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Lithium bis-catechol borate as an effective reductive quencher in photoredox catalysis

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ABSTRACT

The use of lithium bis-catechol borate ($LiB(cat)_2$) as a reductive quencher for the photoredox mediated intermolecular C–H functionalization of various heteroaromatics with bromopyrroloindolines is described. $LiB(cat)_2$ offers a financial benefit over state-of-the-art quenchers currently in use while eliminating the side reactions that typically plague these couplings. The advantage of this methodology is highlighted by the synthesis of C3–C2' (–) gliocladin C. Furthermore, additional examples of reactivity with various bromopyrroloindolines sets the stage for expedient routes towards other pharmaceutically active hexahydropyrroloindoline alkaloids and their analogues.

1. Introduction

In recent years, visible light-mediated catalysis has been extensively studied to develop an array of novel organic transformations.[1–3] Of the myriad methods centered around photo-induced single electron transfer (SET) chemistry, our research program has been particularly interested in the reduction of activated and unactivated C–X bonds.[4,5] Using a photoredox catalyst, an efficient method for the intramolecular radical arylation of electron-rich heterocycles was developed.[6] Traditionally, chemists have employed trialkyl amines as sacrificial reductive quenchers for photocatalytic reactions. However, several unavoidable side reactions can limit the potential of photocatalysis. Of these undesired pathways, hydrogen atom abstraction from trialkyl amine **1** by radicals (**2**) lead to premature reduction of activated halides **(3)** (Fig. 1). Importantly, the rate of unwanted hydrogen atom transfer is competitive with the desired trapping with a heterocycle or activated alkene. In the case of bromopyrroloindolines, which our group has been interested in coupling with heterocycles for natural product syntheses, trialkyl amines reactivity had so far limited their use.

This undesired reactivity initially hampered our efforts to develop redox neutral coupling protocol. We, therefore, introduced commercially available 4-methoxy-*N*,*N*-diphenylaniline **4** as a novel reductive quencher in photoredox catalysis.[7] In the absence of α-protons, the formed *N*-centered radical cation is unable to act as a hydrogen atom donor. Due to the high cost of this reductive quencher,[8] we envisioned employing a less expensive alternative that still avoided the deleterious side reactions seen with trialkyl amines. Similar to trialkyl amines, the redox potential of the novel quencher would have to be in the electrochemical window required for reductive quenching of photocatalysts such as $Ru(bpy)_3^{2+}$ ($E1/2^{II*/I} = +0.77$ V vs SCE)[9] as well as be inexpensively procured. Finally, the new reductive quencher and its oxidized state need to be innocent species in the desired reaction.

The indole aromatic scaffold is ubiquitous in both bioactive natural products and pharmaceuticals,[1] and tremendous effort has been expended to develop methods for the robust and efficient functionalization of the heteroaromatic skeleton. In the same vein, reliable investigation of the bioactivity of the natural frameworks has often relied upon *de novo* synthesis to supply the necessary quantities for study. Indole alkaloids functionalized at both the 2- and 3- carbons of the aromatic scaffold, such as undulifoline,[2] actinophyllic acid,[3] vinblastine and vincristine,[4] piqued our interest into radical indole alkylation as they pose both strategic and methodological challenges (Fig. 1).

2. Results and discussion

Given the previous success of tertiary amines as reductive quenchers, we began looking for other commercially available amines capable of undergoing reductive SET without resulting in

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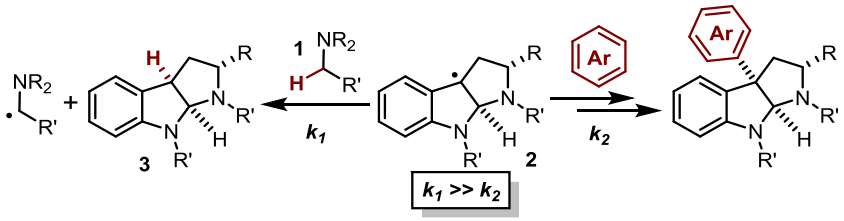


Fig. 1. Off-cycle reactivity with trialkyl amine reductive quenchers.

premature reduction. Our search proved unfruitful; no amine unable to undergo H-atom donation was financially competitive or a productive quencher. In 2006, lithium bis-catechol borate **5** (LiB(-cat)$_2$) was reported as a reductive quencher of photoexcited ruthenium polypyridyl complexes (Fig. 2).[10]

Although not directly available for purchase, borate complexes can readily be synthesized from abundantly-available commodity chemicals: boric acid and catechol. Furthermore, once oxidized, the borate complex is no longer ionic and thus can easily diffuse from the iridium or ruthenium photocatalyst, inhibiting the unproductive back electron transfer process.[11] Detailed herein, this low-cost, inert sacrificial reductant has been shown to operate effectively in our reductive, formal C–H functionalization of electron-rich heterocycles while also enabling a universal method to couple bromopyrroloindolines with electron-rich or electron-poor heterocycles.

The reaction conditions can be varied based on the availability of either coupling partner. If the heterocycle is more precious than the reagents, an excess of halide can be used. Using less than two equivalents of diethyl bromomalonate led to slow reactions and/or poor conversions to the product. Moderate to good yields were observed for electron-rich and electron-poor indoles (Scheme 1, **6**–**8**). Pyrroles and even azaindole were also compatible with this method (**9**–**10**). The starting material was fully consumed within 3 h. It should be noted that in the case of more electron rich heterocycles such as thianaphthene, only decomposition of starting materials was observed (**11**).

The radical coupling with bromopyrroloindolines with various heterocycles was also attempted (Scheme 2). Coupling with indole **12** occurred in 60% isolated yield. The use of LiB(cat)$_2$ enabled a shorter reaction time and a reduced excess of indole compared to trialkyl amine quenchers which was critical to achieve a 50% improvement in yield as the product was prone to decomposition under reaction conditions (Fig. 3). Notably, indole-2-carbaldehyde, **13**, led to isolation of the product in 91% yield, a significant improvement of the key step towards the synthesis of the natural product (+)-gliocladin C. Previous efforts required five equivalents of indole, longer reaction times and resulted in a lower yield (Fig. 3).[12] N-Boc tryptophan was isolated in good yields (**14**, 57%). Pyrrole (**15**) and furan (**16**) were also compatible with our optimized reaction protocol. Lastly, quenching the bromopyrroloindolines radical with butyl vinyl ether afforded the target aldehyde in good yields (**17**, 71%). The resulting aldehyde provides a simple yet useful handle for further transformation. For example, this aldehyde could be used to revisit syntheses of (−)-flustramine B and (+)-nocardiozines.[13] Interestingly, we did not observe poor mass recovery in cases with electron-rich heterocycles, a dramatic improvement compared to our coupling of di-ethyl bromomalonate with said substrates.

Having demonstrated the versatility of the new reductive quencher, we decided to apply this method towards the synthesis of a gliocladin C analogue. Natural gliocladin C is a hexahydropyrroloindoline alkaloid[14] containing a C3-C3′ bisindole motif. Along other natural products of this class of alkaloids, gliocladin C exhibits potent cytotoxic properties against lymphocytic leukemia cell lines ($ED_{50} = 240\ ng\ mL^{-1}$).[15] Novel analogues of gliocladin C are highly desired due to their potential as new anti-cancer therapy leads. Given our previous report,[12] we sought to synthesize the C3-C2′ gliocladin C, **18**, in a quick and efficient manner (Scheme 3). Starting from bromopyrrolindoline **19**, C3-C2′ coupling with indole proceeded smoothly with the catechol borate quencher to isolate **12** in good yield (60%). Boc-deprotection with TMSI followed by N-acylation led to the desired triketopiperazine **20** after an unexpected second N-acylation occurring during silica gel chromatography. Finally, Pd/C dehydrogenation provided **21** and a Lewis acid-mediated deprotection delivered the C3–C2′ unnatural gliocladin C (**18**) in 97% yield.

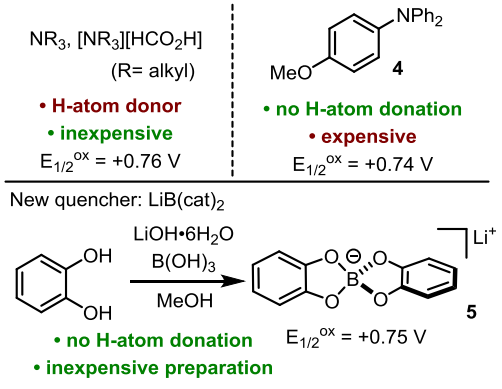
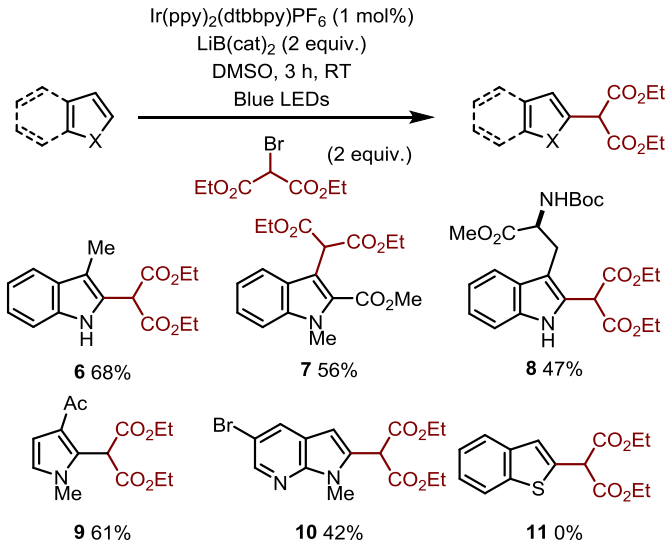


Fig. 2. Comparison of reductive quenchers.



Scheme 1. Malonate coupling scope.