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Regioselective Pd-catalyzed α-alkylation of furans using alkyl iodides†

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Herein, direct alkylation of the C–H bond at the α-position of furans catalyzed by palladium catalyst is reported. This protocol targets α-alkylfurans, achieving moderate to good yields under very practical reaction conditions. With a broad scope of substrates and good functional group tolerance, this method will has promising utility in medicinal chemistry.

Introduction

Alkyl-substituted heteroarene scaffolds are commonly found in drugs and other materials. Among these heteroarenes, α-alkyl-substituted furans are attractive for marketed drugs or active compounds, for example: Lapatinib,[1] a tyrosine kinase inhibitor targeting HER2, was approved for the treatment of breast cancer in 2013; Lafutidine[2] and Ranitidine,[3] classic histamine H2-receptor antagonists, are clinically used for peptic ulcers; Navarixin,[4] a selective CXC chemokine receptor 1/2 antagonist, is currently being used in a phase 2 clinical trial for treatment of chronic obstructive pulmonary disease (Fig. 1). Clearly, as important structures in drug research, the efficient synthesis and construction of α-alkylfurans deserves more attention.

While most direct alkylation reactions of furans fall into two types: (1) Friedel–Crafts alkylation, which usually requires Lewis acids/environmentally harmful solvents[5–7] and has low selectivity and yields for furans; (2) nucleophilic substitution reactions, which need extremely low temperature conditions and strong base to form and stabilize the furan anion.[8–10] Both types of reactions suffer from the limitation of functional group compatibility. Recently, transition-metal-catalyzed C–H functionalization has become a powerful and reliable tool for the direct alkylation of arenes, but most efficient procedures are designed for electron-deficient heteroarenes[11–14] and acidic C–H bonds of azoles.[15–18] As a typical electron-rich heteroarene, transition-metal-catalyzed C–H functionalization for the direct alkylation of furan has been rarely reported. In 2014, Zhou reported Pd-catalyzed alkylations of neutral heteroarenes (like benzoxazole) with alkyl halides,[19] but few furan derivatives were employed as substrates. In 2015, Hartwig accomplished anti-Markovnikov hydroheteroarylation of unactivated alkenes with furans,[20] but this transformation used a highly air-sensitive Ni(0)-*N*-heterocyclic carbene complex and gave only primary and secondary alkyl-substituted products. As far as we know, from 2015 to the present, only a few research papers involving transition-metal-catalyzed C–H alkylation of furans have been published. Evano and Nishikata achieved Cu[21]-and Fe[22]-catalyzed alkylation of heteroarenes with alkyl halides, respectively, *via* a radical pathway; however the coupling partners were limited to tertiary alkyl halides and only a few furan substrates were reported. Furthermore, Bao and Yin employed an Fe catalyst to achieve the alkylation of furans with alkyl diacyl peroxides[23] and aliphatic aldehydes,[24] respectively, but Bao's protocol is restricted because it involves dangerous peroxides and far in excess usage of furans, and Yin's method is strictly confined to acyl-substituted furan substrates and oxidative conditions. Therefore, general and systemic research focused on developing a convenient, practical and, most importantly, a functional-group-tolerant method for direct alkylation of furans is in high demand.

During research on the structure–activity relationship (SAR) of a furan-containing leading compound in our group, the introduction of different alkyl substituents at the α-position of

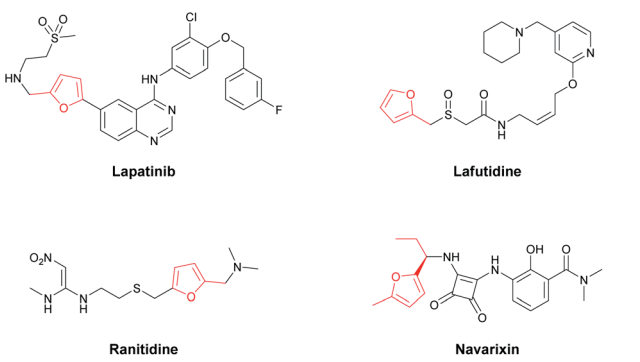

Fig. 1 Drugs with α-alkylfuran scaffolds.

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furan became quite a challenge. So, herein, a general protocol for Pd-catalyzed regioselective α-alkylation of furans with alkyl iodides was developed.

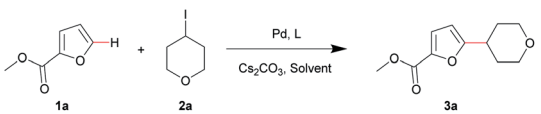
Results and discussion

Tetrahydro-2*H*-pyran is a very familiar pharmacophore in bioactive compounds owing to its unique chemical and physical properties.[25–28] Following screening in previous work, commercially available and easily accessible methyl furan-2-carboxylate (**1a**) and 4-iodotetrahydro-2*H*-pyran (**2a**) were used as substrates for the first synthesis of methyl 5-(tetrahydro-2*H*-pyran-4-yl) furan-2-carboxylate (**3a**) *via* direct C–H alkylation.

Initially, we employed Zhou's optimal conditions for this reaction, but the desired product **3a** was obtained with a low yield (Table 1, entry 1). By increasing the amount of ligand to 10 mol%, the yield of **3a** was slightly increased to 36% (Table 1, entry 2). Several solvents with appropriate boiling points were tested and $PhCF_3$ turned out to be the best choice (Table 1, entries 2–4). Later, the optimization of the reaction conditions focused on the screening of ligands (Table 1, entries 5–12) and Pd catalysts (Table 1, entries 13–16). As a result, $Pd(PPh_3)_4$ and Xantphos were found to be the best combination for this transformation. Subsequently, the replacement of Cs_2CO_3 with K_2CO_3/LiOH/K_3PO_4 failed to give better yields (Table 1, entry 17). Eventually, by adding 10 mol% $Pd(PPh_3)_4$, 20 mol% Xantphos, 2 equiv. (0.6 mmol) Cs_2CO_3 and 3 equiv. (0.9 mmol) **2a**, and extending the reaction time to 48 h, the target compound **3a** was obtained with 74% isolated yield (Table 1, entries 18 and 19).

With the optimal conditions in hand, we first explored the substrate scope of furans (Table 2). This Pd-catalyzed direct C–H alkylation of furans was tolerant of a broad range of functional groups, such as ester, aldehyde, cyano, acetyl, amide and Boc groups. The target compounds were successfully synthesized with moderate to good yields (Table 2, **3a–f** and **3h**). It is noteworthy that no regio-isomers were detected in these reactions even for the preparation of **3c**. 2-Phenylfuran and benzofuran also performed well to give products with good yields (Table 2, **3i** and **3j**). In contrast, from the experimental results, when the 2- or 3-position of furan was substituted with electron-donating groups, the yields were significantly decreased (Table 2, **3g**, **3k** and **3l**). The relatively low yields for electron-donating substituents were due to the low conversion rate: most of the unreacted starting furan could be recovered after the reaction. An electron-withdrawing substituent on the furan ring clearly benefitted the reaction process.

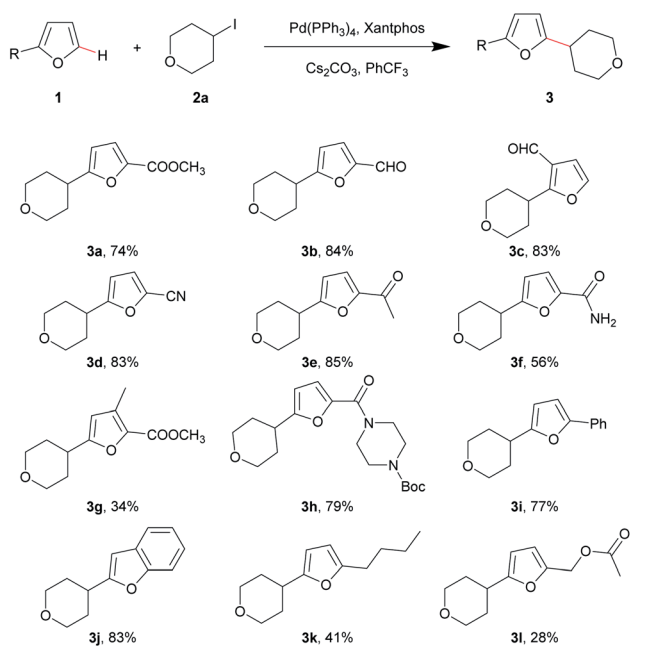
Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst	Ligand	Solvent	Yield (%)[b]
1	$Pd(PPh_3)_4$	dppp	$PhCF_3$	28[c]
2	$Pd(PPh_3)_4$	dppp	$PhCF_3$	36
3	$Pd(PPh_3)_4$	dppp	1,4-dioxane	23
4	$Pd(PPh_3)_4$	dppp	$PhCH_3$	12
5	$Pd(PPh_3)_4$	dppe	$PhCF_3$	27
6	$Pd(PPh_3)_4$	dppb	$PhCF_3$	36
7	$Pd(PPh_3)_4$	dppf	$PhCF_3$	45
8	$Pd(PPh_3)_4$	XPhos	$PhCF_3$	<10%
9	$Pd(PPh_3)_4$	Xantphos	$PhCF_3$	47
10	$Pd(PPh_3)_4$	BINAP	$PhCF_3$	31
11	$Pd(PPh_3)_4$	Johnphos	$PhCF_3$	11
12	$Pd(PPh_3)_4$	—	$PhCF_3$	<10%
13	$Pd(OAc)_2$	Xantphos	$PhCF_3$	ND
14	Pd_2dba_3	Xantphos	$PhCF_3$	<10%
15	$PdCl_2dppf$	Xantphos	$PhCF_3$	28
16	$Pd_2dba_3 \cdot CHCl_3$	Xantphos	$PhCF_3$	<10%
17	$Pd(PPh_3)_4$	Xantphos	$PhCF_3$	<10%[d]
18	$Pd(PPh_3)_4$	Xantphos	$PhCF_3$	58[e]
19	$Pd(PPh_3)_4$	Xantphos	$PhCF_3$	74[f]

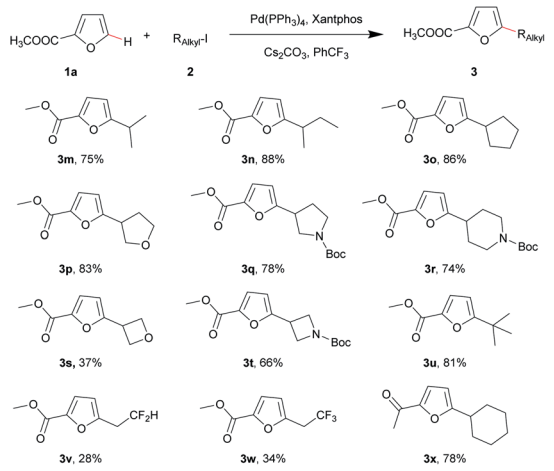
[a] Reaction conditions: methyl furan-2-carboxylate (**1a**, 0.3 mmol), 4-iodotetrahydro-2*H*-pyran (**2a**, 0.6 mmol), Pd catalyst (5 mol%), ligand (10 mol%) and Cs_2CO_3 (0.6 mmol) in 5 mL solvent under Ar at 110 °C for 24 h. [b] Isolated yields. [c] By employing Zhou's optimized conditions. [d] Cs_2CO_3 was replaced with K_2CO_3/LiOH/K_3PO_4, respectively (0.6 mmol). [e] By adding 10 mol% $Pd(PPh_3)_4$ and 20 mol% Xantphos. [f] By adding 10 mol% $Pd(PPh_3)_4$, 20 mol% Xantphos and 0.9 mmol **2a**, extending the reaction time to 48 h. dppp = 1,3-bis(diphenylphosphino) propane; dppe = 1,2-bis(diphenylphosphino)ethane; dppb = 1,4-bis(diphenylphosphino)butane; dppf = 1,1′-bis(diphenylphosphino) ferrocene; XPhos = 2-(dicyclohexylphosphino)-2′,4′,6′-tri-i-propyl-1,1′-biphenyl; Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene; BINAP = 1.1′-binaphthyl-2.2′-diphemyl phosphine; Johnphos = 2-(di-*tert*-butylphosphino)biphenyl.

Table 2 The substrate scope of furans[ab]



[a] Reaction conditions: furans (**1**, 0.3 mmol), 4-iodotetrahydro-2*H*-pyran (**2a**, 0.9 mmol), $Pd(PPh_3)_4$ (10 mol%), Xantphos (20 mol%) and Cs_2CO_3 (0.6 mmol) in 5 mL $PhCF_3$ under Ar at 110 °C for 48 h. [b] Isolated yields.

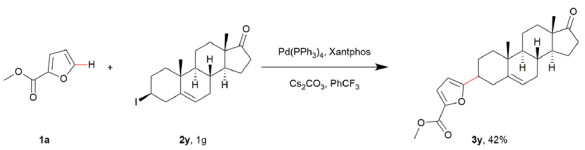
Table 3 The substrate scope of alkyl iodides[ab]



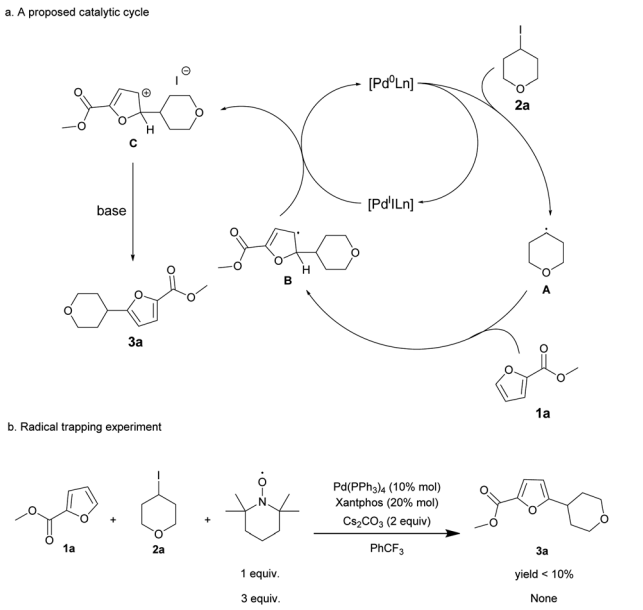
[a] Reaction conditions: methyl furan-2-carboxylate (**1a**, 0.3 mmol), alkyl iodides (**2**, 0.9 mmol), $Pd(PPh_3)_4$ (10 mol%), Xantphos (20 mol%) and Cs_2CO_3 (0.6 mmol) in 5 mL $PhCF_3$ under Ar at 110 °C for 48 h. [b] Isolated yields.

The substrate scope of the alkyl iodides was then examined. Various unactivated/functionalized alkyl iodides (**2**) were treated with **1a** under the optimal conditions (Table 3). Most secondary alkyl iodides afforded products with good yields, except for 3-iodooxetane (Table 3, **3m–3t**). Interestingly, methyl furan-2-carboxylate (**1a**) reacted with iodocyclohexane gave an unsatisfactory result (yield <30%), while 2-acetylfuran performed well with iodocyclohexane to produce **3x** in 78% yield. Furthermore, for tertiary alkyl iodides, 2-iodo-2-methylpropane gave the coupling product **3u** in 81% yield. To our delight, although primary alkyl iodides like 1-iodohexane failed to afford the alkylated product (yield <10%), the first C–H α-difluoroethylation and α-trifluoroethylation of furan using ICH_2CF_2H and ICH_2CF_3 were accomplished with acceptable yields (Table 3, **3v** and **3w**). It is necessary to note that methyl furan-2-carboxylate **1a** did not react with 4-bromotetrahydro-2*H*-pyran, even with 3 equiv. (0.09 mmol) NaI or KI under the optimal conditions.

To further demonstrate the synthetic utility of this method, we employed 3β-iodo-5-androsten-17-one as coupling substrate (Scheme 1). The desired compound **3y** was produced with an acceptable yield of 42% under the optimal conditions. This late-stage modification strongly highlights the importance of this protocol and demonstrates potential applications in medicinal chemistry.



Scheme 1 The reaction of methyl furan-2-carboxylate and 3β-iodo-5-androsten-17-one.



Scheme 2 Possible mechanism and radical trapping experiment.

A proposed mechanism for the Pd-catalyzed radical alkylation of furans is outlined in Scheme 2. It starts with single electron transfer from $[Pd^0Ln]$ to the alkyl iodides, generating an alkyl radical A and $[Pd^IILn]$. The addition of alkyl radical A to **1a** affords a delocalized radical intermediate B, which then produces the corresponding carbocation C and $[Pd^0Ln]$ through single electron transfer. Finally, deprotonation driven by aromatization furnishes the alkylated furans. To test the possibility of single electron transfers, control experiments with our standard conditions were performed in the presence of TEMPO (oxidanyl, $(CH_2)_3(CMe_2)_2NO$). The reaction of **1a** and **2a** with 1 equiv. TEMPO afforded the alkylated product **3a** in low yield (<10%), but it did not give the corresponding product when 3 equiv. TEMPO was employed. This result indicates that the reaction may proceed *via* the described radical pathway.

Conclusions

In conclusion, a regioselective procedure for α-alkylation of furans using alkyl iodides *via* a simple Pd catalyst has been developed. This protocol provides a convenient and practical route to α-alkylfurans with good functional group compatibility and broad substrate scope. After this systemic research for alkylation of furans, the diversification of furan-containing compounds could be more easily achieved. The applications of this method for drug discovery from our group will be published in the near future.

Experimental section

General information

All reagents were purchased from commercial suppliers and used without further purification. The progress of all of the reactions was monitored by thin layer chromatography (TLC)

with standard TLC silica gel plates, and the developed plates were visualized under UV light. All of the compounds were purified by column chromatography. Chromatography was performed on silica gel (100–200 mesh). Nuclear magnetic resonance spectra (^{1}H, ^{13}C NMR) were recorded on Varian Mercury-400 and Bruker Avance III-500/600 spectrometers and $CDCl_3$-d and CD_3OD-d were used as solvent. NMR peaks were calibrated by reference to standard peaks of $CDCl_3$ at 7.26 ppm for ^{1}H and 77.16 ppm for ^{13}C and standard peaks of CD_3OD at 3.31 ppm for ^{1}H and 49.00 ppm for ^{13}C. For peak descriptions, the following abbreviations are used: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet). Electron ionization high-resolution mass spectrometry (EI-HRMS) data were recorded using a Thermo DFS mass spectrometer. ESI-HRMS were recorded using an Agilent QTOF mass spectrometer.

General experimental methods

A 15 mL Schlenk tube equipped with a stirrer bar was charged with $Pd(PPh_3)_4$ (0.03 mmol, 0.1 equiv.), Xantphos (0.06 mmol, 0.2 equiv.), Cs_2CO_3 (0.6 mmol, 2.0 equiv.), furan derivatives (0.3 mmol, 1.0 equiv.), alkyl iodides (0.9 mmol, 3.0 equiv.), and $PhCF_3$ (5 mL). The tube was evacuated and backfilled with Ar 5 times, and the mixture was vigorously stirred in a pre-heated 110 °C oil bath for 48 h. The mixture was diluted with water (90 mL), and extracted three times with ethyl acetate (30 mL). The organic phase was dried over Na_2SO_4, concentrated *in vacuo*, and purified by column chromatography on silica gel.

Characterization data of compounds

Methyl 5-(tetrahydro-2*H*-pyran-4-yl)furan-2-carboxylate (3a). Brown oil (yield 74%). ^{1}H NMR (500 MHz, chloroform-d) δ 7.11 (d, J = 3.4 Hz, 1H), 6.14 (dd, J = 3.5, 0.9 Hz, 1H), 4.03 (ddd, J = 11.5, 4.1, 2.2 Hz, 2H), 3.88 (s, 3H), 3.50 (td, J = 11.7, 2.2 Hz, 2H), 2.97 (tt, J = 11.5, 3.9 Hz, 1H), 1.97 (dtd, J = 12.9, 4.1, 2.4 Hz, 2H), 1.78 (dtd, J = 13.4, 11.6, 4.3 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.71, 159.38, 143.16, 119.16, 106.23, 67.50, 51.90, 34.87, 31.05. HRMS (ESI) m/z calc. for $C_{11}H_{15}O_4$ $[M + H]^+$ 211.0965, found 211.0966.

5-(Tetrahydro-2*H*-pyran-4-yl)furan-2-carbaldehyde (3b). Brown solid (yield 84%). ^{1}H NMR (500 MHz, chloroform-d) δ 9.55 (s, 1H), 7.18 (d, J = 3.6 Hz, 1H), 6.25 (dd, J = 3.6, 0.9 Hz, 1H), 4.04 (ddd, J = 11.5, 4.0, 2.2 Hz, 2H), 3.52 (td, J = 11.7, 2.2 Hz, 2H), 3.00 (tt, J = 11.6, 3.9 Hz, 1H), 1.98 (dtd, J = 13.1, 4.2, 2.4 Hz, 2H), 1.81 (dtd, J = 13.4, 11.6, 4.4 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.29, 165.97, 151.98, 107.27, 67.44, 35.01, 30.87. HRMS (ESI) m/z calc. for $C_{10}H_{13}O_3$ $[M + H]^+$ 181.0859, found 181.0861.

2-(Tetrahydro-2*H*-pyran-4-yl)furan-3-carbaldehyde (3c). Brown solid (yield 83%). ^{1}H NMR (400 MHz, chloroform-d) δ 10.01 (s, 1H), 7.34 (d, J = 2.0 Hz, 1H), 6.71 (d, J = 2.1 Hz, 1H), 4.12–4.06 (m, 2H), 3.55 (td, J = 11.9, 2.1 Hz, 2H), 3.47 (tt, J = 11.9, 3.9 Hz, 1H), 2.05 (dtd, J = 13.6, 12.0, 4.5 Hz, 2H), 1.78 (dtd, J = 11.0, 3.9, 3.2, 1.9 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.75, 166.85, 142.24, 121.53, 108.64, 67.72, 34.38, 31.05. HRMS (EI$^+$): m/z calc. for $C_{10}H_{12}O_3$ $[M]^+$ 180.0781, found 180.0780.

5-(Tetrahydro-2*H*-pyran-4-yl)furan-2-carbonitrile (3d). Brown solid (yield 83%). ^{1}H NMR (500 MHz, chloroform-d) δ 7.02 (d, J = 3.5 Hz, 1H), 6.14 (dd, J = 3.5, 1.0 Hz, 1H), 4.03 (ddd, J = 11.5, 4.0, 2.2 Hz, 2H), 3.51 (td, J = 11.7, 2.2 Hz, 2H), 2.94 (tt, J = 11.5, 3.9 Hz, 1H), 1.93 (dtd, J = 12.9, 4.4, 2.5 Hz, 2H), 1.77 (dtd, J = 13.5, 11.7, 4.4 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.71, 124.79, 123.06, 111.98, 105.80, 67.36, 34.89, 30.82. HRMS (EI$^+$): m/z calc. for $C_{10}H_{11}NO_2$ $[M]^+$ 177.0784, found 177.0785.

1-(5-(Tetrahydro-2*H*-pyran-4-yl)furan-2-yl)ethan-1-one (3e). Brown oil (yield 78%). ^{1}H NMR (400 MHz, chloroform-d) δ 7.13 (d, J = 3.5 Hz, 1H), 6.18 (dd, J = 3.5, 0.9 Hz, 1H), 4.04 (ddd, J = 11.4, 4.0, 2.1 Hz, 2H), 3.52 (td, J = 11.7, 2.3 Hz, 2H), 2.98 (tt, J = 11.6, 3.9 Hz, 1H), 2.44 (s, 3H), 2.01–1.94 (m, 2H), 1.79 (dtd, J = 13.4, 11.6, 4.4 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 186.36, 164.13, 151.61, 118.98, 106.74, 67.47, 34.90, 30.99, 25.93. HRMS (ESI) m/z calc. for $C_{11}H_{15}O_3$ $[M + H]^+$ 195.1016, found 195.1020.

5-(Tetrahydro-2*H*-pyran-4-yl)furan-2-carboxamide (3f). White solid (yield 56%). ^{1}H NMR (500 MHz, chloroform-d) δ 7.08 (d, J = 3.5 Hz, 1H), 6.15 (dd, J = 3.5, 0.9 Hz, 1H), 4.04 (ddd, J = 11.5, 4.0, 2.1 Hz, 2H), 3.52 (td, J = 11.7, 2.2 Hz, 2H), 2.93 (tt, J = 11.6, 3.9 Hz, 1H), 1.97–1.91 (m, 2H), 1.79 (dtd, J = 13.3, 11.6, 4.3 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.69, 160.15, 145.93, 116.30, 106.75, 67.50, 34.83, 31.13. HRMS (ESI) m/z calc. for $C_{10}H_{14}NO_3$ $[M + H]^+$ 196.0968, found 196.0963.

Methyl-3-methyl-5-(tetrahydro-2*H*-pyran-4-yl)furan-2-carboxylate (3g). Brown oil (yield 34%). ^{1}H NMR (400 MHz, chloroform-d) δ 6.01 (s, 1H), 4.02 (ddd, J = 11.7, 4.3, 2.2 Hz, 2H), 3.87 (s, 3H), 3.49 (td, J = 11.7, 2.2 Hz, 2H), 2.91 (tt, J = 11.5, 3.9 Hz, 1H), 2.32 (s, 3H), 1.94 (ddd, J = 13.0, 4.1, 2.0 Hz, 2H), 1.74 (dtd, J = 13.4, 11.6, 4.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.01, 160.16, 138.71, 132.47, 109.64, 67.48, 51.53, 34.67, 31.00, 11.82. HRMS (ESI) m/z calc. for $C_{12}H_{17}O_4$ $[M + H]^+$ 225.1121, found 225.1117.

***tert*-Butyl-4-(5-(tetrahydro-2*H*-pyran-4-yl)furan-2-carbonyl) piperazine-1-carboxylate (3h).** White solid (yield 79%). ^{1}H NMR (600 MHz, methanol-d_4) δ 6.98 (d, J = 3.4 Hz, 1H), 6.26 (dd, J = 3.4, 0.9 Hz, 1H), 3.99 (ddd, J = 11.4, 3.9, 2.0 Hz, 2H), 3.78 (s, 4H), 3.58–3.47 (m, 6H), 3.00 (tt, J = 11.6, 3.9 Hz, 1H), 1.97–1.92 (m, 2H), 1.75 (dtd, J = 13.4, 11.7, 4.3 Hz, 2H), 1.48 (s, 9H). ^{13}C NMR (125 MHz, MeOD) δ 163.05, 161.28, 156.29, 146.65, 119.08, 106.87, 81.70, 68.37, 35.70, 32.19, 28.64. HRMS (ESI) m/z calc. for $C_{19}H_{28}N_2NaO_5$ $[M + Na]^+$ 387.1890, found 387.1900.

4-(5-Phenylfuran-2-yl)tetrahydro-2H-pyran (3i). Brown oil (yield 77%). ^{1}H NMR (400 MHz, chloroform-d) δ 7.65–7.60 (m, 2H), 7.36 (dd, J = 8.5, 7.1 Hz, 2H), 7.25–7.20 (m, 1H), 6.56 (d, J = 3.3 Hz, 1H), 6.08 (dd, J = 3.3, 1.0 Hz, 1H), 4.05 (ddd, J = 11.6, 4.3, 2.4 Hz, 2H), 3.54 (td, J = 11.6, 2.3 Hz, 2H), 2.95 (tt, J = 11.3, 3.9 Hz, 1H), 2.02–1.94 (m, 2H), 1.82 (dtd, J = 13.5, 11.5, 4.3 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.82, 152.45, 131.24, 128.76, 127.08, 123.56, 105.67, 105.63, 67.70, 34.74, 31.43. HRMS (EI$^+$): m/z calc. for $C_{15}H_{16}O_2$ $[M]^+$ 228.1145, found 228.1143.

2-(Tetrahydro-2*H*-pyran-4-yl)benzofuran (3j). White solid (yield 83%). ^{1}H NMR (400 MHz, chloroform-d) δ 7.52–7.49 (m, 1H), 7.44–7.40 (m, 1H), 7.25–7.16 (m, 2H), 6.39 (t, J = 1.0 Hz,

1H), 4.07 (ddd, J = 11.6, 4.1, 2.1 Hz, 2H), 3.56 (td, J = 11.7, 2.3 Hz, 2H), 3.03 (tt, J = 11.4, 3.8 Hz, 1H), 2.06–1.99 (m, 2H), 1.86 (dtd, J = 13.4, 11.5, 4.4 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.06, 154.65, 128.77, 123.55, 122.66, 120.61, 110.97, 100.59, 67.67, 34.98, 31.13. HRMS (EI^+): m/z calc. for $C_{13}H_{14}O_2$ $[M]^+$ 202.0988, found 202.0987.

4-(5-Butylfuran-2-yl)tetrahydro-2*H*-pyran (3k). Colorless oil (yield 41%).^{1}H NMR (600 MHz, chloroform-d) δ 5.90–5.86 (m, 2H), 4.03 (ddd, J = 11.4, 3.9, 2.3 Hz, 2H), 3.52 (td, J = 11.7, 2.2 Hz, 2H), 2.84 (tt, J = 11.4, 3.8 Hz, 1H), 2.59 (t, J = 7.6 Hz, 2H), 1.94–1.89 (m, 2H), 1.74 (dtd, J = 13.4, 11.6, 4.3 Hz, 2H), 1.62 (dt, J = 15.2, 7.5 Hz, 2H), 1.42–1.36 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.20, 155.07, 104.87, 103.66, 67.75, 34.60, 31.46, 30.34, 27.87, 22.45, 13.99. HRMS (EI^+): m/z calc. for $C_{13}H_{20}O_2$ $[M]^+$ 208.1458, found 208.1458.

(5-(Tetrahydro-2*H*-pyran-4-yl)furan-2-yl)methyl acetate (3l). Brown oil (yield 28%). ^{1}H NMR (400 MHz, chloroform-d) δ 6.34 (d, J = 3.1 Hz, 1H), 5.99 (dd, J = 3.1, 1.0 Hz, 1H), 5.02 (s, 2H), 4.07–4.00 (m, 2H), 3.52 (td, J = 11.7, 2.2 Hz, 2H), 2.90 (tt, J = 11.4, 3.8 Hz, 1H), 2.10 (s, 3H), 1.98–1.91 (m, 2H), 1.76 (dtd, J = 13.4, 11.6, 4.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.86, 160.08, 147.85, 111.47, 104.52, 67.64, 58.43, 34.63, 31.23, 21.11. HRMS (EI^+): m/z calc. for $C_{12}H_{16}O_4$ $[M]^+$ 224.1043, found 224.1041.

Methyl-5-isopropylfuran-2-carboxylate (3m). Colorless oil (yield 75%). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.10 (d, J = 3.4 Hz, 1H), 6.11 (dd, J = 3.4, 0.9 Hz, 1H), 3.87 (s, 3H), 3.02 (p, J = 6.9 Hz, 1H), 1.30 (s, 3H), 1.28 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.77, 159.50, 142.89, 119.27, 105.64, 51.82, 28.31, 21.08. HRMS (EI^+): m/z calc. for $C_9H_{12}O_3$ $[M]^+$ 168.0781, found 168.0779.

Methyl-5-(sec-butyl)furan-2-carboxylate (3n). Colorless oil (yield 88%). ^{1}H NMR (400 MHz, chloroform-d) δ 7.12 (d, J = 3.4 Hz, 1H), 6.13 (d, J = 3.4 Hz, 1H), 3.89 (s, 3H), 2.83 (q, J = 6.9 Hz, 1H), 1.77 (dt, J = 13.5, 7.2 Hz, 1H), 1.65–1.54 (m, 1H), 1.28 (d, J = 7.0 Hz, 3H), 0.91 (t, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.88, 159.50, 142.87, 119.26, 106.48, 51.81, 35.15, 28.54, 18.47, 11.58. HRMS (ESI) m/z calc. for $C_{10}H_{15}O_3$ $[M + H]^+$ 183.1016, found 183.1015.

Methyl-5-cyclopentylfuran-2-carboxylate (3o). Colorless oil (yield 86%). ^{1}H NMR (400 MHz, chloroform-d) δ 7.09 (d, J = 3.4 Hz, 1H), 6.12 (d, J = 3.4 Hz, 1H), 3.87 (s, 3H), 3.19–3.09 (m, 1H), 2.11–1.99 (m, 2H), 1.79–1.63 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.32, 159.48, 142.89, 119.33, 106.18, 51.81, 39.07, 31.99, 25.34. HRMS (ESI) m/z calc. for $C_{11}H_{15}O_3$ $[M + H]^+$ 195.1016, found 195.1016.

Methyl-5-(tetrahydrofuran-3-yl)furan-2-carboxylate (3p). Colorless oil (yield 83%). ^{1}H NMR (400 MHz, chloroform-d) δ 7.11 (d, J = 3.5 Hz, 1H), 6.22 (dd, J = 3.4, 0.8 Hz, 1H), 4.10 (dd, J = 8.6, 7.4 Hz, 1H), 3.98 (td, J = 8.2, 5.8 Hz, 1H), 3.94–3.89 (m, 1H), 3.88 (s, 3H), 3.84 (dd, J = 8.6, 6.5 Hz, 1H), 3.55 (p, J = 7.0 Hz, 1H), 2.38–2.28 (m, 1H), 2.19–2.08 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.13, 159.27, 143.56, 119.21, 107.32, 72.06, 68.15, 51.94, 38.74, 31.80. HRMS (ESI) m/z calc. for $C_{10}H_{13}O_4$ $[M + H]^+$ 197.0808, found 197.0814.

***tert*-Butyl 3-(5-(methoxycarbonyl)furan-2-yl)pyrrolidine-1-carboxylate (3q).** Brown oil (yield 78%). ^{1}H NMR (400 MHz, chloroform-d) δ 7.11 (d, J = 3.4 Hz, 1H), 6.21 (d, J = 3.4 Hz, 1H), 3.88 (s, 3H), 3.79–3.72 (m, 1H), 3.55–3.36 (m, 4H), 2.27 (dq, J = 12.1, 6.3 Hz, 1H), 2.10 (dq, J = 12.5, 8.3 Hz, 1H), 1.47 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.23, 159.24, 154.53, 143.70, 119.11, 107.49, 79.64, 51.98, 45.32, 28.66. HRMS (ESI) m/z calc. for $C_{15}H_{21}NNaO_5$ $[M + Na]^+$ 318.1312, found 318.1305.

***tert*-Butyl 4-(5-(methoxycarbonyl)furan-2-yl)piperidine-1-carboxylate (3r).** Brown oil (yield 74%). ^{1}H NMR (400 MHz, chloroform-d) δ 7.11 (d, J = 3.4 Hz, 1H), 6.13 (d, J = 3.5 Hz, 1H), 4.16 (dt, J = 13.3, 3.4 Hz, 2H), 3.88 (s, 3H), 2.89–2.79 (m, 3H), 2.02 (dd, J = 13.8, 3.4 Hz, 2H), 1.60 (qd, J = 12.3, 4.2 Hz, 2H), 1.47 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.56, 159.36, 154.86, 143.18, 119.15, 106.36, 79.76, 51.93, 35.88, 30.32, 28.59. HRMS (ESI) m/z calc. for $C_{16}H_{23}NNaO_5$ $[M + Na]^+$ 332.1468, found 332.1466.

Methyl 5-(oxetan-3-yl)furan-2-carboxylate (3s). White solid (yield 37%). ^{1}H NMR (400 MHz, chloroform-d) δ 7.16 (d, J = 3.5 Hz, 1H), 6.39 (d, J = 3.5 Hz, 1H), 4.97 (dd, J = 8.6, 6.0 Hz, 2H), 4.86 (dd, J = 7.1, 6.0 Hz, 2H), 4.38 (p, J = 7.8 Hz, 1H), 3.90 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.22, 159.15, 143.96, 119.22, 108.20, 75.99, 52.05, 34.14. HRMS (ESI) m/z calc. for $C_9H_{11}O_4$ $[M + H]^+$ 183.0652, found 183.0657.

***tert*-Butyl 3-(5-(methoxycarbonyl)furan-2-yl)azetidine-1-carboxylate (3t).** Brown oil (yield 66%). ^{1}H NMR (400 MHz, chloroform-d) δ 7.14 (d, J = 3.4 Hz, 1H), 6.33 (d, J = 3.4 Hz, 1H), 4.26 (t, J = 8.7 Hz, 2H), 4.07 (dd, J = 8.5, 6.2 Hz, 2H), 3.89 (s, 3H), 3.88–3.82 (m, 1H), 1.46 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.66, 159.18, 156.28, 144.05, 119.18, 108.29, 80.00, 52.05, 28.52, 27.47. HRMS (ESI) m/z calc. for $C_{14}H_{19}NNaO_5$ $[M + Na]^+$ 304.1155, found 304.1149.

Methyl 5-(*tert*-butyl)furan-2-carboxylate (3u). Colorless oil (yield 81%). ^{1}H NMR (400 MHz, chloroform-d) δ 7.08 (d, J = 3.4 Hz, 1H), 6.10 (d, J = 3.4 Hz, 1H), 3.87 (s, 3H), 1.32 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.09, 159.51, 142.85, 119.15, 104.89, 51.76, 33.24, 28.96. HRMS (ESI) m/z calc. for $C_{10}H_{15}O_3$ $[M + H]^+$ 183.1016, found 183.1011.

Methyl 5-(2,2-difluoroethyl)furan-2-carboxylate (3v). Brown oil (yield 28%). ^{1}H NMR (400 MHz, chloroform-d) δ 7.14 (d, J = 3.5 Hz, 1H), 6.38 (d, J = 3.5 Hz, 1H), 6.06 (tt, J = 55.9, 4.6 Hz, 1H), 3.89 (s, 3H), 3.29 (td, J = 16.0, 4.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.06, 151.36 (t, J = 7.3 Hz), 144.49, 119.20, 114.18 (t, J = 241.9 Hz), 111.20, 52.09, 34.15 (t, J = 24.7 Hz). HRMS (ESI) m/z calc. for $C_8H_9F_2O_3$ $[M + H]^+$ 191.0514, found 191.0510.

Methyl 5-(2,2,2-trifluoroethyl)furan-2-carboxylate (3w). Colorless oil (yield 34%). ^{1}H NMR (400 MHz, chloroform-d) δ 7.16 (d, J = 3.5 Hz, 1H), 6.47 (d, J = 3.4 Hz, 1H), 3.90 (s, 3H), 3.56 (q, J = 10.1 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.92, 148.67, 144.92, 124.31 (q, J = 276.9 Hz), 119.04, 111.98, 52.15, 33.93 (q, J = 32.5 Hz). HRMS (EI^+): m/z calc. for $C_8H_7F_3O_3$ $[M]^+$ 208.0342, found 208.0342.

1-(5-Cyclohexylfuran-2-yl)ethan-1-one (3x). Colorless oil (yield 78%). ^{1}H NMR (600 MHz, chloroform-d) δ 7.12 (d, J = 3.5 Hz, 1H), 6.15 (dd, J = 3.6, 0.9 Hz, 1H), 2.72 (tt, J = 11.3, 3.6 Hz, 1H), 2.45 (s, 3H), 2.11–2.04 (m, 2H), 1.83 (dt, J = 12.8, 3.3 Hz, 2H), 1.74 (dddd, J = 13.9, 5.0, 3.3, 1.6 Hz, 1H), 1.49–1.34 (m, 4H), 1.27 (qt, J = 11.9, 3.5 Hz, 1H). ^{13}C NMR (150 MHz,

$CDCl_3$) δ 186.33, 166.45, 151.25, 119.17, 106.25, 37.63, 31.34, 25.98, 25.87. HRMS (ESI) *m/z* calc. for $C_{12}H_{17}O_2$ $[M + H]^+$ 193.1223, found 193.1224.

Methyl 5-((8*R*,9*S*,10*R*,13*S*,14*S*)-10,13-dimethyl-17-oxo-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl)furan-2-carboxylate (3y). White solid (yield 42%). ^{1}H NMR (400 MHz, chloroform-d) δ 7.11 (d, J = 3.4 Hz, 1H), 7.07 (d, J = 3.4 Hz, 1H), 6.23 (dd, J = 3.5, 1.0 Hz, 1H), 6.13 (dd, J = 3.5, 0.8 Hz, 1H), 5.46–5.40 (m, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.21 (s, 1H), 2.79–2.63 (m, 2H), 2.53–2.43 (m, 2H), 2.43–2.36 (m, 3H), 2.17–2.07 (m, 4H), 2.03–1.92 (m, 6H), 1.90–1.79 (m, 3H), 1.74–1.71 (m, 2H), 1.70–1.67 (m, 3H), 1.65 (d, J = 3.4 Hz, 1H), 1.61 (d, J = 3.1 Hz, 1H), 1.59–1.50 (m, 3H), 1.50–1.40 (m, 2H), 1.36–1.33 (m, 1H), 1.32–1.29 (m, 2H), 1.28–1.25 (m, 2H), 1.24–1.15 (m, 2H), 1.08 (s, 3H), 1.06 (s, 3H), 0.90 (s, 3H), 0.88 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 221.31, 221.29, 164.95, 163.51, 159.47, 159.45, 142.89, 142.43, 141.56, 140.23, 121.49, 120.49, 119.23, 119.11, 109.21, 105.88, 51.89, 51.87, 51.83, 50.48, 50.28, 47.65, 47.64, 38.97, 38.95, 37.45, 37.25, 37.22, 35.97, 34.64, 34.54, 34.34, 31.54, 31.48, 31.46, 30.88, 27.35, 25.28, 21.99, 21.95, 20.30, 20.08, 19.61, 19.51, 13.67, 13.66. HRMS (EI^+): *m/z* calc. for $C_{25}H_{32}O_4$ $[M]^+$ 396.2295, found 396.2293.

Author contributions

Conceptualization, C. Y.; methodology, J. Y. and X. Z.; chemical experiments, J. Y. and X. Z.; inspiration and discussions, J. Y., X. Z. and C. Y.; writing—original draft preparation, J. Y. and X. Z.; writing—review and editing, X. Z. and C. Y.

Conflicts of interest

There are no conflicts to declare.

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