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Received

Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x
www.rsc.org/

# Photochemical organocatalytic enantioselective radical γ-functionalization of α-branched enals

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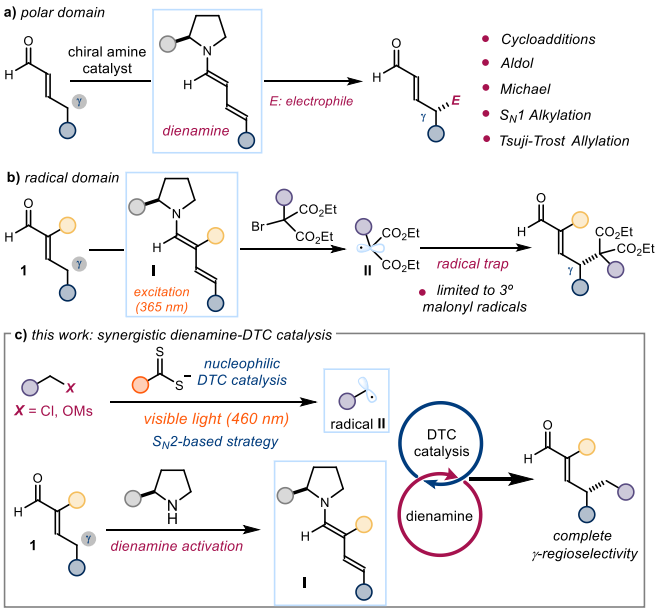
**Reported herein is a rare example of asymmetric catalytic functionalisation of enals at the remote γ-position, proceeding via a radical path. The process requires visible light and exploits the synergistic actions of two distinct organocatalysts. A nucleophilic organic catalyst generates radicals upon $S_N2$-based activation of commercially available alkyl halides and blue light irradiation. Concomitantly, a chiral secondary amine catalyst triggers the formation of a dienamine from α-branched enals. This chiral dienamine intercepts the photogenerated radicals with excellent γ-selectivity and good sterecontrol.**

Remote functionalisation processes exploit the reactivity of one functional group within a substrate to elicit a reaction at a distant position.[1] Despite its synthetic potential, this approach is difficult to achieve in an asymmetric catalytic fashion.[2] This is particularly true for acyclic systems because their flexibility challenges the catalyst's ability to infer remote stereocontrol. One effective method exploits the activation of α,β-unsaturated aldehydes with a chiral amine catalyst (Scheme 1a).[3] The resulting catalytic dienamine intermediate is characterised by vinylogous nucleophilicity,[4] which accounts for the site-selective functionalisation at the remote γ-carbon of carbonyl substrates. The dienamine activation strategy[5] has been widely applied for the asymmetric organocatalytic preparation of chiral molecules bearing remote stereocentres.[3c] Chiral dienamines have been used to catalyse enantioselective cycloaddition reactions,[6] aldol,[7a,b] Michael,[7c,d] $S_N1$ alkylation,[7e,f] and Tsuji-Trost allylation[7g] processes. All these transformations relied on traditional two-electron ionic pathways. In contrast, radical chemistry has found very limited use in dienamine-based catalysis[8] and in stereocontrolled remote functionalisation strategies in general. This lack of application is striking, given that the unique reactivity of radicals is attracting enormous interest from the chemistry community.[9]

Our laboratory recently reported an example of asymmetric catalytic remote functionalisation using radical pathways,[8] which exploited the formation of chiral dienamines **I** from α-branched enals **1** (Scheme 1b). The electrophilic radicals **II**, photogenerated upon direct excitation of the extended enamines **I**, were trapped at the distant γ-position with perfect regioselectivity and good stereocontrol. However, the method's synthetic utility was limited to the use of tertiary bromomalonates as the only suitable radical precursors. This was because the radical generation mechanism depended on the redox properties of the substrates.




**Scheme 1**: a) Dienamine-based catalysis in the polar domain. b) Our previous example of radical remote functionalisation. c) Present work, based on the merger of dienamine and DTC catalysis; DTC: dithiocarbamate.

Recently, we identified a photochemical catalytic strategy for generating radicals that does not rely on the substrates' redox properties.[10] This method exploits the ability of a nucleophilic dithiocarbonyl anion (DTC) organocatalyst to generate radicals **II**

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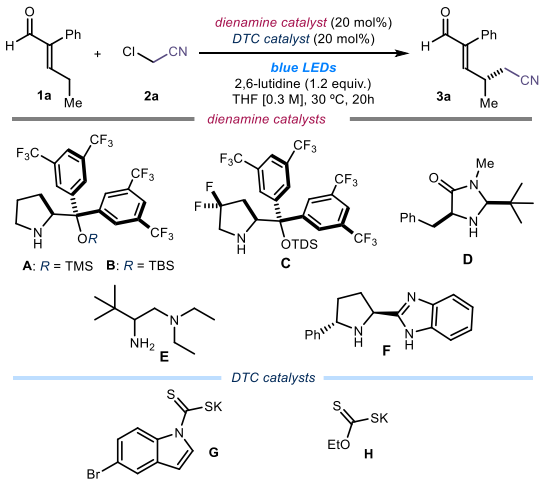
Electronic Supplementary Information (ESI) available: details of experimental procedures, full characterization data, and copies of NMR and HPLC spectra (PDF). See DOI: 10.1039/x0xx00000x

upon blue light irradiation and $S_N2$-based activation of substrates (including alkyl chlorides and mesylates), which would be inert to classical radical-generating strategies (Figure 1c). Herein, we demonstrate how the synergistic merger of DTC organocatalysis and dienamine-based catalysis provides a general platform for the regio- and enantio-selective radical γ-alkylation of α-branched enals.

To test our idea's feasibility, we selected the commercially available chloroacetonitrile **2a** as the radical precursor (Table 1). Initial explorations were performed in THF under irradiation by a blue LED. A variety of chiral amine catalysts (20 mol%) were screened in the presence of enal **1a**. The indole-based DTC catalyst **G** (20 mol%)[10] was used to photogenerate radicals upon $S_N2$-based activation of **2a**. The diarylprolinol silylether catalyst **A**,[11] which has found general application in aminocatalytic asymmetric processes, including via dienamine intermediates,[7a-c] exclusively afforded the γ-functionalised product **3a** in 70% yield and 77:23 enantiomeric ratio (e.r., entry 1).

**Table 1**: Optimisation studies.

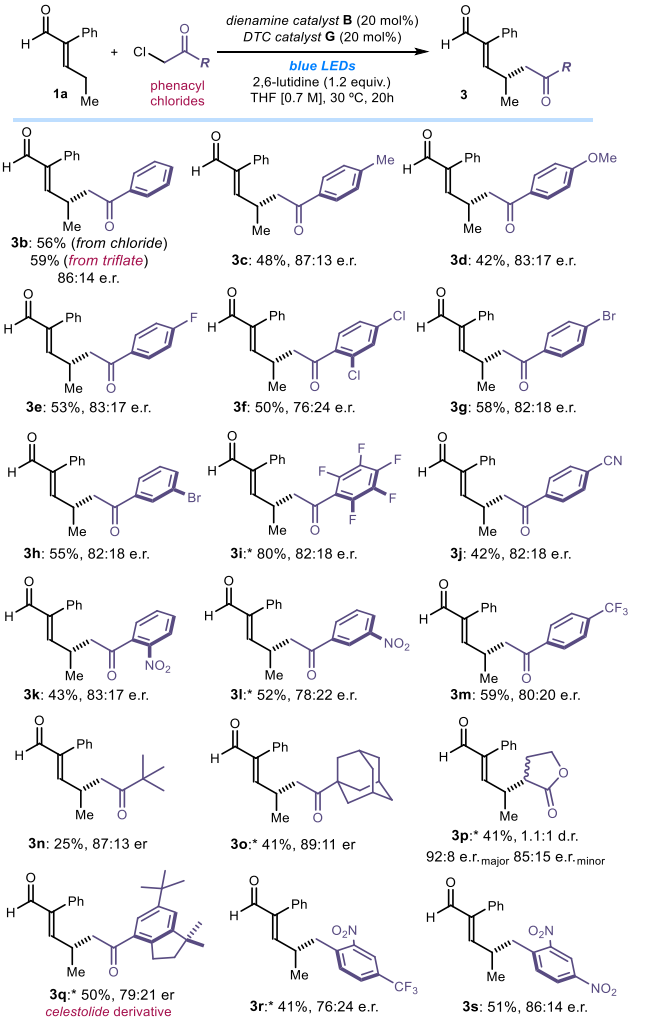



| entry | amine | DTC | deviation | yield **3a** (%) | e.r. **3a** |
|---|---|---|---|---|---|
| 1 | **A** | **G** | none | 70% | 77:23 |
| 2 | **A** | **G** | in toluene | 40% | 77:23 |
| 3 | **A** | **G** | in $CH_3CN$ | 18% | 78:22 |
| 4 | **B** | **G** | none | 57% | 80:20 |
| 5 | **B** | **G** | [THF] = 0.7 M | 70% | 80:20 |
| 6 | **C** | **G** | none | traces | - |
| 7 | **D** | **G** | none | traces | - |
| 8 | **E** | **G** | none | 0% | - |
| 9 | **F** | **G** | none | 0% | - |
| 10 | **B** | **H** | none | 0% | - |
| 11 | **B** | **G** | no light | 0% | - |
| 12 | **B** | - | none | 0% | - |
| 13 | - | **G** | none | 0% | - |

Reactions performed on a 0.2 mmol scale using 20 mol% of both dienamine and DTC catalysts, 3 equivalents of **1a** under irradiation by a blue LED. Enantiomeric ratio measured using UPC[2] analysis on a chiral stationary phase. Yields refer to the isolated product **3a**.

Solvents other than THF negatively impacted reactivity without improving stereocontrol (entries 2 and 3). Swapping the silyl protecting group from trimethylsilyl (TMS, catalyst **A**) to *tert*-butyldimethylsilyl (TBS, catalyst **B**) offered a better enantiocontrol for the remote radical functionalisation (entry 4, 80:20 e.r.). The best results were obtained by increasing the reaction concentration from 0.3 M to 0.7 M (entry 5). Different chiral aminocatalysts were not suitable for this radical transformation, including *gem*-difluorinated diarylprolinol silylether catalyst **C**, the imidazolidinone **D**, and the primary amine **E** (entries 6-9). The use of the commercially available xanthate **H** as the DTC catalyst did not lead to any product formation (entry 10). Control experiments showed that the process was completely inhibited in the absence of aminocatalyst, DTC catalyst, or light, highlighting the essential role of these components (entries 11-13).

Adopting the conditions in Table 1, entry 5, we evaluated the scope of the radical remote alkylation of α-branched enals under the synergistic action of the dienamine catalyst **B** (20 mol%) and the DTC catalyst **G** (20 mol%). Using enal **1a**, we first investigated the alkyl chlorides **1** that could be used as suitable radical precursors (Scheme 2).

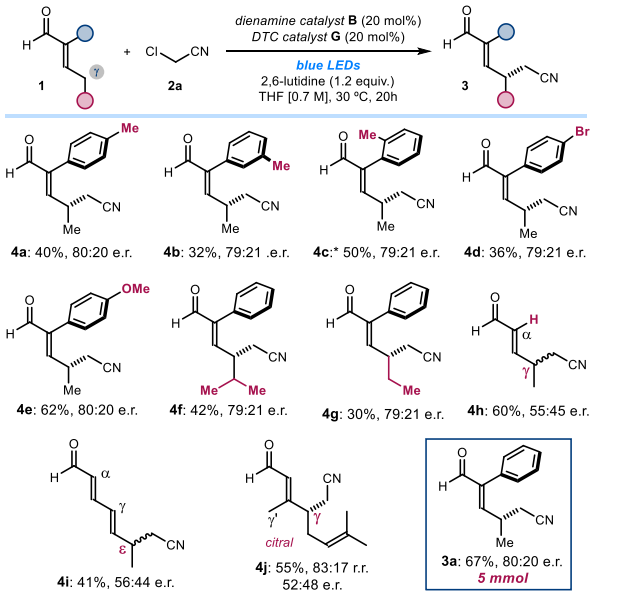



**Scheme 2**: Radical precursors that can participate in the γ-alkylation of enal **1a**. *Using the corresponding bromide as the radical precursor.

A variety of phenacyl chlorides participated smoothly in the process, leading to the γ-alkylation products **3b**-**o** with moderate to good yields and e.r. Importantly, catalyst **G** effectively activated

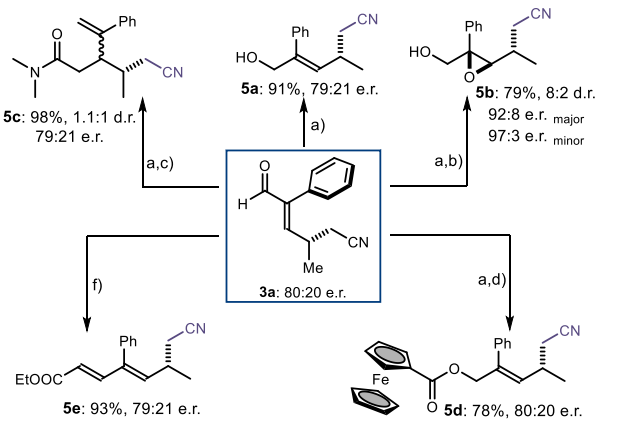
phenacyl triflate towards radical formation via an $S_N2$ path, leading to product **3b** with a yield and enantioselectivity comparable to that of the parent chloride. Both electron-rich (products **3c**, **3d**) and electron-accepting groups (**3j**-**m**) on the aryl moiety of the phenacyl scaffold were well-tolerated. The transformation was largely unaffected by bromine or chlorine substituents in various positions of the aromatic ring (products **3f**-**3h**). Fluorine-containing scaffolds, which are known for their marked activity as bioisosteres in drug design,[12] could also be installed at the γ-position of the aldehyde products (**3e**, **3i**, and **3m**). Aliphatic α-chloro ketones (products **3n** and **3o**) and α-bromo-butyrolactone (**3p**) were suitable radical precursors, offering good enantioselectivity, albeit with reduced reactivity. We also demonstrated that this method is suitable for the direct functionalisation of a biorelevant compound, installing the *celestolide* scaffold within product **3q**. We also generated electron-poor benzyl radicals from the corresponding halides, and trapped them at the remote position (products **3r** and **3s**). A complex *cortisone* derivative, electronically unbiased benzyl chlorides, and α-chloro esters failed to react. A list of unsuccessful and moderately reactive substrates is reported in Figure S7 of the Supporting Information.

We next evaluated the α-branched enals **1** that could participate in the remote radical functionalisation process with chloroacetonitrile **2a** (Scheme 3). Substituents of different electronic natures and in different positions of the α-aryl ring were tolerated well, although they offered somewhat reduced reactivity (products **4a**-**e**). As for the substituents at the enal β position, branched and linear aliphatic chains could be included in the final products (**4f** and **4g**, respectively). The aromatic α-substituent within enals **1** is crucial for this process. For example, an aliphatic group (e.g. using 2-methyl-pentenal, details in Figure S7) completely inhibited the reaction. The lack of substituents (e.g. in pentenal) resulted in the formation of the γ-functionalised product **4h** exclusively, although in almost racemic form. This complete γ-site selectivity is in contrast to the polar dienamine-based reactivity of unsubstituted enals, which generally affords mixtures of α- and γ-functionalised products.[7f,13] The ability to control the site selectivity was further corroborated by an experiment with hepta-2,4-dienal, which may potentially react at the α- and γ-positions but was exclusively alkylated at the more remote ε-carbon, albeit with poor stereocontrol (product **4i**). The lack of stereoselectivity indicates that the α-branched substituent acts as a crucial stereocontrol element, likely by enforcing a preferred conformation of the chiral dienamine intermediate.[14] We also tested the reactivity of citral, which reacted with complete γ-site selectivity, leading to the preferential formation of the more substituted regioisomer **4j**. Finally, we performed the model reaction between **1a** and **2a** on a 5 mmol scale, which proceeded smoothly to afford product **3a** in 67% yield (0.67 g). This result demonstrated that this method is amenable to synthetically useful applications.



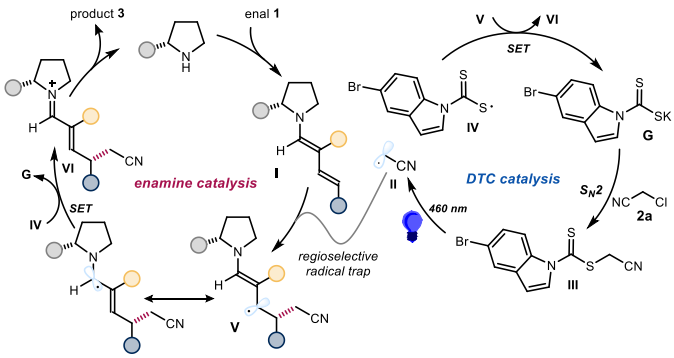

**Scheme 3**: Enals that participate in the γ-alkylation with chloroacetonitrile **2a**. *Product **4c** isolated as 1:1 atropoisomeric ratio; r.r. regiosomeric ratio

One synthetic benefit of this protocol is the installation of a stereocentre remote from the carbonyl group, leaving the α,β-unsaturated system amenable to further transformations. Scheme 4 shows how product **3a** could be readily manipulated to install useful functionalities. Simple reduction led to the enantioenriched allylic alcohol **5a** (path *a*), which was then used as substrate of the venerable Ti-based Sharpless asymmetric epoxidation (path *b*).[15] The chiral epoxy alcohol **5b** featuring three contiguous stereocentres was obtained in good yield and stereocontrol. The allylic alcohol **5a** is also amenable to a [3,3] sigmatropic rearrangement. Applying the Eschenmoser-Claisen conditions,[16] we converted **5a** into the chiral amide **5c** (path *c*). The coupling of **5a** with ferrocenyl carboxylic acid smoothly produced the chiral ferrocenyl ester **5d** in good yield and with no loss of enantiomeric purity (path *d*). Finally, the carbonyl moiety in **3a** engaged in a Wittig olefination, which afforded the ε-enantioenriched unsaturated ester **5e** (path *e*).




**Scheme 4**: Derivatisation of product **3a**. Conditions: *a*) $NaBH_4$, MeOH, 1h, 0 °C; *b*) (-)-diethyl-*D*-tartrate (23 mol%), $Ti(OiPr)_4$ (20 mol%), *t*-BuOOH, DCM, -20 °C; *c*) *N,N*-dimethylacetamide dimethyl acetal, xylene, 110 °C; *d*) ferrocenyl carboxylic acid, oxalyl chloride, DMF; *e*) (carbethoxymethyl)triphenylphosphonium bromide, DCE.

Based on our previous studies on dienamine-based catalysis[7b,14] with α-branched enals and on DTC photochemistry,[10] we propose the mechanism detailed in Scheme 5. Upon nucleophilic substitution of alkyl chloride **2** with the DTC catalyst **G**, the photoactive intermediate **III** is generated. Blue light excitation of **III** triggers a homolytic cleavage, leading to the kinetically stable thiyl radical **IV**[10b,17] and the carbon radical **II**. **II** is then intercepted by the catalytic dienamine **I**, generated upon activation of enal **1** by the chiral amine catalyst, in a regio- and enantioselective fashion. The resulting 5π intermediate **V** ($E1/2_{red}$ = -0.92 to -1.12 V vs. SCE)[18] is then oxidised by an SET by the thiyl radical **II**.[19] The last SET event, which merges the dienamine catalytic cycle with the DTC cycle, accounts for the turnover of the DTC catalyst **G** and the formation of the γ-alkylation product **3**. We measured a quantum yield (Φ) for the model reaction as low as 0.002. This value is consistent with our mechanistic proposal based on the synergistic actions of two distinct organocatalysts, suggesting that a radical chain propagation, if present, is not a dominant path.[20]




**Scheme 5**. Proposed mechanism.

In summary, we have developed a dual organocatalytic platform that accounts for a rare example of asymmetric remote radical functionalisation. The protocol requires commercially available radical precursors and catalysts and leads to the asymmetric γ-alkylation of α-branched enals with excellent γ-regioselectivity. The synthetic usefulness of the process was highlighted by a scale-up reaction and a variety of product manipulations.

This work was supported by Agencia Estatal de Investigación (PID2019-106278GB-I00) and the MCIN/AEI/10.13039/ 501100011033 (CEX2019-000925-S). We thank Dr. Will Hartley and Dr. Martin Berger (ICIQ) for fruitful discussions, and Davide Spinnato (ICIQ) with support with quantum yield measurements.

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