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

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A unique approach has been developed to synthesize trisubstituted 1H-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-1H-pyrrole-3-carbaldehydes employing chiral amine organocatalysts with high efficiency (up to 98% ee, >20:1 d.r.).

Poly-substituted 1H-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 1H-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 selvamycin.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 1H-pyrrole-3-carbaldehydes using amine organocatalysts. Furthermore, this approach has been extended to the enantioselective synthesis of highly enantioenriched trisubstituted 4,5-dihydro-1H-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 1H-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.

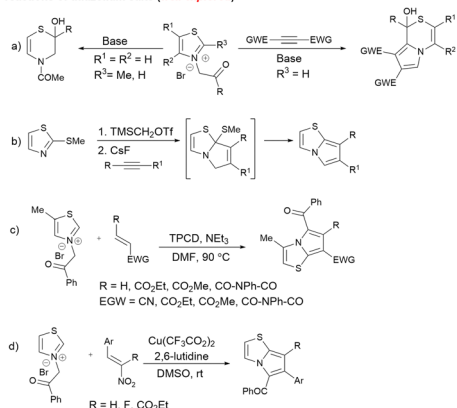
With the optimized reaction conditions in hand, the generality, and functional group tolerance of the domino reactions were

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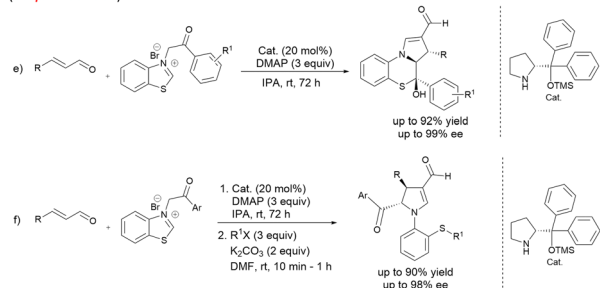
† Electronic supplementary information (ESI) available: Experimental details, ¹H, ¹³C{¹H}, and ¹⁹F NMR spectra, and HPLC chromatogram (PDF). X-ray crystallography data for **3h**. CCDC 2354829. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d4cc06706a>

Previous works

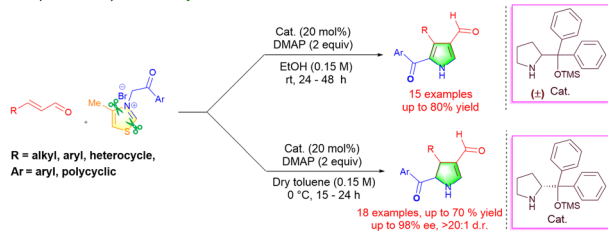
i) Base mediated 1,3-dipolar cycloaddition, nucleophilic addition/rearrangement, and aromatization reactions of thiazolium salts (*well explored*)¹⁰



ii) Organocatalytic asymmetric 1,3-dipolar cycloaddition/rearrangement/ring-opening reaction of benzothiazolium salts (*Our previous works*)¹¹



iii) Organocatalytic asymmetric 1,3-dipolar cycloaddition/ring-opening/ring-cleavage reaction of 4-methyl thiazolium salts (*Present work*) *New reactivity*

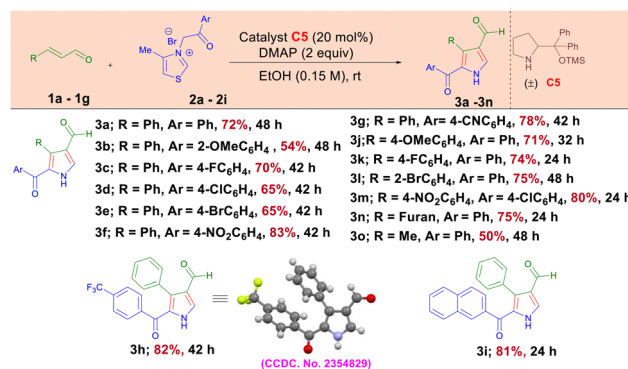


Scheme 1 1,3-Dipolar cycloaddition of thiazolium salts with α,β -unsaturated systems.

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 electron 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 $-\text{NO}_2$, $-\text{CN}$, and $-\text{CF}_3$ 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**

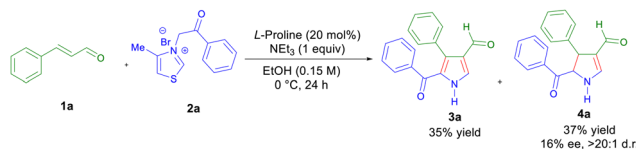


Scheme 2 Substrate scope of trisubstituted-1*H*-pyrrole-3-carbaldehydes.

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 ₂ O	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 ¹H 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.

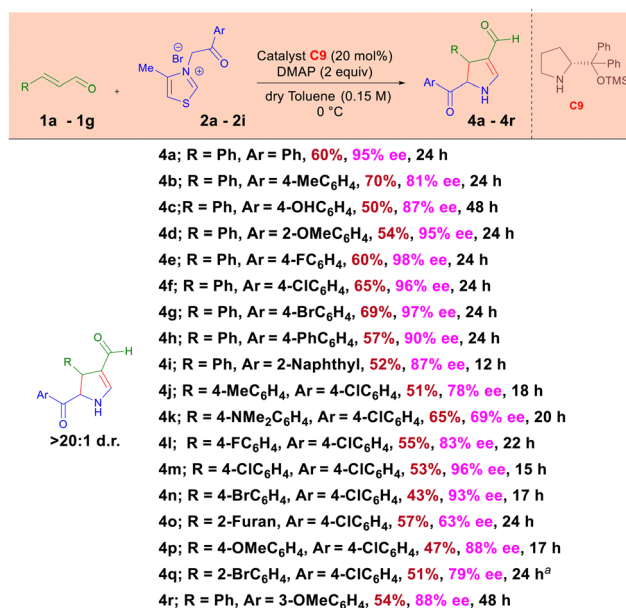
were screened to increase % ee (entries 1–5), and **C9** was the best choice (entry 4). Then, the reaction was carried out with several bases (Table S5, ESI†)¹⁴ to improve the yield and % ee of **4a**.

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.

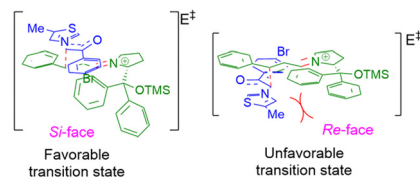
All the domino reactions took place smoothly *via* intermolecular 1,3-dipolar cycloaddition/intramolecular ring-opening/C–S/C–N bond cleavage to afford the chiral trisubstituted-4,5-dihydro-1H-pyrrole-3-carbaldehydes **4a–4r** in good to excellent enantioselectivity (63–98% ee). Gratifyingly, 4-methyl 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 hydropyrrolo-thiazole 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



Scheme 4 Substrate scope for chiral dihydro-1H-pyrrole-3-carbaldehydes.

^a When this reaction was allowed for a longer time, aromatization took place to yield the racemic atropisomeric 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-methylthiazolium anion **III** approaching from the *Si*-face of iminium ion **I**, which is the favorable transition state.

The unfavorable transition state is a 4-methylthiazolium 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-methylthiazolium 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.

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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

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- 14 See the ESI† for more details.
- 15 The comparative study of ref. 6a and 12c with this study is included in the ESI,† Page 91.