ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2025, **61**, 5806

Received 24th December 2024,
Accepted 14th March 2025

DOI: 10.1039/d4cc06706a

rsc.li/chemcomm

Domino 1,3-dipolar cycloaddition/ring-opening/ring-cleavage: synthesis of trisubstituted pyrrole and chiral dihydropyrrole-3-carbaldehydes†

Solai Pandidurai, Maddala Chinababu and Govindasamy Sekar *

A unique approach has been developed to synthesize trisubstituted 1*H*-pyrrole-3-carbaldehydes using 4-methyl thiazolium salts, α,β-unsaturated aldehydes, and organocatalysts *via* a domino 1,3-dipolar cycloaddition/ring-opening/C–S and C–N bond cleavage reaction sequence. This methodology has been successfully extended for the asymmetric synthesis of enantioenriched trisubstituted-4,5-dihydro-1*H*-pyrrole-3-carbaldehydes employing chiral amine organocatalysts with high efficiency (up to 98% ee, >20 : 1 d.r.).

Poly-substituted 1*H*-pyrroles are essential building blocks in many synthetic chemists because of their diverse use in organic synthesis, bioactive molecules, natural products, and catalysis.[1] There are several approaches to accessing diverse poly-substituted 1*H*-pyrroles in the literature.[2] Due to their privileged structure, they can be used in drug discovery, such as antitumor, antibacterial, antiviral, and anti-inflammatory agents, anticancer drugs like veliparib, and antibacterial agents like selvamicin.[3]

Enantioselectively synthesized, highly substituted dihydropyrrole is an essential building block in many bioactive molecules and natural products.[4] Various attractive methods have been designed to synthesize these heterocycles.[5] For instance, cyclopropane ring-opening,[6a] 1,3-dipolar cycloaddition reactions,[6b] domino ring-opening cyclization (DROC),[6c,15] intramolecular iminium ion cyclization,[6d] and intramolecular nucleophilic addition/rearrangement[6e] reactions have been reported in the literature. However, developing an efficient method for the synthesis of highly substituted chiral 4,5-dihydropyrroles from readily accessible starting materials using asymmetric organocatalysts in a greener and sustainable manner is highly warranted.[7]

Cycloaddition is an essential method for the synthesis of complex chiral molecules.[8a] In this regard, 1,3-dipolar cycloaddition[8b,c] using thiazolium azomethine ylides has been known for the past few decades, while less attention has been paid to its development towards asymmetric transformation.[9] Over the past few decades, scientists have successfully developed a series of methods for synthesizing various achiral and racemic heterocyclic compounds using thiazolium salt with various unsaturated systems *via* 1,3-dipolar cycloaddition reactions (Scheme 1(i)).[10] Very recently, our group developed the organocatalytic asymmetric synthesis of chiral heterocycles using benzothiazolium azomethine ylide (Scheme 1(ii)).[11]

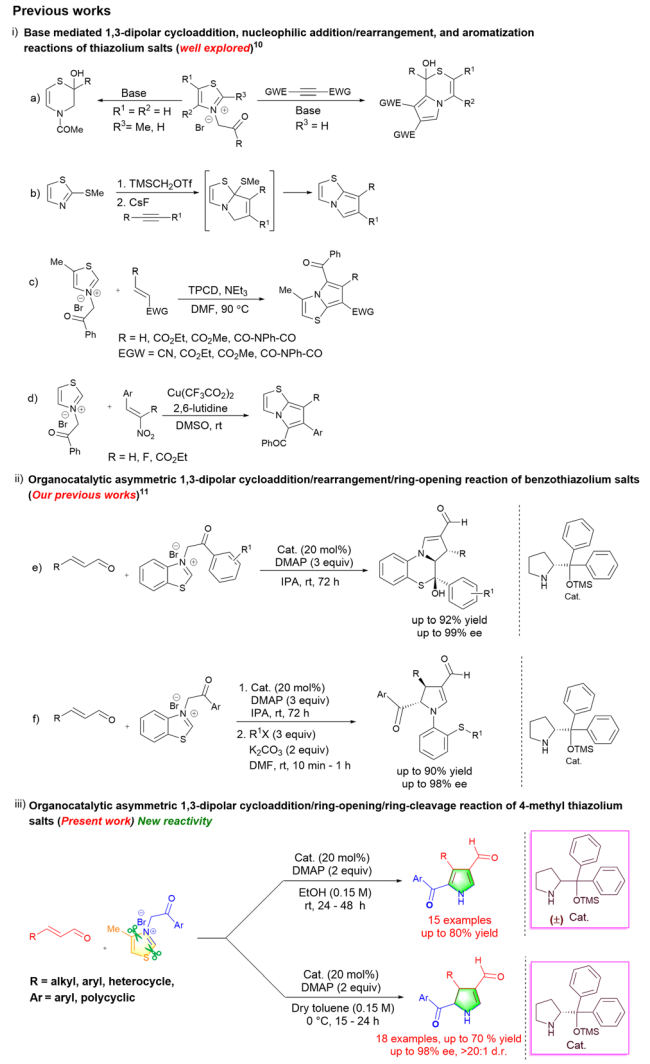
Both thiazolium and benzothiazolium azomethine ylides are expected to have the same reactivity pattern with dipolarophiles to produce a 1,3-dipolar cycloadduct as a common intermediate.[11] This cycloadduct further undergoes ring-opening/rearrangement, yielding various racemic and chiral N,S-heterocyclic compounds in the literature.[11,12,15] However, the cycloadduct experiencing ring-opening followed by unprecedented C–S/C–N bond cleavage towards synthesizing highly substituted five-membered chiral and achiral heterocyclic compounds has not been reported. We present a novel reactivity of 4-methyl thiazolium azomethine ylide with α,β-unsaturated aldehydes, enabling the synthesis of trisubstituted 1*H*-pyrrole-3-carbaldehydes using amine organocatalysts. Furthermore, this approach has been extended to the enantioselective synthesis of highly enantioenriched trisubstituted 4,5-dihydro-1*H*-pyrrole-3-carbaldehydes using chiral amine organocatalyst (Scheme 1(iii)).

The initial reaction commenced with cinnamaldehyde **1a** (0.3 mmol), 4-methyl thiazolium salt **2a** (0.3 mmol), and racemic proline (20 mol%) with NEt_3 as a base, and IPA (isopropyl alcohol) as a solvent at room temperature. This reaction provided an unexpected trisubstituted 1*H*-pyrrole **3a** product with a 30% yield in 48 h. The reaction conditions were varied to increase the yield **3a** with several parameters such as racemic secondary amine catalysts **C1–C5**, bases, and solvents. The results are summarized in Tables S1–S3 (ESI†).[14] For the complete optimization studies, refer to ESI,† Page S3–S4. From the optimization, we found the best-optimized reaction conditions with α,β-unsaturated aldehyde **1a** (1 equiv.), 4-methyl thiazolium salt **2a** (1 equiv.), DMAP (2 equiv.), and catalyst **C5** in EtOH (0.15 M) at room temperature for 48 h.

With the optimized reaction conditions in hand, the generality, and functional group tolerance of the domino reactions were

Department of Chemistry, Indian Institute of Technology Madras, Chennai-600036, India. E-mail: gsekar@iitm.ac.in

† Electronic supplementary information (ESI) available: Experimental details, ^{1}H, $^{13}C\{^{1}H\}$, and ^{19}F NMR spectra, and HPLC chromatogram (PDF). X-ray crystallography data for **3h**. CCDC 2354829. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d4cc06706a

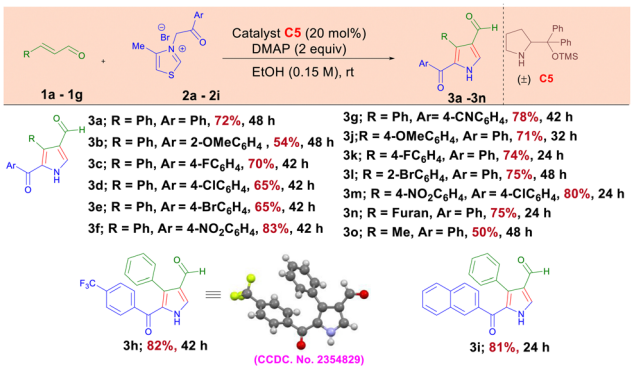


Scheme 1 1,3-Dipolar cycloaddition of thiazolium salts with α,β-unsaturated systems.

investigated with various α,β-unsaturated aldehydes **1** and 4-methyl thiazolium salts **2** with electron-donating and electron-withdrawing groups, halogens, and bulky substituents. All the reactions furnished the desired products **3a–3o** in good yields (Scheme 2).

The simple 4-methyl thiazolium salt gave the product **3a** in 72% yield. The 4-methyl thiazolium salt, having the election donating methoxy group at the *ortho* position, gave product **3b** in a moderate yield of 54% compared to the unsubstituted product **3a**. The reason may be a steric hindrance to *ortho*-OMe substitution on the phenyl ring. Meanwhile, the halogen-substitution at the *para* positions of 4-methyl thiazolium salts delivered **3c–3e** in good yields (Scheme 2). The electron-withdrawing groups such as $-NO_2$, –CN, and $-CF_3$ at the *para* positions of 4-methyl thiazolium salt led to the desired trisubstituted 1*H*-pyrrole products **3f–3h** in 78–83% yields (Scheme 2). The bulky naphthyl group, well tolerated for this domino strategy, led to the product **3i** in 81% yield.

α,β-Unsaturated aldehydes **1** containing an electron-donating methoxy group at the *para* position provided the desired product **3j**

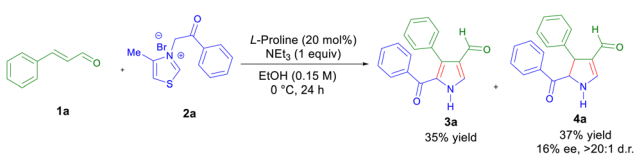


Scheme 2 Substrate scope of trisubstituted-1*H*-pyrrole-3-carbaldehydes.

in 71% yield. The halogen substitution at the *para* position furnished the desired product **3k** in 74% yield. Surprisingly, the bromine substitution at the *ortho* position shows atropisomerism, confirmed by chiral HPLC analysis (Fig. S2 in ESI†),[14] and afforded the desired product **3l** in 75% yield. The electron-withdrawing group at the *para* position delivered the trisubstituted pyrrole product **3m** in 80% yield. The substitution at the 3-position of α,β-unsaturated aldehydes such as the furan ring also offered the desired product **3n** in 75% yield. Delightfully, alkyl substitution at the 3-position of α,β-unsaturated aldehyde also delivered the product **3o** in 50% yield. The structure of compound **3h** was unambiguously confirmed through single-crystal X-ray analysis, and a plausible reaction mechanism is provided in the ESI† (Page S13).[14]

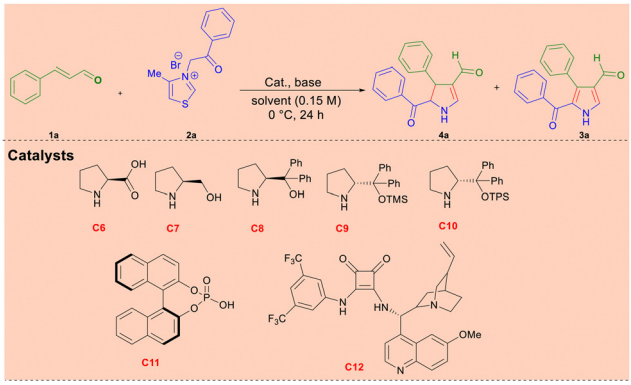
We envisaged that if we could control the reaction rate of the domino synthesis of product **3**, there is a possibility of stopping the reaction at trisubstituted-4,5-dihydro-1*H*-pyrroles. In this case, if we use a chiral amine catalyst, there is a possibility of making the trisubstituted-4,5-dihydro-1*H*-pyrroles in enantioenriched form by an enantioselective domino reaction. So, to slow down the rate of the reaction, the domino reaction was performed at 0 °C, in the presence of L-proline (20 mol%), and NEt_3 (1 equiv.) in EtOH solvent, and the reaction afforded the desired product **3a** in 35% yield, along with the expected chiral trisubstituted-4,5-dihydro-1*H*-pyrrole **4a** 37% yield with 16% ee in >20 : 1 d.r. (Scheme 3 and Table 1, entry 1).

Notably, the domino reaction was successfully controlled at the dihydropyrrole stage by lowering the reaction temperature to 0 °C and achieving the dihydropyrrole in an enantioselective manner. Inspired by the preliminary result, further optimization was done for the enantioselective formation of **4a** and to minimize the formation of **3a**. The domino reaction was optimized with various chiral catalysts, bases, and solvents, and the results are summarized in Table 1.[14] Among the chiral catalysts, **C6–C12**



Scheme 3 Trail reaction for the synthesis of chiral dihydropyrrole.

Table 1 Optimization of the reaction conditions[a]



Entry	Base (equiv.)	Cat. (mol%)	Solvent (0.15 M)	Yield of **4a**[b]	ee[c] (%)	d.r.[d]	Yield of **3a**[b]
1	Net_3 (1)	**C6** (20)	EtOH	37	16	>20 : 1	35
2	Net_3 (1)	**C7** (20)	EtOH	36	10	>20 : 1	10
3	Net_3 (1)	**C8** (20)	EtOH	35	15	>20 : 1	15
4	Net_3 (1)	**C9** (20)	EtOH	40	16	>20 : 1	20
5	Net_3 (1)	**C10** (20)	EtOH	30	12	>20 : 1	25
6	DMAP (1)	**C9** (20)	EtOH	50	65	>20 : 1	25
7	DMAP (2)	**C9** (20)	EtOH	48	85	>20 : 1	12
8	DMAP (2)	**C9** (20)	MeOH	48	48	>20 : 1	12
9	DMAP (2)	**C9** (20)	H_2O	nr	—	—	—
10	DMAP (2)	**C9** (20)	1,2-DCE	10	94	>20 : 1	20
11	DMAP (2)	**C9** (20)	Toluene	25	94	>20 : 1	20
12	DMAP (2)	**C9** (20)	THF	30	96	>20 : 1	30
13	DMAP (2)	**C9** (20)	Dry THF	45	96	>20 : 1	15
14	DMAP (2)	**C9** (20)	Dry toluene	60	96	>20 : 1	10
15[e]	DMAP (1)	**C9** (20)	Dry toluene	45	90	>20 : 1	25
16[f]	DMAP (2)	**C9** (10)	Dry toluene	40	60	>20 : 1	20
17[g]	DMAP (2)	**C9** (5)	Dry toluene	30	20	>20 : 1	35
18	DMAP (2)	**C11** (10)	Dry toluene	—	—	—	60
19	DMAP (2)	**C12** (10)	Dry toluene	—	—	—	65

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.3 mmol), base (1–2 equiv.), catalyst **C6–C12** (10–20 mol%), solvent (0.15 M). [b] Isolated yield. [c] Enantiomeric excess was determined by chiral HPLC. [d] d.r. ratio was determined by ^{1}H NMR using a crude reaction mixture. [e] The reaction was performed using 1 equivalent of DMAP base. [f] The reaction was performed using 10 mol% of the **C9** catalyst. [g] The reaction was performed using 5 mol% of the **C9** catalyst. nr = no reaction.

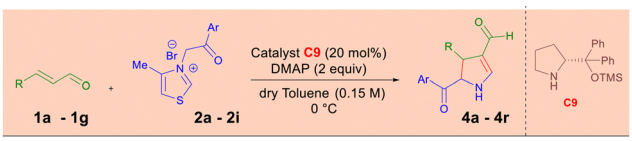
were screened to increase % ee (entries 1–5), and **C9** was the best choice (entry 4). Then, the reaction was carried out with several bases (Table S5, ESI†)[14] to improve the yield and % ee of **4a**.

When DMAP was used as a base, the yield and % ee of product **4a** increased to 50% and 65%, respectively (entry 6). In contrast, other bases failed to give better outcomes (Table S5, ESI†).[14] Increasing DMAP equivalents into two resulted in 48% with 85% ee of the product (entry 7). Notably, when dry toluene was used as a solvent, the domino reaction provided a 60% yield of **4a** with 96% ee (entry 14), and minimizing the formation of aromatic product **3a**. When the quantity of DMAP was decreased by one equivalent, the yield of product **4a** was reduced to 45% with 90% ee (entry 15). Reducing the catalyst loading to 10 mol%, the yield and % ee of product **4a** were also reduced to 40% and 60%, respectively (entry 16).[14] Also, the reaction was performed with other green catalysts, such as **C11** and **C12**, which produced only racemic products (entries 18 and 19).

With the optimized reaction conditions in hand, the generality of the asymmetric domino reaction was investigated with various α,β-unsaturated aldehydes **1**, and 4-methyl thiazolium salts **2** containing electron-donating groups, heterocycles, and bulky aryl groups, and the results are summarized in Scheme 4.

All the domino reactions took place smoothly *via* intermolecular 1,3-dipolar cycloaddition/intramolecular ring-opening/C–S/C–N bond cleavage to afford the chiral trisubstituted-4,5-dihydro-1*H*-pyrrole-3-carbaldehydes **4a–4r** in good to excellent enantioselectivity (63–98% ee). Gratifyingly, 4-methyl thiazolium salts bearing an electron-donating group at the *ortho*, *meta*, and *para* positions exhibited good reactivity and enantioselectivity (**4a–4d** and **4r**; 81–95% ee). The halogen substitution at the *para* positions provided the desired products **4e–4g** in 60–65% yields with 96–98% ee. The 4-biphenyl and bulky substitution containing naphthyl 4-methyl thiazolium salts **4h** and **4i** delivered the desired chiral products in 57% and 52% yield with 90% ee and 87% ee. The decreasing yield of **4d**, **4i**, and **4r** is due to steric hindrance with the thiazolium ring methyl group. As a result, the formation of the hydropyrrolothiazole cycloadduct intermediate is decreased, reducing the yield of the dihydropyrrole product.

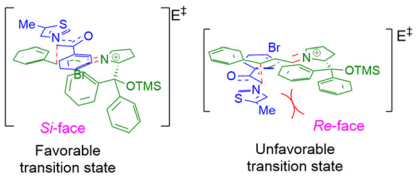
To showcase the functional group tolerance of α,β-unsaturated aldehyde **1**, the domino reaction proceeded with electron-donating groups, halogens, and heterocycle substituents. All the reactions underwent smoothly and yielded the enantioselective domino products **4j–4q** in 63–96% ee (Scheme 4). The cinnamaldehyde-bearing electron-donating group at the *para* position delivered the desired products **4j**, **4k**, and **4p** in good yields with 69–88% ee. The halogen substitution at cinnamaldehyde's *para* and *ortho* positions furnished **4l–4n** and **4q** in 79–96% ee. The reaction was also suitable for substituting at the 3-position of α,β-unsaturated



4a; R = Ph, Ar = Ph, 60%, 95% ee, 24 h
4b; R = Ph, Ar = 4-MeC_6H_4, 70%, 81% ee, 24 h
4c;R = Ph, Ar = 4-OHC_6H_4, 50%, 87% ee, 48 h
4d; R = Ph, Ar = 2-$OMeC_6H_4$, 54%, 95% ee, 24 h
4e; R = Ph, Ar = 4-FC_6H_4, 60%, 98% ee, 24 h
4f; R = Ph, Ar = 4-ClC_6H_4, 65%, 96% ee, 24 h
4g; R = Ph, Ar = 4-BrC_6H_4, 69%, 97% ee, 24 h
4h; R = Ph, Ar = 4-PhC_6H_4, 57%, 90% ee, 24 h
4i; R = Ph, Ar = 2-Naphthyl, 52%, 87% ee, 12 h
4j; R = 4-MeC_6H_4, Ar = 4-ClC_6H_4, 51%, 78% ee, 18 h
4k; R = 4-$NMe_2C_6H_4$, Ar = 4-ClC_6H_4, 65%, 69% ee, 20 h
4l; R = 4-FC_6H_4, Ar = 4-ClC_6H_4, 55%, 83% ee, 22 h
4m; R = 4-ClC_6H_4, Ar = 4-ClC_6H_4, 53%, 96% ee, 15 h
4n; R = 4-BrC_6H_4, Ar = 4-ClC_6H_4, 43%, 93% ee, 17 h
4o; R = 2-Furan, Ar = 4-ClC_6H_4, 57%, 63% ee, 24 h
4p; R = 4-$OMeC_6H_4$, Ar = 4-ClC_6H_4, 47%, 88% ee, 17 h
4q; R = 2-BrC_6H_4, Ar = 4-ClC_6H_4, 51%, 79% ee, 24 h[a]
4r; R = Ph, Ar = 3-$OMeC_6H_4$, 54%, 88% ee, 48 h

>20:1 d.r.

Scheme 4 Substrate scope for chiral dihydro-1*H*-pyrrole-3-carbaldehydes. [a] When this reaction was allowed for a longer time, aromatization took place to yield the racemic atropoisomeric product **3l**.



Scheme 5 Diastereomeric transition state.

aldehydes such as the furan ring and delivered the domino chiral product **4o** in 63% ee.

Gram scale synthesis was performed to check the scalability of both domino methodologies.[14] Also, several control experiments and mechanistic investigations were conducted to probe the reaction mechanism.[14]

Based on our control experiments and previous literature reports,[11] a plausible reaction mechanism has been proposed in the ESI† (Page No. S13).[14] The 4-methylthiazolium salt **2a** will initially react with DMAP to yield azomethine ylides **III**. Subsequently, α,β-unsaturated aldehyde **1a** in the presence of chiral catalyst **C9** will provide iminium ion intermediate **I**. Intermediate **I** will react with azomethine ylide **III** to produce Michael adduct intermediate **IV** *via* a 1,4-addition. The formation of intermediate **IV** is a chiral induction step through the 4-methyl thiazolium anion **III** approaching from the *Si*-face of iminium ion **I**, which is the favorable transition state.

The unfavorable transition state is a 4-methyl thiazolium anion **III** approaching from the *Re*-face of iminium ion **I**. According to our previous report, computational study[11a] shows the favorable and unfavorable diastereomeric transition in Scheme 5 (for a detailed, plausible reaction mechanism, see ESI,† Page S13).[14]

In conclusion, we have developed a new, unusual domino methodology for the synthesis of trisubstituted 1*H*-pyrrole-3-carbaldehydes and enantioenriched dihydro-1*H*-pyrrole-3-carbaldehydes *via* domino 1,3-dipolar cycloaddition/ring-opening/C–S and C–N bond-cleavage reactions of α,β-unsaturated aldehydes with 4-methyl thiazolium salt utilizing organocatalysts. The enantioselective synthesis was achieved with excellent enantio- and diastereoselectivity. We have performed various control experiments and mechanistic studies to confirm the product formation. HRMS analysis confirms that the formation of 1-mercaptopropane-2-one is a by-product. However, a detailed mechanistic investigation is in progress.

G. S. thanks DST-ANRF (CRG/2022/001739) and CSIR (02/0484/23/EMR-11) for financial support and DST-FIST for the instrumentation facility. S. P. thanks IIT Madras for the research fellowship. Dedicated to Prof. Vinod K. Singh (IIT Kanpur) on the occasion of his 65th birthday.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

The authors declare the following competing financial interest(s): a patent is pending for both domino methodologies described herein (Indian patent application numbers: 202441067200 and 202441067175, May 05, 2024).[13]

References

1 D. Tzankova, S. Vladimirova, L. Peikova and M. Georgieva, *J. Chem. Tech. Metall.*, 2018, **53**, 451.
2 (*a*) M. Thwin, B. Mahmoudi, O. A. Ivaschuk and Q. A. Yousif, *RSC Adv.*, 2019, **9**, 15966; (*b*) M. K. Hunjan, S. Panday, A. Gupta, J. Bhaumik, P. Das and J. K. Laha, *Chem. Rec.*, 2021, **21**, 715.
3 (*a*) H. Pourtaher, A. Hasaninejad and A. Iraji, *Sci. Rep.*, 2022, **12**, 15236; (*b*) S. Boussios, P. Karihtala, M. Moschetta, C. Abson, A. Karathanasi, N. Zakynthinakis-Kyriakou, J. E. Ryan, M. Sheriff, E. Rassy and N. Pavlidis, *Invest. New Drugs*, 2020, **38**, 181; (*c*) E. B. Van Arnam, A. C. Ruzzini, C. S. Sit, H. Horn, A. A. Pinto-Tomás, C. R. Currie and J. Clardy, *Proc. Natl. Acad. Sci. U. S. A.*, 2016, **113**, 12940.
4 (*a*) S. Castellano, H. D. G. Fiji, S. S. Kinderman, M. Watanabe, P. de Leon, F. Tamanoi and O. Kwon, *J. Am. Chem. Soc.*, 2007, **129**, 5843; (*b*) E. Fattorusso and O. Taglialatela-Scafati, *Modern Alkaloids: Structure, Isolation, Synthesis and Biology*, Wiley-VCH Verlag GmbH&Co. KGaA, Weinheim, 2008.
5 Studies about synthesis of dihydropyrroles: (*a*) A. Guðmundsson, K. P. J. Gustafson, B. K. Mai, V. Hobiger, F. Himo and J.-E. Bäckvall, *ACS Catal.*, 2019, **9**, 1733; (*b*) D. Wang, Y. Fan, P. Yu and L. Désaubry, *Chem. Commun.*, 2020, **56**, 5584.
6 (*a*) S. Yaragorla, R. Tangellapally and D. Arun, *Eur. J. Org. Chem.*, 2024, e202400238; (*b*) F.-F. Tang, W.-L. Yang, X. Yu and W.-P. Deng, *Catal. Sci. Technol.*, 2015, **5**, 3568; (*c*) M. K. Ghorai and D. P. Tiwari, *J. Org. Chem.*, 2013, **78**, 2617; (*d*) J. Xiang, H. Xie, Z. Li, Q. Dang and X. Bai, *Org. Lett.*, 2015, **17**, 3818; (*e*) K. M. Wen Ting and Chen Zhanguo, *Chin. J. Org. Chem.*, 2019, **39**, 3162.
7 Recent studies on asymmetric catalysis and sustainable methodologies: (*a*) A. Garg, D. Rendina, H. Bendale, T. Akiyama and I. Ojima, *Front. Chem.*, 2024, **12**, 1398397; (*b*) A. Chaskar and R. Darade, *Int. J. Creat. Res. Thoughts.*, 2022, **10**, 2320; (*c*) A. M. Koskinen, *Asymmetric synthesis of natural products*, John Wiley & Sons, 2022.
8 (*a*) X. Liu, H. Zheng, Y. Xia, L. Lin and X. Feng, *Acc. Chem. Res.*, 2017, **50**, 2621; (*b*) K. Wang, L. Yang, Y. Li, H. Li, Z. Liu, L. Ning, X. Liu and X. Feng, *Angew. Chem., Int. Ed.*, 2023, **62**, e202307249; (*c*) F. Zhang, Y. Zhou, H. Zhao, L. Chen, W. Cao and X. Feng, *Precis. Chem.*, 2023, **1**, 423.
9 J. L. García Ruano, A. Fraile, M. R. Martín, G. González and C. Fajardo, *J. Org. Chem.*, 2008, **73**, 8484.
10 (*a*) T. Iwamura, M. Kobayashi, T. Ichikawa, H. Shimizu and T. Kataoka, *J. Chem. Soc., Perkin Trans. 1*, 1996, 629; (*b*) C. R. Berry, C. A. Zificsak, A. C. Gibbs and D. J. Hlasta, *Org. Lett.*, 2007, **9**, 4099; (*c*) Y.-M. Shen, P.-C. Lv, M.-Z. Zhang, H.-Q. Xiao, L.-P. Deng, H.-L. Zhu and C.-Z. Qi, *Monatsh. Chem.*, 2011, **142**, 521; (*d*) V. A. Motornov, A. A. Tabolin and S. L. Ioffe, *New J. Chem.*, 2022, **46**, 4134.
11 (*a*) S. Pandidurai, V. S. Kumar Choutipalli, V. Subramanian and G. Sekar, *Org. Lett.*, 2024, **26**, 2971; (*b*) S. Pandidurai and G. Sekar, *Org. Biomol. Chem.*, 2024, **22**, 8119.
12 (*a*) O. Tsuge, S. Kanemasa and S. Takenaka, *Bull. Chem. Soc. Jpn.*, 1985, **58**, 3320; (*b*) X. Zhang, X. Liu, J. Zhang, D. Zhang, L. Lin and X. Feng, *Org. Chem. Front.*, 2018, **5**, 2126; (*c*) Z.-H. Wang, T. Zhang, L.-W. Shen, X. Yang, Y.-P. Zhang, Y. You, J.-Q. Zhao and W.-C. Yuan, *Molecules*, 2023, **28**, 4410.
13 (*a*) S. Pandidurai, S. Kishor and G. Sekar, *Indian Pat.*, 202441067200, 2024; (*b*) S. Pandidurai and G. Sekar, *Indian Pat.*, 202441067175, 2024.
14 See the ESI† for more details.
15 The comparative study of ref. 6*a* and 12*c* with this study is included in the ESI,† Page 91.