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Direct Stereoselective Installation of Alkyl Fragments at the β-Carbon of Enals via Excited Iminium Ion Catalysis

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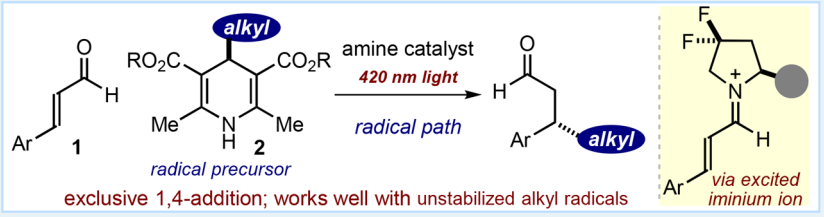
Supporting Information



ABSTRACT: The direct introduction of sp^3 carbon fragments at the β position of α,β-unsaturated aldehydes is greatly complicated by competing 1,2-addition manifolds. Previous catalytic enantioselective conjugate addition methods, based on the use of organometallic reagents or ground-state iminium ion activation, could not provide general and efficient solutions. We report herein that, by turning them into strong oxidants, visible light excitation of chiral iminium ions triggers a stereocontrolled radical pathway that exclusively affords highly enantioenriched β-substituted aldehydes bearing a variety of alkyl fragments.

KEYWORDS: *asymmetric catalysis, organocatalysis, iminium ion, photochemistry, radical reactivity*

The conjugate addition of hard carbon nucleophiles to electron-deficient alkenes is a powerful synthetic method for creating new C−C bonds in a catalytic enantioselective fashion.[1] Over the last 20 years, asymmetric catalytic processes using organometallic reagents have been extensively investigated, allowing the installation of sp^3 carbon fragments within Michael acceptors.[2] Despite the major progress achieved, applying this strategy to α,β-unsaturated aldehydes **1** has proven to be difficult. The main complication stems from the high reactivity of the aldehyde moiety, which enables a competing addition to the carbonyl, ultimately leading to a mixture of 1,2- and 1,4-addition adducts (Figure 1a). This regioselectivity issue was highlighted by Bräse, who reported that the catalytic addition of diethyl zinc to enals could proceed with high enantioselectivity but poor 1,4/1,2 selectivity (ranging from 4:1 to 1:1).[3] Subsequent studies by Alexakis demonstrated that a chiral copper catalyst could promote the addition of both dialkylzinc and Grignard reagents to enals.[4] While the former reacted with high 1,4 regioselectivity but moderate stereocontrol,[4a] Grignard reagents afforded highly enantioenriched β-substituted enals along with a large amount of 1,2-addition adducts.[4b]

Recently, the synthetic potential of the asymmetric conjugate addition technology was greatly expanded by the ground-state reactivity of electron-poor iminium ions **I**. Iminium ion-mediated catalysis has found a myriad of applications in the direct stereo- and regioselective β-functionalization of enals **1** with soft nucleophiles.[5] However, the installation of simple alkyl fragments at the β position of enals through iminium ion activation[6] largely remains an unmet goal.[7] We surmised that the excited-state reactivity of iminium ions,[8] which we recently disclosed, might provide an effective strategy to close this gap in synthetic methodology. Our previous study demonstrated that the photoexcitation of iminium ions can switch on novel reaction pathways that are unavailable to ground-state reactivity. Selective excitation with visible light, by bringing the electron-poor intermediate **I** into an electronically excited state (**I*** in Figure 1b), turns a merely electrophilic species into a strong oxidant, which could trigger the formation of the benzylic radical **III** through single-electron transfer (SET) oxidative cleavage of the silicon−carbon bond within benzyl trimethylsilane **II**. The subsequent stereoselective coupling between **III** and the chiral β-enaminyl radical **IV**, generated from **I*** upon SET, led to the direct β-benzylation of enals.

We reasoned that, if the photochemistry of chiral iminium ions could be used to generate C(sp^3)-centered radicals upon SET oxidation of suitable precursors **2**, it might provide a solution for the direct regioselective installation of alkyl fragments within enals (Figure 1c). However, we found that the original methodology,[8] based on the use of alkyl silanes, was limited to the generation of either benzyl radicals or radicals stabilized by an adjacent heteroatom.[9] This required us to

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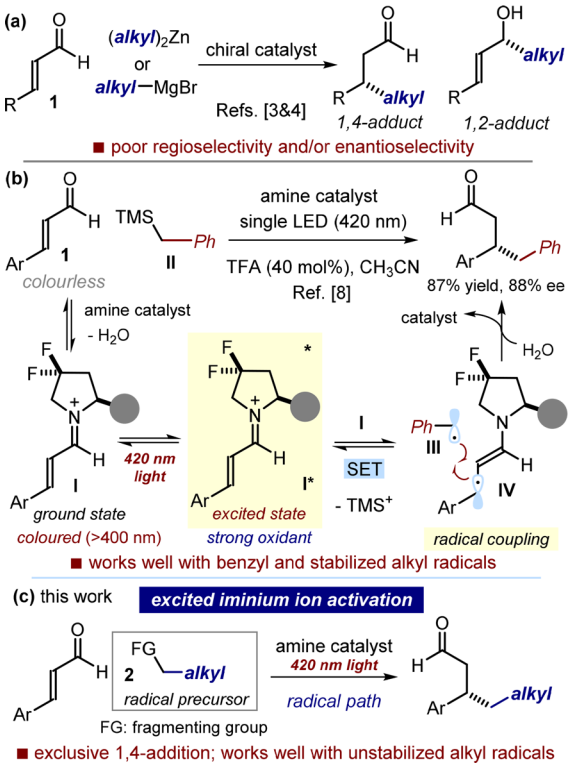


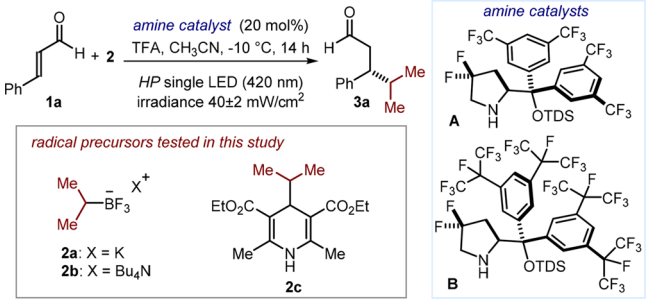
Figure 1. (a) The regioselectivity issue plaguing the development of the enantioselective catalytic conjugate addition of hard organometallic nucleophiles to enals **1**. (b) The previous study demonstrating that light excitation turns iminium ions into chiral oxidants, and the resulting SET-based radical generation mechanism for achieving the enantioselective β-benzylation of enals. (c) The proposed radical-based strategy for the direct and stereoselective installation of alkyl fragments at the β-carbon of enals via excited iminium ion catalysis. SET: single-electron transfer; TMS: trimethylsilyl; filled gray circle represents a bulky substituent on the chiral amine catalyst.

identify alternative precursors **2**. Herein, we detail the successful realization of this idea, which allowed us to directly install alkyl fragments at the β-carbon of enals with perfect regioselectivity and high stereocontrol by using the excited-state reactivity of iminium ions.[10,11]

To test the feasibility of our idea, we selected cinnamaldehyde **1a** as the model substrate while using the *gem*-difluorinated diarylprolinol silylether catalyst **A**[8] to promote the formation of the chiral iminium ion **Ia**. Since the excited iminium ion has a reduction potential (E^*_{red} (**Ia***/**Ia**$^{\bullet-}$)) as high as +2.4 V (vs Ag/Ag$^+$ in CH_3CN), as estimated on the basis of electrochemical and spectroscopic measurements, we surmised that a variety of different precursors **2** could productively undergo a SET oxidation to generate alkyl radicals (Table 1). The experiments were conducted in CH_3CN at −10 °C under irradiation by a single violet high-power light-emitting diode (HP LED, λ_{max} = 420 nm) with an irradiance of 40 mW/cm^2, as controlled by an external power supply (full details of the illumination setup are reported in the Supporting Information, Figure S1).

The use of potassium *iso*-propyl trifluoroborate **2a** (E_{ox} (**2a**$^{\bullet+}$/**2a**) = +1.72 V vs Ag/Ag$^+$ in CH_3CN) as the radical precursor[12] led to the formation of the desired β-alkylated product **3a** in moderate yield and stereoselectivity (entry 1). A cation exchange from potassium (**2a**) to tetrabutylammonium (**2b**, E_{ox} (**2b**$^{\bullet+}$/**2b**) = +1.65 V vs Ag/Ag$^+$ in CH_3CN) greatly

Table 1. Optimization Studies[a]



entry	catalyst	radical precursor **2**	TFA (mol %)	yield (%)[b]	ee (%)
1	**A**	**2a**	40	55	78
2	**A**	**2b**	40	58	79
3	**A**	**2c**	40	70	80
4	**A**	**2c**	80	91	80
5	**B**[c]	**2c**	80	59	87
6	**B**[c]	**2c**	100	67	87
7	**B**[d]	**2c**	100	88 (83)[e]	86

[a]TDS: thexyl-dimethylsilyl. Reactions performed in CH_3CN (0.5 mL) on a 0.1 mmol scale using 3 equiv of **1a** and an irradiance of 40 mW/cm^2. [b]NMR yield of **3a** determined using 1,3,5-trimethoxybenzene as the internal standard. [c]Performed in a 4:1 CH_3CN/perfluorohexane (C_6F_{14}) solvent mixture (0.5 mL). [d]Performed in a 2:1 CH_3CN/C_6F_{14} solvent mixture (0.3 mL). [e]Number in parentheses indicates the yield of the isolated **3a** after chromatographic purification on silica gel.

increased the reagent solubility. However, **2b** offered a similar reactivity in the enantioselective photochemical β-alkylation of **1a** (entry 2). We then focused on the use of *iso*-propyl substituted dihydropyridine **2c** (E_{ox} (**2c**$^{\bullet+}$/**2c**) = +1.41 V vs Ag/Ag$^+$ in CH_3CN). This choice was motivated by the notion that 4-alkyl-1,4-dihydropyridines (alkyl-DHPs), which are readily prepared from aldehydes in one step, easily undergo a homolytic cleavage to form C(sp^3)-centered radicals under oxidative conditions.[13] Pleasingly, the use of **2c** resulted in a clean process, with the β-alkylated aldehyde **3a** formed in fairly good yield and a good level of stereocontrol (entry 3). The reactivity was greatly improved by increasing the amount of trifluoracetic acid (TFA, needed to facilitate the formation of the iminium ion intermediate) from 40 to 80 mol % (entry 4, the use of different acids offered reduced reactivity, see details in Table S1 of the Supporting Information). The chiral amine catalyst **B**, possessing bulkier perfluoro-isopropyl groups on the arene scaffold, was suitable for improving enantiocontrol, but at the expense of reactivity (entry 5, reaction performed in a CH_3CN/perfluorohexane solvent mixture to improve the catalyst's solubility). A final cycle of optimization revealed that a higher concentration of the reaction system and a higher TFA loading (100 mol %) secured a better catalyst turnover along with a satisfactory level of stereocontrol and a perfect 1,4 selectivity (entry 6 and 7).

We also performed some control experiments, which indicated that the process was completely inhibited in the absence of protonated amine catalyst or light.[14] Also the presence of TEMPO resulted in no product formation, which is consistent with a radical mechanism.

We then used the optimized conditions described in Table 1, entry 5 to demonstrate the generality of the β-alkylation process triggered by the photoexcitation of iminium ions (Figure 2). First, we evaluated the possibility of using 4-alkyl-1,4-dihydropyridines, bearing alkyl fragments other than *iso*-

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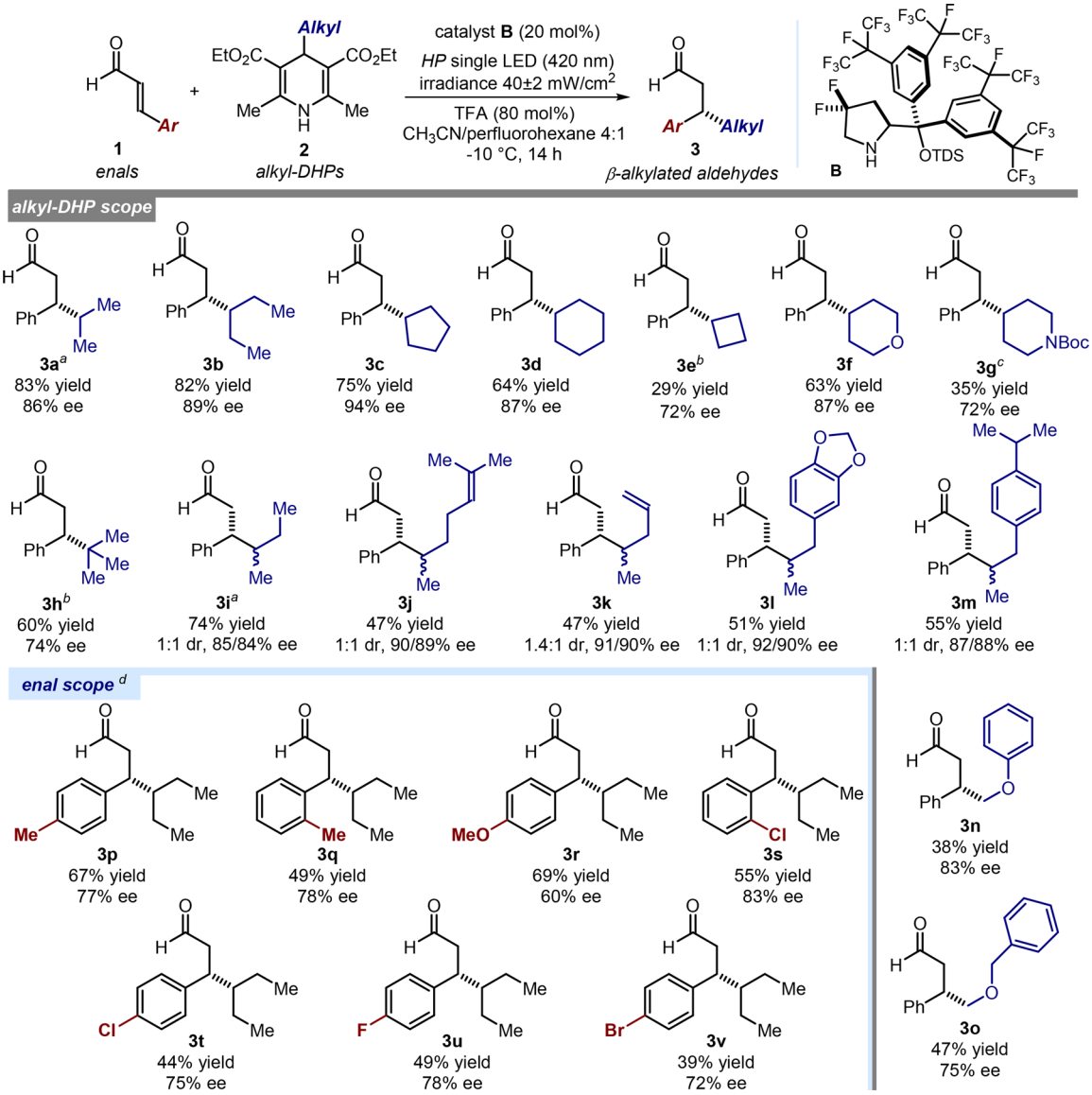

Figure 2. Survey of the enals **1** and the 4-alkyl-1,4-dihydropyridines **2** that can participate in the photochemical catalytic strategy for the asymmetric installation of alkyl fragments at the β position of enals. Reactions performed on a 0.1 mmol scale over 14 h in a 4:1 CH_3CN/perfluorohexane (C_6F_{14}) solvent mixture (0.5 mL) using 3 equiv of **1** and an irradiance of 40 mW/cm^2. Yields and enantiomeric excesses of the isolated products are indicated below each entry (average of two runs per substrate). [a]Performed using 100 mol % of TFA in a 2:1 CH_3CN/C_6F_{14} solvent mixture (0.3 mL). [b]Performed using 40 mol % of TFA and the corresponding tetrabutylammonium trifluoroborate as the radical precursor. [c]Performed in dichloromethane using catalyst **A** and 100 mol % of TFA. [d]Performed in a 2:1 CH_3CN/C_6F_{14} solvent mixture (0.3 mL); TDS: thexyl-dimethylsilyl.

propyl at the C4-position, as radical precursors. Both linear and cyclic fragments could be successfully introduced at the β carbon of cinnamaldehyde **1a**, exclusively leading to the 1,4-adducts with generally good yields and stereocontrol (products **3a**–**m**). An oxygen-containing heterocyclic motif did not hamper the reaction (**3f**), while a piperidine moiety could be installed at the β position of **1a** with good stereocontrol but a poor yield (adduct **3g**). Sterically demanding fragments were accommodated well, as demonstrated with the *tert*-butyl moiety (product **3h**, in this case the corresponding trifluoroborate salt was used as the radical precursor because the corresponding 1,4-dihydropyridine is not easily accessible). The use of alkyl-DHPs bearing a chiral fragment afforded the formation of adducts **3i**–**m**, that have two vicinal stereogenic centers, with high enantiomeric purity, albeit with a poor diastereomeric ratio. Interestingly, alkyl fragments adorned with both alkene and aromatic moieties could be installed, leading to the corresponding products **3j**–**m**. Also primary radicals could successfully engage in this stereoselective coupling reaction when adorned with a stabilizing α-oxygen atom, leading to adducts **3n** and **3o** with moderate yield and good stereoselectivity.

As for the scope of the α,β-unsaturated aldehydes **1**, different substituents at the β aromatic moiety could be accommodated well, regardless of their electronic and steric properties and position on the phenyl ring. The β-alkylation products **3p**–**v** were formed with exclusive 1,4 selectivity, in moderate to good chemical yields and with good stereocontrol. As a limitation of the method, the presence of a β-alkyl fragment in **1** completely inhibited the reaction.[15]

To further expand the synthetic utility of the methodology, the optimized conditions were applied for the stereocontrolled

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preparation of saccharide-containing aldehydes **5**. The 1,4-dihydropyridine **4**, which contains a galactosyl moiety,[16] was used as radical precursor to access the target adducts **5** in fairly good yields and high stereocontrol (Figure 3). The reactions

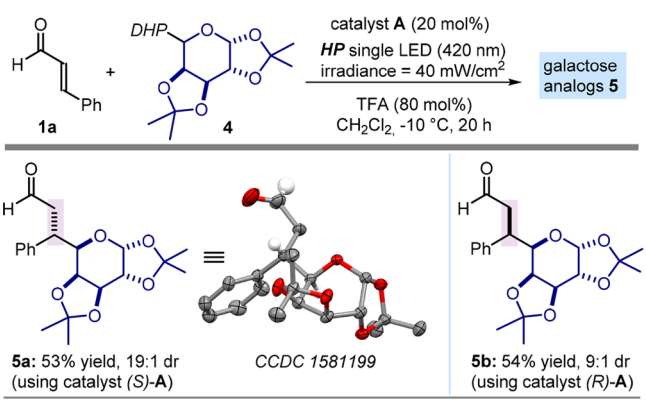

Figure 3. Stereoselective photochemical synthesis of galactose-containing aldehydes **5** under catalyst control; the configuration of the stereocenter highlighted in pink is dictated by the chiral aminocatalyst **A**.

were performed with both enantiomers of the chiral amine catalyst **A**, which provided access to different diastereomers of the galactose derivatives (adducts **5a** and **5b**). These results indicate that the chiral organic catalyst governs the stereoselectivity of the process, and can overwrite the inherent stereochemical information encoded within the chiral substrate **4**. The stereochemistry of product **5a** was established by single crystal X-ray crystallographic analysis.[17]

In summary, we have reported a method for the direct regio- and stereoselective installation of alkyl fragments at the β position of α,β-unsaturated aldehydes. The chemistry relies on the visible light excitation of chiral iminium ions, which turns them into strong oxidants able to generate C(sp^3)-centered radicals from readily available 4-alkyl-1,4-dihydropyridines. Further studies are ongoing in our laboratories to fully explore the excited-state reactivity of chiral iminium ions and its potential in chiral molecule synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.7b03788.

Experimental procedures and spectral data (PDF)
X-ray data (CIF)

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Notes

The authors declare no competing financial interest.

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(14) We recently reported that 4-alkyl-1,4-dihydropyridines, upon light excitation, become strong reducing agents that can activate reagents via SET manifolds while undergoing a homolytic cleavage to generate alkyl radicals, see: Buzzetti, L.; Prieto, A.; Roy, S. R.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2017**, *56*, 15039−15043 However, the isopropyl derivative **2c** cannot absorb light at 420 nm and it is stable upon illumination (see details in Table S2 and Figure S7 of the Supporting Information), which leaves the photoexcitation of iminium ions as the only reaction pathway that can be operative in this system..

(15) Irradiation at 365 nm of a nonenolizable aliphatic enal, bearing a *tert*-butyl group at the β-position, in the presence of substrate **2b** and catalyst **A** afforded trace amounts of the β-alkylation product (about 10% yield after 60 h, as inferred by NMR analysis). Other aliphatic enals (i.e., pentenal and octenal) remained completely unreacted under the same conditions.

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(17) Crystallographic data for compound **5a** has been deposited with the Cambridge Crystallographic Data Centre, accession number CCDC 1581199.

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