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Brønsted acid catalyzed radical addition to quinone methides†

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A fundamental quest for alkyl radical generation under mild conditions through photoinduced Brønsted acid catalysis is addressed. The optimized protocol does not require any organic dyes or transition metal photocatalyst. Under blue light irradiation with diphenyl phosphate as a catalyst and dihydropyridine derivatives as a radical source, functionalized arylmethane derivatives are obtained in high yield.

Development of novel radical reactions underpins the notion behind the advancements in photocatalysis.[1] Lately the emphasis in this field has been upon finding simple yet effective catalytic systems and in this context the discovery of sustainable organocatalytic photochemical reactions has been at the fore front.[2] Amid several principles and concepts in photocatalysis, our lab got interested in hydrogen atom transfer (HAT) reactions[3] which encompass mechanistic possibilities such as sequential electron transfer/proton transfer and concerted proton coupled electron transfer reactions (PCET).[4,5,6]

In photochemical reactions the carbon centered radicals are of great significance and amongst several radical precursors the dihydropyridine derivatives have a special place. Their wide range of applications and ease of synthesis makes them attractive.[7] In general, the photochemical reactions of dihydropyridine derivatives are carried out with a transition metal based catalyst or an organic dye. For these catalysts a cost comparison in Indian rupee (INR) is provided in Scheme 1A. Thus, we envisioned the possibility to develop a transition metal/organic dye free protocol for radical addition with a readily available catalyst.

In this communication, a diphenyl phosphate (DPP) catalyzed photochemical radical addition protocol to access functionalized arylmethane derivatives is reported. The optimized reaction conditions do not involve an external photocatalyst and the catalyst utilized is inexpensive and readily available. Moreover, this method offers a viable route for the synthesis of arylalkylmethylphosphonates, which are prevalent in several biologically active compounds (Scheme 1B).[8] Due to their significance various methods for synthesizing diarylmethyl phosphonates are reported whereas routes for synthesizing arylalkylmethylphosphonates are underexplored.[9] In addition, prior to this work the chemistry of phosphorylated quinomethanes is unfledged in the domain of radical reactions.[10] At the outset of our investigation, we envisaged a mechanistic cycle involving a donor–acceptor complex (Scheme 1C). We reasoned that in the presence of DPP as a catalyst, preorganization of substrates takes place and donor–acceptor complex **I** is obtained. The subsequent electron transfer under blue light irradiation provides **II**, which upon radical addition and protonation delivers **3** in high yield. We also realized that the substituents at the 2,6-position in quinomethane will impart stability to the radical intermediate and thus they will be critical for successful fruition of this reaction.

With this premise, the optimization of the reaction conditions for photochemical radical addition arylation of phosphorylated quinomethanes was initiated. Substrates **1a** and **2a** were chosen as model substrates (Table 1). In blue light irradiation (455 nm) and $CHCl_3$ as the reaction medium, 10 mol% of diphenyl phosphate efficiently catalyzed the radical addition to phosphorylated quinomethane **1a** and furnished **3a** in 90% yield (entry 1). Both the blue light and catalyst were essential for the reaction and in their absence no product was obtained (entries 2 and 3). Lowering the catalyst loading to 5 mol% proved detrimental to the reaction yield and **3a** was obtained in 50% yield (entry 4). The use of dibenzyl phosphate as a catalyst was also effective (entry 5). However, given the easy availability of diphenyl phosphate, it was used for further studies. The effect of commonly used excited state photooxidants was also probed. The reaction in the presence of 5 mol% of these well-established photocatalysts proceeded smoothly and **3a** was obtained in good yield (entries 6–10). The reaction

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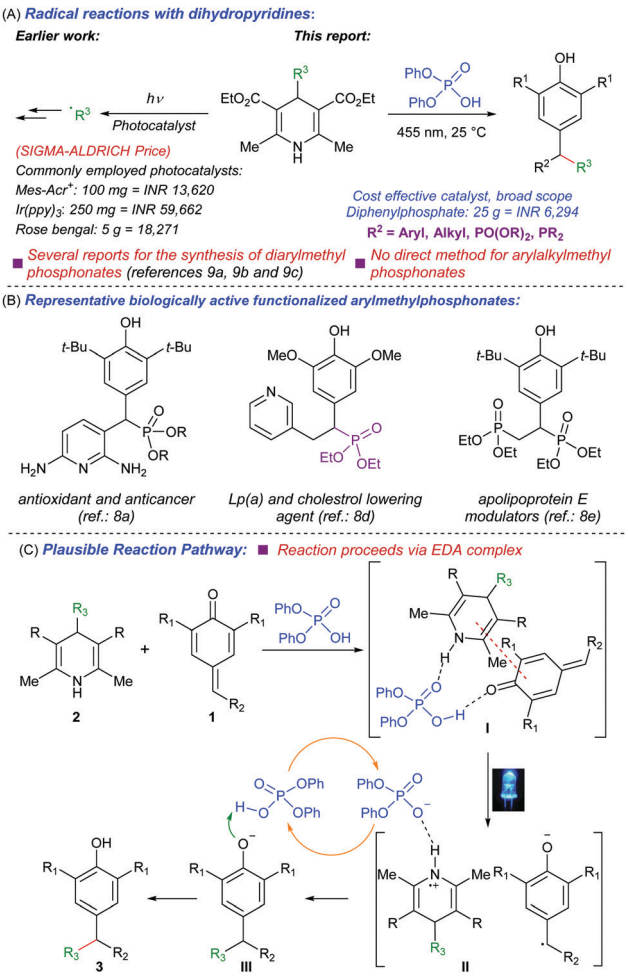
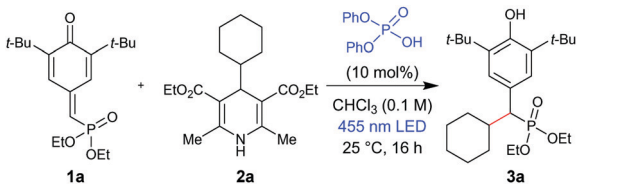


Scheme 1 Photochemistry of quinomethanes.

Table 1 Reaction condition optimization[ab]



Entry	Variation in standard conditions	Yield[b] (%)
1	None	98 (90)[c]
2	No DPP	<5
3	No light	<5
4	5 mol% DPP instead of 10 mol%	50
5	Dibenzyl phosphate instead of DPP	90
6	Mes-Acr$^+$ instead of DPP	86
7	Mes-Acr$^+$ and KH_2PO_4 instead of DPP	68
8	Rose Bengal instead of DPP	86
9	Eosin Y disodium salt instead of DPP	52
10	Ir(ppy)$_3$ instead of DPP	76
11	Green LED instead of Blue	52

[a] Reaction conditions: **1a** (0.1 mmol, 1.0 equiv.), **2a** (0.15 mmol, 1.5 equiv.) and **Catalyst** (0.01 mmol, 0.1 equiv.). [b] ^{1}H-NMR yield. [c] Isolated yield.

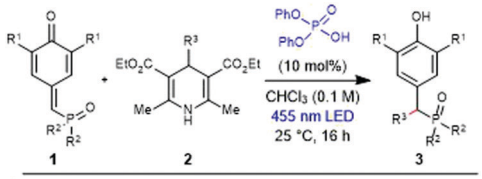
was also conducted under a green LED (entry 11). Although the reaction proceeded smoothly, **3a** was obtained in only 52% yield. In addition, readily available acids such as H_2SO_4, TfOH, TsOH, H_3PO_4 and benzoic acid were also screened and the product **3a** was obtained is moderate to good yield (see the ESI† for details).

The optimum reaction conditions were applied to probe the substrate scope of the reaction. In general, the reaction proceeded smoothly with a broad array of substrates and the products were obtained in excellent yields (Table 2). Initially the scope with respect to phosphorylated quinomethanes was tested (Table 2A). The reaction remained unperturbed by the different ester groups on phosphorylated quinomethanes and products **3a–3j** were obtained in excellent yield. The effect of the *t*-Bu group on phosphorylated quinomethanes was also tested and substrates containing different alkyl groups on the quinone ring furnished **3k–3m** in good yield. At this point, the scope with respect to different radical precursors was also studied (Table 2B). Several alkyl and benzyl radical precursors were well suited and **3n–3v** were obtained in good yields. Notably heteroatom substituted radical sources furnished **3w** and **3x** in good yield. Phosphine oxide substituted quinomethane derivatives also emerged as excellent substrates and **3y–3za** were obtained in good yields. Having explored the scope with phosphorylated quinomethanes, the generality with respect to other *p*-QM's was also tested (Table 3).[11] The aryl and alkyl substituted *p*-QM's furnished **5a–5f** in good yield.

Scaling up the reaction at 1 mmol scale had no detrimental effect and **3i** was obtained in 82% yield (Scheme 2A). The utility of the optimized protocol was further demonstrated through synthetic applications. In the presence of $AlCl_3$ both the *t*-Bu groups from **3y** were removed to provide **6** in 84% yield (Scheme 2A). Subsequently the reaction protocol was applied for the synthesis of an established bioactive compound. Gratifyingly through this Brønsted acid catalyzed photoinduced radical reaction the compound **7**, a Lp(a) and cholesterol lowering agent[8d] was obtained in good yield (Scheme 2B).

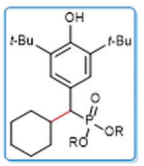
Control experiments were also carried out to understand the reaction mechanism. In the presence of *N*-methylated radical precursor **8**, no reaction was observed (Scheme 2C) This experiment clearly illustrates the pivotal role of N–H of the dihydropyridine radical precursor. The role of additives was also probed. With radical trapping agents such as BHT and TEMPO no measurable reaction was observed (Scheme 2D). The corresponding adducts of BHT and TEMPO with **1a** and cyclohexyl radical of **2a** were characterized through HRMS analysis.[12] Similarly, no measurable reaction was observed in the presence of O_2. These experiments illustrated the involvement of a radical species (Scheme 2D). A light ON–OFF experiment was also carried out and it was concluded that the reaction proceeds only upon blue light irradiation.[12] The reaction exhibited a quantum yield of 0.0216 and thus the possibility of a radical chain process was ruled out.[12] The EDA complex formation (Scheme 1C) was further supported through UV/Visible studies.[12] Through these studies generation of a donor–acceptor complex between **1a** and **2a** with 1 : 1 stoichiometry was

Table 2 Substrate scope[ab]

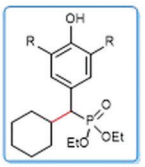


1 2 3

(A) Scope of phosphorylated quinomethides

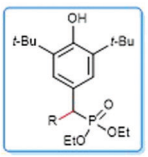


R	Yield (%)
Et (3a)	90
Me (3b)	90
n-Pr (3c)	85
i-Pr (3d)	64
n-Bu (3e)	79
i-Bu (3f)	85
neo-Pent (3g)	91
c-Hex (3h)	73
Ph (3i)	74
Bn (3j)	70



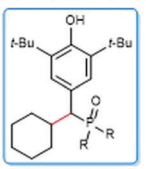
R	Yield (%)
Me (3k)	48
i-Pr (3l)	69
OMe (3m)	64

(B) Scope with Radical Precursors



R	Yield (%)
i-Pr (3n)	87
sec-Bu (3o)	72 (dr = 1:0.7)
t-Bu (3p)	60
c-Pent (3q)	94
3-Pent (3r)	70
Bn (3s)	67[c]
4-$CH_3C_6H_4CH_2$ (3t)	84[c]
4-$ClC_6H_4CH_2$ (3u)	62[c]
(3v)	94 (dr = 1.67:1)
(3w)	95
(3x)	67[d]

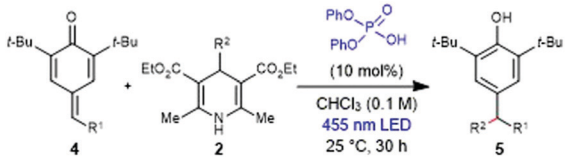
(C) Scope with phosphine oxides



R	Yield (%)
Ph (3y)	51
4-$CH_3C_6H_4$ (3z)	84
4-FC_6H_4 (3za)	79

[a] Reaction conditions: **1** (0.1 mmol, 1.0 equiv.), **2** (0.15 mmol, 1.5 equiv.) and **DPP** (0.01 mmol, 0.1 equiv.). [b] Isolated yield. [c] Reaction time: 30 h. [d] **1** (0.1 mmol, 1.5 equiv.), **2** (0.1 mmol, 1.0 equiv.) and **DPP** (0.01 mmol, 0.1 equiv.).

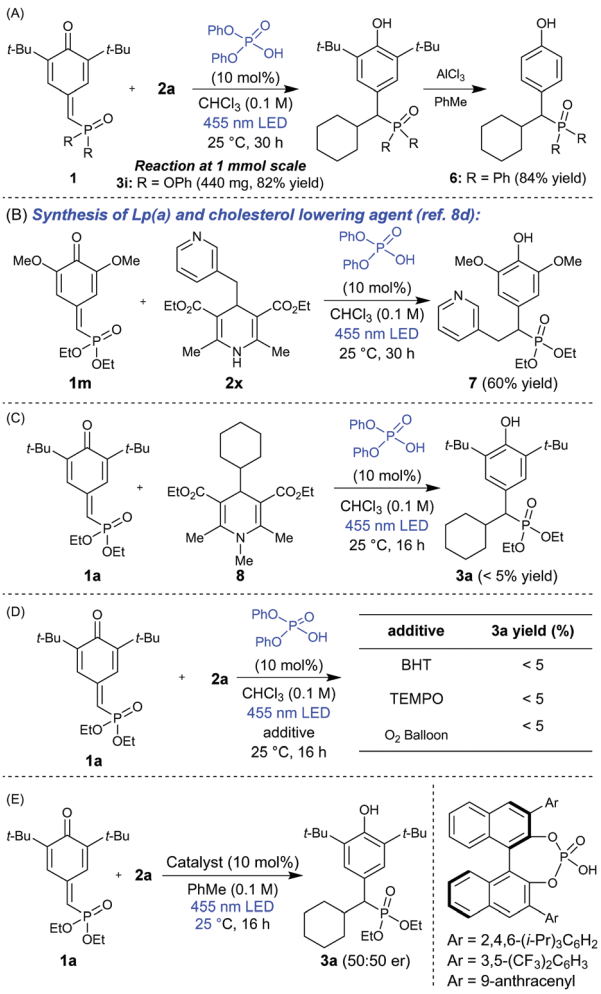
Table 3 Substrate Scope for *p*-QM's[ab]



4 2 5

R^1	R^2	Yield (%)
Ph	c-Hex (**5a**)	68
Ph	i-Pr (**5b**)	73
Ph	Bn (**5c**)	77
Ph	4-$ClC_6H_4CH_2$ (**5d**)	42
4-$CF_3C_6H_4$	c-Hex (**5e**)	44
Me	c-Hex (**5f**)	69

[a] Reaction conditions: **4** (0.1 mmol, 1.0 equiv.), **2** (0.15 mmol, 1.5 equiv.) and **Diphenyl phosphate** (0.01 mmol, 0.1 equiv.). [b] Isolated yield.



Scheme 2 Synthetic utility and control experiments.

established. We were also intrigued by the possibility of direct excitation of 4-substituted Hantzsch ester as an alternative pathway. However, 4-alkyl dihydropyridines tend to undergo blue shift.[7j] In

addition, upon replacing the blue LED with a green LED (530 nm), **3a** was obtained in 52% yield (Table 1, entry 11). This experiment also disfavors the direct excitation pathway. Attempts were also made to develop an asymmetric variant. However, our efforts in this direction yielded a racemic product (Scheme 2E).

In summary, a photoinduced organocatalytic radical addition protocol is developed. This straight forward protocol utilizes no expensive photocatalyst or external additives. The significance of this protocol is demonstrated through broad substrate scope and synthesis of biologically active compounds. Given the wide implications of Brønsted acid catalysis we believe that this simple yet efficient strategy will further expand its horizons and pave the way for further development of sustainable organocatalytic photochemical reactions.

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Conflicts of interest

There are no conflicts to declare.

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12 See ESI† for details.

