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Organocatalytic [10+4] cycloadditions for the synthesis of functionalised benzo[*a*]azulenes†

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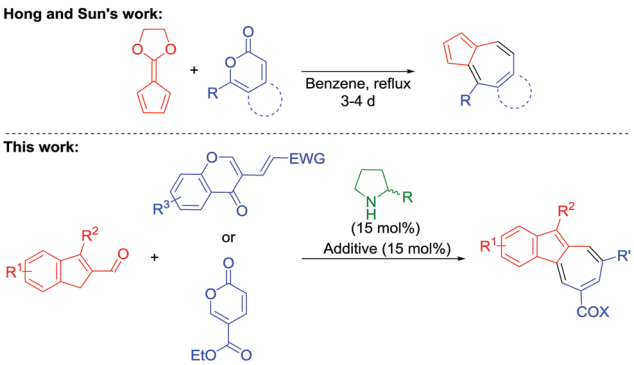
A direct and mild strategy for the synthesis of benzo[*a*]azulenes based on an organocatalytic [10+4] cycloaddition reaction is described. The strategy enables a diversity-oriented approach for the synthesis of various poly-functionalised azulenes from easily accessible starting materials.

Azulenes belong to poly-aromatic hydrocarbons and are composed of a 5-membered ring fused to a 7-membered ring. This platform has recently gathered attention, as azulene derivatives show promising biological activities.[1–3] Furthermore, these compounds demonstrate interesting electronic properties, rendering them attractive as potential materials for various applications,[4–7] and are often coloured compounds important for imaging,[8] dyes[9] and indicators.[10]

Benzo[*a*]azulenes are a subclass of azulenes based on a tricyclic benzo-fused azulene moiety. The first synthesis of benzo[*a*]azulenes dates back to 1947 and involves vapour dehydrogenation of an already built tricyclic core.[11] Since then, several approaches for the synthesis of various types of benzo[*a*]azulenes have been reported. Some rely on the construction of the 5-membered ring by metal catalysis[12] or by cascade reactions from the tropylium cation.[13] The 6-membered ring of benzo[*a*]azulenes can also be constructed *via* Knoevenagel condensation,[14] whereas the 7-membered ring can be obtained by ring expansion of a benzene ring using carbene chemistry.[15] In a more direct strategy, all three cycles have been constructed in a Pt-catalysed cascade sequence.[16] However, all these routes involve complex starting materials.

Cycloaddition reactions provide an easy access to cyclic compounds. 6-Membered rings can be accessed by the Diels–Alder reaction involving 6π-electrons,[17] while higher-order cycloadditions (>6π-electrons) have demonstrated the potential for the construction of larger cyclic compounds.[18] Hong and Sun have described a [6+4] cycloaddition strategy for the synthesis of azulenes and indole-fused azulenes from fulveneketene acetal and α-pyrones (Scheme 1, top).[19] They later developed a variant of this reaction using 6-aminofulvenes.[20] Recently, we have developed an enantioselective organocatalytic [10+4] cycloaddition based on the reaction of indene-2-carbaldehydes with electron-deficient dienes affording a 7-membered ring in tricyclic dihydrobenzo[*a*]azulenes.[21] Inspired by these results, we have been seeking a direct approach towards functionalised aromatic benzo[*a*]azulenes from easily accessible substrates. In the present work, we report the first organocatalytic [10+4] cycloaddition reaction between indene-2-carbaldehydes and chromen-4-one derivatives or α-pyrones enabling the mild synthesis of poly-substituted azulene derivatives (Scheme 1, bottom).



Scheme 1 The approach by Hong and Sun to azulenes and indole-fused azulenes (top) and this work involving organocatalytic reactions of indene-2-carbaldehydes with chromen-4-ones or α-pyrones (bottom).

The investigations were initiated by reacting 3-phenylindene-2-carbaldehyde **1a** with ethyl (*E*)-3-(4-oxo-4*H*-chromen-3-yl)-acrylate **2a** in the presence of **3a** as a catalyst, applying the reported conditions for the enantioselective [10+4] cycloaddition.[21] We were pleased to observe an elimination reaction following the [10+4] cycloaddition, thus rendering traces of the desired aromatic benzo[*a*]azulene **4aa** (Table 1, entry 1). By extending the reaction time to 4 d, the conversion reached only 50% and compound **4aa** was isolated in 15% yield (entry 2).

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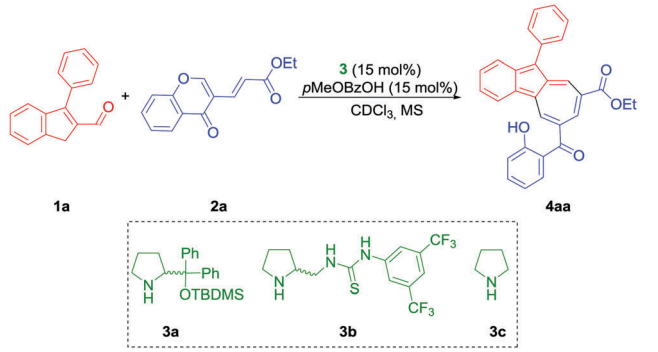
Table 1 Optimisation of the reaction between 3-phenylindene-2-carbaldehyde **1a** and ethyl (*E*)-3-(4-oxo-4*H*-chromen-3-yl)acrylate **2a**[a]



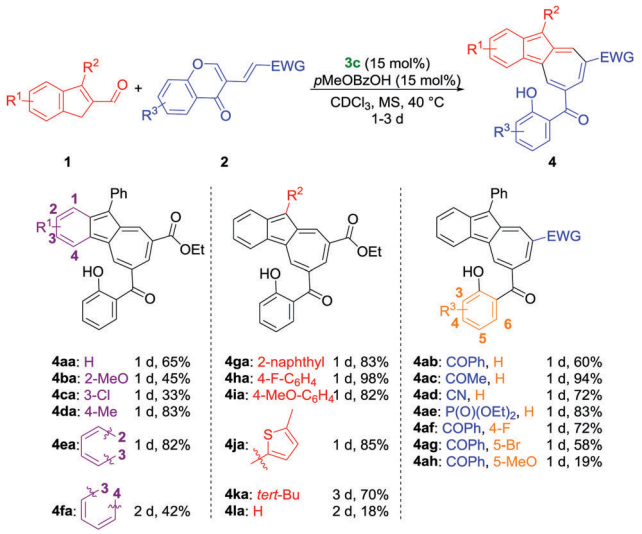
Entry	Catalyst **3**	Temperature	Time (d)	Yield[b] (%)
1	**3a**	RT	1	Trace
2	**3a**	RT	4	15
3[c]	**3b**	RT	3	69
4[c]	**3b**	40 °C	2	70
5	**3c**	40 °C	1	75
6[d]	**3c**	40 °C	1	65

[a] Reaction conditions: **1a** (0.075 mmol), **2a** (0.05 mmol), **3** (15 mol%), *p*MeOBzOH (15 mol%), $CDCl_3$ (filtered over Al_2O_3, 0.2 mL), molecular sieves (MS) 4 Å. [b] Isolated yields. [c] No acid additive was used. [d] In this case: **1a** (0.05 mmol), **2a** (0.075 mmol).

Using a bifunctional thiourea catalyst **3b** afforded **4aa** in 69% yield after 3 d (entry 3). Similar results were obtained when the reaction mixture was stirred at 40 °C for 2 d (entry 4). Since compounds **4** are achiral, we decided to test pyrrolidine **3c** as a simpler catalyst, and **4aa** was produced in 1 d at 40 °C in 75% yield (entry 5). Inverting the **1a**/**2a** ratio to 1/1.5 eased the purification affording **4aa** in 65% yield (entry 6). Although the yield was slightly lower, we retained these conditions for the scope.

We then proceeded to study the scope of this reaction, utilising various indene-2-carbaldehydes **1** (Scheme 2). Introduction of an electron-rich substituent, as well as an electron-poor substituent, gave rise to the desired azulenes (**4ba**, **4ca**) in modest yields, whereas a 4-methyl group in **1** provided **4da** in 83% yield. The tetracyclic compound **4ea** was produced in high yield. In comparison, product **4fa**, obtained from a more sterically hindered starting compound (next to the reactive centre), was formed in 42% yield after 2 d. The presence of other aryl and hetero-aryl substituents (**4ga–4ja**) at the 3-position of indene-2-carbaldehyde was well-tolerated, and a *tert*-butyl substituent (**4ka**), although in this case, a longer reaction time was required. On the other hand, when no 3-substituent in **1** was present, the desired azulene (**4la**) could only be obtained in low yield. We then subjected several chromen-4-one derivatives **2** to the reaction conditions. A large variety of electron-withdrawing groups provided the desired azulenes **4ab–4ae** in high yields. Electron-poor substituents on the benzene ring of chromen-4-one were also viable, delivering the azulene products **4af** and **4ag** in good yields. However, methoxy-substituted **4ah** was obtained in only 19% yield.

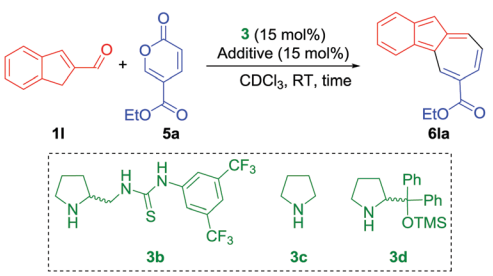
The products obtained are highly colourful and in the ESI† the UV spectra and data of representative compounds (**4aa**, **4ba**, **4ca** (Scheme 2) and **6la** (*vide infra*)) are shown.



Scheme 2 Scope of the organocatalytic reaction between indene-2-carbaldehydes **1** and chromen-4-ones **2**. Reaction conditions: **1** (0.1 mmol), **2** (0.15 mmol), **3c** (15 mol%), *p*MeOBzOH (15 mol%), $CDCl_3$ (0.4 mL, filtered over Al_2O_3), MS 4 Å, 40 °C. Isolated yields.

Encouraged by these results, we decided to expand the potential of the reaction concept to also include ethyl 2-oxo-2*H*-pyran-5-carboxylate **5a** in a reaction with **1l**. In the development of the reaction conditions, the reaction was allowed to reach full conversion before isolation of compound **6la**. We started to screen the reaction conditions with TMS-protected catalyst **3d** in $CDCl_3$ at room temperature. After 3 d, the expected benzo[*a*]azulene **6la** was obtained in 49% yield (Table 2, entry 1). We then considered using pyrrolidine as a catalyst (**3c**), which then rendered **6la** in 52% yield (entry 2). The use of *p*MeOBzOH as an additive furnished the product in 42% yield after 1 d (entry 3). We then hypothesised that the bifunctional catalyst **3b** could help increase the reaction rate

Table 2 Optimisation of the reaction between indene-2-carbaldehyde **1l** and ethyl 2-oxo-2*H*-pyran-5-carboxylate **5a**[a]

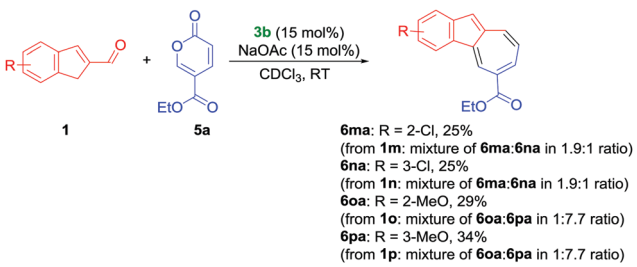


Entry	Catalyst **3**	Time (d)	Additive	Yield[b] (%)
1	**3d**	3	—	49
2	**3c**	3	—	52
3	**3c**	1	*p*MeOBzOH	42
4	**3b**	3	—	41[c]
5	**3b**	6	NaOAc	64

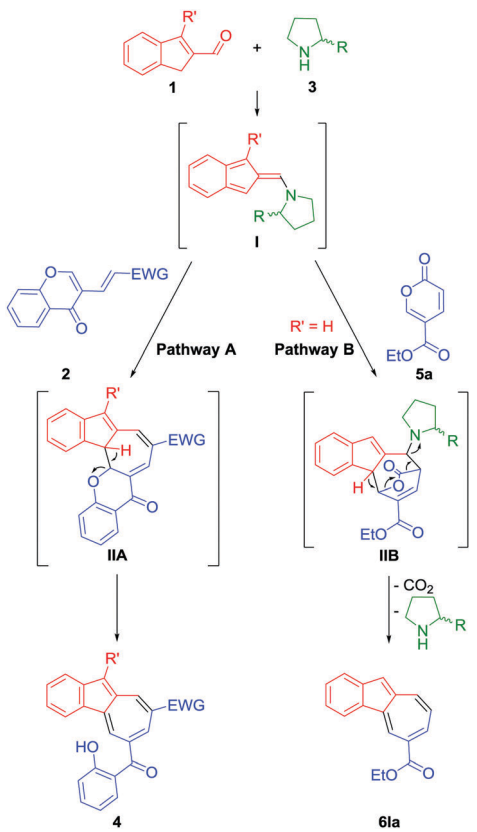
[a] Reaction conditions: **1l** (0.05 mmol), **5a** (0.075 mmol), **3** (15 mol%), additive (15 mol%), $CDCl_3$ (0.2 mL). [b] Isolated yields. [c] NMR conversion.

and by employing this catalyst, **6la** was obtained in 41% yield after 3 d (entry 4). Finally, the addition of NaOAc as a base additive enabled us to reach 64% yield over 6 d (entry 5).

These conditions were then applied to several indene-2-carbaldehydes **1** (Scheme 3). In general, the yields dropped, independent of the electronic effects of the substituents. When indene-2-carbaldehydes **1m** and **1n** were employed, in both cases, isomerisation of the pure aldehyde towards a 1.9 : 1 **1n** : **1m** mixture occurred, leading to an inseparable mixture of the respective products **6ma** and **6na** with the same ratio. A similar pattern was observed when indene-2-carbaldehydes **1o** and **1p** were probed, but a higher **6pa** : **6oa** ratio of 7.7 : 1 was obtained. The introduction of an aryl group at position-3 of the indene **1** impaired the reactivity and no product could be isolated in a significant amount. A study of the scope of α-pyrones **5** was attempted but it turned out to be difficult to synthesise the variants of **5a** bearing another electron-withdrawing group at position-5 or a substituent at position-3. The introduction of aryl groups at either position-4 or position-6 of **5a** proved to be unsuccessful, as no reactivity was observed when such substrates were employed.



Scheme 3 Scope of the organocatalytic reaction between indene-2-carbaldehydes **1** and ethyl 2-oxo-2*H*-pyran-5-carboxylate **5a**. Reaction conditions: **1** (0.1 mmol), **2** (0.15 mmol), **3b** (15 mol%), NaOAc (15 mol%), $CDCl_3$ (0.4 mL), RT for 6–7 d. Isolated yields for the mixture of regioisomers.



Scheme 4 Mechanistic proposal for the formation of benzo[*a*]azulenes **4** and **6la** *via* [10+4] cycloaddition reaction pathways.

The first step in the mechanism for the formation of azulenes is expected to be the generation of an electron-rich 10π-intermediate **I** arising from the condensation of the pyrrolidine moiety of catalyst **3** with the indene-2-carbaldehyde **1** (Scheme 4). Based on mechanistic studies,[21] it is proposed that the [10+4] cycloaddition occurs as a step-wise process. In the case of pathway **A**, involving chromen-4-ones, we surmise that product **4** is formed *via* intermediate **IIA**, involving deprotonation/elimination of the phenolate moiety. When α-pyrone **5a** is used, we propose that the [10+4] cycloaddition produces intermediate **IIB**.[19] Deprotonation of this intermediate concomitantly releases the catalyst, CO_2 and the desired aromatic structure **6la**. In the present stage, we propose that the potential role of the thiourea moiety of **3b** is to activate and direct the electrophile which is possibly also involved in the CO_2 elimination process.

In summary, a new organocatalytic strategy based on a [10+4] cycloaddition reaction for the synthesis of benzo[*a*]azulenes has been developed. It allows for the formation of poly-substituted azulenes in low to high yields under mild conditions from simple and easily accessible substrates.

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Conflicts of interest

The authors declare no conflict of interest.

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