Here, we present a ligand-enabled metallaphotoredox Suzuki-Miyaura cross-coupling protocol for the facile synthesis of diarylmethanes. Specifically, we describe the preparation of a unique class of ligands, 2,4-diarylquinolines, and demonstrate their application in nickel-catalyzed fragment couplings between alkyltrifluoroborates and haloarenes. We detail the synthesis of the most enabling ligand, PPQN$_{2,4}$-di-$\text{OMe}$, on a gram scale via sequential Grignard reaction and Friedländer condensation. We also outline how coupling reactions are performed without external photocatalysts under violet light irradiation.

Publisher’s note: Undertaking any experimental protocol requires adherence to local institutional guidelines for laboratory safety and ethics.
A ligand-enabled metallaphotoredox protocol for Suzuki-Miyaura cross-couplings for the synthesis of diarylmethanes

Jianbin Li,1,2 Chia-Yu Huang,1,2 and Chao-Jun Li1,3,4,*

1Department of Chemistry, FRQNT Centre for Green Chemistry and Catalysis, McGill University, 801 Sherbrooke Street W.,
Montreal, QC H3A 0B8, Canada
2These authors contributed equally
3Technical contact
4Lead contact
*Correspondence: cj.li@mcgill.ca
https://doi.org/10.1016/j.xpro.2022.101618

SUMMARY

Here, we present a ligand-enabled metallaphotoredox Suzuki-Miyaura cross-coupling protocol for the facile synthesis of diarylmethanes. Specifically, we describe the preparation of a unique class of ligands, 2,4-diarylquinolines, and demonstrate their application in nickel-catalyzed fragment couplings between alkyltrifluoroborates and haloarenes. We detail the synthesis of the most enabling ligand, PPQN2,4-di-OMe, on a gram scale via sequential Grignard reaction and Friedländer condensation. We also outline how coupling reactions are performed without external photocatalysts under violet light irradiation.

BEFORE YOU BEGIN

Pioneered by MacMillan, Molander and others (Chan et al., 2022; Huang et al., 2022; Tellis et al., 2016; Twilton et al., 2017), metallaphotoredox cross-couplings have gained exponential growth in both academic and industrial platforms for the last decade. These novel synthetic paradigms could synergize the advantages of rapidly developed molecular photochemistry and well-established transition metal catalysis, thus opening uncharted chemical space for new mechanistic insights and long-sought-after reactivities. A typical metallaphotoredox cross-couplings system mandates two discrete catalysts, which independently manage photocatalysis and organometallic cycles. Although such cooperative patterns have tackled numerous elusive challenges, optimizing these two-component catalytic systems still ranks among the most difficult tasks due to multivariate photocatalyst/metallacatalyst pairing and catalyst/ligand combination.

Significant progress has been made to meet chemists’ aspirations for more efficient chemical synthesis (Li, 2016; Li et al., 2021c, 2022a). In this area, state-of-the-art solutions include Fu’s strategy leveraging multiligand cooperativity (Chen et al., 2021), Ackermann’s and Greaney’s light-harvesting metal-substrate bound complexes (Gandeepan et al., 2019; Sagadevan and Greaney, 2019), metal-embedded covalent-organic framework (Vijeta et al., 2022), among others (Pei et al., 2022). In these elegant precedents, photosensitive species are either generated in situ or incorporated into the conventional ligated metal catalysts, therefore, circumventing exogeneous photocatalysts.

In this context, we contributed to this field by repurposing our previously reported organophotoredox catalyst (Li et al., 2021b) into a photoactive bipyridine-scaffold ligand, which could merge
the dual roles of metallaphotoredox catalysts into a unified entity. Such a setting allows us to perform metallaphotoredox cross-couplings under simplified conditions and generalize a broad range of reactivity features of bipyridyl metal complexes into one single-catalyst set.

The protocol below details the specific steps for PPQN\textsuperscript{2,4-di-OMe} synthesis, which is representative of other family members in this unique class of photoactive ligands. Guidelines of PPQN\textsuperscript{2,4-di-OMe} enabled nickel-catalyzed Suzuki-Miyaura cross-couplings that are applicable for fifteen different potassium benzyltrifluoroborates and sixteen substituted aryl halides are provided. This Ni/PPQN\textsuperscript{2,4-di-OMe} protocol has been extended to other four C-C bond-forming and six C-X bond-forming cross-couplings, either in redox-neutral or net reductive manners. PPQN\textsuperscript{2,4-di-OMe} with other base metals (e.g., Fe, Co and Cu) were also catalytically viable in radical-based fragment couplings. For details of these monocatalytic metallaphotoredox reactions, please refer to (Li et al., 2022b).

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

Preparation of the stock solvents

© Timing: 20.5 h

In this step, two degassed solvents for the reaction are prepared.

*Degassed acetone and methanol solvents*

| Reagent                                      | Final concentration | Amount |
|----------------------------------------------|---------------------|--------|
| Acetone                                      | N/A                 | 80 mL  |
| Methanol                                     | N/A                 | 40 mL  |
| 4 Å molecular sieves (beads, 8–12 mesh)     | N/A                 | 12 g   |

1. Activate 4 Å molecular sieves (MS) as mentioned below:
   a. Place 4 Å MS in a small beaker.
   b. Heat the MS in a 380°C muffle furnace for 12 h.
   c. Transfer the MS to a 50 mL round bottom flask.
   d. Quickly move the round bottom flask into a desiccator under the vacuum.
   e. Cool down the MS to 20°C–30°C.
   f. Seal the round bottom flask with a rubber septum.
   g. Evacuate the round bottom flask and refill it with argon.
   h. Repeat the evacuation-refill cycle twice so that the MS is under an inert atmosphere.
   i. Keep MS with argon before use.

△ CRITICAL: Gloves and beaker pliers would be needed since the beaker will be hot.

Alternatives: Nitrogen could be used as well to store the MS under an inert atmosphere.

2. Prepare the 80 mL acetone solvent as mentioned below:
   a. To a 100 mL round bottom flask is added 80 mL of acetone and 8 g of 4 Å MS.
   b. Seal the round bottom flask with a rubber septum.
   c. Purge the solvent with argon through an inlet needle with another needle outlet for 30 min (Figure 1).
   d. Remove the needles and seal the flask with Teflon tape.
   e. Keep the solvent over 4 Å MS for another 8 h before use.
3. Prepare the 40 mL MeOH solvent as mentioned below:
   a. To a 50 mL round bottom flask are added 40 mL of MeOH and 4 g of 4 Å MS.
   b. Seal the round bottom flask with a rubber septum.
   c. Purge the solvent with argon through an inlet needle, with another needle outlet, for 30 min.
   d. Remove the needles and seal the flask with Teflon tape.
   e. Keep the solvent over 4 Å MS for another 8 h before use.

   △ CRITICAL: Since the potassium alkyltrifluoroborates could be hydrolyzed over time, drying and degassing the solvent properly would be important.

   ♤ Pause point: Dried and degassed solvents could be stored at 20°C–30°C for more than 6 months.

Photochemical setup

♂ Timing: 5 min

In this step, the photochemical setup for the metallaphotoredox Suzuki-Miyaura reaction is presented (Figure 2).

-key resources table-

| REAGENT or RESOURCE | SOURCE | IDENTIFIER |
|---------------------|--------|------------|
| Chemicals, peptides, and recombinant proteins | COMBI-BLOCKS | Cat#OR-9846 |
| 1-(4-Methoxy-pyridin-2-yl)-ethanone, 95% | COMBI-BLOCKS | Cat#TB-3280 |
| Potassium benzyltrifluoroborate, 97% | Sigma-Aldrich | Cat#A89901 |
| 2-Aminobenzonitrile, 98% | Sigma-Aldrich | Cat#470260 |
| 4-Methoxyphenylmagnesium bromide solution, 0.5 M in THF | Sigma-Aldrich | Cat#7632 |

(Continued on next page)
## REAGENT or RESOURCE SOURCE IDENTIFIER

| REAGENT or RESOURCE | SOURCE | IDENTIFIER |
|---------------------|--------|------------|
| Nickel(II) chloride ethylene glycol dimethyl ether complex, 98% | Sigma-Aldrich | Cat#696668 |
| 2,6-Lutidine, 98% | Sigma-Aldrich | Cat#L3900 |
| Sulfuric acid, 95.0%–98.0% | Sigma-Aldrich | Cat#258105 |
| Acetic acid, >99.7% | Sigma-Aldrich | Cat#695092 |
| Hydrochloric acid, 37% | Sigma-Aldrich | Cat#320331 |
| Sodium hydroxide, ≥98% | Sigma-Aldrich | Cat#S5881 |
| Ethyl acetate, >99.8% | Sigma-Aldrich | Cat#270989 |
| Dichloromethane, ≥99.5% | Sigma-Aldrich | Cat#D65100 |
| Acetone, ≥99.5% | Sigma-Aldrich | Cat#179124 |
| Methanol, ≥99.8% | Sigma-Aldrich | Cat#179337 |
| Hexane, mixture of isomers, ≥99% | Sigma-Aldrich | Cat#227064 |
| Tetrahydrofuran (THF), septum-sealed, >99.9% | Fisher Scientific | Cat#6001668 |
| Silica gel for chromatography (40–63 µm, 60 Å) | EMD Chemicals | Cat#105719 |
| Argon, ≥99.999% | Praxair Canada | Cat#E-4563-L |
| Liquid nitrogen | Praxair Canada | Cat#E-4630-L |
| Deuterated chloroform, 99.8% deuterated | Cambridge Isotope Laboratories | Cat#DLM-7-PK |

### Software and algorithms

| SOFTWARE | SOURCE | IDENTIFIER |
|----------|--------|------------|
| TopSpin | Bruker | https://www.bruker.com/en/products-and-solutions/mr/mr-software/topspin.html |
| MassHunter | Agilent | https://www.agilent.com/en/product/software-informatics/mass-spectrometry-software |

### Other

| OTHER | SOURCE | IDENTIFIER |
|-------|--------|------------|
| Microwave tubes (10 mL and 20 mL) | Fisher Scientific | Cat#50-872-808 |
| 390 nm PR160L Kessil lamp | Kessil Science | Not applicable |
| Argon/vacuum Schlenk manifold | Fisher Scientific | Cat#31-501-795 |
| Disposable pasteur pipets | Fisher Scientific | Cat#13-678-20A |
| Preparative thin-layer chromatography (TLC) plate (layer thickness 250 µm) | EMD Chemicals | Cat#105719 |
| 4 Å molecular sieves (beads, 8–12 mesh) | Sigma-Aldrich | Cat#208590 |
| Edward E2M28 vacuum pump | Edwards Vacuum | Cat#A37317984 |
| Cooling pad | Manhattan | Cat#703406 |
| Crimpers (for microwave tubes) | Chemglass Life Sciences | Cat#CG-4930-20 |
| Decappers (for microwave tubes) | Chemglass Life Sciences | Cat#CG-4930-21 |
| Analytical balance MS104TS/00 | METTLER TOLEDO | Cat#3013522 |
| Thermolyne benchtop muffle furnace | Thermo Fisher Scientific | Cat#F48058 |
| 500 MHz AVIIIHD NMR | Bruker | Not applicable |
| Exactive Plus Orbitrap-API | Thermo Fisher Scientific | Cat#DLAEGAAPFALGMCBA |
| Gas chromatography-mass spectrometer | Agilent | Not applicable |
| Teflon-coated magnetic stirring bar | Brand | Cat#137300,137301 |
| Stirring hot plate | Fisher Scientific | Cat#11-497-6A |
| Sand (for sand bath) | Alfa Aesar | Cat#H37933 |
| UV protection goggles | Uline | Cat#S-24605SM |
| 250 mL Separatory funnel | Corning | Cat#6400-250 |
| Filter papers | Fisher Scientific | Cat#09-831 |
| Filter funnel | Fisher Scientific | Cat#S23818 |
| Erlenmeyer flasks | Thermo Fisher Scientific | Cat#4103-0125 |
| Round bottom flasks | Chemglass Life Sciences | Cat#CG-1506 |
| Aluminum crimp caps and PTFE-line silicone septa | Chrom Tech | Cat#5183-4477 |
| Rubber bulbs | Sigma-Aldrich | Cat#Z111597 |
| Rubber septa | Sigma-Aldrich | Cat#Z553964 |
| Spatula | Sigma-Aldrich | Cat#S4147 |
| pH Test paper | Sigma-Aldrich | Cat#1.09521 |
| Weighing papers | Sigma-Aldrich | Cat#WHA10347671 |

(Continued on next page)
**MATERIALS AND EQUIPMENT**

**Reagents**

- (2-Aminophenyl)(4-methoxyphenyl)methanone.
- 1-(4-Methoxy-pyridin-2-yl)-ethanone.
- Potassium benzyltrifluoroborate.
- Iodobenzene.
- Nickel(II) chloride ethylene glycol dimethyl ether complex.
- 2,6-Lutidine.
- Sulfuric acid.
- Acetic acid.
- Sodium hydroxide.
- Ethyl acetate.
- Dichloromethane.
- Acetone.
- Methanol.
- Hexane, mixture of isomers.
- Deionized water.
- Deuterated chloroform.

---

**Continued**

| REAGENT or RESOURCE | SOURCE | IDENTIFIER |
|---------------------|--------|------------|
| Rotary evaporator   | BUCHI  | Not applicable |
| Beaker pliers       | Sigma-Aldrich | Cat# Z225282 |
| Gloves              | Aurelia | Cat#93897 |
| Syringes            | Sigma-Aldrich | Cat#Z683531,Z683558 |
| Disposable needles  | Fisher Scientific | Cat#14-840-88 |
| Stainless syringe needle | Sigma-Aldrich | Cat#Z115606 |
| Fixed Needle Syringes | Thermo Fisher Scientific | Cat#36500505 |
| Cotton              | Sigma-Aldrich | Cat#BR28205-1KG |
| Stand holder        | Thermo Fisher Scientific | Cat#Z509450 |
| Clamps              | Sigma-Aldrich | Cat#Z689815 |
| Clamps holders      | Sigma-Aldrich | Cat#; Z243620 |
| 254 nm compact and handheld UV lamps (for TLC monitoring) | Fisher Scientific | Cat#UV5001614 |
| Dewar flask         | Fisher Scientific | Cat#FB1019623 |
| Heating gun         | Cole-Parmer | Cat#UZ-03026-01 |

**Figure 2. Overview of the photochemical setup**

(i) Microwave reaction tube, rubber septum, and Teflon-coated magnetic stirring bar. (ii) 390 nm PR160L Kessil lamp (5 cm away from the reaction tube). (iii) Clamp stand and stirring hot plate. (iv) Cooling pad for temperature maintenance. (v) Clamp.
**STEP-BY-STEP METHOD DETAILS**

**Part 1: Synthesis of diphenylmethane(2-aminophenyl)(4-methoxyphenyl)methanone**

- **Timing:** 24 h

In this step, the synthesis of diphenylmethane(2-aminophenyl)(4-methoxyphenyl)methanone (3) has been accomplished within 24 h through the Grignard reaction under an argon atmosphere (Scheme 1).

| Reagent                                      | Final concentration | Amount |
|----------------------------------------------|---------------------|--------|
| 4-Methoxyphenylmagnesium bromide solution in THF (0.5 M) | 0.46 M              | 60 mL  |
| 2-Aminobenzonitrile in THF (2.0 M)            | 0.15 M              | 5 mL   |
| Total                                        | N/A                 | 65 mL  |

The procedure was modified from the reported literature (Kobayashi et al., 2009).

1. Dry a 100 mL round bottom flask equipped with a Teflon-coated magnetic stirring bar with a heating gun at 100°C for 20 s.
2. Cool down the round bottom flask to 20°C–30°C in a desiccator under the vacuum.
3. Seal the round bottom flask with a rubber septum and fill with argon.
4. Connect the round bottom flask with an argon balloon.
5. Place the round bottom flask at 0°C (ice bath) with a magnetic stirring bar.
6. Add 60 mL of 0.5 M 4-methoxyphenylmagnesium bromide solution in THF (1, 30 mmol, 3 equiv) to the round bottom flask via syringe.
7. Allow the solution to cool to 0°C for 5 min. 2-Aminobenzonitrile (2, 10 mmol, 1 equiv) in 5 mL of anhydrous THF is added dropwise over 3 min.
   - **CRITICAL:** The addition should be slow because the reaction is exothermic.
   - **Alternatives:** The anhydrous THF sealed by septum is used in this case. It could also be freshly prepared following the preparation of the stock solvents.
8. Stir the mixture for 12 h at 20°C–30°C.
9. Add concentrated HCl (37%) dropwise until the pH of the mixture reaches 3, as indicated by pH test papers.
10. Stir the mixture for another 12 h at 20°C–30°C.
   - **Note:** The addition of HCl is to hydrolyze the imine intermediate.
   - **Pause point:** The crude mixture can be stored at 20°C–30°C for at least 8 h.
Part 2: Purification of diphenylmethane(2-aminophenyl)(4-methoxyphenyl)methanone

© Timing: 5 h

In this step, the pure diphenylmethane(2-aminophenyl)(4-methoxyphenyl)methanone (3) has been obtained within 5 h through extraction and column chromatography.

11. The reaction mixture is unsealed and cooled to 0°C with an ice bath.
12. 10 M NaOH (aqueous solution) is added dropwise until the pH of the mixture reaches 10, as indicated by pH test papers.
13. Remove THF by rotary evaporation (200 mbar at 40°C).
14. Extract the reaction mixture as mentioned below:
   a. Transfer the reaction mixture to a 250 mL separatory funnel.
   b. Add 100 mL of deionized water and 50 mL of EtOAc to the mixture.
   c. Shake the separatory funnel vigorously and let the aqueous phase separate from the organic one.
   d. Transfer the organic and aqueous phases into two separate 250 mL Erlenmeyer flasks.
   e. Put the aqueous phase back into the separatory funnel and add 50 mL of EtOAc.
   f. Repeat steps 14c to 14e twice and combine the organic phase.
15. Discard the aqueous phase in the appropriate waste container.
16. Add an appropriate amount of anhydrous MgSO₄ to remove water residue from the combined organic phase.
17. Filter the suspension into a 500 mL round bottom flask equipped with a funnel and filter paper. Rinse the residue with a minimal amount of EtOAc.
18. Remove the solvent by rotary evaporation (180 mbar at 40°C).
19. Dissolve the crude in 5–10 mL of CH₂Cl₂.
20. Purify the crude by gradient column chromatography (15 cm of silica gel, Ø of the column= 3 cm) using hexane to 5:1 volume mixture of hexane/EtOAc (Rf of 3 in 5:1 hexane/EtOAc = 0.39).
21. Collect the combined fractions containing product 3 and concentrate them under reduced pressure. Troubleshooting 1.
22. Characterize product 3 by NMR spectroscopy (¹H and ¹³C NMR) and gas chromatography-mass spectrometry (GC-MS).

|| Pause point: Diphenylmethane(2-aminophenyl)(4-methoxyphenyl)methanone (3) is shelf-stable. It can be stored at 20°C–30°C in the dark for at least 6 months.

Part 3: Synthesis of PPQN²,₄-di-OMe ligand

© Timing: 16 h

In this step, the synthesis of PPQN²,₄-di-OMe (5) has been accomplished within 16 h upon heating at 140°C under an argon atmosphere (Scheme 2).

| PPQN²,₄-di-OMe | Reagent                              | Final concentration | Amount |
|----------------|--------------------------------------|---------------------|--------|
|                | (2-Aminophenyl)(4-methoxyphenyl)methanone | 0.50 M              | N/A    |
|                | 1-(4-Methoxy-pyridin-2-yl)-ethanone    | 0.66 M              | N/A    |
|                | Acetic acid (AcOH)                    | N/A                 | 8.8 mL |
|                | Total                                 | N/A                 | 8.8 mL |

The following procedure was modified from the reported literature (Muthuramalingam et al., 2017).
23. Add the following reagents to a 20 mL round bottom flask equipped with a Teflon-coated magnetic stirring bar:
   a. Add 1 g of (2-aminophenyl)(4-methoxyphenyl)methanone (3, 4.4 mmol, 1 equiv).
   b. Add 0.87 g of 1-(4-methoxy-pyridin-2-yl)-ethanone (4, 5.8 mmol, 1.3 equiv).
   c. Add 8.8 mL of AcOH.
   d. Add 100 mg of H₂SO₄.

△CRITICAL: Gloves must be worn during the manipulations because AcOH and H₂SO₄ are corrosive.

△CRITICAL: AcOH should be added in a fume hood because it is volatile and irritative.

24. The tube is filled with argon and sealed by an aluminum cap with a polytetrafluoroethylene (PTFE)-lined silicone septum.

   Alternatives: Nitrogen could be used as well to conduct the reaction under an inert atmosphere.

△CRITICAL: The reaction will be heated to reflux and generate internal pressure; therefore, the PTFE-lined silicone septum should not be replaced with a rubber septum.

25. Stir the reaction mixture vigorously in a 140°C pre-heated sand bath for 16 h.

   Alternatives: The oil bath works equally well as the sand bath for heating in this case.

   ⏹️Pause point: The crude mixture can be stored at 20°C–30°C for at least 8 h.

Part 4: Purification of PPQN²,4-di-OMe ligand

⊙Timing: 3 h

In this step, the pure PPQN²,4-di-OMe (5) has been obtained within 3 h through extraction and column chromatography.

26. Cool the reaction down to 20°C–30°C.
27. The reaction mixture is unsealed and cooled to 0°C with an ice bath.
28. 10 M NaOH (aqueous solution) is added dropwise until the pH of the mixture reaches 10, as indicated by pH test papers.

   Alternatives: Before basification, most AcOH could be evacuated by rotary evaporation (100 mbar at 60°C).

29. Extract the reaction mixture as mentioned below:
   a. Transfer the reaction mixture to a 250 mL separatory funnel.
   b. Add 30 mL of deionized water and 50 mL of EtOAc to the mixture.
   c. Shake the separatory funnel vigorously and let the aqueous phase separate from the organic one. Troubleshooting 2.
   d. Transfer the organic and aqueous phases into two separate 250 mL Erlenmeyer flasks.
   e. Put the aqueous phase back into the separatory funnel and add 50 mL of EtOAc.
   f. Repeat steps 29c to 29e twice and combine the organic phase. Troubleshooting 3.
30. Discard the aqueous phase in the appropriate waste container.
31. Add an appropriate amount of anhydrous MgSO₄ to remove water residue from the combined organic phase.
32. Filter the suspension to a 500 mL round bottom flask equipped with a funnel and filter paper. Rinse the residue with a minimal amount of EtOAc.

33. Remove the solvent by rotary evaporation (180 mbar at 40°C).

34. Dissolve the crude in 5–10 mL of CH$_2$Cl$_2$, then add an appropriate amount of silica gel to dry the solution. Before dry loading, remove the solvent residue by rotary evaporation (600 mbar at 40°C).

35. Purify the residue by gradient column chromatography (10 cm of silica gel, Ø of the column=3 cm) using 20:1 to 1:1 volume mixture of hexane/EtOAc (R$_f$ of 5 in 1:1 hexane/EtOAc = 0.33).

36. Collect the combined fractions containing product 5 and concentrate them under reduced pressure. Troubleshooting 4.

37. Recrystallize 5 as mentioned below:
   a. Transfer the collected 5 to a 50 mL round bottom flask and remove the solvent by rotary evaporation.
   b. Add 25 mL of EtOAc to the round bottom flask.
   c. Dissolve 5 by heating the round bottom flask to 60°C with a heating gun.

   **Alternatives:** Hot water bath could be used as well to place the heating gun.

   d. Add 10 mL of hexane dropwise to the round bottom flask.
   e. Cover the round bottom flask with a rubber septum and let it slowly cool back to 20°C–30°C.
   f. After 1 h, the organic layer is removed with a glass pipette. The solid is washed with 5 mL of 10:1 mixture of hexane/EtOAc.
   g. Dry the purified 5 under vacuum.

   **Alternatives:** More 5 could be collected from the combined organic solution through second recrystallization or column purification.

38. Characterize product 5 by NMR spectroscopy (¹H and ¹³C NMR) and high-resolution mass spectrometry (HRMS).

   **Pause point:** PPQN$_2$,$^4$-di-OMe (5) is shelf-stable. It can be stored at 20°C–30°C for at least 6 months.

**Part 5: Synthesis of diphenylmethane**

**Timing:** 20 h

In this step, the synthesis of diphenylmethane (8) has been accomplished within 20 h under 390 nm light irradiation (Scheme 3).

### Diphenylmethane

| Reagent                  | Final concentration | Amount  |
|--------------------------|---------------------|---------|
| PPQN$_2$,$^4$-di-OMe     | 5 mM                | N/A     |
| NiCl$_2$·DME             | 5 mM                | N/A     |
| Potassium benzyltrifluoroborate | 0.15 M       | N/A     |
| Iodobenzene              | 0.10 M              | 22.3 µL |
| 2,6-Lutidine             | 0.35 M              | 81 µL   |
| Acetone                  | N/A                 | 1.9 mL  |
| MeOH                     | N/A                 | 0.10 mL |
| Total                    | N/A                 | 2.1 mL  |
This protocol could apply to the coupling between the other fifteen different potassium benzyltrifluoroborates (Li et al., 2012, 2020, 2021a; Wang et al., 2018) and sixteen aryl halides. For details of the scope of this metallaphotoredox Suzuki-Miyaura coupling, please refer to Li et al. (2022b).

39. To a 10 mL microwave tube equipped with a Teflon-coated magnetic stirring bar are added the following reagents:
   a. Add 3.4 mg of PPQN2,4-di-OMe (5, 10 μmol, 5 mol%).
   b. Add 2.2 mg of NiCl2·DME (10 μmol, 5 mol%).
   c. Add 1 mL of CH2Cl2.

40. The suspension is stirred at 20°C–30°C for 30 min and pre-form the nickel complex.

   △ CRITICAL: Upon complexation, the color of the nickel suspension would change from grass-green to light green.

Alternatives: The solid complex can be stored at 20°C–30°C in a desiccator for at least 1 week.

41. Remove the solvent by rotary evaporation (600 mbar at 40°C).

42. Add the following reagents to the same reaction tube:
   a. Add 59.4 mg of potassium benzyltrifluoroborate (6, 0.30 mmol, 1.5 equiv).
   b. Add 22.3 μL of iodobenzene (7, 0.20 mmol, 1 equiv).
   c. Add 1.9 mL of acetone.
   d. Add 0.10 mL of MeOH.
   e. Add 81 μL of 2,6-lutidine (75 mg, 0.70 mmol, 3.5 equiv).

43. Seal the tube with a rubber septum.

44. Connect the reaction tube to the Schlenk line via a syringe.

45. Perform three freeze-pump-thaw cycles as mentioned below:
   a. Freeze the reaction mixture in a Dewar flask filled with liquid nitrogen for 1 min (Figure 3).
   b. Evacuate the reaction mixture under vacuum for 30 s.
   c. Fill the tube with argon.

   Alternatives: Nitrogen could be used as well to conduct the reaction under an inert atmosphere.

   d. Remove the tube from the Dewar flask and warm the reaction mixture back to 20°C–30°C with a heating gun.
   e. Repeat steps 45a to 45d twice.
Alternatives: Purging the reaction mixture with inert gas for 10 min could be conducted as well to bypass the freeze-pump-thaw cycles.

46. Place the reaction tube in the photochemical setup and turn on the cooling pad to maintain the reaction temperature at 30°C–35°C.

47. Stir the reaction mixture under a 53 W 390 nm PR160L Kessil lamp irradiation (5 cm away from the light source) for 20 h.

△ CRITICAL: UV protection goggles must be worn during the manipulations because high power light source is harmful to the eyes. The light must not point toward other people.

● Pause point: The crude mixture can be stored at 20°C–30°C in the dark for at least 8 h.

Part 6: Purification of diphenylmethane

© Timing: 3 h

In this step, the pure diphenylmethane (8) has been obtained within 3 h through preparative thin-layer chromatography.

48. Unseal the reaction tube.

49. Filter the mixture through a 3 cm silica pad in a glass pipette and collect it with a 25 mL round bottom flask (Figure 4). The residue is rinsed with a minimal amount of EtOAc.

Alternatives: Filtration can remove insoluble salts formed during the reaction and most of the catalyst, simplifying the following purifications. This step could be bypassed but is highly recommended.

50. Remove the solvent by rotary evaporation (180 mbar at 40°C).

51. Purify the crude residue by preparative thin-layer chromatography (Prep. TLC) as mentioned below:
   a. Dissolve the residue in a minimal amount of CH₂Cl₂ and load it onto the Prep. TLC as a thin uniform band using a glass pipette or capillary tube.
   b. Develop the Prep. TLC using an isocratic eluent composed of a 10:1 volume mixture of hexane/EtOAc (Rf of 8 in 10:1 hexane/EtOAc = 0.90) in a glass chamber.
   c. Scrap off the silica band containing the desired product as indicated by a handheld UV lamp.
   d. Collect the product-containing silica gel in a glass pipette and flush it with 5 mL EtOAc into a 25 mL round bottom flask (Figure 5). The residue is rinsed with 10 mL of EtOAc.
   e. Remove the solvent by rotary evaporation (180 mbar at 40°C) to obtain pure 8. Troubleshooting 5.

52. Characterize product 8 by NMR spectroscopy (¹H and ¹³C NMR) and gas chromatography-mass spectrometry (GC-MS).

● Pause point: Diphenylmethane (8) can be stored at 20°C–30°C in the dark for at least 6 months.

EXPECTED OUTCOMES

(2-Aminophenyl)(4-methoxyphenyl)methanone (3) is obtained in 2.07 g (91%) as a yellow solid. PPQN²,4-di-OMe (5) is obtained in 0.92 g (61%) as a white solid. Diphenylmethane (8) is obtained as a colorless solid in 21.8 mg (65%).
QUANTIFICATION AND STATISTICAL ANALYSIS

Analytical data
For (2-aminophenyl)(4-methoxyphenyl)methanone (3):

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.68 (d, J = 8.8 Hz, 2H), 7.46 (d, J = 8.0 Hz, 1H), 7.32-7.24 (m, 1H), 6.95 (d, J = 8.8 Hz, 2H), 6.74 (d, J = 8.3 Hz, 1H), 6.66-6.60 (m, 1H), 5.84 (br, 2H), 3.88 (s, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 197.7, 162.1, 150.0, 134.1, 133.7, 132.2, 131.8, 119.2, 117.1, 115.8, 113.3, 55.4.

GC-MS (EI, m/z) for C$_{14}$H$_{13}$NO$_2$ Calcd: 227.1, found: 227.1.

For PPQN$_{2,4}$-di-OMe (5):

$^1$H NMR (500 MHz, CDCl$_3$) δ 8.56 (d, J = 5.5 Hz, 1H), 8.51 (s, 1H), 8.31–8.21 (m, 2H), 8.02 (dd, J = 8.4, 1.8 Hz, 1H), 7.82–7.71 (m, 1H), 7.57 (d, J = 8.7 Hz, 2H), 7.55–7.51 (m, 1H), 7.09 (d, J = 8.7 Hz, 2H), 6.92 (dd, J = 5.6, 2.6 Hz, 1H), 4.05 (s, 3H), 3.93 (s, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 166.7, 159.8, 158.4, 155.5, 150.3, 149.0, 148.5, 131.0, 130.7, 130.2, 129.3, 127.1, 126.7, 125.9, 119.4, 114.0, 111.2, 106.8, 55.4, 55.4.

HRMS (M+H$^+$) for C$_{22}$H$_{19}$N$_2$O$_2$ Calcd: 343.1441, found: 343.1442.
For diphenylmethane (8):

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.34–7.29 (m, 4H), 7.26–7.18 (m, 6H), 4.02 (s, 2H).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 141.1, 129.0, 128.5, 126.1, 42.0.

GC-MS (EI, m/z) for C$_{13}$H$_{12}$ Calcd: 168.1, found: 168.1.

**LIMITATIONS**
The protocol is limited to aryl halides and benzyl trifluoroborates.

**TROUBLESHOOTING**

**Problem 1**
Yield is lower than expected (major step 21).

**Potential solution**
Grignard reagents are highly reactive and sensitive to moisture and air; therefore, poor quality of the Grignard reagent or containments such as water and acetone residues on the glassware and syringes would cause inefficient transformation. To guarantee the quality of the Grignard reagent, it could also be freshly prepared from 4-bromoanisole and magnesium (Piller et al., 2009).

**Problem 2**
The phase separation is not efficient (major step 29c).

**Potential solution**
5–10 mL of brine could be added to assist the phase separation.

**Problem 3**
There are suspensions between two layers (major step 29f).

**Potential solution**
The PPQN$_{2,4}$-di-OMe (5) might precipitate during extraction due to its low solubility. In this case, heating the side of the separatory funnel to dissolve 5 might be helpful; otherwise, repeating extraction for more times might be required.
Problem 4
Product 5 precipitates in the column (major step 36).

Potential solution
The PPQN2,4-di-OMe (5) could precipitate in the column due to its low solubility in hexane. It will gradually dissolve with the increasing eluent polarity and totally dissolve at a 5:3 to 1:1 volume ratio of hexane/EtOAc co-eluent.

Problem 5
Yield is lower than expected (major step 51e).

Potential solution
This protocol is air-sensitive; therefore, insufficient degas might lead to low yield or no reaction. In addition to using dried and degassed stock solvents, three freeze-pump-thaw cycles are necessary to assure an inert atmosphere. Shake or stir the thawed mixture before the next freezing process is also recommended.

RESOURCE AVAILABILITY
Lead contact
Further information and requests for resources and reagents should be directed to and will be fulfilled by the lead contact, Chao-Jun Li (cj.li@mcgill.ca).

Materials availability
All other data supporting the finding of this study are available within the article or from the lead contact upon reasonable request. This study generated unique ligand and catalyst, and they are available from the lead contact upon reasonable request.

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

This paper does not report the original code.

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

Scheme 1. Diphenylmethane(2-aminophenyl)(4-methoxyphenyl)methanone (3)

Scheme 2. Synthesis of PPQN2,4-di-OMe ligand.
**ACKNOWLEDGMENTS**

The authors are grateful to the Canada Research Chair Foundation (to C.-J.L.), the Canada Foundation for Innovation, the FQRNT Center in Green Chemistry and Catalysis, the Natural Sciences and Engineering Research Council of Canada, and McGill University for supporting our research. The authors would also like to acknowledge the staffs at McGill Chemistry Characterization Facility for their contribution to the compound characterization in this work, specifically, Robin Stein for the NMR, Nadim Saaded and Alexander Wahba on HRMS.

**AUTHOR CONTRIBUTIONS**

J.L. conceived and designed the reaction and conducted some preliminary studies. C.-Y.H. performed the other experiments. J.L. wrote the manuscript with C.-Y.H. The project was under the supervision of C.-J.L. All the authors joined the discussion and gave approval for the final version of the manuscript. J.L. and C.-Y.H. contributed equally to this work.

**DECLARATION OF INTERESTS**

The authors declare no competing interests.

**REFERENCES**

Chen, A.Y., Perry, I.B., Bissonnette, N.B., Buksh, B.F., Edwards, G.A., Frye, L.I., Garry, O.L., Lavagnino, M.N., Li, B.X., Liang, Y., et al. (2022). Metallaphotoredox: the merger of photoredox and transition metal catalysis. Chem. Rev. 122, 1485–1542.

Chen, C., Peters, J.C., and Fu, G.C. (2021). Photoinduced copper-catalysed asymmetric amidation via ligand cooperativity. Nature 596, 250–256.

Gandeepan, P., Koeller, J., Korvorapun, K., Mohr, J., and Ackermann, L. (2019). Visible-light-enabled ruthenium-catalyzed meta-C-H alkylation at room temperature. Angew. Chem. Int. Ed. Engl. 58, 9820–9825.

Huang, C.-Y., Li, J., and Li, C.-J. (2022). Photocatalytic C(sp3)-C(sp3) radical generation via C-H, C-C, and C-X bond cleavage. Chem. Sci. 13, 5465–5504.

Kobayashi, K., Fujita, S., Fukamachi, S., and Konishi, H. (2009). One-pot synthesis of quinoline-cobaloxime dual photocatalytic system for oxidative C-C cross-couplings via H2 release. ACS Catal. 11, 14148–14158.

Li, J., Huang, C.-Y., Han, J.-T., and Li, C.-J. (2021b). Development of a quinolinium/cobaloxime dual photocatalytic system for oxidative C-C cross-couplings enabled by H2 release. ACS Catal. 11, 14148–14158.

Li, J., Huang, C.-Y., and Li, C.-J. (2021c). Deoxygenative functionalizations of aldehydes, ketones and carboxylic acids. Angew. Chem. Int. Ed. Engl. 61, e202112770.

Li, J., Huang, C.-Y., and Li, C.-J. (2022a). Cross-dehydrogenative coupling of unactivated alkanes. Trends Chem. 4, 479–494.

Li, J., Huang, C.-Y., and Li, C.-J. (2022b). Two-in-one metallaphotoredox cross-couplings enabled by a photoactive ligand. Chem. https://doi.org/10.1038/s41786-022-00510-11.

Li, J., Wang, H., Qiu, Z., Huang, C.Y., and Li, C.-J. (2020). Metal-free direct deoxygenative borylation of aldehydes and ketones. J. Am. Chem. Soc. 142, 13011–13020.

Muthuramalingam, S., Khamrang, T., Velusamy, M., and Mayilmurugan, R. (2017). Catalytic fixation of atmospheric carbon dioxide by copper(II) complexes of bidentate ligands. Dalton Trans. 46, 16065–16076.

Pei, C., Empel, C., and Koenigs, R.M. (2022). Visible-light-induced, single-metal-catalyzed, directed C-H functionalization: metal-substrate bound complexes as light-harvesting agents. Angew. Chem. Int. Ed. 134, e202201743.

Piller, F.M., Metzger, A., Schade, M.A., Haag, B.A., Gavryushin, A., and Knochel, P. (2009). Preparation of polyfunctional arylmagnesium, arylzinc, and benzyllic zinc reagents by using magnesium in the presence of LiCl. Chemistry 15, 7192–7202.

Sagadevan, A., and Greaney, M.F. (2019). meta-Selective C-H activation of arenes at room temperature using visible light: dual-function ruthenium catalysis. Angew. Chem. Int. Ed. Engl. 58, 9826–9830.

Tellis, J.C., Kelly, C.B., Primer, D.N., Jouffroy, M., Patel, N.R., and Molander, G.A. (2016). Single-electron transmetalation via photoredox/nickel dual catalysis: unlocking a new paradigm for sp2->sp3 cross-coupling. Acc. Chem. Res. 49, 1429–1439.

Twilton, J., Le, C., Zhang, P., Shaw, M.H., Evans, R.W., and MacMillan, D.W.C. (2017). The merger of transition metal and photocatalysis. Nat. Rev. Chem. 1, 1–19.

Vijeta, A., Casadevall, C., and Reisner, E. (2022). An integrated carbon nitride-nickel photocatalyst for the amination of aryl halides using sodium azide. Angew. Chem. Int. Ed. Engl. 61, e202203176.