

Cite this: *Chem. Sci.*, 2021, 12, 8778

All publication charges for this article have been paid for by the Royal Society of Chemistry

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

Bivas Mondal,<sup>c</sup> Rakesh Maiti,<sup>c</sup> Xing Yang,<sup>c</sup> Jun Xu,<sup>bc</sup> Weiyi Tian,<sup>\*b</sup> Jia-Lei Yan,<sup>ID c</sup> Xiangyang Li<sup>ID \*a</sup> and Yonggui Robin Chi<sup>ID \*ac</sup>

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 enal-derived  $\alpha,\beta$ -unsaturated acyl azolium intermediates. The aryl-dihydropyridazinone products accessed by our protocol can be readily transformed into drugs and bioactive molecules.

Received 6th April 2021  
Accepted 17th May 2021

DOI: 10.1039/d1sc01891d

rsc.li/chemical-science

## 1. Introduction

4,5-Dihydropyridazinones and their derivatives, especially those bearing aryl substituents at the 6-position, display a broad range of pharmacological activities.<sup>1</sup> Some members of this family have already made their way into the market, such as Levosimendan<sup>2</sup> and Pimobendan<sup>3</sup> 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 anti-inflammatory activity),<sup>4</sup> Meribendan (potent PDE III inhibitor),<sup>5</sup> and (R)-DNMDP (cancer cytotoxic modulator),<sup>6</sup> have shown promising activities in biological studies (Fig. 1a). Traditionally, these structural motifs can be accessed by condensation of substituted  $\gamma$ -keto carboxylic acids or their derivatives with hydrazines (Fig. 1b), whereas asymmetric access relies on either chiral resolution of the products<sup>4,5,7</sup> or the use of optically enriched starting materials.<sup>8</sup> It is worth noting that access to chiral starting materials (1,4-dicarbonyl compounds) used in these syntheses remains challenging in organic chemistry.<sup>9</sup> 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).<sup>10</sup>

One asymmetric example of these formal [4 + 2] reactions was demonstrated using isothioureia as the organic catalyst to control enantioselectivity at the C4-position.<sup>10a</sup> 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 carbene-catalyzed reactions for the preparation or modification of bioactive molecules for medicinal and agriculture uses.<sup>11</sup> Herein, we disclose carbene catalyzed asymmetric annulation between N-monosubstituted arylidene hydrazones (precursor of 1,3-dinucleophile) and bromoenals<sup>12</sup> (common 1,3-dinucleophilic hydrazones from trifluoroacetaldehyde and glyoxal derivatives<sup>13</sup> have been explored in NHC-catalyzed reactions<sup>13c,d</sup> 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, –CF<sub>3</sub>)<sup>13</sup> at azomethine carbon have been used widely as 1,3-dinucleophiles after the pioneering study by Vicario<sup>14</sup> 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.<sup>13g,15</sup> 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  $\alpha,\beta$ -unsaturated acyl azolium **I** to form intermediate **III**. Intermediate **III** upon intramolecular proton transfer leads to intermediate **IV** that undergoes cyclization to form 6-aryl-4,5-dihydropyridazinone products with good yields and

<sup>a</sup>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: xyl1@gzu.edu.cn

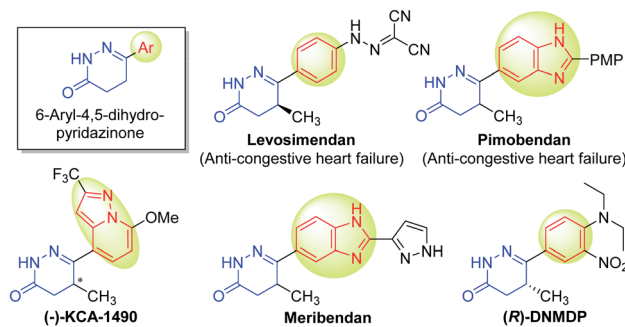
<sup>b</sup>Guizhou University of Traditional Chinese Medicine, Guiyang 550025, China. E-mail: tianweiyi@gzy.edu.cn

<sup>c</sup>Division of Chemistry & Mathematical Science, School of Physical & Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore. E-mail: robinchi@ntu.edu.sg

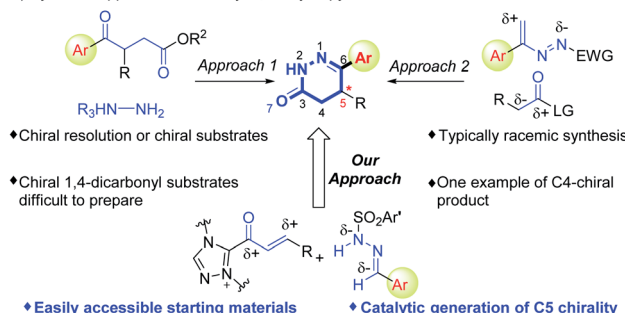
† Electronic supplementary information (ESI) available. CCDC 2062761. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1sc01891d



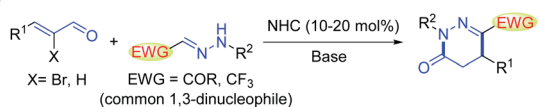
a) Examples of drugs and bioactive molecules bearing 6-aryl-4,5-dihydropyridazinone



b) Synthetic approaches for 6-aryl-4,5-dihydropyridazinones



c) Asymmetric catalytic synthesis of 4,5-dihydropyridazinones with electron withdrawing groups as C6 substitution



d) NHC-catalyzed asymmetric [3+3] annulation of bromoal and arylidene hydrazone (this work)

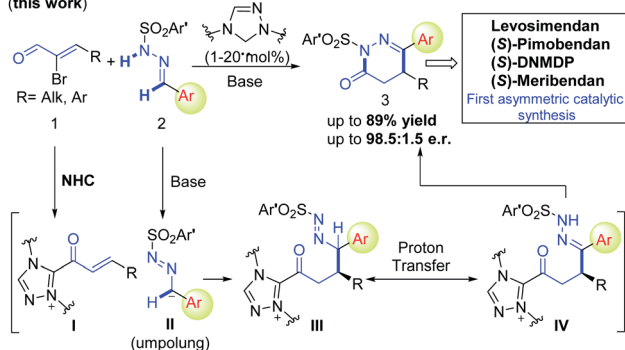
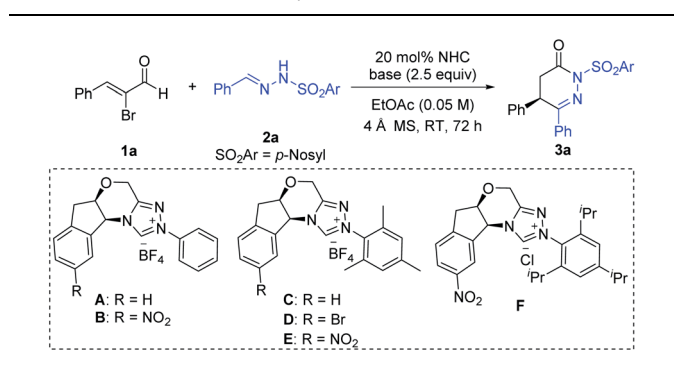


Fig. 1 Strategies to access 6-aryl-4,5-dihydropyridazinones.

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.<sup>4-6,7c-f,8e</sup>

## 2. Results and discussion

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

Table 1 Reaction condition optimization<sup>a</sup>

Entry	Conditions	Yield <sup>b</sup> (%)	e.r. <sup>c</sup>
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 <sup>d</sup>	32–77	92.5 : 7.5–94 : 6
8	E, K <sub>2</sub> CO <sub>3</sub>	72	94 : 6
9	E, K <sub>3</sub> PO <sub>4</sub>	67	93.5 : 6.5
10	E, Cs <sub>2</sub> CO <sub>3</sub>	90	93 : 7
11	E, TMEDA	72(71) <sup>e,f</sup>	95 : 5
12	E, TMEDA	57 <sup>g</sup>	95 : 5

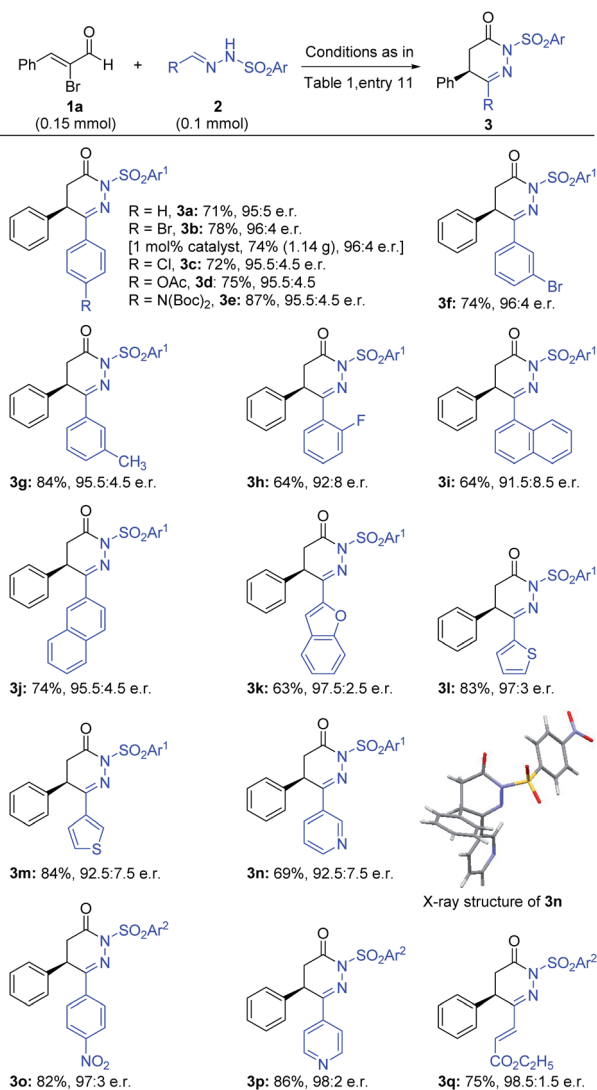
<sup>a</sup> Reaction conditions: **1a** (0.1 mmol), **2a** (0.05 mmol), NHC precat. (20 mol%), base (2.5 equiv.), solvent (0.05 M), 4 Å MS (100 mg ml<sup>-1</sup>) at RT for 72 h. <sup>b</sup> Yields determined by <sup>1</sup>H NMR analysis with 1,3,5-trimethoxybenzene as the internal standard. <sup>c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

model substrates to search for suitable pre-catalysts and reaction conditions, with key results briefed in Table 1 (and also see ESI†). The aminoindanol-derived pre-catalyst with an N-phenyl substituent (**A**)<sup>16</sup> led to the formation of the desired product **3a** in moderate yield and enantioselectivity (Table 1, entry 1). Installing a nitro (-NO<sub>2</sub>) group in the aminoindanol moiety of pre-catalyst **A** (to get pre-catalyst **B**)<sup>17</sup> improved the enantioselectivity, albeit with poor yield (Table 1, entry 2). Replacing the N-phenyl substituent of pre-catalyst **A** with an electron-rich and bulky N-mesityl substituent (to get pre-catalyst **C**)<sup>18</sup> 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 pre-catalyst **D**<sup>19</sup> 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<sub>2</sub>) substituted aminoindanol scaffold containing NHC pre-catalyst **E**<sup>19</sup> 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 pre-catalyst **F**).<sup>19</sup> However, poorer enantioselectivity and yield were detected (Table 1, entry 6). Screening of other solvents showed no additional encouraging improvement in the

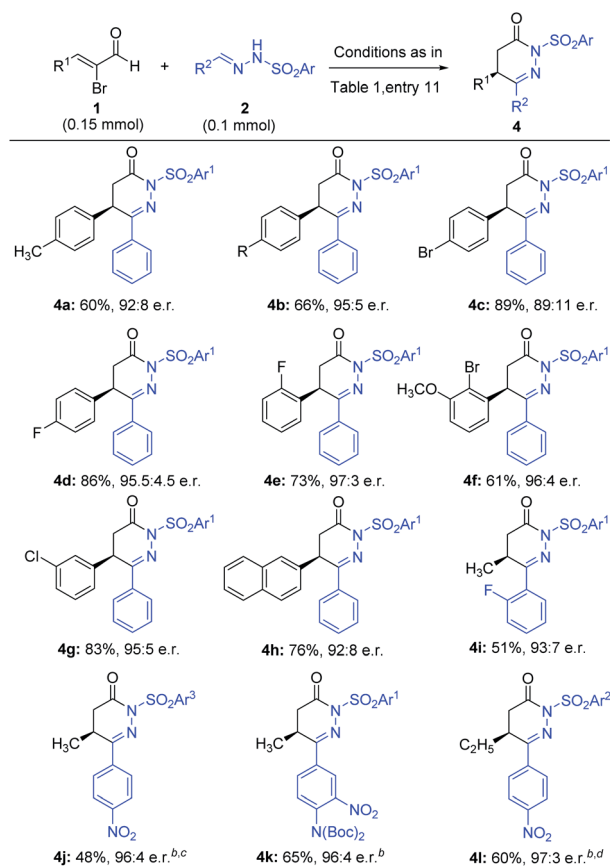
enantioselectivity of our reaction (Table 1, entry 7 and see ESI†). Both organic and inorganic bases were efficient in providing the desired product (Table 1, entries 8–10 and also see ESI†). After further screening of the precatalyst loading parameter, we established that the optimal conditions consist 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  $\alpha$ -bromo cinnamaldehyde (**1a**) as the model substrate and the results are shown in Scheme 1. Different kinds of substituted

phenyl rings [such as halogens,  $-\text{OAc}$ ,  $-\text{N}(\text{Boc})_2$  and methyl groups at the *ortho*, *meta*, and *para* positions] at the azomethine carbon of hydrazones were all tolerated and gave the desired products in good yields and excellent e.r. values (**3a–h**). Interestingly, gram-scale synthesis of **3b** with 1 mol% precatalyst loading could furnish the product in 74% yield and 96 : 4 e.r. The phenyl ring of **2a** could also be replaced with 1-naphthyl and 2-naphthyl without affecting the yield and e.r. value of the products (**3i–j**) significantly. A diverse set of heteroaryls such as 2-benzothiophenyl, 2-thiophenyl, 3-thiophenyl and 3-pyridyl at the azomethine carbon of hydrazones afforded the desired products in excellent yield and e.r. (**3k–3n**). The absolute configuration of **3n** was confirmed by X-ray analysis.<sup>20</sup> Most of the time *p*-nosyl (*p*-Ns) protected hydrazones gave our desired products in excellent outcomes; unfortunately, similar hydrazones bearing a highly electron-deficient phenyl ring at the azomethine position were degraded under our catalytic conditions. Thus, tosyl protected hydrazones (**2o–2p**) were used in our reaction, giving the products (**3o–3p**) in good yields and excellent enantioselectivities. Surprisingly, vinyl substituted



Scheme 1 Scope of hydrazone substrates.<sup>a</sup>Reaction 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.  $\text{SO}_2\text{Ar}^1 = p$ -nosyl,  $\text{SO}_2\text{Ar}^2 = \text{tosyl}$ .



Scheme 2 Scope of  $\alpha$ -bromo enal substrates.<sup>a</sup>Reaction 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.  $\text{SO}_2\text{Ar}^1 = p$ -nosyl,  $\text{SO}_2\text{Ar}^2 = \text{tosyl}$ ,  $\text{SO}_2\text{Ar}^3 = o$ -nosyl. <sup>b</sup>NaOAc and THF were used as the base and solvent, respectively. <sup>c</sup>Reagents were added in a glovebox. The reaction was carried out at 0 °C for 24 h with 20 mol% precatalyst and 0.2 mmol bromo enal. <sup>d</sup>0.2 mmol bromo enal was used.



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 electron-donating and withdrawing substituents at the  $\beta$ -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  $\beta$ -phenyl ring of the bromoenal could also be replaced with the 2-naphthyl 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 molecules<sup>2–6</sup> (Fig. 1a), we further examined the reaction of  $\alpha$ -bromocrotonaldehyde with some hydrazones. For example, hydrazone containing 2-fluoro phenyl for azomethine substitution was coupled with  $\alpha$ -bromocrotonaldehyde 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  $\alpha$ -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  $\alpha$ -bromocrotonaldehyde, for example,  $\beta$ -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  $\alpha,\beta$ -unsaturated acyl azolium is blocked by the catalyst and specifically the presence of the nitro ( $-\text{NO}_2$ ) group on the catalyst makes the *Si*-face less available for the nucleophile. So, it is more favourable to intercept the NHC-bound  $\alpha,\beta$ -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

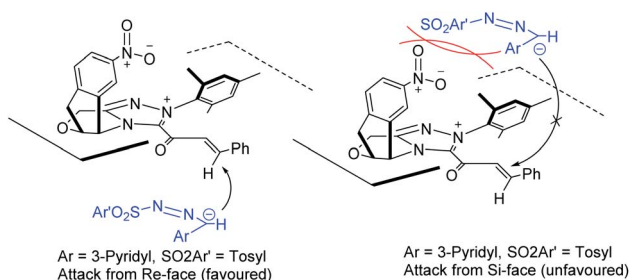
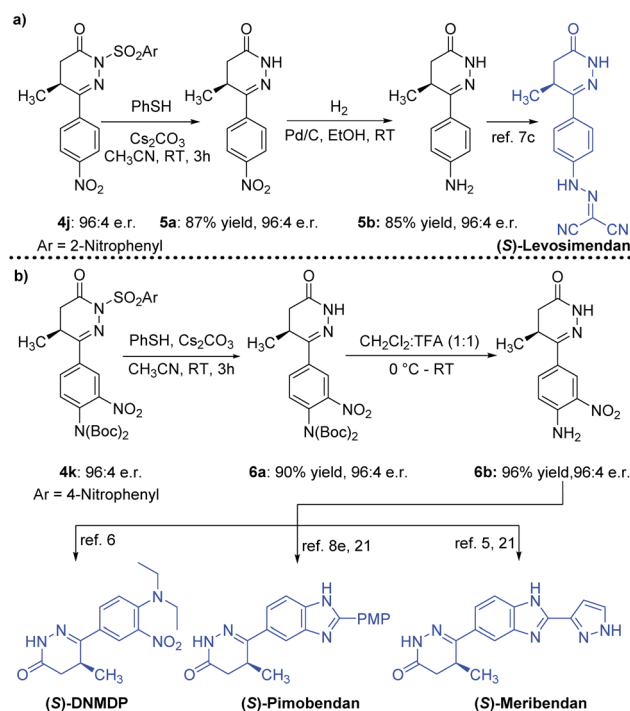


Fig. 2 Proposed TS model for stereoselectivity.



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).<sup>7c</sup> 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 DNMDP<sup>6</sup>, drug Pimobendan<sup>8e,21</sup> and bioactive Meribendan<sup>5,21</sup> (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



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.

## Acknowledgements

We thank Dr Yongxin Li (NTU) for assistance with X-ray structure analysis. We acknowledge financial support from the Singapore National Research Foundation under its NRF Investigatorship (NRF-NRFI2016-06) and Competitive Research Program (NRF-CRP22-2019-0002); the Ministry of Education, Singapore, under its MOE AcRF Tier 1 Award (RG108/16, RG5/19, RG1/18), MOE AcRF Tier 2 (MOE2019-T2-2-117), MOE AcRF Tier 3 Award (MOE2018-T3-1-003); the Agency for Science, Technology and Research (A\*STAR) under its A\*STAR AME IRG Award (A1783c0008, A1783c0010); GSK-EDB Trust Fund; Nanyang Research Award Grant, Nanyang Technological University; the National Natural Science Foundation of China (21772029, 21801051, 21807019, 21961006, 22071036, 22061007, 82360589, 81360589), Frontiers Science Center for Asymmetric Synthesis and Medicinal Molecules, Department of Education, Guizhou Province [Qianjiaohe KY number (2020) 004]; The 10 Talent Plan (Shicengci) of Guizhou Province ([2016] 5649); the Science and Technology Department of Guizhou Province ([2018]2802, [2019]1020); the National Natural Science Foundation of China (No. 31960546); the Program of Introducing Talents of Discipline to Universities of China (111 Program, D20023) at Guizhou University; the Guizhou Province First-Class Disciplines Project [(Yiliu Xueke Jianshe Xiangmu)-GNYL(2017)008], NSFC Grant (81360589), Guizhou University of Traditional Chinese Medicine (China); and Guizhou University.

## Notes and references

- For selected reviews, see: (a) R. Bansal and S. Thota, *Med. Chem. Res.*, 2013, **22**, 2539–2552; (b) S. Dubey and P. A. Bhosle, *Med. Chem. Res.*, 2015, **24**, 3579–3598; for selected examples, see: (c) R. Bansal, D. Kumar, R. Carron and C. de la Calle, *Eur. J. Med. Chem.*, 2009, **44**, 4441–4447; (d) M. Thygesen, H. D. Lehmann, J. Gries, H. Koenig, R. Kretzschmar, J. Kunze, R. Lebkuecher and D. Lenke, *J. Med. Chem.*, 1983, **26**, 800–807; (e) S. Demirayak, A. C. Karaburun, I. Kayagil, K. Erol and B. Sirmagul, *Arch. Pharmacol. Res.*, 2004, **27**, 13–18; (f) S. Ovais, K. Javed, S. Yaseen, R. Bashir, P. Rathore, R. Yaseen, A. D. Hameed and M. Samim, *Eur. J. Med. Chem.*, 2013, **67**, 352–358; (g) J. Singh, V. Saini, A. Kumar and R. Bansal, *Bioorg. Chem.*, 2017, **71**, 201–210; (h) D. Sharma and R. Bansal, *Med. Chem. Res.*, 2016, **25**, 1574–1589.
- For selected examples, see: (a) Z. Papp, I. Édes, S. Fruhwald, S. G. De Hert, M. Salmenperä, H. Leppikangas, A. Mebazaa, G. Landoni, E. Grossini, P. Caimmi, A. Morelli, F. Guarracino, R. H. G. Schwinger, S. Meyer, L. Algotsson, B. G. Wikström, K. Jörgensen, G. Filippatos, J. T. Parissis, M. J. G. González, A. Parkhomenko, M. B. Yilmaz, M. Kivikko, P. Pollesello and F. Follath, *Int. J. Cardiol.*, 2012, **159**, 82–87; (b) M. S. Nieminen, S. Fruhwald, L. M. A. Heunks, P. K. Suominen, A. C. Gordon, M. Kivikko and P. Pollesello, *Heart Lung Vessel*, 2013, **5**, 227–245; (c) A. Mebazaa, M. S. Nieminen, M. Packer, A. Cohen-Solal, F. X. Kleber, S. J. Pocock, R. Thakkar, R. J. Padley, P. Pöder, M. Kivikko and f. t. SURVIVE Investigators, *JAMA*, 2007, **297**, 1883–1891.
- For selected examples, see: (a) J. Brett, C. Wylie and J. Brown, *Clin. Toxicol.*, 2020, **58**, 146–148; (b) M. Baron Toaldo, M. Pollesello and A. Diana, *J. Vet. Cardiol.*, 2020, **28**, 37–47.
- K. Ochiai, N. Ando, K. Iwase, T. Kishi, K. Fukuchi, A. Ohinata, H. Zushi, T. Yasue, D. R. Adams and Y. Kohno, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 5451–5456.
- R. Jonas, M. Klockow, I. Lues, H. Prücher, H. J. Schliep and H. Wurziger, *Eur. J. Med. Chem.*, 1993, **28**, 129–140.
- L. de Waal, T. A. Lewis, M. G. Rees, A. Tsherniak, X. Wu, P. S. Choi, L. Gechijian, C. Hartigan, P. W. Faloon, M. J. Hickey, N. Tolliday, S. A. Carr, P. A. Clemons, B. Munoz, B. K. Wagner, A. F. Shamji, A. N. Koehler, M. Schenone, A. B. Burgin, S. L. Schreiber, H. Greulich and M. Meyerson, *Nat. Chem. Biol.*, 2016, **12**, 102–108.
- For selected examples, see: (a) R. L. Hudkins, A. L. Zulli, R. Dandu, M. Tao, K. A. Josef, L. D. Aimone, R. C. Haltiwanger, Z. Huang, J. A. Lyons, J. R. Mathiasen, R. Raddatz and J. A. Gruner, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 1504–1509; (b) S. Jakkaraj, V. G. Young Jr. and G. I. Georg, *Tetrahedron*, 2018, **74**, 2769–2774; (c) H. Singhanian, EP3424908A1, 2019; (d) M. Harjula, I. Larma, S. Antila and L. Lehtonen, WO 99/16443, 1999; (e) W. Yan, X. Qi, S. Zhao and N. Liu, CN104418810A, 2015; (f) L. Cheng, J. Cai, Q. Fu and Y. Ke, *J. Sep. Sci.*, 2019, **42**, 2482–2490.
- For selected examples, see: (a) Y. Nomoto, H. Takai, T. Ohno, K. Nagashima, K. Yao, K. Yamada, K. Kubo, M. Ichimura, A. Mihara and H. Kase, *J. Med. Chem.*, 1996, **39**, 297–303; (b) T. Seki, A. Kanada, T. Nakao, M. Shiraiwa, H. Asano, K. Miyazawa, T. Ishimori, N. Minami, K. Shibata and K. Yasuda, *Chem. Pharm. Bull.*, 1998, **46**, 84–96; (c) A. Kojima and Y. Kohno, *Tetrahedron*, 2013, **69**, 1658–1662; (d) B. A. Provencher, K. J. Bartelson, Y. Liu, B. M. Foxman and L. Deng, *Angew. Chem., Int. Ed.*, 2011, **50**, 10565–10569; (e) S. Li, CN107344933A, 2017; (f) F. F. Owings, M. Fox, C. J. Kowalski and N. H. Baine, *J. Org. Chem.*, 1991, **56**, 1963–1966.
- For selected examples, see: (a) Y. Kuang, K. Wang, X. Shi, X. Huang, E. Meggers and J. Wu, *Angew. Chem., Int. Ed.*, 2019, **58**, 16859–16863; (b) M. Z. Liang and S. J. Meek, *Angew. Chem., Int. Ed.*, 2019, **58**, 14234–14239; (c) D. Kaldre, I. Klose and N. Maulide, *Science*, 2018, **361**, 664–667; (d) S. Huang, L. Kötzner, C. K. De and B. List, *J. Am. Chem. Soc.*, 2015, **137**, 3446–3449.



- 10 (a) X. Li, K. Gai, Z. Yuan, J. Wu, A. Lin and H. Yao, *Adv. Synth. Catal.*, 2015, **357**, 3479–3484; (b) W. C. Yuan, B. X. Quan, J. Q. Zhao, Y. You, Z. H. Wang and M. Q. Zhou, *J. Org. Chem.*, 2020, **85**, 11812–11821; (c) W. Yin, L. Fang, Z. Wang, F. Gao, Z. Li and Z. Wang, *Org. Lett.*, 2019, **21**, 7361–7364; (d) L. Duan, X. Wang, Y. Gu, Y. Hou and P. Gong, *Org. Chem. Front.*, 2020, **7**, 2307–2312.
- 11 (a) B. Liu, R. Song, J. Xu, P. K. Majhi, X. Yang, S. Yang, Z. Jin and Y. R. Chi, *Org. Lett.*, 2020, **22**, 3335–3338; (b) J. Sun, F. He, Z. Wang, D. Pan, P. Zheng, C. Mou, Z. Jin and Y. R. Chi, *Chem. Commun.*, 2018, **54**, 6040–6043; (c) Y. Liu, Q. Chen, C. Mou, L. Pan, X. Duan, X. Chen, H. Chen, Y. Zhao, Y. Lu, Z. Jin and Y. R. Chi, *Nat. Commun.*, 2019, **10**, 1675; (d) Y. Liu, P. K. Majhi, R. Song, C. Mou, L. Hao, H. Chai, Z. Jin and Y. R. Chi, *Angew. Chem., Int. Ed.*, 2020, **59**, 3859–3863.
- 12 For reviews, see: (a) D. Enders, O. Niemeier and A. Henseler, *Chem. Rev.*, 2007, **107**, 5606–5655; (b) D. M. Flanagan, F. Romanov-Michailidis, N. A. White and T. Rovis, *Chem. Rev.*, 2015, **115**, 9307–9387; (c) X. Chen, H. Wang, Z. Jin and Y. R. Chi, *Chin. J. Chem.*, 2020, **38**, 1167–1202; for selected examples, see: (d) J. Guin, S. De Sarkar, S. Grimme and A. Studer, *Angew. Chem., Int. Ed.*, 2008, **47**, 8727–8730; (e) S. De Sarkar and A. Studer, *Angew. Chem., Int. Ed.*, 2010, **49**, 9266–9269; (f) S. De Sarkar, S. Grimme and A. Studer, *J. Am. Chem. Soc.*, 2010, **132**, 1190–1191; (g) A. Levens, A. Ametovski and D. W. Lupton, *Angew. Chem., Int. Ed.*, 2016, **55**, 16136–16140; (h) X. Y. Chen, Z. H. Gao and S. Ye, *Acc. Chem. Res.*, 2020, **53**, 690–702; (i) A. Ghosh and A. T. Biju, *Angew. Chem., Int. Ed.*, 2021, **60**, 2–15; (j) H. Ohmiya, *ACS Catal.*, 2020, **10**, 6862–6869; (k) S. Mondal, S. R. Yetra, S. Mukherjee and A. T. Biju, *Acc. Chem. Res.*, 2019, **52**, 425–436; (l) T. K. Das and A. T. K. Biju, *Chem. Commun.*, 2020, **56**, 8537–8552; (m) X. Wu, B. Liu, Y. Zhang, M. Jeret, H. Wang, P. Zheng, S. Yang, B. A. Song and Y. R. Chi, *Angew. Chem., Int. Ed.*, 2016, **55**, 12280–12284; (n) X. Wu, L. Zhou, R. Maiti, C. Mou, L. Pan and Y. R. Chi, *Angew. Chem., Int. Ed.*, 2019, **58**, 477–481.
- 13 (a) A. Das, C. M. R. Volla, I. Atodiresei, W. Bettray and M. Rueping, *Angew. Chem., Int. Ed.*, 2013, **52**, 8008–8011; (b) C. M. R. Volla, A. Das, I. Atodiresei and M. Rueping, *Chem. Commun.*, 2014, **50**, 7889–7892; (c) J.-H. Mao, Z.-T. Wang, Z.-Y. Wang and Y. Cheng, *J. Org. Chem.*, 2015, **80**, 6350–6359; (d) C.-L. Zhang, D.-L. Wang, K.-Q. Chen and S. Ye, *Org. Biomol. Chem.*, 2015, **13**, 11255–11262; (e) X. Xu, P. Y. Zavalij, W. Hu and M. P. Doyle, *J. Org. Chem.*, 2013, **78**, 1583–1588; (f) J.-N. Zhu, W.-K. Wang, J. Zheng, H.-P. Lin, Y.-X. Deng and S.-Y. Zhao, *J. Org. Chem.*, 2019, **84**, 11032–11041; (g) W. Wu, X. Yuan, J. Hu, X. Wu, Y. Wei, Z. Liu, J. Lu and J. Ye, *Org. Lett.*, 2013, **15**, 4524–4527.
- 14 M. Fernández, U. Uria, J. L. Vicario, E. Reyes and L. Carrillo, *J. Am. Chem. Soc.*, 2012, **134**, 11872–11875.
- 15 (a) A. C. Mantovani, T. A. C. Goulart, D. F. Back and G. Zeni, *Chem.–Eur. J.*, 2014, **20**, 12663–12668; (b) I. R. Siddiqui, Rahila, P. Rai, H. Sagir and M. A. Waseem, *RSC Adv.*, 2015, **5**, 52355–52360.
- 16 C. D. Campbell, C. Concellón and A. D. Smith, *Tetrahedron: Asymmetry*, 2011, **22**, 797–811.
- 17 S. Kuwano, S. Harada, B. Kang, R. Oriez, Y. Yamaoka, K. Takasu and K. Yamada, *J. Am. Chem. Soc.*, 2013, **135**, 11485–11488.
- 18 M. He, J. R. Struble and J. W. Bode, *J. Am. Chem. Soc.*, 2006, **128**, 8418–8420.
- 19 C. Zhao, F. Li and J. Wang, *Angew. Chem., Int. Ed.*, 2016, **55**, 1820–1824.
- 20 CCDC 2062761 (3n) contains the supplementary crystallographic data for this paper.†
- 21 Q. Tong, J. Chen, X. Cui, Z. Gong and B. Zhang, CN107522663A, 2017.

