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Synthesis of Seven-membered Azepino[3,2,1-*hi*]indoles via Rhodium-Catalyzed Regioselectively C-H Activation/DBU-Catalyzed Intramolecualr Amidation of 7-Phenylindoles in One Pot

Yumeng Yuan†, Guoshuai Pan†, Xiaofeng Zhang†, Buhong Li‡, Shengchang Xiang†, Qiufeng Huang*†

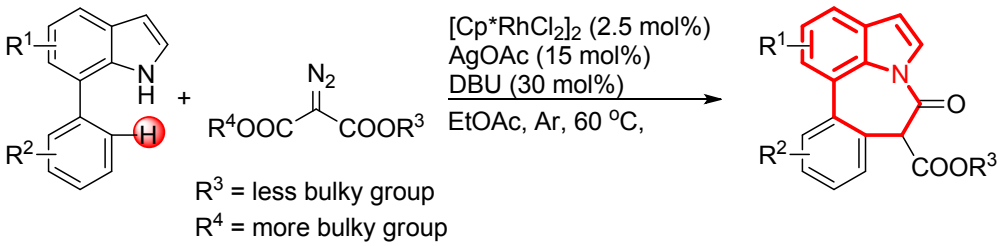
†Fujian Key Laboratory of Polymer Materials, College of Chemistry & Materials Science, Fujian Normal University, Fuzhou, Fujian 350007, P. R. China

‡MOE Key Laboratory of Optoelectronic Science and Technology for Medicine, Fujian Key Laboratory for Photonics Technology, Fujian Normal University, Fuzhou, Fujian 350007, P. R. China

E-mail: qiufenghuang@fjnu.edu.cn

Abstract

An unprecedented rhodium-catalyzed regioselectively C-H activation/DBU-catalyzed intramolecular amidation of 7-arylindoles with diazomalonates is described that provides a straightforward route to seven-membered azepino[3,2,1-*hi*]indoles in good to excellent yields in one pot. A wide range of functional groups, including F, OMe, NPh_2, $SiMe_3$, Cl, CN, CHO, COMe, CO_2Me, CF_3, NO_2 were all well tolerated.



- Tandem C-H activation/amidation in one-pot
- Selectively (*ortho*-C-H activation, mono-C-H activation)
- Mild conditions, excellent yields, gram scale
- High functional group tolerance

INTRODUCTION

Transition-metal-catalyzed C-H bond activation is a versatile synthetic tool for the construction of carbon-carbon bonds and carbon-heteroatom bonds.[1] In particular, transition-metal-catalyzed C-H activation/cyclization is a powerful and distinct method for the synthesis of cyclic and heterocyclic compounds.[2] In this context, recent years have witnessed a lot of efficient methods for the synthesis of five-membered or six-membered cyclic compounds.[3] However, one pot C-H activation/cyclization strategies leading to seven-membered rings have rarely been developed due to entropic factors and transannular interactions.[4] Azepino[3,2,1-*hi*]indoles and their derivatives are important classes of fused tricyclic compounds containing a seven-membered ring that are found in a wide range of natural products and biological active compounds (Figure 1). For example, erythrivarine B was isolated from the flower of Erythrina Variegata,[5] and extracts from the roots of stemonaceae plants were found to contain a class of polycyclic alkaloids which are structurally characterized by the presence of a azepino[3,2,1-*hi*]indole nucleus as show in stenine,[6] stemona-lactam,[7] tuberostemonol,[8] dehydrostenine[9] and tridehydrotuberostemonine.[10] These alkaloids exhibit a wide variety of biological activities, such as antitussive activity, insecticidal activity, anti-inflammatory and so on.[11] The structural diversity associated with biological activities of azepino[3,2,1-*hi*]indoles have attracted the attention of the synthetic community.[12] However, the synthesis of azepino[3,2,1-*hi*]indoles usually requires multistep approaches, and the development of novel strategies for efficient

and straightforward construction of azepino[3,2,1-*hi*]indoles still remains a great challenge. Indole nuclei are ubiquitous structural motifs. Recently, our group and other laboratories have demonstrated that *NH*-indole was explored as an intrinsic directing group which is present in the final product.[13] Herein, we report a regioselective Cp*Rh(III)-catalyzed C-H activation/base-catalyzed intramolecular amidation of 7-phenylindoles with diazomalonates to give the corresponding azepino[3,2,1-*hi*]indoles in good to excellent yields (Scheme 1). This catalytic method offers opportunities for the synthesis of azepino[3,2,1-hi]indoles derivatives' synthesis.

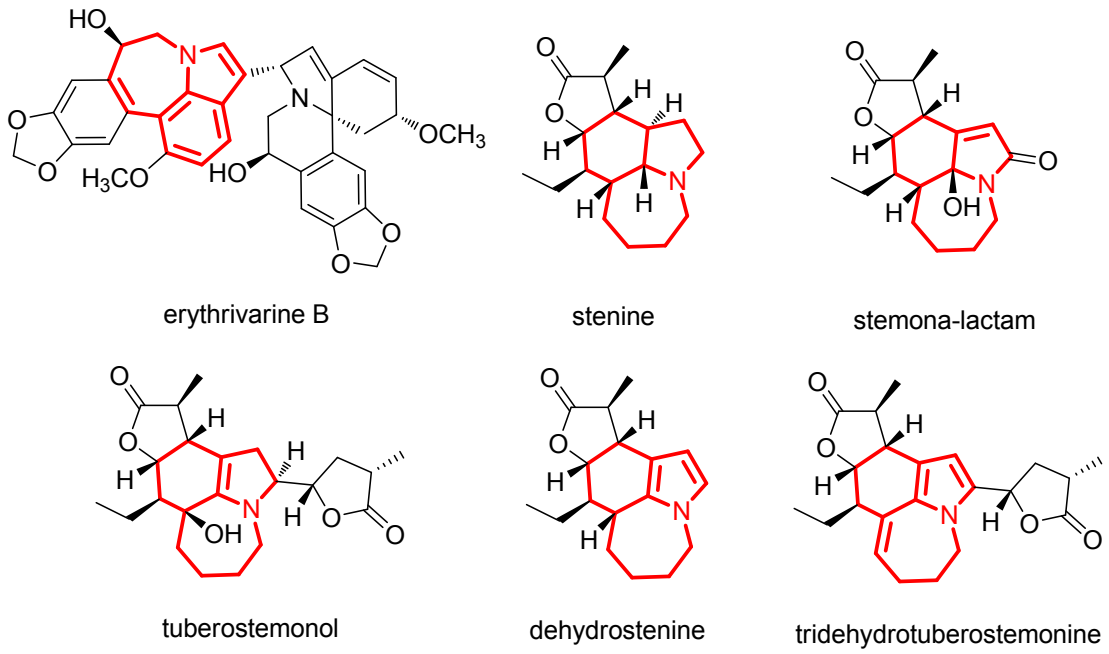
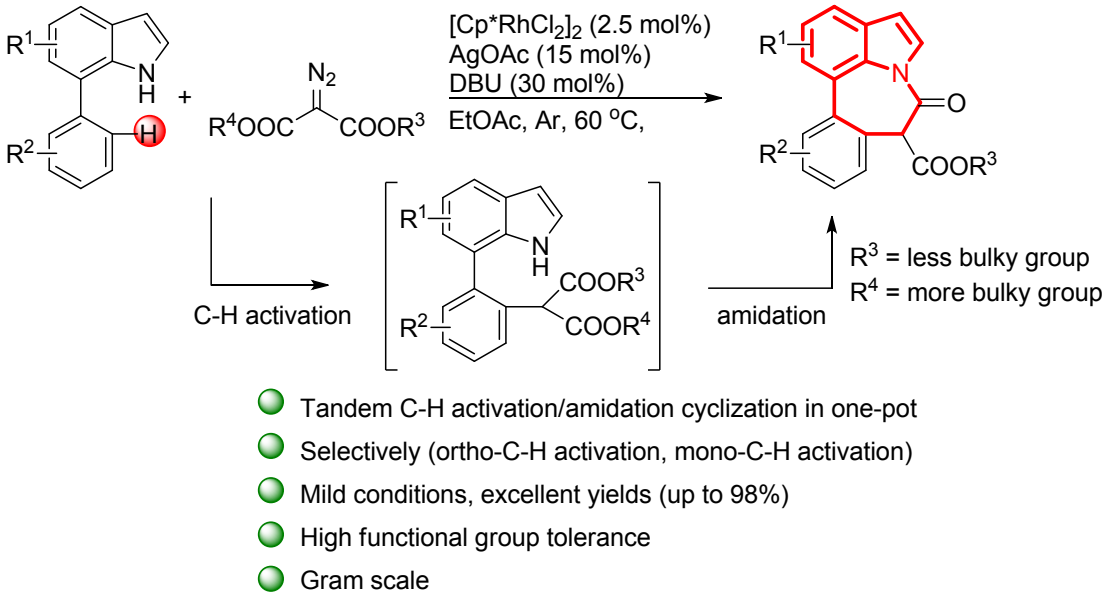


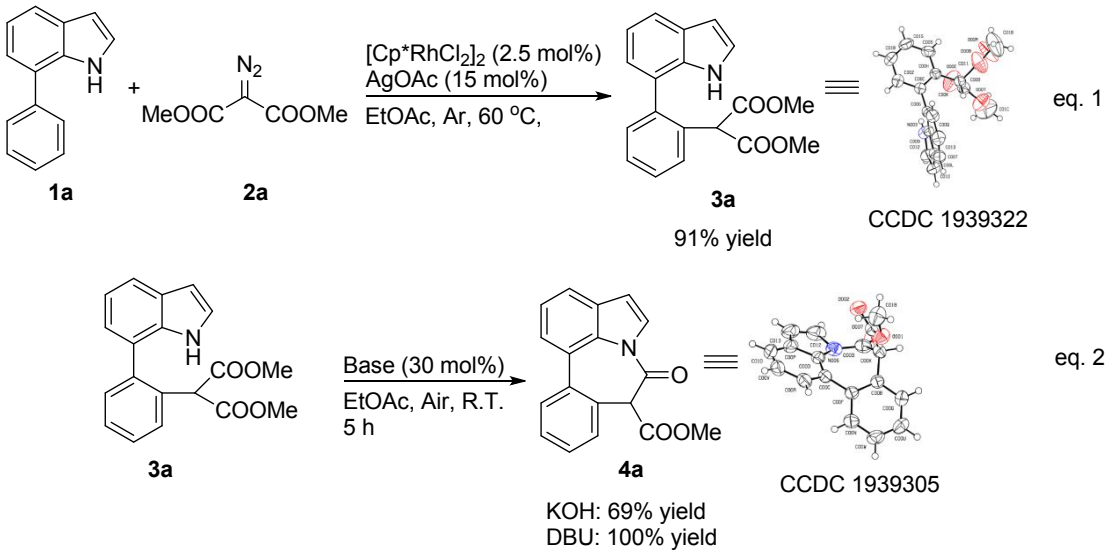
Figure 1. Natural products bearing azepino[3,2,1-*hi*]indole core



Scheme 1 Synthesis of Azepino[3,2,1-*hi*]indoles via Tandem C-H Activation/Amidation in One Pot

RESULT AND DISCUSSION

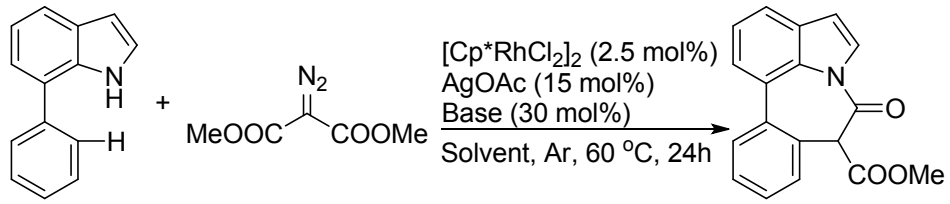
To begin, the experiments were performed with 7-phenyl-1*H*-indole (**1a**, 1 equiv) and dimethyl diazomalonate (**2a**, 1.5 equiv) in the presence of $[Cp^*RhCl_2]_2$ (2.5 mol %) and AgOAc (15 mol %) at 60 °C for 24 h, and the desired mono-substituted product **3a** was obtained selectively in 91% yield (Scheme 2, eq. 1). No disubstituted product[13b-c] or C3-substitituted product[14] was found in the reaction mixture. The structure of **3a** was confirmed by X-ray crystallography (see the Supporting Information). Treating **3a** with 30 mol % KOH in EtOAc resulted in intramolecular amidation to provide 7-membered ring **4a** in 69% yield. Changing the base to DBU afforded **4a** in quantitative yield (Scheme 2, eq. 2). The structure of **4a** was also confirmed by X-ray crystallography (see the Supporting Information). Encourage by the above results, the tandem C-H activation/amidation of 7-phenyl-1*H*-indole with



Scheme 2 Rhodium-Catalyzed *ortho* C-H Coupling of 7-Arylindoles with Diazo Compounds (eq. 1); Base-Catalyzed Intramolecular Amidation Cyclization (eq. 2).

dimethyl diazomalonate leading to azepino[3,2,1-*hi*]indole **4a** in one pot was surveyed (Table 1). It is found that KOH was incompatible with the $[Cp^*RhCl_2]_2$/AgOAc catalyst system; almost no annulated product was formed, and the starting material **1a** was recovered totally (Table 1, entry 1). We reasoned that strong base KOH had an adverse impact on Rhodium-catalyzed *NH*-indole directed C-H activation cycle. To our delight, by changing the base from KOH to DBU, the yield of the desired product was significantly improved to 94% (Table 1, entry 2). Other bases such as Et_3N, KO^tBu, DMAP, LiOH, piperidine, Me_4NOAc and $^nBu_4NOAc$ gave unsatisfactory results (Table 1, entries 3-9). The effect of the solvent on the formation of **4a** was also briefly investigated. In xylene, the reaction proceeded as smoothly as in EtOAc (Table 1, entry 10). However, the use of other solvents such as CH_3CN, 1,4-dioxane, DCM and MeOH resulted in significant decreases of the yields (Table 1, entries 11-15).

Table 1. Optimization of the Reaction Conditions[a]



1a **2a** **4a**

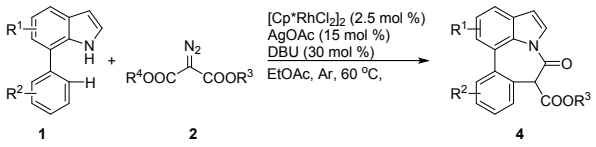
entry	base	solvent	yield (%)[b]
1	KOH	EtOAc	trace
2	DBU	EtOAc	94
3	Et_3N	EtOAc	0
4	KO^tBu	EtOAc	trace
5	DMAP	EtOAc	trace
6	LiOH	EtOAc	0
7	piperidine	EtOAc	trace
8	Me_4NOAc	EtOAc	22
9	$^nBu_4NOAc$	EtOAc	30
10	DBU	xylene	91
11	DBU	CH_3CN	trace
12	DBU	1,4-dioxane	47
13	DBU	DCM	79
14	DBU	DCE	trace
15	DBU	MeOH	0

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.45 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol%), AgOAc (15 mol%), base (30 mol%), solvent (2 mL), argon atmosphere, 60°C, 24 h. [b]isolated yield on the basis of the amount of **1a** used.

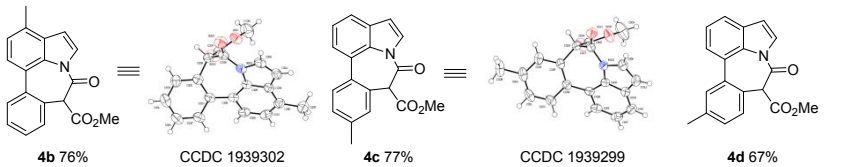
Under the optimal catalytic reaction conditions, the generality of the Rh(III)-catalyzed tandem C-H activation/cyclization was examined (Table 2). The reaction is found to be very sensitive with respect to the positions of substituents. Substituents at the 4 or 5-positions of the indole ring or the 3 or 4-positions of the benzene ring favored the reaction, affording the desired products in good to excellent yields (Table 2. **4b-e**), while substituents on other positions led to complete reaction shutdown (**4f-i**). Notably, a wide range of functional groups, including F, OMe, NPh_2, $SiMe_3$, Cl, CN,

CHO, COMe, CO_2Me, CF_3, NO_2 were all well tolerated (**4e**, **4j**, **4l-t**), providing the corresponding products in 56-95% yields. The diverse groups in the products can serve as a handle for further transformation. Only 18% yield of the desired product was detected when an OH group was present, which is probably a result of the chelating ability of the OH group with Rh metal (see **4w**). It is worth mentioned that 7-naphthylindole and 1,4-diindolylbenzene both coupled smoothly with **2a** to afford the annulated products. The resulting structures **4u** and **4v** may be useful as valuable intermediate for preparing optoelectronic materials. In order to determine if the electronic nature of the substituent affected the reaction, an intermolecular competition experiment was conducted with an equimolar mixture of 7-(4-methoxyphenyl)-1*H*-indole and 7-(4-nitrophenyl)-1*H*-indole. A ratio of 3:1 was obtained between **4j** and **4t** after 12 h, which suggests that electron-rich substrates are favorable to the reaction (Scheme 3, eq. 1). An intermolecular competition reaction between 7-phenyl-1*H*-indole **1a** and its deuterated derivative **1a-D5** gave a KIE value of 2.5, indicating that the C-H bond cleavage might be involved in the rate-determining step (Scheme 3, eq. 2). Next, various diazo compounds were examined under the standard conditions. It is found that the steric effects of the substituents on the diazomaonates play an important role in the cyclization step. Changing the methyl group to ethyl group afforded a lower yield (**4x**, 55%). Diisopropyl 2-diazomalonate was found to couple with **1a** to afford the mono-substituted product **3y** in quantitative yield; and the amidation cyclization of **3y** can not happen in one pot. However, treating **3y** with 30 mol% KOH in DCM

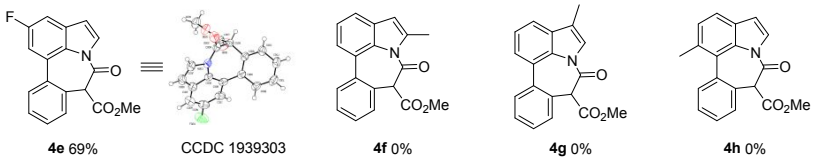
Table 2. Substrate Scope[a]



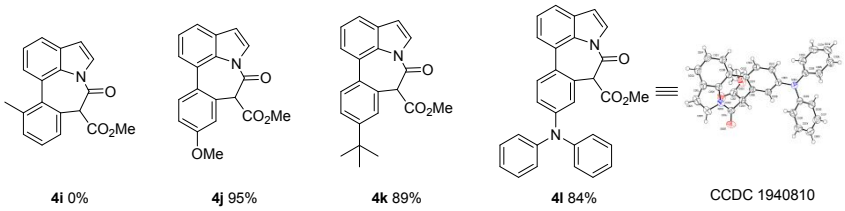
1 2 4



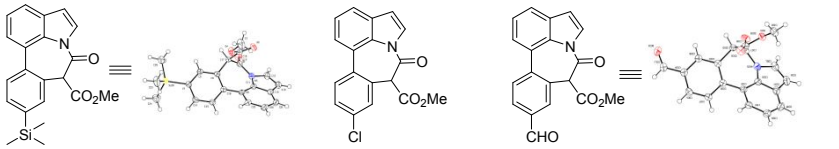
4b 76% CCDC 1939302 **4c** 77% CCDC 1939299 **4d** 67%



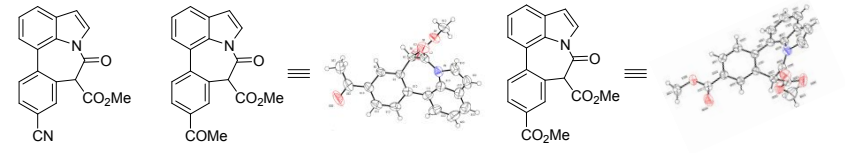
4e 69% CCDC 1939303 **4f** 0% **4g** 0% **4h** 0%



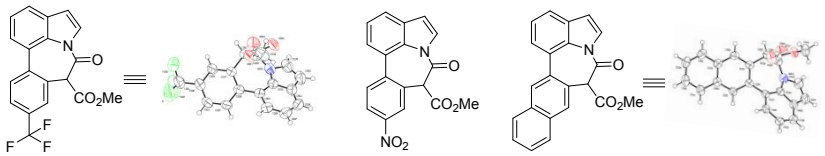
4i 0% **4j** 95% **4k** 89% **4l** 84% CCDC 1940810



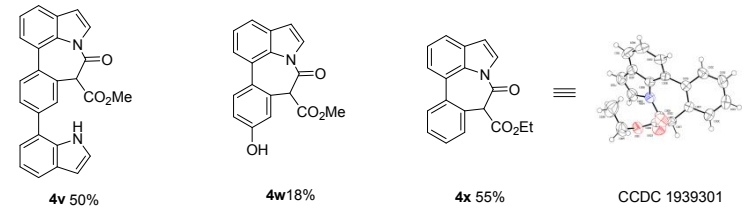
4m 75% CCDC 1940811 **4n** 85% **4o** 93% CCDC 1939304



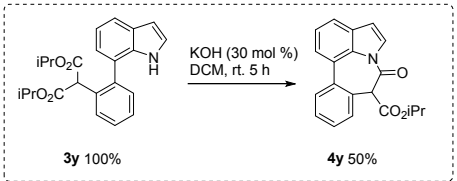
4p 75% **4q** 71% CCDC 1940812 **4r** 90% CCDC 1939300



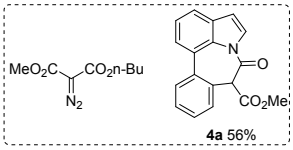
4s 77% CCDC 1940814 **4t** 56% **4u** 98% CCDC 1940815



4v 50% **4w**18% **4x** 55% CCDC 1939301

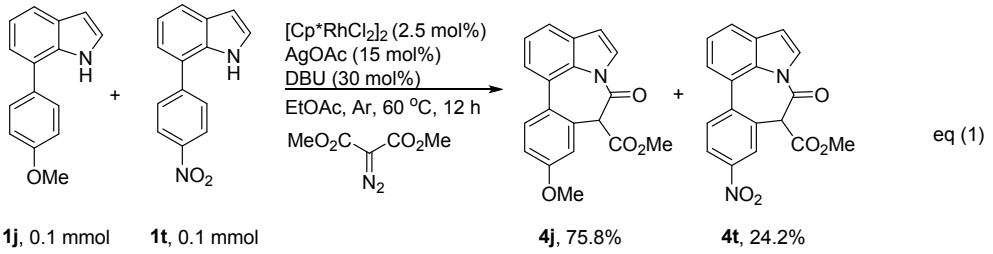


3y 100% **4y** 50%

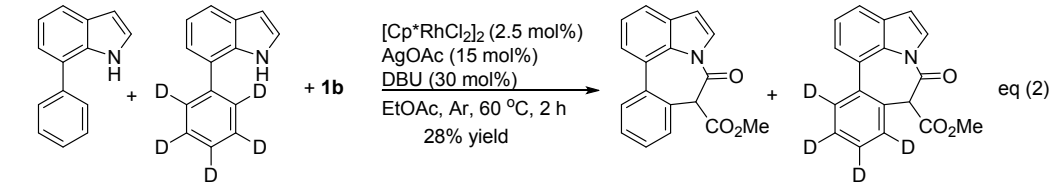


4a 56%

[a]Reaction conditions: **1** (0.3 mmol), **2** (0.45 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol%), AgOAc (15 mol%), DBU (30 mol%), EtOAc (2 mL), argon atmosphere, 60 °C, 24 h; isolated yield.



1j, 0.1 mmol **1t**, 0.1 mmol **4j**, 75.8% **4t**, 24.2%



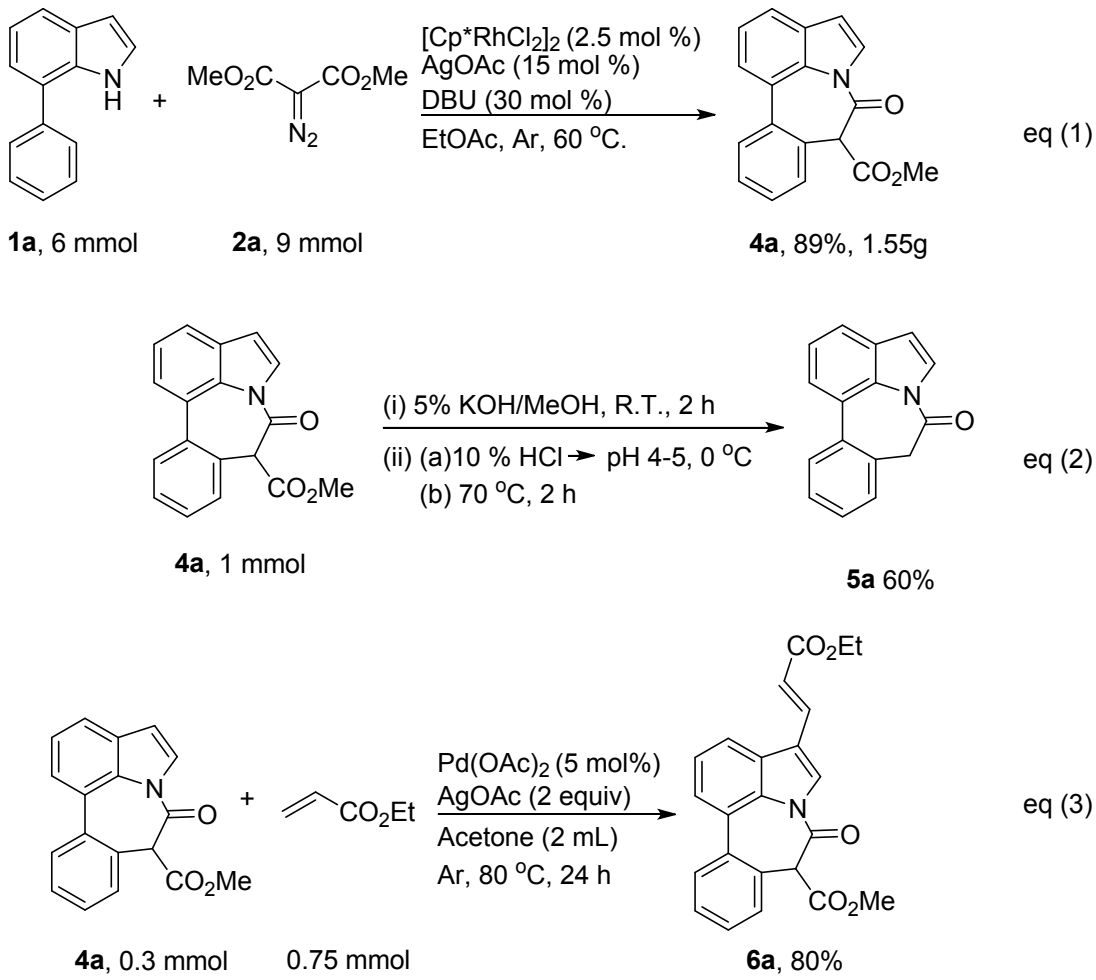
1a, 0.1 mmol **1a-D5**, 0.1 mmol **4a** **4a-D4**

K_H/K_D = 2.5 : 1

Scheme 3. Competition Experiment

delivered cyclization product **4y** in 50% yield. Interestingly, when the unsymmetrical diazomalonate *n*-butyl methyl 2-diazomalonate was employed, the amidation occurred at the more bulky group and reserved the less bulky group in the final product **4a**.

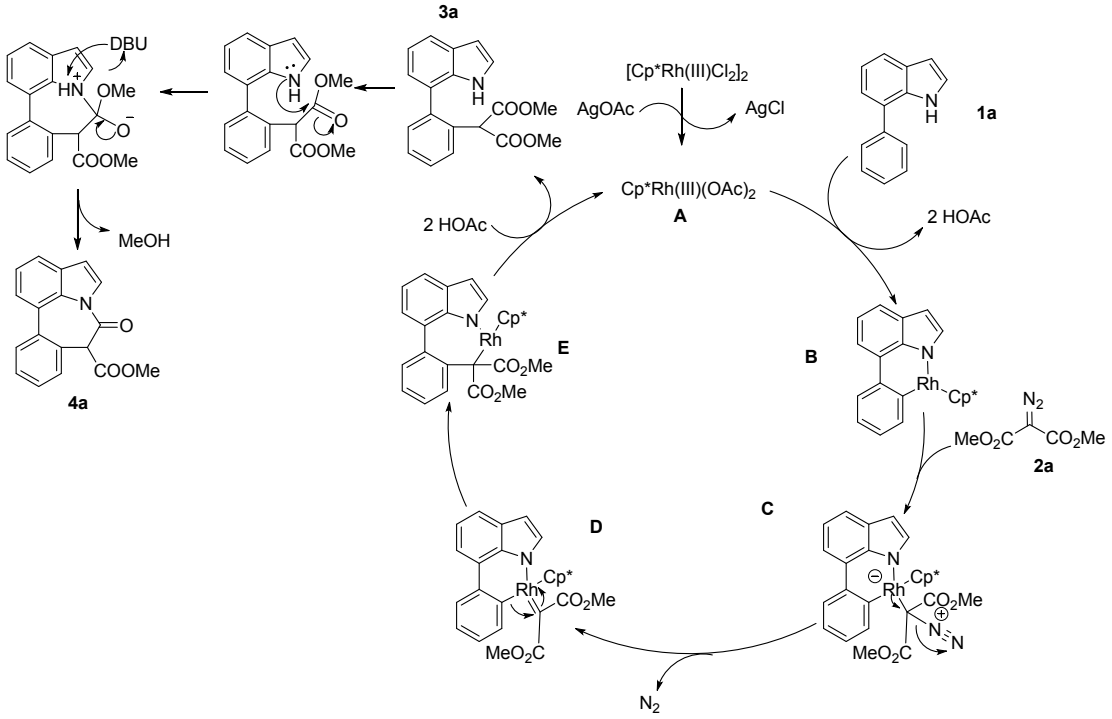
In order to demonstrate the practical application of the methodology, the reaction of **1a** and **2a** was carried out on a gram scale, which provided an 89% yield of **4a** (1.55 g, Scheme 4, eq. 1). Demethoxycarbonylation of **4a** through a saponification and decarboxylation sequence gave benzo[4,5]azepino[3,2,1-*hi*]indol-4(5*H*)-one **5a** in 60% yield (Scheme 4, eq. 2).[15] Finally, **4a** can be efficiently alkenylated at the 3-position with acrylate affording **6a** in 80% yield by a $Pd(OAc)_2$-catalyzed Fujiwara-Moritani reaction (Scheme 4, eq. 3).[16]



Scheme 4. Synthetic Transformations

In fact, several attempts to recrystallize or in situ characterize the key intermediates from the reaction of 7-phenyl-*1H*-indole with equimolar $[Cp^*RhCl_2]_2$ were problematic. However, based on our group's previous research of *NH*-indole-directed C-H bond functionalization,[13a-b] a possible mechanism for the present reaction is depicted briefly in Scheme 5. First, the active Rh(III) species **A** is generated with the assistance of AgOAc, which undergoes N-H bond cleavage and C-H bond cleavage to give six-membered rhodacycle **B**. Then rhodacycle **B** decomposes the diazo compound **2a** to generate metal carbene species **D**; **D** undergoes migratory insertion to produce seven-membered rhodacycle **E**. At this

point, **E** is protonated to afford the coupling product **3a** and regenerate the active Rh(III) catalyst **A**. Finally, **3a** can be converted into the seven-membered product **4a** via intramolecualr amidation in the presence of DBU catalyst.



Scheme 5. Proposed Reaction Mechanism

In conclusion, we have developed a significant advancement to catalytic C-H activation/cyclization. This protocol enables unprecedented general access to the seven-membered azepino[3,2,1-*hi*]indoles. The tandem rhodium-catalyzed C-H coupling of 7-phenylindoles with diazo compounds and DBU-catalyzed intramolecular amidation proceeds in one pot under mild reaction conditions. The reactions have a broad range of substrates giving a variety of functionalized products in high yields. A wide range of functional groups, including F, OMe, NPh_2, $SiMe_3$, Cl, CN, CHO, COMe, CO_2Me, CF_3, NO_2 were all well tolerated. Further applications of this C-H activation/cyclization in the synthesis of related targets are in progress.

Experimental Section

General Method

7-Phenyl-1*H*-indoles (**1**) were synthesized from 7-bromo-*1H*-indoles and Phenylboronic acid via Suzuki coupling.[17] **1a**, **1c**, **1f**, **1h-j**, **1p**, **1s-u** are known compounds, ^{1}H NMR data of the isolated products were in agreement with the literature reports.[18] **1b**, **1d-e**, **1g**, **1k-o**, **1q**, **1v-w** are new compounds. They were characterized by ^{1}H NMR, ^{13}C NMR and HRMS. Diazo compounds (**2**) were prepared according to the reported procedures, and the compounds' spectra data are in agreement with the reports.[19] ^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra at 100 MHz, respectively. ^{1}H chemical shifts (δ) were referenced to TMS, and ^{13}C NMR chemical shifts (δ) were referenced to internal solvent resonance. ESI-HRMS spectra were recorded by using a Q-TOF mass spectrometer. Data collection and structural analysis of the crystal was collected on a Single Crystal Diffractometer equipped with graphite monochromatic Cu/Mo K_{α} radiation (λ=1.54184Å).

7-Phenyl-1*H*-indole (**1a**)**:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.69 – 7.64 (m, 3H), 7.55 – 7.50 (m, 2H), 7.47 (t, J = 7.4 Hz, 1H), 7.26 – 7.20 (m, 3H), 6.64 (dd, *J* = 3.2, 2.1 Hz, 1H).

4-Methyl-7-phenyl-1*H*-indole (**1b**)**:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.64 (dt, *J* = 7.7, 1.5 Hz, 2H), 7.54 – 7.49 (m, 2H), 7.42 – 7.38 (m, 1H), 7.23 (dd, *J* = 3.2, 2.5 Hz, 1H), 7.16 (d, *J* = 7.3 Hz, 1H), 7.03 (dd, J = 7.5, 1.0 Hz, 1H), 6.66 (dd, *J* = 3.2, 2.1 Hz, 1H), 2.63 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 139.4, 133.3,

129.6, 129.1, 128.2, 128.0, 127.1, 123.7, 123.3, 122.0, 120.5, 101.6, 18.7. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{15}H_{14}N$, 208.1121; found, 208.1117.

7-(*p*-Tolyl)-1*H*-indole (**1c**)**:** ^1H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.71 – 7.57 (m, 3H), 7.44 – 7.20 (m, 5H), 6.68 (s, 1H), 2.49 (s, 3H).

7-(*m*-Tolyl)-1*H*-indole (**1d**)**:** ^1H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.68 – 7.63 (m, 1H), 7.48 – 7.44 (m, 2H), 7.41 (td, *J* = 7.2, 1.4 Hz, 1H), 7.25 – 7.19 (m, 4H), 6.64 (dd, *J* = 3.2, 2.1 Hz, 1H), 2.46 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 139.2, 138.8, 133.7, 129.0, 128.9, 128.2, 128.1, 125.7, 125.2, 124.2, 121.8, 120.2, 119.9, 103.0, 21.6. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{15}H_{14}N$, 208.1121; found, 208.1119.

5-Fluoro-7-phenyl-1*H*-indole (**1e**)**:** ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.65 – 7.61 (m, 2H), 7.56 – 7.51 (m, 2H), 7.47 – 7.42 (m, 1H), 7.31 (dd, *J* = 9.3, 2.3 Hz, 1H), 7.25 (t, *J* = 2.9 Hz, 1H), 7.02 (dd, *J* = 10.0, 2.4 Hz, 1H), 6.60 (dd, *J* = 3.1, 2.1 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 158.2 (d, J = 234.5 Hz), 138.1, 130.2, 129.2, 128.5 (d, J = 10.5 Hz), 128.1, 127.9, 126.3 (d, J = 9.4 Hz), 125.9, 110.1 (d, J = 26.6 Hz), 104.6 (d, J = 23.4 Hz), 103.2 (d, J = 4.8 Hz). 19 F NMR (376 MHz, $CDCl_3$)δ -124.7 (t, J = 9.3 Hz). HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{14}H_{11}FN$, 212.0870; found, 212.0865.

2-Methyl-7-phenyl-1*H*-indole (**1f**)**:** ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.67 – 7.63 (m, 2H), 7.55 – 7.50 (m, 3H), 7.43 – 7.38 (m, 1H), 7.19 – 7.13 (m, 2H), 6.33 – 6.27 (m, 1H), 2.45 (s, 3H).

3-Methyl-7-phenyl-1*H*-indole (**1g**)**:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.73 – 7.64 (m, 2H), 7.64 – 7.59 (m, 1H), 7.57 – 7.49 (m, 2H), 7.44 – 7.39 (m, 1H), 7.27 – 7.24 (m, 2H), 7.00 (dd, *J* = 2.3, 1.2 Hz, 1H), 2.40 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 139.3, 134.0, 129.1, 128.6, 128.2, 127.3, 125.4, 121.8, 119.6, 118.1, 112.1, 9.8. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{15}H_{14}N$, 208.1121; found, 208.1116.

6-Methyl-7-phenyl-1*H*-indole (**1h**)**:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.56 – 7.49 (m, 3H), 7.45 – 7.40 (m, 3H), 7.12 – 7.05 (m, 2H), 6.55 (dd, *J* = 3.2, 2.1 Hz, 1H), 2.31 (s, 3H).

7-(*o*-Tolyl)-1*H*-indole (**1i**)**:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.68 (dt, J = 8.0, 0.9 Hz, 1H), 7.40 – 7.30 (m, 4H), 7.24 – 7.18 (m, 2H), 7.10 (dd, J = 7.2, 1.1 Hz, 1H), 6.64 (dd, J = 3.2, 2.1 Hz, 1H), 2.21 (s, 3H).

7-(4-Methoxyphenyl)-1*H*-indole (**1j**)**:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.65 – 7.55 (m, 3H), 7.23 – 7.18 (m, 3H), 7.08 – 7.02 (m, 2H), 6.66 – 6.59 (m, 1H), 3.89 (s, 3H).

7-(4-(*Tert*-butyl)phenyl)-1*H*-indole (**1k**)**:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.65 (ddd, *J* = 6.8, 2.1, 0.7 Hz, 1H), 7.62 – 7.58 (m, 2H), 7.57 – 7.53 (m, 2H), 7.25 – 7.20 (m, 3H), 6.64 (dd, *J* = 3.2, 2.1 Hz, 1H), 1.42 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 150.3, 136.3, 133.8, 128.2, 127.9, 126.0, 125.5, 124.2, 121.8, 120.3, 119.8, 103.0, 34.6, 31.4. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{18}H_{20}N$, 250.1590; found, 250.1584.

4-(1*H*-Indol-7-yl)-*N,N*-diphenylaniline (**1l**)**:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.63 (dd, J = 6.4, 2.2 Hz, 1H), 7.55 – 7.48 (m, 2H), 7.33 – 7.27 (m, 4H), 7.24

– 7.16 (m, 8H), 7.13 (dt, J = 8.7, 1.8 Hz, 1H), 7.09 – 7.04 (m, 2H), 6.63 (dd, J = 3.2, 2.1 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, CDCl3) δ 147.6, 147.2, 133.7, 133.1, 129.3, 129.2, 128.9, 128.2, 127.3, 125.2, 124.5, 124.3, 124.2, 124.0, 123.1, 122.8, 121.6, 120.3, 119.7, 103.1. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{26}H_{21}N_2$, 361.1699; found, 361.1689.

7-(4-(Trimethylsilyl)phenyl)-1*H*-indole (**1m**)**:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.71 – 7.63 (m, 5H), 7.26 – 7.20 (m, 3H), 6.64 (dd, *J* = 3.2, 2.1 Hz, 1H), 0.35 (t, 9H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 139.6, 139.5, 134.1, 133.7, 128.2, 127.5, 125.5, 124.3, 121.8, 120.3, 120.1, 103.0, -1.1. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{17}H_{20}NSi$, 266.1360; found, 266.1352.

7-(4-Chlorophenyl)-1*H*-indole (**1n**)**:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.67 (ddd, *J* = 7.3, 1.9, 0.7 Hz, 1H), 7.60 – 7.56 (m, 2H), 7.51 – 7.47 (m, 2H), 7.24 – 7.18 (m, 3H), 6.64 (dd, *J* = 3.2, 2.0 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 137.7, 133.5, 133.3, 129.5, 129.3, 128.4, 124.5, 124.3, 121.9, 120.4, 120.3, 103.2. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{14}H_{11}ClN$, 228.0575; found, 228.0569.

4-(1*H*-Indol-7-yl)benzaldehyde (**1o**)**:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.06 (s, 1H), 8.51 (s, 1H), 8.03 – 8.00 (m, 2H), 7.84 – 7.81 (m, 2H), 7.71 (ddd, *J* = 7.2, 1.8, 0.7 Hz, 1H), 7.29 – 7.21 (m, 3H), 6.66 (dd, *J* = 3.2, 2.0 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 191.8, 145.7, 135.2, 133.4, 130.6, 128.7, 128.6, 124.7, 124.1, 122.2, 121.2, 120.4, 103.3. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{15}H_{12}NO$, 222.0913; found, 222.0908.

4-(1*H*-Indol-7-yl)benzonitrile (**1p**)**:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.81 – 7.75 (m, 4H), 7.73 – 7.68 (m, 1H), 7.28 – 7.19 (m, 4H), 6.66 (dd, *J* = 3.2, 2.0 Hz, 1H).

1-(4-(1*H*-Indol-7-yl)phenyl)ethan-1-one (**1q**)**:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.11 – 8.06 (m, 2H), 7.77 – 7.73 (m, 2H), 7.70 (dd, J = 7.0, 1.7 Hz, 1H), 7.28 – 7.21 (m, 3H), 6.66 (dd, *J* = 3.1, 2.1 Hz, 1H), 2.65 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 197.8, 144.3, 135.8, 129.2, 128.5, 128.3, 124.7, 124.3, 122.0, 121.0, 120.3, 104.9, 103.2, 26.6. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{16}H_{14}NO$, 236.1070; found, 236.1064.

Methyl 4-(1*H*-indol-7-yl)benzoate (**1r**)**:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 8.17 (d, J = 8.2 Hz, 2H), 7.72 (d, J = 8.2 Hz, 2H), 7.69 (dd, J = 7.0, 2.0 Hz, 1H), 7.27 – 7.21 (m, 3H), 6.65 (dd, *J* = 3.2, 2.1 Hz, 1H), 3.96 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.9, 144.0, 133.4, 130.4, 128.9, 128.5, 128.1, 124.6, 124.4, 122.0, 120.9, 120.3, 103.2, 52.2. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{16}H_{14}NO_2$, 252.1019; found, 252.1012.

7-(4-(Trifluoromethyl)phenyl)-1*H*-indole (**1s**)**:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.80 – 7.75 (m, 4H), 7.72 – 7.68 (m, 1H), 7.26 – 7.22 (m, 3H), 6.66 (dd, *J* = 3.2, 2.0 Hz, 1H).

7-(4-Nitrophenyl)-1*H*-indole (**1t**)**:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 8.39 – 8.35 (m, 2H), 7.85 – 7.80 (m, 2H), 7.75 – 7.71 (m, 1H), 7.32 – 7.20 (m, 3H), 6.67 (dd, *J* = 3.2, 2.0 Hz, 1H).

7-(Naphthalen-2-yl)-1*H*-indole (**1u**)**:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 8.11 (s, 1H), 8.00 (d, *J* = 8.4 Hz, 1H), 7.95 – 7.90 (m, 2H), 7.78 (dd, J = 8.4, 1.7 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.59 – 7.51 (m, 2H), 7.35 (d, *J* = 7.1 Hz, 1H), 7.30 – 7.23 (m, 2H), 6.67 (m, 1H).

1,4-Di(1*H*-indol-7-yl)benzene (**1v**)**:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 2H), 7.80 (s, 4H), 7.69 (d, *J* = 7.2 Hz, 2H), 7.31 – 7.23 (m, 6H), 6.67– 6.65 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 138.4, 133.7, 128.9, 128.4, 127.7, 125.1, 124.4, 121.9, 120.4, 120.3, 103.2. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{22}H_{17}N_2$, 309.1386; found, 309.1379.

4-(1*H*-Indol-7-yl)phenol (**1w**)**:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.64 (d, *J* = 7.0 Hz, 1H), 7.52 (d, J = 8.4 Hz, 2H), 7.27 – 7.17 (m, 3H), 6.97 (d, J = 8.4 Hz, 2H), 6.67 – 6.59 (m, 1H), 5.09 (s, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 154.9, 133.8, 131.8, 129.5, 128.2, 125.2, 124.3, 121.7, 120.3, 119.6, 116.0, 103.0. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{14}H_{12}NO$, 210.0913; found, 210.0908.

General Procedure for the Synthesis of Azepino[3,2,1-*hi*]indoles 4a-4x: Under argon atmosphere, 7-aryl-1*H*-indoles **1**(0.3 mmol), diazo compounds **2** (0.45 mmol, 1.5 equiv.), $[Cp^*RhCl_2]_2$ (4.7 mg, 0.0075 mmol, 2.5mol%), AgOAc (7.5 mg, 0.045 mmol, 15 mol%), DBU (13.5 μL, 0.09 mmol, 30 mmol%) and EtOAc (2 mL) were placed in a 25 mL seal tube. The mixture was heated in oil bath at 60 °C for 24 h and then cooled to room temperature. The crude reaction mixture was diluted with EtOAc to 5 mL, filtered through a celite pad, and then washed with 10 mL EtOAc. The volatiles were removed under reduced pressure, and the residue was subjected to silica gel column chromatography [eluting with petroleum ether/ethyl acetate] to

afford the corresponding product.

Dimethyl 2-(2-(1*H*-indol-7-yl)phenyl)malonate **(3a):** 88 mg (91%); white solid, mp 151-152 °C; Purification (Petroleum ether/ethyl acetate = 10/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.68 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.67 – 7.63 (m, 1H), 7.51 – 7.38 (m, 3H), 7.20 (dd, *J* = 8.0, 7.2 Hz, 1H), 7.14 (dd, *J* = 3.2, 2.4 Hz, 1H), 7.06 (dd, *J* = 7.2, 1.2 Hz, 1H), 6.60 (dd, *J* = 3.2, 2.1 Hz, 1H), 4.72 (s, 1H), 3.68 (s, 3H), 3.63 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.7, 168.9, 138.9, 134.6, 131.7, 130.6, 129.4, 128.5, 128.3, 127.8, 124.6, 123.3, 122.8, 120.4, 119.9, 102.8, 53.8, 52.8. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{19}H_{17}NO_4Na$, 346.1050; found, 346.1051. It was crystallized from cyclohexane/dichloromethane.

Methyl 4-oxo-4,5-dihydrobenzo[4,5]azepino[3,2,1-*hi*]indole-5-carboxylate **(4a):** 82 mg (94%); white solid, mp 128-129 °C; Purification (Petroleum ether/ethyl acetate = 10/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 3.7 Hz, 1H), 7.75 – 7.72 (m, 2H), 7.66 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.56 – 7.47 (m, 3H), 7.41 (t, *J* = 7.7 Hz, 1H), 6.77 (d, *J* = 3.7 Hz, 1H), 5.07 (s, 1H), 3.26 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.3, 165.1, 135.6, 131.8, 131.6, 131.5, 129.6, 129.5, 129.0, 128.6, 127.1, 125.6, 124.2, 123.5, 121.6, 109.8, 62.1, 52.6. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{13}NO_3Na$, 314.0788; found, 314.0788. It was crystallized from cyclohexane/dichloromethane.

Methyl 12-methyl-4-oxo-4,5-dihydrobenzo[4,5]azepino[3,2,1-*hi*]indole-5-carboxylate **(4b):**70 mg (76%); white solid, mp 172-173 °C; Purification (Petroleum ether/ethyl acetate = 10/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 3.8 Hz, 1H), 7.71 (d, *J* =

7.6 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.53 – 7.43 (m, 3H), 7.21 (dd, *J* = 7.8, 0.9 Hz, 1H), 6.81 (d, *J* = 3.8 Hz, 1H), 5.07 (s, 1H), 3.27 (s, 3H), 2.60 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 167.5, 165.0, 135.7, 131.6, 131.5, 131.44, 131.41, 131.1, 129.2, 128.9, 128.3, 126.4, 125.0, 123.5, 123.2, 108.1, 62.1, 52.6, 18.4. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{19}H_{15}NO_3Na$, 328.0944; found, 328.0944. It was crystallized from cyclohexane/dichloromethane.

Methyl 7-methyl-4-oxo-4,5-dihydrobenzo[4,5]azepino[3,2,1-*hi*]indole-5-carboxylate **(4c):** 71 mg (77%); white solid, mp 164-165 °C; Purification (Petroleum ether/ethyl acetate = 10/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 3.7 Hz, 1H), 7.70 (d, *J* = 7.7 Hz, 1H), 7.63 (d, *J* = 7.7 Hz,2H), 7.41 – 7.28 (m, 3H), 6.76 (d, *J* = 3.7 Hz, 1H), 5.01 (s, 1H), 3.25 (s, 3H), 2.45 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 167.4, 165.1, 138.7, 132.8, 132.1, 131.7, 131.5, 129.9, 129.4, 127.1, 125.6, 124.2, 123.3, 121.2, 109.7, 62.1, 52.6, 21.0. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{19}H_{15}NO_3Na$, 328.0944; found, 328.0944. It was crystallized from cyclohexane/dichloromethane.

Methyl 8-methyl-4-oxo-4,5-dihydrobenzo[4,5]azepino[3,2,1-*hi*]indole-5-carboxylate **(4d):** 61 mg (67%); white solid, mp 127-128 °C; Purification (Petroleum ether/ethyl acetate = 10/1).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 3.7 Hz, 1H), 7.72 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.64 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.55 – 7.53 (m, 1H), 7.39 (dd, *J* = 15.7, 7.8 Hz, 2H), 7.29 (d, *J* = 7.7 Hz,1H), 6.76 (d, *J* = 3.7 Hz, 1H), 5.03 (s, 1H), 3.25 (s, 3H), 2.46 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 167.5, 165.3, 139.0, 135.4, 131.8, 131.7,

131.4, 130.2, 129.5, 127.1, 126.9, 125.7, 124.2, 123.4, 121.5, 109.7, 61.7, 52.6, 21.3. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{19}H_{15}NO_3Na$, 328.0944; found, 328.0943.

Methyl 11-fluoro-4-oxo-4,5-dihydrobenzo[4,5]azepino[3,2,1-*hi*]indole-5-carboxylate **(4e):** 64 mg (69%); white solid, mp 140-141 °C; Purification (Petroleum ether/ethyl acetate = 10/1). ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 3.7 Hz, 1H), 7.70 (dd, *J* = 7.3, 1.7 Hz, 1H), 7.57 – 7.43 (m, 4H), 7.33 (dd, *J* = 8.1, 2.4 Hz, 1H), 6.73 (d, *J* = 3.7 Hz, 1H), 5.07 (s, 1H), 3.30 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.1, 164.6, 159.8 (d, $^1J_{C-F}$ = 240.8 Hz), 134.6, 132.9 (d, $^2J_{C-F}$ = 10.5 Hz), 131.7, 129.5 (d, $^3J_{C-F}$ = 4.6 Hz), 129.2 (d, $^3J_{C-F}$ = 4.3 Hz), 128.8, 128.1, 126.8 (d, $^2J_{C-F}$ = 9.2 Hz), 110.7, 110.5, 109.6 (d, $^3J_{C-F}$ = 4.0 Hz), 107.6, 107.4, 62.0, 52.8. ^{19}F NMR (376 MHz, $CDCl_3$)δ-118.9 (t, *J* = 9.0 Hz, 1F).HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{12}FNO_3Na$, 332.0693; found, 332.0693. It was crystallized from cyclohexane/dichloromethane.

Methyl 7-methoxy-4-oxo-4,5-dihydrobenzo[4,5]azepino[3,2,1-*hi*]indole-5-carboxylate **(4j):** 92 mg (95%); white solid, mp 125-126 °C; Purification (Petroleum ether/ethyl acetate = 4/1). ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 3.7 Hz, 1H), 7.67 – 7.63 (m, 2H), 7.60 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.37 (t, *J* = 7.7 Hz, 1H), 7.07 (dd, *J* = 8.7, 2.7 Hz, 1H), 7.01 (d, *J* = 2.7 Hz, 1H), 6.76 (d, *J* = 3.7 Hz, 1H), 5.00 (s, 1H), 3.89 (s, 3H), 3.26 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.2, 164.8, 159.9, 131.7, 131.3, 130.8, 130.7, 128.2, 127.0, 125.4, 124.2, 123.0, 120.8, 116.2, 115.1, 109.8, 62.1, 55.5, 52.6. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{19}H_{15}NO_4Na$, 344.0893; found, 344.0893.

Methyl 7-(*tert*-butyl)-4-oxo-4,5-dihydrobenzo[4,5]azepino[3,2,1-*hi*]indole-5-carboxylate **(4k):** 93 mg (89%); white solid, mp 167-168 °C; Purification (Petroleum ether/ethyl acetate = 10/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 3.7 Hz, 1H), 7.71 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.67 (d, *J* = 8.2 Hz, 1H), 7.63 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.55 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.45 (d, *J* = 2.0 Hz, 1H), 7.39 (t, *J* = 7.7 Hz, 1H), 6.76 (d, *J* = 3.7 Hz, 1H), 5.07 (s, 1H), 3.26 (s, 3H), 1.39 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.5, 165.2, 151.9, 132.8, 131.7, 131.6, 129.2, 129.2, 128.4, 127.0, 126.3, 125.6, 124.2, 123.2, 121.2, 109.7, 62.5, 52.6, 34.7, 31.3. HRMS (ESI) m/z: $[M+H]^+$ Calcd for$C_{22}H_{22}NO_3$, 348.1594; found, 348.1589.

Methyl 7-(diphenylamino)-4-oxo-4,5-dihydrobenzo[4,5]azepino[3,2,1-*hi*]indole-5-carboxylat e **(4l):** 116 mg (84%); white solid, mp 198-199 °C; Purification (Petroleum ether/ethyl acetate = 10/1).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 3.7 Hz, 1H), 7.65 (d, *J* = 7.7 Hz, 1H), 7.60 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.56 (d, *J* = 8.6 Hz, 1H), 7.37 (t, *J* = 7.7 Hz, 1H), 7.31 (td, *J* = 8.5, 7.2 Hz, 4H), 7.21 – 7.15 (m, 5H), 7.13 – 7.07 (m, 3H), 6.75 (d, *J* = 3.7 Hz, 1H), 4.84 (s, 1H), 3.26 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.3, 164.9, 148.4, 147.1, 131.7, 131.3, 130.4, 130.3, 129.5, 128.7, 127.0, 125.5, 125.2, 124.3, 124.2, 123.8, 123.0, 122.6, 120.8, 109.8, 62.1, 52.6. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{30}H_{23}N_2O_3$, 459.1698; found, 459.1698. It was crystallized from cyclohexane/dichloromethane.

Methyl 4-oxo-7-(trimethylsilyl)-4,5-dihydrobenzo[4,5]azepino[3,2,1-*hi*]indole-5-carboxylate **(4m):** 82 mg (75%); white solid, mp 153-154 °C; Purification (Petroleum ether/ethyl acetate = 8/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 3.7 Hz, 1H), 7.76 – 7.71 (m, 2H), 7.69 – 7.64 (m, 2H), 7.59 (d, *J* = 0.8 Hz, 1H), 7.41 (t, *J* = 7.7 Hz, 1H), 6.77 (d, *J* = 3.7 Hz, 1H), 5.12 (s, 1H), 3.26 (s, 3H), 0.35 (t, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.4, 165.2, 141.4, 136.5, 135.9, 133.9, 131.8, 131.6, 128.8, 128.6, 127.1, 125.7, 124.2, 123.4, 121.6, 109.7, 62.3, 52.6, -1.2. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{21}H_{21}NO_3SiNa$, 386.1183; found, 386.1183. It was crystallized from cyclohexane/dichloromethane.

Methyl 7-chloro-4-oxo-4,5-dihydrobenzo[4,5]azepino[3,2,1-*hi*]indole-5-carboxylate **(4n):** 83 mg (85%); white solid, mp 165-166 °C; Purification (Petroleum ether/ethyl acetate = 10/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 3.7 Hz, 1H), 7.70– 7.64 (m, 3H), 7.54 – 7.46 (m, 2H), 7.40 (t, *J* = 7.7 Hz, 1H), 6.77 (d, *J* = 3.7 Hz, 1H), 5.00 (s, 1H), 3.27 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.7, 164.4, 134.5, 134.2, 131.9, 131.4, 131.2, 130.9, 130.7, 129.1, 127.2, 124.5, 124.3, 123.4, 121.9, 109.9, 61.5, 52.8. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{12}ClNO_3Na$, 348.0398; found, 348.0398.

Methyl 7-formyl-4-oxo-4,5-dihydrobenzo[4,5]azepino[3,2,1-*hi*]indole-5-carboxylate **(4o):** 89 mg (93%); white solid, mp 222-223 °C; Purification (Petroleum ether/ethyl acetate = 3/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.11 (s, 1H), 8.04 – 7.99 (m, 2H), 7.92 – 7.88 (m,

2H), 7.77 (dt, *J* = 7.8, 0.6 Hz, 1H), 7.73 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 1H), 6.80 (d, *J* = 3.7 Hz, 1H), 5.19 (s, 1H), 3.27 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 191.1, 166.7, 164.3, 141.5, 135.9, 133.1, 132.1, 131.7, 130.4, 130.3, 129.6, 127.4, 124.4, 124.1, 122.9, 109.9, 61.8, 52.9. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{19}H_{13}NO_4Na$, 342.0737; found, 342.0731. It was crystallized from cyclohexane/dichloromethane.

Methyl 7-cyano-4-oxo-4,5-dihydrobenzo[4,5]azepino[3,2,1-*hi*]indole-5-carboxylate **(4p):** 71 mg (75%); white solid, mp 160-161 °C; Purification (Petroleum ether/ethyl acetate = 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 3.7 Hz, 1H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.82 – 7.78 (m, 2H), 7.76 – 7.71 (m, 2H), 7.45 (t, *J* = 7.7 Hz, 1H), 6.80 (d, *J* = 3.7 Hz, 1H), 5.09 (s, 1H), 3.28 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 166.3, 164.0, 140.3, 135.0, 132.2, 132.2, 131.7, 130.6, 130.3, 127.4, 124.54, 124.51, 124.0, 123.2, 118.0, 112.3, 110.0, 61.4, 53.0. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{19}H_{12}N_2O_3Na$, 339.0740; found, 339.0740.

Methyl 7-acetyl-4-oxo-4,5-dihydrobenzo[4,5]azepino[3,2,1-*hi*]indole-5-carboxylate **(4q):** 71 mg (71%); white solid, mp 149-150 °C; Purification (Petroleum ether/ethyl acetate = 3/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 – 8.06 (m, 2H), 7.88 (d, *J* = 3.7 Hz, 1H), 7.84 – 7.81 (m, 1H), 7.75 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.71 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.43 (tt, *J* = 7.7, 0.6 Hz, 1H), 6.78 (dd, *J* = 3.7 Hz, 1H), 5.17 (s, 1H), 3.26 (s, 3H), 2.68 (t, *J* = 0.6 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 197.0, 166.9, 164.6,

140.2, 136.7, 132.0, 131.7, 131.7, 129.9, 129.9, 128.7, 127.3, 124.6, 124.4, 124.0, 122.7, 109.9, 77.1, 62.0, 52.8, 26.8. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{15}NO_4Na$, 356.0893; found, 356.0888. It was crystallized from cyclohexane/dichloromethane.

Dimethyl 4-oxo-4,5-dihydrobenzo[4,5]azepino[3,2,1-*hi*]indole-5,7-dicarboxylate **(4r):** 94 mg (90%); white solid, mp 170-171 °C; Purification (Petroleum ether/ethyl acetate = 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 – 8.13 (m, 2H), 7.88 (d, *J* = 3.7 Hz, 1H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.74 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.68 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.41 (td, *J* = 7.7, 0.7 Hz, 1H), 6.77 (dd, *J* = 3.7, 0.7 Hz, 1H), 5.16 (s, 1H), 3.96 (d, *J* = 0.7 Hz, 3H), 3.24 (s, 3H).^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.8, 166.2, 164.5, 139.9, 132.8, 131.9, 131.6, 129.9, 129.8, 129.6, 129.6, 127.2, 124.5, 124.3, 123.9, 122.5, 109.7, 61.8, 52.7, 52.3. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{15}NO_5Na$, 372.0842; found, 372.0842. It was crystallized from cyclohexane/dichloromethane.

Methyl 4-oxo-7-(trifluoromethyl)-4,5-dihydrobenzo[4,5]azepino[3,2,1-*hi*]indole-5-carboxylate **(4s):** 83 mg (77%); white solid, mp 149-151 °C; Purification (Petroleum ether/ethyl acetate = 10/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 3.7 Hz, 1H), 7.86 (d, *J* = 8.1 Hz, 1H), 7.79 – 7.70 (m, 4H), 7.44 (t, *J* = 7.7 Hz, 1H), 6.79 (d, *J* = 3.7 Hz, 1H), 5.13 (s, 1H), 3.27 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.6, 164.3, 139.2, 132.0, 131.7, 130.5 (q, J = 33.0 Hz), 130.3, 130.0, 128.4 (q, J = 3.0 Hz), 127.3, 126.5 (q, J = 271 Hz), 125.7 (q, J = 4.0 Hz), 124.4, 124.3, 123.9, 122.6, 109.9, 61.8, 52.8.

^{19}F NMR (376 MHz, $CDCl_3$) δ-62.4 (s, 3F). HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{19}H_{12}F_3NO_3Na$, 382.0661; found, 382.0661. It was crystallized from cyclohexane/dichloromethane.

Methyl 7-nitro-4-oxo-4,5-dihydrobenzo[4,5]azepino[3,2,1-*hi*]indole-5-carboxylate **(4t):** 57 mg (56%); white solid, mp 177-178 °C; Purification (Petroleum ether/ethyl acetate = 5/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 2.4 Hz, 1H), 8.35 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.92 – 7.87 (m, 2H), 7.76 (d, *J* = 7.7 Hz, 2H), 7.46 (dd, *J* = 8.0, 7.5 Hz, 1H), 6.81 (d, *J* = 3.7 Hz, 1H), 5.20 (s, 1H), 3.28 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.2, 163.8, 147.3, 142.1, 132.2, 131.6, 130.6, 130.5, 127.5, 126.6, 124.6, 124.3, 123.7, 123.6, 123.4, 110.0, 61.5, 53.0. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{12}N_2O_5Na$, 359.0638; found, 359.0637.

Methyl 4-oxo-4,5-dihydronaphtho[2',3':4,5]azepino[3,2,1-*hi*]indole-5-carboxylate **(4u):** 101 mg (98%); white solid, mp 169-170 °C; Purification (Petroleum ether/ethyl acetate = 10/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 8.01 – 7.85 (m, 5H), 7.67 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.59 – 7.52 (m, 2H), 7.44 (t, *J* = 7.7 Hz, 1H), 6.78 (d, *J* = 3.7 Hz, 1H), 5.25 (s, 1H), 3.27 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.5, 165.2, 133.3, 133.2, 132.8, 132.1, 131.9, 130.7, 129.2, 128.14, 128.07, 127.5, 127.14, 127.12, 126.9, 126.0, 124.4, 123.5, 121.5, 109.8, 62.4, 52.7. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{22}H_{15}NO_3Na$, 364.0944; found, 364.0944. It was crystallized from cyclohexane/dichloromethane.

Methyl7-(1*H*-indol-7-yl)-4-oxo-4,5-dihydrobenzo[4,5]azepino[3,2,1-*hi*]indole-5-carboxylate **(4v):** 61mg (50%); white solid, mp 208-209 °C; Purification (Petroleum ether/ethyl acetate = 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 7.90 (d, *J* = 3.8 Hz, 1H), 7.87 (d, *J* = 8.1 Hz, 1H), 7.81 – 7.75 (m, 3H), 7.69 (dq, *J* = 7.7, 1.3 Hz, 2H), 7.45 (t, *J* = 7.7 Hz, 1H), 7.31 – 7.22 (m, 3H), 6.80 (d, *J* = 3.7 Hz, 1H), 6.66 (dd, *J* = 3.2, 2.0 Hz, 1H), 5.14 (s, 1H), 3.29 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.2, 164.9, 139.8, 134.6, 133.6, 131.9, 131.6, 131.1, 130.3, 130.3, 128.8, 128.5, 127.2, 125.3, 124.6, 124.4, 124.0, 123.5, 122.0, 121.7, 120.6, 120.4, 109.9, 103.2, 62.1, 52.8. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{26}H_{18}N_2O_3Na$, 429.1210; found, 429.1202.

Methyl 7-hydroxy-4-oxo-4,5-dihydrobenzo[4,5]azepino[3,2,1-*hi*]indole-5-carboxylate **(4w):**17 mg (18%); white solid, mp 124-125 °C; Purification (Petroleum ether/ethyl acetate = 2/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 3.7 Hz, 1H), 7.65 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.63 – 7.58 (m, 2H), 7.38 (t, *J* = 7.7 Hz, 1H), 6.99 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.94 (d, *J* = 2.6 Hz, 1H), 6.76 (d, *J* = 3.7 Hz, 1H), 5.84 (s, 1H), 4.96 (s, 1H), 3.28 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.3, 165.0, 156.4, 131.7, 131.3, 131.1, 130.8, 128.2, 127.0, 125.5, 124.3, 123.1, 120.9, 118.0, 116.6, 110.0, 61.8, 52.8. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{13}NO_4Na$, 330.0737; found, 330.0731.

Ethyl 4-oxo-4,5-dihydrobenzo[4,5]azepino[3,2,1-*hi*]indole-5-carboxylate **(4x):** 51 mg (55%); white solid, mp 119-120 °C; Purification (Petroleum ether/ethyl acetate = 10/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 3.7 Hz, 1H), 7.75 – 7.71 (m, 2H), 7.65 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.55 – 7.46 (m, 3H), 7.40 (t, *J* = 7.7 Hz, 1H), 6.77 (d, *J*

= 3.7 Hz, 1H), 5.05 (s, 1H), 3.82 – 3.74 (m, 1H), 3.72 – 3.64 (m, 1H), 0.60 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.7, 165.3, 135.6, 131.9, 131.7, 131.6, 129.9, 129.5, 129.0, 128.6, 127.2, 125.9, 124.2, 123.6, 121.5, 109.6, 62.3, 61.7, 13.4. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{19}H_{15}NO_3Na$, 328.0944; found, 328.0944. It was crystallized from cyclohexane/dichloromethane.

Diisopropyl 2-(2-(1*H*-indol-7-yl)phenyl)malonate **(3y):** 114 mg (100%); white solid, mp 84-85 °C; Purification (Petroleum ether/ethyl acetate = 10/1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.72 – 7.65 (m, 2H), 7.50 (td, *J* = 7.5, 1.8 Hz, 1H), 7.45 (td, *J* = 7.4, 1.5 Hz, 1H), 7.42 – 7.38 (m, 1H), 7.21 (dd, *J* = 8.0, 7.2 Hz, 1H), 7.17 (dd, *J* = 3.2, 2.5 Hz, 1H), 7.08 (dd, *J* = 7.2, 1.1 Hz, 1H), 6.62 (dd, *J* = 3.2, 2.0 Hz, 1H), 5.07 – 4.94 (m, 2H), 4.62 (s, 1H), 1.24 (dd, *J* = 6.3, 4.3 Hz, 6H), 1.18 (d, *J* = 6.3 Hz, 3H), 1.11 (d, *J* = 6.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.0, 167.8, 139.0, 134.6, 132.2, 130.7, 129.4, 128.3, 127.8, 124.5, 123.7, 123.0, 120.2, 119.9, 102.7, 69.6, 69.2, 54.7, 21.5. HRMS (ESI) m/z: $[M+Na]^+$Calcd for $C_{23}H_{25}NO_4Na$, 402.1676; found, 402.1676.

Procedure for Synthesis of Isopropyl 4-oxo-4,5-dihydrobenzo[4,5]azepino[3,2,1-*hi*]indole-5-carboxylate (4y): Compound **3y** (0.3 mmol) and KOH (0.09 mmol, 30 mol%) were added in an oven-dried sealing tube, then CH_2Cl_2 was added. The reaction mixture was stirred at room temperature for 2 h and then filtered through a plug of silica and washed with EtOAc. The filtrate was concentrated under vacuum and purified by flash column chromatography (petroleum ether/EtOAc = 2/1) to give product **4y** as a white solid.

Isopropyl 4-oxo-4,5-dihydrobenzo[4,5]azepino[3,2,1-*hi*]indole-5-carboxylate

(4y): 48 mg (50%); white solid, mp 135-136 °C; Purification (Petroleum ether/ethyl acetate = 10/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 3.2 Hz, 1H), 7.76 – 7.69 (m, 2H), 7.64 (d, *J* = 7.4 Hz, 1H), 7.55 – 7.45 (m, 3H), 7.39 (td, *J* = 7.7, 2.2 Hz, 1H), 6.76 (t, *J* = 3.1 Hz, 1H), 5.02 (s, 1H), 4.59 – 4.49 (m, 1H), 0.87 (dd, *J* = 6.1, 2.2 Hz, 3H), 0.43 (dd, *J* = 6.1, 2.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.2, 165.5, 135.6, 132.0, 131.7, 131.7, 130.2, 129.5, 128.9, 128.6, 127.3, 126.0, 124.2, 123.6, 121.4, 109.5, 105.0, 69.6, 62.5, 21.1, 20.6. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{17}NO_3Na$, 342.1101; found, 342.1110.

Competition Experiments Between 1j and 1t: The reaction of 7-(4-methoxyphenyl)-1*H*-indole **1j** (22.3 mg, 0.1 mmol), 7-(nitrophenyl)-1*H*-indole **1t** (23.8 mg, 0.1 mmol) was run following the general procedure. After 12 h, the reaction mixture was subjected to silica gel column chromatography [eluting with petroleum ether/ethyl acetate=10:1] to provide the product including **4j** (24.3 mg, 75.8% yield) and **4t** (8.1 mg, 24.2% yield).

Experiments for intermolecular kinetic isotope effects: The reaction of 7-phenyl-1*H*-indole **1a** (19.3 mg, 0.1 mmol), D5-7-phenyl-1*H*-indole **1a-D5** (19.8 mg, 0.1 mmol) was run for 2 h following the general procedure. After the reaction the crude reaction mixture was subjected to silica gel column chromatography [eluting with petroleum ether/ethyl acetate=10:1] to provide the product including **4a** and **4a-D4** (16.8 mg, ~28% yield). This mixture was analyzed by ^{1}H NMR to give the relative ration of two isomers.

4a-D4: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 3.7 Hz, 1H), 7.73 (d, J = 7.8

Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.41 (td, J = 7.8, 0.5 Hz, 1H), 6.77 (d, J = 3.7 Hz, 1H), 5.08 (s, 1H), 3.26 (s, 3H).

Procedure for Synthesis of Benzo[4,5]azepino[3,2,1-*hi*]indol-4(5*H*)-one (5a): Compound **4a** (291.4 mg, 1 mmol) was dissolved in aqueous KOH (5%, 10 mL),and the mixture was stirred at 20 °C for 2 h. HCl (10%) was then added dropwise at 0 °C until pH 2.5 was reached. The resulting mixture was heated at 70 °C for 2 h, basified with NH_4OH (1 mL) and extracted with CH_2Cl_2 (30 mL). The combined organic layers were filtered, and the solvents were evaporated in vacuum to yield an oily residue that was purified by flash-chromatograph on silica gel [PE/EA (10:1-20:1)]. This afforded benzo[4,5]azepino[3,2,1-*hi*]indol-4(5*H*)-one **5a** 140 mg, 0.61 mmol, 60% yield.

Benzo[4,5]azepino[3,2,1-*hi*]indol-4(5*H*)-one **(5a):** 140 mg (60%); white oil; Purification (Petroleum ether/ethyl acetate = 15/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 3.7 Hz, 1H), 7.76 (dd, 1H), 7.70 – 7.66 (m, 2H), 7.47 – 7.41 (m, 4H), 6.73 (d, *J* = 3.8 Hz, 1H), 3.93 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.0, 135.9, 132.7, 132.1, 130.3, 130.1, 128.9, 128.5, 128.0, 126.3, 126.2, 123.9, 123.5, 121.3, 109.0, 45.5. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{16}H_{12}NO$, 234.0913; found, 234.0926.

Procedure for Synthesis of (*E*)-Methyl 1-(3-ethoxy-3-oxoprop-1-en-1-yl)-4-oxo-4,5-dihydrobenzo[4,5]azepino[3,2,1-*hi*]indole-5-carboxylate (6a): Under argon atmosphere, **4a** (0.3 mmol), ethyl acrylate (0.36 mmol, 1.2 equiv.), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 5 mol%), AgOAc (100 mg,

0.6 mmol, 2 equiv.), and acetone (2 mL) were placed in a 25 mL seal tube. The reaction solution was degassed twice and refilled with Ar. The mixture was heated in an oil bath at 80 °C for 24 h and then cooled to room temperature. The crude reaction mixture was diluted with EtOAc to 5 mL, filtered through a celite pad, and then washed with 10 mL EtOAc. The volatiles were removed under reduced pressure, and the residue was subjected to silica gel column chromatography [eluting with petroleum ether/ethyl acetate = 4/1] to afford (*E*)-methyl 1-(3-ethoxy-3-oxoprop-1-en-1-yl)-4-oxo-4,5-dihydrobenzo[4,5]azepino[3,2,1-*hi*]indole-5-carboxylate **6a** (93.46 mg, 0.24 mmol) in 80% yield.

(*E*)-1-(3-Ethoxy-3-oxoprop-1-en-1-yl)-4-oxo-4,5-dihydrobenzo[4,5]azepino[3,2,1-*hi*]indole-5-carboxylate **(6a):** 94 mg (80%); white oil; Purification (Petroleum ether/ethyl acetate = 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.92 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.85 (dd, *J* = 16.2 Hz, 1H), 7.78 (d, *J* = 7.7 Hz, 1H), 7.72 (d, *J* = 7.4 Hz, 1H), 7.56 – 7.47 (m, 4H), 6.60 (d, *J* = 16.2 Hz, 1H), 5.09 (s, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 3.26 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.0, 164.6, 135.4, 135.3, 132.5, 131.6, 129.8, 129.3, 129.2, 129.2, 128.9, 128.9, 126.0, 124.9, 124.5, 120.8, 119.1, 118.9, 61.8, 60.6, 52.8, 14.3. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{23}H_{19}NO_5Na$, 412.1155; found, 412.1148.

Gram-Scale Experiment of 4a: Under argon atmosphere, 7-phenyl-1*H*-indoles **1a** (6 mmol), dimethyl 2-diazomalonate **2a** (9 mmol, 1.5 equiv.), $[Cp^*RhCl_2]_2$ (94 mg, 0.15 mmol, 2.5 mol%), AgOAc (150 mg, 0.9 mmol, 15 mol%), DBU (270 μL, 1.8 mmol, 30 mmol%) and EtOAc (35 mL) were placed in a 100 mL seal tube. The

mixture was heated in oil bath at 60 °C for 24 h and then cooled to room temperature. The crude reaction mixture was diluted with EtOAc to 50 mL, filtered through a celite pad, and then washed with 20 mL EtOAc. The volatiles were removed under reduced pressure, and the residue was subjected to silica gel column chromatography [eluting with petroleum ether/ethyl acetate] to afford the corresponding product **4a** (1.55 g, 89% yield).

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

^{1}H and ^{13}CNMR spectra of all compounds and single crystal X-ray structure (PDF)

Crystal data for **3a**, **4a**, **4b**, **4c**, **4e**, **4l**, **4m**, **4p**, **4q**, **4r**, **4s**, **4u**, **4x** (CIF)

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