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ARTICLE

Alkylation of the α -amino C–H bonds of anilines photocatalyzed by a DMEDA-Cu-Benzophenone complex: Reaction scope and mechanistic studies

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The Cu(II) complex **1** incorporating a BP chromophore is a highly active and chemoselective photocatalyst for the alkylation of α -amino C–H bonds of anilines. The reaction was shown to proceed with a broad substrate scope in the absence of additives. Extensive mechanistic studies were performed, in particular using transient absorption spectroscopy, and spectroscopic signatures of key intermediates were identified in the conditions of catalysis. Finally, the ability of **1** to act as a multitask catalyst was showcased by conducting multi-component CuAAC and olefin hydroalkylation reactions in one-pot.

Introduction

With the advent of photoredox catalysis,¹ the development of light-promoted methodologies for the direct functionalization of C(sp³)–H bonds is developing fast.² In this domain, the direct C(sp³)–H α -alkylation of amines is of particular interest.³ Anilines constitute a prominent class of amines that are found in numerous natural products, agrochemicals and pharmaceuticals.⁴ Consequently, numerous transition metal-catalyzed methodologies have been developed for the direct functionalization of their aromatic C(sp²)–H bonds.⁵ As far as photoredox processes are concerned,³ direct C(sp³)–H bond alkylations proceeding through 1,4-addition of α -aminoalkyl radicals to Michael acceptors have been developed.⁶ The methodologies reported so far combine precious metal-based Ru(II), Ir(III) or Rh(III) photoredox catalysts and visible light irradiation from blue/white LED or CFL light sources (scheme 1A).⁶ In most of these systems it was found that an additive, i.e. a Brønsted acid or base, was necessary to obtain high yields. Interestingly, the reaction of *N,N*-dimethyl anilines with Michael acceptors could be switched by O₂ to afford tetrahydroquinolines resulting from oxidative cyclization of the radical intermediate.^{6d, 7} Furthermore, in the presence of weak electrophiles such as acrylates, low yields of addition products with *N*-methyl anilines (~ 30%) were reported due to competitive oligomerization,^{6a, 6g} a side-reaction that could

A- State of the art Ru^{II} or Ir^{III} photocatalysis

B- Previous attempt using dual (BP)-Cu photocatalysis

C- This work

Scheme 1 Representative examples of Giese-type photocatalyzed C(sp³)–H α -amino alkylations of anilines.

indeed occur when using highly polymerizable Michael acceptors in radical processes.

In the area of photoredox catalysis, dual aromatic carbonyl-transition metal photocatalytic systems are receiving increasing interest.⁸ Aromatic carbonyls are cheap, environmentally-friendly and easily tunable photosensitizers whose triplet

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states, populated following photoexcitation, can mediate single electron transfers (SET) and/or H-atom transfers (HAT). Combining the photocatalytic properties of aromatic carbonyls with first-row transition metal-based catalysts has led to the development of numerous innovative transformations, including the direct functionalization of C(sp³)-H bonds.⁹

We recently reported that the combination of catalytic amounts of Cu(OAc)₂ (2 mol%) and BP (20 mol %) under mild UVA irradiation promoted efficient C(sp³)-H alkylations of ethers, amines, alcohols and alkanes.^{9h} In the absence of copper, oligomerization/polymerization of the Michael acceptors was the dominant reaction. During this study we found that the Cu(OAc)₂-BP combination was poorly efficient for the α -C-H functionalization of the *N,N*-dimethyl aniline **2**. Not only was the polyethylacrylate the major product, but the addition product **4** at full conversion of the acrylate was formed in low yield along with an $\sim$ equimolar amount of the non-separable tetrahydroquinoline by-product **5** (scheme 1B). We now report that when using the photoreducible copper(II) complex **1** (scheme 1C), a photolabile catalyst for the Cu^I-catalyzed azide-alkyne cycloaddition (CuAAC),^{10a} and a photocatalyst for the trifluoromethylation of alkenes,^{10b} *N*-alkyl anilines could be alkylated with high selectivity and broad substrate scope in the absence of additives. Mechanistic studies were performed, in particular using transient absorption spectroscopy, and spectroscopic signatures of key intermediates were identified. Finally, preliminary results show that **1** can be employed as a multi-task catalyst able to perform the C(sp³)-H alkylation and CuAAC reaction in a one-pot photopromoted process applied to the coupling of anilines with azido derivatives.

Results and discussion

We were pleased to find that when testing **1** as photocatalyst at 4 mol % loading, the reaction between the *N,N*-dimethyl aniline **2** and ethyl acrylate **3** proceeded cleanly in acetonitrile, the expected hydroalkylated product **4** being isolated with a very high 91% isolated yield (Table 1) after 2 h of irradiation with a 365 nm LED (see SI for detailed set-up). The use of 370 nm or violet 390 nm LEDs led to similar results (entries 1 and 2). Low-pressure Hg lamps, i.e. type Thin Layer Chromatography Lamp (TLC) or Compact Fluorescent Light bulbs (CFL), could be employed as irradiation sources albeit with longer irradiation times (entries 3 and 4). A significant decrease in yield was observed when reducing the catalyst loading to 2 mol% (entry 5). Using the combination of Cu(OAc)₂ and BP as catalysts and at the same loading as **1** led to a low yield (18 %) of a 2.8:1 non-separable mixture of **4** and **5** (entry 6). The ¹H NMR follow-up revealed that the acrylate conversion was $\sim$ 50% after 4 h irradiation, and that the BP was fully degraded within the first 2 h of reaction. Using BP alone, traces of **4** were formed, while the acrylate was almost intact and the BP fully degraded (entry 7). Using 2 equiv. of the acrylate with respect to the aniline led to a mixture of **4** and overalkylation ($\sim$ 40%) of the second *N*-methyl group of **4** (entry 8). Similarly, reducing the

aniline:acrylate ratio from 3:1 to 2:1 led to a decrease of the yield of **4** accompanied with the formation of $\sim$ 30% of the

Table 1 Alkylation of **2** photocatalyzed by **1**^a

No.	Deviation from standard conditions	Yield ^b
1	370 nm LED, ^c 4 h	86%
2	390 nm LED, ^c 7 h	85%
3	Hg Lamp (type TLC, 6W 365 nm), 7 h	90%
4	CFL (24 W), 17 h	68%
5	1 at 2 mol%, 19 h	43%
6	Cu(OAc) ₂ (4 mol%), BP (8 mol%), 4 h	18% ^d
7	BP (8 mol%) instead of 1 , 2 h	<5%
8	2 (0.1 mmol), 3 (0.2 mmol), 20 h	38%
9	2 (0.2 mmol), 3 (0.1 mmol)	68%
10	Under air, ^e magnetic stirring, 18 h	0%
11	Reaction in the dark, 24 h	0%

^a Standard conditions: Reactions followed by ¹H NMR and conducted in NMR tubes, CD₃CN (1 mL), degassing by Ar bubbling (10 min), LED (Luzchem) placed at $\sim$ 3 cm of the tube (See SI for details). ^b Isolated yields. ^c LED lamps (Kessil) placed at $\sim$ 15 cm from the tube (See SI for details). ^d The acrylate conversion was $\sim$ 50%, products isolated as a 2.8:1 mixture of **4** and bicyclic by-product (see scheme 1). ^e Reaction in a test tube (pyrex, 5 mL) under 1 atm. of air (balloon).

symmetrical bis-alkylated product (entry 9). Finally, no reactivity was observed for reactions conducted under air or in the dark (entries 10, 11).

Using the standard conditions we then evaluated the scope of acceptors (scheme 2). The *N,N*-dimethyl aniline **2** reacted with a wide variety of Michael acceptors including acrylates (**4**, **6-8**), benzyl methacrylate (**9**), methyl 2-acetamidoacrylate (**10**), acrylamides (**11**, **12**), enals (**13**, **14**), 4- and 2-vinylpyridine (**15**, **16**), enones (**17**, **18**) and acrylonitrile (**19**), to afford the corresponding hydroalkylated products in good to excellent isolated yields. A reaction between **2** and **3** conducted on a 1 mmol scale delivered **4** in 75% yield.

Considering the scope of anilines, the reaction of *N,N*-dimethyl anilines with electron-withdrawing or electron-donating groups in para position of the phenyl ring with ethyl acrylate afforded the addition products **20-24** with ethyl acrylate in good to excellent yields. A noticeable limitation is that with 4-Br and 4-Cl phenyl substituents the hydroalkylated products were isolated in low yields and were contaminated by significant amounts of the ATRA adducts resulting from a carbon-halogen bond cleavage. Anilines **24-26** having ortho substituents were obtained in low to good yields. Interestingly, the 4-dimethylaminopyridine (DMAP) and 2-dimethylaminopyridine could be effectively alkylated (**27-29**). The *N*-methyldiphenylaniline and *N*-methylaniline were also found to be suitable substrates, the hydroalkylated products **30-34** being obtained in moderate to good yields. Finally, engaging *N*-phenyl piperidine led to **35** in satisfactory yield.

Based on extensive previous studies on BP photochemistry and radical addition reactions onto olefins, as well as

experiments described below, a reaction mechanism is proposed (scheme 3). Absorption of a UVA photon by BPCO_2^-

Scope of acceptors

Scope of anilines

Scheme 2 Scope of the C(sp³)-H alkylation of anilines catalysed by **1** (0.2 mmol scale of the acceptor). ^a1 mmol scale.

led to the BPCO_2^- singlet excited state which is very rapidly converted through intersystem crossing (ISC) to the BPCO_2^- triplet excited state ($\Phi_{\text{ISC}} = 1$).¹¹ The triplet state ($E_{\text{T}}^{\text{red}} = +1.28$ V vs SCE for BP)^{1b} oxidizes the aniline ($E_{\text{ox}} = +1.122$ V vs SCE in CH₃CN for 4-cyano-*N,N*-dimethylaniline)¹² to afford the aniline radical cation **A** and BPCO_2^- radical dianion **B**. Proton transfer from the relatively acidic intermediate **A** ($\text{pK}_{\text{a}} = 6$ in CH₃CN for the 4-cyano-*N,N*-dimethylaniline)¹² to **B** leads to radical **C** and ketyl radical **E**. As revealed by ¹H NMR and mass spectrometry, **C** was effectively trapped by TEMPO during the reaction between **2** and **3**, leading to < 5% of the hydroalkylation product (Figures S3-S4). The radical **C** rapidly adds on the olefin to afford the relatively electrophilic radical **D** which would rapidly react with the electron rich/reducing Cu(I) and/or Cu(0) species generated in situ by reduction of Cu(II)/Cu(I) by ketyl radical **E** ($E_{\text{red}} = -0.25$ V vs SCE in CH₃CN for BP)¹³ or radical anion **B** ($E_{\text{red}} = -1.72$ V vs SCE in CH₃CN for BP).¹¹ Following the photoreaction by UV-vis showed that complete photoreduction of the Cu(II) occurs within the first 5 min, as shown with the loss of the absorption band centered at 630 nm ascribed to a d-d electronic transition in the d⁹ complex **1** (Figure 1). During the course of the reaction formation of a copper mirror on the tube surface was observed (Figure 1), supporting the assertion that

Cu(0) is generated during the reaction. Additionally, opening the solution to air at the end of the reaction led to a fast color change from yellowish to blue/green showing that reactive reduced copper species are indeed present in solution. From **D** to the product, the reaction should proceed either by outer-sphere electron transfer from Cu(I) and/or Cu(0) followed by protonation, or by an inner-sphere process implying organocopper alkyl-Cu(II) or alkyl-Cu(I) intermediates followed by protodemetalation. When conducting the benchmark reaction by adding 0.5 % D₂O (v/v), ~ 75% of monodeuteration occurred at the α -position of the carbonyl group as determined by NMR and mass spectrometry (Figures S5-S6) confirming that the conversion of **D** to the product does not proceed through direct H-atom abstraction from the aniline, as would be the case for a radical chain mechanism.

To gain additional support for such mechanism, transient absorption spectroscopic studies were conducted in deaerated acetonitrile solution at reaction concentrations ($\lambda_{\text{exc}} = 355$ nm, see Figure 2 and S7-S8 and details in SI). Three samples were

Scheme 3. Proposed reaction mechanism.

Figure 1. UV-vis monitoring of the photoreduction of **1** during the first 5 min of irradiation of a reaction between *N,N*-dimethyl aniline **2** and ethyl acrylate **3**. A vial containing **1** (4 mol%, 0.012 mmol) and CH₃CN (3 mL) is sonicated for 1 minute, followed by the addition of **2** (0.9 mmol) and **3** (0.3 mmol). The solution was transferred to a quartz UV cuvette (1 cm path length) which was closed with a rubber septum. After deaeration by gentle Ar bubbling (10 min), the reaction was then initiated by irradiation with a 365 nm LED placed at ~ 3 cm of the cuvette (Luzchem irradiation set-up). Inset: Photograph of test tubes after hydroalkylation reactions (reaction solution removed) showing the formation of a copper(0) mirror on the tube surface.

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Figure 2. A: TRABS map of BP (0.01 M) – 2 (0.3 M) on a 200 ns scale in acetonitrile ($\lambda_{\text{exc}} = 355$ nm). (Note: The spectrum combines two individual spectra at different wavelength ranges). B: TRABS map of 1 (0.04 M) – 2 (0.3 M) on a 20 ns timescale in acetonitrile ($\lambda_{\text{exc}} = 355$ nm). (Note: The spectrum combines two individual spectra at different wavelength ranges). C: The relaxation of 2 radical cation TRABS band of three samples on 20 ns timescale. In C and D, in addition to a fast decay component ($\tau = 0.6$ ns) in each case: Red: $\tau = 2.8$ ns; blue: $\tau = 4$ ns; black: $\tau = 63$ ns. A long, persistent component was further seen in fully degassed red and blue samples.

measured, i.e. BP + 2, 1 + 2 and 1 + 2 + 3. Monitoring the BP + 2 mixture showed the growth of the 2 radical cation signal at 460 nm and that of the BP radical anion at 650–700 nm – showing that the photoinduced electron transfer process was occurring, as well as the BP triplet absorption signature at 525 nm (Figure 2A). Further, this electron transfer process proved to occur on two different timescales (Figure 2A, C–D, Figure S7). The more rapid process is attributed to a pseudo-intramolecular transfer within a ground-state complex (static) formed in solution as well as a predominant slower diffusion-controlled (dynamic) intermolecular contribution. The wealth of overlapping signals hampered precise determination of sub-nanosecond radical formation rates in each case. Similarly, detailed studies by Mataga conducted in the absence of Cu(II) previously elucidated the presence of both static and dynamic photoinduced electron transfer processes involving benzophenone and dimethyl aniline at similar concentrations in MeCN.¹⁴ While some geminate radical pair recombination

between A and the BP anion radical is observed ($\tau = 0.6$ ns), once formed, the BP anion radical disappears with a time constant around 63 ns in the case of the BP-2 mixture (Figure 2D). However, it is dramatically shortened (circa ten-fold) in the presence of the current copper-BPCO₂[−] 1 (Figure 2B, 2D). This quenching appeared to be substrate-independent with similar rates being observed both in the absence and presence of ethyl acrylate 3 (Figure 2D, Figure S8). Protonation of the radical anion B, forming ketyl radical E was revealed by the presence of a transient absorption band at 560 nm which, like the aniline radical cation A, persisted over a 200 ns time window.

Overall, these studies strongly support the proposed mechanism. However, we are aware that there is still a need to understand the higher efficiency and selectivity of complex 1 compared to Cu(OAc)₂/BP in the reaction between *N*-alkyl anilines and highly polymerizable acrylate acceptors (see Scheme 1B and Table 1, entry 6). Considering the main differences between 1 and Cu(OAc)₂/BP, i.e. the presence of the

DMEDA ligand that will affect the redox properties of Cu(II/I/0) species, and a tighter interaction between the benzophenone and copper in **1** that could favour the copper reduction by intermediates **E** and/or **B** (Scheme 3), we propose that a more effective trapping of radical intermediate **D** might occur with **1**, thus limiting the radical intramolecular cyclization and acrylate oligomerization. Studies are in progress in our group to clarify this particular point.

Scheme 4. One-pot-combined C(sp³)-H bond alkylation/CuAAC reactions photocatalyzed by **1** (0.2 mmol scale)

Finally, as complex **1** is a powerful photolabile catalyst for the CuAAC, we envisioned that tandem C(sp³)-H bond alkylation and CuAAC reactions could be performed with **1** as a multitask catalyst. Satisfyingly, preliminary results showed that the triazoles **36-37** could be obtained in good isolated yields in one-pot transformations by reacting the anilines and azides in the presence of propargyl acrylate (scheme 4). In terms of reactivity, there is thus a clear orthogonality between the two photo-promoted reactions. As very recently underpinned in seminal reports,¹⁵ such a catalyzed process combining two 100 % atom-economical reactions should be of interest not only to access molecular complexity in a one-pot methodology, but also for bioconjugation.

Conclusions

In summary, the Cu(II)-DMEDA complex **1** incorporating a BP chromophore as counterion is a very effective photocatalyst for the direct C(sp³)-H bond alkylations of *N*-alkyl anilines. The reaction is wide in scope, chemoselective with acrylates, and does not require a precious metal or an additive. The proposed mechanism, which merges BP and copper catalytic cycles, is supported by radical scavenging and deuteration experiments, as well as steady-state and transient absorption spectroscopy studies. Interestingly, **1** emerges as a powerful multitask catalyst able to perform photolabile CuAAC and photocatalyzed olefin hydroalkylations in a one-pot process. Considering the chemical diversity and easy accessibility of organic azides, we anticipate that the combined C(sp³)-H bond alkylation/CuAAC process catalyzed by **1** will find multiple applications, such as for bioconjugation.

Experimental

General procedure for the C(sp³)-H alkylations of anilines (Scheme 2): In a test tube (pyrex, 1 cm diameter, 10 cm length) protected from light by aluminum foil, equipped with a magnetic stirrer, complex **1** (0.008 mmol, 5.81 mg) was dissolved in dry acetonitrile (2 mL) and sonicated for 1 minute. Then the acceptor (0.2 mmol, 1 eq) and the aniline (0.6 mmol,

3 eq) were added, and the tube was capped with a rubber septum. The reaction medium was deaerated by gentle argon bubbling during 10 minutes. The reaction was initiated by irradiating the tube at 365 nm with the Luzchem® illuminator setup. After stirring under irradiation at room temperature for 3-48 h, the solvent was removed under reduced pressure, and the crude product was purified by column chromatography over silica gel.

General procedure for the C(sp³)-H/CuAAC reactions (Scheme 4): In a test tube (pyrex, 1 cm diameter, 10 cm length) protected from light by aluminum foil, equipped with a magnetic stirrer, complex **1** (0.008 mmol, 5.81 mg) was dissolved in dry acetonitrile (2 mL) and sonicated for 1 minute. Then the propargyl acrylate (0.2 mmol, 1 eq), the benzyl azide (0.2 mmol, 1 eq) and the aniline (0.6 mmol, 3 eq) were added, and the tube was capped with a rubber septum. The reaction medium was deaerated by gentle argon bubbling during 10 minutes. The reaction was initiated by irradiating the tube at 365 nm with the Luzchem® illuminator setup. After stirring under irradiation at room temperature for 3 h, the solvent was removed under pressure, and the crude product was purified by column chromatography over silica gel.

Transient absorption spectroscopy (TRABS): The transient absorption / time-resolved luminescence set-up was built as follows: a frequency tripled Nd:YAG amplified laser system (30 ps, 30 mJ @1064 nm, 20 Hz, Ekspla model PL 2143) output was used to pump an optical parametric generator (Ekspla model PG 401) producing tunable excitation pulses in the range 410 – 2300 nm. For longer timescales, a tunable nanosecond laser (5 ns, 135 mJ @355 nm from Nd:YAG amplified laser pumping OPO, 10 Hz, Ekspla model NT342B-10-WW); produced tunable excitation pulses in the range 410-2300 nm. The residual fundamental laser radiation was focused in a high pressure Xe filled breakdown cell where a white light pulse for sample probing was produced. All light signals were analyzed by a spectrograph (Princeton Instruments Acton model SP2300) coupled with a high dynamic range streak camera (Hamamatsu C7700, 1ns-1ms). Accumulated sequences (sample emission, probe without and with excitation) of pulses were recorded and treated by HPDTA (Hamamatsu) software to produce two-dimensional maps (wavelength vs delay) of transient absorption intensity in the range 300 – 800 nm. Typical measurement error was better than 10⁻³ O. D. Data were analysed using home-made software developed in LabVIEW 2014 system-design platform and development environment. The trust-region dogleg algorithm (supported by LabVIEW 2014) was applied to determine the set of parameters that best fit the set of input data. The trust-region dogleg algorithm was used instead of Levenberg-Marquardt algorithm, the latter being less stable in most cases during optimization process, because trust region methods are robust, and can be applied to ill-conditioned problems.

Conflicts of interest

There are no conflicts to declare.

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