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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.9b00228 • Publication Date (Web): 18 Mar 2019

Just Accepted

ACS Publications

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Copper-Catalyzed Aerobic 6-endo-trig Cyclization of β,γ-Unsaturated Hydrazones for the Divergent Synthesis of Dihydropyridazines and Pyridazines

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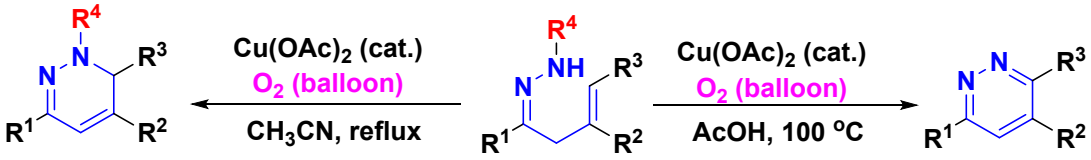


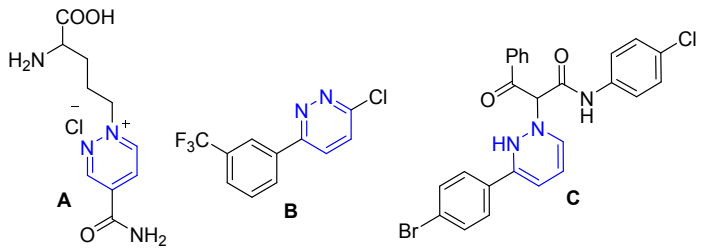
- Controllable and selective diversity-oriented synthesis
- 6-Endo-trig cyclization
- O_2 as the oxidant
- Wide functional group tolerance

ABSTRACT: A divergent synthetic strategy to 1,6-dihydropyridazines and pyridazines through Cu(II)-catalyzed controllable aerobic 6-endo-trig cyclization was developed. The selectivity can be rationally tuned via the judicious choice of reaction solvent. It was found that the 1,6-dihydropyridazines were obtained in moderate to high yields with CH_3CN as the reaction solvent, whereas employment of AcOH directly afforded pyridazines in up to 92% yields, probably arising from the oxidation of the in-situ generated 1,6-dihydropyridazines.

Introduction

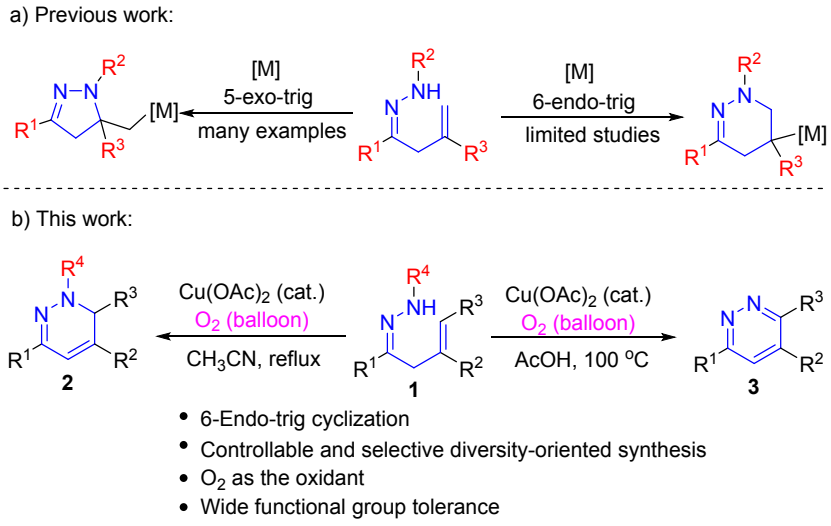
Pyridazine and dihydropyridazine derivatives, which contain unique and valuable N-N bonds, are abundant structural components of bioactive molecules and functional materials (Figure 1).[1] Synthetic efforts for preparing these two scaffolds have been continuously devoted in the past few years. Reactions of the 1,4-dicarbonyl compound with hydrazine[2] or [4+2] cycloadditions of 1,2,4,5-tetrazine with alkynes[3] were the typical methods for the pyridazine synthesis. For dihydropyridazine, while the most progress focused on the construction of 1,4-dihydropyridazines, rare protocols has been developed for the synthesis of 1,6-dihydropyridazines. For example, Lewis acid-mediated ring expansion of methylenecyclopropyl hydrazones and cycloaddition of diazonium salts with dienes has recently been reported for the straightforward synthesis of 1,6-dihydropyridazines.[4] Despite these fascinating achievements, an efficient, controllable strategy for the construction of both pyridazines and 1,6-dihydropyridazines from commercially available starting materials would be highly desirable.

Figure 1. Examples of useful compounds containing pyridazine and 1,6-dihydropyridazine cores.



In recent years, olefin-substituted hydrazones have emerged as an important and versatile reagent for the assembly of diverse substituted aza-heterocycles (Scheme 1).[5] Nevertheless, most developed strategies were restricted to 5-exo-trig cyclization,[6] 6-endo-trig cyclization reaction still face challenge in terms of efficiency and environmental friendliness even if some interesting results have been described. Xiao et al. recently reported a visible-light photocatalyzed 6-endo-trig mode reaction of β-1-styrene-substituted hydrazones for the synthesis of 1,6-dihydropyridazines with TEMPO as the oxidant.[7] Quite recently, Guan et al. reported a strategy to prepare 1,6-dihydropyridazines via a stoichiometric amount of copper salt promoted cyclization of β,γ-unsaturated hydrazones.[8] Therefore, it is necessary to establish a controllable and atom-economical route that allows divergent synthesis of pyridazines and 1,6-dihydropyridazines through 6-endo-trig cyclization of β,γ-unsaturated hydrazones.

Scheme 1. Controllable 6-endo-trig cyclization for dihydropyridazines and pyridazines.



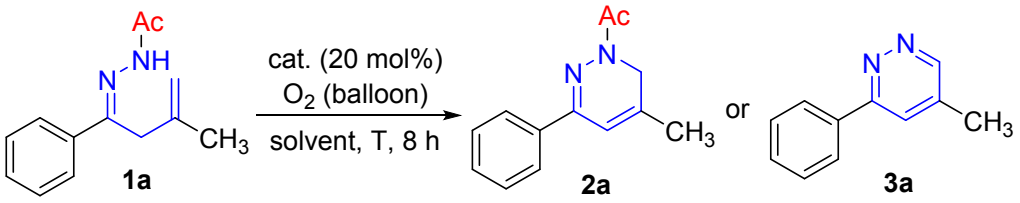
As an environmentally benign alternative to traditional oxidants, molecular oxygen does not give rise to any waste byproducts. Inspired by the biological metalloenzymatic oxidizing systems based on copper and oxygen,[9] Cu-catalyzed aerobic oxidative reactions have gradually became one of the most valuable methods for the C-C bond formation.[10] As part of our continuous efforts to develop regiodivergent catalytic processes of hydrazones,[11] herein we report copper-catalyzed aerobic 6-endo-trig cyclization for pyridazines and 1,6-dihydropyridazines synthesis based on β,γ-unsaturated hydrazones.[12] This Cu-catalyzed aerobic oxidative transformation features synthetic simplicity, broad substrate scope, and good functional group tolerance under mild conditions. The using of O_2 as terminal oxidant made this strategy even more synthetically advantageous, practical and green.

Results and Discussion

We launched our study by subjecting β,γ-unsaturated hydrazones **1a** to various reaction conditions (Table 1). The feasibility of the transformation was first tested by exposing the substrates to catalytic $Cu(OAc)_2$ under balloon pressure of O_2 atmosphere. Gratifyingly, the desired 6-endo-trig cyclization product 1,6-pyridazine **2a** was obtained in 8% isolated yield when the reaction was performed at 70 °C for 8 h (entry 1). No over-oxidation product pyridazine **3a** was observed during the process. Although no product was obtained with dioxane as the solvent, we are pleased to find that reaction conducted in CH_3CN delivered **2a** in 61% yield (entries 2-3). Furthermore, compared with the other Cu catalysts such as CuI, $Cu(OTf)_2$, $Cu(acac)_2$ and $CuCl_2•2H_2O$, $Cu(OAc)_2$ still proved to be the best reaction catalyst choice (entries 4-7). We then

found that 81% yield of **2a** was generated as the sole product by elevating the reaction temperature (entry 8). Attempt to perform the reaction in air or reduce the amount of copper catalyst failed (entries 9-11). Reactions were then conducted with the expectation to deliver pyridazine **3a** with high yield and selectivity. To assist the release of the Ac group, CF_3CO_2H was added to the reaction mixtures. CH_3CN was chosen as solvent in the beginning which afforded no generation of **3a** (entry 12). Delightedly, 74% yield of **3a** was observed as the sole product by switching the reaction solvent to toluene (entry 13). However, replacement of CF_3CO_2H with AcOH gave inferior result (entry 14). Finally, pyridazine **3a** was isolated in 85% yield and excellent selectivity in AcOH with 20 mol% of $Cu(OAc)_2$ as the catalyst under 1 atm O_2 atmosphere (entry 15).

Table 1. Screening of the optimal reaction conditions[a]



entry	cat.	solvent	T (°C)	yield(%)[b]	
				2a	**3a**
1	$Cu(OAc)_2$	Toluene	70	8	nd
2	$Cu(OAc)_2$	Dioxane	70	nd	nd
3	$Cu(OAc)_2$	CH_3CN	70	61	nd
4	CuI	CH_3CN	70	nd	nd
5	$Cu(OTf)_2$	CH_3CN	70	nd	nd
6	$Cu(acac)_2$	CH_3CN	70	nd	nd
7	$CuCl_2•2H_2O$	CH_3CN	70	nd	nd
8	$Cu(OAc)_2$	CH_3CN	reflux	81	nd
9[c]	$Cu(OAc)_2$	CH_3CN	reflux	21	nd
10[d]	$Cu(OAc)_2$	CH_3CN	reflux	46	nd
11[e]	$Cu(OAc)_2$	CH_3CN	reflux	38	nd
12[f]	$Cu(OAc)_2$	CH_3CN	reflux	nd	nd
13[f]	$Cu(OAc)_2$	toluene	100	-	74

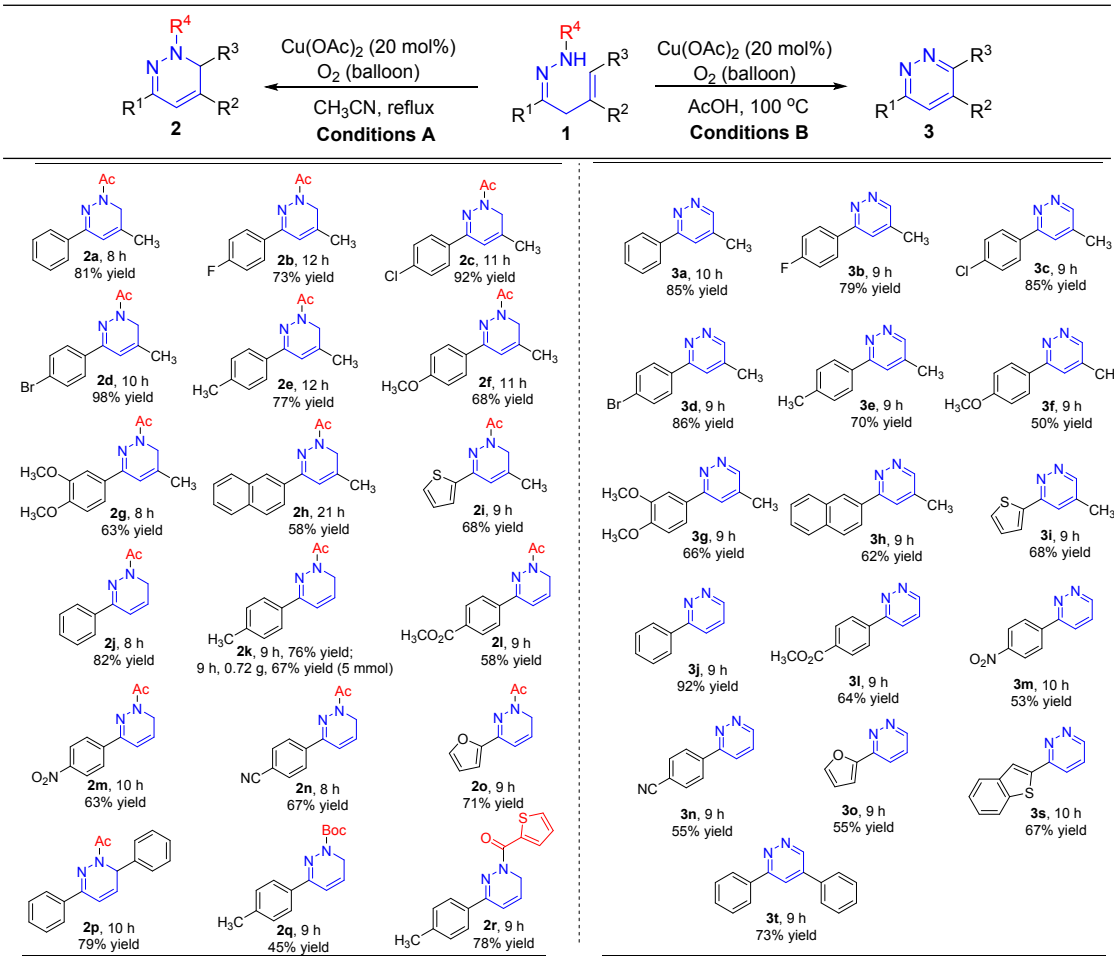
14[g]	$Cu(OAc)_2$	toluene	100	-	40
15[h]	$Cu(OAc)_2$	AcOH	100	-	85

[a]Reaction conditions: **1a** (0.1 mmol), catalysis (20 mol%), O_2 (balloon) in solvent (2.0 mL) for 8 h. [b]Isolated yield. [c]air. [d]10 mol% $Cu(OAc)_2$ was added. [e]5 mol% $Cu(OAc)_2$ was added for 24 h. [f]5 equiv. of CF_3COOH was added for 9 h. [g]5 equiv. of AcOH was added. [h]9 h.

The results shown in Table 2 demonstrate that this approach has a great potential in the divergent synthesis of functionalized dihydropyridazines and pyridazines. As shown in the left section of Table 2, various substituted hydrazone derivatives worked well to provide the desired dihydropyridazines **2** in good to excellent yields with $Cu(OAc)_2$ as the catalyst. It was observed that the reaction was slightly affected by the substitution patterns and electronic property of the substitute on the aromatic ring. Numerous β,γ-unsaturated hydrazones bearing electron-donating (e.g., CH_3, OCH_3) and electron-withdrawing groups (e.g., F, Cl, Br) at the 4-position of the phenyl ring were well tolerated to afford the expected dihydropyridazines **2b**-**2f** with good to high yields (68%-92%). When the 3,4-dimethoxy-substituted β,γ-unsaturated hydrazone was subjected to the reaction conditions, 63% yield of dihydropyridazine **2g** was isolated. Moreover, we found that substrates derived from naphthalenyl and thiophenyl ketones served as suitable substrates to give the corresponding products efficiently (**2h** and **2i**). Then, we examined the possible structural scope of the olefin moiety. Fortunately, different hydrazones with monosubstituted terminal olefin moiety led to the effective formation of pyridazines (**2j**-**2o**) in high yields. A larger-scale preparation of **2k** with slightly decreased efficiency further demonstrate the practicability of the

method. Substrates bearing aryl substituent also proceeded cleanly to provide **2p** in 79% yield. Furthermore, substituent on N atom of **1** was also investigated. *N*-Boc and *N*-2-thienyl-substituted hydrazones **1q** and **1r** also proved to be applicable substrates, leading to **2q** and **2r** in 45% and 78% yields, respectively.

Table 2. Substrate scope of the chemoselective cyclization[a,b]



[a]Conditions A: **1a** (0.1 mmol), $Cu(OAc)_2$ (20 mol%), O_2 (balloon) in CH_3CN (2.0 mL) at reflux for 8 h; conditions B: **1a** (0.1 mmol), $Cu(OAc)_2$ (20 mol%), O_2 (balloon) in AcOH (2 mL) at 100 °C for 9 h. [b]Yields of the isolated products.

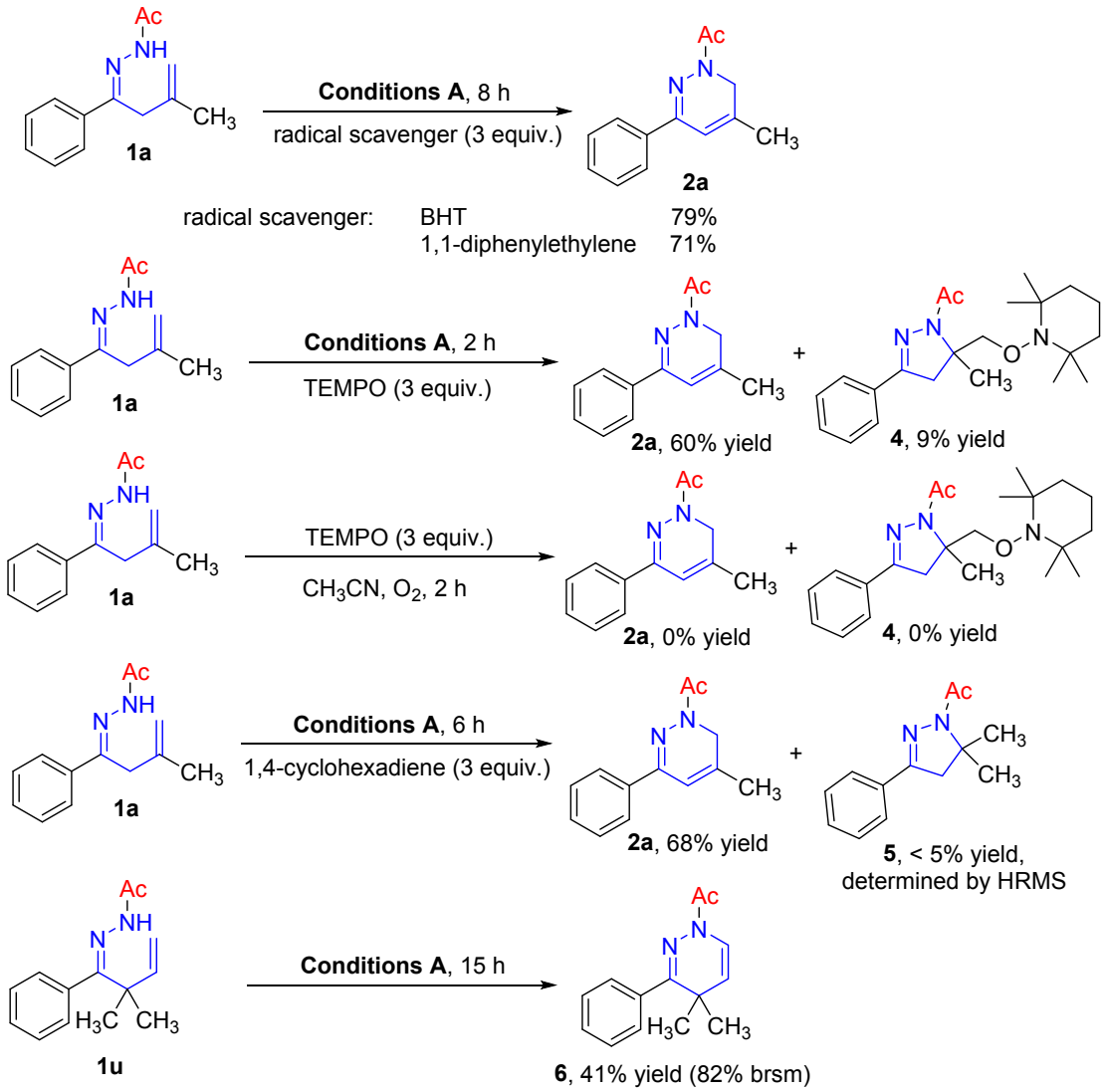
The substrate scope of the pyridazine is shown in the right section of Table 2. Generally, β,γ-unsaturated hydrazones containing either electron-rich or electron-

deficient substituents on the phenyl moiety were well tolerated, generating the desired products as a single isomer (**3a**-**3g**). Naphthalene and heteroarenes were also suitable substrates for this methodology (**3h** and **3i**). Additionally, replacement of the methyl group on the olefin moiety with other substituent furnished the amination products in good yield (**3j**-**3t**).

In order to gain preliminary insight into this transformation, we conducted additional experiments to elucidate the reaction mechanism (Scheme 2). The reaction proceeded smoothly to afford the dihydropyridazine **2a** when an excess amount of radical scavenger, butylated hydroxytoluene (BHT) or 1,1-diphenylethylene was added under the reaction conditions **A**. The results of the inhibition experiments indicate that the transformation may not involve a radical mechanism.[13] However, when 3 equiv. of TEMPO (2,2,6,6-tetramethylpiper-idine-1-oxyl) was added, a five-membered TEMPO trapping product **4** was isolated in 9% yield along with **2a** in 60% yield. No product was observed when Cu catalyst was removed from the above reaction mixture. In an attempt to trap the radical intermediate, the experiment with 1,4-cyclohexadiene as hydrogen atom donor was conducted. While the isolation of the hydrogen atom transfer product **5** failed, the determination of the crude reaction mixture by HRMS clearly confirmed the existence of the HAE product (Please see the SI for details). Furthermore, α-deprotonation of hydrazone, electrophilic addition of the Cu catalyst to the terminal carbon and reductive elimination from the 7-membered intermediate may also led to the formation of the product. However, when 2,2-dimethyl-substituted hydrazone **1u**

was used as substrate, the isolation of 6-endo-trig cyclization product **6** as a sole regio-isomer strongly disfavored this possible reaction pathway.

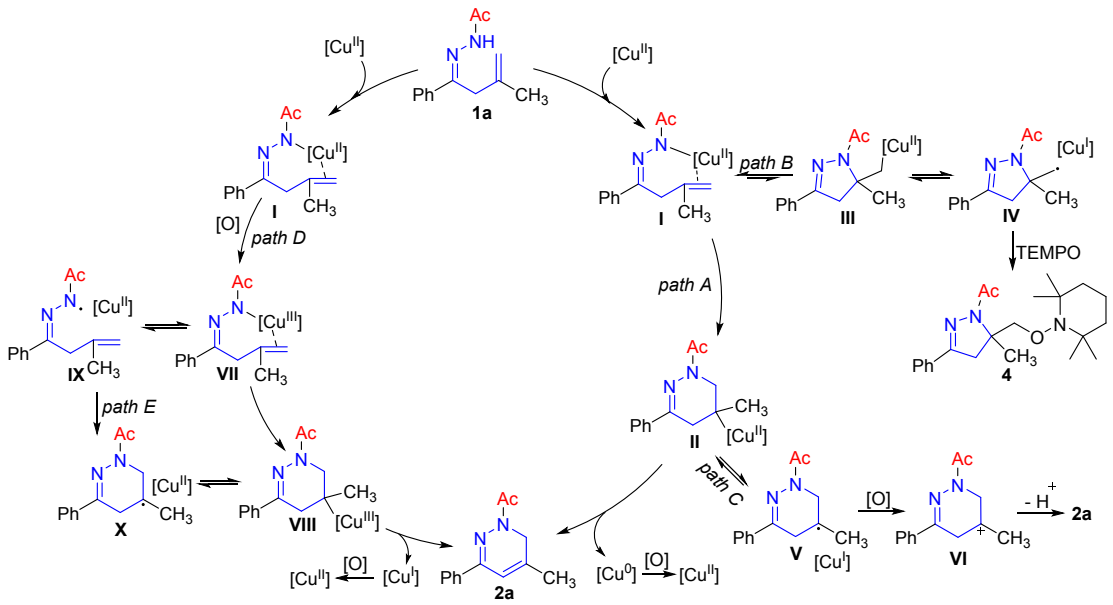
Scheme 2. Mechanism studies.



On the basis of these results as well as the literature reports,[7,8,10] a postulated reaction pathway was summarized in Scheme 3, although a detailed mechanism remains unclear. The interaction of substrate **1a** and copper catalyst first lead to the formation of a copper complex **I**. Carbometalation with the intramolecular alkene subsequently affords the cyclization intermediate **II**. After that, β-H elimination of intermediate **II** offered

delivery of 1,6-dihydropyridazine **2a** and Cu(0),[14] which could be reoxidized to Cu(II) by O_2 to finish the catalytic cycle (path A). Alternatively, 5-exo-trig cyclization of intermediate **I** may lead to the formation of intermediate **III**, which could undergo homocleavage to form the radical intermediate **IV** (path B).[15] The observation of the radical trapping product **4** suggested the possible reaction pathway. However, the absence of 5-exo-trig cyclization side-product under the standard conditions implied that the addition step could be reversible and the equilibration favored the formation of ring opening intermediate **I**. While the homolysis of C-Cu(II) bond of intermediate **II** to afford the C-centered radical intermediate **V** may lead to the formation of the product (path C), a different reaction pathway of Cu(III)/Cu(II)/Cu(I) catalytic cycle could also be involved in the reaction (path D). Furthermore, we cannot exclude another scenario where the homocleavage of C-Cu(III) bond of intermediate **VII** to afford the N-centered radical intermediate **IX**, which then undergoes endo alkene addition to deliver the final product (path E).

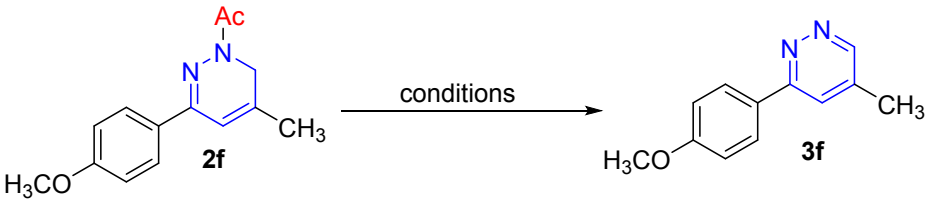
Scheme 3. Proposed reaction mechanism



The possible transformation of dihydropyridazine **2** to pyridazine **3** was also investigated (Scheme 4). The smooth production of **3f** when **2f** was subjected to the conditions **B** (65% yield, the yield based on the recovered starting material (brsm) was as high as 99%) indicated that **3f** was probably formed through the oxidation of **2f**. Removing $Cu(OAc)_2$ from the reaction mixture slowed down the reaction, because only less than 5% of **3f** was afforded when the reaction was continued for 9 h. Extension of the reaction time to 24 h delivered 86% yield of **3f**. Moreover, no reaction took place if $Cu(OAc)_2$ and O_2 were both absent from the reaction mixture. Therefore, we speculated that the single electron oxidation of **2f** by Cu(II) or O_2 may led to the formation of N-centered radical ion intermediate **I** (Scheme 5b). The subsequent oxidation and loss of a hydrogen atom would generate the carbocation **II**, which probably undergoes H_2O-assisted acetyl group cleavage to deliver product **3f**.

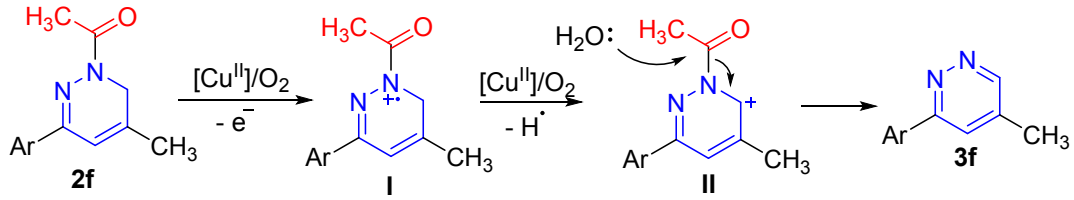
Scheme 4. Study about the transformation of 1,6-dihydropyridazines to pyridazines

a) Control reaction study:



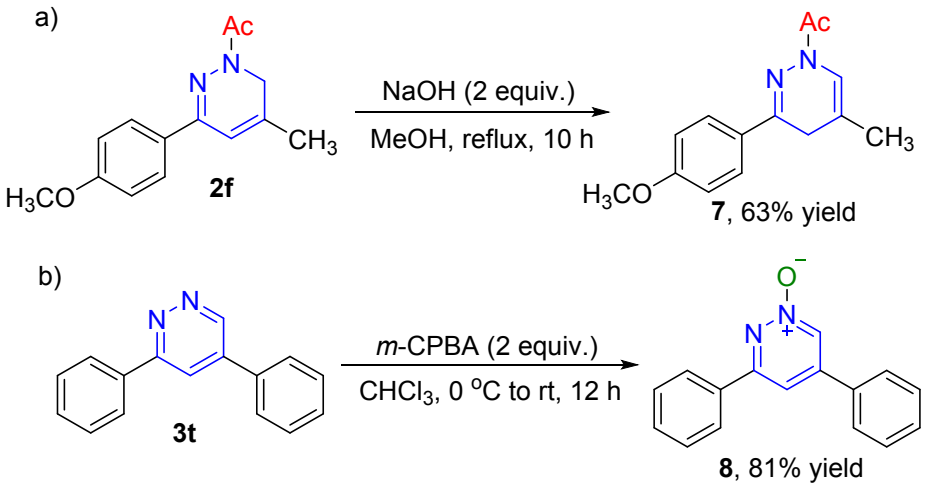
Conditions B, 9 h	65% (99% brsm)
O_2 (balloon), AcOH, 100 °C, 9 h	< 5%
O_2 (balloon), AcOH, 100 °C, 24 h	86%
AcOH, 100 °C, 24 h	0%

b) Proposed reaction pathway:



1,4-Dihydropyridazine and heteroaromatic N-oxides existed in a number of biologically active compounds and were widely employed in transition-metal-catalyzed C-H functionalization reactions.[16] The cyclization product obtained in our studies could be readily transformed by using simple protocols (Scheme 5). For example, treatment of 1,6-dihydropyridazine **2f** with NaOH resulted in the facile formation of C=C bond migration 1,4-dihydropyridazine **7** in 63% yield. Moreover, the oxidation of **3t** gave the pyridazine N-oxide derivative **8** in 81% yield that are not easily obtained by other methods.

Scheme 5. Application of the synthetic methodology.



CONCLUSION

In conclusion, a mild 6-endo-trig cyclization of β,γ-unsaturated hydrazones via copper-catalyzed aerobic system have been developed. The approach allowed controllable and selective access to a diverse range of both pyridazines and 1,6-dihydropyridazines from low-cost and readily available starting materials. The switch in selectivity is attributed to the judicious choice of different reaction solvent. The value of the protocol has been demonstrated by the broad functional group tolerance and the application in the synthesis of bioactive compounds. The mild reaction conditions, synthetic simplicity and the use of O_2 as terminal oxidant make this methodology a sustainable and promising tool in the diversity-oriented complex molecule synthesis. Further investigations to uncover the detailed mechanism are currently underway in our laboratory.

EXPERIMENTAL SECTION

General Methods and Materials. Commercially available materials purchased from Alfa Aesar or Aldrich was used as received. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker AV400 (400 MHz) spectrometer.

Chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ 0.00). ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), dd (doublet of doublets); m (multiplets), and etc. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Carbon nuclear magnetic resonance (^{13}C{^{1}H} NMR) spectra were recorded on a Bruker AV400 (100 MHz) spectrometer. High resolution mass spectral analysis (HRMS) was performed on Waters Q-TOF Premier mass spectrometer. Analytical thin-layer chromatography (TLC) was carried out on Merck 60 F254 pre-coated silica gel plate (0.2 mm thickness). Visualization was performed using a UV lamp.

General Procedure for Preparation of β,γ-Unsaturated Hydrazones 1. To a solution of the β,γ-unsaturated ketone (5 mmol) in methanol was added acetyl hydrazine (1.5 equiv) and acetic acid (0.2 equiv). The mixture was stirred at 60 ^{o}C overnight. After the completion of the reaction as monitored by TLC, the solvent was then concentrated in vacuo. The reaction mixture was extracted with ethyl acetate and the combined extracts were washed with water. The solvent was then removed in vacuo and the resulting crude residue was purified *via* column chromatography on silica gel (4:1 hexanes/EtOAc) to afford the desired hydrazones in 67-97% yield.[8h]

(E)-*N′*-(3-Methyl-1-phenylbut-3-en-1-ylidene)acetohydrazide (1a). White solid, m. p. 141.7-143.3 ^{o}C, Yield: 1.0 g (93%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 7.82-7.64 (m, 2H), 7.42-7.35 (m, 3H), 4.93 (s, 1H), 4.73 (s, 1H), 3.36 (s, 2H), 2.39 (s, 3H), 1.86 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 173.6, 148.1, 137.9, 137.7, 129.3,

128.5, 126.1, 113.3, 35.6, 23.0, 20.5; HRMS (ESI) calcd for $C_{13}H_{17}N_2O$ ($M+H^+$): 217.1335, found: 217.1331.

(Z)-*N′*-(1-(4-Fluorophenyl)-3-methylbut-3-en-1-ylidene)acetohydrazide (1b). White solid, m. p. 153.2-154.1 °C, Yield: 1.1 g (95%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 1H), 7.78-7.68 (m, 2H), 7.14-7.04 (m, 2H), 4.92 (s, 1H), 7.71 (s, 1H), 3.34 (s, 2H), 2.38 (s, 3H), 1.86 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.6, 163.4 (d, J = 249.9 Hz), 147.2, 137.8, 133.8, 128.0 (d, J = 8.3 Hz), 115.4 (d, J = 21.7 Hz), 113.2, 35.5, 22.9, 20.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.8; HRMS (ESI) calcd for $C_{13}H_{16}FN_2O$ ($M+H^+$): 235.1241, found: 235.1242.

(Z)-*N′*-(1-(4-Chlorophenyl)-3-methylbut-3-en-1-ylidene)acetohydrazide (1c). White solid, m. p. 154.1-156.2 °C, Yield: 1.2 g (92%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 7.66 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 4.92 (s, 1H), 4.69 (s, 1H), 3.33 (s, 2H), 2.38 (s, 3H), 1.85 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.6, 147.0, 137.7, 136.1, 135.3, 128.7, 127.4, 113.3, 35.4, 23.0, 20.5; HRMS (ESI) calcd for $C_{13}H_{16}ClN_2O$ ($M+H^+$): 251.0946, found: 251.0949.

(Z)-*N′*-(1-(4-Bromophenyl)-3-methylbut-3-en-1-ylidene)acetohydrazide (1d). White solid, m. p. 154.2-155.7 °C, Yield: 1.3 g (87%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H), 7.59 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 4.92 (s, 1H), 4.68 (s, 1H), 3.32 (s, 2H), 2.38 (s, 3H), 1.85 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.6, 147.0, 137.7, 136.5, 131.6, 127.7, 123.6, 113.3, 35.3, 23.0, 20.5; HRMS (ESI) calcd for $C_{13}H_{16}{}^{79}BrN_2O$($M+H^+$): 295.0441, found: 295.0444.

(Z)-*N′*-(3-Methyl-1-(p-tolyl)but-3-en-1-ylidene)acetohydrazide (1e). White solid, m. p. 167.2-167.8 °C, Yield: 0.98 g (85%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H), 7.62 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 4.91 (s, 1H), 4.72 (s, 1H), 3.34 (s, 2H), 2.38 (s, 3H), 2.37 (s, 3H), 1.85 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 173.6, 148.2, 139.5, 138.0, 134.9, 129.2, 126.0, 113.2, 35.5, 22.9, 21.2, 20.5; HRMS (ESI) calcd for $C_{14}H_{19}N_2O$ ($M+H^+$): 231.1492, found: 231.1488.

(Z)-*N′*-(1-(4-Methoxyphenyl)-3-methylbut-3-en-1-ylidene)acetohydrazide (1f). White solid, m. p. 139.1-140.2 °C, Yield: 1.0 g (82%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 2H), 4.91 (s, 1H), 4.72 (s, 1H), 3.83 (s, 3H), 3.33 (s, 2H), 2.38 (s, 3H), 1.84 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 173.5, 160.6, 147.9, 138.1, 130.2, 127.5, 113.8, 113.2, 55.3, 35.4, 22.9, 20.4; HRMS (ESI) calcd for $C_{14}H_{19}N_2O_2$ ($M+H^+$): 247.1441, found: 247.1449.

(Z)-*N′*-(1-(3,4-Dimethoxyphenyl)-3-methylbut-3-en-1-ylidene)acetohydrazide (1g). White solid, m. p. 142.0-142.9 °C, Yield: 1.0 g (74%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 7.44 (s, 1H), 7.20 (d, *J* = 8.4 Hz, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 4.93 (s, 1H), 4.74 (s, 1H), 3.93 (s, 3H), 3.91 (s, 3H), 3.35 (s, 2H), 2.39 (s, 3H), 1.85 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 173.3, 150.4, 149.0, 147.9, 130.5, 119.5, 113.3, 110.5, 108.7, 55.9, 55.8, 35.4, 22.9, 20.4; HRMS (ESI) calcd for $C_{15}H_{21}N_2O_3$ ($M+H^+$): 277.1547, found: 277.1544.

(E)-*N′*-(3-Methyl-1-(naphthalen-2-yl)but-3-en-1-ylidene)acetohydrazide (1h). White solid, m. p. 153.5-154. 6 °C, Yield: 0.99 g (74%); ^{1}H NMR (400 MHz, $CDCl_3$)

δ 8.88 (s, 1H), 8.08-7.98 (m, 2H), 7.88-7.80 (m, 3H), 7.55-7.44 (m, 2H), 4.94 (s, 1H), 4.77 (s, 1H), 3.47 (s, 2H), 2.44 (s, 3H), 1.90 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 173.7, 148.0, 138.1, 135.0, 133.7, 133.1, 128.5, 128.1, 127.6, 126.8, 126.4, 126.0, 123.4, 113.3, 35.4, 23.0, 20.6; HRMS (ESI) calcd for $C_{17}H_{19}N_2O$ ($M+H^+$): 267.1492, found: 267.1495.

(E)-*N′*-(3-Methyl-1-(thiophen-2-yl)but-3-en-1-ylidene)acetohydrazide (1i). Yellow solid, m. p. 148.5-149.1 °C, Yield: 0.74 g (67%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H), 7.32 (d, J = 5.2 Hz, 1H), 7.23 (d, J = 3.2 Hz, 1H), 7.01 (t, J = 4.4 Hz, 1H), 4.94 (s, 1H), 4.81 (s, 1H), 3.39 (s, 2H), 2.35 (s, 3H), 1.83 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 173.4, 144.1, 143.3, 137.9, 127.8, 127.3, 126.5, 113.6, 36.1, 22.7, 20.3; HRMS (ESI) calcd for $C_{11}H_{15}N_2OS$ ($M+H^+$): 223.0900, found: 223.0894.

(Z)-*N′*-(1-Phenylbut-3-en-1-ylidene)acetohydrazide (1j). White solid, m. p. 110.2-110.9 °C, Yield: 0.98 g (97%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85-8.65 (m, 1H), 7.78-7.72 (m, 2H), 7.42-7.36 (m, 3H), 5.98-5.76 (m, 1H), 5.25-5.10 (m, 2H), 3.52-3.42 (m, 2H), 2.40 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 173.6, 147.6, 137.4, 129.7, 129.4, 128.5, 126.1, 118.4, 31.2, 20.5; HRMS (ESI) calcd for $C_{12}H_{15}N_2O$ ($M+H^+$): 203.1179, found: 203.1184.

Methyl (E)-4-(1-(2-acetylhydrazono)but-3-en-1-yl)benzoate (1l).[8] Yield: 1.87 g (72%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (s, 1H), 8.06 (d, J = 8.1 Hz, 2H), 7.81 (d, J = 8.2 Hz, 2H), 5.89 (ddt, J = 15.7, 10.2, 5.1 Hz, 1H), 5.23 (d, J = 10.2 Hz, 1H), 5.14 (d, J = 17.3 Hz, 1H), 3.94 (s, 3H), 3.48 (d, J = 4.4 Hz, 2H), 2.41 (s, 3H).

(E)-N'-(1-(4-Nitrophenyl)but-3-en-1-ylidene)acetohydrazide (1m). Yellow solid, m. p. 146.8-148.3 °C, Yield: 1.73 g (70%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (br, 1H), 8.25 (d, *J* = 7.6 Hz, 2H), 7.90 (d, *J* = 7.7 Hz, 2H), 5.90 (ddt, *J* = 15.5, 9.7, 4.7 Hz, 1H), 5.26 (d, *J* = 10.2 Hz, 1H), 5.13 (d, *J* = 16.0 Hz, 1H), 3.50 (s, 2H), 2.42 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 173.7, 148.1, 145.2, 143.3, 129.1, 126.9, 123.8, 118.7, 30.9, 20.6; HRMS (ESI) calcd for $C_{12}H_{14}N_3O_3$ ($M+H^+$): 248.1030, found: 248.1028.

(E)-N'-(1-(4-Cyanophenyl)but-3-en-1-ylidene)acetohydrazide (1n). White solid, m. p. 168.6-170.2 °C, Yield: 0.95 g (42%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 7.84 (d, *J* = 7.4 Hz, 2H), 7.68 (d, *J* = 7.4 Hz, 2H), 5.87 (dq, *J* = 15.2, 4.5 Hz, 1H), 5.24 (d, *J* = 10.2 Hz, 1H), 5.12 (d, *J* = 20.0 Hz, 1H), 3.45 (d, *J* = 2.7 Hz, 2H), 2.40 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 173.6, 145.4, 141.5, 132.3, 129.1, 126.6, 118.7, 118.6, 112.7, 30.8, 20.6; HRMS (ESI) calcd for $C_{13}H_{14}N_3O$ ($M+H^+$): 228.1131, found: 228.1128.

(E)-N'-(1-(Furan-2-yl)but-3-en-1-ylidene)acetohydrazide (1o).[8] Yield: 0.98 g (51%); ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 7.49 (s, 1H), 6.75 (s, 1H), 6.48 (s, 1H), 5.82 (ddt, *J* = 16.2, 10.5, 5.5 Hz, 1H), 5.34-5.10 (m, 2H), 3.39 (d, *J* = 4.4 Hz, 2H), 2.36 (s, 3H).

N'-((1E,3E)-1,4-Diphenylbut-3-en-1-ylidene)acetohydrazide (1p).[8] Yield: 1.35 g (97%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.82-7.77 (m, 2H), 7.44-7.38 (m, 4H), 7.33-7.28 (m, 4H), 6.46 (d, *J* = 16.0 Hz, 1H), 6.23 (dt, *J* = 16.2, 5.4 Hz, 1H), 3.59 (d, *J* = 5.2 Hz, 2H), 2.42 (s, 3H).

***tert*-Butyl (*E*)-2-(1-(p-tolyl)but-3-en-1-ylidene)hydrazine-1-carboxylate (1q).**[8] Yield: 1.5 g (55%); ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.68 (d, *J* = 7.5 Hz, 2H), 7.16 (d, *J* = 7.6 Hz, 2H), 5.91 (ddd, *J* = 16.2, 10.8, 5.9 Hz, 1H), 5.20 (dd, *J* = 22.3, 13.9 Hz, 2H), 3.45-3.35 (m, 2H), 2.35 (s, 3H), 1.54 (s, 9H).

(E)-N'-(1-(p-Tolyl)but-3-en-1-ylidene)thiophene-2-carbohydrazide (1r).[8] Yield: 1.84 g (65%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (s, 1H), 8.21 (s, 1H), 7.77 (d, *J* = 7.7 Hz, 2H), 7.66 (s, 1H), 7.25 (d, *J* = 7.3 Hz, 2H), 7.18-7.12 (m, 1H), 6.02-5.87 (m, 1H), 5.28-5.05 (m, 2H), 3.68-3.49 (m, 2H), 2.39 (s, 3H); HRMS (ESI) calcd for $C_{16}H_{16}N_2OS$ ($M+H^+$): 285.1056, found:285.1054.

3-(Benzo[b]thiophen-2-yl)pyridazine (1s). White solid, m.p. 163.2-165.0 °C, Yield: 1.63 g (63%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 1H), 7.78 (d, *J* = 7.2 Hz, 1H), 7.73 (d, *J* = 7.0 Hz, 1H), 7.46 (s, 1H), 7.38-7.30 (m, 2H), 5.88 (ddt, *J* = 15.8, 10.2, 5.3 Hz, 1H), 5.30-5.18 (m, 2H), 3.52 (d, *J* = 3.9 Hz, 2H), 2.40 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 173.5, 143.8, 143.1, 140.4, 139.7, 129.4, 125.8, 124.5, 124.1, 123.5, 122.3, 118.8, 31.2, 20.4; HRMS (ESI) calcd for $C_{14}H_{15}N_2OS$ ($M+H^+$): 259.0900, found: 259.0900.

(E)-*N'*-(1,3-Diphenylbut-3-en-1-ylidene)acetohydrazide (1t). White solid, m. p. 157.3-158.5 °C, Yield: 1.3 g (93%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86-8.74 (m, 1H), 7.80-7.70 (m, 2H), 7.54-7.46 (m, 2H), 7.44-7.34 (m, 6H), 5.50 (s, 1H), 4.97 (s, 1H), 3.81 (s, 2H), 2.38 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 173.7, 148.0, 139.6,

139.5, 137.6, 129.4, 128.6, 128.5, 128.3, 126.2, 125.7, 113.9, 32.9, 20.5; HRMS (ESI) calcd for $C_{18}H_{19}N_2O$ ($M+H^+$): 279.1492, found: 279.1490.

Typical Procedure for the Synthesis of Dihydropyridazine Derivatives 2. To a dry Schlenk tube equipped with a magnetic stir bar, was added β,γ- unsaturated hydrazone **1a** (0.1 mmol), $Cu(OAc)_2$ (20 mol%) and CH_3CN (2 mL). The tube was closed with a rubber stopper and filled with O_2 (balloon). The reaction mixture was then stirred at reflux till **1a** was completely consumed (monitored by TLC). The mixture was then concentrated under reduced pressure and the resulting crude residue was purified *via* column chromatography on silica gel (4:1 hexanes/EtOAc) to afford the desired product **2a** (17.4 mg, 81%).

1-(5-Methyl-3-phenylpyridazin-1(6H)-yl)ethan-1-one (2a). Yellow solid, m. p. 89.1-89.8 °C, Yield: 17.4 mg (81%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.82-7.67 (m, 2H), 7.45-7.30 (m, 3H), 6.28 (s, 1H), 4.35 (s, 2H), 2.42 (s, 3H), 1.94 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 172.9, 145.2, 141.0, 135.7, 129.4, 128.5, 125.6, 112.0, 44.0, 21.2, 21.1; HRMS (ESI) calcd for $C_{13}H_{15}N_2O$ ($M+H^+$): 215.1179, found: 215.1184.

1-(3-(4-Fluorophenyl)-5-methylpyridazin-1(6H)-yl)ethan-1-one (2b). Yellow solid, m. p. 92.8-93.3 °C, Yield: 17.0 mg (73%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.77-7.70 (m, 2H), 7.09 (t, J = 8.4 Hz, 2H), 6.24 (s, 1H), 4.34 (s, 2H), 2.40 (s, 3H), 1.95 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 172.8, 163.49 (d, J = 249.3 Hz), 144.3, 141.3, 131.9, 127.5 (d, J = 8.3 Hz), 115.5 (d, J = 21.7 Hz), 111.8, 44.0, 21.2, 21.1; ^{19}F NMR

(376 MHz, $CDCl_3$) δ -111.7; HRMS (ESI) calcd for $C_{13}H_{14}FN_2O$ ($M+H^+$): 233.1085, found: 233.1089.

1-(3-(4-Chlorophenyl)-5-methylpyridazin-1(6H)-yl)ethan-1-one (2c). Yellow solid, m. p. 93.2-94.1 °C, Yield: 22.8 mg (92%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.2 Hz, 2H), 7.37 (d, *J* = 7.2 Hz, 2H), 6.23 (s, 1H), 4.34 (s, 2H), 2.40 (s, 3H), 1.95 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 172.9, 144.1, 141.3, 135.3, 134.2, 128.7, 126.9, 111.6, 44.0, 21.2, 21.1; HRMS (ESI) calcd for $C_{13}H_{14}ClN_2O$ ($M+H^+$): 249.0789, found: 249.0796.

1-(3-(4-Bromophenyl)-5-methylpyridazin-1(6H)-yl)ethan-1-one (2d). Yellow solid, m. p. 104.1-104.8 °C, Yield: 28.7 mg (98%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.0 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 2H), 6.22 (s, 1H), 4.34 (s, 2H), 2.40 (s, 3H), 1.94 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 172.9, 144.1, 141.4, 134.7, 131.7, 127.1, 123.6, 111.5, 44.1, 21.3, 21.1; HRMS (ESI) calcd for $C_{13}H_{14}BrN_2O$ ($M+H^+$): 293.0284, found: 293.0279.

1-(5-Methyl-3-(p-tolyl)pyridazin-1(6H)-yl)ethan-1-one (2e). Yellow solid, m. p. 96.2-97.1 °C, Yield: 17.6 mg (77%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 6.31-6.27 (m, 1H), 4.33 (s, 2H), 2.41 (s, 3H), 2.38 (s, 3H), 1.93 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 172.9, 145.3, 140.9, 139.5, 132.9, 129.2, 125.5, 112.1, 44.0, 21.3, 21.2, 21.1; HRMS (ESI) calcd for $C_{14}H_{17}N_2O$ ($M+H^+$): 229.1335, found: 229.1339.

1-(3-(4-Methoxyphenyl)-5-methylpyridazin-1(6H)-yl)ethan-1-one (2f). Yellow solid, m. p. 125.5-126.1 °C, Yield: 16.6 mg (68%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.4 Hz, 2H), 6.93 (d, *J* = 8.4 Hz, 2H), 6.26 (s, 1H), 4.32 (s, 2H), 3.84 (s, 3H), 2.40 (s, 3H), 1.94 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 172.7, 160.6, 145.0, 140.9, 128.3, 127.0, 113.9, 112.0, 55.3, 43.9, 21.2, 21.1; HRMS (ESI) calcd for $C_{14}H_{17}N_2O_2$ ($M+H^+$): 245.1285, found: 245.1282.

1-(3-(3,4-Dimethoxyphenyl)-5-methylpyridazin-1(6H)-yl)ethan-1-one (2g). Yellow solid, m. p. 127.3-127.9 °C, Yield: 17.2 mg (63%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.27 (s, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 6.27 (s, 1H), 4.34 (s, 2H), 3.94 (s, 3H), 3.92 (s, 3H), 2.42 (s, 3H), 1.95 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 172.6, 150.4, 149.1, 145.1, 140.9, 128.6, 118.7, 112.0, 110.6, 108.4, 55.9, 55.8, 43.9, 21.2, 21.1; HRMS (ESI) calcd for $C_{15}H_{19}N_2O_3$ ($M+H^+$): 275.1390, found: 275.1396.

1-(5-Methyl-3-(naphthalen-2-yl)pyridazin-1(6H)-yl)ethan-1-one (2h). Yellow solid, m. p. 142.3-143.2 °C, Yield: 15.3 mg (58%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 8.01 (d, *J* = 8.8 Hz, 1H), 7.90-7.80 (m, 3H), 7.58-7.47 (m, 2H), 6.45 (s, 1H), 4.38 (s, 2H), 2.47 (s, 3H), 1.98 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 172.9, 145.0, 141.0, 135.7, 133.8, 133.1, 128.4, 128.3, 127.7, 126.7, 126.5, 125.2, 123.1, 111.9, 44.2, 21.3, 21.2; HRMS (ESI) calcd for $C_{17}H_{17}N_2O$ ($M+H^+$): 265.1335, found: 265.1338.

1-(5-Methyl-3-(thiophen-2-yl)pyridazin-1(6H)-yl)ethan-1-one (2i). Yellow solid, m. p. 135.1-136.2 °C, Yield: 15.0 mg (68%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.30

(m, 2H), 7.26 (s, 1H), 6.22 (s, 1H), 4.33 (s, 2H), 2.38 (s, 3H), 1.94 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 172.6, 141.5, 141.03, 140.96, 127.4, 125.4, 111.6, 44.2, 21.1, 20.9; HRMS (ESI) calcd for $C_{11}H_{13}N_2OS$ ($M+H^+$): 221.0743, found: 221.0736.

1-(3-Phenylpyridazin-1(6H)-yl)ethan-1-one (2j). Yellow Liquid, Yield: 16.4 mg (82%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76-7.70 (m, 2H), 7.45-7.37(m, 3H), 6.48 (d, *J* = 10.0 Hz, 1H), 6.41-6.27 (m, 1H), 4.49 (s, 2H), 2.40 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 173.0, 144.5, 135.4, 130.1, 129.5, 128.6, 125.5, 116.6, 39.9, 21.0; HRMS (ESI) calcd for $C_{12}H_{13}N_2O$ ($M+H^+$): 201.1022, found: 201.1026.

1-(3-(p-Tolyl)pyridazin-1(6H)-yl)ethan-1-one (2k).[8] Yield: 16.2 mg (76%); 0.72 g (67% yield, 5 mmol of substrate **1k** was used); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 7.9 Hz, 2H), 6.47 (d, *J* = 10.1 Hz, 1H), 6.40-6.29 (m, 1H), 4.49 (s, 2H), 2.40 (s, 3H), 2.39 (s, 3H).

Methyl 4-(1-acetyl-1,6-dihydropyridazin-3-yl)benzoate (2l).[8] Yield: 14.9 mg (58%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.1 Hz, 2H), 7.80 (d, *J* = 8.1 Hz, 2H), 6.49 (d, *J* = 10.5 Hz, 1H), 6.42-6.34 (m, 1H), 4.51 (d, *J* = 3.9 Hz, 2H), 3.94 (s, 3H), 2.42 (s, 3H).

1-(3-(4-Nitrophenyl)pyridazin-1(6H)-yl)ethan-1-one (2m). Yellow solid, m. p. 169.5-170.9 °C, Yield: 15.4 mg (63%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.6 Hz, 2H), 7.90 (d, *J* = 8.6 Hz, 2H), 6.50 (d, *J* = 10.3 Hz, 1H), 6.45-6.38 (m, 1H), 4.54 (d, *J* = 3.2 Hz, 2H), 2.43 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 173.1, 148.2,

142.1, 141.3, 130.6, 126.1, 123.9, 115.8, 40.3, 21.1; HRMS (ESI) calcd for $C_{12}H_{12}N_3O_3$ ($M+H^+$): 246.0873, found: 246.0874.

4-(1-Acetyl-1,6-dihydropyridazin-3-yl)benzonitrile (2n). Yellow solid, m. p. 144.8-146.1 °C, Yield: 15.1 mg (67%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.2 Hz, 2H), 7.70 (d, *J* = 7.2 Hz, 2H), 6.46 (d, *J* = 11.3 Hz, 1H), 6.40-6.25 (m, 1H), 4.52 (s, 2H), 2.41 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 173.1, 142.4, 139.5, 132.4, 130.6, 125.9, 118.6, 115.7, 112.7, 40.2, 21.0; HRMS (ESI) calcd for $C_{13}H_{12}N_3O$ ($M+H^+$): 226.0975, found: 226.0974.

1-(3-(Furan-2-yl)pyridazin-1(6H)-yl)ethan-1-one (2o).[8] Yield: 13.5 mg (71%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 6.76 (s, 1H), 6.53-6.46 (m, 1H), 6.39 (d, *J* = 10.7 Hz, 1H), 6.36-6.27 (m, 1H), 4.48 (d, 2H), 2.37 (s, 3H).

1-(3,6-Diphenylpyridazin-1(6H)-yl)ethan-1-one (2p).[8] Yellow Liquid, Yield: 21.8 mg (79%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 4.0 Hz, 2H), 7.46-7,42 (m, 3H), 7.39-7.27 (m, 5H), 6.66 (d, *J* = 9.9 Hz, 1H), 6.47 (dd, *J* = 9.8, 6.0 Hz, 1H), 6.32 (d, *J* = 5.8 Hz, 1H), 2.44 (s, 3H).

***tert*-Butyl 3-(*p*-tolyl)pyridazine-1(6*H*)-carboxylate (2q).**[8] Yield: 12.2 mg (45%); ^{1}HNMR (400MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.8 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 6.44 (d, *J* = 10.0 Hz, 1H), 6.30-6.20 (m, 1H), 4.37 (d, *J* = 3.4 Hz, 2H), 2.36 (s, 3H), 1.57 (s, 9H).

Thiophen-2-yl(3-(p-tolyl)pyridazin-1(6H)-yl)methanone (2r). Yellow solid, m.p.106.4-108.2 °C, Yield: 21.9 mg (78%); ^{1}HNMR (400MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.77 (d, *J* = 7.4 Hz, 2H), 7.60 (s, 1H), 7.27 (d, *J* = 8.6 Hz, 2H), 7.11 (s, 1H), 6.54 (d, *J* = 10.2 Hz, 1H), 6.49-6.39 (m, 1H), 4.71-4.60 (m, 2H), 2.41 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.5, 145.8, 140.0, 135.5, 134.2, 132.8, 132.5, 130.4, 129.4, 126.5, 126.2, 117.1, 40.8, 21.4; HRMS (ESI) calcd for $C_{16}H_{15}N_2OS$ ($M+H^+$): 283.0900, found:283.0899.

Typical Procedure for the Synthesis of Pyridazine Derivatives 3. To a dry Schlenk tube equipped with a magnetic stir bar, was added β-γ unsaturated hydrazone **1a** (0.1 mmol), $Cu(OAc)_2$ (20 mol%) and AcOH (2 mL). The tube was closed with a rubber stopper and filled with O_2 (balloon). The reaction mixture was then stirred at 100 °C till **1a** was completely consumed (monitored by TLC). The reaction mixture was cooled to room temperature and was diluted with H_2O (2 mL), neutralized with a saturated aqueous solution of $NaHCO_3$, and extracted with CH_2Cl_2 (5 mL × 3). The organic extract was washed with brine (2 mL) and dried with Na_2SO_4. After filtration the solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography on silica gel (2:1 hexanes/EtOAc) to afford the desired product **3a** (14.4 mg, 85%).

5-Methyl-3-phenylpyridazine (3a). Brown solid, m. p. 91.3-92.1 °C, Yield: 14.4 mg (85%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1H), 8.06 (d, *J* = 7.2 Hz, 2H), 7.67 (s, 1H), 7.56-7.44 (m, 3H), 2.44 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.9,

151.6, 137.9, 136.4, 129.9, 128.9, 127.1, 124.3, 18.6; HRMS (ESI) calcd for $C_{11}H_{11}N_2$ ($M+H^+$): 171.0917, found: 171.0921.

3-(4-Fluorophenyl)-5-methylpyridazine (3b). Brown solid, m. p. 128.5-129.2 °C, Yield: 14.9 mg (79%); ^1H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 8.06 (t, J = 8.4 Hz, 2H), 7.64 (s, 1H), 7.21 (t, J = 8.4 Hz, 2H), 2.44 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.1 (d, J = 250.0 Hz), 157.9, 151.6, 138.0, 132.5, 129.0 (d, J = 8.6 Hz), 124.0, 116.0 (d, J = 21.7 Hz), 18.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.3; HRMS (ESI) calcd for $C_{11}H_{10}FN_2$ ($M+H^+$): 189.0823, found: 189.0828.

3-(4-Chlorophenyl)-5-methylpyridazine (3c). Brown solid, m. p. 146.4-147.6 °C, Yield: 17.3 mg (85%); ^1H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1H), 8.02 (d, J = 7.2 Hz, 2H), 7.65 (s, 1H), 7.49 (d, J = 7.2 Hz, 2H), 2.44 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 157.7, 151.8, 138.0, 136.2, 134.8, 129.2, 128.4, 124.0, 18.6; HRMS (ESI) calcd for $C_{11}H_{10}ClN_2$ ($M+H^+$): 205.0527, found: 205.0529.

3-(4-Bromophenyl)-5-methylpyridazine (3d). Brown black solid, m. p. 173.1-173.8 °C, Yield: 21.3 mg (86%); ^1H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1H), 7.95 (d, J = 7.2 Hz, 2H), 7.70-7.62 (m, 3H), 2.44 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 157.8, 151.2, 138.1, 135.3, 132.1, 128.6, 124.6, 124.0, 18.6; HRMS (ESI) calcd for $C_{11}H_{10}BrN_2$ ($M+H^+$): 249.0022, found: 249.0015.

5-Methyl-3-(p-tolyl)pyridazine (3e). Brown solid, m. p. 121.5-122.2 °C, Yield: 13.0 mg (70%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1H), 7.96 (d, J = 8.0 Hz, 2H),

7.64 (s, 1H), 7.33 (d, J = 8.0 Hz, 2H), 2.43 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 158.8, 151.4, 140.1, 137.8, 133.5, 129.7, 127.0, 124.0, 21.3, 18.5; HRMS (ESI) calcd for $C_{12}H_{13}N_2$ ($M+H^+$): 185.1073, found: 185.1070.

3-(4-Methoxyphenyl)-5-methylpyridazine (3f). Brown solid, m. p. 145.3-146.2 °C, Yield: 10.1 mg (50%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.95 (s, 1H), 8.03 (d, J = 8.4 Hz, 2H), 7.62 (s, 1H), 7.04 (d, J = 8.4 Hz, 2H), 3.88 (s, 3H), 2.42 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.2, 158.4, 151.1, 137.8, 128.8, 128.5, 123.7, 114.3, 55.4, 18.6; HRMS (ESI) calcd for $C_{12}H_{13}N_2O$ ($M+H^+$): 201.1022, found: 201.1016.

3-(3,4-Dimethoxyphenyl)-5-methylpyridazine (3g). Brown solid, m. p. 149.1-150.6 °C, Yield: 15.2 mg (66%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.95 (s, 1H), 7.84 (s, 1H), 7.63 (s, 1H), 7.51 (d, J = 8.4 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 4.00 (s, 3H), 3.95 (s, 3H), 2.42 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 158.2, 151.2, 150.8, 149.5, 137.7, 129.1, 123.6, 119.6, 111.1, 110.1, 56.1, 56.0, 18.5; HRMS (ESI) calcd for $C_{13}H_{15}N_2O_2$ ($M+H^+$): 231.1128, found: 231.1123.

5-Methyl-3-(naphthalen-2-yl)pyridazine (3h). Brown solid, m. p. 178.3-179.2 °C, Yield: 13.6 mg (62%); ^1H NMR (400 MHz, $CDCl_3$) δ 9.05 (s, 1H), 8.54 (s, 1H), 8.21 (d, J = 8.8 Hz, 1H), 8.01-7.95 (m, 2H), 7.93-7.89 (m, 1H), 7.83 (s, 1H), 7.58-7.50 (m, 2H), 2.47 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 151.4, 134.1, 133.5, 133.3, 128.80, 128.78, 127.7, 127.1, 127.0, 126.6, 124.8, 124.3, 100.0, 18.6; HRMS (ESI) calcd for $C_{15}H_{13}N_2$ ($M+H^+$): 221.1073, found: 221.1069.

5-Methyl-3-(thiophen-2-yl)pyridazine (3i). Brown solid, m. p. 162.4-163.2 °C, Yield: 12.0 mg (68%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 1H), 7.71-7.68 (m, 1H), 7.58 (s, 1H), 7.49 (d, *J* = 8.4Hz, 1H), 7.16 (s, 1H), 2.40 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 154.5, 151.5, 140.7, 137.8, 129.1, 128.0, 126.1, 122.4, 18.5; HRMS (ESI) calcd for $C_9H_9N_2S$ ($M+H^+$): 177.0481, found: 177.0478.

3-Phenylpyridazine (3j). Brown solid, m. p. 92.3-92.8 °C, Yield: 14.5 mg (92%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22-9.16 (m, 1H), 8.08 (d, *J* = 7.2 Hz, 2H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.57-7.49 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 150.0, 146.2, 130.1, 129.0, 127.1, 126.8, 123.9; HRMS (ESI) calcd for $C_{10}H_9N_2$ ($M+H^+$): 157.0760, found: 157.0758.

Methyl 4-(pyridazin-3-yl)benzoate (3l).[8] Yield: 13.7 mg (64%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (d, *J* = 4.9 Hz, 1H), 8.25-8.10 (m, 4H), 7.92 (d, *J* = 8.5 Hz, 1H), 7.59 (dd, *J* = 8.9, 5.0 Hz, 1H), 3.97 (s, 3H).

3-(4-Nitrophenyl)pyridazine (3m). White solid, m. p. 160.3-161.8 °C, Yield:10.7 mg (53%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (d, *J* = 4.8 Hz, 1H), 8.40 (d, *J* = 7.5 Hz, 2H), 8.29 (d, *J* = 7.4 Hz, 2H), 7.96 (d, *J* = 8.6 Hz, 1H), 7.69-7.61 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.4, 150.8, 149.0, 142.2, 128.0, 127.1, 124.3, 124.2; HRMS (ESI) calcd for $C_{10}H_8N_3O_2$ ($M+H^+$): 202.0611, found: 202.0607.

4-(Pyridazin-3-yl)benzonitrile (3n). White solid, m. p. 130.5-131.8 °C, Yield: 10.0 mg (55%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (d, *J* = 4.6 Hz, 1H), 8.23 (d, *J* = 7.2 Hz,

2H), 7.92 (d, *J* = 8.6 Hz, 1H), 7.84 (d, *J* = 7.1 Hz, 2H), 7.66-7.60 (m, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 157.7, 150.7, 140.5, 132.8, 127.7, 127.0, 124.1, 118.4, 113.8; HRMS (ESI) calcd for $C_{11}H_8N_3$ ($M+H^+$): 182.0713, found: 182.0709.

3-(Furan-2-yl)pyridazine (3o).[8] Yield: 8.0 mg (55%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07 (d, *J* = 4.7 Hz, 1H), 7.84 (d, *J* = 8.6 Hz, 1H), 7.62 (s, 1H), 7.50 (dd, *J* = 8.3, 5.0 Hz, 1H), 7.37 (d, *J* = 2.5 Hz, 1H), 6.61 (s, 1H).

3-(Benzo[b]thiophen-2-yl)pyridazine (3s). White solide, m. p. 158.2-159.8 °C, Yield: 14.2 mg (67%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (br, 1H), 7.95-7.87 (m, 3H), 7.86-7.80 (m, 1H), 7.52 (br, 1H), 7.43-7.35 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 141.2, 140.7, 139.9, 125.8, 124.8, 124.4, 123.2, 122.8, 122.7; HRMS (ESI) calcd for $C_{12}H_9N_2S$ ($M+H^+$): 213.0481, found: 213.0477.

3,5-Diphenylpyridazine (3t). Yellow solid, m. p. 175.4-176.1 °C, Yield: 17.0 mg (73%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.42 (s, 1H), 8.14 (d, *J* = 6.8 Hz, 2H), 8.00 (s, 1H), 7.73 (d, *J* = 6.8 Hz, 2H), 7.60-7.52 (m, 6H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 148.4, 139.1, 136.5, 134.9, 130.10, 130.07, 129.5, 129.0, 127.3, 127.2, 121.1; HRMS (ESI) calcd for $C_{16}H_{13}N_2$ ($M+H^+$): 233.1073, found: 233.1077.

Radical inhibition study. To a dry Schlenk tube equipped with a magnetic stir bar, was added β-γ unsaturated hydrazone **1a** (0.05 mmol), $Cu(OAc)_2$ (20 mol%), radical scavenger (BHT or 1,1-diphenylethylene, 3.0 equiv) and CH_3CN (1 mL). The tube was closed with a rubber stopper and filled with O_2 (balloon). The reaction mixture

was then stirred at 80 °C till **1a** was completely consumed (monitored by TLC). The mixture was concentrated under reduced pressure. The resulting crude residue was purified *via* column chromatography on silica gel (4:1 hexanes/EtOAc) to afford the desired product **2a** (BHT, 8.4 mg, 79% yield; 1,1-diphenylethylene, 7.6 mg, 71% yield).

To a dry Schlenk tube equipped with a magnetic stir bar, was added β-γ unsaturated hydrazone **1a** (0.1 mmol), $Cu(OAc)_2$ (20 mol%), TEMPO (3.0 equiv) and CH_3CN (1 mL). The tube was closed with a rubber stopper and filled with O_2 (balloon). The reaction mixture was then stirred at 80 °C till **1a** for 2 h. The mixture was concentrated under reduced pressure. The resulting crude residue was purified *via* column chromatography on silica gel (4:1 hexanes/EtOAc) to afford the desired product **2a** (12.8 mg, 60% yield) and TEMPO trapping product **4** (3.3 mg, 9% yield).

1-(5-Methyl-3-phenyl-5-(((2,2,6,6-tetramethylpiperidin-1-yl)oxy)methyl)-4,5-dihydro-1H-pyrazol-1-yl)ethan-1-one (**4**). Colourless liquid, Yield: 3.3 mg (9%); ^{1}HNMR (600 MHz, $CDCl_3$) δ 7.76-7.68 (m，2H), 7.44-7.39 (m, 3H), 4.38 (d, J = 8.8 Hz, 2H), 3.92 (d, J = 8.8 Hz, 2H), 3.63 (d, J = 17.1 Hz, 2H), 2.98 (d, J = 17.1 Hz, 2H), 2.37 (s, 1H), 1.66 (s, 3H), 1.55-1.35 (m, 6H), 1.20-1.08 (m, 6H), 1.05-0.85 (m, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.8, 152.5, 132.0, 129.8, 128.6, 126.3, 78.3, 66.0, 60.1, 44.7, 39.8, 33.4, 23.3, 22.8, 20.1, 17.0; HRMS (ESI) calcd for $C_{22}H_{33}N_3O$ ($M+H^+$): 372.2646, found: 372.2652.

To a dry Schlenk tube equipped with a magnetic stir bar, was added β-γ unsaturated hydrazone **1a** (0.1 mmol), $Cu(OAc)_2$ (20 mol%), 1,4-cyclohexadiene (3.0

equiv) and CH_3CN (1 mL). The tube was closed with a rubber stopper and filled with O_2 (balloon). The reaction mixture was then stirred at 80 °C till **1a** for 6 h. The mixture was concentrated under reduced pressure. The resulting crude residue was purified *via* column chromatography on silica gel (4:1 hexanes/EtOAc) to afford the desired product **2a** (14.5 mg, 68% yield). The hydrogen atom transfer product **5** was not able to be isolated. However, the determination of the reaction crude mixture by HRMS indicated the existence of **5**. HRMS (ESI) calcd for $C_{13}H_{17}N_2O$ ($M+H^+$): 217.1335, found: 217.1338.

Control reaction with 2,2-dimethyl-substituted hydrazone 1u as substrate. To a dry Schlenk tube equipped with a magnetic stir bar, was added β-γ unsaturated hydrazone **1u** (0.1 mmol), $Cu(OAc)_2$ (20 mol%) and CH_3CN (1 mL). The tube was closed with a rubber stopper and filled with O_2 (balloon). The reaction mixture was then stirred at 100 °C for 15 h. The mixture was concentrated under reduced pressure. The resulting crude residue was purified *via* column chromatography on silica gel (4:1 hexanes/EtOAc) to afford the desired product **6** (9.3 mg, 41% yield) and recovered substrate **1u** (11.5 mg, 50% yield).

1-(4,4-Dimethyl-3-phenylpyridazin-1(4H)-yl)ethan-1-one (**6**).[10], Yield:9.3 mg (41%, 82% brsm); ^1H NMR (400 MHz, $CDCl_3$) δ 7.92-7.73 (m, 2H), 7.55-7.35 (m, 3H), 6.02 (s, 1H), 4.62 (s, 1H), 2.49 (s, 3H), 1.60-1.46 (d, 6H).

Transformation of 1,6-dihydropyridazine to pyridazine. To a dry Schlenk tube equipped with a magnetic stir bar, was added **2f** (0.05 mmol), $Cu(OAc)_2$ (20 mol%) and

AcOH (2 mL). The tube was closed with a rubber stopper and filled with O_2 (balloon). The reaction mixture was then stirred at 100 °C for 9 hours. The reaction mixture was cooled to room temperature and was diluted with H_2O (2 mL), neutralized with a saturated aqueous solution of $NaHCO_3$, and extracted with CH_2Cl_2 (5 mL × 3). The organic extract was washed with brine (2 mL) and dried with Na_2SO_4. After filtration the solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography on silica gel (2:1 hexanes/EtOAc) to afford the desired product **3f** in 65% yield (99% brsm).

To a dry Schlenk tube equipped with a magnetic stir bar, was added **2f** (0.05 mmol) and AcOH (2 mL). The tube was closed with a rubber stopper and filled with O_2 (balloon). The reaction mixture was then stirred at 100 °C for 9 hours. The desired product **3f** was afforded in < 5% yield.

To a dry Schlenk tube equipped with a magnetic stir bar, was added **2f** (0.05 mmol) and AcOH (2 mL). The tube was closed with a rubber stopper and filled with O_2 (balloon). The reaction mixture was then stirred at 100 °C for 24 hours till **1a** was completely consumed (monitored by TLC). The reaction mixture was cooled to room temperature and was diluted with H_2O (2 mL), neutralized with a saturated aqueous solution of $NaHCO_3$, and extracted with CH_2Cl_2 (5 mL × 3). The organic extract was washed with brine (2 mL) and dried with Na_2SO_4. After filtration the solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography on silica gel (2:1 hexanes/EtOAc) to afford the desired product **3f** in 86%.

To a dry Schlenk tube equipped with a magnetic stir bar, was added **2f** (0.05 mmol) and AcOH (2 mL). The tube was closed with a septum, evacuated, and refilled with nitrogen. The reaction mixture was then stirred at 100 ^{o}C for 24 hours. The desired product **3f** was not observed.

Application of the Synthetic Methodology. To a dry Schlenk tube equipped with a magnetic stir bar, was added **2f** (0.05 mmol), NaOH (2 equiv) and MeOH (2 mL). The tube was closed with a septum, evacuated, and refilled with nitrogen. The reaction mixture was then stirred at 90 ^{o}C till **2f** was completely consumed (monitored by TLC). The mixture was concentrated under reduced pressure. The resulting crude residue was purified *via* column chromatographyon silica gel (4:1 hexanes/EtOAc) to afford the desired product **7** in 63% yield.

1-(3-(4-Methoxyphenyl)-5-methylpyridazin-1(4H)-yl)ethan-1-one (7). Yellow solid, m. p. 97.4-98.3 ^{o}C, Yield: 7.7 mg (63%); ^{1}H NMR (400 MHz, CDCl3) δ 7.76 (d, J = 8.2 Hz, 2H), 7.25 (s, 1H), 6.94 (d, J = 8.2 Hz, 2H), 3.86 (s, 3H), 3.13 (s, 2H), 2.44 (s, 3H), 1.79 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.7, 161.0, 144.8, 128.9, 127.2, 115.2, 113.8, 112.3, 55.3, 28.0, 21.3, 19.9; HRMS (ESI) calcd for $C_{14}H_{17}N_2O_2$ ($M+H^+$): 245.1285, found: 245.1286.

To a Schlenk tube equipped with a magnetic stir bar, was added **3t** (0.05 mmol), $CHCl_3$ (1 mL). The tube was frozen to 0 ^{o}C and m-CPBA (0.2 mmol) was slowly added to the reaction mixture. The reaction was then stirred at RT for 12 hours till **3s** was completely consumed (monitored by TLC). The solvent was evaporated and the

resulting crude mixture was washed with DCM (5 mL×3) to afford the desired product **8** in 81% yield.

3,5-Diphenylpyridazine 1-oxide (8). Yellow solid, m. p. 187.4-189.3 °C, Yield: 10.0 mg (81%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 8.10-8.04 (m, 2H), 7.69-7.63 (m, 3H), 7.60-7.56 (m, 3H), 7.54-7.50 (m, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.3, 147.7, 134.0, 133.2, 131.0, 130.9, 130.0, 129.7, 129.1, 127.3, 126.9, 112.1; HRMS (ESI) calcd for $C_{16}H_{13}N_2O$ ($M+H^+$): 249.1022, found: 249.1021.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Copy of NMR spectra for the products (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We gratefully acknowledge the National Natural Science Foundation of China (21502019, 21402027), the Open Project Program of the State Key Laboratory of Photocatalysis on Energy and Environment (SKLPEE-KF201816), the Foundation of Science and Technology on Sanming Institute of Fluorochemical Industry (FCIT201702BR) and Fuzhou University for financial support.

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