Catalytic Enantiodivergent Michael Addition by Subtle Adjustment of Achiral Amino Moiety of Dipeptide Phosphines

HIGHLIGHTS
- Enantiodivergent phosphine-catalyzed Michael addition
- Readily available starting materials, mild reaction conditions
- High efficiency, up to 99% yield and 99% ee
- General substrate scope

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Catalytic Enantiodivergent Michael Addition by Subtle Adjustment of Achiral Amino Moiety of Dipeptide Phosphines

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SUMMARY
Over the past decades, asymmetric catalysis has been intensely investigated as a powerful tool for the preparation of numerous chiral biologically active compounds. However, developing general and practical strategies for preparation of both enantiomers of a chiral molecule via asymmetric catalysis is still a challenge, particularly when the two enantiomers of a chiral catalyst are not easily prepared from natural chiral sources. Inspired by the biologic system, we report herein an unprecedented catalytic enantiodivergent Michael addition of pyridazines to enones by subtle adjustment of achiral amino moiety of dipeptide phosphine catalysts. These two dipeptide phosphine catalysts, P5 and P8, could deliver both enantiomers of a series of N2-alkylpyridazines in good yields (up to 99%) with high enantioselectivities (up to 99% ee) via the catalyst-controlled enantiodivergent addition of pyridazines to enones.

INTRODUCTION
The development of efficient methods to synthesize both enantiomers of a chiral molecule is of great significance, because drug candidates and their isomers may have distinct therapeutic properties or adverse effects (Wermuth, 2008; Jozwiak et al., 2012). Enantiodivergent methodology (Zanoni et al., 2003; Bartok, 2010; Beletskaya et al., 2018) is an attractive route to afford the mirror image products, which can be achieved with the use of both enantiomers of a chiral catalyst, respectively. However, the two enantiomers of the required chiral catalyst are not always available in nature. In biological systems, minor structural changes in functional molecules (proteins, enzymes, and hormones) by noncovalent binding of allosteric regulators or covalent modification of structure-determining functionalities (Li et al., 2012; Lyons et al., 2013; Lasalde et al., 2014) (e.g., cleavage of peptide domains, ionizable groups, and methylation/glycosylation/phosphorylation of H-bond donors) can display a polypeptide-based distinct three-dimensional architecture, leading to turn on/off their function or acquire another function, enabling the timely regulation of intra- or extracellular events with elegant synergy (Zanoni et al., 2003; Harrison, 2004; Heilmann et al., 2004; Li et al., 2012; Lyons et al., 2013; Lasalde et al., 2014) (Scheme 1A). For example, sickle cell anemia is an autosomal recessive genetic disease, caused by a single-base mutation in the beta gene of globin causing glutamate mutated to proline. This sickling leads to the RBC membrane damage and increases the likelihood of rupture and anemia (Gyang et al., 2011). Inspired by this intriguing biological process, we hypothesized that some small structural modifications in conformationally flexible chiral organocatalysts without changing any stereocenter might allow to obtain both stereoisomers in the individual form in asymmetric catalysis as well.

Considerable research efforts have long been devoted to phosphine-catalyzed asymmetric reactions (Cai et al., 2016; Cowen and Miller, 2009; Fan and Kwon, 2013; Gu et al., 2015; Guo et al., 2018; Han et al., 2016; Lee et al., 2015; Li et al., 2015, 2016; Li and Zhang, 2016; Lu et al., 2001; C. Ni et al., 2017; H. Ni et al., 2017; Ni et al., 2018; Sankar et al., 2016; Satpathi and Ramasastry, 2016; C. Wang et al., 2016, 2018; H. Wang et al., 2018; H.-Y. Wang et al., 2016; T. Wang et al., 2016; Wang et al., 2014; Wei and Shi, 2010, 2017; Xie and Huang, 2015; Ye et al., 2008; Zhang et al., 2015; Zhao et al., 2012), whereas the enantiodivergent synthesis directed by chiral natural amine-acid-derived bi- or multifunctional phosphine still poses considerable challenge. Only a few examples of enantiodivergent phosphine-catalyzed reactions were realized so far (Henry et al., 2014; Wang et al., 2015a, 2015b, 2017a, 2017b, 2017c; Ni et al., 2016; Li et al., 2016; Gu et al., 2018; Smaligo et al., 2018) (Scheme 1B), in which the enantioselectivity could be only partially switched by variation of one or multiple stereocenters of phosphine
catalysts. Early Lu group (Wang et al., 2015a, 2015b; 2017a, 2017b, 2017c; Ni et al., 2016) observed that the enantioselectivity of phosphine-catalyzed enantioselective γ-additions of allenoates could be moderately switched by a pair of diastereomers of the chiral catalyst. Kwon group (Henry et al., 2014; Smaligo et al., 2018) reported the enantiodivergent [3 + 2] annulations of allenoates and imines to obtain a series of pyrrolines via a pair of diastereomeric phosphine catalysts. To the best of our knowledge, in the area of phosphine catalysis, switching enantioselectivity to gain both enantiomers in high ee without changing any stereocenter of the phosphine catalyst has not been explored so far. Meanwhile, many efficient catalytic asymmetric reactions have been well established in recent decades; however, asymmetric phosphine-catalyzed Michael addition (Zhong et al., 2013; Huang et al., 2017) to non-terminal electron-deficient alkenes are much less developed and represent a challenging task. In view of the biological significance of N2-alkylated pyridazinones (Van der Mey et al., 2001; Berthel et al., 2009; Allerton
et al., 2009; Rathish et al., 2009; Cilibrizzi et al., 2009; Ahmad et al., 2010; Parveen et al., 2017) (Scheme 2), herein, we report an enantiodivergent phosphine-catalyzed Michael addition of pyridazinones to enones, which provides a rapid access to two enantiomers of \(N^2\)-alkylated pyridazinones in good to excellent enantioselectivity (Scheme 1C). The enantioselectivity was well switched by the subtle variation of the amide moiety of chiral dipeptide phosphine catalyst without changing any stereogenic element.

RESULTS AND DISCUSSION
Research Design
During the course of our study on phosphine-catalyzed (Su et al., 2015; Zhou et al., 2015, 2016a, 2016b, 2017, Chen et al., 2016, Chen and Zhang, 2017; Wang et al., 2017a, 2017b, 2017c; 2018a, 2018b, 2019; Huang et al., 2017; Zhang et al., 2017) diverse transformations of enones, we envisaged that the asymmetric organophosphorus zwitterion intermediate, generated \(\text{in situ}\) by mixing a chiral multifunctional phosphine with methyl acrylate, might provide a mild Brønsted base to activate pyridazinone. The subsequently formed ionic pair, followed by the addition to \(\beta\)-substituted enones was feasible.

The reaction between \(\beta\)-trifluoromethylated enone 1f and pyridazinone 2a was investigated in the presence of chiral phosphine catalyst (Scheme 3) and methyl acrylate in DCM at room temperature (Table 1). The chiral sulfinamide phosphine P1 developed by us (Su et al., 2015; Zhou et al., 2016a) is not efficient to deliver \((-\)\()-3fa\) in low yields along with recovery of 1f (Table 1, entry 1). The variation of the tert-butanesulfinamide to 3,5-bis(trifluoromethyl)benzoyl-derived amide (Wang et al., 2017a, 2017b, 2017c; Zhou et al., 2017) could increase the catalytic activity significantly but only 16% ee was obtained (Table 1, entry 2). The Introduction of a bulkier 3,5-di-tert-butylphenyl group at the ortho-position of the phenyl ring gave similar ee (Table 1, entry 3). Gratifyingly, the desired product was obtained in 98% yield with 31% ee upon the use of N-Boc-D-Val-derived phosphine P4 (Table 1, entry 4). To our delight, its diastereomer N-Boc-L-Val-derived P5 could substantially improve the ee (Table 1, entry 5). To our surprise, the replacement of Boc-amide (P5) with other benzoyl-derived amides (P6–P8) could reverse the enantioselectivity of the reaction to deliver the \((+)\)-3fa as the major enantiomer (Table 1, entries 6–8), in which the catalyst P8 showed promising result (57% ee). Further solvent screening showed toluene is
the best solvent to deliver (+)-3fa in 81% ee (Table 1, entry 12). After further systematic screening, the enantiodivergent phosphine-catalyzed addition of pyridazinones to enone was realized by running the reaction at 20°C under the catalysis of P5 in F5C6CH3 and P8 in toluene, respectively (Table 1, entries 17–19). Lowering the amount of methyl acrylate from 1.0 to 0.5 equivalent would keep the enantioselectivity unchanged but deliver a relatively lower yield (Table 1, entry 20).

Table 1. Screening of Reaction Conditions

| Entry | Cat. | Solvent | Yield (%) | (+/-)-3fa, ee (%) |
|-------|------|---------|-----------|------------------|
| 1     | P1   | DCM     | Trace     | –                |
| 2     | P2   | DCM     | 88        | (−)-3fa, 16      |
| 3     | P3   | DCM     | 90        | (−)-3fa, 17      |
| 4     | P4   | DCM     | 98        | (−)-3fa, 31      |
| 5     | P5   | DCM     | 96        | (−)-3fa, 51      |
| 6     | P6   | DCM     | 99        | (+)-3fa, 26      |
| 7     | P7   | DCM     | 99        | (+)-3fa, 25      |
| 8     | P8   | DCM     | 99        | (+)-3fa, 57      |
| 9     | P8   | CHCl3   | 81        | (+)-3fa, 67      |
| 10    | P8   | THF     | 73        | (+)-3fa, 62      |
| 11    | P8   | Et2O    | 95        | (+)-3fa, 72      |
| 12    | P8   | Toluene | 98        | (+)-3fa, 81      |
| 13    | P8   | PhCF3   | 99        | (+)-3fa, 73      |
| 14    | P8   | o-xylene| 98        | (+)-3fa, 80      |
| 15    | P8   | F5PhCH3 | 97        | (+)-3fa, 79      |
| 16  | P8   | Toluene | 98        | (+)-3fa, 94      |
| 17  | P8   | Toluene | 97        | (+)-3fa, 98      |
| 18  | P5   | Toluene | 95        | (−)-3fa, 86      |
| 19  | P5   | F5PhCH3 | 98        | (−)-3fa, 95      |
| 20  | P8   | Toluene | 90        | (+)-3fa, 98      |

*aNMR yield with CH2Br2 as an internal standard.

*bDetermined by HPLC analysis on a chiral stationary phase.

*cThe reaction was performed at −10°C and the reaction time was 2 h.

*dThe reaction was performed at −20°C and the reaction time was 3 h.

*e50mol% methyl acrylate was used.

The scope of this enantiodivergent hydroamination reaction was subsequently probed. Firstly, the scope of the enantioselective hydroamination reaction under the catalysis of P8 in toluene was investigated (Scheme 4, Method B). Generally, β-trifluoromethyl enones with different substituents on the phenyl ring, regardless
of the substitution patterns and electronic properties, afforded the corresponding products (+)-3 in high yields with excellent ees (Scheme 4, (+)-3aa-(+)-3pa). The absolute configuration of (+)-3da was determined to be $S$ by X-ray crystallographic analysis (see Supplemental Information) and the other products were analogously assigned. In addition, fused aromatic and hetero-aromatic group-substituted enones were also applicable to the reaction, delivering the desired hydroamination products in excellent yields (98%–99%) with 91%–96% ee (Scheme 4, (+)-3qa-(+)-3ta). Enone 1u with a cyclohexenyl substituent produced (+)-3ua in moderate yield with 92% ee (Scheme 4, Method B). Furthermore, the trifluoromethyl group could be replaced by perfluoroethyl, furnishing moderate yield of the desired product (+)-3va in 83% ee. Subsequently, the scope of the pyridazinone component 2 was investigated and all reactions proceeded well with no matter electron-donating or electron-withdrawing substituents (2b-2f) at different positions, providing (+)-3fb-(+)3ff in 93%–98% yields with 90%–99% ees. Then, all the reactions mentioned above were then carried out under the catalysis of P5 as the catalyst in CH$_5$C$_6$F$_5$ at –20°C (Scheme 4). The scope of β-trifluoromethyl enone component is quite general, various aryl (1a-1r), heteroaryl (1s-1t), and cyclohexenyl (1u) substituents (Scheme 4, (−)-3aa–(−)-3ua) were compatible, delivering 75%–96%.
what is more, \( \beta \)-pentafluoroethyl enone (1v) was also compatible to furnish good ee. Pyridazinones 2 with either electron-withdrawing or electron-donating substituents were also well tolerated delivering the desired products in good to excellent yields with excellent ees (\((-)\)-3fb-\((-)\)-3ff).

The scope of 3-aryl acrylates were then investigated (Scheme 5). In most cases, the desired products \((-)\)-5aa-\((-)\)-5pa were obtained in good yields with excellent enantioselectivity by using P5 as the chiral catalyst (Method A). Substrates with various esters (4a–4e) and different aryl substituents (4f–4p) were all compatible, furnishing the corresponding products in 55%–97% yields and 87%–97% ees (\((-)\)-5aa-\((-)\)-5pa). Meanwhile, the reaction proceeded also well to afford the desired products \((+)-5aa-\((+)-5pa\) under the catalysis of P8 (Method B). However, the reaction was found to be somewhat sensitive to the electronic nature of the substituents on the aromatic ring. Electron-donating substituents \((+)-5fa-\((+)-5ha\) led to the desired products in relatively lower yield compared with electron-withdrawing substituents \((+)-5ia-\((+)-5na\). The reaction of heteroaryl- \((4o\) and naphthyl- \((4p\) containing substrates proceeded smoothly to give the corresponding products in 57%–84% yields but with relatively lower enantioselectivities \((+)-5oa-\((+)-5pa\).

To evaluate two chiral dipeptide phosphine catalytic systems on a large scale, 5.0 mmol of \( \beta \)-trifluoromethylated enone 1f and 3-aryl acrylate 4c was used to perform the Michael addition reaction, providing the

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**Scheme 5. Substrate Study with Variation of 3-Aroyl Acrylates 4 and Pyridazinone 2a**

| R      | \((-)\)-5aa, 85% (90%) \(^a\) | \((-)\)-5ba, 75% (89%) | \((-)\)-5ca, 87% (93%) | \((-)\)-5da, 96% (96%) | \((-)\)-5ea, 93% (97%) |
|--------|-------------------------------|------------------------|------------------------|------------------------|------------------------|
|        | \((-)\)-5aa, 87% (84%)        | \((-)\)-5ba, 69% (87%) | \((-)\)-5ca, 90% (81%) | \((-)\)-5da, 64% (83%) | \((-)\)-5ea, 52% (88%) |

\(^a\)Reactions were performed with 1 (0.1 mmol), 2 (0.2 mmol), methyl acrylate (0.1 mol); method A: P5 (0.01 mmol) in F\(_2\)PhCH\(_3\) (1.0 mL) at \(-20^\circ C\); method B: P8 (0.01 mmol) in toluene (1.0 mL) at \(-20^\circ C\). Ee in parenthesis and determined by HPLC analysis on a chiral stationary phase.
corresponding product (+)-3fg and (−)-5ca with excellent yields in 95% and 92% ees. The (−)-5ca could be hydrolyzed under acidic conditions, affording product (−)-6a in 95% yield with 92% ee. The thioester 7a and glucokinase activators analog (Berthel et al., 2009; Allerton et al., 2009; Rathish et al., 2009) amidine 7b could be obtained in 85% and 68% yield, respectively from the compound (−)-6a. Racemic pyridazinone 7c and lactone 7d were both obtained in good yield by treating (−)-6a with either hydrazine hydrate in THF or acetyl chloride, respectively (Scheme 6).

Mechanistic Study
To gain insight of the role of these two hydrogen-bonding interactions, N1-methyl-P5, N1-methyl-P8, N2-methyl-P5, N2-methyl-P8, deuterated P8, and P9 with free terminal amine were then synthesized and subjected to the reaction, respectively (Scheme 7). It is interesting to find that N1-methyl-P5 and N1-methyl-P8 could not catalyze the reaction, indicating that the first N1-H is crucial to the catalytic activity. In addition, both N2-methyl-P5 and N2-methyl-P8 gave (−)-3fa in satisfactory yields with 70% ee. More interestingly, the deuterated catalyst P8 could deliver (+)-3fa in 92% yield but with much lower enantioselectivity. Catalyst P9 also gave (−)-3fa in satisfactory yields with 63% ee. Together, these observations clearly indicated that the second N2-H of P8 is crucial to reverse the enantioselectivity. Subsequently, we wondered whether the stereoselectivities were enhanced by using the pentfluoro toluene. When 1f and 2a were carried out in CH3C6F5, the product (+)-3fa was obtained in 79% yield and slightly lower enantioselectivity (90% ee) compared with toluene (98% ee) as solvent. Simultaneously, we then conducted NMR titration experiments (see the Supplemental Information for details) and observed that hydrogen bond interaction did not exist between pentfluoro toluene and pyridazinone or catalyst, implying the enantioselectivity was not significantly influenced by fluorinated solvent.

Conclusion
In conclusion, we have developed two new chiral dipeptide phosphine catalysts, which showed good performance in enantioselective addition of pyridazinones with enones. The enantioselectivity could be switched by subtle variation of the amino moiety of chiral dipeptide phosphine catalyst without changing any stereocenter of the phosphine catalyst. Both enantiomers of N2-alkylated pyridazinones can be obtained in high yields (up to 99%) with good to excellent enantioselectivity (up to 99% ee) by the use of P5 and P8, respectively. The results of control experiments suggest that a number of hydrogen-bonding interactions play a crucial role in determining the catalytic activity and enantioselectivity reversal (see the Supplemental Information for proposed transition states). The salient features of this work include readily available starting materials, mild reaction conditions, high efficiency, switchable enantioselectivity,
and general substrate scope. Extensions of this concept with other important organic transformations and comprehensive theoretical studies into the reaction mechanism will also be reported in due course.

Limitations of the Study
A brief examination showed that the present method is not compatible with chalcone and (E)-(2-nitrovinyl) benzene for the construction of corresponding N1-alkylated pyridazinones.

Resource Availability
Lead Contact
Further information and requests for resources should be directed to and will be fulfilled by the Lead Contact, J. Zhang (junliangzhang@fudan.edu.cn).

Materials Availability
This study generated new unique reagents, include phosphine catalysts and N2-alkylated pyridazinones.

Data and Code Availability
The data for the X-ray crystallographic structure of (+)-3da has been deposited in the Cambridge Crystallographic DataCenter under accession numbers CCDC: 1839409.

METHODS
All methods can be found in the accompanying Transparent Methods supplemental file.

SUPPLEMENTAL INFORMATION
Supplemental Information can be found online at https://doi.org/10.1016/j.isci.2020.101138.
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Supplemental Information

Catalytic Enantiodivergent Michael Addition by Subtle Adjustment of Achiral Amino Moiety of Dipeptide Phosphines

Huamin Wang, Xiuzheng Li, Youshao Tu, and Junliang Zhang
Transparent Methods

A. General Information

Unless otherwise noted, all reactions were carried out under a nitrogen atmosphere; materials obtained from commercial suppliers were used directly without further purification. The [α]D was recorded using PolAAr 3005 High Accuracy Polarimeter. 1H NMR spectra, 13C NMR spectra, 31P NMR spectra and 19F NMR spectra were recorded on a Bruker 400 (300 or 500) MHz spectrometer in chloroform-d3. Chemical shifts (in ppm) were referenced to tetramethylsilane (δ = 0 ppm) in CDCl3 as an internal standard. 13C NMR spectra were obtained by using the same NMR spectrometers and were calibrated with CDCl3 (δ = 77.00 ppm). The data is being reported as (s = singlet, d = doublet, dd = doublet of doublet, t = triplet, m = multiplet or unresolved, br = broad signal, coupling constant(s) in Hz, integration). Noteworthy, splitting signals between 13C nucleus and 13P nucleus in some chiral phosphine catalysts were difficult to distinguish and these 13C NMR signals were reported as singlet entirely.

Trichloromethane (CHCl3), dichloromethane, dichloroethane and ethyl acetate were freshly distilled from CaH2; tetrahydrofuran (THF), toluene and ether were dried with sodium benzophenone and distilled before use. Reactions were monitored by thin layer chromatography (TLC) using silicycle pre-coated silica gel plates. Flash column chromatography was performed on silica gel 60 (particle size 200-400 mesh ASTM, purchased from Yantai, China) and eluted with petroleum ether/ethyl acetate. The Substrates 1, (Yamazaki et al., 2009; Daniel et al., 2013) and catalysts P1-P9 and P11 were synthesized according to the reported methods. (Su et al., 2015; Zhou et al., 2015; Zhou et al., 2016; Chen et al., 2016; Wang et al, 2015; Wang et al, 2017) All reagents and solvents were used as received from commercial sources (Energy Chemical, Adams-beta®) without further purification.
B. Experimental procedures

Typical Synthetic Procedure and Datas for Novel Chiral Phosphines Catalyst P1-P8.

**Step 1:** to a flask containing a solution of [1,1′-biphenyl]-2-carbaldehyde (4.0 mmol) and tert-butylsulfonamide (6.0 mmol) was added Ti(O'Pr)₄ (8 mmol) and the mixture was stirred at 50°C. Upon reaction completion, the reaction mixture was allowed to cool to room temperature, diluted with EtOAc, and poured to brine with rapid stirring. The resulting suspension was filtered through celite and washed with EtOAc. The combined organic phases were dried over MgSO₄ and the solvents were removed in vacuo. The residue was purified by silica gel chromatography using petroleum ether/EtOAc as the eluent to afford the desired chiral sulfinyl imines, isolated yield: 89%.

**Step 2:** A solution of diphenyl methyl phosphonic lithium (1.5 mmol) that containing TMEDA (1.5 mmol) in anhydrous THF was added to the solution of corresponding chiral sulfinyl imines (1.5 mmol chiral sulfinyl imines in 5 mL anhydrous THF) at room temperature. The mixture was stirred until completion of imine as indicated by TLC, followed by hydrolysis with 10 mL of water and diluted with EtOAc. The organic layer was separated, the aqueous phase was extracted three times with EtOAc (3X10 mL). The combined organic phases were dried over MgSO₄ and the solvents were removed in vacuo. The residue was purified by silica gel chromatography using petroleum ether/EtOAc as the eluent to afford the desired (S,R₅)-P, isolated yield: 51%, 5:1 dr.

**Step 3:** BH₃•THF (3.0 mmol) was added slowly to the solution of (S,R₅)-P (1.0 mmol) in dry THF at -30°C and the reaction mixture was stirred for 2 h until completion of the material as indicated by TLC followed by adding 10 mL of water and 20 mL EtOAc. The aqueous phase was separated and extracted three times with 20 mL EtOAc. The combined organic phases were dried over MgSO₄ and the solvents were removed in vacuo.
**Step 4**: 6 M HCl (1 mL) was added to the above residue which dissolved in MeOH (10 mL) and the reaction mixture was stirred at room temperature for 3 h until completion of material as indicated by TLC analysis, followed by washing with aq NaHCO₃ and 10 mL aq brine water. The organic layers were separated and extracted three times with 20 mL EtOAc. The combined organic phases were dried over MgSO₄ and the solvents were removed in vacuo.

**Step 5**: Et₂NH (5.0 mL) was added to the above residue and the mixture was stirred at 55°C for 6 h under the protection of N₂ until completion of material as indicated by TLC analysis. The solvent was then removed in vacuo and the resulting mixture P0 was used directly for the next step.

**Step 1**: To a stirred solution of N-Boc L-valine (434.6 mg, 2.0 mmol) in anhydrous CH₂Cl₂ (10 mL) was added DCC (226.8 mg, 1.1 mmol), and the resulting mixture was stirred at room temperature for 2 h. The solution was then cooled down to 0°C and the above residue and the mixture in CH₂Cl₂ (5 mL) was added dropwise over 2 minutes. The reaction mixture was further stirred for 1.0 h at 0°C and 1.0 h at room temperature. Water (10 mL) was added to quench the reaction, and the resulting mixture was extracted with dichloromethane several times (3 x 10 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated, the residue was purified by column chromatography (hexane: ethyl acetate = 20:1) to afford P5 (480 mg, 82%) as a white solid.

**Step 2**: To a stirred solution of P5 (116 mg, 0.2 mmol) in anhydrous CH₂Cl₂ (2 mL) at room temperature was added TFA (0.4 mL), and the resulting mixture was stirred for 2 h. The reaction was then quenched with saturated aqueous NaHCO₃ (10 mL), and extracted with CH₂Cl₂ several times (3 x 10 mL). The combined organic extracts
were washed by brine (15 mL), and dried over Na$_2$SO$_4$, filtered and concentrated. The next operation is similar to above method which it afford **P8** (100 mg, 78%) as a yellow solid.

**N2-methyl-P5** were prepared according to the modified procedure of **P5**. To a stirred solution of **N2-methyl-P5** (180 mg, 0.3 mmol) in anhydrous CH$_2$Cl$_2$ (5 mL) at room temperature was added TFA (0.8 mL), and the resulting mixture was stirred for 2 h. The reaction was then quenched with saturated aqueous NaHCO$_3$ (10 mL), and extracted with CH$_2$Cl$_2$ several times (3 × 10 mL). The combined organic extracts were washed by brine (15 mL), and dried over Na$_2$SO$_4$, filtered and concentrated. The next operation is similar to above method which it afford **N2-methyl-P8** (157 mg, 76%) as a light yellow solid.

**Step 1**: To solution of amino phosphine **1** (3 mmol) and Et$_3$N (6.0 mmol) in dry CH$_2$Cl$_2$ (10 mL) at 0°C was added slowly ClCOOMe (4.5 mmol), and the resulting mixture was stirred at room temperature for 2 h. Water (10 mL) was added and the organic layer was separated. The aqueous phase was extracted with CH$_2$Cl$_2$ (2 × 10 mL). The combined organic layers were washed with brine and dried over Na$_2$SO$_4$. Solvent was removed under reduced pressure, and the residue was used directly for the next step. To the solution of the carbamate intermediate in dry THF (10 mL) at 0°C was added slowly LAH in THF (12 mmol), and the resulting mixture was refluxed
for 72 h. After cooling down to room temperature and further to 0°C, the reaction mixture was quenched by addition of water and NaOH (1 M) solution. The insoluble slurry was filtrated off and washed with ethyl acetate. The filtrate was collected and the organic phase was separated. The aqueous layer was extracted with ethyl acetate (3 x 30 mL) several times, and the combined organic layers were washed with brine and dried over Na₂SO₄. Solvent was removed under reduced pressure, and the residue was used directly for the next step.

**Step 2:** Et₂NH (10.0 mL) was added to the above residue and the mixture was stirred at 55°C for 6 h under the protection of N₂ until completion of material as indicated by TLC analysis. The solvent was then removed in vacuo and the resulting mixture *N1*-methyl-*P0* was used directly for the next step.

**Step 1:** To a solution of *N*-Boc-*L*-valine (3 mmol) in dry CH₂Cl₂ (10 mL) at 0°C under N₂ was added HOBt (3.6 mmol), *N*,*N*-diisopropylethylamine (3.6 mmol) and EDCI (3.6 mmol). After stirring for 10 min, crude product *N1*-methyl-*P0* in dry CH₂Cl₂ (10 mL) was introduced at the same temperature. The stirring was continued at 0°C for 1 h and then at room temperature overnight. The mixture was diluted with CH₂Cl₂, washed with saturated aqueous NH₄Cl solution, and the organic layer was dried over Na₂SO₄. Solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 5/1) to afford *N1*-methyl-*P5* as a white solid (800 mg, 44% yield for three steps).

**Step 2:** To a stirred solution of *N1*-methyl-*P5* (0.3 mmol) in anhydrous CH₂Cl₂ (5 mL) at room temperature was added TFA (0.8 mL), and the resulting mixture was stirred for 2 h. The reaction was then quenched with saturated aqueous NaHCO₃ (10 mL), and extracted with CH₂Cl₂ several times (3 × 10 mL). The combined organic
extracts were washed by brine (15 mL), and dried over Na$_2$SO$_4$, filtered and concentrated. The next operation is similar to above method which it afford $N$-$methyl$-$P8$ (125 mg, 60%) as a light yellow solid.

**Typical Procedure for the Hydroamination Reactions, Related to Schem 4 and Schema 5.**

To a flame dried reaction tube with a magnetic stirring bar under N$_2$ at room temperature were added $P8$ (0.01 mmol), pyridazinone $2$ (0.2 mmol) and methyl acrylate (100 mol %), followed by the addition of anhydrous toluene (1.0 mL), and the mixture was stirred at -20$^\circ$C for 10 min before the enones $1/4$ (0.10 mmol) was added. When the reaction was finished (determined by TLC analysis), the crude mixture was purified by column chromatography on silica gel to afford the products $(+)-3/(+)\cdot5$.

To a flame dried reaction tube with a magnetic stirring bar under N$_2$ at room temperature were added $P5$ (0.01 mmol), pyridazinone $2$ (0.2 mmol) and methyl acrylate (100 mol %), followed by the addition of pentafluoromethylbenzene (1.0 mL), and the mixture was stirred at -20$^\circ$C for 10 min before the enones $1/4$ (0.10 mmol) was added. When the reaction was finished (determined by TLC analysis), the crude mixture was purified by column chromatography on silica gel to afford the products
Scaled-up Version of the Michael addition and Transformation of the Products, Related to Scheme 6

To a flame dried reaction tube with a magnetic stirring bar under N₂ at room temperature were added P₈ (0.25 mmol), 4,5-dibromopyridazin-3(2H)-one 2g (6 mmol) and methyl acrylate (50 mol%), followed by the addition of anhydrous toluene (20.0 mL), and the mixture was stirred at -20°C for 10 min before the enones 1f (5 mmol) was added. When the reaction was finished (determined by TLC analysis), the crude mixture was purified by column chromatography on silica gel to afford the product (+)-3fg, 2.4 g, 95% ee.

To a flame dried reaction tube with a magnetic stirring bar under N₂ at room temperature were added P₅ (0.25 mmol), pyridazinone 2a (6 mmol) and methyl acrylate (50 mol %), followed by the addition of anhydrous 1,2,3,4,5-pentafluoro-6-methylbenzene (20.0 mL), and the mixture was stirred at -20°C for 10 min before the enones 4c (5 mmol) was added. When the reaction was finished (determined by TLC analysis), the crude mixture was purified by column chromatography on silica gel to afford the product (-)-5ca, 1.3 g, 92% ee.
A mixture of (-)-5ca (2 mmol) and 20%H2SO4 (0.125 M, 16 mL) was heated at 100°C for 10 h and monitored by TLC. The reaction mixture was poured onto ice/water with vigorously stirring and extracted with EA several times (3 × 10 mL). The combined organic extracts were washed by brine (15 mL), and dried over Na2SO4, filtered and concentrated. The crude mixture was purified by column chromatography on silica gel to afford the product (-)-6a, 517.4 mg, 95% yield, 92% ee.

A flame-dried flask was charged with 6a (0.1 mmol, 1 equiv) and CH2Cl2 (1 mL). The reaction was cooled to 0°C and isobutyl chloroformate (0.11 mmol, 1.1 equiv) and Et3N (0.1 mmol, 1 equiv) were added dropwise. The resulting mixture was stirred vigorously for 10 min under N2, after which time Et3N (0.1 mmol, 1 equiv) and thiophenol (0.22 mmol, 2.2 equiv) were added dropwise. The reaction was stirred at 0°C under N2 for 1 h. The reaction was warmed to room temperature and washed with water, water, and brine. The combined aqueous layers were extracted with CH2Cl2. The combined organic layers were dried (MgSO4), filtered, and concentrated. The crude residue was purified by column chromatography (PE/EA = 2/1) to afford the product 7a, 32.2 mg, 85% yield, 90% ee.
Add 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (1 equivalent), 6a (0.1 mmol, 1 equivalent) and 4-dimethyl-aminopyridine (0.1 equivalent) to a stirred solution of 1-methyl-1H-pyrazol-3-amine (0.1 mmol, 1 equivalent) in methylene chloride at 0°C. Stir the reaction mixture at this temperature for 2 hours, during 2 hours the solution becomes homogeneous. After completion (TLC control using EA as eluent), wash the reaction mixture with water and brine. Dry the organic layer with Na$_2$SO$_4$. The crude residue was purified by column chromatography (EA) to afford the product 7b, 23.9 mg, 68% yield, 93% ee.

To the 6a (0.1 mmol, 1 eq.) in THF (1 mL) was added NH$_2$NH$_2$•H$_2$O (0.2 mmol). The resulting mixture was stirred at 60°C for 1 h. The filtrate was concentrated to dryness under reduced pressure and the crude residue was then diluted in 1 M HCl and extracted with CH$_2$Cl$_2$. The organic layer was washed with water, dried over MgSO$_4$ and evaporated to dryness under reduced pressure. The crude residue was purified by column chromatography (PE/EA = 1/1) to afford the product rac-7c, 21.4 mg, 80% yield.

6a (0.1 mol), acetyl chloride (1 mL) was added and the mixture was stirred at room
temperature for 1 h. The acetyl chloride excess was removed in vacuo. The crude mixture was add H₂O (2 mL) to the reaction mixture and extract the organic layer with EtOAc (5 mL × 3). Evaporate the combined organic phases under reduced pressure. The crude residue was purified by column chromatography (PE/EA = 1/1) to afford the product rac-7d, 16.0 mg, 63% yield.

Synthesis of d-P5 and d-P8, Related to Scheme 7.

A flame-dried round bottom flask equipped with a magnetic stir bar under N₂ was charged with P5 or P8 (0.2 mmol) and d₈-THF (1.0 mL), followed by the addition of D₂O (2.0 mL). The reaction was then heated to 30°C for three hours. The reaction was then diluted with dry dichloromethane (5 mL), filtered through diatomite, dried over sodium sulfate and concentrated. ¹H NMR spectra was recorded on a Bruker300 (or 400) MHz spectrometer in DMSO-d₆.
Table S1. Asymmetric Michael Addition of pyridazinones to enones catalyzed by different chiral phosphines.\(^a\) Related to Table 1.

\[
\begin{array}{c|c|c|c|c}
 & \text{Product} & \text{Conditions} & \text{Yield} & \text{ee} \\
\hline
1f & 2a & \begin{array}{c} 10 \text{ mol \% Cat.} \\ \text{-eq methyl acrylate} \\ \text{DCM, N}_{2}, r.t. \end{array} & (R)-3fa \\
\hline
\text{P1} & \begin{array}{c} \text{Ph}_3\text{P} \\ \text{Ph}_3\text{P} \end{array} & \begin{array}{c} \text{trace} \\ 30 \text{\% yield, 31\% ee} \end{array} & \begin{array}{c} \text{trace} \\ 30 \text{\% yield, 31\% ee} \end{array} \\
\text{P2} & \begin{array}{c} \text{Ph}_3\text{P} \\ \text{Ph}_3\text{P} \end{array} & \begin{array}{c} 90 \text{\% yield, 16\% ee} \\ 90 \text{\% yield, 17\% ee} \end{array} & \begin{array}{c} 90 \text{\% yield, 16\% ee} \\ 90 \text{\% yield, 17\% ee} \end{array} \\
\text{P3} & \begin{array}{c} \text{Ph}_3\text{P} \\ \text{Ph}_3\text{P} \end{array} & \begin{array}{c} \text{trace} \\ 30 \text{\% yield, 31\% ee} \end{array} & \begin{array}{c} \text{trace} \\ 30 \text{\% yield, 31\% ee} \end{array} \\
\text{P4} & \begin{array}{c} \text{Ph}_3\text{P} \\ \text{Ph}_3\text{P} \end{array} & \begin{array}{c} 90 \text{\% yield, 51\% ee} \\ 96 \text{\% yield, 20\% ee} \end{array} & \begin{array}{c} 90 \text{\% yield, 51\% ee} \\ 96 \text{\% yield, 20\% ee} \end{array} \\
\text{P5} & \begin{array}{c} \text{Ph}_3\text{P} \\ \text{Ph}_3\text{P} \end{array} & \begin{array}{c} 90 \text{\% yield, 51\% ee} \\ 96 \text{\% yield, 20\% ee} \end{array} & \begin{array}{c} 90 \text{\% yield, 51\% ee} \\ 96 \text{\% yield, 20\% ee} \end{array} \\
\text{P6} & \begin{array}{c} \text{Ph}_3\text{P} \\ \text{Ph}_3\text{P} \end{array} & \begin{array}{c} 90 \text{\% yield, 51\% ee} \\ 96 \text{\% yield, 20\% ee} \end{array} & \begin{array}{c} 90 \text{\% yield, 51\% ee} \\ 96 \text{\% yield, 20\% ee} \end{array} \\
\text{P7} & \begin{array}{c} \text{Ph}_3\text{P} \\ \text{Ph}_3\text{P} \end{array} & \begin{array}{c} 90 \text{\% yield, 51\% ee} \\ 96 \text{\% yield, 20\% ee} \end{array} & \begin{array}{c} 90 \text{\% yield, 51\% ee} \\ 96 \text{\% yield, 20\% ee} \end{array} \\
\text{P10} & \begin{array}{c} \text{Ph}_3\text{P} \\ \text{Ph}_3\text{P} \end{array} & \begin{array}{c} 90 \text{\% yield, 51\% ee} \\ 96 \text{\% yield, 20\% ee} \end{array} & \begin{array}{c} 90 \text{\% yield, 51\% ee} \\ 96 \text{\% yield, 20\% ee} \end{array} \\
\text{P11} & \begin{array}{c} \text{Ph}_3\text{P} \\ \text{Ph}_3\text{P} \end{array} & \begin{array}{c} 90 \text{\% yield, 51\% ee} \\ 96 \text{\% yield, 20\% ee} \end{array} & \begin{array}{c} 90 \text{\% yield, 51\% ee} \\ 96 \text{\% yield, 20\% ee} \end{array} \\
\text{P12} & \begin{array}{c} \text{Ph}_3\text{P} \\ \text{Ph}_3\text{P} \end{array} & \begin{array}{c} 90 \text{\% yield, 51\% ee} \\ 96 \text{\% yield, 20\% ee} \end{array} & \begin{array}{c} 90 \text{\% yield, 51\% ee} \\ 96 \text{\% yield, 20\% ee} \end{array} \\
\text{P13} & \begin{array}{c} \text{Ph}_3\text{P} \\ \text{Ph}_3\text{P} \end{array} & \begin{array}{c} 90 \text{\% yield, 51\% ee} \\ 96 \text{\% yield, 20\% ee} \end{array} & \begin{array}{c} 90 \text{\% yield, 51\% ee} \\ 96 \text{\% yield, 20\% ee} \end{array} \\
\end{array}
\]

\(^a\) Reaction conditions: 1f (0.1 mmol), 2a (0.2 mmol), methyl acrylate (0.1 mmol) and catalyst (0.01 mmol) in DCM (1 mL) at room temperature for 1 h. NMR yield with CHCl₃ as an internal standard. Determined by HPLC analysis on a chiral stationary phase.
Table S2. Optimization of Reaction Conditions Using Model Substrates.\(^a\) Related to Table 1.

![Chemical structure of 1f and 2a](image)

| Entry | Cat | Temp. (°C) | Solvent          | Yield\(^b\) (%) | Ee\(^c\) (%) |
|-------|-----|------------|------------------|-----------------|--------------|
| 1     | P8  | rt         | CHCl\(_3\)       | 81              | -67          |
| 2     | P8  | rt         | THF              | 73              | -62          |
| 3     | P8  | rt         | Et\(_2\)O        | 95              | -72          |
| 4     | P8  | rt         | toluene          | 98              | -81          |
| 5     | P8  | rt         | PhCF\(_3\)       | 99              | -73          |
| 6     | P8  | rt         | o-xylene         | 98              | -80          |
| 7     | P8  | rt         | F\(_5\)PhCH\(_3\)| 97              | -79          |
| 8     | P6  | rt         | toluene          | 97              | -48          |
| 9     | P7  | rt         | toluene          | 99              | -67          |
| 10    | P8  | -10        | toluene          | 98              | -94          |
| 11    | P8  | -20        | toluene          | 97              | -98          |
| 12    | P5  | -20        | toluene          | 95              | 86           |
| 13    | P6  | -20        | toluene          | 95              | -66          |
| 14    | P7  | -20        | toluene          | 99              | -90          |
| 15    | P5  | -20        | F\(_5\)PhCH\(_3\)| 98              | 95           |
| 26\(^d\) | P8  | -20        | toluene          | 90              | -98          |

[a] Reaction conditions: 1f (0.1 mmol), 2a (0.2 mmol), methyl acrylate (0.1 mmol) and the catalyst (0.01 mmol) in the solvent specified (1.0 mL) at room temperature for 1 h. [b] NMR yield with CH\(_2\)Br\(_2\) as an internal standard. [c] Determined by HPLC analysis on a chiral stationary phase. [d] 50 mol % methyl acrylate was used.
Table S3. Optimization of Reaction Conditions Using Catalyst P5. Related to Table 1.

\[
\text{Cl} \quad \text{CF}_3
\quad \text{O}
\quad \text{Cl} \quad \text{CF}_3
\]

\[
\begin{array}{cccc}
\text{Entry} & \text{Solvent} & \text{Yield}^\text{\textdegree} (%) & \text{ee}^\text{\textdegree} (%) \\
1 & \text{CHCl}_3 & 96 & 45 \\
2 & \text{THF} & 88 & 55 \\
3 & \text{Et}_2\text{C} & 94 & 54 \\
4 & \text{toluene} & 95 & 54 \\
5 & \text{PhCF}_2 & 93 & 53 \\
6 & \text{PhCl} & 95 & 50 \\
7 & \text{FePh} & 90 & 79 \\
8 & \text{Fe}_2\text{PhCH}_3 & 95 & 83 \\
9 & \text{PhF} & 93 & 54 \\
10 & \text{Mesitylene} & 95 & 71 \\
11 & \text{\textalpha}-\text{xylene} & 92 & 59 \\
12 & \text{\textmu}-\text{xylene} & 94 & 59 \\
13 & \text{\textpi}-\text{xylene} & \text{NR} & -- \\
14 & \text{\texteta}-\text{A} & 96 & 47 \\
15^\text{[a]} & \text{FePh} & 94 & 91 \\
16^\text{[a]} & \text{Fe}_2\text{PhCH}_3 & 98 & 95 \\
17^\text{[a]} & \text{PhCF}_2 & 95 & 82 \\
18^\text{[a]} & \text{toluene} & 95 & 86 \\
19^\text{[a]} & \text{\textalpha}-\text{xylene} & \text{NR} & -- \\
20^\text{[a]} & \text{\textmu}-\text{xylene} & 96 & 83 \\
21^\text{[a]} & \text{mesitylene} & 98 & 86 \\
22^\text{[a]} & \text{EtO} & 98 & 77 \\
\end{array}
\]

[a] Reaction conditions: 1f (0.1 mmol) 2a (0.2 mmol) methyl acrylate (0.1 mmol) and P5 (0.01 mmol) in the solvent specified (1 mL) at room temperature for 1 h. \([b]\) NMR yield with CH$_2$Br$_2$ as an internal standard. \([c]\) Determined by HPLC analysis on a chiral stationary phase. \([d]\) The reaction was performed at -20°C and the reaction time was 12 h.
Table S4. Nitrogen nucleophile survey.\(^a\) Related to Scheme 4.

| Method | Nucleophile | Yield | ee (%) | Reaction Conditions | Product | ee (%) | Product |
|--------|-------------|-------|--------|----------------------|---------|--------|---------|
| A      | N1-methyl-P5 | 90%   | 70%    | DMF, 60°C, 3 h       | (+)-3fa |        |         |
| B      | N2-methyl-P8 | 94%   | 70%    | DMF, 60°C, 3 h       | (+)-3fa |        |         |
|        | N2-methyl-P8 | 92%   | 63%    | DMF, 60°C, 3 h       | (+)-3fa |        |         |
|        | D-P5        | 96%   | 95%    | DMF, 60°C, 3 h       | (+)-3fa |        |         |
|        | D-P8        | 92%   | 35%    | DMF, 60°C, 3 h       | (+)-3fa |        |         |

\(^a\) Method A: 1 mol % N2-methyl-P5 in CH2Cl2 at 80°C. Method B: 1 mol % methyl acrylate in toluene at 60°C. Determined by HPLC analysis on a Vydac stationary phase. Boc: 20 mol % 2-methyl-2-phenoxypropanoic acid additive and the reaction was run at room temperature.

Figure S1. Some Control Experiments. Related to Scheme 7.
Figure S2. $^{19}$F-NMR titration experiments. Related to Scheme 7.

Figure S3. Proposed mechanism and transition states. Related to Scheme 7.
Data S1. Characterizations. Related to Scheme 3, Scheme 4, Scheme 5, Scheme 6 and Scheme 7.

The data of P4.

\[ \text{P4; white solid; yield: } 70\% \; [\alpha]_D^{20} = +34.4 \; (c = 1.0, \text{CHCl}_3); \]  
\[ ^1\text{H NMR (500 MHz, CDCl}_3) \delta 7.39-7.37 \; (m, 1H), 7.32 \; (dd, J = 7.1, 5.7 Hz, 6H), 7.28-7.22 \; (m, 7H), 7.15 \; (dd, J = 9.9, 3.8 Hz, 3H), 7.04 \; (t, J = 7.4 Hz, 2H), 5.25 \; (d, J = 6.4 Hz, 1H), 4.94 \; (s, 1H), 3.88 \; (dd, J = 8.1, 5.9 Hz, 1H), 2.89-2.80 \; (m, 2H), 2.32 \; (d, J = 6.1 Hz, 1H), 1.46 \; (s, 9H), 0.90 \; (d, J = 6.8 Hz, 3H), 0.82 \; (d, J = 6.8 Hz, 3H); \]  
\[ ^{13}\text{C NMR (126 MHz, CDCl}_3) \delta 170.57, 155.87, 141.04, 140.49, 140.25, 137.82 \; (d, J = 12.1 Hz), 132.60 \; (d, J = 19.4 Hz), 132.52 \; (d, J = 18.9 Hz), 130.52, 129.31, 128.66, 128.64, 128.58, 128.53, 128.52, 128.48, 128.34, 127.90, 127.17, 127.11, 125.07, 49.14, 48.74 \; (d, J = 14.7 Hz), 36.22, 36.09, 31.61, 30.89, 28.36, 22.67, 19.47, 17.55, 11.92; \]  
\[ ^{31}\text{P NMR (202 MHz, CDCl}_3) \delta -24.45; \]  
HRMS (ESI) m/z calcd. for C\textsubscript{36}H\textsubscript{41}N\textsubscript{2}NaO\textsubscript{3}P [M+Na]\textsuperscript{+} = 603.2747, found 603.2756.

The data of P5.

\[ \text{P5; white solid; yield: } 82\% \; [\alpha]_D^{20} = -6.0 \; (c = 0.33, \text{CHCl}_3); \]  
\[ ^1\text{H NMR (500 MHz, CDCl}_3) \delta 7.42 \; (d, J = 7.4 Hz, 1H), 7.32-7.19 \; (m, 13H), 7.12 \; (t, J = 6.5 Hz, 3H), 6.97 \; (t, J = 7.3 Hz, 2H), 6.71 \; (d, J = 5.0 Hz, 1H), 5.15 \; (dd, J = 10.1, 5.4 Hz, 1H), 5.02 \; (d, J = 5.4 Hz, 1H), 4.97 \; (s, 1H), 3.88 \; (dd, J = 8.1, 5.9 Hz, 1H), 2.89-2.80 \; (m, 2H), 2.32 \; (d, J = 6.1 Hz, 1H), 1.46 \; (s, 9H), 0.90 \; (d, J = 6.8 Hz, 3H), 0.82 \; (d, J = 6.8 Hz, 3H); \]  
\[ ^{13}\text{C NMR (126 MHz, CDCl}_3) \delta 170.57, 155.87, 141.04, 140.49, 140.25, 137.82 \; (d, J = 12.1 Hz), 132.60 \; (d, J = 19.4 Hz), 132.52 \; (d, J = 18.9 Hz), 130.52, 129.31, 128.66, 128.64, 128.58, 128.53, 128.52, 128.48, 128.34, 127.90, 127.17, 127.11, 125.07, 49.14, 48.74 \; (d, J = 14.7 Hz), 36.22, 36.09, 31.61, 30.89, 28.36, 22.67, 19.47, 17.55, 11.92; \]  
\[ ^{31}\text{P NMR (202 MHz, CDCl}_3) \delta -24.45; \]  
HRMS (ESI) m/z calcd. for C\textsubscript{36}H\textsubscript{41}N\textsubscript{2}NaO\textsubscript{3}P [M+Na]\textsuperscript{+} = 603.2747, found 603.2756.
= 8.6 Hz, 1H), 3.85 (t, J = 7.9 Hz, 1H), 2.87-2.76 (m, 1H), 2.32 (dd, J = 13.8, 2.6 Hz, 1H), 2.26-2.20 (m, 1H), 2.03 (d, J = 6.3 Hz, 1H), 1.45 (s, 9H), 0.94-0.86 (m, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 170.88, 156.00, 140.80, 140.70, 140.65, 140.59, 138.06 (d, J = 11.9 Hz), 135.99 (d, J = 12.8 Hz), 132.82 (d, J = 19.9 Hz), 132.20 (d, J = 18.5 Hz), 130.51, 129.34, 128.82, 128.66, 128.60, 128.46, 128.44, 128.41, 128.01, 127.11, 127.06, 124.89, 79.82, 60.29, 49.05 (d, J = 6.4 Hz), 48.75 (d, J = 12.9 Hz), 36.19 (d, J = 17.0 Hz), 30.54, 28.38, 19.63, 18.11, 11.80 (d, J = 2.5 Hz); $^{31}$P NMR (202 MHz, CDCl$_3$) δ -24.43 (s); HRMS (ESI) m/z calcd. for C$_{36}$H$_{42}$N$_2$O$_3$P [M+H]$^+$ = 581.2928, found 581.2941.

The data of P6.

P6; pale yellow solid; yield: 75%; [α]$_D^{20}$ = -14.7 (c = 0.33, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 8.00 (d, J = 8.7 Hz, 2H), 7.80 (d, J = 8.7 Hz, 2H), 7.40-7.09 (m, 17H), 6.97 (t, J = 7.5 Hz, 2H), 5.27-5.20 (m, 1H), 4.53 (t, J = 7.7 Hz, 1H), 2.37-2.32 (m, 1H), 2.27-2.15 (m, 2H), 1.72 (s, 1H), 1.26 (s, 1H), 1.02 (dd, J = 18.4, 6.7 Hz, 6H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 170.33, 165.49, 149.56, 140.62, 140.56, 140.45, 139.34, 137.82 (d, J = 11.5 Hz), 135.96 (d, J = 12.6 Hz), 132.70 (d, J = 19.8 Hz), 132.18 (d, J = 18.9 Hz), 130.58, 129.23, 128.86, 128.68, 128.61, 128.51, 128.43, 128.22, 128.12, 127.22 (d, J = 8.3 Hz), 124.76, 123.59, 59.47, 49.03 (d, J = 13.9 Hz), 36.31 (d, J = 17.4 Hz), 31.38, 19.10 (d, J = 12.1 Hz); $^{31}$P NMR (162 MHz, CDCl$_3$) δ -24.42 (s); HRMS (ESI) m/z calcd. for C$_{38}$H$_{37}$N$_3$O$_4$P [M+H]$^+$ = 630.2516, found 630.2529.

The data of P7.
P7; white solid; yield: 84%; $[\alpha]_D^{20} = -12.0$ ($c = 0.33$, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.24 (s, 2H), 7.96 (s, 1H), 7.34-7.11 (m, 15H), 7.05 (d, $J = 7.1$ Hz, 1H), 6.98 (t, $J = 7.2$ Hz, 3H), 5.27-5.21 (m, 1H), 4.42 (t, $J = 6.3$ Hz, 1H), 2.35 (d, $J = 12.4$ Hz, 1H), 2.25-2.18 (m, 2H), 1.98 (s, 1H), 1.26 (s, 1H), 0.97 (dd, $J = 17.2$, 6.6 Hz, 6H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 167.41 (d, $J = 537.3$ Hz), 140.65, 140.39, 137.83 (d, $J = 11.6$ Hz), 136.12, 135.98, 132.66 (d, $J = 19.8$ Hz), 132.26, 132.07, 131.92, 131.58, 130.50, 129.23, 128.81, 128.61 (d, $J = 7.0$ Hz), 128.47 (d, $J = 6.3$ Hz), 128.37, 128.34, 127.98, 127.50 (d, $J = 2.5$ Hz), 127.12, 126.91, 124.74, 124.84 (q, $J = 273.0$ Hz), 59.76, 31.20, 49.90 (d, $J = 13.8$ Hz), 36.41 (d, $J = 17.2$ Hz), 18.97 (d, $J = 114.3$ Hz); $^{31}$P NMR (162 MHz, CDCl$_3$) $\delta$ -24.37 (s); $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -62.87 (s); HRMS (ESI) m/z calcd. for C$_{40}$H$_{36}$F$_6$N$_2$O$_2$P [M+H]$^+$ = 721.2413, found 721.2421.

The data of P5.

P8; yellow solid; yield: 78%; $[\alpha]_D^{20} = -29.1$ ($c = 0.33$, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.92 (s, 2H), 8.37 (s, 1H), 7.35-7.15 (m, 15H), 6.96 (dd, $J = 25.1$, 18.2 Hz, 4H), 5.17 (d, $J = 4.1$ Hz, 1H), 4.82 (s, 1H), 2.29 (d, $J = 14.5$ Hz, 2H), 2.16 (s, 1H), 1.91 (s, 1H), 1.11 (d, $J = 5.5$ Hz, 3H), 0.96 (d, $J = 5.7$ Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 170.43, 163.38, 148.02, 140.40 (d, $J = 5.7$ Hz), 140.20 (d, $J = 26.6$ Hz), 130.50, 129.23, 128.81, 128.61 (d, $J = 7.0$ Hz), 128.47 (d, $J = 6.3$ Hz), 128.37, 128.34, 127.98, 127.50 (d, $J = 2.5$ Hz), 127.12, 126.91, 124.74, 124.84 (q, $J = 273.0$ Hz), 59.76, 31.20, 49.90 (d, $J = 13.8$ Hz), 36.41 (d, $J = 17.2$ Hz), 18.97 (d, $J = 114.3$ Hz); $^{31}$P NMR (162 MHz, CDCl$_3$) $\delta$ -24.37 (s); $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -62.87 (s); HRMS (ESI) m/z calcd. for C$_{40}$H$_{36}$F$_6$N$_2$O$_2$P [M+H]$^+$ = 721.2413, found 721.2421.
137.80 (d, J = 11.5 Hz), 137.32, 135.45 (d, J = 12.6 Hz), 132.80 (d, J = 20.0 Hz), 131.96 (d, J = 18.4 Hz), 130.29, 129.09, 128.98, 128.54, 128.50, 128.46, 128.23, 128.70 (d, J = 7.4 Hz), 127.63, 127.20 (d, J = 17.4 Hz), 124.59, 121.04, 59.53, 48.86 (d, J = 12.6 Hz), 36.39 (d, J = 17.4 Hz), 32.18, 29.72, 29.38, 22.72, 14.15, 19.05 (d, J = 200.9 Hz); \(^{31}\)P NMR (202 MHz, CDCl\(_3\)) δ -24.59 (s); HRMS (ESI) m/z calcd. for C\(_{38}\)H\(_{36}\)N\(_4\)O\(_6\)P [M+H]\(^+\) = 675.2367, found 675.2384.

The data of \(N1\)-methyl-P5.

\(N1\)-methyl-P5; white solid; yield: 44% yield for three steps; [α]\(^D\)\(_{20}\) = +53.0 (c = 0.33, CHCl\(_3\)); \(^1\)H NMR (500 MHz, CDCl\(_3\)) δ 7.57 (d, J = 7.7 Hz, 1H), 7.40-7.36 (m, 3H), 7.31 (dd, J = 5.8, 2.7 Hz, 4H), 7.29-7.19 (m, 8H), 7.13 (dd, J = 7.4, 1.0 Hz, 1H), 6.95 (d, J = 6.8 Hz, 2H), 5.69 (dd, J = 14.3, 7.6 Hz, 1H), 5.07 (d, J = 9.2 Hz, 1H), 4.24 (dd, J = 9.2, 5.7 Hz, 1H), 2.81 (s, 3H), 2.63 (dd, J = 13.8, 7.4 Hz, 1H), 2.50 (dd, J = 13.7, 9.2 Hz, 1H), 1.91-1.85 (m, 1H), 1.45 (s, 9H), 0.92 (d, J = 6.8 Hz, 3H), 0.81 (d, J = 6.7 Hz, 3H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) δ 171.17, 155.76, 143.08, 140.69, 138.28 (d, J = 14.5 Hz), 137.60 (d, J = 12.9 Hz), 136.69 (d, J = 5.4 Hz), 133.01, 132.86, 132.73, 132.58, 130.66, 128.77, 128.62, 128.55, 128.50, 128.16, 127.49, 127.77 (d, J = 3.2 Hz), 127.13 (d, J = 15.6 Hz), 79.13, 55.31, 52.62, 52.49, 31.59 (d, J = 3.8 Hz), 31.20, 31.14, 31.07, 28.44, 19.86, 17.20; \(^{31}\)P NMR (202 MHz, CDCl\(_3\)) δ -22.75; HRMS (ESI) m/z calcd. for C\(_{37}\)H\(_{43}\)N\(_2\)O\(_3\)P [M+Na]\(^+\) = 617.2904, found 617.2908.

The data of \(N1\)-methyl-P8.
**N1-methyl-P8:*** light yellow solid; yield: 60%; \([\alpha]_D^{20} = +55.3\ (c = 1.0, \text{CHCl}_3);^1\text{H}^1\text{H} \text{NMR (500 MHz, CDCl}_3) \delta 9.00-8.98 (m, 1H), 8.93 (d, \(J = 1.9\ Hz, 2H), 7.46 (d, \(J = 5.8\ Hz, 1H), 7.36-7.30 (m, 9H), 7.24 (dd, \(J = 10.1, 4.5\ Hz, 2H), 7.12 (d, \(J = 6.8\ Hz, 5H), 7.01 (s, 1H), 6.78 (s, 1H), 6.48 (s, 1H), 6.43 (d, \(J = 7.5\ Hz, 2H), 6.36 (s, 1H), 6.25-6.21 (m, 2H), 5.74 (dd, \(J = 10.4, 5.4\ Hz, 1H), 5.04 (d, \(J = 4.1\ Hz, 1H), 3.01 (s, 3H), 2.62-2.60 (m, 1H), 2.48 (d, \(J = 9.4\ Hz, 1H), 2.18-2.16 (m, 1H), 1.88-1.87 (m, 1H), 1.09 (d, \(J = 6.6\ Hz, 3H), 0.84 (d, \(J = 6.6\ Hz, 3H);^13\text{C} \text{NMR (126 MHz, CDCl}_3) \delta 170.94, 170.82, 162.71, 162.67, 153.34, 148.33, 148.28, 148.26, 142.27, 142.19, 140.70, 140.05, 137.84, 137.80, 137.30, 137.19, 132.80, 132.69, 132.64, 132.53, 130.89, 128.94, 128.79, 128.70, 128.65, 128.61, 128.56, 128.33, 127.58 (d, \(J = 5.2\ Hz), 127.30, 126.94, 126.70, 121.08, 120.22, 60.46, 56.59, 55.11, 53.23 (d, \(J = 15.7\ Hz), 50.40, 32.45, 31.77 (d, \(J = 17.0\ Hz), 31.43, 31.10 (d, \(J = 7.2\ Hz), 26.05, 25.22 (d, \(J = 5.7\ Hz), 24.61, 21.09, 20.37, 17.23, 14.24;^31\text{P} \text{NMR (202 MHz, CDCl}_3) \delta -22.13; \text{HRMS (ESI) m/z calcd. for C}_{39}\text{H}_{37}\text{N}_4\text{NaO}_6\text{P [M+Na]}^+ = 711.2343, found 711.2352.\)"

The data of N2-methyl-P5.

**N2-methyl-P5:*** white solid; yield: 79%; \([\alpha]_D^{20} = -35.6\ (c = 1.0, \text{CHCl}_3);^1\text{H} \text{NMR (400 MHz, CDCl}_3) \delta 7.32 (s, 6H), 7.24-7.18 (m, 8H), 7.12-7.09 (m, 3H), 6.93 (t, \(J = 7.5\ Hz, 2H), 6.84 (d, \(J = 6.9\ Hz, 1H), 5.21-5.16 (m, 1H), 4.07 (d, \(J = 11.2\ Hz, 1H), 2.71 (s, 3H), 2.30-2.25 (m, 1H), 2.24-2.19 (m, 1H), 2.17-2.09 (m, 1H), 1.51 (s, 9H);^13\text{C} \text{NMR}}
The data of N1-methyl-P8.

![Structure of N1-methyl-P8](image)

N2-methyl-P8, light yellow solid; yield: 76%; $\alpha$D20 = -39.5 (c = 0.33, CHCl3); $^1$H NMR (400 MHz, CDCl3) $\delta$ 9.06 (s, 1H), 8.55 (d, $J = 1.7$ Hz, 2H), 7.46 (q, $J = 7.7$ Hz, 2H), 7.33-7.29 (m, 6H), 7.24-7.21 (m, 5H), 7.17-7.10 (m, 4H), 6.98 (t, $J = 7.5$ Hz, 2H), 5.29-5.22 (m, 1H), 4.55 (d, $J = 11.3$ Hz, 1H), 2.87 (s, 3H), 2.43-2.30 (m, 2H), 2.28-2.20(m, 1H), 1.05 (d, $J = 6.4$ Hz, 6H); $^{31}$P NMR (122 MHz, CDCl3) $\delta$ -23.57; $^{13}$C NMR (101 MHz, CDCl3) $\delta$ 168.18, 167.57, 148.56, 141.24 (d, $J = 6.0$ Hz), 140.62 (d, $J = 59.0$ Hz), 139.36, 138.31 (d, $J = 11.9$ Hz), 135.96 (d, $J = 13.2$ Hz), 132.85 (d, $J = 20.0$ Hz), 132.14 (d, $J = 18.5$ Hz), 130.79, 129.24, 128.91, 128.70 (d, $J = 7.3$ Hz), 128.55, 128.53, 128.50, 128.49, 127.99, 127.36, 127.25, 124.40, 119.95, 48.23, 48.11, 36.34, 36.17, 33.75, 25.64, 19.69, 19.02; HRMS (ESI) m/z calcd. for C39H37NaNaO6P [M+Na] $^+$ = 711.2343, found 711.2356.

The data of P9.
**P9; white solid; yield: 80%;** [α]_D^{20} = -1.6 (c = 0.33, CHCl₃); ^1^H NMR (500 MHz, CDCl₃) δ 7.92 (d, J = 6.9 Hz, 1H), 7.41-7.38 (m, 3H), 7.31-7.28 (m, 4H), 7.26-7.20 (m, 7H), 7.15-7.11 (m, 3H), 7.00 (dd, J = 11.7, 4.1 Hz, 2H), 5.30-5.27 (m, 1H), 3.18 (d, J = 3.9 Hz, 1H), 2.32 (d, J = 7.4 Hz, 2H), 2.28-2.22 (m, 1H), 1.59 (s, 2H), 0.93 (d, J = 7.0 Hz, 3H), 0.76 (d, J = 6.9 Hz, 3H); ^1^C NMR (126 MHz, CDCl₃) δ 173.45, 141.16 (d, J = 5.9 Hz), 140.94, 140.66, 138.25 (d, J = 11.9 Hz), 137.00 (d, J = 12.7 Hz), 132.64 (d, J = 6.4 Hz), 132.49 (d, J = 6.8 Hz), 130.55, 129.48, 128.60, 128.54, 128.52, 128.47, 128.42, 128.37, 127.84, 125.12, 60.12, 48.28 (d, J = 14.4 Hz), 36.77 (d, J = 16.6 Hz) 30.88, 19.87, 16.21; ^3^P NMR (202 MHz, CDCl₃) δ -23.64; HRMS (ESI) m/z calcd. for C₃₁H₃₄N₂O₆P [M+H]^+ = 481.2403, found 481.2404.

The data of P10.

**P10; white solid;** [α]_D^{20} = -7.8 (c = 0.33, CHCl₃); ^1^H NMR (500 MHz, CDCl₃) δ 7.35-7.22 (m, 14H), 7.17 (d, J = 7.4 Hz, 2H), 7.05 (d, J = 7.2 Hz, 1H), 7.01 (t, J = 7.4 Hz, 2H), 6.46 (s, 1H), 5.19 (d, J = 5.0 Hz, 1H), 4.29 (t, J = 6.9 Hz, 1H), 2.37 (d, J = 11.8 Hz, 1H), 2.30-2.24 (m, 1H), 2.09 (dd, J = 12.9, 6.5 Hz, 1H), 1.65 (s, 1H), 0.96 (d, J = 6.5 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H); ^1^F NMR (376 MHz, CDCl₃) δ -75.65; ^3^P NMR (202 MHz, CDCl₃) δ -24.45; ^1^C NMR (126 MHz, CDCl₃) δ 168.30, 157.20 (q, J = 37.5 Hz), 140.76, 140.44, 140.02 (d, J = 5.6 Hz), 137.63 (d, J = 11.1 Hz), 135.82 (d, J = 13.1 Hz), 132.75 (d, J = 19.8 Hz), 132.21 (d, J = 18.7 Hz), 130.68, 129.24,
129.00, 128.75, 128.69, 128.68, 128.58, 128.53, 128.48, 128.17, 127.32 (d, \( J = 13.9 \) Hz), 115.77 (q, \( J = 287.7 \) Hz), 124.75, 58.66, 49.20 (d, \( J = 13.3 \) Hz), 36.20 (d, \( J = 17.1 \) Hz), 31.76, 21.53, 19.31, 17.89; HRMS (ESI) m/z calcd. for \( \text{C}_{33}\text{H}_{33}\text{F}_{3}\text{N}_{2}\text{O}_{2}\text{P} \) [M+H] \(^+\) = 577.2226, found 577.2229.

**The data of P12.**

\[
\text{P12; white solid; } [\alpha]_D^{20} = -3.3 \text{ (c = 1.0, CHCl}_3\text{);}\]

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.31 (s, 11H), 7.23 (d, \( J = 10.3 \) Hz, 7H), 7.12 (dd, \( J = 9.4, 4.8 \) Hz, 3H), 6.98 (t, \( J = 7.6 \) Hz, 2H), 6.73 (d, \( J = 6.4 \) Hz, 1H), 5.40 (s, 1H), 5.17 (dd, \( J = 15.5, 6.5 \) Hz, 1H), 5.09 (s, 2H), 4.02 (d, \( J = 6.8 \) Hz, 1H), 2.80 (dd, \( J = 12.3, 5.5 \) Hz, 2H), 2.30-2.23 (m, 1H), 2.13-2.04 (m, 1H), 0.95 (d, \( J = 6.7 \) Hz, 3H), 0.89 (d, \( J = 6.6 \) Hz, 3H); \(^{31}\)P NMR (162 MHz, CDCl\(_3\)) \( \delta \) -24.34; \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 170.56, 156.64, 140.80, 140.69, 140.60, 138.12 (d, \( J = 11.9 \) Hz), 136.33, 136.26, 136.13, 132.83 (d, \( J = 19.8 \) Hz), 132.25 (d, \( J = 18.6 \) Hz), 130.54, 129.36, 128.85, 128.71, 128.64, 128.56, 128.51, 128.48, 128.45, 128.16, 128.09, 128.01, 127.16, 127.13, 125.02, 67.02, 60.56, 48.95 (d, \( J = 3.4 \) Hz), 48.76 (d, \( J = 13.3 \) Hz), 36.35 (d, \( J = 16.9 \) Hz), 31.11, 21.57, 19.67, 17.98, 14.27, 11.69 (d, \( J = 4.0 \) Hz); HRMS (ESI) m/z calcd. for \( \text{C}_{39}\text{H}_{40}\text{N}_{2}\text{O}_{3}\text{P} \) [M+H] \(^+\) = 615.2771, found 615.2770.

**The data of P13.**
**P13**; white solid; \([\alpha]_D^{20} = +17.530\) (\(c = 0.33, \text{CHCl}_3\)); \(^1\text{H} \text{NMR (500 MHz, CDCl}_3\) \(\delta 7.39\) (d, \(J = 7.7 \text{ Hz, 1H}\)), 7.31-7.28 (m, 6H), 7.24-7.21 (m, 6H), 7.16-7.13 (m, 3H), 7.04 (t, \(J = 7.3 \text{ Hz, 2H}\)), 6.75 (s, 1H), 5.28-5.25 (m, 1H), 5.13 (s, 1H), 3.68 (s, 2H), 2.32 (d, \(J = 7.3 \text{ Hz, 2H}\)), 1.44 (s, 9H); \(^{31}\text{P} \text{NMR (202 MHz, CDCl}_3\) \(\delta -23.96\); \(^{13}\text{C} \text{NMR (126 MHz, CDCl}_3\) \(\delta 168.31, 156.07, 140.74\) (d, \(J = 46.8 \text{ Hz}\)), 140.43 (d, \(J = 5.8 \text{ Hz}\)), 138.00 (d, \(J = 12.1 \text{ Hz}\)), 137.03 (d, \(J = 12.7 \text{ Hz}\)), 132.72, 132.59, 132.57, 132.44, 130.54, 129.33, 128.67, 128.62, 128.59, 128.53, 128.52, 128.46, 128.37, 127.98, 127.18, 125.25, 60.44, 44.31, 48.73 (d, \(J = 14.9 \text{ Hz}\)), 36.54 (d, \(J = 16.9 \text{ Hz}\)), 28.38, 21.09, 14.24; HRMS (ESI) m/z calcd. for C\(_{33}\)H\(_{36}\)N\(_2\)O\(_3\)P \([\text{M+H}]+ = 539.2458\), found 539.2459.

**\((S)-2-(1,1,1\text{-trifluoro-4-oxo-4-phenylbutan-2-yl})\text{pyridazin-3(2H)-one}\**

\((+)-3aa\); isolated yield: 28.1 mg (95%); colorless sticky oil; \([\alpha]_D^{20} = +291.9\) (\(c = 1.0, \text{CHCl}_3\)); \(^1\text{H} \text{NMR (400 MHz, CDCl}_3\) \(\delta 7.97-7.94\) (m, 2H), 7.72 (dd, \(J = 3.7, 1.6 \text{ Hz, 1H}\)), 7.60 (t, \(J = 7.4 \text{ Hz, 1H}\)), 7.48 (t, \(J = 7.7 \text{ Hz, 2H}\)), 7.14 (dd, \(J = 9.5, 3.7 \text{ Hz, 1H}\)), 6.99 (dd, \(J = 9.5, 1.6 \text{ Hz, 1H}\)), 6.47-6.38 (m, 1H), 4.29 (dd, \(J = 18.1, 10.9 \text{ Hz, 1H}\)), 3.52 (dd, \(J = 18.1, 2.9 \text{ Hz, 1H}\)); \(^{13}\text{C} \text{NMR (101 MHz, CDCl}_3\) \(\delta 193.85, 160.11, 136.59, 135.79, 133.76, 131.04, 130.22, 128.74, 128.06, 124.41\) (q, \(J = 282.8 \text{ Hz}\)), 52.89 (q, \(J = 31.5 \text{ Hz}\)), 35.30; \(^{19}\text{F} \text{NMR (376 MHz, CDCl}_3\) \(\delta -73.16\) (s); Enantiomeric excess: 95%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 80/20; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: \(t_R = 9.69 \text{ min, second peak: } t_R = 13.64 \text{ min}; HRMS (ESI) m/z calcd. for C\(_{14}\)H\(_{11}\)F\(_3\)N\(_2\)NaO\(_2\) \([\text{M+Na}]+ = 319.0665\), found 319.0667.
(S)-2-(1,1,1-trifluoro-4-(4-methoxyphenyl)-4-oxobutan-2-yl)pyridazin-3 (2H)-one

(+)-3ba; isolated yield: 30.0 mg (97%); colorless sticky oil; [α]D20 = +230.3 (c = 1.0, CHCl3); 1H NMR (400 MHz, CDCl3) δ 7.85 (d, J = 8.2 Hz, 2H), 7.71 (dd, J = 3.6, 1.6 Hz, 1H), 7.27 (d, J = 8.0 Hz, 2H), 7.13 (dd, J = 9.5, 3.7 Hz, 1H), 6.98 (dd, J = 9.5, 1.7 Hz, 1H), 6.64-6.37 (m, 1H), 4.25 (dd, J = 18.0, 10.9 Hz, 1H), 3.49 (dd, J = 18.0, 2.9 Hz, 1H), 2.41 (s, 3H); 13C NMR (101 MHz, CDCl3) δ 193.47, 160.16, 144.78, 136.59, 133.41, 131.06, 130.25, 129.45, 128.23, 124.49 (q, J = 282.8 Hz), 52.98 (q, J = 31.4 Hz), 35.20, 21.66 (q, J = 2.6 Hz); 19F NMR (376 MHz, CDCl3) δ -73.14 (s); Enantiomeric excess: 96%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 80/20; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: tR = 10.29 min, second peak: tR = 15.93 min; HRMS (ESI) m/z calcd. for C15H13F3N2NaO2 [M+Na]+ = 333.0821, found 333.0824.
(S)-2-(1,1,1-trifluoro-4-oxo-4-(p-tolyl)butan-2-yl)pyrazin-3(2H)-one

(+)-3ca; isolated yield: 28.7 mg (88%); colorless sticky oil; [α]D\text{20} = +355.6 (c = 1.0, CHCl\text{3}); \textsuperscript{1}H NMR (500 MHz, CDCl\text{3}) δ 7.93 (d, J = 8.9 Hz, 2H), 7.72 (dd, J = 3.6, 1.6 Hz, 1H), 7.13 (dd, J = 9.5, 3.7 Hz, 1H), 7.00-6.93 (m, 3H), 6.45-6.38 (m, 1H), 4.23 (dd, J = 17.9, 11.0 Hz, 1H), 3.87 (s, 3H), 3.46 (dd, J = 17.9, 2.9 Hz, 1H); \textsuperscript{13}C NMR (126 MHz, CDCl\text{3}) δ 192.27, 164.00, 160.14, 136.55, 131.02, 130.41, 130.23, 128.88, 124.46 (q, J = 282.8 Hz), 113.89, 55.51, 52.95 (q, J = 31.3 Hz), 34.90; \textsuperscript{19}F NMR (376 MHz, CDCl\text{3}) δ -73.13 (s); Enantiomeric excess: 93%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 80/20; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: t\text{R} = 14.74 min, second peak: t\text{R} = 24.57 min; HRMS (ESI) m/z calcd. for C\textsubscript{15}H\textsubscript{13}F\textsubscript{3}N\textsubscript{2}NaO\textsubscript{3} [M+Na\textsuperscript{+}] = 349.0770, found 349.0769.
(S)-2-(4-((1,1'-biphenyl)-4-yl)-1,1,1-trifluoro-4-oxobutan-2-yl)pyridazin-3(2H)-one

(+)-3da; isolated yield: 36.1 mg (97%); white solid; $[\alpha]_D^{20} = +321.9$ ($c = 1.0$, CHCl$_3$);

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.02 (d, $J = 8.4$ Hz, 2H), 7.75-7.64 (m, 3H), 7.62-7.60 (m, 2H), 7.51-7.39 (m, 3H), 7.13 (dd, $J = 9.5$, 3.7 Hz, 1H), 6.99 (dd, $J = 9.6$, 1.7 Hz, 1H), 6.49-6.40 (m, 1H), 4.32 (dd, $J = 18.0$, 10.9 Hz, 1H), 3.55 (dd, $J = 18.0$, 2.9 Hz, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 193.40, 160.12, 146.48, 139.55, 136.60, 134.47, 131.04, 130.24, 128.97, 128.68, 128.40, 127.34, 127.22, 124.44 (q, $J = 282.8$ Hz), 52.94 (q, $J = 31.5$ Hz), 35.32; $^{19}$F NMR (376 MHz, CDCl$_3$) δ -73.09 (s); Enantiomeric excess: 95%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 80/20; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: $t_R = 15.51$ min, second peak: $t_R = 27.28$ min; HRMS (ESI) m/z calcd. for C$_{20}$H$_{15}$F$_3$N$_2$O$_2$ [M+Na]$^+$ = 395.0978, found = 395.0977.
(S)-2-(1,1,1-trifluoro-4-(4-fluorophenyl)-4-oxobutan-2-yl)pyridazin-3(2H)-one

(+)-3ea; isolated yield: 30.1 mg (96%); colorless sticky oil; [α]D20 = +269.9 (c = 1.0, CHCl3); 1H NMR (500 MHz, CDCl3) δ 8.01-7.97 (m, 2H), 7.73-7.72 (m, 1H), 7.17-7.13 (m, 3H), 7.00 (dd, J = 9.5, 1.7 Hz, 1H), 6.43-6.39 (m, 1H), 4.26 (dd, J = 18.0, 10.9 Hz, 1H), 3.50 (dd, J = 18.0, 2.9 Hz, 1H); 13C NMR (126 MHz, CDCl3) δ 192.36, 166.16 (d, J = 256.1 Hz), 160.15, 136.71, 132.26 (d, J = 3.0 Hz), 131.15, 130.85 (d, J = 9.5 Hz), 130.31, 124.39 (q, J = 282.8 Hz), 115.99 (d, J = 22.0 Hz), 52.87 (q, J = 31.5 Hz), 35.25; 19F NMR (376 MHz, CDCl3) δ -73.17 (s), -103.67 (s); Enantiomeric excess: 97%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 80/20; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: tR = 10.19 min, second peak: tR = 16.21 min; HRMS (ESI) m/z calcd. for C14H10F4N2NaO2 [M+Na]+ = 337.0571, found 337.0573.
(S)-2-(4-(4-chlorophenyl)-1,1,1-trifluoro-4-oxobutan-2-yl)pyridazin-3(2H)-one

(+)-3fa; isolated yield: 32.0 mg (97%); colorless sticky oil; \([\alpha]_D^{20} = +235.2\) (c = 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.90 (d, J = 8.6 Hz, 2H), 7.73 (dd, J = 3.6, 1.6 Hz, 1H), 7.45 (d, J = 8.5 Hz, 2H), 7.16 (dd, J = 9.5, 3.7 Hz, 1H), 6.99 (dd, J = 9.5, 1.5 Hz, 1H), 6.45-6.36 (m, 1H), 4.25 (dd, J = 18.1, 10.9 Hz, 1H), 3.49 (dd, J = 18.1, 2.9 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 192.73, 160.08, 140.36, 136.66, 134.09, 131.10, 130.26, 129.49, 129.10, 124.32 (q, J = 282.9 Hz), 35.27, 52.83 (q, J = 31.5 Hz); ¹⁹F NMR (376 MHz, CDCl₃) δ -73.17 (s). Enantiomeric excess: 98%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 80/20; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: tᵣ = 10.66 min, second peak: tᵣ = 17.35 min; HRMS (ESI) m/z calcd. for C₁₄H₁₀ClF₃N₂NaO₂ [M+Na]⁺ = 353.0275, found 353.0280.
(S)-2-(4-(4-bromophenyl)-1,1,1-trifluoro-4-oxobutan-2-yl)pyrazidin-3(2H)-one

(+)-3ga; isolated yield: 36.4 mg (97%); colorless sticky oil; [α]$_{D}^{20}$ = +226.1 ($c$ = 1.0, CHCl$_3$); 1H NMR (400 MHz, CDCl$_3$) δ 7.82 (d, $J$ = 8.4 Hz, 2H), 7.73-7.72 (m, 1H), 7.63-7.61 (m, 2H), 7.15 (dd, $J$ = 9.5, 3.7 Hz, 1H), 6.99 (d, $J$ = 9.5 Hz, 1H), 6.44-6.36 (m, 1H), 4.24 (dd, $J$ = 18.1, 10.9 Hz, 1H), 3.49 (dd, $J$ = 18.1, 2.9 Hz, 1H); 13C NMR (126 MHz, CDCl$_3$) δ 193.00, 160.15, 136.75, 134.49, 132.15, 131.19, 130.30, 129.62, 129.17, 124.36 (q, $J$ = 282.8 Hz), 52.81 (q, $J$ = 31.5 Hz), 35.29; 19F NMR (376 MHz, CDCl$_3$) δ -73.16 (s); Enantiomeric excess: 97%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 80/20; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: $t_R$ = 11.43 min, second peak: $t_R$ = 18.57 min; HRMS (ESI) m/z calcd. for C$_{14}$H$_{10}$BrF$_3$N$_2$NaO$_2$ [M+Na]$^+$ = 396.9770, found 396.9773.
(S)-2-(1,1,1-trifluoro-4-(4-iodophenyl)-4-oxobutan-2-yl)pyridazin-3(2H)-one

(+)-3ha; isolated yield: 41.8 mg (99%); white solid; $[\alpha]_D^{20} = +288.3$ ($c = 1.0$, CHCl$_3$);

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.84 (d, $J = 8.5$ Hz, 2H), 7.72 (dd, $J = 3.6$, 1.6 Hz, 1H), 7.66 (d, $J = 8.5$ Hz, 2H), 7.15 (dd, $J = 9.5$, 3.7 Hz, 1H), 6.99 (dd, $J = 9.5$, 1.6 Hz, 1H), 6.44-6.35 (m, 1H), 4.23 (dd, $J = 18.1$, 10.9 Hz, 1H), 3.47 (dd, $J = 18.1$, 3.0 Hz, 1H);

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 193.25, 160.07, 138.08, 136.67, 134.94, 131.11, 130.24, 129.38, 124.29 (q, $J = 282.8$ Hz), 101.98, 52.73 (q, $J = 31.5$ Hz), 35.15; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -73.15 (s); Enantiomeric excess: 95%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 80/20; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: $t_R = 12.58$ min, second peak: $t_R = 20.67$ min; HRMS (ESI) m/z calcd. for C$_{14}$H$_{10}$F$_3$IN$_2$NaO$_2$ [M+Na]$^+$ = 444.9631, found 444.9631.
(S)-2-(1,1,1-trifluoro-4-(4-nitrophenyl)-4-oxobutan-2-yl)pyridazin-3(2H)-one

(+)-3ia; isolated yield: 33.4 mg (98%); colorless sticky oil; [α]D²⁰ = +288.2 (c = 1.0, CHCl₃); 
¹H NMR (400 MHz, CDCl₃) δ 8.33 (d, J = 8.8 Hz, 2H), 8.14 (d, J = 8.8 Hz, 2H), 7.75 (dd, J = 3.6, 1.6 Hz, 1H), 7.19 (dd, J = 9.6, 3.7 Hz, 1H), 7.01 (dd, J = 9.6, 1.6 Hz, 1H), 6.46-6.38 (m, 1H), 4.33 (dd, J = 18.2, 10.8 Hz, 1H), 3.59 (dd, J = 18.3, 3.0 Hz, 1H); 
¹³C NMR (101 MHz, CDCl₃) δ 192.71, 160.07, 150.76, 140.07, 136.86, 131.26, 130.34, 129.24, 124.22 (q, J = 282.9 Hz), 124.02, 52.77 (q, J = 31.7 Hz), 35.89; 
¹⁹F NMR (376 MHz, CDCl₃) δ -73.19 (s); Enantiomeric excess: 97%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 80/20; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: tR = 31.02 min, second peak: tR = 32.74 min; HRMS (ESI) m/z calcd. for C₁₄H₁₀F₃N₃O₄[M+Na]⁺ = 364.0516, found 364.0515.
(S)-4-(4,4,4-trifluoro-3-(6-oxopyridazin-1(6H)-yl)butanoyl)benzonitrile

(+)-3ja; isolated yield: 31.1 mg (97%); colorless sticky oil; [\(\alpha\)]\(_D\)\(^{20}\) = +276.8 (c = 1.0, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.06 (d, \(J = 8.5\) Hz, 2H), 7.80 (d, \(J = 8.5\) Hz, 2H), 7.74 (dd, \(J = 3.6, 1.6\) Hz, 1H), 7.18 (dd, \(J = 9.6, 3.7\) Hz, 1H), 7.01 (dd, \(J = 9.6, 1.6\) Hz, 1H), 6.45-6.36 (m, 1H), 4.29 (dd, \(J = 18.2, 10.8\) Hz, 1H), 3.55 (dd, \(J = 18.2, 3.0\) Hz, 1H), 13C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 192.87, 160.07, 138.62, 136.83, 132.67, 131.25, 130.33, 128.57, 124.23 (q, \(J = 282.9\) Hz), 117.65, 117.12, 52.76 (q, \(J = 31.6\) Hz), 35.68; \(^19\)F NMR (376 MHz, CDCl\(_3\)) \(\delta\) -73.19 (s); Enantiomeric excess: 96%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 80/20; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: \(t_R\) = 23.54 min, second peak: \(t_R\) = 26.24 min; HRMS (ESI) m/z calcd. for C\(_{15}\)H\(_{10}\)F\(_3\)N\(_3\)NaO\(_2\) [M+Na] \(^+\) = 344.0617, found 344.0622.
(S)-2-(1,1,1-trifluoro-4-(4-(methylsulfonyl)phenyl)-4-oxobutan-2-yl) pyridazin-3(2H)-one

(+)-3ka; isolated yield: 29.2 mg (78%); white solid; [α]D20 = +176.2 (c = 1.0, CHCl3);

1H NMR (400 MHz, CDCl3) δ 8.14 (d, J = 8.5 Hz, 2H), 8.07 (d, J = 8.5 Hz, 2H), 7.73 (dd, J = 3.6, 1.6 Hz, 1H), 7.17 (dd, J = 9.6, 3.7 Hz, 1H), 7.01 (dd, J = 9.6, 1.6 Hz, 1H), 6.46-6.37 (m, 1H), 4.31 (dd, J = 18.2, 10.8 Hz, 1H), 3.56 (dd, J = 18.2, 3.0 Hz, 1H), 3.08 (s, 1H); 13C NMR (101 MHz, CDCl3) δ 192.95, 160.08, 144.94, 139.61, 136.81, 131.21, 130.37, 129.02, 127.99, 124.23 (q, J = 282.8 Hz), 52.81 (q, J = 31.7 Hz), 44.26, 35.83; 19F NMR (376 MHz, CDCl3) δ -73.17 (s); Enantiomeric excess: 93%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 90/10; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: τR = 39.94 min, second peak: τR = 50.88 min; HRMS (ESI) m/z calcd. for C15H13F3N2NaO4S [M+Na]+ = 397.0440, found 397.0445.
(S)-2-(1,1,1-trifluoro-4-oxo-4-(4-(trifluoromethyl)phenyl)butan-2-yl)
pyridazin-3(2H)-one

(+)-3la; isolated yield: 35.3 mg (97%); colorless sticky oil; \([\alpha]_D^{20} = +180.2\) (c = 1.0, CHCl₃); ¹H NMR (500 MHz, CDCl₃) \(\delta 8.08\) (d, \(J = 8.1\) Hz, 2H), 7.76-7.73 (m, 3H), 7.20-7.16 (m, 1H), 7.01 (dd, \(J = 9.6, 1.7\) Hz, 1H), 6.46-6.39 (m, 1H), 4.32 (dd, \(J = 18.2, 10.9\) Hz, 1H), 3.55 (dd, \(J = 18.2, 3.0\) Hz, 1H); ¹³C NMR (126 MHz, CDCl₃) \(\delta 193.10, 160.09, 138.31, 136.76, 135.04\) (q, \(J = 32.8\) Hz), 131.18, 130.28, 128.47, 125.85 (q, \(J = 3.7\) Hz), 124.25 (q, \(J = 282.8\) Hz), 123.38 (q, \(J = 272.8\) Hz), 52.72 (q, \(J = 31.6\) Hz), 35.58; ¹⁹F NMR (376 MHz, CDCl₃) \(\delta -63.27\) (s), -73.21 (s); Enantiomeric excess: 96%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 80/20; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: \(t_R = 9.23\) min, second peak: \(t_R = 13.33\) min; HRMS (ESI) m/z calcd. for \(C_{15}H_{10}F_3N_2NaO_2 [M+Na]^+ = 387.0539\), found 387.0544.
(S)-2-(1,1,1-trifluoro-4-(2-nitrophenyl)-4-oxobutan-2-yl)pyridazin-3(2H)-one

(+)-3ma; isolated yield: 31.4 mg (92%); white solid; [α]D20 = +140.9 (c = 1.0, CHCl3);

1H NMR (500 MHz, CDCl3) δ 8.12 (dd, J = 8.2, 0.6 Hz, 1H), 7.84 (dd, J = 3.7, 1.6 Hz, 1H), 7.76-7.73 (m, 1H), 7.66-7.63 (m, 1H), 7.40 (dd, J = 7.6, 1.2 Hz, 1H), 7.22 (dd, J = 9.5, 3.7 Hz, 1H), 7.00 (dd, J = 9.5, 1.6 Hz, 1H), 6.47-6.40 (m, 1H), 4.03 (dd, J = 18.3, 10.8 Hz, 1H), 3.47 (dd, J = 18.3, 2.8 Hz, 1H); 13C NMR (126 MHz, CDCl3) δ 196.41, 160.14, 145.58, 136.96, 136.34, 134.41, 131.40, 131.17, 130.25, 124.07 (q, J = 282.9 Hz), 127.26, 124.65, 52.50 (q, J = 31.9 Hz), 39.44; 19F NMR (376 MHz, CDCl3) δ -73.14 (s); Enantiomeric excess: 90%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 90/10; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: tR = 12.75 min, second peak: tR = 15.98 min; HRMS (ESI) m/z calcd. for C14H10F3N3NaO4 [M+Na]⁺ = 364.0516, found 364.0520.
(S)-2-(1,1,1-trifluoro-4-(3-nitrophenyl)-4-oxobutan-2-yl)pyridazin-3(2H)-one

(+)-3na; isolated yield: 31.0 mg (91%); colorless sticky oil; [α]D20 = +273.3 (c = 1.0, CHCl3); 1H NMR (400 MHz, CDCl3) δ 8.78 (t, J = 1.7 Hz, 1H), 8.47-8.45 (m, 1H), 8.30 (d, J = 7.8 Hz, 1H), 7.76-7.71 (m, 2H), 7.19 (dd, J = 9.6, 3.7 Hz, 1H), 7.01 (dd, J = 9.6, 1.6 Hz, 1H), 6.48-6.39 (m, 1H), 4.35 (dd, J = 18.2, 10.8 Hz, 1H), 3.60 (dd, J = 18.2, 3.0 Hz, 1H); 13C NMR (101 MHz, CDCl3) δ 192.06, 160.03, 148.49, 136.94, 136.83, 133.57, 131.22, 130.28, 130.16, 127.99, 124.18 (q, J = 282.9 Hz), 122.96, 52.72 (q, J = 136.94 Hz), 35.63; 19F NMR (376 MHz, CDCl3) δ -73.17 (s); Enantiomeric excess: 93%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 80/20; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: tR = 15.22 min, second peak: tR = 23.71 min; HRMS (ESI) m/z calcd. for C14H10F3N3O4 [M+Na]+ = 364.0516, found 364.0522.
(S)-2-(4-(3,5-difluorophenyl)-1,1,1-trifluoro-4-oxobutan-2-yl)pyridazin-3(2H)-one

(+)-3oa; isolated yield: 32.9 mg (99%); colorless sticky oil; $[\alpha]_D^{20} = +188.3$ (c = 1.0, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.74 (dd, $J = 3.6$, 1.6 Hz, 1H), 7.49-7.44 (m, 2H), 7.17 (dd, $J = 9.6$, 3.7 Hz, 1H), 7.06 (tt, $J = 8.3$, 2.3 Hz, 1H), 7.01 (dd, $J = 9.6$, 1.6 Hz, 1H), 6.43-6.36 (m, 1H), 4.23 (dd, $J = 18.2$, 10.9 Hz, 1H), 3.48 (dd, $J = 9.6$, 1.6 Hz, 1H); $^{19}$F NMR (376 MHz, CDCl$_3$) δ -73.24, -107.29; $^{13}$C NMR (126 MHz, CDCl$_3$) δ 191.69, 164.12 (d, $J = 11.7$ Hz), 162.11 (d, $J = 11.7$ Hz), 160.10, 136.82, 131.22, 130.35, 138.51 (t, $J = 7.6$ Hz), 124.22 (q, $J = 282.8$ Hz), 52.71 (q, $J = 31.5$ Hz), 35.56; Enantiomeric excess: 96%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 80/20; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: $t_R = 7.987$ min, second peak: $t_R = 12.556$ min; HRMS (ESI) m/z calcd. for C$_{14}$H$_{10}$F$_3$N$_2$O$_2$ [M+H]$^+$ = 333.0657, found = 333.0652.
(S)-2-(4-(3,4-dichlorophenyl)-1,1,1-trifluoro-4-oxobutan-2-yl)pyridazin-3(2H)-one

(+)-3pa; isolated yield: 35.0 mg (96%); colorless sticky oil; [α]D20 = +480.8 (c = 1.0, CHCl3); 1H NMR (400 MHz, CDCl3) δ 8.02 (d, J = 1.9 Hz, 1H), 7.79 (dd, J = 8.4 Hz, 1H), 7.73 (dd, J = 3.6, 1.5 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.16 (dd, J = 9.5, 3.7 Hz, 1H), 7.00 (dd, J = 9.5, 1.5 Hz, 1H), 6.44-6.35 (m, 1H), 4.23 (dd, J = 18.1, 10.9 Hz, 1H), 3.48 (dd, J = 18.1, 3.0 Hz, 1H); 13C NMR (101 MHz, CDCl3) δ 191.86, 160.03, 138.52, 136.73, 135.26, 133.57, 131.14, 130.92, 130.28, 130.08, 127.07, 124.23 (q, J = 282.9 Hz), 52.78 (q, J = 31.6 Hz), 35.35; 19F NMR (376 MHz, CDCl3) δ -73.17 (s); Enantiomeric excess: 94%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 80/20; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: tR = 9.46 min, second peak: tR = 12.75 min; HRMS (ESI) m/z calcd. for C14H9Cl2F3N2NaO2 [M+Na]+ = 386.9885, found = 386.9889.
(S)-2-(1,1,1-trifluoro-4-(naphthalen-1-yl)-4-oxobutan-2-yl)pyridazin-3(2H)-one

(+)-3qa; isolated yield: 33.9 mg (98%); colorless sticky oil; [α]D20 = +148.4 (c = 1.0, CHCl3); 1H NMR (400 MHz, CDCl3) δ 8.57-8.55 (m, 1H), 8.01 (t, J = 7.3 Hz, 2H), 7.85 (dd, J = 7.0, 2.3 Hz, 1H), 7.73 (dd, J = 3.6, 1.6 Hz, 1H), 7.56-7.49 (m, 3H), 7.13 (dd, J = 9.5, 3.7 Hz, 1H), 6.99 (dd, J = 9.5, 1.6 Hz, 1H), 6.54-6.45 (m, 1H), 4.39 (dd, J = 17.9, 11.0 Hz, 1H), 3.59 (dd, J = 17.9, 3.2 Hz, 1H); 13C NMR (101 MHz, CDCl3) δ 197.33, 160.22, 136.70, 133.97, 133.76, 131.11, 130.32, 130.12, 128.49, 128.48, 128.36, 126.69, 125.64, 124.48 (q, J = 282.9 Hz), 124.29, 53.35 (q, J = 31.5 Hz), 38.21, 29.69; 19F NMR (376 MHz, CDCl3) δ -73.03 (s); Enantiomeric excess: 91%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 90/10; flow rate 1.0 ml/min; 25 ºC; 254 nm), first peak: tR = 9.86 min, second peak: tR = 11.99 min; HRMS (ESI) m/z calcd. for C18H13F3N2NaO2 [M+Na]+ = 369.0821, found 369.0819.
(S)-2-(1,1,1-trifluoro-4-(naphthalen-2-yl)-4-oxobutan-2-yl)pyridazin-3(2H)-one

(+)-3ra; isolated yield: 33.9 mg (98%); colorless sticky oil; $[\alpha]_{D}^{20} = +450.6$ ($c = 0.33$, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.48 (s, 1H), 7.97 (d, $J = 8.5$ Hz, 2H), 7.87 (dd, $J = 8.3$, 4.2 Hz, 2H), 7.71 (dd, $J = 3.6$, 1.6 Hz, 1H), 7.63-7.55 (m, 2H), 7.12 (dd, $J = 9.5$, 3.7 Hz, 1H), 6.99 (dd, $J = 9.5$, 1.6 Hz, 1H), 6.53-6.44 (m, 1H), 4.43 (dd, $J = 18.0$, 10.9 Hz, 1H), 3.64 (dd, $J = 18.0$, 2.9 Hz, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 193.81, 160.20, 136.67, 135.87, 133.18, 132.41, 131.12, 130.28, 130.07, 129.63, 128.91, 128.71, 127.83, 127.06, 124.53 (q, $J = 282.8$ Hz), 123.51, 53.08 (q, $J = 31.3$ Hz), 35.39. $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -73.03 (s); Enantiomeric excess: 94%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 80/20; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: $t_R = 11.61$ min, second peak: $t_R = 15.35$ min; HRMS (ESI) m/z calcd. for C$_{18}$H$_{13}$F$_3$N$_2$NaO$_2$ [M+Na]$^+$ = 369.0821, found 369.0822.
(S)-2-(4-(benzo[b]thiophen-2-yl)-1,1,1-trifluoro-4-oxobutan-2-yl)pyridazin-3(2H)-one

(+)-3sa; isolated yield: 34.5 mg (98%); colorless sticky oil; $\alpha_d^{20} = +395.1$ (c = 1.0, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.05 (s, 1H), 7.91 (d, $J$ = 7.9 Hz, 1H), 7.85 (d, $J$ = 8.0 Hz, 1H), 7.73 (dd, $J$ = 3.5, 1.5 Hz, 1H), 7.49-7.40 (m, 2H), 7.13 (dd, $J$ = 9.6, 3.7 Hz, 1H), 6.97 (dd, $J$ = 9.5, 1.5 Hz, 1H), 6.47-6.39 (m, 1H), 4.31 (dd, $J$ = 17.7, 10.9 Hz, 1H), 3.58 (dd, $J$ = 17.7, 3.1 Hz, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 188.22, 160.02, 142.59, 142.07, 138.81, 136.75, 131.15, 130.24, 129.85, 127.84, 126.08, 125.21, 124.23 (q, $J$ = 282.9 Hz), 122.92, 52.76 (q, $J$ = 31.6 Hz), 35.70; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -73.11 (s); Enantiomeric excess: 94%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 80/20; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: $t_R$ = 13.97 min, second peak: $t_R$ = 19.45 min; HRMS (ESI) m/z calcd. for C$_{16}$H$_{11}$F$_3$N$_2$NaO$_2$S [M+Na]$^+$ = 375.0386, found 375.0383.
(S)-2-(1,1,1-trifluoro-4-oxo-4-(thiophen-2-yl)butan-2-yl)pyridazin-3(2H)-one

(+)-3ta; isolated yield: 29.9 mg (99%); colorless sticky oil; [α]D20 = +205.9 (c = 1.0, CHCl3); 1H NMR (400 MHz, CDCl3) δ 7.80 (dd, J = 3.8, 0.9 Hz, 1H), 7.74 (dd, J = 3.6, 1.6 Hz, 1H), 7.68 (dd, J = 4.9, 0.9 Hz, 1H), 7.17-7.13 (m, 2H), 6.97 (dd, J = 9.5, 1.6 Hz, 1H), 6.44-6.35 (m, 1H), 4.18 (dd, J = 17.6, 10.9 Hz, 1H), 3.49 (dd, J = 17.6, 3.1 Hz, 1H); 13C NMR (126 MHz, CDCl3) δ 186.63, 160.02, 142.72, 136.70, 134.55, 132.54, 131.13, 130.21, 128.26, 124.23 (q, J = 282.9 Hz), 52.73 (q, J = 31.5 Hz), 35.76; 19F NMR (376 MHz, CDCl3) δ -73.15 (s); Enantiomeric excess: 96%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 80/20; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: tR = 11.51 min, second peak: tR = 16.85 min; HRMS (ESI) m/z calcd. for C12H9F3N2NaO2S [M+Na]+ = 325.0229, found 325.0229.
(S)-2-(4-(cyclohex-1-en-1-yl)-1,1,1-trifluoro-4-oxobutan-2-yl)pyridazin-3(2H)-one

(+)-3ua; isolated yield: 16.5 mg (55%); colorless sticky oil; $[\alpha]_D^{20}= +249.6$ (c = 0.33, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.75 (dd, $J = 3.7$, 1.6 Hz, 1H), 7.16-7.13 (m, 1H), 7.00-6.96 (m, 2H), 6.30-6.23 (m, 1H), 3.91 (dd, $J = 17.7$, 11.0 Hz, 1H), 3.21 (dd, $J = 17.7$, 2.9 Hz, 1H), 2.27 (dd, $J = 3.6$, 2.2 Hz, 2H), 2.20-2.12 (m, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 194.64, 160.16, 141.39, 138.78, 136.51, 131.06, 131.01, 130.26, 124.49 (q, $J = 282.7$ Hz), 52.99 (q, $J = 31.1$ Hz), 33.90, 26.12, 22.92, 21.55 (d, $J = 40.9$ Hz); $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -73.19 (s); Enantiomeric excess: 92%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 80/20; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: $t_R = 8.09$ min, second peak: $t_R = 10.87$ min; HRMS (ESI) m/z calcd. for C$_{14}$H$_{15}$F$_3$N$_2$NaO$_2$ [M+Na]$^+$ = 323.09787, found 323.0982.
(S)-2-(1,1,1,2,2-pentafluoro-5-oxo-5-phenylpentan-3-yl)pyridazin-3(2H)-
One

(+)-3va; isolated yield: 22.0 mg (64%); colorless sticky oil; [α]D
20
= +94.1 (c = 1.0, CHCl3); 1H NMR (400 MHz, CDCl3) δ 7.96-7.94 (m, 2H), 7.72 (dd, J = 3.6, 1.6 Hz, 1H), 7.60 (t, J = 7.4 Hz, 1H), 7.47 (t, J = 7.7 Hz, 2H), 7.12 (dd, J = 9.6, 3.7 Hz, 1H), 6.97 (dd, J = 9.6, 1.7 Hz, 1H), 6.61-6.65 (m, 1H), 4.32 (dd, J = 18.1, 10.8 Hz, 1H), 3.55 (dd, J = 18.1, 2.3 Hz, 1H); 13C NMR (126 MHz, CDCl3) δ 193.90, 160.09, 136.80, 135.82, 133.85, 131.04, 130.13, 128.81, 128.14, 119.84 (t, J = 35.5 Hz), 117.56 (t, J = 35.4 Hz), 51.09 (t, J = 23.3 Hz), 35.21; 19F NMR (376 MHz, CDCl3) δ -82.53 (s), -120.25 (dd, J = 1710.6, 275.5 Hz); Enantiomeric excess: 83%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 80/20; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: tR = 8.32 min, second peak: tR = 8.97 min; HRMS (ESI) m/z calcd. for C15H11F3N2NaO2 [M+Na]+ = 369.0633, found 369.0628.
(S)-2-(4-(4-chlorophenyl)-1,1,1-trifluoro-4-oxobutan-2-yl)-6-methylpyridin-3(2H)-one

Dazin-3(2H)-one

(+)-3fb; isolated yield: 33.1 mg (96%); colorless sticky oil; [α]D^20 = +254.6 (c = 1.0, CHCl3); ^1H NMR (400 MHz, CDCl3) δ 7.91 (d, J = 8.6 Hz, 1H), 7.45 (d, J = 8.6 Hz, 1H), 7.03 (d, J = 9.6 Hz, 1H), 6.91 (d, J = 9.6 Hz, 1H), 6.40-6.31 (m, 1H), 4.24 (dd, J = 17.9, 10.8 Hz, 1H), 3.45 (dd, J = 17.9, 3.0 Hz, 1H), 2.24 (s, 1H); ^13C NMR (126 MHz, CDCl3) δ 192.95, 159.44, 144.97, 140.27, 134.23, 133.30, 129.97, 129.50, 129.08, 124.38 (q, J = 283.0 Hz), 52.63 (q, J = 31.4 Hz), 35.17, 20.89. ^19F NMR (376 MHz, CDCl3) δ -73.10 (s); Enantiomeric excess: 96%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 80/20; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: t_R = 9.63 min, second peak: t_R = 12.43 min; HRMS (ESI) m/z calcd. for C_{15}H_{12}ClF_{3}N_{2}NaO_{2} [M+Na]^+ = 367.0432, found 367.0435.
(S)-2-(4-(4-chlorophenyl)-1,1,1-trifluoro-4-oxobutan-2-yl)-6-phenylpyridazin-3(2H)-one

(+)-3fc; isolated yield: 39.1 mg (96%); colorless sticky oil; $[\alpha]_D^{20} = +50.3 \ (c = 1.0, \ CHCl_3)$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.89 (d, $J = 8.6$ Hz, 2H), 7.66-7.63 (m, 3H), 7.42-7.40 (m, 5H), 7.08 (d, $J = 9.8$ Hz, 1H), 6.52-6.44 (m, 1H), 4.31 (dd, $J = 17.9, 10.8$ Hz, 1H), 3.55 (dd, $J = 17.9, 3.0$ Hz, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 192.89, 159.44, 145.04, 140.39, 134.30, 134.16, 130.45, 129.83, 129.56, 129.14, 128.99, 125.95, 124.44 (q, $J = 283.0$ Hz), 53.13 (q, $J = 31.4$ Hz), 35.51; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -72.96 (s); Enantiomeric excess: 95%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 80/20; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: $t_R = 10.19$ min, second peak: $t_R = 12.50$ min; HRMS (ESI) m/z calcd. for C$_{20}$H$_{14}$ClF$_3$N$_2$NaO$_2$ [M+Na]$^+$ = 429.0588, found = 429.0592.
(S)-6-chloro-2-(4-(4-chlorophenyl)-1,1,1-trifluoro-4-oxobutan-2-yl)pyridazin-3(2H)-one

(+)-3fd; isolated yield: 33.9 mg (93%); colorless sticky oil; \([\alpha]_D^{20} = +178.8\) (c = 1.0, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.92-7.89 (m, 2H), 7.48-7.45 (m, 2H), 7.16-7.14 (m, 1H), 6.99 (d, J = 9.8 Hz, 1H), 6.33-6.26 (m, 1H), 4.18 (dd, J = 18.2, 10.9 Hz, 1H), 3.49 (dd, J = 18.2, 2.8 Hz, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 192.70, 158.48, 140.53, 138.33, 133.95, 133.90, 132.15, 129.54, 129.16, 124.00 (q, J = 282.9 Hz), 53.09 (q, J = 31.8 Hz), 35.11; ¹⁹F NMR (376 MHz, CDCl₃) δ -73.22 (s); Enantiomeric excess: 92%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 80/20; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: t_R = 9.12 min, second peak: t_R = 11.43 min; HRMS (ESI) m/z calcd. for C₁₄H₉Cl₂F₃N₂NaO₂ [M+Na]⁺ = 386.9885, found 386.9890.
Methyl (S)-1-(4-(4-chlorophenyl)-1,1,1-trifluoro-4-oxobutan-2-yl)-6-oxo-1,6-dihydropyridazine-3-carboxylate

(+)-3fe; isolated yield: 37.0 mg (95%); white solid; [α]_{D}^{20} = +153.3 (c = 1.0, CHCl₃);

$^{1}$H NMR (400 MHz, CDCl₃) δ 7.91 (d, J = 8.6 Hz, 2H), 7.79 (d, J = 9.8 Hz, 1H), 7.46 (d, J = 8.6 Hz, 2H), 7.03 (d, J = 9.8 Hz, 1H), 6.46-6.37 (m, 1H), 4.33 (dd, J = 18.1, 11.1 Hz, 1H), 3.88 (s, 3H), 3.52 (dd, J = 18.1, 2.8 Hz, 1H); $^{13}$C NMR (101 MHz, CDCl₃) δ 192.94, 162.10, 159.37, 140.53, 136.74, 134.09, 131.19, 129.63, 129.14, 124.06 (q, J = 282.9 Hz), 53.79 (q, J = 31.8 Hz), 35.32, 29.68; $^{19}$F NMR (376 MHz, CDCl₃) δ -73.05 (s); Enantiomeric excess: 90%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 90/10; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: t_R = 10.91 min, second peak: t_R = 14.53 min; HRMS (ESI) m/z calcd. for C₁₆H₁₂ClF₃N₂NaO₄ [M+Na]^+ = 411.0330, found 411.0330.
(S)-5-chloro-2-(4-(4-chlorophenyl)-1,1,1-trifluoro-4-oxobutan-2-yl)pyridazin-3(2H)-one

(+)-3ff; isolated yield: 35.8 mg (98%); colorless sticky oil; \([\alpha]_D^{20} = +240.5\) (c = 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.91-7.88 (m, 2H), 7.68 (d, J = 2.4 Hz, 1H), 7.47-7.45 (m, 2H), 7.04 (d, J = 2.4 Hz, 1H), 6.35-6.26 (m, 1H), 4.21 (dd, J = 18.2, 11.1 Hz, 1H), 3.51 (dd, J = 18.2, 2.9 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 192.56, 158.74, 140.53, 139.56, 136.99, 133.91, 129.48, 129.16, 127.52, 124.10 (d, J = 282.7 Hz), 52.95 (q, J = 31.7 Hz), 35.14; ¹⁹F NMR (376 MHz, CDCl₃) δ -73.20 (s); Enantiomeric excess: 99%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 80/20; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: tᵣ = 9.19 min, second peak: tᵣ = 16.77 min; HRMS (ESI) m/z calcd. for C₁₄H₉Cl₂F₃N₂NaO₂ [M+Na]⁺ = 386.9885, found 386.9888.
(S)-4,5-dibromo-2-(4-(4-chlorophenyl)-1,1,1-trifluoro-4-oxobutan-2-yl)pyridazin-3(2H)-one

(+)-3fg; isolated yield: 47.8 mg (98%); white solid; $[\alpha]_{D}^{20} = +223.7\ (c = 1.0, \text{CHCl}_3)$; 
$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.90-7.88 (m, 2H), 7.75 (s, 1H), 7.46 (d, $J = 8.5$ Hz, 2H), 6.32-6.25 (m, 1H), 4.22 (dd, $J = 18.2$, 11.1 Hz, 1H), 3.52 (dd, $J = 18.2$, 2.9 Hz, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 192.47, 156.57, 140.60, 137.92, 133.78, 130.98, 130.92, 129.49, 129.18, 123.94 (q, $J = 282.9$ Hz), 54.57 (q, $J = 31.7$ Hz), 35.19; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -73.06 (s); Enantiomeric excess: 94%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 90/10; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: $t_R = 20.53$ min, second peak: $t_R = 26.39$ min; HRMS (ESI) m/z calcd. for C$_{14}$H$_8$Br$_2$ClF$_3$N$_2$NaO$_2$ [M+Na]$^+$ = 508.8485, found 508.8486.
Methyl (S)-4-(4-chlorophenyl)-4-oxo-2-(6-oxopyridazin-1(6H)-yl)butanoate

(+)-5aa; isolated yield: 27.9 mg (87%); colorless sticky oil; [α]D20 = +16.0 (c = 1.0, CHCl3); 1H NMR (400 MHz, CDCl3) δ 7.92 (d, J = 8.6 Hz, 2H), 7.74 (dd, J = 3.7, 1.6 Hz, 1H), 7.44 (d, J = 8.5 Hz, 2H), 7.20 (dd, J = 9.5, 3.8 Hz, 1H), 6.97 (dd, J = 9.5, 1.6 Hz, 1H), 6.11 (dd, J = 7.8, 5.6 Hz, 1H), 3.91 (dd, J = 17.7, 5.6 Hz, 1H), 3.81 (d, J = 7.9 Hz, 1H), 3.76 (s, 3H); 13C NMR (101 MHz, CDCl3) δ 194.41, 169.50, 160.11, 139.97, 136.32, 134.59, 131.46, 130.10, 129.59, 129.01, 58.57, 52.96, 38.13; Enantiomeric excess: 84%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 70/30; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: tR = 17.62 min, second peak: tR = 21.70 min; HRMS (ESI) m/z calcd. for C15H13ClN2NaO4 [M+Na]+ = 343.0456, found 343.0453.
Benzyl (S)-4-oxo-2-(6-oxopyridazin-1(6H)-yl)-4-phenylbutanoate

(+)-5ba; isolated yield: 25.0 mg (69%); colorless sticky oil; \([\alpha]_D^{20} = +7.4\) (c = 1.0, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.96 (d, $J$ = 7.6 Hz, 2H), 7.71-7.70 (m, 1H), 7.58 (t, $J$ = 7.4 Hz, 1H), 7.46 (t, $J$ = 7.7 Hz, 2H), 7.34-7.26 (m, 5H), 7.17 (dd, $J$ = 9.5, 3.8 Hz, 1H), 6.97 (dd, $J$ = 9.4, 1.3 Hz, 1H), 6.20 (t, $J$ = 6.7 Hz, 1H), 5.25-5.18 (m, 2H), 3.91 (d, $J$ = 6.5 Hz, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 195.51, 169.14, 160.20, 136.23, 136.20, 135.19, 133.52, 131.43, 130.06, 128.69, 128.54, 128.32, 128.20, 128.03, 67.59, 58.62, 38.11; Enantiomeric excess: 87%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 70/30; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: $t_R = 21.07$ min, second peak: $t_R = 27.84$ min; HRMS (ESI) m/z calcd. for C$_{21}$H$_{18}$N$_2$NaO$_4$ [M+Na]$^+$ = 385.1159, found 385.1164.

Ethyl (S)-4-oxo-2-(6-oxopyridazin-1(6H)-yl)-4-phenylbutanoate

(+)-5ca; isolated yield: 27.0 mg (90%); colorless sticky oil; \([\alpha]_D^{20} = +1.9\) (c = 1.0, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.99 (d, $J$ = 7.5 Hz, 2H), 7.74 (d, $J$ = 2.3 Hz, 1H), 7.59 (t, $J$ = 7.3 Hz, 1H), 7.48 (t, $J$ = 7.6 Hz, 2H), 7.19 (dd, $J$ = 9.5, 3.8 Hz, 1H), 6.98 (d, $J$ = 9.4 Hz, 1H), 6.12 (dd, $J$ = 7.3, 6.1 Hz, 1H), 4.23 (q, $J$ = 6.8 Hz, 2H), 3.90 (t, $J$ = 6.0 Hz, 2H), 1.24 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 195.63,
isopropyl (S)-4-oxo-2-(6-oxopyridazin-1(6H)-yl)-4-phenylbutanoate

(+)-5da; isolated yield: 20.0 mg (64%); colorless sticky oil; [α]D20 = +2.3 (c = 1.0, CHCl3); 1H NMR (500 MHz, CDCl3) δ 8.00-7.98 (m, 2H), 7.74 (dd, J = 3.6, 1.6 Hz, 1H), 7.59 (dd, J = 10.6, 4.2 Hz, 1H), 7.48 (dd, J = 11.0, 4.4 Hz, 2H), 7.19 (dd, J = 9.5, 3.8 Hz, 1H), 6.97 (dd, J = 9.5, 1.7 Hz, 1H), 6.09 (dd, J = 7.7, 5.8 Hz, 1H), 5.11-5.06 (m, 1H), 3.92-3.82 (m, 2H), 1.24 (d, J = 6.3 Hz, 3H), 1.20 (d, J = 6.2 Hz, 3H); 13C NMR (126 MHz, CDCl3) δ 195.72, 168.71, 160.20, 136.26, 136.15, 133.50, 131.43, 130.01, 128.70, 128.20, 69.89, 58.83, 38.07, 21.69, 21.60; Enantiomeric excess: 83%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 70/30; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: tR = 9.25 min, second peak: tR = 10.60 min; HRMS (ESI) m/z calcd. for C17H18N2NaO4 [M+Na] + = 337.1159, found 337.1156.
tert-butyl (S)-4-oxo-2-(6-oxopyridazin-1(6H)-yl)-4-phenylbutanoate

(+)-5ea; isolated yield: 17.1 mg (52%); colorless sticky oil; [$\alpha$]$_D$ = +2.5 ($c = 1.0$, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.99 (d, $J = 7.8$ Hz, 2H), 7.73 (d, $J = 3.6$ Hz, 1H), 7.58 (t, $J = 7.3$ Hz, 1H), 7.47 (t, $J = 7.6$ Hz, 2H), 7.18 (dd, $J = 9.5$, 3.8 Hz, 1H), 6.96 (d, $J = 9.4$ Hz, 1H), 6.03 (t, $J = 6.8$ Hz, 1H), 3.85 (d, $J = 6.8$ Hz, 2H), 1.44 (s, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 195.81, 168.26, 160.23, 136.32, 135.99, 133.45, 131.30, 130.00, 128.68, 128.21, 82.80, 59.33, 38.06, 27.89; Enantiomeric excess: 88%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 70/30; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: $t_R = 7.16$ min, second peak: $t_R = 9.37$ min; HRMS (ESI) m/z calcd. for C$_{18}$H$_{20}$N$_2$NaO$_4$ [M+Na]$^+$ = 351.1315, found 351.1320.

Ethyl (S)-4-oxo-2-(6-oxopyridazin-1(6H)-yl)-4-(p-tolyl)butanoate
(+)-5fa; isolated yield: 15.4 mg (49%); colorless sticky oil; [α]D20 = +12.5 (c = 1.0, CHCl3); 1H NMR (400 MHz, CDCl3) δ 7.88 (d, J = 8.2 Hz, 2H), 7.72 (dd, J = 3.7, 1.5 Hz, 1H), 7.26 (d, J = 7.9 Hz, 2H), 7.18 (dd, J = 9.5, 3.8 Hz, 1H), 6.96 (dd, J = 9.5, 1.5 Hz, 1H), 6.11 (dd, J = 7.5, 6.0 Hz, 1H), 4.23 (qd, J = 7.1, 1.3 Hz, 2H), 3.86 (dd, J = 6.7, 3.7 Hz, 2H), 2.41 (s, 3H), 1.23 (t, J = 7.1 Hz, 3H); 13C NMR (101 MHz, CDCl3) δ 195.17, 169.24, 160.17, 144.31, 136.09, 133.85, 131.32, 130.02, 129.34, 128.30, 61.99, 58.74, 38.00, 21.67, 14.03; Enantiomeric excess: 82%, determined by HPLC (Chiralpak AD-H, hexane/i-ProOH = 70/30; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: tR = 12.81 min, second peak: tR = 16.17 min; HRMS (ESI) m/z calcd. for C17H18N2NaO4[M+Na]+ = 337.1159, found 337.1158.

Ethyl (S)-4-(4-methoxyphenyl)-4-oxo-2-(6-oxopyridazin-1(6H)-yl)butanoate

(+)-5ga; isolated yield: 10 mg (30%); white solid; [α]D20 = +20.2 (c = 0.33, CHCl3); 1H NMR (500 MHz, CDCl3) δ 7.97 (d, J = 8.6 Hz, 2H), 7.74 (d, J = 3.6 Hz, 1H), 7.18 (dd, J = 9.4, 3.7 Hz, 1H), 6.95 (dd, J = 12.2, 9.2 Hz, 3H), 6.11 (t, J = 6.7 Hz, 1H), 4.25-4.21 (m, 2H), 3.87 (s, 3H), 3.85-3.83 (m, 2H), 1.24 (t, J = 7.1 Hz, 3H); 13C NMR
(126 MHz, CDCl$_3$) $\delta$ 194.07, 169.36, 163.76, 160.21, 136.16, 131.38, 130.51, 130.04, 129.33, 113.81, 62.03, 58.80, 55.54, 37.74, 14.07; Enantiomeric excess: 77%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 70/30; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: $t_R = 17.79$ min, second peak: $t_R = 24.43$ min; HRMS (ESI) m/z calcd. for C$_{17}$H$_{18}$N$_2$NaO$_5$ [M+Na]$^+ = 353.1108$, found 353.1113.

Ethyl (S)-4-([(1,1'-biphenyl]-4-yl)-4-oxo-2-(6-oxopyridazin-1(6H)-yl)-Butanoate

(+)-5ha; isolated yield: 24.8 mg (66%); colorless sticky oil; $[\alpha]_D^{20} = +44.2$ (c = 1.0, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.06 (d, $J = 8.4$ Hz, 2H), 7.74 (dd, $J = 3.7$, 1.5 Hz, 1H), 7.69 (d, $J = 8.4$ Hz, 2H), 7.62 (d, $J = 7.3$ Hz, 2H), 7.47 (t, $J = 7.4$ Hz, 2H), 7.40 (t, $J = 7.3$ Hz, 1H), 7.18 (dd, $J = 9.5$, 3.8 Hz, 1H), 6.97 (dd, $J = 9.5$, 1.5 Hz, 1H), 6.14 (dd, $J = 7.7$, 5.8 Hz, 1H), 4.27-4.21 (m, 2H), 3.98-3.86 (m, 2H), 1.25 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 195.18, 169.21, 160.19, 146.14, 139.77, 136.16, 135.01, 131.37, 130.06, 128.99, 128.80, 128.33, 127.30, 127.29, 62.05, 58.78, 38.15, 14.06; Enantiomeric excess: 81%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 70/30; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: $t_R = 18.93$ min, second peak: $t_R = 34.60$ min; HRMS (ESI) m/z calcd. for C$_{22}$H$_{20}$N$_2$NaO$_4$ [M+Na]$^+ = 399.1315$, found 399.1314.
Ethyl (S)-4-(4-fluorophenyl)-4-oxo-2-(6-oxopyridazin-1(6H)-yl)butanoate

(+)-5ia; isolated yield: 22.3 mg (70%); colorless sticky oil; \([\alpha]_D^{20} = +1.7\) (c = 1.0, CHCl_3); \(^1\)H NMR (500 MHz, CDCl_3) \(\delta\) 8.03-8.00 (m, 2H), 7.74 (dd, \(J = 3.7, 1.6\) Hz, 1H), 7.20 (dd, \(J = 9.5, 3.8\) Hz, 1H), 7.14 (t, \(J = 8.6\) Hz, 2H), 6.97 (dd, \(J = 9.5, 1.6\) Hz, 1H), 6.10 (dd, \(J = 7.9, 5.6\) Hz, 1H), 4.26-4.20 (m, 2H), 3.90 (dd, \(J = 17.6, 7.9\) Hz, 1H), 3.80 (dd, \(J = 17.6, 7.9\) Hz, 1H), 1.23 (t, \(J = 7.1\) Hz, 3H); \(^1^9\)F NMR (376 MHz, CDCl_3) \(\delta\) -104.43; \(^{13}\)C NMR (126 MHz, CDCl_3) \(\delta\) 194.09, 169.06, 165.95 (d, \(J = 255.3\) Hz), 160.14, 136.22, 132.75 (d, \(J = 2.9\) Hz), 131.43, 130.86 (d, \(J = 9.4\) Hz), 130.06, 62.08, 115.81 (d, \(J = 21.9\) Hz), 58.75, 38.03, 14.02; Enantiomeric excess: 82%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 70/30; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: \(t_R = 12.11\) min, second peak: \(t_R = 14.38\) min; HRMS (ESI) m/z calcd. for \(\text{C}_{16}\text{H}_{15}\text{FN}_{2}\text{NaO}_{4}\) [M+Na] \(^+\) = 341.0908, found 341.0905.

Ethyl (S)-4-(4-chlorophenyl)-4-oxo-2-(6-oxopyridazin-1(6H)-yl)butanoate

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(+)-5ja; isolated yield: 27.1 mg (81%); colorless sticky oil; $[\alpha]_D^{20} = +19.6$ (c = 1.0, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.93 (d, $J = 8.6$ Hz, 2H), 7.75 (dd, $J = 3.7, 1.5$ Hz, 1H), 7.45 (d, $J = 8.6$ Hz, 2H), 7.21 (dd, $J = 9.5, 3.8$ Hz, 1H), 6.98 (dd, $J = 9.5, 1.5$ Hz, 1H), 6.10 (dd, $J = 7.9, 5.6$ Hz, 1H), 4.26-4.20 (m, 2H), 3.90 (dd, $J = 17.7, 5.5$ Hz, 1H), 3.81 (dd, $J = 17.7, 8.0$ Hz, 1H), 1.24 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 194.53, 169.07, 160.17, 139.98, 136.53, 134.53, 131.52, 130.10, 129.64, 129.03, 62.17, 58.67, 38.07, 14.07; Enantiomeric excess: 83%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 70/30; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: $t_R = 14.48$ min, second peak: $t_R = 17.87$ min; HRMS (ESI) m/z calcd. for C$_{16}$H$_{15}$ClN$_2$O$_4$[M+Na]$^+$ = 357.0613, found 357.0608.

Ethyl (S)-4-(4-bromophenyl)-4-oxo-2-(6-oxopyridazin-1(6H)-yl)butanoate

(+)-5ka; isolated yield: 33.0 mg (87%); colorless sticky oil; $[\alpha]_D^{20} = +20.3$ (c = 1.0, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.85 (d, $J = 8.5$ Hz, 2H), 7.73 (dd, $J = 3.7, 1.6$ Hz, 1H), 7.61 (d, $J = 8.5$ Hz, 2H), 7.19 (dd, $J = 9.5, 3.8$ Hz, 1H), 6.96 (dd, $J = 9.5, 1.6$ Hz, 1H), 6.09 (dd, $J = 7.9, 5.6$ Hz, 1H), 4.26-4.19 (m, 2H), 3.89 (dd, $J = 17.7, 5.6$ Hz,
1H), 3.78 (dd, J = 17.7, 7.9 Hz, 1H), 1.23 (t, J = 7.1 Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 194.71, 168.99, 160.12, 136.25, 135.02, 132.00, 131.46, 130.06, 129.70, 128.69, 62.10, 58.70, 38.05, 14.04; Enantiomeric excess: 79%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 70/30; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: t$_R$ = 14.46 min, second peak: t$_R$ = 17.99 min; HRMS (ESI) m/z calcd. for C$_{16}$H$_{15}$BrN$_2$NaO$_4$ [M+Na]$^+$ = 401.0107, found 401.0101.

Ethyl (S)-4-oxo-2-(6-oxopyridazin-1(6H)-yl)-4-(4-(trifluoromethyl)phenyl)-butanoate

(+)-5la; isolated yield: 25.0 mg (68%); colorless sticky oil; [α]$_D^{20}$ = +1.8 (c = 1.0, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 8.10 (d, J = 8.2 Hz, 2H), 7.75 (d, J = 7.3 Hz, 3H), 7.21 (dd, J = 9.5, 3.8 Hz, 1H), 6.99 (dd, J = 9.5, 1.4 Hz, 1H), 6.11 (dd, J = 7.8, 5.7 Hz, 1H), 4.27-4.21 (m, 2H), 3.96 (dd, J = 17.7, 5.6 Hz, 1H), 3.83 (dd, J = 17.7, 7.9 Hz, 1H), 1.24 (t, J = 7.1 Hz, 3H); $^{19}$F NMR (282 MHz, CDCl$_3$) δ -63.14; $^{13}$C NMR (126 MHz, CDCl$_3$) δ 194.88, 168.94, 160.16, 138.88, 136.36, 134.59 (t, J = 32.7 Hz), 131.54, 130.14, 128.57, 125.80 (q, J = 3.7 Hz), 123.53 (q, J = 272.7 Hz), 62.23, 58.67, 38.38, 14.05; Enantiomeric excess: 82%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 70/30; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: t$_R$ = 11.00 min, second peak: t$_R$ = 14.45 min; HRMS (ESI) m/z calcd. for C$_{17}$H$_{15}$F$_3$N$_2$NaO$_4$ [M+Na]$^+$ = 391.0876, found 391.0875.
Ethyl (S)-4-(4-cyanophenyl)-4-oxo-2-(6-oxopyridazin-1(6H)-yl)butanoate

(+)-5ma; isolated yield: 28.6 mg (88%); colorless sticky oil; [α]_D^{20} = +15.1 (c = 1.0, CHCl₃); ^1H NMR (500 MHz, CDCl₃) δ 8.09 (d, J = 8.4 Hz, 2H), 7.80 (d, J = 8.4 Hz, 2H), 7.75 (dd, J = 3.8, 1.6 Hz, 1H), 7.23 (dd, J = 9.5, 3.8 Hz, 1H), 6.99 (dd, J = 9.5, 1.6 Hz, 1H), 6.09 (dd, J = 7.6, 5.8 Hz, 1H), 4.27-4.20 (m, 2H), 3.97 (dd, J = 17.7, 5.8 Hz, 1H), 3.79 (dd, J = 17.7, 7.7 Hz, 1H), 1.24 (t, J = 7.1 Hz, 3H); ^13C NMR (126 MHz, CDCl₃) δ 194.62, 168.81, 160.11, 139.18, 136.43, 132.62, 131.61, 130.15, 128.65, 117.89, 116.69, 62.27, 58.67, 38.39, 14.04; Enantiomeric excess: 83%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 70/30; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: t_R = 16.64 min, second peak: t_R = 19.78 min; HRMS (ESI) m/z calcd. for C₁₇H₁₅N₃NaO₄ [M+Na]^+ = 348.0955, found 348.0960.

Ethyl (S)-4-(3,4-dichlorophenyl)-4-oxo-2-(6-oxopyridazin-1(6H)-yl)-
Butanoate
(+)-5na; isolated yield: 35.0 mg (95%); colorless sticky oil; [α]$_D^{20} = +13.4$ (c = 1.0, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 8.05 (s, 1H), 7.81 (dd, J = 8.4, 1.0 Hz, 1H), 7.75 (dd, J = 2.2, 1.5 Hz, 1H), 7.57-7.55 (m, 1H), 7.21 (dd, J = 9.5, 3.8 Hz, 1H), 6.97 (d, J = 9.5 Hz, 1H), 6.07 (t, J = 6.7 Hz, 1H), 4.26-4.20 (m, 2H), 3.89 (dd, J = 17.7, 5.6 Hz, 1H), 3.75 (dd, J = 17.7, 7.8 Hz, 1H), 1.25-1.22 (m, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 193.63, 168.88, 160.13, 138.09, 136.38, 135.74, 133.39, 131.57, 130.86, 130.20, 130.11, 127.24, 62.22, 58.65, 38.11, 14.05; Enantiomeric excess: 80%, determined by HPLC (Chiralpak OD-H to OD-H, hexane/i-PrOH = 60/40; flow rate 0.5 ml/min; 25 °C; 254 nm), first peak: t$_R$ = 69.93 min, second peak: t$_R$ = 74.21 min; HRMS (ESI) m/z calcld. for C$_{16}$H$_{14}$Cl$_2$N$_2$NaO$_4$ [M+Na]$^+$ = 391.0223, found 391.0220.

Ethyl (S)-4-(benzo[b]thiophen-2-yl)-4-oxo-2-(6-oxopyridazin-1(6H)-yl)butanoate

(+)-5oa; isolated yield: 29.9 mg (84%); colorless sticky oil; [α]$_D^{20} = +33.1$ (c = 1.0, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 8.05 (s, 1H), 7.88 (dd, J = 13.8, 7.9 Hz, 2H), 7.74 (dd, J = 3.7, 1.6 Hz, 1H), 7.49-7.39 (m, 2H), 7.19 (dd, J = 9.5, 3.8 Hz, 1H), 6.96
(dd, $J = 9.5, 1.5$ Hz, 1H), 6.10 (dd, $J = 8.0, 5.7$ Hz, 1H), 4.28-4.20 (m, 2H), 4.00-3.86 (m, 2H), 1.24 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 190.01, 168.89, 160.16, 142.74, 142.60, 139.01, 136.33, 131.53, 130.07, 129.67, 127.66, 126.08, 125.12, 123.00, 62.17, 58.84, 38.54, 14.05; Enantiomeric excess: 70%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 70/30; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: $t_R = 15.02$ min, second peak: $t_R = 17.21$ min; HRMS (ESI) m/z calcd. for C$_{18}$H$_{16}$N$_2$NaO$_4$S [M+Na]$^+ = 379.0723$, found 379.0723.

Ethyl (S)-4-(naphthalen-2-yl)-4-oxo-2-(6-oxopyridazin-1(6H)-yl)butanoate

(+)-5pa; isolated yield: 20.0 mg (57%); colorless sticky oil; $[\alpha]_D^{20} = +47.1$ (c = 1.0, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.52 (s, 1H), 8.03 (dd, $J = 8.6, 1.6$ Hz, 1H), 7.96 (d, $J = 8.0$ Hz, 1H), 7.90-7.86 (m, 2H), 7.74 (dd, $J = 3.7, 1.6$ Hz, 1H), 7.63-7.54 (m, 2H), 7.18 (dd, $J = 9.5, 3.8$ Hz, 1H), 6.97 (dd, $J = 9.5, 1.6$ Hz, 1H), 6.17 (dd, $J = 7.7, 5.8$ Hz, 1H), 4.29-4.21 (m, 2H), 4.09-3.97 (m, 2H), 1.25 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 195.53, 169.26, 160.23, 136.23, 135.74, 133.60, 132.45, 131.45, 130.07, 129.63, 128.70, 128.56, 127.81, 126.91, 123.75, 62.09, 58.91, 38.16, 14.08; Enantiomeric excess: 79%, determined by HPLC (Chiralpak AD-H to AD-H, hexane/i-PrOH = 60/40; flow rate 0.5 ml/min; 25 °C; 254 nm), first peak: $t_R = 39.78$ min, second peak: $t_R = 41.53$ min; HRMS (ESI) m/z calcd. for C$_{20}$H$_{18}$N$_2$NaO$_4$ [M+Na]$^+ = 373.1159$, found 373.1151.
\((R)\)-2-(1,1,1-trifluoro-4-oxo-4-(p-tolyl)butan-2-yl)pyridazin-3(2H)-one

\((-\text{3ba})\); isolated yield: 30.7 mg (99%); colorless sticky oil; \([\alpha]_D^{20} = -298.4\) (c = 1.0, CHCl₃); Enantiomeric excess: 96%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 80/20; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: \(t_R = 9.286\) min, second peak: \(t_R = 14.768\) min.
(R)-2-(1,1,1-trifluoro-4-(4-methoxyphenyl)-4-oxobutan-2-yl)pyridazin-3(2H)-one

![Chemical Structure](image)

(-)-3ca; isolated yield: 29.3 mg (90%); colorless sticky oil; \([\alpha]_D^{20} = -320.6 \ (c = 1.0, \text{CHCl}_3)\); Enantiomeric excess: 95%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 80/20; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: \(t_R = 12.734\) min, second peak: \(t_R = 21.611\) min.

(R)-2-(4-([1,1'-biphenyl]-4-yl)-1,1,1-trifluoro-4-oxobutan-2-yl)pyridazin-3(2H)-one

![Chemical Structure](image)

(-)-3da; isolated yield: 36.8 mg (99%); white solid; \([\alpha]_D^{20} = -256.1 \ (c = 1.0, \text{CHCl}_3)\);
Enantiomeric excess: 95%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 80/20; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: $t_R = 13.774$ min, second peak: $t_R = 24.216$ min.

(R)-2-(1,1,1-trifluoro-4-(4-fluorophenyl)-4-oxobutan-2-yl)pyridazin-3(2H)-one

(-)-3ea; isolated yield: 29.8 mg (95%); colorless sticky oil; $[\alpha]_D^{20} = -243.1$ ($c = 1.0$, CHCl$_3$); Enantiomeric excess: 94%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 90/10; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: $t_R = 8.954$ min, second peak: $t_R = 14.645$ min.

(R)-2-(4-(4-chlorophenyl)-1,1,1-trifluoro-4-oxobutan-2-yl)pyridazin-3(2H)-one

(R)-2-(4-(4-chlorophenyl)-1,1,1-trifluoro-4-oxobutan-2-yl)pyridazin-3(2H)-one

- one
(-)-3fa; isolated yield: 31.2 mg (95%); colorless sticky oil; \([\alpha]_D^{20} = -284.5\) (c = 1.0, CHCl3); Enantiomeric excess: 95%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 80/20; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: \(t_R = 9.908\) min, second peak: \(t_R = 16.340\) min.

(R)-2-(4-(4-bromophenyl)-1,1,1-trifluoro-4-oxobutan-2-yl)pyridazin-3(2H)-one

(-)-3ga; isolated yield: 36.8 mg (98%); colorless sticky oil; \([\alpha]_D^{20} = -307.4\) (c = 1.0, CHCl3); Enantiomeric excess: 93%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 80/20; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: \(t_R = 10.333\) min, second peak: \(t_R = 17.299\) min.
(R)-2-(1,1,1-trifluoro-4-(4-iodophenyl)-4-oxobutan-2-yl)pyridazin-3(2H)-one

\[ \text{(-)-3ha; isolated yield: 38.0 mg (90\%); colorless sticky oil; } [\alpha]_{D}^{20} = -272.9 \text{ (c = 1.0, CHCl}_3) \]; Enantiomeric excess: 93\%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 80/20; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: \( t_{R} = 11.318 \text{ min, second peak: } \text{tr} = 18.690 \text{ min.} \]

(\text{R})-2-(1,1,1-trifluoro-4-(4-nitrophenyl)-4-oxobutan-2-yl)pyridazin-3(2H)-one

\[ \text{(-)-3ia; isolated yield: 30.0 mg (88\%); colorless sticky oil; } [\alpha]_{D}^{20} = -284.1 \text{ (c = 1.0, CHCl}_3) \]; Enantiomeric excess: 91\%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 70/30; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: \( t_{R} = 18.031 \text{ min, second peak: } \text{tr} = 40.589 \text{ min.} \]
(R)-4-(4,4,4-trifluoro-3-(6-oxopyridazin-1(6H)-yl)butanoyl)benzonitrile

\[
\text{NC} \quad \text{CF}_3
\]

(-)-3ja; isolated yield: 31.5 mg (98%); colorless sticky oil; \([\alpha]_D^{20} = -299.2 \ (c = 1.0, \text{CHCl}_3)\); Enantiomeric excess: 91%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 80/20; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: \(t_R = 18.918\) min, second peak: \(t_R = 22.761\) min.

(R)-2-(1,1,1-trifluoro-4-(4-(methylsulfonyl)phenyl)-4-oxobutan-2-yl)pyridazin-3(2H)-one

\[
\text{MeO}_2\text{S} \quad \text{CF}_3
\]

(-)-3ka; isolated yield: 35.9 mg (96%); yellow oil; \([\alpha]_D^{20} = -220.1 \ (c = 1.0, \text{CHCl}_3)\); Enantiomeric excess: 91%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH =
90/10; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: \( t_R = 32.345 \) min, second peak: \( t_R = 41.491 \) min.

\[
(R)-2-(1,1,1\text{-trifluoro}-4\text{-oxo}-4-(4\text{-(trifluoromethyl)phenyl})\text{butan-2-yl}) \\
\text{pyridazin-3(2H)-one}
\]

\[
\begin{align*}
\text{F}_3\text{C} & \quad \text{O} \quad \text{N} \quad \text{CF}_3 \\
\end{align*}
\]

\((-\)-3la; isolated yield: 32.4 mg (89%); yellow oil; \([\alpha]_D^{20} = -278.9 \) (c = 1.0, CHCl₃); Enantiomeric excess: 93%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 80/20; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: \( t_R = 7.929 \) min, second peak: \( t_R = 11.515 \) min.

\[
(R)-2-(1,1,1\text{-trifluoro}-4\text{-(2-nitrophenyl)-4-oxobutan-2-yl})\text{pyridazin-3(2H)-one}
\]
(-)-3ma; isolated yield: 32.4 mg (95%); yellow oil; \([\alpha]_D^{20} = -127.3\, (c = 1.0, \text{CHCl}_3)\); Enantiomeric excess: 75%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 80/20; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: \(t_R = 11.818\) min, second peak: \(t_R = 15.631\) min.

(R)-2-(1,1,1-trifluoro-4-(3-nitrophenyl)-4-oxobutan-2-yl)pyridazin-3(2H)-one

(-)-3na; isolated yield: 32.1 mg (94%); colorless sticky oil; \([\alpha]_D^{20} = -263.0\, (c = 1.0, \text{CHCl}_3)\); Enantiomeric excess: 92%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 80/20; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: \(t_R = 13.409\) min, second peak: \(t_R = 23.927\) min.
(R)-2-(4-(3,5-difluorophenyl)-1,1,1-trifluoro-4-oxobutan-2-yl)pyridazin-3(2H)-one

(-)-3oa: isolated yield: 31.0 mg (93%); colorless sticky oil; $[\alpha]_D^{20} = -209.6$ ($c = 1.0$, CHCl$_3$); Enantiomeric excess: 93%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 80/20; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: $t_R = 7.975$ min, second peak: $t_R = 12.459$ min.

(R)-2-(4-(3,4-dichlorophenyl)-1,1,1-trifluoro-4-oxobutan-2-yl)pyridazin-3(2H)-one

(R)-2-(4-(3,4-dichlorophenyl)-1,1,1-trifluoro-4-oxobutan-2-yl)pyridazin-3(2H)-one
**(-)-3pa:** isolated yield: 35.8 mg (98%); white solid; \([\alpha]_D^{20} = -286.6 (c = 1.0, \text{CHCl}_3)\); Enantiomeric excess: 95%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 80/20; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: \(t_R = 7.905\) min, second peak: \(t_R = 11.792\) min.

$$\text{(R)-2-(1,1,1-trifluoro-4-(naphthalen-1-yl)-4-oxobutan-2-yl)pyridazin-3(2H)-one}$$

$$\text{(-)-3qa}$$; isolated yield: 33.9 mg (98%); colorless sticky oil; \([\alpha]_D^{20} = -181.2 (c = 1.0, \text{CHCl}_3)\); Enantiomeric excess: 85%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 80/20; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: \(t_R = 8.340\) min, second peak: \(t_R = 10.875\) min.

$$\text{(R)-2-(1,1,1-trifluoro-4-(naphthalen-2-yl)-4-oxobutan-2-yl)pyridazin-3(2H)-one}$$
**(-)-3ra;** isolated yield: 33.9 mg (98%); colorless sticky oil; [α]D\(^{20}\) = -422.3 (c = 1.0, CHCl\(_3\)); Enantiomeric excess: 93%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 80/20; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: t\(_R\) = 10.523 min, second peak: t\(_R\) = 14.709 min.

\[
(R)-2-(4-(benzo[b]thiophen-2-yl)-1,1,1-trifluoro-4-oxobutan-2-yl)pyridazin-3(2H)-one
\]

**(-)-3sa;** isolated yield: 34.1 mg (97%); colorless sticky oil; [α]D\(^{20}\) = -384.1 (c = 1.0, CHCl\(_3\)); Enantiomeric excess: 92%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 80/20; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: t\(_R\) = 12.571 min, second peak: t\(_R\) = 17.941 min.
(R)-2-(1,1,1-trifluoro-4-oxo-4-(thiophen-2-yl)butan-2-yl)pyridazin-3(2H)-one

(-)-3ta; isolated yield: 28.7 mg (95%); yellow oil; $[\alpha]_D^{20} = -278.5$ ($c = 1.0$, CHCl$_3$); Enantiomeric excess: 96%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 80/20; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: $t_R = 10.632$ min, second peak: $t_R = 15.932$ min.

(R)-2-(4-(cyclohex-1-en-1-yl)-1,1,1-trifluoro-4-oxobutan-2-yl)pyridazin-3(2H)-one

(-)-3ua; isolated yield: 12.0 mg (40%); colorless sticky oil; $[\alpha]_D^{20} = -235.5$ ($c = 0.33$, CHCl$_3$); Enantiomeric excess: 90%, determined by HPLC (Chiralpak AD-H,
hexane/i-PrOH = 80/20; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: $t_R = 7.266$ min, second peak: $t_R = 9.892$ min.

(R)-2-(1,1,1,2,2-pentafluoro-5-oxo-5-phenylpentan-3-yl)pyridazin-3(2H)-one

![Image](image1.png)

(-)-3ua: isolated yield: 22.0 mg (64%); colorless sticky oil; Enantiomeric excess: 83%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 80/20; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: $t_R = 7.857$ min, second peak: $t_R = 8.661$ min.

(R)-2-(4-(4-chlorophenyl)-1,1,1-trifluoro-4-oxobutan-2-yl)-6-methylpyridazin-3(2H)-one

![Image](image2.png)

(-)-3fb: isolated yield: 22.0 mg (64%); white solid; $[\alpha]_D^{20} = -222.3$ (c = 1.0, CHCl₃);
Enantiomeric excess: 96%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 80/20; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: $t_R = 9.167$ min, second peak: $t_R = 12.150$ min.

$(R)$-2-(4-(4-chlorophenyl)-1,1,1-trifluoro-4-oxobutan-2-yl)-6-phenylpyridazin-3(2H)-one

(-)-3fc; isolated yield: 39.5 mg (97%); colorless sticky oil; $[\alpha]_D^{20} = -76.6$ ($c = 1.0$, CHCl$_3$); Enantiomeric excess: 92%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 80/20; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: $t_R = 9.624$ min, second peak: $t_R = 11.733$ min.

$(R)$-6-chloro-2-(4-(4-chlorophenyl)-1,1,1-trifluoro-4-oxobutan-2-yl)pyridazin-3(2H)-one

$(R)$-6-chloro-2-(4-(4-chlorophenyl)-1,1,1-trifluoro-4-oxobutan-2-yl)pyridazin-3(2H)-one
(-)-3fd; isolated yield: 35.0 mg (96%); white solid; $[\alpha]_D^{20} = -188.3$ ($c = 1.0$, CHCl$_3$); Enantiomeric excess: 92%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 80/20; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: $t_R$ = 8.770 min, second peak: $t_R$ = 11.389 min.

Methyl (R)-1-(4-(4-chlorophenyl)-1,1,1-trifluoro-4-oxobutan-2-yl)-6-oxo-1,6-dihydropyridazine-3-carboxylate

(-)-3fe; isolated yield: 38.1 mg (98%); white solid; $[\alpha]_D^{20} = -228.9$ ($c = 1.0$, CHCl$_3$); Enantiomeric excess: 90%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 80/20; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: $t_R$ = 10.047 min, second peak: $t_R$ = 13.182 min.
(R)-5-chloro-2-(4-(4-chlorophenyl)-1,1,1-trifluoro-4-oxobutan-2-yl)pyridazin-3(2H)-one

(-)-3ff; isolated yield: 35.4 mg (97%); colorless sticky oil; $[\alpha]_{D}^{20} = -257.0$ (c = 1.0, CHCl$_3$); Enantiomeric excess: 92%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 80/20; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: $t_R = 8.833$ min, second peak: $t_R = 16.246$ min.

Methyl (R)-4-(4-chlorophenyl)-4-oxo-2-(6-oxopyridazin-1(6H)-yl)butanoate

(-)-5aa; isolated yield: 27.2 mg (85%); colorless sticky oil; $[\alpha]_{D}^{20} = -17.1$ (c = 1.0, CHCl$_3$); Enantiomeric excess: 90%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 70/30; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: $t_R = 17.67$ min, second peak: $t_R = 21.60$ min.
Benzyl (R)-4-oxo-2-(6-oxopyridazin-1(6H)-yl)-4-phenylbutanoate

\[
\text{(-)-5ba; isolated yield: 27.2 mg (75\%); colorless sticky oil; } [\alpha]_D^{20} = -6.2 \text{ (c = 1.0, CHCl}_3\text{); Enantiomeric excess: 89\%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 70/30; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: } t_R = \text{20.88min, second peak: } t_R = \text{27.51 min.}
\]

Ethyl (R)-4-oxo-2-(6-oxopyridazin-1(6H)-yl)-4-phenylbutanoate

\[
\text{(-)-5ca; isolated yield: 26.1 mg (87\%); colorless sticky oil; } [\alpha]_D^{20} = -9.0 \text{ (c = 1.0, CHCl}_3\text{); Enantiomeric excess: 93\%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 70/30; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: } t_R = \text{11.60 min.}
\]
min, second peak: $t_R = 13.86$ min.

**isopropyl (R)-4-oxo-2-(6-oxopyridazin-1(6H)-yl)-4-phenylbutanoate**

(-)-5da; isolated yield: 30.1 mg (96%); colorless sticky oil; $[\alpha]_D^{20} = -11.7$ ($c = 1.0$, CHCl$_3$); Enantiomeric excess: 96%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 70/30; flow rate 1.0 ml/min; 25°C; 254 nm), first peak: $t_R = 11.30$ min, second peak: $t_R = 13.18$ min.

**tert-butyl (R)-4-oxo-2-(6-oxopyridazin-1(6H)-yl)-4-phenylbutanoate**

(-)-5ea; isolated yield: 30.5 mg (93%); colorless sticky oil; $[\alpha]_D^{20} = -6.5$ ($c = 1.0$, CHCl$_3$); Enantiomeric excess: 97%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 70/30; flow rate 1.0 ml/min; 25°C; 254 nm), first peak: $t_R = 8.35$
min, second peak: $t_R = 11.40$ min.

Ethyl (R)-4-oxo-2-(6-oxopyridazin-1(6H)-yl)-4-(p-tolyl)butanoate

(-)-5fa; isolated yield: 22.0 mg (70%); colorless sticky oil; $[\alpha]_D^{20} = -22.5$ ($c = 1.0$, CHCl$_3$); Enantiomeric excess: 96%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 70/30; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: $t_R = 12.88$ min, second peak: $t_R = 16.06$ min.

Ethyl (R)-4-(4-methoxyphenyl)-4-oxo-2-(6-oxopyridazin-1(6H)-yl)butanoate

(-)-5ga; isolated yield: 18 mg (55%); colorless sticky oil; $[\alpha]_D^{20} = -35.5$ ($c = 0.33$, CHCl$_3$).
CHCl$_3$); Enantiomeric excess: 95%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 70/30; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: t$_R$ = 17.26 min, second peak: t$_R$ = 24.46 min.

Ethyl (R)-4-([1,1'-biphenyl]-4-yl)-4-oxo-2-(6-oxopyridazin-1(6H)-yl)-butanoate

(-)-5ha; isolated yield: 27.1 mg (72%); colorless sticky oil; [α]$_D^{20}$ = -56.9 (c = 1.0, CHCl$_3$); Enantiomeric excess: 95%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 70/30; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: t$_R$ = 18.81 min, second peak: t$_R$ = 33.07 min.

Ethyl (R)-4-(4-fluorophenyl)-4-oxo-2-(6-oxopyridazin-1(6H)-yl)butanoate
(-)-5ia; isolated yield: 28.9 mg (91%); colorless sticky oil; \([\alpha]_D^{20} = -2.0\) (\(c = 1.0,\) CHCl\(_3\)); Enantiomeric excess: 94%, determined by HPLC (Chiralpak AD-H, hexane/\(i\)-PrOH = 70/30; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: \(t_R = 14.33\) min, second peak: \(t_R = 17.68\) min.

Ethyl \((R)-4-(4-chlorophenyl)-4-oxo-2-(6-oxopyridazin-1(6H)-yl)butanoate\)

(-)-5ja; isolated yield: 30.2 mg (90%); colorless sticky oil; \([\alpha]_D^{20} = -20.6\) (\(c = 1.0,\) CHCl\(_3\)); Enantiomeric excess: 95%, determined by HPLC (Chiralpak AD-H, hexane/\(i\)-PrOH = 70/30; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: \(t_R = 17.85\) min, second peak: \(t_R = 22.48\) min.
Ethyl (R)-4-(4-bromophenyl)-4-oxo-2-(6-oxopyridazin-1(6H)-yl)butanoate

(-)-5ka; isolated yield: 34.9 mg (92%); colorless sticky oil; $\left[\alpha\right]_D^{20} = -25.4$ ($c = 1.0$, CHCl$_3$); Enantiomeric excess: 94%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 70/30; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: $t_R = 16.58$ min, second peak: $t_R = 21.28$ min.

Ethyl (R)-4-oxo-2-(6-oxopyridazin-1(6H)-yl)-4-(4-(trifluoromethyl)phenyl)butanoate

(-)-5la; isolated yield: 25.8 mg (70%); colorless sticky oil; $\left[\alpha\right]_D^{20} = -3.4$ ($c = 1.0$, CHCl$_3$); Enantiomeric excess: 94%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 70/30; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: $t_R = 8.79$ min, second peak: $t_R = 11.59$ min.
Ethyl \((R)\)-4-(4-cyanophenyl)-4-oxo-2-(6-oxopyridazin-1(6H)-yl)butanoate

![Chemical structure of compound 5a](image)

\((-\textbf{5a})\); isolated yield: 28.3 mg (87%); colorless sticky oil; \([\alpha]_{D}^{20} = -19.1\ (c = 1.0, \text{CHCl}_3)\); Enantiomeric excess: 87%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 70/30; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: \(t_R = 15.97\) min, second peak: \(t_R = 18.99\) min.

Ethyl \((R)\)-4-(3,4-dichlorophenyl)-4-oxo-2-(6-oxopyridazin-1(6H)-yl)butanoate

![Chemical structure of compound 5a](image)

\((-\textbf{5a})\); isolated yield: 35.1 mg (95%); colorless sticky oil; \([\alpha]_{D}^{20} = -23.1\ (c = 1.0, \text{CHCl}_3)\); Enantiomeric excess: 95%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 70/30; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: \(t_R = 15.97\) min, second peak: \(t_R = 18.99\) min.
CHCl$_3$); Enantiomeric excess: 93%, determined by HPLC (Chiralpak OD-H to OD-H, hexane/i-PrOH = 60/40; flow rate 0.5 ml/min; 25 °C; 254 nm), first peak: $t_R = 68.16$ min, second peak: $t_R = 73.29$ min.

Ethyl (R)-4-(benzo[b]thiophen-2-yl)-4-oxo-2-(6-oxopyridazin-1(6H)-yl)-butanoate

(-)-50a; isolated yield: 33.1 mg (93%); colorless sticky oil; $[\alpha]_D^{20} = -55.8$ (c = 1.0, CHCl$_3$); Enantiomeric excess: 95%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 70/30; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: $t_R = 16.57$ min, second peak: $t_R = 18.92$ min.

Ethyl (R)-4-(naphthalen-2-yl)-4-oxo-2-(6-oxopyridazin-1(6H)-yl)butanoate
(−)-5pa; isolated yield: 31.2 mg (89%); colorless sticky oil; \([\alpha]_D^{20} = -77.8\ (c = 1.0, \text{CHCl}_3)\); Enantiomeric excess: 96%, determined by HPLC (Chiralpak AD-H to AD-H, hexane/\text{i-PrOH} = 60/40; flow rate 0.5 ml/min; 25 °C; 254 nm), first peak: \(t_R = 41.05\) min, second peak: \(t_R = 42.63\) min.

(\(R\))-4-oxo-2-(6-oxopyridazin-1(6H)-yl)-4-phenylbutanoic acid

(−)-6a; white solid; The enantiomeric excess of 6a as determined by chiral HPLC analysis on Chiralpak AD-H after esterification with TMSCH\(_2\)N\(_2\), (hexanes:2-propanol = 70:30, flow rate 1.0 mL/min; 25 °C; 254 nm); minor enantiomer \(t_R =12.15\) min, major enantiomer \(t_R = 14.19\) min; \([\alpha]_D^{20} = +2.8\ (c = 1.0, \text{CHCl}_3)\); \(^1\)H NMR (500 MHz, MeOD) \(\delta\) 8.00 (d, \(J = 7.6\) Hz, 2H), 7.87 (d, \(J = 2.6\) Hz, 1H), 7.62 (t, \(J = 7.4\) Hz, 1H), 7.50 (t, \(J = 7.6\) Hz, 2H), 7.40 (dd, \(J = 9.4, 3.7\) Hz, 1H), 7.02 (d, \(J = 9.2\) Hz, 1H), 6.09 (dd, \(J = 8.2, 5.4\) Hz, 1H), 4.01-3.90 (m, 2H); \(^{13}\)C NMR (126 MHz, MeOD) \(\delta\) 196.38, 137.16, 136.32, 133.29, 132.50, 129.00, 128.47, 128.43, 127.89, 127.84, 58.15, 48.19, 48.02, 37.80; HRMS (ESI) m/z calcd. for C\(_{14}\)H\(_{12}\)N\(_2\)NaO\(_4\) [M+Na]\(^+\) = 295.0689, found 295.0685.
S-\((p\text{-tolyl})\) \((R)\)-4-oxo-2-(6-oxopyridazin-1(6\(H\))-yl)-4-phenylbutanethioate

\[7a, \text{ red solid; } [\alpha]_D^{20} = +125.9 \text{ (c = 1.0, CHCl}_3); \]
\[\text{\(^1\)H NMR (500 MHz, CDCl}_3) \delta 7.97-7.95 (m, 2H), 7.79 (dd, } J = 3.7, 1.6 \text{ Hz, 1H}), 7.57 (dd, } J = 10.5, 4.3 \text{ Hz, 1H}), 7.45 (t, } J = 7.7 \text{ Hz, 2H}), 7.29 (d, } J = 8.1 \text{ Hz, 2H}), 7.22-7.19 (m, 3H), 7.01 (dd, } J = 9.5, 1.7 \text{ Hz, 1H}), 6.41 (dd, } J = 8.2, 5.4 \text{ Hz, 1H}), 4.00-3.90 (m, 2H), 2.35 (s, 3H); \]
\[\text{\(^{13}\)C NMR (126 MHz, CDCl}_3) \delta 195.63, 195.25, 160.35, 140.06, 136.71, 136.16, 134.69, 133.55, 131.53, 130.23, 130.14, 128.70, 128.21, 122.76, 64.09, 38.51, 21.35; \]
Enantiomeric excess: 90\%, determined by HPLC (Chiralpak AD-H, hexane/i-PrOH = 70/30; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: } t_R = 21.61 \text{ min, second peak: } t_R = 22.84 \text{ min; HRMS (ESI) m/z calcd. for } \text{C}_{21}\text{H}_{18}\text{N}_{2}\text{O}_{3}\text{S [M+Na]}^+ = 401.0930, \text{ found 401.0929.}

\((R)\)-N-(1-methyl-1\(H\)-pyrazol-3-yl)-4-oxo-2-(6-oxopyridazin-1(6\(H\))-yl)-4-
Phenylbutanamide

7b, yellow solid; $[\alpha]_D^{20} = +49.0$ ($c = 1.0$, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.53 (s, 1H), 8.00 (d, $J = 7.6$ Hz, 2H), 7.78 (d, $J = 2.5$ Hz, 1H), 7.55 (d, $J = 7.3$ Hz, 1H), 7.45 (t, $J = 7.6$ Hz, 2H), 7.18-7.15 (m, 2H), 7.00-6.97 (m, 1H), 6.58 (d, $J = 1.7$ Hz, 1H), 6.30 (t, $J = 6.8$ Hz, 1H), 3.99-3.97 (m, 2H), 3.77 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 196.22, 165.83, 160.96, 146.44, 136.87, 136.26, 133.48, 131.39, 130.76, 129.83, 128.65, 128.22, 125.73, 97.61, 57.95, 38.17; Enantiomeric excess: 92%, determined by HPLC (Chiralpak AS-H, hexane/i-PrOH = 50/50; flow rate 1.0 ml/min; 25 °C; 254 nm), first peak: $t_R = 22.650$ min, second peak: $t_R = 45.612$ min; HRMS (ESI) m/z calcd. for C$_{18}$H$_{17}$N$_3$NaO$_3$ [M+Na]$^+$ = 374.1224, found 374.1220.

6'-phenyl-4',5'-dihydro-6H-[1,4'-bipyridazine]-3',6(2'II)-dione

7c, white solid; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.77 (s, 1H), 7.87 (d, $J = 2.2$ Hz, 1H), 7.72-7.70 (m, 2H), 7.43-7.41 (m, 2H), 7.23 (dd, $J = 9.5$, 3.7 Hz, 1H), 7.00 (d, $J = 9.3$ Hz, 1H), 5.96 (dd, $J = 13.4$, 7.4 Hz, 1H), 3.60 (dd, $J = 16.4$, 13.6 Hz, 1H), 3.39 (dd, $J = 16.6$, 7.4 Hz, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 163.41, 160.35, 150.44, 137.26, 135.09, 131.53, 130.22, 129.98, 128.74, 125.89, 53.02, 28.28; HRMS (ESI) m/z calcd. for C$_{14}$H$_{12}$NaNaO$_2$ [M+Na]$^+$ = 291.0852, found 291.0849.
2-(2-oxo-5-phenyl-2,3-dihydrofuran-3-yl)pyridazin-3(2H)-one

7d, white solid; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.80 (dd, \(J = 3.8, 1.6\) Hz, 1H), 7.68-7.67 (m, 2H), 7.44-7.43 (m, 3H), 7.23 (dd, \(J = 9.5, 3.8\) Hz, 1H), 6.98 (dd, \(J = 9.5, 1.6\) Hz, 1H), 6.29 (d, \(J = 2.6\) Hz, 1H), 5.88 (d, \(J = 2.7\) Hz, 1H); \(^1^3\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 171.06, 159.52, 156.55, 137.40, 131.96, 130.62, 130.14, 128.78, 127.48, 125.42, 98.03, 62.57; HRMS (ESI) m/z calcd. for C\(_{14}\)H\(_{10}\)N\(_2\)O\(_3\) [M+Na]\(^+\) = 277.0584, found 277.0584.

X-Ray Crystallographic Analysis

**Determination of the Absolute Configurations of the Product (+)-3da**

Figure S4. X ray structure of (+)-3da (CCDC 1839409). Related to Scheme 4.
Data S2. Spectra of Products. Related to Scheme 3, Scheme 4, Scheme 5, Scheme 6 and Scheme 7.
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