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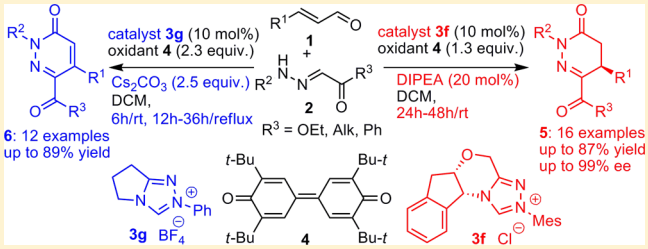
N-Heterocyclic Carbene-Catalyzed Oxidative Annulations of α,β-Unsaturated Aldehydes with Hydrazones: Selective Synthesis of Optically Active 4,5-Dihydropyridazin-3-ones and Pyridazin-3-ones

Jian-Hui Mao, Zi-Tian Wang, Zhan-Yong Wang, and Ying Cheng*

College of Chemistry, Beijing Normal University, Beijing 100875, China

Supporting Information

ABSTRACT: A novel and efficient method for the highly enantioselective synthesis of chiral 4,5-dihydropyridazin-3-one derivatives has been developed based on the chiral N-heterocyclic carbene-catalyzed oxidative annulation between α,β-unsaturated aldehydes and hydrazones. Meanwhile, the selective synthesis of either 4,5-dihydropyridazin-3-ones or pyridazin-3-one derivatives from the same reactants has been achieved by simply varying catalytic and reaction conditions.



INTRODUCTION

Members of the 4,5-dihydropyridazin-3(2*H*)-one and pyridazin-3(2*H*)-one families have been demonstrated to possess a wide range of biological activities.[1] Some of them have been used in commercial pharmaceuticals and agrochemicals. For example, both Levosimendan[2] and Pimobendan[3] are calcium sensitizers and inhibitors of phosphodiesterase with positive inotropic effects, which have been used in the treatment of heart failures. A larger number of 4,5-dihydropyridazin-3-one derivatives, such as CI-930,[4] MCI-154,[5] and compounds **A**–**C**,[6−8] have been reported to inhibit phosphodiesterases and have positive inotropic/vasodilator effects or anti-inflammatory activities (Figure 1). In addition, 4,5-dihydropyridazin-3-one compounds also have anticancer,[9] anticonvulsant,[10] and hypotensive activities,[11] etc. Pyridazin-3-one derivatives, on the other hand, also are known to possess widespread and powerful pharmacologic properties, varying from antiulcer,[12] antihistamine,[13] antitumor,[14] and anti-inflammatory[15] activities to inhibitory activity to HIV-1 reverse transcriptase,[16] phosphodiesterases,[17] platelet aggregation,[18] etc. Various substituted pyridazin-3-ones were reported to have insecticide,[19] acaricide,[19] and herbicide activities.[20]

Due to their broad and powerful pharmacologic activities, the syntheses of 4,5-dihydropyridazin-3-one and pyridazin-3-one compounds have attracted continuous interest from both organic and medicinal chemists. The most frequently used strategy for the construction of a 4,5-dihydropyridazin-3-one or a pyridazin-3-one ring is based on the condensation of a hydrazine or substituted hydrazines with γ-carbonyl acids or their derivatives.[7,8,11,21−25] Another method for the formation of dihydropyridazin-3-ones or pyridazin-3-ones is to utilize a hydrazone of a 1,2-dicarbonyl compound as a substrate to react with ethyl cyanoacetate,[26] phosphonium ylides of carboxylates,[27] 2-benzylidenecyanoacetate, or 2-benzylidenemalononitrile,[28] followed by intramolecular cyclization. In recent years, several new methods, including the $AgNO_3$-catalyzed multicomponent radical reaction of aryldiazonium salts with pent-4-enoate and sodium triflinate,[29] the copper-catalyzed multicomponent reaction of aldehydes with hydrazines and alkynylesters,[30] the KSF-catalyzed multicomponent cyclocondensation of γ-keto acids with thiosemicarbazide and phenacyl bromide,[31] the Brønsted acid assisted Lewis base catalyzed asymmetric reaction between hydrazones and α,β-unsaturated aldehydes,[32] and the reaction between aryldiazonium salts and potassium 2-furantrifluoroborate,[33] have been developed for the construction of 4,5-dihydropyridazin-3-ones or pyridazin-3-ones. Although it has been shown that the (+)- and (−)-enantiomers of the 4,5-dihydropyridazin-3-one derivatives have different bioactivities on the physiological system,[34] the studies on the asymmetric synthesis of chiral 4,5-dihydropyridazin-3-ones are very limited. Enantiomerically pure 4,5-dihydropyridazin-3-one compounds are obtained mainly from the transformations of chiral reactants,[23e,35a] the chiral substrate induced asymmetric reaction,[24b] the lipase-catalyzed resolution of racemates of 4,5-dihydropyridazin-3-one derivatives,[35b] or the resolution of racemic reactants by a chiral reagent.[34c] Recently, Rueping and co-workers[32] reported the chiral Brønsted acid assisted amine-catalyzed asymmetric reaction between *N*-aryltrifluoromethylhydrazones and α,β-unsaturated aldehydes, which produced good yields of 1,4-dihydropyridazine derivatives with excellent enantioselectivity via the dehydration of two diastereomeric 2,3,4,5-tetrahydropyridazin-3-ol intermediates. The oxidation of the 2,3,4,5-tetrahydropyridazin-3-ol intermediate by PCC could provide 4,5-dihydropyridazin-3-one in excellent yield; however, no ee value was reported. Ye and co-workers reported the highly efficient and enantioselective cinchona alkaloid-catalyzed

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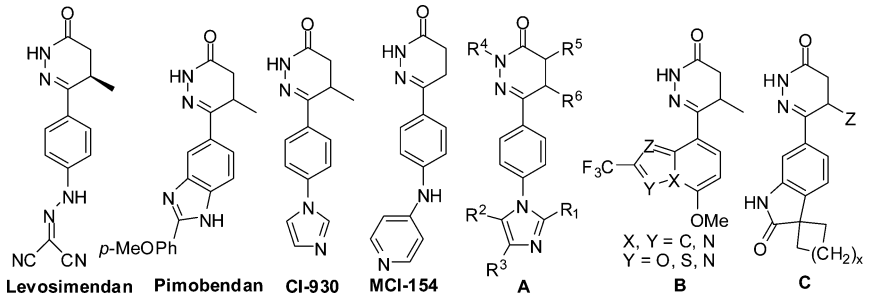
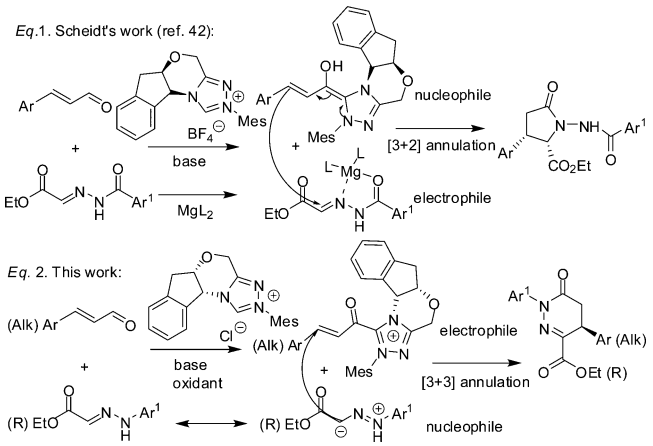


Figure 1. Some pharmacologically active 4,5-dihydropyridazin-3-one derivatives.

asymmetric annulation of α,β-unsaturated acid chlorides with azodicarboxylates and the chiral NHC-catalyzed annulation of γ-(methoxycarbonyloxy)-α,β-unsaturated aldehydes with azodicarboxylates. Both of them generated chiral 1,2-dihydropyridazin-3-ones rather than 4,5-dihydropyridazin-3-ones.[36,37] To the best of our knowledge, the direct construction of enantiopure 4,5-dihydropyridazin-3-ones by chiral catalysis has not been reported yet. Therefore, the development of highly efficient and enantioselective reactions for the preparation of enantiomercally pure 4,5-dihydropyridazin-3-one compounds is of great importance.

Oxidative N-heterocyclic carbene (NHC) catalysis has attracted increasing attention in recent years.[38] Oxidative NHC-catalyzed reactions of α,β-unsaturated aldehydes, which initially form α,β-unsaturated acylazolium intermediates, undergo annulation reactions with various nucleophilic substrates to produce diverse cyclic compounds. For instance, in the presence of a quinone oxidant, the NHC-catalyzed reaction of α,β-unsaturated aldehydes or 3-bromoenals with 1,3-diones produces 3,4-dihydropyran-2-one or pyran-2-one derivatives.[39] On the other hand, under the oxidative NHC catalysis conditions, the annulation of α,β-unsaturated aldehydes with imines or enamines produces dihydropyridin-2-ones.[40] In addition, the γ-activation of α,β-unsaturated aldehydes has also been achieved by means of oxidative NHC catalysis, allowing the γ-addition of 3-alkylenals to the carbonyls of trifluoromethyl ketones or isatins to form dihydropyran-2-one derivatives.[41] In 2010, Scheidt and co-workers reported the cooperative chiral NHC/Lewis acid catalyzed reaction of α,β-unsaturated aldehydes with *N*-acylhydrazones to produce *N*-benzamido substituted γ-lactams with high stereoselectivity via a formal [3 + 2] annulation.[42] In Scheidt's reaction, the α,β-unsaturated aldehydes act as nucleophiles via the Breslow intermediates to add to the electrophilic imine groups of hydrazones that are activated by a Lewis acid (Scheme 1, eq 1). We envisioned that, under the cooperative NHC/oxidant catalysis, α,β-unsaturated aldehydes would behave as electrophiles via α,β-unsaturated acylazolium intermediates to undergo a formal [3 + 3] annulation with the nucleophilic hydrazones to yield 4,5-dihydropyridazin-3-one compounds (Scheme 1, eq 2). Herein we report a novel method for the enantioselective synthesis of chiral dihydropyridazin-3-ones and the selective synthesis of either 4,5-dihydropyridazin-3-ones or pyridazin-3-ones from oxidative NHC catalysis of the reaction between α,β-unsaturated aldehydes and hydrazones by varying the catalytic and reaction conditions.

Scheme 1. Comparison between the Reactions of α,β-Unsaturated Aldehydes with Hydrazones under Scheidt's and Our Catalytic Conditions



RESULTS AND DISCUSSION

The first experiment on the feasibility of the [3 + 3] annulation reaction between enals and hydrazones was carried out with cinnamaldehyde **1a** and ethyl 2-(*N*-phenylhydrazono)acetate **2a** as substrates. We initiated our study by examining the reaction of **1a** with **2a** employing a variety of chiral triazolium salts **3a**−**3f** bearing a different fused ring or a varied *N*-substituent as NHC precursors. The NHC catalysts **3a′**−**3f′** were generated in situ from the deprotonization of triazolium salts **3a**−**3f** with DBU in dichloromethane at ambient temperature. In the presence of DBU (20 mol %) and quinone oxidant **4** (1.3 equiv), a bicyclic triazolium salt **3a** (10 mol %) was found to be almost inactive in catalyzing the reaction of enal **1a** with hydrazone **2a** (**1a**:**2a** = 1.3:1). However, the pyrrolidine- (**3b**) and morpholine-fused triazolium salt (**3c**) were able to promote the reaction to produce (+)-1,4-diphenyl-4,5-dihydropyridaz-6-one-3-carboxylate **5a** in good yields (73%−84%) with low enantioselectivity (33%−49% ee) (Table 1, entries 2 and 3). When tetracyclic triazolium salts **3d**−**3f** were utilized as precatalysts, the reactions catalyzed by *N*-phenyl- (**3d**) and *N*-mesityl (2,4,6-trimethylphenyl) substituted triazolium salt **3f** provided 68%−72% yields of (−)-**5a** with 59%−74% ee (Table 1, entries 4 and 6). However, only a trace amount of product was isolated from the reaction catalyzed by *N*-perfluorophenyl substituted triazolium salt **3e**. Since the best enantioselectivity was observed from the reaction using *N*-mesityltriazolium salt **3f** as a precatalyst, the reaction conditions were further optimized by varying the bases, solvents, and reaction temperature in the presence of triazolium salt **3f**. It was found that the replacement of DBU by a strong base, *t*-BuOK or KOH, diminished the chemical yield or both the yield and ee value of **5a** (Table 1, entries 7, 8). Pleasingly, the employment of Cs_2CO_3 or diisopropylethylamine (DIPEA)

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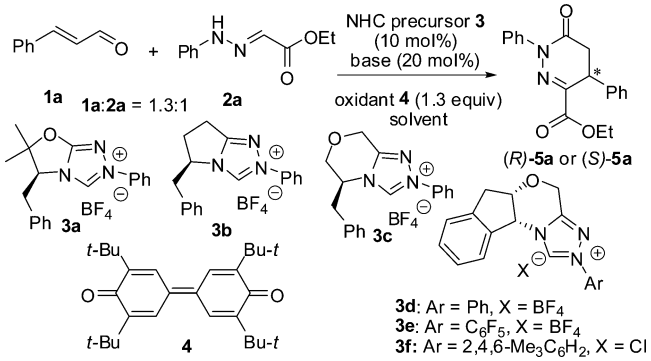
Table 1. Optimization of Reaction Conditions for the Chiral NHC-Catalyzed Oxidative Annulation of Cinnamaldehyde 1a with 2-(*N*-Phenylhydrazono)acetate 2a



entry	NHC precursor **3**	base	solvent	temp.	time (h)	yield of **5a** (%)[a]	ee (%)[b]
1	**3a**	DBU	DCM	rt	24	trace	–
2	**3b**	DBU	DCM	rt	24	84	49[c]
3	**3c**	DBU	DCM	rt	24	73	33[c]
4	**3d**	DBU	DCM	rt	24	72	59[d]
5	**3e**	DBU	DCM	rt	24	9	–
6	**3f**	DBU	DCM	rt	24	68	74[d]
7	**3f**	*t*-BuOK	DCM	rt	24	50	94[d]
8	**3f**	KOH	DCM	rt	24	43	12[d]
9	**3f**	Cs_2CO_3	DCM	rt	24	81	92[d]
10	**3f**	**DIPEA**	**DCM**	**rt**	**24**	**87**	**96**[d]
11	**3f**	DIPEA	THF	rt	48	8	–
12	**3f**	DIPEA	toluene	rt	48	28	59[d]
13	**3f**	DIPEA	CH_3CN	rt	24	88	70[d]
14	**3f**	DIPEA	DCM	0 °C	48	55	96[d]
15	**3f**	DIPEA	DCM	reflux	24	70	92[d]

[a]Isolated yields. [b]Determined by HPLC analysis on a OD-H column. [c](+)-Enantiomer. [d](−)-Enantiomer.

as a base led to the improvement of chemical yield of **5a** to 81% or 87%, respectively, with excellent enantioselectivity (92%−96% ee) also being obtained (Table 1, entries 9, 10). In the presence of *N*-mesityltriazolium salt **3f**, DIPEA, and quinone **4**, the use of THF, toluene, or acetonitrile as reaction media caused the decrease of both chemical yield and enantioselectivity (Table 1, entries 11−13). In dichloromethane, either a decease in reaction temperature to 0 °C or increase to the boiling point of solvent was not beneficial to the yield of product (Table 1, entries 14−15).

The optimized reaction conditions were adopted for further studies of the reaction scope (Table 2). With respect to the α,β-unsaturated aldehyde substrates, cinnamaldehyde **1a** and its analogues **1b** and **1c** bearing an electron-donating group (4-Me and 4-MeO) reacted with 2-(*N*-phenylhydrazono)acetate **2a** to produce 4,5-dihydropyridazin-6-one-3-carboxylates **5a**−**5c** in 71%−87% yields with excellent enantioselectivity (96%−99% ee) (Table 2, entries 1−3). However, the cinnamaldehydes **1d** and **1e** substituted by an electron-withdrawing group (4-Br and 4-Ac) gave products **5d** and **5e** in 51−72% yields with lower enantioselectivity (64%−67% ee) (Table 2, entries 4 and 5). The lower chemical yield of product **5e** derived from the strong electron-withdrawing acetyl substituted cinnamaldehyde **1e** is probably due to the lower stability of **1e** than other cinnamaldehydes **1a**−**1d**. It was found that the substitution pattern of cinnamaldehydes also influenced the outcome of the reaction, as 3-methylcinnamaldehyde **1f** produced a higher yield (87%) of product than that of 2-methylcinnamaldehyde **1g** (67%). The enantioselectivity was however not affected (96%−98% ee) (Table 2, entries 6 and 7). In comparison to the aromatic enals, the reactions of aliphatic enals **1h** and **1i** produced lower yields of products **5h** and **5i** (47%−49%) with 93%−96% ee, probably because the aliphatic enals were less stable under the reaction conditions (Table 2, entries 8 and 9). We next examined the chiral NHC-catalyzed oxidative annulation of cinnamaldehyde **1a** with different hydrazones. It was found that the substituents attached to hydrazones **2** influenced both the chemical yields and enantioselectivity. For example, while *N*-(4-methoxyphenyl)- (**2b**), *N*-(4-methylphenyl)- (**2c**), and *N*-(4-bromophenyl)hydrazonoacetate (**2d**) reacted with enal **1a** to give products **5j**−**5l** in 69%−79% yields with 90%−95% ee, the reaction of *N*-(4-trifluoromethylphenyl)hydrazonoacetate **2e** with **1a** formed product **5m** in moderate yield (51%) and enantioselectivity (74% ee) (Table 2, entries 10−13). The *N*-(4-trifluoromethylphenyl)hydrazonoacetate **2e** produced a lower yield of product than other *N*-arylhydrazonoacetates **2a**−**2d**, probably because the strong electron-withdrawing trifluoromethyl group decreased the nucleophilicity of hydrazone **2e**. When 2-(*N*-arylhydrazono)acetates were replaced by 2-(arylhydrazono)ketones **2f**−**2h**, the reactions of **1a** with 2-(arylhydrazono)ketones **2f**−**2h** proceeded smoothly to produce 6-carbonyl-4,5-dihydropyridazin-3-ones **5n**−**5p** in 60%−83% yields with excellent enantioselectivity (94%−97% ee) (Table 2, entries 14−16). The acetyl substituted hydrazone **2f** gave a better yield of product than the bulky isobutyryl and benzoyl substituted hydrazones **2g** and **2h**, probably due to the larger steric hindrances of **2g** and **2h**. The reaction between cinnamaldehyde **1a** and *N*-benzoylhydrazone

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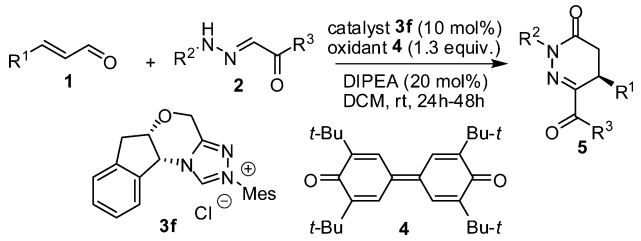
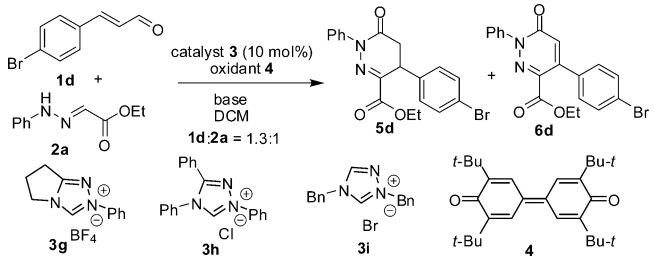
Table 2. Enantioselective Synthesis of Chiral 4,5-Dihydropyridazinone Derivatives 5



entry	1	R^1	2	R^2	R^3	time (h)	yield of 5 (%)[a]	ee (%)[b]
1	**1a**	Ph	**2a**	Ph	OEt	24	**5a**: 87	96
2	**1b**	4-$MeOC_6H_4$	**2a**	Ph	OEt	48	**5b**: 71	99
3	**1c**	4-MeC_6H_4	**2a**	Ph	OEt	24	**5c**: 72	98
4	**1d**	4-BrC_6H_4	**2a**	Ph	OEt	24	**5d**: 72	67
5	**1e**	4-AcC_6H_4	**2a**	Ph	OEt	24	**5e**: 51	64
6	**1f**	3-MeC_6H_4	**2a**	Ph	OEt	24	**5f**: 87	96
7	**1g**	2-MeC_6H_4	**2a**	Ph	OEt	24	**5g**: 67	98
8	**1h**	*n*-Pr	**2a**	Ph	OEt	48	**5h**: 49	93
9	**1i**	*i*-Pr	**2a**	Ph	OEt	48	**5i**: 47	96
10	**1a**	Ph	**2b**	4-$MeOC_6H_4$	OEt	24	**5j**: 79	93
11	**1a**	Ph	**2c**	4-MeC_6H_4	OEt	24	**5k**: 78	95
12	**1a**	Ph	**2d**	4-BrC_6H_4	OEt	24	**5l**: 69	90
13	**1a**	Ph	**2e**	4-$CF_3C_6H_4$	OEt	24	**5m**: 51	74
14	**1a**	Ph	**2f**	Ph	Me	24	**5n**: 83	94
15	**1a**	Ph	**2g**	Ph	*i*-Pr	24	**5o**: 69	97
16	**1a**	Ph	**2h**	Ph	Ph	24	**5p**: 60	95
17	**1a**	Ph	**2i**	PhCO	OEt	24	NR	

[a]Isolated yields. [b]Determined by HPLC analysis on a OD-H column (the details of HPLC separation conditions for each product **5** have been listed in the Supporting Information).

Table 3. Optimization of Reaction Conditions for Selective Synthesis of Pyridazin-3-One 6d Using Achiral NHC Catalysts



				reaction conditions			
entry	catalyst 3	base (equiv)	oxidant 4 (equiv)	*T* (h)/rt	*T* (h)/reflux	yield of 5d (%)	yield of 6d (%)
1	**3g**	DIPEA (0.2)	1.3	10	–	71	–
2	**3h**	DIPEA (0.2)	1.3	10	–	54	–
3	**3i**	DIPEA (0.2)	1.3	10	–	51	–
4	**3g**	DBU (0.2)	1.3	10	–	58	–
5	**3g**	Cs_2CO_3 (0.2)	1.3	10	–	96	–
6	**3g**	Cs_2CO_3 (0.2)	2.3	24	–	87	–
7	**3g**	Cs_2CO_3 (1.2)	2.3	24	–	74	12
8	**3g**	Cs_2CO_3 (2.5)	2.3	24	–	61	26
9	**3g**	**Cs_2CO_3 (2.5)**	**2.3**	**6**	**24**	**trace**	**83**

2i, which were the substrates of Scheidt's reaction (see eq 1 in Scheme 1), was also examined under our oxidative NHC catalysis conditions. However, no reaction of **1a** with **2i** occurred. This was probably attributable to the much weaker nucleophilicity of *N*-acylhydrazones in comparison to *N*-arylhydrazones (Table 2, entry 17). The results summarized in Table 2 indicated that the products **5d**, **5e**, and **5m** containing an electron-withdrawing group have lower enantiomeric excess values (64%−74% ee). That is probably because the electron-withdrawing substituents enhance the acidity of the proton in the stereogenic center of **5** and therefore causes the partial racemization of products **5d**, **5e**, and **5m** under the basic reaction conditions.

During the preparation of racemic 4,5-dihydropyridazin-3-ones **5** using an achiral NHC catalyst, we detected a trace amount of pyridazin-3-ones **6** in some cases. It was also observed that 4,5-dihydropyridazin-3-ones **5** could be oxidized into pyridazin-3-ones **6** upon treatment with the oxidant **4** and

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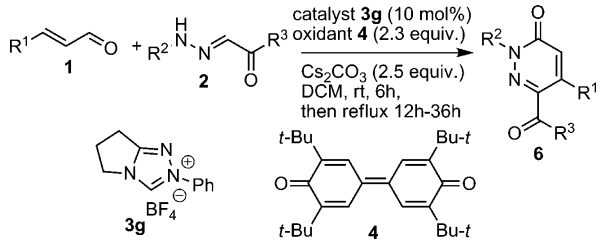
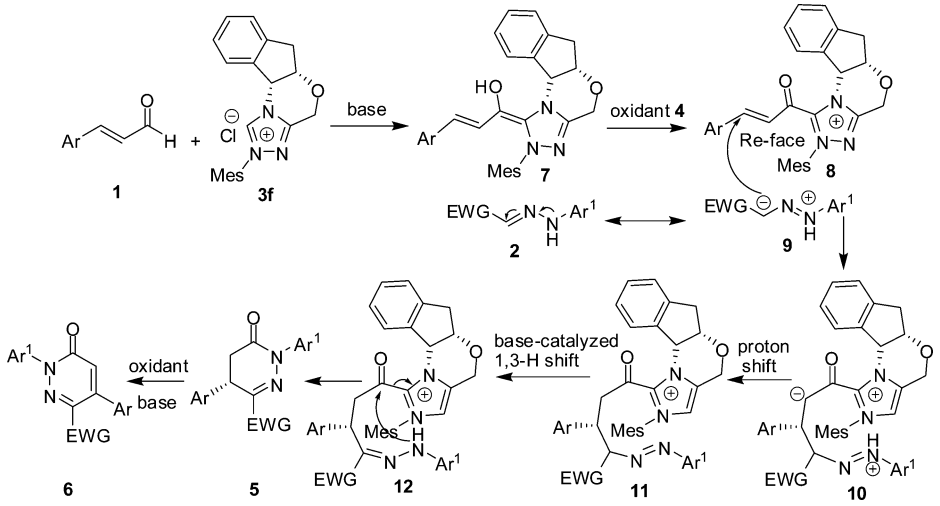
Table 4. Selective Synthesis of Pyridazin-3-ones 6



entry	1	R^1	2	R^2	R^3	reaction conditions	yield of 6 (%)[a]
1	**1a**	Ph	**2a**	Ph	OEt	6 h/rt, 15 h/reflux	**6a**: 89
2	**1b**	4-$MeOC_6H_4$	**2a**	Ph	OEt	6 h/rt, 24 h/reflux	**6b**: 71
3	**1c**	4-MeC_6H_4	**2a**	Ph	OEt	6 h/rt, 17 h/reflux	**6c**: 78
4	**1d**	4-BrC_6H_4	**2a**	Ph	OEt	6 h/rt, 24 h/reflux	**6d**: 83
5	**1e**	4-AcC_6H_4	**2a**	Ph	OEt	6 h/rt, 17 h/reflux	**6e**: 75
6	**1a**	Ph	**2b**	4-$MeOC_6H_4$	OEt	6 h/rt, 12 h/reflux	**6j**: 82
7	**1a**	Ph	**2c**	4-MeC_6H_4	OEt	6 h/rt, 36 h/reflux	**6k**: 84
8	**1a**	Ph	**2d**	4-BrC_6H_4	OEt	6 h/rt, 12 h/reflux	**6l**: 67
9	**1a**	Ph	**2e**	4-$CF_3C_6H_4$	OEt	6 h/rt, 33 h/reflux	**6m**: 74
10	**1a**	Ph	**2f**	Ph	Me	6 h/rt, 17 h/reflux	**6n**: 58
11	**1a**	Ph	**2g**	Ph	*i*-Pr	6 h/rt, 30 h/reflux	**6o**: 41
12	**1a**	Ph	**2h**	Ph	Ph	6 h/rt, 18 h/reflux	**6p**: 52

[a]A trace amount of racemic **5** was detected without isolation in some reactions.

Scheme 2. Proposed Mechanism for the Formations of 4,5-Dihydropyridazin-3-ones 5 and Pyridazin-3-ones 6 from NHC-Catalyzed Oxidative Annulation between α,β-Unsaturated Aldehydes and Hydrazones



a base. We expected that the selective synthesis of pyridazin-3-ones **6** from the NHC-catalyzed oxidative annulation between enals **1** and hydrazones **2** might be achieved by varying the catalytic conditions. Thus, we scrutinized the reaction conditions for the selective synthesis of pyridazin-3-ones **6** using the model reaction of *p*-bromocinnamaldehyde **1d** with 2-(*N*-phenylhydrazono)acetate **2a**. The achiral triazolium salts were employed as catalysts in this reaction, as pyridazin-3-ones **6** were achiral compounds. Since pyridazin-3-ones **6** were derived from 4,5-dihydropyridazin-3-ones **5**, we first optimized the reaction conditions by screening carbene catalysts and bases in order to obtain a high yield of racemic 4,5-dihydropyridazin-3-one **5d**. As indicated by the results in Table 3, in the presence of DIPEA (20 mol %) and quinone oxidant **4** (1.3 equiv) at ambient temperature, dihydropyrrolo[2,1-*c*]triazolium salt **3g** appeared as the most efficient catalyst for the formation of racemic **5d** among the examined achiral triazolium salts **3g**−**3i** (Table 3, entries 1−3). On the other hand, in the reactions catalyzed by triazolium salt **3g**, Cs_2CO_3 was most beneficial to the reaction compared to DIPEA and DBU (Table 3, entries 4−6). Having had the optimized catalysts in hand, we then increased the loading of the oxidant and base to promote the transformation of 4,5-dihydropyridazin-3-one **5d** to pyridazin-3-one **6d**. At ambient temperature, the increase of oxidant **4** to 2.3 equiv alone did not promote the reaction at all. Increasing the loadings of both oxidant and Cs_2CO_3 to 2.3 and 1.2 equiv, respectively, led to the formation of **5d** in 74% yield along with the formation of **6d** in only 12% yield. A further increase in the loading of Cs_2CO_3 to 2.5 equiv improved the yield of **6d** to 26%, with the isolation of a 61% yield of **5d** (Table 3, entry 8). Since the oxidation of **5d** to **6d** was inefficient at ambient temperature, the reaction temperature was then elevated to the boiling point of solvent to accelerate this transformation. To avoid the oxidation of cinnamaldehyde to cinnamic acid at high

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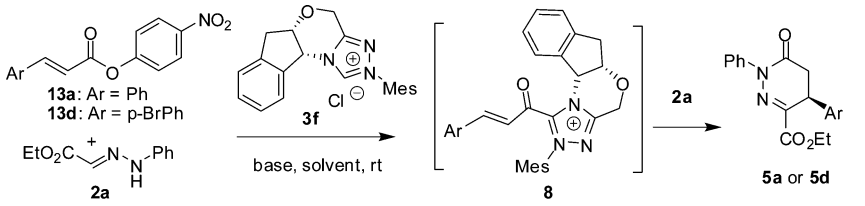
Scheme 3. Chiral NHC-Catalyzed Reaction of *p*-Nitrophenyl *α,β*-Unsaturated Esters 13 with Hydrazones 2



Reaction conditions:
(a) 10 mol% of **3f**, 20 mol% DIPEA, DCM, rt, 24 h
(b) 20 mol% of **3f**, 100 mol% DBU, THF, rt, 14 h
(c) 20 mol% of **3f**, 100 mol% DBU, THF, rt, 24 h
(d) 20 mol% of **3f**, 100 mol% DIPEA, DCM, rt, 24 h
(e) 20 mol% of **3f**, 120 mol% DIPEA, DCM, rt, 24 h

Yield (ee value):
5a: 14% (92% ee); **5d**: trace
5a: 12% (6% ee); **5d**: 4% (0% ee)
5a: 11% (0% ee); **5d**: 8% (4% ee)
5a: 14% (92% ee); **5d**: 10% (91% ee)
5a: 11% (90% ee); **5d**: 19% (89% ee)

temperature, the reaction was carried out initially in dichloromethane at ambient temperature for 6 h to form dihydropyridazinone **5d**, followed by heating the reaction mixture in refluxing solvent for 24 h to promote the oxidation of **5d** into pyridazin-3-one **6d**. Delightfully, an 83% yield of pyridazin-3-one **6d** was isolated from the reaction catalyzed by triazolium salt **3g** (10 mol %), Cs_2CO_3 (2.5 equiv), and oxidant **4** (2.3 equiv) in refluxing dichloromethane (Table 3, entry 9).

The generality for the selective synthesis of pyridazin-3-ones **6** from *α,β*-unsaturated aldehydes **1** and hydrazones **2** was then investigated by using dihydropyrrolotriazolium salt **3g** (10 mol %), Cs_2CO_3 (2.5 equiv), and oxidant **4** (2.3 equiv) as a catalytic system in dichloromethane. The reactions catalyzed by the achiral carbene **3g′** are more reactive than the reactions catalyzed by the bulky chiral carbene **3f′**. Thus, the reactions were first carried out at ambient temperature for 6 h to form dihydropyridazinone **5**, and then in refluxing dichloromethane for another period of time to finish the oxidation of **5** into pyridazin-3-ones **6**. It was found that this reaction tolerated both electron-rich and -deficient enals, as cinnamaldehyde **1a** and cinnamaldehydes **1b−1e** substituted by methyl, methoxy, bromo, and acetyl groups reacted effectively with 2-(*N*-phenylhydrazono)acetate **2a** to produce pyridazin-3-ones **6a−6e** in good yields (71%−89%) (Table 4, entries 1−5). With respect to the hydrazone substrates, the variation of the substituents of 2-(*N*-arylhydrazono)acetates **2** only marginally affected the reaction, as substrates **2b−2e** attached by either an electron-donating or -withdrawing group reacted equally well with enal **1a** to afford 67%−84% yields of products **6j−6m** (Table 4, entries 6−9). The reactions of 2-(arylhydrazono)-ketones **2f−2h** with **1a** proceeded analogously albeit the corresponding products **6n−p** were obtained in slightly lower yields (Table 4, entries 10−12).

To account for the formations of 4,5-dihydropyridazin-3-ones **5** and pyridazin-3-ones **6** from *α,β*-unsaturated aldehydes and hydrazones, a cascade reaction pathway was proposed in Scheme 2. Interaction between the NHC catalyst and cinnamaldehydes **1** forms homoenolate intermediates **7**, which are oxidized into *α,β*-unsaturated acylazolium salts **8** by oxidant **4**. The hydrazones **2** act as *C*-nucleophiles, probably via the resonance structures **9** (see the resonance structures **2** and **9** in ref 43a), to undergo Michael addition toward *α,β*-unsaturated acylazolium salts **8**, forming diazene intermediates **10**. A proton transformation of **10** yields the diazene compounds **11**. To avoid the steric hindrance of the Indane ring, the nucleophiles **9** attack preferentially to the Re-face of *α,β*-unsaturated acylazolium salts **8** to form a *S*-configured stereogenic carbon center. (In the case of 2-hexenal **1h**, this chiral center is *R*-configured.) The absolute configuration of product (*S*)-**5l**, which contains an *N*-bromophenyl group, was established by X-ray diffraction analysis (see Supporting Information). Theoretically, the hydrazones **2** could act as either a *C*- or *N*-nucleophile toward Michael acceptors. In this work, however, no regioisomer of 4,5-dihydropyridazin-3-ones **5** was detected. In fact, the regioselective Carba-Michael rather than Aza-Michael additions of different hydrazones to enals and enones catalyzed by amine catalysts have been documented in literature.[43] In the presence of a base catalyst, diazene compounds **11** probably undergo a base-catalyzed 1,3-H migration to form the amino substituted imines **12** (a similar [1,3]-hydride shift of diazenes to imine has been reported in ref 43a). The intramolecular cyclization of **12** leads to the formation of 4,5-dihydropyridazin-3-ones **5**. Finally, a base-catalyzed oxidation of 4,5-dihydropyridazin-3-ones **5** by quinone **4** affords pyridazin-3-ones **6**.

It is worth mentioning that Chi and co-workers reported in 2013 that the chiral NHC **3f′**-catalyzed annulation of *α,β*-unsaturated esters with *N*-Ts imines produced 3,4-dihydropyridin-2-ones in moderate to good yields with excellent enantioselectivity.[44] In their reaction, the key intermediates, *α,β*-unsaturated acylazolium salts **8**, were derived from the addition of chiral carbene **3f′** to 4-nitrophenyl *α,β*-unsaturated esters. We envisioned that the chiral NHC-catalyzed reaction between 4-nitrophenyl *α,β*-unsaturated esters, and hydrazones would also provide an alternative route to enantiomerically pure 4,5-dihydropyridazin-3-ones **5**. Thus, we examined the reactions of 4-nitrophenyl cinnamate **13a** and 4-nitrophenyl *p*-bromocinnamate **13d** with 2-(*N*-phenylhydrazono)acetate **2a** catalyzed by chiral NHC catalyst **3f** in the absence of oxidant **4**. Disappointingly, under our reaction conditions (10 mmol % of **3f**, 20 mmol % DIPEA, DCM, rt, 24 h) or Chi's conditions (20 mmol % of **3f**, 100 mmol % DBU, THF, rt, 14 h), all reactions gave 4,5-dihydropyridazin-3-one products in very low yields (4%−14% yields) (Scheme 3). Meanwhile, although the reaction in dichloromethane displayed excellent enantioselectivity (92% ee), the products **5a** and **5d** were racemized in the reactions conducted in THF solvent. Since most of the hydrazone **2a** was unconsumed in these reactions, we considered that the acidic 4-nitrophenol released from 4-nitrophenyl cinnamate probably inhibits the nucleophilicity of hydrazone **2a**. To neutralize the *p*-nitrophenol, we then used an excess amount of DIPEA in the reactions of **13a** and **13d** with **2a** in DCM. However, the chemical yields of products **5a** and **5d** were not significantly improved in these reactions (Scheme 3). The outcomes of these reactions clearly showed that the chiral NHC-catalyzed reaction of *p*-nitrophenyl *α,β*-unsaturated esters **13** with hydrazones **2** is not an efficient method for the synthesis of 4,5-dihydropyridazin-3-ones **5**.

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CONCLUSION

In summary, we have developed an efficient method for enantioselective synthesis of chiral 4,5-dihydropyridazin-3-one derivatives with high enantioselectivity from the chiral NHC-catalyzed oxidative annulation reaction of α,β-unsaturated aldehydes with hydrazones. Meanwhile, the selective syntheses of 4,5-dihydropyridazin-3-ones and pyridazin-3-ones have been achieved by varying catalytic and reaction conditions. This work provided not only a new strategy for the construction of enantiopure 4,5-dihydropyridazin-3-ones and pyridazin-3-one compounds but also new chemical entities of potential biological properties and valuable intermediates subject to further elaborations owing to their functional structures.

EXPERIMENTAL SECTION

General Procedure for Enantioselective Synthesis of Chiral 4,5-Dihydropyridazin-3-one Derivatives 5. Under a nitrogen atmosphere and at room temperature, α,β-unsaturated aldehydes **1** (1.3 mmol), hydrazones **2**[43a,45] (1 mmol), chiral *N*-mesityl-indeno-[2,1-*b*]triazolo[4,3-*d*][1,4]oxazinium salt **3f**[46] (37 mg, 0.1 mmol), and oxidant **4**[47] (530 mg, 1.3 mmol) were mixed in dry dichloromethane (15 mL), and then DIPEA (26 mg, 0.2 mmol) was added using a microsyringe. The reaction mixture was stirred at room temperature (20−30 °C) for 24−48 h until the enals **1** and hydrazones **2** were almost completely consumed. After removal of the solvent, the residue was chromatographed on a silica gel column eluting with a mixture of petroleum ether, ethyl acetate, and triethylamine (PE/EA/Et_3N = 10:1.5:0.1−10:3:0.1) to give products **5** in 47%−87% yields.

(S)-Ethyl 1,4-Diphenyl-4,5-dihydropyridaz-6-one-3-carboxylate ***5a***. White crystals, 280 mg, 87%, ee 96%, $[\alpha]^{20}_D$ = −52.0° (*c* = 0.5, acetone), mp 108−109 °C; IR ν (cm^{-1}) 1716, 1696; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.50 (dd, *J* = 8.8, 1.6 Hz, 2H), 7.43 (t, *J* = 7.2 Hz, 2H), 7.29−7.36 (m, 4H), 7.23−7.27 (m, 2H), 4.59 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.25−4.36 (m, 2H), 3.13 (dd, *J* = 16.8, 8.4 Hz, 1H), 2.99 (dd, *J* = 16.8, 2.0 Hz, 1H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 164.2, 163.0, 144.7, 140.3, 137.4, 129.4, 128.8, 128.0, 127.4, 126.9, 125.1, 62.2, 38.5, 35.4, 14.1; HRMS (ESI-TOF): $[M + H]^+$ calcd for $C_{19}H_{19}N_2O_3$: 323.1396; found: 323.1404.

(S)-Ethyl 4-(4-Methoxyphenyl)-1-phenyl-4,5-dihydropyridaz-6-one-3-carboxylate ***5b***. White crystals, 250 mg, 71%, ee 99%, $[\alpha]^{20}_D$ = −2.8° (*c* = 1.0, acetone), mp 98−99 °C; IR ν (cm^{-1}) 1713, 1696; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.43 (d, *J* = 8.0 Hz, 2H), 7.36 (t, *J* = 7.2 Hz, 2H), 7.25 (t, *J* = 7.6 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 2H), 6.79 (d, *J* = 8.4 Hz, 2H), 4.46 (dd, *J* = 8.4, 1.6 Hz, 1H), 4.19−4.29 (m, 2H), 3.71 (s, 3H), 3.03 (dd, *J* = 17.2, 8.4 Hz, 1H), 2.89 (dd, *J* = 16.8, 1.6 Hz, 1H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 164.4, 163.0, 159.3, 145.0, 140.3, 129.4, 128.8, 128.0, 127.4, 125.1, 114.7, 62.2, 55.3, 37.7, 35.5, 14.1; HRMS (ESI-TOF): $[M + H]^+$ calcd for $C_{20}H_{21}N_2O_4$: 353.1501; found: 353.1501.

(S)-Ethyl 4-(4-Methylphenyl)-1-phenyl-4,5-dihydropyridaz-6-one-3-carboxylate ***5c***. White crystals, 242 mg, 72%, ee 98%, $[\alpha]^{20}_D$ = −29.8° (*c* = 0.51, acetone), mp 68−70 °C; IR ν (cm^{-1}) 1708; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.49 (d, *J* = 7.7 Hz 2H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7.1 Hz, 1H), 7.14 (d, *J* = 9.8 Hz 2H), 7.12 (d, *J* = 8.2 Hz 2H), 4.55 (dd, *J* = 8.1, 1.2 Hz, 1H), 4.27−4.34 (m, 2H), 3.11 (dd, *J* = 16.8, 8.4 Hz, 1H), 2.96 (dd, *J* = 16.8, 1.6 Hz, 1H), 2.32 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 164.4, 163.0, 144.9, 140.3, 137.8, 134.3, 130.0, 128.8, 127.4, 126.7, 125.1, 62.3, 38.1, 35.5, 21.1, 14.1; HRMS (ESI-TOF): $[M + H]^+$ calcd for $C_{20}H_{21}N_2O_3$: 337.1552; found: 337.1561.

(S)-Ethyl 4-(4-Bromophenyl)-1-phenyl-4,5-dihydropyridaz-6-one-3-carboxylate ***5d***. White crystals, 288 mg, 72%, ee 67%, $[\alpha]^{20}_D$ = −9.3° (*c* = 1.0, acetone), oil; IR ν (cm^{-1}) 1732, 1697; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.47−7.50 (m, 4H), 7.44 (t, *J* = 8.4 Hz, 2H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.13 (d, *J* = 8.8 Hz, 2H), 4.56 (dd, *J* = 8.4, 1.6 Hz, 1H), 4.26−4.38 (m, 2H), 3.13 (dd, *J* = 16.8, 8.4 Hz, 1H), 2.96 (dd, *J* = 16.8, 2.0 Hz, 1H), 1.33 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 163.9, 162.9, 144.0, 140.2, 136.4, 132.5, 128.8, 128.6, 127.5, 125.0, 122.1, 62.4, 37.9, 35.1, 14.1; HRMS (ESI-TOF): $[M + H]^+$ calcd for $C_{19}H_{18}BrN_2O_3$: 401.0501; found: 401.0511.

(S)-Ethyl 4-(4-Acetylphenyl)-1-phenyl-4,5-dihydropyridaz-6-one-3-carboxylate ***5e***. White crystals, 186 mg, 51%, ee 64%, $[\alpha]^{20}_D$ = +3.8° (*c* = 0.5, acetone), mp 125−126 °C; IR ν (cm^{-1}) 1738, 1703, 1681; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.94 (d, *J* = 8.4 Hz, 2H), 7.49 (dd, *J* = 8.2, 1.6 Hz, 2H), 7.44 (t, *J* = 8.2 Hz, 2H), 7.32−7.36 (m, 3H), 4.65 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.27−3.38 (m, 2H), 3.17 (dd, *J* = 16.8, 8.4 Hz, 1H), 2.99 (dd, *J* = 16.8, 2.0 Hz, 1H), 2.59 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 197.3, 163.9, 162.9, 143.8, 142.5, 140.1, 136.8, 129.4, 128.9, 127.6, 127.2, 125.0, 62.5, 38.4, 35.1, 26.6, 14.1; HRMS (ESI-TOF): $[M + H]^+$ calcd for $C_{21}H_{21}N_2O_4$: 365.1501; found: 365.1495.

(S)-Ethyl 4-(3-Methylphenyl)-1-phenyl-4,5-dihydropyridaz-6-one-3-carboxylate ***5f***. White crystals, 294 mg, 87%, ee 96%, $[\alpha]^{20}_D$ = −70.4° (*c* = 0.51, acetone), mp 70−71 °C; IR ν (cm^{-1}) 1705; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.50 (dd, *J* = 8.2, 1.4 Hz, 2H), 7.44 (t, *J* = 8.2 Hz, 2H), 7.32 (tt, *J* = 7.3, 1.3 Hz, 1H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.10 (d, *J* = 7.6 Hz, 1H), 7.04 (s, 1H), 7.2 (d, *J* = 8.0 Hz, 1H), 4.55 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.24−4.35 (m, 2H), 3.11 (dd, *J* = 16.8, 8.4 Hz, 1H), 2.97 (dd, *J* = 17.2, 2.0 Hz, 1H), 2.32 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 164.3, 163.0, 144.8, 140.4, 139.1, 137.3, 129.2, 128.81, 128.79, 127.6, 127.4, 125.1, 123.8, 62.2, 38.4, 35.5, 21.5, 14.1; HRMS (ESI-TOF): $[M + H]^+$ calcd for $C_{20}H_{21}N_2O_3$: 337.1552; found: 337.1544.

(S)-Ethyl 4-(2-Methylphenyl)-1-phenyl-4,5-dihydropyridaz-6-one-3-carboxylate ***5g***. White crystals, 225 mg, 67%, ee 98%, $[\alpha]^{20}_D$ = −0.6° (*c* = 1.0, Acetone), mp 85−86 °C; IR ν (cm^{-1}) 1737, 1710; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.55 (td, *J* = 8.4, 1.2 Hz, 2H), 7.45 (dt, *J* = 8.0, 2.0 Hz, 2H), 7.33 (tt, *J* = 7.6, 1.2 Hz, 1H), 7.24 (d, *J* = 7.6 Hz, 1H), 7.17 (dt, *J* = 7.2, 1.2 Hz, 1H), 7.15−7.11 (dt, *J* = 7.2, 1.2 Hz, 1H), 6.96 (d, *J* = 7.6 Hz, 1H), 4.76 (dd, *J* = 8.8, 2.0 Hz, 1H), 4.22−4.29 (m, 2H), 3.12 (dd, *J* = 16.8, 8.8 Hz, 1H), 2.82 (dd, *J* = 16.9, 2.4 Hz, 1H), 2.45(s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl3) δ (ppm) 163.8, 162.9, 145.2, 140.4, 135.4, 131.6, 128.8, 128.1, 127.4, 127.0, 125.4, 125.0, 62.2, 35.6, 34.9, 19.4, 14.0; HRMS (ESI-TOF): $[M + H]^+$ calcd for $C_{20}H_{21}N_2O_3$: 337.1552; found: 337.1544.

(R)-Ethyl 1-Phenyl-4-propyl-4,5-dihydropyridaz-6-one-3-carboxylate ***5h***. Oil, 141 mg, 49%, ee 93%, $[\alpha]^{20}_D$ = −280.4° (*c* = 0.5, acetone); IR ν (cm^{-1}) 1703; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.46 (td, *J* = 8.8, 1.4 Hz, 2H), 7.40 (dt, *J* = 7.4, 2.3 Hz, 2H), 7.29 (tt, *J* = 7.2, 1.2 Hz, 1H), 4.31−4.40 (m, 2H), 3.30−3.35 (m, 1H), 2.71−2.81 (m, 2H), 1.46−1.69 (m, 5H), 1.36 (t, *J* = 7.2 Hz, 3H), 0.95 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 165.1, 163.2, 147.3, 140.4, 128.7, 127.3, 125.1, 62.1, 32.6, 32.4, 19.5, 14.2, 13.8; HRMS (ESI-TOF): $[M + H]^+$ calcd for $C_{16}H_{21}N_2O_3$: 289.1552; found: 289.1557.

(S)-Ethyl 4-Isopropyl-1-phenyl-4,5-dihydropyridaz-6-one-3-carboxylate ***5i***. Oil, 134 mg, 47%, ee 96%, $[\alpha]^{20}_D$ = −251.2° (*c* = 0.68, acetone); IR ν (cm^{-1}) 2964, 2878, 1704, 1157, 693; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.45 (td, *J* = 8.4, 2.0 Hz, 2H), 7.41 (dt, *J* = 7.6, 2.0 Hz, 2H), 7.29 (tt, *J* = 7.2, 1.6 Hz, 1H), 4.35 (q, *J* = 6.8 Hz, 2H), 3.17−3.21 (m, 1H), 2.83 (dd, *J* = 17.2, 1.6 Hz, 1H), 2.73 (dd, *J* = 17.2, 8.0 Hz, 1H), 2.04−2.14 (m, 1H), 1.37 (t, *J* = 7.2 Hz, 3H), 1.03 (d, *J* = 7.2 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 165.3, 163.6, 146.5, 140.4, 128.7, 127.2, 125.0, 62.1, 38.7, 30.2, 29.9, 20.2, 18.8, 14.4; HRMS (MALDI-TOF): $[M + H]^+$ calcd for $C_{16}H_{21}N_2O_3$: 289.1547; found: 289.1545.

(S)-Ethyl 1-(4-Methoxyphenyl)-4-phenyl-4,5-dihydropyridaz-6-one-3-carboxylate ***5j***. White crystals, 278 mg, 79%, ee 93%, $[\alpha]^{20}_D$ = −71.4° (*c* = 0.51, acetone), mp 98−99 °C; IR ν (cm^{-1}) 1707, 1690; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.38 (td, *J* = 8.8, 2.0 Hz, 2H), 7.28−7.34 (m, 3H), 7.23−7.25 (m, 2H), 6.95 (td, *J* = 9.2, 2.0 Hz, 2H), 4.58 (dd, *J* = 8.0, 2.0 Hz, 1H), 4.25−4.34 (m, 2H), 3.83 (s, 3H), 3.12 (dd, *J* = 16.8, 8.4 Hz, 1H), 2.98 (dd, *J* = 16.8, 2.0 Hz, 1H), 1.30 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 164.4, 163.0, 158.8, 144.4, 137.4, 133.4, 129.4, 128.0, 126.9, 126.6, 114.1, 62.2, 55.5, 38.4, 35.3, 14.1; HRMS (ESI-TOF): $[M + H]^+$ calcd for $C_{20}H_{21}N_2O_4$: 353.1501; found: 353.1494.

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(S)-Ethyl 1-(4-Methylphenyl)-4-phenyl-4,5-dihydropyridaz-6-one-3-carboxylate ***5k***. White crystals, 262 mg, 78%, ee 95%, $[\alpha]^{20}_{D}$ = −59.6° (*c* = 0.57, acetone), mp 119−120 °C; IR *ν* (cm^{-1}) 1715, 1696; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* (ppm) 7.32−7.37 (m, 4H), 7.28−7.30 (m, 1H), 7.22−7.25 (m, 4H), 4.57 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.26−4.32 (m, 2H), 3.12 (dd, *J* = 16.8, 8.0 Hz, 1H), 2.97 (dd, *J* = 16.8, 2.0 Hz, 1H), 2.37 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* (ppm) 164.3, 163.0, 144.5, 137.9, 137.5, 137.4, 129.42, 129.37, 128.0, 126.9, 125.0, 62.2, 38.5, 35.4, 21.1, 14.1; HRMS (ESI-TOF): $[M + H]^+$ calcd for $C_{20}H_{21}N_2O_3$:337.1547; found: 337.1551.

(S)-Ethyl 1-(4-Bromophenyl)-4-phenyl-4,5-dihydropyridaz-6-one-3-carboxylate ***5l***. White crystals, 275 mg, 69%, ee 90%, $[\alpha]^{20}_{D}$ = −53.5° (*c* = 0.54, acetone), mp 108−109 °C; IR *ν* (cm^{-1}) 1720, 1691; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* (ppm) 7.55 (td, *J* = 8.8, 2.0 Hz, 2H), 7.42 (td, *J* = 8.8, 2.0 Hz, 2H), 7.29−7.36 (m, 3H), 7.20−7.22 (m, 2H), 4.59 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.26−4.35 (m, 2H), 3.11 (dd, *J* = 16.8, 8.0 Hz, 1H), 2.98 (dd, *J* = 16.8, 2.0 Hz, 1H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* (ppm) 164.2, 162.8, 145.2, 139.3, 137.2, 131.8, 129.4, 128.1, 126.8, 126.4, 120.8, 62.3, 38.5, 35.4, 14.1; HRMS (ESI-TOF): $[M + H]^+$ calcd for $C_{19}H_{18}BrN_2O_3$: 401.0501; found: 401.0492.

(S)-Ethyl 1-(4-(Trifluoromethyl)phenyl)-4-phenyl-4,5-dihydropyridaz-6-one-3-carboxylate ***5m***. White crystals, 197 mg, 51%, ee 74%, $[\alpha]^{20}_{D}$ = −28.2° (*c* = 0.55, acetone), mp 102−103 °C; IR *ν* (cm^{-1}) 1746, 1703; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* (ppm) 7.71 (d, *J* = 9.3 Hz, 2H), 7.69 (d, *J* = 9.3 Hz, 2H), 7.30−7.36 (m, 3H), 7.20−7.22 (m, 2H), 4.62 (dd, *J* = 8.0, 2.0 Hz, 1H), 4.28−4.35 (m, 2H), 3.15 (dd, *J* = 17.2, 8.4 Hz, 1H), 3.02 (dd, *J* = 16.8, 2.0 Hz, 1H), 1.32 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* (ppm) 164.3, 162.7, 145.6, 143.0, 137.0, 129.5, 129.0 (q, J_{CF} = 32 Hz), 128.2, 126.8, 125.9 (q, J_{CF} = 4 Hz), 124.7, 123.9 (q, J_{CF} = 271 Hz), 62.5, 38.5, 35.5, 14.1; HRMS (ESI-TOF): $[M + H]^+$ calcd for $C_{20}H_{18}F_3N_2O_3$: 391.1270; found: 391.1273.

(S)-6-Acetyl-2,5-diphenyl-4,5-dihydropyridazin-3-one ***5n***. White crystals, 243 mg, 83%, ee 94%, $[\alpha]^{20}_{D}$ = −95.9° (*c* = 0.49, acetone), mp 97−98 °C; IR *ν* (cm^{-1}) 1707, 1688; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* (ppm) 7.46 (td, *J* = 8.0, 1.6 Hz, 2H), 7.46 (dt, *J* = 7.2, 2.0 Hz, 2H), 7.35 (tt, *J* = 7.2, 1.2 Hz, 1H), 7.30 (dt, *J* = 7.2, 1.2 Hz, 2H), 7.24−7.28 (m, 1H), 7.20 (td, *J* = 8.4, 1.6 Hz, 2H), 4.68 (dd, *J* = 6.4, 3.6 Hz, 1H), 3.05 (dd, *J* = 17.2, 3.2 Hz, 1H), 3.00 (d, *J* = 14.0 Hz, 1H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* (ppm) 196.0, 164.8, 150.4, 140.3, 137.5, 129.3, 128.8, 127.9, 127.4, 126.9, 124.8, 35.4, 35.0, 24.8; HRMS (ESI-TOF): $[M + H]^+$ calcd for $C_{18}H_{17}N_2O_2$: 293.1290; found: 293.1293.

(S)-6-Isobutyryl-2,5-diphenyl-4,5-dihydropyridazin-3-one ***5o***. White crystals, 220 mg, 69%, ee 97%, $[\alpha]^{20}_{D}$ = −110.7° (*c* = 0.53, acetone), mp 79−80 °C; IR *ν* (cm^{-1}) 1703, 1687; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* (ppm) 7.46 (td, *J* = 8.4, 2.0 Hz, 2H), 7.46 (dt, *J* = 7.2, 2.0 Hz, 2H), 7.23−7.36 (m, 4H), 7.18 (td, *J* = 7.2, 1.6 Hz, 2H), 4.69 (dd, *J* = 6.4, 3.2 Hz, 1H), 3.69−3.79 (m, 1H), 3.06 (dd, *J* = 17.0, 3.9 Hz, 1H), 3.01 (d, *J* = 13.9 Hz, 1H), 1.06 (d, *J* = 6.8 Hz, 3H), 1.04 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* (ppm) 202.0, 164.8, 149.2, 140.5, 137.6, 129.3, 128.8, 127.8, 127.3, 126.8, 124.7, 35.7, 35.0, 33.9, 18.8, 18.6; HRMS (ESI-TOF): $[M + H]^+$ calcd for $C_{20}H_{21}N_2O_2$: 321.1603; found: 321.1597.

(S)-6-Benzoyl-2,5-diphenyl-4,5-dihydropyridazin-3-one ***5p***. White crystals, 213 mg, 60%, ee 95%, $[\alpha]^{20}_{D}$ = −113.7° (*c* = 0.51, acetone), mp 69−70 °C; IR *ν* (cm^{-1}) 1698, 1645; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* (ppm) 8.00 (d, *J* = 7.2 Hz, 2H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.51 (d, *J* = 7.6 Hz, 2H), 7.42 (t, *J* = 7.2 Hz, 4H), 7.28−7.35 (m, 5H), 4.90 (dd, *J* = 7.6, 2.0 Hz, 1H), 3.18 (dd, *J* = 17.2, 8.0 Hz, 1H), 3.10 (dd, *J* = 17.2, 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* (ppm) 189.7, 164.5, 150.7, 140.4, 137.5, 135.9, 133.0, 130.7, 129.4, 128.8, 128.1, 128.0, 127.2, 126.8, 124.6, 37.0, 35.2; HRMS (ESI-TOF): $[M + H]^+$ calcd for $C_{23}H_{19}N_2O_2$: 355.1447; found: 355.1446.

General Procedure for Selective Synthesis of Pyridazin-3-One Derivatives 6. Under a nitrogen atmosphere and at room temperature, *α,β*-unsaturated aldehydes **1** (0.65 mmol), hydrazones **2** (0.5 mmol), dihydropyrrolo[2,1-*c*]triazolium salt **3g** (14 mg, 0.05 mmol), and oxidant **4** (469 mg, 1.15 mmol) were mixed in dry dichloromethane (15 mL), and then Cs_2CO_3 (407 mg, 1.25 mmol) was added. The reaction mixture was stirred at room temperature (20−30 °C) for 6 h and then refluxed with stirring for another 12−36 h until dihydropyridazin-3-one intermediates **5** were almost completely converted into pyridazin-3-ones **6**. After removal of the solvent, the residue was chromatographed on a silica gel column eluting with a mixture of petroleum ether, ethyl acetate, and dichloromethane (PE/EA/DCM = 10:1.5:1−10:3:2) to give products **6** in 41%−89% yields.

Ethyl 1,4-Diphenylpyridaz-6-one-3-carboxylate ***6a***. White crystals, 143 mg, 89%, mp 118−119 °C; IR *ν* (cm^{-1}) 1739, 1669; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* (ppm) 7.68 (d, *J* = 7.6 Hz, 2H), 7.52 (d, *J* = 7.6 Hz, 2H), 7.45−7.49 (m, 3H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.36−7.38 (m, 2H), 7.02 (s, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 1.09 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* (ppm) 163.3, 159.3, 144.8, 140.8, 139.3, 134.8, 129.6, 129.5, 128.9, 128.8, 128.7, 127.4, 125.4, 62.2, 13.7; HRMS (MALDI-TOF): $[M + H]^+$ calcd for $C_{19}H_{17}N_2O_3$: 321.1234; found: 321.1233.

Ethyl 4-(4-Methoxyphenyl)-1-phenylpyridaz-6-one-3-carboxylate ***6b***. White crystals, 124 mg, 71%, mp 146−147 °C; IR *ν* (cm^{-1}) 1726, 1672; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* (ppm) 7.66 (d, *J* = 8.0 Hz, 2H), 7.50 (t, *J* = 7.2 Hz, 2H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.31 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 6.99 (s, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 3.87 (s, 3H), 1.16 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* (ppm) 163.7, 160.9, 159.5, 144.3, 140.8, 139.5, 128.9, 128.7, 128.6, 126.8, 125.4, 114.3, 62.3, 55.4, 13.8; HRMS (MALDI-TOF): $[M + H]^+$ calcd for $C_{20}H_{19}N_2O_4$: 351.1339; found: 351.1342.

Ethyl 4-(4-Methylphenyl)-1-phenylpyridaz-6-one-3-carboxylate ***6c***. White crystals, 130 mg, 78%, mp 121−122 °C; IR *ν* (cm^{-1}) 1737, 1671; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* (ppm) 7.66 (d, *J* = 8.8 Hz, 2H), 7.49 (t, *J* = 7.2 Hz, 2H), 7.41 (t, *J* = 7.2 Hz, 1H), 7.26 (s, 4H), 6.99 (s, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 2.41 (s, 3H), 1.13 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* (ppm) 163.5, 159.4, 144.7, 140.8, 139.8, 139.4, 131.8, 129.5, 129.1, 128.8, 128.6, 127.3, 125.4, 62.2, 21.3, 13.7; HRMS (MALDI-TOF): $[M + H]^+$ calcd for $C_{20}H_{19}N_2O_3$:335.1390; found: 335.1391.

Ethyl 4-(4-Bromophenyl)-1-phenylpyridaz-6-one-3-carboxylate ***6d***. White crystals, 165 mg, 83%, mp 140−141 °C; IR *ν* (cm^{-1}) 1731, 1678; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* (ppm) 7.59 (d, *J* = 8.0 Hz, 2H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.44 (t, *J* = 8.0 Hz, 2H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 2H), 6.91 (s, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 1.09 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* (ppm) 163.0, 159.1, 143.8, 140.7, 138.5, 133.8, 132.0, 129.6, 129.0, 128.9, 128.8, 125.3, 124.1, 62.4, 13.8; HRMS (MALDI-TOF): $[M + H]^+$ calcd for $C_{19}H_{16}BrN_2O_3$: 399.0339; found: 399.0340.

Ethyl 4-(4-Acetylphenyl)-1-phenylpyridaz-6-one-3-carboxylate ***6e***. White crystals, 135 mg, 75%, mp 189−190 °C; IR *ν* (cm^{-1}) 1736, 1680; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* (ppm) 8.06 (d, *J* = 8.0 Hz, 2H), 7.68 (d, *J* = 8.0 Hz, 2H), 7.52 (t, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.44 (t, *J* = 7.2 Hz, 1H), 7.02 (s, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 2.66 (s, 3H), 1.14 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* (ppm) 197.1, 162.9, 159.0, 144.0, 140.6, 139.4, 138.2, 137.6, 129.9, 128.93, 128.85, 128.6, 127.7, 125.3, 62.4, 26.7, 13.8; HRMS (MALDI-TOF): $[M + H]^+$ calcd for $C_{21}H_{19}N_2O_4$: 363.1339; found: 363.1340.

Ethyl 1-(4-Methoxyphenyl)-4-phenylpyridaz-6-one-3-carboxylate ***6j***. White crystals, 143 mg, 82%, mp 121−122 °C; IR *ν* (cm^{-1}) 1721, 1674; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* (ppm) 7.59 (td, *J* = 9.0, 2.0 Hz, 2H), 7.46−7.47 (m, 3H), 7.35−7.37 (m, 2H), 6.99−7.01 (m, 3H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.85 (s, 3H), 1.08 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* (ppm) 162.4, 158.6, 158.5, 143.7, 138.0, 133.9, 132.8, 128.5, 128.3, 127.7, 126.3, 125.6, 113.1, 61.2, 54.6, 12.6; HRMS (MALDI-TOF): $[M + H]^+$ calcd for $C_{20}H_{19}N_2O_4$: 351.1339; found: 351.1340.

Ethyl 1-(4-Methylphenyl)-4-phenylpyridaz-6-one-3-carboxylate ***6k***. White crystals, 140 mg, 84%, mp 108−109 °C; IR *ν* (cm^{-1}) 1736, 1672; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* (ppm) 7.54 (d, *J* = 8.4 Hz, 2H), 7.45−7.48 (m, 3H), 7.35−7.38 (m, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 7.01 (s, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 2.41 (s, 3H), 1.08 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* (ppm) 163.4, 159.4,

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144.7, 139.1, 138.8, 138.3, 134.9, 129.54, 129.49, 129.3, 128.8, 127.4, 125.2, 62.2, 21.2, 13.7; HRMS (ESI-TOF): $[M + H]^+$ calcd for $C_{20}H_{19}N_2O_3$: 335.1396; found: 335.1395.

Ethyl 1-(4-Bromophenyl)-4-phenylpyridaz-6-one-3-carboxylate ***6l***. White crystals, 133 mg, 67%, mp 112−113 °C; IR ν (cm^{-1}) 1729, 1678; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.63 (d, J = 9.2 Hz, 2H), 7.60 (d, J = 9.0 Hz, 2H), 7.45−7.48 (m, 3H), 7.35−7.37 (m, 2H), 7.00 (s, 1H), 4.19 (q, J = 7.1 Hz, 2H), 1.09 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 163.2, 159.1, 144.9, 139.7, 139.6, 134.6, 132.0, 129.7, 129.5, 128.8, 127.3, 126.9, 122.5, 62.3, 13.6; HRMS (MALDI-TOF): $[M + H]^+$ calcd for $C_{19}H_{16}BrN_2O_3$: 399.0339; found: 399.0338.

Ethyl 1-(4-(Trifluoromethyl)phenyl)-4-phenylpyridaz-6-one-3-carboxylate ***6m***. White crystals, 143 mg, 74%, mp 144−145 °C; IR ν (cm^{-1}) 1744, 1668; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.88 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 8.5 Hz, 2H), 7.47−7.49 (m, 3H), 7.36−7.39 (m, 2H), 7.03 (s, 1H), 4.20 (q, J = 7.2 Hz, 2H), 1.10 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 163.1, 159.1, 145.1, 143.4, 139.9, 134.5, 130.5 (q, J_{CF} = 33 Hz), 129.8, 129.6, 128.9, 127.3, 126.1 (q, J_{CF} = 3 Hz), 125.7, 123.7 (q, J_{CF} = 270 Hz), 62.4, 13.7; HRMS (MALDI-TOF): $[M + Na]^+$ calcd for $C_{20}H_{15}F_3N_2O_3Na$: 411.0927; found: 411.0929.

6-Acetyl-2,5-diphenyl°pyridazin-3-one ***6n***. White crystals, 84 mg, 58%, mp 162−163 °C; IR ν (cm^{-1}) 1705, 1670; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.72 (d, J = 8.8 Hz, 2H), 7.54 (t, J = 8.0 Hz, 2H), 7.43−7.48 (m, 4H), 7.26−7.29 (m, 2H), 6.94 (s, 1H), 2.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 195.4, 159.4, 145.3, 142.5, 140.9, 135.3, 130.3, 129.1, 128.9, 128.7, 128.4, 127.6, 125.1, 27.3; HRMS (MALDI-TOF): $[M + H]^+$ calcd for $C_{18}H_{15}N_2O_2$: 291.1128; found: 291.1129.

6-Isobutyryl-2,5-diphenylpyridazin-3-one ***6o***. White crystals, 65 mg, 41%, mp 139−140 °C; IR ν (cm^{-1}) 1705, 1678; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.71 (td, J = 7.2, 1.4 Hz, 2H), 7.53 (dt, J = 7.2, 1.8 Hz, 2H), 7.42−7.47 (m, 4H), 7.25−7.27 (m, 2H), 6.95 (s, 1H), 3.73−3.62 (m, 1H), 1.17 (d, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 201.5, 159.4, 145.7, 142.4, 140.9, 135.3, 130.3, 129.2, 128.9, 128.7, 128.5, 127.3, 125.2, 36.3, 18.2; HRMS (MALDI-TOF): $[M + H]^+$ calcd for $C_{20}H_{19}N_2O_2$: 319.1441; found: 319.1439.

6-Benzoyl-2,5-diphenylpyridazin-3-one ***6p***. White crystals, 92 mg, 52%, mp 180−181 °C [lit.:[48] mp 180−181 °C].

■ ASSOCIATED CONTENT

Supporting Information

General procedure for the synthesis of racemic 4,5-dihydropyridazin-3-ones **5**, the copies of HPLC chromatographs for products **5**, ^1H NMR and ^{13}C NMR spectra of enantiopure 4,5-dihydropyridazin-3-ones **5** and pyridazin-3-one products **6** excluding the known compound **6p**, single crystal data of enantiopure **5l** (CIF). The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00784.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ycheng2@bnu.edu.cn.

Notes

The authors declare no competing financial interest.

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