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# Visible light catalyzed reaction of α-bromochalcones with chalcones: direct access to the urundeuvine scaffold†

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The α-keto vinyl radicals generated from α-bromochalcones under visible light photoredox catalyzed conditions were trapped by chalcones. The subsequent intramolecular cyclization of the resulting benzylic radicals led to the synthesis of dihydronaphthalenes, which were conveniently oxidized to the corresponding naphthalenes. The strategy was adopted successfully for synthesizing derivatives of urundeuvine chalcones, which are otherwise accessible only from natural sources.

## Introduction

The dihydronaphthalene motif is widely distributed in several medicinal molecules of natural/synthetic origin such as cannabisins, magnoshinin, trioxifene, negundin B, urundeuvines, *etc.*[1] (Fig. 1) and has been implicated in hepatitis C NS5B polymerase inhibitors, aldosterone synthase (CYP11B2) inhibitors and recently in tubulin binding inhibitors.[2] The dihydronaphthalene scaffold also serves as the precursor to several other valuable scaffolds and molecules such as indatraline, mutisianthol, trikentrin, podophyllotoxin, epipodophyllotoxin, *etc.*[3]

Owing to the importance of the dihydronaphthalene scaffold in synthetic and medicinal chemistry, it is always desirable to develop newer and more efficient strategies for its synthesis. Other than the classical method of naphthalene dearomatization[4] for dihydronaphthalene scaffold synthesis, there are several other strategies based on the arylation of alkynes, rearrangement of vinylcyclopropanes, Friedel–Crafts reaction, RCM reaction, Diels–Alder reaction, Heck reaction, Grignard reaction, [2 + 2] cycloaddition, and metal–carbene radical chemistry.[5]

In recent years, several useful protocols for C–C as well as C–heteroatom bond formation have been reported under visible light photoredox catalyzed conditions.[6] Although visible light photoredox catalyzed radical cyclizations have been reported frequently for the synthesis of various carbocycles, heterocycles, and fused polycyclic scaffolds,[7] the examples of dihydronaphthalene synthesis under photoredox catalysis are rare.[8,9a]

The research group of Professor Reiser identified α-bromochalcones as the source of α-keto vinyl radicals under visible light catalysis[9] and trapped them intermolecularly with various terminal alkenes for the synthesis of dihydronaphthalene scaffolds.[9a] We hereby report the successful use of chalcones as the coupling partners with α-bromochalcones under photoredox conditions, yielding 1,2,3-trisubstituted-1,2-dihydronaphthalenes (Scheme 1).

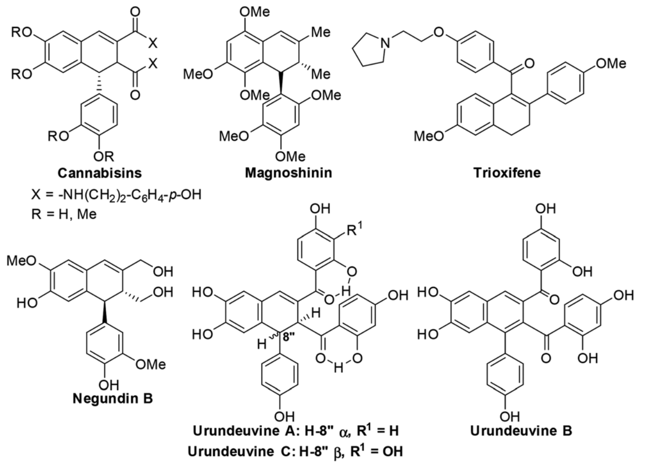

**Fig. 1** 1,2-Dihydronaphthalene core in natural/synthetic medicinal molecules.

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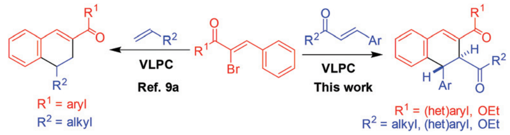


**Scheme 1** Dihydronaphthalene scaffold from α-bromochalcones under visible light catalysis.

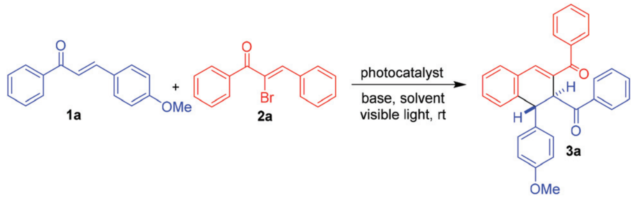
## Results and discussion

For preliminary investigations chalcone **1a** and α-bromochalcone **2a** ($E_{red}$ = −0.88 V *vs.* SCE)[9] were selected as the model substrates in a 1 : 1 ratio, and the reactions were carried out in DMSO in the presence of $Na_2CO_3$ (Table 1).

The polypyridyl complexes of Ir known as the preferred photocatalysts for the generation of α-keto vinyl radicals from α-bromochalcones were selected as photocatalysts for initial reactions (entries 1 and 2). Product **3a** was formed in a diastereomerically pure form, albeit in low yields. The product was assigned the *trans*-configuration on the basis of coupling constant by $^1H$ NMR spectroscopy. The yield of **3a** was even lower with other photocatalysts *viz.* eosin Y and $Ru(bpy)_3Cl_2$ (entries 3 and 4), prompting us to optimize other conditions with *fac*-[Ir(ppy)$_3$], which provided the product in the best yield obtained so far. Further optimization of the solvent and base used in the reaction revealed $K_3PO_4$ and DMSO as the most suitable base and solvent, respectively, affording the product in a modest 55% yield (entry 9). Next, reducing the amount of the photocatalyst to 0.5 mol% as well as increasing to 2 mol% caused reduction in the yield of **3a** (entries 10 and 11). Furthermore, changing the ratio of substrates **1a** : **2a** in favor of **2a** (entry 12) did not improve the yield but taking **1a** : **2a** in a 2 : 1 ratio provided **3a** in 75% isolated yield (entry 13). The necessity of excess radical trapping agent **1a** in the reaction mixture can be explained considering that the reductive dehalogenation of α-bromochalcones and photodimerization of chalcones were major side reactions.[10] Additional optimization of reaction conditions confirmed that 2 equivalents of $K_3PO_4$ were preferable over 1 or 3 equivalents considering product yield and reaction economy (entries 14 and 15). Moreover, key control experiments were performed to establish the significance of both visible light and photocatalyst in the reaction since no product formation was noticed in the absence of a photocatalyst or visible light (entries 16 and 17).

After optimizing the reaction conditions, we decided to investigate the scope of reaction in terms of chalcones **1** and α-bromochalcones **2**. First, α-bromochalcone **2a** was reacted with several chalcones **1** in order to investigate their potential under optimized conditions (Table 2).

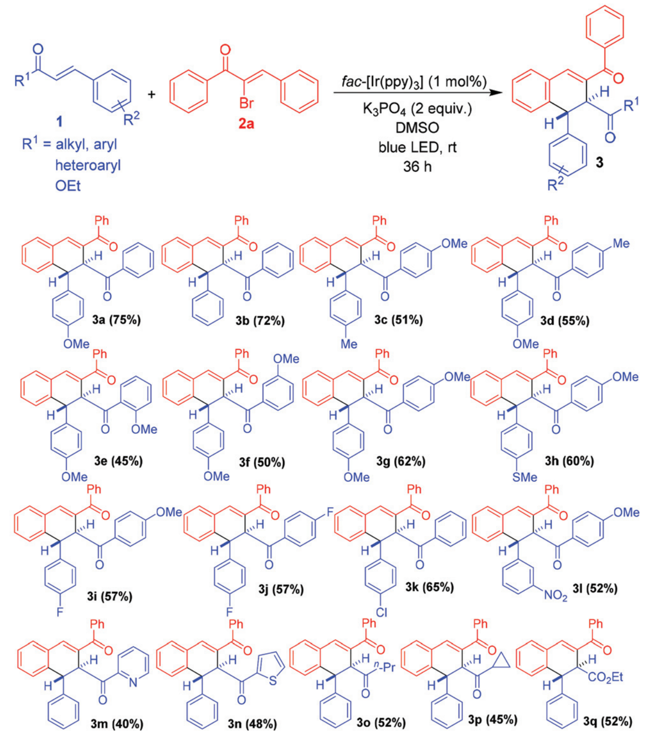
**Table 1** Optimization of reaction conditions[a]



| Entry | 1a : 2a | Photocatalyst (mol%), base (equiv.), solvent | Yield of 3a[b] (%) |
|---|---|---|---|
| 1 | 1 : 1 | *fac*-[Ir(ppy)$_3$] (1), $Na_2CO_3$ (2), DMSO | 40(33)[c] |
| 2 | 1 : 1 | [Ir{dF(CF$_3$)ppy}$_2$(dtb-bpy)]PF$_6$ (1), $Na_2CO_3$ (2), DMSO | 35 |
| 3[d] | 1 : 1 | Eosin Y (1), $Na_2CO_3$ (2), DMSO | 21 |
| 4 | 1 : 1 | [Ru(bpy)$_3$Cl$_2$] (1), $Na_2CO_3$ (2), DMSO | 12 |
| 5 | 1 : 1 | *fac*-[Ir(ppy)$_3$] (1), $Na_2CO_3$ (2), DMF | 32 |
| 6 | 1 : 1 | *fac*-[Ir(ppy)$_3$] (1), $Na_2CO_3$ (2), MeCN | 24 |
| 7 | 1 : 1 | *fac*-[Ir(ppy)$_3$] (1), $K_2CO_3$ (2), DMSO | 31 |
| 8 | 1 : 1 | *fac*-[Ir(ppy)$_3$] (1), $NaHCO_3$ (2), DMSO | 47 |
| 9 | 1 : 1 | *fac*-[Ir(ppy)$_3$] (1), $K_3PO_4$ (2), DMSO | 55 |
| 10 | 1 : 1 | *fac*-[Ir(ppy)$_3$] (0.5), $K_3PO_4$ (2), DMSO | 43 |
| 11 | 1 : 1 | *fac*-[Ir(ppy)$_3$] (2), $K_3PO_4$ (2), DMSO | 45 |
| 12 | 0.75 : 1 | *fac*-[Ir(ppy)$_3$] (1), $K_3PO_4$ (2), DMSO | 49 |
| 13 | 2 : 1 | *fac*-[Ir(ppy)$_3$] (1), $K_3PO_4$ (2), DMSO | 81(75)[c] |
| 14 | 2 : 1 | *fac*-[Ir(ppy)$_3$] (1), $K_3PO_4$ (1), DMSO | 62 |
| 15 | 2 : 1 | *fac*-[Ir(ppy)$_3$] (1), $K_3PO_4$ (3), DMSO | 80 |
| 16 | 2 : 1 | **No photocatalyst**, $K_3PO_4$ (2), DMSO | 0 |
| 17 | 2 : 1 | *fac*-[Ir(ppy)$_3$] (1), $K_3PO_4$ (2), DMSO, no light | 0 |

[a] **2a** (0.3 mmol) with specified amounts of **1a**, photocatalyst and base were irradiated in solvent (3.0 mL) with a 450 nm blue LED for 36 h under $N_2$. [b] NMR yields. [c] Isolated yield. [d] A 530 nm green LED was used.

**Table 2** Scope of reaction: variation of chalcones **1** (**1a–1q**)[a]

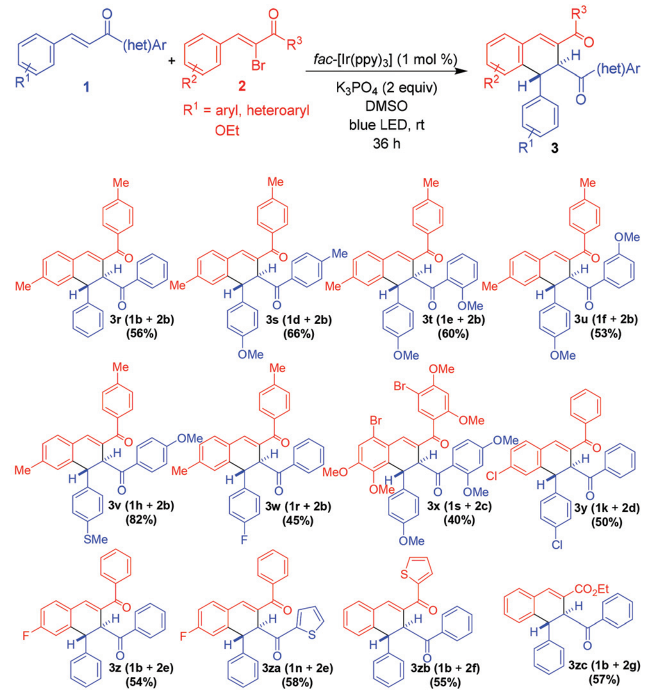


[a] Reaction conditions: **1** (0.6 mmol), **2** (0.3 mmol), *fac*-[Ir(ppy)$_3$] (0.003 mmol), $K_3PO_4$ (0.6 mmol), DMSO (3 mL), blue light at rt under $N_2$.

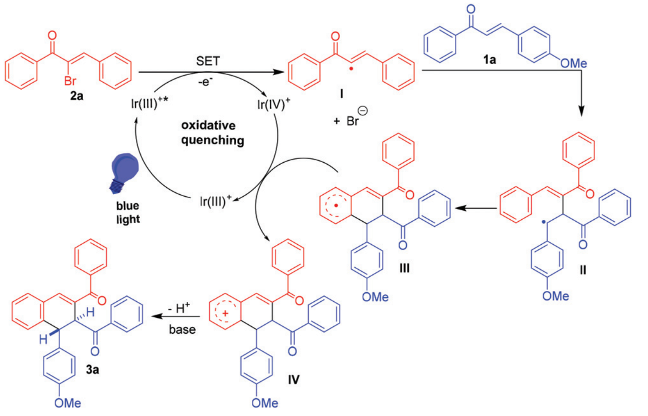
The chalcones with unsubstituted aryl rings (**1b**), with electron-releasing groups (**1a**, **1c–1h**) or with electron-withdrawing groups (**1i–1l**) on one or both the aryl rings reacted smoothly with **2a** under optimized reaction conditions. The heteroaryl chalcones **1m–1n** also provided the desired products with **2a**, though in lower yields. Furthermore, the α,β-unsaturated alkyl styryl ketones **1o**, **1p** and α,β-unsaturated ester **1q** could also be successfully employed in the reaction with **2a**, providing the corresponding dihydronaphthalenes **3o**, **3p** and **3q**, respectively.

After utilizing the wide range of chalcones **1** in the reaction, we aimed to investigate the scope of α-bromochalcones **2** in the reaction (Table 3). The α-bromochalcone bearing electron releasing methyl groups **2b** reacted well with unsubstituted chalcone **1b** as well as with chalcones bearing substituents of different electronic characters, including methyl, methoxy, thiomethyl and halogens, affording the corresponding products **3r–3w**. Furthermore, α-bromochalcones with halogen substituents **2c–2e** reacted smoothly with several chalcones, including the heteroaryl chalcone **1n**, affording the corresponding dihydronaphthalenes **3x–3za** in moderate yields. Also, the α-bromo-thienyl-styryl ketone **2f** and α-bromo acrylate **2g** coupled effectively with **1b** to provide the desired products **3zb** and **3zc** in 55% and 57% yield, respectively. Although in most cases the *trans*-isomer was the exclusive product, in a few cases traces of the *cis*-isomer (<5%) were also noticed by $^1$H NMR of the crude product. The stereochemistry of the major products was assigned on the basis of single crystal X-ray analysis of **3l** and **3x**[11] (see the ESI†).

Table 3 Scope of reaction: variation of α-bromochalcones **2** (**2b–2g**)[a]



[a] Reaction conditions: **1** (0.6 mmol), **2** (0.3 mmol), *fac*-[Ir(ppy)$_3$] (0.003 mmol), K$_3$PO$_4$ (0.6 mmol), DMSO (3 mL), blue light at rt under N$_2$.

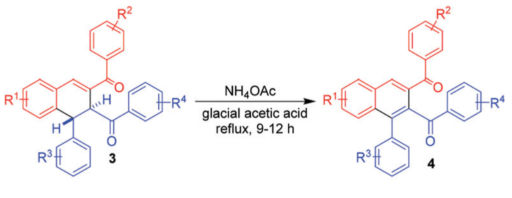


Scheme 2 Plausible reaction mechanism.

The mechanism of the reaction congruous with the related reports can be depicted as shown in Scheme 2.[9,12] The reaction expectedly follows the oxidative quenching cycle of the photocatalyst which initially gets excited by blue light to [*fac*-Ir(III)(ppy)$_3$*]. This excited photocatalyst reduces the α-bromochalcone **2a** by single-electron transfer, generating the α-ketovinyl radical **I**. Radical **I** adds to the α-carbon of chalcone **1a**, leading to the formation of benzylic radical **II**. The benzylic radical is trapped intramolecularly by the aryl ring of α-bromochalcone, generating radical species **III**. Oxidation of radical intermediate **III** effected by the strong oxidant [*fac*-Ir(IV)(ppy)$_3$]$^+$ completes the catalytic cycle and produces cyclohexadienyl cation **IV**. Finally, cation **IV** undergoes deprotonation in the presence of a base to provide the dihydronaphthalene product **3a**.

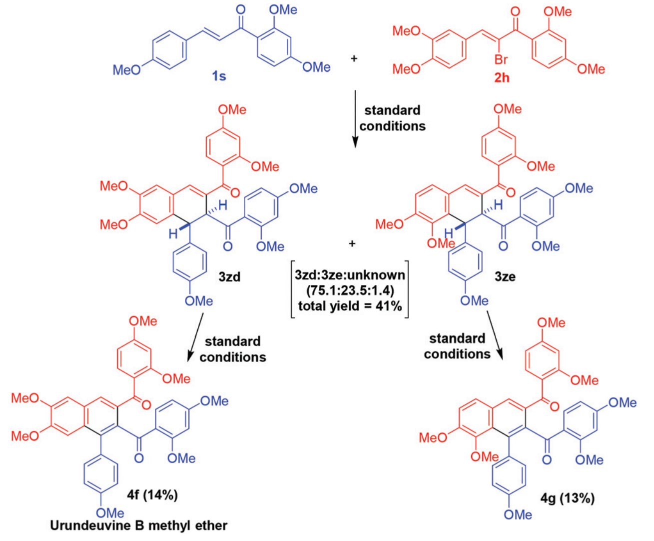
Furthermore, the dihydronaphthalenes **3** were readily oxidized into the corresponding naphthalenes **4** upon heating with ammonium acetate in glacial acetic acid, as exemplified by few representative examples (Scheme 3).

After establishing the general nature and applicability of the reaction to provide dihydronaphthalenes and naphthalenes, we planned to verify its application for the synthesis of natural dimeric chalcones namely, urundeuvine **A** and urundeuvine **B** (Fig. 1). We first attempted the synthesis of a methyl



**4a**: R$^1$ = R$^2$ = H, R$^3$ = 4-Me, R$^4$ = 4-OMe (56%)
**4b**: R$^1$ = R$^2$ = H, R$^3$ = 4-OMe, R$^4$ = 3-OMe (60%)
**4c**: R$^1$ = R$^2$ = H, R$^3$ = 4-OMe, R$^4$ = 4-OMe (30%)
**4d**: R$^1$ = R$^2$ = 4-Me, R$^3$ = 4-OMe, R$^4$ = 3-OMe (50%)
**4e**: R$^1$ = R$^2$ = 4-Me, R$^3$ = 4-SMe, R$^4$ = 4-OMe (30%)

Scheme 3 Dihydronaphthalenes **3** to naphthalenes **4**.



**Scheme 4** Application of the methodology in the synthesis of natural product derivatives.

ether derivative of urundeuvine **A** through the reaction between the corresponding trimethoxy chalcone **1s** and tetramethoxy α-bromochalcone **2h** under optimized conditions. The reaction resulted in a mixture of three products in 75.1 : 23.5 : 1.4 ratio in 41% total yield (determined by HPLC; see the ESI†). While the product in 1.4% amount could not be isolated, the other two products were characterized as regioisomers **3zd** (75.1%) and **3ze** (23.5%) (Scheme 4). Both the regioisomers were assigned the *trans* configuration on the basis of their analogy with other products.[13] Although our method could not provide the natural urundeuvine **A** (*cis*-isomer of **3zd**), the methyl ether derivatives of natural urundeuvine **B** **4f** and regioisomer **4g** were isolated in 14% and 13% yield, respectively, by subjecting **3zd** and **3ze** to the standard oxidation conditions after separating them by preparative HPLC (Scheme 4). The efforts to demethylate **4f** to obtain urundeuvine **B** and to apply the protocol for accessing other natural products including urundeuvine **C** and negundin B are currently underway in our group.

## Conclusions

In conclusion, we developed a novel method for the synthesis of dihydronaphthalenes under visible light catalysis by employing conveniently accessible starting materials. This practically simple strategy represents the first example of electron deficient alkenes being utilized to trap the α-keto vinyl radicals generated from α-bromochalcones. The reaction exhibited high functional group tolerance and a wide range of both chalcones and α-bromo chalcones reacted efficiently under the reaction conditions. The protocol was applied successfully for the synthesis of derivatives of urundeuvine chalcones, which are otherwise accessible only from the bark of the *Myracrodruon urundeuva* plant.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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