1. Introduction

This review focuses on Csp3−Csp3 bond-forming processes that, by overall formal nucleophilic substitution, result in an electrophile losing a leaving group and becoming attached at the α-carbon of an aldehyde (Scheme 1). Direct Csp3−Csp3 bond formation at the α-carbon of an aldehyde by oxidative coupling, where the non-aldehydic partner typically loses a proton or proton equivalent (e.g., an organosilyl group), is also discussed. The emphasis is on recent developments (up to mid 2013), particularly asymmetric transformations; however, to put the newer work in context, an overview of significant older and established strategies is also
included. Rather than just simply present relevant transformations, an attempt has also been made to provide likely principal underlying reaction pathways and, where relevant, catalytic cycles and origins of asymmetric induction. α-Substituted aldehydes arising from heteroatom incorporation, or C–C bond formation resulting in attachment to Csp² centres (e.g., α-arylation/α-vinylation), or by addition processes to C=O (e.g., aldol), to C=N (e.g., Mannich), to C=C (e.g., Michael), constitute large areas of important synthetic chemistry, but lie outside the scope of the present review.

α-Alkyl-substituted aldehydes are used extensively in synthesis. Numerous transformations are possible for such compounds, including addition reactions with a wide range of nucleophiles (especially involving C–C bond formation). As such, chiral, non-racemic, α-alkyl-substituted aldehydes constitute substrates in attractive strategies to reach more complex asymmetric molecular frameworks. Chiral α-alkylated aldehydes may also show useful olfactory properties. Not surprisingly, there has been substantial interest in the development of methodology to access these valuable chiral building blocks. Several recent reviews cover aspects of progress in asymmetric ‘α-alkylation’ of aldehydes; in the present more broader overview, we place the significant achievements they summarise in the context of the long-standing challenge of direct (i.e., single-step) installation of a simple alkyl group at the α-position of an aldehyde.

2. Methods to prepare racemic α-alkyl-substituted aldehydes

While this review principally concerns asymmetric alkylation, α-alkylation of aldehydes in a racemic manner is itself often problematic, typically more so than with ketones, and the difficulties encountered cannot be ignored in the design of stereo-controlled approaches.

2.1. Enolates and related oxo-intermediates

For alkylation in a racemic manner, a variety of enolate-based methods have been examined; however, the techniques developed are far from general. Successful formation of the enolate is highly dependent on conditions for deprotonation, which often do not prevent reaction of the enolate with the aldehyde precursor and this gives rise to mixtures of products (Scheme 2). In some instances, the aldehyde is so electrophilic that the bases used may also competitively undergo 1,2-addition to the carbonyl group. Additionally, reactions may suffer from the base used (e.g., LDA) acting as a hydride transfer agent, reducing the aldehyde to the corresponding alcohol (Scheme 2). Aside from the issue of clean aldololate generation, depending on the electrophile employed, reactions may also suffer from polyalkylation, competing C- and O-alkylation, and other side reactions, among which aldol addition/condensation, Cannizzaro and Tishchenko products are commonly observed (Scheme 2).

Despite the above challenges, certain enolate approaches have shown some success. C- vs O-Enolate alkylation can be biased by the use of larger counter-cations (e.g., K vs Li) and less polar solvents. In the gas-phase O-alkylation of aldenolates is favoured. Non-polar solvents more closely mimic a gas-phase environment and thus under such conditions the size of the counter-cation greatly influences the extent of electrophilic attack at oxygen—larger ions provide greater steric encumberment at oxygen, and promote C-alkylation. Biphasic conditions have also proved effective for generation of some aldenolates. In such systems, a phase transfer catalyst (e.g., Bu4N+X−) is used to solvate small amounts of hydroxide into the organic phase, in turn generating small amounts of the enolate, which reacts with the alkyl halide present. Such alkylations are limited to more reactive halides (e.g., allylic/benzyl halides and MeI), as with less ‘active’ alkyl halides (e.g., i-PrI) self-condensation of the aldehyde dominates. Aldol condensation is less problematic for potassium enolates since potassium is a poor chelator, therefore, the aldolate and precursor enolate are likely to be in equilibrium so allowing alkylation to reach completion. However, while O-alkylation may be suppressed using potassium enolates (vide supra), this is generally only successful for reactions involving more reactive halides. Reactions between aldenolates and unactivated alkyl halides, regardless of 

![Scheme 1. Scope of review.](image1)

![Scheme 2. Competing reactions in aldehyde α-alkylations.](image2)
the counter-cation, are prone to undesirable mixtures of O- and C-alkylation products.

Metal enolates of less electropositive elements, such as tin, where the metal–oxygen bond is more covalent in nature, give better yields of C-alkylation.5 Early studies by Odic and Pereyre demonstrated high C-alkylation regioselectivity could be achieved using tri-\(\text{Bu}\)Sn enolates.11 Subsequent work by Jung and Blum demonstrated this to be an effective strategy for alkylation of acetaldehyde, albeit less so for less reactive electrophiles such as EtI (40%, Scheme 3).12

More recently, Baba et al. showed that manipulation of the coordination number at tin (from four to five) can give remarkable changes in chemoselectivity of tin enolates, at least for those derived from cyclic and acyclic ketones (Scheme 4).13 Jacobsen et al. have exploited this type of reactivity for asymmetric alkylation of ketones, including for the generation of all-carbon-substituted quaternary stereocentres;14 however, this chemistry has not been extended to aldehydes, possibly due to accessibility of the tin enolates, which are typically prepared by transmetallation from other metal enolates or from enol acetates (e.g., using tri-\(\text{Bu}\)Sn methoxide, Scheme 3).

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Monoalkylations with S\(\text{N}1\)-active electrophiles (2\(^+\) and 3\(^+\) alkyl halides) are routinely performed using silyl enol ethers in the presence of a Lewis acid (LA, Scheme 6).17 The covalent Si–O bond prevents unwanted side reactions but also lowers reactivity, therefore, silyl enol ethers react only with activated (typically as carbocations) alkylation agents.5b Their lower reactivity is actually of benefit since aza-enolates and enamines, which are often useful for alkylation with S\(\text{N}2\)-mode electrophiles (Section 2.2), typically undergo elimination reactions with S\(\text{N}1\)-active electrophiles, thus silyl enol ethers offer a complementary reactivity mode.18

In recent years, Brønsted acid catalysis has shown utility in alkylation with S\(\text{N}1\)-active electrophiles (Scheme 7). Synergistic amino-/acid-catalysed systems are covered within the context of chiral organocatalysis (Section 4). Regarding racemic S\(\text{N}1\) alkylation, in 2011 Chi et al. reported a monocatalytic system relying on a Brønsted acid to facilitate both formation of a carbocation (from a suitable alcohol precursor) and also tautomerisation to the reactive enol form of the aldehyde.19 A series of common acid catalysts in conjunction with a broad range of diaryl methanol-derived carbocation electrophiles (notably including ‘less stabilised’ carbocation substrates) and aliphatic aldehydes were tested, which gave the corresponding \(\alpha\)-substituted aldehydes in high yields. Almost contemporaneously, Guo et al. reported similar findings.20 Both studies showed limited success for diastereosymmetric benzhydryl electrophiles (i.e., Ar\(^1\) ≠ Ar\(^2\), Scheme 7). However, the use of ‘less stabilised’
carbocations is advantageous to amine/acid co-catalysis, which does not tolerate such substrates. The systems that were examined show strong solvent dependencies and the $pK_a$ of the acid also influences reaction yields. Improved yields were observed by Guo et al. at elevated reaction temperature. In contrast, the conditions of Chi et al. gave efficient conversion at ambient temperature for many of the aldehydes examined, though higher temperatures were required for some reactions involving ‘less stabilised’ electrophiles. In this work it was found that $t$-BuOH (1 equiv) additive was required in some instances to suppress self-redox reactions of ether intermediate 1, which is formed during the reaction; the tert-butyl ether will form but the product is less susceptible to self-redox (Scheme 7). While both catalytic systems represent novel strategies to alkylations with $S_N1$-active electrophiles, a potential limitation of this chemistry is the reaction stoichiometry with valuable aldehydes, as significant excesses of aldehydes are used [3 equiv (Chi) and 10 equiv (Guo)].

2.2. Enamines, aza-enolates, and related nitrogen intermediates

Seminal work by Stork et al. established the use of enamines as non-charged enolate equivalents. While this work provided an exemplary solution to previously problematic $\alpha$-monoalkylation of ketones [via ketenamines (3 → 4 [R^4=alkyl/aryl], Scheme 9)], alkylation of aldenamines is more limited. Reactive (activated) electrophiles, such as benzylic, allylic and propargylic halides, are suitable reaction partners for aldenamines since $N$-alkylation is reversible with benzylic halides, and in the case of allylic and propargylic halides C-alkylation is achieved by reaction at N followed by [3,3] sigmatropic rearrangement (e.g., 3 → 5 → 6 → 4, Scheme 9). However, the less-hindered nature of aldenamines compared with their ketenamine counterparts invariably results in irreversible $N$-alkylation (3 → 2 [R^4=H], Scheme 9) with weaker...
electrophiles, i.e., simple alkyl halides. Furthermore, synthesis of aldenamines \( \text{I} (R^2=\text{H}) \) is intrinsically more difficult due to the high reactivity of the aldehyde and the basicity of the secondary amines employed, which can lead to aldol side reactions. Aldenamines are also prone to hydrolysis, oxidation and polymerisation. Enamines are typically prepared through condensation according to the method first reported by Mannich and Davidsen in 1936. The mechanismal sequence involves formation of an intermediate aminal, which upon destructive distillation generates the enamine. Several alternative enamine syntheses have also been reported, though substitution about nitrogen is often a limiting factor—more sterically hindered amines generally return lower yields of the corresponding aldenamines, which is unfortunate since these enamines are more prone to C-alkylation (vide infra).

Curphey et al. were the first to demonstrate that sterically hindered (about N) aldenamines can circumvent the problem of N-alkylation. For example, ethylation of enamine 9, prepared by \( \text{K}_2\text{CO}_3 \)-mediated condensation from amine 7 and valeraldehyde (8), gave the desired \( \alpha \)-ethylated aldehyde 10 in good yield (Scheme 10). In contrast, a comparatively less reactive alkyl halide, BuI, provided the corresponding aldehyde 11 in significantly lower yield (24%, Scheme 10), although Hodgson et al. have shown since that the efficiency for this alkylation can be higher (54%).

Further work by Hodgson et al. expanded on this chemistry to demonstrate that severely hindered aldenamines can circumvent the problem of N-alkylation. For example, ethylation of enamine 9, prepared by \( \text{K}_2\text{CO}_3 \)-mediated condensation from amine 7 and valeraldehyde (8), gave the desired \( \alpha \)-ethylated aldehyde 10 in good yield (Scheme 10). In contrast, a comparatively less reactive alkyl halide, BuI, provided the corresponding aldehyde 11 in significantly lower yield (24%, Scheme 10), although Hodgson et al. have shown since that the efficiency for this alkylation can be higher (54%).

\[
\begin{align*}
7 & \overset{\text{Bu}^+}{\underset{n\text{Bu}^-}{\text{NH}}} \quad \overset{\text{O}}{\underset{\text{C}_2\text{H}_5}{\text{O}}} \quad \overset{\text{K}_2\text{CO}_3}{\text{Et}_2\text{O}, \text{rt, 16 h}} \quad \overset{\text{Bu}^+}{\underset{n\text{Bu}^-}{\text{NH}}} \quad \overset{\text{O}}{\underset{\text{C}_2\text{H}_5}{\text{O}}} \\
71\% & \text{MeCN, } \Delta \\
\text{then } \text{NaOAc / } \text{AcOH / } \text{H}_2\text{O} \\
9 & \overset{\text{R} = \text{Et}}{\underset{\text{R}}{\text{O}}} \quad \overset{\text{O}}{\underset{\text{C}_2\text{H}_5}{\text{O}}} \\
10 & 78\% (R = \text{Et}) \\
11 & 24-54\% (R = n\text{Bu})
\end{align*}
\]

Scheme 10. Synthesis and C-alkylation of a sterically hindered aldenamine.

Aldenamine 14 was prepared by eliminative (\(-\text{LiO}) \) insertion of hindered lithium amide 13 into the \( \alpha \)-lithiated derivative of terminal epoxide 12. Synthesis of the aldenamine is a potential limitation of this chemistry, as classical condensation is not possible owing to the hindered nature of the amine 13 (Li=H), and the lithium amide—epoxide methodology used to generate the enamine is in this case modest yielding and restricted to enamines of low molecular weight (since the enamine is sensitive to hydrolysis and purification is by distillation).

Due to the issues of aldenamine N-alkylation with unhindered enamines and the limited methodology available for preparation of hindered aldenamines, \( \alpha \)-monoalkylation of aldehydes is more commonly achieved by way of the enamine salt 17 [also termed aza-enolate (Scheme 12)]. Such metalloenamines 17, which are formed by deprotonation of aldimes 16 (readily prepared by condensation of a primary amine and aldehyde) with an appropriate organometallic reagent (e.g., LDA or RMgX), are not susceptible to N-alkylation and are highly nucleophilic (at the \( \beta \)-carbon) towards less active \( S_2 \)-mode alkylating agents, such as simple alkyl halides; the product aldime 18 is then hydrolysed to give the \( \alpha \)-alkylated aldehyde 19. One of the great benefits of this chemistry is that it can be adapted to an efficient asymmetric version (see discussion of Enders’ SAMP/RAMP hydrazone process, Section 3). However, a drawback of this chemistry is the strongly basic conditions necessary to form the aza-enolate.

Efficient direct generation of \( \alpha \)-alkylated aldehydes is also possible from nitrile precursors by way of a three-step one-pot synthesis (Scheme 13). Reaction of a primary or secondary nitrile with DIBAL-H forms the corresponding aluminium imide 20 readily at 0 °C. Addition of an appropriate base [LDA–HMPA (or \( n\)-BuLi, which is limited to benzylic substrates (\( R^1 \) or \( R^2=\text{aryl} \)) and requires \( 1:1 \text{Et}_2\text{O/hexane solvent mixture to give useful yields} \)] gives rise to a lithium–aluminium complex that can be C-alkylated with a broad range of alkylating agents (notably including \( i\)-PrI).

### 3. Chiral auxiliary-based methodology to access enantioenriched \( \alpha \)-alkyl-substituted aldehydes

Currently, one of the more popular methods to access enantioenriched \( \alpha \)-alkyl-substituted aldehydes is Enders’ SAMP/RAMP hydrazone chemistry (Scheme 14). Hydrazone derivatives 22, which are readily formed by condensation of aldehydes and a chiral, non-racemic hydrazine auxiliary, such as commercially available \((S)-1\)-amino-2-methoxymethylpyrrolidine (21, SAMP), undergo facile deprotonation and alkylation with simple alkyl halides. This strategy routinely provides high levels of asymmetric induction, and a host of other related auxiliaries are now available offering potential to optimise stereoselectivity, if required. However, while this chemistry is capable of attaining very high levels of diastereoadjustment, it is not without limitations. One
constraint is the requirement for very low reaction temperatures (typically between −80 °C and −120 °C). Furthermore, an additional step (e.g., ozonolysis or hydrolytic cleavage mediated by Mel and acid; Scheme 14) is required to retrieve the aldehyde from alkylated hydrazone 23; and the byproduct of this cleavage (a toxic nitrosamine when ozone is used) also requires further manipulation (reduction) to regenerate the auxiliary 21, which can often only partially be recovered.38

Alternative (enolate) approaches, such as those developed by Evans (Scheme 15),39 Myers (Scheme 16),40 and Oppolzer (Scheme 17)41 perform alkylations at a higher oxidation level, and also constitute well-established routes to enantioenriched α-alkyl-substituted aldehydes. These methods consistently produce high levels of chirality transfer, and oxazolidinone 24 (R=H, Evans), pseudoephedrine 27 (Myers) and camphorsultam 30 (Oppolzer) chiral auxiliaries are all commercially available. Precursors 25/28/31 to the enolates are routinely prepared in high yield by simple substitution of the appropriate acyl chloride (or {mixed}anhydride). An additional advantage of Myers’ methodology is that N-acyl products 28/29 are often crystalline, providing a means to increase (chiral) purity through re-crystallisation. However, the indirect nature of these methodologies is a disadvantage, requiring an additional reduction step in each case to access the aldehyde, which in certain cases can be problematic (e.g., endo vs exo N-acyl oxazolidinone cleavage); this latter problem can be minimised by use of a modified auxiliary (e.g., Davies’ ‘SuperQuat’,42 R=Me; Scheme 15). Additionally, while Evans’ oxazolidinone is a powerful auxiliary for alkylations involving activated electrophiles [e.g., reaction of imide 25 (R′=Me) with BnBr gave imide 26 (R′=Me, R″=Bn) in excellent yield (92%) and dr (>99%)] alklylation with simple alkyl halides is less successful [e.g., ethylation of imide 25 (R′=Me) with EtI gave imide 26 (R′=Me, R″=Et) in only 36% yield].3 Although more efficient for alklylation with unactivated alkyl halides, Myers’ asymmetric alklylations require the addition of a large excess of LiCl to increase reaction rate and inhibit O-alkylation of the free hydroxyl group on the auxiliary.

Given the efficiency of alklylations between hindered aldenamines and simple alkyl halides (Section 2.2), Hodgson considered

![Scheme 13. α-Alkylation via metallated aluminium imide.](image)

![Scheme 14. Enders’ hydrazone asymmetric alklylation.](image)

![Scheme 15. Evans’ strategy for asymmetric alklylation.](image)
the possibility of using chiral, non-racemic, hindered aldenamines for asymmetric intermolecular SN2 alkylation. In 2008, Hodgson and Kaka reported the first ‘direct’ synthesis of enantioenriched mono-α-alkyl-substituted aldehydes 34a,b involving intermolecular nucleophilic substitution, by way of C-alkylation of chiral piperidine-derived enamines 33a,b (Scheme 18).43 In this work, diastereocontrol was achieved using chiral trialkylpiperidine auxiliaries 32a,b (Li=H), where the derived aldenamines 33a,b were found to alkylate in moderate to high yield. While stereoselectivity could be improved by installation of a sterically more demanding substituent α- to N on the piperidine (Me→i-Pr, 33b→34b, Scheme 18), this resulted in diminished yields of alkylation. Computational analysis44 indicated that the C-6 Me substituent resides axial in the ground state conformation of enamine 33a (i.e., 33(ax) {R=Me}, Fig. 1) in order to minimise A1,3 strain, which is present in the ring-flipped conformer (33 eq), Fig. 1). Conversely, the C-6 i-Pr substituent in enamine 33b lies equatorial in the ground state (33 eq) {R=i-Pr}, Fig. 1). This minimises more significant 1,3-diaxial interactions imposed by the isopropyl substituent but reduces the reactivity of the enamine (in the ground state), since the olefinic component twists orthogonal to the nitrogen lone pair rendering the enamine inactive to C-alkylation.22a,23,45 While the reactive axial conformation (where N lone pair–π overlap becomes possible) is attainable at elevated temperatures for enamine 33b increasing the size of the substituent at this position (e.g., exchanging i-Pr for t-Bu) is predicted to lower enamine reactivity and in turn reduce yields of alkylation.

In this work, diastereocontrol was achieved using chiral trialkylpiperidine auxiliaries 32a,b (Li=H), where the derived aldenamines 33a,b were found to alkylate in moderate to high yield. While stereoselectivity could be improved by installation of a sterically more demanding substituent α- to N on the piperidine (Me→i-Pr, 33b→34b, Scheme 18), this resulted in diminished yields of alkylation. Computational analysis44 indicated that the C-6 Me substituent resides axial in the ground state conformation of enamine 33a (i.e., 33(ax) {R=Me}, Fig. 1) in order to minimise A1,3 strain, which is present in the ring-flipped conformer (33 eq), Fig. 1). Conversely, the C-6 i-Pr substituent in enamine 33b lies equatorial in the ground state (33 eq) {R=i-Pr}, Fig. 1). This minimises more significant 1,3-diaxial interactions imposed by the isopropyl substituent but reduces the reactivity of the enamine (in the ground state), since the olefinic component twists orthogonal to the nitrogen lone pair rendering the enamine inactive to C-alkylation.22a,23,45 While the reactive axial conformation (where N lone pair–π overlap becomes possible) is attainable at elevated temperatures for enamine 33b increasing the size of the substituent at this position (e.g., exchanging i-Pr for t-Bu) is predicted to lower enamine reactivity and in turn reduce yields of alkylation.

In the exploration of more reactive enamines, the present authors considered tropane 35a (Scheme 19).46 It was believed enamines derived from the conformationally locked tropane 35a would give improved reactivity compared with enamine 33b and, given the structural similarity between these auxiliaries, a similar degree of stereoccontrol might be attained. Ethylation of tropane-derived enamine 37a with EtI proceeded in high yield but
showed a substantial reduction in $\text{er}$, interestingly with opposing
diastereofacial selectivity. The observed facial preference was found
to be consistent with DFT studies. Subsequent DFT calculations
predicted formal expansion of the embedded pyrrolidine would
give significantly improved $\text{er}$ (85:15), with the originally envisaged
sense of asymmetric induction. Indeed, ethylation of the corre-
sponding homotropane-derived enamine $37b$ proceeded with antici-
patated enantioinduction and a higher degree of stereoselectivity,
albeit lower than for aldehydes with enamine $33b$. The en-
amines themselves were prepared according to a modified pro-
cedure based on Hansson and Wickberg’s earlier work; this
involves an unusual Grignard addition
and cascade reactions.4e For organocatalytic asymmetric
breakthroughs include organocatalysed aldol, Mannich, tandem
progress in asymmetric
4. Organocatalytic aldime diastereomer.
dependent, as the approach relies on selective crystallisation of one
iminium49 and enamine50 catalysis have resulted in dramatic
continued as the approach relies on selective crystallisation of one
iminium49 and enamine50 catalysis have resulted in dramatic

**Scheme 19.** Tropane- and homotropane-derived enamines for asymmetric $\alpha$-alkylation.

4.1. $\text{SN}_2$ alkylation

Asymmetric aldenamine catalysis has found utility in a wide
range of transformations.51 In 2004, List and Vignola reported the
first aminocatalytic intramolecular $\alpha$-alkylation of aldehydes as
a powerful method for asymmetric ring formation (Scheme 21).54
Aldehydes containing a leaving group at the $\omega$-position under-
went cyclisation in the presence of catalytic (S)-$\alpha$-methyl pro-
line in moderate to high yields, with excellent stereoselectivity.
Computational studies provided support for the significant rise in
asymmetric induction when using $\alpha$-methyl proline compared with
proline, which was seen to provide a stronger bias for reaction
proceeding through an anti-enamine in the transition state
(Scheme 21).55 This slow (24–48 h), below ambient temperature,
enamine alkylation process is facilitated by cyclisations leading to
five- and three-membered rings, but in this case also in the tran-
sition state (necessarily containing a three-atom linear arrange-
mation which includes simple alkyl based-electrophiles has yet to be
found, and has been termed a ‘Holy Grail’ of organocatalysis.4c

**Scheme 20.** CIDR of racemic $\alpha$-alkyl-substituted aldehydes.

4. Organocatalytic $\alpha$-alkylation

Over the last dozen years or so, groundbreaking studies on
iminion59 and enamine60 catalysis have resulted in dramatic
progress in asymmetric $\alpha$-functionalisation of aldehydes.51 Notable
breakthroughs include organocatalysed aldol, Mannich, tandem
and cascade reactions.56 For organocatalytic asymmetric $\alpha$-alkyl-
aldehyde, several ingenious methods have been developed
for specific classes of partner substrates.52 However, a general so-
lution which includes simple alkyl based-electrophiles has yet to be
found, and has been termed a ‘Holy Grail’ of organocatalysis.4c

**Scheme 20.** CIDR of racemic $\alpha$-alkyl-substituted aldehydes.

Intermediate enamine underwent preferential intramolecular $C$-
alkylation (intramolecular N-alkylation of the E-enamine is not
generically feasible), rather than intermolecular aldolisation.
However, attempts to develop this reactivity intermolecularly
proved unsuccessful, with self-aldolisation dominating.56 Attem-
pted reaction of propionaldehyde with BnBr, catalysed by proline in
the presence of Et$_3$N resulted in benzylation of the catalyst, giving
N-benzylproline and N-benzylproline benzyl ester.54 These studies
indicate that amine-catalysed intermolecular alkylation of aldehydes through enamine SN₂-like reaction with simple alkylating agents is less preferred than self-aldolisation and catalyst alkylation.

Although organocatalysed intermolecular α-alkylation of aldehydes with simple alkyl halides has yet to be achieved, Palomo et al. have developed an asymmetric intermolecular α-allylation (Scheme 22). In this work, a base additive (e.g., DABCO, carefully chosen to avoid racemisation of the product aldehyde) is used to activate a 2-(bromomethyl)acrylate towards attack by a proline-derived enamine generated in situ. While the overall reaction constitutes a simple substitution, DFT studies indicate the reaction is assisted by the electron-accepting ester group present on the allylating agent and support an initial Michael-type conjugate addition, followed by elimination.

Building on this work, Palomo et al. have recently reported a procedure for the α-allylation of aldehydes with 3-substituted-2-(bromomethyl)acrylates that generates two contiguous stereocentres with excellent diastereo- and enantioselectivity (Scheme 23). However, a large excess of aldehyde is required.
Despite the difficulties mentioned above of using purely SN2-active electrophiles in alkylations, a variety of intramolecular SN2 processes (including domino alkylations) have been reported since List and Vignola’s seminal paper; generally, these procedures utilise proline-derived catalysts. A sub-category of reactions within this class are based on conjugate addition to chiral α,β-unsaturated iminium ions (formed by condensation of the aminocatalyst and an enal) where the nucleophile contains a (halide) leaving group, which is subsequently displaced by cyclisation of the enamine intermediate. For example, Cordova and Wang have demonstrated asymmetric cyclopropanation in excellent yields and enantioselectivities using this concept (Scheme 24). A potential reaction pathway is also indicated in Scheme 24. Under the reaction conditions, iminium ions are generated in situ from condensation of the Jørgensen–Hayashi proline-derived aminocatalyst with enals. Concurrent enolisation of the bromomalonate substrate provides the Michael donor for 1,4-addition. Following conjugate addition, the transient enamine intermediate undergoes SN2 intramolecular alkylation, followed by in situ hydrolysis to provide the cyclopropane adduct.

In 2008, Enders et al. reported a remarkable alternative strategy to create an enamine intermediate, which undergoes intramolecular alkylation with the creation of an all-carbon quaternary stereocentre (Scheme 26). In this work, an in situ generated aldehyde-derived enamine undergoes preferential intermolecular Michael addition with an ω-iodo-substituted nitroalkene. Proton transfer neutralises zwitterion 41 (evidently outcompeting potential intramolecular alkylation α- to the nitro group) to give the cyclisation precursor.

### 4.2. Cation alkylation

#### 4.2.1. Brønsted acid co-catalysis.

In addition to the enamine-catalysed SN2 aldehyde α-alkylations described in Section 4.1, SN1-based processes have been a focus of considerable interest. Initial findings in the laboratories of Petrini and Melchiorre, concerning alkylation of an α-proline enamine by a carbocation formed in situ from a bisaryl sulfonate (Scheme 27), inspired new avenues of research in this area. For example, Cozzi et al. have utilised this reactivity mode to α-alkylate aldehydes with benzhydrol substrates (Scheme 27).

Since this area was last reviewed, a number of papers have been published reporting similar modes of alkylation. Several of these new methods merge transition metal Lewis acid- and amino-catalysis, and are discussed in the next section (Section 4.2.2). Under Brønsted acid catalysis, Ji et al. have very recently documented a strategy for enantioselective generation of 3-indolylalkoxindoles by way of asymmetric alkylation of aldehydes with 3-hydroxy-3-indolylxindoles facilitated by an imidazolidinone (Scheme 28). While a variation of this method of α-alkylation has found application in the total synthesis of (+)-gliocladin C.

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**Scheme 24.** Enantioselective cyclopropanation of α,β-unsaturated aldehydes.

**Scheme 25.** Cyclopentanes by tandem conjugate addition/α-alkylation.
a limitation of these methodologies is the requirement for functionality in the electrophile that is capable of promoting generation of the transient carbocation.

Loh et al. have reported an ‘acid-free’ method of SN1-activation using trifluoroethanol (Scheme 29). While this chemistry has obvious benefits for acid-sensitive substrates, high temperatures are required and although the chemistry expands the utility of fluorinated solvents, expense and toxicity are potential drawbacks.

With organocatalytic \( \alpha \)-alkylation using secondary (benzhydryl-type) alcohols now well-established, the pursuit of more elaborate tandem reactions is underway. For example, Behr,
Christmann et al. have reported a one-pot hydroformylation/SN1 alkylation (Scheme 30). A range of terminal alkenes were examined, which gave moderate to excellent yields with good stereocontrol. Conjugated alkenes did not undergo reaction.

An alternative approach to methods employing alcohols for SN1 α-alkylations has been developed by Tian et al., which recognises the potential of N-doubly benzylic sulfonamides as SN1-substrates (Scheme 31). Under the acidic reaction conditions, a sulfonamide undergoes C–N cleavage generating a stabilised carbocation that subsequently reacts with an in situ generated chiral aldenamine. The acid and amine catalyst are regenerated on hydrolysis of the resulting iminium ion 42.

In the same study, tropylium hexafluorophosphate was examined as a cationic electrophile, and α-alkylations proceeded in comparably high yields and excellent enantioselectivities (Scheme 33). Of particular merit in the area of cationic organocatalytic transformations is a strategy conceived by Cozzi et al. that achieves formal asymmetric α-methylation of aldehydes (Scheme 34). In this work, enamines derived from an imidazolidinone undergo highly stereoselective addition to 1,3-benzodithiolylium tetrafluoroborate in good yield. The resulting aldehydes are reduced to their corresponding alcohols in order to avoid post-reaction epimerisation. Subsequent reduction with Raney Ni of the 1,3-
benzodithiol group provides access to the enantioenriched 2-methylated alcohol. Furthermore, the 1,3-benzodithiol group in the product following alkylation–reduction can be easily metalated and then alkylated (with alkyl halides) to provide longer chain alkyl groups in the \( \alpha \)-position, without degrading the enantiopurity of the aldehyde. While this is a significant advance towards the ‘Holy Grail’,\(^{4c} \) it is still an indirect approach (as the \( \alpha \)-alkylated aldehyde is not directly obtained from the alkylation step).

Cozzi et al. have subsequently extended this methodology to access all-carbon quaternary stereocentres from \( \alpha \)-substituted propanal (Scheme 35).\(^ {74} \) In this work, a range of readily accessible amino acids, primary amines and an imidazolidinone were examined as potential organocatalysts; however, all proved unsuitable. Subsequent examination of a series of \( \text{cinchona} \) alkaloid-derived primary amines established a good organocatalyst candidate. Further enhancement of asymmetric induction was achieved by introducing a chiral acidic additive [\((-\)-CSA]. Interestingly, enantiofacial selectivity could be reversed by changing the solvent (from MeCN to CH\(_2\)Cl\(_2\)); an experimental result in congruence with findings by Melchiorre et al. in asymmetric sulfa-Michael additions to \( \alpha \)-branched enones.\(^ {75} \) \( \alpha \)-Alkyl-substituted propanals gave the corresponding quaternary alkylation adducts in high yield (76–79\%) but enantioselectivity in these cases was lower (66:34 to 73:27 er) than with \( \alpha \)-aryl systems.

4.2.2. Lewis acid co-catalysis. Cozzi et al. have exploited indium salts as co-catalyst for \( \alpha \)-allylation of aldehydes with allylic alcohols (Scheme 36).\(^ {76} \) In this work, a range of readily accessible amino acids, primary amines and an imidazolidinone were examined as potential organocatalysts; however, all proved unsuitable. Subsequent examination of a series of \( \text{cinchona} \) alkaloid-derived primary amines established a good organocatalyst candidate. Further enhancement of asymmetric induction was achieved by introducing a chiral acidic additive [\((-\)-CSA]. Interestingly, enantiofacial selectivity could be reversed by changing the solvent (from MeCN to CH\(_2\)Cl\(_2\)); an experimental result in congruence with findings by Melchiorre et al. in asymmetric sulfa-Michael additions to \( \alpha \)-branched enones.\(^ {75} \) \( \alpha \)-Alkyl-substituted propanals gave the corresponding quaternary alkylation adducts in high yield (76–79\%) but enantioselectivity in these cases was lower (66:34 to 73:27 er) than with \( \alpha \)-aryl systems.
Examination of a variety of indium salts established InBr$_3$ as the preferred catalyst. Screening of solvents showed significant solvent dependency, with CH$_2$Cl$_2$ proving to be the only effective solvent for such transformations. The choice of organocatalyst also proved critical; whereas proline or the Jørgensen–Hayashi prolinol silyl ether gave no trace of product, MacMillan’s imidazolidinone gave efficient conversion and high stereocontrol. A limitation of this chemistry is the substrate scope, where large vinylic substituents are required to promote diastereoselectivity in the reaction and the aromatic substituents are necessary for stabilisation of the intermediate carbocation. The observed syn-selectivity likely arises from different steric demands of the 1,1-diphenyl tether and the Ar group in postulated syn- and anti-transition states, with greater steric interaction envisaged between the 1,1-diphenylethenyl group and imidazolidinone tert-butyl group.

In 2012, Xiao reported a similar cooperative catalysis system to achieve stereoselective $\alpha$-benzhydrylation with symmetrical (and unsymmetrical) diarylmethanols (Scheme 37).
In the same year, Cozzi et al. published similar findings, using a combination of In(OTf)$_3$ with a MacMillan imidazolidinone (Scheme 38). This method allows the use of substrates that cannot form stable carbocations through Brønsted acid catalysis (c.f., Section 4.2.1). It demonstrates the coupling of alcohols possessing an alkyl tether ($R^2$=alkyl), although an electron-rich benzylic 4-$(Me_2N)C_6H_4$ group is required for successful reaction and modest $dr$s are observed.

Rueping et al. have applied similar dual catalysis to the synthesis of chromenes in modest $dr$s (Scheme 39). Following reduction, the absolute configuration of the major alcohol diastereomer was determined to be $S,R$ through CD- and NMR-spectroscopy. Suggested competing transitions states are illustrated in Scheme 39, which depict reaction of the enamine at the $Si$- and $Re$-faces of the oxonium intermediate; favourable $\pi$-stacking interactions may bias $Si$-face addition.

In 2010, MacMillan and Allen merged organocatalysis and Lewis acid catalysis to achieve $\alpha$-trifluoromethylation (Scheme 40). In this work, 3,3-dimethyl-1-trifluoromethyl-1,2-benziodoxole (Togni’s reagent) is used as the $\alpha$-trifluoromethylation agent. It is proposed that aldenamine 43 reacts with iodonium salt 44 (formed by copper-assisted $I$–$O$ cleavage of Togni’s reagent) through an addition/reductive elimination sequence (the latter occurring with retention of configuration) that furnishes iminium 45 and liberates the Lewis acid catalyst. Hydrolysis regenerates the organocatalyst and provides the $\alpha$-trifluoromethylated aldehyde.

4.2.3. Hydrogen-bond co-catalysis. Following a rather different cationic ($S_N1$-type) pathway to those described previously, is Jacobsen et al. enantioselective $\alpha$-benzhydrylation of $\alpha$-aryl propanals catalysed by primary aminothiourea derivatives (Scheme 41). In this work, the anion-binding properties of aminothioureas are exploited to generate a carbocation from a neutral benzhydryl bromide substrate by anion abstraction, which then undergoes attack by in situ generated enamine. Where non-primary amines were employed as potential H-bond catalysts no reaction was observed. Additionally, the urea moiety was found to be crucial—if amino-carbamate catalysts were employed no reaction was observed. The suggested reaction pathway is illustrated in Scheme 41. The possibility of an $S_N2$-type pathway was ruled out based on Hammet and kinetic isotope studies, and through competition experiments. This chemistry is an elegant approach to the construction of aldehydes with $\alpha$-quaternary stereocentres. However, as with the $S_N1$-processes discussed earlier, this
Scheme 40. Enantioselective α-trifluoromethylation.

Scheme 41. Hydrogen-bond catalysed α-benzhydrylation.
methodology is restricted to electrophiles that can generate stabilised carbocations.

4.3. Dehydrogenative \( \alpha \)-alkylation

The xanthyl group has also been introduced at the \( \alpha \)-position of aldehydes in an asymmetric manner by way of dehydrogenative electro-organocatalysis, albeit with modest enantioselectivity (Scheme 42). Electrochemical investigations and control experiments favour an enamine radical cation—xanthene radical coupling pathway (c.f., Scheme 61), though a xanthene cationic intermediate cannot be entirely dismissed since no homocoupled products could be isolated.

Following preliminary benzylic C—H activation studies for \( \alpha \)-alkylation of aldehydes performed by Cozzi et al. (which were mediated by DDQ at \(-25\) °C acting as oxidant), Cui, Jiao et al. have developed an asymmetric intermolecular dehydrogenative aldehyde \( \alpha \)-xanthylation procedure facilitated by molecular oxygen as oxidant (Scheme 43). Under the acidic conditions either of the two peroxides shown in Scheme 43 could be formed, which subsequently liberate hydrogen peroxide and the corresponding benzylic (xanthyl) carbocation.

In related work, Xiao et al. have modified Cozzi’s original DDQ procedure; by replacing MacMillan’s imidazolidinone with the Jørgensen–Hayashi catalyst they were able to slightly reduce catalyst loading (from 20 to 10 mol %) and perform reactions involving xanthyl and tropylium cations at rt.

4.4. Transition metal co-catalysis

4.4.1. Allylation. Recent research has demonstrated the power of merging transition metal and organo-catalysis. In 2006, Córdova and Ibrahem reported that palladium and enamine catalysis can work in synergy to achieve intermolecular \( \alpha \)-allylation of aldehydes in high yield and chemoselectivity (Scheme 44), the latter referring to the avoidance of catalyst N-allylation—a persisting problem in the attempts to achieve transition metal-free organocatalytic \( \alpha \)-alkylation (see also Section 4.1).

In this chemistry, an enamine is allylated by an allylic acetate after the latter is activated through \( \pi \)-allyl palladium formation. Preliminary investigation of chiral, non-racemic pyrrolidine and proline derivatives with the aim of developing an asymmetric process led to good levels of asymmetric induction (up to 87:13 er), but yields were poor (5–45%). Subsequent optimisation studies showed solvent to be important for both reactivity and stereocontrol, with DMSO giving the highest levels of conversion and DMF the best er; using a 1:1 mixture of these solvents at reduced temperature gave significantly improved yields and excellent levels of asymmetric induction (Scheme 45). The aldehydes formed were directly reduced to the corresponding alcohols to
minimise epimerisation. Breit et al. also successfully examined al\-lylic alcohols as partners for aldehyde (and ketone) $\alpha$-allylations under proline/Pd co-catalysis but did not achieve ‘efficient enantioinduction’.90

Ibrahim, Cordova et al. have very recently extended amine and Pd(0) co-catalysis to enantioselective intramolecular aldehyde $\alpha$-allylation, where the precursor enamine intermediate is obtained in situ by reversible Michael addition of a substituted malonate or cyanoacetate to an enal activated as the corresponding iminium; up to four stereocentres, including one quaternary carbon, are created in this process.91

In 2007, Mukherjee and List published an alternative enamine-based route to $\alpha$-allylated aldehydes employing a chiral phosphoric acid catalyst [(R)-TRIP] in combination with palladium, which together mediate high enantioselectivity through a Tsuji–Trost-type mechanism (Scheme 46).92 Here an allylic secondary amine acts as both a source of the allylic palladium and the aldehyde-derived enamine. The phosphoric acid co-catalyst functions both as...
a Brønsted acid and a counteranion/ligand for the π-allyl inter-
termEDIATE, imparting facial selectivity on the attacking nucleo-
phile. This chemistry is also applicable to α,α-disubstituted aldehyde
(R1 and R2 s H, see e.g., in Scheme 46), providing a novel route to all-carbon quaternary stereocentres.

Jiang and List subsequently extended the above methodology, replacing the original benzhydryl amino-allylating reagent by benzhydrylamine and simple allylic alcohols (Scheme 47).93

In addition to palladium sources, gold complexes have recently been shown to be effective co-catalysts for asymmetric intramolecular α-allylation.94 Bandini et al. utilised a cationic gold complex in combination with MacMillan’s imidazolidinone to effect α-allylation through an anti/anti SN20 reaction sequence (Scheme 48). The putative reaction cycle involves initial condensation of aldehyde and MacMillan’s imidazolidinone catalyst, accelerated by benzoic acid. Electrophilic activation of the Z-allylic alchohol present in the resulting enamine by cationic gold (which is less effective for thermodynamically more stable E-allylic alcohols) promotes anti-carboauration, the product of which undergoes anti-β-hydroxy elimination to give iminium ion. Subsequent hydrolysis

While promising ers have been achieved by both Córdova and by List, since these reactions proceed via palladium π-allyl com-
plexes they are restricted to allylations giving γ,δ-unsaturated aldehydes.
furnishes the \( \pi \)-allylated aldehyde and regenerates the organocatalyst. With secondary alcohols (i.e., \( R = H \), Scheme 48), a variety of prolinol and imidazolidinone organocatalysts were employed with varying degrees of success. An interesting aspect of the results obtained with secondary alcohols is the observed discrimination between (\( R \))- and (\( S \))-enantiomers by the dual catalytic system: with the (\( S \))-imidazolidinone shown, (\( S \))-configured secondary alcohol (\( R=CH_2CH_2Ph, X=NTs \)), Scheme 48 provided the corresponding product [42%, 49:1 \( E/Z \) ratio, 99:1 (88:12) \( e.r. \)], while \( R \)-alcohol failed to react.

### 4.4.2. Propargylation

Expanding on their earlier work concerning enantioselective propargylic substitution reactions, Nishibayashi et al. have developed a ruthenium-assisted alkylation of in situ generated enamines 46 with propargylic alcohols to give \( \pi \)-propargylated aldehydes (Scheme 49). The proposed reaction pathway proceeds by initial formation of an allenylidene ruthenium complex 47 by reaction of propargyl alcohol with the transition metal catalyst (a thiolate-bridged diruthenium complex). Lack of an analogous reaction for internal alkynes provides support for an allenyldiene intermediate. Subsequent attack of aldenamine 46 [formed in situ as the \( \text{anti}-(\text{E}) \)-enamine (energetically favoured)] at the \( \gamma \)-position of the allenyldiene complexes 47 generates a diastereomeric mixture of allynyl iminium complex 48 (as a consequence of \( Re-/Si \)-facial attack of allenyldiene 47, by contrast, only the \( Si \)-face of enamine 46 is attacked due to steric shielding of the \( Re \)-face by the prolinol substituents). Hydrolysis of the allynyl iminium ion complex 48 and subsequent ligand exchange with propargyl alcohol continues the catalytic cycle and liberates the product diastereomeric propargylic aldehydes, which were directly reduced to the corresponding alcohols.

Slightly higher diastereoselectivity [\( \sim 4:1 \) (syn/anti)] was subsequently observed using propargylic pentafluorobenzoates under CuOTf/enamine co-catalysis (Scheme 50). Excess BINAP is used to prevent dissociation of diposphine from copper. The role of BINAP is not specified, but it is not to impart stereoccontrol (racemic BINAP gives similarly high \( d.r. \)); however, diposphine additive is essential—without BINAP complex reaction mixtures were formed.

In 2011, Nishibayashi et al. reported a strategy for enantioselective propargylation with internal alkynes employing \( \text{InBr}_3 \) (acting as Lewis acid) in conjunction with a MacMillan imidazolidinone organocatalyst, which gave the corresponding \( \pi \)-propargylated aldehydes in excellent yields as diastereomeric mixtures with high enantiopurity.

Contemporaneously, Cozzi et al. utilised indium triflate with a marginally different MacMillan imidazolidinone catalyst to facilitate propargylation (with internal alkynes, \( FG \)-organosilyl, aryl, alkyl) under synthetically mild conditions on water (c.f., \( CH_2Cl_2 \) used by Nishibayashi), which gave significantly improved diastereoselectivity (Scheme 51).

In comparison to Nishibayashi’s Ru/Cu work, this catalyst combination gives opposite diastereoselectivity. Furthermore, if \( FG \)=TMS facile desilylation of the product aldehydes with \( K_2CO_3/MeOH \) provides an efficient route to the anti-terminal alkyne, thus offering a stereo-complementary method to the above ruthenium-catalysed work.

### 4.5. Radical and electron transfer processes

#### 4.5.1. SOMO activation

In early 2007, MacMillan et al. reported a novel mode of activation for organocatalytic reactions of aldehydes, termed SOMO activation. Typically, organocatalytic reactions are catalysed by either LUMO lowering iminium catalysis and/or HOMO raising enamine catalysis. MacMillan’s chemistry intersects these two reaction modes utilising SOMO activation.

In MacMillan’s work involving C–C bond formation, selective one-electron oxidation [using ceric ammonium nitrate (CAN)] of a transient enamine, formed by condensation of an aldehyde and imidazolidinone catalyst, provides a SOMO-activated radical cation that is reactive to electron neutral but \( \pi \)-rich SOMO nucleophiles (SOMOphiles), such as allylic silanes, with high levels of facial discrimination (Scheme 52). Further one-electron oxidation of the resulting dative-stabilised \( \beta \)-silyl radical generates a \( \beta \)-silyl stabilised cation, which undergoes alkene-generating desilylation. This chemistry provides an attractive approach to enantioenriched \( \pi \)-allylated aldehydes, which is conceptually different to those methods developed by Cordova and List (Section 4.4.1). The process tolerates a range of solvents (DME identified as optimal) and, importantly, aldehyde...
Scheme 49. Ru-complex catalysed enantioselective α-propargylation of aldehydes.

Scheme 50. Cu-BINAP catalysed enantioselective α-propargylation of aldehydes.
epimerisation or polyallylation was not observed with extended reaction times.

MacMillan et al. have since utilised this same mechanistic paradigm in intramolecular $\alpha$-allylation, which enabled the construction of five-, six- and seven-membered carbocycles, as well as tetrahydropyrans and piperidines in high yield and with promising levels of stereocontrol (Scheme 53). Addition of water (2 equiv)—which assists solubilisation of CAN—and for some substrates exchanging the solvent (DME by acetone) and base [NaHCO$_3$ by 2,6-di-tert-butylpyridine (2,6-DTBP)], gave improved reaction efficiency and asymmetric induction.

Utilising a similar SOMO activation platform, MacMillan et al. reported an asymmetric method for $\alpha$-enolation of aldehydes (Scheme 54). In this chemistry, a SOMO-activated radical cation is accessed in a similar manner to that discussed above, which then couples with a silyl enol ether. Further one-electron oxidation of the resulting $\alpha$-silyloxy radical 49 by CAN generates an oxonium ion that on desilylation and iminium hydrolysis gives an enantioenriched $\gamma$-ketoaldehyde.

The scope of organo-SOMO chemistry was usefully expanded, by exchanging the electron-rich olefinic coupling partners (allyl/enol silanes) for simple, non-activated, styrenes.
With styrenes, the carbocation 50, resulting from oxidation of benzylic radical 51, does not undergo ready E1 elimination (due to the absence of a suitable \( \beta \)-activation/leaving group, unlike with allyl/enol silanes) and is preferentially trapped by nitrate anion [released through reduction of the Ce(IV) oxidant] to form the corresponding nitrate ester (3:1 dr). The latter proved a useful handle for further transformations, such as hydrogenolysis (thus achieving overall aldehyde-\( \alpha \)-homobenzylation in

\[ \text{Scheme 53. Intramolecular } \alpha \text{-allylation through organo-SOMO catalysis.} \]

[Suggested Reaction Pathway:]

\[ \text{Scheme 54. Enantioselective } \alpha \text{-enolation.} \]
an enantioselective manner) and heterocycle formation through borohydride reduction—cyclisation (Scheme 55). While outside the scope of this review, it is noteworthy that this organo-SOMO catalysis can also be utilised in $\alpha$-vinylation with vinyl trifluoroborates.$^{107}$

In 2013, the SOMO activation mode was extended to intramolecular $\alpha$-allylation of unactivated aldehyde—olefin substrates (Scheme 56).$^{108}$ In this chemistry, ferric oxidation of an in situ generated aldenamine forms the enamine radical cation, which undergoes radical cyclisation and subsequent one electron oxidation to give tertiary carbocation 52. Subsequent deprotonation/hydrolysis regenerates the organocatalyst and liberates the ‘homo-ene’ product. Chair-$\mathcal{E}$ geometry in the transition state rationalises the observed trans diastereoselectivity, whereas regioselective formation of the less substituted alkene may reflect minimisation of allylic strain. Overall, this process can be viewed as a dehydrogenative coupling. Aside from being intramolecular, it also differs from those intermolecular examples comprising Section 4.3, since in the present case the hydrogen atom removed from the aldehyde partner is not lost from the carbon becoming

Scheme 55. Enantioselective $\alpha$-carboxoxidation.

Scheme 56. Enantioselective intramolecular aldehyde $\alpha$-allylation with trialkyl-substituted alkenes.
attached at the aldehyde $\alpha$-position (but rather from an allylic site).

4.5.2. Photoredox organocatalysis. In 2008, Nicewicz and MacMillan facilitated aldehyde $\alpha$-alkylations by way of single electron transfer (SET) using a dual catalytic system of an imidazolidinone salt and photoredox catalyst,\textsuperscript{109,110} which is widely recognised as a landmark achievement in the field of organocatalysis (Scheme 57).\textsuperscript{4a,b}

The reaction pathway is rationalised by two intertwined catalytic cycles (Scheme 58) and follows an antipodal reactivity compared with the above methodology using allylic silanes (Scheme 52). Initiation of the reaction occurs through application of a suitable light source (e.g., a household 15 W fluorescent light bulb), which excites the photoredox catalyst $[\text{Ru}(\text{bpy})_2^{2+}]$ (bpy = 2,2'-bipyridine) to a higher energy state ($^*\text{Ru}(\text{bpy})_2^{2+}$). This excited species oxidises a sacrificial quantity of (in situ generated) enamine, creating a reduced ruthenium complex $\text{Ru}(\text{bpy})_2^{2+}$. The latter enters into a productive catalytic cycle by single electron transfer to the electron-deficient organohalide substrate, regenerating $\text{Ru}(\text{bpy})_2^{2+}$ and forming, by loss of halide anion, a radical 53, which reacts with the enamine. This last step leads to an $\alpha$-amino radical 54, which through SET to excited $^*\text{Ru}(\text{bpy})_2^{2+}$ provides iminium 55, closing the photoredox catalytic cycle. The organocatalytic cycle is closed by subsequent hydrolysis of iminium ion 55. A base additive, 2,6-lutidine, neutralises the HBr byproduct. This chemistry offers an elegant and efficient strategy for $\alpha$-alkylation of aldehydes (high yields and efficiencies, synthetic simplicity, and compatibility with a wide range of substrates); however, it does require electrophilic organohalide partners that contain a capto radical-stabilising functional group (FG) or groups, such as benzoyl. In contrast to the previous section (4.5.1) where a SOMO-activated enamine radical cation reacts with $\pi$-rich systems, here the neutral but electron-rich enamine reacts with electron-deficient radicals.

The rarity and associated toxicity issues of ruthenium-based catalysts have prompted investigation of replacement photoredox catalysts in the above chemistry. For example, Zeitler et al. examined Eosin Y, an organic xanthene dye sensitizer, which proved a good substitute showing comparable photoredox properties to the transition metal complex.\textsuperscript{111} Performing reactions with Eosin Y under microflow conditions was found to be additionally advantageous—reducing reaction times from 18 h to 45 min.\textsuperscript{112} Another ‘green’ method has been reported by Ferroud et al. where the ruthenium-based catalyst was exchanged for Rose Bengal, an alternative organic dye sensitizer.\textsuperscript{113} König et al. have

![Scheme 57. Dual organo- and photoredox catalysis for asymmetric $\alpha$-alkylation.](image1)

![Scheme 58. Dual organo- and photoredox catalytic system.](image2)
also recently demonstrated the utility of heterogeneous catalysis, using inorganic semiconductors [e.g., PbBiO$_2$Br, blue light ($\lambda$=440 nm)] in place of ruthenium or dye photo-sensitisers. Another notable extension of MacMillan’s work is the development, by He and Duan, of chiral metal–organic frameworks (MOFs) that house the organocatalyst (in this case, L- or D-pyrrolidine-2-ylimidazole) and photoactive unit (4,4’$'$-nitrotribenzoate). These heterogeneous reaction systems simplify recovery and re-use of the catalysts (since they are embedded within a Zn-based solid support), and help to reduce heavy metal contamination of the product. Additional benefits of MOFs are the reduced hazards and costs, not only in the reactions themselves, but also in terms of disposal. While these latter modifications are encouraging, with the exception of König et al. (who also tested bromoacetophenone and 2,4-dinitrobenzyl bromide), an α-bromo malonate was the only electrophilic partner examined.

MacMillan has extended his photoredox/organocatalysis strategy to α-benzylation of aldehydes (Scheme 59). In this work, an iridium photoredox catalyst [fac-Ir(ppy)$_3$ (ppy = 2-phenylpyridine)] was used to facilitate s-bond cleavage of the benzylic bromide to give the key electrophilic benzyl radical. Following a similar mechanism to that illustrated in Scheme 58 for α-alkylation, α-benzylation was achieved using organocatalyst 57 in high yield and er; however, this chemistry is limited to reactions with benzylic bromides that have electron-withdrawing aryl motifs; attempted reaction with simple benzyl bromide (56, Ar=Ph) proved unsuccessful.

![Scheme 59. Asymmetric α-benzylation through organo-photoredox catalysis.](image)

The MacMillan laboratory has also shown photoredox organocatalysis to be an efficient method for preparation of α-perfluoroalkylated aldehydes (Scheme 60). Preliminary investigation of a range of aldehyde substrates showed broad functional group compatibility, achieving trifluoromethylation ($R^2$=R$^3$=F) in excellent yields and high ers (analysed as the alcohol, following reduction with NaBH$_4$) with an iridium photoredox catalyst [Ir(p-ppy)$_2$(dbt-bpy) (dbt-bpy=4,4’-di-tert-butyl-2,2’-bipyridine)] and imidazolidinone organocatalyst 59; carrying out the reaction at −20 °C avoids racemisation. Subsequent examination of a series of fluoroalkyl halides 58 ($R^2$ and/or $R^3$=F) showed similar propensity for formation of the corresponding α-perfluoroalkylated aldehydes, with comparable stereoselectivity.

Most recently, Melchiorre et al. have shown that visible light only (household 23 W compact fluorescent light (CFL) bulb or sunlight) will facilitate enamine-catalysed enantioselective α-benzylation and α-phenacylation of aldehydes (Scheme 61), including generation of a quaternary stereocentre through benzylolation of 2-phenylpropanal. Mechanistic studies support a process involving formation of an electron donor/acceptor (EDA) complex between enamine and electron-poor benzylic (or phenacyl) halide, followed by (sun)light-assisted electron transfer, then bromide loss from the radical anion. In-cage combination of the resulting electron-deficient benzylic (or 2-keto) radical with the enamine radical cation followed by the usual iminium hydrolysis provides the α-substituted aldehyde and regenerates the organocatalyst. This work is notable for photochemical asymmetric catalysis in the absence of a photosensitizer. It provides access to similar adducts obtained through MacMillan photoredox catalysis (see Scheme 57), albeit with slightly lower enantioselectivity for phenacylation. The latter may be partly due to the different organocatalysts favoured to generate the EDA complex, and/or to the nature of the radical–radical cation C=C bond-forming event (c.f., Scheme 42), which is slightly different to the radical addition to the neutral enamine proposed in the photoredox chemistry (Scheme 58).

![Scheme 60. Enantioselective α-perfluoroalkylation.](image)
5. Summary

Alkyl-bearing stereogenic centres are ubiquitous both in natural and synthetic compounds of interest. Enantioenriched \( \alpha \)-alkyl-substituted aldehydes provide a convenient way of introducing such groups into molecules, since aldehydes are highly reactive and demonstrate predictable chemoselectivity. However, typical enolate approaches to prepare these building blocks are thwarted by an array of possible side reactions. As a consequence, powerful auxiliary-based strategies to generate enantioenriched \( \alpha \)-alkyl aldehydes have been developed through enamine salts, or the ‘stability’ of higher oxidation level enolates. Although these methodologies are well-established, they are not without limitations—a requirement for stoichiometric quantities of the auxiliary, the use of strong bases to generate enolate intermediates and an additional step to cleave the auxiliary/reveal the aldehyde are common drawbacks to these strategies. Efforts to improve overall efficiency have seen the development of chiral hindered aldenamines, which are able to alkylate in high yield (overcoming problematic N-alkylation), confer moderate to high enantioselectivity, and obtain the aldehyde in a one-pot reaction from the enamine. Especially significant organocatalysis-based advances to \( \alpha \)-alkyl-substituted aldehydes have been made, which involve a variety of reaction modes (intramolecular Sn2, Sn1, SOMO). While methods discussed in this review are capable of achieving asymmetric \( \alpha \)-alkylation, either directly or indirectly, the challenge still remains for development of straightforward strategies to enantioenriched \( \alpha \)-alkylated aldehydes that can exploit the synthetic/commercial availability of simple alkyl electrophiles (halides or halide equivalents).

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Biographical sketch

David M. Hodgson obtained his first degree in Chemistry at Bath University. After a Ph.D. at Southampton University in the field of natural product synthesis (with P.J. Parsons) and a research position at Schering, he was appointed in 1990 to a lectureship at Reading University. In 1995 he moved to the Chemistry Department at Oxford University, where he is now a Professor of Chemistry. In recognition of achievements by his research group, he has received a GSK Award for Innovative Organic Chemistry, a Pfizer Academic Award and an AstraZeneca Research Award in Organic Chemistry, and the Royal Society of Chemistry Bader Award. His research interests are broadly in the development and application of synthetic methods, particularly asymmetric generation and transformations of carbenoids.

Andrew Charlton studied Chemistry [MChem (Hons)] at The University of Edinburgh, which included a year in industry with GlaxoSmithKline and a research project on arylene chemistry with Mike Greaney. He then moved to the University of Oxford (Trinity College) for Ph.D. research under the supervision of David M. Hodgson, obtaining his doctorate in 2013. His work was sponsored by an EPSRC Pharma studentship, and involved the asymmetric synthesis of tropanes and homotropanes and their evaluation in enamines for the generation of $\alpha$-alkyl-substituted aldehydes.