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Article

4,5-Dihydro-2*H*-pyridazin-3-ones as a Platform for the Construction of Chiral 4,4-Disubstituted-dihydropyridazin-3-ones †

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Abstract

4,5-Dihydro-2*H*-pyridazin-3-ones (DHPDOs) are important synthetic as well as naturally occurring heterocycles. We herein report the synthesis of various 4-monofunctionalized 4,5-dihydro-2*H*-pyridazin-3-ones and their use as starting materials to access 4,4-disubstituted dihydropyridazin-3-ones in an asymmetric fashion. By using chiral ammonium salt phase-transfer catalysts, conjugate additions of these scaffolds to classical acrylate-based Michael acceptors, as well as quinone methides, can be carried out with moderate to good enantioselectivities and in reasonable yields, affording a new pathway to dihydropyridazin-3-one derivatives with an all-carbon stereocenter.

Keywords: organic chemistry; Meldrum's acid; asymmetric synthesis; phase-transfer catalysis; pyridazinones

1. Introduction

The 4,5-dihydro-2*H*-pyridazin-3-one scaffold (DHPDO; Scheme 1A) represents an important structural motif that can be frequently found in a variety of synthetic and naturally occurring biologically active 6-membered *N*-containing heterocycles [1–12]. Not surprisingly, several research groups have developed catalytic asymmetric syntheses of DHPDO derivatives which are either mono-substituted at the C5- [13,14], or the C4-position (α -position of the carbonyl functionality) [15–22]. Furthermore, (chiral) substituted 4,5-dihydropyridazinone derivatives are useful building blocks and may be considered as masked γ -amino acid (γ -AA) derivatives [23,24], after reduction of the hydrazone moiety or cleavage of the N-N bond [16,25–29]. In that domain, several of these potentially medically interesting heterocycles contain one or two substituents at the 4-position [5,11]. However, to the best of our knowledge, the asymmetric catalytic elaboration of α,α -disubstituted DHPDOs, containing a quaternary stereocenter has not been covered yet. Thus, the development of reliable strategies to access different α -functionalized DHPDOs straightforwardly, even in an asymmetric manner, represents a worthwhile goal. Our groups have a long-standing interest in asymmetric synthesis and functionalization of chiral heterocycles, i.e., those that can be considered as masked α - and β -amino acids [30–33].



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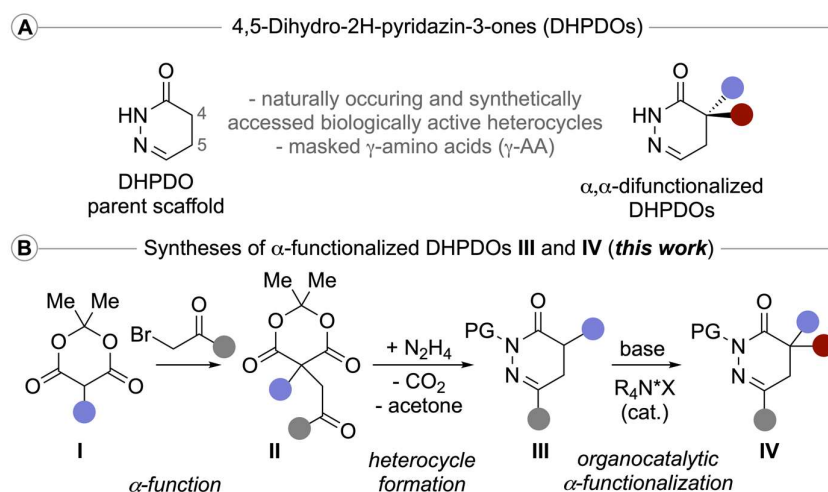
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Scheme 1. (A) General structures of DHPDOs and (B) the herein investigated strategy to access α -functionalized DHPDOs III and IV starting from Meldrum's acid derivatives I.

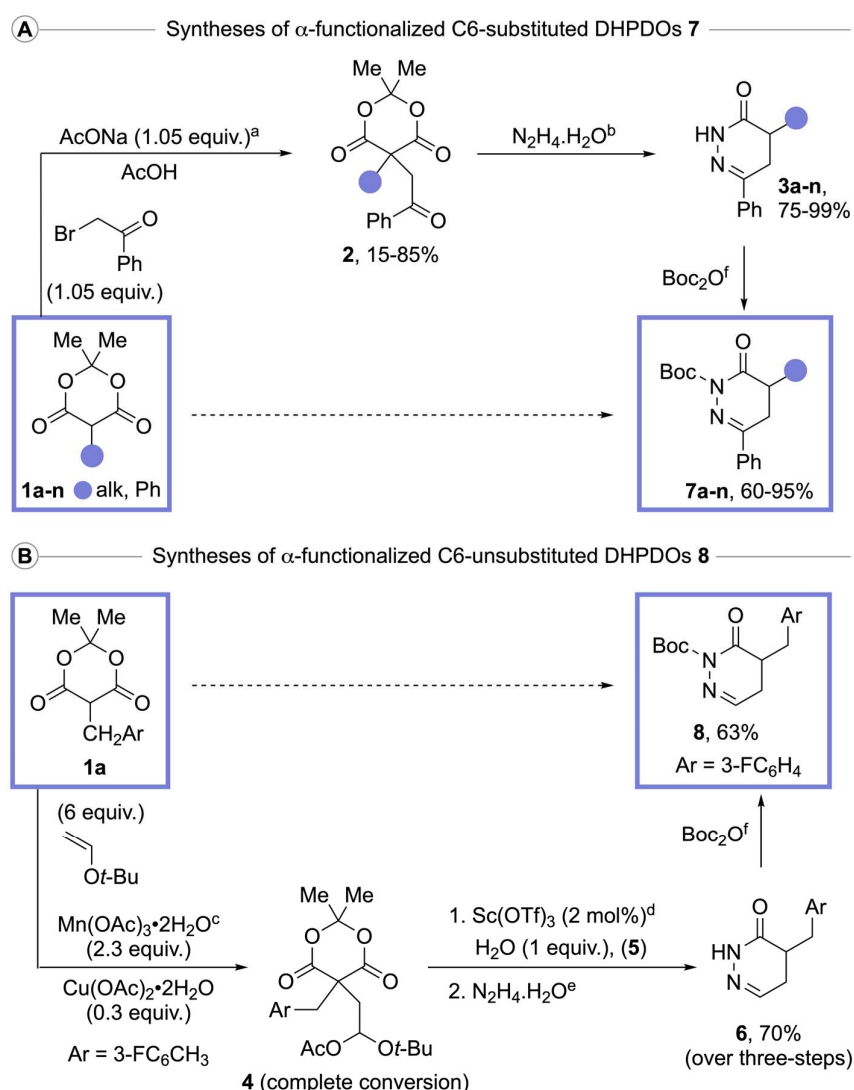
In line with our general research interests and the aforementioned value of chiral 4,5-dihydro-2H-pyridazin-3-ones, we now set out to establish versatile synthesis routes to access various α -functionalized DHPDOs III based on hydrazine and Meldrum's acid chemistry, i.e., derivatives I [34–37] (Scheme 1). The easily accessible compounds I were believed to allow the elaboration of appropriately functionalized precursors II, which can be seen as 1,4-ketoester equivalents enabling the synthesis of DHPDOs III upon treatment with hydrazine (Scheme 1B). We herein furthermore report a strategy which demonstrates the organocatalytic asymmetric α -functionalization of DHPDO compounds III with different Michael-type acceptors under chiral ammonium salt phase-transfer catalytic conditions en route to the construction of new heterocyclic derivatives IV with an all-carbon stereocenter [38–42].

2. Results and Discussion

2.1. Syntheses of Pyridazinones

At the onset, we sought a straightforward and versatile route to α -functionalized DHPDOs in order to allow the investigation of the catalytic asymmetric α -alkylation reactions (III to IV, Scheme 1). Inspired by the pioneering contribution of Tóth and collaborators [43], we exploited the readily available substituted Meldrum's acid derivatives 1 as convenient precursors of 1,4-ketoester equivalents (Scheme 2) [11,44,45]. After an alkylation step of 1 with α -bromoacetophenone under basic conditions, producing access to products 2, the facile condensation of hydrazine led to a series of free NH-containing DHPDOs 3 in good yields. On the other hand, in the purpose of expanding the scope of DHPDO substrates, we tackled the introduction of the $\text{CH}_2\text{CH}_2\text{CHO}$ motif. However, this turned out to be not a trivial task on Meldrum's acid derivatives 1, according to the weak nucleophilic properties of its corresponding anion [34–37]. By revisiting Parsons' conditions, in the presence of manganese(III) acetate as a single-electron oxidant, we found that *tert*-butyl vinyl ether smoothly underwent a radical addition of the model benzylated Meldrum's acid derivative 1a, yielding product 4 [46,47]. This *tert*-butyl derived acetal 4 was easily deprotected into the corresponding aldehyde 5 in 15 min using $\text{Sc}(\text{OTf})_3$ as a Lewis acid [48]. (We initially tried the commonly employed *n*-butyl vinyl ether as radical reaction partner [46], but the transformation proved to be less efficient than with *tert*-butyl vinyl ether, and the corresponding addition product was reluctant to be deprotected into aldehyde without leading to decomposition events under forced conditions). This rather unstable aldehyde has to be rapidly engaged in the subsequent condensation with hydrazine at 60 °C, affording

the DHPDO **6** in excellent 70% yield over three steps. Eventually, in order to explore the reactivity of various molecular platforms, the *N*-Boc-protected DHPDOs **7** and **8** were also synthesized.



Conditions (a) AcONa (1.05 equiv.), AcOH (1 equiv.), DMF, 20 °C, 24 h. (b) $\text{N}_2\text{H}_4\cdot\text{H}_2\text{O}$ (4 equiv.), DMF, 20 °C, 24 h. (c) $\text{Mn}(\text{OAc})_3\cdot 2\text{H}_2\text{O}$ (2.3 equiv.), $\text{Cu}(\text{OAc})_2\cdot 2\text{H}_2\text{O}$ (0.3 equiv.), DCM, 50 °C, 36 h. (d) $\text{Sc}(\text{OTf})_3$ (2 mol%), H_2O (1 equiv.), 20 °C, MeNO_2 , 15 min.. (e) $\text{N}_2\text{H}_4\cdot\text{H}_2\text{O}$ (4 equiv.), DMF, 60 °C, 24 h. (f) Boc_2O (1.2 equiv.), DMAP (0.2 equiv.), DCM, 20 °C, 19 h.

Scheme 2. Elaboration of α -functionalized DHPDOs **7–8** starting from Meldrum's acid derivatives, either (A) C6-substituted **7** or (B) C6-unsubstituted derivatives **8**.

2.2. α -Functionalizations of Pyridazinones

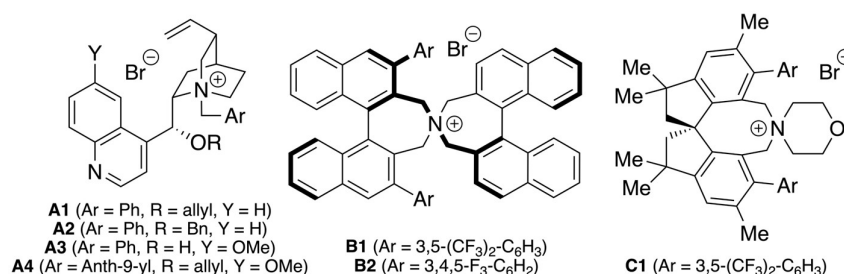
With a robust route for the syntheses of differently functionalized pyridazinones **3** and **6**, as well as the *N*-protected derivatives **7** and **8** at hand, we next focused on the asymmetric α -functionalization of these heterocycles. We started our investigations by testing the quaternary ammonium salt-catalysed Michael addition of the parent compound **7a** to acrylate **9a** (Table 1 gives a condensed overview of the most significant results obtained by using the catalysts depicted in Figure 1).

Table 1. Optimization of the Quatsalt-catalysed Michael addition of pyridazinone **7a** to acrylate **9a**.¹

$\text{7a (Ar = 3-FC}_6\text{H}_4\text{)} + \text{9a} \xrightarrow[\text{base, solvent, room temp.}]{\text{R}_4\text{NX (10 mol\%)}} \text{10a}$

Entry	R ₄ NX	Solvent	Base (Eq.)	t (h)	Conv. (%) ²	10a (%) ³	e.r. ⁴
1	A1	CH ₂ Cl ₂	Cs ₂ CO ₃ (1.5)	3	70	70	55:45
2	A2	CH ₂ Cl ₂	Cs ₂ CO ₃ (1.5)	3	55	55	54:46
3	A3	CH ₂ Cl ₂	Cs ₂ CO ₃ (1.5)	3	10	10	n.d.
4	A4	CH ₂ Cl ₂	Cs ₂ CO ₃ (1.5)	3	90	85	54:46
5	A4	THF	Cs ₂ CO ₃ (1.5)	3	100	95	52:48
6	A4	toluene	Cs ₂ CO ₃ (1.5)	3	80	80	52:48
7	A4	CH ₂ Cl ₂	K ₃ PO ₄ (1.5)	3	40	35	50:50
8	B1	CH ₂ Cl ₂	Cs ₂ CO ₃ (1.5)	3	40	30	40:60
9	B2	CH ₂ Cl ₂	Cs ₂ CO ₃ (1.5)	3	40	35	43:57
10	C1	CH ₂ Cl ₂	Cs ₂ CO ₃ (1.5)	3	90	85	36:64
11	C1	CH ₂ Cl ₂	K ₃ PO ₄ (1.5)	3	25	25	36:64
12	C1	THF	Cs ₂ CO ₃ (1.5)	3	95	50	42:58
13	C1	toluene	Cs ₂ CO ₃ (1.5)	3	30	25	10:90
14	C1	toluene	Cs ₂ CO ₃ (1.5)	18	80	75	15:85
15	C1	toluene	Cs ₂ CO ₃ (1.5)	40	100	90	19:81
16	C1	toluene	Cs ₂ CO ₃ (3)	18	100	90 (54)	19:81
17 ⁵	C1	toluene	Cs ₂ CO ₃ (3)	18	40	40	10:90

¹ All reactions were run using 0.1 mmol **7a**, 0.3 mmol **9a**, the indicated base and 10 mol% of the indicated catalyst in the given solvent (0.1 M) at room temperature unless otherwise stated. ² Based on remaining **7a** calculated from the ¹H NMR spectrum of the crude product using nitromethane as an internal standard (rounded in increments of 5%). ³ NMR yields using nitromethane as an internal standard (rounded in increments of 5%)—isolated yields given in brackets. ⁴ Determined by HPLC using a chiral stationary phase (given as ratio of (–):(+)–enantiomer⁵ at 0 °C.

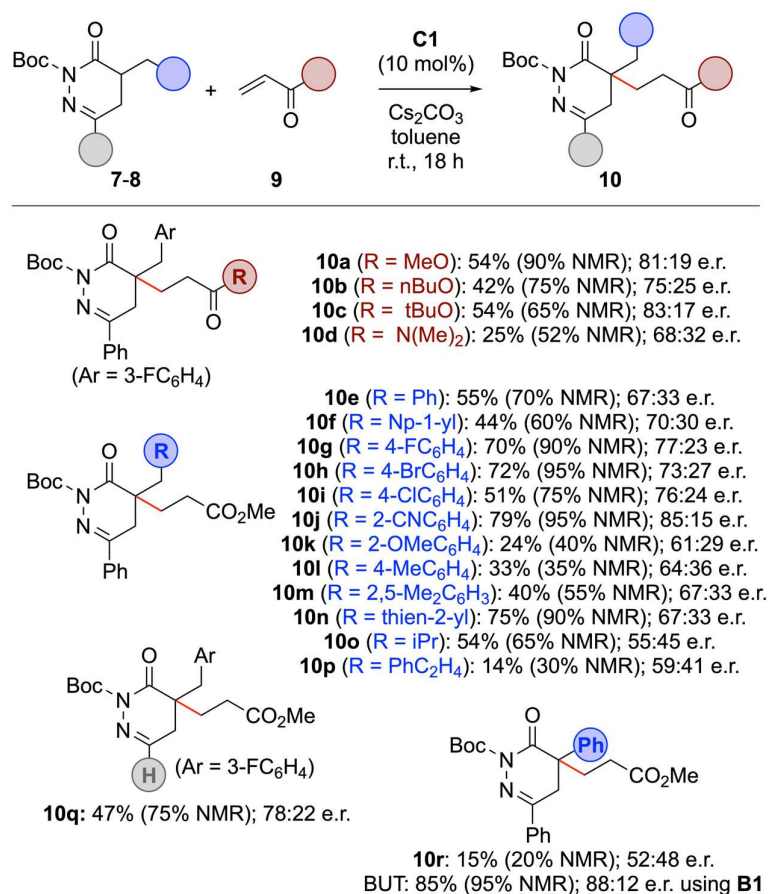
**Figure 1.** Chiral ammonium salt catalysts R₄NX used herein.

First experiments using the well-established Cinchona alkaloid-based Quatsalts **A** showed that the 1,4-addition of **7a** to **9a** is possible in principle, but the enantioselectivities obtained for product **10a** were disappointing (entries 1–4) [38–42]. Also, varying the base and solvent did not allow us to achieve any notable levels of enantiodifferentiation (entries 5–7 give illustrative examples of a broader screening). Thus, we focused on alternative catalyst scaffolds. Unfortunately, the commercially available Maruoka catalysts **B** allowed for low conversions and low enantioselectivities only (entries 8 and 9; other conditions were tested as well, but did not lead to any improvement) [49].

Interestingly, the recently introduced spirobiindane-based salt **C1** was the only catalyst scaffold that gave reasonable conversion combined with somewhat more promising levels of enantioselectivities under the initially chosen conditions (entry 10) [50–52]. Variation of base and solvent (entries 10–13) revealed that Cs₂CO₃ in toluene allows for notable enantioselectivities (up to 90:10 e.r.), but conversion was slow (entry 13). While increased

reaction times resulted in more practical rates of conversion, this was accompanied by a slight decrease in enantioselectivity (entries 13–15). Such a decrease in enantioselectivity with increased reaction progress can most likely be rationalized by a change of the catalyst's integrity, i.e., its counter anion or also some catalyst degradation over the course of several catalyst turnovers. Using a slightly larger excess of base (3 eq.) at room temperature finally gave product **10a** with a high NMR yield of around 90% and a moderate enantioselectivity of 81:19 e.r. (entry 16). Unfortunately, the reaction became again much slower when carried out at 0 °C (entry 17). Noteworthy, the isolated yield of **10a** was lower than expected from the NMR yield (54% vs 90%; entry 16), which can be explained by a partial retro-Michael reaction of **10a** under the applied “classical” normal-phase silica gel column chromatography conditions (as observed by the formation of notable amounts of starting material **7a** again; this obstacle can to some extent be reduced, but not totally suppressed by using basified high-quality silica gel).

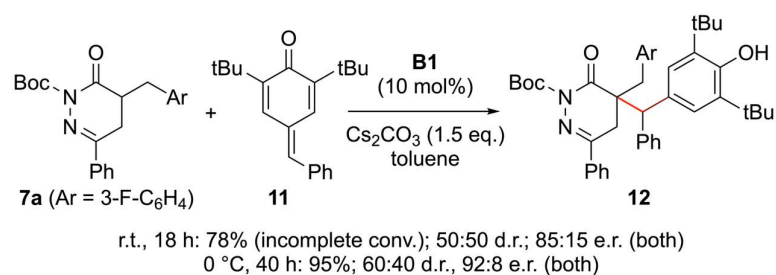
Having identified operationally reliable conditions that represent a reasonable compromise between conversion (yield) and enantioselectivity, we next investigated the generality of this protocol (Scheme 3). Testing different acrylates **9** first revealed that the ester functionality does not massively influence the outcome of this transformation (products **10a–c**). Interestingly, even the poorly electrophilic dimethylacrylamide was transformed into the corresponding Michael adduct **10d** in 32:68 er while in moderate NMR yield of 52%. Variations of the (hetero)benzylic α -substituents of starting materials **7** were investigated next (products **10e–k** and **10n**). Unfortunately, enantioselectivities were only modest as well, while conversion rates and yields somewhat depended on the nature of the benzylic groups (i.e., Me-containing electron-rich aryl groups led to lower yields as exemplified for products **10m** and **10n**). Other alkyl substituents were less well tolerated in terms of yield and e.r. (**10l**, **10p**).



Scheme 3. Application scope for the asymmetric 1,4-addition of compounds **7** and **8** to various acceptors **9**.

The use of the 6-H containing DHPDO **8** was also reasonably well tolerated, producing product **10q** in comparable yield and enantiopurity as for the 4-Ph-substituted analogue **10a**. Furthermore, we also tested an α -Ph-containing DPHDO and hereby made an interesting observation (product **10r**). While the standard conditions using Quatsalt **C1** resulted in low yield and racemic product formation only, the use of Maruoka's catalyst **B1** resulted in high yield and good e.r. of 88:12. This result, which is in clear contrast to the observations made when optimizing the parent reaction using α -alkylated pyridazinone **7a** (Table 1), clearly underscore the difficulties in predicting a suited catalyst for a given transformation and the importance of proper catalyst screening for differently substituted starting materials!

In addition to using classical 1,4-acceptors **9**, we also tested if compounds **7** may undergo 1,6-additions to *para*-quinone methides (*p*-QMs) such as compound **11** (Scheme 4) [53–56]. We quickly realized that the addition of **7a** to **11** is a rather rapid and high-yielding process under quaternary ammonium salt catalysis conditions, affording the corresponding adduct **12** in up to 95% yield. When using chiral Quatsalts, the diastereoselectivity was always low (<60:40 d.r.)—this limitation is not rare. Reactions of enolate species to *p*-QMs could also not be overcome by any alteration of the reaction conditions. In contrast, enantioselectivities for both diastereomers were up to 92:8 e.r. when using Maruoka's catalyst **B1** at 0 °C.



Scheme 4. 1,6-addition of compound **7a** to *p*-QM **11**.

3. Experimental Details

Detailed experimental procedures and analytical details can be found in the online supporting information.

General procedure for the synthesis of N-Boc 4,5-dihydropyridazinone derivatives **7**.

Compounds 2: C5-monosubstituted Meldrum's acid derivatives **1** (4.9 mmol), 2-bromoacetophenone (1.05 g, 5.3 mmol) and sodium acetate (435 mg, 5.3 mmol) were introduced into a round-bottom flask (N_2 atmosphere). The mixture was dissolved in DMF (5 mL, 0.98 M), and acetic acid (0.29 mL, 4.9 mmol) was added dropwise at room temperature (vigorous stirring). After a night, the solvent was evaporated under reduced pressure. The crude product was dissolved in DCM and washed with a mixture of $\text{H}_2\text{O}/\text{Na}_2\text{CO}_3$ (sat.) (9:1), and then with brine. The resulting organic phase was dried over anhydrous Na_2SO_4 , filtrated, and finally the solvent was evaporated under reduced pressure. The crude reaction mixture was triturated with Et_2O to give products **2a–o** (exact experimental and analytical details can be found in the online supporting information).

Compounds 3: C5-disubstituted Meldrum's acid derivative **2** (3.3 mmol) was solubilized in DMF (11 mL, 0.3 M) first (N_2 atmosphere). At 0 °C, under vigorous stirring, hydrazine monohydrate (0.65 mL, 13.3 mmol) was added dropwise. The reaction was stirred for 24 h at room temperature, then the solvent was evaporated under reduced pressure. The crude was dissolved in DCM and washed with an aqueous acidic solution (pH 3–4) and then with brine. The combined organic phases were dried over anhydrous Na_2SO_4 and finally, the

solvent was evaporated under reduced pressure, producing products **3** (exact experimental and analytical details can be found in the online supporting information).

Compounds **7**: Boc₂O (938.5 mg, 4.3 mmol) and DMAP (87.5 mg, 716 μmol) were introduced in a round-bottom flask (N₂ atmosphere). The N-unsubstituted 4,5-dihydropyridazinone **3** (3.58 mmol) was dissolved in anhydrous DCM (24 mL, 0.15 M) and introduced slowly into the round-bottom flask at room temperature. The solution was vigorously stirred overnight. Then, the solvent was evaporated under reduced pressure and the crude mixture was purified by silica gel column chromatography producing **7** (exact experimental and analytical details can be found in the online supporting information).

General procedure for the quaternary ammonium salt-catalyzed Michael addition of pyridazinones to Michael acceptors.

Spirobiindane-based ammonium salt **C1** (9.2 mg, 0.01 mmol) and Cs₂CO₃ (98 mg, 0.3 mmol) were introduced into a 2 mL vial at room temperature. The N-Boc dihydropyridazinone derivative **7** or **8** (0.1 mmol) was dissolved in toluene (1 mL, 0.1 M) and added to the vial followed by the Michael acceptor **9** (0.3 mmol). The mixture was stirred at room temperature for 18 h (1100 rpm). The crude mixture was filtered through a pad of silica gel using EtOAc as an eluent. Then, the crude mixture was purified by silica gel column chromatography producing the corresponding α,α-difunctionalized pyridazinone derivatives **10** (exact experimental and analytical details can be found in the online supporting information).

4. Conclusions

We herein introduced a straightforward route for the synthesis of various 4-monofunctionalized 4,5-dihydro-2*H*-pyridazin-3-ones. These heterocycles can then be employed as starting materials to access various 4,4-disubstituted dihydropyridazin-3-ones in an asymmetric fashion upon using chiral ammonium salt phase-transfer catalysts. More specifically, several conjugate addition reactions of these scaffolds to acrylate-based Michael acceptors (1,4-additions) as well as quinone methides (1,6-additions) were carried out with moderate to good enantioselectivities and in reasonable yields, allowing the construction and control of pyridazinone derivatives with an all-carbon stereocenter. Parts of this research have been presented at the 29th International Electronic Conference on Synthetic Organic Chemistry [57].

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/molecules31010083/s1>, Full experimental details and characterization of intermediates and products. NMR spectra and HPLC traces. Reference [58] is cited in the supplementary materials.

Author Contributions: Conceptualization, M.W. and J.-F.B.; methodology, M.W. and J.-F.B.; investigation, P.J.H., G.B. and W.N.; resources, M.W. and J.-F.B.; data curation, P.J.H. and W.N.; writing—original draft preparation, M.W. and J.-F.B.; writing—review and editing, P.J.H., W.N., M.W. and J.-F.B.; visualization, M.W. and J.-F.B.; supervision, M.W. and J.-F.B.; project administration, M.W. and J.-F.B.; funding acquisition, M.W. and J.-F.B. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Ma, X.; Sun, P.; Wang, J.; Huang, X.; Wu, J. Pyridazine and pyridazinone compounds in crops protection: A review. *Mol. Divers* **2024**, *29*, 5085–5100. [[CrossRef](#)] [[PubMed](#)]
2. Bansal, R.; Thota, S. Pyridazin-3(2H)-ones: The versatile pharmacophore of medicinal significance. *Med. Chem. Res.* **2013**, *22*, 2539–2552. [[CrossRef](#)]
3. Dubey, S.; Bhosle, P.S. Pyridazinone: An important element of pharmacophore possessing broad spectrum of activity. *Med. Chem. Res.* **2015**, *24*, 3579–3598. [[CrossRef](#)]
4. Shaik, B.B.; Chandrasekaran, B.; Obakachi, V.A.; Mokoena, S.; Mohite, S.B.; Kushwaha, B.; Kushwaha, N.S.; Karpoormath, R. Pyridazinone: A privileged scaffold for synthetic and biomedical applications. *J. Mol. Struct.* **2025**, *1326*, 140948.
5. Singh, J.; Sharma, D.; Bansal, R. Pyridazinone: An Attractive Lead for Anti-Inflammatory and Analgesic Drug Discovery. *Future Med. Chem.* **2017**, *9*, 95–127. [[CrossRef](#)]
6. Yu, S.; Yu, J.-T.; Pan, C. Advances in the synthesis of functionalized tetrahydropyridazines from hydrazones. *Org. Biomol. Chem.* **2024**, *22*, 7753–7766. [[CrossRef](#)]
7. Nieminen, M.S.; Fruhwald, S.; Heunks, L.M.A.; Suominen, P.K.; Gordon, A.C.; Kivikko, M.; Pollesello, P. Levosimendan: Current data, clinical use and future development. *Heart Lung Vessels* **2013**, *5*, 227–245.
8. Ünlü, S.; Banoglu, E.; Küpelib, E.; Yeşilada, E.; Şahina, M.F.; Ökçelika, B. Investigations of New Pyridazinone Derivatives for the Synthesis of Potent Analgesic and Anti-Inflammatory Compounds with Cyclooxygenase Inhibitory Activity. *Arch. Pharm. Pharm. Med. Chem.* **2003**, *336*, 406–412.
9. Friebe, W.-G.; Müller-Beckmann, B.; Kampe, W.; Kling, L.; von der Saal, W.; Mertens, A. Nonsteroidal Cardiotonics. 3. New 4,5-Dihydro-6-(1J3r-indol-5-yl)pyridazin-3(2fIT)-ones and Related Compounds with Positive Inotropic Activities. *J. Med. Chem.* **1990**, *33*, 2870–2875.
10. Imran, M.; Asif, M. Biologically Active Pyridazines and Pyridazinone Derivatives: A Scaffold for the Highly Functionalized Compounds. *Russ. J. Bioorg. Chem.* **2020**, *46*, 726–744. [[CrossRef](#)]
11. Kurose, A.; Ishida, Y.; Hirata, G.; Nishikata, T. Direct α -Tertiary Alkylations of Ketones in a Combined Copper–Organocatalyst System. *Angew. Chem. Int. Ed.* **2021**, *60*, 10620–10625. [[CrossRef](#)] [[PubMed](#)]
12. Ng, T.M.H. Levosimendan, a new calcium-sensitizing inotrope for heart failure. *Pharm. Pharmacotherapy* **2004**, *24*, 1366–1384. [[CrossRef](#)] [[PubMed](#)]
13. Matsuda, K.; Arima, K.; Akiyama, S.; Yamada, Y.; Abe, Y.; Suenaga, H.; Hashimoto, J.; Shin-ya, K.; Nishiyama, M.; Wakimoto, T. A Natural Dihydropyridazinone Scaffold Generated from a Unique Substrate for a Hydrazine-Forming Enzyme. *J. Am. Chem. Soc.* **2022**, *144*, 12954–12960. [[CrossRef](#)] [[PubMed](#)]
14. Liu, R.-X.; Ma, S.-F.; Chen, Y.-L.; Ma, L.-F.; Wang, J.-D.; Zham, Z.-J. Tetrodecadazinone, a novel tetrodecamycin-pyridazinone hybrid with anti-liver fibrosis activity from *Streptomyces* sp. HU051. *Bioorg. Chem.* **2022**, *119*, 105573. [[CrossRef](#)]
15. Provencher, B.A.; Bartelson, K.J.; Liu, Y.; Foxman, B.M.; Deng, L. Structural Study-Guided Development of Versatile Phase Transfer Catalysts for Asymmetric Conjugate Additions of Cyanide. *Angew. Chem. Int. Ed.* **2011**, *50*, 10565–10569. [[CrossRef](#)]
16. Shen, L.-T.; Sun, L.-H.; Ye, S. Highly Enantioselective γ -Amination of α,β -Unsaturated Acyl Chlorides with Azodicarboxylates: Efficient Synthesis of Chiral γ -Amino Acid Derivatives. *J. Am. Chem. Soc.* **2011**, *133*, 15894–15897. [[CrossRef](#)]
17. Mao, J.-H.; Wang, Z.-T.; Wang, Z.-Y.; Cheng, Y. N-Heterocyclic Carbene-Catalyzed Oxidative Annulations of α,β -Unsaturated Aldehydes with Hydrazones: Selective Synthesis of Optically Active 4,5-Dihydropyridazin-3-ones and Pyridazin-3-ones. *J. Org. Chem.* **2015**, *80*, 6350–6359. [[CrossRef](#)]
18. Zhang, C.-L.; Wang, D.-L.; Chen, K.-Q.; Ye, S. N-Heterocyclic carbene-catalyzed [3+3] cyclocondensation of bromoenals with hydrazones: Highly enantioselective synthesis of dihydropyridazines. *Org. Biomol. Chem.* **2015**, *13*, 11255–11262. [[CrossRef](#)]
19. Zhang, Z.-J.; Song, J. An isothioureia-catalyzed asymmetric formal [4 + 2] cycloaddition of in situ generated azoalkenes with C1 ammonium enolates. *Org. Chem. Front.* **2018**, *5*, 2578–2582. [[CrossRef](#)]
20. Mondal, B.; Maiti, R.; Yang, X.; Xu, J.; Tian, W.; Yan, J.-L.; Li, X.; Chi, Y.R. Carbene-catalyzed enantioselective annulation of dinucleophilic hydrazones and bromoenals for access to aryl-dihydropyridazinones and related drugs. *Chem. Sci.* **2021**, *12*, 8778–8783. [[CrossRef](#)]
21. Li, X.; Gai, K.; Yuan, Z.; Wu, J.; Lin, A.; Yao, H. Organocatalyzed Formal [4+2] Cycloaddition of in situ Generated Azoalkenes with Arylacetic Acids: An Efficient Approach to the Synthesis of 4,5-Dihydropyridazin-3(2H)-ones. *Adv. Synth. Catal.* **2015**, *357*, 3479–3484. [[CrossRef](#)]

22. Zhou, Y.; Zhou, H.; Xu, J. N-Heterocyclic Carbene-Promoted [4+2] Annulation of α -Chloro Hydrazones with α -Chloro Aliphatic Aldehydes to Access Enantioenriched Dihydropyridazinones. *J. Org. Chem.* **2022**, *87*, 3677–3685.
23. Ordóñez, M.; Cativiela, C. Stereoselective synthesis of γ -amino acids. *Tetrahedron Asymmetry* **2007**, *18*, 3–99. [[CrossRef](#)]
24. Ordóñez, M.; Cativiela, C.; Romero-Estudillo, I. An update on the stereoselective synthesis of γ -amino acids. *Tetrahedron Asymmetry* **2016**, *27*, 999–1055. [[CrossRef](#)]
25. Boatman, P.D.; Ogbu, C.O.; Eguchi, M.; Kim, H.-O.; Nakanishi, H.; Cao, B.; Shea, J.P.; Kahn, M. Secondary Structure Peptide Mimetics: Design, Synthesis, and Evaluation of β -Strand Mimetic Thrombin Inhibitors. *J. Med. Chem.* **1999**, *42*, 1367–1375. [[CrossRef](#)]
26. Alvarez-Ibarra, C.; Csáký, A.G.; de la Oliva, C.G. Diastereoselective Synthesis of α -Methylpyroglutamates from α,β -Didehydro α -Amino Acids. *Eur. J. Org. Chem.* **2002**, *2002*, 4190–4194. [[CrossRef](#)]
27. Alvarez-Ibarra, C.; Csáký, A.G.; de la Oliva, C.G. Diastereoselective Synthesis and Estimation of the Conformational Flexibility of 6-Oxoperhydropyridazine-3-carboxylic Acid Derivatives. *J. Org. Chem.* **2002**, *67*, 2789–2797. [[CrossRef](#)]
28. Gardiner, J.; Abell, A.D. A diastereoselective synthesis of the tetrahydropyridazinone core of 2-oxo-1,6-diazobicyclo[4.3.0]nonane-9-carboxylate-based peptidomimetics starting from (S)-phenylalanine. *Tetrahedron Lett.* **2003**, *44*, 4227–4230. [[CrossRef](#)]
29. Keck, G.E.; Heumann, S.A. Diastereoselective Synthesis of Cyclopentapyridazinones via Radical Cyclization: Synthetic Studies Toward Halichlorine. *Org. Lett.* **2008**, *10*, 4783–4786. [[CrossRef](#)]
30. Cadart, T.; Berthonneau, C.; Levacher, V.; Perrio, S.; Brière, J.-F. Enantioselective Phase-Transfer Catalyzed α -Sulfanylation of Isoxazolidin-5-ones: An Entry to $\beta^{2,2}$ -Amino Acid Derivatives. *Chem. Eur. J.* **2016**, *22*, 15261–15264. [[CrossRef](#)]
31. Cadart, T.; Levacher, V.; Perrio, S.; Brière, J.-F. Construction of Isoxazolidin-5-ones with a Tetrasubstituted Carbon Center: Enantioselective Conjugate Addition Mediated by Phase-Transfer Catalysis. *Adv. Synth. Catal.* **2018**, *360*, 1499–1509. [[CrossRef](#)]
32. Röser, K.; Prameshuber, L.; Jahangir, S.; Mallojjala, S.C.; Hirschi, J.S.; Waser, M. Chiral Quaternary Ammonium Salt-Catalyzed Enantioselective Addition Reactions of Hydantoins. *Helv. Chim. Acta* **2024**, *107*, e202300234. [[CrossRef](#)]
33. Eitzinger, A.; Winter, M.; Schörghenheimer, J.; Waser, M. Quaternary $\beta^{2,2}$ -amino acid derivatives by asymmetric addition of isoxazolidin-5-ones to *para*-quinone methides. *Chem. Commun* **2020**, *56*, 579–582.
34. Dumas, A.M.; Fillion, E. Meldrum's Acids and 5-Alkylidene Meldrum's Acids in Catalytic Carbon–Carbon Bond-Forming Processes. *Acc. Chem. Res.* **2010**, *43*, 440–454. [[CrossRef](#)] [[PubMed](#)]
35. Pair, E.; Cadart, T.; Levacher, V.; Brière, J.-F. Meldrum's Acid: A Useful Platform in Asymmetric Organocatalysis. *ChemCatChem* **2016**, *8*, 1882–1890.
36. Brosge, F.; Singh, P.; Almqvist, F.; Bolm, C. Selected applications of Meldrum's acid—a tutorial. *Org. Biomol. Chem.* **2021**, *19*, 5014–5027. [[CrossRef](#)]
37. Beucher, H.; Levacher, V.; Oudeyer, S.; Brière, J.-F. Recent advances of asymmetric catalytic transformations of alkylidene Meldrum's acid derivatives. *Chem. Commun.* **2025**, *61*, 6555–6566.
38. Shirakawa, S.; Maruoka, K. Recent Developments in Asymmetric Phase-Transfer Reactions. *Angew. Chem. Int. Ed.* **2013**, *52*, 4312–4348.
39. Qia, D.; Sun, J. Recent Progress in Asymmetric Ion-Pairing Catalysis with Ammonium Salts. *Chem. Eur. J.* **2019**, *25*, 3740–3751.
40. Otevreil, J.; Waser, M. Asymmetric Phase-Transfer Catalysis—From Classical Applications to New Concepts. In *Asymmetric Organocatalysis: New Strategies, Catalysts, and Opportunities*; Albrecht, L., Albrecht, A., Dell'Amico, L., Eds.; Wiley-VCH: Weinheim, Germany, 2023; Volume 2, pp. 71–120.
41. Albanese, D.C.M.; Penso, M. New Trends in Asymmetric Phase Transfer Catalysis. *Eur. J. Org. Chem.* **2023**, *26*, e202300224. [[CrossRef](#)]
42. Lee, H.-J.; Maruoka, K. Asymmetric phase-transfer catalysis. *Nat. Rev. Chem.* **2024**, *8*, 851–869. [[CrossRef](#)] [[PubMed](#)]
43. Tóth, G.; Molnár, S.; Tamás, T.; Borbély, I. An Efficient Synthesis of 4,5-Dihydro-3(2H)-pyridazinone Derivatives. *Synth. Commun.* **2006**, *27*, 3513–3523. [[CrossRef](#)]
44. Ramachary, D.B.; Kishor, M.; Ramakumar, K. A novel and green protocol for two-carbon homologation: A direct amino acid/ K_2CO_3 -catalyzed four-component reaction of aldehydes, active methylenes, Hantzsch esters and alkyl halides. *Tetrahedron Lett.* **2006**, *47*, 651–656. [[CrossRef](#)]
45. Ramachary, D.B.; Reddy, G.B. Towards organo-click reactions: Development of pharmaceutical ingredients by using direct organocatalytic bio-mimetic reductions. *Org. Biomol. Chem.* **2006**, *4*, 4463–4468. [[CrossRef](#)]
46. Bar, G.; Parsons, A.F.; Thomas, C.B. Manganese(III) acetate-mediated alkylation of β -keto esters and β -keto amides: An enantio- and diastereo-selective approach to substituted pyrrolidinones. *Org. Biomol. Chem.* **2003**, *1*, 373–380. [[CrossRef](#)]
47. Snider, B.B.; Smith, R.B. Mn(III)-based oxidative free-radical cyclizations of alkenyl Meldrum's acids. *Tetrahedron* **2002**, *58*, 25–34. [[CrossRef](#)]
48. Aggarwal, V.K.; Fonquerna, S.; Vennall, G.P. $Sc(OTf)_3$, an Efficient Catalyst for Formation and Deprotection of Geminal Diacetates (Acylals); Chemoselective Protection of Aldehydes in Presence of Ketones. *Synlett* **1998**, *1998*, 849–850. [[CrossRef](#)]

49. Lee, H.-J.; Maruoka, K. Recent Asymmetric Phase-Transfer Catalysis with Chiral Binaphthyl-Modified and Related Phase-Transfer Catalysts over the Last 10 Years. *Chem. Rec.* **2023**, *23*, e202200286.
50. Xu, C.; Qi, Y.; Yang, X.; Li, X.; Li, Z.; Bai, L. Development of C₂-Symmetric Chiral Spirocyclic Phase-Transfer Catalysts: Synthesis and Application to Asymmetric Alkylation of Glycinate Schiff Base. *Org. Lett.* **2021**, *23*, 2890–2894. [[CrossRef](#)]
51. Xu, C.; Yang, X. Chiral Ammonium Salt Catalyzed Asymmetric Alkylation of Unactivated Amides. *Synlett* **2022**, *33*, 664–668. [[CrossRef](#)]
52. Zebrowski, P.; Röser, K.; Chrenko, D.; Pospisil, J.; Waser, M. Enantioselective β -Selective Addition of Isoxazolidin-5-ones to Allenoates Catalyzed by Quaternary Ammonium Salts. *Synthesis* **2023**, *55*, 1706–1713. [[PubMed](#)]
53. Caruana, L.; Fochi, M.; Bernardi, L. The Emergence of Quinone Methides in Asymmetric Organocatalysis. *Molecules* **2015**, *20*, 11733–11764. [[CrossRef](#)] [[PubMed](#)]
54. Lima, C.G.S.; Pauli, F.P.; Costa, D.C.S.; de Souza, A.S.; Forezi, L.S.M.; Ferreira, V.F.; de Carvalho da Silva, F. *para*-Quinone Methides as Acceptors in 1,6-Nucleophilic Conjugate Addition Reactions for the Synthesis of Structurally Diverse Molecules. *Eur. J. Org. Chem.* **2020**, *2020*, 2650–2692.
55. Wang, J.-Y.; Hao, W.-J.; Tu, S.-J.; Jiang, B. Recent developments in 1,6-addition reactions of *para*-quinone methides (*p*-QMs). *Org. Chem. Front.* **2020**, *7*, 1743–1778. [[CrossRef](#)]
56. Li, X.; Li, Z.; Sun, J. Quinone methides and indole imine methides as intermediates in enantioselective catalysis. *Nat. Synth.* **2022**, *1*, 426–438. [[CrossRef](#)]
57. Henry, P.J.; Burel, G.; Nzegge, W.; Waser, M.; Brière, J.-F. Catalytic Synthesis of Versatile Chiral Heterocycles: En Route to γ -Amino Acid Derivatives. *Chem. Proc.* **2025**, *18*, 70. [[CrossRef](#)]
58. Chidipudi, S.R.; Khan, I.; Lam, H.W. Functionalization of Csp³-H and Csp²-H Bonds: Synthesis of Spiroindenes by Enolate-Directed Ruthenium-Catalyzed Oxidative Annulation of Alkynes with 2-Aryl-1,3-dicarbonyl Compounds. *Angew. Chem. Int. Ed.* **2012**, *51*, 12115–12119. [[CrossRef](#)]

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