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Stereospecific Copper(II)-Catalyzed Tandem Ring Opening/Oxidative Alkylation of Donor-Acceptor Cyclopropanes with Hydrazones: Synthesis of Tetrahydropyridazines

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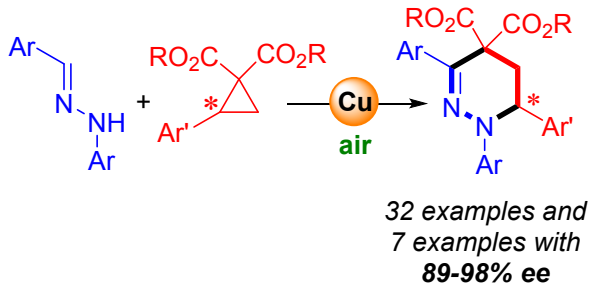


ABSTRACT: Aerobic copper(II)-catalyzed tandem ring opening and oxidative C-H alkylation of donor-acceptor cyclopropanes with bisaryl hydrazones is accomplished to produce tetrahydropyridazines, in which copper(II) plays dual role as a Lewis acid as well as redox catalyst. The reaction is stereospecific and optically active cyclopropanes can be reacted with high optical purities (89-98% *ee*). The substrate scope, functional group tolerance, dual role of the copper(II) catalyst and the use of air as an oxidant are the important practical features. A product bearing a 3-bromoaryl group can be subjected to Pd-catalyzed Suzuki-coupling with boronic acid in high yield.

INTRODUCTION

Donor-acceptor (D-A) cyclopropanes are the versatile building blocks in organic synthesis.[1] Ring strain (27.5 kcal mol^{-1})[2] and vicinal substitution pattern of donor and acceptor groups make them to have a propensity to undergo ring-opening, rearrangement and cycloaddition reactions.[3,4] To

date, [3+n] (n = 2, 3, 4) cycloaddition of D-A cyclopropanes with [1,n]-dipolarophiles have been extensively investigated to construct carbo- and heterocycles.[5] Thereby, harnessing the reactivity of D-A cyclopropanes as the 1,3-zwitterion equivalents in the synthesis of heterocycles is emerging as a valuable asset in synthetic chemistry. Tetrahydropyridazines and their synthetic analogues represent an imperative class of aza-heterocycles as they display unique biological properties (Fig. 1).[6] Significant synthetic contribution has thus been made for the construction of tetrahydropyridazine scaffolds. Of the strategies developed, base promoted [4+2]-cycloaddition of *in situ* generated 1,2-diaza-1,3-butadienes with alkenes is studied thoroughly to assemble tetrahydropyridazines.[7] Recently, Werz and co-workers reported a [3+3]-cycloaddition of *in-situ* generated nitrile imines with D-A cyclopropanes using $TiCl_4$ to give tetrahydropyridazines at moderate temperature (Scheme 1a).[8] Soon after, they have also shown the nucleophilic ring opening of D-A cyclopropanes with naphthoquinones using $SnCl_2$, which acts as both a Lewis

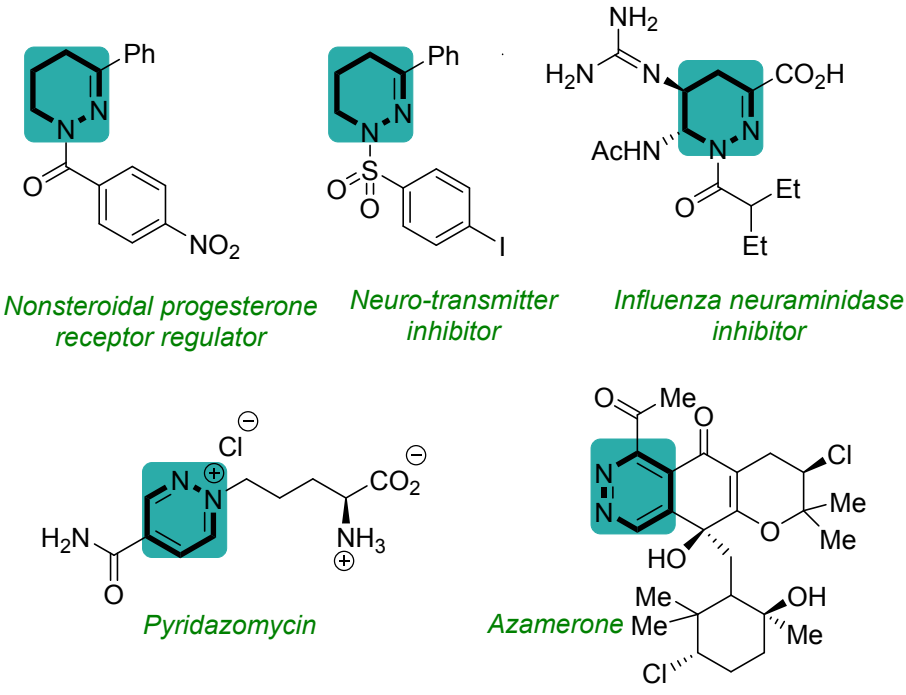
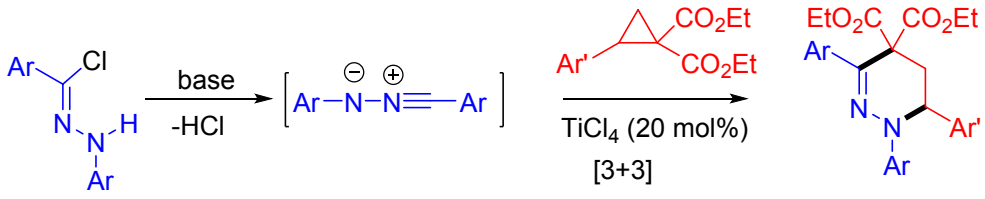


Figure 1. Some examples of biologically important tetrahydropyridazine scaffolds

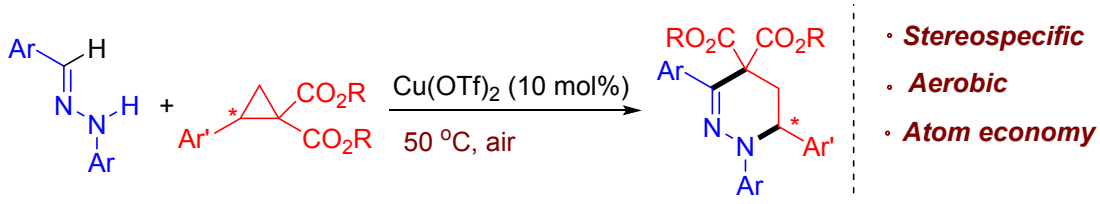
acid as well as a redox catalyst.[3e] This strategy provides an effective synthetic tool for the construction of tetrahydropyridazine scaffolds with readily accessible cyclopropanes. Development of a stereospecific strategy for tetrahydropyridazine structural frameworks using the optically active D-A cyclopropanes[4a,4g-h,5e] would thus be valuable. Further, the use of C–H functionalization to assemble molecules has witnessed a dramatic advancement in recent years.[9] Herein, we present an aerobic[10] stereospecific copper(II)-catalyzed tandem[11a] nucleophilic ring (S_N2) opening and intramolecular oxidative C(sp^2)-H alkylation[11b] of D-A cyclopropanes with bisaryl hydrazones to afford tetrahydropyridazines (Scheme 1b). Optically active D-A cyclopropanes can be coupled in high optical purities (89-98% *ee*). The reaction is atom economical and generates water as the by-product.

Scheme 1. Synthesis of Tetrahydropyridazines using D-A Cyclopropanes

a. Previous study: [3+3]-cycloaddition with nitrile imines

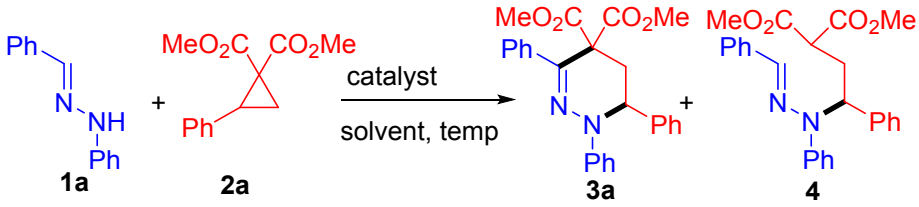


b. This study: tandem ring-opening/oxidative C-H alkylation using Cu as Lewis acid and redox catalyst



RESULTS AND DISCUSSION

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst (10 mol%)	solvent	yield[b] (%)	
			3a	**4**
1	$Cu(OTf)_2$	toluene	41	47
2	$Cu(OTf)_2$	CH_2Cl_2	30	56
3	$Cu(OTf)_2$	$(CH_2Cl)_2$	63	27
4	$Cu(OTf)_2$	THF	10	17
5	$Cu(OTf)_2$	PhCl	19	24
6	$Sc(OTf)_3$	$(CH_2Cl)_2$	5	81
7	$Zn(OTf)_2$	$(CH_2Cl)_2$	n.d.	trace
8	$Yb(OTf)_3$	$(CH_2Cl)_2$	36	55
9	AgOTf	$(CH_2Cl)_2$	n.d.	23
10[c]	$Cu(OTf)_2$	$(CH_2Cl)_2$	82	trace
11[d]	$Cu(OTf)_2$	$(CH_2Cl)_2$	70	trace
12	-	$(CH_2Cl)_2$	n.d.	n.d.

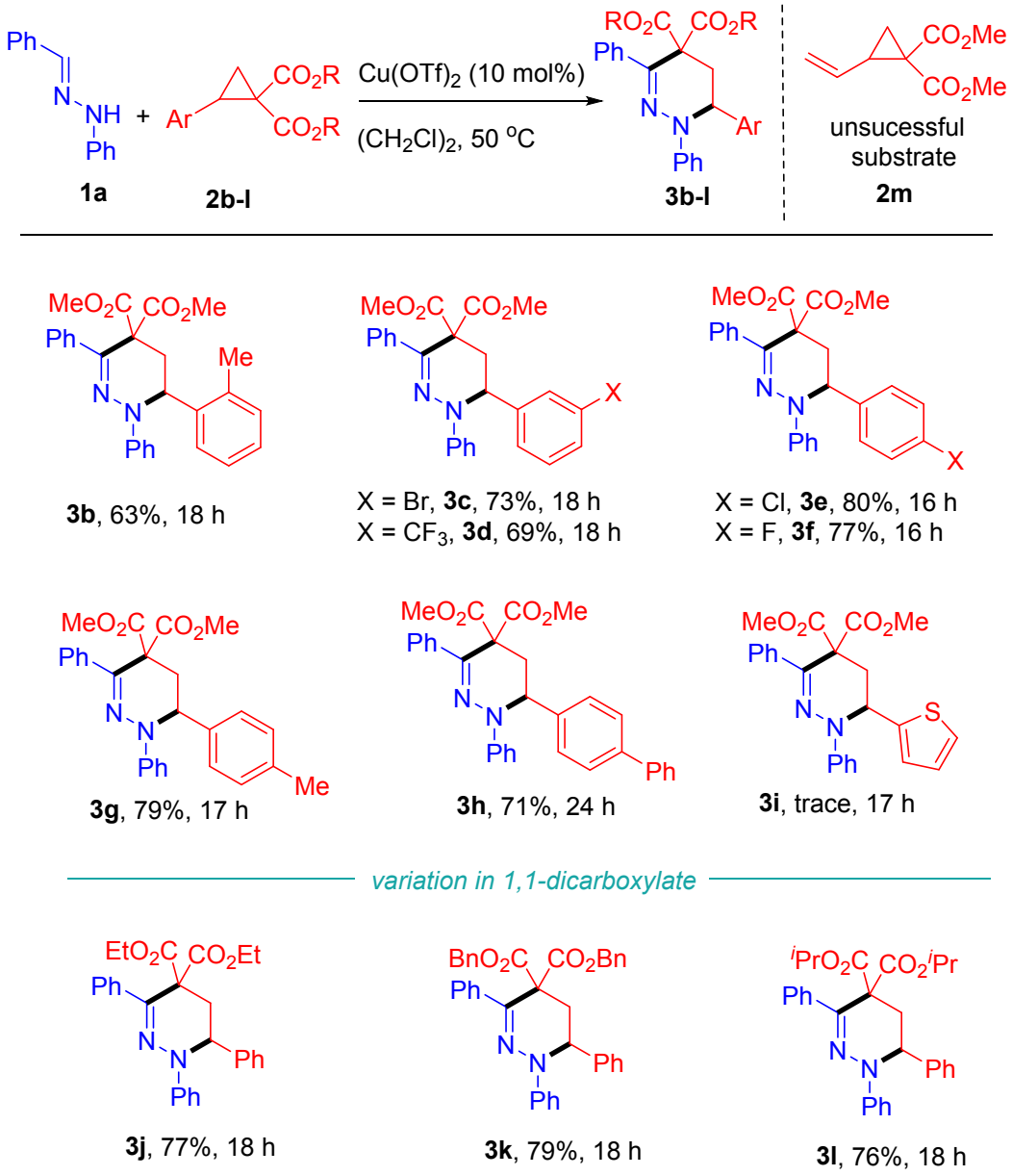
[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.22 mmol), catalyst (10 mol%), solvent (1.5 mL), rt, 16 h. [b]Isolated yield. [c]Reaction at 50 °C. [d]Reaction at 80 °C. n.d. = not detected.

Our optimization studies commenced with (*E*)-1-benzylidene-2-phenylhydrazine **1a** and D-A cyclopropane **2a** as the test substrates, utilizing a series of Lewis acids and solvents (Table 1). Gratifyingly, tetrahydropyridazine **3a** was produced in 41% yield along with 47% uncyclized **4**, when the reaction was carried out employing 10 mol % $Cu(OTf)_2$ for 16 h in toluene at room temperature (entry 1). Subsequent screening of solvents led to enhance the yield to 63% utilizing $(CH_2Cl)_2$, whereas CH_2Cl_2, THF and chlorobenzene produced inferior results (entries 2-5). In a set of Lewis acid catalysts screened, $Cu(OTf)_2$, $Sc(OTf)_3$, $Zn(OTf)_2$, $Yb(OTf)_3$ and AgOTf, the former yielded superior results (entries 3 and 6-9). Gladly, increasing of reaction temperature to 50 ^oC improved the yield to 82% with a trace amount of **4** (entry 10). Further increment of temperature (80 ^oC), however, led to drop the yield to 70%, which might be due to the low stability of the imine C=N bond (entry 11).[12] A control experiment confirmed that **3a** was not formed in the absence of the catalyst (entry 12).

Having identified the optimized reaction conditions, the scope of the procedure was assessed engaging the substituted 2-aryl cyclopropane-1,1-dicarboxylates **2b-l** with hydrazone **1a** as a representative example (Scheme 2). Cyclopropane **2b** with 2-methyl substituent at the aryl ring furnished tetrahydropyridazine **3b** in 63% yield. Similarly, 3-bromo **2c** and 3-trifluoromethyl **2d** substituted cyclopropanes in the aryl ring provided **3c** and **3d** in 73 and 69% yields, respectively. Reactions of the cyclopropanes bearing 4-chloro **2e**, 4-fluoro **2f**, 4-methyl **2g** and 4-phenyl **2h** functionalities at the aryl ring afforded the target products **3e-h** in 71-80% yields, while the 2-thienyl containing cyclopropane **2i** was incompatible and produced a trace amount of **3i**. Interestingly, 1,1-diester variants of D-A cyclopropanes, such as **2j-l** successfully participated in the reaction to provide aza-heterocycles **3j-l** in 76-79% yields. Under these conditions, vinyl

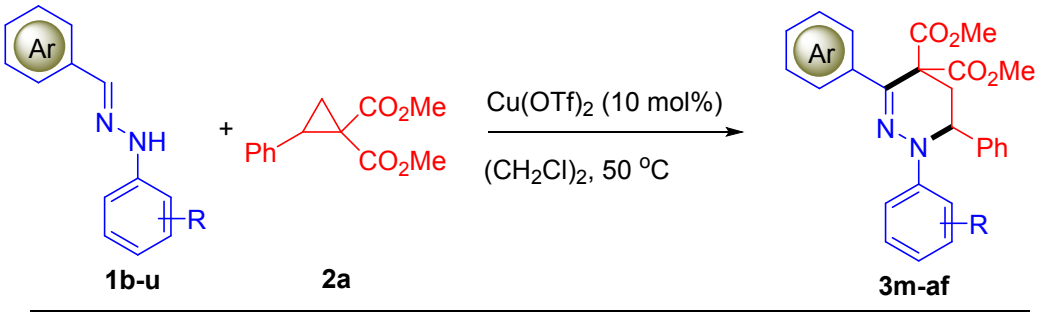
cyclopropane **2m** was an unsuccessful substrate, which may be due to the less electrophilic nature of the C2 carbon compared to that of 2-aryl substituted cyclopropanes **2a-l**.

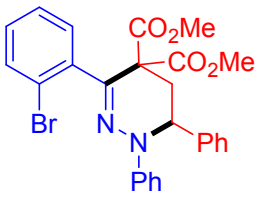
Scheme 2. Substrate Scope with Respect to D-A Cyclopropanes[a-c]



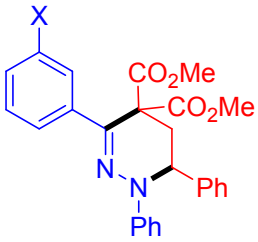
[a]Reaction conditions: **1a** (0.2 mmol), **2b-l** (0.22 mmol), $Cu(OTf)_2$ (10 mol%), $(CH_2Cl)_2$ (1.5 mL), 50 °C. [b]Isolated yield. Bn = benzyl. [c]Accompanied ~5% of uncyclized products.

Scheme 3. Substrate Scope with Respect to Hydrazones[a-c]

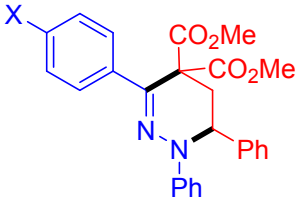




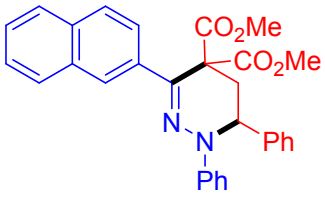
3m, 64%, 16 h



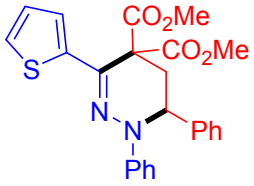
X = Br, **3n**,74%, 17 h
X = CH_3, **3o,** 80%, 16 h
X = CF_3, **3p**, 70%, 18 h



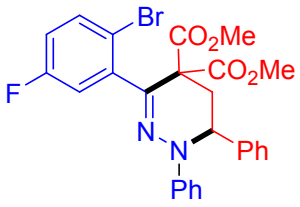
X = OAc, **3q**, 63%, 22 h
X = Br, **3r**, 75%, 16 h
X = Cl, **3s**,81%, 17 h
X = CN, **3t**, 69%, 22 h
X = F, **3u**, 80%, 16 h
X = Me, **3v**, 81%, 17 h
X = Ph, **3w**, 73%, 16 h
X = NO_2, **3x**, 61%, 22 h



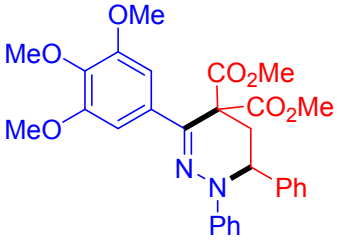
3y, 69%, 20 h



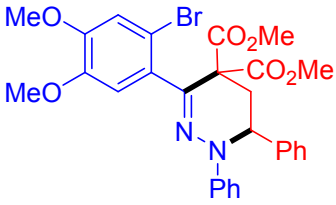
3z,74%, 21 h



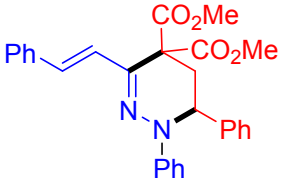
3aa, 66%, 24 h



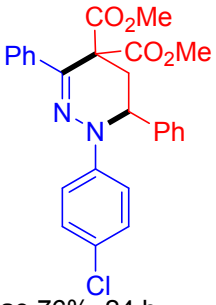
3ab, 77%, 22 h



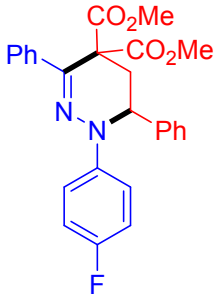
3ac, 73%, 24 h



3ad, 62%, 24 h



3ae,76%, 24 h



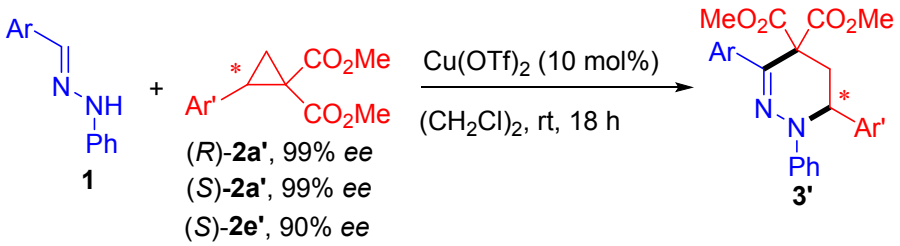
3af, 73%, 24 h

[a]Reaction conditions: **1b-u** (0.2 mmol), **2a** (0.22 mmol), $Cu(OTf)_2$ (10 mol%), $(CH_2Cl)_2$ (1.5 mL), 50 °C. [b]Isolated yield. [c]Accompanied ~5% of uncyclized products.

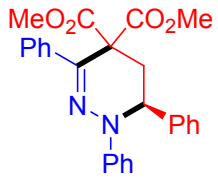
Next, the scope of the procedure was extended for the synthesis of functionalized tetrahydropyridazines with a series of hydrazones **1b-u** using D-A cyclopropane **2a** as the representative example (Scheme 3). *N*-Phenyl substituted hydrazones bearing both the electron-donating and -withdrawing groups in the aryl rings can be readily cross-coupled. To mention, the 2-bromo derivative **1b** resulted in **3m** with 64% yield. The substrates having 3-bromo **1c**, 3-methyl **1d** and 3-trifluoromethyl **1e** groups afforded the heterocycles **3n-p** in 70-80% yields. Similar results were observed for hydrazones containing 4-substituents with acetoxy **1f**, bromo **1g**, chloro **1h**, cyano **1i**, fluoro **1j**, methyl **1k**, phenyl **1l** and nitro **1m** functionalities, delivering the target products **3q-x** in 61-81% yields. Notably, 2-naphthyl **1n** and 2-thienyl **1o** substrates conveyed **3y** and **3z** in 69 and 74% yields, respectively. To our delight, di- and tri-substituted hydrazones **1p-r** were found to be compatible, furnishing the heterocycles **3aa-ac** in 66-77% yields. In addition, C-styryl substituted hydrazone **1s** participated in the reaction to give **3ad** in 62% yield. Moreover, 4-chloro **1t** and 4-fluoro **1u** substitution on the *N*-phenyl ring of hydrazones underwent reaction to afford **3ae** and **3af** in 76 and 73% yields, respectively.

To reveal the stereoselectivity, the coupling of a series of hydrazones was investigated with optically active D-A cyclopropanes (*R*)-**2a′** and (*S*)-**2a′** as the representative examples (Scheme 4). Hydrazone **1a** underwent reaction with (*R*)-**2a′** to give **3a′** in 91% *ee*, while hydrazones containing 4-cyano **1i**, 4-methyl **1k** and 4-fluoro **1j** substituents in the aryl ring produced tetrahydropyridazines **3t′-u′** in 95-98% *ee*. Similarly, cyclopropane (*S*)-**2e′** having a 4-chloro group in the aryl ring on reaction with hydrazone **1a** conveyed **3e′** in 89% *ee*. Parallel results were

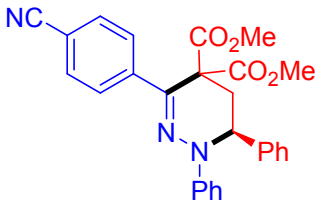
Scheme 4. Enantiospecific Synthesis of Tetrahydropyridazines[a,b]



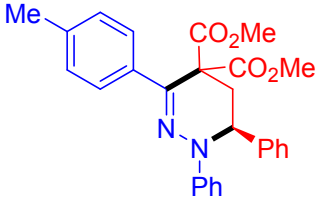
from (R)-cyclopropane



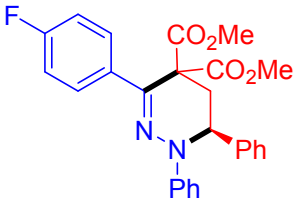
3a', 68%, 91% *ee*



3t', 64%, 95% *ee*



3v', 78%, 98% *ee*



3u', 76%, 98% *ee*

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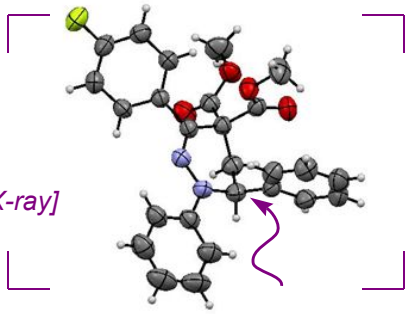
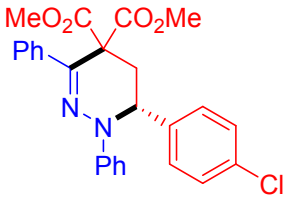
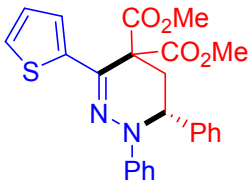


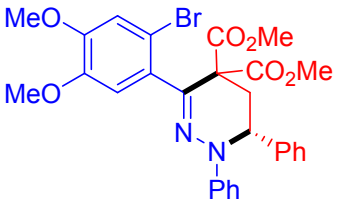
from (S)-cyclopropane



3e', 74%, 89% *ee*



3z', 70%, 94% *ee*

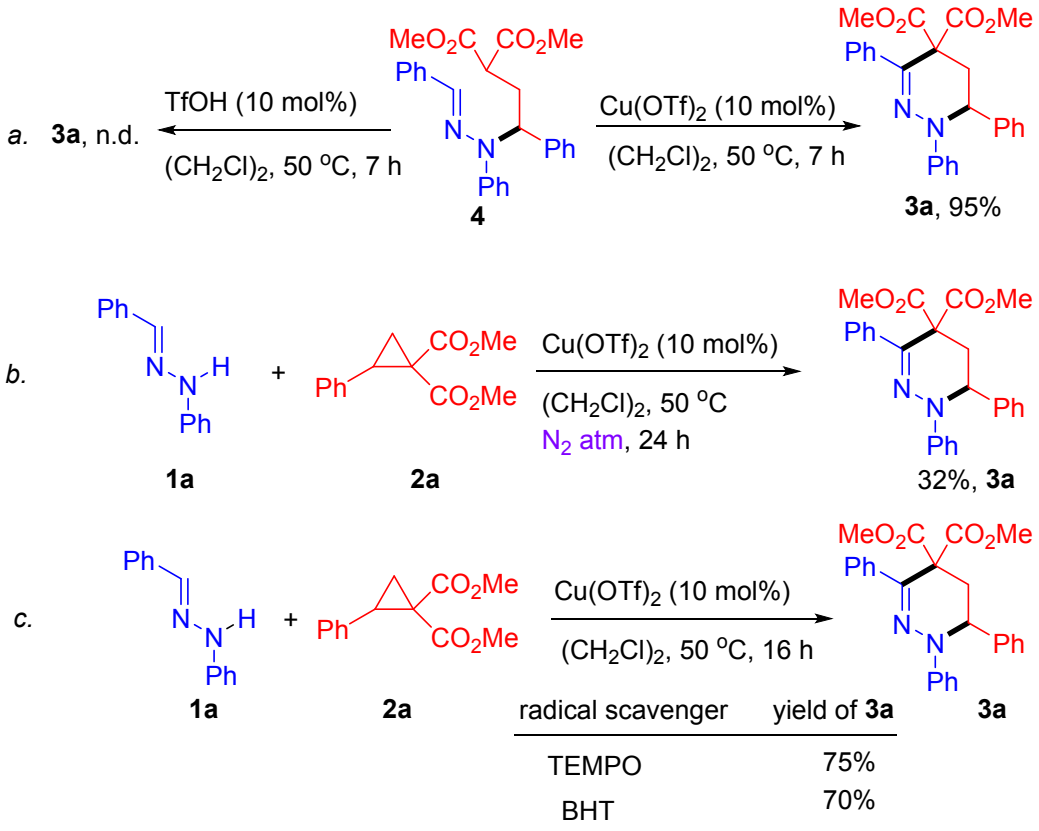


3ac', 67%, 92% *ee*

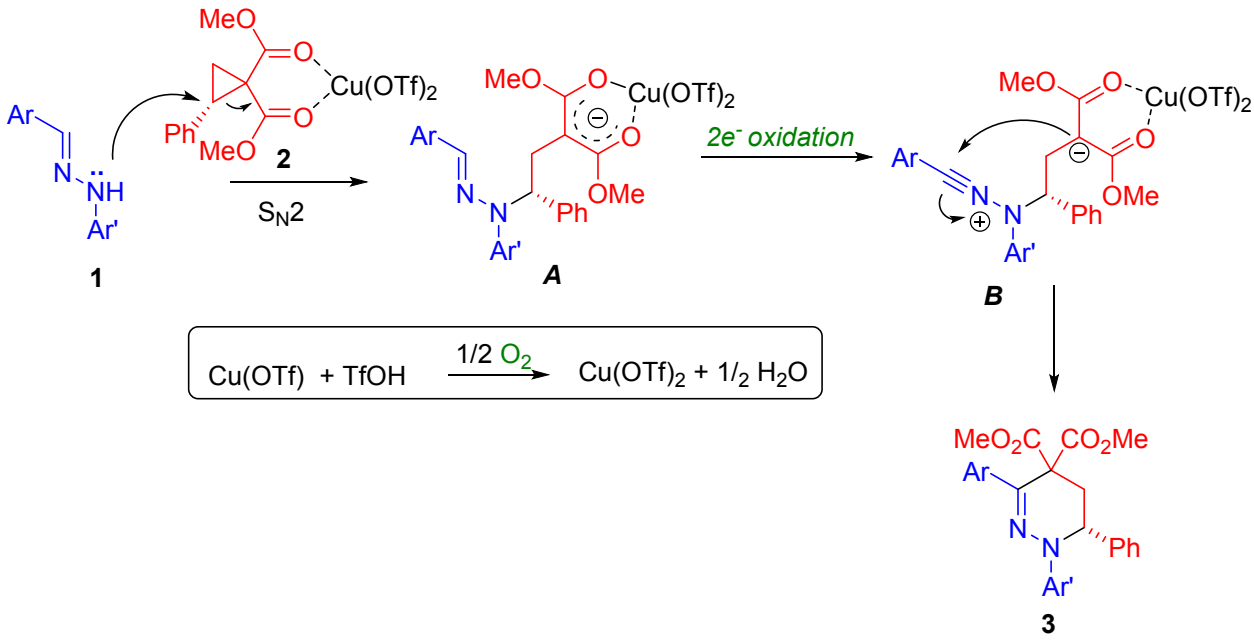
[a]Reaction conditions: **1** (0.2 mmol), **2´** (0.22 mmol), $Cu(OTf)_2$ (10 mol%), $(CH_2Cl)_2$ (1.5 mL), rt, 18 h. [b]Isolated yield.

perceived utilizing hydrazones **1o** and **1r** on reaction with (*S*)-**2a´**, affording **3z′** and **3ac´** in 94 and 92% *ee,* respectively. The absolute configuration of **3u´** was determined using a single-crystal X-ray analysis (see the Supporting Information). These results suggest that the reaction may proceed through a S_N2 ring opening of D-A cyclopropanes and the construction of functionalized tetrahydropyridazines can be achieved with high optical purities.

Scheme 5. Preliminary Mechanistic Investigations



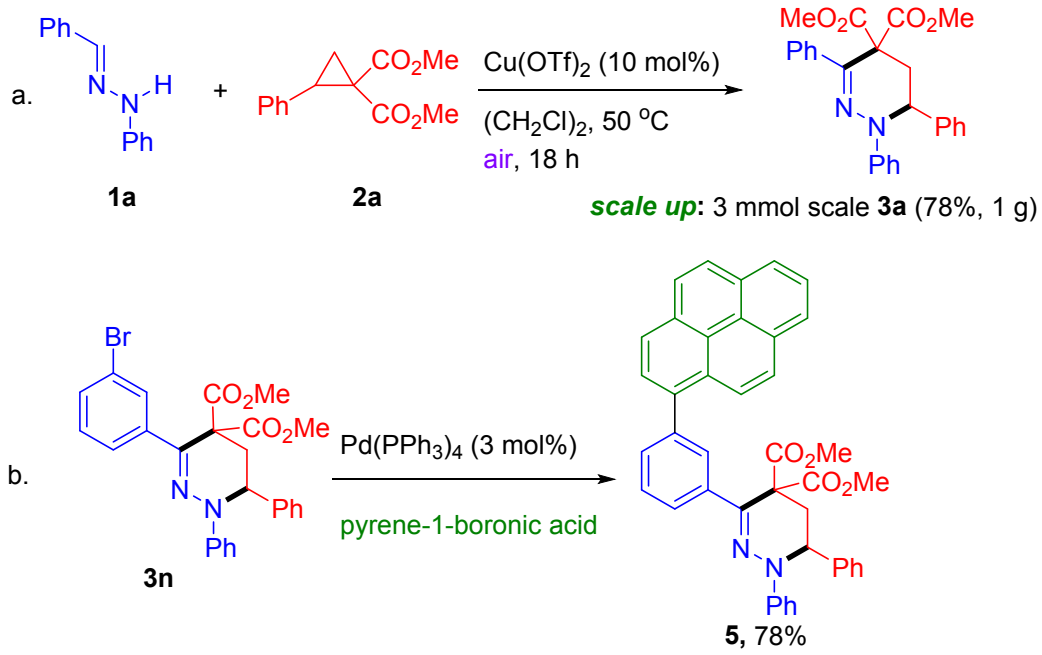
Scheme 6. Proposed Reaction Pathway



To gain insight into the reaction pathway, the reaction of **4** was performed employing 10 mol % $Cu(OTf)_2$ in $(CH_2Cl)_2$ and the tetrahydropyridazine **3a** was obtained in 95% yield (Scheme 5a). Hence, the reaction likely to proceed via a ring opening of D-A cyclopropane. In addition, the cyclization of **4** was ineffective with TfOH, which implies that the cyclization may not occur via Bronsted acid catalysis. Consequently, the standard reaction of **1a** and **2a** under N_2 atmosphere resulted in diminished yield of **3a** (32%), bolstered the involvement of an aerobic oxidative pathway (Scheme 5b).[11b] Further, the radical scavenger experiments independently in presence of 1 equiv 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and 1 equiv of 2,6-di-*tert*-butyl-4-methylphenol (BHT) do not impede the product formation, which invalidates a radical pathway (Scheme 5c). Thus, $Cu(OTf)_2$-catalyzed S_N2 ring opening of D-A cyclopropanes **2** with hydrazones **1** can deliver ***A*** with inverted configuration. The $Cu(OTf)_2$-catalyzed $2e^-$ oxidation[11c] of ***A*** can produce an *N*-amino nitrilium ion[11a] ***B*** (Scheme 6). The Lewis acid catalyzed

intramolecular cyclization of ***B*** can lead to the formation of the target heterocycle **3**. Aerobic oxidation of Cu(OTf) with TfOH can regenerate $Cu(OTf)_2$ to complete the catalytic cycle. The proposed catalytic cycle explains the dual role of $Cu(OTf)_2$ as a redox catalyst for the oxidation of imine to nitrile as well as Lewis acid catalyst for the nucleophilic ring opening and addition of the enolate to nitrile to produce the target heterocycle **3**.

Scheme 7. Synthetic Applications



To display the synthetic utility, the scale-up synthesis was conducted on a 3 mmol scale and **3a** was obtained in 78% yield (Scheme 7a). In addition, a bromo bearing tetrahydropyridazine **3n** was transformed to **5** in 78% yield via Suzuki coupling using pyrene-1-boronic acid (Scheme 7b).

CONCLUSIONS

In summary, an aerobic copper-catalyzed tandem reaction of the readily accessible hydrazones with D-A cyclopropanes have been demonstrated for the construction of tetrahydropyridazine structural frameworks via a sequential nucleophilic ring opening (S_N2) and aerobic oxidative C-C bond formation. The method offers a potential route to access optically pure tetrahydropyridazines. The substrate scope, air as the oxidant and functional group compatibility are the importance practical features.

EXPERIMENTAL SECTION

General Information. $Cu(OTf)_2$ (98%), $Sc(OTf)_3$ (99%), $Zn(OTf)_2$ (98%), $Yb(OTf)_3$ (99.99%) and AgOTf (≥98.0%) were purchased from Aldrich and used as received. Merck silica gel G/GF 254 plates were utilized for analytical TLC. Rankem silica gel (60-120 mesh) was employed for column chromatography. Bruker Avance III 600 and 400 MHz spectrometers were used for recording NMR (^1H and ^{13}C) spectra utilizing $CDCl_3$ as the solvent and TMS (Me_4Si) as an internal standard. Chemical shifts (δ) and spin-spin coupling constant (*J*) are reported in ppm and in Hz, respectively, and other data are reported as follows: s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet and br s = broad singlet. Melting points were determined using a Büchi B-540 apparatus and are uncorrected. Optical rotations were determined by using a PerkinElmer-343 Polarimeter with a 50 mm path length cell at 589 nm at 25 °C. HPLC analysis was carried out using Waters-2489 with Daicel Chiralcel AD-H and Chiralpak IC column using 2-propanol and *n*-hexane as an eluent. IR spectra were collected on Perkin Elmer FT-IR spectrometer. Q-Tof ESI-MS instrument (model HAB 273) was used for mass spectra. Single crystal X-ray data were

collected on a Bruker SMART APEX II equipped with a CCD area detector using Mo/Kα radiation and the structure was solved by direct method using SHELXL-16 (Göttingen, Germany).

General Procedure for the Preparation of Bisaryl Hydrazones.[13] To a stirred solution of aryl hydrazine (2 mmol) in EtOH (5 mL) was added aldehyde (1.6 mmol) slowly. The mixture was stirred at 60 ^{o}C in an oil bath for 30 min. The precipitated bisaryl hydrazone was filtered, washed with EtOH (5 mL), dried and used without further purification. Bisaryl hydrazones (**1a-b**, **1g**, **1i**, **1o**, **1s**),[13c] (**1c**, **1k**, **1n**, **1t-u**),[13e] (**1d**, **1m**),[13d] **1f**,[13b] (**1h**, **1j**)[13f] and **1q**[13a] are known compounds. While the hydrazones **1e**, **1l**, **1p** and **1r** are new compounds whose characterization data are presented.

(*E*)-1-Phenyl-2-(3-(trifluoromethyl)benzylidene)hydrazine 1e. Synthesized according to the given procedure in 81% yield (342.1 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.80 (s, 1H), 7.71 (s, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 1H), 7.34-7.31 (m, 2H), 7.16-7.15 (m, 2H), 6.93 (t, *J* = 7.2 Hz, 1H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 144.2, 136.2, 135.26, 135.22, 131.4 (q, $J_{C\text{-}F}$ = 31.95 Hz), 129.3, 129.0, 126.3 (q, $J_{C\text{-}F}$ = 201.75 Hz), 124.7 (q, $J_{C\text{-}F}$ = 3.45 Hz), 122.7 (q, $J_{C\text{-}F}$ = 3.6 Hz), 120.6, 112.9; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{14}H_{12}F_3N_2$: 265.0947, found 265.0953.

(*E*)-1-([1,1'-Biphenyl]-4-ylmethylene)-2-phenylhydrazine 1l. Synthesized according to the given procedure in 85% yield (369.9 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.4 Hz, 3H), 7.64-7.58 (m, 5H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.36-7.34 (m, 1H), 7.28 (t, *J* = 8.4 Hz, 2H), 7.13 (d, *J* = 7.8 Hz, 2H), 6.88 (t, *J* = 7.2 Hz, 1H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 144.6, 141.0, 140.6, 136.8, 134.3, 129.3, 128.8, 127.4, 127.3, 126.9, 126.6, 120.1, 112.7; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{17}N_2$: 273.1386, found 273.1390.

(*E*)-1-(2-Bromo-5-fluorobenzylidene)-2-phenylhydrazine 1p. Synthesized according to the given procedure in 87% yield (406.4 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.96-7.94 (m, 2H), 7.76-7.75 (m, 1H), 7.48-7.46 (m, 1H), 7.31-7.28(m, 2H), 7.13-7.11 (m, 2H), 6.93-6.90 (m, 1H), 6.87-6.84 (m, 1H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 162.8 ($J_{C\text{-}F}$ = 244.5 Hz), 143.9, 134.57, 134.56, 134.1 ($J_{C\text{-}F}$ =7.95 Hz), 129.4, 120.8, 116.7, 116.5, 113.3 ($J_{C\text{-}F}$ =24.3 Hz), 113.0; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{13}H_{11}BrFN_2$: 293.0084, found 293.0088.

(*E*)-1-(2-Bromo-4,5-dimethoxybenzylidene)-2-phenylhydrazine 1r. Synthesized according to the given procedure in 84% yield (448.8 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.77 (s, 1H), 7.55 (s, 1H), 7.28 (t, *J* = 7.8 Hz, 2H), 7.10 (d, *J* = 7.8 Hz, 2H), 6.96 (s, 1H), 6.88 (t, *J* = 7.2 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 149.9, 148.6, 144.5, 136.2, 129.3, 126.6, 120.2, 115.0, 113.6, 112.7, 108.5, 56.1, 56.0. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{15}H_{16}BrN_2O_2$: 335.0390, found 335.0389.

General Procedure for the Preparation of D-A Cyclopropanes.[14] To a stirred solution of the aldehyde (5 mmol) in benzene (10 mL), dimethyl malonate (5 mmol, 660 mg), piperidine (0.5 mmol, 50 μL) and acetic acid (0.5 mmol, 28 μL) were added. The flask was equipped with a Dean-Stark trap and condenser, and the solution was heated to reflux in an oil bath. After completion, evaporation of the solvent gave a residue that was purified by silica gel column chromatography using ethyl acetate and hexane.

Sodium hydride (4 mmol, 60% dispersion in mineral oil, 96 mg) was suspended in anhydrous DMF (10 mL) under nitrogen. Trimethylsulfoxonium iodide (3.85 mmol, 847 mg) was added and the solution was stirred for 1 h at room temperature. A solution of the appropriate benzylidene malonate (3.5 mmol) in anhydrous DMF (1 mL) was added, and the reaction mixture was allowed

to stir over night at room temperature. After completion, the solution was poured onto a mixture of ice and 2 M HCl (5 mL) and extracted with diethyl ether (25 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on a silica gel column chromatography using n-hexane and ethyl acetate as an eluent to give cyclopropanes. All the synthesized cyclopropanes **2a**,[14f] **2b**,[14a] **2c**,[14c] **2d**,[14g] **2e-g**,[14f] **2h**,[14b] **2i-j**,[14f] and **2k-l**[14e] are known compounds.

General Procedure for the Preparation of Enantio-enriched Cyclopropanes 2a′ and **2e**[4b,14h]

To a stirred solution of chiral 1-phenylethane-1,2-diol (2.2 mmol, 304 mg) in CH_2Cl_2 (5 mL) at 0 °C, was added NEt_3 (6.5 mmol, 1 mL). After 10 minutes, a solution of MsCl (5.4 mmol, 618 mg) in CH_2Cl_2 (1 mL) was added for 1 h dropwise. The resultant mixture was warmed to room temperature, and the stirring was continued for an additional 4 h. The reaction mixture was then poured into 1M HCl (5 mL) and extracted using CH_2Cl_2 (3 x 10 mL). The combined organic layer was washed successively with 1M HCl (5 mL), saturated $NaHCO_3$ (5 mL) and water (5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue, which was used in the next step.

To a suspension of NaH (60% in mineral oil, 0.9 mmol, 22 mg) in THF (5 mL) was added a solution of dimethylmalonate (0.6 mmol, 79 mg) in THF (0.5 mL) for 20 min at 0 °C. The resultant mixture was treated with a solution of the above prepared bismesylate (0.3 mmol, 88 mg) in THF (0.5 mL) dropwise (0 °C). The reaction mixture was then stirred under reflux for 24 h in an oil bath, poured into water (2 mL) and extracted with EtOAc (3 x 5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using ethyl acetate and hexane as an eluent to afford the known enantio-enriched cyclopropanes **2a′** and **2e′.**[4b, 14h]

General Procedure for the Synthesis of Tetrahydropyridazines. Bisaryl hydrazone **1** (0.2 mmol), cyclopropane **2** (0.22 mmol) and $Cu(OTf)_2$ (0.02 mmol, 7.23 mg) were stirred in $(CH_2Cl)_2$ (1.5 mL) at 50 °C using $CaCl_2$ guard tube in an oil bath. Progress of the reaction was monitored using TLC with ethyl acetate and *n*-hexane as an eluent. After completion, the reaction mixture was cooled to room temperature and diluted with CH_2Cl_2 (10 mL), and washed with water (5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on a silica gel column chromatography using *n*-hexane and ethyl acetate as an eluent to give tetrahydropyridazines **3**.

Procedure for the Enantiospecific Tetrahydropyridazine Synthesis. Bisaryl hydrazone **1** (0.2 mmol), optically active cyclopropanes (0.22 mmol) and $Cu(OTf)_2$ (0.02 mmol, 7.23 mg) were stirred at room temperature for 18 h. The work-up was carried out as above described general procedure for the synthesis of tetrahydropyridazines. The *ee* was determined using chiral HPLC analysis.

Gram-scale Synthesis of 3a. Hydrazone **1a** (3 mmol, 588 mg), cyclopropane **2a** (3.3 mmol, 772 mg) and $Cu(OTf)_2$ (10 mol %, 108 mg) were stirred in $(CH_2Cl)_2$ (10 mL) at 50 °C using $CaCl_2$ guard tube in an oil bath. Progress of the reaction was monitored using TLC with ethyl acetate and *n*-hexane as an eluent. After completion, the reaction mixture was cooled to room temperature and diluted with CH_2Cl_2 (3 x 10 mL), and washed with water (10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on a silica gel column chromatography using *n*-hexane and ethyl acetate as the eluent to give **3a** in 78% yield (1 gm).

Dimethyl 1,3,6-triphenyl-5,6-dihydropyridazine-4,4(1*H*)-dicarboxylate 3a. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.43; colorless solid; mp 160-161 °C; yield 68% (58

mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.2 Hz, 2H), 7.39 (t, *J* = 7.2 Hz, 2H), 7.33-7.31 (m, 5H), 7.29-7.25 (m, 3H), 7.20 (d, *J* = 7.2 Hz, 2H), 6.94 (t, *J* = 7.2 Hz, 1H), 5.34-5.33 (m, 1H), 3.54 (s, 3H), 3.27 (dd, *J* = 13.8, 3.0 Hz, 1H), 3.13 (s, 3H), 2.93 (dd, *J* = 13.2, 6.0 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 170.7, 168.6, 145.9, 138.2, 138.2, 133.7, 129.1, 128.8, 128.1, 127.8, 127.7, 127.2, 126.9, 120.9, 114.5, 53.9, 53.4, 53.2, 52.5, 33.9; IR (KBr) 2948, 2928, 1753, 1743, 1726, 1594, 1556, 1489, 1449, 1434, 1367, 1348, 1241, 1217, 1172, 1068 cm^{-1}; **3a′**: $[\alpha]_D^{25}$ = +17.95 (c= 0.08, $CHCl_3$); HPLC analysis: 91% *ee* [Daicel CHIRALCEL AD-H column, hexane/*i*PrOH = 97:3, flow rate: 1 mL /min, λ = 254 nm, t_R = 14.44 min (minor), 16.40 min (major)]; HRMS (ESI) m/z [M+H]+ calcd for $C_{26}H_{25}N_2O_4$: 429.1809, found 429.1810.

Dimethyl 1,3-diphenyl-6-(o-tolyl)-5,6-dihydropyridazine-4,4(1*H*)-dicar-boxylate 3b. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.42; yellow solid; mp 141-142 °C; yield 63% (55.6 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.2 Hz, 2H), 7.27 (t, *J* = 7.2 Hz, 2H), 7.22-7.20 (m, 1H), 7.16-7.10 (m, 5H), 7.05 (t, *J* = 8.0 Hz, 1H), 6.90 (t, *J* = 8.0 Hz, 1H), 6.82-6.77 (m, 2H), 5.29-5.27 (m, 1H), 3.46 (s, 3H), 3.13 (dd, *J* = 13.2, 3.2 Hz, 1H), 3.06 (s, 3H), 2.71 (dd, *J* = 13.6, 6.0 Hz, 1H), 2.44 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 171.0, 168.6, 145.7, 138.2, 135.7, 134.8, 133.0, 131.1, 129.1, 128.1, 127.8, 127.7, 127.1, 127.0, 126.4, 120.9, 114.4, 53.5, 53.3, 52.6, 51.9, 31.4, 19.2; IR (KBr) 2949, 2853, 1742, 1597, 1562, 1491, 1459, 1444, 1462, 1329, 1268, 1249, 1181, 1172, 1070 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{27}N_2O_4$: 443.1965, found 443.1965.

Dimethyl 6-(3-bromophenyl)-1,3-diphenyl-5,6-dihydropyridazine-4,4(1*H*)-dicarboxylate 3c. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.38; yellow solid; mp 159-162 °C; yield 73% (73.8 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.8 Hz, 2H), 7.37-7.33 (m, 4H),

7.30-7.27 (m, 1H) 7.26-7.23 (m, 4H), 7.15 (t, J = 7.8 Hz, 1H), 7.07 (d, J = 7.8 Hz, 1H), 6.93-6.90 (m, 1H), 5.25-5.24 (m, 1H), 3.50 (s, 3H), 3.22 (s, 3H), 3.18 (dd, J = 13.2, 2.4 Hz, 1H), 2.87 (dd, J =13.8, 6.0 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ 170.5, 168.5, 145.6, 140.9, 137.9, 133.9, 131.0, 130.5, 129.7, 129.2, 128.2, 128.0, 127.1, 125.6, 122.8, 121.2, 114.4, 53.4, 53.2, 52.7, 33.6; IR (KBr) 3057, 2947, 1752, 1745, 1595, 1496, 1425, 1366, 1216, 1068 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{24}BrN_2O_4$: 507.0914, found 507.0913.

Dimethyl 1,3-diphenyl-6-(3-(trifluoromethyl)phenyl)-5,6-dihydropyri-dazine-4,4(1*H*)-dicarboxy-late 3d. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.25; colorless solid; mp 80-82 °C; yield 69% (68.4 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 7.2 Hz, 2H), 7.54-7.52 (m, 2H), 7.42-7.35 (m, 3H), 7.32-7.24 (m, 6H), 6.95-6.92 (m, 1H), 5.37-5.35 (m, 1H), 3.53 (s, 3H), 3.24 (dd, J = 13.6, 2.8Hz, 1H), 3.12 (s, 3H), 2.95 (dd, J = 13.6, 6.0 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ 170.4, 168.5, 145.6, 139.6, 137.9, 134.1, 131.3 (q, J_{C-F} = 31.9 Hz), 130.5, 129.4, 129.2, 128.2, 128.0, 127.2, 126.7 (q, J_{C-F} = 270.4 Hz), 124.7 (q, J_{C-F} = 3.3 Hz), 123.7 (q, J_{C-F} = 3.7 Hz), 121.3, 114.4, 53.5, 53.4, 53.2, 52.6, 33.5; IR (KBr) 2953, 2924, 2852, 1734, 1597, 1559, 1496, 1444, 1434, 1367, 1328, 1265, 1243, 1166, 1069 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{24}F_3N_2O_4$: 497.1683, found 497.1688.

Dimethyl 6-(4-chlorophenyl)-1,3-diphenyl-5,6-dihydropyridazine-4,4(1*H*)-dicarboxylate 3e. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.43; brown solid; mp 190-192 °C; yield 74% (68.4 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 7.6 Hz, 2H), 7.37 (t, J = 6.8 Hz, 2H), 7.33-7.25 (m, 7H), 7.13 (d, J = 8.4 Hz, 2H), 6.95-6.91 (m, 1H), 5.29-5.27 (m, 1H), 3.53 (s, 3H), 3.22-3.18 (m, 4H), 2.91 (dd, J = 13.6, 5.6 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 170.5, 168.6, 145.6, 138.0, 136.8, 134.0, 133.5, 129.1, 128.9, 128.4, 128.1, 127.9, 127.2, 121.1, 114.4,

53.38, 53.35, 53.32, 52.6, 33.7; IR (KBr) 2950, 1746, 1760, 1596, 1577, 1494, 1457, 1443, 1365, 1266, 1241, 1216, 1067 cm^{-1}; **3e′**: $[\alpha]_D^{25}$ = +10.39 (c= 0.08, $CHCl_3$); HPLC analysis: 89% *ee* [Daicel CHIRALCEL AD-H column, hexane/^{i}PrOH = 97:3, flow rate: 1 mL /min, λ = 254 nm, t_R = 18.01 min (major), 23.57 min (minor)]; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{24}ClN_2O_4$: 463.1419, found 463.1440.

Dimethyl 6-(4-fluorophenyl)-1,3-diphenyl-5,6-dihydropyridazine-4,4(1*H*)-dicarboxylate 3f. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.42; brown solid; mp 168-169 °C; yield 77% (68.6 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.2 Hz, 2H), 7.33 (t, *J* = 7.2 Hz, 2H), 7.28 (d, 7.2 Hz, 1H), 7.23-7.22 (m, 4H),7.13-7.09 (m, 2H), 6.95 (t, *J* = 8.8 Hz, 2H), 6.91-6.87 (m, 1H), 5.26-5.24 (m, 1H), 3.49 (s, 3H), 3.18-3.15 (m, 4H), 2.86 (dd, *J* = 13.6, 6.0 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 170.5, 168.6, 163.4 (J_{C-F} = 244.9 Hz), 145.7, 138.0, 133.94, 133.90, 129.1, 128.7 (J_{C-F} = 8.1 Hz), 128.1, 127.9, 127.2, 121.1, 115.8 (J_{C-F} = 21.5 Hz), 114.4, 53.36, 53.30, 53.2, 52.5, 33.9; IR (KBr) 2949, 1741, 1596, 1560, 1456, 1489, 1345, 1260, 1218, 1155, 1091, 1066 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{24}FN_2O_4$: 447.1715, found 447.1731.

Dimethyl 1,3-diphenyl-6-(*p*-tolyl)-5,6-dihydropyridazine-4,4(1*H*)-dicarboxylate 3g. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.41; colorless solid; mp 167-168° C; yield 79% (69.8 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.2 Hz, 2H), 7.37 (t, *J* = 7.8 Hz, 2H), 7.32-7.29 (m, 3H),7.28-7.25 (m, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 7.07 (d, *J* = 7.8 Hz, 2H), 6.92 (t, *J* = 7.2 Hz, 1H), 5.30-5.28 (m, 1H), 3.53 (s, 3H), 3.23 (dd, *J* = 13.8, 3.0 Hz, 1H), 3.14 (s, 3H), 2.89 (dd, *J* = 13.2, 5.4 Hz, 1H), 2.32 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 170.8, 168.6, 145.8, 138.2, 137.3, 134.9, 133.4, 129.4, 129.0, 128.1, 127.7, 127.1, 126.8, 120.8, 114.4, 53.5,

53.3, 53.2, 52.5, 33.9, 21.2; IR (KBr) 2949, 1740, 1597, 1556, 1452, 1364, 1260, 1243, 1189, 1173, 1066 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{27}N_2O_4$: 443.1965, found 443.1961.

Dimethyl 6-([1,1'-biphenyl]-4-yl)-1,3-diphenyl-5,6-dihydropyrid-azine-4,4(1*H*)-dicarboxylate 3h. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.33; colorless solid; mp 86-87 °C; yield 71% (71.5 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.0 Hz, 2H), 7.58-7.54 (m, 4H), 7.45 (t, *J* = 7.2 Hz, 2H), 7.40-7.25 (m, 10H), 6.94 (t, *J* = 6.8 Hz, 1H), 5.39-5.36 (m, 1H), 3.54 (s, 3H), 3.29 (dd, *J* = 13.6, 2.8 Hz, 1H), 3.13 (s, 3H), 2.95 (dd, *J* = 13.6, 5.6 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.7, 168.6, 145.9, 140.6, 140.5, 138.2, 137.2, 133.7, 129.1, 129.0, 128.1, 127.8, 127.6, 127.45, 127.42, 127.2, 127.1, 121.0, 114.5, 53.6, 53.4, 53.3, 52.5, 33.8; IR (KBr) 2950, 2924, 2852, 1734, 1598, 1557, 1493, 1443, 1366, 1263, 1242, 1225, 1206, 1112, 1068 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{32}H_{29}N_2O_4$: 505.2122, found 505.2126.

Diethyl 1,3,6-triphenyl-5,6-dihydropyridazine-4,4(1*H*)-dicarboxylate 3j. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.68; brown solid; mp 125-126 °C; yield 77% (70.2 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.0 Hz, 2H), 7.24 (t, *J* = 7.2 Hz, 2H), 7.20-7.11 (m, 8H), 7.07 (d, *J* = 7.2 Hz, 2H), 6.79 (t, *J* = 6.8 Hz, 1H), 5.20-5.18 (m, 1H), 3.97-3.89 (m, 1H), 3.87-3.79 (m, 1H), 3.51-3.43 (m, 1H), 3.32-3.24 (m, 1H), 3.11 (dd, *J* = 13.6, 2.8 Hz, 1H), 2.79 (dd, *J* = 13.2, 5.6 Hz, 1H), 0.92 (t, *J* = 6.8 Hz, 3H), 0.83 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.1, 168.2, 145.9, 138.5, 138.3, 134.3, 129.0, 128.7, 127.9, 127.79, 127.72, 127.6, 126.9, 120.8, 114.5, 62.4, 61.8, 54.0, 53.7, 33.8, 13.7, 13.6; IR (KBr) 2925, 1749, 1721, 1594, 1561, 1444, 1490, 1364, 1329, 1266, 1226, 1176, 1068 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{29}N_2O_4$: 457.2122, found 457.2131.

Dibenzyl 1,3,6-triphenyl-5,6-dihydropyridazine-4,4(1*H*)-dicarboxylate 3k. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.65; yellow solid; mp 80-81 °C; yield 79% (91.6 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.64 (m, 2H), 7.21-7.11 (m, 16H), 7.09-7.07 (m, 2H), 6.98-6.96 (m, 2H), 6.90 (d, *J* = 6.8 Hz, 2H), 6.81-6.77 (m, 1H), 5.18-5.16 (m, 1H), 4.85-4.77 (m, 2H), 4.49 (d, *J* = 12.4 Hz, 1H), 4.14 (d, *J* = 12.4 Hz, 1H), 3.15 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.83 (dd, *J* = 13.6, 6.0 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.9, 168.1, 145.8, 138.4, 138.1, 135.0, 134.6, 133.8, 129.0, 128.8, 128.6, 128.55, 128.53, 128.3, 128.1, 127.8, 127.7, 127.4, 127.0, 120.9, 114.6, 68.2, 67.5, 54.0, 53.9, 53.7, 34.1; IR (KBr) 2923, 2858, 1732, 1638, 1597, 1492, 1454, 1171, 1116, 1064 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{38}H_{33}N_2O_4$: 581.2435, found 581.2447.

Diisopropyl 1,3,6-triphenyl-5,6-dihydropyridazine-4,4(1*H*)-dicarboxylate 3l. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.66; yellow solid; mp 112-113 °C; yield 76% (73.5 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86-7.83 (m, 2H), 7.38-7.36 (m, 2H), 7.32-7.25 (m, 7H), 7.23-7.20 (m, 3H), 6.89 (t, *J* = 6.8 Hz, 1H), 5.27-5.25 (m, 1H), 4.89 (m, 1H), 4.27 (m, 1H), 3.15 (dd, *J* = 13.6, 3.6 Hz, 1H), 2.92 (dd, *J* = 13.2, 5.6 Hz, 1H), 1.12 (d, *J* = 6.0 Hz, 3H), 1.09 (d, *J* = 6.4 Hz, 3H), 0.96 (d, *J* = 6.4 Hz, 3H), 0.92 (d, *J* = 6.0 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.5, 166.9, 144.9, 138.0, 137.4, 133.9, 127.9, 127.7, 127.0, 126.8, 126.77, 126.72, 125.9, 119.7, 113.7, 69.2, 69.1, 53.3, 53.1, 33.1, 20.48, 20.41, 20.2, 20.0; IR (KBr) 2981, 1734, 1637, 1497, 1455, 1372, 1341, 1266, 1238, 1226, 1204, 1175, 1106, 1060 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{30}H_{33}N_2O_4$: 485.2435, found 485.2447.

Dimethyl-3-(2-bromophenyl)-1,6-diphenyl-5,6-dihydropyridazine-4,4(1*H*)-dicarboxylate 3m. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.38; brown solid; mp 108-109 °C; yield 64% (64.7 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.54 (dd,

J = 8.0, 1.2 Hz, 1H), 7.27-7.21 (m, 3H), 7.20-7.15 (m, 3H), 7.13-7.08 (m, 5H), 6.81-6.77 (m, 1H), 5.22-5.20 (m, 1H), 3.33 (s, 3H), 3.03-3.02 (m, 2H), 2.97 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 168.8, 168.6, 146.1, 138.64, 138.61, 133.0, 132.3, 132.0, 129.5, 129.0, 128.7, 127.7, 127.1, 126.8, 124.8, 121.1, 114.8, 54.94, 54.91, 53.1, 52.5, 32.4; IR (KBr) 2951, 2924, 2853, 1735, 1597, 1573, 1496, 1450, 1432, 1367, 1330, 1264, 1238, 1171, 1066 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{24}BrN_2O_4$: 507.0914, found 507.0915.

Dimethyl-3-(3-bromophenyl)-1,6-diphenyl-5,6-dihydropyridazine-4,4(1*H*)-dicarboxylate 3n. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.39; colorless solid; mp 141-142 °C; yield 74% (74.8 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.66 (d, *J* = 9.0 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 2H), 7.28-7.23 (m, 5H), 7.21 (t, *J* = 8.4 Hz, 1H), 7.16 (d, *J* = 7.2 Hz, 2H), 6.96-6.93 (m, 1H), 5.33-5.32 (m, 1H), 3.58 (s, 3H), 3.25 (dd, *J* = 13.8, 3.0 Hz, 1H), 3.12 (s, 3H), 2.89 (dd, *J* = 13.8, 6.0 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ 170.5, 168.4, 145.6, 140.1, 137.8, 131.9, 130.6, 130.0, 129.6, 129.2, 128.8, 127.8, 126.8, 125.6, 122.3, 121.3, 114.6, 53.9, 53.5, 53.1, 52.6, 33.7; IR (KBr) 2950, 2924, 1741, 1734, 1595, 1497, 1328, 1262, 1218, 1060 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{24}BrN_2O_4$: 507.0914, found 507.0915.

Dimethyl 1,6-diphenyl-3-(*m*-tolyl)-5,6-dihydropyridazine-4,4(1*H*)-dicarboxylate 3o. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.41; yellow solid; mp 98-99 °C; yield 80% (70.7 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.22-7.12 (m, 8H), 7.09 (d, *J* = 7.6 Hz, 2H), 7.03 (d, *J* = 7.2 Hz, 1H), 6.83-6.79 (m, 1H), 5.22-5.20 (m, 1H), 3.44 (s, 3H), 3.13 (dd, *J* = 13.6, 3.2 Hz, 1H), 3.02 (s, 3H), 2.81 (dd, *J* = 13.6, 5.6 Hz, 1H), 2.30 (s, 3H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ 170.8, 168.7, 145.9, 138.2, 138.1, 137.6, 133.8, 129.1,

128.8, 128.6, 128.0, 127.8, 127.7, 126.9, 124.3, 120.8, 114.4, 53.8, 53.35, 53.32, 52.5, 33.9, 21.9; IR (KBr) 2952, 2924, 2853, 1736, 1687, 1596, 1559, 1496, 1433, 1265, 1226, 1068 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{27}N_2O_4$: 443.1965, found 443.1973.

Dimethyl 1,6-diphenyl-3-(3-(trifluoromethyl)phenyl)-5,6-dihydro-pyridazine-4,4(1*H*)-dicarboxy-late 3p. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.25; colorless solid; mp 98-99 °C; yield 70% (69.4 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.48 (t, *J* = 8.0 Hz, 1H), 7.33-7.23 (m, 7H), 7.17 (d, *J* = 7.2 Hz, 2H), 6.98-6.91 (m, 1H), 5.36-5.34 (m, 1H), 3.56 (s, 3H), 3.27 (dd, *J* = 13.2, 2.8 Hz, 1H), 3.13 (s, 3H), 2.91 (dd, *J* = 13.6, 5.6 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.5, 168.4, 145.6, 138.9, 137.9, 132.0, 130.6, 130.4, 130.3, 129.2, 128.8, 128.6, 127.9, 126.8, 124.2 (q, J_{C-F} =3.6 Hz), 123.9 (q, J_{C-F} =3.6 Hz), 121.5, 114.6, 54.0, 53.4, 53.2, 52.6, 33.8; IR (KBr) 2955, 2923, 1761, 1727, 1592, 1565, 1497, 1488, 1369, 1339, 1266, 1219, 1168, 1070 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{24}F_3N_2O_4$: 497.1683, found: 497.1689.

Dimethyl 3-(4-acetoxyphenyl)-1,6-diphenyl-5,6-dihydropyri-dazine-4,4(1*H*)-dicarboxylate 3q. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane, R_f = 0.29; colorless solid; mp 168-169 °C; yield 63% (61.2 mg); ^1H NMR (600 MHz, $CDCl_3$) δ 7.80 (d, *J* = 9.0 Hz, 2H), 7.31-7.23 (m, 7H), 7.16 (d, *J* = 7.8 Hz, 2H), 7.09 (d, *J* = 9.0 Hz, 2H), 6.93-6.90 (m, 1H), 5.32-5.31 (m, 1H), 3.54 (s, 3H), 3.24 (dd, *J* = 13.8, 3.0 Hz, 1H), 3.11 (s, 3H), 2.90 (dd, *J* = 13.2, 5.4 Hz, 1H), 2.32 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 170.7, 169.5, 168.6, 150.3, 145.7, 138.0, 135.9, 132.7, 129.1, 128.8, 128.2, 127.7, 126.8, 121.1, 121.0, 114.4, 53.7, 53.4, 53.3, 52.6, 33.7, 21.4; IR (KBr) 2924, 2850, 1750, 1686, 1597, 1497, 1435, 1369, 1197 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{27}N_2O_6$: 487.1864, found 487.1860.

Dimethyl 3-(4-bromophenyl)-1,6-diphenyl-5,6-dihydropyriazine-4,4(1*H*)-dicarboxylate 3r. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.39; yellow solid; mp 187-188 °C; yield 75% (75.9 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.8 Hz, 2H), 7.38 (d, *J* = 8.8 Hz, 2H), 7.21-7.11 (m, 7H), 7.05 (d, *J* = 7.2 Hz, 2H), 6.85-6.80 (m, 1H), 5.22- 5.20 (m, 1H), 3.45 (s, 3H), 3.13 (dd, *J* = 13.6, 2.8 Hz, 1H), 3.00 (s, 3H), 2.77 (dd, *J* = 13.2, 6.0 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 170.4, 168.3, 145.5, 137.7, 137.0, 132.2, 131.0, 128.9, 128.6, 128.5, 127.6, 126.6, 121.7, 121.0, 114.3, 53.7, 53.2, 53.0, 52.4, 33.5; IR (KBr) 2951, 2924, 2853, 1734, 1636, 1597, 1549, 1497, 1489, 1332, 1266, 1244, 1226, 1173, 1068 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{24}BrN_2O_4$: 507.0914, found 507.0910.

Dimethyl 3-(4-chlorophenyl)-1,6-diphenyl-5,6-dihydropyri-dazine-4,4(1*H*)-dicarboxylate 3s. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.41; brown solid; mp 151-152 °C; yield 81% (74.8 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.4 Hz, 2H), 7.33-7.29 (m, 4H), 7.28-7.23 (m, 5H), 7.16 (d, *J* = 7.8 Hz, 2H), 6.94-6.92 (m, 1H), 5.33-5.31 (m, 1H), 3.56 (s, 3H), 3.25 (dd, *J* = 13.8, 3.0 Hz, 1H), 3.11 (s, 3H), 2.89 (dd, *J* = 13.8, 6.0 Hz, 1H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 170.6, 168.5, 145.6, 137.9, 136.7, 133.6, 132.3, 129.1, 128.8, 128.4, 128.2, 127.8, 126.8, 121.2, 114.4, 53.8, 53.4, 53.1, 52.6, 33.7; IR (KBr) 2952, 1755, 1726, 1598, 1549, 1498, 1489, 1451, 1399, 1373, 1337, 1212, 1173, 1068 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{24}ClN_2O_4$: 463.1419, found: 463.1429.

Dimethyl 3-(4-cyanophenyl)-1,6-diphenyl-5,6-dihydropyri-dazine-4,4(1*H*)-dicarboxylate 3t. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.21; yellow solid; mp 178-179 °C; yield 64% (58 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 9.0 Hz, 2H), 7.32-7.24 (m, 7H), 7.14 (d, *J* = 7.8 Hz, 2H), 7.00-6.95(m, 1H), 5.37-5.36 (m, 1H), 3.58 (s,

3H), 3.29 (dd, J = 13.8, 3.0 Hz, 1H), 3.11 (s, 3H), 2.87 (dd, J = 13.8, 5.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.5, 168.2, 145.4, 142.5, 137.5, 131.9, 131.4, 129.2, 128.9, 128.0, 127.2, 126.7, 121.9, 119.3, 114.9, 110.6, 54.1, 53.5, 52.8, 52.7, 33.8; IR (KBr) 2949, 1734, 1597, 1563, 1494, 1450, 1368, 1329, 1260, 1185, 1108, 1034 cm^{-1}; **3t′**: $[\alpha]_D^{25}$ = +24 (c= 0.1, $CHCl_3$); HPLC analysis: 95% *ee* [Daicel CHIRALCEL AD-H column, hexane/^{i}PrOH = 97:3, flow rate: 1 mL /min, λ = 215 nm, t_R = 38.32 min (minor), 48.39 min (major)]; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{24}N_3O_4$: 454.1761, found 454.1770.

Dimethyl 3-(4-fluorophenyl)-1,6-diphenyl-5,6-dihydropyridazine-4,4(1*H*)-dicarboxylate 3u. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane, R_f = 0.42; colorless solid; mp 175-176 °C; yield 76% (67.7 mg); ^1H NMR (600 MHz, $CDCl_3$) δ 7.78-7.75 (m, 2H), 7.31 (t, J = 7.2 Hz, 2H), 7.28-7.23 (m, 5H), 7.17 (d, J = 7.2 Hz, 2H), 7.05 (t, J = 8.4 Hz, 2H), 6.93-6.90 (m, 1H), 5.32-5.31 (m, 1H), 3.53 (s, 3H), 3.24 (dd, J = 13.8, 3.0 Hz, 1H), 3.11 (s, 3H), 2.89 (dd, J = 13.2, 5.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 170.6, 168.6, 163.4 ($J_{C\text{-}F}$ = 245.7 Hz), 145.7, 138.0, 134.4 ($J_{C\text{-}F}$ = 3.3 Hz), 132.6, 129.1, 129.1 ($J_{C\text{-}F}$ = 7.8 Hz), 128.8, 127.8, 126.8, 121.0, 115.1 ($J_{C\text{-}F}$ = 21.3 Hz), 114.4, 53.7, 53.4, 53.4, 52.6, 33.6; IR (KBr) 2947, 1750, 1738, 1600, 1554, 1508, 1496, 1453, 1328, 1240, 1216, 1174, 1160, 1067 cm^{-1}; **3u′**: $[\alpha]_D^{25}$ = +32 (c=0.1, $CHCl_3$); HPLC analysis: 98% ee [Daicel CHIRALPAK IC column, hexane/^{i}PrOH = 97:3, flow rate: 1 mL /min, λ = 254 nm, t_R = 8.40 min (major), 9.80 min (minor)]; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{24}FN_2O_4$: 447.1715, found 447.1718.

Dimethyl 1,6-diphenyl-3-(p-tolyl)-5,6-dihydropyridazine-4,4(1*H*)-dicarboxylate 3v. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.41; yellow solid; mp 141-142 °C; yield 78% (69 mg); ^1H NMR (600 MHz, $CDCl_3$) δ 7.69 (d, J = 7.8 Hz, 2H), 7.31-7.28 (m, 4H),

7.25 (t, J = 7.2 Hz, 3H), 7.18-7.16 (m, 4H), 6.91 (t, J = 7.2 Hz, 1H), 5.31-5.30 (m, 1H), 3.55 (s, 3H), 3.24 (dd, J = 13.8, 3.0 Hz, 1H), 3.11 (s, 3H), 2.91 (dd, J = 13.8, 6.0 Hz, 1H), 2.37 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 170.8, 168.6, 145.9, 138.2, 137.6, 135.4, 133.7, 129.0, 128.8, 128.7, 127.6, 127.0, 126.8, 120.7, 114.3, 53.6, 53.3, 53.2, 52.5, 33.8, 21.3; IR (KBr) 2949, 1759, 1727, 1595, 1575, 1493, 1449, 1430, 1367, 1327, 1272, 1184, 1071 cm^{-1}; **3v′**: $[\alpha]_D^{25}$ = +29.33 (c=0.15, $CHCl_3$); HPLC analysis: 98% ee [Daicel CHIRALPAK IC column, hexane/^{i}PrOH = 97:3, flow rate: 1 mL /min, λ = 254 nm, t_R = 12.41 min (major), 14.45 min (minor)]; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{27}N_2O_4$: 443.1965, found 443.1964.

Dimethyl 3-([1,1'-biphenyl]-4-yl)-1,6-diphenyl-5,6-dihydropyri-dazine-4,4(1*H*)-dicarboxylate 3w. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.33; yellow solid; mp 87-88 °C; yield 73% (73.5 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 8.4 Hz, 2H), 7.63-7.57 (m, 4H), 7.44 (t, J = 7.2 Hz, 2H), 7.36-7.32 (m, 1H), 7.30-7.20 (m, 7H), 7.17 (d, J = 7.2 Hz, 2H), 6.90 (t, J = 6.8 Hz, 1H), 5.33-5.30 (m, 1H), 3.55 (s, 3H), 3.25 (dd, J = 13.6, 2.8 Hz, 1H), 3.11 (s, 3H), 2.90 (dd, J = 13.6, 5.6 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.8, 168.6, 145.9, 140.9, 140.3, 138.1, 137.2, 133.3, 129.1, 128.9, 128.8, 127.7, 127.4, 127.1, 126.9, 126.7, 121.0, 114.5, 53.8, 53.4, 53.2, 52.5, 34.0; IR (KBr) 2949, 1758, 1597, 1562, 1541, 1495, 1432, 1450, 1328, 1216, 1172, 1065 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{32}H_{29}N_2O_4$: 505.2122, found 505.2134.

Dimethyl 3-(4-nitrophenyl)-1,6-diphenyl-5,6-dihydropyridazine-4,4(1*H*)-dicarboxylate 3x. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.16; yellow solid; mp 182-183 °C; yield 61% (57.7 mg); ^1H NMR (600 MHz, $CDCl_3$) δ 8.22 (d, J = 9.6 Hz, 2H), 7.95 (d, J = 9.6 Hz, 2H), 7.33-7.30 (m, 5H), 7.28-7.25 (m, 2H) 7.15 (d, J = 6.6 Hz, 2H), 7.01-6.98 (m, 1H), 5.389-

5.384 (m, 1H), 3.59 (s, 3H), 3.33 (dd, *J* = 13.2, 2.4 Hz, 1H), 3.12 (s, 3H), 2.89 (dd, *J* = 13.8, 6.0 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ 170.5, 168.2, 146.7, 145.3, 144.3, 137.4, 131.1, 129.3, 128.9, 128.0, 127.2, 126.7, 123.5, 122.1, 115.0, 54.2, 53.7, 52.83, 52.81, 33.8; IR (KBr) 2956, 2924, 2852, 1733, 1596, 1543, 1512, 1491, 1451, 1435, 1378, 1366, 1263, 1213, 1105, 1069 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{24}N_3O_6$: 474.1660, found 474.1659.

Dimethyl 3-(naphthalen-2-yl)-1,6-diphenyl-5,6-dihydropyri-dazine-4,4(1*H*)-dicar-boxylate 3y. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.31; brown solid; mp 182-183 °C; yield 69% (65.9 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 8.8, 3.0 Hz, 1H), 7.96 (s, 1H), 7.75-7.71 (m, 3H), 7.38-7.33 (m, 2H), 7.24-7.14 (m, 7H), 7.12-7.08 (m, 2H), 6.83 (t, *J* = 7.2 Hz, 1H), 5.26-5.23 (m, 1H), 3.39 (s, 3H), 3.19 (dd, *J* = 13.6, 3.2 Hz, 1H), 3.03 (s, 3H), 2.84 (dd, *J* = 13.6, 6.0 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 170.8, 168.7, 145.9, 138.2, 135.7, 133.6, 133.3, 133.0, 129.1, 128.8, 128.7, 127.7, 127.6, 127.6, 126.9, 126.1, 126.1, 126.0, 125.4, 121.1, 114.6, 53.9, 53.4, 53.3, 52.5, 34.0; IR (KBr) 2948, 1754, 1726, 1595, 1557, 1495, 1450, 1431, 1365, 1248, 1223, 1174, 1105, 1069 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{30}H_{27}N_2O_4$: 479.1965, found 479.1971.

Dimethyl 1,6-diphenyl-3-(thiophen-2-yl)-5,6-dihydropyridazine-4,4(1*H*)-dicarboxylate 3z. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.32; brown solid; mp 185-186 °C; yield 70% (60.7 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20-7.13 (m, 7H), 7.11 (d, *J* = 4.8 Hz, 1H), 7.05 (d, *J* = 7.2 Hz, 2H), 6.90-6.89 (m, 1H), 6.85-6.79 (m, 2H), 5.23-5.20 (m, 1H), 3.55 (s, 3H), 3.17 (dd, *J* = 13.2, 2.4 Hz, 1H), 3.03 (s, 3H), 2.80 (dd, *J* = 13.6, 5.2 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ 170.7, 167.9, 145.4, 143.9, 137.5, 129.8, 129.1, 128.8, 127.3, 126.7, 125.1, 124.4, 121.1, 114.4, 53.58, 53.56, 53.0, 52.6, 33.5; IR (KBr) 2949, 2840, 1747, 1733, 1595, 1558, 1497,

1450, 1433, 1322, 1242, 1225, 1177, 1067 cm^{-1}; **3z′**: $[\alpha]_D^{25}$ = +17.91 (c= 0.07, $CHCl_3$); HPLC analysis: 94% ee [Daicel CHIRALCEL AD-H column, hexane/^{i}PrOH = 97:3, flow rate: 1 mL /min, λ = 254 nm, t_R = 19.79 min (minor), 21.03 min (major)]; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{23}N_2O_4S$: 435.1373, found 435.1380.

Dimethyl 3-(2-bromo-5-fluorophenyl)-1,6-diphenyl-5,6-dihydro-pyridazine-4,4(1*H*)-dicarboxylate 3aa. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.38; yellow solid; mp 149-150 °C; yield 66% (69.1 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 10.0, 3.2 Hz, 1H), 7.51-7.47 (m, 1H), 7.25 (t, *J* = 6.8 Hz, 2H), 7.19-7.08 (m, 7H), 6.86-6.78 (m, 2H), 5.22-5.20 (m, 1H), 3.35 (s, 3H), 3.07-2.98 (m, 2H), 2.97 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.6, 168.4, 162.6 (J_{C-F}=245.5 Hz), 145.9, 140.3 (J_{C-F}=8.6 Hz), 138.2, 134.0 (J_{C-F}=8.1 Hz), 130.9 (J_{C-F}=2.2 Hz), 129.0, 128.7, 127.8, 127.0, 121.4, 119.6 (J_{C-F}=23.6 Hz), 119.0 (J_{C-F}=3.4 Hz), 116.8 (J_{C-F}=22.2 Hz), 114.8, 54.8, 54.6, 53.2, 52.6, 32.2; IR (KBr) 3068, 2947, 1749, 1738, 1576, 1492, 1325, 1260, 1062 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{23}BrFN_2O_4$: 525.0820, found 525.0821.

Dimethyl 1,6-diphenyl-3-(3,4,5-trimethoxyphenyl)-5,6-dihydro-pyridazine-4,4(1*H*)-dicarboxylate 3ab. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.11; yellow solid; mp 101-102 °C; yield 77% (79.7 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.28 (m, 3H), 7.26-7.22 (m, 4H), 7.17 (d, *J* = 7.2 Hz, 2H), 7.08 (s, 2H), 6.93-6.89 (m, 1H), 5.33-5.31 (m, 1H), 3.89 (s, 6H), 3.88 (s, 3H), 3.57 (s, 3H), 3.15 (dd, *J* = 13.2, 2.8 Hz, 1H), 3.12 (s, 3H), 2.89 (dd, *J* = 13.6, 6.0 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 170.7, 168.4, 152.6, 145.5, 137.9, 133.6, 133.0, 128.9, 128.6, 127.6, 126.7, 120.8, 114.1, 104.5, 60.9, 56.0, 53.6, 53.4, 53.2, 52.3, 33.6; IR (KBr) 2951,

2929, 1732, 1687, 1588, 1495, 1451, 1432, 1369, 1261, 1202, 1172, 1063 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{29}H_{31}N_2O_7$: 519.2126, found 519.2132.

Dimethyl 3-(2-bromo-4,5-dimethoxyphenyl)-1,6-diphenyl-5,6-dihydropyridazine-4,4(1*H*)-dicar-boxylate 3ac. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.08; brown solid; mp 159-160 °C; yield 67% (75.8 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.32 (t, *J* = 7.2 Hz, 2H), 7.24-7.15 (m, 7H), 7.08 (s, 1H), 6.88-6.85 (m, 1H), 5.27-5.25 (m, 1H), 3.89 (s, 3H), 3.84 (s, 3H), 3.42 (s, 3H), 3.13-3.06 (m, 2H), 3.03 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.0, 168.8, 149.2, 147.7, 146.2, 138.6, 131.7, 130.8, 129.0, 128.7, 127.7, 127.1, 121.1, 115.6, 114.9, 114.8, 114.6, 56.3, 56.1, 55.0, 54.8, 53.1, 52.4, 32.1; IR (KBr) 2952, 2850, 1735, 1598, 1497, 1439, 1387, 1328, 1263, 1208, 1172,1065 cm^{-1}; **3ac′**: $[\alpha]_D^{25}$ = -42.50 (c= 0.08, $CHCl_3$); HPLC analysis: 92% ee [Daicel CHIRALCEL AD-H column, hexane/^{i}PrOH = 97:3, flow rate: 1 mL /min, λ = 254 nm, t_R = 27.17 min (major), 45.49 min (minor)]; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{28}BrN_2O_6$: 567.1125, found 567.1122.

Dimethyl (*E*)-1,6-diphenyl-3-styryl-5,6-dihydropyridazine-4,4(1*H*)-dicarboxylate 3ad. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.13; yellow solid; mp 96-97 °C; yield 62% (56.2 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.2 Hz, 2H), 7.26-7.21 (m, 2H), 7.19-7.11 (m, 8H), 7.04-6.99 (m, 3H), 6.85-6.81 (m, 1H), 6.78 (d, *J* = 16.4 Hz, 1H), 5.23-5.21 (m, 1H), 3.68 (s, 3H), 3.10 (dd, *J* = 13.6, 3.2 Hz, 1H), 3.06 (s, 3H), 2.82 (dd, *J* = 13.6, 5.6 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.7, 168.3, 145.7, 137.7, 137.6, 133.1, 129.2, 129.1, 128.8, 128.7, 127.77, 127.74, 126.86, 126.82, 126.4, 121.2, 114.7, 53.8, 53.6, 52.7, 52.6, 33.2; IR (KBr) 2954, 2923, 2852, 1734,1596, 1542, 1496, 1450, 1434, 1371, 1264, 1224, 1197, 1102, 1067 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{27}N_2O_4$: 455.1965, found 455.1966.

Dimethyl 1-(4-chlorophenyl)-3,6-diphenyl-5,6-dihydropyridazine-4,4(1*H*)-dicarboxylate 3ae. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.41; yello solid; mp 139-140 °C; yield 76% (70.2 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.2 Hz, 2H), 7.36 (t, *J* = 7.2 Hz, 2H), 7.31 (t, *J* = 7.2 Hz, 3H), 7.26-7.24 (m, 1H), 7.20-7.19 (m, 4H), 7.15 (d, *J* = 7.2 Hz, 2H), 5.27-5.25 (m, 1H), 3.53 (s, 3H), 3.23 (dd, *J* = 13.2, 3.0 Hz, 1H), 3.11 (s, 3H), 2.92 (dd, *J* = 13.8, 6.0 Hz, 1H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 170.5, 168.5, 144.4, 137.9, 137.7, 134.5, 129.0, 128.9, 128.2, 128.0, 127.9, 127.2, 126.8, 125.8, 115.6, 53.8, 53.38, 53.35, 52.6, 33.9; IR (KBr) 2951, 2924, 1757, 1727, 1557, 1489, 1370, 1329, 1223, 1212, 1069 cm^{-1}; HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{26}H_{24}ClN_2O_4$: 463.1419, found 463.1419.

Dimethyl 1-(4-fluorophenyl)-3,6-diphenyl-5,6-dihydropyridazine-4,4(1*H*)-dicarboxylate 3af. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.42; yellow solid; mp 97-98 °C; yield 73% (65.1 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.2 Hz, 2H), 7.38-7.25 (m, 6H), 7.22-7.15 (m, 4H), 6.94 (t, *J* = 8.4 Hz, 2H), 5.25-5.23 (m, 1H), 3.54 (s, 3H), 3.21 (dd, *J* = 13.6, 3.2 Hz, 1H), 3.13 (s, 3H), 2.92 (dd, *J* = 13.6, 5.6 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 170.4, 168.4, 158.8 ($J_{C\text{-}F}$ = 237.9 Hz), 142.1 ($J_{C\text{-}F}$ = 2.2 Hz), 137.9, 137.8, 133.6, 130.4, 128.6, 127.9, 127.6 ($J_{C\text{-}F}$ = 3.1 Hz), 126.9, 126.6, 115.57 ($J_{C\text{-}F}$ = 28.9 Hz), 115.50, 54.0, 53.2, 53.1, 52.4, 33.8; IR (KBr) 2952, 2852, 1735, 1689, 1599, 1505, 1444, 1369, 1330, 1266, 1226, 1176, 1070 cm^{-1}; HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{26}H_{24}FN_2O_4$: 447.1715, found 447.1717.

Dimethyl (*E*)-2-(2-(2-benzylidene-1-phenylhydrazineyl)-2-phenyl-ethyl)malonate 4. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.58; yellow liquid; yield 81% (69.6 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.2 Hz, 2H), 7.37-7.31 (m, 6H), 7.30-7.21 (m, 6H), 6.95 (d, *J* = 7.2 Hz, 2H), 4.58 (dd, *J* = 10.8, 4.8 Hz, 1H), 3.89-3.87 (m, 1H), 3.76 (s, 3H),

3.73 (s, 3H), 3.29-3.24 (m, 1H), 2.63-2.58 (m, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 170.1, 145.1, 141.1, 136.9, 134.8, 129.7, 128.6, 128.5, 127.8, 127.75, 127.72, 127.1, 126.7, 126.0, 67.9, 52.7, 52.7, 49.6, 33.8; IR (neat) 2924, 2853, 1758, 1728, 1597, 1563, 1494, 1452, 1435, 1364, 1338, 1263, 1228, 1189, 1070 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{27}N_2O_4$: 431.1965, found 431.1966.

Dimethyl-1,6-diphenyl-3-(3-(pyren-1-yl)phenyl)-5,6-dihydropyridazine-4,4(1*H*)-dicarboxylate 5. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.42; colorless solid; mp 208-209 °C; yield 78% (48.9 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28-8.19 (m, 4H), 8.15-8.10 (m, 2H), 8.08-8.02 (m, 4H), 7.91 (d, *J* = 6.8 Hz, 1H), 7.58-7.53 (m, 2H), 7.33-7.26 (m, 6H), 7.24-7.20 (m, 3H), 6.89 (t, *J* = 7.2 Hz, 1H), 5.35-5.33 (m, 1H), 3.57 (s, 3H), 3.27 (dd, *J* = 13.6, 3.2 Hz, 1H), 3.11 (s, 3H), 2.96 (dd, *J* = 13.6, 5.6 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ 170.8, 168.6, 145.8, 140.9, 138.3, 138.1, 138.0, 133.4, 131.6, 131.2, 130.7, 130.1, 129.5, 129.1, 128.8, 128.7, 128.2, 127.8, 127.64, 127.62, 127.60, 126.9, 126.2, 126.1, 125.6, 125.2, 125.17, 125.13, 125.0, 124.8, 121.0, 114.5, 53.9, 53.4, 52.6, 33.9, 32.1; FT-IR(neat) 2924, 2853, 1758, 1728, 1597, 1563, 1494, 1452, 1364, 1338, 1263, 1228, 1189, 1070 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{42}H_{33}N_2O_4$: 629.2435, found 629.2429.

ASSOCIATED CONTENT

Supporting Information.

HPLC chromatograms, crystal data and NMR spectra (^{1}H and ^{13}C) of the products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The author declares no competing financial interest.

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REFERENCES

(1) For some recent reviews on D-A cyclopropanes, see: (a) Reissig, H.-U.; Zimmer, R. Donor−Acceptor-Substituted Cyclopropane Derivatives and Their Application in Organic Synthesis. *Chem. Rev*. **2003**, *103*, 1151-1196. (b) Carson, C. A.; Kerr, M. A. Heterocycles from Cyclopropanes: Applications in Natural Product Synthesis. *Chem. Soc. Rev*. **2009**, *38*, 3051-3060. (c) Cavitt, M. A.; Phun, L. H.; France, S. Intramolecular Donor–Acceptor Cyclopropane Ring-Opening Cyclizations. *Chem. Soc. Rev*. **2014**, *43*, 804-818. (d) de Nanteuil, F.; De Simone, F.; Frei, R.; Benfatti, F.; Serrano, E.; Waser, J. Cyclization and Annulation Reactions of Nitrogen-Substituted Cyclopropanes and Cyclobutanes. *Chem. Commun*. **2014**, *50*, 10912-10928. (e) Schneider, T. F.; Kaschel, J.; Werz, D. B. A New Golden Age for Donor-Acceptor Cyclopropanes.

Angew. Chem. Int. Ed. **2014**, *53*, 5504-5523. (f) Grover, H. K.; Emmett, M. R.; Kerr, M. A. Carbocycles from Donor–Acceptor Cyclopropanes. *Org. Biomol. Chem*. **2015**, *13*, 655-671.

(2) (a) Gordon, M. S. Ring Strain in Cyclopropane, Cyclopropene, Silacyclopropane and Silacyclopropene. *J. Am. Chem. Soc*. **1980**, *102*, 7419-7422. (b) Kreft, A.; Lücht, A.; Grunenberg, J.; Jones, P. G.; Werz, D. B. Kinetic Studies of Donor–Acceptor Cyclopropanes: The Influence of Structural and Electronic Properties on the Reactivity. *Angew. Chem. Int. Ed*. **2019**, *58*, 1955-1959.

(3) For some recent examples, see: (a) Sparr, C.; Gilmour, R. Cyclopropyl Iminium Activation: Reactivity Umpolung in Enantioselective Organocatalytic Reaction Design. *Angew. Chem. Int. Ed*. **2011**, *50*, 8391-8395. (b) Xia, Y.; Liu, X.; Zheng, H.; Lin, L.; Feng, X. Asymmetric Synthesis of 2,3-Dihydropyrroles by Ring Opening/Cyclization of Cyclopropyl Ketones Using Primary Amines. *Angew. Chem. Int. Ed*. **2015**, *54*, 227-230. (c) Wallbaum, J.; Garve, L. K. B.; Jones, P. G.; Werz, D. B. Ring-Opening Regio-, Diastereo-, and Enantioselective 1,3-Chlorochalcogenation of Cyclopropyl Carbaldehydes. *Chem. Eur. J.* **2016**, *22*, 18756-18759. (d) Pilsl, L. K. A.; Ertl, T.; Reiser, O. Enantioselective Three-Step Synthesis of Homo-β-proline: A Donor–Acceptor Cyclopropane as Key Intermediate. *Org. Lett*. **2017**, *19*, 2754-2757. (e) Lücht, A.; Patalag, L.J.; Augustin, A. U.; Jones, P. G.; Werz, D. B. Reactions of Donor–Acceptor Cyclopropanes with Naphthoquinones: Redox and Lewis Acid Catalysis Working in Concert. *Angew. Chem. Int. Ed.* **2017**, *56*, 10587-10591. (f) Das, S.; Daniliuc, C. G.; Studer, A. Lewis Acid Catalyzed Stereoselective Dearomative Coupling of Indolylboron Ate Complexes with Donor–Acceptor Cyclopropanes and Alkyl Halides. *Angew. Chem. Int. Ed.* **2018**, *57*, 4053-4057. (g) Novikov, R. A.; Denisov, D. A.; Potapov, K. V.; Tkachev, Y. V.; Shulishov, E. V.; Tomilov, Y. V. Ionic Ga-Complexes of Alkylidene- and Arylmethylidenemalonates and their Reactions with Acetylenes:

An In-Depth Look into the Mechanism of the Occurring Gallium Chemistry. *J. Am. Chem. Soc.* **2018**, *140*, 14381-14390.

(4) For some recent examples, see: (a) Pohlhaus, P. D.; Johnson, J. S. Enantiospecific Sn(II)- and Sn(IV)-Catalyzed Cycloadditions of Aldehydes and Donor−Acceptor Cyclopropanes. *J. Am. Chem. Soc*. **2005**, *127*, 16014-16015. (b) Sapeta, K.; Kerr, M. A. The Cycloaddition of Nitrones with Homochiral Cyclopropanes. *J. Org. Chem*. **2007**, 72, 8597-8599. (c) Jackson, S. K.; Karadeolian, A.; Driega, A. B.; Kerr, M. A. Stereodivergent Methodology for the Synthesis of Complex Pyrrolidines. *J. Am. Chem. Soc*. **2008**, *130*, 4196-4201. (d) Parsons, A. T.; Smith, A. G.; Neel, A. J.; Johnson, J. S. Dynamic Kinetic Asymmetric Synthesis of Substituted Pyrrolidines from Racemic Cyclopropanes and Aldimines: Reaction Development and Mechanistic Insights. *J. Am. Chem. Soc*. **2010**, *132*, 9688-9692. (e) Xing, S.; Pan, W.; Liu, C.; Ren, J.; Wang, Z. Efficient Construction of Oxa- and Aza-[n.2.1] Skeletons: Lewis Acid Catalyzed Intramolecular [3+2] Cycloaddition of Cyclopropane 1,1-Diesters with Carbonyls and Imines. *Angew. Chem. Int. Ed*. **2010**, *49*, 3215-3218. (f) Goldberg, A. F. G.; O'Connor, N. R.; Craig, R. A.; Stoltz, B. M. Lewis Acid Mediated (3 + 2) Cycloadditions of Donor–Acceptor Cyclopropanes with Heterocumulenes. *Org. Lett.* **2012**, *14*, 5314-5317. (g) Das, S.; Chakrabarty, S.; Daniliuc, C. G.; Studer, A. Tetrahydroquinolines via Stereospecific [3+3]-Annulation of Donor-Acceptor Cyclopropanes with Nitrosoarenes. *Org. Lett*. **2016**, *18*, 2784-2787. (h) Chagarovskiy, A. O.; Vasin, V. S.; Kuznetsov, V. V.; Ivanova, O. A.; Rybakov, V. B.; Shumsky, A. N.; Makhova, N. N.; Trushkov, I. V. [3+3]-Annulation of Donor-Acceptor Cyclopropanes with Diaziridines. *Angew. Chem., Int. Ed.* **2018**, *57*, 10338-10342.

(5) For some recent examples, see: (a) Grover, H. K.; Emmett, M. R.; Kerr, M. A. γ-Substituted Butanolides from Cyclopropane Hemimalonates: An Expedient Synthesis of Natural (*R*)-

Dodecan-4-olide. *Org. Lett.* **2013**, *15*, 4838-4841. (b) Liu, H.; Yuan, C.; Wu, Y.; Xiao, Y.; Guo, H. $Sc(OTf)_3$-Catalyzed [3+3] Cycloaddition of Cyclopropane 1,1-Diesters with Phthalazinium Dicyanomethanides. *Org. Lett*. **2015**, *17*, 4220-4223. (c) Xu, H.; Hu, J.-L.; Wang, L.; Liao, S.; Tang, Y. Asymmetric Annulation of Donor–Acceptor Cyclopropanes with Dienes. *J. Am. Chem. Soc.* **2015**, *137*, 8006-8009. (d) Garve, L. K. B.; Pawliczek, M.; Wallbaum, J.; Jones, P. G.; Werz, D. B. [4+3] Cycloaddition of Donor–Acceptor Cyclopropanes with Amphiphilic Benzodithioloimine as Surrogate for *ortho*-Bisthioquinone. *Chem. Eur. J*. **2016**, *22*, 521-525 and cited therein.

(6) For biological properties, see: (a) Hughes, P.; Clardy, J. Total Synthesis of 3(*S*)-Carboxy-4(S)-Hydroxy-2,3,4,5-Tetrahydropyrida-zine, An Unusual Amino Acid Constituent of Luzopeptin A. *J. Org. Chem.* **1989**, *54*, 3260-3264. (b) Küchenthal, C. H.; Maison, W. Synthesis of Cyclic Hydrazine A-Carboxylic Acids. *Synthesis* **2010**, *2010*, 719-740. (c) Oelke, A. J.; France, D. J.; Hofmann, T.; Wuitschik, G.; Ley, S. V. Piperazic Acid-Containing Natural Products: Isolation, Biological Relevance and Total Synthesis. *Nat. Prod. Rep*. **2011**, *28*, 1445-1471. (d) Dardíc, D.; Lauro, G.; Bifulco, G.; Laboudie, P.; Sakhaii, P.; Bauer, A.; Vilcinskas, A.; Hammann, P. E.; Plaza, A. Svetamycins A-G, Unusual Piperazic Acid-Containing Peptides from Streptomyces sp. *J. Org. Chem*. **2017**, *82*, 6032-6043.

(7) For examples, see: (a) Reichelt, I.; Reissig, H.-U. Eine einfache und flexible Synthese für 4,5-Dihydro-2H-3-pridazinone. *Synthesis* **1984**, 786-787. (b) Gladow, D.; Reissig, H.-U. Synthesis of Perfluoroalkyl Substituted γ-Lactones and 4,5-Dihydropyridazin-3(2H)-ones via Donor-Acceptor Cyclopropanes. *Helv. Chim. Acta*. **2012**, *92*, 1818-1830. (c) Zhong, X.-R.; Lv, J.; Luo, S.-Z. [4+2] Cycloaddition of in situ Generated 1,2-Diaza-1,3-dienes with simple Olefins: Facile Approaches to Tetrahydropyridazines. *Org. Lett*. **2015**, *17*, 1561-1564. (d) Yang, X.-L.; Peng, X.-X.; Chen, F.;

Han, B. TEMPO-Mediated Aza-Diels-Alder Reaction: Synthesis of Tetrahydropyridazines Using Ketohydrazones and Olefins. *Org. Lett.* **2016**, *18*, 2070-2073. (e) Deng, Y.-M.; Pei, C.; Arman, H.; Dong, K.-Y.; Xu, X.-F.; Doyle, M. P. Syntheses of Tetrahydropyridazine and Tetrahydro-1,2-diazepine Scaffolds Through Cycloaddition Reactions of Azoalkenes with Enol Diazoacetates. *Org. Lett*. **2016**, *18*, 5884-5887. (f) Wei, L.; Zhu, Q.; Song, Z.-M.; Liu, K.; Wang, C.-J. Catalytic Asymmetric Inverse Electron Demand Diels-Alder Reaction of Fulvenes with Azoalkenes. *Chem. Commun*. **2018**, *54*, 2506-2509. (g) Dey, R.; Kumar, P.; Banerjee, P. Lewis Acid Catalyzed Annulation of Cyclopropane Carbaldehydes and Aryl Hydrazines: Construction of Tetrahydropyridazines and Application Toward a One-Pot Synthesis of Hexahydropyrrolo[1,2-b]pyridazines. *J. Org. Chem.* **2018**, *83*, 5438-5449. (h) Huo, H.; Runa, A.; Gong, Y. Formal [3 + 3] Cycloaddition Reactions between Electron-Deficient Cyclopropenes and Hydrazones: A Route to Alkyl 1,4,5,6-Tetrahydropyridazine-3-carboxylates. *J. Org. Chem*. **2019**, *84*, 2093-2101.

(8) Garve, L. K. B.; Petzold, M.; Jones, P. G.; Werz, D. B. [3+3]-Cycladdition of Donor-Acceptor Cyclopropanes with Nitrile Imines Generated in Situ: Access to Tetrahydropyridazines. *Org. Lett.* **2016**, *18*, 564-567.

(9) For some recent reviews, see: (a) Li, C.-J. Cross-Dehydrogenative Coupling (CDC): Exploring C-C Bond Formations beyond Functional Group Transformations *Acc. Chem. Res*. **2009**, *42*, 335-344. (b) Cho, S. H.; Kim, J. Y.; Kwak, J. Chang. S. Recent Advances in The Transition Metal-Catalyzed Twofold Oxidative C–H Bond Activation Strategy for C–C and C–N Bond Formation. *Chem. Soc. Rev*. **2011**, *40*, 5068-5083. (c) Allen, S. E.; Walvoord, R. R.; Padilla-Salinas, R.; Kozlowski. M. C. Aerobic Copper-Catalyzed Organic Reactions. *Chem. Rev.*, **2013**, *113*, 6234-6458. (d) Guo, X.-X.; Gu, D.-W.; Wu, Z.; Zhang. W. Copper-Catalyzed C–H Functionalization Reactions: Efficient Synthesis of Heterocycles. *Chem. Rev.* **2015**, *115*, 1622-1651. (e) Liu, C.;

Yuan, J.; Gao, M.; Tang, S.; Li, W.; Shi, R.; Lei, A. Oxidative Coupling between Two Hydrocarbons: An Update of Recent C–H Functionalizations. *Chem. Rev*. **2015**, *115*, 12138-12204. (f) Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J. Mild Metal-Catalyzed C–H Activation: Examples and Concepts. *Chem. Soc. Rev*. **2016**, *45*, 2900-2936.

(10) For examples, see: (a) Punniyamurthy, T.; Velusamy, S.; Iqbal, J. Recent Advances in Transition Metal Catalyzed Oxidation of Organic Substrates with Molecular Oxygen. *Chem. Rev*., **2005**, *105*, 2329-2364. (b) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. Cu(II)-Catalyzed Functionalizations of Aryl C−H Bonds Using O_2 as an Oxidant. *J. Am. Chem. Soc*., **2006**, *128*, 6790-6791. (c) Shi, Z.; Zhang, C.; Tanga, C.; Jiao, N. Recent Advances in Transition-Metal Catalyzed Reactions using Molecular Oxygen as the Oxidant. *Chem. Soc. Rev.* **2012**, *41*, 3381-3430.

(11) (a) Grigg, R.; Dowling, M.; Jordan, M. W.; Sridharan, V.; Thianpatanagul, S. X=Y-ZH Systems as Potential 1,3-Dipoles: Part 13. Prototropic Generation of Azomethine Imines from Hydrazones. *Tetrahedron* **1987**, *43*, 5873-5887. (b) Tietze, L. F. Domino Reactions in Organic Synthesis. *Chem. Rev*. **1996**, *96*, 115-136. (c) McCann, S. D.; Stahl, S. S. Copper-Catalyzed Aerobic Oxidations of Organic Molecules: Pathways for Two-Electron Oxidation with a Four-Electron Oxidant and a One-Electron Redox-Active Catalyst. *Acc. Chem. Res.* **2015**, *48*, 1756-1766.

(12) For stability of hydrazone, see: (a) Johnson, S. M.; Petrassi, H. M.; Palaninathan, S. K.; Mohamedmohaideen, N. N.; Purkey, H. E.; Nochols, C.; Chiang, K. P.; Walkup, T.; Sacchettini, J. C.; Sharpless, K.B.; Kelly, J. W. Bisaryloxime Ethers as Potent Inhibitors of Transthyretin Amyloid Fibril Formation. *J. Med. Chem*. **2005**, *48*, 1576-1587. (b) Kalia, J.; Raines, R. T. Hydrolytic Stability of Hydrazones and Oximes. *Angew. Chem., Int. Ed*. **2008**, *47*, 7523-7526.

(13) (a) Kokel, B.; Menichi, G.; Huebert-Habart, M. A. Convenient One-Pot Conversion of Arene- and Heteroarenecarboxaldehyde Phenylhydrazones into Nitriles via Reaction with *N,N*-Dimethyldichloromethaniminium Chloride. *Synthesis* **1985**, 201-202. (b) Dikusar, E. A.; Potkin, V. I. Synthesis and Properties of Substituted Benzaldehyde Phenylhydrazones. *Russ. J. Gen. Chem.* **2009**, *79*, 953-956. (c) Li, P.; Wu, C.; Zhao, J.; Rogness, D. C.; Shi, F. Synthesis of Substituted 1H-Indazoles from Arynes and Hydrazones. *J. Org. Chem*. **2012**, *77*, 3149-3158. (d) Borazjani, M. K.; Safaei, H. R.; Panahandeh, M.; Kiani, A. R.; Kiani, M.; Mofarahi, M. Oxidized Single-Walled Carbon Nanotubes (SWCNs-COOH) as a New Catalyst for the Protection of Carbonyl Groups as Hydrazones. *S. Afr. J. Chem*. **2013**, *66*, 279-281. (e) Ding, Y.; Li, H.; Meng, Y.; Zhang, T.; Li, J.; Chena, Q.-Y.; Zhu, C. Direct Synthesis of Hydrazones by Visible Light Mediated Aerobic Oxidative Cleavage of the C=C Bond. *Org. Chem. Front*. **2017**, *4*, 1611-1614. (f) Zabaleta, N.; Uria, U.; Reyes, E.; Carrillo, L.; Vicario, J. L. Ion-Pairing Catalysis in The Enantioselective Addition of Hydrazones to *N*-Acyldihydropyrrole Derivatives. *Chem. Commun*. **2018**, *54*, 8905-8908.

(14) For the preparation of D-A cyclopropanes, see: (a) Dias, D. A.; Kerr, M. A. Domino Synthesis of Bridged Bicyclic Tetrahydro-1,2-oxazines: Access to Stereodefined 4-Aminocyclohexanols. *Org. Lett*. **2009**, *11*, 3694-3697. (b) Chagarovskiy, A. O.; Ivanova, O. A.; Rakhmankulov, E. R.; Budynina, E. M.; Trushkov, I. V.; Melnikov, M. Y. Lewis Acid-Catalyzed Isomerization of 2-Arylcyclopropane-1,1-dicarboxylates: A New Efficient Route to 2-Styrylmalonates. *Adv. Synth. Catal*. **2010**, *352*, 3179-3184. (c) Novikov, R. A.; Tarasova, A. V.; Korolev, V. A.; Timofeev, V. P.; Tomilov, Y. V. A New Type of Donor-Acceptor Cyclopropane Reactivity: The Generation of Formal 1,2- and 1,4-Dipoles. *Angew. Chem., Int. Ed.* **2014**, *53*, 3187-3191. (d) Diez, E. S.; Vesga, D. L.; Reyes, E.; Uria, U.; Carrillo, L.; Vicario, J. L. Organocatalytically Generated Donor-

Acceptor Cyclopropanes in Domino Reactions. One-Step Enantioselective Synthesis of Pyrrolo[1,2-a]quinolones. *Org. Lett.* **2016**, *18,* 1270-1273. (e) Kaga, A.; Gandamana, D. A.; Tamura, S.; Demirelli, M.; Chiba, S. [3+2]-Annulation of Donor–Acceptor Cyclopropanes with Vinyl Azides. *Synlett* **2017**, *28*, 1091-1095. (f) Richmond, E.; Vukovic, V. D.; Moran, J. Nucleophilic Ring Opening of Donor−Acceptor Cyclopropanes Catalyzed by a Brønsted Acid in Hexafluoroisopropanol. *Org. Lett.* **2018**, *20*, 574-577. (g) Augustin, A. U.; Busse, M.; Jones, P. G.; Werz, D. B. Formal Insertion of Thioketenes into Donor-Acceptor Cyclopropanes by Lewis Acid Catalysis. *Org. Lett*. **2018**, *20*, 820-823. (h) Petzold, M.; Jones, P. G.; Werz, D. B. (3+3)-Annulation of Carbonyl Ylides with Donor–Acceptor Cyclopropanes: Synergistic Dirhodium(II) and Lewis Acid Catalysis. *Angew. Chem., Int. Ed.* **2019**, *58*, 6225-6229.