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Amine–*N*-heterocyclic carbene cascade catalysis for the asymmetric synthesis of fused indane derivatives with multiple chiral centres†

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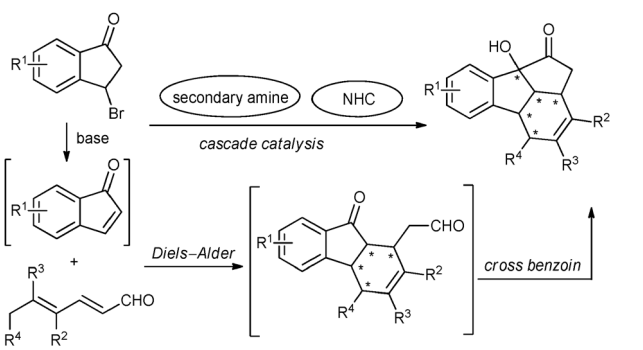
An aminocatalytic asymmetric Diels–Alder reaction of 2,4-dienals and labile 1-indenones *in situ* generated from 3-bromo-1-indanones was developed, producing highly fused indane products with multiple chiral centres followed by a cascade *N*-heterocyclic carbene-mediated benzoin condensation.

The development of multiple catalytic systems for cascade reactions has been provoking increasing interest in organic synthesis in recent years, owing to their high efficacy in the construction of complex products from simple starting materials without the need for isolation and purification of intermediates.[1,2] This strategy appears especially remarkable when some intermediates are unstable. While being efficient and attractive, the examples of such reactions remain relatively limited because of a main challenge of cascade catalysis that each catalyst must be compatible with not only other catalysts but also all reagents and intermediates during the course of the reaction. Recently, much focus has been placed on cascade reactions with multiple organocatalysis, since organocatalysis has emerged as a promising area with unique advantages.[3] In particular, the seminal studies by Rovis[4] have shown that it is possible to utilise secondary amine and *N*-heterocyclic carbene (NHC) *simultaneously* to realize cascade reactions with the incorporation of multiple catalytic cycles in a single procedure. Very recently, Melchiorre[5] and our group[6] independently demonstrated that the newly developed trienamine catalysis[7] could also be effectively combined with NHC catalysis to access complex chiral products; nevertheless, both reactions have to be conducted in a *sequential* catalytic pattern.

Fused indane frameworks have been widely witnessed in a number of natural products or biologically active materials.[8] Apparently, the Diels–Alder reaction of 1-indenones would be one of the most straightforward methods to construct the related hydrofluorene carbocycles.[9] Although these types of electrophiles have been successfully applied in various catalytic asymmetric reactions,[10] catalytic stereoselective Diels–Alder reaction of 1-indenones has been scarcely explored in the literature, probably due to their high tendency for polymerisation.[11] In our continuing interest in the application of 2,4-dienals *via* trienamine activation,[7] we envisioned that 1-indenones should be used as more reactive dienophiles to react with trienamine intermediates to afford the corresponding Diels–Alder cycloadducts,[12] which can be further transformed to fused indane derivatives followed by an NHC-catalysed intramolecular benzoin condensation. Moreover, labile 1-indenones could be generated *in situ* from relatively more stable 3-bromo-1-indanone precursors in the presence of a suitable base,[9g] which might be compatible with both secondary amine[13] and NHC catalysis. Thus, a highly efficient cascade catalytic process would be developed to produce fused indane compounds with multiple stereogenic centres, as outlined in Scheme 1.

Based on the above considerations, we initially tested the reaction of 3-bromo-1-indanone **3a** and 2,4-dienal **4a** in $CHCl_3$ with a catalytic amount of amine[14] **1a** and excess triethylamine that has been proved to be effective for generating 1-indenone from **3a**.[9g] Unfortunately, no desired Diels–Alder cycloadduct was detected (Table 1, entry 1). The same results were obtained with K_2CO_3 (entry 2). Since an acid is generally necessary for trienamine catalysis,[7] we turned our attention to some carboxylate salts, which could



Scheme 1 A multiple reaction process to access fused indane frameworks *via* amine and NHC cascade catalysis.

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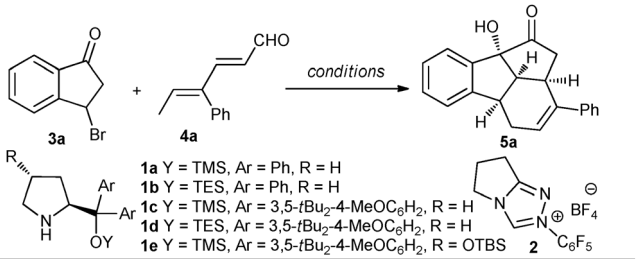
Table 1 Screening studies of the cascade reaction of 3-bromo-1-indanone **3a** and 2,4-dienal **4a**[a]



Entry	1	Solvent	Base	t (h)	Yield[b] (%)	ee[c] (%)
1	**1a**	$CHCl_3$	NEt_3	24	/	/
2	**1a**	$CHCl_3$	K_2CO_3	24	/	/
3	**1a**	$CHCl_3$	NaOAc	6	32	71
4	**1a**	$CHCl_3$	$PhCO_2Na$	5	40	88
5	**1a**	$CHCl_3$	$PhCO_2Na$	4	57	88
6	**1a**	Toluene	$PhCO_2Na$	5	40	81
7	**1a**	CH_3CN	$PhCO_2Na$	5	/	/
8	**1a**	Dioxane	$PhCO_2Na$	5	/	/
9	**1b**	$CHCl_3$	$PhCO_2Na$	4	57	89
10	**1c**	$CHCl_3$	$PhCO_2Na$	5	47	91
11	**1d**	$CHCl_3$	$PhCO_2Na$	5	47	91
12	**1e**	$CHCl_3$	$PhCO_2Na$	5	30	94

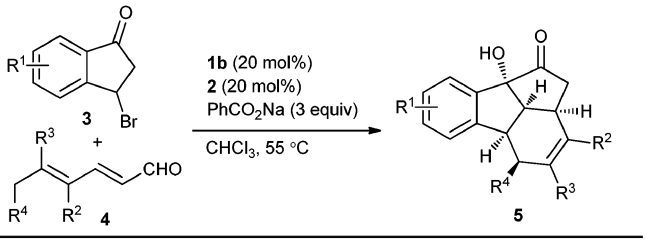
[a] For entries 1–4, reactions were performed with **3a** (0.2 mmol), **4a** (0.1 mmol), **1a** (0.02 mmol) and base (0.3 mmol) in $CHCl_3$ (1 mL) at 55 °C. After **4a** was consumed, salt **2** (0.02 mmol) was added and the mixture was stirred at 55 °C for 30 minutes. For entries 5–12, reactions were performed with **3a** (0.2 mmol), **4a** (0.1 mmol), **1** (0.02 mmol), salt **2** (0.02 mmol) and base (0.3 mmol) in solvent (1 mL) at 55 °C. [b] Isolated yield. [c] Determined by chiral HPLC analysis; dr >19 : 1.

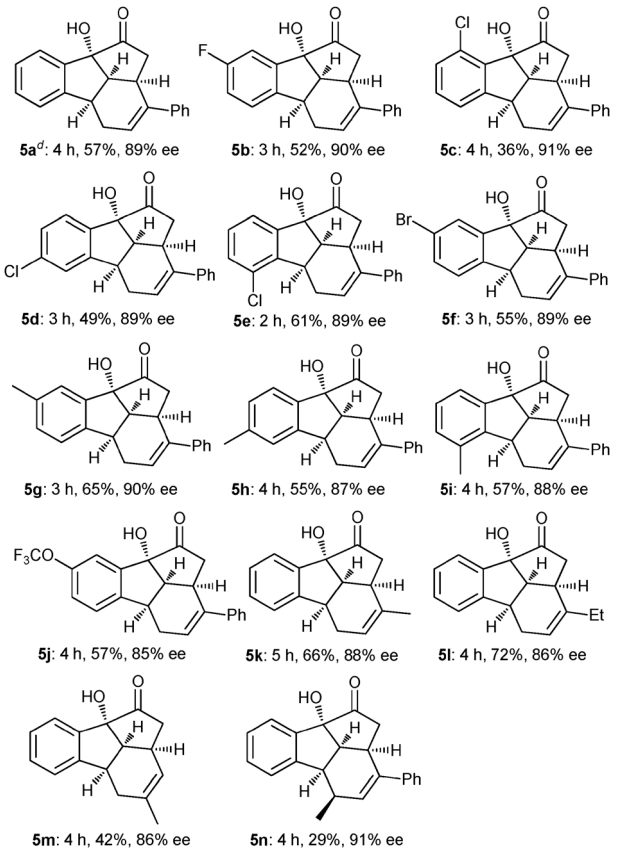
generate the required acids to promote the Diels–Alder reaction after dehydrobromination. As expected, the corresponding *endo*-selective DA adduct could be formed by using NaOAc as the base, but it was contaminated with the side products resulting from the polymerisation of 1-indenone, and slow decomposition was observed even after purification. It was pleasing that, after adding NHC precursor **2**, a sequential cross benzoin reaction could proceed smoothly to deliver the highly complex product **5a** with excellent diastereoselectivity and moderate enantioselectivity, albeit in low yield (entry 3). The DA reaction occurred more rapidly when sodium benzoate was used. A high ee value was obtained from the benzoin reaction, but the yield was still unsatisfactory (entry 4).

Although our previous attempts to combine amine and NHC catalysis with 2,4-dienal substrates in a single procedure were unsuccessful,[6] we gratifyingly found that this multiple dehydrobromination–DA cycloaddition–cross benzoin condensation process of 3-bromo-1-indanone **3a** and 2,4-dienal **4a** took place smoothly by simply combined with excess sodium benzoate and catalytic amount of amine **1a** and NHC precursor **2** together. Product **5a** was isolated after 4 hours in an even higher yield with retained stereoselectivity (entry 5). Subsequently, this cascade catalysis was investigated in other solvents. Both yield and enantioselectivity were reduced in toluene (entry 6), and the desired product **5a** was not obtained in CH_3CN or 1,4-dioxane (entries 7 and 8). Later, we tested other amine catalysts **1b**–**1e** (entries 9–12). Slightly improved ee values were generally observed, while decreased yields were attained with bulkier catalysts **1c**–**1e** (entries 10–12).

With the optimal conditions in hand, we next explored a series of 3-bromo-1-indanone **3** and 2,4-dienals **4** in the presence of amine **1b**,

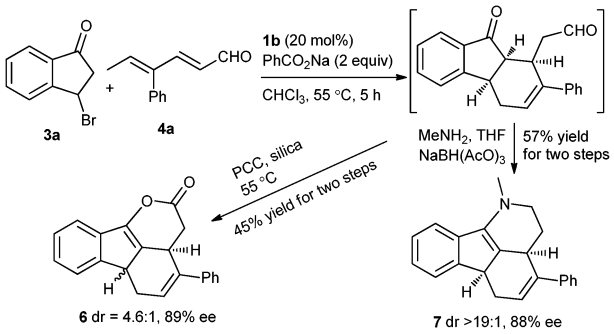
Table 2 Substrate scope and limitations[a,b,c]





[a] Reactions were performed with **3a** (0.2 mmol), **4a** (0.1 mmol), **1b** (0.02 mmol), salt **2** (0.02 mmol) and base (0.3 mmol) in $CHCl_3$ (1 mL) at 55 °C. [b] Isolated yield. [c] ee determined by chiral HPLC analysis; dr >19 : 1. [d] The absolute configuration of **5a** was determined by X-ray analysis after conversion to 2,4-dinitrobenzenehydrazone, see ESI. The other products were assigned by analogy.

NHC precursor **2** (20 mol%) and 3 equivalent of sodium benzoate. The reactions were conducted at 55 °C in $CHCl_3$ and generally completed within 5 hours. The results are summarised in Table 2. For the reactions with 4-phenyl-2,4-hexadienal **4a,** the *in situ* generated 1-indenones with electron-withdrawing groups exhibited higher reactivity, and the fused products **5b**–**5f** were obtained in fair to moderate yields and with exclusive diastereoselectivity and high enantioselectivity. It was noteworthy that the relay NHC catalysis was crucial for the formation of these carbocycles. If the reactions were conducted in a *sequential* manner, very low yields were observed due to the instability of such DA intermediates. In addition, 1-indenone bearing electron-denoting groups also showed good reactivity under the cascade catalysis, and the fused indanes **5g**–**5j** were produced in moderate yields and with a similar good stereoselectivity. On the other hand, more 2,4-dienals were explored in the reactions with 3-bromo-1-indanone **3a**.



Scheme 2 Sequential transformations with the DA intermediate.

The corresponding indane derivatives **5k–5n** were obtained in low to good yields and with retained high enantioselectivity. It should be noted that simple 2,4-hexadienal gave a complex mixture in the reaction with **3a**.

Apart from the cascade NHC-catalysed cross benzoin reaction with the DA intermediates, a sequential transformation could also be adopted to produce fused indane compounds with more structural diversity. As illustrated in Scheme 2, PCC oxidation of the DA cycloadduct from 3-bromo-1-indanone **3a** and 2,4-dienal **4a** could give a lactone product **6** with good diastereoselectivity. More importantly, a tetrahydropyridine derivative **7** with potential use in medicinal chemistry could be separated as a single diastereomer after a domino reductive amination–enamine formation process.[13]

In conclusion, we have presented an amine–NHC cascade catalytic reaction of 3-bromo-1-indanones and 2,4-dienals, which involves a multiple base-promoted dehydrobromination, asymmetric Diels–Alder reaction *via* trienamine activation and the NHC-catalysed intramolecular cross benzoin condensation process. An array of fused indane derivatives with high molecular complexity and multiple stereogenic centres were efficiently produced in a single procedure with high stereoselectivity. Moreover, other selected transformations with the Diels–Alder cycloadducts leading to more diverse and complex scaffolds further illustrate the synthetic usefulness of this methodology.

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