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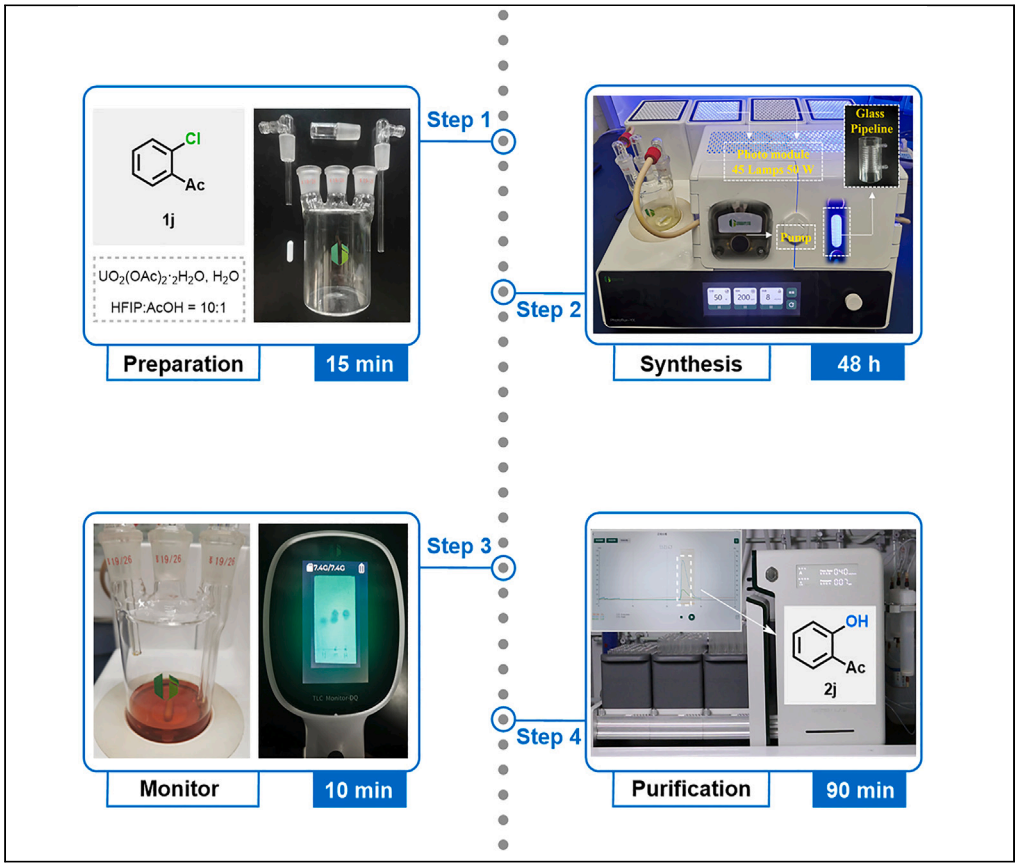
Protocol

Protocol for hydroxylating aryl chlorides catalyzed by photouranium with water under ambient conditions



Here, we present a protocol for the hydroxylation of aryl chlorides catalyzed by photouranium with water under ambient conditions. We describe steps for gram-scale hydroxylation of 2′-chloroacetophenone using our self-designed continuous-flow photoreactor. We then detail procedures for obtaining 2′-hydroxyacetophenone using our self-designed rapid separation and purification instrument. This protocol is not suitable for polycyclic and heterocyclic aryl chlorides.

Publisher's note: Undertaking any experimental protocol requires adherence to local institutional guidelines for laboratory safety and ethics.

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Highlights

Monitor the reaction via TLC Monitor-DQ

Small-scale parallel synthesis via PhotoSyn-10

Steps for purifying of the crude product via AutoSepa-MJL Late-stage

Steps for gram-scale preparation via continuous flow photoreactor Photoflux-YX

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Protocol for hydroxylating aryl chlorides catalyzed by photouranium with water under ambient conditions

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SUMMARY

Here, we present a protocol for the hydroxylation of aryl chlorides catalyzed by photouranium with water under ambient conditions. We describe steps for gram-scale hydroxylation of 2′-chloroacetophenone using our self-designed continuous-flow photoreactor. We then detail procedures for obtaining 2′-hydroxyacetophenone using our self-designed rapid separation and purification instrument. This protocol is not suitable for polycyclic and heterocyclic aryl chlorides.
For complete details on the use and execution of this protocol, please refer to Sun et al.[1]

BEFORE YOU BEGIN

Phenolic compounds are widely found in pharmaceuticals, pesticides, materials, and natural products.[2] Aryl chlorides, with their diverse types, abundant reserves, and low cost, typically serve as pivotal raw materials for various functional group transformations.[3] Therefore, synthesizing high-valued phenolic products from commercially available aryl chlorides holds practical industrial value. However, The C_{sp2}–Cl bond in aryl chlorides has a high bond dissociation energy of up to 400 kJ/mol, posing significant challenges for activation and transformation, often requiring stringent reaction conditions.[4] Pioneering work by Buchwald has highlighted the initial advancements in C−Cl activation,[5] leading to catalytic $2e^-$ oxidative addition.[6–12] Subsequent breakthroughs are achieved through rhodium-catalyzed $2e^-$ umpolung nucleophilic aromatic substitution (S_NAr)[13,14] and single-electron reduction strategies.[15–17] Since Sorensen's first application of photo-excited uranyl in the selective fluorination of cycloalkanes,[18] photouranium chemistry has made significant strides.[19–26] Our research in uranyl photoredox catalysis has harnessed the exceptional oxidative potential (E^o = +2.60 V vs. standard hydrogen electrode (SHE)) of the photo-excited uranyl ion ($*U^{VI}O_2^{2+}$) under blue light irradiation in ambient conditions.[27–31] This method combines synergistic water splitting via hydrogen atom transfer (HAT) with cation-radical accelerated S_NAr through single electron transfer (SET), which facilitates oxygen atom transfer (OAT), efficiently converting inert aryl chlorides into versatile phenols. For details of synthetic technology, please refer to Sun et al.[1]

Preparation of the reagents and setting up the equipment

A complete list of reagents and equipment can be found in the "key resources table" and "materials and equipment".

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Chemicals, peptides, and recombinant proteins		
2′-Chloroacetophenone (AR)	Leyan	CAS: 2142-68-9
Uranyl acetate (depleted uranium)	SPI-Chem	CAS: 6159-44-0
1,1,1,3,3,3-Hexafluoro-2-propanol (AR)	Macklin	CAS: 920-66-1
Acetic acid (AR)	Macklin	CAS: 64-19-7
Dichloromethane (AR)	Greagent	CAS: 75-09-2
Methanol (AR)	Greagent	CAS: 67-56-1
Silica gel for chromatography (100–200 mesh, AR)	Greagent	CAS: 63231-67-4
Silica gel for chromatography (300–400 mesh, AR)	Greagent	CAS: 63231-67-4
Quartz sand (AR)	Sinopharm	CAS: 14808-60-7
Petroleum ether (AR)	Greagent	CAS: 8032-32-4
Ethyl acetate (AR)	Greagent	CAS: 141-78-6
Deuterated chloroform, 99.8 atom%D	J&K Scientific	CAS: 865-49-6
Other		
TLC Monitor-DQ	ECNUGreenLab	Cat# DQA1601
Photoflux-YX	ECNUGreenLab	N/A
AutoSepa-MJL	ECNUGreenLab	N/A
PhotoSyn-10	ECNUGreenLab	Cat# YLA0026
LED light	ECNUGreenLab	Cat# YLA0026
Gloves	3M	Cat# WX300953410
Thin-layer chromatography (TLC plates 0.25 mm)	Leyan	Cat# C100053
Electronic balance	Sartorius	Cat#BSA124S
Low-temperature pump	Shanghai Xiangya	Cat# LC-310
Water circulating multi-purpose vacuum pump	Shanghai Xiangya	Cat# SHB-III
Absorbent cotton	Tansoole	Cat# 02025831
Vial (10 mL)	Synthware	Cat# V315010
Rotary evaporator	Heidolph	Cat# Hei-Vap Value
Splash-proof ball	LH Labware	Cat# LH-163-202
400 MHz NMR spectrometer	Bruker	N/A
Schlenk bottle (25 mL)	Synthware	Cat# F891925
Eggplant-shaped flask (100 mL)	Synthware	Cat# F319100
Eggplant-shaped flask (250 mL)	Synthware	Cat# F319250
Stir bar (2 cm)	N/A	N/A
Magnetic stirrer	Synthware	Cat# S360033
Hollow glass plug	Synthware	Cat# S401926
Chromatographic column empty column (100 mL)	Wuxi Tianyan	Cat# DB05

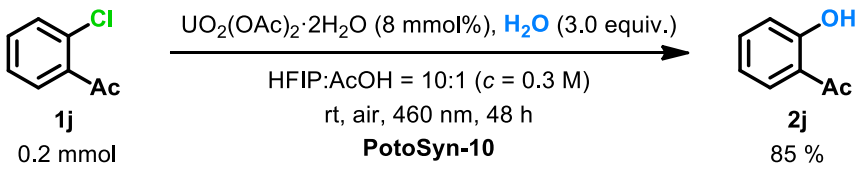
MATERIALS AND EQUIPMENT

Reagent	Storage	Shelf life
2′-Chloroacetophenone (AR)	25°C	more than two years
Uranyl acetate (depleted uranium)	25°C	more than two years
1,1,1,3,3,3-Hexafluoro-2-propanol (AR)	25°C	more than two years
Acetic acid (AR)	25°C	more than two years

STEP-BY-STEP METHOD DETAILS

Part 1: Synthesis of 2′-hydroxyacetophenone (2j)

Timing: 48 h



Scheme 1. The synthetic pathway of 0.2 mmol 1j

In this step, the synthesis of 2′-hydroxyacetophenone **2j** (Scheme 1; Scheme 2) has been accomplished by Photoflux-YX (Figure 1; Figure 2).

1. Reaction set up (Scheme 2; Table 1; Figure 3).
   a. Add the 2′-Chloroacetophenone **1j** (3.08 g, 20.0 mmol, 1.0 equiv.), $UO_2(OAc)_2 \cdot 2H_2O$ (680 mg, 1.6 mmol, 0.08 equiv.), acetic acid (6.0 mL), hexafluoroisopropanol (60 mL), H_2O (60 mmol, 1.08 g, 3.0 equiv.) and a 2 cm stir bar to a 100 mL three-necked flask (troubleshooting 1, 2 and 3).

   Note: Some of the uranium acetate is initially insoluble, but this does not affect the subsequent reaction. Under blue light irradiation, it eventually all dissolves.

   b. Equip the flask with glass plugs, and an inlet and outlet of micro tube made of glass tubing.
   c. Pump the reaction mixture into the microtube at a rate of 8.0 mL/min and then return to the flask.
      i. Irradiate this circulatory system with blue LEDs (460 nm, 50 W) for 48 h.
      ii. Set the stirring rate at 200 rpm (Figure 1 and Figure 3A).
   d. After 48 h, monitor the reaction using TLC (petroleum ether/ethyl acetate = 50:1) with UV light detection at 254 nm via TLC Monitor-DQ (Figure 3B, 3C, and 3D, troubleshooting 1 and 4).

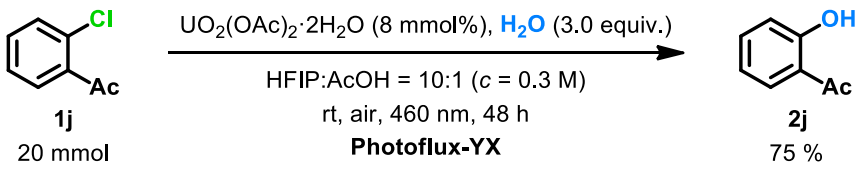
   Note: If the reaction does not complete, it is better to consider extending the reaction time or increasing the power of light.

Part 2: Purification of the crude product

Timing: 90 min (step 2: 30 min, step 3: 1 h)

This section completes the purification of the desired product **2j**.

2. work-up (30 min).
   a. Pump dichloromethane (30 mL) into the microtube to quench the reaction, followed by methanol (30 mL) to wash the tube (Figure 3E).
   b. Transfer the mixture to a 250 mL round-bottom flask.
   c. Remove the solvent by rotary evaporation (40°C, 80 rpm, 0.090–0.095 MPa) to obtain the crude product (Figure 3F and 3G).
3. Purification via AutoSepa-MJL (1 h) (Figure 4; Figure 5).



Scheme 2. General procedures for phenols

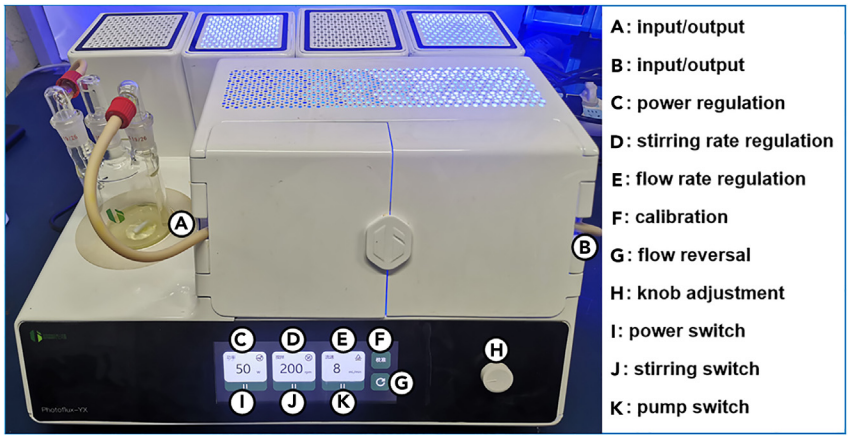


Figure 1. Photoflux-YX touch screen interface

The function of each module has been described (A–K).

(A) Input/output

(B) Input/output

(C) Power regulation

(D) Stirring rate regulation

(E) Flow rate regulation

(F) Calibration

(G) Flow reversal

(H) Knob adjustment

(I) Power switch

(J) Stirring switch

(K) Pump switch

a. Dilute the concentrated crude mixture with 100 mL dichloromethane.

b. Add 25 g of silica gel (100–200 mesh).

c. Swirl the flask and evaporate the solvent under vacuum (40°C, 80 rpm, 0.090–0.095 MPa) (Figure 3H).

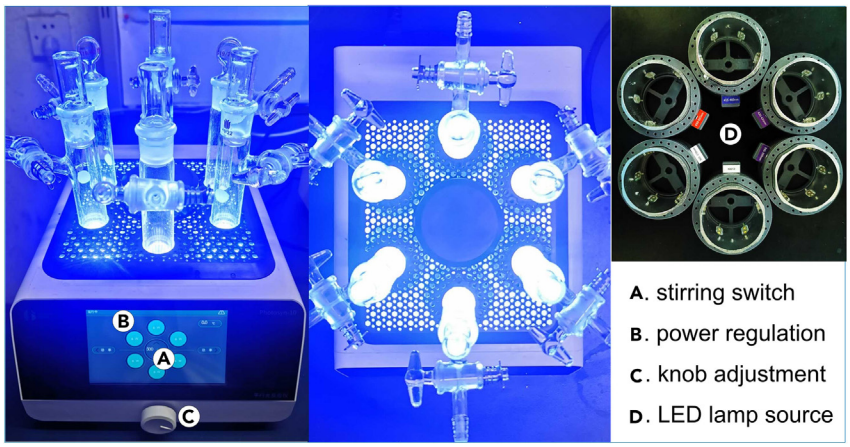


Figure 2. Parallel photoreactor PhotoSyn-10 for small scale

The operating panel adjusts the optical power and magneton speed.

(A) Stirring switch

(B) Power regulation

(C) Knob adjustment

(D) LED lamp source

Table 1. Quantification of reagents, solvent, and product

Reagent	MW (g/mol)	m (g)	n (mmol)	Equiv.	V (mL)	Conc (M)	Yield (%)
1j	154	3.08	20.0	1.0			
$UO_2(OAc)_2 \cdot 2H_2O$	424	0.68	1.6	0.08			
H_2O	18	1.08	60.0	3.0			
acetic acid					6.0		
hexafluoroisopropanol					60.0	0.30	
2j	136	2.05					75

Note: Absorbent cotton is placed inside the splash-proof ball to prevent silica gel from splashing during vacuum evaporation.

d. Add silica gel (10 cm, 300–400 mesh) to the empty silica gel column.
   i. Load the free-flowing silica gel and quartz sand (2 cm) to the column.
   ii. Secure the cover and mount it on the AutoSepa-MJL (Figure 3I).
e. Open the software and configure the solvent system to petroleum ether/ethyl acetate.
   i. Start with pure petroleum ether for the first 10 min.
   ii. Increase the ethyl acetate concentration linearly to 5% over the next 10 min.
   iii. Maintain the solvent ratio after 20 min.
   iv. Set the flow rate to 45 mL/min and use threshold collection mode (Figure 5 and troubleshooting 5).

Note: Some of the collected test tubes may contain impurities along with the desired compound, necessitating further confirmation by TLC.

f. The separation began, and the absorption peak appeared from 24 min to 28 min (Figure 5).
g. Use TLC (petroleum ether/ethyl acetate = 50/1) with UV-light detection (254 nm) to analyze the fractions.
h. Collect the fractions containing the product (R_f = 0.6).
i. Remove the solvent using rotary evaporation (40°C, 80 rpm, 0.090–0.095 MPa) to obtain the pure product (Figure 3J).
j. Identify and characterize the product by ^{1}H-NMR, ^{13}C-NMR and GCMS.

EXPECTED OUTCOMES

The 2′-hydroxyacetophenone **2j** is obtained as a light yellow liquid with a 75% yield (2.05 g, purity > 95.0%).

QUANTIFICATION AND STATISTICAL ANALYSIS

Analytical data

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.22 (d, *J* = 1.6 Hz, 1H), 7.59–7.55 (m, 1H), 7.35–7.30 (m, 1H), 6.85–6.82 (m, 1H), 6.78–6.73 (m, 1H), 2.48–2.45 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 204.1, 161.9, 135.9, 130.4, 119.2, 118.5, 117.8 26.0.

GCMS (EI) [M] Calculated for $C_8H_8O_2$ 136, Found 136.

LIMITATIONS

The protocol is not suitable for polycyclic and heterocycle aryl chlorides, due to the higher redox potential and lower electron density that hamper the excited uranyl ions for single-electron oxidation, such as 1-chloronaphthalene and 3-chloropyridine.

Figure 3. At different stages of the reaction

TROUBLESHOOTING

Problem 1

Step 1a and 1d: Yield is lower than expected.

Potential solution

The reaction time can be further extended, additional optical power added or the reaction fluid in the three-neck flask can be reduced by increasing the number of microtubules in series.

Problem 2

Step 1a: uranium acetate may be radioactive.

Potential solution

Natural uranium consists of three isotopes: ^{238}U, ^{235}U, and ^{234}U, with natural abundances of 99.28%, 0.71%, and 0.006%, respectively. Only ^{235}U and ^{234}U are radioactive, while the radiation from ^{238}U is

Figure 4. Rapid separation and purification instrument: AutoSepa-MJL

less than 199 microsieverts, posing almost no harm to the human body. Currently, commercial uranium available on the market is treated depleted uranium, which contains almost no ^{235}U and ^{234}U, making it safe for use.[32,33]

Problem 3

Step 1a: at the beginning of the reaction, the uranium acetate did not completely dissolve.

Potential solution

Some of the uranium acetate is initially insoluble, but this does not affect the subsequent reaction. Under blue light irradiation, it eventually all dissolves.

Problem 4

Step 1d: the raw material **1j** is not fully transformed and the polarity of the raw material and the product is similar.

Potential solution

The raw material **1j** will be fully transformed by extending the reaction time or by using an eluent with a higher proportion of petroleum ether through the column.

Problem 5

Step 3e: excessive pressure in the silica gel column caused the machine to stop.

Potential solution

To ensure there is no blockage at the bottom of the silica gel column, place a layer of cotton at the base before filling it with silica gel.

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Xuefeng Jiang (xfjiang@chem.ecnu.edu.cn).

Technical contact

Technical questions on executing this protocol should be directed to and will be answered by the technical contact, Leiyang Bai (lybai@chem.ecnu.edu.cn).

Materials availability

This study did not generate new unique reagents, all compounds have been described in the original article; see Sun et al.[1]

Data and code availability

All data reported in this paper will be shared by the lead contact upon request.

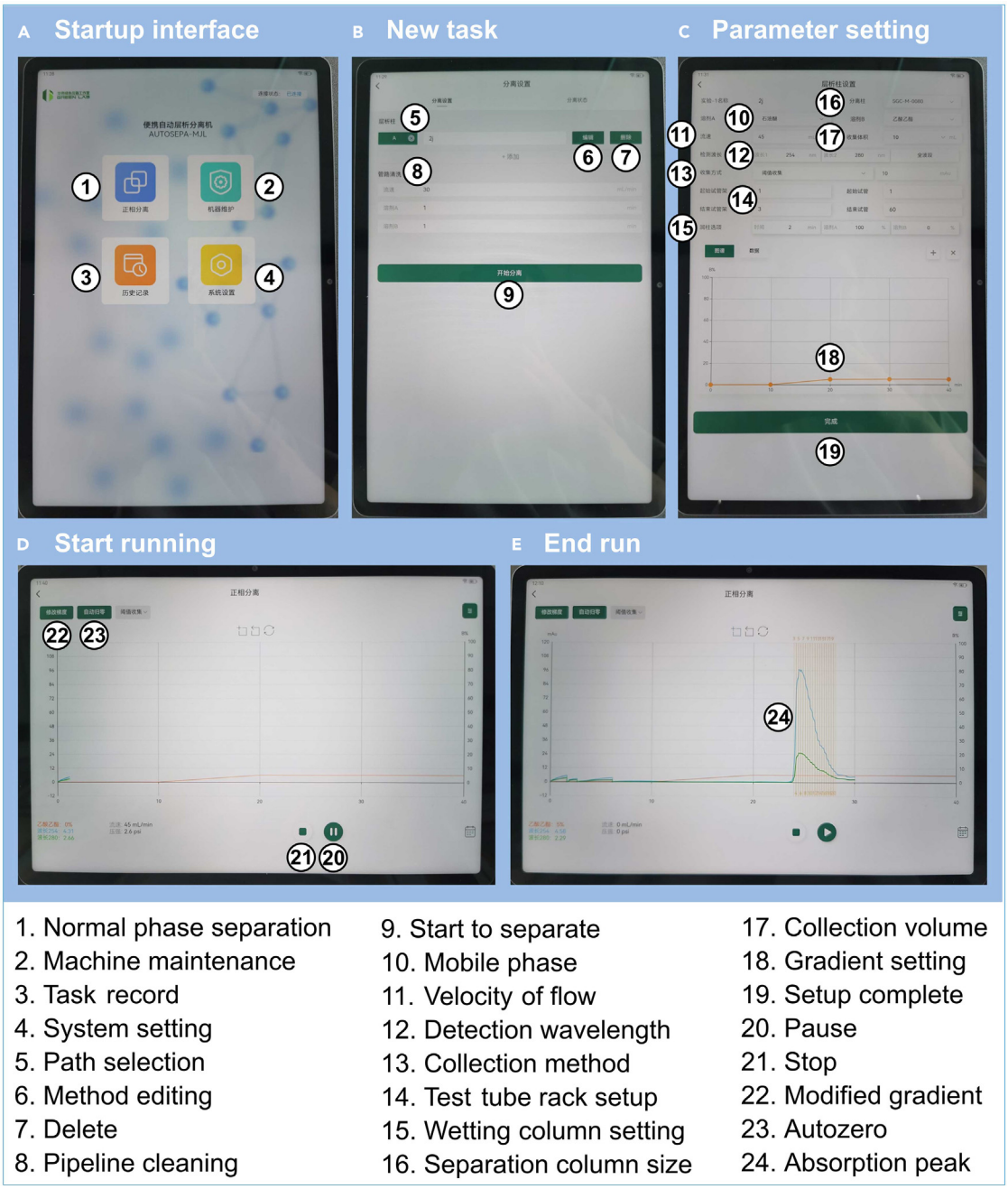


Figure 5. Software interface setup of AutoSepa-MJL

(A) Startup interface

(B) New task

(C) Parameter setting

(D) Start running

(E) End run

This paper does not report the original code.

Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

The published article includes all [datasets/code] generated or analyzed during this study, see Sun et al.[1]

ACKNOWLEDGMENTS

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AUTHOR CONTRIBUTIONS

X.J., C.L., and L.B. designed and wrote the protocol with inputs from all the authors. C.L. and L.B. performed the experimental data. X.J. supervised the project. All authors approved the final version of the manuscript for submission.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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