Diastereodivergent synthesis of enantioenriched α,β-disubstituted-γ-butyrolactones via cooperative N-heterocyclic carbene/Ir catalysis

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The stereodivergent synthesis of natural product frameworks via a single transformation using simple starting materials is a significant challenge. The prevalence of γ-butyrolactones in biologically active natural products has long motivated the development of enantioselective strategies towards their synthesis. Herein, we report an enantio- and diastereodivergent [3+2] annulation reaction for the synthesis of α,β-disubstituted-γ-butyrolactones through cooperative N-heterocyclic carbene (NHC) organocatalysis and iridium catalysis. This method overcomes the challenges of merging NHC organocatalysis with Ir catalysis by the appropriate choice of ligands. The use of two chiral catalysts allowed control over the relative and absolute configuration of the two formed stereocentres, thereby providing selective access to all four possible stereoisomers of the γ-lactone products. The transformation could be extended to the synthesis of δ-lactams via [4+2] annulation. The synthetic utility of this methodology was illustrated in the concise synthesis of the naturally occurring lignan (−)-hinokinin.

Introduction

In the last two decades, N-heterocyclic carbene (NHC) organocatalysis has evolved into a versatile tool for the construction of organic molecules with rich stereochemistry by the generation of a diverse set of catalytic intermediates.[1-6] Recent developments in the field have broadened the synthetic utility of carbene organocatalysis by combining it with Lewis acids,[7-9] Brønsted acids,[10,11] hydrogen bond donors[12-14] and others[15-18] to achieve cooperative catalytic systems that promote otherwise inaccessible reactivity.[19,20] The merger of NHC-bound nucleophiles with electrophilic species generated via transition-metal (TM) catalytic cycles has very recently contributed to enlarging the synthetic applicability of NHC organocatalysis even further. However, the developed

systems have so far been limited to the use of palladium as the transition-metal catalyst[21-25] and the potential of merging other metals with carbene catalysis remains an underexplored area. The challenge associated to the development of such kind of dual catalytic systems lies on the strong, irreversible coordination of NHCs to transition metals, which can lead to the disruption of the individual desired reactivity. This strong binding affinity has indeed been largely exploited and NHC-transition metal complexes find broad applications in modern chemistry (Fig. 1a).[5]

γ-Butyrolactones are ubiquitous motifs in natural products, pharmaceuticals, fragrances and flavouring agents that display a wide range of structural frameworks and substitution patterns (Fig. 1b).[26,27] The broad pharmacological activities of γ-butyrolactones (which includes antioxidant, anticarcinogenic and antiviral, among others), as well as their industrial relevance has long motivated the development of synthetic methods for their enantioselective synthesis. Despite the progress in this field, there is a lack of catalytic asymmetric methods for the diastereo- and enantioselective installation of stereocentres at the γ-butyrolactone ring and in particular, versatile methods for the enantioselective synthesis of α,β-disubstituted γ-butyrolactones are still needed.[28,29] Among the multiple strategies developed towards the synthesis of substituted γ-butyrolactones, NHC-catalysed [3+2] annulations of homoenolate intermediates (acting as 1,3-dipoles) with electrophilic carbonyl derivatives provide access to β,γ-disubstituted γ-butyrolactones (Fig. 1c).[30-32] However, due to unfavourable steric interactions between the α-substituent and the NHC scaffold in the homoenolate intermediate, these strategies fail to provide direct access to α-substituted γ-butyrolactones when using α-substituted enals.[33]

We envisioned that γ-lactones bearing α,β-substituents could be accessed following a different C–C bond connection coming from an enolate (two-carbon synthon) and a β-carbocationic alkoxy synthon. Encouraged by the high stereocontrol imparted by NHC catalysts on the α-functionalization of carbonyl derivatives,[34] we anticipated that the addition of an NHC-enolate to a suitable electrophile followed by lactonization would give access to the desired scaffolds. As for the electrophile, we rationalized that metal-allyl species, arising from oxidative addition of allylic electrophiles to a transition metal, would be ideal β-carbocationic alkoxy synthons. Given the known preference of Ir-π-allyl intermediates for branched over linear addition,[35] these species seemed well suited for nucleophilic addition of the NHC-enolate leading to the formation of the desired five-membered rings (Fig. 1d). Additionally, the possibility of controlling the absolute and relative configuration of the two newly-formed vicinal stereocentres using two chiral catalysts[36-38] would allow access to all four stereoisomers of the γ-lactone product. As the different diastereo- and enantiomers of a molecule bearing multiple stereogenic centres are known to present distinct biological activities,[39] a method giving access to the set of stereoisomers of a relevant scaffold from the same starting materials would be highly valuable. Herein, we describe a stereodivergent dual catalytic transformation merging NHC organocatalysis with Ir catalysis for the synthesis of all four stereoisomers of α,β-disubstituted-γ-butyrolactones, via [3+2] annulations. The dual catalytic system is also applicable to the synthesis of δ-lactams, via [4+2] annulations. The synthetic utility of the developed method is exemplified in the concise synthesis of the lignan (−)-hinokinin.

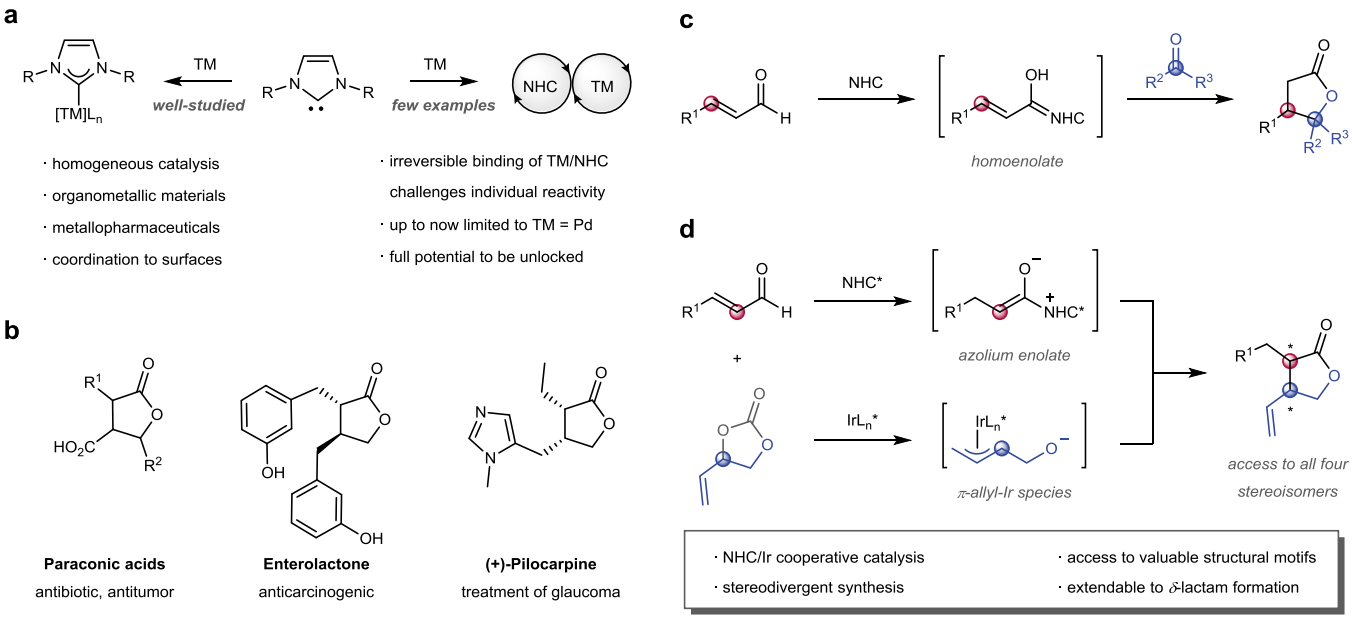


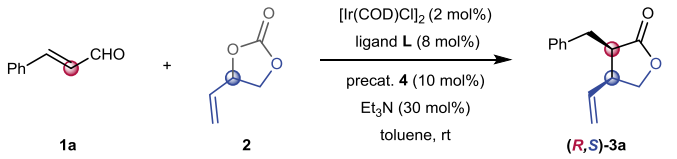
Fig. 1. Examples of γ-Butyrolactones and their synthesis by NHC organocatalysis. **a**, NHCs as ligands for transition metals or as organocatalysts in cooperative catalytic systems. **b**, representative examples of naturally-occurring γ-butyrolactones. **c**, synthesis of β,γ-disubstituted γ-butyrolactones via homoenolate intermediates. **d**, our design principle towards the synthesis of α,β-disubstitued γ-butyrolactones via NHC/Ir dual catalysis (this work). Coloured circles highlight atoms where key stereocentres are formed. TM, transition metal.

Results

Optimization studies

In order to test the validity of our hypothesis, the reaction of *trans*-cinnamaldehyde **1a** and vinylethylene carbonate (VEC) **2**, in presence of widely used triazolium NHC precatalyst **4a**, was used as a starting point. At the outset of our studies, we anticipated that the main challenge would be the identification of an appropriate ligand for the metal catalyst. Thus, we turned our attention towards ligands that have been used extensively in Ir-catalysed allylic alkylation. However, when using phosphoramidite **L1** no formation of the desired product was observed (Table 1, entry 1).[40] Encouragingly, the use of (P-olefin)-ligand **L2**, developed by Carreira,[41] afforded the desired enolate

addition product **3a** (*cis*-lactone as the major product), albeit in low yield and with low diastereoselectivity, but with high enantioselectivity (entry 2). Further screening of different (P-olefin)-ligands in combination with NHC precatalysts (entries 3-6), uncovered SPINOL derived ligand **L4** and NHC precatalyst **4c** as the optimal combination for the generation of the desired *cis*-lactone **3a** in good yield (78%), and with excellent diastereo- and enantioselectivity (entry 6).



Entry	Precat.	Ligand	Yield **3a** (%)	dr	ee (%)
1	**4a**	**L1**	0	-	-
2	**4a**	**L2**	12	75:25	99
3	**4a**	**L3**	11	91:9	>99
4	**4b**	**L3**	48	94:6	99
5	**4c**	**L3**	47	>95:5	97
6	**4c**	**L4**	78	>95:5	>99

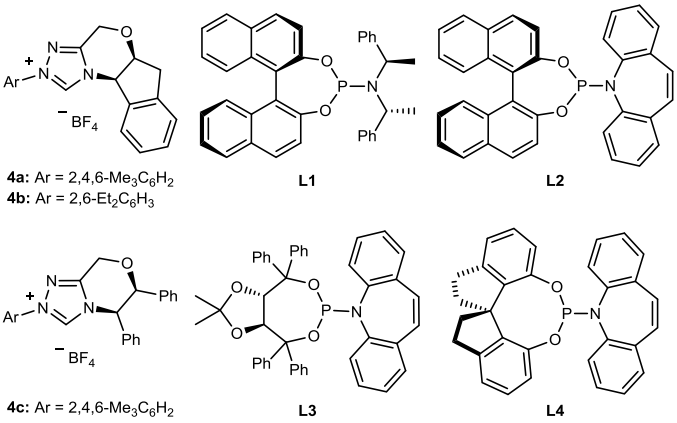


Table 1. Reaction optimization. Reaction conditions: to a solution of $[Ir(COD)Cl]_2$ (2 mol%), ligand (8 mol%) and NHC precatalyst (10 mol%) in toluene (0.1 M) under Ar, were added **1a** (0.15 mmol), **2** (0.1 mmol) and Et_3N (30 mol%). The reaction was stirred for 48 h. Yield and diastereomeric ratio (dr) were determined by GC. Enantiomeric excess (ee) was determined by chiral GC. rt, room temperature; COD, 1,5-cyclooctadiene; precat., precatalyst.

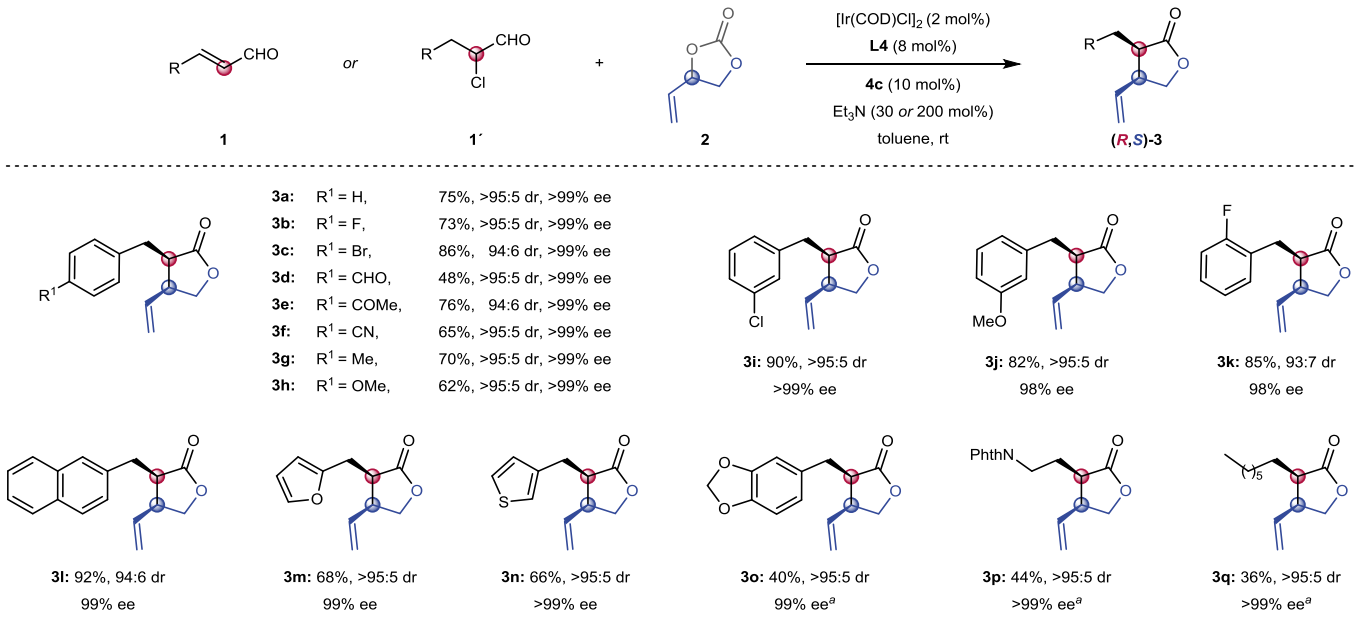


Fig. 2. Scope of the *cis*-selective [3+2] annulation reaction. Reaction conditions: to a solution of $[Ir(COD)Cl]_2$ (2 mol%), **L4** (8 mol%) and **4c** (10 mol%) in toluene (0.1 M) under Ar, were added **1** or **1´** (0.3 mmol), **2** (0.2 mmol) and Et_3N (30 mol% for **1** or 200 mol% for **1´**). The reaction was stirred for 48-96 h. Yields of isolated *cis*-lactone product are shown. The dr was determined by GC or ^1H NMR analysis of crude reaction mixture. The ee was determined by chiral HPLC or chiral GC. [a] Using the corresponding α-chloro aldehyde. NPhth, phthalimide.

cis-α,β-disubstituted-γ-butyrolactones via [3+2] annulation

Having established the optimized conditions, we explored the generality of our dual catalytic system (Fig. 2). First, a diverse array of aryl enals was examined: both electron-donating, and electron-withdrawing groups (R^1) in the *para* position of the phenyl ring were well tolerated and delivered the corresponding [3+2] annulated products (**3a**-**3h**) in good yields, with excellent diastereoselectivity (94:6 to >95:5 dr) and enantioselectivity (>99% ee). As shown by examples **3i**-**3k**, substituents at the *meta*- and *ortho*-position were also tolerated, and polyaromatic- and heteroaryl-substituted enals were compatible, as well (**3l-3n**). Longer reaction times and failure to reach full conversion were observed when using electron-rich enals as substrates. However, this could be easily circumvented by using the corresponding α-chloro aldehydes, which are more

reactive starting materials for the generation of NHC-enolates,[42] as exemplified by **3o**. The poor reaction outcome for aliphatic enals could be overcome in a similar fashion (**3p** and **3q**). The absolute configuration of **3c** was determined by analogy to that of derivative **3c'**, which was established by single-crystal diffraction analysis (see Supplementary Methods 6 and Supplementary Fig. 7).

Diastereodivergent [3+2] annulation

In order to harness our design principle for the diastereodivergent synthesis of γ-lactones, we investigated if it was possible to access the *trans*-diastereomer of **3a** by simply taking the enantiomer of the (P-olefin)-ligand **L4** while keeping the same enantiomer of NHC **4c**. However, the desired diastereoselectivity switch was not observed, and instead the *trans*-isomer was still obtained as the minor product (*cis*:*trans* = 54:46). After screening different NHC precatalysts, we found that NHC precatalyst **4a**, having a chloride counter anion, with **ent-L4** was able to induce the desired diastereoselectivity switch, providing the *trans*-isomer as the major product. It is worth mentioning that, in general, NHC precatalysts with chloride counter anions showed superior reactivity compared to the corresponding NHC precatalysts bearing BF_4 counter anions (Supplementary Table 2). Next, the generality of the stereodivergency was demonstrated by the synthesis of all four isomers of γ-lactone **3a** using the four possible combinations of NHC precatalyst **4a**(Cl) with (P-olefin)-ligand **L4** (Fig. 3). The scope of the diastereodivergent transformation was explored with respect to the aldehyde counterpart, for which a variety of functional groups were well tolerated, affording the desired *cis*- or *trans*-lactones in good yields (Fig. 4a).

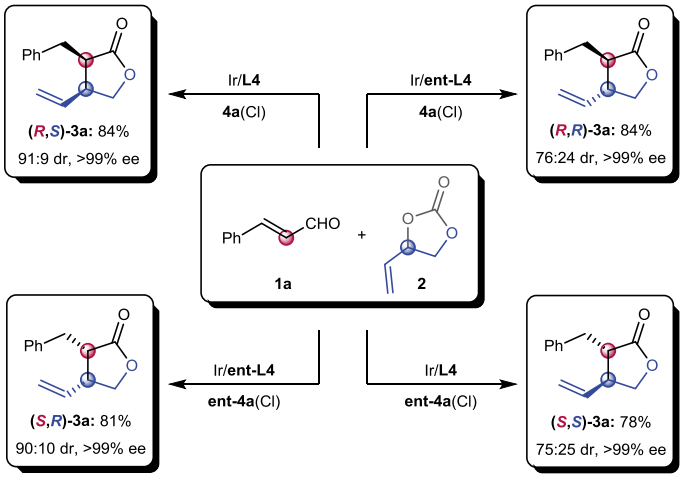


Fig. 3. Diastereodivergent synthesis of all four isomers of γ-butyrolactone 3a. Reaction conditions: to a solution of $[Ir(COD)Cl]_2$ (2 mol%), **L4** or **ent-L4** (8 mol%), **4a** or **ent-4a**(Cl) in toluene (0.1 M) under Ar, were added **1a** (0.3 mmol), **2** (0.2 mmol) and NMM (30 mol%). The reaction was stirred for 24 h. Isolated product yields (*cis*- and *trans*-isomers together) are shown. The dr was determined by GC analysis of crude reaction mixtures. The ee was determined by chiral GC. NMM, *N*-methylmorpholine.

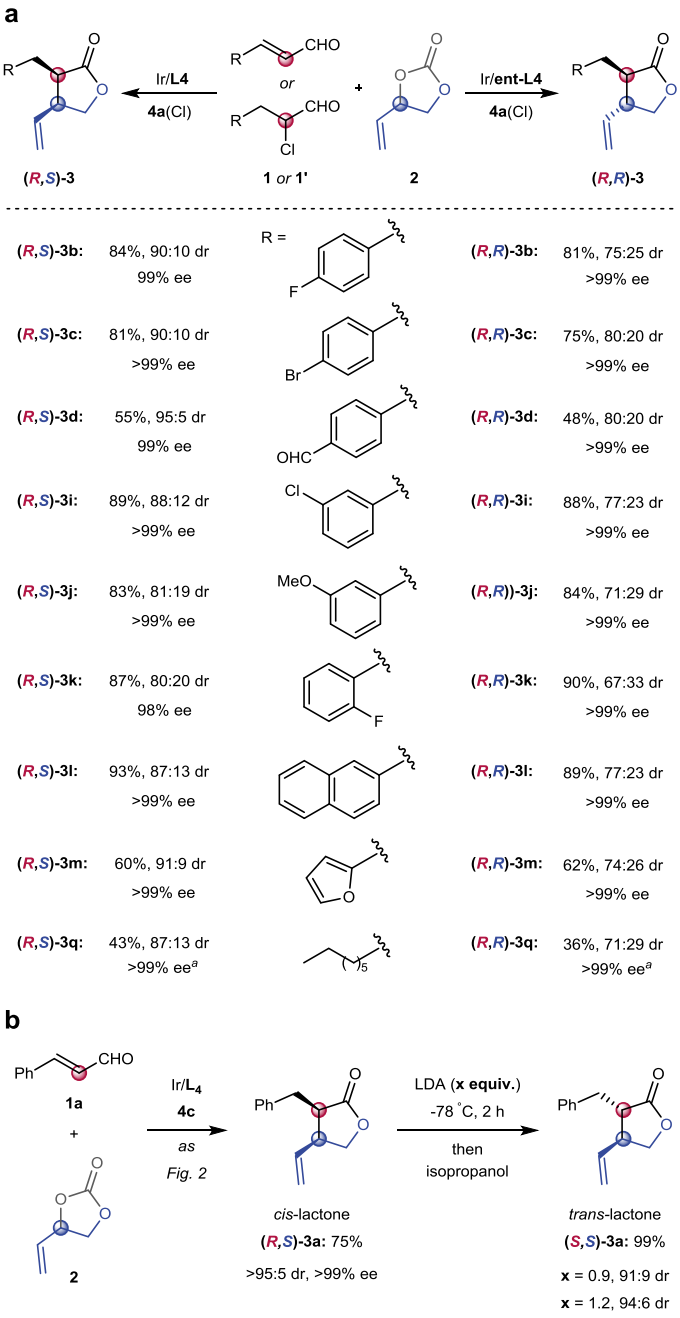


Fig. 4. Diastereodivergent [3+2] annulation reaction and isomerization of *cis*-lactones. a, Scope of the diastereodivergent [3+2] annulation reaction giving access to *cis*- or *trans*- γ-lactones. Reaction conditions: to a solution of $[Ir(COD)Cl]_2$ (2 mol%), **L4** or **ent-L4** (8 mol%) and **4a**(Cl) (10 mol%) in toluene (0.1 M) under Ar, were added **1** or **1´** (0.3 mmol), **2** (0.2 mmol) and NMM (30 mol% for **1** or 200 mol% for **1´**). The reaction was stirred for 24 h. Isolated product yields (*cis*- and *trans*-isomers together) are shown. The dr was determined by ^{1}H NMR analysis of crude reaction mixture. The ee was determined by chiral HPLC or chiral GC. [a] Using the corresponding α-chloro aldehyde. **b**, Isomerization of *cis*-lactones to *trans*-lactones under basic conditions (see Supplementary Methods 5 for details).

As shown in Fig. 3 and Fig. 4a, the *cis*-lactone products are formed with excellent diastereoselectivity, whereas the corresponding *trans*-lactones have a slightly lower selectivity using the current set of optimized conditions for the [3+2] annulation reactions. To overcome this shortcoming, we reasoned that *trans*-lactones could alternatively be obtained with high diastereoselectivity via a separate isomerization reaction of the corresponding *cis*-lactones, under basic conditions, as the *trans*-isomer is likely to be thermodynamically and kinetically more favoured. Indeed, when *cis*-lactone **3a** was treated with lithium diisopropylamide (LDA) (under both thermodynamic and kinetic conditions), the *trans*-lactone was obtained with high diastereoselectivity, offering an attractive and alternative route for the synthesis of *trans*-lactones with high diastereoselectivity (Fig. 4b).

Access to *δ*-lactams via [4+2] annulation

The developed dual NHC/Ir catalytic system is also amenable to the synthesis of *δ*-lactams by using *N*-benzoyl-protected vinyl benzoxazinanones as substrates (Fig. 5). Due to a mismatch in kinetics, sluggish reactions were observed when using enals as substrates, as the carbamate substrate rearranged to the corresponding *N*-benzoyl-1,2-dihydroquinoline via the much faster iridium catalysed allylic rearrangement. To minimize this side-reaction, *α*-chloro hydrocinnamaldehyde was used as substrate for the organocatalytic cycle. Various substituents at different positions of the benzoxazinanone were tolerated and the corresponding products **6aa-6ae** were obtained in low to moderate yields, but with good diastereoselectivity and excellent enantioselectivity (>99% ee). The absolute configuration of **6ab** was determined by single crystal diffraction analysis. The diastereodivergent synthesis of *δ*-lactams could also be achieved, albeit with low yield (20%) and

moderate diastereoselectivity (*trans*:*cis* = 75:25), yet very high enantioselectivity (98%) by using **ent-L4** as the ligand to form *trans*-*δ*-lactam **(*R,R*)-6aa** (see Supplementary Methods 4.5)

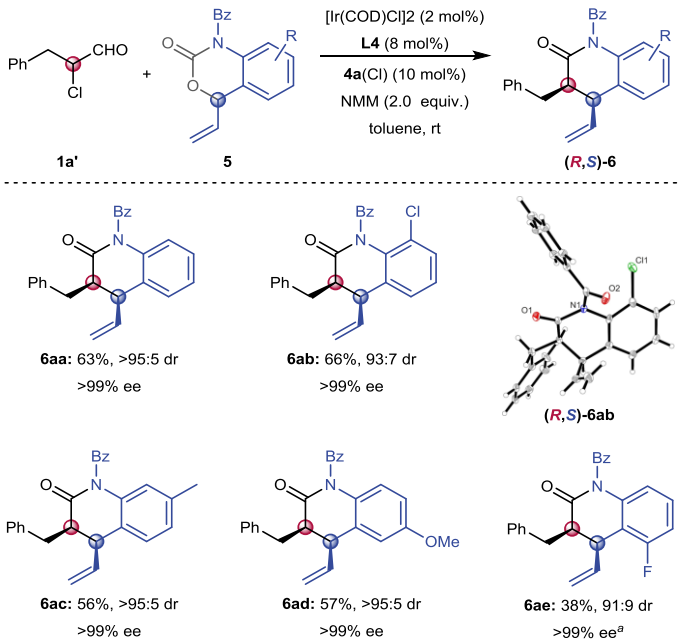


Fig. 5. Scope of the [4+2] annulation for the formation of *cis*-*δ*-lactams. Reaction conditions: to a solution of $[Ir(COD)Cl]_2$ (2 mol%), **L4** (8 mol%) and **4c**(Cl) (10 mol%) in toluene (0.1 M) under Ar, were added **1a´** (0.3 mmol), **5** (0.2 mmol and NMM (200 mol%). The reaction was stirred for 12 h. Yields of isolated *cis*-*δ*-lactam product are shown. The dr was determined by ^{1}H NMR analysis of crude reaction mixtures. The ee was determined by chiral HPLC. [a] The reaction mixture was stirred for 48 hours. Bz, benzoyl.

Application to the synthesis of natural lignan (−)-hinokinin

The synthetic utility of our dual catalytic process was demonstrated by applying this methodology to the total synthesis of naturally occurring lignan (−)-hinokinin, which displays anti-inflammatory, antimicrobial,[43] and modulatory effects on human GABA transporter activities[44] (Fig. 6). Starting from *α*-chloro aldehyde **1o´** and vinylethylene carbonate **2**, *trans*-lactone **(*R,R*)-3o** was obtained in good yield and with excellent enantioselectivity. Alternatively, **(*R,R*)-3o** can also be obtained in quantitative yield by isomerization of **(*S,R*)-3o** upon treatment with LDA with excellent levels of

diastereoselectivity (>95:5 dr) (see Supplementary Methods 7). Next, dihydroxylation of the double bond followed by oxidative cleavage furnished aldehyde **7**. The required benzodioxole substituent was introduced via a Nozaki-Hiyama-Kishi reaction of **7** with aryl iodide **8** to generate an epimeric mixture of alcohols (**9**).[45] Finally, hydrogenolysis of the C–OH bond using Pd/C as catalyst, afforded (−)-hinokinin (**10**) in overall good yield and with excellent enantioselectivity.

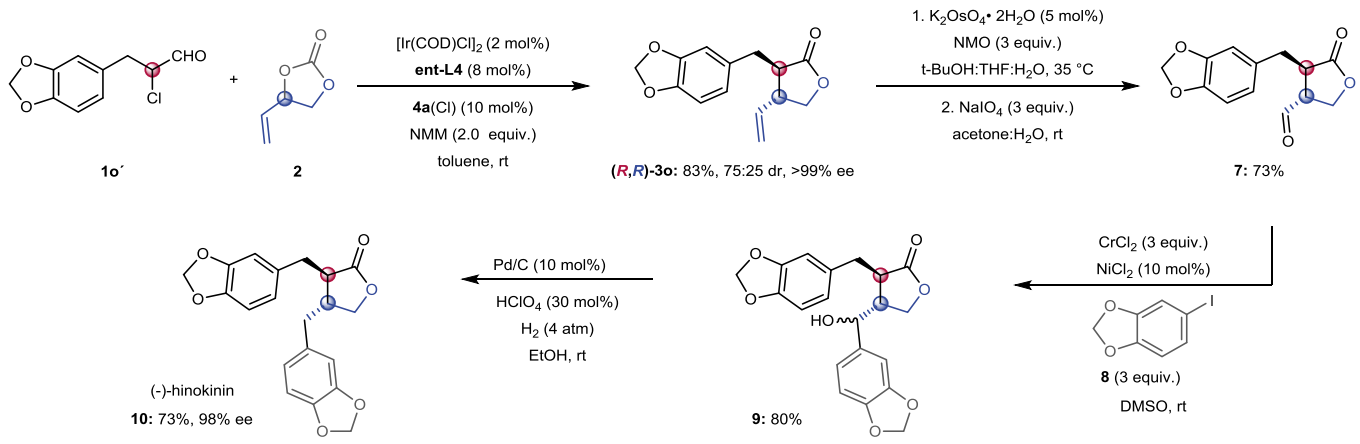


Fig. 6. Application of the [3+2] annulation to the synthesis of (−)-hinokinin. See Supplementary Methods 7 for experimental details. NMO, *N*-methylmorpholine-*N*-oxide.

Discussion

Mechanistic studies

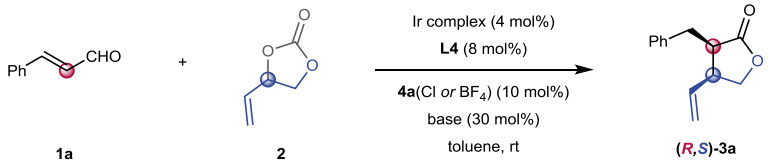
A series of experiments was carried out to gain insight into the active Ir species involved in the dual NHC/Ir catalysed transformation (Fig. 7a). A striking counter-anion effect was observed as reactivity was only obtained when using either an Ir precatalyst containing chloride anions, or an NHC precatalyst with chloride counter anions, or both. For example, when $Ir(COD)_2BF_4$ in presence of NHC precatalyst **4a** with BF_4 as counter anion was used, no reaction occurred (entry 1). Interestingly, reactivity could be re-established when the reaction was carried out in presence of sub-stoichiometric amounts of tetrabutyl ammonium chloride (TBACl), or when **4a**(Cl) was used as

the NHC precatalyst (entries 2 & 3). These results could indicate the necessity of a coordinating anion in the reaction mixture that can bind to the Ir centre. Next, the effect of the Ir:(P-olefin)-ligand:NHC ratio was investigated: while moderate yields were observed when using a 1:1 ratio of Ir:(P-olefin)-ligand, optimal results in terms of yield and selectivity were obtained with a 1:2 ratio (Supplementary Table 5). This result prompted us to investigate the catalytic competency of different Ir species. The use of isolated Ir(**L4**)$_2$Cl (complex **11**) in catalytic amounts, and otherwise identical reaction conditions, provided compound **3a** in a similar outcome as for the standard reaction conditions (Fig. 7a, entry 4); however, in a separate experiment ligand exchange was observed between complex **11** and NHC **4a** to form Ir(**L4**)(**4a**)Cl (complex **12**) (see Supplementary Methods 8.6). Indeed, in-situ generated complex **12** led to the formation of **3a** when carrying out the reaction in presence of 10 mol% NHC precatalyst **4a**(Cl) (entry 5) but no product was observed in absence of the latter (entry 6). Interestingly, no reaction occurred when Ir(**4a**)(COD)Cl (complex **13**) was used in catalytic amounts, in the presence of 8 mol% **L4** and under otherwise identical reaction conditions (entry 7).[46-48]

Based on these preliminary mechanistic investigations, we propose the reaction to begin with the formation of (*Z*)-enol intermediate **B** from α,β-unsaturated aldehyde via homoenolate formation followed by facile β-protonation[49] (or from α-chloroaldehydes via base-mediated elimination of chloride[42]) (Fig. 7b). When **4a**(Cl) is used as NHC precatalyst, the *re*-face of the formed enolate intermediate is shielded by the substituents on the NHC. In the second catalytic cycle, initial formation of Ir(**L4**)$_2$Cl is followed by ligand exchange to generate Ir(**L4**)(**4a**)Cl, which is tentatively proposed as the catalytically active species. Upon Ir-mediated decarboxylation, VEC **2** forms the iridium π-allyl intermediate **C**, which was identified by ESI-MS analysis of crude reaction mixtures (see Supplementary Methods 8.7). By analogy to DFT calculations by Sunoj and co-workers,[50] the

re-face of intermediate **C** would be shielded, making the *si*-face available to nucleophilic attack when **L4** is used as ligand. Finally, nucleophilic attack from enolate **B** to the branched position of the Ir-π-allyl moiety of **C** via an open transition state **D**, followed by lactonization of the acyl azolium species **E** delivers **(*R*,*S*)-3** and regenerates the free NHC and Ir catalysts.

a



Entry	Ir complex	NHC Precat.	Base	Deviation	Yield **3a** (%)	dr	ee (%)
1	$Ir(COD)_2BF_4$	**4a**(BF_4)	Et_3N	-	0	-	-
2	$Ir(COD)_2BF_4$	**4a**(BF_4)	Et_3N	TBACl (10 mol%) added	45	>95:5	>99
3	$Ir(COD)_2BF_4$	**4a**(Cl)	Et_3N	-	71	94:6	>99
4	Ir(**L4**)$_2$Cl	**4a**(Cl)	NMM	no **L4**	88	82:12	>99
5	Ir(**L4**)(**4a**)Cl	**4a**(Cl)	Et_3N	no **L4**	52	91:9	>99
6	Ir(**L4**)(**4a**)Cl	-	Et_3N	no **L4**	0	-	-
7	Ir(**4a**)(COD)Cl	**4a**(Cl)	NMM	-	0	-	-

b

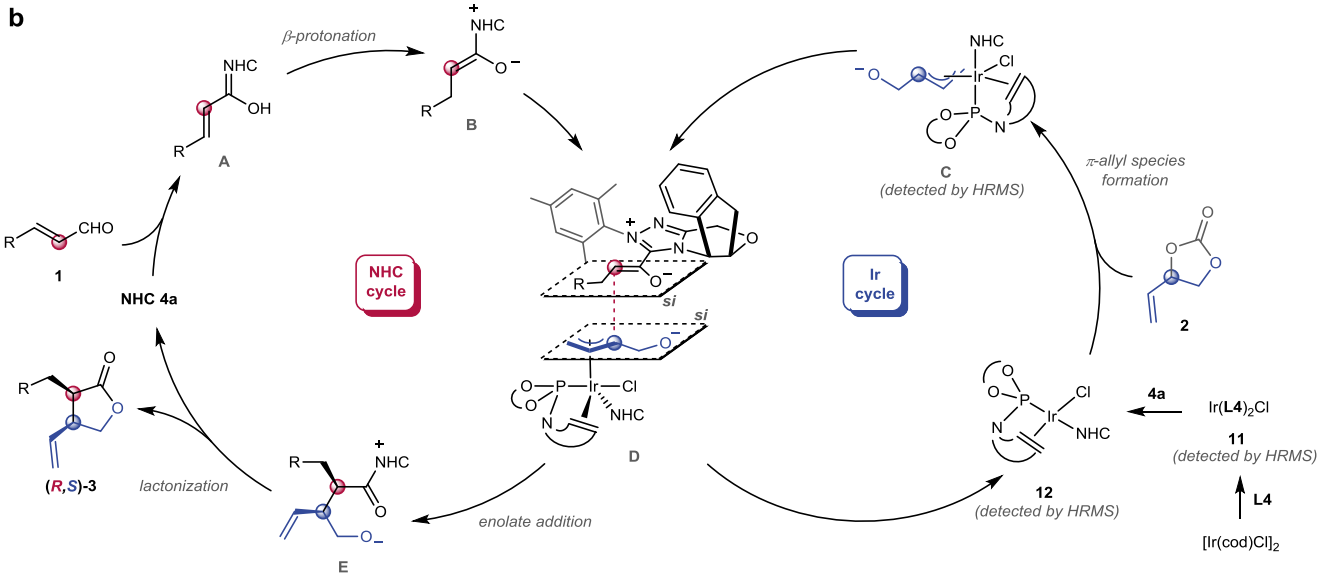


Fig. 7. Mechanistic insights into the [3+2] annulation: a, Effect of the counter-anion and Ir complexes on the reaction outcome. Reaction conditions: to a solution of Ir complex (4 mol%), **L4** (8 mol%) and **4a** (10 mol%) in toluene (0.1 M) under Ar, were added **1a** (0.15 mmol), **2** (0.1 mmol) and base (30 mol%). The reaction was stirred for 24 h. Yield and dr were determined by GC. ee was determined by chiral GC. **b**, Proposed NHC/Ir dual catalytic cycle for the formation of α,β-disubstituted-γ-butyrolactones.

Conclusion

In conclusion, we have developed a cooperative process that merges NHC organocatalysis with Ir catalysis. The success of this cooperative system stems from the careful selection of the appropriate set of NHC organocatalyst and ligand for the iridium catalyst. Our method grants control over the absolute and relative stereochemistry of the two newly-formed stereocentres, thereby giving access to all four isomers of the γ-butyrolactone motifs in a predictable manner. The products obtained from this stereodivergent [3+2] annulation are valuable motifs that are present in the core of numerous natural products. The practical utility of the developed methodology has been illustrated by applying it to the synthesis of the lignan (−)-hinokinin. Importantly, the possibility of merging NHC-bound nucleophiles with transition-metal activated electrophiles using a metal other than Pd has been demonstrated. We hope that our study will aid the development of dual catalytic systems based on transition metal/organocatalysis, and enable the discovery of new stereodivergent asymmetric transformations.

Methods

General procedure for cooperative NHC/Ir catalysed [3+2] and [4+2] annulation reactions.

A flame-dried Schlenk tube equipped with a magnetic stir bar was charged with the indicated NHC precatalyst (0.02 mmol, 10 mol%). Then the Schlenk tube was taken into a glove box and charged with $[Ir(COD)Cl]_2$ (0.004 mmol, 2 mol%) and P-olefin ligand (0.016 mmol, 8 mol%). Outside the glovebox, toluene (2.0 mL, 0.1 M) was added to the Schlenk tube under positive pressure of argon and the solution was stirred for 3-4 minutes. After that, enal **1** or α-chloro aldehyde **1´** (0.3 mmol, 1.5 equiv.) were added. Next, for the [3+2] annulation reaction, vinyl carbonate **2** (0.2 mmol, 1.0 equiv.) or for the [4+2] annulation, vinyl carbamate **5** (0.2 mmol, 1.0 equiv.) was added, followed

by Et_3N or NMM (0.06 mmol, 30 mol% for enals or 0.4 mmol, 200 mol% for α-chloro aldehydes). The resulting mixture was stirred at room temperature for the specified time. After the reaction was over, the reaction mixture was filtered through a small pad of silica and washed with EtOAc. The diastereomeric ratio was determined by ^1H NMR or GC analysis of crude reaction mixture. Purification by silica gal column chromatography afforded the desired lactone **3** or lactam **6**. (See Supplementary Methods 4 for more details on experimentation and characterization data.)

Data availability

Crystallographic data for the structures reported in this Article have been deposited at the Cambridge Crystallographic Data Centre, under deposition numbers CCDC Nr.: 1907670 (**(*R*,*S*)-3c′**) and CCDC Nr.: 1907671 (**(*R*,*S*)-6ab**). Copies of the data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/. All other data supporting the findings of this study are available within the Article and its Supplementary Information, or from the corresponding author upon reasonable request.

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S. S., E. S., S. M., and F. G. designed, performed and analysed the experiments. C. G. D. performed the crystallographic studies. S. S., E. S. and F. G. co-wrote the manuscript. All authors contributed to discussions.

Competing interests

The authors declare no competing interests.

Additional information

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