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Visible-light promoted de Mayo reaction by zirconium catalysis†

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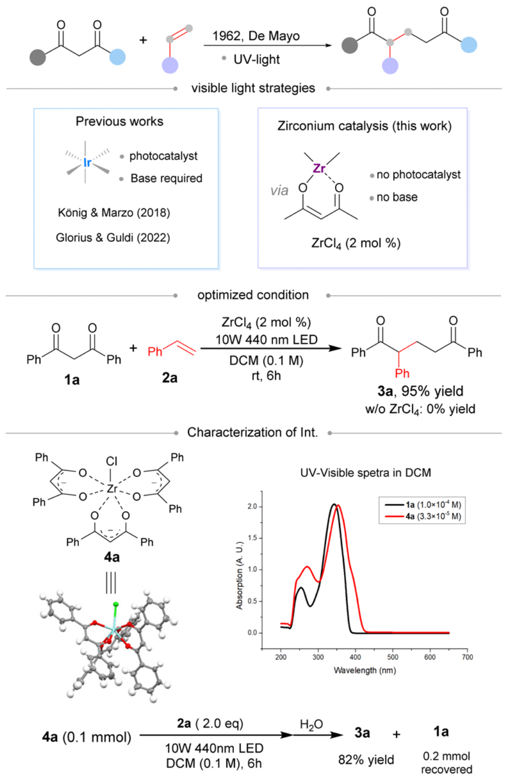
Zirconium catalysis with $ZrCl_4$ was developed to facilitate a de Mayo reaction under visible light conditions without any external photosensitizer and additive.

In 1962, de Mayo reported the photo-coupling of 1,3-dicarbonyls and alkenes under UV light irradiation. This reaction becomes a versatile route toward the access of 1,5-ketocarbonyl compounds (Scheme 1, top).[1–3] However, a typical de Mayo reaction requires ultra violet light for effective conversion. The development of a visible light-process is not achieved until the renaissance of photochemical catalysis in organic synthesis.[4,5] In 2018, Marzo and König reported a visible light-promoted de Mayo reaction catalyzed by an external iridium-based photosensitizer.[6] A similar visible light process was also developed for the synthesis of medium-sized rings by Guldi and Glorius.[7] In both cases, a basic additive was essential in order to facilitate the enol formation. Herein, we report a visible light-promoted de Mayo reaction by zirconium catalysis without any external photosensitizer or basic additive.

Zirconium complexes have been widely applied in organic synthesis as Lewis acid catalysts due to their low cost and toxicity, high stability and a high-coordination number.[8] One interesting feature is their tendency to form stabilized zirconium enolates.[8–10] For example, $ZrCl_4$ easily forms enolate complex **4a** with diketone **1a**. The complex **4a** is easily crystalized and shows strong absorption at 430 nm, which is red shifted compared with that of parent **1a** (Scheme 1, below).[11] Moreover, absorption of **4a** would further red-shift to 445 nm at a reaction concentration of 2.0×10^{-3} mol L^{-1} (see Fig. S2, ESI†), showing significant absorption in the range of visible light. Though widely explored in chemical synthesis,[8,9] zirconium enolate has not been examined in photochemical reactions. We examined the de Mayo reaction of Zr enolate **4a** with styrene under visible light irradiation. To our delight, the reaction proceeded smoothly to give the desired adduct **3a** in 82% yield. A $ZrCl_4$-catalyzed version was hence further pursued.[12]

In our initial experiments, 1,3-diphenylpropanedione (**1a**) and styrene (**2a**) were employed as model substrates for the visible light de Mayo reaction. Under optimized conditions, 2 mol% loading of $ZrCl_4$ is sufficient for complete conversion



Scheme 1 Visible light strategies for a catalytic de Mayo reaction, optimized conditions and characterization of the intermediate.[a] Optical absorption spectra, recorded in DCM in 1 cm path quartz cuvettes, [**1a**] = 1.0×10^{-4} mol L^{-1}, and [**4a**] = 3.3×10^{-5} mol L^{-1}.

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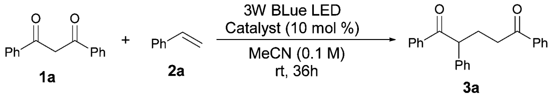
under 440 nm visible light. In contrast, no reaction was observed in the absence of $ZrCl_4$ (Scheme 1, middle). The reaction did not proceed at all in the presence of only a base (Table 1, entries 1–3). Other Lewis acids have also been investigated; $HfCl_4$ and $ZrCl_4$ were identified as the two viable catalysts (Table 1, entries 4–8) and $ZrCl_4$ was selected for further development as it is much more cheap. Other zirconium salts such as ZrF_4 or $Zr(OTf)_4$ were ineffective for the reaction (Table 1, entries 7 and 8). The change of solvent improved the yield greatly, and the loading of **2a** could be further decreased with similar reactivity (Table 1, entries 9 and 10). Increasing the light power led to an enhanced reaction rate and the reaction was completed in 6 hours with 2 mol% loading of the catalyst (Table 1, entries 11 and 12).

With the optimized conditions in hand, we examined the scope of styrene derivatives (Table 2). Substituents on styrenes such as methyl (Table 2, entries 2 and 3, **3b and 3c**), MeO- (entry 4, **3d**), halogen (entries 5–8, **3e–3h**), trifluoromethyl (entry 9, **3i**) or AcO (entry 10, **3j**) were well tolerated to afford the desired products in good yields. 2-Vinylnaphthalene was also compatible, delivering **3k** in a quantitative yield (Table 2, entry 11). 1,1-Disubstituted aryl alkenes worked well under the present conditions (Table 2, entries 12–17). 2-Aryl-1-propenes bearing a MeS- or BocNH- moiety were equally applicable (Table 2, entries 13 and 14, **3l** and **3n**). Diaryl alkene **2o** provided a good yield of 79% (Table 2, entry 15), and cyclopropyl- or acetoxyl-substituted alkene was well tolerated, too (entries 16 and 17, **3p** and **3q**).

Aromatic internal alkenes were next examined. Both *E*- and *Z*-isomers of β-methylstyrene worked but with varying diastereoselectivity. In both cases, the reaction afforded syn-selective adducts as the major diastereoisomers (Table 2, entry 18, **3r**). Notably, trisubstituted alkenes such as **2s** and **2t** also reacted well in this process, delivering moderate yields within 24 hours (Table 2, entries 19 and 20). The reactions with other aromatic alkenes such as benzofuran-substituted alkene **5a** and thiophene derivative **5b** proceeded smoothly to give the desired products with 77% and 87% isolated yields, respectively (Table 2, entries 21 and 22, **6a** and **6b**).

Table 1 Optimization of reaction conditions[a]



Entry	Catalyst	Ratio (**1a** : **2a**)	Solvent	Yield (%)
1	K_2CO_3	1 : 5	MeCN	NR
2	H_3PO_4	1 : 5	MeCN	NR
3	Quinuclidine	1 : 5	MeCN	NR
4	$AlCl_3$	1 : 5	MeCN	NR
5	$HfCl_4$	1 : 5	MeCN	62
6	$ZrCl_4$	1 : 5	MeCN	63
7	ZrF_4	1 : 5	MeCN	NR
8	$Zr(OTf)_4$	1 : 5	MeCN	NR
9	$ZrCl_4$	1 : 5	DCM	91
10	$ZrCl_4$	1 : 2	DCM	89
11[b]	$ZrCl_4$	1 : 2	DCM	98
12[c]	$ZrCl_4$	1 : 2	DCM	95

[a] Reactions were performed at room temperature in 1.0 mL of solvent with **1a** (0.1 mmol), **2a** (0.5 mmol), and cat (10 mol%) under a 3 W blue LED in nitrogen for 36 h. Yield of the isolated product. [b] 10 W 440 nm LED, 3 h. [c] 2 mol% $ZrCl_4$ loading, 10 W 440 nm LED, for 6 h.

Aliphatic alkenes were also found to be applicable, showing moderate to good reactivity (Table 2, entries 23–28, **6c–6h**). The reaction occurred with enamide to give the expected adduct **6f** in 72% yield (Table 2, entry 26). *N*-Cbz-protected piperidine was also compatible, providing **6g** in 60% yield (Table 2, entry 27). Cyclohexene worked to give a moderate 41% yield (Table 2, entry 28, **6h**). The reaction also tolerated dienes such as butadiene and 2,3-dimethyl butadiene and a selective reaction of one of the two identical double bonds was generally observed (Table 2, entries 29 and 30, **6i** and **6j**). When (*R*)-cinene **5k** was applied, a regioselective reaction at the terminal double bond was observed to give de Mayo adduct **6k** in a quantitative yield with 1.3 : 1 dr (Table 2, entry 31).

The scope of diketones was also examined. Both EDGs- and EWG-substituted aromatic diketones performed well in the reaction, giving good to excellent yields of the corresponding products (Table 2, entries 37–42, **7a–7f**). Aliphatic ketones were also workable with high yields of the desired adducts (Table 2, entries 43–46, **7g–7j**). In these cases, a shorter-wavelength light of 400 nm was applied for effective conversion. Apart from diketones, β-ketoamides were compatible in the reaction with light irradiation at 400 nm in the presence of 10 mol% of $ZrCl_4$ (Table 2, entries 47–50, **7k–7n**).

To demonstrate the synthetic potential of this methodology, alkene derivatives of natural products and pharmaceuticals were investigated in the reaction. Fenofibrate derivative **5l** performed well in this process, delivering **6l** in 81% yield after 18 hours (Table 2, entry 32). Ibuprofen and celestolide derivatives were also compatible, and the desired products were isolated in excellent yields (Table 2, entries 33 and 34, **6m** and **6n**). To our delight, androsterone derivative **5p** was also reactive to give an alkene insertion adduct **6p** in 49% yield after 4 days (Table 2, entry 35).

Mechanistically, the reaction is proposed to proceed *via* a photo-excited Zr enolate intermediate **4a*** (Scheme 2). Subsequent photo-[2+2] and retro-aldol reactions lead to the desired adduct. The observed regioselectivity with asymmetric β-ketocarbonyls can be understood by considering the extent of conjugation in the enolate intermediate (*e.g.* **4a**/**4a***) and the relative stability of the diradical intermediate involved in the photo-[2+2] process (see Scheme S1, ESI† for details).[6,7]

In concluon, we developed a $ZrCl_4$ catalyzed de Mayo reaction under visible light conditions without any external photosensitizer or additive. The visible light zirconium catalysis proceeds *via* a photoactive Zr enolate intermediate, and 2% loading of $ZrCl_4$ suffices to promote the reaction for a wide variety of alkenes and 1,3-dicarbonyls.

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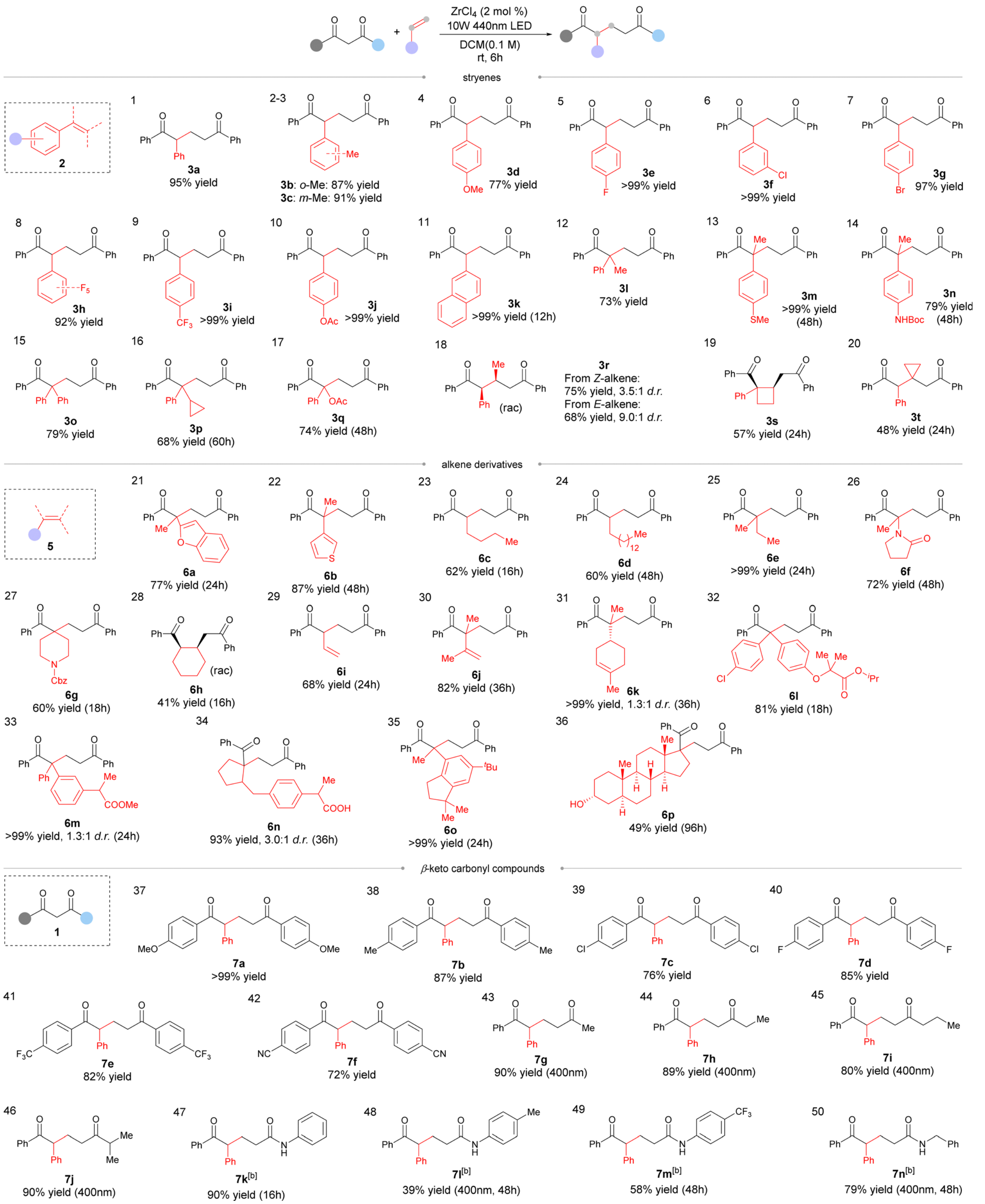
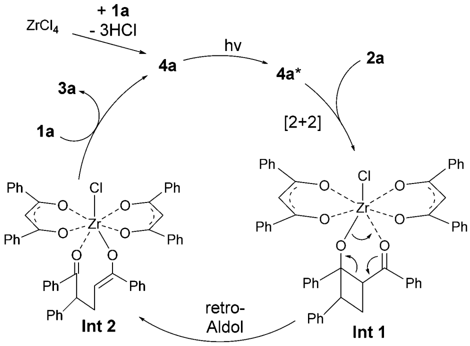
Table 2 Scope of the reaction[a]



[a] Reactions were performed at room temperature in 1.0 mL DCM with **1** (0.1 mmol), **2** or **5** (0.2 mmol) and $ZrCl_4$ (2 mol%) under a 10 W 440 nm LED for 6 h. Yield of the isolated product. [b] 10 mol% $ZrCl_4$ loading.



Scheme 2 Proposed mechanism of the reaction.

Conflicts of interest

There are no conflicts to declare.

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