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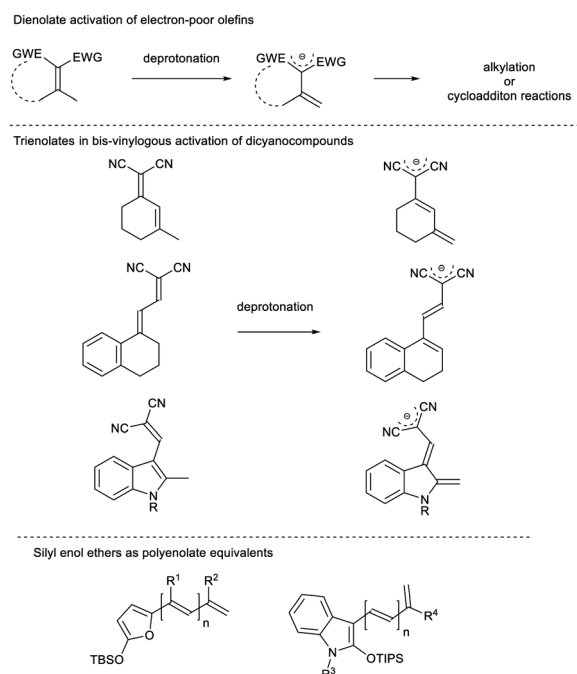
In this manuscript, the application of pentaenolate intermediates in the allylic alkylation of indene-2-carbaldehydes with Morita–Baylis–Hillman (MBH) carbonates is described. The reaction has been carried out in a highly enantio- and diastereoselective manner due to the use of a chiral tertiary amine as a nucleophilic catalyst. The developed reactivity constitutes the first application of organocatalytic pentaenolate activation in asymmetric synthesis, expanding the arsenal of catalytic methods.

One of the primary goals of contemporary organic chemistry is to develop novel synthetic tools and reactivities to broaden the range of chemical transformations.¹ Interestingly, one of the simplest modifications of an already established reactivity can be achieved by applying the principle of vinylogy, which is defined as the transmission of electronic properties through a conjugated double bond system. This concept was first introduced in 1926 by Ludwig Claisen and, in the nearly 100 years since then, has brought about the development of an enormous number of new reaction pathways. It is also worth noting that the concept of vinylogy has been readily employed in asymmetric organocatalysis.² Within the organocatalytic vinylogous reactivities, a great deal of attention has been devoted to the development of various polyenolate species³ and polyenamine chemistry.⁴ Generation of polyenolate intermediates under Brønsted base activation primarily uses pronucleophiles bearing two electron-withdrawing groups installed at a position enabling stabilization of negatively charged carbanions, thus providing an easily-affordable carbon vinylogous nucleophile (Scheme 1, top).⁵ This approach has been mainly exploited in the dienolate reactivity, where electron-poor olefin is functionalized at the γ -position, giving access to different alkylation and formal cycloaddition products. Interestingly, only a few

Pentaenolate activation in the organocatalytic allylic alkylation of indene-2-carbaldehydes†

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examples of trienolate reactivity⁶ which use doubly unsaturated dicyanocompounds as substrates are known (Scheme 1, middle). Moreover, this idea has led to the use of dicyano-indole-based olefins in such reactions, which proved to be a convenient method for the dearomatization of heterocyclic indole rings *via* the formation of trienolate.⁷ Further development of the potential of polyenolates by adding more conjugated double bonds to the system was carried out using multi-unsaturated silyl enol ethers under chiral metal complex catalysis (Scheme 1, bottom).⁸ On the other hand, great advances in vinylogous reactions have been possible due to the development of polyenamine reactivity (Scheme 2, top).⁴ This involves the formation of enamine from diversely designed, both linear and cyclic, unsaturated aldehydes or ketones under aminocatalytic conditions. Recently,

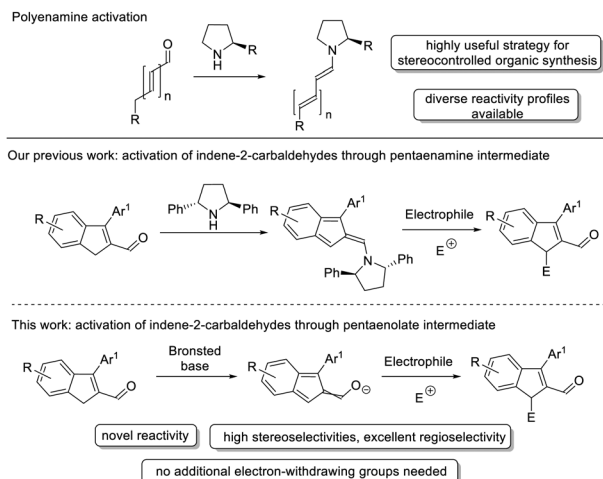


Scheme 1 Polyenolates in stereocontrolled organic synthesis.

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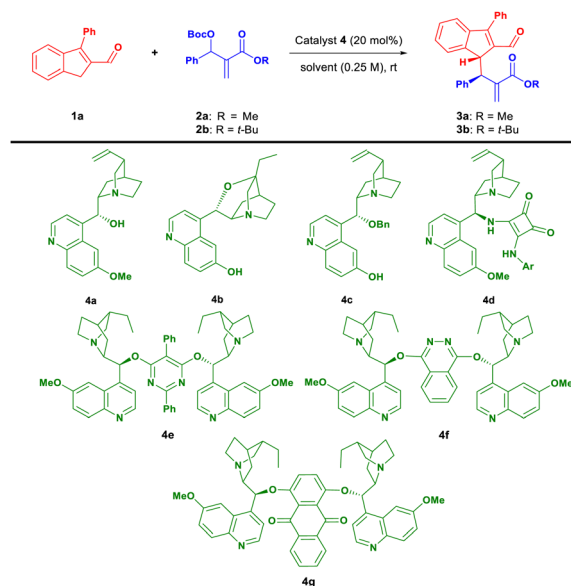


Scheme 2 Polyamines in organic synthesis and the objectives of our study.

the aminocatalytic activation of indene-2-carbaldehydes⁹ providing formal pentaenamine alkylation products has been developed in our laboratories (Scheme 2, middle).¹⁰

Inspired by our previous results, we decided to attempt organocatalytic pentaenolate alkylation using indene-2-carbaldehydes under basic conditions (Scheme 2, bottom). Morita–Baylis–Hillman (MBH) carbonates were selected as model electrophiles for the devised reactivity due to the fact that their ability to participate in the asymmetric allylic alkylations is well-recognized.¹¹ It was anticipated that the application of chiral tertiary amines as nucleophilic catalysts would ensure high stereocontrol of the process.

Optimization studies were performed using 3-phenylindene-2-carbaldehyde **1a** and MBH carbonate **2a** as model reactants (Table 1). To our delight, commercially available quinine **4a** promoted the reaction with moderate conversion (Table 1, entry 1). However, product **3a** was racemic. Therefore, catalyst screening was carried out. The application of β -isocupreidine **4b** or cupreine derivative **4c** as a catalyst improved the conversion of **1a** but the product **3a** was either racemic (Table 1, entry 2) or the reaction stereoselectivity was low (Table 1, entry 3). It was found that when a catalyst **4d** bearing H-bond donor moieties was employed, the reactivity was not observed (Table 1, entry 4). Next, the ability of the three dimeric cinchona alkaloid catalysts **4e–g** to promote the desired reaction was investigated (Table 1, entries 5–7). We were pleased to observe that the use of **4g** led to an increase in the enantioselectivity of the developed reaction. However, the diastereoselectivity was still unsatisfactory. Consequently, the influence of the bulkiness of the ester group in **2** on the stereochemical reaction outcome was evaluated. To our delight, the use of an MBH-carbonate **2b** bearing a sterically demanding *tert*-butyl group led to an increase in the diastereoselectivity of the process (Table 1, entries 8 and 9). Next in the optimization part of the study, the influence of the concentration (Table 1, entry 10) and relative ratio of substrates (Table 1, entry 11) on the reaction outcome was evaluated. The modification of the concentration (from 0.25 M to 0.5 M) led to a significant improvement in the conversion while also ensuring high stereoselectivity of the

Table 1 Pentaenolate activation in the allylic alkylation of indene-2-carbaldehydes **1** – optimization studies^a

	2	Cat.	Solvent	Time	Conv. (yield) ^b [%]	dr ^c	er ^d
1	2a	4a	CH ₂ Cl ₂	24	60	2 : 1	50 : 50
2	2a	4b	CH ₂ Cl ₂	24	> 95	2 : 1	50 : 50
3	2a	4c	CH ₂ Cl ₂	24	80	2.3 : 1	55 : 45
4	2a	4d	CH ₂ Cl ₂	24	< 5	n. d.	n. d.
5	2a	4e	CH ₂ Cl ₂	24	50	2.5 : 1	85 : 15
6	2a	4f	CH ₂ Cl ₂	24	20	2 : 1	n. d.
7	2a	4g	CH ₂ Cl ₂	24	77	2.8 : 1	95 : 5
8	2b	4g	CH ₂ Cl ₂	24	26	5 : 1	n. d.
9	2b	4g	CH ₂ Cl ₂	48	40	5 : 1	95 : 5
10 ^e	2b	4g	CH ₂ Cl ₂	48	85	5 : 1	95 : 5
11 ^f	2b	4g	CH ₂ Cl ₂	48	80	5 : 1	95 : 5
12 ^{ef}	2b	4g	CH ₂ Cl ₂	48	> 95(79)	5 : 1	95 : 5
13 ^{ef}	2b	4g	Et ₂ O	48	40	5.2 : 1	n. d.
14 ^{ef}	2b	4g	Toluene	48	34	5 : 1	n. d.
15 ^{ef}	2b	4g	MTBE	48	50	5 : 1	n. d.
16 ^{ef}	2b	4g	THF	48	92	4.7 : 1	96 : 4
17 ^{ef}	2b	4g	DCE	48	> 95	4 : 1	93 : 7
18 ^{efg}	2b	4g	CH ₂ Cl ₂	48	> 95(63)	4.7 : 1	95 : 5

^a Reactions performed on a 0.05 mmol scale using **1a** (1 equiv.) and **2** (1.2 equiv.) in 0.2 mL of the solvent. ^b Conversion as determined by ¹H NMR for **3** of a crude reaction mixture. In parentheses yield of isolated **3** is given. ^c Determined for **3** by ¹H NMR of a crude reaction mixture. ^d Determined by a chiral stationary phase HPLC for **3**. ^e Reaction performed in 0.1 mL of the solvent. ^f Reaction performed using **1a** (1.0 equiv.) and **2** (2.0 equiv.). ^g Reaction performed on a 1.5 mmol scale.

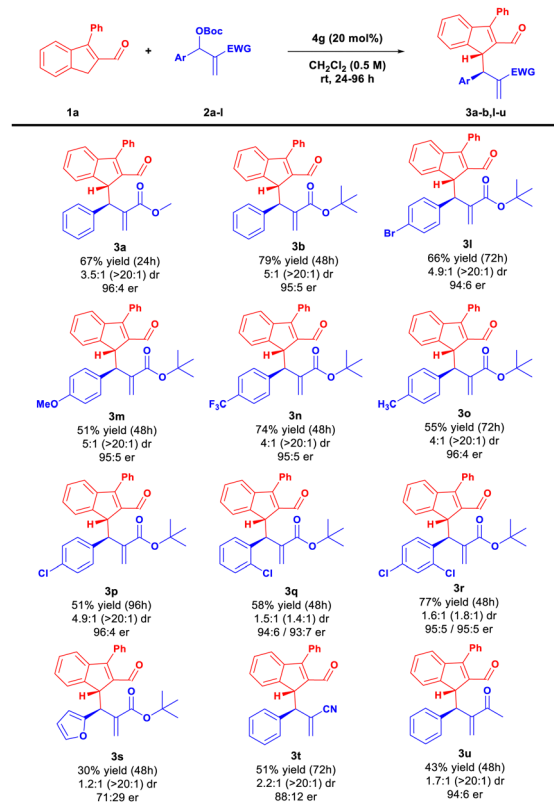
process. The use of a 2-fold excess of MBH carbonate **2b** had a similar effect on the reaction outcome (Table 1, entry 11). Subsequently, solvent screening was performed. Among the tested solvents (Table 1, compare entries 12–17), dichloromethane proved the most suitable reaction medium for the developed allylic alkylation as it provided the best stereoselectivity and efficiency of the process (Table 1, entry 12). It is worth noticing that the developed reaction was readily carried out on a 30-fold higher scale generating **3b** with similar results (Table 1, entry 18).

Once the optimal reaction conditions were established, the scope and limitations of the method were examined. Initially, a

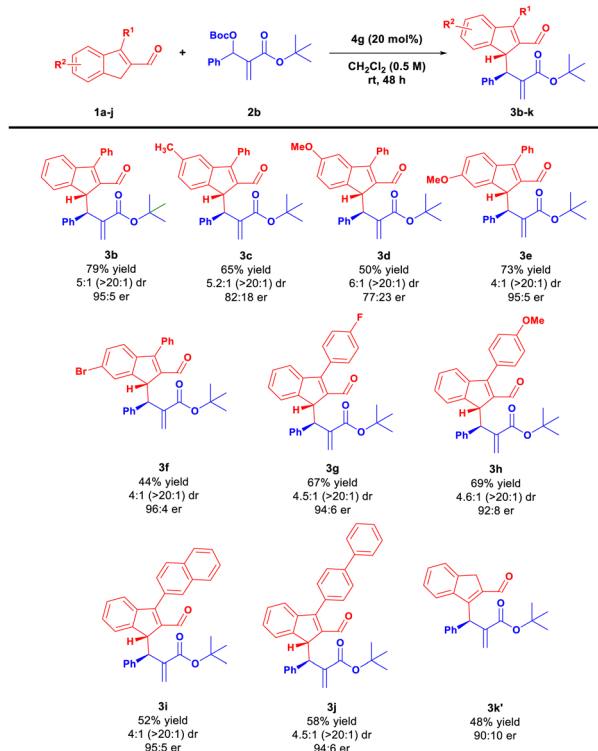


variety of indene-2-carbaldehydes **1a–j** were reacted with **2b** under optimized conditions (Scheme 3). Surprisingly, 5-methyl- and 5-methoxy-indene-2-carbaldehydes **1b–c** provided products **3c–d** with good diastereoselectivity but with lower yield and diminished enantioselectivity, presumably for steric reasons. The use of 6-bromo or 6-methoxy-substituted aldehydes **1d–e** led to products **3e–f** with good diastereo- and enantioselectivities. Transformation proved unbiased toward the presence of both electron-withdrawing and electron-donating substituents at the 3-position of **1** (Scheme 3, compounds **3g–h**). Replacing the phenyl ring at the 3 position of **1** by more sterically demanding 2-naphthyl or 1,1'-biphenyl substituents afforded access to the desired products **3i–j** in lower yields but with good stereoselectivities. Interestingly, the use of unsubstituted indene-2-carbaldehyde **1j** led to the isomeric product **3k'** with the double bond at a different position in the indene framework. A plausible explanation is that, under the reaction conditions, the initially generated product **3k** underwent isomerization (*via* deprotonation/protonation mechanism) to give more substituted olefin **3k'**.

The second part of the study focused on the use of structurally diversified MBH carbonates **2a–l**. To our delight, carbonate **2c** bearing a bromine substituent at the *para* position gave access to the desired product **3l** with good yield and stereoselectivity. The electron-donating groups appear to have an effect on the reactivity since substrate **2d** and **2f** gave access to **3m,o** with lower yield but satisfying stereoselectivity. It was



Scheme 4 Pentaenolate activation in the allylic alkylation of indene-2-carbaldehydes **1** – MBH carbonates **2** scope. Yields of isolated products **3** are given. Diastereomeric ratios as determined by ^1H NMR of a crude reaction mixture. In parentheses dr of the isolated product is given.

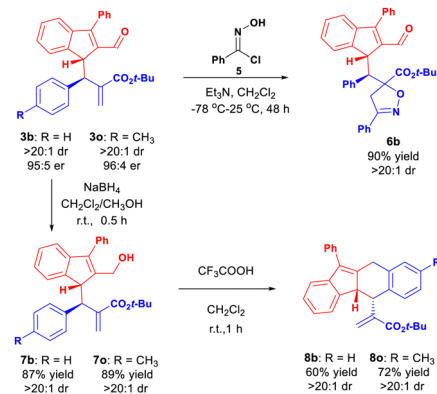


Scheme 3 Pentaenolate activation in the allylic alkylation of indene-2-carbaldehydes **1** – indene-2-carbaldehydes **1** scope. Yields of isolated products **3** are given. Diastereomeric ratios as determined by ^1H NMR of a crude reaction mixture. In parentheses dr of the isolated product is given.

found that the presence of electron-withdrawing groups on the aromatic ring in **2e** did not significantly influence the reaction outcome. The position of substituents on the aromatic ring in **2** had a significant influence on the diastereoselectivity of the developed transformation (Scheme 4, compare **3p** vs. **3q**). The *ortho*-substituted carbonate **2h** provided product **3q** with moderate yield, good enantioselectivity, and low diastereoselectivity. The use of the double substitution pattern on the aryl ring in **2** was also possible but with diminished diastereoselectivity (Scheme 4, product **3r**). Substrate **2j** bearing a heteroaromatic ring reacted to give **3s** with low yield and stereoselectivity. In the last part of the study, the possibility to modify the electron-withdrawing-group in the MBH carbonate **2** was investigated. The desired products **3t–u** were produced in moderate yields and with low diastereoselectivity. As for the cyano-group-substituted MBH carbonate **2k**, slightly lower enantioselectivity was observed after longer reaction time. Attempts to expand the scope of the reaction by including MBH-carbonates **2** derived from aliphatic aldehydes were unsuccessful. Under the optimized conditions, the formation of complex reaction mixtures was observed.

In order to demonstrate the synthetic utility of the allylic alkylation product **3**, the selected transformations of **3** were attempted. Initially, the dipolar (3+2)-cycloaddition involving the alkene moiety in **3b** with the dipole generated from imidoyl chloride **5** under basic conditions was performed to give **6b** in a





Scheme 5 Pentaenolate activation in the allylic alkylation of indene-2-carbaldehydes **1** – transformations of **3b**.

very good yield. Subsequently, the reaction sequence involving the reduction of **3b,o** with NaBH₄ to alcohols **7b,o** followed by acid-induced intramolecular Friedel–Crafts alkylation was performed. Products **8b,o** containing an additional six-membered ring were efficiently obtained (Scheme 5). Both reaction sequences occurred with the preservation of the optical purity of **3b,o** as all products were obtained as single diastereoisomers (Scheme 5). The absolute configuration of product **3b** was unambiguously determined by single crystal X-ray diffraction analysis of **3b**.¹² The stereochemistry of products **3** and as well as **6–8** was assigned by analogy.

In conclusion, we have demonstrated the possibility to generate highly extended pentaenolate species using asymmetric organocatalysis. In contrast to classical activation of indene-2-carbaldehydes **1** (via polyenamine formation),^{9,10} their use as pentaenolate precursors generated under basic conditions is unprecedented in the literature. Allylic alkylation of **1** with MBH-carbonates **2** was efficiently carried out under nucleophilic catalysis conditions using dimeric cinchona alkaloid derivative **4g** as a reaction promotor. The advantages of this methodology are its broad scope, high efficiency, and excellent stereoselectivity. Further studies leading to the expansion of pentaenolate activation to more-demanding linear substrates are on-going in our laboratories.

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Conflicts of interest

There are no conflicts to declare.

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- CCDC 2192825 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

