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α-Alkylation of ketimines using visible light photoredox catalysis†

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A novel α-alkylation of *N*-diphenylphosphinoyl ketimines with α-bromocarbonyl compounds has been accomplished using visible light photoredox catalysis. The reaction proceeds under remarkably mild conditions: at 35 °C, in 20 hours, under blue light irradiation (1 W), in the presence of a tertiary amine and catalytic amounts of Ru- and Ni-based complexes. Chemoselective transformation of the products provides access to 1,4-dicarbonyl compounds, protected GABA analogues and γ-lactams.

In recent years, photoredox catalysis has emerged as a powerful methodology to construct C–C bonds under mild conditions, typically involving visible light irradiation and the use of a catalytic amount of an organic dye or metal complex.[1] In the continuation of our work on new reactivity of imines under photoredox catalysis,[2] we were interested in studying the behaviour of ketimines with the aim of achieving C–C bond formation at the α-position (Fig. 1). The general approach for the α-alkylation of carbonyl compounds involves their conversion into carbon nucleophiles (such as enamines,[3] enolates and enol silyl ethers, either pre-formed or formed *in situ*) followed by S_N2 reaction with alkyl halides (Fig. 1, top). Photoredox catalysis has recently added a new dimension to this long-established reactivity, uncovering novel mechanistic pathways and often allowing the reactions to be carried out without the use of organometallic reagents nor strong bases. Since MacMillan's seminal work on the enantioselective alkylation of aldehydes through merging photoredox catalysis with aminocatalysis,[4] alkylations of aldehydes,[5] ketones,[6] 2-acylimidazoles[7] and silyl enol ethers[8] with α-halocarbonyl compounds under light irradiation have been reported. In this context we speculated that, if a similar reactivity could be extended to a new class of substrates, *i.e.* ketimines, a mild method for the generation of valuable γ-imino esters would be realised (Fig. 1, bottom). Synthetic manipulation of the products would provide access not only to 1,4-dicarbonyl compounds,[8] but also to γ-amino esters (protected analogues of the neurotransmitter γ-aminobutyric acid, GABA),[9] and to γ-lactams, which are found in both natural and synthetic molecules possessing a range of biological properties.[10] However, we anticipated a series of challenges in the development of the reaction: (i) the C=N and C=O bonds of the substrates must survive the reaction conditions; (ii) overalkylation should be controlled; (iii) reductive dehalogenation of the α-bromocarbonyl compound should be avoided.

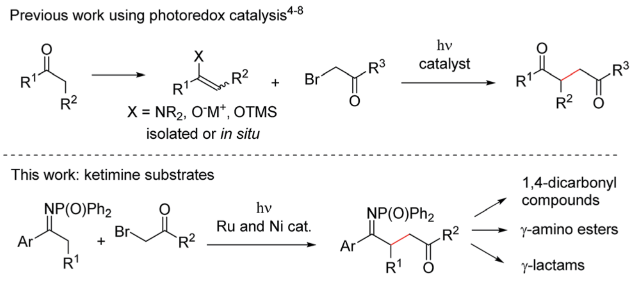

Fig. 1 Photoredox-catalysed α-alkylation of carbonyl compounds and derivatives.

Keeping these considerations in mind, we began our investigation by studying then optimising a model reaction between *N*-diphenylphosphinoyl acetophenone-derived ketimine **1a** and ethyl bromoacetate **2**, using *N*,*N*-diisoproprylamine (DIPEA) as a base, 5 mol% $[Ru(bpy)_3]Cl_2 \cdot 6H_2O$ and 5 mol% $[NiCl_2(PPh_3)_2]$ (Table 1, see ESI for full data†).[11] Pleasingly, the desired alkylation reaction proceeded with encouraging conversion in polar solvents that were able to solubilise all components (Table 1, entries 1–5). DMF was selected as the solvent of choice due to the good yield and the clean reaction profile (entry 5, 56% conversion, 50% yield for the desired ketimine **3a**). A range of photocatalysts were then screened for performance (entries 6–9) and $[Ru(bpy)_3]Cl_2 \cdot 6H_2O$ was confirmed to be the most effective. Among the Ni(II) salts that were tested, inexpensive nickel(II) acetate tetrahydrate was found to promote the reaction without significant detriment to the yield (45%, entry 10). Several organic and inorganic bases were trialled and their stoichiometry was varied. When using triethanolamine (TEOA) instead of DIPEA, the reaction proceeded to nearly full conversion (95%, entry 11), however the NMR yield for the alkylated ketimine **3a**

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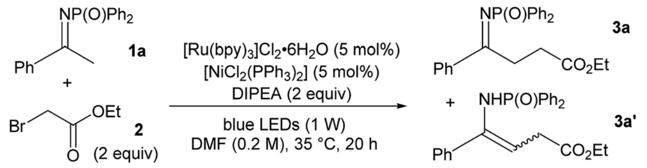
† Electronic supplementary information (ESI) available: Optimisation tables, experimental procedures, characterisation data, copies of ^1H and ^{13}C NMR spectra, NMR and luminescence quenching studies. See DOI: 10.1039/c7ra09248b

Table 1 Optimisation and control experiments for the reaction of *N*-diphenylphosphinoyl ketimine **1a** and ethyl bromoacetate **2**



Entry	Change to conditions above	Conversion[a] (%)	Yield[a] **3a** + **3a′** (%)
1	Acetone	29	21 + 3
2	CH_3CN	34	34 + 0
3	MeOH	51	32 + 14
4	DMSO	59	34 + 23
5	—	56	50 + 5
6	Eosin Y disodium form	53	41 + 5
7	$[Ru(bpz)_3](PF_6)_2$	37	35 + 2
8	$[Ir\{dF(CF_3)ppy\}_2(dtbpy)]PF_6$	23	16 + 7
9	$[Ir(ppy)_2(dtbpy)]PF_6$	31	29 + 0
10	$Ni(OAc)_2 \cdot 4H_2O$	55	45 + 8
11	$N(CH_2CH_2OH)_3$	95	28 + 21
12	second addition of DIPEA and **2**[b]	72	45 + 14
13	Without $[NiCl_2(PPh_3)_2]$	38	28 + 10
14	Without DIPEA	12	0
15	In the dark	0	0
16	Without $[Ru(bpy)_3]Cl_2 \cdot 6H_2O$	7	4 + 2

[a] Consumption of ketimine **1a** (conversion) and NMR yields for **3a** and **3a′** determined by ^{31}P and ^{1}H NMR analysis of the reaction mixture after work-up using mesitylene as an internal standard. [b] 2 further equivalents of DIPEA and bromoacetate **2** were added after 7 hours.

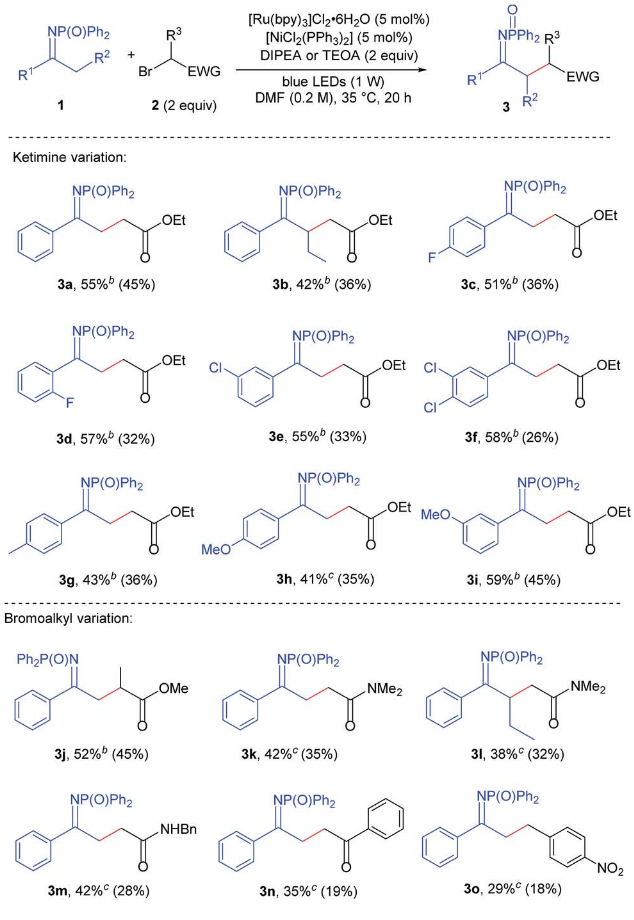
was a modest 28%. The poor yield observed in this case is explained by the formation of *E* and *Z* enamines **3a′** (21%) and dialkylated product (41%). Similarly, the addition of 2 further equivalents of both DIPEA and bromoacetate **2** enhanced the conversion to 72% (entry 12), but the yield for **3a** remained 45%.

Control experiments were run to gather more information (Table 1). Omission of $[NiCl_2(PPh_3)_2]$ resulted in a lower yield of the product, showing that Ni(II), although not essential for reactivity, improved the conversion (entry 13). No product formation was observed in the absence of base or light, thus ruling out simple radical or S_N2-type reactivity, while small amounts of **3a** were formed under light irradiation without photocatalyst[12] (entries 14–16).

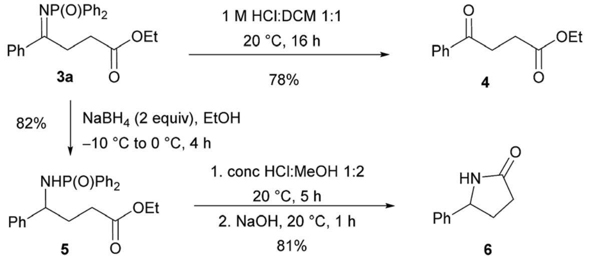
At this point the substrate scope of the reaction was assessed, using $[Ru(bpy)_3]Cl_2 \cdot 6H_2O$ (5 mol%), $[NiCl_2(PPh_3)_2]$ (5 mol%) and 2 equivalents of either DIPEA or TEOA. With respect to acetophenone-derived ketimine **1a**, substrates possessing electron-withdrawing groups on the aromatic ring were generally found to be more reactive. The most appropriate base to carry out their alkylation was DIPEA, that when compared to TEOA minimised the amounts of dialkylated product and enamine tautomers arising from the reaction. Aryl methyl ketimines **1c–1f**, bearing F and Cl substituents in the *para*, *meta* and *ortho* positions of the aromatic ring were alkylated affording 51–58% NMR yields of products (ketimine plus enamine tautomers, Table 2, compounds **3c–3f**). Isolated yields for the ketimine tautomers were lower (26–36%), as these compounds were prone to tautomerise to the enamine form. In line with this trend, electron-rich ketimines **1g** and **1h** were found to be less reactive than the model substrate.[13] Alkylated ketimines with *p*-methyl (**3g**), *p*-methoxy (**3h**) and *m*-methoxy (**3i**) substituents on the aromatic ring were obtained in 35–45% yields.

Next, the substrate scope on the bromoalkyl component was investigated.[14] The use of ethyl 2-bromopropionate delivered product **3j** in 45% yield. Electron-withdrawing groups different from an ester could be used, although they showed lower reactivity, thus requiring the use of TEOA as a base. 2-Bromoacetamides were found to be compatible alkylating agents, delivering compounds **3k** and **3m** in 35% and 28% yield, respectively. 2-Bromoacetophenone effected the alkylation of the model ketimine in 19% yield (**3n**). Alkylating agents lacking the α-carbonyl group were not suitable reaction partners, with *p*-nitrobenzyl bromide affording product **3o** in 18% yield.

Table 2 Substrate scope for the α-alkylation of *N*-diphenylphosphinoyl ketimines[a]



[a] Reactions performed on 0.2 mmol scale. Reaction yields (ketimine product plus enamine tautomers) determined by ^{1}H NMR analysis of the reaction mixture after work-up using mesitylene as an internal standard. Isolated yields, given in parentheses, refer to spectroscopically pure product in predominantly ketimine tautomeric form as obtained after chromatographic purification. [b] DIPEA as a base. [c] TEOA as a base.



Scheme 1 Synthetic transformations of product **3a**.

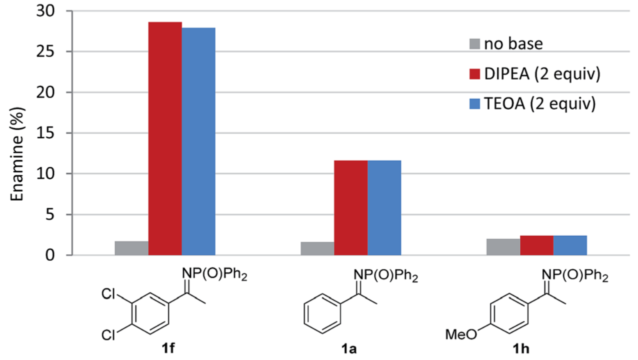


Fig. 2 Percentage of enamine present in a 0.2 M solution of **1f**, **1a** and **1h** in DMSO-d_6 after 5 hours, as determined by ^{1}H and ^{31}P NMR analysis.

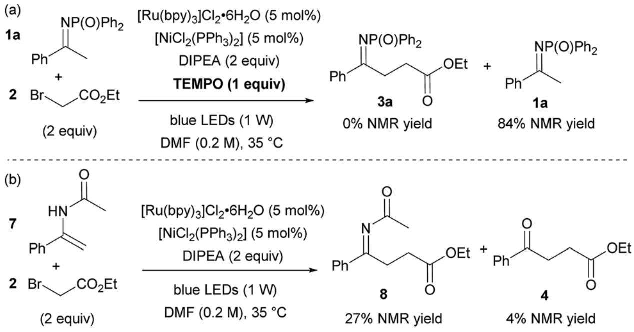
Elongating the alkyl chain on the ketimine did not affect the reactivity significantly. Indeed ketimine **1b** possessing a *n*-propyl chain could be alkylated with ethyl bromoacetate and 2-bromo-*N*,*N*-dimethylacetamide obtaining compounds **3b** and **3l** with isolated yields (32–36%) nearly comparable to those of ketimine **1a**.

To demonstrate synthetic applicability, chemoselective transformations of compound **3a** were performed (Scheme 1). The imine functionality was hydrolysed to afford γ-keto ester **4** in 78% yield. Alternatively, reduction of the C═N bond using sodium borohydride provided γ-amino ester **5** in 82% yield. The latter compound could be deprotected and then cyclised in a one-pot procedure, affording γ-lactam **6** in 81% yield.

Finally, a series of experiments were performed to investigate the mechanism of the reaction. Addition of 1 equivalent of TEMPO inhibited product formation, indicating that radical intermediates are involved in the reaction (Scheme 2a). When *N*-DPP ketimine **1a** was replaced by enamide **7**, formation of the expected alkylated product **8** (alongside hydrolysed ketoester **4** and unreacted starting material, Scheme 2b) was observed, suggesting that the addition of an electron-deficient radical to an enamide double bond is the likely pathway, in accordance with the intramolecular mechanism postulated by Rueping for the cyclisation of α-chloroenamides.[10b] This mechanistic hypothesis, at first glance, appears to conflict with the observation that electron-rich ketimines are less reactive than electron-poor ones. However, this apparent discrepancy is explained by the unfavourable ketimine/enamine equilibrium of electron-rich substrates. The ketimine : enamine ratio for 3 different substrates in the presence of DIPEA and TEOA was determined by NMR experiments (Fig. 2).[15] Using either base, electron-poor ketimine **1f** derived from 3′,4′-dichloroacetophenone existed in equilibrium with a higher percentage of enamine tautomer when compared to standard ketimine **1a** and electron-rich substrate **1h** possessing a *p*-methoxyphenyl group. No significant changes to the ketimine : enamine ratio were detected after 1 h or upon addition of 5 mol% [$NiCl_2(PPh_3)_2$], indicating that the equilibrium position for the tautomerism is reached relatively quickly and is not influenced by [$NiCl_2(PPh_3)_2$].

Light/dark cycle experiments (see ESI†) confirmed that the reaction proceeds only under light irradiation. Spectroscopic studies were then performed to determine which species was responsible for the quenching of the luminescence emitted by the excited Ru^{2+} photocatalyst (Fig. 3, see ESI for details†).[16] Whilst DMF solutions of DIPEA and of 3′,4′-dichloroacetophenone-derived ketimine **1f** with 2 equivalents of TEOA (ketimine : enamine ratio 79 : 21 by ^{31}P NMR) were found to quench the luminescence of *[$Ru(bpy)_3$]$^{2+}$, ketimines **1a**, **1f**, TEOA and ethyl bromoacetate **2** did not.

On the basis of these observations and of literature precedents,[4] we propose the mechanism depicted in Scheme 3 for the visible-light promoted, Ru-catalysed α-alkylation of *N*-diphenylphosphinoyl ketimine **1a** with ethyl bromoacetate **2**. The photoexcited ruthenium catalyst is reductively quenched by DIPEA or the enamine form of the starting material to a Ru(I)



Scheme 2 Experiments to investigate the mechanism of the reaction.

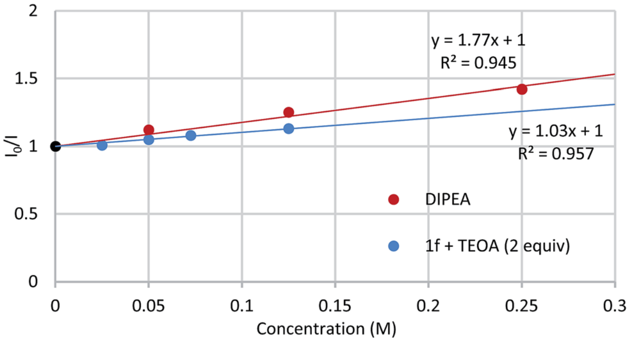
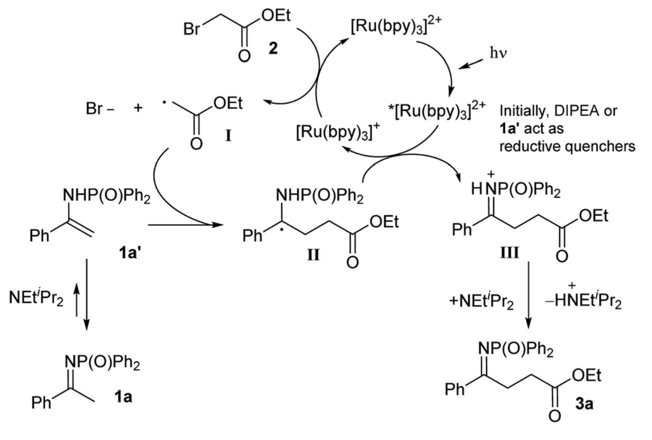


Fig. 3 Luminescence quenching studies. [$Ru(bpy)_3$]$Cl_2\cdot 6H_2O$ 1 μM in DMF, λ(excitation) 452 nm, λ(emission) 620 nm.

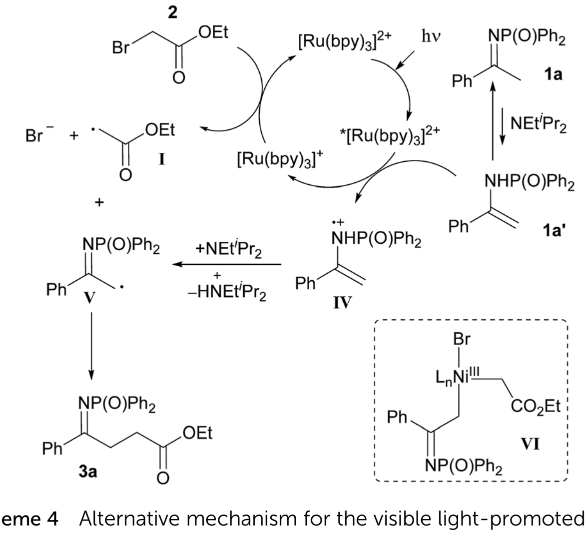


Scheme 3 Proposed mechanism for the visible light-promoted, Ru-catalysed α-alkylation of *N*-diphenylphosphinoyl ketimine **1a** with ethyl bromoacetate **2**.

species ($E_{1/2}^{\mathrm{II/I}} = -1.33$ V *vs.* SCE in CH_3CN),[17] which is then able to reduce ethyl bromoacetate ($E_{1/2}^{\mathrm{red}} = -1.08$ V *vs.* SCE in CH_3CN)[18] generating the α-carbonyl radical **I**. This electron-deficient radical attacks the electron-rich double bond of the enamine tautomer (**1a′**) of the starting material, leading to the formation of α-amino radical **II**. The latter ($E_{1/2}^{\mathrm{red}} = ca.\ -1.0$ V *vs.* SCE in CH_3CN)[19] can be oxidised to the protonated product **III** by $^*[\mathrm{Ru(bpy)_3}]^{2+}$ ($E_{1/2}^{\mathrm{II^*/I}} = +0.77$ V *vs.* SCE in CH_3CN),[17] or by the less oxidising but more abundant bromoacetate **2**, in the case a radical chain mechanism is operative.[20] Finally, deprotonation of compound **III** affords product **3a**. Depending on the nature of the ketimine and on reaction conditions, **3a** may tautomerise and undergo a second alkylation.

At present, we cannot exclude an alternative mechanism based on the coupling between enamine radical cation **IV** (or radical **V**) with the α-carbonyl radical **I** (Scheme 4).[21]

The beneficial effect of $[\mathrm{NiCl_2(PPh_3)_2}]$ on yield and conversion might be linked to its ability to stabilise the radical species generated during the reaction or promote a more efficient reaction pathway.[22] Based on the Stern–Volmer studies,[23] it is not possible to rule out electron transfer[24] or energy transfer processes[25,26] from the excited photocatalyst to the nickel complex. Alternatively, the intermediacy of organonickel(III) species such as **VI**, from which C–C bond-forming reductive elimination would take place, can be imagined (see ESI for discussion†).[22] Under this hypothesis, reductive elimination from organonickel(III) intermediate **VI** would help to overcome the unfavourable electronic effects associated with the direct coupling of the two electron-poor radicals **I** and **V**.



Scheme 4 Alternative mechanism for the visible light-promoted, Ru-catalysed α-alkylation of *N*-diphenylphosphinoyl ketimine **1a** with ethyl bromoacetate **2**.

In summary, a mild α-alkylation of *N*-diphenylphosphinoyl ketimines with α-bromocarbonyl compounds has been accomplished in moderate yields using nickel and ruthenium light-promoted catalysis. The mechanism, investigated through a combination of control, NMR and luminescence quenching experiments, likely proceeds *via* the attack of an α-carbonyl radical to the enamine tautomer of the starting material. The product γ-imino esters were easily transformed into 1,4-dicarbonyl compounds, GABA analogues and γ-lactams. Further studies to elucidate the role of the nickel cocatalyst are ongoing in our laboratories and the results will be disclosed in due course.

Conflicts of interest

There are no conflicts to declare.

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13 *N*-DPP ketimines derived from *tert*-butyl methyl ketone, cyclohexyl methyl ketone and 2-acetylthiophene gave the α-alkylated products using TEOA in 15%, 22% and 22% NMR yields respectively (see Table S1 in the ESI†).

14 When using ethyl iodoacetate and chloroacetate, **3a** was obtained in 36% and 12% NMR yield respectively. Benzyl bromide, ethyl bromodifluoroacetate and diethyl bromomalonate were not suitable reaction partners (see Table S1 in the ESI†).

15 Given the similar reaction profile, DMSO-d_6 was chosen as a cheaper alternative to DMF-d_7 to avoid peak overlap.

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