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Carbene-catalyzed enantioselective annulation of dinucleophilic hydrazones and bromoenals for access to aryl-dihydropyridazinones and related drugs⁺

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4,5-Dihydropyridazinones bearing an aryl substituent at the C6-position are important motifs in drug molecules. Herein, we developed an efficient protocol to access aryl-dihydropyridazinone molecules *via* carbene-catalyzed asymmetric annulation between dinucleophilic arylidene hydrazones and bromoenals. Key steps in this reaction include polarity-inversion of aryl aldehyde-derived hydrazones followed by chemo-selective reaction with enalderived α , β -unsaturated acyl azolium intermediates. The aryl-dihydropyridazinone products accessed by our protocol can be readily transformed into drugs and bioactive molecules.

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1. Introduction

4,5-Dihydropyridazinones and their derivatives, especially those bearing aryl substituents at the 6-position, display a broad range of pharmacological activities.1 Some members of this family have already made their way into the market, such as Levosimendan² and Pimobendan³ which are used for the treatment of heart disease of humans and animals respectively (Fig. 1a). Other members of this family, such as (-)-KCA 1490 (bonchodilatory and antiinflammatory activity),4 Meribendan (potent PDE III inhibitor),5 and (R)-DNMDP (cancer cytotoxic modulator),6 have shown promising activities in biological studies (Fig. 1a). Traditionally, these structural motifs can be accessed by condensation of substituted yketo carboxylic acids or their derivatives with hydrazines (Fig. 1b), whereas asymmetric access relies on either chiral resolution of the products^{4,5,7} or the use of optically enriched starting materials.⁸ It is worth noting that access to chiral starting materials (1,4-dicarbonyl compounds) used in these syntheses remains challenging in organic chemistry.9 Another approach to construct these heterocyclic moieties involves formal [4 + 2] cycloaddition between in situ generated 3-aryl azoalkenes and two carbon synthons (Fig. 1b).10

"State Key Laboratory Breeding Base of Green Pesticide and Agricultural Bioengineering, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University, Huaxi District, Guiyang 550025, China. E-mail: xyli1@gzu.edu.cn One asymmetric example of these formal [4 + 2] reactions was demonstrated using isothiourea as the organic catalyst to control enantioselectivity at the C4-position.^{10 α} There is no success in catalytic asymmetric access to C5 stereogenic center (Fig. 1a) of these 4,5-dihydropyridazinones.

We're interested in designing N-heterocyclic carbenecatalyzed reactions for the preparation or modification of bioactive molecules for medicinal and agriculture uses.11 Herein, we disclose carbene catalyzed asymmetric annulation between N-monosubstituted arylidene hydrazones (precursor of 1,3-dinucleophile) and bromoenals¹² (common 1,3-dinucleophilic hydrazones from trifluoroacetaldehyde and glyoxal derivatives13 have been explored in NHC-catalyzed reactions13c,d as demonstrated in Fig. 1c) to afford highly enantiopure 6-aryl-4,5-dihydropyridazinones (Fig. 1d). N-Monosubstituted hydrazones containing an electron-withdrawing group (e.g., -COR, -CF₃)¹³ at azomethine carbon have been used widely as 1,3dinucleophiles after the pioneering study by Vicario¹⁴ in 2012. In contrast, N-monosubstituted hydrazones from aryl aldehydes rarely showed such character as 1,3-dinucleophiles. This is probably because of the comparatively less stable anionic character at azomethine carbon and an unfordable tendency for proton transfer to regenerate a N-centered nucleophile (Fig. 1d). Therefore, aryl aldehyde-derived N-monosubstituted hydrazones were barely used as precursors of effective 1,3-dinucleophiles in asymmetric catalysis.13g,15 Key steps in our reaction involve the Umpolung of arylidene hydrazone (2) to form intermediate II followed by chemo-selective 1,4-addition to NHC-bound α,β -unsaturated acyl azolium I to form intermediate III. Intermediate III upon intramolecular proton transfer leads to intermediate IV that undergoes cyclization to form 6aryl-4,5-dihydropyridazinone products with good yields and

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a) Examples of drugs and bioactive molecules bearing 6-arvl-4.5-dihydropyridazinone

Fig. 1 Strategies to access 6-aryl-4,5-dihydropyridazinones.

high enantioselectivities. A broad range of hydrazones from aryl and heteroaryl aldehydes were well tolerated under our reaction conditions. Straightforward transformations of our products lead to clinically approved drugs (Levosimendan and Pimobendan) and several other bioactive molecules without any erosion of the e.r. values (Scheme 3). It is worth mentioning that previously reported procedures to access these drugs and bioactive molecules comprised longer steps and used chiral resolutions or chiral starting materials.^{4–6,7c-f,8e}

2. Results and discussion

We initiated our studies using readily available α -bromo cinnamaldehyde **1a** and *p*-nosyl protected hydrazone **2a** as the



Entry	Conditions	$\operatorname{Yield}^{b}(\%)$	e.r. ^c
1	A, TMEDA	44	78.5:21.5
2	B, TMEDA	21	90:10
3	C, TMEDA	74	71:29
4	D, TMEDA	64	87:13
5	E, TMEDA	72	95:5
6	F, TMEDA	48	89.5:10.5
7	E , TMEDA, solvents ^d	32-77	92.5:7.5-94:6
8	E, K_2CO_3	72	94:6
9	E, K_3PO_4	67	93.5:6.5
10	E, Cs_2CO_3	90	93:7
11	E, TMEDA	$72(71)^{e,f}$	95:5
12	E, TMEDA	57 ^g	95:5

^{*a*} Reaction conditions: **1a** (0.1 mmol.), **2a** (0.05 mmol), NHC precat. (20 mol%), base (2.5 equiv.), solvent (0.05 M), 4Å MS (100 mg ml⁻¹) at RT for 72 h. ^{*b*} Yields determined by ¹H NMR analysis with 1,3,5-trimethoxybenzene as the internal standard. ^{*c*} The e.r. value was determined *via* chiral-phase HPLC analysis. ^{*d*} See ESI. ^{*e*} Isolated yield was given in parentheses. ^{*f*} 10 mol% precatalyst and 0.075 mmol of **1a** were used. ^{*g*} 5 mol% precatalyst was used. MS = molecular sieves, TMEDA = tetramethylethylenediamine.

model substrates to search for suitable precatalysts and reaction conditions, with key results briefed in Table 1 (and also see ESI[†]). The aminoindanol-derived precatalyst with an N-phenyl substituent (A)¹⁶ led to the formation of the desired product 3a in moderate yield and enantioselectivity (Table 1, entry 1). Installing a nitro (-NO₂) group in the aminoindanol moiety of precatalyst A (to get precatalyst B)17 improved the enantioselectivity, albeit with poor yield (Table 1, entry 2). Replacing the N-phenyl substituent of precatalyst A with an electron-rich and bulky N-mesityl substituent (to get precatalyst C)18 gave the product in improved yield (74%), although the e.r. value dropped down to 71 : 29 (Table 1, entry 3). As expected, switching to more sterically hindered NHC precatalyst D19 with a bromo atom on the aminoindanol motif further boosted the e.r. value, although a diminishing yield was obtained (Table 1, entry 4). Ultimately, we found out that the use of nitro $(-NO_2)$ substituted aminoindanol scaffold containing NHC precatalyst E¹⁹ could give the desired product in 72% yield and 95:5 e.r (Table 1, entry 5). In the hope for further improvement, we replaced the mesityl group of E with the bulky 1,3,5-triisopropyl phenyl group (to get precatalyst F).19 However, poorer enantioselectivity and yield were detected (Table 1, entry 6). Screening of other solvents showed no additional encouraging improvement in the

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enantioselectivity of our reaction (Table 1, entry 7 and see ESI[†]). Both organic and inorganic bases were efficient in providing the desired product (Table 1, entries 8–10 and also see ESI[†]). After further screening of the precatalyst loading parameter, we established that the optimal conditions consist of ethyl acetate as the solvent and TMEDA as the base in the presence of 10 mol% precatalyst loading, providing the corresponding product without any change in the reaction outcomes (comparing entry 5 and entry 11). Further decrease in the precatalyst loading (5 mol%) resulted in low yield without affecting the enantioselectivity (Table 1, entry 12).

With the optimized reaction conditions in hand (Table 1, entry 11), we moved to evaluate the generality of this reaction. The scope of various hydrazones was examined first with α -bromo cinnamaldehyde (1a) as the model substrate and the results are shown in Scheme 1. Different kinds of substituted





Scheme 1 Scope of hydrazone substrates.^aReaction conditions as in Table 1, entry 11. Yields (after silica gel chromatography purification) based on **2**. Reaction time 72–84 h. The e.r. value was determined *via* chiral-phase HPLC analysis. $SO_2Ar^1 = p$ -nosyl, $SO_2Ar^2 = tosyl$.



Scheme 2 Scope of α -bromoenal substrates.^aReaction conditions as in Table 1, entry 11. Yields (after silica gel chromatography purification) based on 2. Reaction time 72–84 h. The e.r. value was determined via chiral-phase HPLC analysis. SO₂Ar¹ = p-nosyl, SO₂Ar² = tosyl, SO₂Ar³ = o-nosyl. ^bNaOAc and THF were used as the base and solvent, respectively. ^cReagents were added in a glovebox. The reaction was carried out at 0 °C for 24 h with 20 mol% precatalyst and 0.2 mmol bromoenal. ^d0.2 mmol bromoenal was used.

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hydrazone **2q** was also compatible to provide the corresponding product (**3q**) in 75% yield and 98.5 : 1.5 e.r.

We next examined the scope of bromoenals, and the results are summarized in Scheme 2. Different kinds of electrondonating and withdrawing substituents at the β -phenyl ring (such as methyl, halogens, and methoxyl at the ortho, meta, and para positions) of the bromoenal worked well under our reaction conditions and gave the annulated products in good to excellent yields and high enantioselectivities (4a-4g). The β phenyl ring of the bromoenal could also be replaced with the 2napthyl ring without affecting the result significantly (4h). As a 5-methyl substituent in 6-aryl-4,5-dihydropyridazinone is crucial from the viewpoint of existing drugs and bioactive molecules²⁻⁶ (Fig. 1a), we further examined the reaction of α bromocrotonaldehyde with some hydrazones. For example, hydrazone containing 2-fluoro phenyl for azomethine substitution was coupled with α-bromocrotonaldehvde to obtain the product 4i in moderate yield and excellent enantioselectivity. With the aim to prepare precursors of clinical drugs and bioactive molecules utilizing our methodology, products 4j and 4k were obtained in moderate to good yields and excellent enantioselectivities by coupling corresponding hydrazones with α -bromocrotonaldehyde. Notably, in the case of 4j *o*-nosyl protected hydrazone was used over p-nosyl protected hydrazone due to its instability under our reaction conditions and the reagents were added inside a glove box, as we found the hydrazone decomposed under our reaction conditions and hence resulted in lower yield, when the reagents were added outside. Higher homologues of α -bromocrotonaldehyde, for example, β -ethyl substituted bromoenal have also been used to couple with hydrazone derived from 4-nitrobenzaldehyde to give product 4l in good yield and excellent enantioselectivity. Notably, in the case of 4l tosyl protected hydrazone instead of nosyl protected hydrazone was used, to avoid the decomposition of the hydrazone under the reaction conditions.

A rationale for the reaction stereoselectivity is illustrated in Fig. 2 for product **3n** based on the absolute configuration of **3n**. The *Si*-face of the NHC-bound α , β -unsaturated acyl azolium is blocked by the catalyst and specifically the presence of the nitro (–NO₂) group on the catalyst makes the *Si*-face less available for the nucleophile. So, it is more favourable to intercept the NHC-bound α , β -unsaturated acyl azolium from the *Re*-face resulting in the formation of the (*R*)-**3a** stereoselectively.

The chiral 4,5-dihydropyridazinone molecules from our catalytic reaction were readily transformed to marketed drugs



Fig. 2 Proposed TS model for stereoselectivity.



Scheme 3 Synthesis of marketed-drugs and bioactive molecules.

and other bioactive molecules (Scheme 3). For example, intermediate **5b**, the precursor of Levosimendan (clinical drug), was obtained without any degradation of the e.r. value from optically enriched **4j** (96 : 4 e.r.) through thiophenol mediated nosyl deprotection, followed by Pd/C-catalyzed hydrogenation (Scheme 3a).^{7c} Successive deprotection of the *p*-nosyl group and two Boc groups of the product **4k** (96 : 4 e.r.) gave the intermediate **6b** in high yield without any erosion of the e.r. value (Scheme 3b). Intermediate **6b** is the precursor for cancer cytotoxic modulator DNMDP⁶, drug Pimobendan^{8e,21} and bioactive Meribendan^{5,21} (Scheme 3b).

3. Conclusions

In summary, we have developed a carbene-catalyzed enantioselective formal [3 + 3] annulation strategy for the construction of 6-aryl-4,5-dihydropyridazinones. The reaction proceeds *via* the Umpolung of aryl aldehyde-derived hydrazones followed by chemoselective 1,4-addition to the NHC-bound acyl azolium intermediate. A broad scope of functional groups is well tolerated on both of the bromoenal and hydrazone substrates, with all the corresponding products afforded in good to excellent yields and enantioselectivities. Scalable synthesis with low precatalyst loading (1 mol%) could also give the annulated products in good results. Applications of our reaction products allow enantiomeric access to marketed drugs and bioactive molecules.

Author contributions

B. Mondal conducted most of the experiments and wrote the initial manuscript draft. R. Maiti, X. Yang, J. Xu, and J.-L. Yan

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performed part of the experiments. W. Tian and X. Li contributed to product design regarding potential bioactivities. Y. R. Chi conceptualized and directed the project and finalized the manuscript draft. All authors contributed to discussions.

Conflicts of interest

There are no conflicts to declare.

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