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\( \alpha \)-Alkylation of ketimines using visible light photoredox catalysis‡

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A novel \( \alpha \)-alkylation of \( N \)-diphenylphosphinoyl ketimines with \( \alpha \)-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. Chemoselsective transformation of the products provides access to 1,4-dicarbonyl compounds, protected GABA analogues and \( \gamma \)-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. In the continuation of our work on the new reactivity of imines under photoredox catalysis, we were interested in studying the behaviour of ketimines with the aim of achieving C–C bond formation at the \( \alpha \)-position (Fig. 1). The general approach for the \( \alpha \)-alkylation of carbonyl compounds involves their conversion into carbon nucleophiles (such as enamines, enolates and enol silyl ethers, either pre-formed or formed in situ) followed by \( \text{SN}_2 \) 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, alkylations of aldehydes, ketones, 2-acylimidazoles and silyl enol ethers with \( \alpha \)-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 \( \gamma \)-imino esters would be realised (Fig. 1, bottom). Synthetic manipulation of the products would provide access not only to 1,4-dicarbonyl compounds, but also to \( \gamma \)-amino esters (protected analogues of the neurotransmitter \( \gamma \)-amino butyric acid, GABA), and to \( \gamma \)-lactams, which are found in both natural and synthetic molecules possessing a range of biological properties. 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 \( \alpha \)-bromocarbonyl compound should be avoided.

Keeping these considerations in mind, we began our investigation by studying then optimising a model reaction between \( N \)-diphenylphosphinoyl acetonophenone-derived ketimine 1a and ethyl bromoacetate 2, using \( N,N \)-diisopropylamine (DIPEA) as a base, 5 mol% [Ru(bpy)\(_3\)]Cl\(_2\)-6H\(_2\)O and 5 mol% [NiCl\(_2\)(PPh\(_3\))\(_2\)] (Table 1, see ESI for full data†). 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\(_2\)-6H\(_2\)O was confirmed to be the most effective. Among the Ni\([\text{II}]\) 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 triethanolamine (TEOA) instead of DIPEA, the reaction proceeded to nearly full conversion (95%, entry 11), however the NMR yield for the alkylated ketimine 3a...
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 [NiCl2(PPh3)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 SN2-type reactivity, while small amounts of 3a were formed under light irradiation without photocatalyst (entries 14–16).

At this point the substrate scope of the reaction was assessed, using [Ru(bpy)3]Cl2·6H2O (5 mol%), [NiCl2(PPh3)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 according 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 alkylation 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). Alkylation agents lacking the a-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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Change to conditions above</th>
<th>Conversion (a)</th>
<th>Yield (a)</th>
<th>3a + 3a' (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acetone</td>
<td>29</td>
<td>21 + 3</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>CH3CN</td>
<td>34</td>
<td>34 + 0</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>MeOH</td>
<td>51</td>
<td>32 + 14</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>DMSO</td>
<td>59</td>
<td>34 + 23</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>—</td>
<td>56</td>
<td>50 + 5</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Rosin Y disodium form</td>
<td>53</td>
<td>41 + 5</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>[Ru(bpy)3]2[PF6]2</td>
<td>37</td>
<td>35 + 2</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>[Ir(dF(C6F5)ppy)2(dbppy)]PF6</td>
<td>23</td>
<td>16 + 7</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>[Ir(ppy)2(dbppy)]PF6</td>
<td>31</td>
<td>29 + 0</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Ni(OAc)2·4H2O</td>
<td>55</td>
<td>45 + 8</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Ni(CH3CH2OH)</td>
<td>95</td>
<td>28 + 21</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>second addition of DIPEA and 2 b</td>
<td>72</td>
<td>45 + 14</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Without [NiCl2(PPh3)2]</td>
<td>38</td>
<td>28 + 10</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Without DIPEA</td>
<td>12</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>In the dark</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Without [Ru(bpy)3]Cl2·6H2O</td>
<td>7</td>
<td>4 + 2</td>
<td></td>
</tr>
</tbody>
</table>

* Consumption of ketimine 1a (conversion) and NMR yields for 3a and 3a' determined by 31P and 1H NMR analysis of the reaction mixture a with mesitylene as an internal standard. b Further equivalents of DIPEA and bromoacetate 2 were added after 7 hours.
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=\(\equiv\)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 \(\equiv\)chloroenamides.\(^{10}\) 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% [NiCl2(\(\equiv\)PPh3)2]\(^{\text{**}}\), indicating that the equilibrium position for the tautomerism is reached relatively quickly and is not influenced by [NiCl2(\(\equiv\)PPh3)2]\(^{\text{**}}\).

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\(^{2+}\), ketimines 1f, 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% [NiCl2(\(\equiv\)PPh3)2]\(^{\text{**}}\), indicating that the equilibrium position for the tautomerism is reached relatively quickly and is not influenced by [NiCl2(\(\equiv\)PPh3)2]\(^{\text{**}}\).

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 \(\equiv\)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(0)
species \([E_{1/2}^{\text{red}} = -1.33 \text{ V vs. SCE in CH}_3\text{CN}]\)\(^{17}\) which is then able to reduce ethyl bromoacetate \([E_{1/2}^{\text{red}} = -1.08 \text{ V vs. SCE in CH}_3\text{CN}]\)\(^{18}\) generating the \(\alpha\)-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 \(\alpha\)-amino radical \((II)\). The latter \([E_{1/2}^{\text{red}} = ca. -1.0 \text{ V vs. SCE in CH}_3\text{CN}]\)\(^{19}\) can be oxidised to the protonated product \((III)\) by \([\text{Ru(bpy)}_3]^{2+}\) \([E_{1/2}^{\text{red}} = +0.77 \text{ V vs. SCE in CH}_3\text{CN}]\)\(^{17}\) 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 \(\alpha\)-carbonyl radical \((I)\) (Scheme 4).\(^{21}\)

The beneficial effect of \([\text{NiCl}_2(\text{PPh}_3)_2]\) 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 \((V)\).

In summary, a mild \(\alpha\)-alkylation of \(N\)-diphenylphosphinoyl ketimines with \(\alpha\)-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 \(\alpha\)-carbonyl radical to the enamine tautomer of the starting material. The product \(\gamma\)-imino esters were easily transformed into 1,4-dicarbonyl compounds, GABA analogues and \(\gamma\)-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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5. (a) E. Arceo, I. D. Jurberg, A. Álvarez-Fernández and P. Melchorre, *Nat. Chem.*, 2013, 5, 750–756; (b) M. Silvi,
11 \([\text{NiCl}_2(\text{PPh}_3)_2]\) was chosen based on reports for Reformatsky reactions of bromoacetates, where it has been identified as a highly effective catalyst: J. C. Adrian Jr and M. L. Snapper, \textit{J. Org. Chem.}, 2007, \textbf{68}, 2143–2150.

12 This might be due to the direct, uncatalysed photoexcitation of 1a’, the enamine tautomer of the starting ketimine (ref. 5b and 20) or of a donor–acceptor complex between enamine 1a’ and ethyl bromoacetate (ref. 5a).

13 N-DPP ketimines derived from \textit{tert}-butyl methyl ketone, cyclohexyl methyl ketone and 2-acetylthiophene gave the \(\alpha\)-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-\(d_6\) to avoid peak overlap.


23 Luminescence quenching studies with \([\text{NiCl}_2(\text{PPh}_3)_2]\) were undertaken (see ESI†), but due to inner filter effects they did not provide any conclusive evidence of quenching.

