ACS OMEGA

http://pubs.acs.org/journal/acsodf

Article

Synthesis of Functionalized Tetrahydroquinoline Containing Indole Scaffold via Chemoselective Annulation of Aza-*ortho*-quinone Methide Precursor

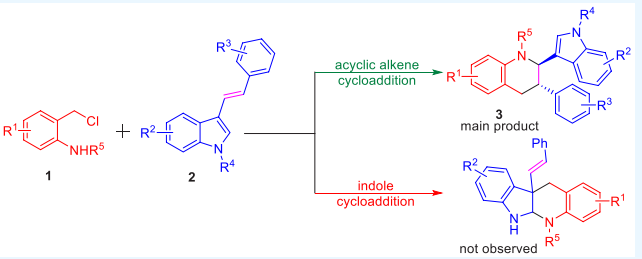
Xiaoke Zhang,* Qianlu Xing, Zhengxing Gou, Song Gan, Wenjuan Wang, Ziwei Li, Huawu Shao,* and Chaoyong Wang*

Cite This: *ACS Omega* 2023, 8, 22352−22360

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: The chemoselective annulation of aza-*ortho*-quinone methide generated by in situ *o*-chloromethyl sulfonamide has been achieved with bifunctional acyclic olefin. This efficient approach provides access to the diastereoselective synthesis of functionalized tetrahydroquinoline derivatives containing indole scaffolds through the inverse-electron-demand aza-Diels−Alder reaction under mild reaction conditions with excellent results (up to 93% yield, > 20:1 dr). Moreover, this article realized the cyclization of α-halogeno hydrazone with electron-deficient alkene affording the tetrahydropyridazine derivatives, which had never been reported.

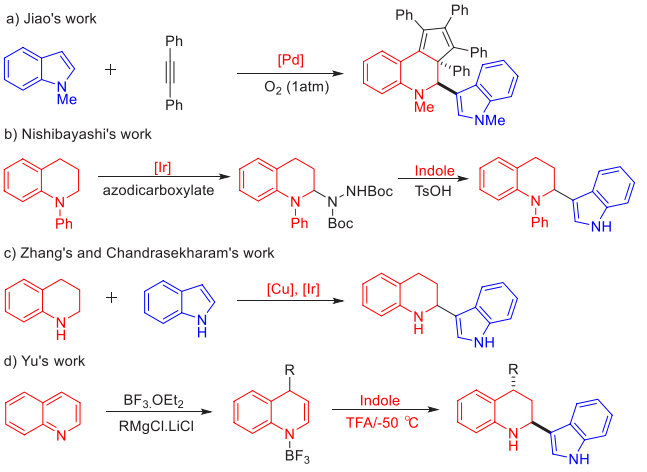


INTRODUCTION

Recent research indicated *N*-biheteroarenes play an important role in dyes and pharmaceuticals, such as antibacterial agent 2-(1*H*-indol-3-yl)tetrahydroquinoline.[1] Tetrahydroquinoline and indole skeleton widely exist in the core structure of the natural product and exhibits a broad spectrum of biological activities, respectively.[2] Therefore, it is of great value to construct the tetrahydroquinoline-indole linked heterobiarene framework for the discovery of functional and pharmaceutically active molecules. To date, these methods for the synthesis of tetrahydroquinoline containing indole scaffold are very limited. An early example, Jiao's group developed a selective ring-expansion reaction mediated by the $Pd(OAc)_2$ providing the polysubstituted tetrahydroquinoline-indole scaffold (Scheme 1a).[3] In 2012, the C−H amination of tetrahydroquinoline was contributed by Nishibayashi and co-workers affording biheteroarenes with the assistance of a visible-light-photoredox catalyst (Scheme 1b).[4] Later, Zhang and Chandrasekharam's group disclosed a Cu/Ir-catalyzed direct α-functionalization strategy through the dehydrogenative cross $C(sp^3)$-$C(sp^2)$ coupling of tetrahydroquinolines and indoles (Scheme 1c).[5] Recently, the dearomative double nucleophilic addition to quinolines accessing tetrahydroquinoline was described by Yu's group (Scheme 1d).[6] Although some efficient strategies have been established, it limited their application using a metal catalyst, oxidation, or harsh reaction condition. Thus, it is still highly desirable to exploit a mild, metal-free, and easy-to-operate method for constructing the tetrahydroquinoline skeleton bearing indole.

Aza-*ortho*-quinone methides (aza-*o*-QMs) generated in situ via the *o*-chloromethyl sulfonamide were widely employed as the four atoms building blocks for the construction of N-containing heterocyclic compounds through [4 + *n*] annulation reaction.[7−10] Especially, the [4 + 2] cycloaddition reaction attracted extensive attention since the Diels−Alder reaction of aza-*o*-QMs with C2 synthons has been disclosed by

Scheme 1. Synthesis of Tetrahydroquinoline

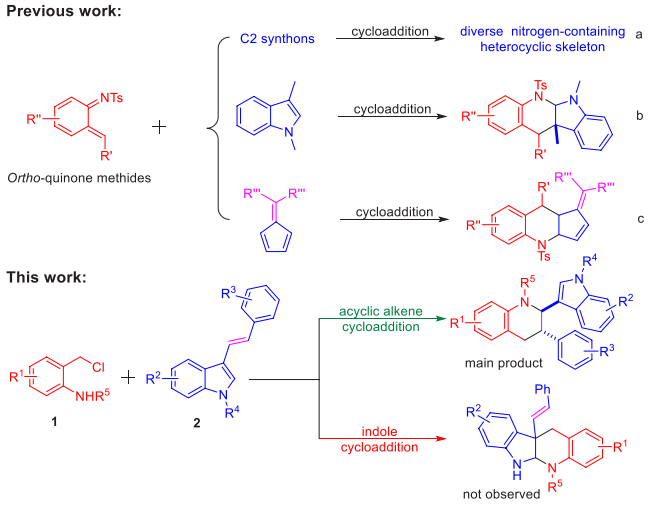


Received: November 1, 2022
Accepted: February 21, 2023
Published: June 13, 2023

https://doi.org/10.1021/acsomega.2c07036
ACS Omega 2023, 8, 22352−22360

Corey's group.[11] In 2019, Liu's group discovered the cycloaddition reaction between 1,3,5-triazinane and *o*-chloromethyl sulfonamide could form various tetrahydroquinazoline derivatives with the assistance of the base.[12] Besides, much effort has been devoted to developing the cycloaddition of aza-*o*-QMs with a cyclic alkene, such as furan, azlactone, bicyclic alkene oxabenzonorbornene, and [60] fullerene affording diverse quinoline scaffold through hetero-Diels–Alder reaction (Scheme 2a).[13−15] Moreover, You's group reported a concise

Scheme 2. [4 + 2] Annulation of Aza-*ortho*-quinone Methides

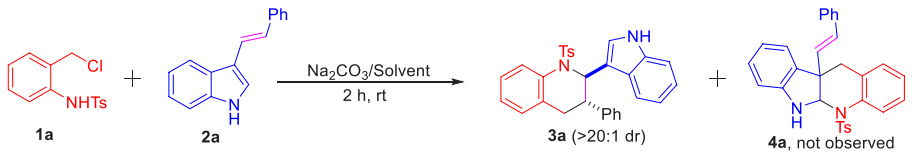


synthesis of tetrahydro-5*H*-indolo[2,3-*b*]quinoline using *o*-chloromethyl sulfonamide and 1,3-dimethyl-1*H*-indole as the substances (Scheme 2b).[16] It is worth noting that the cycloaddition product of acyclic olefin was not detected, while the substrate contains acyclic olefin and cyclic olefin functional groups (Scheme 2c).[17] Furthermore, because indole has excellent reactivity,[16,18] there is no example of the chemoselective intermolecular [4 + 2] annulation of aza-*ortho*-quinone methide with 1,2 disubstituted acyclic olefin in the presence of acyclic olefin and indole. Achievement of such a transformation is particularly challenging, because of (1) the potential competing dimerization of the aza-*o*-QMs and self-nucleophilic addition reaction;[14b,19] (2) it may suppress the occurrence of this transformation that indole could react with aza-*o*-QMs;[16,18] (3) compared with acyclic olefin, cyclic olefins have priority reactivity.[17,18] In view of our continued interest in the annulation reaction of aza-*ortho*-quinone methides,[7c,9e,19] we envisioned the chemoselective annulation of aza-*ortho*-quinone methide **1** with 3-vinylindoles **2**[20] would occur, which could provide a mild and metal-free method to form the functionalized tetrahydroquinoline containing indole framework.

RESULTS AND DISCUSSION

With these considerations in mind, we began our investigation using *o*-chloromethyl sulfonamide **1a** as the four-atom building blocks and bifunctional acyclic olefin **2a** as the C2 synthon under the basic conditions to screen effective parameters. The initial experiment was performed in the presence of KOH (0.2 mmol), **1a** (0.15 mmol), and **2a** (0.1 mmol) in dichloromethane (DCM) at room temperature. The corresponding [4 + 2] annulation product **3a** was obtained in 48% isolated yield (Table 1, entry 1). The structure of **3a** was identified through NMR analysis and confirmed by X-ray crystallographic analysis.[21] Interestingly, the cycloaddition product **4a** between indole and aza-*o*-QMs was not obtained, which indicated the

Table 1. Screening of Optimal Reaction Conditions[a]



entry	base	solvent	yield of **3a** (%)[b]
1	KOH	DCM	48
2	NaOH	DCM	50
3	KO^{t}Bu	DCM	19
4	DBU	DCM	<10
5	TEA	DCM	<5
6	TEDA	DCM	trace
7	K_2CO_3	DCM	71
8	Na_2CO_3	DCM	83
9	Cs_2CO_3	DCM	67
10	$KHCO_3$	DCM	79
11	Na_2CO_3	DCE	42
12	Na_2CO_3	$CHCl_3$	74
13	Na_2CO_3	MeCN	86
14	**Na_2CO_3**	**THF**	90
15[c]	Na_2CO_3	THF	76[c]
16[d]	Na_2CO_3	THF	84[d]

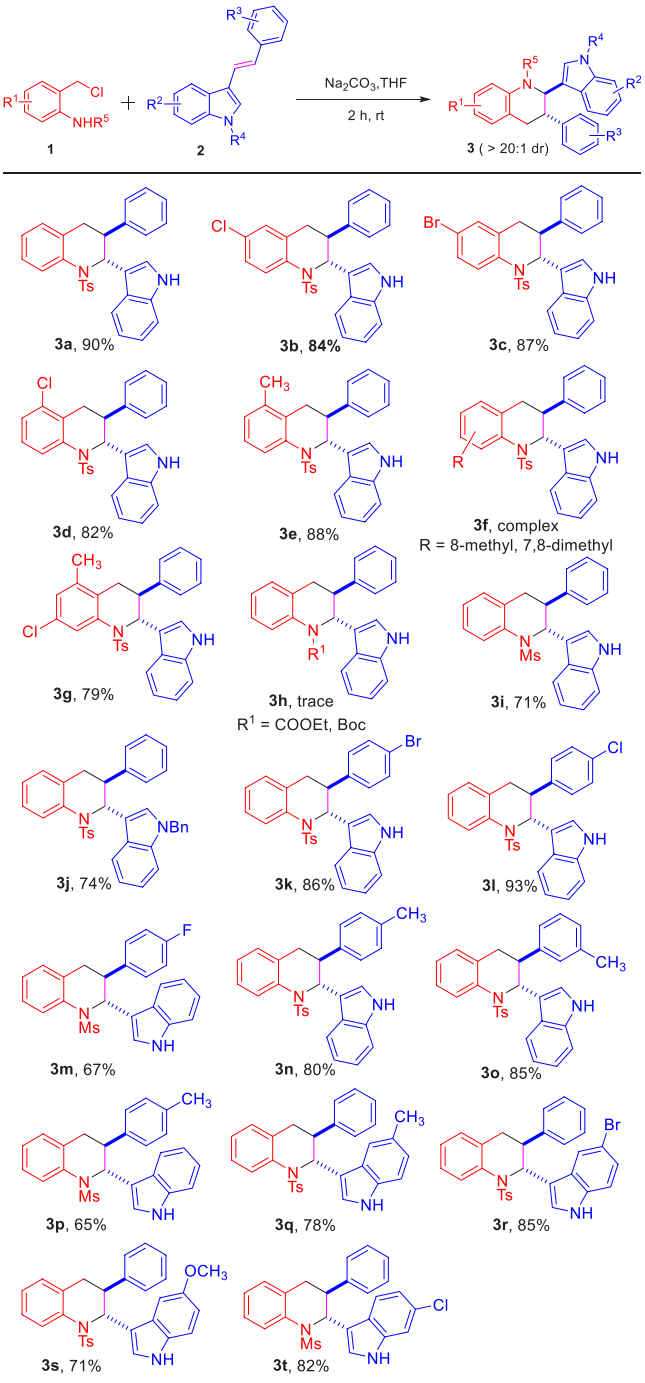
[a]Reaction conditions: **1a** (0.15 mmol), **2a** (0.1 mmol), and base (0.2 mmol) were reacted for 2 h at room temperature. The dr value was determined by the crude ^{1}HNMR analysis. **4a** was not detected in this transformation. [b]Isolated yield based on **2a**. [c]Reaction was performed at 0 °C. [d]Reaction was performed at 66 °C.

https://doi.org/10.1021/acsomega.2c07036
ACS Omega 2023, 8, 22352−22360

reaction has excellent selectivity. As shown in Table 1, screening of various bases was conducted at room temperature (Table 1, entries 1−10). These results indicated: (1) the type of base has a significant impact on this transformation (Table 1, entries 1−3 vs entries 4−6); (2) organic base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), triethylamine (TEA), and 1,4-diazabicyclo[2.2.2]octane (TEDA) could not effectively promote the annulation proceeding (Table 1, entries 4−6); and (3) inorganic bases presented a better performance in yield (Table 1, entries 7−10), and Na_2CO_3 was proven to be the appropriate base for this cycloaddition reaction with 83% yield (Table 1, entry 8). To find the optimal condition, various solvents were screened with Na_2CO_3 as the base. Moderate yields (42%−86%) were provided in dichloroethane (DCE), trichloromethane ($CHCl_3$), and acetonitrile (MeCN) (Table 1, entries 11−13). The best yield (90%) was afforded using THF (Table 1, entry 14). In addition, raising and decreasing the temperature could not further improve the yield of **3a** (Table 1, entries 15−16).

With the aforementioned optimal reaction conditions established, the scope of *o*-chloromethyl sulfonamides **1** and bifunctional acyclic olefin **2** with various substituted groups was examined. As shown in Table 2, the first part of the substrate scope was screened using (*E*)-3-styryl-1*H*-indole **2a** and the aza-*ortho*-quinone methides **1** bearing various substituted phenyl rings as the starting material. A series of *o*-chloromethyl sulfonamides **1** bearing different electron-withdrawing substituents (−Cl, −Br) on the 3- or 4- position of aromatic ring underwent smoothly, offering the [4 + 2] annulation product in good to excellent yield (**3b**, **3c**, and **3d**). Besides, the tetrahydroquinoline derivative **3e** featuring electron-donating groups on the aromatic group was formed in 88% yield under standard conditions. However, when the methyl group was at the 7- and 8-positions on the aromatic ring of **1**, the reaction mixture was so complicated that the expected product could not be obtained. Significantly, starting material **1** containing different electrical properties of the group on the aromatic ring was tolerated in this reaction providing the desired product **3g** in 79% yield. Subsequently, the effect of substrates possessing different protecting groups on this reaction was studied. Due to the strong electron-withdrawing group (−COOEt) and large sterically hindered group (−Boc) could block the cyclization process, **3h** could not be accessed. To our delight, *N*-(2-(chloromethyl) phenyl) methanesulfonamide was compatible with the [4 + 2] cycloaddition reaction affording **3i** in 71% yield with >20:1 dr. Encouraged by these promising results, 3-vinylindole **2** containing different substituents was synthesized to further evaluate the generality of this transformation. First, the substituted group on the nitrogen atom of indole was tested. When switching the hydrogen atom to the benzyl group, the desired compound **3j** could be obtained in 74%. Furthermore, this protocol was amenable to the 3-vinylindole substrates with electron-withdrawing groups, such as −F, −Cl, −Br groups and delivered the corresponding product **3k**−**3m** in good to excellent yields with high diastereoselectivities (67%−93% yields, >20:1 dr). Moreover, when the methyl group is on the 3- or 4- position of the benzene ring, tetrahydroquinoline skeletons bearing indole were achieved as a single diastereoisomer in 80% and 85% yields, respectively (**3n**, **3o**). Compared with **3i**, **3m**, and **3p**, it was found that the [4 + 2] annulation between the mesyloxy-protected *o*-chloromethyl sulfonamide **1** and bifunctional acyclic olefin **2** containing an electron-withdrawing or electron-donating group could proceed smoothly, giving the desired product with excellent diastereoselectivity. In addition, bifunctional olefin **2** with a methyl or Br group at the five positions on the indole ring could also work well under the optimal reaction conditions, providing the cycloaddition products **3q**−**3r** in moderate yields (78%, 85%, >20:1 dr). In addition, the ether functional group was also compatible in this process, giving the cycloaddition product **3s** in 71%. Furthermore, **3t** could be delivered in 82% yield via this conversion using the Cl substituted group at the

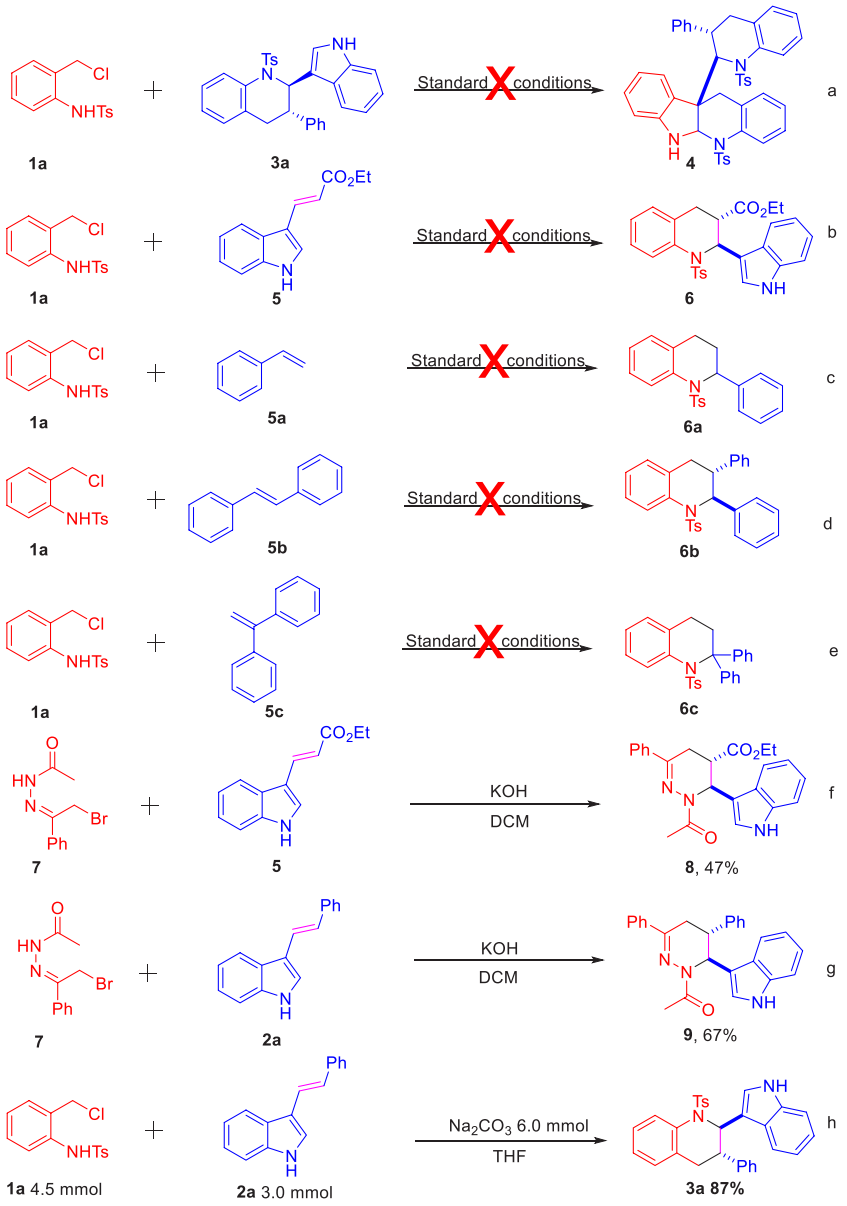
Table 2. Substrate Scope of Reaction[a]



[a]Reaction conditions: **1** (0.15 mmol), **2** (0.1 mmol), and Na_2CO_3 (0.2 mmol) were reacted at room temperature. The dr value was determined by the crude ^{1}HNMR analysis; [b]Isolated yield based on **2**.

https://doi.org/10.1021/acsomega.2c07036
ACS Omega 2023, 8, 22352−22360

Scheme 3. Gram-Scale Reactions and Transformations



six positions on the indole ring and aza-*o*-QMs **1a** as the starting materials.

Encouraged by these excellent results, the cyclization of *o*-chloromethyl sulfonamide **1a** with tetrahydroquinoline scaffold bearing indole **3a** was performed. To our disappointment, the desired product **4** could not be afforded (Scheme 3a). Although various bifunctional olefins, such as ethyl (*E*)-3-(1*H*-indol-3-yl) acrylate **5**, styrene **5a**, (*E*)-1,2-diphenylethene **5b**, and ethene-1,1-diyldibenzene **5c**, were applied in this process, the [4 + 2] cycloaddition product could not be furnished, which indicated bifunctional acyclic olefins containing indole is necessary for this transformation (Scheme 3b−e). Our previous work showed the reactivity of α-halogeno hydrazone **7** is similar to **1a**,[9e] and the [4 + 2] annulation reaction between α-halogeno hydrazone **7** and the electron-deficient bifunctional acyclic olefin **5** has been studied, utilizing DCM as the solvent in the presence of KOH. This process proceeded smoothly affording the tetrahydropyridazine **8** in 47% yield (>20:1 dr) (Scheme 3f), which had never been reported. Moreover, α-halogeno hydrazone was a good C4 building block for the synthesis of 1-(6-(1*H*-indol-3-yl)-3,5-diphenyl-5,6-dihydropyridazin-1(4H)-yl)ethan-1-one **9** (Scheme 3g). To gain insight into the utility of this chemoselective cyclization of aza-*ortho*-quinone methide precursor, a gram-scale experiment was performed under standard conditions. Expected cycloaddition product **3a** was generated in 87% yield with excellent dr (>20:1) (Scheme 3h).

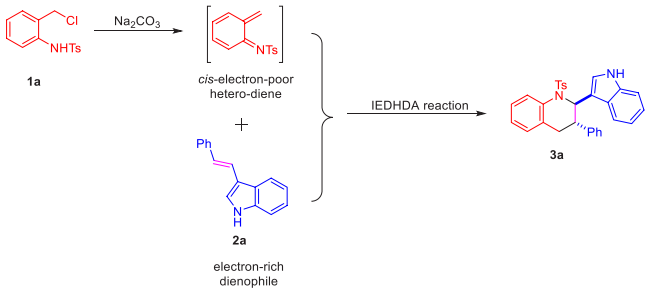
A plausible mechanism was proposed as shown in Scheme 4. The *cis*-electron-poor heterodiene intermediate was generated by **1a**, in situ, under basic conditions. Meanwhile, 3-vinylindole **2a** was employed as the electron-rich dienophile. Then, the inverse-electron-demand hetero-Diels−Alder reaction between **2a** and *cis*-electron-poor heterodiene would occur delivering **3a.**

CONCLUSIONS

In conclusion, we herein developed an inverse-electron-demand hetero-Diels−Alder reaction between aza-*ortho*-

https://doi.org/10.1021/acsomega.2c07036
ACS Omega 2023, 8, 22352−22360

Scheme 4. Proposed Mechanism for Forming Product 3



quinone methide precursor and bifunctional acyclic olefin mediated by an inorganic base. This strategy provided a convenient method to produce the highly functionalized tetrahydroquinoline derivative containing indole scaffold under mild reaction conditions with excellent results (63−91% yields, >20:1 dr). Furthermore, our approach realized the cyclization of α-halogeno hydrazone with electron-deficient alkene which had never been reported.

EXPERIMENTAL SECTION

General Information. The ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer with chloroform-*d* and dimethyl sulfoxide-d_6 as the solvent. High-resolution mass spectra (HRMS) were recorded on an FT-ICR MS spectrometer. Column chromatography was performed on silica gel 200−300 mesh. azoalkene precursors **1** and bifunctional acyclic olefin **2** were synthesized according to literature methods.[9b,20b,22]

General Procedure for the Preparation of Dihydropyrazole 3. To a stirred solution of the aza-*ortho*-quinone methide precursor **1** (0.15 mmol) and Na_2CO_3 (0.2 mmol) in THF (2 mL) at room temperature, bifunctional acyclic olefin **2** (0.1 mmol) was added. After 2 h, bifunctional acyclic olefin **2** disappeared, as indicated by the TLC. The mixture was concentrated in vacuo, and the crude product was purified by flash chromatography eluting with (petroleum ether/ethyl acetate 10:1) to afford the products **3**.

*2-(1H-Indol-3-yl)-3-phenyl-1-tosyl-1,2,3,4-tetrahydroquinoline (**3a**).* Ethyl acetate/petroleum ether = 1:10 as an eluent, yellow solid (43 mg, 90%). MP: 164.4−175.9 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.89 (d, J = 2.6 Hz, 1H), 7.55−7.50 (m, 1H), 7.45−7.29 (m, 6H), 7.28−7.17 (m, 5H), 7.06−6.91 (m, 5H), 6.81 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H), 5.54 (d, J = 9.3 Hz, 1H), 3.31 (ddd, J = 12.4, 9.3, 3.4 Hz, 1H), 2.54−2.50 (m, 1H), 2.37 (s, 3H), 1.92 (dd, J = 14.2, 12.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 143.80, 142.19, 136.51, 136.16, 135.78, 135.35, 129.71, 128.57, 127.74, 127.39, 127.27, 126.89, 126.21, 124.85, 123.83, 120.99, 119.01, 118.56, 115.63, 111.76, 61.41, 50.08, 33.36, 21.07. HRMS (ESI): m/z calcd for $C_{30}H_{26}N_2NaO_2S$ [M + Na]$^+$: 501.1607, found 501.1601.

*6-Chloro-2-(1H-indol-3-yl)-3-phenyl-1-tosyl-1,2,3,4-tetrahydroquinoline (**3b**).* Ethyl acetate/petroleum ether = 1:10 as an eluent, yellow solid (43 mg, 84%). MP: 109.1−121.2 °C. ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.01 (s, 1H), 7.63 (d, J = 8.6 Hz, 1H), 7.44−7.35 (m, 2H), 7.30 (dd, J = 8.8, 2.0 Hz, 2H), 7.23−7.09 (m, 7H), 7.01 (d, J = 8.0 Hz, 1H), 6.93 (ddd, J = 8.0, 6.9, 1.1 Hz, 1H), 6.87−6.80 (m, 2H), 6.78 (d, J = 2.3 Hz, 1H), 5.50 (d, J = 9.1 Hz, 1H), 3.39 (ddd, J = 12.2, 9.1, 3.6 Hz, 1H), 2.50 (dd, J = 14.5, 3.5 Hz, 1H), 2.42 (s, 3H), 2.10 (dd, J = 14.5, 11.5 Hz, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*): δ 143.95, 142.03, 136.78, 136.60, 136.29, 135.47, 131.27, 129.68, 128.68, 127.78, 127.68, 127.64, 127.62, 127.28, 127.20, 124.96, 123.43, 122.01, 119.74, 119.58, 116.61, 111.58, 62.44, 49.45, 33.12, 21.75. HRMS (ESI): m/z calcd for $C_{30}H_{25}ClN_2NaO_2S$ [M + Na]$^+$: 535.1217, found 535.1217.

*6-Bromo-2-(1H-indol-3-yl)-3-phenyl-1-tosyl-1,2,3,4-tetrahydroquinoline (**3c**).* Ethyl acetate/petroleum ether = 1:10 as an eluent, yellow solid (48 mg, 87%). MP: 138.5−142.4 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.97 (d, J = 2.4 Hz, 1H), 7.57 (d, J = 8.6 Hz, 1H), 7.44 (dd, J = 8.6, 2.3 Hz, 1H), 7.39−7.35 (m, 2H), 7.31 (d, J = 8.3 Hz, 1H), 7.27 (d, J = 2.3 Hz, 1H), 7.22−7.16 (m, 5H), 7.13 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 7.03 (d, J = 8.0 Hz, 1H), 6.95 (ddd, J = 8.0, 6.9, 1.0 Hz, 1H), 6.88−6.83 (m, 2H), 6.81 (d, J = 2.5 Hz, 1H), 5.52 (d, J = 9.0 Hz, 1H), 3.44−3.38 (m, 1H), 2.51 (dd, J = 14.7, 3.7 Hz, 1H), 2.42 (s, 3H), 2.14 (dd, J = 14.6, 11.3 Hz, 1H). ^{13}C NMR (100 Hz, Chloroform-*d*) δ 143.94, 142.03, 136.78, 136.71, 136.31, 136.05, 130.62, 130.59, 129.68, 128.70, 127.90, 127.64, 127.32, 127.22, 124.97, 123.39, 122.08, 119.65, 119.15, 116.70, 111.55, 62.34, 49.27, 32.96, 21.76. HRMS (ESI): m/z calcd for $C_{30}H_{25}BrN_2NaO_2S$ [M + Na]$^+$: 579.0712, found 579.0718.

*5-Chloro-2-(1H-indol-3-yl)-3-phenyl-1-tosyl-1,2,3,4-tetrahydroquinoline (**3d**).* Ethyl acetate/petroleum ether = 1:10 as an eluent, yellow solid (42 mg, 82%). MP: 186.8−191.6 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.00 (s, 1H), 7.59 (d, J = 7.4 Hz, 1H), 7.33−7.10 (m, 12H), 6.99−6.87 (m, 3H), 6.79 (d, J = 2.5 Hz, 1H), 5.64 (d, J = 8.4 Hz, 1H), 3.47 (ddd, J = 10.3, 8.4, 4.0 Hz, 1H), 2.97 (dd, J = 15.4, 4.1 Hz, 1H), 2.40 (s, 3H), 2.18 (dd, J = 15.4, 10.4 Hz, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 143.95, 142.18, 138.42, 136.76, 136.44, 132.59, 131.93, 129.64, 128.72, 127.70, 127.66, 127.38, 127.20, 126.32, 125.01, 124.25, 123.38, 122.13, 119.73, 119.65, 116.65, 111.55, 61.91, 48.19, 29.55, 21.75. HRMS (ESI): m/z calcd for $C_{30}H_{25}ClN_2NaO_2S$ [M + Na]$^+$: 535.1217, found 535.1214.

*2-(1H-Indol-3-yl)-5-methyl-3-phenyl-1-tosyl-1,2,3,4-tetrahydroquinoline (**3e**).* Ethyl acetate/petroleum ether = 1:10 as an eluent, yellow solid (44 mg, 88%). MP: 118.9−124.6 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.88 (d, J = 2.7 Hz, 1H), 7.36−7.19 (m, 10H), 7.12−6.97 (m, 5H), 6.91 (d, J = 2.6 Hz, 1H), 6.87−6.81 (m, 1H), 5.61 (d, J = 8.8 Hz, 1H), 3.34 (ddt, J = 11.0, 8.7, 3.8 Hz, 1H), 2.58 (dd, J = 14.8, 3.8 Hz, 1H), 2.35 (s, 3H), 2.17 (s, 3H), 1.85 (dd, J = 14.9, 11.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 143.72, 142.53, 136.47, 136.14, 135.96, 135.00, 133.15, 129.59, 128.58, 127.46, 127.39, 126.99, 126.88, 126.32, 124.89, 123.73, 123.46, 121.04, 119.06, 118.59, 115.68, 111.74, 60.75, 49.00, 29.37, 21.07, 19.05. HRMS (ESI): m/z calcd for $C_{31}H_{28}N_2NaO_2S$ [M + Na]$^+$: 515.1764, found 515.1763.

*7-Chloro-2-(1H-indol-3-yl)-5-methyl-3-phenyl-1-tosyl-1,2,3,4-tetrahydroquinoline (**3g**).* Ethyl acetate/petroleum ether = 1:10 as an eluent, yellow solid (42 mg, 79%). MP: 108.7−119.1 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.92 (s, 1H), 7.63 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.32−7.27 (m, 2H), 7.17−7.09 (m, 4H), 7.01 (d, J = 2.4 Hz, 1H), 6.89 (ddd, J = 8.1, 7.0, 1.0 Hz, 1H), 6.77−6.67 (m, 4H), 5.26 (d, J = 9.8 Hz, 1H), 3.21 (ddd, J = 13.2, 9.7, 3.2 Hz, 1H), 2.49 (s, 3H), 2.31 (dd, J = 14.1, 3.3 Hz, 1H), 2.25 (s, 3H), 2.01 (t, J = 13.7 Hz, 1H). ^{13}C NMR (100 Hz, Chloroform-*d*) δ 144.21, 142.10, 141.53, 141.25, 136.88, 136.58, 134.39, 132.66, 130.08, 129.82, 128.53, 128.10, 127.47, 127.08, 125.09, 125.03, 123.28, 122.08, 119.73, 119.68, 116.50, 111.42, 63.06, 51.23, 34.44, 21.85, 19.63. HRMS (ESI): m/z calcd for $C_{31}H_{27}ClN_2NaO_2S$ [M + Na]$^+$: 5491374, found 5491374.

https://doi.org/10.1021/acsomega.2c07036
ACS Omega 2023, 8, 22352−22360

*2-(1H-Indol-3-yl)-1-(methylsulfonyl)-3-phenyl-1,2,3,4-tetrahydroqui-noline (**3i**).* Ethyl acetate/petroleum ether = 1:10 as an eluent, yellow solid (28 mg, 71%). MP: 129.8−134.7 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.99 (s, 1H), 7.61 (d, *J* = 8.2 Hz, 1H), 7.36−7.15 (m, 11H), 7.02 (ddd, *J* = 8.1, 7.1, 1.0 Hz, 1H), 6.82 (d, *J* = 2.5 Hz, 1H), 5.82 (d, *J* = 7.6 Hz, 1H), 3.62 (td, *J* = 8.2, 4.3 Hz, 1H), 3.18 (dd, *J* = 15.2, 8.7 Hz, 1H), 2.95 (dd, *J* = 15.2, 4.4 Hz, 1H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 142.17, 137.36, 136.74, 131.03, 128.80, 128.64, 127.98, 127.59, 127.20, 124.79, 124.54, 123.68, 122.39, 121.68, 119.92, 119.59, 115.78, 111.64, 61.27, 46.81, 40.28, 32.33. HRMS (ESI): *m*/*z* calcd for $C_{24}H_{22}N_2NaO_2S$ [M + Na]$^+$: 425.1294, found 425.1299.

*2-(1-Benzyl-1H-indol-3-yl)-3-phenyl-1-tosyl-1,2,3,4-tetrahydroquinoline (**3j**).* Ethyl acetate/petroleum ether = 1:10 as an eluent, yellow solid (42 mg, 74%). MP: 164.1−168.7 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.69 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.42−7.38 (m, 2H), 7.34 (td, *J* = 7.8, 1.6 Hz, 1H), 7.25−7.05 (m, 12H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.90 (dd, *J* = 6.9, 1.4 Hz, 3H), 6.81 (dd, *J* = 6.6, 2.9 Hz, 2H), 6.77 (s, 1H), 5.41 (d, *J* = 9.6 Hz, 1H), 5.22−5.09 (m, 2H), 3.35 (ddd, *J* = 12.6, 9.6, 3.3 Hz, 1H), 2.51 (dd, *J* = 14.2, 3.4 Hz, 1H), 2.40 (s, 3H), 2.15−2.07 (m, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 143.57, 142.53, 137.62, 137.02, 136.87, 136.66, 135.76, 129.49, 128.71, 128.49, 127.69, 127.61, 127.58, 127.56, 127.48, 127.28, 127.22, 127.03, 126.53, 126.24, 125.93, 121.69, 120.31, 119.32, 116.03, 110.06, 62.73, 50.59, 49.89, 33.55, 21.73. HRMS (ESI): *m*/*z* calcd for $C_{37}H_{32}N_2NaO_2S$ [M + Na]$^+$: 591.2077, found 591.2070.

*3-(4-Bromophenyl)-2-(1H-indol-3-yl)-1-tosyl-1,2,3,4-tetrahydroquinoline (**3k**).* Ethyl acetate/petroleum ether = 1:10 as an eluent, yellow solid (48 mg, 86%). MP: 168.5−173.2 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.02 (s, 1H), 7.61 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.38−7.02 (m, 12H), 6.98 (ddd, *J* = 8.0, 6.9, 1.0 Hz, 1H), 6.82−6.74 (m, 3H), 5.59 (d, *J* = 8.2 Hz, 1H), 3.47 (ddd, *J* = 10.0, 8.2, 4.2 Hz, 1H), 2.94 (dd, *J* = 15.5, 4.2 Hz, 1H), 2.41 (s, 3H), 2.19 (dd, *J* = 15.5, 10.0 Hz, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ143.93, 141.07, 138.25, 136.65, 136.27, 132.56, 131.65, 131.05, 129.49, 129.25, 127.66, 127.18, 126.18, 124.71, 123.85, 123.35, 122.12, 120.92, 119.63, 119.42, 116.05, 111.51, 61.51, 47.17, 31.92, 21.61. HRMS (ESI): *m*/*z* calcd for $C_{30}H_{25}BrN_2NaO_2S$ [M + Na]$^+$: 579.0712, found 579.0719.

*3-(4-Chlorophenyl)-2-(1H-indol-3-yl)-1-tosyl-1,2,3,4-tetrahydroquinoline (**3l**).* Ethyl acetate/petroleum ether = 1:10 as an eluent, yellow solid (48 mg, 93%). MP: 114.0−123.7 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.99 (s, 1H), 7.61 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.36−7.26 (m, 4H), 7.26−7.06 (m, 8H), 6.98 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.86−6.80 (m, 3H), 5.59 (d, *J* = 8.3 Hz, 1H), 3.48 (ddd, *J* = 10.0, 8.2, 4.1 Hz, 1H), 2.95 (dd, *J* = 15.5, 4.2 Hz, 1H), 2.41 (s, 3H), 2.19 (dd, *J* = 15.5, 10.1 Hz, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 144.06, 140.70, 138.42, 136.79, 136.46, 132.99, 132.70, 131.30, 129.63, 129.04, 128.85, 127.80, 127.33, 126.35, 124.90, 124.05, 123.45, 122.29, 119.80, 119.60, 116.29, 111.63, 61.72, 47.33, 29.35, 21.76. HRMS (ESI): *m*/*z* calcd for $C_{30}H_{25}ClN_2NaO_2S$ [M + Na]$^+$: 535.1217, found 535.1213.

*3-(4-Fluorophenyl)-2-(1H-indol-3-yl)-1-(methylsulfonyl)-1,2,3,4-tetrahydroquinoline (**3m**).* Ethyl acetate/petroleum ether = 1:10 as an eluent, yellow solid (28 mg, 67%). MP: 242.3−244.6 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.14 (s, 1H), 7.53 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.38−7.31 (m, 2H), 7.26−7.16 (m, 6H), 7.07−6.99 (m, 3H), 6.82 (d, *J* = 2.5 Hz, 1H), 5.68 (d, *J* = 8.2 Hz, 1H), 3.54 (dt, *J* = 8.6, 4.4 Hz, 1H), 3.14 (dd, *J* = 14.9, 9.6 Hz, 1H), 2.92 (dd, *J* = 15.0, 4.1 Hz, 1H), 2.51 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 140.57, 137.19, 136.62, 132.78, 131.18, 129.14, 128.60, 128.49, 128.20, 127.58, 124.57, 123.68, 122.34, 121.87, 119.89, 119.39, 115.15, 111.62, 61.13, 47.11, 40.69, 32.67. HRMS (ESI): *m*/*z* calcd for $C_{24}H_{21}FN_2NaO_2S$ [M + Na]$^+$: 443.1200, found 443.1209.

*2-(1H-Indol-3-yl)-3-(p-tolyl)-1-tosyl-1,2,3,4-tetrahydroquinoline (**3n**).* Ethyl acetate/petroleum ether = 1:10 as an eluent, yellow solid (39 mg, 80%). MP: 110.8−114.9 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.00 (d, *J* = 2.5 Hz, 1H), 7.59 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.35−7.08 (m, 10H), 7.01 (d, *J* = 7.8 Hz, 2H), 6.95 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.81−6.76 (m, 3H), 5.60 (d, *J* = 8.5 Hz, 1H), 3.43 (ddd, *J* = 10.5, 8.5, 4.0 Hz, 1H), 2.94 (dd, *J* = 15.3, 4.0 Hz, 1H), 2.40 (s, 3H), 2.30 (s, 3H), 2.13 (dd, *J* = 15.4, 10.6 Hz, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 143.91, 139.17, 138.42, 136.78, 136.76, 136.46, 132.53, 132.21, 129.59, 129.35, 127.61, 127.52, 127.38, 126.35, 125.02, 124.40, 123.46, 122.05, 119.77, 119.57, 116.63, 111.56, 62.00, 47.90, 29.75, 21.74, 21.19. HRMS (ESI): *m*/*z* calcd for $C_{31}H_{28}N_2NaO_2S$ [M + Na]$^+$: 515.1764, found 515.1763.

*(1H-indol-3-yl)-3-(m-tolyl)-1-tosyl-1,2,3,4-tetrahydroquinoline (**3o**).* Ethyl acetate/petroleum ether = 1:10 as an eluent, yellow solid (41 mg, 85%). MP: 109.9−118.6 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.05 (s, 1H), 7.60 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.39−7.35 (m, 2H), 7.33−6.91 (m, 11H), 6.79 (d, *J* = 2.5 Hz, 1H), 6.72 (d, *J* = 1.8 Hz, 1H), 6.69 (dt, *J* = 7.4, 1.6 Hz, 1H), 5.64 (d, *J* = 8.5 Hz, 1H), 3.46−3.40 (m, 1H), 2.97 (dd, *J* = 15.3, 4.1 Hz, 1H), 2.41 (s, 3H), 2.25 (s, 3H), 2.15 (dd, *J* = 15.3, 10.7 Hz, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 143.95, 142.19, 138.44, 138.26, 136.77, 136.51, 132.49, 132.23, 129.64, 128.54, 128.32, 127.92, 127.63, 127.40, 126.41, 124.99, 124.78, 124.51, 123.43, 121.99, 119.72, 119.51, 116.61, 111.56, 61.89, 48.48, 29.87, 21.72, 21.57. HRMS (ESI): *m*/*z* calcd for $C_{31}H_{28}N_2NaO_2S$ [M + Na]$^+$: 515.1764, found 515.1763.

*2-(1H-indol-3-yl)-1-(methylsulfonyl)-3-(p-tolyl)-1,2,3,4-tetrahydroquinoline (**3p**).* Ethyl acetate/petroleum ether = 1:10 as an eluent, yellow solid (27 mg, 65%). MP: 196.4−201.1 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.11 (d, *J* = 2.5 Hz, 1H), 7.58 (d, *J* = 7.7 Hz, 1H), 7.31−7.22 (m, 4H), 7.17−7.12 (m, 2H), 7.07−6.93 (m, 5H), 6.75 (d, *J* = 2.5 Hz, 1H), 5.77 (d, *J* = 7.7 Hz, 1H), 3.55 (ddd, *J* = 8.8, 7.7, 4.3 Hz, 1H), 3.12 (dd, *J* = 15.1, 8.9 Hz, 1H), 2.90 (dd, *J* = 15.2, 4.3 Hz, 1H), 2.41 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 139.14, 137.33, 136.75, 136.72, 131.33, 129.26, 128.73, 127.78, 127.50, 124.77, 124.53, 123.75, 122.24, 121.76, 119.77, 119.54, 115.62, 111.71, 61.35, 46.62, 40.26, 32.59, 21.14. HRMS (ESI): *m*/*z* calcd for $C_{25}H_{24}N_2NaO_2S$ [M + Na]$^+$: 439.1451, found 439.1456.

*2-(5-Methyl-1H-indol-3-yl)-3-phenyl-1-tosyl-1,2,3,4-tetrahydroquinoline (**3q**).* Ethyl acetate/petroleum ether = 1:10 as an eluent, yellow solid (38 mg, 78%). MP: 176.3−183.2 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.84 (s, 1H), 7.60 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.35−7.08 (m, 11H), 6.99−6.92 (m, 3H), 6.82 (d, *J* = 1.7 Hz, 1H), 6.78 (d, *J* = 2.5 Hz, 1H), 5.67 (d, *J* = 8.1 Hz, 1H), 3.47 (ddd, *J* = 10.0, 8.0, 4.2 Hz, 1H), 2.96 (dd, *J* = 15.5, 4.2 Hz, 1H), 2.40 (s, 3H), 2.30 (s, 3H), 2.24 (dd, *J* = 15.5, 10.1 Hz, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ143.88, 142.33, 138.58, 136.61, 135.06, 132.69, 131.70, 129.62, 128.72, 127.79, 127.51, 127.43, 127.18, 126.18,

https://doi.org/10.1021/acsomega.2c07036
ACS Omega 2023, 8, 22352−22360

125.25, 124.07, 123.74, 123.29, 119.56, 116.40, 111.10, 61.80, 48.09, 29.46, 21.74, 21.68. HRMS (ESI): m/z calcd for $C_{31}H_{28}N_2NaO_2S$ $[M + Na]^+$: 515.1764, found 515.1769.

*2-(5-Bromo-1H-indol-3-yl)-3-phenyl-1-tosyl-1,2,3,4-tetrahydroquinoline (**3r**).* Ethyl acetate/petroleum ether = 1:10 as an eluent, yellow solid (47 mg, 85%). MP: 145.5−153.6 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.16 (s, 1H), 7.66 (dd, J = 7.4, 1.9 Hz, 1H), 7.35−7.05 (m, 13H), 6.90−6.86 (m, 2H), 6.75 (d, J = 1.9 Hz, 1H), 5.52 (d, J = 8.8 Hz, 1H), 3.27 (ddd, J = 10.9, 8.7, 3.8 Hz, 1H), 2.95 (dd, J = 15.2, 3.8 Hz, 1H), 2.42 (s, 3H), 2.09 (dd, J = 15.3, 11.0 Hz, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 144.22, 141.79, 138.12, 135.96, 135.25, 132.56, 132.39, 129.73, 128.79, 127.80, 127.72, 127.40, 127.34, 126.70, 126.55, 124.84, 124.67, 124.27, 122.20, 116.64, 112.99, 112.83, 61.95, 49.21, 29.75, 21.76. HRMS (ESI): m/z calcd for $C_{30}H_{25}BrN_2NaO_2S$ $[M + Na]^+$: 579.0712, found 579.0711.

*2-(5-Methoxy-1H-indol-3-yl)-3-phenyl-1-tosyl-1,2,3,4-tetrahydroquinoline (**3s**).* Ethyl acetate/petroleum ether = 1:10 as an eluent, yellow solid (36 mg, 71%). MP: 122.4−127.8 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.84 (s, 1H), 7.73 (dd, J = 8.0, 1.1 Hz, 1H), 7.46−7.41 (m, 2H), 7.37−7.32 (m, 1H), 7.26−7.09 (m, 8H), 6.84 (ddt, J = 5.8, 2.6, 1.3 Hz, 2H), 6.79−6.72 (m, 2H), 6.31 (d, J = 2.4 Hz, 1H), 5.43 (d, J = 9.4 Hz, 1H), 3.48 (s, 3H), 3.35−3.28 (m, 1H), 2.50 (dd, J = 14.1, 3.5 Hz, 1H), 2.42 (s, 3H), 2.10 (dd, J = 14.0, 12.6 Hz, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 153.73, 143.65, 142.66, 137.12, 136.83, 135.99, 131.88, 129.55, 128.59, 127.74, 127.60, 127.58, 127.38, 127.25, 127.09, 126.37, 125.42, 123.77, 117.12, 112.53, 112.12, 101.55, 62.62, 55.52, 50.81, 33.90, 21.74. HRMS (ESI): m/z calcd for $C_{31}H_{28}N_2NaO_3S$ $[M + Na]^+$: 531.1713, found 515.1710.

*2-(6-Chloro-1H-indol-3-yl)-3-phenyl-1-tosyl-1,2,3,4-tetrahydroquinoline (**3t**).* Ethyl acetate/petroleum ether = 1:10 as an eluent, yellow solid (36 mg, 82%). MP: 125.4−130.8 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.00 (s, 1H), 7.63−7.58 (m, 1H), 7.34−7.11 (m, 10H), 6.98 (dd, J = 8.6, 1.9 Hz, 1H), 6.82 (d, J = 2.5 Hz, 1H), 5.76 (d, J = 7.9 Hz, 1H), 3.52 (td, J = 8.5, 4.2 Hz, 1H), 3.17 (dd, J = 15.1, 9.1 Hz, 1H), 2.93 (dd, J = 15.1, 4.2 Hz, 1H), 2.46 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 141.94, 137.16, 137.09, 131.36, 128.78, 128.72, 128.41, 127.93, 127.74, 127.33, 124.84, 124.23, 123.44, 122.06, 120.74, 120.45, 116.32, 111.59, 61.16, 47.49, 40.15, 32.58. HRMS (ESI): m/z calcd for $C_{24}H_{21}ClN_2NaO_2S$ $[M + Na]^+$: 459.0904, found 459.0908.

General Procedure for the Preparation of 8. To a stirred solution of ethyl (*E*)-3-(1*H*-indol-3-yl)acrylate **5** (0.1 mmol) in DCM (2 mL) at room temperature in the presence of KOH (2 mmol), α-halogeno hydrazone **7** (0.15 mmol) was added. After 8 h, **5** disappeared, as indicated by TLC. The mixture was concentrated in vacuo, and the crude product was purified by flash chromatography eluting with (petroleum ether/ethyl acetate 10:1) to afford the product **8** in 47%.

*Ethyl 2-Acetyl-3-(1H-indol-3-yl)-6-phenyl-2,3,4,5-tetrahydropyridazine-4-carboxylate (**8**).* Ethyl acetate/petroleum ether = 1:8 as an eluent, white solid (18 mg, 47%). MP: 191.4−198.3 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.19 (s, 1H), 7.82−7.71 (m, 2H), 7.65 (d, J = 7.7 Hz, 1H), 7.45−7.26 (m, 4H), 7.15 (dtd, J = 18.1, 7.2, 1.2 Hz, 2H), 6.70 (d, J = 2.8 Hz, 1H), 6.61 (s, 1H), 4.29−4.07 (m, 2H), 3.55−3.47 (m, 1H), 3.02 (dt, J = 17.9, 1.7 Hz, 1H), 2.50 (s, 3H), 2.35 (dd, J = 17.8, 6.7 Hz, 1H), 1.31−1.23 (m, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 172.19, 171.78, 145.80, 137.31, 136.93, 129.50, 128.57, 125.59, 124.55, 122.58, 121.83, 119.97, 118.70, 113.81, 111.70, 61.59, 47.11, 39.31, 29.84, 21.68, 14.34. HRMS (ESI): m/z calcd for $C_{23}H_{23}N_3NaO_3$ $[M + Na]^+$: 412.1632, found 412.1637.

General Procedure for the Preparation of 9. To a stirred solution of **2a** (0.1 mmol) in DCM (2 mL) at room temperature in the presence of KOH (2 mmol), α-halogeno hydrazone **7** (0.15 mmol) was added. After 8 h, **2a** disappeared, as indicated by the TLC. The mixture was concentrated in vacuo, and the crude product was purified by flash chromatography eluting with (petroleum ether/ethyl acetate 10:1) to afford the product **9** in 67%.

*1-(6-(1H-Indol-3-yl)-3,5-diphenyl-5,6-dihydropyridazin-1(4H)-yl)ethan-1-one (**9**).* Ethyl acetate/petroleum ether = 1:10 as an eluent, yellow solid (26 mg, 67%). MP: 221.5−227.6 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.27 (s, 1H), 7.85−7.78 (m, 2H), 7.77−7.69 (m, 1H), 7.41 (dd, J = 5.4, 1.9 Hz, 3H), 7.32−7.19 (m, 6H), 7.19−7.11 (m, 2H), 6.70−6.65 (m, 1H), 6.27 (s, 1H), 3.88−3.82 (m, 1H), 2.85 (d, J = 18.1 Hz, 1H), 2.69 (dd, J = 18.3, 7.1 Hz, 1H), 2.48 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 172.62, 146.43, 142.39, 137.38, 136.95, 129.57, 128.95, 128.66, 127.17, 126.94, 125.55, 124.83, 122.38, 121.58, 119.80, 118.78, 115.20, 111.74, 51.03, 38.32, 24.79, 21.78. HRMS (ESI): m/z calcd for $C_{26}H_{23}N_3NaO$ $[M + Na]^+$: 416.1733, found 416.1742.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c07036.

^{1}H, ^{13}C{^{1}H} NMR spectra for all of the products (PDF)

Accession Codes

CCDC 2205697 contains the supplementary crystallographic data for compound **3e**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

■ AUTHOR INFORMATION

Corresponding Authors

Xiaoke Zhang − *Central Laboratory, Chongqing University Fuling Hospital, Chongqing 408000, PR China; Zunyi Medical University, Zunyi, Guizhou 563000, China;* orcid.org/0000-0003-0423-5790; Email: xiaokezhang53@163.com

Huawu Shao − *Natural Products Research Centre, Chengdu Institute of Biology, Chinese Academy of Sciences, Chengdu 610041, China*; Email: shaohw@cib.ac.cn

Chaoyong Wang − *Central Laboratory, Chongqing University Fuling Hospital, Chongqing 408000, PR China*; Email: cqwchy@21cn.com

Authors

Qianlu Xing − *Department of Pediatrics, The Second Affiliated Hospital of Zunyi Medical University, Zunyi, Guizhou 563000, China*

Zhengxing Gou − *Central Laboratory, Chongqing University Fuling Hospital, Chongqing 408000, PR China*

Song Gan − *Zunyi Medical University, Zunyi, Guizhou 563000, China*

Wenjuan Wang − *Zunyi Medical University, Zunyi, Guizhou 563000, China*

Ziwei Li − *Central Laboratory, Chongqing University Fuling Hospital, Chongqing 408000, PR China*

Complete contact information is available at:
https://pubs.acs.org/10.1021/acsomega.2c07036

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for financial support from the Youth Science and Technology Personal Growth Project of the Educational Department of Guizhou Province (KY [2021] 227), the Guizhou Province Science and Technology plan program of China (QKHPTRC [2019]-034) and CK1187-029.

■ REFERENCES

(1) (a) Goebel, G. L.; Hohnen, L.; Borgelt, L.; Hommen, P.; Qiu, X. Q.; Lightfoot, H.; Wu, P. Small molecules with tetrahydroquinoline-containing Povarov scaffolds as inhibitors disrupting the Protein−RNA interaction of LIN28−let-7. *Eur. J. Med. Chem.* **2022**, *228*, 114014. (b) Shen, S. D.; Picci, C.; Ustinova, K.; Benoy, V.; Kutil, Z.; Zhang, G. P.; Tavares, M. T.; Pavlíček, J.; Zimprich, C. A.; Robers, M. B.; BosCh, L. V.; Bařinka, C.; Langley, B.; Kozikowski, A. P. Tetrahydroquinoline-capped histone deacetylase 6 inhibitor SW-101 ameliorates pathological phenotypes in a Charcot−Marie−Tooth type 2A mouse model. *J. Med. Chem.* **2021**, *64* (8), 4810. (c) Yadav, P.; Kumar, A.; Althagafi, I.; Nemaysh, V.; Rai, R.; Pratap, R. The recent development of tetrahydro-quinoline/isoquinoline based compounds as anticancer agents. *Curr. Top. Med. Chem.* **2021**, *21* (17), 1587.

(2) (a) Hoemann, M. Z.; Xie, R. L.; Rossi, R. F.; Meyer, S.; Sidhu, A.; Cuny, G. D.; Hauske, J. R. Potent in vitro methicillin-resistant staphylococcus aureus activity of 2-(1*H*-indol-3-yl) tetrahydroquinoline derivatives. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 129. (b) Zhou, M. X.; Gu, L. B.; Li, W.; Wu, Z. Z. WO 2021050721, 2021. (c) Cuny, G. D.; Hauske, J. R.; Heefner, D. L.; Hoemann, M. Z.; Kumaravel, G.; Melikian-Badalian, A.; Rossi, R. F.; Xie, R. L. WO 2000034265 A2, 2000. (d) Zeng, H. H.; Cao, R.; Zhang, H. B. Combined 3D-QSAR modeling and molecular docking study on quinoline derivatives as inhibitors of P-selectin. *Chem. Biol. Drug. Des.* **2009**, *74*, 596. (e) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. Aryl−aryl bond formation one century after the discovery of the Ullmann reaction. *Chem. Rev.* **2002**, *102* (5), 1359. (f) Li, C. J. Cross-dehydrogenative coupling (CDC): exploring C−C bond formations beyond functional group transformations. *Acc. Chem. Res.* **2009**, *42* (2), 335.

(3) Shi, Z. Z.; Zhang, B.; Cui, Y. X.; Jiao, N. Palladium-catalyzed ring-expansion reaction of indoles with alkynes: from indoles to tetrahydroquinoline derivatives under mild reaction conditions. *Angew. Chem., Int. Ed.* **2010**, *49*, 4036.

(4) Miyake, Y.; Nakajima, K.; Nishibayashi, Y. Direct sp^3 C-H amination of nitrogen-containing benzoheterocycles mediated by visible-light-photoredox catalysts. *Chem.—Eur. J.* **2012**, *18*, 16473.

(5) (a) Chen, X. W.; Zhao, H.; Chen, C.; Jiang, H. F.; Zhang, M. Iridium-catalyzed dehydrogenative α-functionalization of (hetero)-aryl-fused cyclic secondary amines with indoles. *Org. Lett.* **2018**, *20*, 1171. (b) Ramana, D. V.; Chandrasekharam, M. Copper-catalyzed direct oxidative α-functionalization of tetrahydroquinoline in water under mild conditions. *Adv. Synth. Catal.* **2018**, *360* (21), 4080.

(6) Wang, D.; Wang, Z. T.; Liu, Z. L.; Huang, M. D.; Hu, J. Y.; Yu, P. Strategic C−C bond-forming dearomatization of pyridines and quinolines. *Org. Lett.* **2019**, *21*, 4459.

(7) For some selected examples about [4 + 3] annulation, see: (a) Wang, L.; Li, S.; Blumel, M.; Philipps, A. R.; Wang, A.; Puttreddy, R.; Rissanen, K.; Enders, D. Asymmetric synthesis of spirobenzazepinones with atroposelectivity and spiro-1,2-diazepinones by NHC-catalyzed [3 + 4] annulation reactions. *Angew. Chem., Int. Ed.* **2016**, *55*, 11110. (b) Mei, G. J.; Zhu, Z. Q.; Zhao, J. J.; Bian, C. Y.; Chen, J.; Chen, R. W.; Shi, F. Brønsted acid-catalyzed stereoselective [4 + 3] cycloadditions of *ortho*-hydroxybenzyl alcohols with N,N-cyclic azomethine imines. *Chem. Commun.* **2017**, *53*, 2768. (c) Zhang, X.; Pan, Y.; Liang, P.; Pang, L.; Ma, X.; Jiao, W.; Shao, H. Oxadiazepine synthesis by formal [4 + 3] cycloaddition of *o*-chloromethyl arylsulfonamides with nitrones promoted by $NaHCO_3$. *Adv. Synth. Catal.* **2018**, *360*, 3015. (d) Wang, X. Y.; Li, Z. F.; Feng, C.; Zhen, Q.; Guo, M. Z.; Yao, Y. N.; Zou, X. Y.; Wang, P. F.; Hou, Y. L.; Gong, P. A [4 + 3] Cycloaddition Reaction of Aza-ortho-quinone Methides with C,N-Cyclic Azomethine Imines for Synthesis of 1,2,4-Triazepines. *Synlett.* **2021**, *32*, 2090. (e) Meng, Z. R.; Yang, W. R.; Zheng, J. [4 + 3]-Cycloaddition of aza-o-quinone methides and azomethine imines to make 1,2,4-triazepines. *Tetrahedron Lett.* **2019**, *60*, 1758. (f) Long, W. Y.; Chen, S. Q.; Zhang, X. H.; Fang, L.; Wang, Z. Y. Diversity-oriented synthesis of 1,2,3,5-tetrahydrobenzo[*e*]-[1,2,4]oxadiazepines and 2,3-dihydro-1H-benzo[e][1,2,4] triazepines by base-induced [4 + 3] annulation reactions. *Tetrahedron.* **2018**, *74* (42), 6155. (g) Guo, Z. Y.; Jia, H.; Liu, H. L.; Wang, Q. J.; Huang, J. X.; Guo, H. C. A [4 + 3] Annulation Reaction of aza-o-Quinone Methides with Arylcarbohydrazonoyl Chlorides for Synthesis of 2,3-Dihydro-1H-benzo[e][1,2,4]triazepines. *Org. Lett.* **2018**, *20* (10), 2939. (h) Zheng, Y. S.; Tu, L.; Gao, L. M.; Huang, R.; Feng, T.; Sun, H.; Wang, W. X.; Li, Z. H.; Liu, J. K. Accessing benzooxadiazepines via formal [4 + 3] cycloadditions of aza-o-quinone methides with nitrones. *Org. Biomol Chem.* **2018**, *16* (15), 2639. (i) Zhi, Y.; Zhao, K.; Shu, T.; Enders, D. Synthesis of Benzotriazepine Derivatives via [4 + 3] Cycloaddition of Aza-o-quinone Methide Intermediates and Azomethine Imines. *Synthesis.* **2016**, *48* (02), 238. (j) Chen, L.; Yang, G. M.; Wang, J.; Jia, Q. F.; Wei, J.; Du, Z. Y. An efficient [4 + 3] cycloaddition reaction of aza-o-quinodimethanes with C,N-cyclic azomethine imines: stereoselective synthesis of 1,2,4-triazepines. *RSC Adv.* **2015**, *5*, 76696.

(8) For some selected examples about [4 + 2] annulation, see: (a) Li, L. Z.; Wang, C. S.; Guo, W. F.; Mei, G. X.; Shi, F. Catalytic asymmetric [4 + 2] cycloaddition of in Situ generated *o*-quinone methide Imines with *o*-hydroxystyrenes: diastereo- and enantioselective construction of tetrahydroquinoline frameworks. *J. Org. Chem.* **2018**, *83* (2), 614. (b) Boal, B. W.; Schammel, A. W.; Garg, N. K. An interrupted fischer indolization approach toward fused indoline-containing natural products. *Org. Lett.* **2009**, *11*, 3458. (c) Liao, H. H.; Hsiao, C. C.; Atodiresei, I.; Rueping, M. Multiple hydrogen-bond activation in asymmetric brønsted acid catalysis. *Chem.—Eur. J.* **2018**, *24*, 7718. (d) Alden-Danforth, E.; Scerba, M. T.; Lectka, T. Asymmetric cycloadditions of *o*-quinone methides employing chiral ammonium fluoride precatalysts. *Org. Lett.* **2008**, *10* (21), 4951. (e) Lee, A.; Younai, A.; Price, C. K.; Izquierdo, J.; Mishra, R. K.; Scheidt, K. A. Enantioselective annulations for dihydroquinolones by in situ generation of azolium enolates. *J. Am. Chem. Soc.* **2014**, *136* (30), 10589. (f) Mukhina, O. A.; Kuznetsov, D. M.; Cowger, T. M.; Kutateladze, A. G. Amino azaxylylenes photogenerated from *o*-amido imines: photo assisted access to complex spiro-poly-heterocycles. *Angew. Chem., Int. Ed.* **2015**, *54*, 11516. (g) Kretzschmar, M.; Hodik, T.; Schneider, C. Brønsted acid catalyzed addition of enamides to *ortho*-quinone methide imines—an efficient and highly enantioselective synthesis of chiral tetrahydroacridines. *Angew. Chem., Int. Ed.* **2016**, *55*, 9788. (h) Ji, H. J.; He, C. L.; Gao, H. J.; Fu, W. J.; Xu, J. F. DBU-Promoted Formal [4 + 2] Annulation Reactions of o-Chloromethyl Anilines with Azlactones. *Synthesis.* **2021**, *53*, 1349. (i) Zheng, Y. S.; Tu, L.; Li, N.; Huang, R.; Feng, T.; Sun, H.; Li, Z. H.; Liu, J. K. Inverse-Electron-Demand [4 + 2]-Cycloaddition of 1,3,5-triazinanes: Facile Approaches to Tetrahydroquinazolines. *Adv. Synth. Catal.* **2019**, *361* (j), 44. (i) Han, S.; Vogt, F.; May, J. A.; Krishnan, S.; Gatti, M.; Virgil, S. C.; Stoltz, B. M. Evolution of a Unified, Stereodivergent Approach to the Synthesis of Communesin F and Perophoramidine. *J. Org. Chem.* **2015**, *80*, 528. (k) Schammel, A. W.; Chiou, G.; Garg, N. K. Interrupted Fischer Indolization Approach toward the Communesin Alkaloids and Perophoramidine. *Org. Lett.* **2012**, *14* (17), 4556. (l) Schammel, A. W.; Boal, B. W.; Zu, L. S.; Mesganaw, T.; Garg, N. K. Exploration of the interrupted Fischer indolization reaction. *Tetrahedron.* **2010**, *66* (26), 4687. (m) Rahul, P.; Veena, S.; Jubi, J. Inverse Electron Demand Diels Alder Reaction

https://doi.org/10.1021/acsomega.2c07036
ACS Omega 2023, 8, 22352−22360

of Aza-*o*-Quinone Methides and Enaminones: Accessing 3-Aroyl Quinolines and Indeno[1,2-b]quinolinones. *J. Org. Chem.* **2022**, *87* (21), 13708. (n) May, J. A.; Stoltz, B. The structural and synthetic implications of the biosynthesis of the calycanthaceous alkaloids, the communesins, and nomofungin. *Tetrahedron.* **2006**, *62* (22), 5262. (n) May, J. A.; Zeidan, R. K.; Stoltz, B. M. Biomimetic approach to communesin B (a.k.a. nomofungin). *Tetrahedron. Lett.* **2003**, *44* (6), 1203.

(9) For some selected examples about [4 + 1] annulation, see: (a) Sharma, H. A.; Hovey, M. T.; Scheidt, K. A. Azaindole synthesis through dual activation catalysis with *N*-heterocyclic carbenes. *Chem. Commun.* **2016**, *52*, 9283. (b) Yang, Q. Q.; Xiao, C.; Lu, L. Q.; An, J.; Tan, F.; Li, B. J.; Xiao, W. J. Synthesis of indoles through highly efficient cascade reactions of sulfur ylides and *N*-(*ortho*-chloromethyl) aryl amides. *Angew. Chem., Int. Ed.* **2012**, *51*, 9137. (c) Chen, M. W.; Cao, L. L.; Ye, Z. S.; Jiang, G. F.; Zhou, Y. G. A mild method for generation of *o*-quinone methides under basic conditions. The facile synthesis of *trans*-2,3-dihydrobenzofurans. *Chem. Commun.* **2013**, *49*, 1660. (d) Huang, H.; Yang, Y.; Zhang, X. Y.; Zeng, W. L.; Liang, Y. Transition-metal-free approach to synthesis of indolines from *N*-(*ortho*-chloromethyl) aryl amides and iodonium ylides. *Tetrahedron. Lett.* **2013**, *54*, 6049. (e) Zhang, X. K.; Wang, H. B.; Li, Z. W.; Shu, Y.; Gan, S.; Zhang, X. F.; Shao, H. W.; Wang, C. Y. Chemodivergent synthesis of aza-Heterocycles with a quarternary carbon center *via* [4 + 1] annulation between azoalkenes and α-bromo carbonyl compounds. *ACS. Omega.* **2022**, *7*, 40963. (f) Yang, Q. Q.; Wang, Q.; An, J.; Chen, J. R.; Lu, L. Q.; Xiao, W. J. Construction of optically active indolines by formal [4 + 1] annulation of sulfur ylides and *N*-(*ortho*-chloromethyl) aryl amides. *Chem.—Eur. J.* **2013**, *19*, 8401. (g) Zhang, Y.; Liu, T. D.; Liu, L.; Guo, H. Y.; Zeng, H. Y.; Bi, W.; Qiu, G. Y. S.; Gao, W.; Ran, X.; Yang, L.; Du, G. B.; Zhang, L. P. Palladium-Catalyzed Preparation of N-Substituted Benz[c, d]indol-2-imines and N-Substituted Amino-1-naphthylamides. *J. Org. Chem.* **2022**, *87* (13), 8515. (h) Li, H.; Yu, Z.; Sun, H.; Liu, B.; Wang, X.; Shao, Z.; Wang, M.; Xie, W.; Yao, X.; Yao, Q.; Zhi, Y. Efficient Synthesis of 2,3′-Spirobi (Indolin)-2′-Ones and Preliminary Evaluation of Their Damage to Mitochondria in HeLa Cells. *Front. Pharmacol.* **2022**, *12*, 821518. (i) Hua, T. B.; Chao, F.; Wang, L.; Yan, C. Y.; Xiao, C.; Yang, Q. Q.; Xiao, W. J. Tandem Phospha-Michael Addition/N-Acylation/ Intramolecular Wittig Reaction of aza-o-Quinone Methides: Approaches to 2,3-Disubstituted Indoles. *Adv. Synth. Catal.* **2020**, *362* (13), 2615. (j) Gui, H. Z.; Wu, X. Y.; Wei, Y.; Shi, M. A Formal Condensation and [4 + 1] Annulation Reaction of 3-Isothiocyanato Oxindoles with Aza-o-Quinone Methides. *Adv. Synth. Catal.* **2019**, *361* (23), 5466. (k) Jong, J. A. W.; Bao, X.; Wang, Q.; Zhu, J. P. Formal [4 + 1] cycloaddition of o-aminobenzyl chlorides with isocyanides: synthesis of 2-amino-3-substituted indoles. *Helv. Chim. Acta* **2019**, *102* (3), No. e1900002.

(10) For some selected examples about the generation of *ortho*-quinone methide, see: (a) Walden, D. M.; Jaworski, A. A.; Johnston, R. C.; Hovey, M. T.; Baker, H. V.; Meyer, M. P.; Scheidt, K. A.; Cheong, P. H. Y. Formation of aza-*ortho*-quinone methides under room temperature conditions: Cs_2CO_3 effect. *J. Org. Chem.* **2017**, *82* (14), 7183. (b) Liao, H. H.; Miñoza, S.; Lee, S. C.; Rueping, M. Aza-*ortho*-quinone methides as reactive intermediates: generation and utility in contemporary asymmetric synthesis. *Chem.—Eur. J.* **2022**, *28*, No. e202201112. (c) Lewis, R. S.; Garza, C. J.; Dang, A. T.; Pedro, T. K. A.; Chain, W. J. Michael additions of highly basic enolates to *ortho*-quinone methides. *Org. Lett.* **2015**, *17* (9), 2278. (d) Pathak, T. P.; Sigman, M. S. A. Applications of *ortho*-quinone methide intermediates in catalysis and asymmetric synthesis. *J. Org. Chem.* **2011**, *76*, 9210. (e) Liu, X. J.; Wang, K.; Guo, W. G.; Liu, Y.; Li, C. An organic-base catalyzed asymmetric 1,4-addition of tritylthiol to in situ generated aza-o-quinone methides at the H_2O/DCM interface. *Chem. Commun.* **2019**, *55*, 2668.

(11) Steinhagen, H.; Corey, E. J. A convenient and versatile route to hydroquinolines by inter- and intramolecular aza-Diels−Alder pathways. *Angew. Chem., Int. Ed.* **1999**, *38*, 1928.

(12) Zheng, Y. S.; Tu, L.; Li, N.; Huang, R.; Feng, T.; Sun, H.; Li, Z. H.; Liu, J. K. Inverse-electron-demand [4 + 2]-cycloaddition of 1,3,5-triazinanes: facile approaches to tetrahydroquinazolines. *Adv. Synth. Catal.* **2019**, *361*, 44.

(13) Wang, H. Q.; Ma, W. J.; Sun, A.; Sun, X. Y.; Jiang, C.; Zhang, Y. C.; Shi, F. (4 + 2) Cyclization of aza-*o*-quinone methides with azlactones: construction of biologically important dihydroquinolinone frameworks. *Org. Biomol. Chem.* **2021**, *19*, 1334.

(14) (a) Lei, L.; Liang, Y. F.; Liang, C.; Qin, J. K.; Pan, C. X.; Su, G. F.; Mo, D. L. Copper (i)-catalyzed [4+ 2] cycloaddition of aza-*ortho*-quinone methides with bicyclic alkenes. *Org. Biomol. Chem.* **2021**, *19*, 3379. (b) Lei, L.; Yao, Y.-Y.; Jiang, L.-J.; Lu, X.; Liang, C.; Mo, D.-L. Synthesis of furo [3,2-*b*] quinolines and furo[2,3-*b*:4,5-*b*] diquinolines through [4 + 2] cycloaddition of aza-*o*-quinone methides and furans. *J. Org. Chem.* **2020**, *85*, 3059.

(15) Jiang, S. P.; Lu, W. Q.; Liu, Z.; Wang, G. W. Synthesis of fullerotetrahydroquinolines *via* [4 + 2] cycloaddition reaction of [*60*] fullerene with in situ generated aza-*o*-quinone methides. *J. Org. Chem.* **2018**, *83*, 1959.

(16) Shao, W.; Xu-Xu, Q. F.; You, S. L. Highly diastereoselective synthesis of polycyclic indolines through formal [4 + 2] propargylic cycloaddition of indoles with ethynyl benzoxazinanones. *Chem.—Asian J.* **2020**, *15* (16), 2462.

(17) Cheng, H.; Yan, D. C.; Wang, G.; He, Z. L. [4+ 2]-Cycloaddition reactions of aza-*o*-quinone methides with fulvenes: construction of tetrahydroquinoline derivatives. *Synlett.* **2022**, *33* (08), 795.

(18) (a) Dandia, A.; Sachdeva, H.; Ahmed, N.; Joshi, K. One pot Synthesis of fluorine containing diastereoisomeric spiro [3*H*-indol-3,2'-oxiran]-2(1H)-ones and their conversion to 5a, 10b-dihydrdro-5*H*,6*H*-indole[2,3-*b*] quinoline-11-ones. *Heterocycl. Commun.* **2000**, *6* (2), 181. (b) Wu, H. X.; Xue, F.; Xiao, X.; Qin, Y. Total synthesis of (+)-perophoramidine and determination of the absolute configuration. *Angew. Chem., Int. Ed.* **2010**, *132* (40), 14052. (c) Robertson, F. J.; Kenimer, B. D.; Wu, J. Direct annulation and alkylation of indoles with 2-aminobenzyl alcohols catalyzed by TFA. *Tetrahedron.* **2011**, *67*, 4327. (d) Luo, M.; Chen, J. X.; Yu, L. Q.; Wei, W. G. Concise Synthesis of Polycyclic Indoline Scaffolds through an InIII-Catalyzed Formal [4 + 2] Annulation of 2,3-Disubstituted Indoles with o-Aminobenzyl Alcohols. *Eur. J. Org. Chem.* **2017**, *18*, 2652.

(19) Zhang, X. K.; Pan, Y.; Liang, P.; Ma, X. F.; Jiao, W.; Shao, H. W. An effective method for the synthesis of 1,3-dihydro-2H-indazoles via N-N bond formation. *Adv. Synth. Catal.* **2019**, *361*, 5552.

(20) (a) Tu, M. S.; Chen, K. W.; Wu, P.; Zhang, Y. C.; Liu, X. Q.; Shi, F. Advances in organocatalytic asymmetric reactions of vinylindoles: powerful access to enantioenriched indole derivatives. *Org. Chem. Front.* **2021**, *8*, 2643. (b) Guan, X. K.; Liu, G. F.; An, D.; Zhang, H.; Zhang, S. Q. Chiral imidodiphosphoric acid-catalyzed highly diastereo- and enantioselective synthesis of poly-substituted 3,4-dihydro-2*H*-pyrans: [4 + 2] cycloadditions of β, γ-unsaturated α-ketoesters and 3-vinylindoles. *Org. Lett.* **2019**, *21*, 5438. (c) Zhu, Z. Q.; Shen, Y.; Sun, X. X.; Tao, J. Y.; Liu, J. X.; Shi, F. Catalytic asymmetric [3 + 2] cycloadditions of C-3 unsubstituted 2-indolylmethanols: regio-, diastereo- and enantioselective construction of the cyclopenta[*b*]indole framework. *Adv. Synth. Catal.* **2016**, *358*, 3797. (d) Tan, B.; Hernández-Torres, G.; Barbas, C. F. Highly efficient hydrogen-bonding catalysis of the Diels−Alder reaction of 3-vinylindoles and methyleneindolinones provides carbazolespirooxindole skeletons. *J. Am. Chem. Soc.* **2011**, *133* (32), 12354.

(21) CCDC 2205697 contains the supplementary crystallographic data for compound **3a**.

(22) Wagner, A. M.; knezevic, C. E. K.; Wall, J. L.; Sun, V. L.; Buss, J. A.; Allen, L. T.; Wenzel, A. G. Green synthesis of novel chalcone and coumarin derivatives via Suzuki coupling reaction. *Tetrahedron. Lett.* **2012**, *53*, 833.

https://doi.org/10.1021/acsomega.2c07036
ACS Omega 2023, 8, 22352−22360