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

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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,ß-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,ß-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 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

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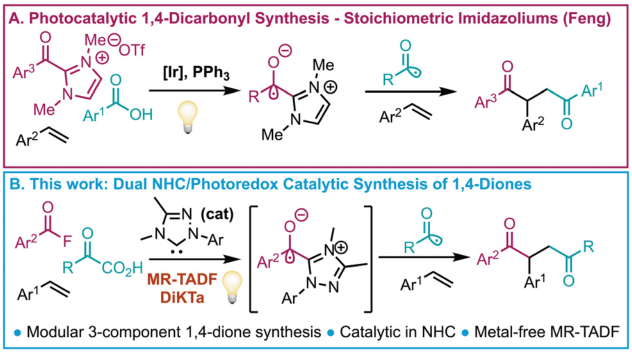
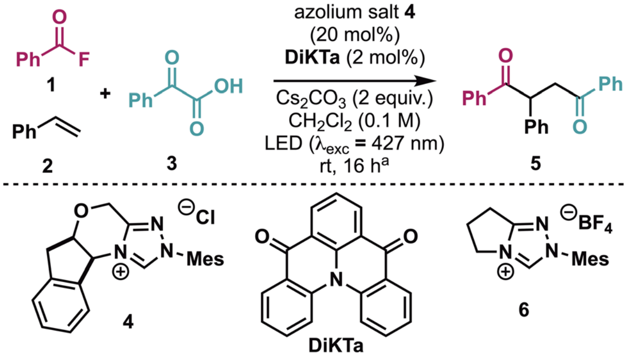


Scheme 1 (A) Previous work using stoichiometric imidazolium species.[18] (B) Present work using catalytic NHCs and **DiKTa** as the photocatalyst.

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†).

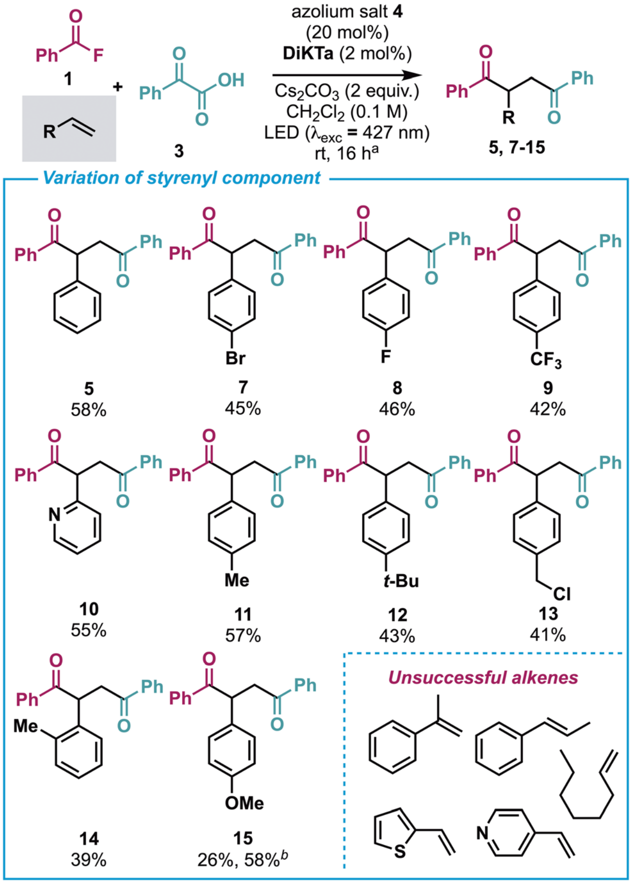


Entry	Deviation from optimized conditions	Yield (%)^b
1	**no deviation**	**61 (58)**
2	azolium salt **6** *instead* of **4**	42
3	$[Ir(ppy)_2(dtbbpy)](PF_6)$ *instead* of **DiKTa**	54
4	Toluene *instead of* CH_2Cl_2	54
5	CH_3CN *instead of* CH_2Cl_2	48
6	No **DiKTa**	0
7	No azolium salt **4**	5
8	No light	0

Scheme 2 Optimization of the NHC/photoredox catalysed 1,4-dione synthesis^a. ^{a} Conditions: **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 (λ_{exc} = 427 nm), rt, 16 h. ^{b} ^1H-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 $[Ir(ppy)_2(dtbbpy)](PF_6)$ 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†).

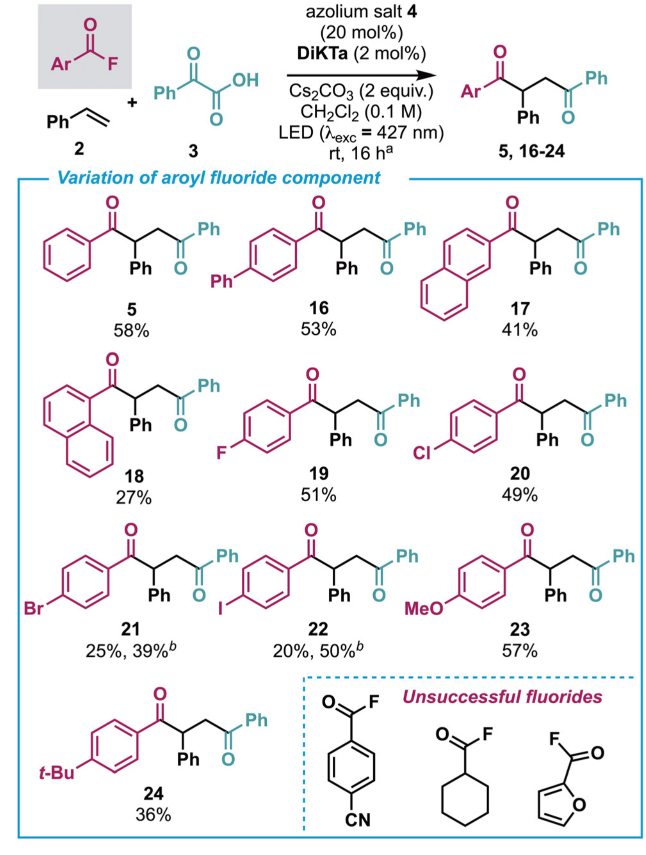
With the optimized conditions in hand (Scheme 2, entry 1), the scope and limitations of this NHC/photoredox dual catalysed synthesis of 1,4-diketones was developed. Using benzoyl fluoride **1** and phenylglyoxylic acid **3** a variety of terminal alkene derivatives was explored in this process (Scheme 3). Incorporation of halogenated (*para*-Br, *para*-F) as well as electron-withdrawing (*para*-CF_3) 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. ^{a} All reactions performed using **1** (0.40 mmol), **3** (0.15 mmol) and an alkene (0.10 mmol). ^{b} Conditions: **1** (0.40 mmol), alkene (0.20 mmol), **3** (0.40 mmol), $[Ir(ppy)_2(dtbbpy)](PF_6)$ (1.5 mol%), azolium salt **4** (15 mol%), toluene (0.05 M), rt, N_2, LED (λ_{exc} = 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.[20] Substrates that proved unsuccessful under the developed conditions included α- and ß-methyl styrene, 2-vinylthiophene, oct-1-ene and 4-vinylpyridine.

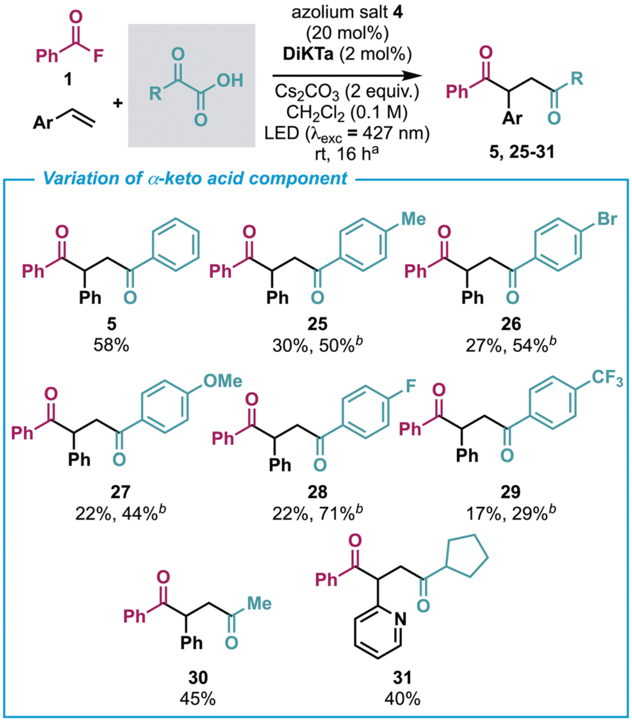
With the alkene scope established, attention turned to variation of the benzoyl fluoride component and the synthesis of unsymmetric 1,4-diketones (Scheme 4). In each case ∼5% of the symmetrical 1,4-diketone product was also observed, likely formed through the same process as reported by Wu and co-workers.[13] 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 unsymmetric 1,4-diketones. Unsuccessful substrates for the benzoyl fluoride component included *para*-cyanobenzoyl fluoride, cyclohexane carbonyl fluoride and 2-furanoyl fluoride.



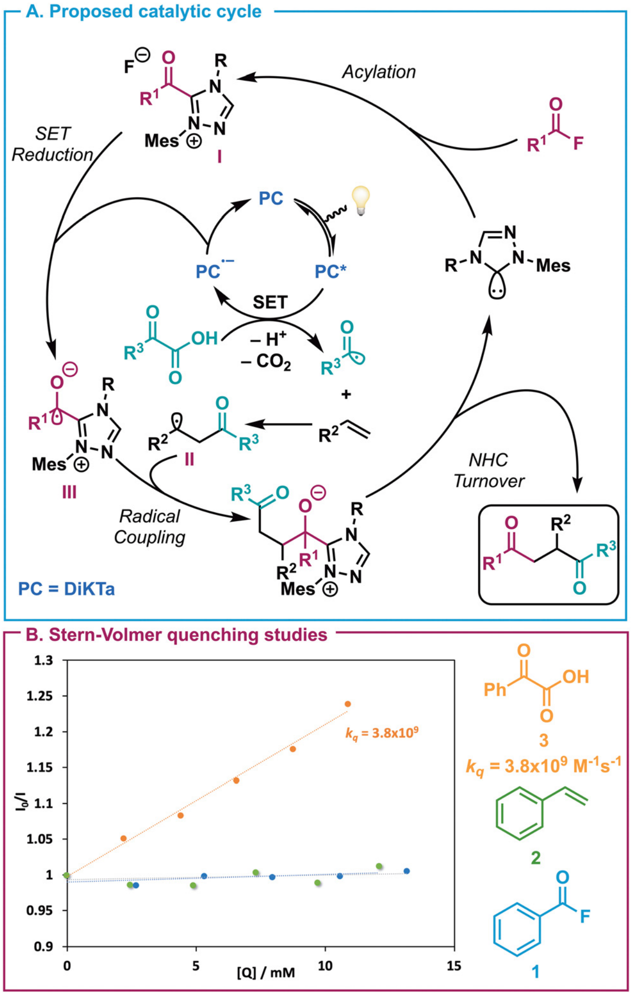
Scheme 4 Scope of the Benzoyl fluorides used in the synthesis of 1,4-diones[a]. [a] All reactions performed using **2** (0.1 mmol), **3** (0.15 mmol) and a benzoyl fluoride (0.40 mmol). [b] Conditions: **1** (0.60 mmol), alkene (0.20 mmol), **3** (0.60 mmol), [Ir(ppy)$_2$(dtbbpy)](PF$_6$) (1.5 mol%),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

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-workers[18]] leads to the acyl azolium ion pair intermediate **I**. Simultaneously the MR-TADF photocatalyst **DiKTa** (E_{red}(PC*/PC$^{•-}$) = 1.49 V *vs.* SCE) is generated in its excited state by absorption. This oxidizes the α-keto acid *via* SET (E_{ox}([PhCOCO$_2$][/K]) = 1.03 *vs.* SCE in DMSO),[21] which undergoes decarboxylation to generates the key acyl radical



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), [Ir(ppy)$_2$(dtbbpy)](PF$_6$) (1.5 mol%), azolium salt **4** (15 mol%), toluene (0.05 M), rt, N$_2$, LED (λ_{exc} = 456 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 3.8×10^9 $M^{-1}s^{-1}$. 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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