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Direct, enantioselective α-alkylation of aldehydes using simple olefins

Andrew G. Capacci, Justin T. Malinowski, Neil J. McAlpine, Jerome Kuhne and David W. C. MacMillan*

Although the α-alkylation of ketones has already been established, the analogous reaction using aldehyde substrates has proven surprisingly elusive. Despite the structural similarities between the two classes of compounds, the sensitivity and unique reactivity of the aldehyde functionality has typically required activated substrates or specialized additives. Here, we show that the synergistic merger of three catalytic processes—photoredox, enamine and hydrogen-atom transfer (HAT) catalysis—enables an enantioselective α-aldehyde alkylation reaction that employs simple olefins as coupling partners. Chiral imidazolidinones or prolinols, in combination with a thiophenol, iridium photoredox catalyst and visible light, have been successfully used in a triple catalytic process that is temporally sequenced to deliver a new hydrogen and electron-borrowing mechanism. This multicatalytic process enables both intra- and intermolecular aldehyde α-methylene coupling with olefins to construct both cyclic and acyclic products, respectively. With respect to atom and step-economy ideals, this stereoselective process allows the production of high-value molecules from feedstock chemicals in one step while consuming only photons.

The stereoselective α-alkylation of carbonyl compounds has long been a fundamental transformation within the field of organic chemistry. In the 1980s, the seminal research of Evans, Meyers, Oppolzer, Seebach and Myers[1] demonstrated that chiral auxiliaries can offer a general approach to the enantioselective construction of α-carbonyl stereocentres[2,3], which today remains the method of choice for enolate-based fragment coupling. In recent years a variety of novel catalytic methods have been developed for asymmetric α-carbonyl alkylation, including (1) phase transfer additions of glycine-derived imines, (2) chiral triamine ligation of ketone-derived lithium enolates, and (3) the use of Jacobsen's Cr (salen) complex with pre-formed stannous enolates[4–6]. Given these important advances, the direct, enantioselective formation of α-alkyl carbonyls from simple, abundant organic building blocks remains an elusive yet important goal.

Over the last two decades, secondary amine-mediated organocatalysis has enabled the development of mild methods for the catalytic generation of reactive HOMO-raised enamine nucleophiles[7–10]. This activation platform has found broad utility in a variety of α-functionalization reactions, most notably the enantioselective formation of C–O, C–N, C–X and C–C bonds[11]. Despite these efforts, the α-alkylation of carbonyl compounds using alkyl halides remains an elusive transformation, mainly due to limitations involving competitive self-aldol reactions and/or catalyst alkylation[12].

In 2007 we first demonstrated that open-shell, radical pathways can enable the enantioselective α-functionalization of carbonyl compounds via a SOMO activation pathway[13]. This process occurs via stoichiometric oxidation of a transiently formed enamine to generate a 3πe$^-$ enaminyl radical intermediate. This electrophilic SOMO species can then be intercepted by a variety of prefunctionalized olefins and, following an additional oxidation event, can lead to a number of α-functionalized adducts[14,15]. While the generality of this 3πe$^-$ enaminyl radical activation mode has been demonstrated, widescale adoption has been restricted due to (1) the requirement of two equivalents of a stoichiometric oxidant per bond formation and (2) the need for pre-generated π-nucleophilic olefin partners (for example, silyl ketene acetals, allyl silanes) that can engage the electrophilic 3πe$^-$ enaminyl radical.

Recently, we questioned whether photoredox catalysis and organocatalysis might be successfully merged to enable the enantioselective α-alkylation of carbonyl compounds using simple, unactivated olefin coupling partners and without the requirement of stoichiometric oxidants (Fig. 1). We recognized that the

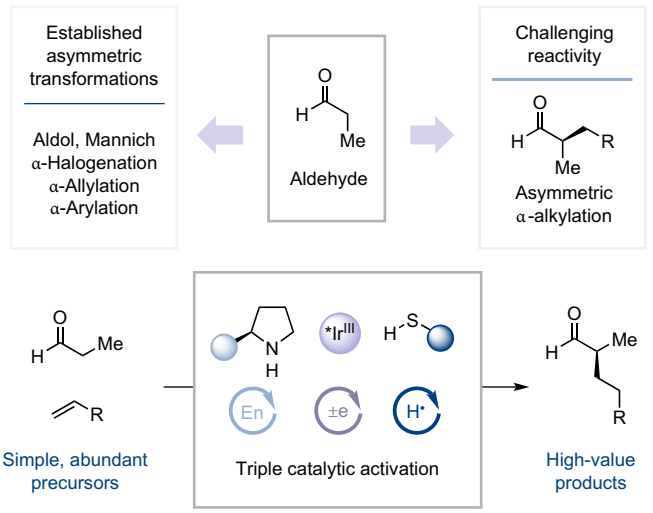


Figure 1 | Direct enantioselective α-alkylation of aldehydes with olefins via triple catalytic activation. Aldehydes are known to be efficient substrates for a number of fundamental carbonyl α-functionalization transformations for selective C–O, C–N, C–X and C–C bond formation. Despite this, the catalytic, asymmetric α-alkylation of aldehydes has remained a challenge. This transformation has now been accomplished through the merger of secondary amine organocatalysis, photoredox catalysis and HAT catalysis to produce α-alkyl carbonyl products from simple olefin and aldehyde substrates.

Merck Center for Catalysis at Princeton University, Princeton, New Jersey 08544, USA. *e-mail: dmacmill@princeton.edu

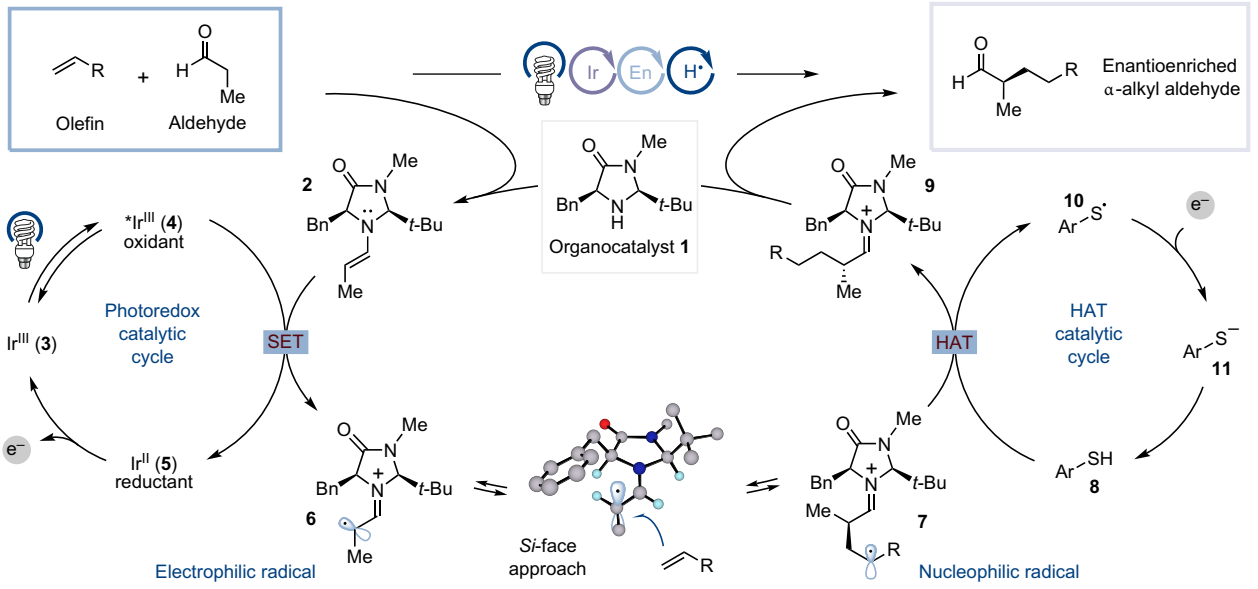


Figure 2 | Proposed mechanism for aldehyde α-alkylation via photoredox, HAT and organocatalysis. Condensation of organocatalyst **1** with an aldehyde substrate initiates the catalytic cycle. Concurrently, irradiation of iridium photocatalyst **3** generates an excited state species (**4**). This intermediate can then oxidize enamine **2** through single electron transfer (SET) and generate the 3πe⁻ enaminyl radical **6**. Reversible radical addition across an olefin substrate then produces the carbon radical **7**, which is trapped through HAT with thiol HAT catalyst **8**. Hydrolysis of iminium **9** provides the enantioenriched α-alkyl aldehyde and regenerates amine catalyst **1**. Finally, reduction of thiyl radical **10** by the Ir(II) species (**5**) subsequently regenerates thiol catalyst **8** as well as the Ir(III) catalyst **3** to complete the remaining redox cycles.

combination of both the SOMO and photoredox activation modes might enable hydrogen atom and electron borrowing to achieve enaminyl radical formation before coupling with an olefin substrate[16]. The generation of simple olefin adducts was deemed feasible, provided the initial enaminyl radical–olefin addition event could be rendered non-reversible. To this end, we rationalized that the use of a third catalytic cycle, involving a reductive hydrogen-atom transfer, would capture the radical intermediate arising from the olefin addition step[17–19], thereby ensuring that the overall mechanism is redox-neutral (that is, non-oxidative, with only photons being consumed in the process).

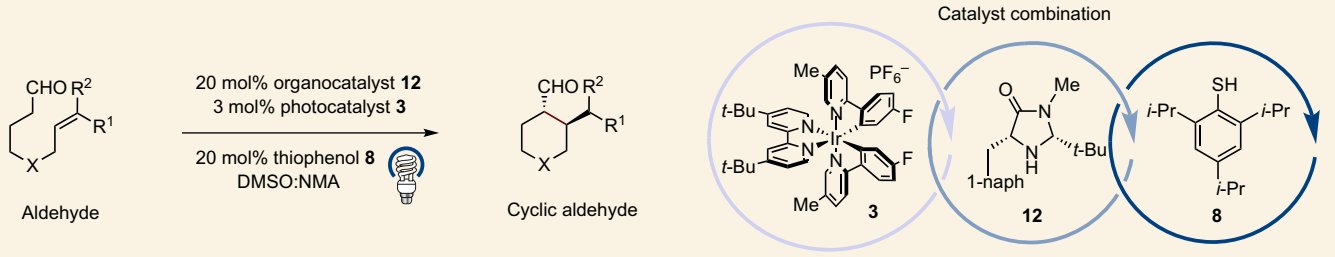
From a conceptual standpoint, we hypothesized that three catalytic cycles could be used in concert to enable this unique alkylation: (1) amine catalysis (= enamine formation), (2) photoredox catalysis (= enamine oxidation to generate an activated 3πe⁻ enaminyl radical and reduction of a thiyl radical), and (3) HAT catalysis (= hydrogen-atom transfer to the alkyl radical species after olefin addition) (Fig. 2). As such, a critical feature of this transformation would be the identification of three highly selective yet independent catalysts and their controlled interface. For example, a selective HAT catalyst would be required to successfully discriminate between trapping of the initial electrophilic 3πe⁻ enaminyl radical intermediate and the alkyl radical species generated following olefin coupling. Second, given the reversible nature of the olefin addition event, the kinetic efficiency of the HAT catalyst would dictate the retention or loss of enantiocontrol gained in the SOMO-addition step. Finally, the redox activity of the three catalysts would be interdependent, and efficient regeneration of the ground-state photocatalyst and HAT catalyst would require a multicatalytic process that is temporally synchronized.

Merging photoredox, organocatalysis and HAT catalysis

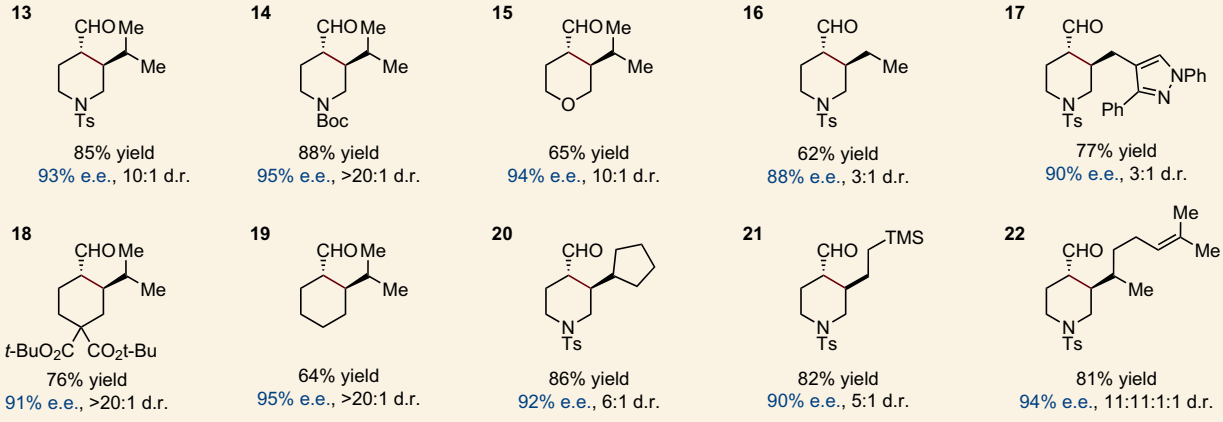
A detailed description of our proposed mechanism for the enantioselective α-alkylation of aldehydes is outlined in Fig. 2. We presumed that the process would begin with condensation of amine catalyst **1** and an aldehyde substrate to provide enamine **2**. Concurrently, irradiation of the iridium photocatalyst **3** $Ir(Fmppy)_2(dtbbpy)PF_6$ (Fmppy = 2-(4-fluorophenyl)-4-(methylpyridine), dtbbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine) with visible light would produce the long-lived (τ = 1.2 μs) excited-state complex **4** (ref. 20). This highly oxidizing charge transfer species ($E^{red}_{1/2}$ [$*Ir^{III}/Ir^{II}$] = +0.77 V versus saturated calomel electrode, SCE) would be capable of mediating a single-electron transfer (SET) from the electron-rich enamine **2** to generate reduced Ir^{II} complex **5** and the critical 3πe⁻ enaminyl radical species **6**. This electrophilic radical should then rapidly undergo addition to an olefin coupling partner to generate a new C–C bond, a stereogenic centre and a secondary alkyl radical. At this stage we hypothesized that this nucleophilic radical **7** would participate in a HAT event with a sufficiently acidic and weak S–H bond (HAT catalyst **8**, thiophenol S–H BDE = 78 kcal mol^{-1})[21]. This HAT process is governed both by the polarity match and relative bond strengths of the donor and acceptor species, and is expected to rapidly trap the alkyl radical species at near diffusion control[22]. Following HAT, hydrolysis of iminium ion **9** would liberate the organocatalyst while also providing an enantioenriched aldehyde product. Finally, thiyl radical **10** ($E^{red}_{1/2}$[$PhS^{\bullet}/PhS^{-}$] = +0.02 V versus SCE in dimethylsulfoxide)[23] engages in a SET event with the highly reducing Ir^{II} complex **5** ($E^{red}_{1/2}$[Ir^{III}/Ir^{II}] = –1.50 V versus SCE) to regenerate both the ground state Ir^{III} complex **3** as well as the HAT thiol catalyst after protonation of thiolate **11**.

We first tested the proposed aldehyde alkylation on an intramolecular variant to determine if enantioselective ring formation was feasible using this mechanism. As shown in Table 1, heterocyclic or carbocyclic rings were readily generated with high efficiency and enantiocontrol using this tricatalytic method. For example, *N*-tethered aldehydic olefins with either sulfonamide or carbamate protecting groups are tolerated, giving rise to piperidine adducts in high yield (**13** and **14**, 85% yield, 93% e.e. and 88% yield, 95% e.e., respectively). Moreover, an ether-linked system provided the desired *trans*-disubstituted tetrahydropyran with useful efficiency (**15**, 65% yield, 94% e.e.). Carbocycles were also prepared in good yield via this protocol, as exemplified by the *gem*-diester-containing substrate **18** (76% yield, 91% e.e.). Notably, the reaction proceeded well using an unsubstituted alkyl tether to generate the

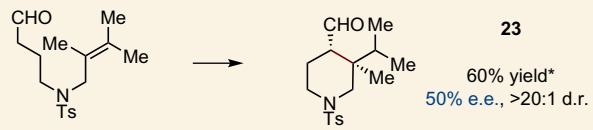
Table 1 | Tether and olefin scope of enantioselective intramolecular α-alkylation of aldehydes.



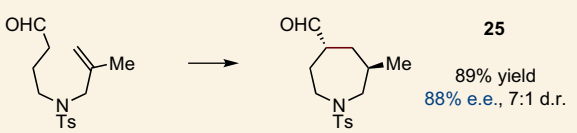
6-*exo* cyclization



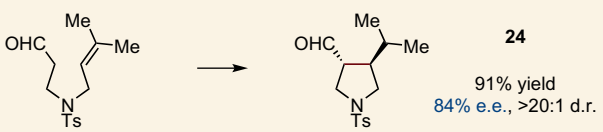
6-*exo* formation of quaternary centre

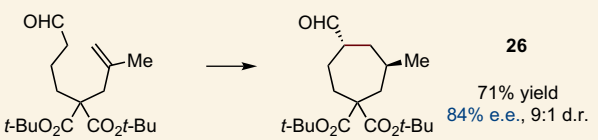


7-*endo* cyclization



5-*exo* cyclization





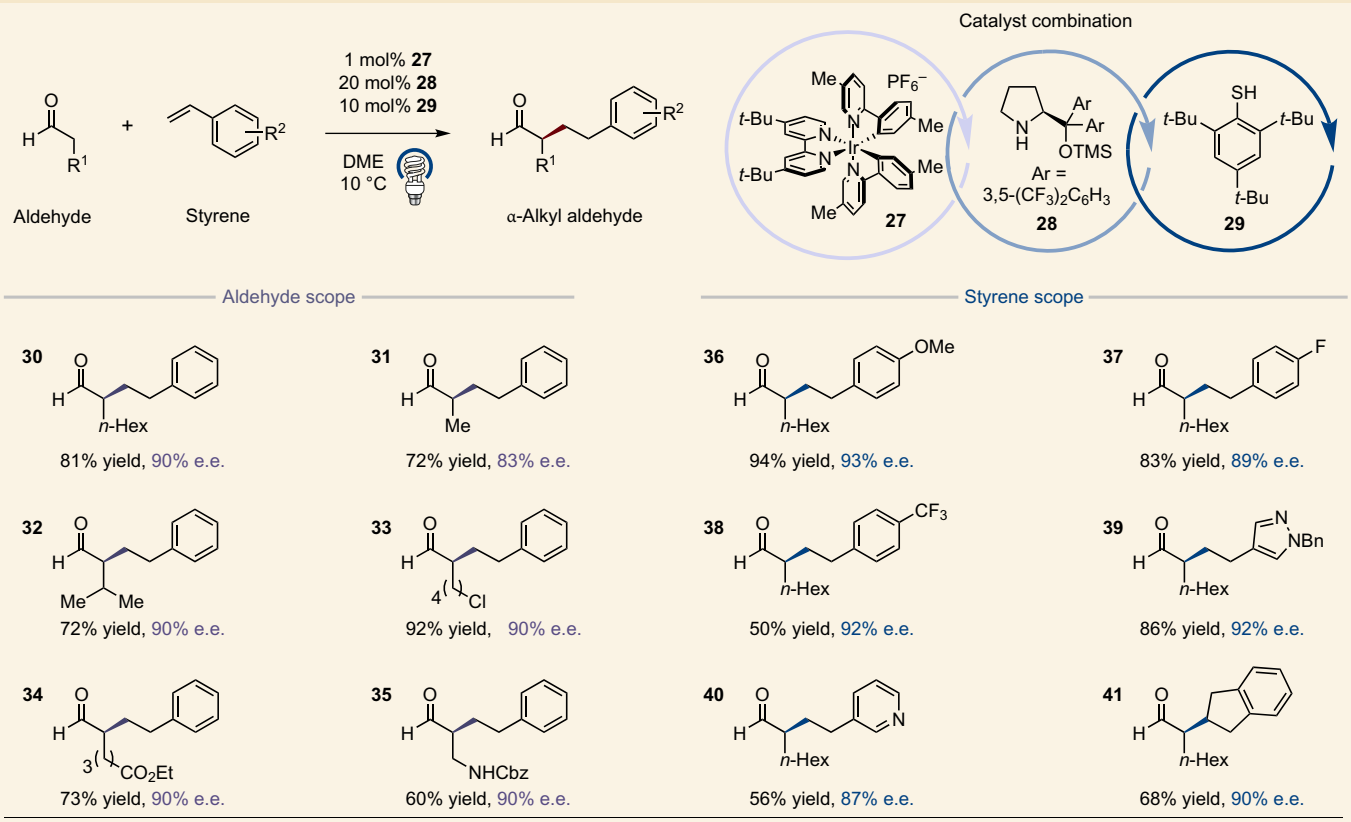
For each product number (in bold), data are reported as percent isolated yield, and diastereomeric ratio (d.r.) was determined by ^{1}H NMR. *(*R*)-2-*tert*-butyl-3-methylimidazolidin-4-one (20 mol%) was used. NMA, *N*-methyl acetamide; Me, methyl; Ts, tosyl; Boc, *tert*-butyl carbamoyl; TMS, trimethylsilyl; Ph, phenyl. See Supplementary Information for experimental details.

disubstituted cyclohexane product (**19**, 64% yield, 95% e.e., >20:1 d.r.). We also explored the formation of a substituted pyrrolidine product through a 5-*exo* cyclization and were pleased to obtain the product in excellent yield and moderate stereoselectivity (**24**, 91% yield, 84% e.e.). The diminished enantioinduction observed in this case is probably due to the enhanced reversibility of the alkylation step as the Baeyer ring strain in five-membered rings exceeds that of six-membered analogues[24].

Next, we turned our attention to the alkene component in this intramolecular variant. Trisubstituted olefins proved to be highly efficient (**20** and **22**, 86% yield, 92% e.e. and 81% yield, 94% e.e., respectively). As might be expected, trisubstituted olefins that incorporate two prochiral carbons achieve high diastereocontrol at the stereocentres involved in ring formation, yet effectively no selectivity in the HAT step (**22**, 11:11:1:1 d.r.). It should be noted that, in the case of the geraniol-derived example **22**, where multiple olefins are present in the tethered aldehyde substrate, only the proximal alkene undergoes radical addition. Notably, 1,2-disubstituted olefins were also effective in the transformation (**16**, **17** and **21**, 62–82% yield, 88–90% e.e.). However, superior efficiency was observed in the cases where radical-stabilization was possible after the cyclization event (**17**, **21** versus **16**). Perhaps most notably, quaternary carbon stereocentres could also be formed via a tethered tetrasubstituted olefin using (*R*)-2-*tert*-butyl-3-methylimidazolidin-4-one, albeit with lower enantiocontrol (**23**, 60% yield, 50% e.e., >20:1 d.r.). Moreover, we also found that seven-membered rings could be formed through a 7-*endo* cyclization to provide the corresponding azepanes or cycloheptanes in excellent yields (**25** and **26**, 89% yield, 88% e.e. and 71% yield, 84% e.e., respectively). This process is believed to occur through reversible 6-*exo* and 7-*endo* radical cyclizations that ultimately favour the formation of the more thermodynamically stable tertiary radical intermediate before intermolecular HAT.

Having successfully demonstrated this enantioselective α-formyl alkylation in a unimolecular sense, we next turned our attention to an intermolecular variant. Initially we focused on widely available styrene coupling partners, given their established propensity as radicalphiles[25]. Indeed, we observed excellent efficiency and selectivity in this case using a less oxidizing heteroleptic iridium(III) photocatalyst, $Ir(dmppy)_2(dtbbpy)PF_6$ (ref. 26)

Table 2 | Aldehyde and styrene scope of enantioselective intermolecular α-alkylation.



For each product number (in bold), data are reported as percent isolated yield. Cbz, benzyl carbamoyl; Bn, benzyl. See Supplementary Information for experimental details.

(dmppy = 2-(4-methylphenyl)-4-(methylpyridine)) (**27**) and the diarylsilylprolinol organocatalyst, α,α-bis[3,5-bis(trifluoromethyl) phenyl]-2-pyrrolidine-methanol trimethylsilyl ether (**28**). Moreover, the use of a more sterically congested thiophenol catalyst **29** was required in this case to overcome side reactions arising from thiol-ene type processes.

With these conditions in hand, we found that a variety of substituted aldehydes provided the desired alkylated products in good yield and selectivity (Table 2). Interestingly, 6-chlorohexanal provided the desired product (**33**) in high efficiency rather than the alternative 6-*exo*-tet intramolecular enamine alkylation adduct. Moreover, β,β-disubstituted and β-amino aldehydes were well-tolerated in the transformation (**32** and **35**, 72% yield, 90% e.e. and 60% yield, 90% e.e., respectively). Next, we examined the effect of the aromatic group of the styrene component. Notably, we found that a variety of electron-rich and electron-deficient vinyl arenes can be employed while retaining excellent enantioselectivity (**36**–**38**, 50–94% yield, 89–93% e.e.). Additionally, heteroaromatics in the form of 3-vinyl pyridine and a 4-vinyl pyrazole were shown to be viable substrates (**39** and **40**, 86% yield, 92% e.e. and 56% yield, 87% e.e., respectively). Furthermore, 1,2-disubstituted styrenes could also be employed, as exemplified by indene, to generate the corresponding alkylation adduct in excellent yield and enantiocontrol (**41**, 68% yield, 90% e.e.).

Finally, we examined this α-alkylation manifold with simple olefin coupling partners. Although terminal olefins were found to be less reactive (see Supplementary Information), π-nucleophilic 1,1-disubstituted olefins were found to be suitable, with moderate to useful levels of efficiency. As shown in Fig. 3, we were pleased to find that this triple catalytic activation mode allows methylenecyclopentane and methylenecyclohexane to participate in the desired alkylation event with high levels of enantiocontrol. We attribute the viability of these substrates to be due, in part, to the reversible photocatalytic generation of the key 3πe⁻ enaminyl radical intermediate and subsequent interaction with the HAT catalyst only after addition across the olefin substrate.

In summary, we have developed a novel reaction platform where simple aldehyde substrates undergo coupling with a wide variety of olefin reaction partners to enantioselectively produce α-alkyl carbonyl adducts. This visible light-mediated transformation is accomplished via a hydrogen atom and electron borrowing mechanism that involves three discrete catalytic cycles that are temporally matched to function in concert. This multicatalytic process enables both intra- and intermolecular coupling of aldehydes to construct both cyclic and acyclic products, respectively. We expect the capacity of employing feedstock chemicals in a new enantioselective coupling reaction that employs visible light will find utility across a number of research and industrial applications.

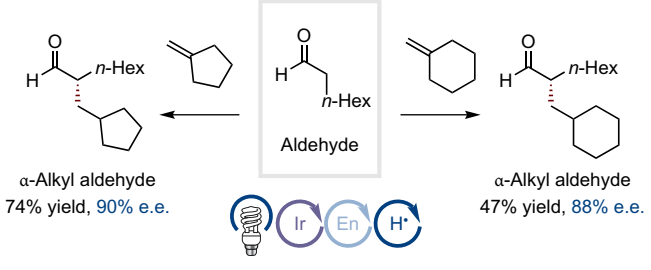


Figure 3 | Intermolecular α-alkylation of aldehydes with non-functionalized olefins. Intermolecular coupling between 1,1-disubstituted olefins and octanal. Data are reported as percent isolated yield. Reaction conditions: 1 mol% **27**, 20 mol% **28**, 10 mol% **29**, DME, blue LED light, −65 °C.

Data availability. The data supporting the findings of this study are available within the paper and its Supplementary Information.

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Author contributions

A.G.C., J.T.M., N.J.M. and J.K. performed and analysed experiments. A.G.C., J.T.M., N.J.M., J.K. and D.W.C.M. designed experiments to develop the intramolecular variant of this reaction and probe its utility. A.G.C., N.J.M., and D.W.C.M. designed experiments to develop the intermolecular variant of this reaction and probe its utility. A.G.C. and D.W.C.M. prepared this manuscript.

Additional information

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Competing financial interests

The authors declare no competing financial interests.