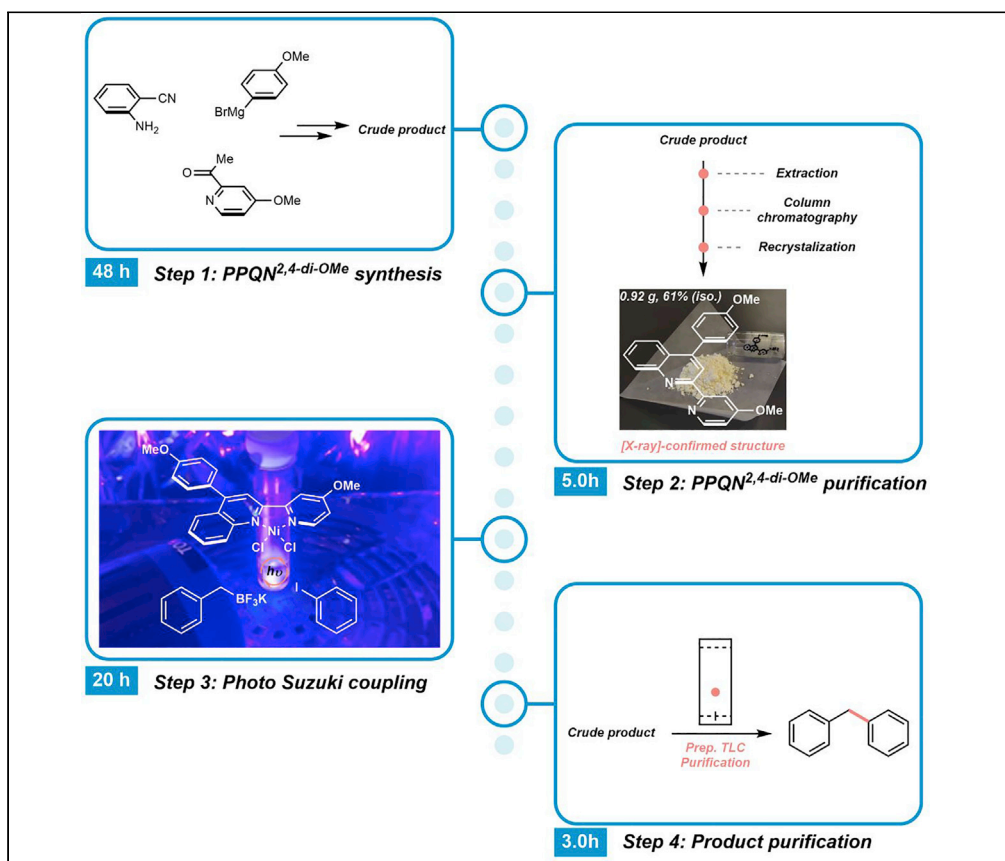


Protocol

A ligand-enabled metallaphotoredox protocol for Suzuki-Miyaura cross-couplings for the synthesis of diarylmethanes



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-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.

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Highlights
Design of a photoactive ligand for single-catalyst metallaphotoredox cross-couplings

Two-step synthesis of the photoactive ligand under transition metal-free conditions

C(sp³)-C(sp²) Suzuki-Miyaura cross-couplings under Ni-metallaphotoredox catalysis

Diarylmethane synthesis from readily available benzyltrifluoroborates and aryl halides

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Protocol

A ligand-enabled metallaphotoredox protocol for Suzuki-Miyaura cross-couplings for the synthesis of diarylmethanes

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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, PPQN^{2,4-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. For complete details on the use and execution of this protocol, please refer to Li et al. (2022b).

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 exogenous 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^{2,4-di-OMe} synthesis, which is representative of other family members in this unique class of photoactive ligands. Guidelines of PPQN^{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^{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^{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.



Figure 1. Solvent degassing setup

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		
1-(4-Methoxy-pyridin-2-yl)-ethanone, 95%	COMBI-BLOCKS	Cat#OR-9846
Potassium benzyltrifluoroborate, 97%	COMBI-BLOCKS	Cat#TB-3280
2-Aminobenzonitrile, 98%	Sigma-Aldrich	Cat#A89901
4-Methoxyphenylmagnesium bromide solution, 0.5 M in THF	Sigma-Aldrich	Cat#470260
Iodobenzene, 98%	Sigma-Aldrich	Cat#17632

(Continued on next page)

Continued

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)	SiliCycle	Cat#R12030B
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

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

Other

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#30133522
Thermolyne benchtop muffle furnace	Thermo Fisher Scientific	Cat#F48058
500 MHz AVIIIHD NMR	Bruker	Not applicable
Exactive Plus Orbitrap-API	Thermo Fisher Scientific	Cat#QLAAEGAAPFALGMBCA
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)

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#UVP95001614
Dewar flask	Fisher Scientific	Cat#FB1019623
Heating gun	Cole-Parmer	Cat#UZ-03026-01

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.

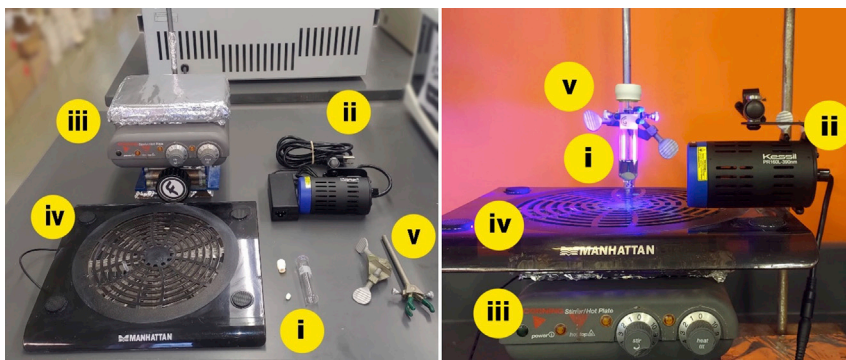


Figure 2. Overview of the photochemical setup

(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).

Diphenylmethane(2-aminophenyl)(4-methoxyphenyl)methanone		
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.

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

4. Connect the round bottom flask with an argon balloon.

Alternatives: The argon balloon is used to balance the inner pressure during the chemical injection. Nitrogen could serve the same purpose in this step.

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:

Alternatives: The Grignard reagent could be freshly prepared following other reported literature.

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.

- The reaction mixture is unsealed and cooled to 0°C with an ice bath.
- 10 M NaOH (aqueous solution) is added dropwise until the pH of the mixture reaches 10, as indicated by pH test papers.
- Remove THF by rotary evaporation (200 mbar at 40°C).
- Extract the reaction mixture as mentioned below:
 - Transfer the reaction mixture to a 250 mL separatory funnel.
 - Add 100 mL of deionized water and 50 mL of EtOAc to the mixture.
 - Shake the separatory funnel vigorously and let the aqueous phase separate from the organic one.
 - Transfer the organic and aqueous phases into two separate 250 mL Erlenmeyer flasks.
 - Put the aqueous phase back into the separatory funnel and add 50 mL of EtOAc.
 - Repeat steps 14c to 14e twice and combine the organic phase.
- Discard the aqueous phase in the appropriate waste container.
- Add an appropriate amount of anhydrous MgSO₄ to remove water residue from the combined organic phase.
- 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.
- Remove the solvent by rotary evaporation (180 mbar at 40°C).
- Dissolve the crude in 5–10 mL of CH₂Cl₂.
- 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 (R_f of **3** in 5:1 hexane/EtOAc = 0.39).
- Collect the combined fractions containing product **3** and concentrate them under reduced pressure. [Troubleshooting 1](#).
- 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 PPQN^{2,4-di-OMe} ligand

⌚ Timing: 16 h

In this step, the synthesis of PPQN^{2,4-di-OMe} (**5**) has been accomplished within 16 h upon heating at 140°C under an argon atmosphere ([Scheme 2](#)).

PPQN ^{2,4-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:
- Add 1 g of (2-aminophenyl)(4-methoxyphenyl)methanone (**3**, 4.4 mmol, 1 equiv).
 - Add 0.87 g of 1-(4-methoxy-pyridin-2-yl)-ethanone (**4**, 5.8 mmol, 1.3 equiv).
 - Add 8.8 mL of AcOH.
 - 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 PPQN^{2,4-di-OMe} ligand

⌚ **Timing:** 3 h

In this step, the pure PPQN^{2,4-di-OMe} (**5**) has been obtained within 3 h through extraction and column chromatography.

- Cool the reaction down to 20°C–30°C.
- The reaction mixture is unsealed and cooled to 0°C with an ice bath.
- 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:
- Transfer the reaction mixture to a 250 mL separatory funnel.
 - Add 30 mL of deionized water and 50 mL of EtOAc to the mixture.
 - Shake the separatory funnel vigorously and let the aqueous phase separate from the organic one. [Troubleshooting 2](#).
 - Transfer the organic and aqueous phases into two separate 250 mL Erlenmeyer flasks.
 - Put the aqueous phase back into the separatory funnel and add 50 mL of EtOAc.
 - 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 CH₂Cl₂, 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



Figure 3. Freezing the reaction mixture in liquid nitrogen

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 PPQN^{2,4-di-OMe} (**5**, 10 μ mol, 5 mol%).
 - b. Add 2.2 mg of NiCl₂·DME (10 μ mol, 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.

Δ 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 μ L 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 μ L 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 (R_f 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. PPQN^{2,4-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%).

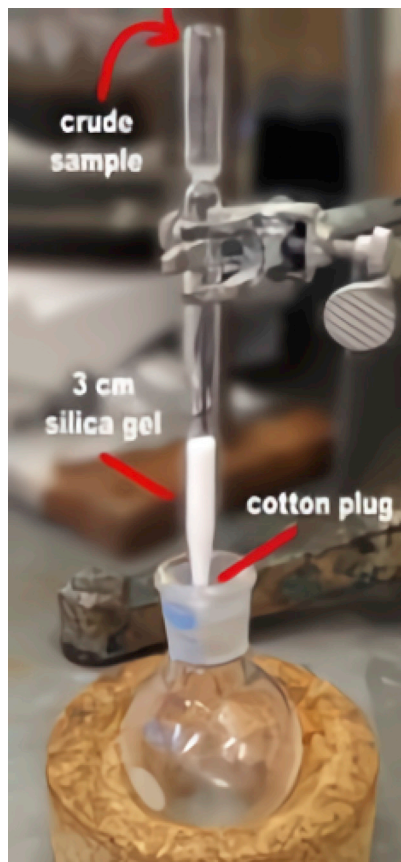


Figure 4. Filtration with a silica pad

QUANTIFICATION AND STATISTICAL ANALYSIS

Analytical data

For (2-aminophenyl)(4-methoxyphenyl)methanone (**3**):

$^1\text{H NMR}$ (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).

$^{13}\text{C NMR}$ (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 $\text{C}_{14}\text{H}_{13}\text{NO}_2$ Calcd: 227.1, found: 227.1.

For PPQN^{2,4-di-OMe} (**5**):

$^1\text{H NMR}$ (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).

$^{13}\text{C NMR}$ (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 ($\text{M}+\text{H}^+$) for $\text{C}_{22}\text{H}_{19}\text{N}_2\text{O}_2$ Calcd: 343.1441, found: 343.1442.

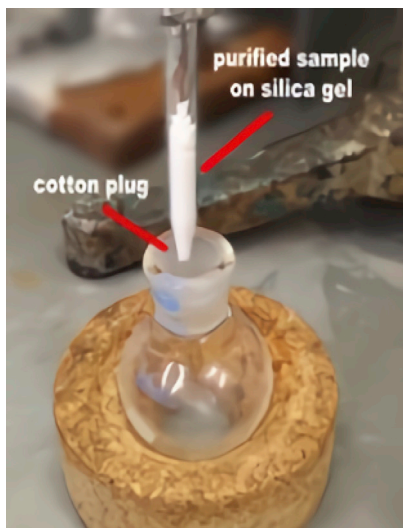


Figure 5. Purification of the product-containing silica gel

For diphenylmethane (8):

^1H 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 $\text{C}_{13}\text{H}_{12}$ 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

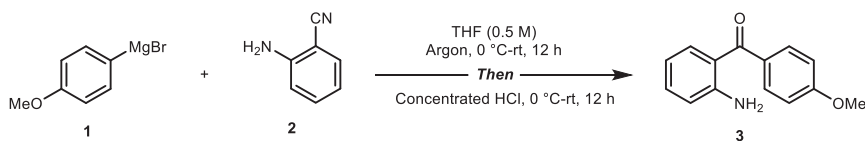
5–10 mL of brine could be added to assist the phase separation.

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.



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

Problem 4

Product **5** precipitates in the column (major step 36).

Potential solution

The PPQN^{2,4-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

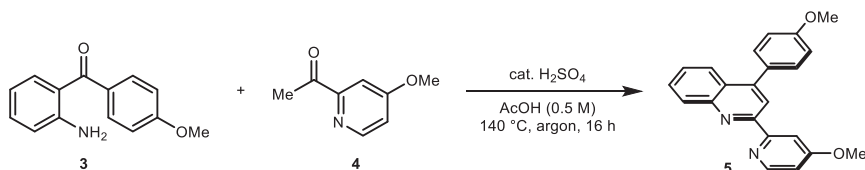
All other data supporting the finding of this study are available within the article or from the [lead contact](#) upon reasonable request. This studies generated unique ligand and catalyst, and they are available from the [lead contact](#) upon reasonable request.

Data and code availability

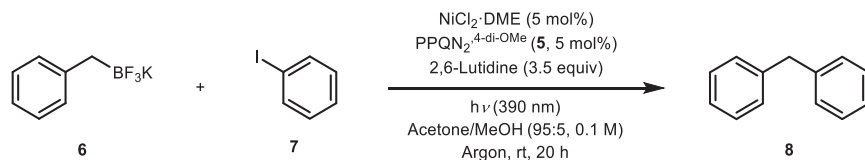
All data reported in this paper will be shared by the [lead contact](#) upon reasonable request.

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 2. Synthesis of PPQN^{2,4-di-OMe} ligand.



Scheme 3. Synthesis of diphenylmethane (8)

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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.

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