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Copper-Catalyzed Alkylation of Silyl Enol Ethers with Sterically Hindered α-Bromocarbonyls: Access to the Histamine H_3 Receptor Antagonist

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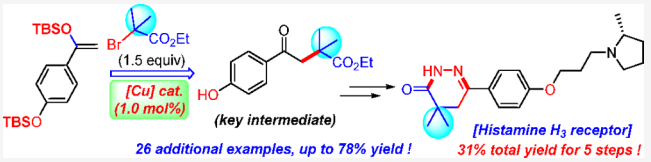
ABSTRACT: A general and efficient copper-catalyzed alkylation of silyl enol ethers with functionalized alkyl bromides has been developed for the synthesis of the sterically hindered γ-ketoesters. The transformation was induced through C(sp^3)-halogen activation of commercially available sterically hindered alkyl bromides under mild conditions in good results. The strategy could be used for the synthesis of biologically active histamine H_3 receptor (H_3R) antagonist for medicinal purposes.



INTRODUCTION

The γ-ketoester moieties are arguably the most important and versatile building blocks in organic synthesis. For example, they are useful synthetic precursors in many fundamental transformations, such as the Paal–Knorr reaction for the construction of five-membered heterocyclic compounds.[1] Meanwhile, they exist in a variety of bioactive compounds, such as the matrix metalloproteinases inhibitor (**A**),[2a] bioavailable tankyrase inhibitor (**B**),[2b] or cannabinoid receptor 1 inhibitor (**C**)[2c] (Figure 1). In this context, γ-ketoesters with sterically hindered groups, such as the geminal dimethyl centers, are prevalent intermediates in medicinal chemistry, due to their excellent biological properties.[3] For example, these scaffolds have been found in the histamine H_3 receptor antagonist (**D**)[3a] and inhibitors of 17β-HSD1 (**E**)[3b] (Figure 1). Thus, the development of diverse synthetic approaches for the construction of these compounds in organic synthesis and medicinal chemistry has been a hot topic.[4,5]

Generally, these functional products could be obtained by treating 2,2-dimethylsuccinic anhydride as a substrate in the presence of a copper-catalytic system with Grignard reagents or a stoichiometric amount of aluminum chloride in the reactions with substituted benzenes[4,3d] (a, Scheme 1). However, it is still quite limited in the substrate scope; moreover, the acid group ($-CO_2H$) needs further diversification.[4] In recent years, the utilization of alkyl halides, especially with the bench stable and commercially available alkyl α-bromocarboxylates, has been studied as one as the most efficient strategies for the construction of these compounds[5] (Scheme 1b). For example, in 2014, the Zhang group developed an efficient visible-light-induced reaction with sterically hindered alkyl α-bromocarboxylates and enamines by Ru-photoredox catalysis to afford γ-ketoesters in generally good yields.[5a] Later on, the same type of products were accessed with different Ir-based phtocatalysts with vinylarenes.[5b] In 2016, Loh and Xu developed a palladium-catalyzed alkylation reaction of enamides with α-bromo-substituted carbonyls. In the reaction, a stoichiometric amount of silver salt was also required. Further applications of the corresponding products could be transformed into γ-ketoesters (Scheme 1b).[5c] Despite these significant advances,[5] limitations of these strategies, such as the use of noble Ru and Ir photocatalysts[5a,b] or Pd/Ag salts in the system,[5c] make the development of new practical routes highly desirable. It has been well-known that the alkyl radical could be induced by a cheap and earth abundant copper catalyst[6−8] and continued the author interest in functionalized alkyl halides in organic chemistry;[9] herein, the author wish to develop a general and efficient copper-catalyzed alkylation of silyl enol ethers with functionalized alkyl bromides for the synthesis of the sterically hindered γ-ketoesters (Scheme 1c).

RESULTS AND DISCUSSION

Initially, the investigation was studied with *tert*-butyldimethyl-((1-phenylvinyl)oxy)silane (**1a**) and ethyl 2-bromo-2-methyl-propanoate (**2a**) as the model substrates to test the possibility.[6] The desired product **3a** could be obtained in 21% yield, when the reaction was conduct with CuI (3.0 mol %) and PMDTA (1.5 equiv) in EtOH (entry 1, Table 1). Delightedly, when PMDTA (5.0 mol %) and $NaHCO_3$ (1.5 equiv) were used, a remarkable 51% yield was obtained (entry 2, Table 1). The control experiments showed that the copper salt, ligand, and base were all inevitable (entries 3−5). Other ligands or bases

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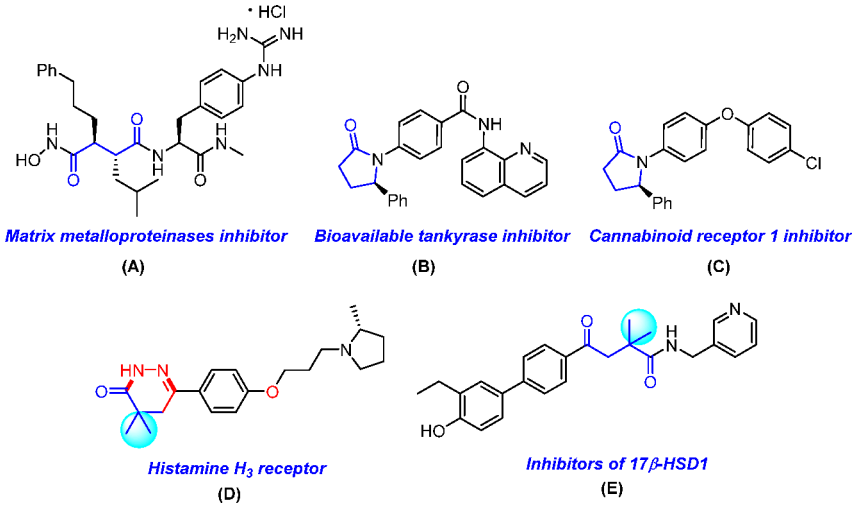
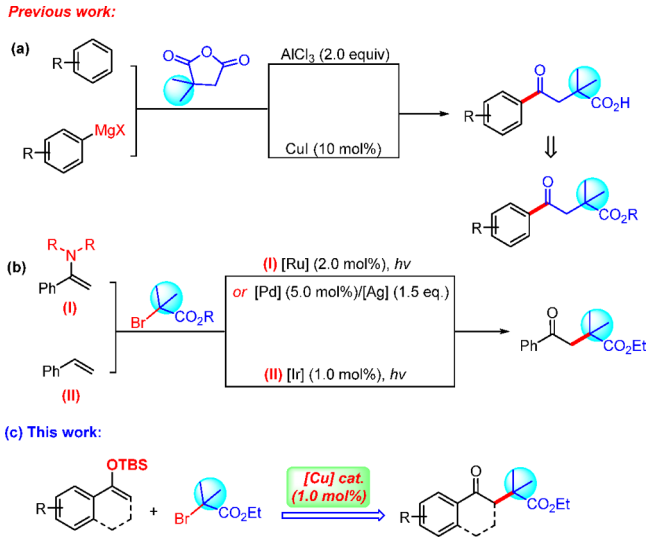


Figure 1. Bioactive compounds derived from γ-ketoesters.

Scheme 1. Strategies to Sterically Hindered γ-Ketoesters with Geminal Dimethyl Groups



were screened (entries 11−15), such as Na_2CO_3 (45%), K_2CO_3 (10%), and NaOAc (22%), or copper species (entries 16−20) were proven less effective. Interesting, other solvents, such as DCE (63%, entry 21) or dioxane (78%, entry 23), were used; product **3a-1** was obtained as the only side product in a good yield, and no obvious product **3a** could be identified. At last, reducing the amount of the copper catalyst (1.0 mol %) gave a similar result of **3a-1** (84%, entry 29). Since the step of **3a-1** was high-yielding and clean, the direct hydrolysis for product **3a** could proceed in a 75% total yield in a one-pot two-step protocol as the best reaction condition (entry 29).

Then, the scope of silyl enol ethers and ethyl 2-bromo-2-methylpropanoate (**2a**) was investigated to illustrate the possibility of the reaction (Scheme 2). It showed that silyl enol ether derivatives have a good functional group tolerance in this protocol. Different substituent groups, such as, electron-donating (e.g., Me−, OMe−) or electron-withdrawing (F−, Cl−, Br−, or CF_3−), even the strong electron-withdrawing (NO_2−), at different positions of the aromatic rings, could generate the desired products **3a−3n** in generally good yields (36−78%). It should be noted that the starting material could not be consumed completely in the formation of **3f**, **3g**, **3m**, and **3o**, due to the steric or electronic effects. Importantly, when EtOH was used as the solvent, a significant beneficial effect on the reaction outcome was observed,[7d] affording **3f** (49%), **3g** (36%), **3m** (45%), and **3o** (52%) in moderate yields. Furan- or thiophene-fused silyl enol ethers could be converted to the desired products **3k−3l** in 52−78% yields. In addition, silyl enol ethers with alkene or alkyne groups could also be used as the coupling partners to give the corresponding products **3p−3r** in moderate yields (46−64%). Unfortunately, alkyl enol ether derivatives were unsuitable substrates for transformations when the starting materials were decomposed in the reaction.

Encouraged by the above results, a range of alkyl bromides were studied for further examination of the substrate scope[6,10,11] (Scheme 3). The alkyl bromides with different substituents, such as methyl, benzyl, or ethyl groups, all could be used in the transformation smoothly, giving the desired products **4a−4h** in good yields (30−74%).

It is noteworthy that the pyridazin-3-one derivatives are versatile building blocks and have been extensively studied due to the unique biological properties.[12] Meanwhile, the γ-ketoester compounds are versatile synthetic precursors to these heterocycles.[2,3] Since the step of products **3** or **4** was high-yielding and clean, the direct one-pot three-step protocol reaction conditions for the synthesis of pyridazin-3-one derivatives have been conducted (Scheme 4). A 1.0 mmol scale reaction in the formation of pyridazin-3-one derivatives **5a−5f** could be achieved in good results successfully.

It has been known that the histamine H_3 receptor (H_3R) is localized primarily presynaptically in the brain and as an inhibitory heteroreceptor regulating the release of multiple neurotransmitters.[13] The identification of compound (*R*)-4,4-dimethyl-6-(4-(3-(2-methylpyrrolidin-1-yl)propoxy)phenyl)-4,5-dihydropyridazin-3(2*H*)-one **6e** as a lead candidate for potential use in the treatment of cognitive disorders has been well studied.[3a] To further explore the synthetic utility of the strategies, the important biologically active histamine H_3 receptor (H_3R) antagonist **6e** could be accessed with the present copper-catalyzed alkylation of silyl enol ethers as the key strategy for medicinal purposes (Scheme 5).

Some control experiments were examined in order to investigate the mechanism of the reaction. For example, TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) or BHT (buty-

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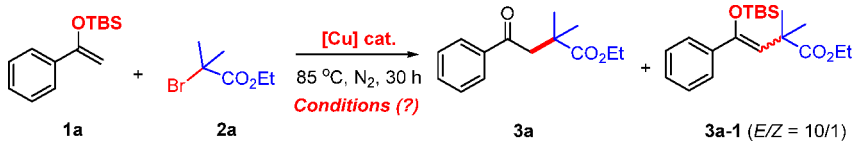
Table 1. Examination of the Reaction Conditions[a]



1a 2a 3a 3a-1 (*E*/*Z* = 10/1)

entry	catalyst (mol %)	ligand (mol %)	base (equiv)	solvent	yield 3a[b]	yield 3a-1[b]
1	CuI (3.0)		PMDTA (1.5)	EtOH	21	
2	CuI (3.0)	PMDTA (5.0)	$NaHCO_3$ (1.5)	EtOH	51	
3		PMDTA (5.0)	$NaHCO_3$ (1.5)	EtOH		
4	CuI (3.0)		$NaHCO_3$ (1.5)	EtOH		
5	CuI (3.0)	PMDTA (5.0)		EtOH		
6	CuI (3.0)	DIPEA (5.0)	$NaHCO_3$ (1.5)	EtOH	13	
7	CuI (3.0)	bipy (5.0)	$NaHCO_3$ (1.5)	EtOH	26	
8	CuI (3.0)	phen (5.0)	$NaHCO_3$ (1.5)	EtOH	20	
9	CuI (3.0)	L-proline (5.0)	$NaHCO_3$ (1.5)	EtOH	18	
10	CuI (3.0)	TMEDA (5.0)	$NaHCO_3$ (1.5)	EtOH	17	
11	CuI (3.0)	PMDTA (5.0)	Na_2CO_3 (1.5)	EtOH	45	
12	CuI (3.0)	PMDTA (5.0)	K_2CO_3 (1.5)	EtOH	10	
13	CuI (3.0)	PMDTA (5.0)	KOAc (1.5)	EtOH	<5	
14	CuI (3.0)	PMDTA (5.0)	NaOAc (1.5)	EtOH	22	
15	CuI (3.0)	PMDTA (5.0)	Cs_2CO_3 (1.5)	EtOH	<5	
16	CuCl (3.0)	PMDTA (5.0)	$NaHCO_3$ (1.5)	EtOH	39	
17	CuBr (3.0)	PMDTA (5.0)	$NaHCO_3$ (1.5)	EtOH	41	
18	$CuCl_2$ (3.0)	PMDTA (5.0)	$NaHCO_3$ (1.5)	EtOH	47	
19	$CuBr_2$ (3.0)	PMDTA (5.0)	$NaHCO_3$ (1.5)	EtOH	47	
20	$Cu(OAc)_2$ (3.0)	PMDTA (5.0)	$NaHCO_3$ (1.5)	EtOH	45	
21	CuI (3.0)	PMDTA (5.0)	$NaHCO_3$ (1.5)	DCE		63
22	CuI (3.0)	PMDTA (5.0)	$NaHCO_3$ (1.5)	MeCN	34	30
23	CuI (3.0)	PMDTA (5.0)	$NaHCO_3$ (1.5)	dioxane	<5	78
24	CuI (3.0)	PMDTA (5.0)	$NaHCO_3$ (1.5)	THF		54
25	CuI (3.0)	PMDTA (5.0)	$NaHCO_3$ (1.5)	toluene		45
26	CuI (3.0)	PMDTA (5.0)	$NaHCO_3$ (1.5)	dioxane		<5[c]
27	CuI (1.0)	PMDTA (3.0)	$NaHCO_3$ (1.2)	EtOH	56[e]	
28	CuI (1.5)	PMDTA (5.0)	$NaHCO_3$ (1.5)	dioxane	(76)[d]	84
29	CuI (1.0)	PMDTA (3.0)	$NaHCO_3$ (1.2)	dioxane	(75)[d,e]	84
30	CuI (1.5)	PMDTA (5.0)	$NaHCO_3$ (1.5)	dioxane		<5[f]
31	CuI (1.5)	PMDTA (5.0)	$NaHCO_3$ (1.5)	EtOH	<5[f]	

[a]Unless otherwise noted, PMDTA = pentamethyldiethylenetriamine; DIPEA = *N*,*N*-diisopropylethylamine; bipy = 2,2′-bipyridine; phen = 1,10-phenanthroline; TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethanediamine. Reaction conditions: in N_2, **1a** (1.0 equiv, 0.40 mmol), **2a** (2.0 equiv, 0.80 mmol), [Cu] (1.0−3.0 mol %), ligand (3.0−5.0 mol %), base (1.2−1.5 equiv) in solvent (2.0 mL), 85 °C, 30 h. [b]Isolated yield. [c]At 65 °C. [d]For the product requiring acid hydrolysis, aqueous HCl (2 M, 30 equiv) was used and stirred at rt for 24 h. [e]**1a** (1.0 equiv, 0.60 mmol) and **2a** (1.5 equiv, 0.90 mmol) were used. [f]Trimethyl((1-phenylvinyl)oxy)silane was used.

lated hydroxytoluene) was used as the radical scavengers.[6,10] The reaction was completely inhibited, and no desired product **3a** was obtained (Scheme 6a,b). Excitedly, the alkyl radical could be trapped by 1,1-diphenylethylene[10] (Scheme 6c,d), indicating that the radical species were involved in the reaction.[6,10]

On the basis of the control experiments and reported literature,[6,10] a plausible mechanism was proposed (Scheme 7). First, functionalized alkyl bromide **2a** was reduced by the Cu(I) catalyst to give Cu(II) species **A** and the alkyl radical **B**.[6] Then, radical addition of **B** to the terminal C═C bond of the silyl enol ether (**1a**) affords intermediate **C**. Subsequently, single-electron transfer (SET) oxidation by **A** affords **D**, which then undergoes deprotonation in the aid of the base, giving product **3a-1**, with regeneration of the Cu(I) catalyst concurrently. Finally, hydrolysis of **3a-1** affords the target product **3a**.

CONCLUSIONS

In summary, a general and efficient copper-catalyzed alkylation of silyl enol ethers with functionalized alkyl bromides has been developed for the synthesis of the sterically hindered γ-ketoesters. The transformation was induced through $C(sp^3)$−halogen activation of commercially available sterically hindered alkyl bromides under mild conditions with a wide functional group and substrate scope tolerance in good results. The strategy could be used for the synthesis of the biologically active histamine H_3 receptor (H_3R) antagonist in medicinal chemistry.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, all commercially available reagents were obtained from commercial suppliers and used directly without further purification. ^1H NMR, $^{13}C\{^1H\}$ NMR, or ^{19}F NMR spectra were recorded on a 400 MHz Bruker FT-NMR spectrometer. All chemical shifts are given as δ values (ppm) with tetramethylsilane (TMS) as the internal standard; the peak patterns are indicated as follows: singlet (s), doublet (d), triplet (t), quartet (q), and

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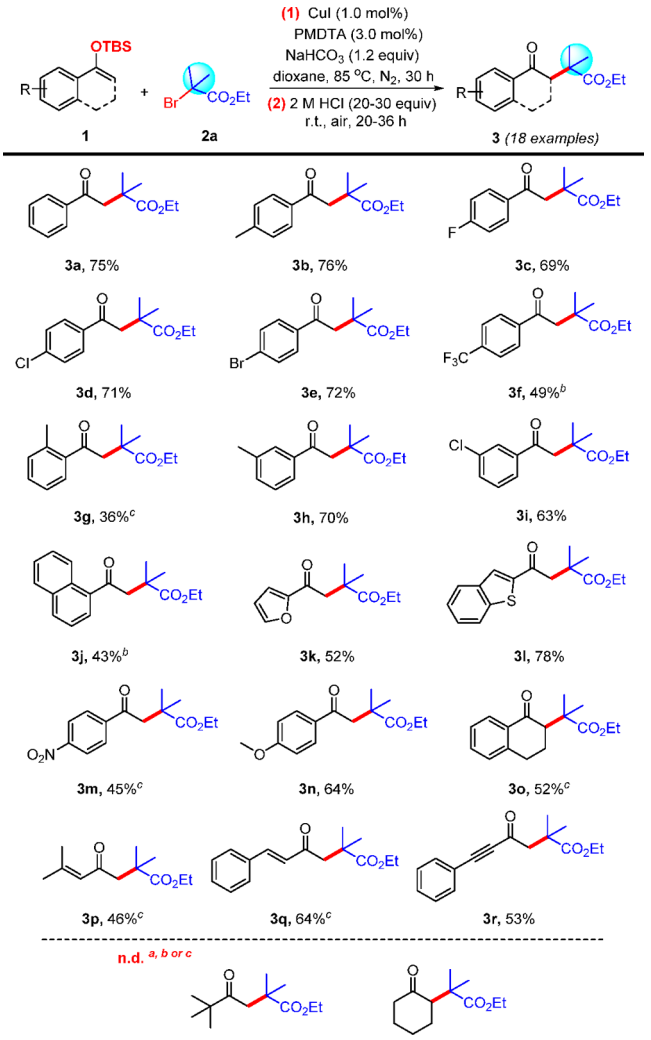
Scheme 2. Scope of the Silyl Enol Ethers[a]



[a]Reaction conditions: (1) in N_2, **1** (1.0 equiv, 0.60 mmol), **2a** (1.5 equiv, 0.90 mmol), CuI (1.0 mol %), PMDTA (3.0 mol %), $NaHCO_3$ (1.2 equiv, 0.72 mmol) in dioxane (2.0 mL), 85 °C, 30 h; (2) for product requiring acid hydrolysis, aqueous HCl (2 M, 20−30 equiv) was added and stirred at rt for 20−36 h. [b]In EtOH (2.0 mL), 65 °C, 45 h (without acid hydrolysis). [c]In EtOH (2.0 mL), 85 °C, 45 h (without acid hydrolysis).

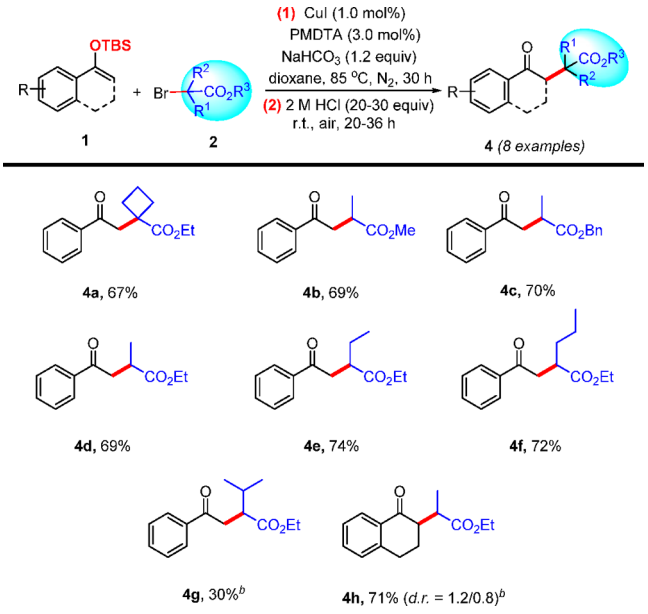
multiplet (m). The coupling constants, *J*, are reported in hertz (Hz). All high-resolution mass (HRMS) analysis was detected on a LC/MSD TOF spectrometer system with electrospray ionization (ESI). All melting points were detected on a Mel-Temp apparatus, and the results were uncorrected. All IR data was obtained on an ATR-FTIR spectrometer. All reactions were monitored by thin-layer chromatography (TLC) with commercially available silica gel plates (GF254) under UV light (254 or 365 nm). Flash chromatography was performed on silica gel (200−300 mesh, Qindao, China).

Preparation of the Starting Materials. *Preparation of the Silyl Enol Ethers.* The silyl enol ethers **1a−1u** were prepared according to the reported literature procedures,[14] and all were known compounds.

Preparation of the Alkyl Bromides. The alkyl bromides **2a−2h** were obtained from commercial sources and used directly without further purification.

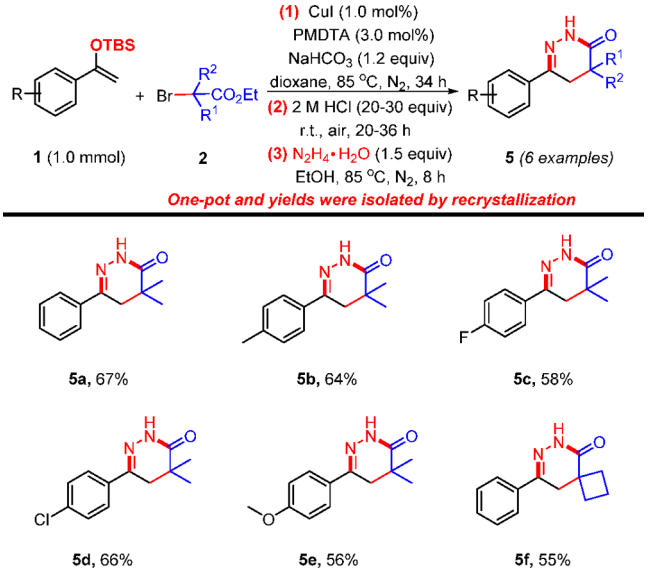
General Procedures. *General Procedures for the Preparation of **3** or **4**.* (Step 1) Under air, alkyl bromide **2** (1.5 equiv, 0.90 mmol) was added to the mixture of **1** (1.0 equiv, 0.60 mmol), CuI (1.0 mol %, 1.1 mg), PMDTA (Pentamethyldiethylenetriamine, 3.0 mol %, 3.1 mg), and $NaHCO_3$ (1.2 equiv, 0.72 mmol, 60.5 mg) in 1,4-dioxane (2.0 mL)

Scheme 3. Scope of the Alkyl Bromides[a]



[a]Reaction conditions: (1) in N_2, **1** (1.0 equiv, 0.60 mmol), **2** (1.5 equiv, 0.90 mmol), CuI (1.0 mol %), PMDTA (3.0 mol %), $NaHCO_3$ (1.2 equiv, 0.72 mmol) in dioxane (2.0 mL), 85 °C, 30 h; (2) for product requiring acid hydrolysis, aqueous HCl (2 M, 20−30 equiv) was added and stirred at rt for 20−36 h. [b]In EtOH (2.0 mL), 65 °C, 30 h (without acid hydrolysis).

Scheme 4. Synthetic Scope of Pyridazin-3-one Derivatives[a]



[a]Reaction conditions: (1) in N_2, **1** (1.0 equiv, 1.0 mmol), **2** (1.5 equiv, 1.5 mmol), CuI (1.0 mol %), PMDTA (3.0 mol %), $NaHCO_3$ (1.2 equiv, 1.2 mmol) in dioxane (3.0 mL), 85 °C, 34 h; (2) for product requiring acid hydrolysis, aqueous HCl (2 M, 20−30 equiv) was added and stirred, rt, 20−36 h; (3) in N_2, hydrazine monohydrate (80% aq, 1.5 equiv, 1.5 mmol), EtOH (2.0 mL), 85 °C, 8 h; all yields were isolated by recrystallization.

in a dry 35 mL Schlenk tube. Then the mixture was degassed with N_2 and heated at 85 °C (oil bath) for 30 h. After completion of the reaction, it was cooled to room temperature for the next step.

(Step 2) For product requiring acid hydrolysis, aqueous HCl (2 M, 20−30 equiv) was added and stirred at rt for 20−36 h. The mixture was

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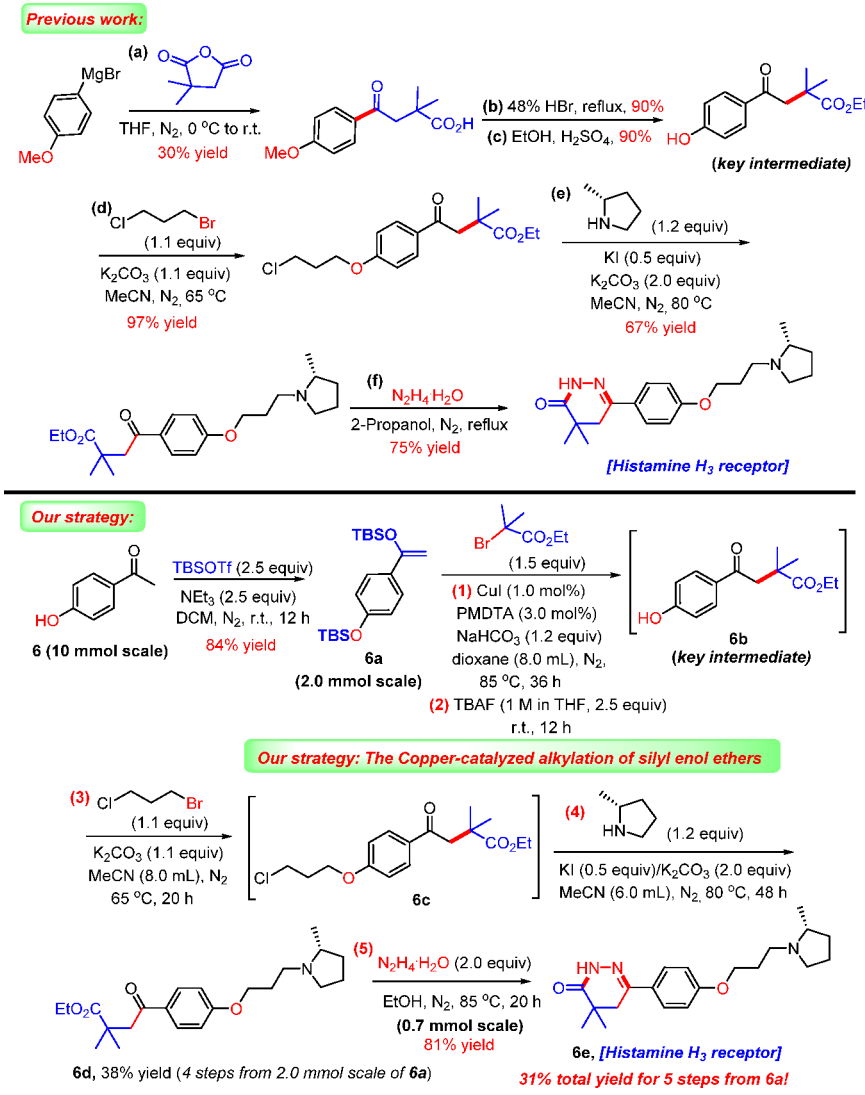
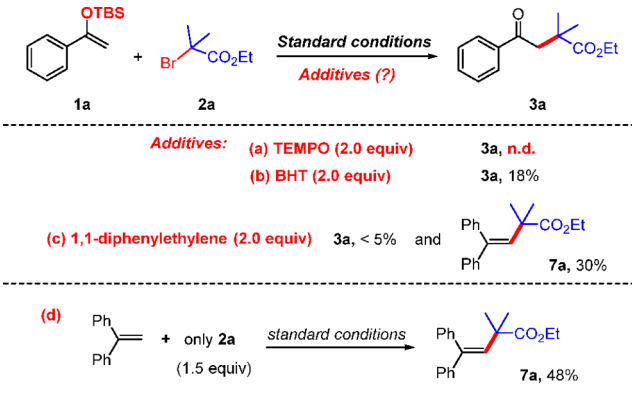
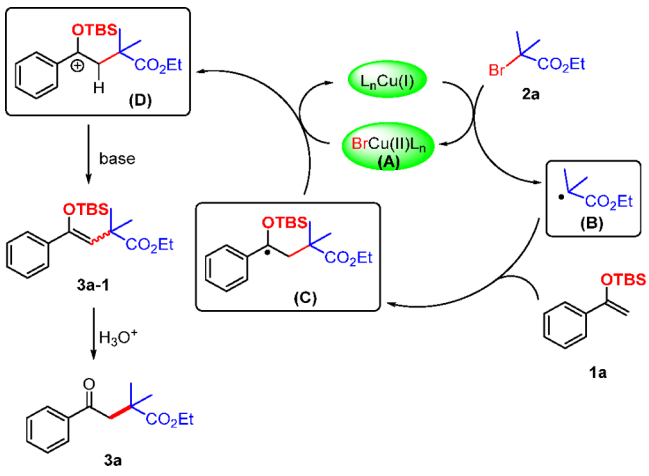
Scheme 5. Application in the Synthesis of the Histamine H_3 Receptor Antagonist



Scheme 6. Control Experiments



Scheme 7. Plausible Mechanism



quenched with saturated Na_2CO_3 (aq) and then extracted with ethyl acetate, and the organic layer was dried over Na_2SO_4. The resulting solution was concentrated under reduced pressure and purified by flash chromatography on silica gel (eluent: ethyl acetate/petroleum ether) to give the desired products **3** or **4**.

General Procedures for the Preparation of ***5****.* (Step 1) Under air, alkyl bromide **2** (1.5 equiv, 1.5 mmol) was added to the mixture of **1** (1.0 equiv, 1.0 mmol), CuI (1.0 mol %, 1.9 mg), PMDTA (pentamethyldiethylenetriamine, 3.0 mol %, 5.2 mg), and $NaHCO_3$ (1.2 equiv, 1.2 mmol, 100.8 mg) in 1,4-dioxane (3.0 mL) in a dry 35 mL Schlenk tube. Then the mixture was degassed with N_2 and heated at 85 °C (oil bath) for 34 h. After completion of the reaction, it was cooled to room temperature for the next step.

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(Step 2) For product requiring acid hydrolysis, aqueous HCl (2 M, 20−30 equiv) was added and stirred at rt for 20−36 h. The mixture was quenched with saturated Na_2CO_3 (aq) and then extracted with ethyl acetate, and the organic layer was dried with Na_2SO_4. The resulting solution was concentrated under reduced pressure. The residue was used without any purification for the next step.

(Step 3) In a N_2 atmosphere, hydrazine monohydrate (80% aq, 1.5 equiv, 1.5 mmol, 94.0 mg) in EtOH (2.0 mL) was added to the above mixture and heated at 85 °C (oil bath) for 8 h. After completion of the reaction, it was cooled to room temperature and quenched with water and then extracted with ethyl acetate, and the organic layer was dried with Na_2SO_4. The resulting solution was concentrated under reduced pressure and purified by recrystallization with petroleum ether to give the desired products **5**.

Preparation of the Histamine H_3 Receptor Antagonist 6e. (Step 1) Under air, ethyl 2-bromo-2-methylpropanoate (**2a**, 1.5 equiv, 3.0 mmol, 585.2 mg) was added to a mixture of **6a** (1.0 equiv, 2.0 mmol, 729.4 mg), CuI (1.0 mol %, 3.8 mg), PMDTA (pentamethyldiethylenetriamine, 3.0 mol %, 10.4 mg), and $NaHCO_3$ (1.2 equiv, 2.4 mmol, 201.6 mg) in 1,4-dioxane (8.0 mL) in a dry 50 mL Schlenk tube. Then the mixture was degassed with N_2 and heated at 85 °C (oil bath) for 36 h. After completion of the reaction, it was cooled to room temperature.

(Step 2) In N_2, TBAF (tetrabutylammonium fluoride, 1.0 M in THF, 2.5 equiv, 5.0 mmol, 5.0 mL) was added to the above mixture and stirred at rt for 12 h. The mixture was quenched with water and then extracted with ethyl acetate, and the organic layer was dried with Na_2SO_4. The resulting solution was concentrated under reduced pressure to give the desired crude product **6b**. The residue was used directly without any purified for the next step.

(Step 3) Under air, 1-bromo-3-chloropropane (1.1 equiv, 2.2 mmol, 346.4 mg) and K_2CO_3 (1.1 equiv, 2.2 mmol, 303.6 mg) were added to the crude **6b** in MeCN (8.0 mL) in a dry 50 mL Schlenk tube. Then the mixture was degassed with N_2 and heated at 65 °C (oil bath) for 20 h. After completion of the reaction, it was cooled to room temperature. The mixture was quenched with water and then extracted with ethyl acetate, and the organic layer was dried with Na_2SO_4. The resulting solution was concentrated under reduced pressure to give the desired crude product **6c**. The residue was used directly without any purified for the next step.

(Step 4) In N_2, (*R*)-2-methyl-pyrrolidine (1.2 equiv, 2.4 mmol, 204.4 mg) was added to the mixture of KI (0.5 equiv, 1.0 mmol, 166.0 mg), K_2CO_3 (2.0 equiv, 4.0 mmol, 552.0 mg), and crude **6c** in MeCN (6.0 mL) in a dry 35 mL Schlenk tube. The mixture was heated at 80 °C (oil bath) for 48 h. The mixture was quenched with water and then extracted with ethyl acetate, and the organic layer was dried with Na_2SO_4. The resulting solution was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: MeOH/DCM = 1:10, R_f = 0.45) to give the desired product **6d** (pale yellow oil, 287.0 mg, 38% yield from 2.0 mmol scale of **6a**).

(Step 5) In N_2, hydrazine monohydrate (80% aq, 2.0 equiv, 1.4 mmol, 88.0 mg) in EtOH (2.0 mL) was added to **6d** (1.0 equiv, 0.7 mmol, 263.0 mg) in a dry 15 mL Schlenk tube; then the mixture was heated at 85 °C (oil bath) for 20 h. After completion of the reaction, it was cooled to room temperature and quenched with water and then extracted with ethyl acetate, and the organic layer was dried with Na_2SO_4. The resulting solution was concentrated under reduced pressure and purified by recrystallization with petroleum ether to give the desired product **6e** (white solid, 194.7 mg, 81% yield).

Characterization Data. *Ethyl 4-((tert-Butyldimethylsilyl)oxy)-2,2-dimethyl-4-phenylbut-3-enoate (**3a-1**):* yellow oil; R_f = 0.65 (ethyl acetate/petroleum ether = 1:15) (0.6 mmol scale, 176.0 mg, 84% yield; isomer mixtures were isolated in *E*/*Z* = 10:1, detected by ^{1}H NMR) ATR-FTIR (cm^{-1}) 2956, 2930, 2858, 1731, 1650, 1253, 1137, 1075, 836, 809, 779, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.33 (m, 2H), 7.32−7.27 (m, 4H), 5.16 (s, 0.1H), 4.83 (s, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.67 (q, *J* = 7.2 Hz, 0.2H), 1.42 (s, 6.6H), 1.28 (t, *J* = 7.2 Hz, 3.3H), 0.92 (s, 9.9H), −0.15 (s, 6.6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 177.2, 176.8, 150.6, 140.6, 128.6, 128.1, 127.8, 127.6, 127.5, 117.2, 115.8, 60.3, 41.7, 28.2, 26.7, 26.0, 25.6, 18.3, 14.2, 13.9, −3.4, −4.6; HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{33}O_3Si^+$ 349.2193, found 349.2185.

*Ethyl 2,2-Dimethyl-4-oxo-4-phenylbutanoate (**3a**):*[5a] yellow oil; R_f = 0.30 (ethyl acetate/petroleum ether = 1:15) (0.6 mmol scale, 105.4 mg, 75% yield) ATR-FTIR (cm^{-1}) 2976, 1725, 1686, 1189, 1124, 752, 690; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95−7.93 (m, 2H), 7.57−7.53 (m, 1H), 7.47−7.43 (m, 2H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.29 (s, 2H), 1.32 (s, 6H), 1.20 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 197.6, 177.3, 137.0, 133.0, 128.5, 127.9, 60.5, 48.4, 40.0, 25.7, 14.1.

*Ethyl 2,2-Dimethyl-4-oxo-4-(p-tolyl)butanoate (**3b**):*[11e] yellow oil; R_f = 0.30 (ethyl acetate/petroleum ether = 1:15) (0.6 mmol scale, 113.0 mg, 76% yield) ATR-FTIR (cm^{-1}) 2974, 2932, 1726, 1683, 1606, 1181, 1124, 807; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84−7.82 (m, 2H), 7.25−7.23 (m, 2H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.26 (s, 2H), 2.40 (s, 3H), 1.30 (s, 6H), 1.20 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 197.2, 177.4, 143.8, 134.5, 129.2, 128.0, 60.4, 48.3, 39.9, 25.7, 21.6, 14.0; HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{21}O_3^+$ 249.1485, found 249.1486; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{20}NaO_3^+$ 271.1305, found 271.1303.

*Ethyl 4-(4-Fluorophenyl)-2,2-dimethyl-4-oxobutanoate (**3c**):* yellow oil; R_f = 0.30 (ethyl acetate/petroleum ether = 1:15) (0.6 mmol scale, 104.8 mg, 69% yield) ATR-FTIR (cm^{-1}) 2976, 1724, 1686, 1597, 1228, 1189, 1154, 827; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99−7.94 (m, 2H), 7.14−7.09 (m, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.26 (s, 2H), 1.31 (s, 6H), 1.20 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 196.0, 177.3, 165.7 (d, $^1J_{C-F}$ = 253.0 Hz), 133.4 (d, $^4J_{C-F}$ = 2.9 Hz), 130.5 (d, $^3J_{C-F}$ = 9.3 Hz), 115.6 (d, $^2J_{C-F}$ = 21.7 Hz), 60.5, 48.3, 40.0, 25.7, 14.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −105.26 to −105.33 (m, 1F); HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{17}FNaO_3^+$ 275.1054, found 275.1055.

*Ethyl 4-(4-Chlorophenyl)-2,2-dimethyl-4-oxobutanoate (**3d**):*[15] yellow oil; R_f = 0.30 (ethyl acetate/petroleum ether = 1:15) (0.6 mmol scale, 115.2 mg, 71% yield) ATR-FTIR (cm^{-1}) 2976, 1725, 1686, 1588, 1474, 1189, 1090, 1006, 815; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89−7.85 (m, 2H), 7.43−7.40 (m, 2H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.24 (s, 2H), 1.31 (s, 6H), 1.20 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 196.4, 177.2, 139.4, 135.2, 129.3, 128.8, 60.5, 48.3, 40.0, 25.7, 14.0.

*Ethyl 4-(4-Bromophenyl)-2,2-dimethyl-4-oxobutanoate (**3e**):*[16] yellow solid; R_f = 0.35 (ethyl acetate/petroleum ether = 1:15) (0.6 mmol scale, 134.8 mg, 72% yield); mp 44−46 °C; ATR-FTIR (cm^{-1}) 2976, 1725, 1686, 1588, 1474, 1189, 1090, 1006, 815; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81−7.78 (m, 2H), 7.60−7.57 (m, 2H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.24 (s, 2H), 1.31 (s, 6H), 1.20 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 196.6, 177.2, 135.7, 131.8, 129.4, 128.2, 60.6, 48.3, 40.0, 25.7, 14.0.

*Ethyl 2,2-Dimethyl-4-oxo-4-(4-(trifluoromethyl)phenyl)-butanoate (**3f**):* pale yellow oil; R_f = 0.35 (ethyl acetate/petroleum ether = 1:15) (0.6 mmol scale, 89.0 mg, 49% yield) ATR-FTIR (cm^{-1}) 2979, 1727, 1694, 1322, 1167, 1124, 1064, 1009, 827, 770, 603; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05−8.03 (m, 2H), 7.73−7.71 (m, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.29 (s, 2H), 1.33 (s, 6H), 1.20 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 196.7, 177.1, 139.6, 134.3 (q, $^2J_{C-F}$= 32.6 Hz), 128.2, 125.6 (q, $^3J_{C-F}$ = 3.7 Hz), 123.5 (q, $^1J_{C-F}$ = 271.1 Hz), 60.6, 48.6, 40.1, 25.7, 14.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.09 (s, 3F); HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{17}F_3NaO_3^+$ 325.1022, found 325.1024.

*Ethyl 2,2-Dimethyl-4-oxo-4-(o-tolyl)butanoate (**3g**):* yellow oil; R_f = 0.40 (ethyl acetate/petroleum ether = 1:15) (0.6 mmol scale, 53.0 mg, 36% yield) ATR-FTIR (cm^{-1}) 2975, 1726, 1686, 1185, 1119, 755; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61−7.59 (m, 1H), 7.37−7.33 (m, 1H), 7.24−7.22 (m, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.20 (s, 2H), 2.46 (s, 3H), 1.30 (s, 6H), 1.22 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 202.0, 177.3, 138.1, 137.8, 131.8, 131.1, 128.1, 125.5, 60.5, 51.4, 40.2, 25.7, 21.1, 14.1; HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{21}O_3^+$ 249.1485, found 249.1486; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{20}NaO_3^+$ 271.1305, found 271.1301.

*Ethyl 2,2-Dimethyl-4-oxo-4-(m-tolyl)butanoate (**3h**):* yellow oil; R_f = 0.40 (ethyl acetate/petroleum ether = 1:15) (0.6 mmol scale, 104.6

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mg, 70% yield) ATR-FTIR (cm^{-1}) 2975, 1726, 1684, 1171, 1124, 1026, 775, 690; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75−7.72 (m, 2H), 7.38−7.31 (m, 2H), 4.13 (q, J = 7.2 Hz, 2H), 3.28 (s, 2H), 2.40 (s, 3H), 1.31 (s, 6H), 1.20 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.8, 177.4, 138.3, 137.0, 133.8, 128.4, 128.3, 125.1, 60.4, 48.5, 40.0, 25.7, 21.3, 14.1; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{15}H_{21}O_3^+$ 249.1485, found 249.1484; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{15}H_{20}NaO_3^+$ 271.1305, found 271.1300.

*Ethyl 4-(3-Chlorophenyl)-2,2-dimethyl-4-oxobutanoate (**3i**):* pale yellow oil; R_f = 0.30 (ethyl acetate/petroleum ether = 1:15) (0.6 mmol scale, 101.4 mg, 63% yield) ATR-FTIR (cm^{-1}) 2976, 1725, 1690, 1571, 1350, 1301, 1187, 1125, 1027, 783, 717, 680; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90−7.89 (m, 1H), 7.82−7.79 (m, 1H), 7.53−7.51 (m, 1H), 7.41−7.37 (m, 1H), 4.12 (q, J = 7.2 Hz, 2H), 3.25 (s, 2H), 1.31 (s, 6H), 1.20 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 196.4, 177.1, 138.4, 134.8, 132.9, 129.9, 128.0, 126.0, 60.6, 48.5, 40.0, 25.7, 14.1; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{14}H_{18}ClO_3^+$ 269.0939, found 269.0940; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{14}H_{17}ClNaO_3^+$ 291.0758, found 291.0753.

*Ethyl 2,2-Dimethyl-4-(naphthalen-1-yl)-4-oxobutanoate (**3j**):* yellow oil; R_f = 0.35 (ethyl acetate/petroleum ether = 1:15) (0.6 mmol scale, 74.1 mg, 43% yield) ATR-FTIR (cm^{-1}) 2975, 1724, 1680, 1176, 1089, 1026, 801, 773; ^1H NMR (400 MHz, $CDCl_3$) δ 8.55−8.53 (m, 1H), 7.98−7.96 (m, 1H), 7.88−7.83 (m, 2H), 7.59−7.52 (m, 2H), 7.51−7.47 (m, 1H), 4.16 (q, J = 7.2 Hz, 2H), 3.37 (s, 2H), 1.37 (s, 6H), 1.23 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 202.3, 177.3, 136.1, 133.8, 132.4, 129.9, 128.3, 127.8, 127.1, 126.4, 125.6, 124.3, 60.6, 51.9, 40.4, 25.7, 14.1; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{18}H_{21}O_3^+$ 285.1485, found 285.1480; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{18}H_{20}NaO_3^+$ 307.1305, found 307.1300.

*Ethyl 4-(Furan-2-yl)-2,2-dimethyl-4-oxobutanoate (**3k**):* yellow oil; R_f = 0.35 (ethyl acetate/petroleum ether = 1:7) (0.6 mmol scale, 70.0 mg, 52% yield) ATR-FTIR (cm^{-1}) 2977, 1723, 1675, 1568, 1468, 1301, 1151, 1126, 1027, 763, 595; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55−7.54 (m, 1H), 7.15−7.14 (m, 1H), 6.51−6.50 (m, 1H), 4.11 (q, J = 7.2 Hz, 2H), 3.12 (s, 2H), 1.29 (s, 6H), 1.19 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 187.0, 177.0, 152.7, 146.1, 116.7, 112.2, 60.5, 47.7, 40.1, 25.6, 14.0; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{12}H_{17}O_4^+$ 225.1121, found 225.1122; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{12}H_{16}NaO_4^+$ 247.0941, found 247.0936.

*Ethyl 4-(Benzo[b]thiophen-2-yl)-2,2-dimethyl-4-oxobutanoate (**3l**):* yellow solid; R_f = 0.30 (ethyl acetate/petroleum ether = 1:15) (0.6 mmol scale, 136.2 mg, 78% yield); mp 65−66 °C; ATR-FTIR (cm^{-1}) 2979, 1717, 1656, 1514, 1195, 1119, 739, 723, 581; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.90−7.85 (m, 2H), 7.48−7.38 (m, 2H), 4.14 (q, J = 7.2 Hz, 2H), 3.32 (s, 2H), 1.35 (s, 6H), 1.22 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 192.3, 177.0, 143.8, 142.4, 139.0, 128.9, 127.4, 125.9, 125.0, 123.0, 60.7, 48.6, 40.4, 25.7, 14.1; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{16}H_{19}O_3S^+$ 291.1049, found 291.1044; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{16}H_{18}NaO_3S^+$ 313.0869, found 313.0864.

*Ethyl 2,2-Dimethyl-4-(4-nitrophenyl)-4-oxobutanoate (**3m**):* pale yellow solid; R_f = 0.25 (ethyl acetate/petroleum ether = 1:15) (0.6 mmol scale, 75.0 mg, 45% yield); mp 65−67 °C; ATR-FTIR (cm^{-1}) 2979, 1721, 1687, 1600, 1518, 1344, 1193, 854, 743, 685; ^1H NMR (400 MHz, $CDCl_3$) δ 8.31−8.28 (m, 2H), 8.10−8.07 (m, 2H), 4.13 (q, J = 7.2 Hz, 2H), 3.30 (s, 2H), 1.34 (s, 6H), 1.21 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 196.2, 176.9, 150.2, 141.3, 128.9, 123.8, 60.7, 48.8, 40.2, 25.7, 14.1; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{14}H_{18}NO_5^+$ 280.1179, found 280.1183; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{14}H_{17}NNaO_5^+$ 302.0999, found 302.1000.

*Ethyl 4-(4-Methoxyphenyl)-2,2-dimethyl-4-oxobutanoate (**3n**):* yellow oil; R_f = 0.20 (ethyl acetate/petroleum ether = 1:15) (0.6 mmol scale, 101.7 mg, 64% yield) ATR-FTIR (cm^{-1}) 2979, 1720, 1686, 1600, 1517, 1344, 1193, 1123, 853, 743; ^1H NMR (400 MHz, $CDCl_3$) δ 7.93−7.90 (m, 2H), 6.93−6.90 (m, 2H), 4.12 (q, J = 7.2 Hz, 2H), 3.86 (s, 3H), 3.24 (s, 2H), 1.30 (s, 6H), 1.20 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 196.1, 177.5, 163.4, 130.2, 130.1, 113.6, 60.4, 55.4, 48.1, 40.0, 25.7, 14.1; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{15}H_{21}O_4^+$ 265.1434, found 265.1427; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{15}H_{20}NaO_4^+$ 287.1254, found 287.1245.

*Ethyl 2-Methyl-2-(1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-propanoate (**3o**):* pale yellow oil; R_f = 0.25 (ethyl acetate/petroleum ether = 1:15) (0.6 mmol scale, 82.0 mg, 52% yield) ATR-FTIR (cm^{-1}) 2978, 1726, 1681, 1599, 1456, 1125, 1028, 745; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01−7.99 (m, 1H), 7.48−7.45 (m, 1H), 7.31−7.24 (m, 2H), 4.23−4.17 (m, 2H), 3.17−3.03 (m, 3H), 2.27−2.22 (m, 1H), 1.97−1.86 (m, 1H), 1.28−1.24 (m, 6H), 1.18 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.8, 178.2, 143.7, 133.2, 132.8, 128.5, 127.4, 126.6, 60.4, 55.1, 42.6, 29.8, 25.4, 24.1, 18.9, 14.1; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{16}H_{21}O_3^+$ 261.1485, found 261.1481; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{16}H_{20}NaO_3^+$ 283.1305, found 283.1299.

*Ethyl 2,2,6-Trimethyl-4-oxohept-5-enoate (**3p**):* pale yellow oil; R_f = 0.35 (ethyl acetate/petroleum ether = 1:15) (0.6 mmol scale, 58.4 mg, 46% yield) ATR-FTIR (cm^{-1}) 2975, 1727, 1688, 1621, 1445, 1299, 1189, 1154, 1125, 770; ^1H NMR (400 MHz, $CDCl_3$) δ 5.99 (t, J = 1.0 Hz, 1H), 4.12 (q, J = 7.2 Hz, 2H), 2.71 (s, 2H), 2.10 (d, J = 1.0 Hz, 3H), 1.85 (d, J = 1.0 Hz, 3H), 1.21 (s, 6H), 1.21 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 198.2, 177.4, 155.2, 123.7, 60.3, 53.7, 40.0, 27.6, 25.5, 20.7, 14.1; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{12}H_{21}O_3^+$ 213.1485, found 213.1481; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{12}H_{20}NaO_3^+$ 235.1305, found 235.1298.

*Ethyl (E)-2,2-Dimethyl-4-oxo-6-phenylhex-5-enoate (**3q**):* pale yellow oil; R_f = 0.25 (ethyl acetate/petroleum ether = 1:15) (0.6 mmol scale, 100.4 mg, 64% yield) ATR-FTIR (cm^{-1}) 2975, 1724, 1692, 1660, 1611, 1354, 1300, 1181, 1124, 1073, 1027, 977, 747, 689; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54−7.50 (m, 3H), 7.39−7.38 (m, 3H), 6.70 (d, J = 16.0 Hz, 1H), 4.14 (q, J = 7.2 Hz, 2H), 2.98 (s, 2H), 1.28 (s, 6H), 1.23 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.7, 177.2, 142.4, 134.4, 130.4, 128.9, 128.2, 126.2, 60.5, 50.5, 40.1, 25.6, 14.1; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{16}H_{21}O_3^+$ 261.1485, found 261.1480; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{16}H_{20}NaO_3^+$ 283.1305, found 283.1300.

*Ethyl 2,2-Dimethyl-4-oxo-6-phenylhex-5-ynoate (**3r**):* yellow oil; R_f = 0.40 (ethyl acetate/petroleum ether = 1:15) (0.6 mmol scale, 82.0 mg, 53% yield) ATR-FTIR (cm^{-1}) 2977, 2199, 1726, 1670, 1300, 1192, 1154, 1128, 1073, 1026, 758, 688; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57−7.55 (m, 2H), 7.47−7.43 (m, 1H), 7.39−7.36 (m, 2H), 4.14 (q, J = 7.2 Hz, 2H), 3.00 (s, 2H), 1.29 (s, 6H), 1.23 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 185.1, 176.6, 133.0, 130.7, 128.6, 119.8, 90.4, 87.9, 60.7, 54.7, 40.3, 25.5, 14.0; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{16}H_{19}O_3^+$ 259.1329, found 259.1326; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{16}H_{18}NaO_3^+$ 281.1148, found 281.1144.

*Ethyl 1-(2-Oxo-2-phenylethyl)cyclobutane-1-carboxylate (**4a**):* yellow oil; R_f = 0.35 (ethyl acetate/petroleum ether = 1:15) (0.6 mmol scale, 99.2 mg, 67% yield) ATR-FTIR (cm^{-1}) 2979, 2939, 1720, 1683, 1448, 1352, 1319, 1176, 1094, 750, 689, 569; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98−7.95 (m, 2H), 7.58−7.54 (m, 1H), 7.48−7.44 (m, 2H), 4.14 (q, J = 7.2 Hz, 2H), 3.58 (s, 2H), 2.67−2.60 (m, 2H), 2.08−1.94 (m, 4H), 1.20 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.8, 176.1, 136.7, 133.1, 128.5, 127.9, 60.5, 46.2, 44.4, 30.1, 16.2, 14.1; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{15}H_{19}O_3^+$ 247.1329, found 247.1326; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{15}H_{18}NaO_3^+$ 269.1148, found 269.1141.

*Methyl 2-Methyl-4-oxo-4-phenylbutanoate (**4b**):*[5a] yellow oil; R_f = 0.35 (ethyl acetate/petroleum ether = 1:15) (0.6 mmol scale, 85.2 mg, 69% yield) ATR-FTIR (cm^{-1}) 2975, 2951, 1731, 1683, 1449, 1274, 1212, 1167, 1002, 754, 689; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97−7.95 (m, 2H), 7.58−7.54 (m, 1H), 7.47−7.43 (m, 2H), 3.69 (s, 2H), 3.48 (dd, J = 7.8 Hz, 17.6 Hz, 1H), 3.17−3.08 (m, 1H), 3.02 (dd, J = 5.4 Hz, 17.6 Hz, 1H), 1.27 (d, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 198.0, 176.5, 136.5, 133.2, 128.5, 128.0, 51.9, 41.9, 34.8, 17.3.

*Benzyl 2-Methyl-4-oxo-4-phenylbutanoate (**4c**):* yellow oil; R_f = 0.40 (ethyl acetate/petroleum ether = 1:15) (0.6 mmol scale, 118.4 mg, 70% yield) ATR-FTIR (cm^{-1}) 2973, 1730, 1683, 1450, 1122, 1160, 1002, 751, 690; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98−7.95 (m, 2H), 7.59−7.55 (m, 1H), 7.48−7.44 (m, 2H), 7.38−7.30 (m, 5H), 5.15 (dd, J = 12.4 Hz, 19.6 Hz, 2H), 3.51 (dd, J = 8.0 Hz, 17.7 Hz, 1H), 3.25−3.16 (m, 1H), 3.05 (dd, J = 5.4 Hz, 17.7 Hz, 1H), 1.30 (d, J = 7.0 Hz, 3H);

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$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 198.0, 175.8, 136.5, 136.0, 133.2, 128.6, 128.5, 128.1, 128.0, 127.9, 66.4, 41.8, 34.9, 17.3; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{18}H_{19}O_3^+$ 283.1329, found 283.1327; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{18}H_{18}NaO_3^+$ 305.1148, found 305.1142.

*Ethyl 2-Methyl-4-oxo-4-phenylbutanoate (**4d**)*:[5a,11e] yellow oil; R_f = 0.30 (ethyl acetate/petroleum ether = 1:15) (0.6 mmol scale, 91.2 mg, 69% yield) ATR-FTIR (cm^{-1}) 2978, 1728, 1684, 1449, 1212, 1172, 754, 690; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98−7.95 (m, 2H), 7.58−7.54 (m, 1H), 7.48−7.44 (m, 2H), 4.14 (q, J = 7.2 Hz, 2H), 3.48 (dd, J = 7.8 Hz, 17.5 Hz, 1H), 3.15−3.06 (m, 1H), 3.01 (dd, J = 5.4 Hz, 17.5 Hz, 1H), 1.26 (t, J = 7.2 Hz, 3H), 1.24 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 198.1, 176.0, 136.6, 133.1, 128.5, 128.0, 60.6, 41.9, 35.0, 17.3, 14.1.

*Ethyl 2-Ethyl-4-oxo-4-phenylbutanoate (**4e**)*: yellow oil; R_f = 0.30 (ethyl acetate/petroleum ether = 1:15) (0.6 mmol scale, 104.0 mg, 74% yield) ATR-FTIR (cm^{-1}) 2967, 1726, 1684, 1448, 1210, 1163, 1028, 755, 689; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98−7.95 (m, 2H), 7.58−7.54 (m, 1H), 7.47−7.43 (m, 2H), 4.21−4.09 (m, 2H), 3.49−3.42 (m, 1H), 3.06−2.94 (m, 2H), 1.76−1.62 (m, 2H), 1.25 (t, J = 7.2 Hz, 3H), 0.97 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 198.3, 175.3, 136.6, 133.1, 128.5, 128.0, 60.4, 41.7, 39.9, 25.2, 14.2, 11.5; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{14}H_{19}O_3^+$ 235.1329, found 235.1330; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{14}H_{18}NaO_3^+$ 257.1148, found 257.1143.

*Ethyl 2-(2-Oxo-2-phenylethyl)pentanoate (**4f**)*: yellow oil; R_f = 0.30 (ethyl acetate/petroleum ether = 1:15) (0.6 mmol scale, 106.5 mg, 72% yield) ATR-FTIR (cm^{-1}) 2959, 2933, 1728, 1686, 1448, 1213, 1170, 754, 690; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98−7.95 (m, 2H), 7.57−7.53 (m, 1H), 7.47−7.43 (m, 2H), 4.20−4.09 (m, 2H), 3.49−3.42 (m, 1H), 3.07−3.00 (m, 2H), 1.73−1.64 (m, 1H), 1.60−1.51 (m, 1H), 1.43−1.33 (m, 2H), 1.25 (t, J = 7.2 Hz, 3H), 0.93 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 198.3, 175.7, 136.6, 133.1, 128.5, 128.0, 60.4, 40.4, 40.1, 34.3, 20.3, 14.2, 13.9; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{15}H_{21}O_3^+$ 249.1485, found 249.1481; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{15}H_{20}NaO_3^+$ 271.1305, found 271.1292.

*Ethyl 2-Isopropyl-4-oxo-4-phenylbutanoate (**4g**)*:[17] pale yellow oil; R_f = 0.40 (ethyl acetate/petroleum ether = 1:15) (0.6 mmol scale, 44.6 mg, 30% yield) ATR-FTIR (cm^{-1}) 2963, 1724, 1685, 1173, 756, 690, 560; ^1H NMR (400 MHz, $CDCl_3$) δ 7.99−7.96 (m, 2H), 7.58−7.54 (m, 1H), 7.48−7.44 (m, 2H), 4.21−4.09 (m, 2H), 3.54−3.46 (m, 1H), 3.01−2.91 (m, 2H), 2.11−2.02 (m, 1H), 1.25 (t, J = 7.2 Hz, 3H), 0.99 (d, J = 7.0 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 198.8, 174.8, 136.8, 133.1, 128.5, 128.0, 60.4, 46.5, 37.3, 30.1, 20.2, 19.9, 14.2.

*Ethyl 2-(1-Oxo-1,2,3,4-tetrahydronaphthalen-2-yl)propanoate (**4h**)*: pale yellow oil; R_f = 0.35 (ethyl acetate/petroleum ether = 1:15) (0.6 mmol scale, 104.2 mg, 71% yield; dr = 1.2:0.8) ATR-FTIR (cm^{-1}) 2979, 2938, 1727, 1680, 1599, 1455, 1184, 741; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02−8.00 (m, 1H), 7.48−7.43 (m, 1H), 7.31−7.27 (m, 1H), 7.24−7.22 (m, 1H), 4.18 (qd, J = 7.2 Hz, 1.0 Hz, 1.2H), 4.11 (q, J = 7.2 Hz, 0.8H), 3.21−2.96 (m, 3.6H), 2.90−2.85 (m, 0.4H), 2.20−2.05 (m, 1.4H), 1.98−1.87 (m, 0.6H), 1.30−1.24 (m, 3H), 1.20−1.15 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 198.1, 197.9, 176.1, 174.6, 143.9, 143.7, 133.3, 133.2, 132.5, 132.3, 128.6, 128.5, 127.4, 126.6, 126.5, 60.5, 60.4, 50.5, 50.2, 39.2, 38.7, 29.3, 29.0, 25.8, 25.2, 14.2, 14.1, 13.3, 13.1; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{15}H_{19}O_3^+$ 247.1329, found 247.1329; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{15}H_{18}NaO_3^+$ 269.1148, found 269.1142.

*4,4-Dimethyl-6-phenyl-4,5-dihydropyridazin-3(2H)-one (**5a**)*:[12] white solid; R_f = 0.30 (ethyl acetate/petroleum ether = 1:5) (1.0 mmol scale, 136.0 mg, 67% yield); mp 144−146 °C; ATR-FTIR (cm^{-1}) 3213, 3093, 2919, 1657, 1612, 1341, 1241, 763, 694, 578; ^1H NMR (400 MHz, $CDCl_3$) δ 8.60 (br, s, 1H), 7.73−7.70 (m, 2H), 7.44−7.40 (m, 3H), 2.81 (s, 2H), 1.25 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.3, 150.8, 136.0, 129.8, 128.6, 125.8, 37.1, 34.0, 23.9.

*4,4-Dimethyl-6-(p-tolyl)-4,5-dihydropyridazin-3(2H)-one (**5b**)*: white solid; R_f = 0.30 (ethyl acetate/petroleum ether = 1:5) (1.0 mmol scale, 138.0 mg, 64% yield); mp 142−146 °C; ATR-FTIR (cm^{-1}) 3208, 3093, 2922, 1658, 1613, 1332, 1238, 809, 657, 562; ^1H NMR (400 MHz, $CDCl_3$) δ 8.52 (br, s, 1H), 7.62−7.60 (m, 2H), 7.24−7.21 (m, 2H), 2.78 (s, 2H), 2.39 (s, 3H), 1.24 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.4, 150.9, 140.0, 133.2, 129.3, 125.7, 37.1, 34.0, 23.9, 21.3; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{13}H_{17}N_2O^+$ 217.1335, found 217.1332.

*6-(4-Fluorophenyl)-4,4-dimethyl-4,5-dihydropyridazin-3(2H)-one (**5c**)*: white solid; R_f = 0.30 (ethyl acetate/petroleum ether = 1:5) (1.0 mmol scale, 128.0 mg, 58% yield); mp 145−147 °C; ATR-FTIR (cm^{-1}) 3223, 3096, 2968, 2920, 1655, 1611, 1507, 1336, 840, 776, 564; ^1H NMR (400 MHz, $CDCl_3$) δ 8.66 (br, s, 1H), 7.73−7.68 (m, 2H), 7.13−7.07 (m, 2H), 2.77 (s, 2H), 1.24 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.2, 163.6 (d, $^1J_{C-F}$ = 248.7 Hz), 149.7, 132.2 (d, $^4J_{C-F}$ = 3.4 Hz), 127.7 (d, $^3J_{C-F}$ = 8.6 Hz), 115.7 (d, $^2J_{C-F}$ = 21.8 Hz), 37.1, 34.0, 23.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −110.87 to −110.94 (m, 1F); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{12}H_{14}FN_2O^+$ 221.1085, found 221.1083.

*6-(4-Chlorophenyl)-4,4-dimethyl-4,5-dihydropyridazin-3(2H)-one (**5d**)*: white solid; R_f = 0.35 (ethyl acetate/petroleum ether = 1:5) (1.0 mmol scale, 157.0 mg, 66% yield); mp 146−148 °C; ATR-FTIR (cm^{-1}) 3205, 3087, 2966, 2928, 1667, 1610, 1330, 1237, 1092, 828, 805, 753, 623, 584, 552; ^1H NMR (400 MHz, $CDCl_3$) δ 8.66 (br, s, 1H), 7.67−7.64 (m, 2H), 7.40−7.37 (m, 2H), 2.77 (s, 2H), 1.24 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.2, 149.6, 135.8, 134.4, 128.8, 127.0, 36.9, 34.0, 23.9; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{12}H_{14}ClN_2O^+$ 237.0789, found 237.0786.

*6-(4-Methoxyphenyl)-4,4-dimethyl-4,5-dihydropyridazin-3(2H)-one (**5e**)*: white solid; R_f = 0.20 (ethyl acetate/petroleum ether = 1:5) (1.0 mmol scale, 130.0 mg, 56% yield); mp 161−164 °C; ATR-FTIR (cm^{-1}) 3203, 3092, 2930, 1672, 1614, 1600, 1510, 1460, 1333, 1251, 1170, 819, 797, 559, 543; ^1H NMR (400 MHz, $CDCl_3$) δ 8.65 (br, s, 1H), 7.69−7.65 (m, 2H), 6.95−6.91 (m, 2H), 3.84 (s, 3H), 2.76 (s, 2H), 1.23 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.4, 160.9, 150.6, 128.6, 127.3, 113.9, 55.4, 37.0, 34.0, 23.9; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{13}H_{17}N_2O_2^+$ 233.1285, found 233.1278.

*8-Phenyl-6,7-diazaspiro[3.5]non-7-en-5-one (**5f**)*: white solid; R_f = 0.35 (ethyl acetate/petroleum ether = 1:5) (1.0 mmol scale, 118.2 mg, 55% yield); mp 155−157 °C; ATR-FTIR (cm^{-1}) 3222, 3094, 2950, 2923, 1660, 1336, 1241, 753, 682; ^1H NMR (400 MHz, $CDCl_3$) δ 8.62 (br, s, 1H), 7.75−7.71 (m, 2H), 7.46−7.40 (m, 3H), 3.09 (s, 2H), 2.62−2.55 (m, 2H), 2.10−2.00 (m, 2H), 1.91−1.84 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 172.1, 150.7, 136.1, 129.8, 128.6, 125.7, 38.8, 34.4, 28.7, 15.2; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{13}H_{15}N_2O^+$ 215.1179, found 215.1173.

*tert-Butyl((1-(4-((tert-butyldimethylsilyl)oxy)phenyl)vinyl)oxy)-dimethylsilane (**6a**)*: pale yellow oil; R_f = 0.50 (NEt_3/petroleum ether = 1:50) (10 mmol scale, 3.06 g, 84% yield) ATR-FTIR (cm^{-1}) 2955, 2930, 2857, 1604, 1506, 1253, 1004, 912, 830, 777, 682; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50−7.46 (m, 2H), 6.80−6.77 (m, 2H), 4.77 (d, J = 1.6 Hz, 1H), 4.31 (d, J = 1.6 Hz, 1H), 1.00 (s, 9H), 0.98 (s, 9H), 0.20 (s, 6H), 0.19 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 155.8, 155.7, 130.9, 126.5, 119.5, 89.2, 25.8, 25.6, 18.3, 18.2, −4.4, −4.7; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{20}H_{37}O_2Si_2^+$ 365.2327, found 365.2316.

*Ethyl (R)-2,2-Dimethyl-4-(4-(3-(2-methylpyrrolidin-1-yl)propoxy)-phenyl)-4-oxobutanoate (**6d**)*:[3a] pale yellow oil; R_f = 0.45 (MeOH/DCM = 1:10) (2.0 mmol scale, 287.0 mg, 38% yield) ATR-FTIR (cm^{-1}) 2963, 1723, 1675, 1598, 1234, 1170, 1125, 827, 732; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90−7.86 (m, 2H), 6.91−6.87 (m, 2H), 4.10 (q, J = 7.2 Hz, 2H), 4.09−4.05 (m, 2H), 3.30−3.24 (m, 1H), 3.22 (s, 2H), 3.08−3.01 (m, 1H), 2.53−2.44 (m, 1H), 2.36−2.30 (m, 1H), 2.28−2.21 (m, 1H), 2.13−2.02 (m, 2H), 2.01−1.92 (m, 1H), 1.90−1.69 (m, 2H), 1.55−1.45 (m, 1H), 1.28 (s, 6H), 1.18 (t, J = 7.2 Hz, 3H), 1.15 (d, J = 6.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 196.1, 177.4, 162.7, 130.1, 130.0, 114.0, 66.3, 60.9, 60.4, 53.8, 50.6, 48.0, 39.9, 32.4, 27.8, 25.7, 21.4, 18.3, 14.0.

*(R)-4,4-Dimethyl-6-(4-(3-(2-methylpyrrolidin-1-yl)propoxy)-phenyl)-4,5-dihydropyridazin-3(2H)-one (**6e**)*:[3a] white solid; R_f = 0.40 (MeOH/DCM = 1:10) (0.7 mmol scale, 194.7 mg, 81% yield); mp 117−121 °C; ATR-FTIR (cm^{-1}) 3202, 3094, 2959, 2919, 1664, 1606, 1510, 1331, 1247, 1175, 830, 573, 550; ^1H NMR (400 MHz, $CDCl_3$) δ 8.59 (br, s, 1H), 7.66−7.64 (m, 2H), 6.93−6.91 (m, 2H), 4.09−4.04 (m, 2H), 3.25−3.20 (m, 1H), 3.05−2.98 (m, 1H), 2.75 (s, 2H), 2.40−

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2.35 (m, 1H), 2.28−2.13 (m, 2H), 2.07−2.00 (m, 2H), 1.99−1.90 (m, 1H), 1.85−1.69 (m, 2H), 1.51−1.42 (m, 1H), 1.23 (s, 6H), 1.13 (d, J = 6.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.3, 160.3, 150.6, 128.4, 127.2, 114.5, 66.5, 60.4, 53.9, 50.7, 37.0, 34.0, 32.6, 28.3, 23.9, 21.6, 18.8; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{20}H_{30}N_3O_2^+$ 344.2333, found 344.2318.

*Ethyl 2,2-Dimethyl-4,4-diphenylbut-3-enoate (**7a**):*[10a] pale yellow oil; R_f = 0.30 (ethyl acetate/petroleum ether = 1:50) (0.6 mmol scale, 85.2 mg, 48% yield) ATR-FTIR (cm^{-1}) 2971, 1728, 1239, 1133, 1029, 760, 698; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.29 (m, 3H), 7.28−7.19 (m, 5H), 7.15−7.13 (m, 2H), 6.10 (s, 1H), 3.71 (q, J = 7.2 Hz, 2H), 1.31 (s, 6H), 1.13 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 176.3, 143.2, 141.4, 139.2, 134.1, 130.0, 128.0, 127.8, 127.2, 127.1, 127.0, 60.4, 43.9, 27.8, 13.9.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02277.

Copies of ^1H, $^{13}C\{^1H\}$, or ^{19}F spectra and HRMS spectra for all new products (PDF)

FAIR data, including the primary NMR FID files, for compounds **3a−3r**, **4a−4h**, **5a−5f**, **6a**, **6d−6e**, and **7a** (ZIP)

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Notes

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■ REFERENCES

(1) (a) Paal, C. Ueber die Derivate des Acetophenonacetessigesters und des Acetonylacetessigesters. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 2756−2767. (b) Knorr, L. Synthese von Furfuranderivaten aus dem Diacetbernsteinsäureester. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 2863−2870. (c) Minetto, G.; Raveglia, L. F.; Sega, A.; Taddei, M. MicrowaveAssisted Paal−Knorr Reaction-Three-Step Regiocontrolled Synthesis of Polysubstituted Furans, Pyrroles and Thiophenes. *Eur. J. Org. Chem.* **2005**, *2005*, 5277−5288.

(2) For selected examples, see: (a) Fujisawa, T.; Igeta, K.; Odake, S.; Morita, Y.; Yasuda, J.; Morikawa, T. Highly Water-Soluble Matrix Metalloproteinases Inhibitors and Their Effects in A Rat Adjuvant-Induced Arthritis Model. *Bioorg. Med. Chem.* **2002**, *10*, 2569−2581. (b) Bregman, H.; Chakka, N.; Guzman-Perez, A.; Gunaydin, H.; Gu, Y.; Huang, X.; Berry, V.; Liu, J.; Teffera, Y.; Huang, L.; Egge, B.; Mullady, E. L.; Schneider, S.; Andrews, P. S.; Mishra, A.; Newcomb, J.; Serafino, R.; Strathdee, C. A.; Turci, S. M.; Wilson, C.; DiMauro, E. F. Discovery of Novel, Induced-Pocket Binding Oxazolidinones as Potent, Selective, and Orally Bioavailable Tankyrase Inhibitors. *J. Med. Chem.* **2013**, *56*, 4320−4342. (c) Liu, H.; He, X.; Phillips, D.; Zhu, X.; Yang, K.; Lau, T.; Wu, B.; Xie, Y.; Nguyen, T. N.; Wang, X. Compounds and Compositions as Inhibitors of Cannabinoid Receptor 1 Activity. WO2008076754, 2008.

(3) For selected examples, see: (a) Hudkins, R. L.; Aimone, L. D.; Dandu, R. r.; Dunn, D.; Gruner, J. A.; Huang, Z.; Josef, K. A.; Lyons, J. A.; Mathiasen, J. R.; Tao, M.; Zulli, A. L.; Raddatz, R. 4,5-Dihydropyridazin-3-one Derivatives as Histamine H_3 Receptor Inverse Agonists. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 194−198. (b) Allan, G. M.; Vicker, N.; Lawrence, H. R.; Tutill, H. J.; Day, J. M.; Huchet, M.; Ferrandis, E.; Reed, M. J.; Purohit, A.; Potter, B. V. L. Novel Inhibitors of 17β-Hydroxysteroid Dehydrogenase Type 1: Templates for Design. *Bioorg. Med. Chem.* **2008**, *16*, 4438−4456. (c) Yuan, Q.; Liu, D.; Zhang, W. Synthesis of Chiral γ-Lactams via in Situ Elimination/Iridium-Catalyzed Asymmetric Hydrogenation of Racemic γ-Hydroxy γ-Lactams. *Org. Lett.* **2017**, *19*, 1886−1889. (d) Yuan, Q.; Liu, D.; Zhang, W. Iridium-Catalyzed Asymmetric Hydrogenation of β,γ-Unsaturated γ-Lactams: Scope and Mechanistic Studies. *Org. Lett.* **2017**, *19*, 1144−1147.

(4) Lhommet, G.; Fréville, S.; Thuy, V.; Petit, H.; Célérier, J. P. A General and Versatile Synthesis of 4- and 5-Oxoacids. *Synth. Commun.* **1996**, *26*, 3897−3901.

(5) (a) Hu, B.; Chen, H.; Liu, Y.; Dong, W.; Ren, K.; Xie, X.; Xu, H.; Zhang, Z. Visible Light-Induced Intermolecular Radical Addition: Facile Access to γ-Ketoesters from Alkyl-Bromocarboxylates and Enamines. *Chem. Commun.* **2014**, *50*, 13547−13550. (b) Fang, X.-X.; Wang, P.-F.; Yi, W.; Chen, W.; Lou, S.-C.; Liu, G.-Q. Visible-Light-Mediated Oxidative Coupling of Vinylarenes with Bromocarboxylates Leading to γ-Ketoesters. *J. Org. Chem.* **2019**, *84*, 15677−15684. (c) Ding, R.; Huang, Z.-D.; Liu, Z.-L.; Wang, T.-X.; Xu, Y.-H.; Loh, T.-P. Palladium-Catalyzed Cross-Coupling of Enamides with Sterically Hindered α-Bromocarbonyls. *Chem. Commun.* **2016**, *52*, 5617−5620.

(6) For selected examples, see: (a) Nishikata, T.; Noda, Y.; Fujimoto, R.; Sakashita, T. An Efficient Generation of a Functionalized Tertiary-Alkyl Radical for Copper-catalyzed Tertiary-Alkylative Mizoroki-Heck type Reaction. *J. Am. Chem. Soc.* **2013**, *135*, 16372−16375. (b) Zhang, X.; Yi, H.; Liao, Z.; Zhang, G.; Fan, C.; Qin, C.; Liu, J.; Lei, A. Copper-Catalysed Direct Radical Alkenylation of Alkyl Bromides. *Org. Biomol. Chem.* **2014**, *12*, 6790−6793. (c) Chen, X.; Liu, X.; Mohr, J. T. Cu-Catalyzed Stereoselective γ-Alkylation of Enones. *J. Am. Chem. Soc.* **2016**, *138*, 6364−6367. For selected reviews, see: (d) Ouyang, X.-H.; Song, R.-J.; Li, J.-H. Developments in the Chemistry of α-Carbonyl Alkyl Bromides. *Chem. - Asian J.* **2018**, *13*, 2316−2332.

(7) (a) Che, C.; Zheng, H.; Zhu, G. Copper-Catalyzed *trans*-Carbohalogenation of Terminal Alkynes with Functionalized Tertiary Alkyl Halides. *Org. Lett.* **2015**, *17*, 1617−1620. (b) Hu, M.; Song, R.-J.; Ouyang, X.-H.; Tan, F.-L.; Wei, W.-T.; Li, J.-H. Copper-Catalyzed Oxidative [2 + 2+1] Annulation of 1,*n*-Enynes with α-Carbonyl Alkyl Bromides through C−Br/C−H Functionalization. *Chem. Commun.* **2016**, *52*, 3328−3331. (c) Noda, Y.; Nishikata, T. A Highly Efficient Cu Catalyst System for the Radical Reactions of α-Bromocarbonyls. *Chem. Commun.* **2017**, *53*, 5017−5019. (d) Theunissen, C.; Wang, J.; Evano, G. Copper-Catalyzed Direct Alkylation of Heteroarenes. *Chem. Sci.* **2017**, *8*, 3465−3470. (e) Nakamura, K.; Nishikata, T. Tandem Reactions Enable Trans- and Cis-Hydro-Tertiary-Alkylations Catalyzed by a Copper Salt. *ACS Catal.* **2017**, *7*, 1049−1052.

(8) (a) Zhou, Z.; Behnke, N. E.; Kürti, L. Copper-Catalyzed Synthesis of Hindered Ethers from α-Bromo Carbonyl Compounds. *Org. Lett.* **2018**, *20*, 5452−5456. (b) Gockel, S. N.; Buchanan, T. L.; Hull, K. L. Cu-Catalyzed Three-Component Carboamination of Alkenes. *J. Am. Chem. Soc.* **2018**, *140*, 58−61. (c) Ye, Z.; Cai, X.; Li, J.; Dai, M. Catalytic Cyclopropanol Ring Opening for Divergent Syntheses of γ-Butyrolactones and δ -Ketoesters Containing All-Carbon Quaternary Centers. *ACS Catal.* **2018**, *8*, 5907−5914.

(9) (a) Li, D.; Mao, T.; Huang, J.; Zhu, Q. Copper-Catalyzed Bromodifluoroacetylation of Alkenes with Ethyl Bromodifluoroacetate. *J. Org. Chem.* **2018**, *83*, 10445−10452. (b) Li, D.; Yang, W.-C. Copper-Catalyzed Regioselective Alkylation of Heteroarenes with Functionalized Alkyl Halides. *Tetrahedron Lett.* **2019**, *60*, 1792−1795. (c) Li, D.; Shen, X. Iron-Catalyzed Regioselective Alkylation of 1,4-Quinones and Coumarins with Functionalized Alkyl Bromides. *Org. Biomol. Chem.* **2020**, *18*, 750−754.

(10) For selected examples, see: (a) Liu, C.; Tang, S.; Liu, D.; Yuan, J.; Zheng, L.; Meng, L.; Lei, A. Nickel-Catalyzed Heck-Type Alkenylation of Secondary and Tertiary α-Carbonyl Alkyl Bromides. *Angew. Chem., Int. Ed.* **2012**, *51*, 3638−3641. (b) Nakatani, A.; Hirano, K.; Satoh, T.; Miura, M. Nickel-Catalyzed Direct Alkylation of Heterocycles with α-Bromo Carbonyl Compounds: C3-Selective Functionalization of 2-Pyridones. *Chem. - Eur. J.* **2013**, *19*, 7691−7695. (c) Zhang, F.; Du, P.; Chen, J.; Wang, H.; Luo, Q.; Wan, X. Co-Catalyzed Synthesis of 1,4-Dicarbonyl Compounds Using TBHP Oxidant. *Org. Lett.* **2014**, *16*, 1932−1935. (d) Fan, J.-H.; Wei, W.-T.; Zhou, M.-B.; Song, R.-J.; Li, J.-H. Palladium-Catalyzed Oxidative Difunctionalization of Alkenes with α-Carbonyl Alkyl Bromides Initiated through a Heck-type Insertion: A Route to Indolin-2-ones. *Angew. Chem., Int. Ed.* **2014**, *53*, 6650−6654. (e) Fan, J.-H.; Yang, J.; Song, R.-J.; Li, J.-H. Palladium-Catalyzed Oxidative Heck-Type Alkylation/Aryl Migration/Desulfonylation between Alkenes with α-Carbonyl Alkyl Bromides. *Org. Lett.* **2015**, *17*, 836−839.

(11) (a) Ye, Z.; Gettys, K. E.; Shen, X.; Dai, M. Copper-Catalyzed Cyclopropanol Ring Opening C_{sp3}−C_{sp3} Cross-Couplings with (Fluoro)Alkyl Halides. *Org. Lett.* **2015**, *17*, 6074−6077. (b) Li, Z.; Garcia-Dominguez, A.; Nevado, C. Nickel-Catalyzed Stereoselective Dicarbofunctionalization of Alkynes. *Angew. Chem., Int. Ed.* **2016**, *55*, 6938−6941. (c) Yamane, Y.; Yoshinaga, K.; Sumimoto, M.; Nishikata, T. Iron-Enhanced Reactivity of Radicals Enables C−H Tertiary Alkylations for Construction of Functionalized Quaternary Carbons. *ACS Catal.* **2019**, *9*, 1757−1762. (d) Iwasaki, M.; Kazao, Y.; Ishida, T.; Nishihara, Y. Synthesis of Oxygen-Containing Heterocyclic Compounds by Iron-Catalyzed Alkylative Cyclization of Unsaturated Carboxylic Acids and Alcohols. *Org. Lett.* **2020**, *22*, 7343−7347. (e) Roy Chowdhury, S.; Singh, D.; Hoque, I. U.; Maity, S. Organic Dye-Catalyzed Intermolecular Radical Coupling of α-Bromocarbonyls with Olefins: Photocatalytic Synthesis of 1,4-Ketocarbonyls Using Air as an Oxidant. *J. Org. Chem.* **2020**, *85*, 13939−13950.

(12) For selected examples, see: (a) Combs, D. W.; Reese, K.; Cornelius, L. A. M.; Gunnet, J. W.; Cryan, E. V.; Granger, K. S.; Jordan, J. J.; Demarest, K. T. Nonsteroidal Progesterone Receptor Ligands. 2. High-Affinity Ligands with Selectivity for Bone Cell Progesterone Receptors. *J. Med. Chem.* **1995**, *38*, 4880−4884. (b) Lim, Y. J.; Angela, M.; Buonora, P. T. Conversion of γ-Bicyclic Lactams to 4,5-Dihydro-2H-pyridazin-3-ones. *Tetrahedron Lett.* **2003**, *44*, 7799−7801.

(13) For selected reviews, see: (a) Leurs, R.; Bakker, R. A.; Timmerman, H.; de Esch, I. J. The Histamine H_3 Receptor: From Gene Cloning to H_3 Receptor Drugs. *Nat. Rev. Drug Discovery* **2005**, *4*, 107−120. (b) Raddatz, R.; Tao, M.; Hudkins, R. L. Histamine H_3 Antagonists for Treatment of Cognitive Deficits in CNS Diseases. *Curr. Top. Med. Chem.* **2010**, *10*, 153−169. (c) Berlin, M.; Boyce, C. W.; de Lera Ruiz, M. Histamine H_3 Receptor as a Drug Discovery Target. *J. Med. Chem.* **2011**, *54*, 26−53.

(14) Khan, I.; Reed-Berendt, B. G.; Melen, R. L.; Morrill, L. C. FLP-Catalyzed Transfer Hydrogenation of Silyl Enol Ethers. *Angew. Chem., Int. Ed.* **2018**, *57*, 12356−12359.

(15) Marchington, A. F.; Lewis, T.; Clough, J. M.; Worthington, P. A.; Dalziel, J. 1-(Tetrahydrofurylmethyl)azoles. US4518415, 1985, A.

(16) Anja, G.; Maria, Q.-S.; Thomas, M.; Judith, G.; Niels, B.; Nils, G.; Naomi, B.; Ulf, B.; Roland, N.; Maren, O.; Christine, K. C.; Stefan, K.; Hartmut, R.; Jörg, W.; Benjamin, B.; Sven, C.; Roman, H. Dihydropyridazinones Substituted with Phenylureas. WO2018/86703, 2018, A1.

(17) Fujii, T.; Hirao, T.; Ohshiro, Y. Oxovanadium-Induced Oxidative Desilylation for the Selective Synthesis of 1,4-Diketones. *Tetrahedron Lett.* **1992**, *33*, 5823−5826.

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