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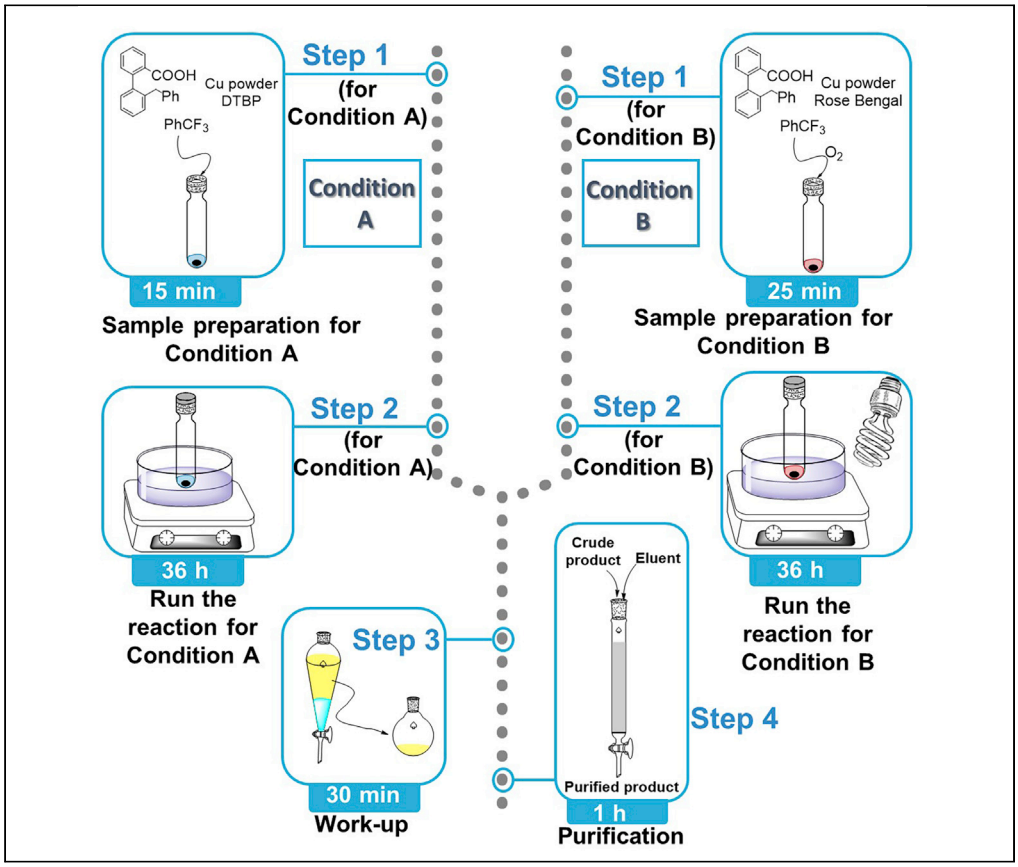
Protocol for chemo- and regioselective C(sp^3)–H activation using a heterogeneous copper powder-catalyzed reaction



Here, we present a protocol for the synthesis of dibenzo[c,e]oxepin-5(7H)-ones starting from 2′-alkyl-[1,1′-biphenyl]-2-carboxylic acids. This technique uses two copper(0)-catalyzed benzylic C(sp^3)–H activation strategies taking either *di*-tertbutyl peroxide or gaseous oxygen as an oxidant. We detail a photocatalytic thermal approach for copper powder-catalyzed reaction with oxygen. We also describe a procedure for catalyst recycling in both the strategies. The product has been successfully synthesized both in mmol and gram scale.

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

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Highlights

Chemo- and regioselective benzylic C(sp^3)–H activation

Copper powder is used as recyclable catalyst, no copper salt required

Sustainable copper/rose bengal dual catalysis replacing peroxide with oxygen

Synthesis of dibenzooxepinones: seven-membered biaryl lactones

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Protocol for chemo- and regioselective C(sp^3)–H activation using a heterogeneous copper powder-catalyzed reaction

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SUMMARY

Here, we present a protocol for the synthesis of dibenzo[c,e]oxepin-5(7H)-ones starting from 2′-alkyl-[1,1′-biphenyl]-2-carboxylic acids. This technique uses two copper(0)-catalyzed benzylic C(sp^3)−H activation strategies taking either *di*-tert-butyl peroxide or gaseous oxygen as an oxidant. We detail a photocatalytic thermal approach for copper powder-catalyzed reaction with oxygen. We also describe a procedure for catalyst recycling in both the strategies. The product has been successfully synthesized both in mmol and gram scale.

For complete details on the use and execution of this protocol, please refer to Nandi et al. (2022).

BEFORE YOU BEGIN

In the last two decades, huge development has been realized in the C−H activation field to ease the direct functionalization of C−H bond avoiding the pre-functionalization step (Crabtree and Lei, 2017; Rogge et al., 2021; Yi et al., 2017). Despite the progress, achieving high chemo-, regio- or stereoselectivity still remains as a tough task in absence of directing groups (Dalton et al., 2021; Lerchen et al., 2018). Thus, for the non-directed C(sp^3)−H bond activation, choosing weaker C(sp^3)−H bonds (e.g., benzyl, allyl etc.) over unbiased strong alkyl C(sp^3)−H bonds have been more fruitful (Feng et al., 2012; Golden et al., 2022; Liu et al., 2013, 2020; Lu et al., 2017; Manna et al., 2020; Nandi and Jana, 2022; Rout et al., 2014; Suh et al., 2020; Vasilopoulos et al., 2017).

Including the aforementioned literatures, plenty of the prior intra-/intermolecular benzylic-C(sp^3)−H /C(sp^2)−H activation strategies have been developed with copper catalysis (Begam et al., 2022; Guo et al., 2015b; Hu et al., 2020; Liang et al., 2020; Tran et al., 2014; Zhang et al., 2017). The Bois group achieved five- and six-membered lactones through Cu(II) catalyzed intramolecular C(sp^3)−H acyloxylation (Sathyamoorthi and Du Bois, 2016). Besides, following Martin (Gallardo-Donaire and Martin, 2013), other groups (Bhunia et al., 2019; Li et al., 2013, 2018; Ramirez et al., 2015; Shao et al., 2018; Tao et al., 2018) accessed six-membered lactones via intramolecular C(sp^2)−H activation of ortho-aryl benzoic acids using metal/metal-free conditions. Though use of bulk copper is worth aspiring (Guo et al., 2015a; Meng et al., 2020) for its low cost and easier handling, different copper salts have been used in most of the cases.

Inspired from these precedents, we hypothesized to synthesize dibenzo[c,e]oxepin-5(7H)-ones from 2′-alkyl-[1,1′-biphenyl]-2-carboxylic acids via C(sp^3)−H activation. Dibenzooxepinones, consisting of seven-membered lactone rings are quite prevalent in various natural products, bio-active

Table 1. Preparation of "vessel A" solution

Chemical	Final concentration	Amount
2′-benzyl-[1,1′-biphenyl]-2-carboxylic acid (stored at room temperature)	0.06 M	42.4 mg
Copper powder (stored at room temperature)	0.02 M	2.5 mg
DTBP (stored at 4°C)	0.13 M	74 μL
α,α,α-Trifluorotoluene	N/A	3 mL

compounds (Altemöller et al., 2009; Aly et al., 2008; Colombel et al., 2010). Recently, we have successfully realized the hypothesis taking copper(0) powder as the catalyst in two related yet distinct methodologies (Nandi et al., 2022), either using di-tertbutyl peroxide (DTBP) as oxidant or by efficiently replacing hazardous DTBP with molecular oxygen (O_2) taking additional help of photocatalysis. For both the strategies, the catalyst is easily recovered by filtration and recycled. Contrary to the previously available reports for synthesizing dibenzooxepinones, (Zhang et al., 2015), we have been able to execute it in fewer steps avoiding the pre-activation of substrate using low-cost copper as catalyst.

Therefore, the current protocol describes the stepwise synthesis of 7-phenyldibenzo[c,e]oxepin-5(7H)-one starting from 2′-benzyl-[1,1′-biphenyl]-2-carboxylic acid utilizing two distinct methodologies, both catalyzed by easily available copper(0) powder. For complete use of this protocol, please refer to (Nandi et al., 2022).

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".

Preparation of reaction vessel for "condition A"

Timing: 15 min

In this step, reaction vessel for Condition A is get ready. One pressure tube with Teflon cap labeled as "vessel A" containing solution of 2′-benzyl-[1,1′-biphenyl]-2-carboxylic acid, copper powder and di-tert butyl peroxide (DTBP) in α,α,α-Trifluorotoluene.

Note: Reaction vessel needs to be prepared fresh every time.

1. Preparation of "vessel A" (Table 1).
   a. In one 15 mL pressure tube with Teflon cap, place one magnetic stir-bar.
   b. Weigh out 42.4 mg (0.2 mmol) of 2′-benzyl-[1,1′-biphenyl]-2-carboxylic acid to the pressure tube.
   c. Add 2.5 mg of Cu powder (0.04 mmol).
   d. Add 3 mL of α,α,α-Trifluorotoluene to the pressure tube with a syringe.
   e. Add 74 μL (0.4 mmol) of DTBP with a microsyringe.

⚠ CRITICAL: DTBP is potentially explosive in nature. It should be handled with care. However, no such incident took place in our laboratory. Add DTBP at ambient condition in the fume hood promptly. And do not leave the reagent container opened in the air. Unfailingly, assure to close the container soon after taking the reagent.

   f. Seal the tube.

⚠ CRITICAL: All the reactants need to be efficiently put into the vessel so that any of the particle do not adhere to the mouth or inner wall of the pressure tube.

Table 2. Preparation of "vessel B" solution

Chemical	Final concentration	Amount
2′-benzyl-[1,1′-biphenyl]-2-carboxylic acid (stored at room temperature)	0.06 M	42.4 mg
Copper powder (stored at room temperature)	0.02 M	2.5 mg
rose bengal (RB) (stored at room temperature)	0.001 M	2.0 mg
α,α,α-Trifluorotoluene	N/A	3 mL

Preparation of reaction vessel for "condition B"

Timing: 25 min

In this step, reaction vessel for Condition B is arranged. One Teflon bushing pressure tube labeled as "vessel B" containing solution of 2′-benzyl-[1,1′-biphenyl]-2-carboxylic acid, copper powder, rose bengal (RB) in α,α,α-Trifluorotoluene is prepared.

Note: Reaction vessel needs to be prepared fresh every time.

2. Preparation of "vessel B" (Table 2).
   a. In one 15 mL pressure tube with Teflon cap, place one magnetic stir-bar.
   b. Weigh out 42.4 mg (0.2 mmol) of 2′-benzyl-[1,1′-biphenyl]-2-carboxylic acid to the pressure vessel.
   c. Add 2.5 mg of Cu powder (0.04 mmol).
   d. Add 2.0 mg of RB (0.002 mmol).
   e. Add to the pressure tube 3 mL of α,α,α-Trifluorotoluene with a syringe.
   f. Purge the tube with ultra-high purity (UHP) grade O_2 gas for one minute and readily seal with the cap.

⚠ CRITICAL: All the reactants need to be efficiently put into the vessel so that any of the particle do not remain sticked to the mouth or inner wall of the pressure tube.

Instrumental set-up for "condition A" (set-up A)

Timing: 30 min

Here, beside setting up the heater cum stirrer and clamp to perform the reaction under optimal conditions, some key parameters such as temperature, rotation speed are also set. And this would be denoted as "set-up A".

3. Set-up the heater cum stirrer.
   a. Equip the IKA stirrer (IKA WORKS INC. 3581201 C-MAG HS 7 IKAMAG Hot Plate Magnetic Stirrer, Glass Ceramics Heating Plate, 115 V in a fume hood (Figure 1A).
   b. Take one dry and clean borosilicate glass flat-bottom bowl (1 L) for making the oil bath.
   c. Fill the bowl with silicone oil.
   d. Place the oil filled bowl on the magnetic stirrer.
   e. Set one clamp on the stirrer so that the "vessel A" can be set.
   f. Hang and dip one thermometer to the oil, vertically. Troubleshooting 2.
4. Digital screen interface of the stirrer.
   a. Turn on the stirrer.
   b. Set the temperature so that the oil bath temperature reaches to 110°C. (In our case, setting digital reading of 145 was sufficient) (Figure 1C, yellow box).
   c. Set the rotation regulator at in between 1 and 2 (500 rpm) (Figure 1C, red box).

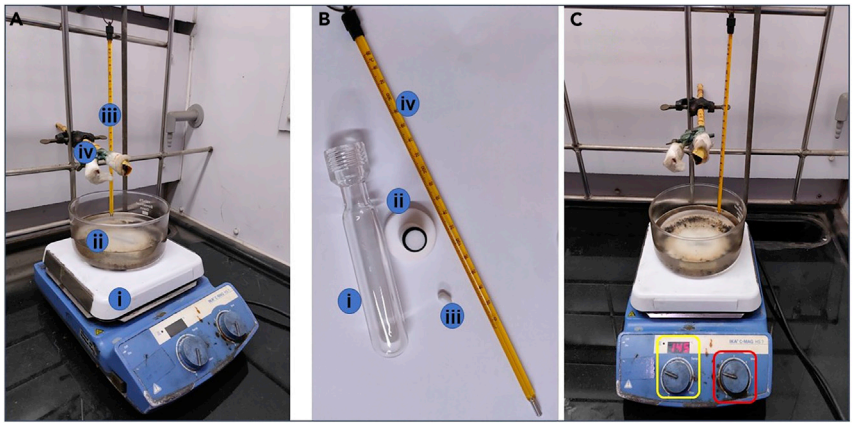


Figure 1. Overview of the "reaction set-up A"

(A) Instrumental set-up: (i) IKA hot plate magnetic stirrer, (ii) oil bath, (iii) clamp, (iv) hanging thermometer dipped in oil.

(B) Zoom in on the required accessories: (i) 15 mL pressure-tube, (ii) Teflon cap of the pressure tube, (iii) magnet bar, (iv) thermometer.

(C) The instrumental "set-up A". Yellow box: temperature interface. Red box: rotation regulator.

Instrumental set-up for "condition B" (set-up B)

Timing: 30 min

In this step, just like the previous one, beside setting up the magnetic stirrer and clamp to perform the reaction under optimal conditions, some key parameters such as temperature, rotation speed are also set. And this would be denoted as "set-up B".

5. Set-up the heater cum stirrer.
   a. Equip the IKA stirrer (IKA WORKS INC. 3581201 C-MAG HS 7 IKAMAG Hot Plate Magnetic Stirrer, Glass Ceramics Heating Plate, 115 V) in a fume hood (Figure 2A).
   b. Place an oil bath on the stirrer, similar to "set-up A".
   c. Set one clamp on the stirrer so that the "vessel A" can be set.
   d. Hang and dip one thermometer to the oil, vertically. Troubleshooting 2.

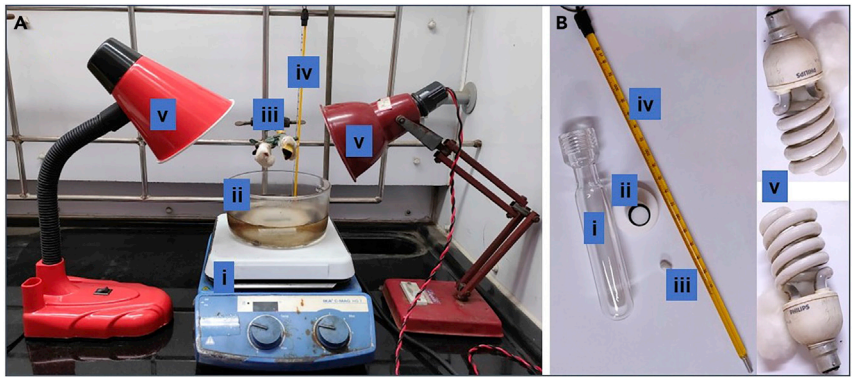


Figure 2. Overview of the "reaction set-up B"

(A) Instrumental set-up: (i) IKA hot plate magnetic stirrer, (ii) oil bath, (iii) clamp, (iv) hanging thermometer dipped in oil, (v) CFL stands.

(B) Zoom in on the required accessories: (i) 15 mL pressure-tube, (ii) Teflon cap of the pressure tube, (iii) magnet bar, (iv) thermometer, (v) CFLs.

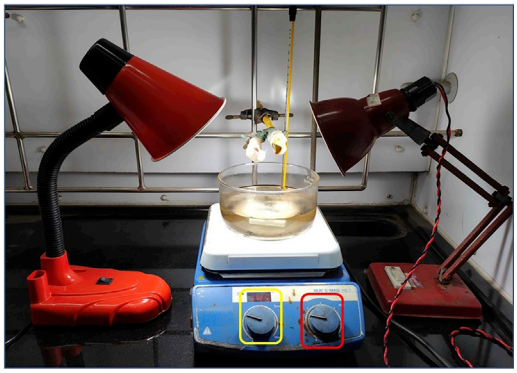


Figure 3. The instrumental "set-up B"
Yellow box: temperature interface. Red box: rotation regulator.

e. Set two white 23 W compact fluorescent lamps (CFLs) (Phillips Tornado T2 23W WW B22 220–240 V 1BC/6) in light-stands.
f. Place the lamps each at opposite sides of the magnetic stirrer so that the lamps remain headed towards oil bath at 5 cm apart.

6. Digital screen interface of the stirrer.
   a. Turn on the stirrer (Figure 3).
   b. Set the temperature so that the oil bath temperature reaches to 110°C. (In our case, setting digital reading of 145 was sufficient (Figure 3, yellow box).
   c. Set the rotation speed regulator at in between 1 and 2 (500 rpm) (Figure 3, red box).
   d. Turn on two CFLs.

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Chemicals, peptides, and recombinant proteins		
Copper (powder, <425 μm, 99.5% trace metals basis)	Sigma-Aldrich	CAS 7440-50-8
2′-benzyl-[1,1′-biphenyl]-2-carboxylic acid	Synthesized at our lab	(Nandi et al., 2022)
Di-tert-butyl peroxide	Sigma-Aldrich	CAS 110-05-4
Rose bengal	Sigma-Aldrich	CAS 632-69-9
α,α,α-Trifluorotoluene	Sigma-Aldrich	CAS 98-08-8
Other		
IKA WORKS INC. 7 IKAMAG Hot Plate Magnetic Stirrer	IKA	Ident. No. 0003581222
Microsyringe 50 μL, 700 series, removable needle	Hamilton	Cat. No. 20788
Tornado T2 23W WW B22 220–240 V 1BC/6	Philips	Product code: 872790092972001
Oil bath, flat bottom	Pyrex	Item code: 1470/12D
Round bottom flask	Borosil	Product code: 4380A16
Pressure tube, 15 mL	Sigma-Aldrich	Product code: Z181099
Separating funnel	Borosil	Product code: 6400017
Erlenmeyer (conical) flask	Borosil	Product code: 4980021
Reagent bottles	Borosil	Product code: 1501021
Chromatography column	Borosil	Product code: 6100063
Thin layer chromatography using aluminum TLC plate, silica gel coated with flourescent indicator F254	Supelco	Cat no.: 105554
Silica gel for chromatography, Silica gel 60 (0.040–0.063 mm) for column chromatography (230–400 mesh ASTM)	Millipore	CAS No.: 112926-00-8

(*Continued on next page*)

Continued		
REAGENT or RESOURCE	SOURCE	IDENTIFIER
Elecopto UV Cabinet for Chromatography analysis	Elecopto	Item part number: EO-111 ASIN: B089GNGKCC Buying link: https://www.amazon.in/Elecopto-UV-Cabinet-Chromatography-analysis/dp/B089GNGKCC/ref=sr_1_5?crid=2IK85T9EVYP2Q&keywords=uv+cabinet&qid=1653478071&sprefix=uv+cabinet+%2Caps%2C217&sr=8-5
Bruker-Avance 600 MHz NMR spectrometer	Bruker	N/A

MATERIALS AND EQUIPMENT

Reagents		
Reagents	Storage temperature	Maximum time for storage
2′-benzyl-[1,1′-biphenyl]-2-carboxylic acid	room temperature	more than two years
Copper powder	room temperature	more than two years
rose bengal (RB)	room temperature	more than two years
α,α,α-Trifluorotoluene	room temperature	more than two years
Di-tert-butyl peroxide	5°C	two years
Ultra-high purity (UHP) O_2	room temperature	more than two years

STEP-BY-STEP METHOD DETAILS

Part 1A: Synthesis of 7-phenyldibenzo[c,e]oxepin-5(7H)-one via "condition A"

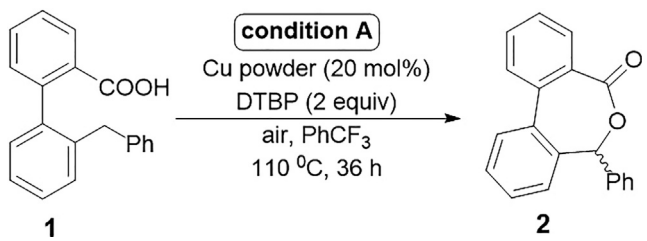
Timing: 36 h

In this step, the synthesis of 7-phenyldibenzo[c,e]oxepin-5(7H)-one **2** (Scheme 1) has been accomplished within 36 h on heating. As per the previous discussion, 2′-benzyl-[1,1′-biphenyl]-2-carboxylic acid is converted to the product **2** on heating it at 110°C with Cu powder as catalyst and DTBP as oxidant.

1. Set up the reaction (Figure 4). Troubleshooting 1.
   a. Deal with the "set up A" for the reaction under "condition A".
   b. Ensure that the stirrer is on and rotation speed is set at regulator reading 1 and 2.
   c. Ensure that the temperature is set rightly.
   d. Check the temperature reading in the thermometer. Troubleshooting 2.

   Pause point: Once the oil bath temperature reaches at 110°C, the equipment is ready to be run for the reaction and throughout the reaction, this temperature is required to be maintained.

2. Run the reaction.
   a. Dip the properly capped "vessel A" to the oil bath of "set up A" and attach it to the clamp.



Scheme 1. General scheme of the reaction under "condition A"

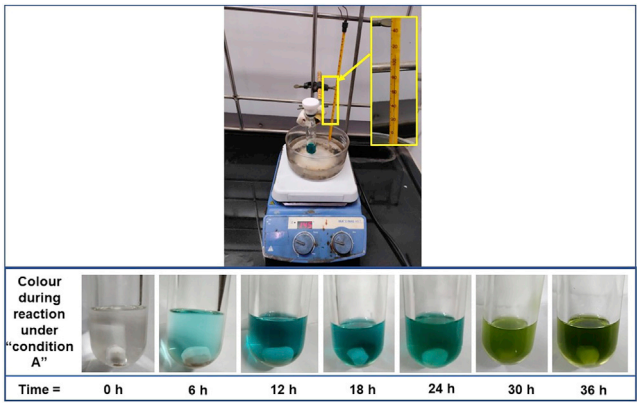


Figure 4. Running the reaction at 110°C and color change time-by-time

⚠ CRITICAL: Ensure that the reaction solvent front inside the "vessel A" is completely under the oil front in such a way that the headspace of the vessel is not immersed into oil either.

b. Ensure that the magnetic stir-bar is stirring properly.
c. At the calculated time, to stop the heating, reduce the temperature to 0 (at digital screen) so that the reaction temperature gradually reduces to the room temperature. The progress of the reaction is checked by TLC.

Note: During the reaction under "condition A", an evident color change of the reaction solution could be observed as depicted in "Figure 4". As shown, the color changes from colorless to blue to green. At the end of the reaction, green color appears and reaction becomes turbid, which indirectly refers to the reaction completion, additional to TLC.

d. Check the temperature of the bath using thermometer, hung vertically in the oil bath (troubleshooting 2). When the temperature reduces to room temperature, raise the pressure vessel from the oil and wash the outer wall with hexane and tissue paper.
e. Switch off the magnetic stirrer.

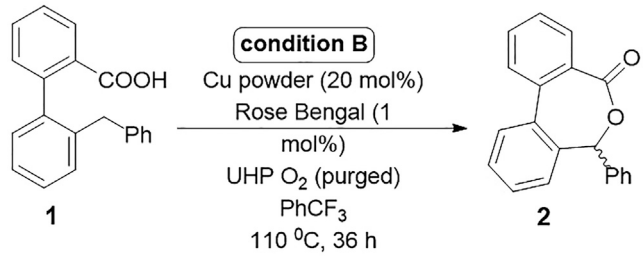
Part 1B: Synthesis of 7-phenyldibenzo[c,e]oxepin-5(7H)-one via "condition B"

Timing: 36 h

In this step, the synthesis of 7-phenyldibenzo[c,e]oxepin-5(7H)-one **2** (Scheme 2) has been accomplished within 36 h on heating. As per the previous discussion, 2′-benzyl-[1,1′-biphenyl]-2-carboxylic acid is converted to the product **2** on heating it at 110°C with Cu powder as catalyst and DTBP as oxidant.

3. Set up the reaction (Figure 6). Troubleshooting 1.
   a. Deal with the "set up B" for the reaction under "condition B".
   b. Ensure that the stirrer is on and rotation regulator is set at in between 1 and 2.
   c. Ensure that the temperature is set rightly.
   d. Ensure that both the lights are on.
   e. Check the temperature reading in the thermometer. Troubleshooting 2.

Pause point: Once the oil bath temperature reaches at 110°C, the equipment is ready to be run for the reaction, and throughout the reaction, this temperature is must to be maintained.



Scheme 2. General scheme of the reaction under "condition B"

4. Run the reaction.
   a. Dip the properly capped "vessel B" to the oil bath of "set up B" and attach it to the clamp.

   ⚠ CRITICAL: Ensure that the reaction solvent front inside the "vessel A" is completely under the oil front in such a way that the headspace of the vessel is not immersed into oil either.

   b. Ensure that the magnetic stir-bar is stirring properly.
   c. At the calculated time, reduce the temperature to 0 (at digital screen) so that the reaction temperature gradually reduces to the room temperature.
   d. Switch off the lights.
   e. Check the temperature in thermometer (troubleshooting 2). When the temperature reduces to room temperature, raise the pressure vessel from the oil and wash the outer wall with hexane and tissue paper.
   f. Switch of the magnetic stirrer.

Part 2A: Catalyst recycling of "condition A"

Timing: 2 h

As at the end of the reaction, the reaction medium became extremely turbid (Figure 7A) and full of dispersed CuNPs (indicated from transmission electron microscope image i.e., TEM) (Nandi et al., 2022), recyclability was checked. After one batch of the reaction, it was filtered, washed with ethyl

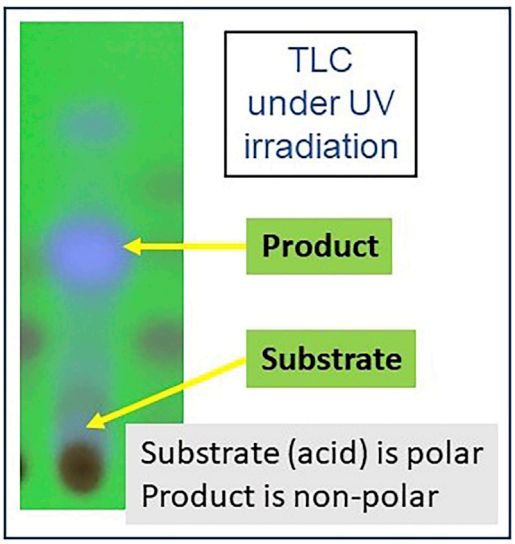


Figure 5. Image of TLC (run with 10% EtOAc in hexane) from reaction mixture

Figure 6. Running the reaction at 110°C under CFL irradiation

acetate and another batch of reaction was set up with the residue. Similarly subsequent four batches were repeated and the result was satisfactory.

5. Filter the residue and set-up a new batch.
   a. After completion, let the pressure tube settle as that allows the residues to be precipitated better.
   b. Isolate the precipitate by simple filtration by a funnel under air.
   c. Wash the filtrand with ethyl acetate for several times (Figure 7A).
   d. With filtrate, follow steps 3–16 (Part 2A) to isolate the product.
   e. Let the filtrand dry under air for 1 h. It will be used as catalyst for subsequent batches.
   f. Take back the recovered catalyst to another clean oven-dried pressure tube (Figure 7A).
   g. As the filtrand would be used as catalyst, prepare the reaction vessel as discussed earlier except the external addition of copper powder.
   h. Run the reaction similarly for 36 h.
   i. Follow steps 5a–5h (Part 2A).

Part 2B: Catalyst recycling of "condition B"

Timing: 2 h

Similarly, as "condition A", the catalyst was recycled in case of "condition B".

6. Filter the residue and set-up a new batch.
   a. Filter the residue and set-up a new batch of reaction following exactly similar manner as performed for "condition A" following steps 5a–5i (Part 2A).

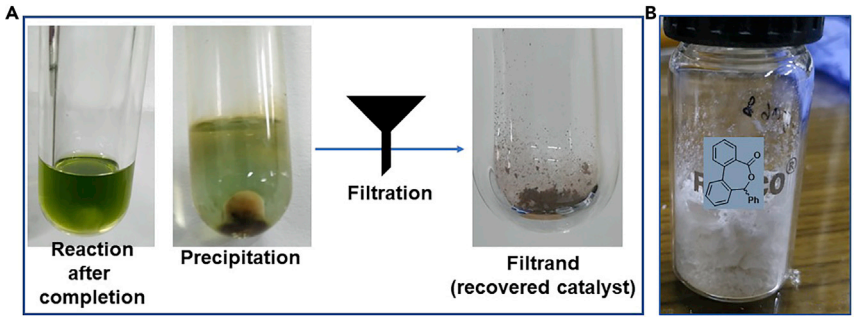


Figure 7. Practical utility of the protocol
(A) Recycling the catalyst, (B) Scale-up reaction under "condition B"

Part 3: Purification of the crude material

Timing: 1.5 h

Purify the crude material in similar manner for each type of reaction (under "condition A", "condition B" or "catalyst recycling").

7. Upon completion of the reaction,
   a. transfer the reaction mixture to a 125 mL separatory funnel.
   b. Add 30 mL of deionized water and 30 mL of ethyl acetate (EtOAc).
   c. Shake the separatory funnel vigorously.
   d. Let it settle so that the aqueous phase is separated from the organic one.

   Note: The thin-layer chromatography (TLC) (run with 10% ethyl acetate in hexane solution) from the reaction mixture looks like Figure 5, under UV irradiation (365 nm).

8. Transfer the separated aqueous phase and organic phase, each in one 250 mL Erlenmeyer flask.
9. Take back the aqueous phase to the separatory funnel and add 30 mL of EtOAc to it.
10. Then,
    a. Shake the separatory funnel vigorously.
    b. Let the two phases to separate.
    c. Transfer those similarly in their corresponding Erlenmeyer flasks.
11. For two times, repeat steps 9 and 10.
12. Transfer the combined organic phase into the separatory funnel and add 30 mL of deionized water to it. Shake the funnel vigorously and let it be stable so that the organic phase is separated from the aqueous one.
13. Take the aqueous phase and discard it in the proper waste container.
14. For additional two times, repeat steps 12 and 13.
15. Now, add 30 mL of Brine to the separatory funnel containing the organic phase and repeat step 14.
16. Take the organic phase in a 100 mL round bottom flask by filtering it through anhydrous sodium sulphate (Na_2SO_4) bed taken in a funnel.
17. Evaporate the solvent under reduced pressure in rotatory evaporator. (45°C, 240 mmHg, ~15 min).
18. Therefore,
    a. Add 1 mL of dichloromethane (DCM) and 200 mg of silica (mesh size: 230–400) to the dried crude material taken in round bottom flask.
    b. Swirl the flask gently.
    c. Evaporate the solvent under reduced pressure (40°C, 800 mbar, ~5 min).
19. Perform column chromatography to purify the crude product (25 cm of silica, Ø of the column= 3.0 cm) eluting 97:3 (by volume) mixture of hexane/ethyl acetate (~300 mL).
20. Combine the collected fractions containing pure product and remove the solvent under vacuum to achieve the desired product. Troubleshooting 3.

EXPECTED OUTCOMES

Condition A

7-phenyldibenzo[c,e]oxepin-5(7H)-one **2** appears as a white solid obtained in 82% isolated yield (34.4 mg).

Condition B

7-phenyldibenzo[c,e]oxepin-5(7H)-one **2** appears as a white solid obtained in 72% yield (30.2 mg). Troubleshooting 4.

Catalyst recycling

For condition A, the yields were 82%, 75%, 66%, and 48% from respective batches. Troubleshooting 5.

For "condition B", the yields were 72%, 68%, 65% and 55% from respective batches. Troubleshooting 5.

QUANTIFICATION AND STATISTICAL ANALYSIS

Analytical data

For 7-phenyldibenzo[c,e]oxepin-5(7H)-one (**2**).

^{1}H NMR (600 MHz, Chloroform-d) δ 8.03 (d, *J* = 7.8 Hz, 1H), 7.65–7.75 (m, 3H), 7.58 (t, *J* = 7.2 Hz, 1H), 7.41–7.52 (m, 6H), 7.29 (t, *J* = 7.2 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 6.25 (s, 1H).

^{13}C NMR (150 MHz, Chloroform-d) δ 169.42, 138.56, 138.46, 137.29, 135.73, 132.68, 131.46, 130.73, 129.54, 128.90, 128.78, 128.55, 128.52, 128.45, 128.40, 127.38, 126.97, 78.99.

HRMS(ESI^{+}): Calculated for $C_{20}H_{14}O_2Na$ $[M+Na]^{+}$: 309.0891; found: 309.0444.

Scaling-up the reaction under "condition B"

Under "condition B", we performed a reaction in 5 mmol scale, and the expected 7-phenyldibenzo [c,e]oxepin-5(7H)-one was isolated in 62% yield (650.2 mg).

Under "condition B", we performed a reaction in 10 mmol scale, and gratifyingly, the expected 7-phenyldibenzo[c,e]oxepin-5(7H)-one was isolated in 68% yield (1.426 g) (Figure 7B).

LIMITATIONS

The protocol is only limited to 7-membered lactone formation.

TROUBLESHOOTING

Problem 1

Step 1, step 3: The temperature does not fix at 110°C according to thermometer reading.

Potential solution

The magnetic stirrers cum heaters can behave differently on different occasions. While setting 145 digitally was adequate for us to reach oil bath temperature at 110°C, at another environment, it could be insufficient. But the main requirement is reaching the reaction temperature to 110°C. To attain that, set the instrumental temperature (digital reading) accordingly.

Problem 2

Steps 1d, 2d, 3e, 4e: The thermometer reading is fluctuating over time.

Potential solution

Please take care that the thermometer should not touch the bottom of the bath to avoid erroneous temperature measurements.

Problem 3

Step 19: Yield is lower than expected.

Potential solution

Check that the amount of solvent is taken as required. The headspace volume is important for the reaction.

Problem 4
Yield is lower than expected.

Potential solution
Check whether the reaction tube was fully purged with O_2 efficiently and capped. Since, O_2 is the main oxidant here, slight deviation might affect the reaction yield enormously.

Problem 5
Yield is lower than expected.

Potential solution
Be assured to use the filtrand soon after filtration and drying within 1 h. Failing which, resting the residue under air for longer time might affect the reaction outcome.

RESOURCE AVAILABILITY

Lead contact
Further information and requests for resources and reagents should be directed to and will be fulfilled by the lead contact, Ranjan Jana (rjana@iicb.res.in).

Materials availability
This study did not generate new unique reagents.

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

This paper does not report original code.

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

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AUTHOR CONTRIBUTIONS
S.N. and R.J. designed and wrote the protocol with inputs from all the authors. S.N. and S.M. performed the experimental data. R.J. supervised the project.

DECLARATION OF INTERESTS
The authors declare no competing interests.

REFERENCES
Altemöller, M., Gehring, T., Cudaj, J., Podlech, J., Goesmann, H., Feldmann, C., and Rothenberger, A. (2009). Total synthesis of graphislactones A, C, D, and H, of ulocladol, and of the originally proposed and revised structures of graphislactones E and F. Eur. J. Org. Chem. 2130–2140.

Aly, A.H., Edrada-Ebel, R., Indriani, I.D., Wray, V., Müller, W.E.G., Totzke, F., Zirrgiebel, U., Schächtele, C., Kubbutat, M.H.G., Lin, W.H., et al. (2008). Cytotoxic metabolites from the fungal endophyte alternaria sp. and their subsequent detection in its host plant polygonum senegalense. J. Nat. Prod. *71*, 972–980.

Begam, H.M., Nandi, S., and Jana, R. (2022). A directing group switch in copper-catalyzed electrophilic C–H amination/migratory annulation cascade: divergent access to benzimidazolone/benzimidazole. Chem. Sci. *13*, 5726–5733.

Bhunia, S.K., Das, P., Nandi, S., and Jana, R. (2019). Carboxylation of aryl triflates with CO_2 merging palladium and visible-light-photoredox catalysts. Org. Lett. *21*, 4632–4637.

Colombel, V., Joncour, A., Thoret, S., Dubois, J., Bignon, J., Wdzieczak-Bakala, J., and Baudoin, O. (2010). Synthesis of antimicrotubule dibenzoxepines. Tetrahedron Lett. *51*, 3127–3129.

Dalton, T., Faber, T., and Glorius, F. (2021). C–H activation: toward sustainability and applications. ACS Cent. Sci. *7*, 245–261.

Feng, J., Liang, S., Chen, S.-Y., Zhang, J., Fu, S.-S., and Yu, X.-Q. (2012). A metal-free oxidative esterification of the benzyl C—H bond. Adv. Synth. Catal. *354*, 1287–1292.

Gallardo-Donaire, J., and Martin, R. (2013). Cu-catalyzed mild C(sp2)–H functionalization assisted

by carboxylic acids en route to hydroxylated arenes. J. Am. Chem. Soc. *135*, 9350–9353.

Golden, D.L., Suh, S.-E., and Stahl, S.S. (2022). Radical C(sp3)–H functionalization and cross-coupling reactions. Nat. Rev. Chem. *6*, 405–427.

Guo, S., Yuan, Y., and Xiang, J. (2015a). Copper-catalyzed oxidative alkenylation of C(sp3)–H bonds via benzyl or alkyl radical addition to β-nitrostyrenes. New J. Chem. *39*, 3093–3097.

Guo, X.-X., Gu, D.-W., Wu, Z., and Zhang, W. (2015b). Copper-catalyzed C–H functionalization reactions: efficient synthesis of heterocycles. Chem. Rev. *115*, 1622–1651.

Hu, H., Chen, S.-J., Mandal, M., Pratik, S.M., Buss, J.A., Krska, S.W., Cramer, C.J., and Stahl, S.S. (2020). Copper-catalysed benzylic C–H coupling with alcohols via radical relay enabled by redox buffering. Nat. Catal. *3*, 358–367.

Crabtree, R.H., and Lei, A. (2017). Introduction: CH activation. Chem. Rev. *117*, 8481–8482.

Lerchen, A., Knecht, T., Koy, M., Ernst, J.B., Bergander, K., Daniliuc, C.G., and Glorius, F. (2018). Non-directed cross-dehydrogenative (hetero) arylation of allylic C(sp3)−H bonds enabled by C−H activation. Angew. Chem. Int. Ed. Engl. *57*, 15248–15252.

Luo, S., Li, L., Yang, Q., and Jia, Z. (2018). Organocatalytic electrochemical C–H lactonization of aromatic carboxylic acids. Synthesis *50*, 2924–2929.

Li, Y., Ding, Y.-J., Wang, J.-Y., Su, Y.-M., and Wang, X.-S. (2013). Pd-catalyzed C–H lactonization for expedient synthesis of biaryl lactones and total synthesis of cannabinol. Org. Lett. *15*, 2574–2577.

Liang, Q., Walsh, P.J., and Jia, T. (2020). Copper-catalyzed intermolecular difunctionalization of styrenes with thiosulfonates and arylboronic acids via a radical relay pathway. ACS Catal. *10*, 2633–2639.

Liu, H., Shi, G., Pan, S., Jiang, Y., and Zhang, Y. (2013). Palladium-catalyzed benzylation of carboxylic acids with toluene via benzylic C–H activation. Org. Lett. *15*, 4098–4101.

Liu, S., Achou, R., Boulanger, C., Pawar, G., Kumar, N., Lusseau, J., Robert, F., and Landais, Y. (2020). Copper-catalyzed oxidative benzylic C(sp3)–H amination: direct synthesis of benzylic carbamates. Chem. Commun. *56*, 13013–13016.

Lu, B., Zhu, F., Sun, H.-M., and Shen, Q. (2017). Esterification of the primary benzylic C–H bonds with carboxylic acids catalyzed by ionic iron(III) complexes containing an imidazolinium cation. Org. Lett. *19*, 1132–1135.

Manna, K., Begam, H.M., Samanta, K., and Jana, R. (2020). Overcoming the deallylation problem: palladium(II)-Catalyzed chemo-regio-and stereoselective allylic oxidation of aryl allyl ether, amine, and amino acids. Org. Lett. *22*, 7443–7449.

Meng, H., Xu, Z., Qu, Z., Huang, H., and Deng, G.-J. (2020). Copper(0)/PPh3-Mediated bisheteroannulations of o-nitroalkynes with methylketoximes accessing pyrazo-fused pseudoindoxyls. Org. Lett. *22*, 6117–6121.

Nandi, S., and Jana, R. (2022). Toward sustainable photo-/electrocatalytic carboxylation of organic substrates with CO_2. Asian J. Org. Chem. *2022*, e202200356.

Nandi, S., Mondal, S., and Jana, R. (2022). Chemo- and regioselective benzylic C(sp3)–H oxidation bridging the gap between hetero- and homogeneous copper catalysis. iScience *25*, 104341.

Ramirez, N.P., Bosque, I., and Gonzalez-Gomez, J.C. (2015). Photocatalytic dehydrogenative lactonization of 2-arylbenzoic acids. Org. Lett. *17*, 4550–4553.

Rogge, T., Kaplaneris, N., Chatani, N., Kim, J., Chang, S., Punji, B., Schafer, L.L., Musaev, D.G., Wencel-Delord, J., Roberts, C.A., et al. (2021). C–H activation. Nat. Rev. Methods Primers *1*, 43.

Rout, S.K., Guin, S., Ali, W., Gogoi, A., and Patel, B.K. (2014). Copper-catalyzed esterification of alkylbenzenes with cyclic ethers and cycloalkanes via C(sp3)–H activation following cross-dehydrogenative coupling. Org. Lett. *16*, 3086–3089.

Sathyamoorthi, S., and Du Bois, J. (2016). Copper-catalyzed oxidative cyclization of carboxylic acids. Org. Lett. *18*, 6308–6311.

Shao, A., Zhan, J., Li, N., Chiang, C.-W., and Lei, A. (2018). External oxidant-free dehydrogenative lactonization of 2-arylbenzoic acids via visible-light photocatalysis. J. Org. Chem. *83*, 3582–3589.

Suh, S.-E., Chen, S.-J., Mandal, M., Guzei, I.A., Cramer, C.J., and Stahl, S.S. (2020). Site-selective copper-catalyzed azidation of benzylic C–H bonds. J. Am. Chem. Soc. *142*, 11388–11393.

Tao, X.-Z., Dai, J.-J., Zhou, J., Xu, J., and Xu, H.-J. (2018). Electrochemical C−O bond formation: facile access to aromatic lactones. Chemistry *24*, 6932–6935.

Tran, B.L., Driess, M., and Hartwig, J.F. (2014). Copper-catalyzed oxidative dehydrogenative carboxylation of unactivated alkanes to allylic esters via alkenes. J. Am. Chem. Soc. *136*, 17292–17301.

Vasilopoulos, A., Zultanski, S.L., and Stahl, S.S. (2017). Feedstocks to pharmacophores: Cu-catalyzed oxidative arylation of inexpensive alkylarenes enabling direct access to diarylalkanes. J. Am. Chem. Soc. *139*, 7705–7708.

Yi, H., Zhang, G., Wang, H., Huang, Z., Wang, J., Singh, A.K., and Lei, A. (2017). Recent advances in radical C–H activation/radical cross-coupling. Chem. Rev. *117*, 9016–9085.

Zhang, J., Shi, D., Zhang, H., Xu, Z., Bao, H., Jin, H., and Liu, Y. (2017). Synthesis of dibenzopyranones and pyrazolobenzopyranones through copper(0)/selectfluor system-catalyzed double CH activation/oxygen insertion of 2-arylbenzaldehydes and 5-arylpyrazole-4-carbaldehydes. Tetrahedron *73*, 154–163.

Zhang, X.-S., Zhang, Y.-F., Li, Z.-W., Luo, F.-X., and Shi, Z.-J. (2015). Synthesis of dibenzo[c, e]oxepin-5(7H)-ones from benzyl thioethers and carboxylic acids: rhodium-catalyzed double C−H activation controlled by different directing groups. Angew. Chem. Int. Ed. Engl. *54*, 5478–5482.