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Visible-Light-Driven Synthesis of 1,3,4-Trisubstituted Pyrroles from Aryl Azides

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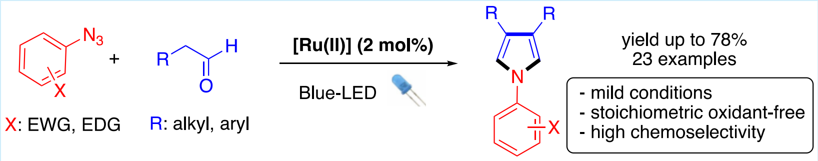
Supporting Information



ABSTRACT: The synthesis of 1,3,4-trisubstituted pyrroles via visible-light mediated photoredox catalyzed condensation of arylazides and aldehydes has been reported herein. The methodology avoids the use of stoichiometric oxidants and provides the corresponding *N*-containing arenes in good yields (up to 78%) and mild conditions. Mechanistic rationale is provided via a dedicated and combined spectroscopic/experimental investigations.

The construction of (hetero)arenes, together with their site-selective functionalization and dearomatization processes represents one of the current milestones in chemical synthetic methodology related to aromatic compounds.[1]

In this context, pyrroles are key building blocks for the realization of a wide range of functional materials as well as bioactive compounds,[2] however their preparation is not always a trivial synthetic task due to their peculiar and extraordinary reactivity profile. Therefore, mild experimental conditions should always be targeted during the design of a new synthetic route to pyrrolyl derivatives.[3] Among the most performing synthetic sequences available for pyrroles, the condensation of aldehydic compounds with anilines under oxidative conditions[4a] is gaining growing credits with the development of catalytic,[4b] metal-free[4c] and ball-milling mediated[4d] approaches (Figure 1).

In all cases, however, the employment of a stoichiometric oxidant is required in order to form the α-formyl or α-imino radical derivatives (see inset Figure 1).

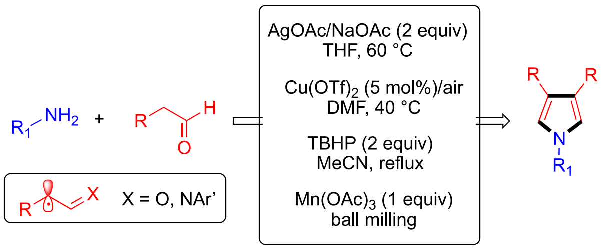


Figure 1. State-of-the-art synthesis of pyrroles via oxidative condensation of anilines with aldehydes.

The advent of visible-light photoredox catalysis brought new ideas and possibility for the generation of high-energy chemical species, such as radicals as well as charged intermediates, under mild reaction conditions.[5] Such an approach has been extensively employed also in the site-selective functionalization of arenes[6] and, though to a lesser extent, in the direct formation of (hetero)aromatic compounds[7] with limitations related to intramolecular metal cocatalyzed methodologies.[8]

In continuation to our ongoing interests in the chemistry of aromatic compounds[9] and visible-light assisted functionalization of arenes[10,11] we present herein an unprecedented mild protocol for the preparation of densely substituted pyrroles by means of photoredox production of the key carbon centered radical intermediate.

In order to avoid concomitant oxidative processes involving the aniline reaction partner, we decided to adopt azides as nitrogen-based reagents[12] that are known to produce the corresponding aniline counterparts via photoreductive SET protocol under protic conditions.[13] Concomitantly, the *in situ* generated [Ru(III)] acts as the oxidant for the α-carbonyl radical formation (Scheme 1). In the present working plan, the arylazide would play the double role of nitrogen source to be incorporated into the heteroaromatic core and "formal" stoichiometric oxidant of the whole process.

This protocol would enable the realization of an unprecedented stoichiometric oxidant-free synthesis of site-selective substituted pyrroles under desirable mild conditions.

At the outset of the optimization stage, we identified in the arylazide **1a** and phenylacetaldehyde **2a** the model substrates to be condensed under photocatalytic regime. Upon an

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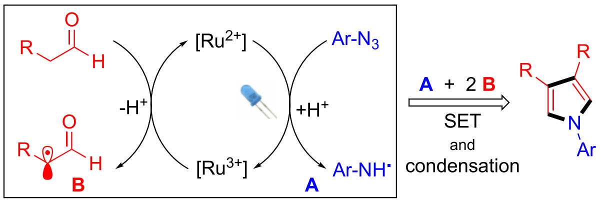
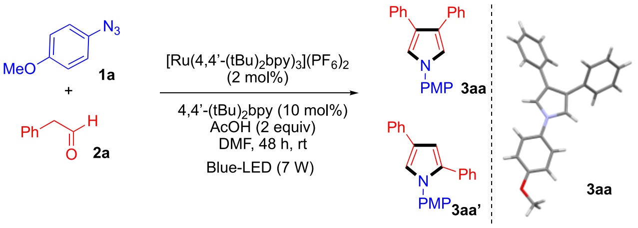
Scheme 1. Working Plan of the Present Visible-Light-Assisted Synthesis of Pyrroles



extensive survey of reaction conditions involving solvent, light source, photosensitizer and additives (see SI for a complete list of attempts), the concomitant employment of $[Ru(4,4'-(tBu)_2bpy)_3](PF_6)_2$ (2 mol %), 4,4′-(*t*Bu)$_2$bpy (10 mol %) and AcOH (2 equiv) in DMF enabled the isolation of the *N*-PMP-3,4-diphenyl pyrrole **3aa** in 74% yield and 87:13 ratio with respect to the isomeric *N*-PMP-2,4-diphenyl pyrrole **3aa'**[14] (Table 1, entry 1, *vide infra* for mechanistic considerations).

Table 1. Optimization of the Reaction Conditions[a]



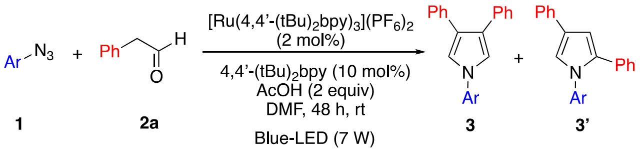
run	deviation from optimal	yield 3/3′[b] (%)	3/3′[c]
1		74	87/13
2	dark	NR	
3	blue LED (1 W)	62	85/15
4	with morpholine (0.5 equiv)	73	87/13
5	with DIPEA (0.5 equiv)	65	86/14
6	acid free	37	84/16
7[d]	no degassing	traces	--
8	no 4,4′-(*t*Bu)$_2$bpy	24	87/13
9	DMSO as the solvent	55	84/16
10	no [Ru(II)]	12	ND
11	[Ir(III)] (2 mol %)	67	84/16
12	Eosin-Y	18	85/15
13	$[Ru(bpy)_3](PF_6)_2$	65	84/16
14	$[Ru(4,4'-(tBu)_2bpy)_3]Cl_2$	68	84/16
15	*p*-anisidine instead of **1a**	NR	

[a] Reaction conditions: **1a** (0.14 M). **1a**/**2a**: 1/2.5. Under anhydrous conditions and degassed solvent. [b] Determined after flash chromatography as a **3**/**3′** mixture. [c] Determined on the reaction crude by GC–MS. [d] With reagent grade DMF. PMP: 4-MeOC$_6$H$_4$. [Ir(III)]: $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$. NR: no reaction. ND: not determined.

From the data collected in Table 1 some conclusions can be drawn. First of all, light irradiation proved to be essential (entries 1 vs 2/3). In particular, no reaction was observed in the dark and a slight drop in chemical yield was obtained when using a 1 W blue-LED irradiation (62%, entry 3). The addition of an external reductant such as morpholine or DIPEA (entries 4,5) did not affect significantly the reaction course. In contrast, the absence of protic source (entry 6), the presence of oxygen (entry 7) and removal of 4,4′-(*t*Bu)$_2$bpy as an additive (entry 8) were proven detrimental for the whole protocol.[15] Additionally, the impact of the presence and nature of the photosensitizer (PS) on the reaction profile was evaluated through dedicated experiments (entries 10–14), highlighting the role of $[Ru(4,4'-(tBu)_2bpy)_3](PF_6)_2$ as the elective photocatalyst for the reaction. Finally, the replacement of **1a** with *p*-anisidine caused the failure of the protocol; this evidence suggests that the photocatalyzed reduction of the arylazide is critical for generating high energy radical species in the reaction machinery (*vide infra*).

With the optimal conditions in hands, the scope and the versatility of the methodology toward the realization of a library of pyrrole derivatives were assessed. To this aim, two sets of experiments namely: condensation of different arylazides (**1b-k**) with phenylacetaldehyde **2a** and *p*-MeO-phenylazide (**1a**) with a range of aldehydes (**2b–m**) were carried out and the results reported in the Table 2 and Scheme 2, respectively.

Table 2. Scope of the Reaction: Azide[a]



run	Ar	yield 3/3′[b] (%)	3/3′[c]
1	C$_6$H$_5$ (**3ba**)	51	90/10
2	4-CH$_3$C$_6$H$_4$ (**3ca**)	78	84/16
3	3-CH$_3$C$_6$H$_4$ (**3da**)	74	80/20
4	2-OCH$_3$C$_6$H$_4$ (**3ea**)	50	83/17
5	4-*n*OBuC$_6$H$_4$ (**3fa**)	75	83/17
6	3,4-(CH$_3$)$_2$C$_6$H$_3$ (**3ga**)	47	81/19
7	2,4-(CH$_3$)$_2$C$_6$H$_3$ (**3ha**)	63	88/12
8	4-FC$_6$H$_4$ (**3ia**)	62	85/15
9	3-BrC$_6$H$_4$ (**3ja**)	45	80/20
10	4-BrC$_6$H$_4$ (**3ka**)	53	80/20

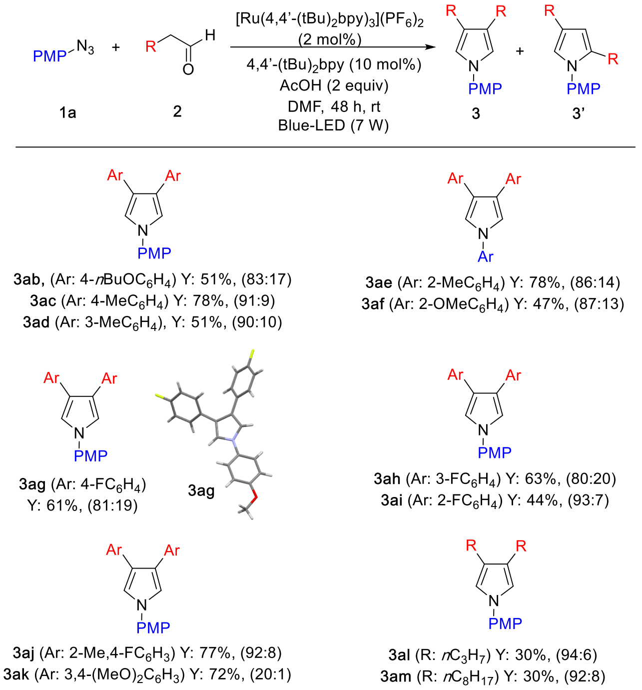
[a] Reaction conditions: **1** (0.14 M). **1**/**2a**: 1/2.5. Under anhydrous conditions and degassed solvent. [b] Determined after flash chromatography as a **3**/**3′** mixture. [c] Determined on the reaction crude by GC–MS.

Variously substituted arylazides were effectively employed in the synthesis of pyrroles regardless the phenyl substitution pattern. In particular, *ortho*, *meta* and *para* substitutions were efficiently tolerated as well as the presence of both electron-rich (**1c-h**) and electron-deficient (**1i-k**) functional groups did not affect the visible-light assisted protocol, delivering the corresponding *N*-aryl-diphenyl-pyrroles **3** in good yields (up to 78%) and moderate to good regioselectivity (**3**:**3′** up to 90:10). Moreover, mono and disubstitutions (**1g** and **1h**) at the *ortho*, *meta* and *para* positions of the aromatic ring of the aldehydic compound were fully compatible with the protocol.

In addition, the orthogonal electronic properties of functional groups located at the arenes of the phenylacetaldehyde (EDG: **2b-f** and EWG: **2h-i**) were adequately tolerated (Scheme 2). The protocol was also suitable for *ortho*-substituted compounds (yield up to 78% in the case of **2e**). Finally, aliphatic linear aldehydes were also tested under best conditions. Although a moderate yield was observed (30% yield), the corresponding 3,4-dialkyl-pyrroles **3al** and **3am** were isolated in excellent regioselectivity (up to 94:6).

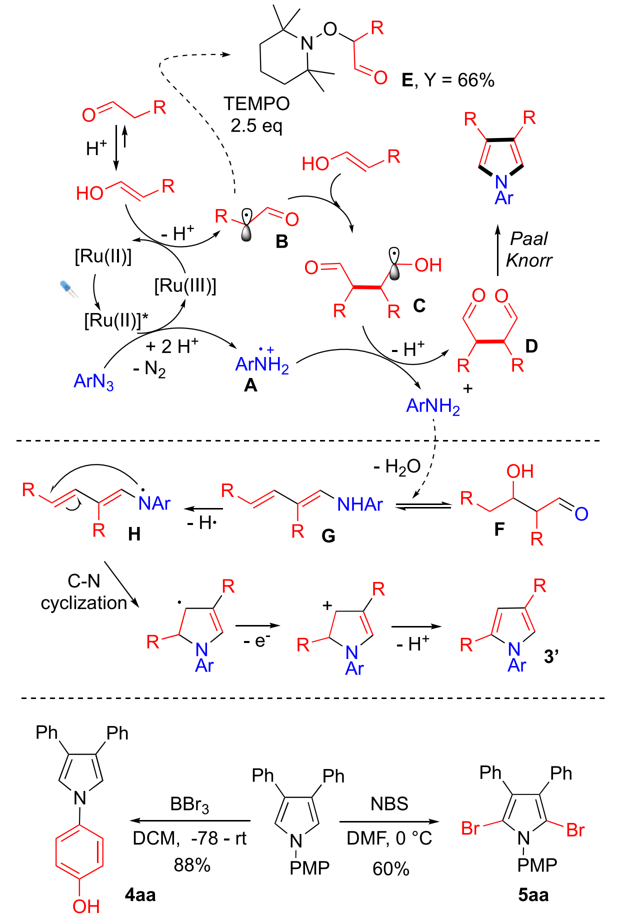
Mechanistically, the catalytic process represented in the Scheme 3 (upper part) is postulated. Stern–Volmer quenching

Scheme 2. Scope of the Reaction: Aldehyde[a]



[a]Reaction conditions: **1** (0.14 M). **1a**/**2**: 1/2.5. Under anhydrous conditions and degassed solvent. The **3**:**3′** ratio is shown in parentheses. PMP: 4-MeOC$_6$H$_4$. The X-ray structure of **3ag** is also reported (see the SI).

Scheme 3. Mechanistic Hypotheses for the Formation of 3 (Top) and Minor Isomer 3′ (Middle); Examples of Chemical Manipulation of Pyrrole 3aa (Bottom)



experiments were performed to investigate the interaction of photoexcited catalyst with the substrates and pointed out the role of arylazide **1** in the process (see SI).

Once generated under visible light irradiation, the photoexcited [Ru(II)]* complex undergoes oxidative quenching (E (Ru(II)*/Ru(III) = −1.20 V vs SCE)[16a] by the arylazide (E = −0.39 V vs SCE for *p*-NO$_2$-phenylazide),[16b] leading to formation of an anilino radical[16c] that would be subsequently protonated to radical cation **A**.[16d] Then, transient [Ru(III)] (E (Ru(III)/Ru(II) = 2.16 Vs SCE),[16a] species could act as a SET oxidant for the enolized aldehyde affording, after deprotonation, the *α*-carbonyl-radical **B** and restoring the catalytically active [Ru(II)] adduct. The presence of **B** was proved by carrying out the reaction in the presence of TEMPO (2.5 equiv), where the adduct **E**[17] was isolated in (66% yield, see SI for further details).

Therefore, trapping of **B** with a second molecule of aldehyde would deliver the *α*-hydroxy-radical **C**[18] that undergoes oxidation to the corresponding 1,4-dialdehyde **D** by **A**.[19] Final condensation of **D** with the *in situ* formed aniline would afford the pyrrole **3** via Paal-Knorr-type condensation. In the Scheme 3 (lower part), a tentative reaction picture to account the formation of the minor 2,4-disubstituted pyrroles **3′** has been presented. In this regard, the *in situ* aldol adduct **F** could undergo acid catalyzed dehydration and consequent enamine formation (**G**) with acid catalyzed condensation with aniline.[20] Annulation reaction (C−N bond formation)[21] followed by SET oxidation and proton loss from the C(2)-site would result into the formation of **3′**.

Finally, the synthetic manipulability of pyrroles **3** was undisclosed by subjecting compound **3aa** to site-selective OMe cleavage (BBr$_3$, DCM, - 78 °C) and bromination (NBS, 0 °C, DMF). Under very mild conditions, the corresponding pyrrolyl-phenol **4aa** and *α*,*α*′-Br$_2$ pyrrole **5aa** were isolated in good yields (88% and 60%, respectively, Scheme 3 lower).

In conclusion, an unprecedented visible-light photoredox catalyzed route to trisubstituted pyrroles is documented by condensing enolizable aldehydes and arylazides. The methodology by means of catalytic amounts of [Ru(II)] as the photocatalyst and 7 W blue-LED irradiation enables the replacement of classic stoichiometric oxidants (i.e., TBHP, Mn(III) salts) for the realization of *α*-carbonyl radicals **B** with the concomitant photoinduced reduction of azides.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02731.

General methods, experimental data, and crystallographic data (PDF)
NMR spectra (PDF)

Accession Codes

CCDC 1945119−1945120 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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§Y.L. and A.P. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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