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Lewis acid Catalyzed Annulation of Cyclopropane Carbaldehydes and Aryl Hydrazines: Construction of Tetrahydropyridazines and Application Towards One-pot Synthesis of Hexahydropyrrolo[1,2-*b*]pyridazines

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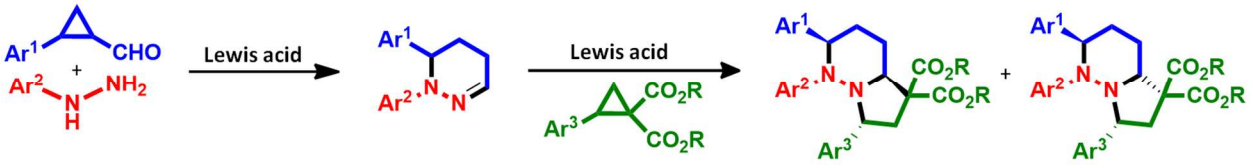
Abstract



In this report, a facile synthesis of tetrahydropyridazines via Lewis acid catalyzed annulation reaction of cyclopropane carbaldehydes and aryl hydrazines has been demonstrated. Moreover, the generated tetrahydropyridazine further participated in cycloaddition reaction with donor-acceptor cyclopropanes to furnish hexahydropyrrolo[1,2-*b*]pyridazines. We also performed these two steps in one pot in a consecutive manner. In addition, a monodecarboxylation reaction of hexahydropyrrolo[1,2-*b*]pyridazine was achieved with a good yield.

Introduction.

Nitrogen-containing heterocycles are coveted structural frameworks, present in numerous molecules of biological importance.[1] In this regard, tetrahydropyridazines and hydropyrrolo[1,2-*b*]pyridazines are of particular interest. Bemoradan acts as a

cardiotonic agent and RWJ25333 shows affinity towards PR binding of human bone cell, are the representative examples of the molecule carrying tetrahydropyridazine as a core cyclic structural motif (Figure 1).[2] Tetrahydropyrrolo[1,2-*b*]pyridazine, having antimicrobial activity is the example of molecule which poses hydropyrrolo[1,2-*b*]pyridazine moiety.[3]

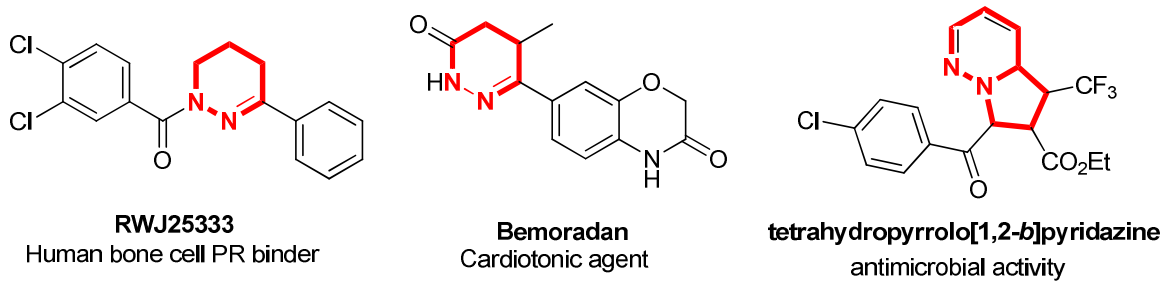


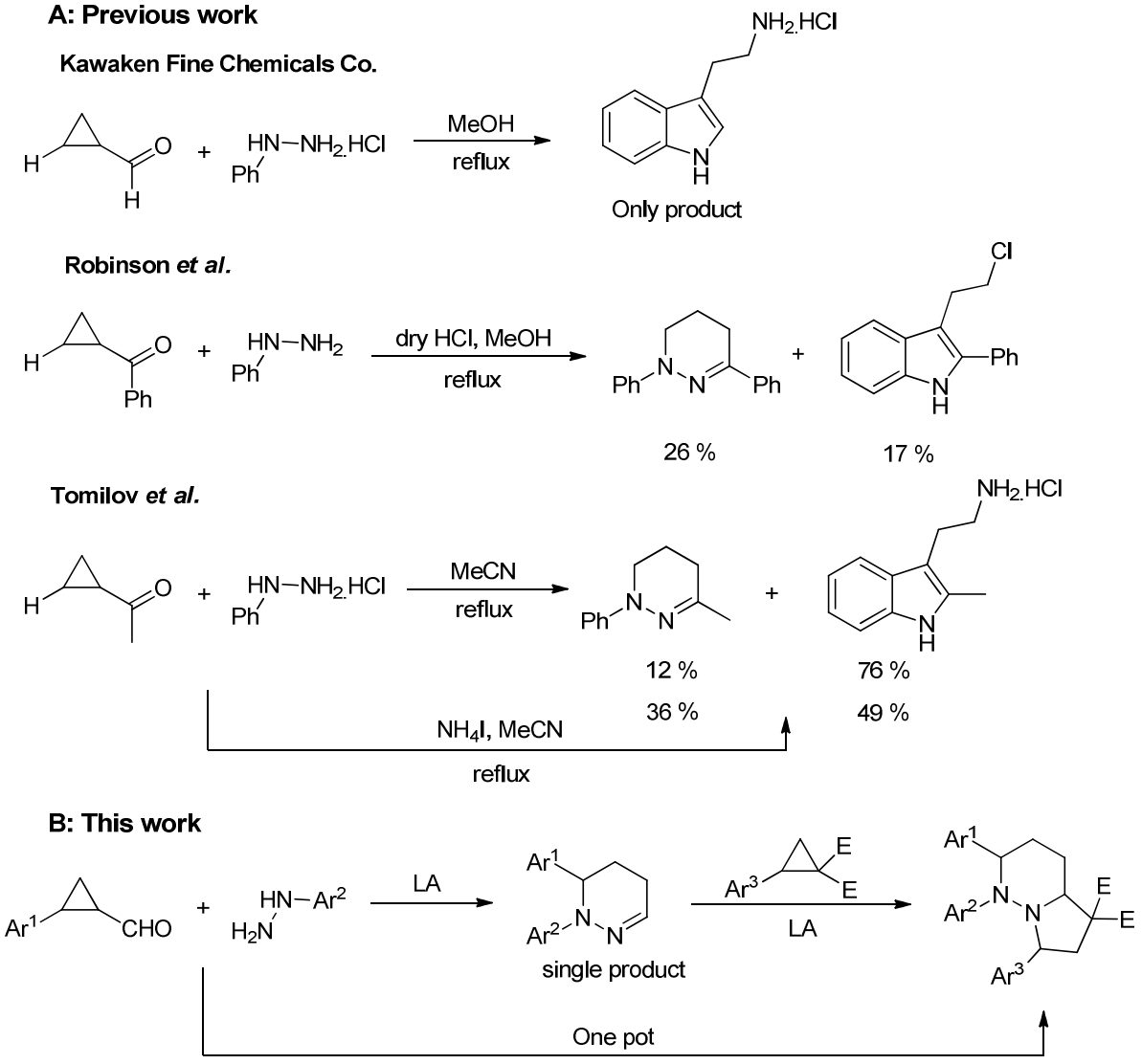
Figure 1. Tetrahydropyridazine and hydropyrrolo[1,2-*b*]pyridazine present in bio-active molecules.

Consequently, the development of an efficient route to synthesize these structural motifs using readily accessible starting materials is of greater interest.

In this regard, due to convenient preparation, easy handling, and inevitable reactivity, cyclopropanes have extensively been used as versatile building blocks in organic syntheses for construction of diverse carbocycles, heterocycles, and functionalized open-chain compounds.[4] Among various cyclopropane derivatives, Lewis acid catalyzed reactions of donor-acceptor cyclopropanes (DAC) have been studied widely.[5] Whereas, cyclopropane carbaldehydes have been used for organocatalyzed ring opening reactions.[6] But the Lewis acid catalyzed reaction of cyclopropane carbaldehydes are scared. The annulation of cyclopropane carbaldehyde and phenyl

hydrazine hydrochloride was studied firstly by Kawaken Fine Chemicals Co. in 1984 (Scheme 1 A)[7] and tryptamines were formed as the sole product.

Scheme 1. Reactivity of cyclopropyl ketone/cyclopropane carbaldehyde with phenyl hydrazine

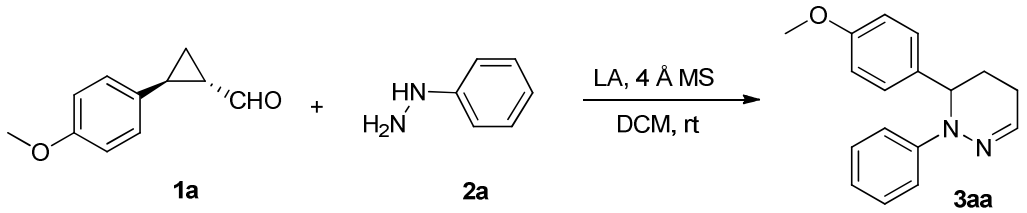


In 1987, Robinson *et al*. documented that, in the presence of dry HCl in refluxing methanol, cyclopropyl ketone and phenyl hydrazine react to afford a mixture of 1,3-diphenyl-1,4,5,6-tetrahydropyridazine (26% yield) and 2-phenyl-3-(2-chloroethyl) indole

(17% yield).[8] Following these reports, Tomilov *et al*. demonstrated two complementary reaction conditions, in refluxing acetonitrile, cyclopropyl ketone and phenyl hydrazine hydrochloride react to produce tryptamines as the major product along with the formation of trace amount tetrahydropyridazine.[9] Whereas, in the presence of NH_4I at reflux in acetonitrile, cyclopropyl ketone and phenyl hydrazine hydrochloride react to furnish a mixture of tetrahydropyridazine and tryptamine.[10] In the second case, product ratio varies from substrate to substrate, in some cases, tetrahydropyridazine became the major product and in some instances tryptamines produced as the primary product. In all of these reports, reaction proceeds through ring opening of cyclopropyl hydrazone by halide ion, following the ring closing and Fischer rearrangement of the ring-opened intermediate, tetrahydropyridazine and tryptamines were formed respectively. To the best of our knowledge, there is no report about the formation of tetrahydropyridazine as the exclusive product. Keeping these reactivities in mind, we anticipated that through imine activation by Lewis acid, cyclopropyl hydrazone would undergo selectively ring opening by *α-N*itrogen to deliver tetrahydropyridazine as the sole product rather than ring opening by halide ion and Fischer rearrangement towards the formation of a mixture of tetrahydropyridazine and tryptamine.

Herein, we report a Lewis acid catalyzed annulation of cyclopropane carbaldehydes and aryl hydrazines to furnish tetrahydropyridazines as the exclusive product along with a broad substrate scope. The produced tetrahydropyridazines undergo Lewis acid catalyzed [3+2]-cycloaddition reaction with DACs to delivered hexahydropyrrolo[1,2-*b*]pyridazines, a biologically important structural frameworks (Scheme 1 B).

Result and Discussion: At the outset of our investigation, *p*-methoxy-substituted phenyl ring containing cyclopropane carbaldehyde (**1a**) and phenyl hydrazine (**2a**) were taken as model substrates to identify the optimal conditions for this annulation reaction (Table 1). **Table 1.** Lewis acid catalyzed annulation of cyclopropane carbaldehyde and aryl hydrazine: optimization of reaction conditions[a]



1a **2a** **3aa**

entry	Lewis acid	LA [mol%]	yield [%][b]	time (h)
1	-	-	n.p.[c]	48
2	MgI_2	20	59	10
3	$Bi(OTf)_3$	20	47	06
4	$Yb(OTf)_3$	20	69	4.5
5	$BF_3.OEt_2$	20	74	05
6	$TiCl_4$	20	73	05
7	$Cu(OTf)_2$	20	56	08
8	$Sc(OTf)_3$	20	55	08
9	$Sn(OTf)_2$	20	63	07
10	$InCl_3$	20	74	05

[a]Reactions were carried out with 1 equiv of **1a** and 1 equiv of **2a** in the presence molecular sieves (4 Å) in dichloromethane solvent. [b]Isolated yield. [c]n.p. = no product formation.

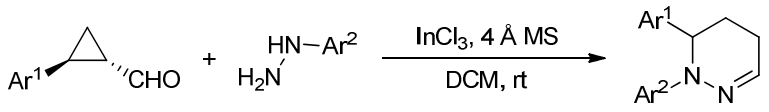
Consistent knowledge gained from the success of our previous study on the reactivity of cyclopropanes and other strained rings,[11] drive us to start this optimization survey in

dichloromethane solvent. Extensive screening of commercially available Lewis acids (Table 1) elucidated that most of them could able to catalyze this annulation reaction. To our satisfaction, 20 mol% $InCl_3$ or $BF_3.OEt_2$ as a catalyst furnished the desired product in 74% yield. Among them, for easy handling, $InCl_3$ was picked as the catalyst of choice. It is important to note that absence of a Lewis acid inhibited the formation of the desired product.

With the optimized conditions in hand, we probed the scope and limitation of this annulation reaction with various cyclopropane carbaldehydes and aryl hydrazines, and the obtained results are summarized in Table 2. Cyclopropane carbaldehyde bearing 4-methoxyphenyl, phenyl and 4-fluorophenyl ring in it's vicinal position (**1a, 1c,** and **1d**) provided the good yield. Whereas cyclopropane carbaldehyde carrying 3,4-dimethoxy-substituted phenyl ring (**1b**) leads to lowering the yield as well as the reaction time, perhaps this is due to the high electron donating capability of two methoxy substituents which making the cyclopropane carbaldehyde more active, thus susceptible to decomposition. A naphthyl-substituted and a heterocycle incorporated cyclopropane carbaldehyde (**1e**, **1f**) were also efficiently transformed into the expected product. To explore the scope of aryl hydrazines in the mentioned annulation reaction, we employed a series of aryl hydrazines bearing differently substituted phenyl ring. To our delight, hydrazine derivative bearing electron donating-substituted phenyl ring like tolyl and 4-isopropyl phenyl hydrazine (**2f**, **2g**) gave higher yield. Whereas, 4-methoxy phenyl hydrazine (**2h**) furnished the desired product with a poor yield. This may be due to the high electron donating capability of methoxy substituent; activated phenyl ring undergoes in diverse reaction towards formation of some undesired product. Hydrazine

derivative bearing electron withdrawing substituted phenyl ring like 4-chloro, 4-bromo and 4-cyano phenylhydrazine (**2c**, **2d**, **2e**) render the corresponding annulated product with reduced yield along with a longer reaction time. The reason may be the electron withdrawing ability of those substituent (choro, bromo, and cyano) making corresponding aryl hydrazine less reactive. A benzyl containing hydrazine derivative (**2i**) was also efficiently converted into

Table 2. Lewis acid catalyzed annulation of cyclopropane carbaldehyde and aryl hydrazine: substrate scope[a]



1 **2** **3**

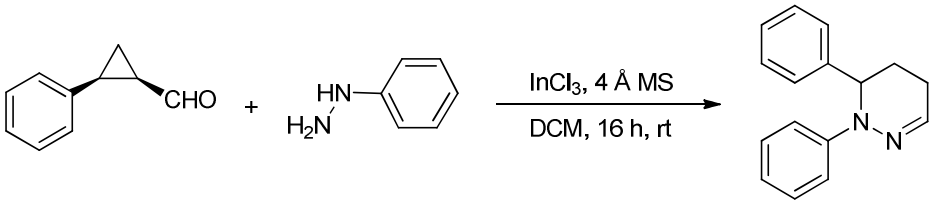
entry	**1**	**2**	Ar^1	Ar^2	time (h)	yield [%] [b]
3aa	**1a**	**2a**	4-methoxy phenyl	phenyl	05	74
3ba	**1b**	**2a**	3,4-dimethoxy phenyl	phenyl	04	57
3ca	**1c**	**2a**	phenyl	phenyl	05	75
3da	**1d**	**2a**	4-fluoro phenyl	phenyl	05	71
3ea	**1e**	**2a**	1-napthyl	phenyl	05	57
3fa	**1f**	**2a**	2-furyl	phenyl	4.5	68
3ab	**1a**	**2b**	4-methoxy phenyl	4-fluoro phenyl	05	70
3ac	**1a**	**2c**	4-methoxy phenyl	4-chloro phenyl	06	64
3ad	**1a**	**2d**	4-methoxy phenyl	4-bromo phenyl	06	62
3ae	**1a**	**2e**	4-methoxy phenyl	4-cyano phenyl	08	56
3af	**1a**	**2f**	4-methoxy phenyl	tolyl	4.5	75
3ag	**1a**	**2g**	4-methoxy phenyl	4-isopropyl phenyl	4.5	75

3ah	**1a**	**2h**	4-methoxy phenyl	4-methoxy phenyl	11	42
3ai	**1a**	**2i**	4-methoxy phenyl	benzyl	06	67

[a]Unless otherwise specified, all reactions were carried out in DCM at rt with 1 equiv of **1** and 1 equiv of **2** in presence of $InCl_3$ (20 mol %) and 4 Å molecular sieves (200 weight %). Isolated yields are reported.

the desired product. In order to emphasize the generous applicability of the protocol, we synthesize annulated product **3aa** in gram-scale (starting with 1.50 g of **1a**, **3aa** was obtained in 68% yield) under the same optimize conditions. To elucidate whether both isomers (*cis* and *trans*) of cyclopropane carbaldehyde can be utilized as the efficient substrates, we did the control experiment with *cis* 2-phenylcyclopropanecarbaldehyde (**1c')** (scheme 2), which in turn gave the desired product **3ca** in a lower yield and with longer reaction time than that of in *trans* 2-phenylcyclopropanecarbaldehyde (**1c**) (Table 2, entry **3ca**). Therefore, from this control experiment we conclude that in the mentioned annulation reaction *trans* isomer of cyclopropane carbaldehyde is more efficient substrate than the *cis* one.

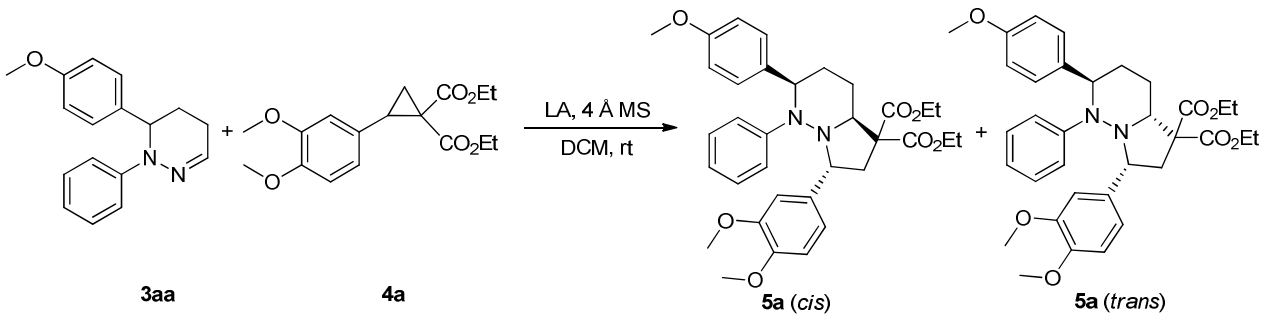
Scheme 2. Control experiment with *cis* cyclopropane carbaldehyde



1c' **2a** **3ca** (42%)

We next utilized the annulated product tetrahydropyridazine **3aa** in [3+2]-cycloaddition reaction with DAC. Initially, to optimize the reaction conditions, we employed tetrahydropyridazine **3aa** and DAC **4a** as model substrate (Table 3). In the beginning, 10 mol% $Yb(OTf)_3$ was used as a catalyst, and the expected product was formed in 50% yield with 52:48 diastereomeric ratio (Table 3). Consequently, this result prompted us to raise the loading of $Yb(OTf)_3$ up to 20 mol%, which delivered the desired product

with the best yield. Further increment of catalyst facilitated the dimerization and decomposition of DAC, thus leads to decrease the yield of the desired cycloadduct. However, a superficial increment of diastereomeric ratio was observed with MgI_2 and $InCl_3$, but in both cases the yield was not satisfactory. Weak Lewis acid like $Cu(OTf)_2$ could not catalyze the reaction, whereas strong Lewis acid like $Bi(OTf)_3$, $BF_3.OEt_2$ and $TiCl_4$ provided an unidentified **Table 3**. Lewis acid catalyzed [3+2]-cycloadditions of tetrahydropyridazine and DAC: optimization of reaction conditions[a]



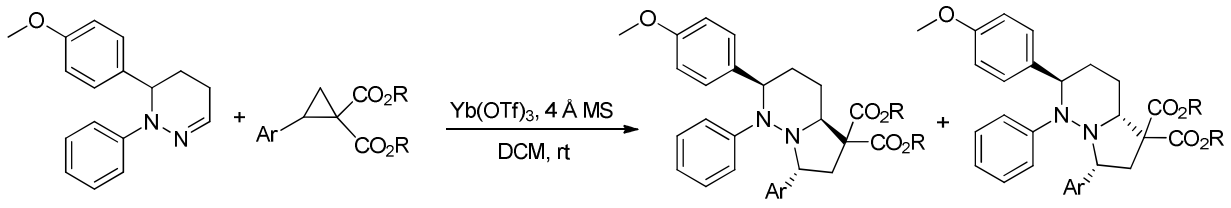
entry	Lewis acid	LA [mol%]	solvent	yield (%)[b]	time (h)	dr[e] (cis:trans)
1	-	-	DCM	n.r.[c]	48	-
2	MgI_2	20	DCM	30	06	60:40
3	$BF_3.OEt_2$	20	DCM	c.m.[d]	04	-
4	$TiCl_4$	20	DCM	c.m.[d]	04	-
5	$Cu(OTf)_2$	20	DCM	n.r.[c]	08	-
6	$Bi(OTf)_3$	20	DCM	c.m.[d]	06	-
7	$InCl_3$	20	DCM	40	07	60:40
8	$Yb(OTf)_3$	10	DCM	50	08	52:48
9	$Yb(OTf)_3$	20	DCM	65	05	52:48
10	$Yb(OTf)_3$	40	DCM	56	04	52:48

[a]Reactions were carried out with 1 equiv of **3aa** and 1 equiv of **4a** in presence of molecular sieves (4 Å). [b]Isolated yields. [c]n.r. = no reaction. [d]c.m. = complex mixture. DCM = dichloromethane. [e]dr = diastereomeric ratio was determined by ^{1}H NMR analysis of the reaction mixture.

complex mixture. It is crucial to note that no reaction was taking place in the absence of Lewis acid. The geometry of both diastereomers (*cis* and *trans*) was determined by NOE experiment, and the geometry of the major diastereomer was further supported by single crystal X-ray structure (Figure 2).[13]

Having developed the optimized reaction conditions, we then evaluated the substrate scope and limitation with various DACs, and the outcomes are depicted in Table 4. DAC (**4a**) bearing 3,4-dimethoxy-substituted phenyl ring in it's vicinal position delivered the

Table 4. Lewis acid catalyzed [3+2]-cycloaddition of tetrahydropyridazine and DAC: substrate scope[a]



3 **4** **5** (*cis*) **5** (*trans*)

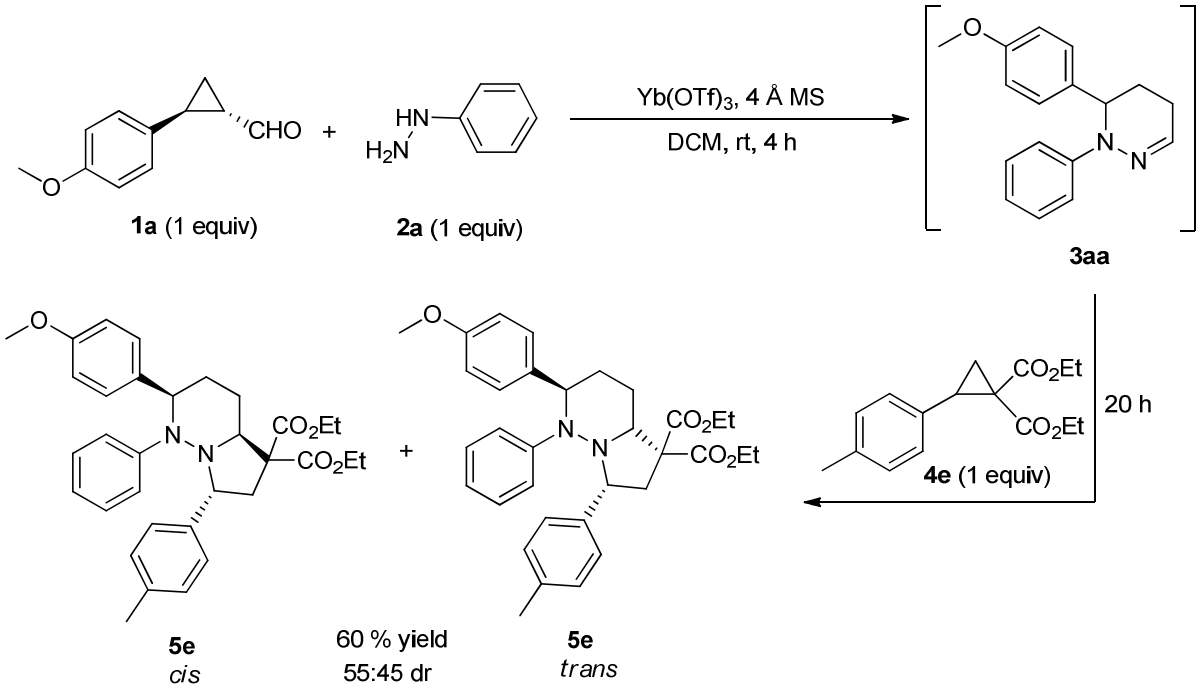
entry	3	4	Ar	CO_2R	time (h)	yield [%] [b]	dr[c] (*cis*:*trans*)
5a	**3aa**	**4a**	3,4-dimethoxy phenyl	CO_2Et	05	65	52:48
5b	**3aa**	**4b**	3,4-dimethoxy phenyl	CO_2Me	05	63	-
5c	**3aa**	**4c**	3,4-dimethoxy phenyl	CO_2Bn	05	64	60:40
5d	**3aa**	**4d**	4-methoxy phenyl	CO_2Et	05	65	65:35
5e	**3aa**	**4e**	tolyl	CO_2Et	08	73	55:45
5f	**3aa**	**4f**	2- tolyl	CO_2Et	08	68	57:43
5g	**3aa**	**4g**	phenyl	CO_2Et	10	69	53:47

5h	**3aa**	**4h**	4-fluoro phenyl	CO_2Et	12	65	50:50
5i	**3aa**	**4i**	2-furyl	CO_2Et	4.5	62	67:33
5j	**3aa**	**4j**	2-thiophenyl	CO_2Et	4.5	63	70:30

[a]Unless otherwise specified, all reactions were carried out in DCM at rt with 1 equiv of **3** and 1 equiv of **4** in presence of $Yb(OTf)_3$ (20 mol %) and 4 Å molecular sieves (200 weight %). [b]Isolated yields are reported. [c]dr (*cis:trans*) was determined by ^1H NMR analysis of reaction mixture.

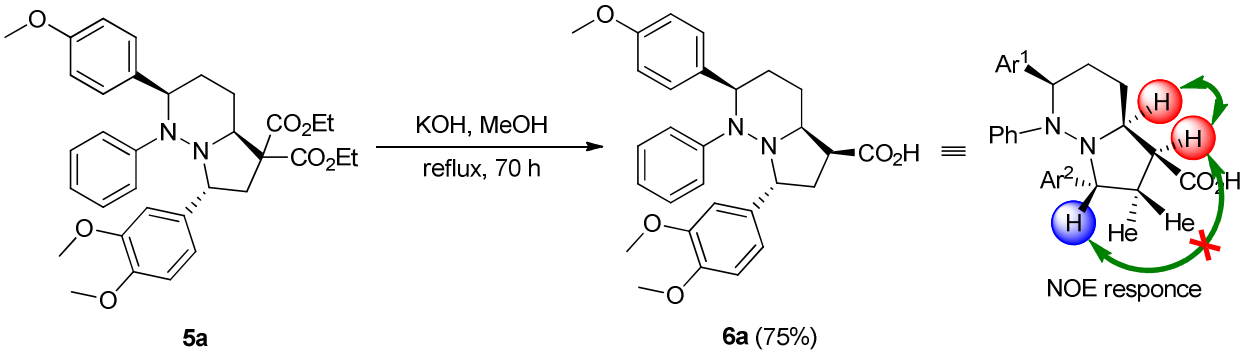
the cycloadduct **5a** in a moderate yield along with a poor diastereomeric ratio. However, a substantial improvement of diastereomeric ratio was observed in the case of the DAC bearing 4-methoxyphenyl ring (**4d**). The DAC bearing tolyl ring (**4e**) gave the highest yield. Relatively less activated DAC, like phenyl and 4-fluoro phenyl-containing DAC (**4g**, **4h**) delivered the cycloadduct with longer reaction time. *o*-Tolyl-containing DAC (**4f**) was employed to examine the effect of *ortho*-substituted phenyl ring on the cycloaddition reaction, convenient conversion into the corresponding cycloadduct (**5f**) indicating the broad substrate tolerance of this methodology. To check the effect of the size of the ester functionality in the mentioned transformation, we exposed a series of DAC bearing different ester group (**4a**, **4b**, **4c**), but no such profound consequence was noticed.

Scheme 3. One pot synthesis of hexahydropyrrolo[1,2-*b*]pyridazine



Having a series of cycloadduct in hand, we conducted these two reactions in one pot via *in situ* formation of tetrahydropyridazine (**3aa**) and it's cycloaddition with DAC (**4e**). Notably, the desired cycloadduct (**5e**) was obtained in moderate yield (Scheme 3). Moreover, to exhibit the potentiality of the developed methodology, we carried out a

Scheme 4. Monodecarboxylation of **5a**



monodecarboxylation reaction of **5a** (Scheme 4). Upon reflux with alcoholic KOH, **5a** easily converted into corresponding monoacid **6a** in good yield.[12] The geometry of **6a** was

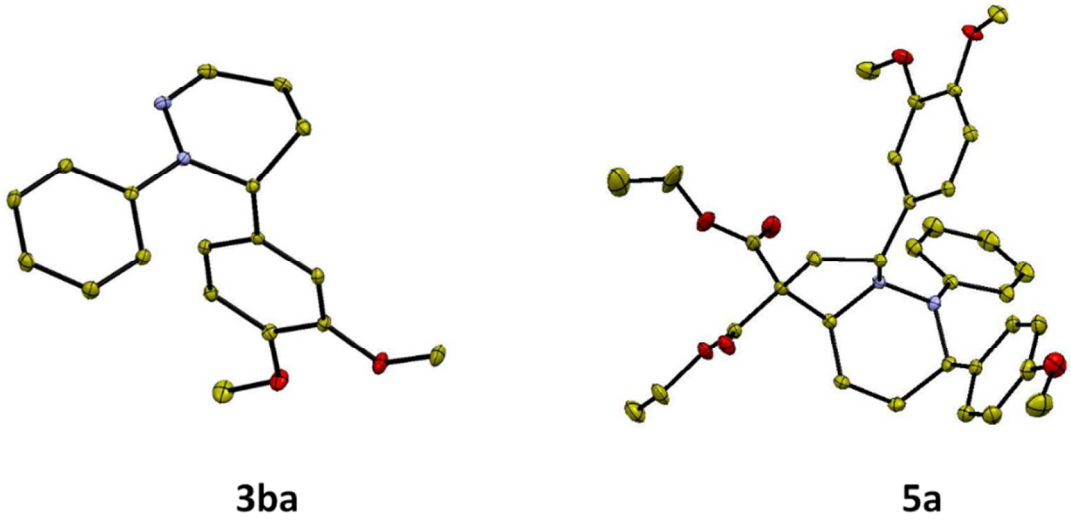
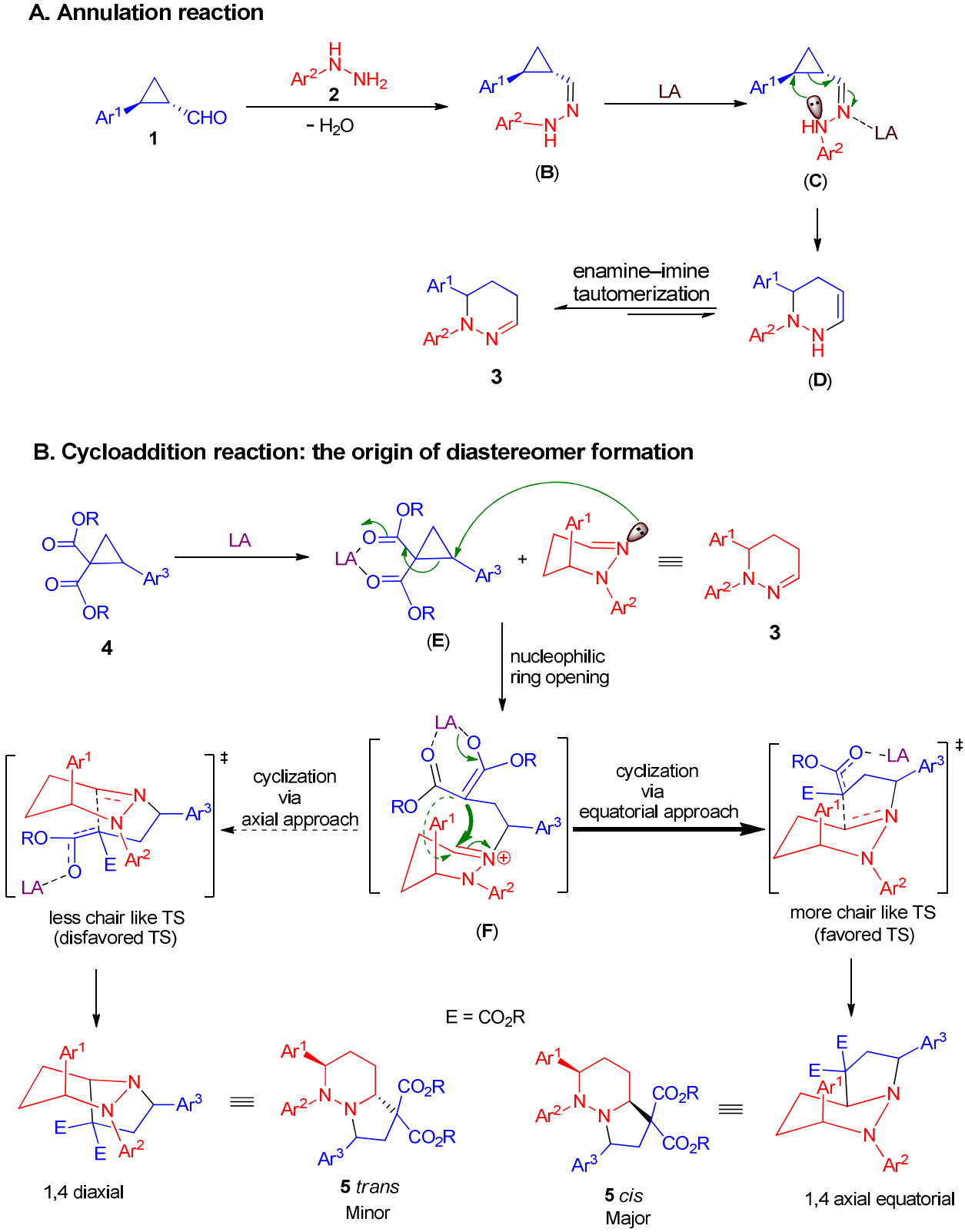


Figure 2. X-ray structure of **3ba** and **5a** (Hydrogen atoms are omitted for the sake of clarity).

Scheme 5. Plausible mechanism for annulation and cycloaddition reaction



unambiguously determined by NOE experiment. In order to clarify the observed

diastereomer formation, on the basis of other literature reports and our experimental outcomes, a plausible mechanism for both the annulation and cycloaddition reaction has been sketched in scheme 5. Initially, cyclopropane carbaldehyde (**1**) and aryl hydrazine (**2**) underwent a condensation reaction to form a transient cyclopropyl hydrazone (**B**) (Scheme 5 A). Upon imine activation by Lewis acid, cyclopropyl hydrazone form an activated intermediate (**C**), which undergoes an intramolecular cyclization reaction via cyclopropane ring opening by *α-N*itrogen atom to give intermediate **D**. Following the enamine-imine tautomerization into more stable imine form, intermediate **D** gave desired tetrahydropyridazine **3**. For cycloaddition reaction, initially Lewis acid activates the DAC (**4**) to form an activated Lewis acid-DAC complex **E** (Scheme 5 B) which undergoes a nucleophilic ring opening by imine nitrogen of tetrahydropyridazine **3** to afford an open chain intermediate **F**. Upon cyclization, intermediate **F** gave hexahydropyrrolo[1,2-*b*]pyridazine (**5**) as the desired cycloadduct. Cyclization can happen either through equatorial approach or axial approach. In equatorial approach, the reaction proceeds through a more chair like TS, which is more favored TS, thus leads to the *cis* isomer as a major diastereomer, whereas, in axial approach, the reaction proceeds through a less chair like TS (disfavored TS) and leads to the *trans* isomer as a minor diastereomer.

Conclusion: In summary, we have developed a convenient route for the synthesis of hexahydropyrrolo[1,2-*b*]pyridazines via Lewis acid catalyzed annulation reactions of cyclopropane carbaldehydes and aryl hydrazines, followed by [3+2]-cycloaddition reactions with DACs. Finally, we displayed a one-step version of the protocol by employing annulation and cycloaddition reaction in one pot. Additionally a

monodecraboxylation of hexahydropyrrolo[1,2-*b*]pyridazine has also been performed. We believe that the developed protocol would serve as a tool for the rapid synthesis of tetrahydropyridazine and hexahydropyrrolo[1,2-*b*]pyridazine motifs.

Experimental section

General information

All reactions were carried out under an inert atmosphere with oven-dried glassware. All solvents and reagents were obtained from commercial sources and were purified following the standard procedure prior to use. Powdered molecular sieves 4 Å (MS 4 Å) was dried at 200 °C under vacuum prior to use. The developed chromatogram was analyzed by UV lamp (254 nm) or *p*-anisaldehyde solution. Products were purified by flash chromatography on silica gel (mesh size 230–400). Unless otherwise specified, all the ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$. Chemical shifts of ^{1}H and ^{13}C NMR spectra are expressed in parts per million (ppm). All coupling constants are absolute values and are expressed in Hertz. The description of the signals includes the following: s = singlet, d = doublet, dd = doublet of doublet, t = triplet, dt = doublet of triplet, q = quartet, br = broad, and m = multiplet.

General procedure for preparation of *trans*-2-arylcyclopropanecarbaldehydes (for the reaction schemes, see scheme S1 in supporting information)[14]

1) To a mixture of triethyl phosphonoacetate (1.1 equiv.), DBU (0.035 equiv.), and finely ground K_2CO_3 (2 equiv.) was added ArCHO (1 equiv.) and the resulting mixture was stirred using a magnetic stirrer for 4 h at room temperature under argon atmosphere. Ethyl acetate was added to the crude mixture and the solid was filtered off. The solid

was rinsed with ethyl acetate and the combined filtrate was concentrated. The resulting oil was distilled under reduced pressure using a bulb-to-bulb apparatus (10 mm Hg/240 °C) to give corresponding alkene (yield 84%) (E:Z = 99:1).

2) A suspension of TMSOI (1.2 equiv.) and NaH (1.5 equiv.) in anhydrous DMSO (15 mL) was stirred for 1 h. A DMSO solution (14 mL) of alkene (14 mmol, 1 equiv) was added at 0 °C. The reaction mixture was stirred at 55 °C for 24 h. Another suspension of TMSOI (0.3 equiv.) and NaH (0.3 equiv.) in DMSO (10 mL) was added to the reaction mixture and reaction was stirred at 65 °C for 84 h. The solution was poured into a brine solution and extracted with ethyl acetate. Combined organic layer was washed with water and dried over $MgSO_4$, concentrated and purified by silica gel column to afford corresponding cyclopropane derivative as a white solid (60-80% yield).

3) To a stirred solution of LAH (1.5 equiv.) in 7 mL diethyl ether was added dropwise a solution of cyclopropane ester (0.90 mmol, 1equiv.) in 3 mL diethyl ether under N_2 atmosphere. After addition was completed the reaction mixture was refluxed for another 6 h. The reaction mixture was then cooled to rt, and the excess LAH was destroyed by water. 15 mL of 10% H_2SO_4 and 8 mL of ether was added and the aqueous layer was extracted several times with diethyl ether. The combined organic layer was washed with water and 5% $NaHCO_3$, dried over $MgSO_4$ and concentrated in a rotary evaporator (90-95% yield). Without any further purification, the crude material (a colorless oil) was used for next step.

4) To a solution of cyclopropane alcohol (6.8 mmol, 1 equiv.) in dry DCM (14 mL), PCC (2 equiv.) was added in a portion-wise manner through a solid addition tube under N_2

atmosphere. After 3 h reaction mixture was filtered through a small plug of celite and concentrated in vacuo. The crude mixture was purified by silica gel column chromatography using ethyl acetate in hexane as an eluent. Starting from aryl aldehyde the 2-arylcyclopropanecarbaldehydes was obtained in 40-50% overall yield.

***trans*-2-(4-methoxyphenyl)cyclopropanecarbaldehyde (1a)**[14(e)]

4-methoxybenzaldehyde (1.0 g, 7.35 mmol), **1a** (0.62 g, 3.53 mmol), overall yield: 48%, colorless crystal, in final step **1a** was purified by silica gel column chromatography with ethyl acetate/hexane (1:9) as eluent. **^{1}H NMR (400 MHz):** δ 9.30 (d, *J* = 4.99 Hz, 1H), 7.05 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 3.79 (s, 3H) 2.63-2.57 (m, 1H), 2.13-2.07 (m, 1H), 1.73-1.67 (m, 1H), 1.51-1.46 (m, 1H).

***trans*-2-(3,4-dimethoxyphenyl)cyclopropanecarbaldehyde (1b)**

3,4-dimethoxybenzaldehyde (1.0 g, 6.02 mmol), **1b** (0.53 g, 2.59 mmol), overall yield: 43%, white solid, in final step **1b** was purified by silica gel column chromatography with ethyl acetate/hexane (2:8) as eluent. **^{1}H NMR (400 MHz):** δ 9.28 (d, *J* = 4.5 Hz, 1H), 6.77 (d, *J* = 8.3 Hz, 1H), 6.65 (d, *J* = 8.2 Hz, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 2.62-2.55 (m, 1H), 2.13-2.06 (m, 1H), 1.71-1.65 (m, 1H), 1.51-1.46 (m, 1H). **^{13}C-NMR (100 MHz)**: δ 199.9, 149.1, 148.1, 131.4, 118.4, 111.3, 110.1, 56.0, 33.7, 26.6, 16.2. **IR (neat)**: 2956, 2835, 2733, 1697, 1589, 1516, 1463, 1253, 1232, 1139, 1024, 972, 852, 761 cm^{-1}. **HRMS** (ESI, Q-TOF) m/z: [M + H]+ Calculated for $C_{12}H_{15}O_3$ 207.1021, found 207.1003.

***trans*-2-phenylcyclopropanecarbaldehyde (1c)**[14(g)]

Benzaldehyde (1.0 g, 9.43 mmol), **1c** (0.69 g, 4.72 mmol), overall yield: 50%, white solid, in final step **1c** was purified by silica gel column chromatography with ethyl acetate/hexane (1:9) as eluent. **^{1}H NMR (400 MHz):** δ 9.32 (d, *J* = 4.5 Hz, 1H), 7.33-7.20 (m, 3H), 7.12(d, *J* = 8.3 Hz, 2H), 2.66-2.60 (m, 1H), 2.21-2.15 (m, 1H), 1.77-1.71 (m, 1H), 1.51-1.46 (m, 1H).

***trans*-2-(4-fluorophenyl)cyclopropanecarbaldehyde (1d)**[6a]

4-fluorobenzaldehyde (1.0 g, 8.06 mmol), **1d** (0.66 g, 4.03 mmol), overall yield: 50%, white solid, in final step **1d** was purified by silica gel column chromatography with ethyl acetate/hexane (1:9) as eluent. **^{1}H NMR (400 MHz):** δ 9.32 (d, *J* = 4.5 Hz, 1H), 7.09-7.05 (m, 2H), 6.98 (t, *J* = 8.7 Hz, 2H), 2.64-2.58 (m, 1H), 2.15-2.09 (m, 1H), 1.74-1.69 (m, 1H), 1.51-1.45 (m, 1H).

***trans*-2-(naphthalen-1-yl)cyclopropanecarbaldehyde (1e)**

1-naphthaldehyde (1.0 g, 6.41 mmol), **1e** (0.53 g, 2.69 mmol), overall yield: 42%, pale yellow oil, in final step **1e** was purified by silica gel column chromatography with ethyl acetate/hexane (1:9) as eluent. **^{1}H NMR (400 MHz):** δ 9.54 (d, *J* = 8.6 Hz, 1H), 8.14 (d, *J* = 8.6 Hz, 1H), 7.88 (d, *J* = 7.1 Hz, 1H), 7.79 (d, *J* = 8.6 Hz, 1H), 7.60-7.50 (m, 2H), 7.41 (t, *J* = 7.1 Hz, 1H), 7.29 (t, *J* = 7.1 Hz, 1H), 2.22-2.16 (m, 1H), 1.88-1.82 (m, 1H), 1.72-1.67 (m, 2H). **^{13}C-NMR (100 MHz)**: δ 200.5, 128.7, 128.0, 126.5, 126.1, 123.7, 31.9, 24.5, 15.2. **IR (neat)**: 3045, 2825, 2725, 1697, 1595, 1508, 1394, 1168, 1031, 1014, 933, 860, 796, 775 cm^{-1}. **HRMS** (ESI, Q-TOF) m/z: [M + H]+ Calculated for $C_{14}H_{13}O$ 197.0966, found 197.0949.

***trans*-2-(furan-2-yl)cyclopropanecarbaldehyde (1f)**[14(e)]

furan-2-carbaldehyde (1.0 g, 10.41 mmol), **1f** (0.64 g, 4.69 mmol), overall yield: 45%, pale yellow oil, in final step **1f** was purified by silica gel column chromatography with ethyl acetate/hexane (1:9) as eluent. **^{1}H NMR (400 MHz):** δ 9.36 (d, *J* = 4.3 Hz, 1H), 7.27-7.25 (m, 1H), 6.30-6.28 (m, 1H), 6.10 (d, *J* = 3.3 Hz, 1H), 2.65-2.59 (m, 1H), 2.32-2.26 (m, 1H), 1.69-1.64 (m, 1H), 1.62-1.56 (m, 1H).

General procedure for preparation of *cis*-2-phenylcyclopropanecarbaldehyde 1c' (for the reaction scheme, see scheme S2 in supporting information)[14(f), 14(g)]

To a suspension of styrene (3.0 g, 28.8 mmol) and $Rh_2(OAc)_4$ (40 mg, 0.09 mmol) in CH_2Cl_2 at room temperature was added ethyl diazoacetate (3.28 g, 28.8 mmol) via syringe pump and over the course of 12 hours. Once the addition was complete, the green mixture was stirred for another 12 hours, and then filtered through a short pad of silica gel to afford the desired cyclopropane derivative as a mixture of diastereoisomers (*trans*:*cis* = 60:40) in 88% yield. The mixture was separated by flash chromatography (typical eluent, diethyl ether/pentane 2:8). The desired *cis* ethyl 2- phenylcyclopropane carboxylate was obtained as a clear oil (32% yield).

The reduction of *cis* ethyl 2-phenylcyclopropanecarboxylate to *cis* 2-phenylcyclopropylmethanol, and the oxidation of *cis* 2-phenylcyclopropylmethanol to *cis* 2-phenylcyclopropanecarbaldehyde was carried out following the general procedure described in the preparation of *trans* cyclopropanecarbaldehydes.

Styrene (1.0 g, 9.61 mmol), **1C'** (0.34 g, 2.34 mmol), overall yield: 24%, colorless oil, in final step **1C'** was purified by silica gel column chromatography with ethyl acetate/hexane (1:9) as eluent. **^{1}H NMR (400 MHz):** δ 8.66 (d, *J* = 6.6 Hz, 1H), 7.33-

7.20 (m, 5H), 2.82 (q, *J* = 8.3, 15.9 Hz, 1H), 2.16-2.09 (m, 1H), 1.90-1.85 (m, 1H), 1.61-1.55 (m, 1H).

General procedure for preparation of aryl hydrazine free bases (for the reaction scheme, see scheme S3 in supporting information)[15]

Phenylhydrazine (**2a**) was commercially available as their free base. The other aryl hydrazine free bases (**2b-2i**) were prepared by neutralization of the corresponding commercially available hydrochloride salts according to the following procedure.

To a solution of arylhydrazine hydrochloride in water (0.5 M), K_2CO_3 (1.5 equiv) was added and the mixture was stirred for 15 min at room temperature. The aqueous layer was extracted with dichloromethane and the organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to afford arylhydrazine as a white solid (around 90% yield).

General procedure for preparation of aryl cyclopropane-1,1-dicarboxylate derivatives (for the reaction scheme, see scheme S4 in supporting information)[16]

Sodium hydride (2.5 equiv) was taken in a two-neck, round-bottom flask and washed three to four times with dry hexane. Trimethylsulfoxonium iodide (2.5 equiv) was added and the mixture suspended in anhydrous DMSO under a nitrogen atmosphere. The mixture was cooled to 0 °C and stirred for 30 min. A solution of the appropriate benzylidene malonate (1 equiv) in anhydrous DMSO was added, and the reaction mixture was allowed to stir at room temperature. Upon completion of the reaction (as determined by TLC analysis), the solution was poured into ice and extracted with diethyl ether. The combined organic layers were washed once with brine, dried over sodium

sulfate, filtered and concentrated in vacuo to give the crude product, which was purified by silica gel column chromatography with ethyl acetate/hexane as eluent. Aryl cyclopropane-1,1-dicarboxylate derivatives was obtained in 70-80% yield.

Diethyl 2-(3,4-dimethoxyphenyl)cyclopropane-1,1-dicarboxylate (4a)[11a]

Reaction time: 5 h, diethyl 2-(3,4-dimethoxybenzylidene)malonate (1.0 g, 3.24 mmol), **4a** (0.76 g, 2.36 mmol), yield: 73%, colorless oil, purified by silica gel column chromatography with ethyl acetate/hexane (2:8) as eluent. **^{1}H NMR (400 MHz):** δ 6.76-6.72 (m, 3H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.89 (q, *J* = 7.1 Hz, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.17 (t, *J* = 8.5 Hz, 1H), 2.12 (dd, *J* = 8.3, 5.1 Hz, 1H), 1.68 (dd, *J* = 8.1, 5.3 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H), 0.92 (t, J = 7.1 Hz, 3H).

Dimethyl 2-(3,4-dimethoxyphenyl)cyclopropane-1,1-dicarboxylate (4b) [11a]

Reaction time = 5 h, dimethyl 2-(3,4-dimethoxybenzylidene)malonate (1.0 g, 3.56 mmol), **4b**, (0.79 g, 2.68 mmol), yield: 75%, colorless solid, purified by silica gel column chromatography with ethyl acetate/hexane (3:7) as eluent. **^{1}H NMR (400 MHz):** δ 6.77-6.71 (m, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.78 (s, 3H), 3.40 (s, 3H), 3.18 (t, *J* = 8.5 Hz, 1H), 2.15 (dd, *J* = 8.2, 5.0 Hz, 1H), 1.72(dd, *J* = 9.2, 5.0 Hz, 1H).

Dibenzyl 2-(3,4-dimethoxyphenyl)cyclopropane-1,1-dicarboxylate (4c) [11a]

Reaction time = 5 h, dibenzyl 2-(3,4-dimethoxybenzylidene)malonate (1.0 g, 2.31 mmol), **4c**, (0.77 g, 1.73 mmol), yield: 75%, white solid, purified by silica gel column chromatography with ethyl acetate/hexane (2:8) as eluent. **^{1}H NMR (400 MHz):** δ 7.37-7.26 (m, 6H), 7.25-7.18 (m, 3H), 6.93 (d, *J* = 7.6 Hz, 1H), 6.69 (s, 3H), 5.27-5.17 (m,

2H), 4.81-4.78 (m. 2H), 3.85 (s, 3H), 3.72 (s, 3H), 3.23 (t, *J* = 8.9 Hz, 1H), 2.19 (dd, *J* = 8.0, 5.0 Hz, 1H), 1.73 (dd, *J* = 8.9, 5.0 Hz, 1H).

Diethyl 2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate (4d) [11a]

Reaction time = 5 h, diethyl 2-(4-methoxybenzylidene)malonate (1.0 g, 3.59 mmol), **4d**, (0.77 g, 2.64 mmol), yield: 74%, colorless oil, purified by silica gel column chromatography with ethyl acetate/hexane (1:9) as eluent. **^{1}H NMR (400 MHz):** δ 7.12 (d, *J* = 8.6 Hz, 2H), 6.79 (d, *J* = 8.6 Hz, 2H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.84 (q, *J* = 7.1 Hz, 2H), 3.75 (s, 3H), 3.75 (s, 3H), 3.15 (t, *J* = 8.8 Hz, 1H), 2.19-2.11 (m, 1H), 1.68-1.65 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.90 (t, *J* = 7.1 Hz, 3H).

Diethyl 2-(*p*-tolyl)cyclopropane-1,1-dicarboxylate (4e) [11a]

Reaction time = 5 h, diethyl 2-(*p*-methylbenzylidene)malonate (1.0 g, 3.81 mmol), **4e** (0.78 g, 2.82 mmol), yield: 74%, colorless oil, purified by silica gel column chromatography with ethyl acetate/hexane (1:9) as eluent. **^{1}H NMR (400 MHz):** δ 7.10-7.06 (m, 4H), 4.25-4.20 (m, 2H), 3.86 (q, *J* = 7.1 Hz, 2H), 3.17 (t, *J* = 8.2 Hz, 1H), 2.29 (s, 3H), 2.15-2.13 (m, 1H), 1.69-1.67 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.89 (t, *J* = 7.1 Hz, 3H).

Diethyl 2-(*o*-tolyl)cyclopropane-1,1-dicarboxylate (4f) [11a]

Reaction time = 6 h, diethyl 2-(*o*-methylbenzylidene)malonate (1.0 g, 3.81 mmol), **4f**, (0.73 g, 2.64 mmol), yield: 70%, colorless oil, purified by silica gel column chromatography with ethyl acetate/hexane (1:9) as eluent. **^{1}H-NMR (400 MHz):** δ 7.16-6.91 (m, 4H), 4.15-4.10 (m, 2H), 3.66-3.62 (m, 2H), 3.03 (t, *J* = 8.7 Hz, 1H), 2.24 (s,

3H), 2.16 (dd, *J* = 8.1, 5.0 Hz, 1H), 1.56 (dd, *J* = 5.0, 9.1 Hz, 1H), 1.17 (t, *J* = 7.1 Hz, 3H), 0.66 (t, *J* = 7.1 Hz, 3H).

Diethyl 2-phenylcyclopropane-1,1-dicarboxylate (4g) [11a]

Reaction time = 6 h, diethyl 2-benzylidenemalonate (1.0 g, 4.03 mmol), **4g**, (0.71 g, 2.71 mmol), yield: 67%, colorless oil, purified by silica gel column chromatography with ethyl acetate/hexane (1:9) as eluent. **^{1}H-NMR (400 MHz):** δ 7.27-7.17 (m, 5H), 4.30-4.15 (m, 2H), 3.81 (q, *J* = 14.3, 7.1 Hz, 2H), 3.20 (t, *J* = 8.7 Hz, 1H), 2.17 (dd, *J* = 7.8, 5.0 Hz, 1H), 1.69 (dd, *J* = 9.2, 5.1 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.84 (t, *J* = 7.3 Hz, 3H).

Diethyl 2-(4-fluorophenyl)cyclopropane-1,1-dicarboxylate (4h) [16d]

Reaction time = 6 h, diethyl 2-(4-fluorobenzylidene)malonate (1.0 g, 3.75 mmol), **4h**, (0.73 g, 2.60 mmol), yield: 69%, colorless oil, purified by silica gel column chromatography with ethyl acetate/hexane (1:9) as eluent. **^{1}H-NMR (400 MHz):** δ ^{1}H-NMR (400 MHz): δ 7.17-7.16 (m, 2H), 6.93 (t, *J* = 8.6 Hz, 2H), 4.24-4.19 (m, 2H), 3.86-3.83 (m, 2H), 3.16 (t, *J* = 7.9 Hz, 1H), 2.11 (dd, *J* = 7.7, 5.1 Hz, 1H), 1.68 (dd, *J* = 9.1, 8.4 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.89 (t, *J* = 7.1 Hz, 3H).

Diethyl 2-(furan-2-yl)cyclopropane-1,1-dicarboxylate (4i) [11a]

Reaction time = 4 h, diethyl 2-(furan-2-ylmethylene)malonate (1.0 g, 4.20 mmol), **4i** (0.75 g, 2.98 mmol), yield: 71%, colorless oil, purified by silica gel column chromatography with ethyl acetate/hexane (2:8) as eluent. **^{1}H-NMR (400 MHz):** δ 7.29 (br, 1H), 6.27 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.12 (d, *J* = 3.2 Hz, 1H), 4.24-4.19 (m, 2H), 4.02

(q, *J* = 14.2, 7.1 Hz, 2H), 3.08 (t, *J* = 8.6 Hz, 1H), 2.05 (dd, *J* = 7.7, 5.0 Hz, 1H), 1.77 (dd, *J* = 9.5, 5.0 Hz, 1H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.07 (t, *J* = 7.1 Hz, 3H).

Diethyl 2-(thiophen-2-yl)cyclopropane-1,1-dicarboxylate (4j)

Reaction time = 5 h, diethyl 2-(thiophen-2-ylmethylene)malonate (1.0 g, 3.93 mmol), **4j** (0.73 g, 2.72 mmol), yield: 70%, light yellow oil, purified by silica gel column chromatography with ethyl acetate/hexane (2:8) as eluent. **^{1}H-NMR (400 MHz):** δ 7.13 (d, *J* = 5.1 Hz, 1H), 6.87 (dd, *J* = 5.2, 3.5 Hz, 1H), 6.82-6.80 (m, 1H), 4.29-4.16 (m, 2H), 3.97-3.89 (m, 2H), 3.25 (t, *J* = 8.5 Hz, 1H), 2.10 (dd, *J* = 7.8, 5.0 Hz, 1H), 1.77 (dd, *J* = 9.1, 5.0 Hz, 1H), 1.27 (t, *J* = 7.3 Hz, 3H), 0.96 (t, *J* = 7.0 Hz, 3H). **^{13}C-NMR (100 MHz):** δ 169.5, 166.4, 138.3, 126.7, 126.1, 124.9, 61.9, 61.4, 38.1, 26.9, 20.7, 14.1, 13.8. **IR (neat)**: 2980, 1718, 1444, 1369, 1319, 1273, 1201, 1126, 1022, 848, 698 cm^{-1}. **HRMS** (ESI, Q-TOF) m/z: [M + H]+ Calculated for $C_{13}H_{17}O_4S$ 269.0848, found 269.0836.

Representative procedure for Lewis acid catalyzed annulation reaction between cyclopropane carbaldehydes (1) and aryl hydrazines (2)

To a round-bottom flask equipped with a magnetic stir bar was charged with 4 Å MS (200 wt%), and $InCl_3$ (0.2 equiv) under nitrogen atmosphere. A DCM solution of cyclopropane carbaldehyde (1 equiv) and aryl hydrazine (1 equiv) was added and stirred at room temperature until completion of the reaction (as monitored by TLC). The reaction mixture was passed through a small pad of celite, and solvent was evaporated on a rotary evaporator. The crude mixture was further purified by column chromatography on silica gel with ethyl acetate/hexane as eluent.

6-(4-methoxyphenyl)-1-phenyl-1,4,5,6-tetrahydropyridazine (3aa)

Reaction time: 5 h**, 1a** (0.05 g, 0.28 mmol), **2a** (0.03 g, 0.28 mmol), **3aa** (0.05g, 0.21 mmol), yield: 74%, reddish yellow viscous liquid, R_f = 0.56 (ethyl acetate/hexane 1:9).

^{1}H-NMR (400 MHz): δ 7.21 (t, *J* = 8.5 Hz, 2H), 7.10 (dd, *J* = 8.1, 15.3 Hz, 4H), 6.85 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 7.3 Hz, 2H), 5.17 (br, 1H), 3.78 (s, 3H), 2.25-1.99 (m, 3H), 1.95-1.82 (m, 1H). **^{13}C-NMR (100 MHz)**: δ 158.7, 146.9, 135.5, 133.0, 129.0, 127.2, 119.5, 114.2, 113.3, 55.7, 55.3, 24.4, 18.9. **IR (neat)**: 2924, 2848, 1595, 1510, 1498, 1263, 1176, 1132, 1024, 941, 840, 810, 756 cm^{-1}. **HRMS** (ESI, Q-TOF) m/z: [M + H]+ Calculated for $C_{17}H_{19}N_2O$ 267.1497, found 267.1481.

6-(3,4-dimethoxyphenyl)-1-phenyl-1,4,5,6-tetrahydropyridazine (3ba)

Reaction time: 4 h, **1b** (0.06 g, 0.28 mmol), **2a** (0.03 g, 0.28 mmol), **3ba** (0.05 g, 0.16 mmol), yield: 57%, pale yellow needle like crystal, melting point: 98 °C, R_f = 0.57 (ethyl acetate/hexane 2:8).

^{1}H-NMR (400 MHz): δ 7.21 (t, *J* = 8.7 Hz, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), 6.85-6.75 (m, 3H), 6.70-6.65 (m, 2H), 5.14 (br, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 2.24-2.01 (m, 3H), 1.97-1.85 (m, 1H). **^{13}C-NMR (100 MHz)**: δ 149.2, 148.0, 146.9, 135.5, 133.6, 128.9, 119.59, 118.3, 113.4, 111.3, 109.0, 56.1, 55.9, 24.4, 19.0. **IR (neat)**: 2922, 2835, 1595, 1516, 1502, 1413, 1249, 1234, 1182, 1085, 1024, 748, 717, 692 cm^{-1}. **HRMS** (ESI, quadrupole) m/z: [M + H]+ Calculated for $C_{18}H_{21}N_2O_2$ 297.1603, found 297.1594

1,6-diphenyl-1,4,5,6-tetrahydropyridazine (3ca)

Reaction time: 5 h, **1c** (0.04 g, 0.28 mmol), **2a** (0.03 g, 0.28 mmol), **3ca** (0.05 g, 0.21 mmol), yield: 75%, pale yellow viscous liquid, R_f = 0.72 (ethyl acetate/hexane 1:9).

^{1}H-NMR (400 MHz): δ 7.29 (t, *J* = 7.7 Hz, 2H), 7.25-7.06 (m, 7H), 6.82-6.75 (m, 2H), 5.18 (br, 1H), 2.24-1.92 (m, 3H), 1.90-1.79 (m, 1H). **^{13}C-NMR (100 MHz)**: δ 146.8, 141.1, 135.5, 129.0, 128.8, 127.1, 126.1, 119.5, 113.3, 56.2, 24.3, 18.9. **IR (neat)**: 2924, 2852, 1608, 1496, 1448, 1369, 1319, 1300, 1238, 1076, 939, 755 cm^{-1}. **HRMS** (ESI, Q-TOF) m/z: [M + H]+ Calculated for $C_{16}H_{17}N_2$ 237.1392, found 237.1371.

6-(4-fluorophenyl)-1-phenyl-1,4,5,6-tetrahydropyridazine (3da)

Reaction time: 5 h, **1d** (0.04 g, 0.28 mmol), **2a** (0.03 g, 0.28 mmol), **3da** (0.05 g, 0.2 mmol), yield: 71%, reddish yellow viscous liquid, R_f = 0.75 (ethyl acetate/hexane 1:9).

^{1}H-NMR (400 MHz): δ 7.12 (t, *J* = 8.8 Hz, 2H), 7.02 (t, *J* = 8.7 Hz, 4H) 6.91 (t, *J* = 8.6 Hz, 2H) 6.74 (q, *J* = 7.1, 14.0 Hz, 2H), 5.10 (br, 1H), 2.16-2.07 (m, 1H), 2.05-1.93 (m, 2H), 1.82-1.70 (m, 1H). **^{13}C-NMR (100 MHz)**: δ 161.9 (d, J_{CF} = 245.5 Hz), 146.6, 136.7 (d, J_{CF} = 3.0 Hz), 135.6, 129.0, 127.7 (d, J_{CF} = 7.8 Hz), 119.6, 115.7 (d, J_{CF} = 21.9 Hz), 113.2, 55.6, 24.3, 18.7. **^{19}F-NMR (376 MHz)**: δ -115.60 (s, 1F), **IR (neat)**: 2926, 2852, 1506, 1496, 1220, 1014, 943, 690, 624, 580 cm^{-1}. **HRMS** (ESI, Q-TOF) m/z: [M + H]+ Calculated for $C_{16}H_{16}N_2F$ 255.1298, found 255.1273.

6-(naphthalen-1-yl)-1-phenyl-1,4,5,6-tetrahydropyridazine (3ea)

Reaction time: 5 h, **1e** (0.05 g, 0.28 mmol), **2a** (0.03 g, 0.28 mmol), **3ea** (0.04 g, 0.16 mmol), yield: 57%, reddish brown viscous liquid, R_f = 0.71 (ethyl acetate/hexane 1:9).

^{1}H-NMR (400 MHz): δ 8.11 (d, *J* = 8.3 Hz, 1H), 7.95 (d, *J* = 7.7 Hz, 1H) 7.78 (d, *J* = 8.2 Hz, 1H) 7.63 (t, *J* = 6.8 Hz, 1H), 7.57 (t, *J* = 7.3 Hz, 1H), 7.35 (t, *J* = 7.3 Hz, 1H), 7.17 (t, *J* = 6.3 Hz, 3H), 7.11 (d, *J* = 9.2 Hz, 2H), 6.87 (d, *J* = 4.5 Hz, 1H), 6.80 (t, *J* = 6.8 Hz,

1H), 5.95 (br, 1H), 2.38-2.26 (m, 2H), 2.14-2.05 (m, 1H), 1.95-1.84 (m, 1H). **^{13}C-NMR (100 MHz)**: δ 146.6, 135.5, 134.6, 134.4, 129.5, 129.4, 128.9, 128.0, 126.5, 125.7, 125.6, 124.6, 122.4, 119.5, 113.2, 53.9, 22.5, 19.2. **IR (neat)**: 3047, 2927, 1595, 1496, 1338, 1301, 1263, 1132, 1039, 937, 800, 742 cm^{-1}. **HRMS** (ESI, Q-TOF) m/z: [M + H]+ Calculated for $C_{20}H_{19}N_2$ 287.1548, found 287.1525.

6-(furan-2-yl)-1-phenyl-1,4,5,6-tetrahydropyridazine (3fa)

Reaction time: 4.5 h, **3f** (0.045g, 0.28 mmol), **2a** (0.03g, 0.28 mmol), **3fa** (0.044g, 0.19 mmol), yield: 68%, yellow viscous liquid, R_f = 0.73 (ethyl acetate/hexane 1:9). **^{1}H-NMR (400 MHz)**: δ 7.31 (s, 1H), 7.19 (t, J = 8.9 Hz, 2H), 7.11 (d, J = 8.5 Hz, 2H), 6.80 (t, *J* = 7.1 Hz, 1H), 6.73 (d, *J* = 4.2 Hz, 1H), 6.21 (dd, *J* = 1.9, 3.3 Hz, 1H), 5.97 (d, *J* = 3.3 Hz, 1H) 5.20 (br, 1H), 2.35-2.29 (m, 1H), 2.10-1.89 (m, 3H). **^{13}C-NMR (100 MHz)**: δ 152.4, 146.82, 142.0, 136.1, 129.0, 119.8, 113.4, 110.4, 107.7, 50.9,31.5, 30.3, 21.5, 19.7. **IR (neat)**: 2931, 1597, 1576, 1346, 1292, 1278, 1170, 1132, 1072, 1006, 937, 745 cm^{-1}. **HRMS** (ESI, quadrupole) m/z: [M + H]+ Calculated for $C_{14}H_{15}N_2O$ 227.1184, found 227.1166

1-(4-fluorophenyl)-6-(4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine (3ab)

Reaction time: 5 h, **1a** (0.05 g, 0.28 mmol), **2b** (0.036 g, 0.28 mmol), **3ab** (0.056 g, 0.19 mmol), yield: 70%**,** light reddish oil, R_f = 0.76 (ethyl acetate/hexane 1:9)**.**

^{1}H-NMR (400 MHz): δ 7.08-7.00 (m, 4H), 6.93-6.82 (m, 4H), 6.79-6.76 (m, 1H), 5.09 (br, 1H), 3.77 (s, 3H) 2.26-2.14 (m, 1H), 2.13-2.01 (m, 2H), 1.94-1.82 (m, 1H). **^{13}C-NMR (100 MHz):** δ 158.7, 157.0 (d, J_{C-F} = 237.6 Hz), 143.4, 135.4, 132.8, 127.2, 115.4 (d, J_{C-F} = 22.1 Hz), 114.4 (d, J_{C-F} = 7.0 Hz), 114.2, 56.0, 55.3, 24.5, 18.8. **^{19}F-NMR (376 MHz):**

δ -126.05 (s, 1F) **IR (neat)**: 2927, 2835, 1608, 1520, 1220, 1128, 1097, 1068, 1024, 941, 815, 692 cm^{-1}. **HRMS** (ESI, Q-TOF) m/z: [M + H]+ Calculated for $C_{17}H_{18}N_2OF$ 285.1403, found 285.1375.

1-(4-chlorophenyl)-6-(4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine (3ac)

Reaction time: 6 h, **1a** (0.05 g, 0.28 mmol), **2c** (0.04 g, 0.28 mmol), **3ac** (0.055 g, 0.18 mmol), yield: 64%**,** pale yellow viscous liquid**,** R_f = 0.75 (ethyl acetate/hexane 1:9).

^{1}H-NMR (400 MHz): δ 7.13 (d, *J* = 8.6 Hz, 2H), 7.03 (d, *J* = 8.2 Hz, 4H) 6.83 (t, *J* = 8.6 Hz, 3H), 5.11 (br, 1H), 3.77 (s, 3H), 2.24-2.01 (m, 3H), 1.94-1.82 (m, 1H). **^{13}C-NMR (100 MHz)**: δ 158.7, 145.4, 136.2, 132.4, 128.7, 127.1, 124.2, 114.3, 114.2, 55.7, 55.3, 24.4, 18.7. **IR (neat)**: 2954, 2926, 1610, 1490, 1247, 1176, 1024, 943, 827, 810, 734 cm^{-1}. **HRMS** (ESI, Q-TOF) m/z: [M + H]+ Calculated for $C_{17}H_{18}N_2OCl$ 301.1108, found 301.1095.

1-(4-bromophenyl)-6-(4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine (3ad)

Reaction time: 6 h, **1a** (0.05 g, 0.28 mmol), **2d** (0.053 g, 0.28 mmol), **3ad** (0.06 g, 0.17 mmol), yield: 62%**,** reddish white oil, R_f = 0.74 (ethyl acetate/hexane 1:9).

^{1}H-NMR (400 MHz): δ 7.18 (d, *J* = 9.2 Hz, 2H), 6.92 (dd, *J* = 8.7, 17.3 Hz, 4H) 6.79-6.71 (m, 3H), 5.02 (br, 1H), 3.69 (s, 3H), 2.15-1.93 (m, 3H), 1.85-1.74 (m, 1H). **^{13}C-NMR (100 MHz)**: δ 158.8, 145.8, 136.3, 132.3, 131.6, 127.1, 114.8, 114.2, 111.6, 55.6, 55.3, 24.4, 18.7. **IR (neat)**: 2953, 2854, 1614, 1587, 1510, 1487, 1369, 1249, 1176, 1132, 1022, 939, 827, 760, 509 cm^{-1}. **HRMS** (ESI, Q-TOF) m/z: [M + H]+ Calculated for $C_{17}H_{18}N_2OBr$ 345.0603, found 345.0558.

4-(6-(4-methoxyphenyl)-5,6-dihydropyridazin-1(4H)-yl)benzonitrile (3ae)

Reaction time: 8 h, **1a** (0.05 g, 0.28 mmol), **2e** (0.037 g, 0.28 mmol), **3ae** (0.05 g, 0.16 mmol), yield: 56%, reddish brown viscous liquid, R_f = 0.47 (ethyl acetate/hexane = 2:8).

^{1}H-NMR (400 MHz): δ 7.44 (d, J = 9.2 Hz, 2H), 7.14 (d, J = 9.1 Hz, 2H), 7.00 (d, J = 8.5 Hz, 2H), 6.93 (br, 1H), 6.85 (d, J = 8.7 Hz, 2H), 5.18 (br, 1H), 3.77 (s, 3H), 2.26-2.06 (m, 3H), 1.97-1.84 (m, 1H). **^{13}C-NMR (100 MHz)**: δ 159.0, 149.6, 139.1, 133.3, 131.4, 127.0, 120.2, 114.4, 113.0, 101.3, 55.5, 55.3, 24.4, 18.8. **IR (neat)**: 2926, 2852, 2218, 1600, 1508, 1371, 1323, 1265, 1249, 1176, 1026, 939, 831, 735, 702 cm^{-1}, **HRMS** (ESI, Q-TOF) m/z: [M + H]+ Calculated for $C_{18}H_{18}N_3O$ 292.1450, found 292.1431.

6-(4-methoxyphenyl)-1-(p-tolyl)-1,4,5,6-tetrahydropyridazine (3af)

Reaction time: 4.5 h, **1a** (0.05 g, 0.28 mmol), **2f** (0.03 g, 0.28 mmol), **3af** (0.06 g, 0.21 mmol), yield: 75%**,** colourless oil, R_f = 0.64 (ethyl acetate/hexane 1:9).

^{1}H-NMR (400 MHz): δ 7.06 (d, *J* = 8.7 Hz, 2H), 7.00 (s, 4H), 6.84 (d, *J* = 8.6 Hz, 2H), 6.76 (br, 1H), 5.13 (br, 1H), 3.77 (s, 3H), 2.24 (s, 3H), 2.22-2.00 (m, 3H), 1.94-1.82 (m, 1H). **^{13}C-NMR (100 MHz)**: δ 158.6, 144.7, 134.9, 133.1, 129.5, 128.6, 127.2, 114.2, 113.3, 55.8, 55.3, 24.4, 20.5, 18.9, **IR (neat)**: 2924, 2854, 1608, 1570, 1490, 1442, 1282, 1246, 1176, 1132, 1024, 943, 806 cm^{-1}. **HRMS** (ESI, Q-TOF) m/z: [M + H]+ Calculated for $C_{18}H_{21}N_2O$ 281.1654, found 281.1632.

1-(4-isopropylphenyl)-6-(4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine (3ag)

Reaction time: 4.5 h, **1a** (0.05 g, 0.28 mmol), **2g** (0.04 g, 0.28 mmol), **3ag** (0.065 g, 0.21 mmol), yield: 75%**,** light yellow viscous liquid, R_f = 0.63 (ethyl acetate/hexane 1:9).

^{1}H-NMR (400 MHz): δ 7.10-7.01 (m, 6H), 6.85 (d, *J* = 8.7 Hz, 2H), 6.76 (br, 1H), 5.13 (br, 1H), 3.78 (s, 3H), 2.81 (q, *J* = 7.1, 14.0, 20.8 Hz, 1H), 2.21-1.98 (m, 3H), 1.94-1.81 (m, 1H), 1.19 (d, *J* = 6.9 Hz, 6H). **^{13}C-NMR (100 MHz)**: δ 158.6, 145.0, 139.8, 134.8, 133.3, 127.2, 126.8, 114.2, 113.2, 55.9, 55.3, 33.2, 24.4, 24.3, 24.2, 18.9. **IR (neat)**: 2954, 2833, 1608, 1488, 1369, 1246, 1024, 943, 908, 827, 729, 648, 605 cm^{-1}, **HRMS** (ESI, Q-TOF) m/z: [M + H]+ Calculated for $C_{20}H_{25}N_2O$ 309.1967, found 309.1957.

1,6-bis(4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine (3ah)

Reaction time: 11 h, **1a** (0.05 g, 0.28 mmol), **2h** (0.04 g, 0.28 mmol), **3ah** (0.04 g, 0.12 mmol), yield: 42%**,** yellow viscous liquid, R_f = 0.41 (ethyl acetate/hexane 1:9).

^{1}H-NMR (400 MHz): δ 7.05 (dd, *J* = 15.1, 8.3 Hz, 4H), 6.84 (d, *J* = 8.6 Hz, 2H), 6.79-6.72 (m, 3H), 5.08 (br, 1H), 3.77 (s, 3H), 3.73 (s, 3H), 2.23-2.13 (m, 1H), 2.12-2.00 (m, 2H), 1.94-1.82 (m, 1H). **^{13}C-NMR (100 MHz)**: δ 158.6, 153.3, 141.3, 134.5, 133.3, 127.2, 114.6, 114.3, 114.1, 56.1, 55.7, 55.3, 24.5, 18.8. **IR (neat)**: 2929, 2831, 1608, 1504, 1240, 1174, 1130, 1035, 1022, 1022, 943, 821 cm^{-1}, **HRMS** (ESI, Q-TOF) m/z: [M + H]+ Calculated for $C_{18}H_{21}N_2O_2$ 297.1603, found 297.1606.

1-benzyl-6-(4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine (3ai)

Reaction time: 6 h, **1a** (0.05 g, 0.28 mmol), **2i** (0.04 g, 0.28 mmol), **3ai** (0.05 g, 0.19 mmol), yield: 67%**,** yellow viscous liquid, R_f = 0.58 (ethyl acetate/hexane 1:9).

^{1}H-NMR (400 MHz): δ 7.30-7.16 (m, 7H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.77 (br, 1H), 4.35 (d, *J* = 14.2 Hz, 1H), 3.85 (d, *J* = 14.6 Hz, 1H), 3.82 (s, 3H), 3.67 (dd, *J* = 9.5, 3.8 Hz, 1H), 2.26-1.87 (m, 4H). **^{13}C-NMR (100 MHz)**: δ 137.7, 134.6, 129.0, 128.5, 128.1, 127.0,

114.1, 59.2, 58.3, 55.4, 28.8, 23.2. **IR (neat)**: 3026, 2927, 2833, 1610, 1510, 1492, 1452, 1298, 1228, 1172, 1024, 831, 727, 698 cm^{-1}, **HRMS** (ESI, Q-TOF) m/z: [M + H]+ Calculated for $C_{18}H_{21}N_2O$ 281.1654, found 281.1635.

Representative procedure for Lewis acid catalyzed [3+2]-cycloaddition reactions of tetrahydropyridazine and DAC

Procedure: To a round-bottom flask equipped with a magnetic stir bar was charged with 4 Å MS (200 wt%), and $Yb(OTf)_3$ (0.2 equiv) under a nitrogen atmosphere. A DCM solution of tetrahydropyridazine (1 equiv) and DAC (1 equiv) was added and stirred at room temperature until completion of the reaction (as monitored by TLC). The reaction mixture was passed through a small pad of celite, and the solvent was evaporated on a rotary evaporator. The crude mixture was further purified by column chromatography on silica gel with ethyl acetate/hexane as eluent.

In the mentioned cycloaddition reaction two diastereomer (*cis* and *trans*) has been formed. These diastereomers are very close in polarity, thus difficult to separate them. For characterization purpose, we have isolated the minor diastereomer (*trans*) for one entry (**5a**). For others entrees we have isolated only major diastereomer (*cis*) and the diastereomeric ratio (*cis:trans*) was determined by ^1H NMR analysis of reaction mixture (for details dr value see Table 4).

Diethyl 7-(3,4-dimethoxyphenyl)-2-(4-methoxyphenyl)-1-phenylhexahydropyrrolo[1,2-*b*]pyridazine-5,5(1H)-dicarboxylate (5a, *cis* diastereomer)

Reaction time: 5 h, **3aa** (0.05 g, 0.19 mmol), **4a** (0.06 g, 0.19 mmol), **5a** (0.07 g, 0.12 mmol), yield: 65%, yellow niddle like crystal, melting point: 90 °C R_f = 0.65 (ethyl acetate/hexane 2:8).

^{1}H-NMR (400 MHz): δ 7.33 (d, *J* = 8.2 Hz, 2H), 7.27-7.16 (m, 4H), 6.77 (d, *J* = 8.6 Hz, 3H), 6.69 (s, 1H), 6.63 (d, *J* = 8.2 Hz, 1H), 6.31 (d, *J* = 8.1 Hz, 1H), 4.65 (br, 1H), 4.43 (dd, *J* = 3.6, 6.3 Hz, 1H), 4.35-4.23 (m, 2H), 4.22-4.12 (m, 2H), 4.03 (t, J = 8.0 Hz, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 3.48 (s, 3H), 2.89 (dd, *J* = 8.9, 14.1 Hz, 1H), 2.45 (d, *J* = 13.9 Hz, 1H), 2.12-2.01 (m, 1H), 1.85 (q, *J* = 11.8, 24.9 Hz, 1H), 1.73 (dd, *J* = 7.6, 14.0 Hz, 1H), 1.44-1.36 (m, 1H), 1.30-1.20 (m, 6H). **^{13}C-NMR (100 MHz**): δ 171.6, 169.3, 158.4, 152.8, 148.6, 147.5, 135.0, 134.2, 128.9, 127.9, 119.7, 118.9, 115.5, 113.7, 110.2, 109.9, 62.9, 61.8, 61.7, 60.3, 57.4, 55.7, 55.6, 55.4, 38.5, 22.8, 16.4, 14.2, 14.1. **IR (neat)**: 2933, 1730, 1595, 1512, 1263, 1176, 1028, 725 cm^{-1}. **HRMS** (ESI, Q-TOF) m/z: [M + H]+ Calculated for $C_{34}H_{41}N_2O_7$ 589.2914, found 589.2916.

Diethyl 7-(3,4-dimethoxyphenyl)-2-(4-methoxyphenyl)-1-phenylhexahydropyrrolo[1,2-*b*]pyridazine-5,5(1H)-dicarboxylate (5a *trans* diastereomer)

Colorless viscous liquid **^{1}H-NMR (400 MHz)**: δ 7.10 (d, *J* = 8.6 Hz, 2H), 6.98-6.82 (m, 4H), 6.77-6.70 (m, 5H), 6.63-6.52 (m, 1H), 4.90-4.83 (m, 1H), 4.73 (dd, J = 6.2, 9.4 Hz, 1H), 4.34 (d, J = 12.7 Hz, 1H), 4.31-4.11 (m, 4H), 3.81 (s, 3H), 3.74 (s, 3H), 3.68 (s, 3H), 3.26 (dd, *J* = 9.2, 14.5 Hz, 1H), 2.31 (dd, *J* = 6.1, 14.5 Hz, 1H), 2.19-2.10 (m, 2H), 1.89-1.76 (m, 1H), 1.66-1.60 (m, 1H), 1.26-1.20 (m, 6H). **^{13}C-NMR (100 MHz)**: δ 171.3,

169.2, 158.4, 148.8, 148.4, 135.4, 133.8, 128.1, 127.6, 120.2, 120.0, 119.8, 113.9, 110.6, 61.9. 61.8, 60.6, 59.5, 57.4, 55.9, 55.6, 55.3, 53.4, 38.0, 24.3, 23.2, 14.2. **IR (neat)**: 2935, 2855, 1732, 1595, 1512, 1463, 1247, 1176, 1138, 1062, 1028, 962, 827, 804, 724 cm^{-1}. **HRMS** (ESI, Q-TOF) m/z: [M + H]+ Calculated for $C_{34}H_{41}N_2O_7$ 589.2914, found 589.2936.

Dimethyl 7-(3,4-dimethoxyphenyl)-2-(4-methoxyphenyl)-1-phenylhexahydropyrrolo[1,2-*b*]pyridazine-5,5(1H)-dicarboxylate (5b)

Reaction time: 5 h, **3aa** (0.05 g, 0.19 mmol), **4b** (0.056 g, 0.19 mmol), **5b** (0.07 g, 0.12 mmol), Yield: 63%**,** Pale yellow amorphous solid, melting point: 150 °C, R_f = 0.51 (ethyl acetate/hexane 2:8).

^{1}H-NMR (400 MHz): δ 7.28 (d, *J* = 7.8 Hz, 2H), 7.24-7.18 (m, 2H), 7.14 (d, *J* = 8.5 Hz, 2H), 6.74 (d, *J* = 8.7 Hz, 3H), 6.64 (s, 1H), 6.60 (d, *J* = 8.3 Hz, 1H), 6.27 (d, *J* = 8.3 Hz, 1H), 4.63 (br, 1H), 4.39 (dd, *J* = 3.8, 11.7 Hz, 1H), 3.99 (t, *J* = 8.3 Hz, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 3.73 (s, 3H), 3.72 (s, 3H), 3.45 (s, 3H), 2.85 (dd, J = 9.0, 14.1 Hz, 1H), 2.42 (d, *J* = 14.2 Hz, 1H), 2.00-1.97 (m, 1H), 1.80 (q, J = 12.7, 25.0 Hz, 1H), 1.70 (dd, *J* = 7.3, 13.8 Hz, 1H), 1.37-1.28 (m, 1H). **^{13}C-NMR (100 MHz)**: δ 172.0, 169.8, 158.5, 152.8, 148.6, 147.5, 134.9, 134.2, 128.9, 127.9, 119.7, 119.0, 115.5, 113.7, 110.3, 109.9, 63.0, 60.2, 57.6, 57.4, 55.8, 55.5, 55.4, 53.0, 52.9, 38.6, 22.8, 16.5. **IR (neat)**: 2951, 2848, 1732, 1595, 1510, 1263, 1246, 746 cm^{-1}. **HRMS** (ESI, Q-TOF) m/z: [M + H]+ Calculated for $C_{32}H_{37}N_2O_7$ 561.2601, found 561.2599.

Dibenzyl 7-(3,4-dimethoxyphenyl)-2-(4-methoxyphenyl)-1-phenylhexahydropyrrolo[1,2-*b*]pyridazine-5,5(1H)-dicarboxylate (5c)

Reaction time: 5 h, **3aa** (0.05 g, 0.19 mmol), **4c** (0.084 g, 0.19 mmol), **5c** (0.09 g, 0.12 mmol), yield: 64%, off-white amorphous sloid, melting point: 130 °C, R_f = 0.63 (ethyl acetate/hexane 2:8).

^{1}H-NMR (400 MHz): δ 7.36-7.12 (m, 16H), 6.76 (d, *J* = 8.6 Hz, 3H), 6.65 (s, 1H), 6.61 (d, *J* = 7.9 Hz, 1H), 6.28 (d, *J* = 8.2 Hz, 1H), 5.16-5.08 (m, 4H), 4.63 (br, 1H), 4.45 (dd, *J* = 3.7, 11.3 Hz, 1H), 4.03 (t, J = 8.1 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 3.44 (s, 3H), 2.90 (dd, *J* = 8.6, 14.3 Hz, 1H), 2.38 (d, *J* = 14.1 Hz, 1H), 2.01-1.96 (m, 1H), 1.84-1.73 (m, 2H), 1.34-1.27 (m, 1H). **^{13}C-NMR (100 MHz)**: δ 171.2, 169.0, 158.5, 152.8, 148.6, 147.5, 135.3, 135.1, 134.9, 134.3, 128.9, 128.7, 128.6, 128.6, 128.4, 128.4, 128.2, 127.9, 119.7, 118.9, 115.5, 113.7, 110.3, 109.9, 67.6, 67.5, 63.1, 60.5, 57.6, 57.5, 55.8, 55.5, 55.4, 38.6, 29.8, 22.8, 16.5. **IR (neat)**: 2926, 2850, 1732, 1595, 1510, 1454, 1263, 1028, 746 cm^{-1}. **HRMS** (ESI, Q-TOF) m/z: [M + H]+ Calculated for $C_{44}H_{45}N_2O_7$ 713.3227, found 713.3235.

Diethyl 2,7-bis(4-methoxyphenyl)-1-phenylhexahydropyrrolo[1,2-*b*]pyridazine-5,5(1H)-dicarboxylate (5d)

Reaction time: 5 h, **3aa** (0.05 g, 0.19 mmol), **4d** (0.06 g, 0.19 mmol), **5d** (0.068 g, 0.12 mmol), yield: 65%, pale yellow amorphous solid, melting point: 95 °C, R_f = 0.47 (ethyl acetate/hexane 1:9).

^{1}H-NMR (400 MHz): δ 7.30 (d, *J* = 7.8 Hz, 2H), 7.26-7.19 (m, 4H), 6.87-6.75 (m, 5H), 6.65 (d, *J* = 8.7 Hz, 2H), 4.66 (br, 1H), 4.41 (dd, *J* = 4.1, 11.0 Hz, 1H), 4.36-4.12 (m, 4H), 4.03 (t, J = 8.3 Hz, 1H), 3.84 (s, 3H), 3.71 (s, 3H), 2.89 (dd, *J* = 9.0, 14.3 Hz, 1H), 2.43 (d, *J* = 14.3 Hz, 1H), 2.11-2.00 (m, 1H), 1.87 (t, *J* = 12.6 Hz, 1H), 1.77 (dd, *J* = 7.3,

14.1 Hz, 1H), 1.43-1.35 (m, 1H), 1.29-1.23 (m, 6H), **^{13}C-NMR (100 MHz)**: δ 171.6, 169.37, 158.5, 158.4, 152.7, 134.6, 134.5, 128.8, 128.6, 128.0, 118.6, 115.1, 113.7, 113.2, 62.8, 61.8, 61.7, 60.5, 57.5, 57.3, 55.4, 55.1, 38.7, 22.7, 16.6, 14.2, 14.1. **IR (neat)**: 2916, 2848, 1730, 1620, 1512, 1263, 1244, 1174, 1033, 829, 736 cm^{-1}. **HRMS** (ESI, Q-TOF) m/z: [M + H]+ Calculated for $C_{33}H_{39}N_2O_6$ 559.2808, found 559.2787.

Diethyl 2-(4-methoxyphenyl)-1-phenyl-7-(*p*-tolyl)hexahydropyrrolo[1,2-*b*]pyridazine-5,5(1H)-dicarboxylate (5e)

Reaction time: 8 h, **3aa** (0.05 g, 0.19 mmol), **4e** (0.053 g, 0.19 mmol), **5e** (0.075 g, 0.14 mmol), yield: 73%, pale yellow gum, R_f = 0.54 (ethyl acetate/hexane 1:9).

^{1}H-NMR (400 MHz): δ 7.28 (d, *J* = 7.8 Hz, 2H), 7.25-7.18 (m, 4H), 6.90 (d, J = 8.0 Hz, 2H), 6.83-6.73 (m, 5H), 4.65 (br, 1H), 4.40 (dd, *J* = 4.0, 11.2 Hz, 1H), 4.34-4.11 (m, 4H), 4.04 (t, J = 8.1 Hz, 1H), 3.83 (s, 3H), 2.89 (dd, *J* = 9.3, 14.0 Hz, 1H), 2.41 (d, *J* = 14.9 Hz, 1H), 2.21 (s, 3H), 2.10-1.99 (m, 1H), 1.85 (t, *J* = 12.4 Hz, 1H), 1.76 (dd, *J* = 6.9, 14.1 Hz, 1H), 1.42-1.33 (m, 1H), 1.28-1.20 (m, 6H). **^{13}C-NMR (100 MHz)**: δ 171.6, 169.3, 158.5, 152.7, 139.6, 136.2, 134.5, 128.8, 128.7, 128.0, 127.5, 118.7, 115.2, 113.8, 63.28, 61.9, 61.8, 60.6, 57.5, 57.4, 55.5 ,38.6, 22.8, 21.1, 16.7, 14.2, 14.1. **IR (neat)**: 2929, 2856, 1732, 1595, 1510, 1452, 1365, 1242, 1176, 1093, 1060, 815, 734, 694 cm^{-1}. **HRMS** (ESI, Q-TOF) m/z: [M + H]+ Calculated for $C_{33}H_{39}N_2O_5$ 543.2859, found 543.2858.

Diethyl 2-(4-methoxyphenyl)-1-phenyl-7-(*o*-tolyl)hexahydropyrrolo[1,2-*b*]pyridazine-5,5(1H)-dicarboxylate (5f)

Reaction time: 8 h, **3aa** (0.05 g, 0.19 mmol), **4f** (0.053 g, 0.19 mmol), **5f** (0.07 g, 0.13 mmol), Yield: 68%**,** pale yellow gum, R_f = 0.54 (ethyl acetate/hexane 1:9).

^{1}H-NMR (400 MHz): δ 7.37 (d, *J* = 7.8 Hz, 2H), 7.30-7.28 (m, 3H), 7.11 (d, *J* = 8.7 Hz, 2H), 7.00 (t, *J* = 7.8 Hz, 1H), 6.93 (d, *J* = 7.5 Hz, 2H), 6.84 (t, *J* = 7.4 Hz, 1H), 6.70 (d, *J* = 8.7 Hz, 2H), 4.65 (br, 1H), 4.49 (dd, *J* = 4.1, 7.7 Hz, 1H), 4.33-4.08 (m, 5H), 3.79 (s, 3H), 2.96 (dd, *J* = 9.1, 13.9 Hz, 1H), 2.44 (d, *J* = 14.5 Hz, 1H), 2.14-2.04 (m, 1H), 2.00-1.84 (m, 1H), 1.64 (dd, *J* = 7.9, 13.6 Hz, 1H), 1.57 (s, 3H) , 1.45-1.37 (m, 1H), 1.27 (t, *J* = 7.2, 3H), 1.21 (t, *J* = 6.9, 3H). **^{13}C-NMR (100 MHz)**: δ 171.3, 169.4, 158.5, 152.8, 140.6, 135.4, 134.4, 129.5, 128.9, 127.3, 126.2, 126.0, 125.7, 119.0, 115.8, 113.9, 61.9, 61.8, 60.3, 59.5, 57.6, 56.9, 55.5, 36.1, 22.2, 18.7, 16.3, 14.2, 14.1. **IR (neat)**: 2931, 2854, 1732, 1595, 1510, 1490, 1462, 1365, 1246, 1060, 1031, 947, 858, 825 cm^{-1}. **HRMS** (ESI, Q-TOF) m/z: [M + H]+ Calculated for $C_{33}H_{39}N_2O_5$ 543.2859, found 543.2848.

Diethyl 2-(4-methoxyphenyl)-1,7-diphenylhexahydropyrrolo[1,2-*b*]pyridazine-5,5(1H)-dicarboxylate (5g)

Reaction time: 10 h, **3aa** (0.05 g, 0.19 mmol), **4g** (0.05 g, 0.19 mmol), **5g** (0.07 g, 0.13 mmol), yield: 69%, pale yellow gum, R_f = 0.59 (ethyl acetate/hexane 1:9).

^{1}H-NMR (400 MHz): δ 7.31 (d, *J* = 8.8 Hz, 2H), 7.25-7.19 (m, 4H), 7.12-7.08 (m, 3H), 6.95-6.91 (m, 2H), 6.82-6.76 (m, 3H), 4.67 (br, 1H), 4.43 (dd, *J* = 4.0, 11.4 Hz, 1H), 4.35-4.15 (m, 4H), 4.09 (t, *J* = 8.2 Hz 1H), 3.83 (s, 3H), 2.92 (dd, *J* = 9.3, 14.2 Hz, 1H), 2.44 (d, *J* = 13.7 Hz, 1H), 2.12-2.02 (m, 1H), 1.88 (t, *J* = 12.3 Hz, 1H), 1.80 (dd, *J* = 7.1, 14.2, 1H), 1.44-1.36 (m, 1H) 1.30-1.21 (m, 6H). **^{13}C-NMR (100 MHz)**: δ 171.5, 169.3,

158.5, 152.7, 142.6, 134.5, 128.8, 128.0, 127.9, 127.6 ,126.8, 118.8, 115.3, 113.8, 63.5, 61.9, 61.8, 60.6, 57.5, 57.4, 55.5, 38.5, 22.7, 16.6, 14.2, 14.1. **IR (neat)**: 2933, 2846, 1732, 1595, 1490, 1474, 1452, 1246, 1176, 1029, 825, 746 cm^{-1}. **HRMS** (ESI, Q-TOF) m/z: [M + H]+ Calculated for $C_{32}H_{37}N_2O_5$ 529.2702, found 529.2701.

Diethyl 7-(4-fluorophenyl)-2-(4-methoxyphenyl)-1-phenylhexahydropyrrolo[1,2-*b*]pyridazine-5,5(1H)-dicarboxylate (5h)

Reaction time: 12 h, **3aa** (0.05 g, 0.19 mmol), **4h** (0.053 g, 0.19 mmol), **5h** (0.067 g, 0.12 mmol), yield: 65%, pale yellow gum, R_f = 0.51 (ethyl acetate/hexane 1:9).

^{1}H-NMR (400 MHz): δ 7.32-7.22 (m, 4H), 7.19 (d, *J* = 7.8 Hz, 2H), 6.89-6.84 (m, 2H), 6.82-6.75 (m, 5H),4.66 (br, 1H), 4.41 (dd, *J* = 4.0, 11.2 Hz, 1H), 4.36-4.12 (m, 4H), 4.05 (t, *J* = 8.1 Hz, 1H), 3.84 (s, 3H), 2.89 (dd, *J* = 9.3, 14.0 Hz, 1H), 2.44 (d, *J* = 14.9 Hz, 1H), 2.11-2.00 (m, 1H), 1.85 (q, J = 12.4 Hz, 1H), 1.73 (dd, *J* = 6.9, 14.1 Hz, 1H), 1.44-1.36 (m, 1H), 1.29-1.23 (m, 6H). **^{13}C-NMR (100 MHz)**: δ 170.3 (d, $J_{C\text{-}F}$ = 231.3 Hz), 163.0, 158.6, 152.6, 138.2 (d, $J_{C\text{-}F}$ = 2.8 Hz), 134.4, 129.0 (d, $J_{C\text{-}F}$ = 7.8 Hz), 128.9, 128.0, 127.8 (d, $J_{C\text{-}F}$ = 7.5 Hz), 118.9, 115.2, 114.8 (d, $J_{C\text{-}F}$ = 21.3 Hz), 113.8, 62.7, 61.9 (d, $J_{C\text{-}F}$ = 9.3 Hz), 57.4 (d, $J_{C\text{-}F}$ = 19.3 Hz), 55.5, 38.5, 22.6, 16.5, 14.2 (d, $J_{C\text{-}F}$ = 8.5 Hz). **^{19}F-NMR (376 MHz):** δ -116.34 (s, 1F) **IR (neat)**: 2929, 2852, 1732, 1595, 1508, 1490, 1444, 1365, 1249, 1174, 1031, 829, 731, 696 cm^{-1}. **HRMS** (ESI, Q-TOF) m/z: [M + H]+ Calculated for $C_{32}H_{36}N_2O_5F$ 547.2608, found 547.2637.

Diethyl 7-(furan-2-yl)-2-(4-methoxyphenyl)-1-phenylhexahydropyrrolo[1,2-*b*]pyridazine-5,5(1H)-dicarboxylate (5i)

Reaction time: 4.5 h, **3aa** (0.05 g, 0.19 mmol), **4i** (0.047 g, 0.19 mmol), **5i** (0.06 g, 0.12 mmol), yield: 62%, light green amorphous solid, melting point: 125 °C, R_f = 0.53 (ethyl acetate/hexane 1:9).

^{1}H-NMR (400 MHz): δ 7.36 (d, *J* = 8.5 Hz, 2H), 7.22-7.11 (m, 5H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.73 (t, *J* = 7.2 Hz, 1H), 6.12 (dd, *J* = 1.8, 3.2 Hz, 1H), 5.93 (d, *J* = 3.0 Hz, 1H), 4.70 (t, *J* = 5.0 Hz, 1H), 4.35-4.14 (m, 6H), 3.83 (s, 3H), 2.87 (dd, *J* = 10.2, 14.1 Hz, 1H), 2.37-2.30 (m, 1H), 2.25 (dd, *J* = 4.9, 14.0 Hz, 1H), 2.11-2.01 (m, 1H), 1.73 (q, *J* = 11.7, 17.4 Hz, 1H), 1.47-1.38 (m, 1H), 1.32-1.18 (m, 6H). **^{13}C-NMR (100 MHz)**: δ 170.6, 168.9, 158.6, 155.5, 152.0, 141.3, 134.7, 128.8, 127.8, 118.3, 114.0, 113.8, 110.0, 106.6, 61.9, 61.8, 61.1, 57.6, 57.3, 57.0, 55.3, 34.0, 29.7, 24.0, 18.0, 14.1, 14.1. **IR (neat)**: 2931, 1732, 1595, 1510, 1492, 1263, 1176, 1031, 736, 702 cm^{-1}. **HRMS** (ESI, Q-TOF) m/z: [M + H]+ Calculated for $C_{30}H_{35}N_2O_6$ 519.2495, found 519.2474.

Diethyl 2-(4-methoxyphenyl)-1-phenyl-7-(thiophen-2-yl)hexahydropyrrolo[1,2-*b*]pyridazine-5,5(1H)-dicarboxylate (5j)

Reaction time: 4.5 h, **3aa** (0.05 g, 0.19 mmol), **4j** (0.05 g, 0.19 mmol), **5j** (0.063 g, 0.12 mmol), yield: 63%**,** light yellow block type crystal, R_f = 0.53 (ethyl acetate/hexane 2:8).

^{1}H-NMR (400 MHz): δ 7.31 (d, *J* = 8.0 Hz, 2H), 7.27-7.19 (m, 4H), 6.98 (d, *J* = 5.1 Hz, 1H), 6.82 (d, *J* = 8.6 Hz, 2H), 6.76 (t, *J* = 6.8, 1H), 6.72 (dd, *J* = 3.2, 4.9 Hz, 1H), 6.46 (d, *J* = 3.1 Hz, 1H), 4.68 (br, 1H), 4.42-4.09 (m, 6H), 3.81 (s, 3H), 2.98 (dd, *J* = 9.7, 14.3 Hz, 1H), 2.37 (d, *J* = 13.9 Hz, 1H), 2.09-1.94 (m, 2H), 1.76 (q, *J* = 12.0,14.3 Hz, 1H), 1.41-1.32 (m, 1H), 1.27-1.20 (m, 6H). **^{13}C-NMR (100 MHz)**: δ 171.0, 169.0, 158.7, 152.4, 148.3, 134.4, 128.7, 128.0, 125.9, 124.6, 124.3, 118.9, 115.3, 113.8, 62.0, 61.9

,60.6, 59.1, 57.6, 57.5, 55.4, 38.2, 22.1, 17.1, 14.2, 14.1. **IR (neat)**: 2922, 2850, 1732, 1597, 1510, 1489, 1463, 1365, 1242, 1168, 1093, 1062, 1029, 827, 754, 696 cm^{-1}. **HRMS** (ESI, Q-TOF) m/z: [M + H]+ Calculated for $C_{30}H_{35}N_2O_5S$ 535.2267, found 535.2236.

Procedure for one-pot synthesis of 5e

To a round-bottom flask equipped with a magnetic stir bar was charged with 4 Å MS (200 wt%), and $InCl_3$ (0.4 equiv) under nitrogen atmosphere. A DCM solution of cyclopropane carbaldehyde (1 equiv) and aryl hydrazine (1 equiv) was added and stirred at room temperature. After full consumption of the starting materials (as monitored by TLC) a DCM solution of DAC (1 equiv) was added and stirred at room temperature until completion of the reaction (as monitored by TLC). The reaction mixture was passed through a small pad of celite, and solvent was evaporated on a rotary evaporator. The crude mixture was further purified by column chromatography on silica gel with ethyl acetate/hexane as eluent.

Procedure for monodecarboxylation of 5a[12]

Compound **5a** (1equiv.) and KOH (4 equiv.) was dissolved in dry methanol under an inert atmosphere and stirred at reflux condition for 70 h. The reaction mixture was cooled down to room temperature and acidified with 2N HCl solution. The organic layer was extracted with CH_2Cl_2, dried with Na_2SO_4 and evaporated in vacuo. The compound was purified by silica gel coloum using with ethyl acetate/hexane as eluent.

Reaction time: 70 h, **5a** (0.05 g, 0.08 mmol), **6a** (0.031 g, 0.06 mmol), Yield: 75%, pale yellow oil, R_f = 0.15 (ethyl acetate/hexane 5:5).

^{1}H-NMR (400 MHz): δ 7.16 (t, *J* = 8.4 Hz, 2H), 7.10 (d, *J* = 8.7 Hz, 2H), 7.03 (d, *J* = 7.9 Hz, 2H), 6.92 (s, 1H), 6.77-6.68 (m, 4H), 6.58 (d, *J* = 3.6, 1H), 4.61 (t, *J* = 8.3, 1H), 4.35-4.30 (m, 1H), 4.27 (dd, *J* = 5.3, 10.2 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.61 (s, 3H), 3.02-2.93 (m, 1H), 2.40-2.31 (m, 1H), 2.28-2.19 (m, 1H), 2.09-2.00 (m, 1H), 1.94 (q, *J* = 10.8, 23.7 Hz, 1H), 1.90-1.73 (m, 2H). **^{13}C-NMR (100 MHz)**: δ 179.0, 158.5, 153.4, 148.7, 147.9, 136.2, 134.3, 128.8, 127.1, 120.0, 118.4, 113.9, 113.6, 110.4, 110.1, 68.5, 62.8, 56.9, 55.8, 55.6, 55.4, 46.8, 36.8, 29.8, 25.3, 24.1. **IR (neat)**: 2935, 2835, 1705, 1595, 1510, 1489, 1263, 1244, 1174, 1026, 808, 746, 698 cm^{-1}. **HRMS** (ESI, Q-TOF) m/z: $[M+H]^+$ Calculated for $C_{29}H_{33}N_2O_5$ 489.2389, found 489.2392.

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ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H, ^{13}C NMR, and IR spectra, mass data of all new compounds and single-crystal X-ray data are available in Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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