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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,^{1–3} in large part due to their utility as precursors of various heterocycles such as furans,⁴ thiophenes,⁵ and pyrroles.⁶ 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 α,β -unsaturated ketone, such as employed in the Stetter reaction.¹ The Stetter reaction uses substoichiometric amounts of an N-heterocyclic carbene (NHC) in the presence of an aldehyde and an α,β -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,^{7,8} they are currently limited to the use of 1,3-diketones in combination with an appropriate α -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

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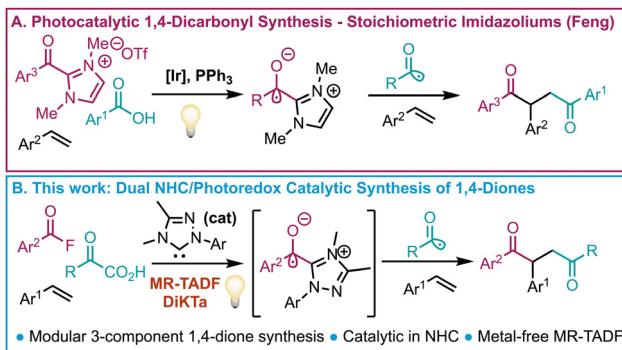
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Dual NHC/photoredox catalytic synthesis of 1,4-diketones using an MR-TADF photocatalyst (DiKTA)†

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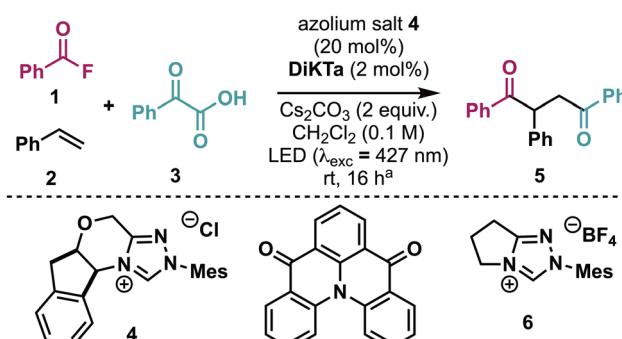
radical-radical coupling. This strategy has been executed successfully by the groups of Ackermann,⁹ Gilmour,¹⁰ Larionov,¹¹ Li,¹² and Wu.¹³ However, these examples are either limited to only symmetric 1,4-diketones or are restricted in terms of the scope of the acyl radical or alkenes available. The challenge 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, α -ketoacids, is well-known.^{10,13,14} 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.⁹ 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,^{15–17} which could act as the second acyl radical required for this transformation. During the course of our investigations Feng *et al.*¹⁸ 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 α -keto acid in combination with the organic multi-resonant thermally activated delayed fluorescent (MR-TADF) photocatalyst DiKTA, recently reported by us,¹⁹ 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



Scheme 1 (A) Previous work using stoichiometric imidazolium species.¹⁸ (B) Present work using catalytic NHCs and DiKTA as the photocatalyst.

et al.²⁰ 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[†]). Using azolium salt precatalyst **4** in the presence of Cs_2CO_3 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[†]). The use of Cs_2CO_3 as the base was found to be decisive, with substitution by alternative inorganic bases leading to diminished product yield (see ESI[†]).

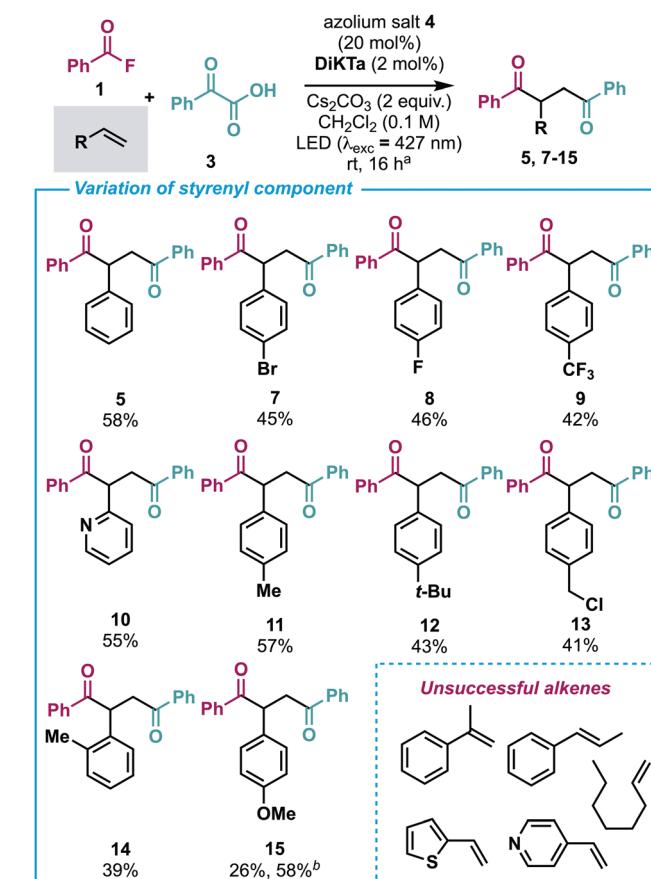


Entry	Deviation from optimized conditions	Yield (%) ^b
1	no deviation	61 (58)
2	azolium salt 6 instead of 4	42
3	$[\text{Ir}(\text{ppy})_2(\text{dtbbpy})](\text{PF}_6)$ instead of DiKTA	54
4	Toluene instead of CH_2Cl_2	54
5	CH_3CN instead of CH_2Cl_2	48
6	No DiKTA	0
7	No azolium salt 4	5
8	No light	0

Scheme 2 Optimization of the NHC/photoredox catalysed 1,4-dione synthesis^a. ^aConditions: **1** (0.40 mmol), **2** (0.10 mmol), **3** (0.15 mmol), DiKTA (2 mol%), azolium salt **4** (20 mol%), CH_2Cl_2 (0.10 M), rt, N_2 , LED ($\lambda_{\text{exc}} = 427 \text{ nm}$), rt, 16 h. ^b $^1\text{H-NMR}$ yield with 1,3,5-trimethoxybenzene as the internal standard. Isolated yield in parentheses.

Various photocatalysts were also evaluated (see ESI[†]), with for example $[\text{Ir}(\text{ppy})_2(\text{dtbbpy})](\text{PF}_6)$ 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[†]). 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[†]).

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*-CF₃) 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^a. ^aAll reactions performed using **1** (0.40 mmol), **3** (0.15 mmol) and an alkene (0.10 mmol). ^bConditions: **1** (0.40 mmol), alkene (0.20 mmol), **3** (0.40 mmol), $[\text{Ir}(\text{ppy})_2(\text{dtbbpy})](\text{PF}_6)$ (1.5 mol%), azolium salt **4** (15 mol%), toluene (0.05 M), rt, N_2 , LED ($\lambda_{\text{exc}} = 456 \text{ nm}$), rt, 16 h.

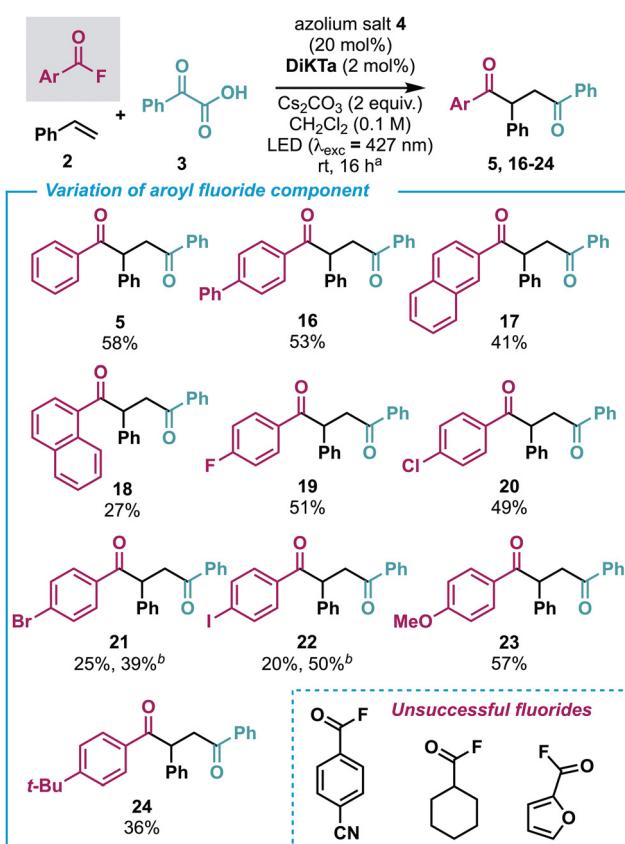
1,4-diketone (**15**) in lower yields. However, **15** could be obtained in an improved yield when using an Ir-based photocatalyst and changing reaction stoichiometries.²⁰ Substrates that proved unsuccessful under the developed conditions included α - and β -methyl styrene, 2-vinylthiophene, oct-1-ene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

With the alkene scope established, attention turned to variation of the benzoyl fluoride component and the synthesis of unsymmetrical 1,4-diketones (Scheme 4). In each case $\sim 5\%$ of the symmetrical 1,4-diketone product was also observed, likely formed through the same process as reported by Wu and co-workers.¹³ Trace amounts of the corresponding 1,2-dione, where effectively the styrene component has been excluded, were also detected. Larger π -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.²⁰ Pleasingly, electron-donating groups such as *para*-methoxy (**23**) and *para*-*t*-Bu (**24**) gave good yields of the corresponding

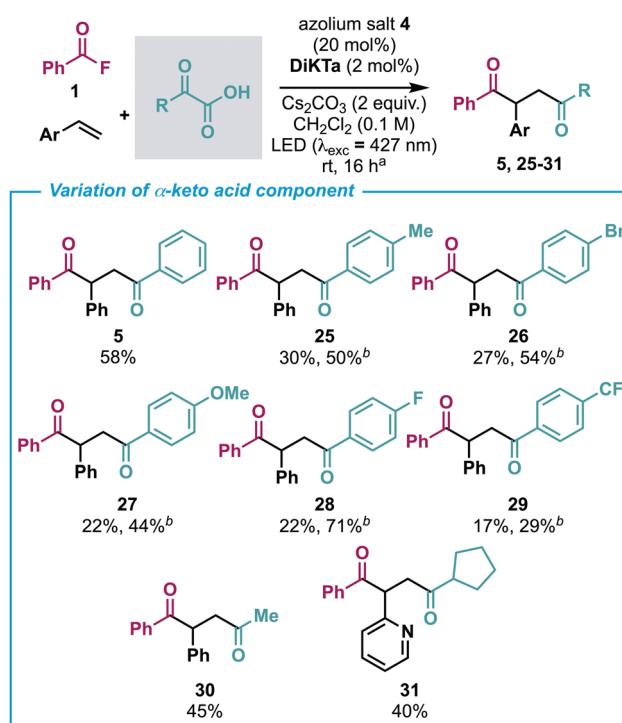
unsymmetrical 1,4-diketones. Unsuccessful substrates for the benzoyl fluoride component included *para*-cyanobenzoyl fluoride, cyclohexane carbonyl fluoride and 2-furanoyl fluoride.

Given these promising results in terms of the breadth of both the alkene and benzoyl fluoride components, the scope of possible α -ketoacids was evaluated next (Scheme 5). Surprisingly, even seemingly small changes to the structure of the α -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 α -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-workers¹⁸] 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 α -keto acid *via* SET ($E_{\text{ox}}([\text{PhCOCO}_2]\text{/[K]}) = 1.03 \text{ vs. SCE in DMSO}$),²¹ which undergoes decarboxylation to generates the key acyl radical

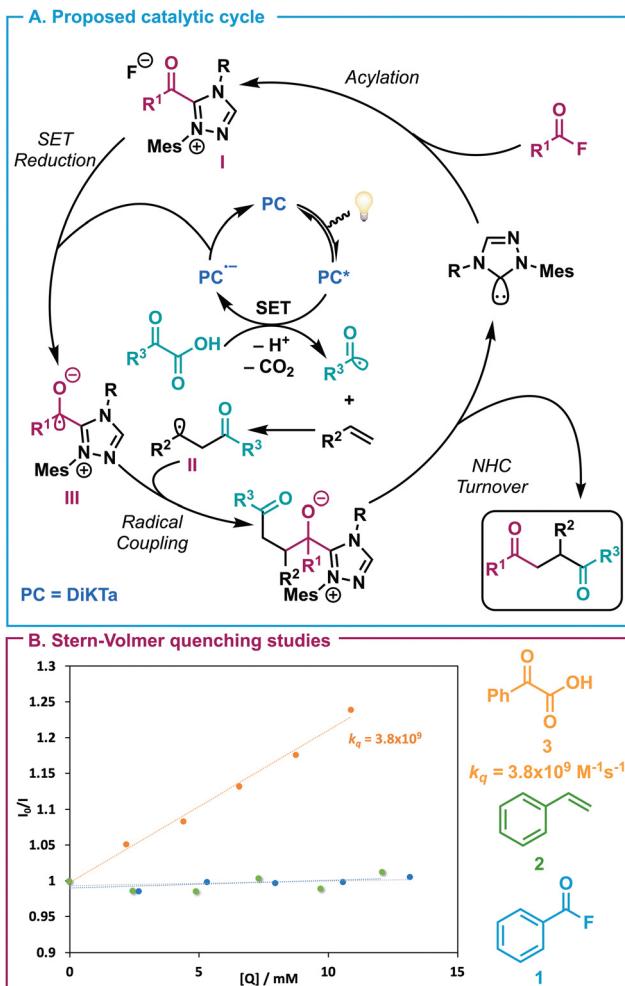


Scheme 4 Scope of the Benzoyl fluorides used in the synthesis of 1,4-diones^a. ^a All reactions performed using **2** (0.1 mmol), **3** (0.15 mmol) and a benzoyl fluoride (0.40 mmol). ^b Conditions: **1** (0.60 mmol), alkene (0.20 mmol), **3** (0.60 mmol), $[\text{Ir}(\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$ (1.5 mol%), azolium salt **4** (15 mol%), toluene (0.05 M), rt, N_2 , LED ($\lambda_{\text{exc}} = 456 \text{ nm}$), rt, 16 h.



Scheme 5 Scope of the α -keto acids used in the synthesis of 1,4-diones^a. ^a All reactions performed using **1** (0.4 mmol), an α -keto acid (0.15 mmol) and an alkene (0.1 mmol). ^b Conditions: **1** (0.60 mmol), alkene (0.20 mmol), **3** (0.60 mmol), $[\text{Ir}(\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$ (1.5 mol%), azolium salt **4** (15 mol%), toluene (0.05 M), rt, N_2 , 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 α -keto acids catalysed by a dual

catalytic NHC/photoredox system using the recently developed MR-TADF organophotocatalyst **DiKTA**.²² During the development of this system Zhang and co-workers published a similar methodology requiring an iridium-containing photocatalyst.²⁰ 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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