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EDGE ARTICLE

Enantioselective direct α -alkylation of cyclic ketones by means of photo-organocatalysis

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We report here the first asymmetric catalytic alkylation of unmodified ketones with alkyl halides. This metal-free approach, which requires light in order to proceed, provides a rare example of highly enantioselective photochemical catalytic processes. An easily available cinchona-based primary amine catalyst guides both the stereoselectivity-defining event and, through the transient formation of photon-absorbing chiral electron donor-acceptor complexes, the photo-activation of the substrates.

Introduction

The asymmetric α -alkylation of ketones with alkyl halides is a fundamental transformation that generates a new carbon-carbon bond while forging a stereogenic center.¹ Effective variants mainly rely upon the use of chiral auxiliaries,² while only sparse catalytic strategies allow for high levels of efficiency and stereoselectivity to be achieved.³ All of these approaches, however, require the pre-formation of metal enolate precursors. The asymmetric catalytic alkylation of *unmodified* ketones with alkyl halides, although highly desirable, has remained limited to phase transfer catalytic activation of specific substrates.⁴ An effective alternative for the direct functionalization of simple ketones was recently devised in that a single electron chemical oxidation of chiral enamines, transiently generated upon condensation of a secondary amine catalyst with cyclic ketones, can be used to stereoselectively react an allylsilane.⁵ This study demonstrated the potential of open-shell reactivity for enabling transformations which are inaccessible through classical “polar” pathways,⁶ yet it could not solve the challenge of using alkyl halides as the reagent.⁷ Herein, we describe how we have successfully addressed this synthetic issue.

Design Plan

Recently, our laboratory discovered that the photochemical activity of in-situ generated chiral electron donor-acceptor (EDA) complexes can drive the stereoselective α -alkylation of unmodified aldehydes with alkyl halides.⁸ The success of this photochemical, metal-free asymmetric alkylation of aldehydes (Figure 1) relied upon the formation of colored EDA complexes

III.⁹ These are molecular aggregations which occurred in the ground state upon association of the transiently generated electron-rich enamine II [the donor, formed from the condensation of an aldehyde I ($R^1 = H$) and a chiral secondary amine I ($R = \text{alkyl}$)] with the electron-accepting alkyl bromide 2.

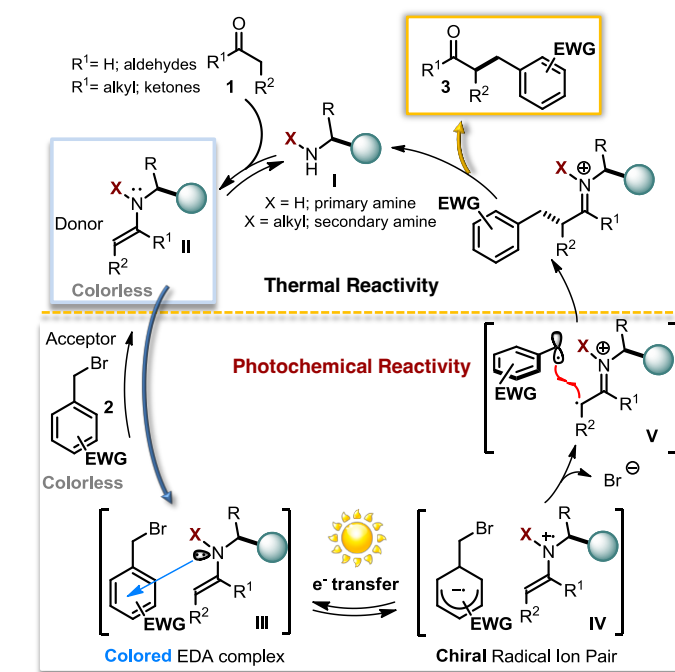


Figure 1. Mechanistic proposal for the photochemical organocatalyzed direct α -alkylation of ketones: exploiting the photochemical activity of the in-situ generated chiral EDA (electron donor-acceptor) complexes III to access radical reactivity patterns; EWG: electron withdrawing group; filled grey circles represent the chiral fragment of the aminocatalyst scaffold; X = H for primary amines, X = alkyl for secondary amine catalysts; $R^1 = H$ for aldehydes, $R^1 = \text{alkyl}$ for ketones.

Visible light irradiation of the colored EDA complex III induced an electron transfer to occur, which allowed access to open-shell reactive species under very mild conditions. Facile

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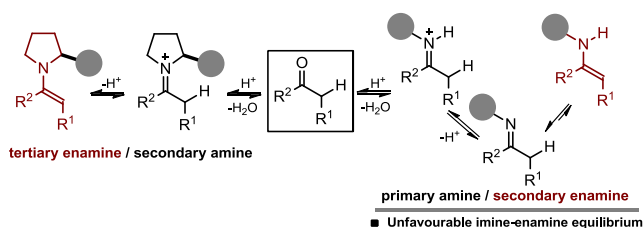
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[†] Electronic Supplementary Information (ESI) available: complete experimental procedures and full compound characterization, including HPLC traces and NMR spectra (PDF).

fragmentation of the bromide anion from the ion pair **IV** productively rendered the positively charged intermediate **V**, which brought two radicals within a geometrically restricted chiral space and in very close proximity. This condition facilitated a stereocontrolled radical combination within the solvent cage to form a new carbon-carbon bond while forging the α -carbonyl stereogenic center of the final product **3**.

We recently wondered if the catalytic principles inherent to the photochemical strategy depicted in Figure 1 could be successfully translated to ketonic systems ($R^1 = \text{alkyl}$ in **1**), thereby providing an unreported catalytic method for their direct and enantioselective α -alkylation. Despite the superficial similarities between aldehydes and ketones, the latter are characterized by increased steric impediments which largely limit the use of chiral secondary amine catalysts. A possible solution may be found in the superior ability of primary amines to effectively condense with sterically biased carbonyls.¹⁰ However, this option would bring about other issues, since the resulting secondary enamines have a tendency to spontaneously rearrange to the more stable imine (Scheme 1).^{10b-c} This unfavorable imine-enamine equilibrium may greatly reduce the concentration of the electron-rich enamine (intermediate **II** in Figure 1), the donor species required for the formation of the photochemically active EDA complex of type **III**. Other concerns arise from the electronic properties of the resulting secondary enamine, which should have the suitable ionization potential (IP)¹¹ to engage in a light-driven electron transfer within the EDA complex. Moreover, an effective chiral primary amine catalyst, capable of inferring a high level of stereocontrol during the carbon-carbon bond forming event, is required.



Scheme 1. The behavior of secondary and primary amines in condensation with enolizable carbonyl compounds.

Results and Discussion

To test the feasibility of our plan, we investigated the potential of a variety of chiral primary amines (20 mol%) to activate cyclohexanone **1a** toward the benzylation with 2,4-dinitrobenzyl bromide **2a**, an alkylating agent which was crucial to the successful implementation of the asymmetric photochemical alkylation of aldehydes.^{8,12} The experiments were conducted using a household full-spectrum 23 W compact fluorescent light (CFL) bulb to irradiate the reaction mixture. Selected explorative studies are summarized in Table 1. We initially confirmed that a chiral secondary amine could not promote the transformation to any extent (entry 1), while primary amines showed promising (entries 2&3) or even excellent reactivity (entry 4). Only the quinidine-derived primary amine **A**¹³ (20 mol%), used in combination with TFA (40 mol%) as the acidic co-catalyst, provided a satisfactory level of enantioselectivity (88% enantiomeric excess, *ee*, entry 2), albeit with only moderate reactivity.

The cinchona-based catalysts of type **A** have an established potential to induce high enantioselectivity in thermal reactions of ketones, also proceeding via enamine formation.^{13b-e} Still, the efficiency of **A** in the photochemical benzylation was rather surprising to us. This is because of the possible deactivation pathways the catalyst could undergo: in particular, the bridgehead nitrogen in the quinuclidine core is easily amenable to a direct benzylation¹⁴ or alternative degradative radical patterns.¹⁵ In line with this scenario, we did indeed observe that the conversion of the model reaction catalyzed by the amine **A** reached a standstill after twelve hours. The arrest of the reactivity indicated that the chiral catalyst could not resist the reaction conditions over the time. Evaluation of the reaction media, characterized by different dielectric constants, did not provide a solution to the deactivation problem (entries 5-7). We eventually found that the catalyst efficiency can be preserved when performing the reaction under cryogenic conditions (0 °C). This allowed the isolation of the final benzylation product **3a** in a good chemical yield and with a slightly improved optical purity (60% yield, 90% *ee*, entry 8). The use of the pseudo-enantiomeric primary amine catalyst **E**, derived from quinine, granted access to the opposite optical antipode of the benzylated product **3a** (entry 9).

Table 1 Explorative Studies.^a

entry	catalyst	solvent	T [°C]	conv. (%) ^b	<i>ee</i> (%) ^c
1 ^d	D	toluene	25	<5	n.d.
2	A	toluene	25	45	88
3 ^e	C	toluene	25	45	42
4 ^e	B	toluene	25	90	18
5	A	CHCl ₃	25	<5	n.d.
6	A	MTBE	25	19	68
7	A	DMSO	25	<5	n.d.
8	A	toluene	0	60 ^f	90
9	E	toluene	0	50 ^f	90 ^g
10 ^h	A	toluene	40	<5	n.d.
11	-	toluene	25	<5	n.d.
12 ⁱ	A	toluene	0	<5	n.d.

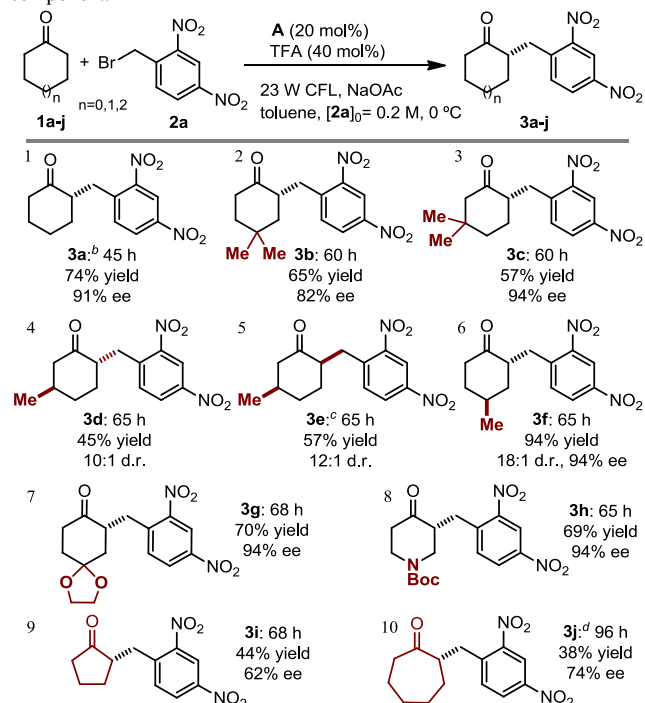
^a TFA: trifluoroacetic acid; NaOAc: sodium acetate; n.d.: not determined; CFL: compact fluorescent light. Reactions performed on a 0.1 mmol scale over 45 hours using 4 equiv. of **1a** and 2 equiv. of NaOAc, [**2a**]₀ = 0.2 M, and a 23 W CFL bulb to illuminate the reaction vessel. ^b Determined by ¹H NMR analysis of the crude reaction mixture. ^c Determined by HPLC analysis on a chiral column. ^d Reaction carried out without the acidic additive. ^e Reaction performed with 20 mol% of benzoic acid instead of 40 mol% of TFA. ^f Yield of the isolated product **3a** after purification on silica gel. ^g Reaction leading to the (*R*) enantiomer of **3a**. ^h Reaction performed in the dark. ⁱ Reaction performed in air.

Control experiments revealed how the careful exclusion of light or of the aminocatalyst **A** completely suppressed the process, even upon heating at 40 °C (entries 10&11). The inhibition of the reactivity observed when performing the

transformation under an aerobic atmosphere (entry 12) was consonant with a radical mechanism being operative.¹⁶ We also performed trapping experiments in the presence of a radical scavenger. When 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO, 5 0.5 equiv.) was added to the reaction mixture, the alkylation product **3a** was not detected after prolonged exposure to light (24 h).

We then evaluated the synthetic potential of the photochemical organocatalytic ketone alkylation strategy. As highlighted in 10 Table 2, entry 1, the method is amenable for synthetically useful purposes, since a slightly higher efficiency was observed when running the reaction on a 1 mmol scale.

Table 2 Scope of the photochemical ketone α -benzylation: the ketone 15 component.^a



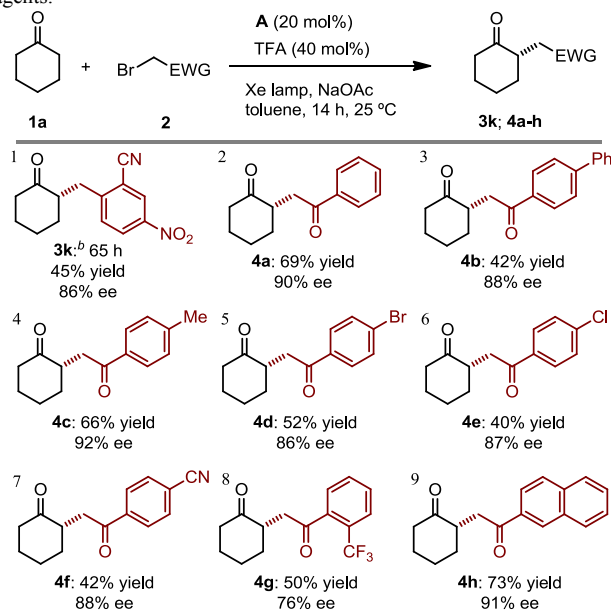
^a TFA: trifluoroacetic acid; NaOAc: sodium acetate; CFL: compact fluorescent light. Reactions performed at 0 °C on a 0.2 mmol scale, using 20 4 equiv. of **1a** and 2 equiv. of NaOAc, $[2a]_0 = 0.2$ M, and three 23 W CFL bulbs to illuminate the reaction vessel. Enantiomeric excess of the isolated products **3** determined by HPLC analysis on a chiral column. ^b Reaction performed on a 1 mmol scale. ^c Using catalyst **E**. ^d 10 equiv. of the starting ketone **1j** were used.

Experiments that probe the scope of the ketone component 30 have revealed that a variety of six-membered carbocycles and heterocycles can be readily employed in this asymmetric alkylation reaction (entries 1-8, 82-94% ee). The steric prominence of a geminal dimethyl pattern at the 4-position of the cyclohexane ring did not affect the efficiency of the reaction (entry 2). The same substitution pattern at the cyclohexanone 3-position resulted in a remarkable complete positional selectivity, the benzylation occurring at the α -carbon atom more distant from the encumbered site (entry 3, **3c**: 94% ee, >20:1 regio-control). 35 The same regioselectivity was observed in the benzylation of the enantiopure (*R*)-3-methylcyclohexanone: remarkably, the opposite diastereoselectivity obtained when using the pseudo-enantiomeric catalysts **A** and **E** (entries 4&5, *trans* and *cis*-selectivity, respectively) illustrated the ability of the cinchona-

40 based catalyst to override the inherent bias of the resident stereogenicity in the alkylation of enantiopure chiral ketones. As detailed in entry 6, 4-methyl-cyclohexanone was effectively desymmetrized, leading to the corresponding benzylated product **3f** with a high level of diastereo- and enantio-selectivity. In 45 addition, the reaction conditions were mild enough to tolerate the presence of ketals (**3g**: 94% ee, entry 7), while N-Boc piperidin-4-one could also be successfully benzylated (**3h**: 94% ee, entry 8). Finally, five- and seven-membered cyclic ketones were competent substrates of this photochemical strategy, albeit with 50 reduced efficiency (entries 9&10, products **3i** & **3j**). At the present stage of investigation, we could not extend the cinchona-based catalytic system to include linear ketones, since a much lower reactivity was observed.

Importantly, we found that this new protocol can be readily 55 extended to other bromide-containing acceptors (see Table 3 for the scope of the alkyl halides). In addition to electron-deficient benzylic systems (entry 1, product **3k**), a broad array of phenacyl bromides can productively participate in the enantioselective photochemical alkylation of cyclohexanone **1a** (entries 2-9, 60 products **4a-h**, 76 to 92% ee). We found that the alkylation to give products **4** proceeds better when using a xenon lamp (*Asashi Spectra Co., Ltd.*) to irradiate the reaction mixture. Under these conditions, the photochemical reaction could be conducted at ambient temperature and over a 14-hour period of time.¹⁷ Control 65 experiments, performed for all the reactions presented here, revealed how the absence of light illumination completely suppressed the process.

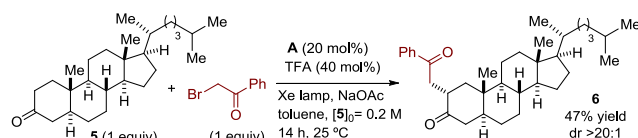
Table 3 Scope of the photochemical ketone α -alkylation: the alkylating 70 agents.^a



^a TFA: trifluoroacetic acid; NaOAc: sodium acetate. Reactions performed at room temperature on a 0.2 mmol scale using 4 equiv. of **1a** and 2 75 equiv. of NaOAc, $[2]_0 = 0.2$ M. A 300 W xenon lamp (300-600 nm) was used to illuminate the reaction vessel. Enantiomeric excess of the isolated products **3k** and **4** determined by HPLC analysis on a chiral column. ^b Reaction performed at 0 °C for 65 hours and using three 23 W CFL bulbs to illuminate the reaction vessel.

80 Finally, the synthetic utility of our method was demonstrated in the photochemical alkylation of the steroid 5 α -cholestan-3-one

(5) with 2-bromo acetophenone, which led to the corresponding product 6 with excellent regio- and stereocontrol (Scheme 2, 47% yield, dr > 20:1, >20:1 regiocontrol).



Scheme 2.

Our proposed mechanism, according to Figure 1, involves highly-organized EDA complexes as critical intermediates that play an explicit role in determining reactivity. In order to investigate the transient formation of a ground-state EDA aggregation, we measured the optical absorption spectra of the separate reaction components involved in the alkylation (Figure 2). Immediately after mixing a toluene solution of the cinchona catalyst A/TFA combination with the cyclohexanone 1a and the bromide 2a, a marked yellow color developed, while the optical absorption spectrum showed a bathochromic displacement in the visible spectral region, diagnostic of an EDA complex (blue line in Figure 2). Interestingly, in the absence of TFA, no evidence for the EDA complex formation was collected (green line). This result is consonant with the notion that the condensation of the cinchona-based primary amine with a carbonyl substrate is greatly inhibited in the absence of acid,^{10a,13a} a condition which does not allow for the formation of an enamine-based EDA complex. This is in agreement with the negligible reactivity observed in the A-catalyzed alkylation performed in the absence of TFA.

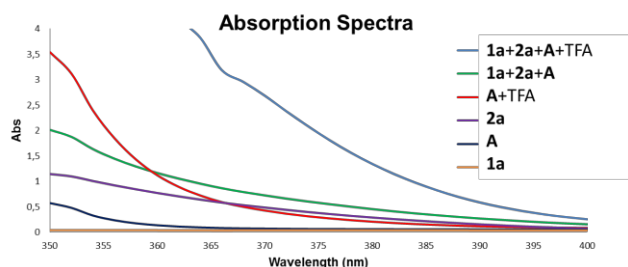


Figure 2. Optical absorption spectra recorded in toluene in 1 mm path quartz cuvettes using a Shimadzu 2401PC UV-visible spectrophotometer. [A] = [2a] = 0.04 M; [1a] = 2 M; [TFA] = 0.08 M.

Conclusions

We have developed a direct methodology for the intermolecular asymmetric alkylation of cyclic ketones with alkyl bromides, leading to the formation of the α -alkylated products with high levels of regio-, diastereo-, and enantio-selectivity. The process is catalyzed by a simple chiral primary amine and is photochemical in nature, since it requires light in order to proceed. In our laboratories, we are currently investigating further applications of photo-organocatalysis, where key transient intermediates of organocatalytic asymmetric processes in the ground state actively participate in the photo-excitation of substrates. We expect that this approach will be useful for developing new asymmetric radical processes.

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- 15 As mentioned in Ref. 12, some tertiary amines can be electron-rich enough to engage in EDA complex formation with nitro-aromatics.
- 16 A plausible explanation for the absence of reactivity under an aerobic atmosphere is that molecular oxygen can easily quench a triplet state resulting from relaxation of the initial excited EDA singlet, thereby interrupting the ET process leading to the radical ion pair **IV** (Figure 1).
- 17 The photochemical alkylation of **1a** with phenacyl bromides leading to products **4** could also be promoted by a simple 15 W-black light CFL bulb ($\lambda_{\text{max}} = 360$ nm), although with a decreased reactivity. However, the use of the Xe lamp with a cut-off filter at 385nm did not promote the transformation. Interestingly, the same cut-off experiment, when conducted for the benzylation with **2a**, did not reduce the reaction rate, indicating that absorption in the visible region is sufficient for this reaction to occur.
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