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## Dual NHC/photoredox catalytic synthesis of 1,4-diketones using an MR-TADF photocatalyst (DiKTA)<sup>†</sup>

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**The use of the recently reported organic multi-resonant thermally activated delayed fluorescence (MR-TADF) photocatalyst DiKTA allows for the modular synthesis of 1,4-diketones under mild and metal-free conditions. The reaction proceeds via a three-component relay process in the presence of an N-heterocyclic carbene (NHC) organocatalyst.**

The development of synthetic methodologies to produce 1,4-diketones is a well-studied area of research,<sup>1–3</sup> in large part due to their utility as precursors of various heterocycles such as furans,<sup>4</sup> thiophenes,<sup>5</sup> and pyrroles.<sup>6</sup> While a number of disconnections are possible, perhaps the most commonly used synthetic strategy follows the umpolung approach of disconnecting the 1,4-diketone into a nucleophilic acyl group equivalent and an  $\alpha,\beta$ -unsaturated ketone, such as employed in the Stetter reaction.<sup>1</sup> The Stetter reaction uses substoichiometric amounts of an N-heterocyclic carbene (NHC) in the presence of an aldehyde and an  $\alpha,\beta$ -unsaturated ketone to furnish the desired 1,4-diketones via a nucleophilic Breslow intermediate. Another possible disconnection would involve generating the 1,4-diketone from three distinct fragments. While such processes have been developed employing conventional two electron mechanisms,<sup>7,8</sup> they are currently limited to the use of 1,3-diketones in combination with an appropriate  $\alpha$ -ketoaldehyde. As a more general approach, the 1,4-diketone may be disconnected into two acyl radical components and an alkene, which in the forward direction would involve a radical addition of one acyl group to the alkene, followed by a subsequent

radical-radical coupling. This strategy has been executed successfully by the groups of Ackermann,<sup>9</sup> Gilmour,<sup>10</sup> Larionov,<sup>11</sup> Li,<sup>12</sup> and Wu.<sup>13</sup> However, these examples are either limited to only symmetric 1,4-diketones or are restricted in terms of the scope of the acyl radical or alkenes available. The challenge of making unsymmetric 1,4-diketones using this strategy is significant, as the two acyl radicals must offer distinct reactivity to avoid forming a mixture of symmetric and unsymmetric products. Acyl radical generation and subsequent addition to alkenes using photoredox catalysis from commercially available, or simple to prepare,  $\alpha$ -ketoacids, is well-known.<sup>10,13,14</sup> Application to achieve selective formation of the desired unsymmetric 1,4-diketones requires another acyl radical, or equivalent, that must be generated simultaneously but itself will not react with the alkene. In a recent report Wang and Ackermann accomplished this transformation selectively through the use of metallaphotoredox catalysis using a tungsten polyoxometalate photocatalyst and a nickel co-catalyst.<sup>9</sup> As an alternative, we envisaged that an acyl azolium intermediate, generated from an NHC catalyst and an appropriate electrophile, could undergo reduction through single electron transfer (SET) to the corresponding NHC-stabilised ketyl radical,<sup>15–17</sup> which could act as the second acyl radical required for this transformation. During the course of our investigations Feng *et al.*<sup>18</sup> published the use of triphenylphosphine in combination with NHC/photoredox dual catalysis using an iridium(III) photocatalyst for the generation of acyl radicals from benzoic acids generated *in situ*. However, to achieve the challenging synthesis of unsymmetric 1,4-diketones, the use of stoichiometric acyl azoliums was required (Scheme 1A). Building upon this work, we considered that using an  $\alpha$ -keto acid in combination with the organic multi-resonant thermally activated delayed fluorescent (MR-TADF) photocatalyst DiKTA, recently reported by us,<sup>19</sup> would allow for the preparation of unsymmetric 1,4-diketones in a modular, metal-free, three-component relay reaction using NHC/photoredox dual catalysis (Scheme 1B). During the preparation of this manuscript Zhang

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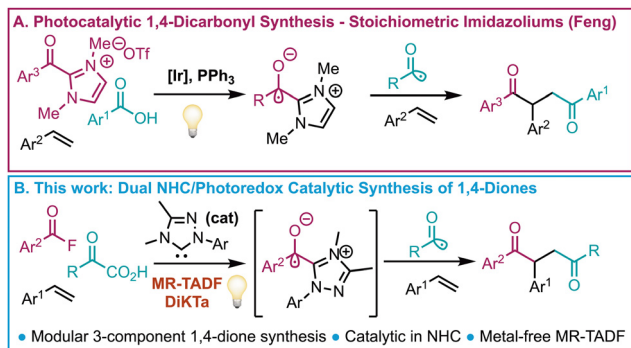
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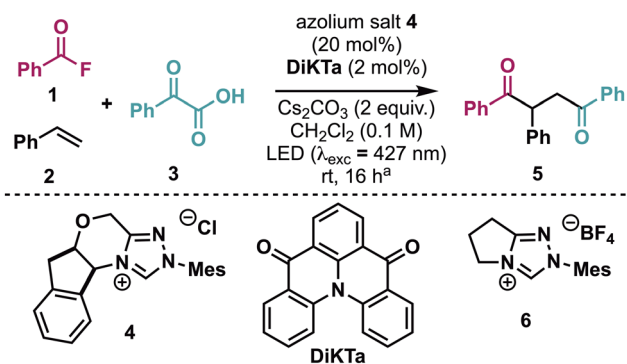




**Scheme 1** (A) Previous work using stoichiometric imidazolium species.<sup>18</sup> (B) Present work using catalytic NHCs and **DiKTa** as the photocatalyst.

*et al.*<sup>20</sup> published a similar study that relied upon the use of an Ir-based photocatalyst.

Initial exploration used the reaction of commercially available benzoyl fluoride **1**, styrene **2** and phenylglyoxylic acid **3** (Scheme 2 and ESI<sup>†</sup>). Using azolium salt pre-catalyst **4** in the presence of Cs<sub>2</sub>CO<sub>3</sub> as a base and **DiKTa**, under photoexcitation using a 427 nm LED, the corresponding 1,4-dione **5** was isolated in good yield (entry 1). A range of alternative NHC catalysts such as **6** were tested but resulted in decreased product yield (entry 2 and ESI<sup>†</sup>). The use of Cs<sub>2</sub>CO<sub>3</sub> as the base was found to be decisive, with substitution by alternative inorganic bases leading to diminished product yield (see ESI<sup>†</sup>).

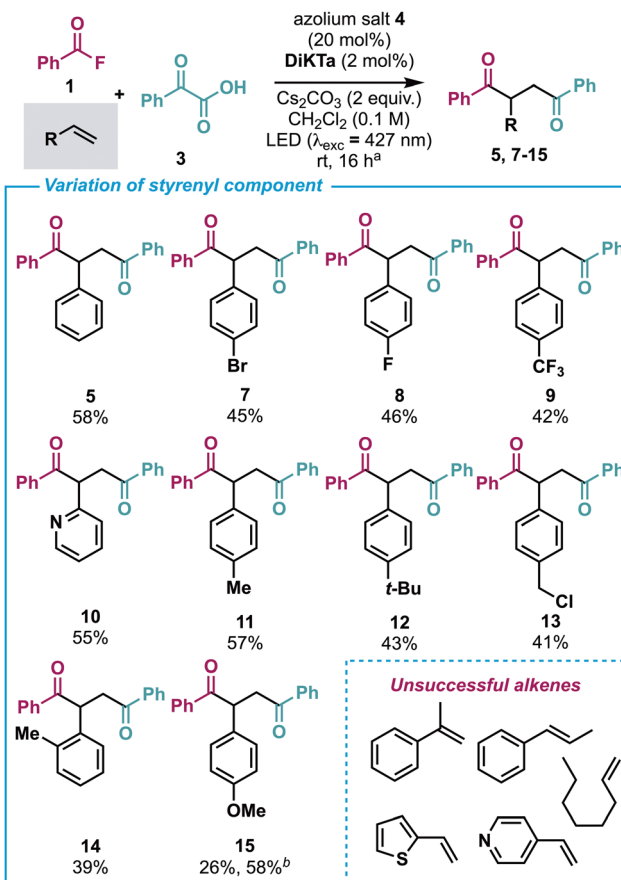


Entry	Deviation from optimized conditions	Yield (%) <sup>b</sup>
1	no deviation	61 (58)
2	azolium salt <b>6</b> instead of <b>4</b>	42
3	[Ir(ppy) <sub>2</sub> (dtbbpy)](PF <sub>6</sub> ) instead of <b>DiKTa</b>	54
4	Toluene instead of CH <sub>2</sub> Cl <sub>2</sub>	54
5	CH <sub>3</sub> CN instead of CH <sub>2</sub> Cl <sub>2</sub>	48
6	No <b>DiKTa</b>	0
7	No azolium salt <b>4</b>	5
8	No light	0

**Scheme 2** Optimization of the NHC/photoredox catalysed 1,4-dione synthesis.<sup>a</sup> Conditions: **1** (0.40 mmol), **2** (0.10 mmol), **3** (0.15 mmol), **DiKTa** (2 mol%), azolium salt **4** (20 mol%), CH<sub>2</sub>Cl<sub>2</sub> (0.10 M), rt, N<sub>2</sub>, LED (λ<sub>exc</sub> = 427 nm), rt, 16 h. <sup>b</sup><sup>1</sup>H-NMR yield with 1,3,5-trimethoxybenzene as the internal standard. Isolated yield in parentheses.

Various photocatalysts were also evaluated (see ESI<sup>†</sup>), with for example [Ir(ppy)<sub>2</sub>(dtbbpy)](PF<sub>6</sub>) giving **5** in a slightly reduced yield (entry 3). The use of alternative solvents such as toluene and acetonitrile were found to be mildly detrimental to product yield (entries 4–5 and ESI<sup>†</sup>). Control experiments verified the co-requirement of photocatalyst, NHC and light (entries 6–8). Observed side-products included a dimerization product of the initial radical addition intermediate, and an esterification product of benzoin (see ESI<sup>†</sup>).

With the optimized conditions in hand (Scheme 2, entry 1), the scope and limitations of this NHC/photoredox dual catalysed synthesis of 1,4-diketones was developed. Using benzoyl fluoride **1** and phenylglyoxylic acid **3** a variety of terminal alkene derivatives was explored in this process (Scheme 3). Incorporation of halogenated (*para*-Br, *para*-F) as well as electron-withdrawing (*para*-CF<sub>3</sub>) substituents within the styrene component were tolerated, giving the desired 1,4-diketones in 42–46% yield (7–9). Incorporation of the heteroaromatic 2-vinyl pyridine variant produced comparable yield of product (**10**). The incorporation of alkyl substituents at the *para* position were well tolerated (**11–13**), while *ortho* substitution (to give **14**) or electron-donating (*para*-MeO) substituents delivered the



**Scheme 3** Scope and limitations of the styrenes used in the synthesis of 1,4-diones.<sup>a</sup> All reactions performed using **1** (0.40 mmol), **3** (0.15 mmol) and an alkene (0.10 mmol). <sup>b</sup> Conditions: **1** (0.40 mmol), alkene (0.20 mmol), **3** (0.40 mmol), [Ir(ppy)<sub>2</sub>(dtbbpy)](PF<sub>6</sub>) (1.5 mol%), azolium salt **4** (15 mol%), toluene (0.05 M), rt, N<sub>2</sub>, LED (λ<sub>exc</sub> = 456 nm), rt, 16 h.



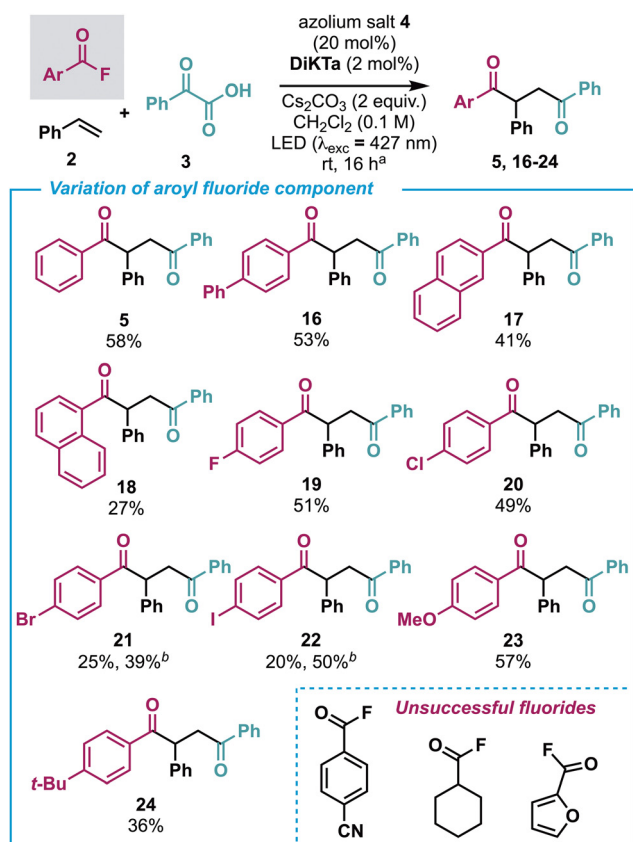
1,4-diketone (**15**) in lower yields. However, **15** could be obtained in an improved yield when using an Ir-based photocatalyst and changing reaction stoichiometries.<sup>20</sup> Substrates that proved unsuccessful under the developed conditions included  $\alpha$ - and  $\beta$ -methyl styrene, 2-vinylthiophene, oct-1-ene and 4-vinylpyridine.

With the alkene scope established, attention turned to variation of the benzoyl fluoride component and the synthesis of unsymmetric 1,4-diketones (Scheme 4). In each case ~5% of the symmetrical 1,4-diketone product was also observed, likely formed through the same process as reported by Wu and co-workers.<sup>13</sup> Trace amounts of the corresponding 1,2-dione, where effectively the styrene component has been excluded, were also detected. Larger  $\pi$ -systems such as biphenyl (**16**) and 2-naphthyl (**17**) were well tolerated, although lower yields resulted from the use of 1-naphthyl (**18**), perhaps due to increased steric congestion. *para*-fluoro- (**19**) and *para*-chloro- (**20**) substituted benzoyl fluorides worked well; however, *para*-bromo (**21**) and *para*-iodo (**22**) derivatives gave reduced product yield. However, **21** and **22** could be obtained in improved yields using alternative conditions with the Ir-based photocatalyst.<sup>20</sup> Pleasingly, electron-donating groups such as *para*-methoxy (**23**) and *para*-*t*-Bu (**24**) gave good yields of the corresponding

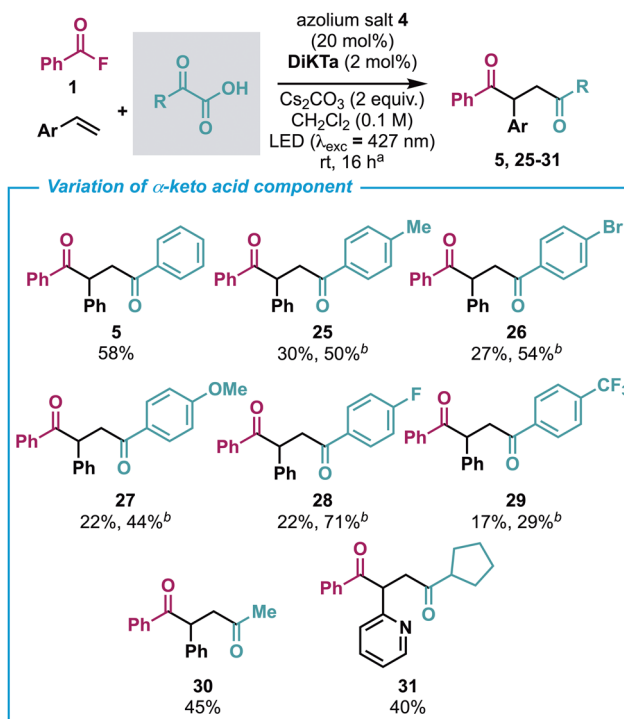
unsymmetric 1,4-diketones. Unsuccessful substrates for the benzoyl fluoride component included *para*-cyanobenzoyl fluoride, cyclohexane carbonyl fluoride and 2-furanoyl fluoride.

Given these promising results in terms of the breadth of both the alkene and benzoyl fluoride components, the scope of possible  $\alpha$ -ketoacids was evaluated next (Scheme 5). Surprisingly, even seemingly small changes to the structure of the  $\alpha$ -ketoacid such as the addition of a *para*-methyl substituent gave significantly lower yields of the corresponding 1,4-dione (**25**). This also proved to be the case for other substituents such as *para*-bromo, *para*-methoxy, *para*-fluoro and *para*-trifluoromethyl (**26–29**). However, using the alternative Ir photocatalyst-based catalytic conditions the yields for each of these substrates could be improved. Pleasingly, the use of pyruvic acid under standard conditions gave the corresponding 1,4-diketone (**30**) while the use of alkyl  $\alpha$ -keto acids could be extended to the cyclopentyl variant with the use of 2-vinyl pyridine to give the corresponding 1,4-diketone (**31**).

A mechanism is proposed for the three-component transformation (Scheme 6A). Acylation of the *in situ* generated NHC by benzoyl fluoride [or by a bis(acyl) carbonate intermediate as proposed by Feng and co-workers<sup>18</sup>] leads to the acyl azolium ion pair intermediate **I**. Simultaneously the MR-TADF photocatalyst **DiKTA** ( $E_{\text{red}}(\text{PC}^*/\text{PC}^{\bullet-}) = 1.49 \text{ V vs. SCE}$ ) is generated in its excited state by absorption. This oxidizes the  $\alpha$ -keto acid *via* SET ( $E_{\text{ox}}([\text{PhCOCO}_2]/[\text{K}]) = 1.03 \text{ vs. SCE}$  in DMSO),<sup>21</sup> which undergoes decarboxylation to generate the key acyl radical

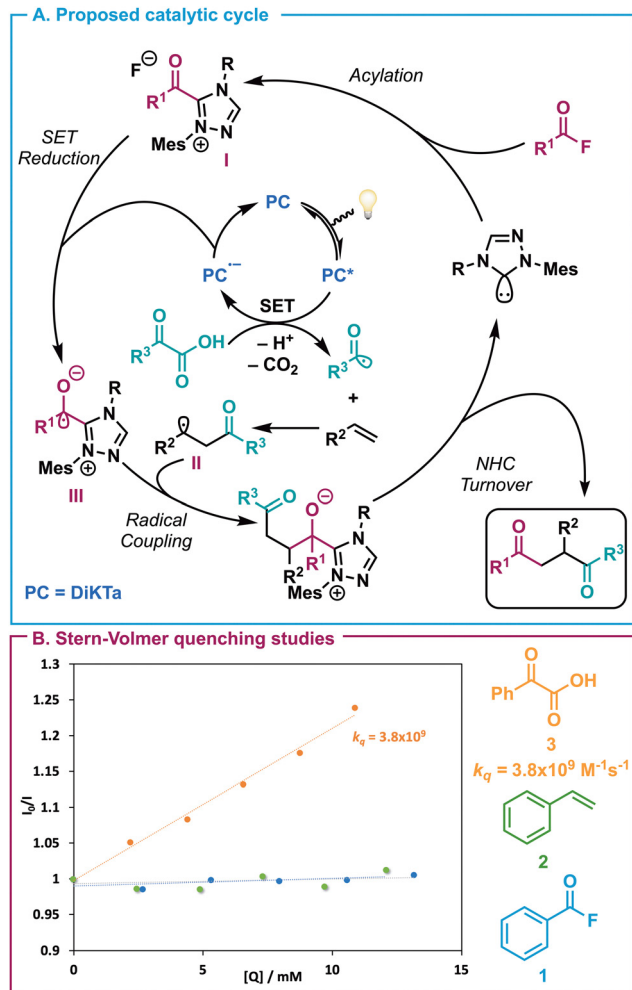


**Scheme 4** Scope of the Benzoyl fluorides used in the synthesis of 1,4-diones<sup>a</sup>. <sup>a</sup>All reactions performed using **2** (0.1 mmol), **3** (0.15 mmol) and a benzoyl fluoride (0.40 mmol). <sup>b</sup>Conditions: **1** (0.60 mmol), alkene (0.20 mmol), **3** (0.60 mmol), [Ir(ppy)<sub>2</sub>(dtbbpy)](PF<sub>6</sub>) (1.5 mol%), azolium salt **4** (15 mol%), toluene (0.05 M), rt, N<sub>2</sub>, LED ( $\lambda_{\text{exc}} = 456 \text{ nm}$ ), rt, 16 h.



**Scheme 5** Scope of the  $\alpha$ -keto acids used in the synthesis of 1,4-diones<sup>a</sup>. <sup>a</sup>All reactions performed using **1** (0.4 mmol), an  $\alpha$ -keto acid (0.15 mmol) and an alkene (0.1 mmol). <sup>b</sup>Conditions: **1** (0.60 mmol), alkene (0.20 mmol), **3** (0.60 mmol), [Ir(ppy)<sub>2</sub>(dtbbpy)](PF<sub>6</sub>) (1.5 mol%), azolium salt **4** (15 mol%), toluene (0.05 M), rt, N<sub>2</sub>, LED ( $\lambda_{\text{exc}} = 456 \text{ nm}$ ), rt, 16 h.





Scheme 6 (A) Proposed mechanism of NHC/photoredox dual catalysed synthesis of 1,4-diones. (B) Stern–Volmer quenching studies.

intermediate. Addition of this acyl species to the least substituted terminus of the styrene generates the corresponding stabilised radical **II**. The reduced photocatalyst is oxidized *via* single electron reduction of **I** to generate NHC-stabilised ketyl intermediate **III**, closing the photocatalytic cycle. Subsequent radical-radical coupling of **II** and **III** give intermediate **IV**. Release of the NHC catalyst furnishes the desired 1,4-diketone product and completes the catalytic cycle. To support this mechanistic proposal, Stern–Volmer quenching studies of benzoyl fluoride **1**, styrene **2** and phenylglyoxylic acid **3** were undertaken (Scheme 6B). These studies revealed that quenching occurs in the presence of **3** with a rate constant,  $k_q$ , of  $3.8 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$ . Fluorescence quenching was not observed in the presence of **1** or **2**. While these investigations support the plausibility of the proposed mechanism, they do not rule out the possibility of an alternative oxidative quenching mechanism.

In summary, we have developed a modular synthetic route to unsymmetric 1,4-diketones through the combination of benzoyl fluorides, styrenes and  $\alpha$ -keto acids catalysed by a dual

catalytic NHC/photoredox system using the recently developed MR-TADF organophotocatalyst **DiKTA**.<sup>22</sup> During the development of this system Zhang and co-workers published a similar methodology requiring an iridium-containing photocatalyst.<sup>20</sup> Certain substrates performed better under their conditions, although most 1,4-diones were obtained in comparable yields using the metal-free conditions described herein. Further work will probe alternative strategies to utilise the reactivity of **DiKTA** in other photocatalytic transformations.

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## Conflicts of interest

There are no conflicts to declare.

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