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Intermolecular C−H Quaternary Alkylation of Aniline Derivatives Induced by Visible-Light Photoredox Catalysis

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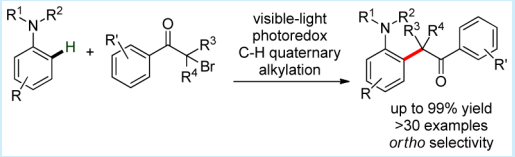
Supporting Information

ABSTRACT: The intermolecular direct C−H alkylation of aniline derivatives with α-bromo ketones to build a quaternary carbon center was reported with a visible-light catalysis procedure. The reaction covers a variety of functional groups with good to excellent yields. A regioselectivity favoring the *ortho* position for the amine group was observed and investigated with Fukui indices and spectral methods.



The intermolecular construction of quaternary carbon centers poses a challenge and has received considerable attention and synthetic effort from the synthetic community. Direct alkylation of an aromatic compound with a tertiary carbon center could give the corresponding quaternary carbon centers. In comparison to the well-established intramolecular tertiary alkylation of arenes with transition-metal catalysis,[1] visible-light catalysis,[2] and metal-free procedures,[3] intermolecular coupling is challenging because of the steric disadvantage as well as the entropy penalty. The direct C−H alkylation of aromatic compounds has been implemented via photoredox catalysis with examples being provided by the difluoroalkylation,[4] trifluoromethylation,[5] oxoallylation,[6] arylation,[7] etc.[8] Nevertheless, the visible-light photoredox-catalyzed intermolecular alkylation of aromatic compounds with tertiary carbon has not been reported.[9]

α,α-Dimethyldesoxybenzoin has a quaternary carbon center and was applied as a key intermediate in the synthesis of an estrogen receptor modulator (Figure 1).[10] The synthetic

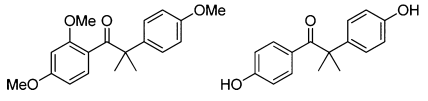
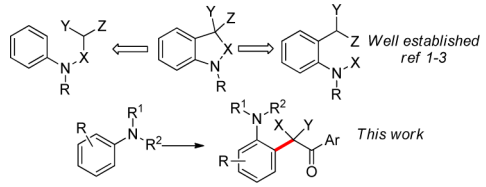


Figure 1. Compounds for estrogen receptor modulation.

strategy for preparation of the dimethyldesoxybenzoin focused on the α-alkylation of less hindered ketones, which required the generation of anionic carbon species with strong base. Herein, we report our study on the syntheses of α,α-dialkyldesoxybenzoins using direct C−H alkylation of electron-rich aniline derivatives with tertiary α-bromo carbonyl compounds induced by visible-light photoredox catalysis (Scheme 1).

At the outset, an electron-rich aniline derivative **1a** and α-bromo isobutyrophenone **2a** were chosen as standard

Scheme 1. Intra-/Intermolecular C−H Quaternary Alkylation of Arene



substrates to optimize the reaction parameters (Table 1). At first, a variety of bases typically employed in photoredox catalysis were evaluated, and sodium acetate was the optimal choice (entries 1−6). It was noted that when the bases with carbonate anion were used in the photoredox catalysis, monodemethylation occurred as a side reaction due to the water generated in situ (entries 1 and 2). In turn, a test of solvents such as DCM and DMSO confirmed that acetonitrile was the preferred medium (entries 7 and 8). Next, several photocatalysts were screened, including common transition-metal complexes and organic dyes in MeCN, to ensure complete dissolution of the catalyst. The alkylation product **3aa** could be prepared with iridium complexes (entries 11−13). The best result was achieved with ruthenium complex giving rise to the **3aa** in 72% isolated yield. When the catalyst loading was decreased to 0.5 mol %, the yield remained at the 73% mark (entries 14 and 15). On the other hand, an organic dye such as eosin Y gave rise to inferior results (entry 16).

With the optimized conditions established (Table 1, entry 15), we turned to substrate scope exploration. Initially, a series of aniline derivatives were evaluated with *p*-cyano-substituted **2b**, which simplified the product characterization and gave

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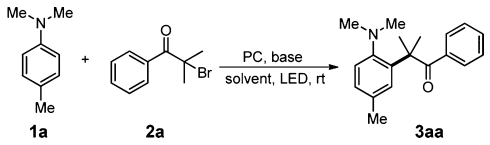
Table 1. Reaction Optimization[a]

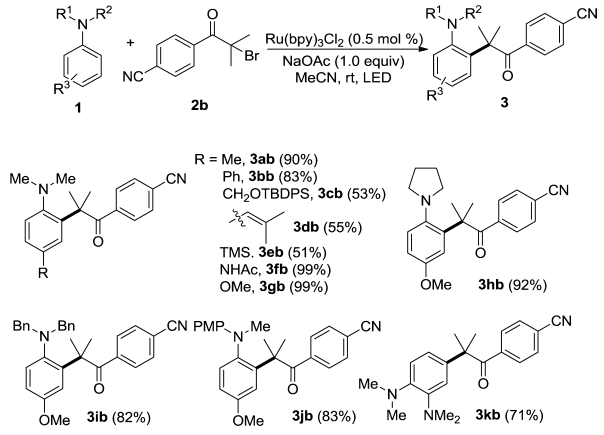


entry	catalyst	base	solvent	yield[b] (%)
1	$Ru(bpy)_3Cl_2$	Cs_2CO_3	MeCN	60
2	$Ru(bpy)_3Cl_2$	Na_2CO_3	MeCN	40
3	$Ru(bpy)_3Cl_2$	HCOONa	MeCN	62
4	$Ru(bpy)_3Cl_2$	KOAc	MeCN	43
5	$Ru(bpy)_3Cl_2$	K_2HPO_4	MeCN	38
6	$Ru(bpy)_3Cl_2$	NaOAc	MeCN	67
7	$Ru(bpy)_3Cl_2$	NaOAc	DCM	10
8	$Ru(bpy)_3Cl_2$	NaxOAc	DMSO	42
9		NaOAc	MeCN	8
10	$Ru(bpy)_3Cl_2$	NaOAc	MeCN	0[c]
11	*fac*-Ir(ppy)$_3$	NaOAc	MeCN[d]	80
12	$Ir(ppy)_2(dtbbpy)PF_6$	NaOAc	MeCN[d]	74
13	$Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$	NaOAc	MeCN[d]	42
14	$Ru(bpy)_3Cl_2$	NaOAc	MeCN[d]	81 (72)[e]
15	$Ru(bpy)_3Cl_2$[f]	NaOAc	MeCN[d]	80 (73)[e]
16	eosin Y	NaOAc	MeCN[d]	trace

[a]The reaction was carried out with **1a** (0.10 mmol), **2a** (0.12 mmol), base (0.10 mmol), and photocatalyst (1.0 mol %) in MeCN (0.5 mL), 24 W blue LEDs, 1 h. [b]NMR yield (DMAP as the internal standard). [c]No light. [d]1.5 mL. [e]Isolated yield in parentheses. [f]0.5 mol %.

improved yields in comparison to **2a** (Scheme 2, **3ab**). Compound **1b** with a phenyl group at the *para* position

Scheme 2. Scope of Anilines 1[a]

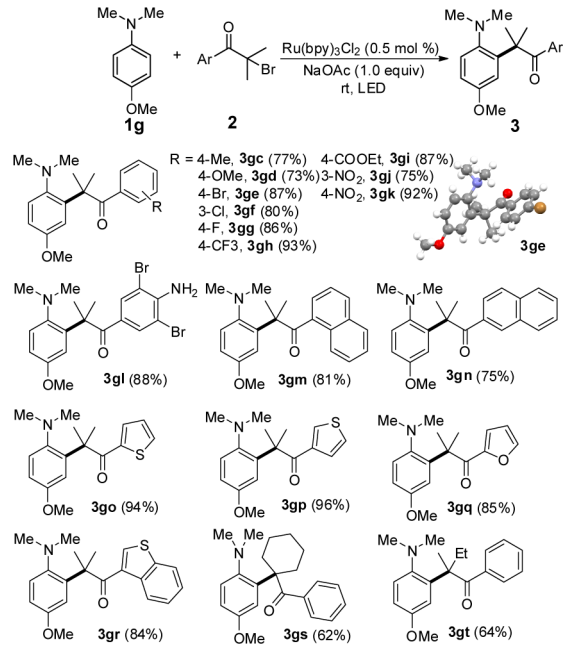


[a]**1** (0.20 mmol), **2b** (0.24 mmol), NaOAc (0.2 mmol), and $Ru(bpy)_3Cl_2$ (0.5 mol %) in MeCN (3.0 mL), 24 W blue LEDs, rt, 1 h, isolated yield after SiO_2 chromatography.

could be converted to the desired **3bb** in 83% yield. The *O*-silyl group remained intact during the reaction to obtain **3cb**; it was obtained in 53% yield. Dimethylaniline with a conjugated alkene at the *para* position was also compatible with this protocol, affording **3db** in 55% yield. Subsequently, other anilines substituted with additional heteroatoms were evaluated. Molecule **3eb** with a TMS group was prepared in moderate yield. 4-Acetamide-substituted aniline **1f** gave the corresponding product **3fb** in almost quantitative yield. The same trend was observed when electron-donating methoxy was presented at the *para* position in the aniline substrate **1g**. The products **3gb** and **3hb** were accessed with the standard reaction conditions in excellent yields. Our screening of anilines **1i** with an *N*,*N*-dibenzyl substituent and **1j** with an *N*-4-(methoxyphenyl)-*N*-methyl substituent gave the corresponding products **3ib** and **3jb** in greater than 80% yield. It was noted that only monoalkylation of **1j** occurred when 1 equiv of **2b** was applied. Substrate **1k** with diamine functionality was subjected to this photoredox alkylation reaction, and a single product **3kb** was generated in 71% yield as the only regioisomer.

In turn, a series of α-bromo ketones **3** were subjected to the alkylation reaction with dimethyl-*p*-anisidine **1g** in the presence of 0.5 mol % of $Ru(bpy)_3Cl_2$ (Scheme 3). It was observed that

Scheme 3. Scope of α-Bromo Ketones 2[a]



[a]**1g** (0.20 mmol), **2** (0.24 mmol), NaOAc (0.20 mmol), and $Ru(bpy)_3Cl_2$ (0.5 mol %) in MeCN (3.0 mL), 24 W blue LEDs, rt, 1 h, isolated yield after chromatography.

substrates with electron-donating groups provided the corresponding products in >70% yield (**3gc**,**gd**). To our delight, electron-withdrawing groups, such as fluoride, chloride, and bromide, enhanced the yield to more than 80% (**3ge**−**gg**). Here, the alkylation *ortho* to the amine group was confirmed by X-ray analysis of a crystal of **3ge**. By increasing the electronic deficiency of ketones with a CF_3 group, an excellent yield was achieved in the case of product **3gh**. Product **3gi** with ester substitution was obtained in 87% yield as well. The *m*-nitroisobutyrophenone was also a valid substrate, giving **3gj** with 75% yield. An even better result was achieved for **3gk** with a *p*-nitro group. Compound **3gl** bearing an unprotected amino group could be prepared with the same protocol in 88% yield. Products **3gm** and **3gn** with α-naphthalenyl and β-naphthalenyl groups were also prepared in 81% and 75% yield, respectively. In addition, heterocyclic ketones could be applied in the alkylation reaction. To our delight, the thiophene-yl, benzothiophene-yl, and furyl functionalities were all compatible with this protocol and gave rise to the corresponding products **3go**−**gr** in good to excellent yield. Consequently, more bulky

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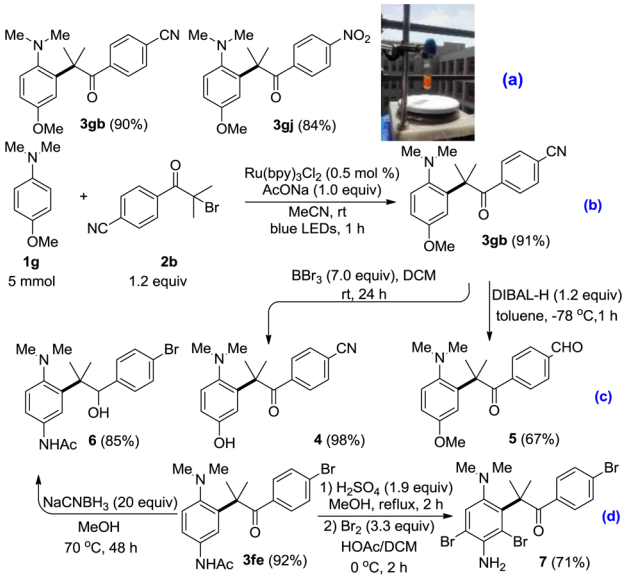
ketones like **2s** and **2t** were prepared and evaluated in the reaction with **1g** under the same conditions. Again, a similar reaction occurred in acceptable yield (**3gs**,**gt**).

To test the robustness of this photoredox alkylation reaction, we carried out the reaction to prepare **3gb** and **3gj** with sunlight instead of LEDs. The reaction was finished within 1 h with comparable yields of 90% and 84% (Scheme 4, a). To

Scheme 4. Applications of Quaternary Alkylation



discover the scalability of this catalytic reaction, a gram-scale reaction was set up with the LEDs kept at 24 W. A complete conversion ensured within 1 h, and the isolated yield of **3gb** was 91% (Scheme 4, b). This compound was subjected to several transformations of its functionalities to give the phenol **4** and aldehyde **5** smoothly (Scheme 4, c). Another compound **3fe** was converted to alcohol **6** with $NaCNBH_3$ in 85% yield. A two-step transformation of hydrolysis and bromination afforded the aniline **7** in 71% of overall yield from **3fe** (Scheme 4, d).

In order to gain insight into the mechanistic course of this reaction, a fluorescent-quenching experiment was conducted with **1a** and **2a**, respectively. A predominant reductive quenching was detected (Figure 2), suggesting the reaction proceeds via the Ru^{I}–Ru^{II} pathway. Therefore, a possible mechanism is proposed in Scheme 5a. At the beginning of the reaction, the excited ruthenium catalyst enters the catalytic cycle. A single-electron transfer from the Ru^{I} to α-bromo isobutyrophenone **2** results in the mesolytic cleavage to the isobutyrophenone radical **A**, which could be captured with

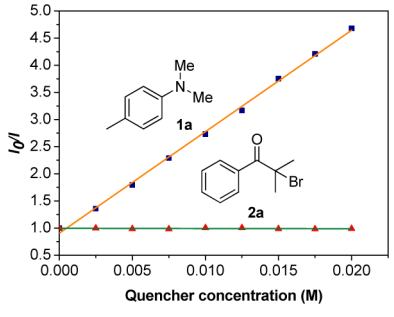
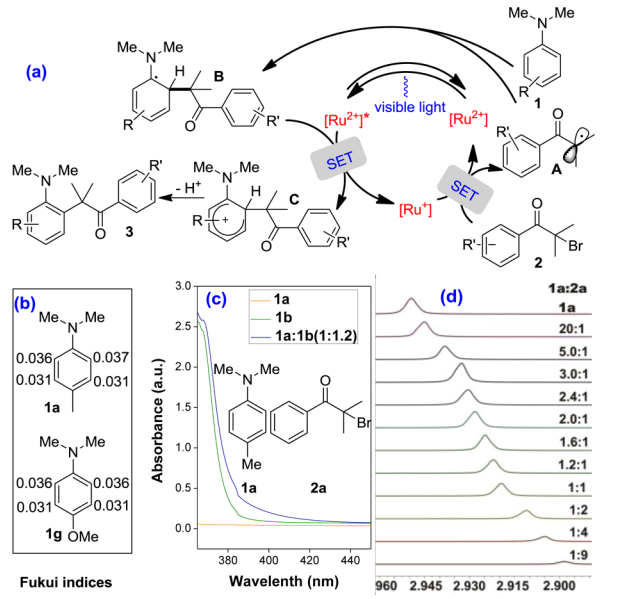


Figure 2. Fluorescent quenching of $Ru(bpy)_3Cl_2$.

Scheme 5. Proposed Mechanism



TEMPO (see the SI). The addition of **A** to aniline **1** generates the neutral radical species **B** that is oxidized with the excited Ru^{II} with release of the cationic intermediate **C**. The final deprotonation gives the desired molecule **3**. Note that the regioselectivity during the radical addition to the aniline favors the carbon *ortho* to the amine group. To elucidate this selectivity, a DFT calculation of Fukui indices on the aniline ring of **1a** and **1g** was conducted using the B3LYP/6-311g++(d,p) level of theory (Scheme 5b). It was found that the carbon *ortho* to the amine group is more reactive than that *ortho* to the methyl or methoxy group. The interaction between two substrates was observed in the UV–vis spectrum (Scheme 5c) and via NMR titration (Scheme 5d) where the amine group was essential. This interaction might facilitate the substitution adjacent to the nitrogen as well.

In summary, we have demonstrated the first visible-light catalytic C–H quaternary alkylation using aniline derivatives and the tertiary radical from α-bromo ketones. The reaction works with a variety of functionalities as well as heterocycles. The reaction could be run on gram scale and be accomplished with sunlight directly. In this reaction, the regioselectivity favors the *ortho* position to N substitution through a radical addition mechanism.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02179.

X-ray data for compound **3ge** (CIF)

Procedure for the preparation of substrates and photoredox catalysis, characterization of new compounds, spectra, experimental and computational study of the mechanism (PDF)

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Notes

The authors declare no competing financial interest.

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