

Cite this: *Chem. Sci.*, 2022, 13, 11513

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# Dynamic kinetic resolution of $\gamma,\gamma$ -disubstituted indole 2-carboxaldehydes via NHC-Lewis acid cooperative catalysis for the synthesis of tetracyclic $\epsilon$ -lactones†

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The ubiquity of  $\epsilon$ -lactones in various biologically active compounds inspired the development of efficient and enantioselective routes to these target compounds. Described herein is the enantioselective synthesis of indole-fused  $\epsilon$ -lactones by the N-heterocyclic carbene (NHC)-Lewis acid cooperative catalyzed dynamic kinetic resolution (DKR) of *in situ* generated  $\gamma,\gamma$ -disubstituted indole 2-carboxaldehydes. The Bi(OTf)<sub>3</sub>-catalyzed Friedel-Crafts reaction of indole-2-carboxaldehyde with 2-hydroxy phenyl *p*-quinone methides generates  $\gamma,\gamma$ -disubstituted indole 2-carboxaldehydes, which in the presence of NHC and Bi(OTf)<sub>3</sub> afforded the desired tetracyclic  $\epsilon$ -lactones in up to 93% yield and >99 : 1 er. Moreover, preliminary studies on the mechanism of this formal [4 + 3] annulation are also provided.

Received 5th July 2022

Accepted 27th August 2022

DOI: 10.1039/d2sc03745a

rsc.li/chemical-science

## Introduction

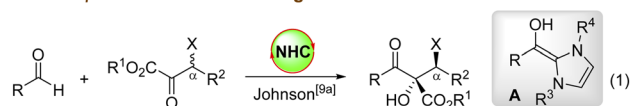
Functionalized  $\epsilon$ -lactones are important structural motifs present in various biologically active compounds and this core is responsible for the flavor and aroma in many natural products.<sup>1</sup> For instance, the natural products rubellins A and B have the benzo-fused  $\epsilon$ -lactone moiety connected to the anthraquinone unit, and they exhibit photodynamic activity.<sup>2</sup> Moreover, 9-dehydroxyurotinone and 2-O-methyl-9-dehydroxyurotinone have a dibenzo-fused  $\epsilon$ -lactone core, and they are useful due to their antimicrobial and cytotoxic activity.<sup>3</sup> Given the potential applications of  $\epsilon$ -lactone-containing compounds, the development of rapid and facile routes for the enantioselective synthesis of  $\epsilon$ -lactone derivatives have received remarkable attention. The Baeyer-Villiger oxidation of cyclohexanones constitutes one of the traditional approaches to access  $\epsilon$ -lactones.<sup>4</sup> Moreover, transition metal-catalyzed ring-expansion reactions and carbonylation processes could also provide straightforward access to  $\epsilon$ -lactones.<sup>5</sup> Herein, we report the enantioselective synthesis of tetracyclic indole-fused  $\epsilon$ -lactones by the N-heterocyclic carbene (NHC)-Lewis acid catalyzed dynamic kinetic resolution (DKR) of *in situ* generated  $\gamma,\gamma$ -disubstituted indole 2-carboxaldehydes.<sup>6,7</sup>

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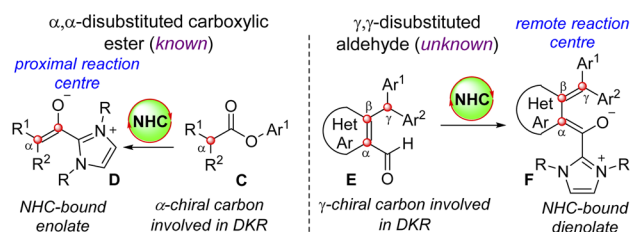
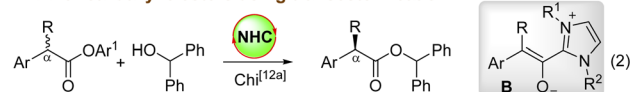
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† Electronic supplementary information (ESI) available. Details on experimental procedures, characterization data of all compounds. CCDC 2131951. For ESI and crystallographic data in CIF or other electronic format see <https://doi.org/10.1039/d2sc03745a>

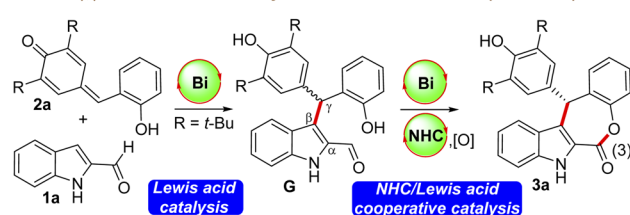
### DKR for $\beta$ -halo $\alpha$ -ketoesters using cross-benzoin reaction



### DKR for carboxylic esters using transesterification



### DKR of $\gamma,\gamma$ -disubstituted aldehydes via NHC-dienolates (this work)



Remote stereocontrol Good yields and Good selectivity  
NHC-bound dienolate intermediates First DKR with enantioinduction at the  $\gamma$ -position

Scheme 1 NHC-catalyzed DKR strategies.



Table 1 Optimization of the reaction conditions<sup>a</sup>

entry	Variation of the standard conditions <sup>a</sup>	Yield of 3a <sup>b</sup> (%)	er of 3a <sup>c</sup>	Yield of 3a' <sup>b</sup> (%)	Yield of 3a'' <sup>b</sup> (%)
1	None	68	95 : 5	<5	<5
2	5 Instead of 4	62	86 : 14	<5	<5
3	6 Instead of 4	11	86 : 14	<5	66
4	7 Instead of 4	19	81 : 19	<5	<5
5	K <sub>2</sub> CO <sub>3</sub> instead of Cs <sub>2</sub> CO <sub>3</sub>	36	91 : 9	<5	25
6	KOt-Bu instead of Cs <sub>2</sub> CO <sub>3</sub>	<5	-Nd-	<5	<5
7	DABCO instead of Cs <sub>2</sub> CO <sub>3</sub>	<5	-Nd-	<5	<5
8	THF instead of toluene	<5	-Nd-	71	<5
9	DME instead of toluene	<5	-Nd-	67	<5
10	Mesitylene instead of toluene	22	91 : 9	<5	18
11	Sc(OTf) <sub>3</sub> instead of Bi(OTf) <sub>3</sub>	52	92 : 8	<5	<5
12	CF <sub>3</sub> SO <sub>3</sub> H instead of Bi(OTf) <sub>3</sub>	60	91 : 9	<5	<5
13	10 mol% of 4 instead of 20 mol%	31	95 : 5	<5	48
14	1.0 equiv. of 8 instead of 2.0 equiv.	39	94 : 6	<5	28

<sup>a</sup> Standard conditions: **1a** (0.12 mmol), **2a** (0.168 mmol), **4** (20 mol%), Bi(OTf)<sub>3</sub> (20 mol%), Cs<sub>2</sub>CO<sub>3</sub> (60 mol%), **8** (2.0 equiv.), toluene (2.0 mL), 18 °C and 36 h. <sup>b</sup> Yields of the column chromatography purified products are provided. <sup>c</sup> The er was established by HPLC analysis on a chiral stationary phase.

NHC-catalyzed DKR strategies are employed for the conversion of racemic substrates to enantiomerically pure products.<sup>8</sup> Generally, carbene-catalyzed DKR approaches are applicable to racemic carbonyl compounds, where the enantioinduction takes place at the  $\alpha$ -carbon centre. For instance, Goodman and Johnson reported the DKR of  $\beta$ -halo  $\alpha$ -ketoesters by utilizing the NHC-catalyzed cross-benzoin reaction, where the reaction proceeds *via* the generation of the nucleophilic Breslow intermediate **A** (Scheme 1, eqn (1)).<sup>9–11</sup> Moreover, Chi and co-workers demonstrated the NHC-catalyzed DKR of  $\alpha$ -alkyl  $\alpha$ -aryl carboxylic esters *via* the transesterification strategy, and the NHC-enolate **B** is the key intermediate (eqn (2)).<sup>12</sup> In all these cases, the  $\alpha$ -carbon center is involved in the DKR process, where the generated chiral center is proximal to the reacting center (generation of **D** from **C**), and intriguingly, the synthesis of enantioenriched  $\gamma$ -substituted carboxylic esters from racemic starting materials *via* the DKR process is not known.<sup>13</sup> This will be interesting as the  $\gamma$ -carbon center will be remote from the reacting carbonyl center and enantioinduction will be challenging (conversion of **E** to **F**). In this context, we envisioned the NHC-catalyzed DKR of the  $\gamma,\gamma$ -disubstituted aldehyde **G** derived from the unprotected indole-2-carboxaldehyde,<sup>14</sup> which can be generated *in situ* by the Lewis

acid-catalyzed Friedel–Crafts reaction of indole 2-aldehyde **1a** with the *o*-hydroxyphenyl-substituted *p*-quinone methide **2a**. This formal [4 + 3] annulation reaction afforded indole-fused  $\epsilon$ -lactone **3a** in good yields and selectivities. The optimal Lewis acid was Bi(OTf)<sub>3</sub>, which plays dual roles: (a) in catalyzing the initial Friedel–Crafts reaction generating **G**, and (b) then the involvement in the DKR process for the esterification reaction in cooperation with NHCs.<sup>15</sup> Intriguingly, although NHC-catalyzed DKR strategies are known for the enantioselective synthesis of  $\beta$ -lactones,  $\gamma$ -lactones and  $\delta$ -lactones, the related DKR strategies for  $\epsilon$ -lactones are unknown. It may be noted in this context that NHC-catalyzed synthesis of fused  $\epsilon$ -lactones by the [4 + 3] annulation of *o*-quinone methides with enal-derived homoenolates was uncovered independently by Ye's<sup>16</sup> and Scheidt's groups.<sup>17</sup> Moreover, a related NHC-homoenolate route for the synthesis of spiroindole  $\epsilon$ -lactones (without involving the DKR process) is demonstrated by Li's<sup>18a</sup> and Enders' groups.<sup>18b</sup>

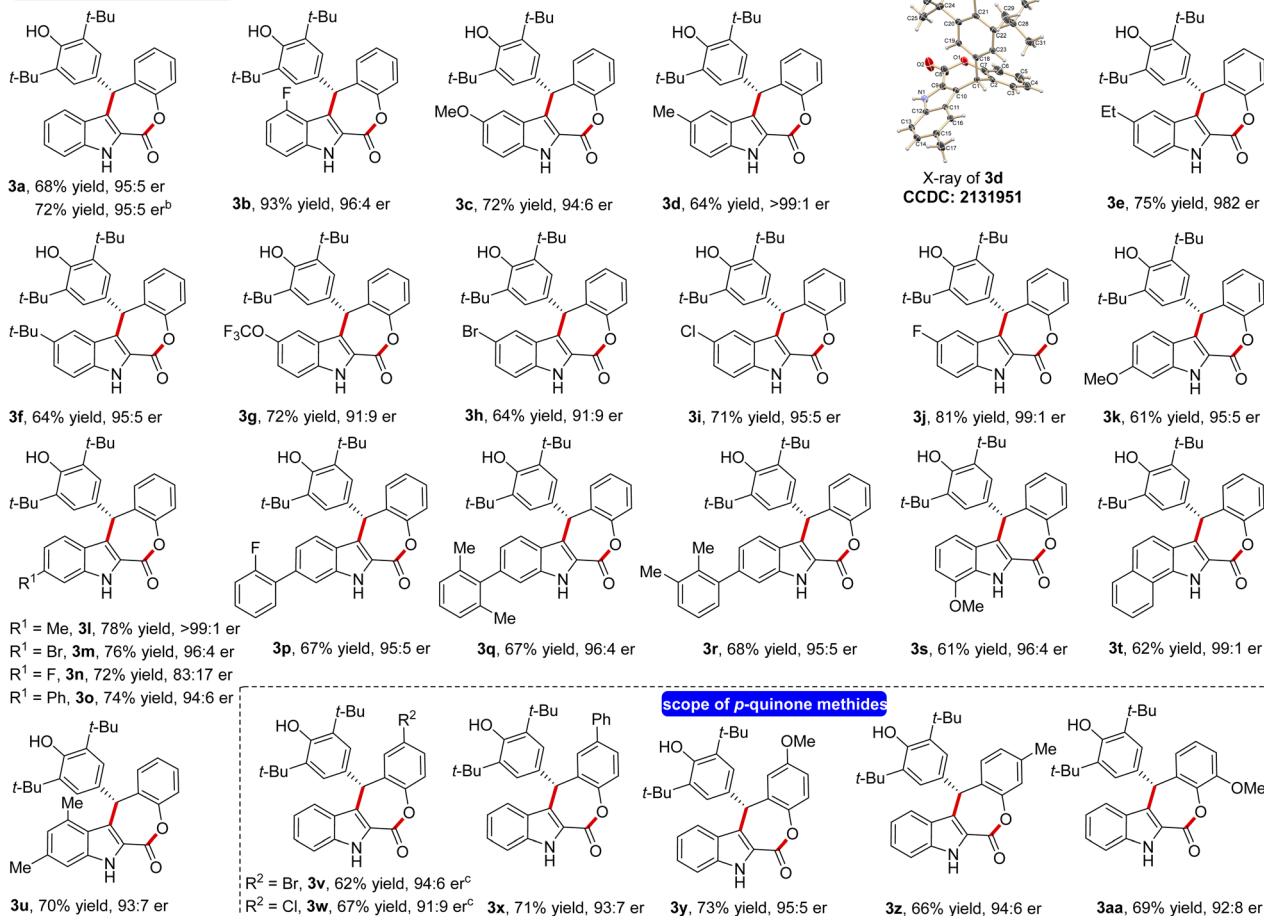
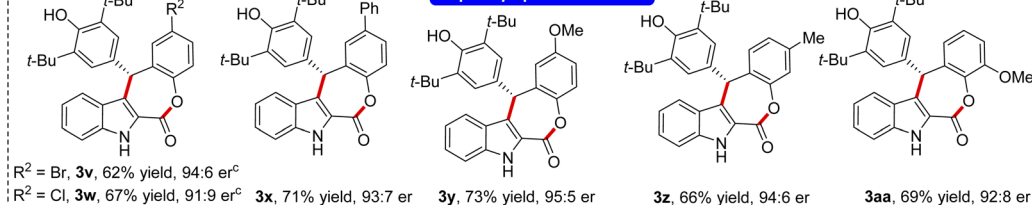
## Results and discussion

Driven by the idea of inducing stereocontrol at a remote position using the DKR strategy, the present study was initiated by

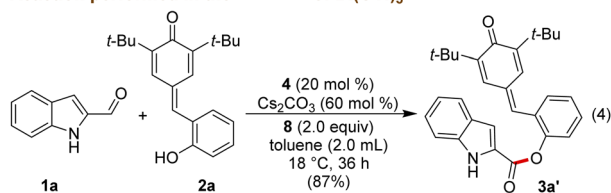




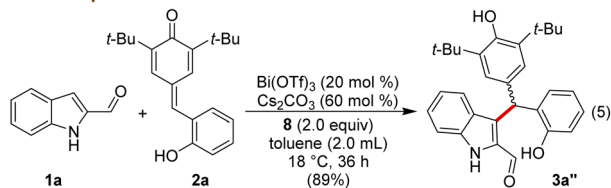
## Scope of indole 2-aldehydes

scope of *p*-quinone methides

Scheme 2 <sup>a</sup> Reaction conditions: **1** (0.25 mmol), **2** (1.4 equiv.), **4** (20 mol%), Bi(OTf)<sub>3</sub> (20 mol%), Cs<sub>2</sub>CO<sub>3</sub> (60 mol%), **8** (2.0 equiv.), toluene (4.0 mL), 18 °C and 36 h. Given are isolated yields of the column chromatography purified products. The er was established by HPLC analysis on a chiral stationary phase. <sup>b</sup> The yield and er for a 1.0 mmol scale reaction. <sup>c</sup> The reaction performed at 10 °C for 48 h.

Reaction performed in the absence of Bi(OTf)<sub>3</sub>

## Reaction performed in the absence of NHC



Scheme 3 Control experiments.

treating indole 2-carboxaldehyde **1a** with the *p*-quinone methide **2a** in the presence of NHC generated from the chiral triazolium salt **4** using Cs<sub>2</sub>CO<sub>3</sub> as the base under oxidative conditions using the bisquinone **8**. Interestingly, under these conditions, the desired indole-fused ε-lactone **3a** was formed in 68% yield and a 95 : 5 enantiomeric ratio (er) (Table 1, entry 1). The product **3a** was formed by the initial Friedel–Crafts reaction of **1a** with **2a** catalyzed by Bi(OTf)<sub>3</sub> (generating *in situ* **3a'**), followed by the NHC/Lewis acid-catalyzed DKR *via* a stereo-selective esterification reaction. Notably, the ester **3a'** (formed by the esterification of **1a** with the phenol moiety of **2a**),<sup>19</sup> and the Friedel–Crafts product **3a''** were not isolated under these conditions. Moreover, compared to the carbene formed from **4**, other chiral triazolium salts 5–7 provided less yield and selectivity of **3a** (entries 2–4). The screening of other bases and solvents revealed that Cs<sub>2</sub>CO<sub>3</sub> is the optimal base and toluene is



Reaction performed in the absence of Bi(OTf)<sub>3</sub>Reaction performed in the presence of Bi(OTf)<sub>3</sub>

Scheme 4 Role of a Lewis acid in the DKR process.

the best solvent for this transformation (entries 5–10). The use of Sc(OTf)<sub>3</sub> as the Lewis acid and CF<sub>3</sub>SO<sub>3</sub>H as the Brønsted acid for initiating the Friedel–Crafts reaction was also not efficient (entries 11 and 12). In addition, performing the reaction with 10 mol% of **4** or using 1.0 equiv. of **8** resulted in an incomplete reaction with the isolation of the Friedel–Crafts adduct **3a''** maintaining high selectivity (entries 13,14). Hence, entry 1 was selected as the best condition for the substrate scope analysis.<sup>20</sup>

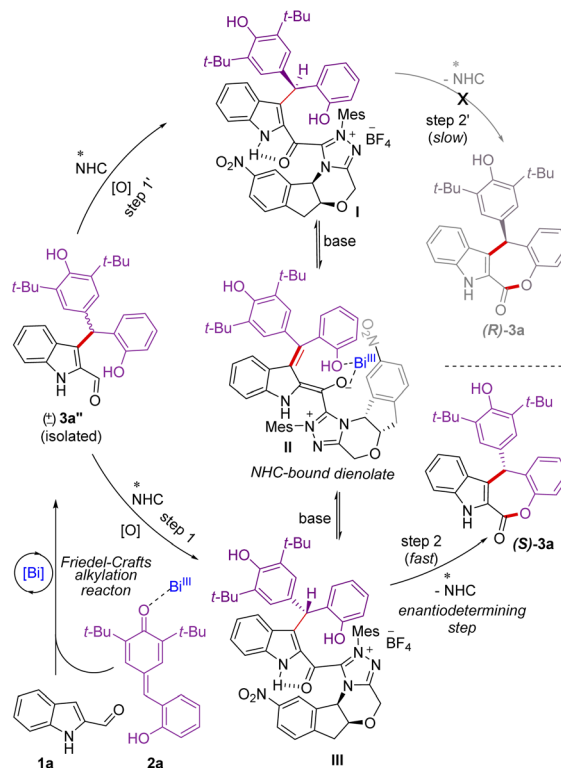
Having the optimized reaction conditions in hand, the scope and limitations of the present NHC-catalyzed DKR has been examined. First, the variation of the indole 2-carboxaldehyde has been studied. The unsubstituted parent aldehyde worked well and 4-fluoro substituted aldehyde furnished the tetracyclic  $\epsilon$ -lactone **3b** in 93% yield and 96 : 4 er (Scheme 2). The formation of **3a** in 72% yield and 95 : 5 er on a 1.0 mmol scale indicates that the present DKR process is scalable and practical. A variety of electronically different substituents at the 5-position of indole 2-carboxaldehyde was well tolerated under the optimized conditions and the corresponding  $\epsilon$ -lactones were formed in good yields and selectivities (**3c–3j**). In the case of the methyl derivative **3d**, the structure and the absolute stereochemistry of the chiral center were confirmed using X-ray analysis of the crystals.<sup>21</sup> Moreover, substrates bearing different groups at the 6-position of indole 2-carboxaldehyde underwent a smooth NHC-catalyzed annulation reaction to afford the desired products in good yields and er values (**3k–3r**). In addition, the reaction using 7-methoxy indole 2-carboxaldehyde furnished the product **3s** in 61% yield and 96 : 4 er. Furthermore, disubstituted indole -aldehydes also provided good yield of the target product thus expanding the scope of this annulation (**3t** and **3u**).

Next, the variation in the *o*-hydroxyphenyl-substituted *p*-quinone methide was studied. The *p*-quinone methides having –Br, –Cl, Ph and –OMe groups at the 5-position are well tolerated under the present conditions and the desired annulated products are formed in reasonable yields and selectivities (**3v–3y**). Moreover, –Me and –OMe groups at the 4- and 3-position of **2** did not affect the reaction outcome and the target  $\epsilon$ -lactones are formed in good yields and er values (**3z** and **3aa**).

To get insight into the mechanism of the reaction, a few mechanistic experiments were performed. When the reaction of **1a** was performed with **2a** in the absence of Bi(OTf)<sub>3</sub>, the reaction furnished the ester product **3a'** in 87% yield, and **3a** was not formed under these conditions (Scheme 3, eqn (4)). Notably, related esterification reactions catalyzed by NHCs are reported by Studer and co-workers.<sup>19</sup> Moreover, treatment of **1a** with **2a** in the absence of NHC resulted in the formation of the Friedel–Crafts adduct **3a''** in 89% yield (eqn (5)).

The lack of the desired product **3a** formation in the absence of either Bi(OTf)<sub>3</sub> or NHC indicates the role of these two catalysts for the direct and enantioselective synthesis of the  $\epsilon$ -lactone **3a**. To get further insight into the role of Bi(OTf)<sub>3</sub> in the DKR process, the Friedel–Crafts alkylation product **3a''** was treated with NHC generated from **4** under oxidative conditions in the absence of Bi(OTf)<sub>3</sub>. This reaction afforded **3a** in 65% yield and 79 : 21 er (Scheme 4, eqn (6)). Interestingly, when the same reaction was conducted in the presence of Bi(OTf)<sub>3</sub> the product **3a** was formed in 62% yield and an improved er of 93 : 7 shedding light on the role of a Lewis acid in the DKR process (eqn (7)).<sup>22</sup> It is reasonable to assume that the Bi(III) Lewis acid is involved in coordination with the NHC-bound dienolate and the phenolic –OH moiety for the facile dienolate protonation and intramolecular acylation.<sup>23,24</sup>

Mechanistically, in the presence of Lewis acidic Bi(OTf)<sub>3</sub>, indole 2-carboxaldehyde **1a**<sup>25</sup> adds to the *p*-quinone methide **2a** generating *in situ* the racemic  $\gamma,\gamma$ -disubstituted indole 2-carboxaldehyde **3a''** through an intermolecular Friedel–Crafts alkylation reaction (Scheme 5). Under oxidative conditions, the



Scheme 5 Proposed mechanism of the reaction.





