Template-Directed meta-Selective Olefination of Aryl C–H Bonds

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Method Article

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Abstract

The most common bond in many organic compounds is the C–H bond. Hence, it is a great challenge to selectively cleave a particular C–H bond in the presence of multiple ones. One of most widely used approach to this problem is the use of □-chelating directing groups[1]. However, the insertion of the transition metal is strictly restricted to the ortho-C–H bond through a six- or seven-membered cyclic pre-transition state \(TS). Although many strategies have been developed to selectively functionalize meta- and para-C–H bonds[2–4], this newly developed template approach overcomes the intrinsic steric and electronic bias of the substrates, and allows for the activation of remote C–H bonds.

Introduction

The most common bond in many organic compounds is the C–H bond. Hence, it is a great challenge to selectively cleave a particular C–H bond in the presence of multiple ones. One of most widely used approach to this problem is the use of □-chelating directing groups[1]. However, the insertion of the transition metal is strictly restricted to the ortho-C–H bond through a six- or seven-membered cyclic pre-transition state \(TS). Although many strategies have been developed to selectively functionalize meta- and para-C–H bonds[2–4], this newly developed template approach overcomes the intrinsic steric and electronic bias of the substrates, and allows for the activation of remote C–H bonds.

Reagents

• Palladium pivalate \(Sigma-Aldrich, cat. no. 721611) • Palladium\(II) acetate \(Sigma-Aldrich, cat. no. 205869) • Ethyl acrylate, contains 10-20 ppm MEHQ as inhibitor \(Sigma-Aldrich, cat. no. E9706) • Silver pivalate \(made from silver nitrate and pivalic acid) • Silver acetate \(Sigma-Aldrich, cat. no. 85140) • Ac-Gly-OH \(Novabiochem cat. no. 04-12-8006) • 1,2-Dichloroethane, anhydrous grade \(Sigma-Aldrich, cat. no. 284505) • 1,1,1,3,3,3-Hexafluoro-2-propanol \(Oakwood Products, cat. no. 003409) • Celite® 545 coarse \(EMD Chemical, cat. no. CX0574-3) • 2 M Hydrochloric acid \(prepared from concentrated HCl, EMD Chemicals, ACS grade, cat. no. HX0603-75) • Diethyl ether, \(Fisher Chemical, Anhydrous; BHT Stabilized/Certified ACS; cat. no. E13820) • Ethyl acetate, \(EMD Chemical, Reagent A.C.S, cat. no. CX0240-3) • Hexanes, \(Avantor Performance Materials, AR A.C.S grade, cat. no. MK518922) • Thin-layer chromatography plates on glass backing, silica gel 60 F254 \(Merck) • Potassium permanganate thin-layer chromatography visualizing stain • Preparative TLC plates, 500 µm with fluorescent indicator \(Sigma-Aldrich, cat. no. Z513032)

Equipment

• Magnetic hotplate stirrer \(IKA® RCT Basic or Corning PC420D) • Digital temperature probe • Oil bath \(Silicone oil from Alfa Aesar, cat. no. A12728-0E) • Pressure vessels, heavy wall, with a Teflon bushing, 15 mL or 30 ml \(Chemglass, cat. no. CG-1880-01 or CG-1880-02) • Disposable syringes \(Norm-Ject cat. no. 53548-000) • Disposable needles \(BD Presicion needle, cat. no. 305196) • Teflon-coated magnetic stirrer

bar \(various brand?) • Balloon fitted to disposable 2.5 mL syringe barrel • Büchner filter funnels with inner joints and coarse frit, 15mL • Rotary evaporator \(Heidolph) • Pyrex chromatographic column \(approx. diameter 3 cm) • NMR tubes

Procedure

Toluene derivatives 1) On the same piece of weighing paper, weigh all the solids. Weigh the substrate \(0.10 mmol) first, followed by Pd\(OPiv)2 \(3.0 mg, 0.010 mmol, 0.10 equiv.) and AgOPiv \(62.7 mg, 0.30 mmol, 3.0 equiv.). The solids were carefully transferred into the bottom of a 15 mL pressure vessel equipped with a Teflon-coated magnetic stirrer bar. 2) Add ethyl acrylate \(16.5 µL, 0.15 mmol, 1.5 equiv.) to the solid mixture. 3) Wash down the solids on the sides of wall with 1,2-dichloroethane \(1.0 mL). 4) Cap the tube and submerge it into a pre-heated 90 °C \(controlled by a digital temperature probe) oil bath. 5) Cover the tube and oil bath with aluminum foil and leave the reaction stirring for a total of 42–48 hours. 6) Lift vessel out of the oil bath and submerge it into ice bath for 10 minutes. 7) Filter the reaction mixture through a short pad of Celite® into a scintillation vial and wash the tube and Celite® pad three times with 2 mL of diethyl ether. Evaporate the solvent to dryness using a rotary evaporator. 8) Purify the desired product by preparative silica gel thin-layer chromatography eluting with hexane:ethyl acetate to yield the desired olefinated product. **Hydrocinnamic acid derivatives** 1) On the same piece of weighing paper, weigh all the solids sequentially as followed: Pd\(OAc)2 \(2.3 mg, 0.010 mmol, 10 mol%), Ac-Gly-OH \(2.4 mg, 0.020 mmol, 20 mol%), AgOAc \(50 mg, 0.30 mmol, 3.0 equiv.) and the substrate \(0.10 mmol). The solids were carefully transferred into the bottom of a 35 mL pressure vessel pre-equipped with a Teflon-coated magnetic stirrer bar. 2) HFIP \(1,1,1,3,3,3-Hexafluoro-2-propanol) \(0.60 mL) was added to the mixture to wash down the solids on the sides of wall, followed by ethyl acrylate \(22 µL, 2.0 equiv.) and then another 0.60 mL of HFIP. 3) Cap the tube tightly and submerge it into a pre-heated 90 °C \(controlled by a digital temperature probe) oil bath. 4) Leave the reaction stirring for 24 hours. 5) Lift vessel out of the oil bath and filtrate the reaction mixture through a short pad of Celite® into a 50 ml round bottom flask after it cools down. 6) Evaporate the solvent to dryness using a rotary evaporator. 7) Isolate the desired product by preparative silica gel thin-layer chromatography eluting with hexane:ethyl acetate to yield the desired olefinated product.

Timing

Toluene derivatives: 42 hours \(electron-donating substituents); 48 hours \(electron-withdrawing substituents) Hydrocinnamic acid derivatives: 24 hours

Troubleshooting

Toluene derivatives Poor separation of the major meta-isomer from the minor isomers: Preparative thin-layer chromatography is usually the first choice to achieve better separation. Repetitive running of the thin-layer chromatography using less polar eluent is recommended to achieve good resolution. Hydrocinnamic acid derivatives Problem: Poor separation of mono-olefinated meta-isomer from the di-

olefinated meta-isomer \(when applicable), and poor separation of the major meta-isomer from the trace minor isomers for some substrates. Solutions: Especially for those substrates with di-olefinated product, preparative thin-layer chromatography is usually employed to achieve better separation. Repetitive developing of the thin-layer chromatography \(3 to 5 times) using relative less polar eluent is recommended

Anticipated Results

Typical isolated yield of toluene derivatives should be 46–98% depending on the substituents on the aromatic ring and olefins used. Typical yield of hydrocinnamic acid derivatives should be 67–93% depending on the substituents on the aromatic ring. Longer reaction time than 24 hours may lead to more di-olefinated products; however, shorter reaction time could cause incomplete reaction.

References

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