nature communications

Article

https://doi.org/10.1038/s41467-025-67390-4

Concise synthesis of chiral tricyclic γ-lactams via synergistic isothiourea/Ir catalyzed asymmetric [3 + 2] annulation

Received: 16 September 2025

Accepted: 28 November 2025

Published online: 07 December 2025

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Accessing *trans*-fused *N*-fused tricyclic frameworks with multiple contiguous stereocenters remains a major challenge in synthesis. We report a synergistic isothiourea/Ir-catalyzed [3 + 2] annulation of arylacetic acid esters with azabenzonorbornadienes, providing *trans*-fused tricyclic γ-lactams with three contiguous tertiary stereocenters in high regio-, enantio-, and diastereoselectivity. The method tolerates diverse arylacetates, heterocycles, and pharmaceutically relevant carboxylates, and is amenable to gram-scale synthesis. Mechanistic studies support a cooperative cycle involving C1-ammonium enolate formation and enantioselective S_N2' attack on the Ir-activated azabenzonorbornadiene. Downstream functionalizations, including epoxidation, hydrogenation, and amino alcohol formation, demonstrate the versatility of the products. This work establishes a concise and efficient platform for constructing sterically challenging *trans*-fused tricyclic γ-lactams, highlighting the potential of synergistic catalysis for complex stereocontrolled transformations.

The stereoselective construction of fused heterocyclic architectures is of great importance in pharmaceutical research, as their three-dimensional complexity imparts distinct physicochemical and biological properties[1–3]. Among these, chiral *N*-fused tricyclic frameworks represent privileged scaffolds in natural products, bioactive molecules, and catalysts, exemplified by strigolactam, carboxylic acid receptors, rivastigmine analogs, and chiral NHC precursors (Fig. 1A)[4–7]. Conventional approaches to *N*-fused tricyclic skeletons bearing multiple stereocenters, particularly chiral tricyclic γ-lactams, typically rely on multistep de novo synthetic routes that are both laborious and resource-intensive[8]. Recently, Zhang and co-workers reported a direct ruthenium-catalyzed tandem dynamic kinetic resolution (DKR)/asymmetric reductive amination (ARA)/lactamization of ketoesters with ammonium salts, which furnishes *cis*-fused tricyclic lactams in a single step but requires high-pressure hydrogen gas and offers limited modularity (Fig. 1B)[9]. Given the broad utility of these structurally complex motifs, the development of efficient and general synthetic strategies to access chiral tricyclic γ-lactams from readily available starting materials remains a critical goal.

Synergistic catalysis has emerged as a powerful platform for the stereoselective construction of structurally complex molecules[10–15]. Over the past two decades, isothiourea (ITU) catalysis has become a particularly versatile organocatalytic strategy, enabling significant advances in asymmetric transformations, especially in synergistic settings[16,17]. Since the seminal report by Snaddon and co-workers in 2016[18], synergistic catalysis involving chiral C(1)-ammonium enolates—generated via ITU-catalyzed substitution of electron-deficient aryl esters followed by deprotonation—has driven remarkable progress in the asymmetric functionalization of esters (Fig. 1C). A wide range of electrophiles, including η^3-allyl species and imines, have been successfully coupled through synergistic ITU/transition-metal and ITU/organocatalysis, affording chiral α-functionalized esters[19–30]. Despite these achievements, synergistic annulative transformations for the construction of pharmaceutically preferred chiral heterocycles remain largely underexplored[31,32]. Thus, expanding the scope of ITU-mediated synergistic catalysis to efficiently access pharmaceutically relevant heterocycles is highly desirable.

Strained azabicyclic olefins, particularly azabenzonorbornadienes—a distinctive subclass defined by a bridgehead nitrogen atom and an

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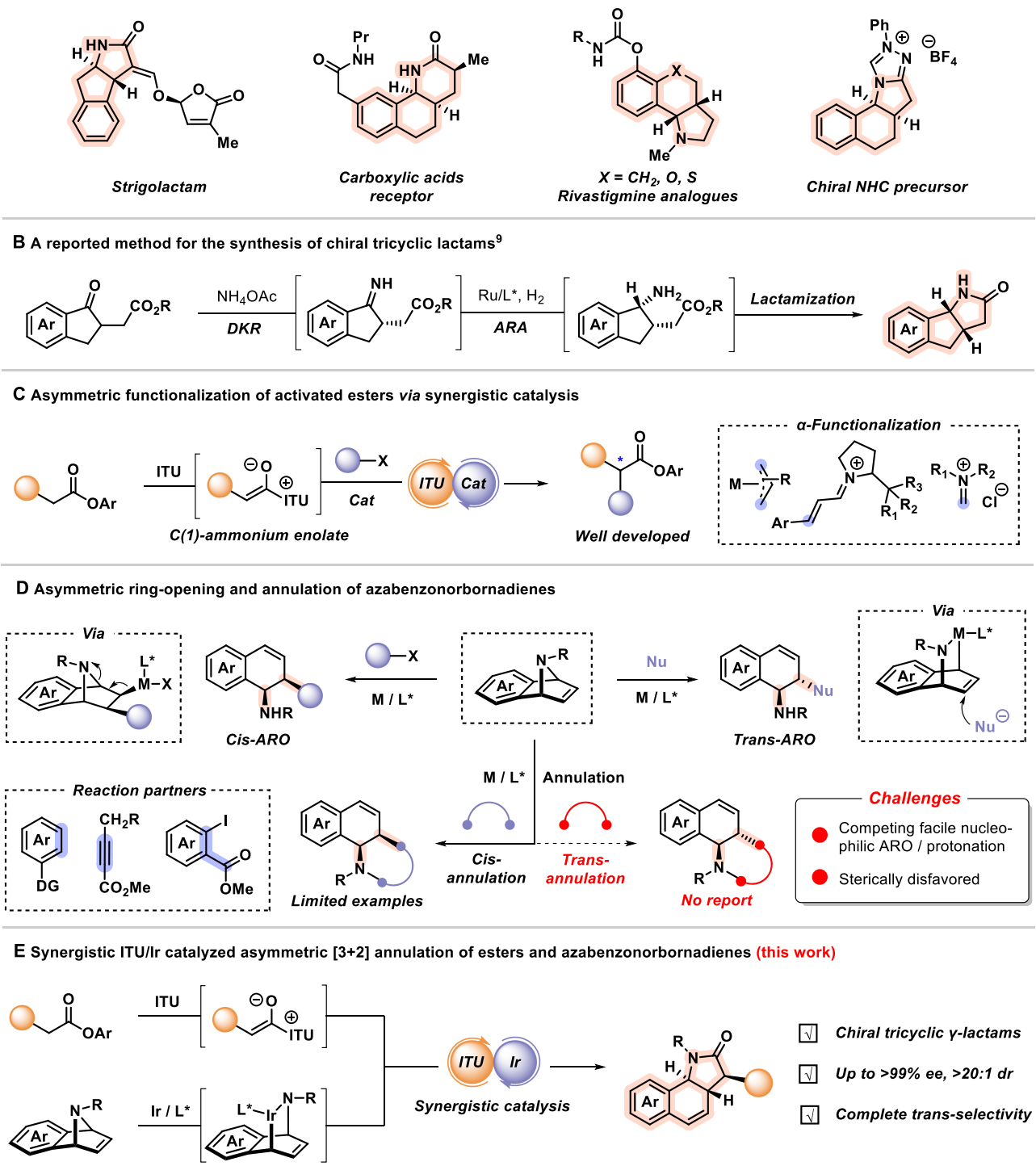

Fig. 1 | Background and reaction development. A Chiral N-fused tricyclic scaffold as a privileged motif in functional molecules. **B** A reported method for the synthesis of chiral tricyclic lactams[9]. **C** Asymmetric functionalization of activated esters via synergistic catalysis. **D** Asymmetric ring-opening and annulation of azabenzonorbornadienes. **E** Synergistic ITU/Ir catalyzed asymmetric [3 + 2] annulation of esters and azabenzonorbornadienes (this work).

internal C = C bond—offer powerful platforms for complexity generation through transition-metal-catalyzed asymmetric ring-opening (ARO) reactions (Fig. 1D)[33–35]. The bridgehead nitrogen and olefin moieties enable metal coordination and promote selective C–N bond cleavage, while the substantial ring strain (~5.2kcal/mol) arising from shortened bond distances renders the ring-opening process energetically favorable[34]. Mechanistically, this transformation can proceed via carbometallation followed by β-heteroatom elimination to afford *cis*-ring-opening products[36–49], or through oxidative C–N insertion followed by S_N2' nucleophilic displacement to yield *trans*-ring-opening products (Fig. 1D, top)[50–63]. To date, only three examples of asymmetric annulation of azabenzonorbornadienes have been reported, employing organic halides, alkynes, or directing-group (DG)-arenes as coupling partners[64–66]. These strategies, integrating asymmetric ring-

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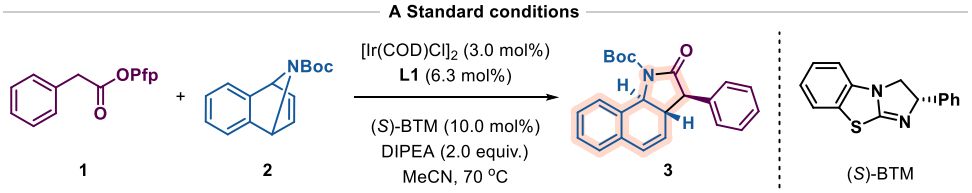

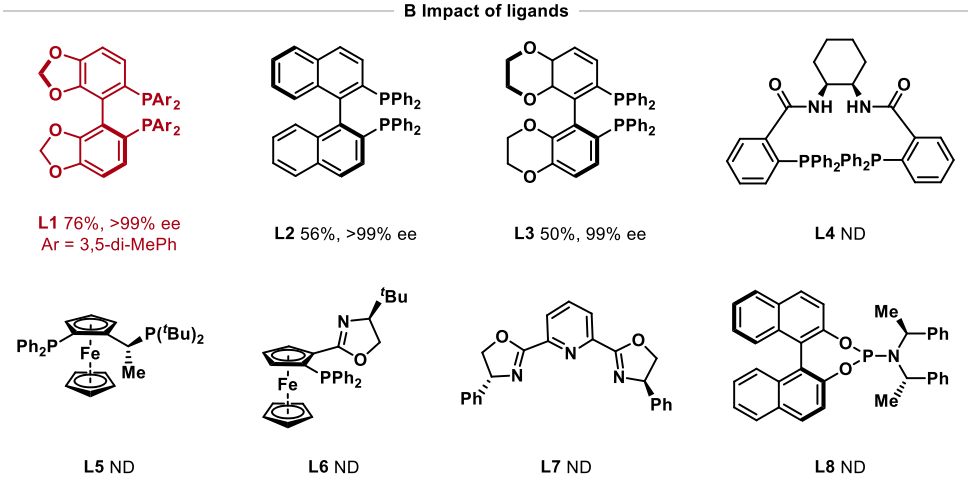

C Impact of reaction condition

Entry	Change in reaction conditions	yield (%)[a]	ee (%)[b]
1	**none**	**76**	**>99**
2	rt or 40 °C instead of 70 °C	ND	/
3	DCE instead of MeCN	ND	/
4	THF instead of MeCN	ND	/
5	DMSO instead of MeCN	ND	/
6	Cu, Co, Rh, Ni, Pd, Ru instead of Ir	ND	/
7	1% instead of 3% $[Ir(COD)Cl]_2$	14	>99
8	5% (*S*)-BTM instead of 10% (*S*)-BTM	56	>99
9	(*R*)-BTM instead of (*S*)-BTM	50	90
10	w/o $[Ir(COD)Cl]_2$ and **L1**	ND	/
11	w/o (*S*)-BTM	35	>99
12	w/o DIPEA	22	>99

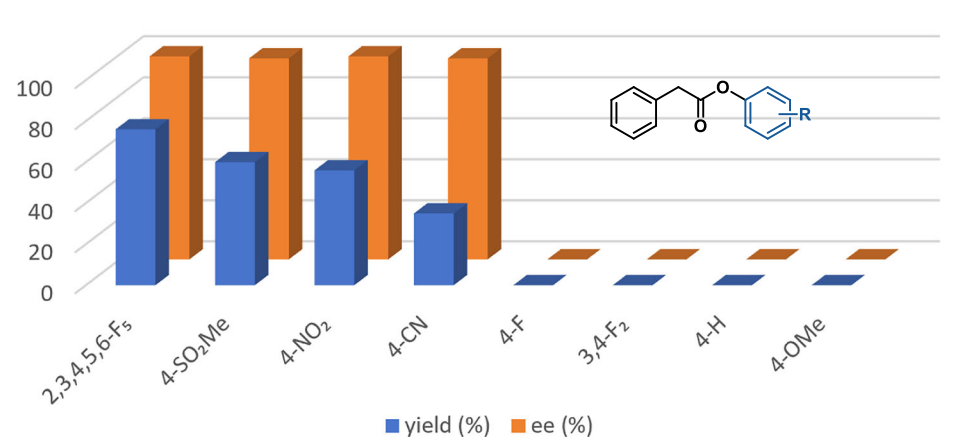

Fig. 2 | Optimization of reaction parameters. A Standard conditions. **B** Impact of ligands. **C** Impact of reaction condition. **D** Impact of leaving group of esters. Reaction conditions: **1** (0.2 mmol, 1.0 equiv.), **2** (0.44 mmol, 2.2 equiv.), $[Ir(COD)Cl]_2$ (3.0 mol%), **L1** (6.3 mol%), (*S*)-BTM (10.0 mol%), DIPEA (2.0 equiv.), MeCN (2.0 mL), 70 °C, 10 h. [a] Isolated yield. [b] The enantiomeric excess (ee) was determined by HPLC analysis. See Section VI in the SI for complete screening details.

opening with oxidative insertion, oxidative cyclization, or transition-metal-catalyzed C–H activation, exclusively afford *cis*-fused annulated products. Despite this progress, the asymmetric construction of sterically disfavored *trans*-fused frameworks remains elusive, hindered by competing facile nucleophilic ARO/protonation pathways and the substantially higher ring strain of *trans*-fusion (Fig. 1D, bottom). Consequently, the development of a general catalytic asymmetric strategy to access enantio- and diastereoselectively enriched *trans*-fused

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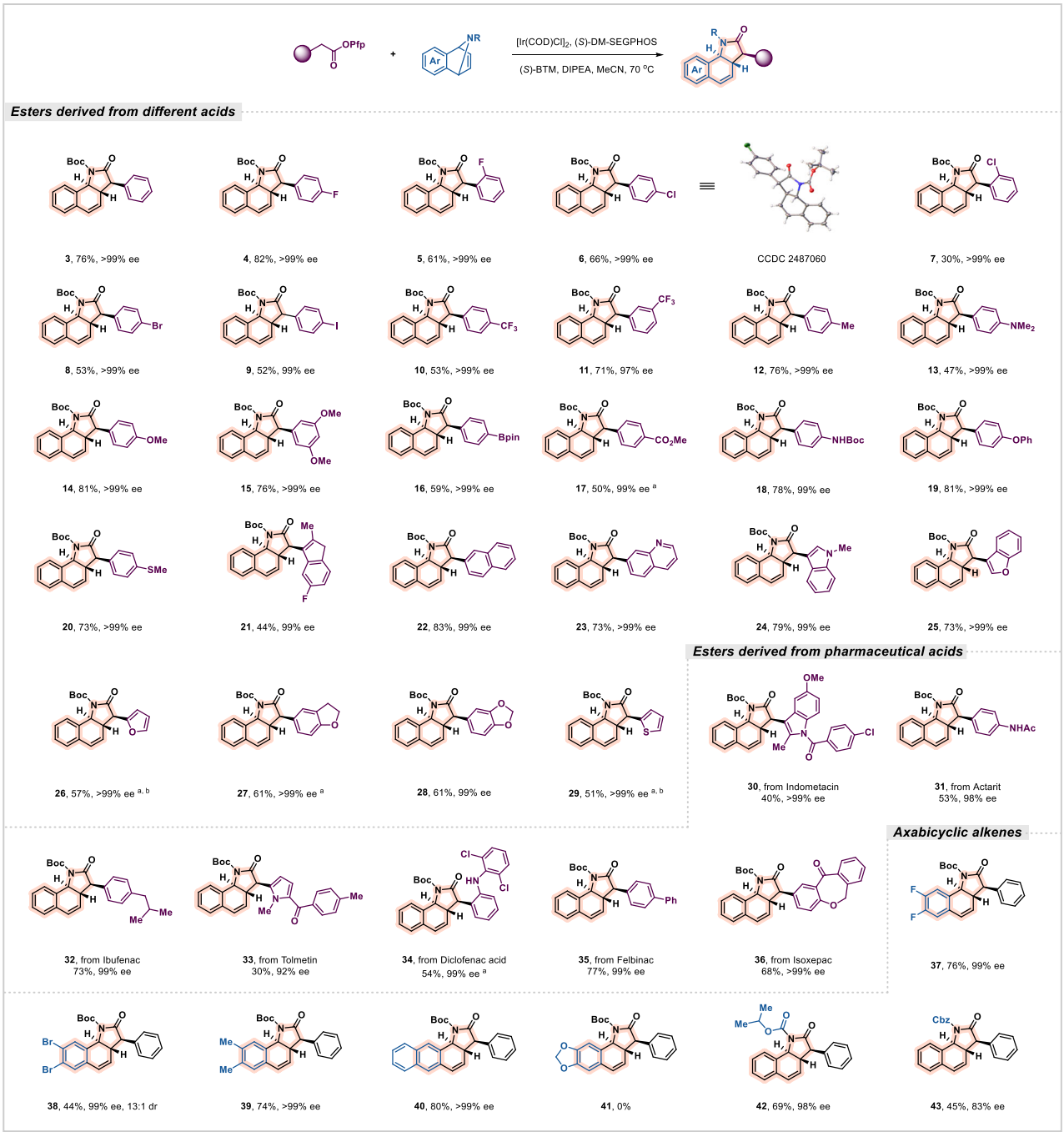

Fig. 3 | Substrate scope of the asymmetric [3 + 2] annulation. Reaction conditions: **1** (0.2 mmol, 1.0 equiv.), **2** (0.44 mmol, 2.2 equiv.), $[Ir(COD)Cl]_2$ (3.0 mol%), **L1** (6.3 mol%), (*S*)-BTM (10.0 mol%), DIPEA (2.0 equiv.), MeCN (2.0 mL), 70 °C, 10 h. Isolated yield. Unless otherwise noted, all products were obtained with > 20:1 *dr*. [a] (*S*)-BINAP instead of (*S*)-DM-SEGPHOS. [b] After recrystallization. See Section IV in the SI for complete details.

products from azabenzonorbornadienes represents a compelling and unmet challenge.

Building on the sustained interest in strained oxa/azabicyclic alkenes[67] and the growing potential of synergistic catalysis, we now disclose a general asymmetric [3 + 2] annulation of actived arylacetic acid esters with azabenzonorbornadienes, enabled by synergistic ITU/Ir catalysis (Fig. 1E). This strategy provides streamlined access to a broad family of *trans*-fused tricyclic γ-lactams—structural motifs that have remained synthetically elusive—bearing three contiguous tertiary stereocenters with excellent levels of regio-, and enantio-, and diastereoselectivity. The modularity of this protocol, together with its ability to forge sterically disfavored *trans*-fused architectures from readily available starting materials, highlights its potential as a powerful platform for the synthesis of pharmaceutically relevant heterocycles.

Results

Optimization studies

We initiated our investigation by employing aryl acetic acid pentafluorophenyl esters **1** and azabenzonorbornadiene **2** as model substrates in MeCN at 70 °C (Fig. 2). Under a synergistic catalytic system comprising $[Ir(COD)Cl]_2$/(*S*)-DM-SEGPHOS **(L1)** and (*S*)-BTM, with

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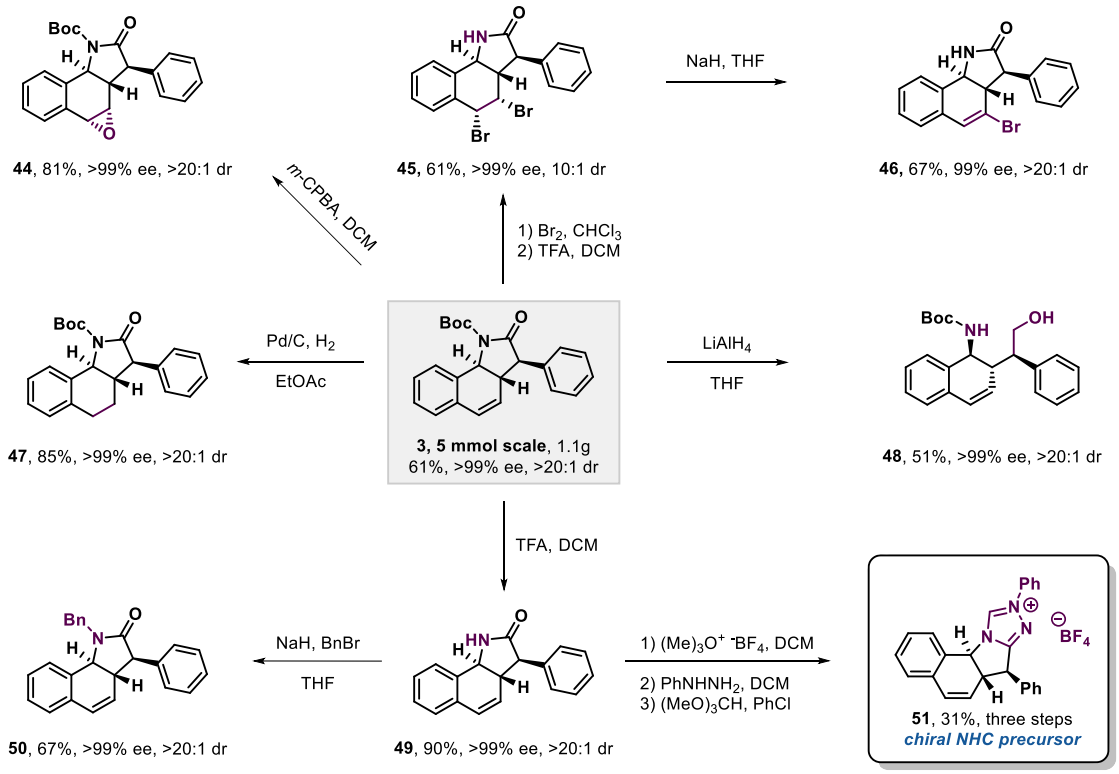

Fig. 4 | **Synthetic applications.** See Supplementary Fig. S1 in the SI for complete details.

DIPEA as the base, the asymmetric [3 + 2] annulation proceeded smoothly, delivering the chiral *trans*-fused tricyclic γ-lactam in 76% yield with excellent enan-tioselectivity (>99% ee) and diastereoselectivity (>20:1 *dr*). Alternative diphosphine ligands (**L2** and **L3**) also promoted the transformation, albeit with slightly diminished yields. In contrast, other common ligand classes—including Trost ligand (**L4**), Josiphos (**L5**), ᵗBu-Phosferrox (**L6**), Ph-Pybox (**L7**), and phosphoramidite (**L8**)—failed to catalyze the reaction, with most starting material recovered. Lowering the temperature to room temperature or 40 °C completely halted the reaction, and no conversion was observed in alternative solvents such as DCE, THF, or DMSO. Other metal precursors, including CuOTf, $Co(acac)_2$, $NiCl_2$, $Pd(OAc)_2$, $RuCl_2$, and various rhodium complexes, were also ineffective (see Supplementary Fig. S6 in the SI for details). Reducing the catalyst loading was feasible but resulted in diminished yields. Several common chiral isothiourea catalysts were also evaluated; however, none afforded promising results (see Supplementary Fig. S7 in the SI). Replacing (*S*)-BTM with (*R*)-BTM led to decreases in both yield and enantioselectivity. Control experiments confirmed that $[Ir(COD)Cl]_2$/**L1** was essential; although the reaction still proceeded without either (*S*)-BTM or DIPEA, yields were significantly reduced. Finally, evaluation of the ester leaving group revealed that only strongly electron-deficient phenol derivatives (4-SO_2Me, 4-NO_2, 4-CN) afforded the product with moderately diminished yields, whereas weakly electron-deficient (4-F, 3,4-F_2), neutral (4-H), and electron-rich (4-OMe) esters failed to promote the transformation. These results underscore the crucial role of a strongly electron-withdrawing leaving group for successful reaction outcomes.

Substrate scope

With optimized conditions in hand, we explored the substrate scope of the asymmetric [3 + 2] annulation (Fig. 3). The method tolerated a broad range of functional groups and accommodated electronically and structurally diverse pentafluorophenyl esters and azabicyclic alkenes. Arylacetates bearing electron-withdrawing groups such as halogens (F, Cl, Br, I; **4** – **9**) or -CF_3 (**10**,**11**) underwent smooth transformation. The absolute configuration of compound **6** was determined via X-ray crystallography (CCDC 2487060). Electron-rich substrates containing Me (**12**), NMe_2 (**13**), and OMe (**14, 15**) groups also reacted with excellent stereoselectivity. Notably, substrates with highly reactive functionalities—including boronic ester (**16**), ester (**17**), and NHBoc (**18**)—were compatible without significant complications. Substrates bearing OPh (**19**), SMe (**20**), or alkenyl (**21**) groups similarly furnished the desired products in high efficiency. Polycyclic and heterocyclic substrates—including naphthalene (**22**), quinoline (**23**), indole (**24**), benzofuran (**25**), furan (**26**), dihydrobenzofuran (**27**), benzodioxole (**28**), and thiophene (**29**)—also underwent the reaction with high enantioselectivity (99- > 99% ee). A range of pharmaceutically relevant carboxyla-tes, including derivatives of Indometacin (**30**), Actarit (**31**), Ibufenac (**32**), Tolmetin (**33**), Diclofenac acid (**34**), Felbinac (**35**), and Isoxepac (**36**), provided satisfactory yields. Various secondary carboxylic acid esters were also found to be ineffective (see Supplementary Fig. S9 in the SI). Symmetric azabicyclic alkenes with substituents such as F (**37**), Br (**38**), methyl (**39**), and naphthalene (**40**) underwent the desired [3 + 2] annulation in moderate to high yields with excellent stereocontrol. The benzodioxole-derived azabicyclic alkene (**41**) was unsuitable due to competitive isomerization under transition-metal catalysis[68]. Compared to Boc protection, isopropoxycarbonyl (**41**) and benzyloxycarbonyl groups (**42**) led to reduced enantioselectivity, highlighting that bulky protecting groups on the bridgehead nitrogen are crucial for achieving high enantioselectivity.

Synthetic applications

The practicality and robustness of this methodology were further demonstrated through gram-scale synthesis and diverse downstream derivatizations (Fig. 4). The gram-scale reaction of carboxylic ester **1** with azabicyclic alkene **2** afforded product **3** in 61% yield, >99% ee, and >20:1 *dr*. Epoxidation of the olefin in **3** with *m*-CPBA proceeded smoothly to give **44** without loss of stereochemical integrity.

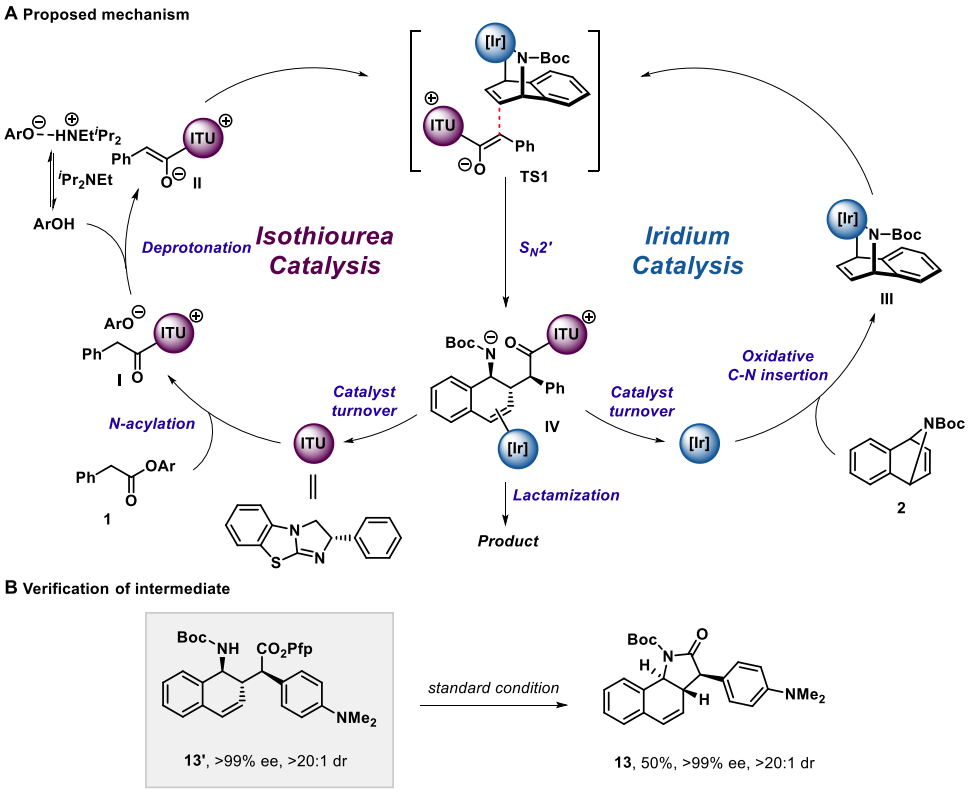

Fig. 5 | Mechanism studies. A Proposed mechanism. **B** Verification of intermediate.

Chemoselective hydrogenation of the alkene using Pd/C under H_2 furnished the saturated product **47**, while treatment of **3** with $LiAlH_4$ yielded amino alcohol **48**. Sequential dibromination and Boc deprotection of **3** provided **45**, and subsequent NaH-mediated HBr elimination afforded vinyl bromide **46**. Following Boc deprotection, the resulting amine **49** was protected as a benzyl derivative (**50**) and could also be elaborated into a chiral NHC precursor **51** via a three-step sequence.

Mechanistic studies

Combining our mechanistic studies with literature precedents[51,52], we propose a plausible catalytic cycle for this cooperative process (Fig. 5). The acyl ammonium ion pair **I** is formed upon acylation of the isothiourea Lewis base catalyst by arylacetic acid ester **1**, followed by deprotonation with the aryloxide counterion to generate the reactive C1-ammonium enolate **II**. Concurrently, the [Ir] catalyst coordinates to azabenzonorbornadiene **2** on the *exo* face and promotes C–N bond cleavage to form intermediate **III**. Nucleophilic attack of enolate **II** on the *endo* face of **III** at the C3 position occurs via TS1 through an S_N2' pathway, delivering intermediate **IV**. Subsequent lactamization furnishes the [3 + 2] annulation product **3** and regenerates both catalysts. Notably, the byproduct **13'**, generated via aryloxy rebound and protonation of the NMe_2-containing intermediate **IV**, can be converted to the final product **13** in 50% yield with >99% ee and >20:1 *dr* under the standard conditions, providing strong support for the proposed mechanism.

In summary, we have developed a general and highly stereoselective [3 + 2] annulation of arylacetic acid esters with azabenzonorbornadienes, enabled by synergistic isothiourea/Ir catalysis. This strategy provides streamlined access to *trans*-fused tricyclic γ-lactams bearing three contiguous tertiary stereocenters with excellent regio-, enantio-, and diastereoselectivity. The methodology exhibits broad substrate scope, tolerating diverse electronic and steric environments, including functionalized arylacetates, heterocycles, and pharmaceutically relevant carboxylates. Key features of this approach include the use of readily available starting materials, the ability to construct sterically disfavored *trans*-fused frameworks, and the potential for further structural elaboration through versatile downstream derivatizations. Mechanistic studies support a cooperative catalytic cycle involving C1-ammonium enolate generation and enantioselective S_N2' attack on the Ir-activated azabenzonorbornadiene.

Methods

General procedure of synergistic ITU/Ir catalyzed asymmetric [3 + 2] annulation of esters and azabenzonorbornadienes

In an atmosphere-controlled glovebox $[Ir(COD)Cl]_2$ (0.006 mmol, 3.0 mol%) and (*S*)-DM-SEGPHOS (0.0126 mmol, 6.3 mol%) were added to a 2-dram vial charged with a stir bar, followed by the addition of anhydrous MeCN (2.0 mL). The mixture was stirred at room temperature for 20 min. Carboxylic ester (0.20 mmol, 1.0 equiv.), azabicyclic alkene (0.44 mmol, 2.2 equiv.), (*S*)-BTM (0.02 mmol, 10.0 mol%) and DIPEA (0.40 mmol, 2.0 equiv.) were added to another 2-dram vial charged with a stir bar. Subsequently, the solution of Ir catalyst was transferred into this vial. The vial was sealed with a PTFE-lined cap and removed from the glovebox. The reaction was stirred at 70 °C in an aluminum block. Upon completion of the reaction (10 h), the mixtures were concentrated in vacuo and directly purified by silica gel column chromatography to afford the final product. The *ee* values were determined by HPLC using a Daicel chiral column.

Data availability

All data, including experimental details, characterization data, NMR and HPLC, are available in the Supplementary Information. Crystallographic data for the structure reported in this Article have been deposited at the Cambridge Crystallographic Data Center, under deposition number CCDC 2487060 (6). Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif. All other data are available from the corresponding author upon request.

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Acknowledgements

This work was supported by the Beijing Municipal Natural Science Foundation (2232015), National Natural Science Foundation of China (22471011), Beijing Nova Program (20230484447).

Author contributions

D.K. designed the project and directed the work; G.X. developed the catalytic method; G.X. and M.Y. performed all synthetic experiments. D.K. and G.X. wrote the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41467-025-67390-4.

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Peer review information *Nature Communications* thanks Baomin Fan and the other anonymous reviewer(s) for their contribution to the peer review of this work. A peer review file is available.