5

Carbon–Carbon Bond Formation

5.1 Carbon–Carbon Forming Reactions (Single Bonds)

5.1.1 Aldol Reactions

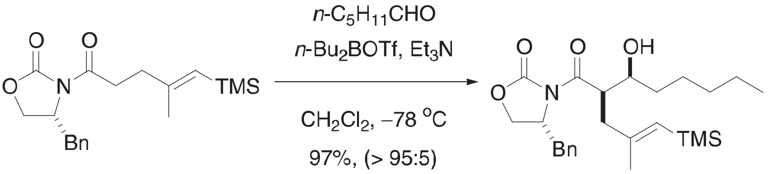
Reviews: (a) Vicarion, J. L.; Badia, D.; Carillo, L.; Reyes, E.; Etxebarria, J. *Curr. Org. Chem.* **2005,** *9*, 219–235. (b) Mahrwald, R. Ed. In *Modern Aldol Reactions*; Wiley-VCH: Weinheim, 2004; Vol. 1., pp. 1–335 (c) Mahrwald, R. Ed. In *Modern Aldol Reactions*; Wiley-VCH: Weinheim, 2004; Vol. 2., pp. 1–345.(d) Machajewski, T. D.; Wong, C.-H. *Angew. Chem. Int. Ed.* **2000,** *39*, 1352–1375. (e) Carriera, E. M. In Modern Carbonyl Chemistry; Otera, J.; Wiley-VCH: Weinheim, 2000; Chapter 8: Aldol Reaction: Methodology and Stereochemistry, 227–248. (f) Paterson, I.; Cowden, C. J.; Wallace, D. J. In Modern Carbonyl Chemistry; Otera, J.; Wiley-VCH: Weinheim, 2000; Chapter 9: Stereoselective Aldol Reactions in the Synthesis of Polyketide Natural Products, pp. 249–298. (g) Franklin, A. S.; Paterson, I. Contemp. Org. Synth. **1994,** *1* 317–338. (h) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, Fl.; 1984; Vol. 3., Chapter 2: The Aldol Addition Reaction, pp. 111–212. (i) Mukaiyama, T. *Org. React.* **1982,** *28*, 203–331.

5.1.1.1 With Boron Enolates

Since the early 1980s, aldol condensations involving boron enolates have gain great importance in asymmetric synthesis, particularly the synthesis of natural products with adjacent stereogenic centers bearing hydroxyl and methyl groups. (*Z*)-Boron enolates tend to give a high diastereoslectivity preference for the *syn*-stereochemistry while (*E*)-boron enolates favor the *anti*-stereochemistry. Because the B–O and

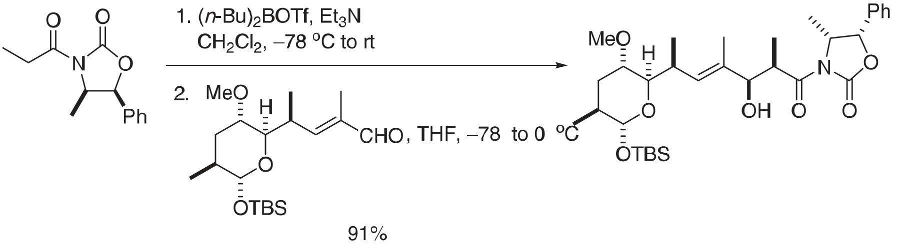
B–C bonds are shorter than other metals with oxygen and carbon, the six membered Zimmerman–Traxler transition state in the aldol condensation tends to be more compact which accentuates steric interactions, thus leading to higher diastereoselectivity. When this feature is coupled with a boron enolate bearing a chiral auxillary, high enantioselectivity is achieved. Boron enolates are generated from a ketone and boron triflate in the presence of an organic base such as triethylamine. Reviews: (a) Abiko, A. *Acc. Chem. Res.* **2004,** *37*, 387–395. (b) Cowden, C. J. *Org. React.* **1997,** *51*, 1–200.

5.1.1.1.1 Evans Aldol (With Two Oxazolidinone Chiral Auxillaries)



A 250-mL round-bottomed flask was charged with the oxazolidinone (3.24, 9.37 mmol) in CH_2Cl_2 (20 mL). The solution was cooled in an ice bath and then dibutylboron triflate (2.83 mL, 11.3 mmol) was added dropwise, followed by triethylamine (1.70 mL, 12.2 ml). The resulting yellow solution was stirred at 0 °C for 10 min. The ice bath was replaced with a dry ice–acetone bath (–78 °C), and freshly distilled hexanal (1.35 mL, 11.3 mmol) was added by syringe over a 5-min period. The reaction mixture was stirred at –78 °C for 1 h, warmed to 0 °C for 2 h, and quenched by addition of pH 7 buffer (15 mL) and methanol (15 mL). A mixture of methanol:30% aqueous H_2O_2 solution (2:1, 10 mL) was then added dropwise, and the biphasic mixture was stirred vigorously at room temperature for 1 h. The mixture was diluted with water (100 mL) and the layers were separated. The aqueous layer was washed with CH_2Cl_2 (2×), and the combined organic layers were washed with saturated aqueous sodium bicarbonate, dried over magnesium sulfate, and concentrated. The crude product was purified by flash chromatography (SiO_2) eluting with hexanes:EtOAc (85:15) to afford 3.62 g (97%) of the alcohol as a pale yellow oil.

Reference: Durham, T. B.; Blanchard, N.; Savall, B. M.; Powell, N. A.; Roush, W. R. *J. Am. Chem. Soc.* **2004,** *126*, 9307–9317.

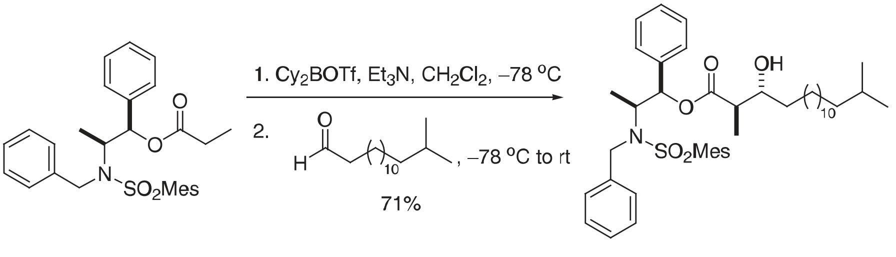


Di-*n*-butylboron-triflate (4.71 g, 18.9 mmol) was added dropwise with stirring to a solution of the imide (4.50 g, 19.3 mmol) in CH_2Cl_2 (35 mL) at –78 °C. The cooling bath was removed, and the resulting mixture was stirred at room temperature until the solution became homogeneous. The mixture was re-cooled to −78 °C, and triethylamine (3.14 mL, 22.5 mL) was added dropwise. After 0.5 h at −78 ºC, the reaction was warmed to 0 °C, maintained at this temperature for 1 h, and re-cooled to −78 °C. A solution of the enaldehyde (2.34 g, 6.60 mmol) in tetrahydrofuran (THF 30 mL) was added via a cannula, and the mixture was stirred for 0.5 h at −78 °C and then at 0 °C for 1 h. Phosphate buffer (30 mL of 0.25 M, pH = 7) and then 30% hydrogen peroxide in methanol (60 mL, 1:1 v/v) were added. The resulting cloudy mixture was diluted with a sufficient volume of methanol to produce a nearly homogeneous solution and subsequently stirred at 0 °C for 1 h. The majority of the methanol (about 75 mL) was removed under reduced pressure (*caution*: the water bath temperature was < 30 °C), and the resulting solution was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with saturated sodium bicarbonate (1 × 50 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford a pale yellow oil that was purified by flash chromatography by gradient elution, first with hexanes:ether (7:3) to elute excess oxazolidinone and then with hexanes:ether (1:1) to give 3.50 g (91%) of the aldol adduct as a white foam.

Reference: Martin, S. F.; Dodge, J. A.; Burgess, L. E.; Limberakis, C.; Hartmann, M. *Tetrahedron* **1996,** *52*, 3229–3246.

5.1.1.1.2 Masamune Aldol

The Masamune aldol condensation, in common with the Evans aldol condensation, involves a boron enolate of an ester containing a norephedrine derived chiral auxillary; however, unlike the latter, the Masamune aldol delivers a 3-hydroxy-2-methyl carbonyl moiety with the *anti*-stereochemistry. Crucial to the success of this reaction is the use of dicyclohexylboron triflate to generate the boron enolate. *Note*: *in the Evans' aldol condensation, dibutylboron triflate is utilized.*



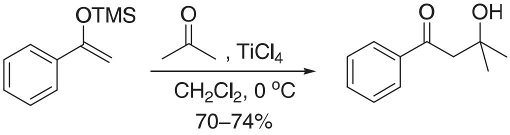
To a stirred solution of the ester (734 mg, 1.53 mmol) and triethylamine (0.52 mL, 3.67 mmol) in CH_2Cl_2 (8 mL) at −78 °C was added dropwise a solution of dicyclohexylboron triflate (1.0 M in hexane, 3.4 mL, 3.4 mmol) over 20 min. The resulting mixture was stirred at this temperature for 2 h before a solution of the aldehyde (442 mg, 1.84 mmol) in CH_2Cl_2 (15 mL) was introduced. Stirring was continued for 1 h at −78 °C before the mixture was allowed to reach ambient temperature over a period of 2 h. The reaction was quenched with a pH 7 buffer solution (6 mL), the mixture was diluted with methanol (21 mL), and 30% hydrogen peroxide (3.1 mL) was added carefully. The mixture was then vigorously stirred overnight before it was concentrated. The residue was partitioned between water and CH_2Cl_2, and the combined organic phases were dried over sodium sulfate and evaporated. The residue was purified by flash chromatography eluting with a gradient of hexane:EtOAc (30:1 to 9:1) to give 862 mg (71%) over the alcohol as a colorless syrup.

References: Fürstner, A.; Caro-Ruiz, J.; Prinz, H.; Waldmann, H. *J. Org. Chem.* **2004,** *69*, 459–467. Abiko, A. Synthesis of the ester: *Org. Syn.* **2002,** *79*, 109–113.

5.1.1.2 Mukaiyama Aldol

The enol silane can be prepared from aldehydes, ketones, esters, and thioesters. The asymmetric Mukaiyama aldol reaction has also been developed using chiral substrates and Lewis acids.

5.1.1.2.1 Standard



Synthesis of the silylenol ether

To a four-necked flask, equipped with a mechanical stirrer, a reflux condenser with a nitrogen inlet, a thermometer, and a pressure-equalizing dropping funnel, was added 36 g (0.30 mol) of acetone and 41.4 g (0.41 mol) of triethylamine under a nitrogen atmosphere. To this mixture, stirred at room temperature under nitrogen, was added via the dropping funnel 43.2 g (0.40 mol) of chlorotrimethylsilane over 10 min. The flask was then immersed in a water bath and the contents were warmed to 35°C. The water bath was removed and the dropping funnel was charged with a solution of 60 g (0.40 mol) of sodium iodide in 350 mL of acetonitrile. This solution was added to the stirred mixture in the flask at such a rate that the temperature of the reaction was maintained at 34–40 °C without external heating or cooling. The addition required approximately 1 h. When the addition was complete, the reaction mixture was stirred for a further 2 h at room temperature. The contents of the flask were then poured into ice-cold water, and the aqueous mixture was extracted three times with pentane. After extraction, the organic layer was dried over potassium carbonate and then concentrated with a rotary evaporator under reduced pressure. The crude product was a mixture of 97% of the desired silyl enol ether and 3% of acetophenone, as shown by gas chromatography. The crude product was distilled in a Claisen flask at a pressure of about 40 mm. After a small forerun (about 3 g), 52.3 g (91%) of silyl enol ether, bp 124–125.5°C, was obtained. The purity of this material was approximately 98%, as judged by gas chromatography and ^1H NMR spectroscopy.

Aldol

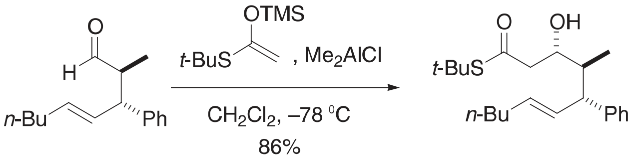
A 500-mL three-necked flask was fitted with a stirring bar, a rubber stopper, a 100-mL pressure-equalizing dropping funnel, and a three-way stopcock that is equipped with a balloon of argon gas. The flask was charged with dry methylene chloride (140 mL) and cooled in an ice bath. Titanium tetrachloride (11.0 mL) was added by a syringe with stirring by a magnetic stirrer, and a solution of 6.5 g of acetone in methylene chloride (30 mL) was added dropwise over a 5-min period. On completion of this addition a solution of 19.2 g of acetophenone trimethylsilyl enol ether in methylene chloride (15 mL) was added dropwise over a 10-min period, and the mixture was stirred for 15 min.

The reaction mixture is poured into ice water (200 mL) with vigorous stirring and the organic layer was separated. The aqueous layer was extracted with two 30-mL portions of methylene chloride. The combined methylene chloride extracts were washed with two 60-mL portions of a 1:1 mixture of saturated aqueous sodium bicarbonate and water, and then with brine. The methylene chloride solution was dried over sodium sulfate and the methylene chloride was removed using a rotary evaporator.

The residue was dissolved in 30 mL of benzene, and the solution was transferred to a chromatographic column (50-mm diameter) consisting of 600 mL of silica gel. The product was eluted sequentially with (a) 1 L of 4:1 (v/v) hexane:EtOAc and (b) 1.5 L of 2:1 (v/v) hexane:EtOAc (flash chromatography). The initial 900 mL of the eluent was discarded. Concentration of the later fractions (about 1.3 L) under reduced pressure yielded the pure product as an oil. The total yield was 12.2–12.8 g (70–74%).

Reference: Mukaiyama, T.; Narasaka, K. *Org. Syn.* **1993,** *Coll. Vol. 8*, 323.

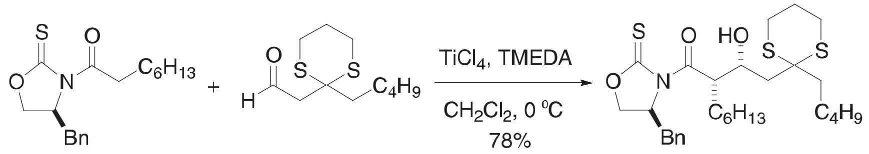
5.1.1.2.2 Asymmetric Mukaiyama

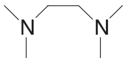


To the aldehyde (0.100g, 0.494 mmol) in CH_2Cl_2 (5 mL) was added (1-*tert*-butylsulfanyl-vinyloxy)-trimethylsilane (131 mg, 0.641 mmol), and the flask was immersed in a −78 °C cooling bath. To the mixture was added a solution of dimethylaluminum chloride (1.0 M in hexanes, 0.74 mL, 0.74 mmol) dropwise, and the reaction was stirred for 1 h at −78 °C. The reaction was quenched by the addition of 10% w/v citric acid in MeOH and slowly raised to ambient temperature; stirring was continued for 1 h. The reaction was diluted with water, and the aqueous layer was extracted with ether (3 ×). The combined organic layers were dried over sodium sulfate, filtered, and the crude product mixture was concentrated in vacuo. The remaining volatiles were removed under high vacuum. Purification via flash chromatography (SiO_2, 10:1 hexanes/EtOAc) afforded 143 mg (86%) of the β-hydroxythioester as a clear viscous oil.

Reference: Stevens, B. D.; Bungard, C. J.; Nelson, S. G. *J. Org. Chem.* **2006,** *71*, 6397–6402.

5.1.1.3 Crimmins' Asymmetric Aldol (Thione Chiral Auxillary)



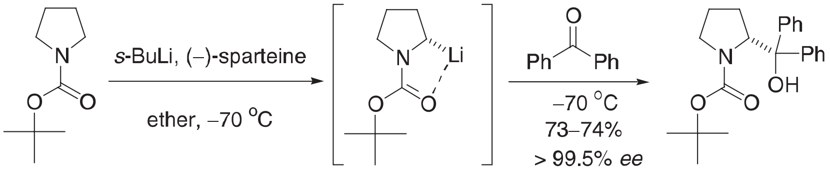


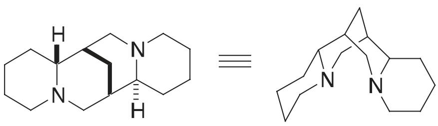
TMEDA

$TiCl_4$ (0.44 mL, 3.99 mmol) was added dropwise to a solution of the thione (1.061g, 3.32 mmol) in dry CH_2Cl_2 (16 mL) and stirred at 0 °C under N_2. After 10 min, dry *N,N,N´N´*-tetramethylethylenediamine (TMEDA 1.65 mL, 8.3 mmol) was added dropwise. The dark solution was then stirred at 0 °C for 0.5 h before the aldehydes (1.540 g, 6.64 mmol) were introduced dropwise. The reaction mixture was stirred at the same temperature for 2 h. Aqueous NH_4Cl (30 mL) was introduced, followed by diethyl ether (300 mL). The phases were separated, and the organic phase was washed with aqueous NH_4Cl (2 × 50 mL) and water, dried (Na_2SO_4), and filtered. The solvents were removed, and the resulting oily residue was chromatographed on silica gel eluting with n-hexane/EtOAc (9:1 to 3:1) to give 1.422 g (78%) of the *syn*-aldol adduct as a pale yellow sticky oil.

Reference: Wu, Y.; Sun, Y.-P. *J. Org. Chem.* **2006,** *71*, 5748–5751.

5.1.2 Asymmetric Deprotonation





(–)-sparteine

An oven-dried, 2-L, three-necked flask, equipped with a magnetic stir bar and a thermocouple, was charged with (–)-sparteine (30.2 mL, 131 mmol), *N*-Boc-pyrrolidine (15.0 g, 87.6 mmol), and anhydrous ether (900 mL). The solution was cooled to –70 °C (dry ice/acetone bath). To this solution was added *sec*-butyllithium (96 mL, 1.16 M in cyclohexane, 111 mmol) dropwise over a period of 35 min. The reaction was then stirred at –70°C for 5.5 h.

After this interval, a solution of benzophenone (25.5 g, 140 mmol) in anhydrous ether (200 mL) was added dropwise over a period of 1.25 h. The dark green to greenish-yellow suspension was maintained at −70 °C for 2.0 h, and the reaction was then quenched by dropwise addition of glacial acetic acid (8.5 mL, 150 mmol) over a period of 15 min. The resulting lemon-yellow suspension was allowed to warm slowly to room temperature over a period of 12 h, during which time the mixture becomes cream colored.

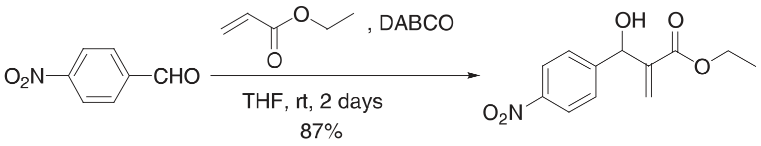
After the solution was warmed to 25 °C, 5% phosphoric acid (H_3PO_4) (150 mL) was added to the reaction mixture, and the resulting biphasic mixture was stirred for 20 min. The layers were partitioned, and the organic phase was washed with additional 5% H_3PO_4 (3 × 150 mL). Combined aqueous phases were extracted with ether (3 × 200 mL). The original organic phase and the ethereal extracts were combined, washed with brine (200 mL), dried over magnesium sulfate ($MgSO_4$), filtered, and the solvents were removed under reduced pressure to afford crude product as an off-white solid. The crude (*R*)-(+)-2-(diphenylhydroxymethyl)-*N*-(tert-butoxycarbonyl)pyrrolidine was purified by recrystallization from a mixture of hexanes-EtOAc (~ 675 mL, 20:1, v/v) affording in two crops 20.9–22.0 g (73–74%) of analytically pure product as a white solid having greater than 99.5% *ee*.

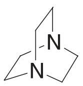
Sparteine was recovered by making the aqueous phases basic with aqueous 20% sodium hydroxide (160 mL). The aqueous phase was extracted with Et_2O (4 × 150 mL), and the combined organic phases were dried over potassium carbonate (K_2CO_3), filtered, and the solvents removed under reduced pressure to afford 30.3 g (98%) of crude recovered sparteine as a pale yellow oil. Fractional distillation of the residual oil from calcium hydride (CaH_2) afforded 27.0 g of sparteine (88%) suitable for reuse.

Reference: Nikolic, N. A.; Beak, P. *Org. Syn.* **1998,** *Coll. Vol. 9*, 391–397.

5.1.3 Baylis–Hillman Reaction

The Baylis–Hillman reaction has become a very powerful carbon–carbon bond forming reaction in the past 20 years. A typical reaction involves an activated olefin (i.e., an acrylate) and an aldehyde in the presence of a tertiary amine such as diazobicyclo-[2.2.2]octane (DABCO) to form an α-methylhydroxyacrylate. A host of activated olefins have been utilized including acrylates, acroleins, α,β-unsaturated ketones, vinylsulfones, vinylphosphonates, vinyl nitriles, *etc*. The Baylis–Hillman has been successfully applied inter- and intramolecularly. In addition, there are numerous examples of asymmetric Baylis–Hillman reactions. Reviews: (a) Ciganek, E. *Org. React.* **1997,** *51*, 201–478. (b) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996,** *52*, 8001–8062. (c) Fort, Y.; Berthe, M. C.; Caubere, P. *Tetrahedron* **1992,** *48*, 6371–6384.





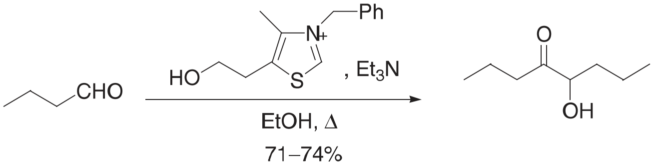
DABCO

To a stirred solution of the aldehyde (1.0 g, 2.92 mmol) in THF (6 mL) were added DABCO (0.15 g, 1.32 mmol) and ethyl acrylate (0.8 mL, 7.28 mmol). The reaction mixture was stirred at room temperature for 24 h. The solvent was removed to give a residue which was purified by chromatography (silica gel) eluting with hexane:EtOAc (8.5:1.5) to afford 1.62 g (97%) of the ethyl acrylate as a syrup.

Reference: Krishna, P. R.; Kannan, V.; Ilangovan, A.; Sharma, G. V. M. *Tetrahedron: Asymmetry* **2001,** *12*, 829–837.

5.1.4 Benzoin Condensation

In the traditional benzoin condensation, aromatic and heteroaryl aldehydes are converted to α-hydroxy ketones in the presence of a catalytic amount of cyanide ion. Since the discovery of this reaction in the early 20th century, improvements have made, including the use of quaternary thiazolium salts as the catalyst. This improvement has broadened the scope of this reaction to include aliphatic aldehydes to deliver acyloins. Review: Hassner, A.; Lokanatha Rai, K. M. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I. Eds.; Pergamon Press: Oxford, 1991; Vol. 1, Chapter 2.4: The Benzoin and Related Acyl Anion Equivalent Reactions, pp. 541–577.

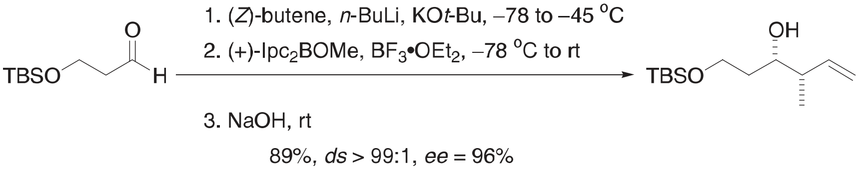


A 500 ml, three-necked, round-bottomed flask was equipped with a mechanical stirrer, a short gas inlet tube, and an efficient reflux condenser fitted with a potassium hydroxide drying tube. The flask was charged with 3-benzyl-5-(2-hydroxyethyl)-4-methyl1,3-thiazolium chloride (13.4 g, 0.05 mol), 72.1 g (1.0 mol) of butyraldehyde, triethylamine (30.3 g, 0.3 mol), and absolute ethanol (300 mL). A slow stream of nitrogen was begun, and the mixture was stirred and heated in an oil bath at 80 °C. After 1.5 h the reaction mixture was cooled to room temperature and concentrated by rotary evaporation. The residual yellow liquid was poured into CH_2Cl_2 (150 mL) which was then used to extract the aqueous mixture. The aqueous layer was extracted with another portion of CH_2Cl_2 (150 mL). The combined organic layers were washed with saturated sodium bicarbonate (300 mL) and water (300 mL). The organic layer was then concentrated under reduced pressure. The crude product was purified via distillation through a 20-cm Vigreux column to afford 51–54 g (71–74%) of the product as a light-yellow liquid.

Reference: Stetter, H.; Kuhlmann, H. *Org. Syn.* **1990,** *Coll. Vol. VII*, 95–99.

5.1.5 Brown Asymmetric Crotylation

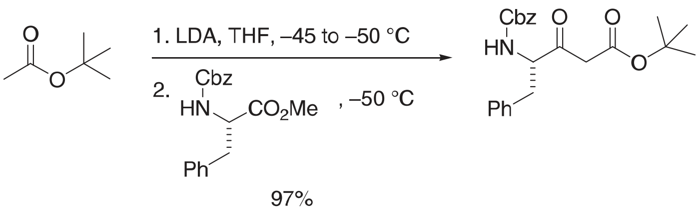
The Brown asymmetric crotylation is a highly regioselective and stereospecific reaction. Many organoboranes are now commercial available. Reviews: (a) Denmark, S. E.; Almstead, N. G. In *Modern Carbonyl Chemistry*; Otera, J, Ed.; Wiley-VCH: Weinheim, 2000; Chapter 10: Allylation of Carbonyls: Methodology and Stereochemistry, pp. 299–402. (b) Chemler, S. R.; Roush, W. R. In *Modern Carbonyl Chemistry*; Otera, J.; Wiley-VCH: Weinheim, 2000; Chapter 11: Recent Applications of the Allylation Reaction to the Synthesis of Natural Products, pp. 403–490.



To a solution of potassium *tert*-butoxide (2.84 g, 24.0 mmol) in THF (40 mL) at −78 °C was cannulated a solution of *cis*-butene (15 mL, 167 mmol). *n*-BuLi (1.6 M in hexanes, 15.5 mL, 24.8 mmol) was then added dropwise, and the yellow mixture was stirred at −78 °C for 5 min and at −45 °C for 20 min. The resulting orange solution was cooled to −78 °C, and a solution of (+)-*B*-diisopinocamphenylmethoxyborane (9.05 g, 28.6 mmol) in diethyl ether (20 mL) was added dropwise over approximately 20 min. The resulting white solution was stirred at −78 °C for 45 min. Boron trifluoride etherate (4.4 mL, 34.2 mmol) was added dropwise followed after 5 min by addition of a solution of 3-(*tert*-butyldimethyl-silyloxy)propionaldehyde (3.76 g, 20.0 mmol) in THF (12 mL). The resulting solution was stirred at room temperature for 15 h. The reaction mixture was neutralized with dilute HCl and washed with diethyl ether. The combined organic layers were washed with brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. The resulting crude product was purified via flash chromatography on silica gel eluting with hexane:EtOAc (9:1) to deliver 4.34 g (89%, 95% *ee*) of the homoallylic alcohol as a colorless oil.

Reference: Wang, P.; Kim, Y.-J.; Navarro-Villalobos, M.; Rohde, B. D.; Gin, D. Y. *J. Am. Chem. Soc.* **2005,** *127*, 3256–3257.

5.1.6 Claisen Condensation



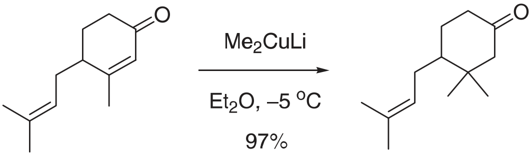
A solution of *tert*-butyl acetate (4.0 equivalents) in THF was added dropwise to a mixture of dry THF and lithium diisopropylamide (LDA 3.5 equivalents in THF) with stirring at − 45 °C. After stirring at −45 °C for 60 min, a solution of the methyl ester was added while maintaining the internal temperature below −50 °C. The resulting mixture was stirred at −50 °C for 60 min and then poured into 1 M HCl and extracted with toluene. The organic layer was then washed with 5% $NaHCO_3$, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a crude product. The crude product was purified by column chromatography to give 97% yield of the β-keto ester.

Reference: Honda, Y.; Katayama, S.; Kojima, M.; Suzuki, T.; Izawa, K. *Org. Lett.* **2002,** *4*, 447–449.

5.1.7 Cuprates

The stability of organocuprates depends on the temperature. For instance, Ph_2CuLi is stable at room temperature while Me_2CuLi is better used at 0 °C. For other unstable organocuprates, the reactions are preferably carried out at −30 °C or lower if the rates of the reactions allow. Reviews: (a) Krause, N.; Gerold, A. *Angew. Chem. Int. Ed.* **1997**, *36*, 186–204. (b) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992,** *41,* 135–631. (c) Lipshutz, B. H. *Synthesis* **1987,** 325–341. (d) Normant, J. F. *Synthesis* **1972,** 63–80.

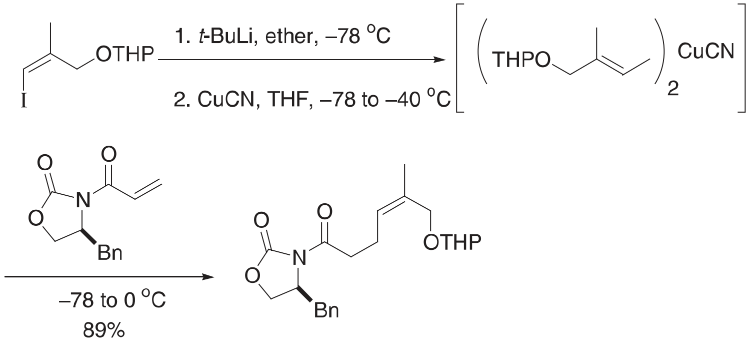
5.1.7.1 Lower Order Cuprates



To a −5 °C slurry of copper(I) iodide (9.83 g, 50.56 mmol) in ether (250 mL) was added dropwise methyl lithium (1.4 M in ether, 72.2 mL, 101.12 mmol). The resulting light-tan solution was stirred for 60 min at −5 °C before a solution of the enone (4.5 g, 25.28 mmol) in ether (100 mL) was added over 10 min via an addition funnel. The bright-yellow reaction mixture was stirred for an additional 10 min at −5 °C until all of the starting material appeared to be consumed by thin layer chromatography (TLC). After quenching with saturated NH_4Cl/NH_4OH solution (250 mL), the layers were separated, and the aqueous layer was extracted with ether (2 × 250 mL). The combined organic layers were dried over magnesium sulfate and concentrated to a yellow oil. The crude product was purified by passing it through a silica gel plug eluting with hexanes:EtOAc (9:1) to afford 4.76 g (97%) of the ketone as a pale yellow oil.

Reference: Spessard, S. J.; Stoltz, B. M. *Org. Lett.* **2002,** *4*, 1943–1946.

5.1.7.2 High Order Cuprates (Cyanocuprates)

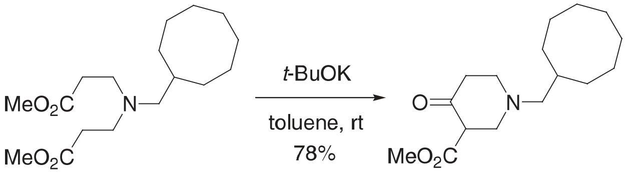


To a stirred solution of *t*-BuLi (1.3 M in pentane, 48 mL, 62.4 mmol) in diethyl ether (63 mL) at −78 °C was added a solution of the vinyl iodide (10.27 g, 36.4 mmol) in diethyl ether (75 mL) via a syringe pump over 20 min. After 20 min, the slurry was rapidly transferred to a precooled solution of copper cyanide (1.58 g, 17.7 mmol) in THF (122 mL) at −78 °C. After 1 h at −78 °C and 5 min at −40 °C, the solution was re-cooled to −78 °C, and a precooled solution of the oxazolidinone (3.40 g, 14.7 mmol) in THF (86 mL) was added via a cannula. An additional amount of THF (25 mL) was added to rinse the flask. After 30 min, the solution was warmed to 0 °C, and after a further 10 min the reaction was quenched with saturated aqueous ammonium chloride (300 mL) and extracted with ether (3 × 150 mL). The organic extracts were dried (magnesium sulfate) and concentrated in vacuo. The crude product was purified by chromatography (silica gel) eluting with ether: petroleum ether (15:85 to 50:50) to give 5.05 g (89%) of the oxazolidinone as a colorless oil.

Reference: White, J. D.; Carter, R. G.; Sundermann, K. F. *J. Org. Chem.* **1999,** *64*, 684–685.

5.1.8 Dieckmann Condensation

The Dieckmann condensation is an intramolecular variant of the Claisen condensation where a diester is converted to a β-ketoester. Typically, an alkoxide is used as the base to form the enolate which attacks the remaining ester to form the carbocycle. Five- and six-membered rings are formed readily with this method. Reviews: (a) Davis, B. R.; Garrett, P. J. In *Comprehensive Organic Synthesis,* Trost, B. M.; Fleming, I. Eds.; Pergamon Press: Oxford, 1991; Vol. 2, Chapter 3.6: Acylation of Esters, Ketones, and Nitriles, pp. 806–829. (b) Schaefer, J. P.; Bloomfield, J. *J. Org. React.* **1967,** *15*, 1–203.



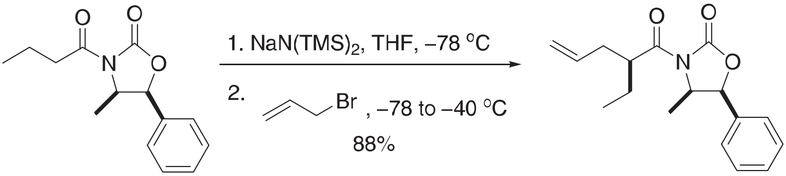
Potassium *tert*-butoxide (4.3 g, 38.34 mmol) was added in 1 portion to a solution of the diester (8 g, 25.56 mmol) in toluene (80 mL) at 0 °C. After being stirred at the same temperature for 30 min, the reaction mixture was kept at room temperature overnight. Water (100 mL) was added, the phases were separated, and the aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic extracts were dried and evaporated. The residue was purified by flash chromatography eluting with EtOAc:light petroleum (1:9) to give 5.6 g (78%) of the keto-ester as an orange oil.

Reference: De Risi, C.; Pollini, G. P.; Trapella, C.; Peretto, I.; Ronzoni, S.; Giardina, G. A. M. *Bioorg. Med. Chem.* **2001,** *9*, 1871–1877.

5.1.9 Enolate Alkylations

5.1.9.1 *Asymmetric Alkylation With Chiral Oxazolidinones*

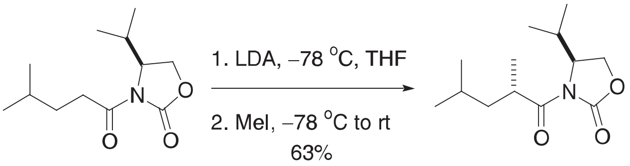
5.1.9.1.1 *Norephedrine-Derived Oxazolidinone*



Sodium bis-trimethylsilylamide (1 M in THF, 6.4 mL, 6.4 mmol) was added dropwise to the imide (1.4 g, 5.7 mmol) in THF (15 mL) at −78 °C. The mixture was stirred at −78 °C for 2 h, allyl bromide (2.5 mL, 29 mmol) was then added via a syringe, and the mixture was stirred for another 3 h at −40 °C. The reaction was quenched with aqueous ammonium chloride (10 mL) at −78 °C and then warmed slowly to room temperature. The mixture was extracted with EtOAc (2 × 20 mL), and the combined organic layers were washed with 5% sodium bicarbonate, brine, dried, and concentrated. The crude product was purified via chromatography eluting with petroleum ether:ether (7:1) to give 1.4 g (88%) of the olefin.

Reference: Wee, A. G. H.; Yu, Q. *J. Org. Chem.* **2001,** *66*, 8935–8943.

5.1.9.1.2 *Valinol-Derived Oxazolidinone*

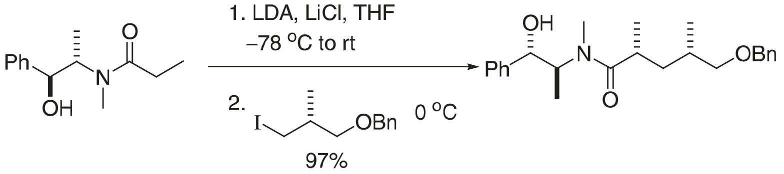


A solution of diisopropylamine (3.42 mL, 24.4 mmol) in THF (30 mL) was cooled to −30 °C and *n*-BuLi in hexanes (2.5 M, 8.45 mL, 21.12 mmol) was added. After stirring the mixture for 45 minutes, a solution of the oxazolidinone (3.69 g, 16.25 mmol) in THF (20 mL) was added at −78 °C. The mixture was stirred at −78 °C for 1 h and iodomethane (5.06 mL, 81.3 mmol) was then added. After stirring for 30 min, the solution was allowed to reach room temperature. The mixture was extracted with ether, and the organic layer extract was washed with saturated ammonium chloride solution, saturated sodium bicarbonate, and brine. The dried solution (sodium sulfate) was concentrated in vacuo, and the residue was purified using flash chromatography eluting with 5% EtOAc and then 10% EtOAc in hexanes. This material was then crystallized from hexanes at −15 °C to deliver 2.47 g (63%) of the oxazolidinone as colorless crystals.

Reference: Guerlavais, V.; Carroll, P. J.; Joullié, M. M. *Tetrahedron: Asymmetry* **2002,** *13*, 675–680.

5.1.9.2 *Myers' Asymmetric Alkylation*

The Myers' asymmetric alkylation is a reaction between the enolate of a pseudoephedrine amide and an alkyl iodide in the presence of lithium chloride to give α-substituted amides with high diastereoselectivity. It has been noted that the lithium chloride must be anhydrous and flame-dried immediately before use. The α-substituted amides can then be transformed to the corresponding carboxylic acids (acid or base hydrolysis), alcohols (reduction with LiH_2NBH_3), aldehydes [reduction with $LiAlH(OEt_3)_3$], and ketones (nucleophilic attack by alkyllithium reagents). Review: Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997,** *119*, 6496–6511.



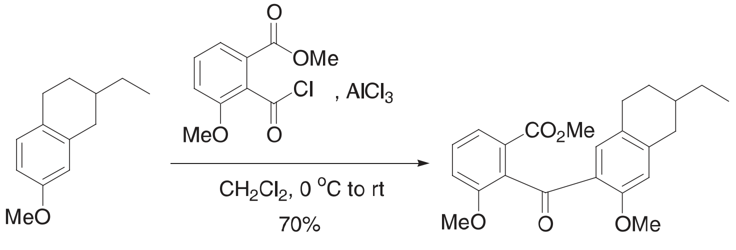
A solution of *n*-butyllithium (2.50 M in hexanes, 27.96 mL, 69.9 mmol) was added via a cannula to a suspension of lithium chloride (9.39 g, 222 mmol) and diisopropylamine (10.6 mL, 75.3 mmol) in THF (50 mL) at −78 °C. The resulting suspension was warmed to 0 °C briefly and then cooled to −78 °C. An ice-cooled solution of the amide (8.12 g, 36.7 mmol) in THF (100 mL, followed by a 4 mL rinse) was added via a cannula. The mixture was stirred at −78 °C for 1 h, at 0 °C for 15 min at 23 °C for 5 min. The mixture was cooled to 0 °C and the iodide (5.08 g, 17.5 mmol) was added neat to the reaction via a cannula. After being stirred for 18.5 h at 0 °C, the reaction mixture was treated with half-saturated aqueous ammonium chloride solution (180 mL), and the resulting mixture was extracted with EtOAc (4 × 100 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with ether:hexanes (65:35) to afford 6.52 g (97%) of the amide as a white solid.

Reference: Vong, B. G.; Abraham, S.; Xiang, A. X.; Theodorakis, E. A. *Org. Lett.* **2003,** *5*, 1617−1620.

5.1.10 Friedel–Crafts Reaction

The Friedel–Crafts reaction includes both alkylation and acylation although here only acylation is exemplified. For the Friedel–Crafts acylation, the electrophile could be either an acid chloride or an anhydride. The catalyst could be either a Lewis or protic acid.

Review: Bandini, M.; Melloni, A.; Ronchi-Umami, A. *Angew. Chem. Int. Ed.* **2004,** *43*, 550–556.

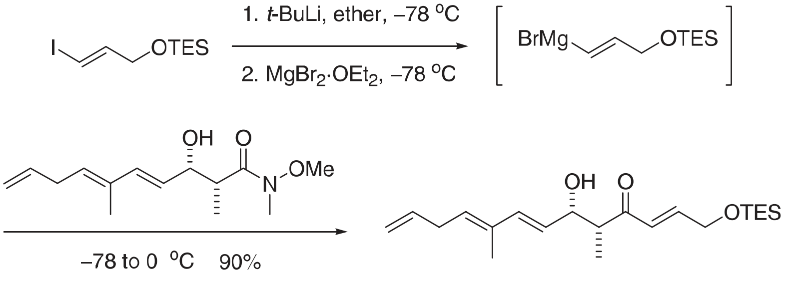


The anisole derivative (380 mg, 2 mmol) in dry CH_2Cl_2 (5 mL) under a nitrogen atmosphere was cooled to 0 °C. Anhydrous aluminum chloride (400 mg, 3 mmol) was added slowly and the mixture was stirred for 15 min. The acid chloride (456 mg, 2 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and at room temperature overnight. After the reaction was deemed complete by TLC, the reaction mixture was poured on a mixture of crushed ice (5 g) and concentrated HCl (2 mL). The quenched reaction was stirred for 10 min and then extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with water (20 mL), brine (20 mL), and dried over sodium sulfate. The filtrate was then evaporated. The crude product was purified by column chromatography eluting with 20% EtOAc/petroleum ether to afford 535 mg (70%) of the ketone as a semi-solid.

Reference: Patil, M. L.; Borate, H. B.; Ponde, D. E.; Deshpande, V. H. *Tetrahedron* **2002,** *58*, 6615–6620.

5.1.11 Grignard Reaction (Organomagnesium Reagents)

The Grignard reaction involves an organomagnesium reagent reacting with an electrophile to form a new carbon–carbon bond. Organomagnesium reagents are readily prepared via several methods (see chapter 1). Magnesium reduction of an organohalide with magnesium turnings in the presence of an initiator such as iodine (*the initiator is necessary to remove the layer of magnesium oxide*) is the classical method (see chapter 1 for this method). However, in the past few decades halide–magnesium exchange has gained in popularity by allowing an organohalide to react with *i*-PrMgCl or *i*-PrMgBr and form the new organomagnesium reagent at low temperature (< 0 °C). Also, it is sometimes convenient to form these reagents via a metal–metal exchange by treating an organolithium reagent with $MgBr_2{\cdot}Et_2O$ or $MgCl_2{\cdot}Et_2O$ at low temperature (−70 °C). When forming the Grignard reagent, it is paramount that an ethereal solvent such as diethyl ether or THF is used because these solvents help stabilize these species via chelation. A variety of simple and functionalized aryl, heteroaryl, alkynyl, alkenyl, and alkylmagnesium reagents have been prepared. These reagents react readily with a host of electrophiles such as aldehydes, ketones, epoxides, allyl halides, etc. Reviews: (a) Knochel, P.; Dohle, W.; Gommerman, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem. Int. Ed.* **2003,** *42*, 4302–4320. (b) Franzén, R. G. *Tetrahedron* **2000,** *56*, 685–691. (c) Wakefield, B. J. *Organomagnesium Methods in Organic Synthesis*; Academic Press: San Diego, 1995. (d) Ashby, E. C.; Laemmle, J.; Neumann, H. M. *Acc. Chem. Res.* **1974,** *7*, 272–280.



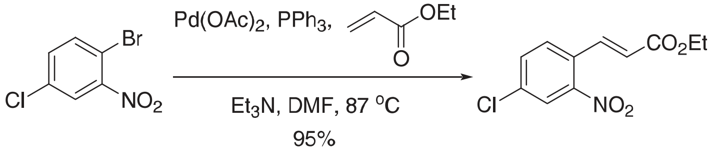
3-Triethylsilyloxy-1-iodo propene (5.56 g, 18.6 mmol) was dissolved in diethyl ether (50 mL) and cooled to −78 °C, and *tert*-BuLi (1.7 M in pentane, 19.5 mL, 33.1 mmol) was added dropwise. After 15 min at −78 °C, freshly prepared $MgBr_2 \cdot OEt_2$ (20.0 mL of a 0.83 M solution in 5:1 ether/benzene) was added via a cannula and stirring was continued at this temperature for 15 min. The amide (1.05 g, 4.14 mmol) was added as a solution in ether (30 mL) via a cannula followed by an ether rinse (3 mL). After 30 min at −78 °C, the cold bath was replaced with an ice bath, and the mixture was stirred for 2 h at 0 °C. The reaction mixture was cannulated into a vigorously stirred biphasic mixture of 0.5 N HCl (100 mL) and CH_2Cl_2 (100 mL) that was cooled to 0 °C. (*Note: HCl is required for this quench, as a milder acid such as ammonium chloride resulted in significant 1,4-addition of liberated N,O-dimethylhydroxylamine to the enone.*) The resulting mixture was extracted with CH_2Cl_2 (3 × 100 mL), and the combined extracts were washed with dilute aqueous sodium bicarbonate (100 mL), dried over magnesium sulfate, and concentrated. The crude product was purified by chromatography eluting with hexanes/EtOAc (9:1) to afford 1.35 g (90%) of the enone as a clear colorless oil.

Reference: Vanderwal, C. D.; Vosburg, D. A. Weiler, S.; Sorensen, E. J. *J. Am. Chem. Soc*. **2003,** *125*, 5393–5407.

5.1.12 Heck Coupling

The palladium catalyzed reaction between an aryl-X (X = I, Br, Cl, OTf, OTs, N_2^+) and an olefin is referred as the Heck reaction. In the traditional Heck reaction, the most common palladium catalysts include $Pd(OAc)_2$, $PdCl_2$, $Pd(PPh_3)_4$, and $Pd_2(dba)_3$; however, in the past 20 years, the literature has been enriched with a number of ligands that have improved the yields of the Heck reaction, and in numerous cases made the reaction possible. In situations where less reactive organohalides undergo the Heck sluggishly or not at all (i.e., arylchloride, electron-rich arylhalide), these electron-rich ligands accelerate the oxidative addition step with the organohalide. The types of ligands include monodenate phosphines, chelating diphosphines, phosphites, and palladacycles, to name a few. The range of olefinic coupling partners is also broad which includes α,β-unsaturated esters, α,β-unsaturated nitriles, styrene derivatives, isolated olefins, etc. The Heck reaction has been successfully used inter- and intramolecularly. Reviews: (a) Gurry, P. J.; Kiely, D. *Curr. Org. Chem.* **2004,** *8*, 781–794. (b) Dounay, A. B.; Overman, L. E. *Chem. Rev*. **2003,** *103*, 2945–2964. (c) Link, J. T. *Org. React*. **2002,** *60*, 157–534. (d) Whitcombe, N. J.; Hii, K. K. Gibson, S. E. *Tetrahedron* **2001,** *57*, 7431–7574. (e) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev*. **2000,** *100*, 3009–3066. (f) Shibasaki, M.; Boden, C. D. J.; Kojma, A. *Tetrahedron* **1997,** *53*, 7371–7395. (g) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995,** *28*, 2–7. (h) de Meijere, A; Meyer, F. E. *Angew. Chem. Int. Ed*. **1994,** *33*, 2379–2411. (i) Heck, R. F. *Org. React*. **1982,** *27*, 345–390. (j) Heck, R. F. *Acc. Chem. Res.* **1979,** *12*, 146–151.

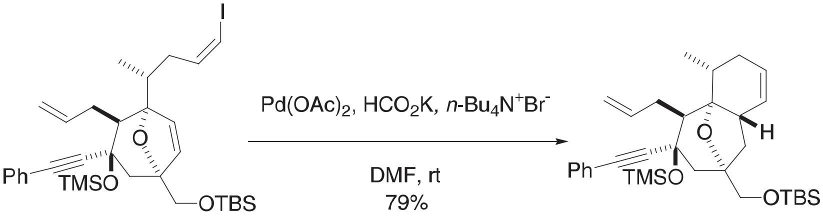
5.1.12.1 Standard Heck



2-Chloro-5-bromonitro-benzene (30.0 g, 127 mmol), $Pd(OAc)_2$ (285 mg, 1.27 mmol), and triphenylphosphine (666 mg, 2.54 mmol) in dimethylformamide (360 mL) were added to triethylamine (24.7 mL, 178 mmol) and ethyl acrylate (138 mL, 1.27 mol). The reaction was stirred at 87 °C for 10 h, cooled to room temperature, and poured into a separatory funnel containing toluene (300 mL). The mixture was washed with 1 N HCl (300 mL) and water (2 × 200 mL). The organic extracts were concentrated to an oil that was crystallized in hexanes (60 mL). The solid was filtered to afford 30.8 g (95%) of the ester.

Reference: Caron, S.; Vazquez, E; Stevens, R. W.; Nakao, K.; Koike, H.; Murata, Y. *J. Org. Chem.* **2003,** *68*, 4104–4107.

5.1.12.2 Jeffrey's Ligandless Conditions

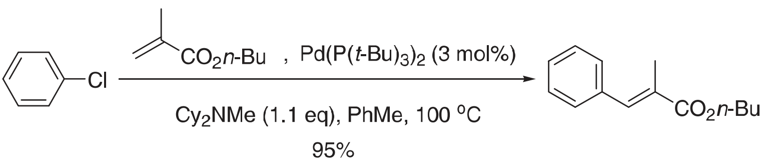


To a mixture of the vinyl iodide (580 mg, 0.858 mmol), potassium formate (217 mg, 2.57 mmol) and tetra-*n*-butylammonium bromide (277 mg, 0.858 mmol) in dimethylformamide (DMF, 34 mL) was added $Pd(OAc)_2$ (9.6 mg, 0.043 mmol) at room temperature. The reaction was stirred for 24 h at room temperature in the dark. After TLC indicated the disappearance of starting material, the reaction mixture was poured into water and extracted with hexanes (3 × 60 mL). The combined organic extracts were dried ($MgSO_4$), filtered, concentrated, and purified by flash chromatography to give 373 mg (79%) of the diene as a colorless oil.

Reference: Lee, K.; Cha, J. K. *J. Am. Chem. Soc.* **2001,** *123*, 5590–5591.

5.1.12.3 Heck Reactions of Aryl Chlorides (Fu Modification)

The Heck reaction of aryl chlorides tends to require reaction temperatures that exceed 120 °C. The aryl chloride lacks reactivity relative to an arylbromide or aryliodide because of the bond dissociation energy. The bond strength order is $sp^2C–Cl > sp^2C–Br > sp^2C–I$. The Fu modification decreases the reaction temperature significantly, and with activated chlorides the reaction can be run at room temperature in the presence of $Pd(P(t\text{-}Bu)_3)_2$ or $Pd_2(dba)_3$ and *N*-methyldicyclohexylamine (Cy_2NMe).

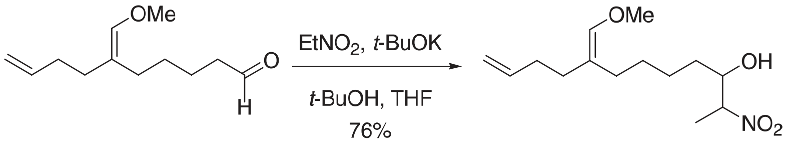


An oven-dried, 250-mL, three-necked, round-bottomed flask equipped with a reflux condenser (fitted with an argon inlet adapter), rubber septum, glass stopper, and a Teflon-coated magnetic stir bar was cooled to room temperature under a flow of argon. The flask was charged with ($Pd(P(t\text{-}Bu)_3)_2$) (0.482 g, 0.943 mmol, 3.0 mol% Pd) and again purged with argon. Toluene (32 mL) was added, and the mixture was stirred at room temperature, resulting in a homogeneous brown–orange solution. Chlorobenzene (3.20 mL, 31.5 mmol), Cy_2NMe (7.50 mL, 35.0 mmol), and butyl methacrylate (5.50 mL, 34.6 mmol) were then added successively via a syringe. The resulting mixture was allowed to stir at room temperature for 5 min, resulting in a homogeneous light-orange solution. The rubber septum was then replaced with a glass stopper, and the flask was heated in a 100°C oil bath under a positive pressure of argon for 22 h. On heating, the solution became a bright canary-yellow in color, and within 10–15 min the formation of a white precipitate (the amine hydrochloride salt) was observed. On completion of the reaction, shiny deposits of palladium metal formed on the sides of the flask, and a large quantity of white precipitate was present. The reaction mixture was allowed to cool to room temperature and then diluted with 100 mL of diethyl ether. The resulting solution was washed with 100 mL of H_2O, and the aqueous layer was extracted with three 50-mL portions of diethyl ether. The combined organic phases were washed with 100 mL of brine and then concentrated by rotary evaporation. Any residual solvent was removed at 0.5 mm. The crude product, a dark-brown oil, was then purified by flash column chromatography to afford 6.67–6.72 g (95%) of the α,β-unsaturated ester as a pale red–orange liquid. This liquid appears to be pure by ^1H and ^{13}C NMR spectroscopy; however, if desired, the discoloration can be removed by filtering the product through a small column of silica gel (3 cm diameter × 10 cm height) which furnishes 6.49–6.62 g (95–96%) of α,β-unsaturated ester as a clear colorless liquid.

Reference: Littke, A. F.; Fu, G. C. *Org. Syn.* **2004,** *81*, 63–70.

5.1.13 Henry Reaction (Nitro Aldol)

The Henry reaction or the nitroaldol is a classical reaction where the α-anion of an alkylnitro compound reacts with an aldehyde or ketone to form a β-nitroalcohol adduct. Over the decades, the Henry reaction has been used to synthesize natural products and pharmaceutical intermediates. In addition, asymmetric catalysis has allowed this venerable reaction to contribute to a plethora of stereoselective aldol condensations. Reviews: (a) Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A. *Front. Nat.Prod. Chem.* **2005,** *1*, 37-41. (b) Ono, N. In *The Nitro Group in Organic Synthesis*; Wiley-VCH: Weinheim, 2001; Chapter 3: The Nitro-Aldol (Henry) Reaction, pp. 30-69. (c) Luzzio, F. A. *Tetrahedron* **2001,** *57*, 915–945.



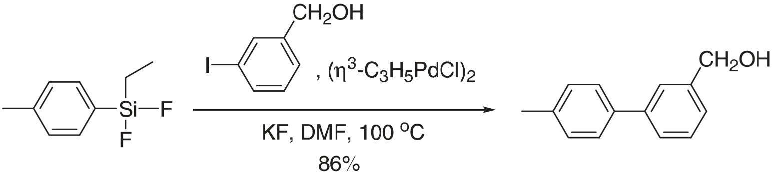
To a solution of the aldehyde (480 mg, 2.44 mmol) and nitroethane (525 μL, 7.32 mmol) in t-BuOH/THF (1:1, 4.0 mL) was added t-BuOK (48 mg, 0.48 mmol) at room temperature. After 20 min, the mixture was diluted with ether (20 mL) and water (20 mL). The separated organic layer was washed with brine (20 mL), and the aqueous layers were back-extracted with ether (2 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by chromatography (silica gel) eluting with hexane:EtOAc (4:1) to afford 500 mg (76%) of the aldol adduct as a pale yellow oil which constituted an inseparable mixture of diastereomers.

Reference: Denmark, S. E.; Gomez, L. *J. Org. Chem.* **2003,** *68*, 8015–8024.

5.1.14 Hiyama Cross-Coupling Reaction

The palladium cross-coupling reaction between an aryl or vinylsilane with an organohalide in the presence of a fluoride source is referred to as the Hiyama reaction. Fluoride sources such as TASF $[(Et_2N)_3S^+(Me_3SiF_2)^-]$, TBAF (tetrabutylammonium fluoride), KF, and CsF activate the silane towards metallation (without these activators, reactions usually do not occur). This reaction is tolerant of a wide array of functionality, including aldehydes, ketones, and esters. Coupling partners include arylhalides and vinylhalides. The silane nucleophile has been extended to include aryl- and vinylsilanols as well as aryltrimethoxysilanes. Reviews: (a) Denmark, S. E.; Ober, M. H. *Aldrichimica Acta* **2003,** *36*, 76–85. (b) Hiyama, T. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.; deMeijere, A., Eds.; Wiley-Interscience: New York, 2002; Chapter III.2.4: Overview of Other Palladium-Catalyzed Cross-Coupling Protocols, pp. 285–301. (c) Hiyama, T. *J. Organomet. Chem.* **2002,** *653*, 58–61. (d) Hiyama, T.; Shirakawa, E.. In *Topics in Current Chemistry: Cross-coupling Reactions A Practical Guide*. Miyaura, N., Ed; Springer-Verlag: Berlin, 2002; Vol. 219, Organosilicon Compounds, pp. 61–85. (e) Hiyama, T. In *Metal-Catalyzed Cross-coupling Reactions*; Diedrich, F.; Stang, P. J., Eds.; Wiley-VCH: New York, 1998; Chapter 10: Organosilicon Compounds in Cross-Coupling Reactions, pp. 421–453.

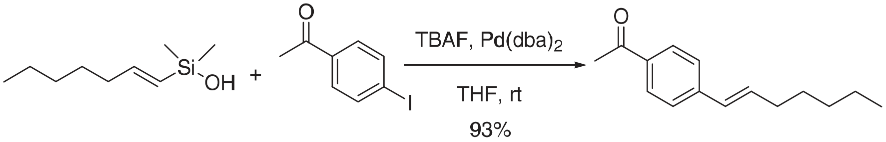
5.1.14.1 Standard Hiyama



To a suspension of potassium fluoride (350 mg, 6.0 mmol, spray dried) in DMF (50 mL) were added ethyldifluoro-(4-methyl)silane (560 mg, 3.0 mmol), 3-iodobenzyl alcohol (250 mg, 2.0 mmol), and $(\eta^3\text{-}C_3H_5PdCl)_2$ (37 mg, 0.1 mmol). The resulting mixture was stirred at 100 °C for 15 h, cooled to room temperature, poured into saturated aqueous sodium bicarbonate solution, and extracted with diethyl ether (3 × 20 mL). The combined ethereal layer was then dried over magnesium sulfate. The solvent was removed under reduced pressure. The crude material was purified by silica gel chromatography eluting a mixture of hexane:EtOAc (5:1) to give 340 mg (86%) of 3-hydroxymethyl-4′-methylbiphenyl as a colorless solid.

Reference: Hatanaka, Y; Goda, K.; Okahara, Y.; Hiyama, T. *Tetrahedron* **1994,** *50*, 8301–8316.

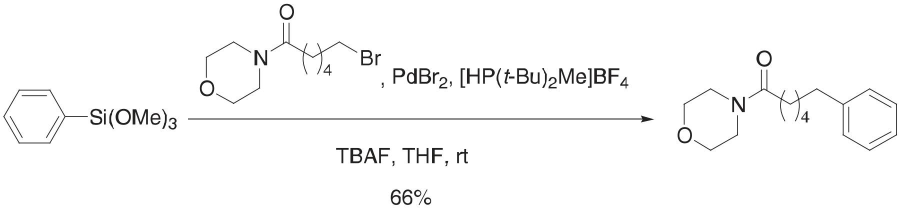
5.1.14.2 Denmark Modification



Tetrabutylammonium fluoride (631 mg, 2.34 mmol) was dissolved in dry THF (2 mL) at room temperature under an atmosphere of dry nitrogen. The silanol (201 mg, 1.17 mmol) was added neat and the mixture was stirred for 10 min at room temperature. 4´-iodoacetophenone (246 mg, 1.0 mmol) was added to the mixture followed by $Pd(dba)_2$ (29 mg). The reaction mixture was stirred at room temperature for 10 min. The mixture was then filtered through a plug silica gel eluting with ether (100 mL).The solvent was removed in vacuo. The resulting residue was then purified by reverse phase chromatography (RPC18) eluting with methanol/H_2O (9/1) followed by Kugelrohr distillation to afford 201 mg (93%) of (*E*)-alkene as a colorless oil.

Reference: Denmark, S. E.; Wehrli, D. *Org. Lett*. **2000,** *2*, 565–568.

5.1.14.3 Fu Modification (Room Temperature Coupling)

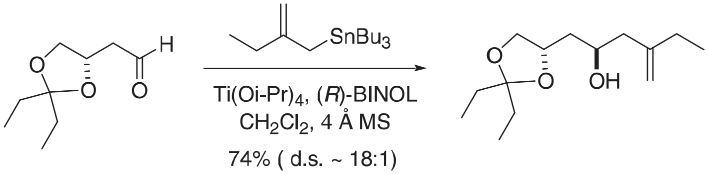


In the air, $PdBr_2$ (10.6 mg, 0.040 mmol) and $[HP(t\text{-Bu})_2Me]BF_4$ (24.8 mg, 0.10 mmol) were placed in a vial equipped with a stir bar. The vial was closed with a septum screwcap, and evacuated and refilled with argon three times. Tetrahydrofuran (2.4 mL) and tetrabutylammnoium fluoride [0.10 mL of 1.0 M (typically in THF), 0.10 mmol] were added, and the resulting mixture was stirred vigorously for 30 min at room temperature. To the resulting homogeneous orange–yellow solution was added $(MeO)_3SiPh$ (0.225 mL, 1.20 mmol), tetrabutylammonium fluoride [2.3 mL of 1.0 M (typically in THF), 2.3 mmol), and the alkyl bromide (264 mg, 1.00 mmol). The reaction mixture was stirred vigorously for 14 h at room temperature. The reaction mixture was then filtered through a short pad of silica gel (washed with ~ 100 mL of ether or EtOAc) and concentrated. The crude product was purified by chromatography eluting with EtOAc:hexane (25:75) to deliver 172 mg (66%) of the morpholine amide as a colorless oil.

Reference: Lee, J.-Y.; Fu, G. C. *J. Am. Chem. Soc*. **2003,** *125*, 5616–5617.

5.1.15 Keck Stereoselective Allylation

The stannane reagents involved in the Keck stereoselective allylation are toxic and caution must be exercised in dealing with them. The catalyst is comprised of 1 equivalent of Ti(O*i*-Pr)$_4$ and 2 equivalents of (*R*)-(+)-BINOL. There are a variety of ways to generate the Ti-BINOL catalyst, and the enantioselectivity varies depending on the method of generation (see Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc*. **1993,** *115*, 8467–8468 and Keck, G. E.; Krishnamurthy, D.; Grier M. C. *J. Org. Chem*. **1993,** *58*, 6543-6544). Reviews: (a) Gung, B. W. *Org. React*. **2004,** *64*, 1–113. (b) Denmark, S. E.; Almstead, N. G. In Modern Carbonyl Chemistry; *Otera, J, Ed.;* Wiley-VCH: Weinheim, 2000; Chapter 10: Allylation of Carbonyls: Methodology and Stereochemistry, pp. 299–402. (c) Chemler, S. R.; Roush, W. R. In Modern Carbonyl Chemistry. Otera, J.; Wiley-VCH: Weinheim, 2000; Chapter 11: Recent Applications of the Allylation Reaction to the Synthesis of Natural Products, pp. 403–490. (d) Denmark, S. E.; Fu, J. *Chem. Rev*. **2003,** *103*, 2763–2793.



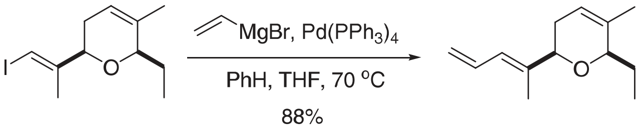
Under argon, to a solution of (*R*)-(+)-BINOL (0.132 g, 0.46 mmol) over 4 Å molecular sieves (0.732 g) in methylene chloride (2.8 mL) was added Ti(O*i*-Pr)$_4$ (0.069 mL, 0.23 mmol). The resulting deep solution was stirred at ambient temperature for 1.5 h then treated with a solution of the aldehyde (0.5 g, 2.9 mmol) in methylene chloride (1.3 mL). The solution was stirred for 2 min, cooled to 0 °C, treated with the allylstannane (1.15 g, 3.2 mmol) over 2 min, and maintained at this temperature for 4.5 h. The reaction was then quenched with saturated sodium bicarbonate, extracted with EtOAc (3×), dried over magnesium sulfate, and concentrated in vacuo. The crude product was purified via flash chromatography using EtOAc:hexanes (1:9) to afford 0.495 g (70%) of the *anti*-alcohol and 28 mg (4%) of the *syn*-alcohol as colorless oils.

Reference: Smith, III, A. B.; Doughty, V. A.; Sfouggatakis, C.; Bennett, C. S.; Koyanagi, J.; Takeuchi, M. *Org. Lett*. **2002,** *4*, 783–786.

5.1.16 Kumada Coupling

The palladium catalyzed reaction between an organomagnesium reagent (Grignard reagent) and organohalide or organotriflate is the Kumada coupling. Although the Kumada coupling has been applied to a variety of coupling partners, the nucleophilic nature of the organomagnesium reagent deems it incompatible with susceptible functionality such as aldehydes, ketones, esters, epoxides, etc. Reviews: (a) Knochel, P.; Krosovskiy; Sapountzis, I. In *Handbook of Functionalized Organometallics*. Knochel, P. Ed.; Wiley-VCH: Weinheim, 2005; Vol. 1, pp. 155–158. (b) Hassan, J.; Sevignon, M; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev*. **2002,** *102*, 1359.

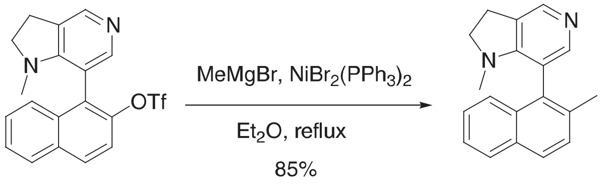
5.1.16.1 *With a Palladium Catalyst*



To the vinyl iodide (1.442 g, 4.938 mmol) in benzene (100 mL) was added vinyl magnesium bromide (1.0 M in THF, 19.75 mL, 19.75 mmol) and tetrakis(triphenylphosphine) palladium (286 mg, 0.247 mmol). *Note: degassing of the solvent is usually recommended for palladium cross-coupling reactions*. This reaction mixture was heated to 60–70 °C for 30 min, diluted with hexanes, and filtered through a pad of silica. After evaporation of the solvents, bulb to bulb Kugelrohr distillation provided 834 mg (88%) of the triene as a colorless oil.

Reference: Liu, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001,** *123*, 10772–10773.

5.1.16.2 *With a Nickel Catalyst*



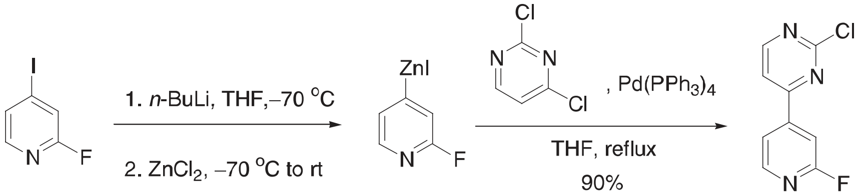
To a solution of the triflate (1.08 g, 2.65 mmol) in ether (17 mL) was added $NiBr_2(PPh_3)_2$ (59 mg, 0.080 mmol) followed by methylmagnesium bromide (3.0 M in ether, 2.2 mL, 6.6 mmol). The mixture was then refluxed for 24 h. The reaction mixture was quenched with water (30 mL) and diluted with CH_2Cl_2 (30 mL). *Note: it is advisable to cool the reaction mixture to 0 °C as an excess of the Grignard reagent is used*. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated in vacuo. The residue was purified by flash chromatography eluting with EtOAc to EtOAc:triethylamine (98:2) to give 618 mg (85%) of the pyridine as a white solid.

Reference: Spivey, A. C.; Fekner, T.; Spey, S. E.; Adams, H. *J. Org. Chem.* **1999,** *64*, 9430–9443.

5.1.17 Negishi Coupling

The palladium catalyzed reaction between an organozinc reagent and an organohalide, or organotriflate is referred as the Negishi coupling. Reviews: (a) Negishi, E,; Hu, Q.; Huang, Z.; Qian, M.; Wang, G. *Aldrichimica Acta* **2005,** *38*, 71–88. (b) Knochel, P.; Leuser, H.; Gong, L.-Z.; Perrone, S.; Kneisel, F. F. In *Handbook of Functionalized Organometallics*. Knochel, P. Ed. Wiley-VCH: Weinheim, 2005; Vol. 1, Chapter 7: Polyfunctional Zinc Organometallics for Organic Synthesis, pp. 316–325. (c) Lessene, G. *Aust. J. Chem.* **2004,** *57*, 107–117. (d) Negishi, E. In *Handbook of Organopalladium Chemistry for Organic Synthesis*. Negishi, E.; deMeijere, A., Eds.; Wiley-Interscience: New York, 2002; Chapter III.2: Palladium-Catalyzed Carbon–Carbon Cross-Coupling, pp. 229–247.

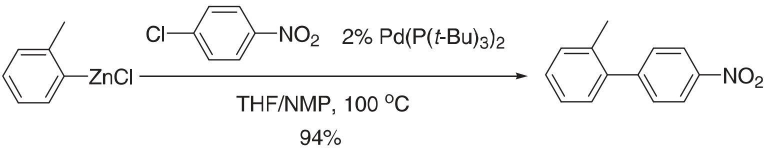
5.1.17.1 Standard



4-Iodo-2-fluoropyridine (15.52 g, 69.60 mmol) was dissolved in dry THF (150 mL) and cooled to −70 °C. Then *n*-BuLi (73.08 mmol, typically a solution in hexanes) was added, and the reaction was stirred at −70 °C for 20 min. Subsequently, dry zinc chloride (10.44 g, 76.61 mmol) was added as a solution in dry THF (60 mL) while keeping the temperature below −60 °C. (*Use an internal thermometer.*) The reaction mixture was then warmed to room temperature whereupon tetrakis (triphenylphosphine)palladium (0.40 g, 0.35 mmol) and 2,4-dichloropyrimidine (7.26 g, 48.73 mmol) in THF (100 mL) were added, and the reaction mixture was refluxed until complete conversion. The reaction mixture was poured into a 10% aqueous EDTA solution and extracted with CH_2Cl_2. The crude material was purified by flash chromatography eluting with petroleum ether:EtOAc (10:1) to deliver 9.17 g (90%) of the pyrimidine as beige crystals.

Reference: Stanetty, P.; Hattinger, G.; Schnürch, M.; Mihovilovic, M. D. *J. Org. Chem.* **2005,** *70*, 5215–5220.

5.1.17.2 Fu Modification



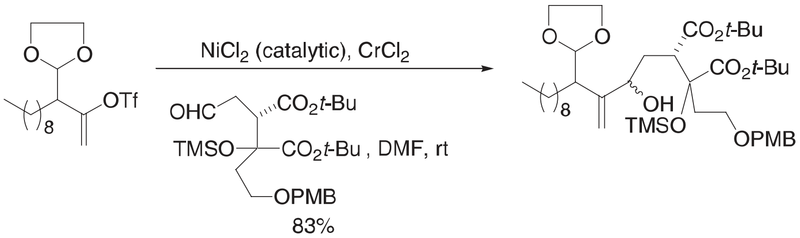
Under argon, $ZnCl_2$ (0.5 M in THF, 3.15 mL, 1.6 mmol) was added by syringe to a Schlenk tube. *o*-Tolylmagnesium chloride (1.0 M in THF, 1.5 mL, 1.5 mmol) was then added dropwise, and the resulting mixture was stirred at room temperature for 20 min. NMP (2.2 mL) was added by syringe. After 5 min, $Pd(P(t\text{-}Bu)_3)_2$ (10.2 mg, 0.020 mmol) and 1-chloro-4-nitrobenzene (158 mg, 1.0 mmol) were added. The Schlenk tube was closed at the Teflon stopcock, and the reaction mixture was stirred in a 100 °C oil bath for 2 h. It was then allowed to cool to room temperature, and aqueous hydrochloric acid (1.0 M, 6 mL) was added. The resulting mixture was extracted with ether (4 × 8 mL), and the organic extracts were combined, washed with water (5 × 10 mL), dried ($MgSO_4$), and concentrated to afford a yellow solid. The crude product was purified via flash chromatography eluting with 3% ether in hexanes to furnish 200 mg (94%) of the biaryl as a pale-yellow solid.

Reference: Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001,** *123*, 2719–2724.

5.1.18 Nozaki–Hiyama–Kishi Reaction (Organochromium Reagents)

The formation of carbinols using organochromium reagents has come to be known as the Nozaki–Hiyama–Kishi reaction. A wide array of organochromium reagents have been generated, including alkenyl, alkynyl, allyl, aryl, and propargyl species. In general, they are formed from organohalides (usually bromides or iodides) and a mixture of $CrCl_2/NiCl_2$. The $NiCl_2$ is absolutely essential for reliable formation of these reagents. Organochromium reagents are chemoselective for aldehydes but do react with ketones to form carbinols. In addition to there chemoselectivity, these reagents have low basicity and are compatible with enolizable aldehydes and ketones, tolerate a multitude of functional groups, and add to aldehydes under mild conditions (*ambient temperature*).

Reviews: (a) Takai, K. *Org. React.* **2004,** *64*, 253–612. (b) Fürstner, A. *Chem. Rev.* **1999,** *99*, 991–1046. (c) Wessjohann, L. A.; Scheid, G. *Synthesis* **1999,** 1–36. (d) Cintas, P. *Synthesis* **1992,** 248–257.

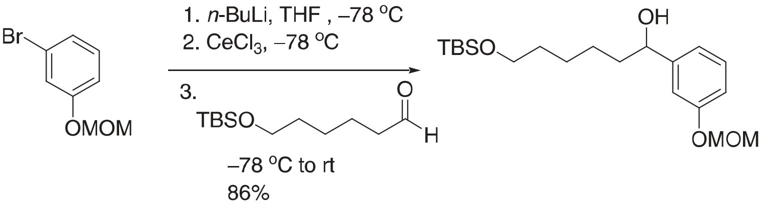


A mixture of $NiCl_2$ (11.0 mg, 0.0849 mmol) and $CrCl_2$ (493 mg, 3.88 mmol) in degassed DMF (3 mL) was stirred at 0 °C for 10 min. A solution of the aldehyde (505 mg, 0.962 mmol) in DMF (3 mL) and a solution of the triflate (653 mg, 1.68 mmol) in DMF (3 mL) was added to the mixture at room temperature, and the resulting mixture was stirred at room temperature for 25 h. The reaction mixture was diluted with water and extracted with ether, washed with saturated sodium chloride, dried, and concentrated. The crude product was purified via chromatography eluting with *n*-hexane:EtOAc (5:1) to give 610.4 mg (83%) of a diastereomeric mixture of allylic alcohols.

Reference: Hirai, K.; Ooi, H.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *Org. Lett.* **2003,** *5*, 857–859.

5.1.19 Organocerium Reagent Addition to a Carbonyl

Organocerium reagents are generated in situ. They are typically synthesized by the reaction of an organolithium reagent or organomagnesium reagent and dry cerium chloride ($CeCl_3$). As $CeCl_3$ is commercially available as the heptahydrate, the water may be driven off by heating the finely ground solid at 140 °C at 0.5 torr. Cerium reagents offer several advantages over organolithium reagents. They are less basic and hence they work well when enolizable aldehydes or ketones are the coupling partners. Although they are less basic, the reagents are more nucleophilic. Also, organocerium reagents react preferentially in a 1,2-fashion with α,β-unsaturated carbonyl electrophiles. Review: Liu, H.-J.; Shia, K.-S.; Shang, X.; Zhu, B.-Y. *Tetrahedron* **1999,** *55*, 3803–3830.



A 250-mL, argon-flushed, three-necked flask was charged with anhydrous cerium chloride (9.90 g, 40.2 mmol) in dry THF (50 mL). The mixture was stirred for 4 h at room temperature and occasionally sonicated in an ultrasound cleaning bath (30 min) until the mixture became a fine white suspension. The flask was then cooled to −78 °C. In a separate 100-mL. argon-flushed, three-necked flask, 3-methoxymethylphenyl bromide (8.14 g, 37.5 mmol) was dissolved in dry THF (30 mL). After the solution was cooled to −78 °C, *n*-BuLi (1.6 M in hexanes, 23.5 mL, 37.6 mmol) was added via a syringe and the resulting brown solution was stirred for 15 min. The solution was then transferred to the flask containing the cerium chloride suspension by means of a transfer needle. The reaction mixture was stirred for 1 h at −78 °C upon which the solution turned an intense yellow. The aldehyde (5.75 g, 25 mmol) was added, and the mixture was stirred overnight while it was allowed to slowly come to room temperature. After the reaction was quenched with sodium bicarbonate (50 mL), the mixture was transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with water and brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with cyclohexane:EtOAc (6:1) to give 7.83 g (86%) of the alcohol as a colorless oil.

Reference: Kaiser, F.; Schwink, L.; Velder, J.; Schmalz, H.-G. *J. Org. Chem.* **2002,** *67*, 9248–9256.

5.1.20 Organolithium Reagents

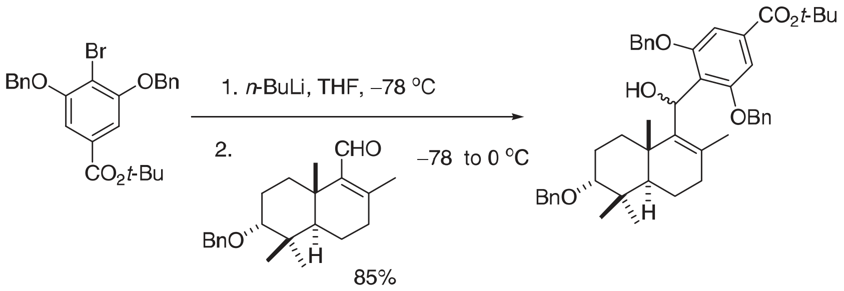
Organolithium reagents have become one of the most important classes of organometallic compounds in modern organic synthesis for forming carbon–carbon bonds between arylithiums, alkenyllithiums, alkynyllithium, alkyl lithiums, and an electrophile (i.e., aldehydes, ketones, esters, amides, epoxides, etc). Organolithium reagents are often prepared in situ from the appropriate arylhalide, alkenylhalide, etc., and a commercially available organolithium (i.e., *n*-BuLi, *sec*-BuLi, *tert*-BuLi) at low temperatures (i.e., −70 °C). A rapid halogen–metal exchange occurs to deliver the newly formed organolithium reagent and the butylhalide. The rate of the metal halogen exchange occurs as follows: R–I > R–Br >> R–Cl. The exchange is not trivial as the equilibrium process is sensitive to solvent (usually THF or diethyl ether), temperature, and rate of addition of the commercial lithium reagent. Lithium metal and dissolving metal reductions are used, but seen less frequently with the availability of the butyllithiums. Also, metallations of alkynes, aryl-, and heteroaryl ring systems are achieved with *n*-, *sec*-, and *tert*-butyllithium. Often a directing group is present with aryl compounds. Reviews: (a) Yus, M.; Foubelo, F. Polyfunctional Lithium

Organometallics for Organic Synthesis. In *Handbook of Functionalized Organometallics*; Knochel, P., Ed.; Wiley-VCH: Weinheim, 2005; Vol. 1, pp. 7–43. (b) Chincilla, R.; Nájera, C. *Tetrahedron* **2005,** *61*, 3139–3176**.** (c) Najera, C.; Yus, M. *Curr. Org. Chem.* **2003,** *7*, 867–926. (d) Sotomayor, N.; Lete, E. *Curr. Org. Chem.* **2003,** *7*, 275–300. (e) Nájera, C.; Sansano, J. M.; Yus, M. *Tetrahedron* **2003,** *59*, 9255–9303. (f) Wakefield, B. J. *Organolithium Methods*; Academic Press: San Diego (USA), 1988.

5.1.20.1 Halogen–Lithium exchange

5.1.20.1.1 With n-BuLi

When using *n*-BuLi, Wurtz coupling is a possibility. This is a S_N2 reaction between the newly formed organolithium reagent and *n*-butylhalide (formed as a consequence of the metal–halogen exchange). See also organolithium generation in chapter 1.

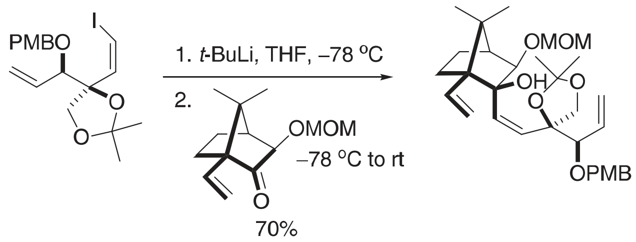


To a solution of the arylbromide (2.58 g, 5.50 mmol) in dry THF (50 mL) was added *n*-BuLi (1.6 M in hexane, 3.44 mL, 5.50 mmol) at −78 °C under nitrogen. (*Note: the metal– halogen exchange process is exothermic so care is usually taken to add the organolithium reagent dropwise. It is also advisable to use an internal thermometer to closely monitor the reaction mixture temperature.*) The mixture was stirred for 10 min at −78 °C under nitrogen. Then, the aldehyde (1.19 g, 3.66 mmol) in dry THF (20 mL) was added, and the mixture was stirred at −78 °C for 1 h, warmed to 0 °C, and stirred for an additional 1 h. Saturated ammonium chloride was then added to quench the reaction. The solvent was removed under vacuum, and the resulting residue was dissolved in EtOAc, washed with 1 N HCl, saturated aqueous sodium bicarbonate, and brine (3×), and then dried over magnesium sulfate. After solvent removal, the crude product was purified by flash chromatography eluting with a gradient of hexane:EtOAc (100:1 to 20:1) to give 2.23 g (85%) of diastereomeric carbinols as a white semi-solid (the authors noted ~ 10% of impurities based on ^{1}H NMR).

Reference: Deng, W.-P; Zhong, M.; Guo, X.-G. Kende, A. S. *J. Org. Chem.* **2003,** *68*, 7422–7427.

5.1.20.1.2. With t-BuLi

Two equivalents of *t*-BuLi are used. One equivalent is required for the metal–halogen exchange, and the second equivalent reacts with the resulting *tert*-butyl halide to form isobutylene and a second equivalent of lithium halide.

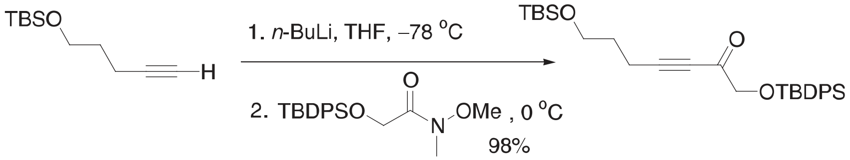


A –78 °C solution of the vinyl iodide (1.05 g, 2.44 mmol) in dry THF (12 mL) was treated with *t*-BuLi (1.7 M in hexanes, 3.2 mL, 5.44 mmol). (*Note: the metal–halogen exchange process is exothermic so care is usually taken to add the organolithium reagent dropwise. It is also advisable to use an internal thermometer to closely monitor the reaction mixture temperature.*) After 2 min, the ketone (500 mg, 2.23 mmol) in THF (3 mL) was introduced via a syringe. The yellow mixture was stirred for 20 min, warmed to room temperature, quenched with saturated sodium bicarbonate solution, and extracted with ether. (*Note: it is prudent to cool the reaction mixture to 0 °C or lower prior to quenching even though these authors did not.*) The combined organic layers were washed with brine (2×), dried, and concentrated. The crude product was purified via chromatography eluting with 10% EtOAc in hexanes to afford 836 mg (70%) of the secondary alcohol as a colorless oil.

Reference: Paquette, L. A.; Montgomery, F. J.; Wang, T.-Z. *J. Org. Chem.* **1995,** *60*, 7857–7864.

5.1.20.2. Metallations

5.1.20.2.1 Alkynes

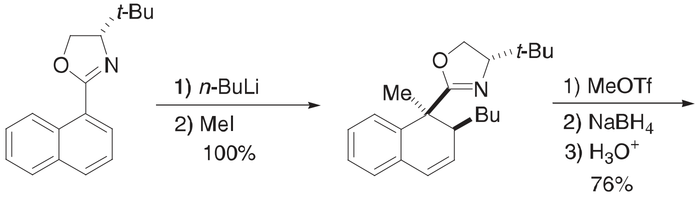


To a –78 °C solution of the alkyne (1.57 g, 7.92 mmol) in THF (25 mL) was added a solution of *n*-BuLi (2.5 M in hexanes, 3.33 mL, 8.32 mmol). The reaction mixture was stirred for 20 min and then a solution of the Weinreb amide (3.11 g, 8.71 mmol) in THF (5 mL) was added via a cannula. The reaction was allowed to warm to 0 °C and stirred for 2 h. The reaction mixture was then re-cooled to –78 °C and treated with 0.5 N HCl (5 mL). The mixture was allowed to warm to ambient temperature and stirred for 30 min. The mixture was diluted with ether and a saturated solution of sodium bicarbonate. The aqueous layer was separated and extracted with ether (3 × 30 mL). The combined ethereal extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated to dryness. The residue was purified by column chromatography eluting with hexanes:ether (20:1) to give 3.87 g (98%) of the ketone as a clear oil.

Reference: Roush, W. R.; Barda, D. A.; Limberakis, C.; Kunz, R. K. *Tetrahedron* **2002,** *58*, 6433–6454.

5.1.20.2.2. Ortho-metallations

Reviews: (a) Clark, R. D.; Jahangir, A. *Org. React.* **1995,** *47*, 1–314. (b) Snieckus, V. *Chem Rev.* **1990,** *90*, 879–933.



A solution of the naphthyloxazoline (200 mg, 0.79 mmol) in THF was cooled to −78°C and a solution of *n*-butyllithium (0.79 mL, 1.5 M in hexanes, 1.19 mmol) was added dropwise. The mixture was stirred at −78 °C for 2 h and then iodomethane (1.21 mL, 2.37 mmol) was added. The mixture was warmed to room temperature, stirred for 1 h, and then quenched with saturated aqueous ammonium chloride (30 mL). The mixture was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel to afford 259 mg (100%) of the dihydronaphthalene as a colorless oil.

Aldehyde

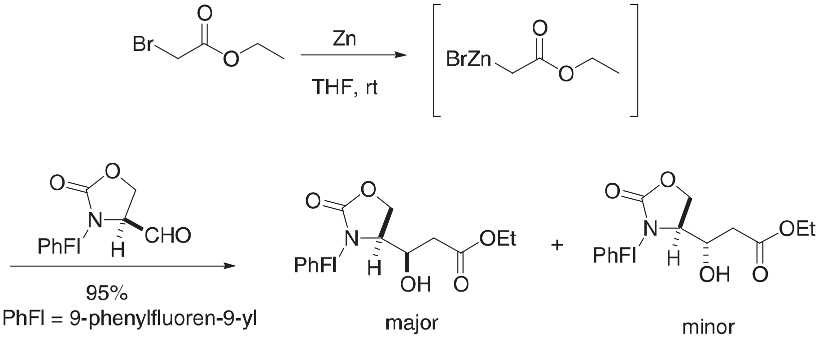
To a solution of the dihydronaphthalene (250 mg, 0.77 mmol) in CH_2Cl_2 (5 mL) was added methyl trifluoromethanesulfonate (227 mg, 1.38 mmol). The mixture was stirred at room temperature until the starting material had been completely consumed, as judged by TLC analysis (3 h). The mixture was cooled to 0 °C and a solution of $NaBH_4$ (111 mg, 2.92 mmol) in 4:1 MeOH:THF (3 mL) was slowly added. The mixture was warmed to room temperature and then quenched with saturated aqueous ammonium chloride (50 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The resulting material was dissolved in 4:1 THF/H_2O (5 mL), and oxalic acid (485 mg, 3.85 mmol) was added. The reaction mixture was stirred at room temperature for 12 h and then quenched with saturated aqueous sodium bicarbonate (50 mL). The resulting mixture was extracted with CH_2Cl_2 and the combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude aldehyde was purified by flash chromatography on silica gel to afford 134 mg (76%) of the aldehyde as a colorless oil.

Reference: Rawson, D. J.; Meyers, A. I. *J. Org. Chem.* **1991,** *56*, 2292–2294.

5.1.21 Reformatsky Reaction (Organozinc)

The traditional Reformatsky reaction involves the conversion of a α-haloester to a α-organozinc ester in the presence of zinc metal and an initiator such as I_2 or 1,2-diiodoethane (*the initiator is necessary to remove the layer of zinc oxide*). The resulting organozinc reagent then reacts with an aldehyde or ketone to deliver a β-hydroxy ester. Other zinc sources such as Rieke zinc^{TM}, dissolving lithium reductions with zinc chloride, and many others have been reported. Over the past several decades this reaction has evolved to include other metals such as chromium, samarium iodide (Kagan reagent), and indium. In addition, the number of electrophiles has increased and some include nitriles, esters, lactones, epoxides, aziridines, and Michael acceptors. The Reformatsky reaction has been reported inter- and intramolecularly and used in asymmetric synthesis.

Reviews: (a) Ocampo, R.; Dolbier, Jr. W. R. *Tetrahedron* **2004,** *60*, 9325–9374. (b) Fürstner, A. *Synthesis* **1989,** 571–590.



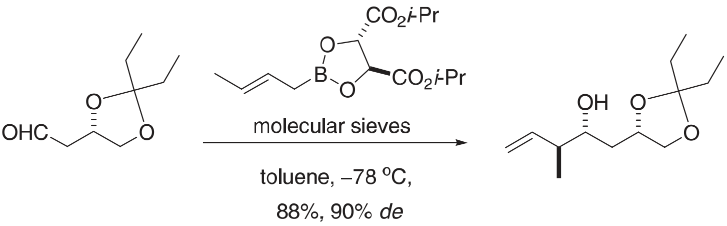
Ethyl bromoacetate (1.14 mL, 10 mmol) was added slowly to a mixture of the aldehyde (2.29g, 6 mmol) and acid-washed zinc dust (0.78 g, 12 mmol) in dry THF (40 mL) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred vigorously for 2 h before the addition of aqueous ammonium chloride (20 mL) and brine (20 mL). After filtration through Celite, the precipitate was washed well with EtOAc (4 × 10 mL) and the organic phase was separated. The aqueous phase was extracted with EtOAc (4 × 10 mL), the combined organic extracts were dried (magnesium sulfate), and the solvent was removed under reduced pressure to give an oily residue. The material was purified by flash chromatography, eluting with hexane:EtOAc (4:1), and delivered 1.92 g (72%) of the major diastereomer as a colorless oil followed by 512 mg (23%) of the minor diastereomer as a colorless oil for a total yield of 2.43 g (95%).

Reference: Ding, Y.; Wang, J.; Abboud, K. A.; Xu, Y.; Dolbier, Jr., W. R.; Richards, N. G. L. *J. Org. Chem.* **2001,** *66*, 6381–6388.

5.1.22 Roush Crotylation

While the Roush crotylboronate reagent takes a whole day to prepare, it works extremely well with regard to both yield and stereoselectivity, especially for the matched substrates.

Reviews: (a) Denmark, S. E.; Almstead, N. G. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim: 2000; Chapter 10: Allylation of Carbonyls: Methodology and Stereochemistry, pp. 299–402. (b) Chemler, S. R.; Roush, W. R. In *Modern Carbonyl Chemistry*; Otera, J. Ed.; Wiley-VCH: Weinheim: 2000; Chapter 11: Recent Applications of the Allylation Reaction to the Synthesis of Natural Products, pp. 403–490. (c) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003,** *103*, 2763–2793.



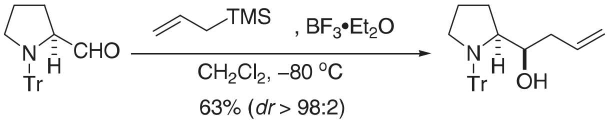
A solution of (*R*,*R*)-diisopropyltartrate (*E*)-crotylboronate (46.0g, 0.152 mol) in dry toluene (1 L) was treated with powdered 4 Å molecular sieves (6 g) at –78 °C. A solution of the aldehyde (13.1 g, 0.076 mol) in dry toluene (50 mL) was cooled to –78 °C and added dropwise into the suspension via a cannula. The resultant mixture was stirred at –78 °C for 1 h before an aqueous solution of sodium hydroxide (2 N, 70 mL) was added. The mixture was warmed to 0 °C, stirred for 30 min, and filtered through a pad of Celite. The aqueous layer was extracted with ether (3 × 250 mL) and the combined organic phases were washed with brine (200 mL), dried over magnesium sulfate, filtered, and concentrated in vacuo. The crude product was purified via flash chromatography eluting with hexanes:EtOAc (7:1) to afford 15.2 g (88%, 90% *d.e.*) of the alcohol as a colorless oil.

Reference: Smith, III, A. B.; Zheng, J. *Tetrahedron* **2002,** *58*, 6455–6471.

5.1.23 Sakurai Reaction

The Sakurai allylation works with a variety of Lewis acid catalysts such as $TiCl_4$, $AlCl_3$, $SnCl_4$, $EtAlCl_2$, in addition to BF_3·OEt. Reviews: (a) Denmark, S. E.; Almstead, N. G. In *Modern Carbonyl Chemistry;* Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; Chapter 10: Allylation of Carbonyls: Methodology and Stereochemistry, pp. 299–402. (b) Chemler, S. R.; Roush, W. R. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; Chapter 11: Recent Applications of the Allylation Reaction to the Synthesis of Natural Products, pp. 403–490. (c) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003,** *103*, 2763–2793.

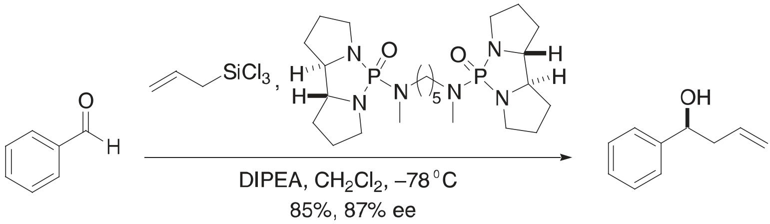
5.1.23.1 Traditional



To the aldehyde (0.511 g, 1.5 mmol) in dry CH_2Cl_2 (15 mL) under argon was added allyltrimethylsilane (0.48 mL, 3 mmol) followed by boron trifluoride etherate (0.19 mL, 1.5 mmol) at –80 °C. The reaction was followed by TLC. After 5 h of stirring at –80 °C, the reaction was hydrolyzed with a 2:1 mixture of saturated aqueous ammonium chloride solution and ammonia (28% in water). The layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic phases were dried over anhydrous magnesium sulfate and the solvents removed in vacuo. The solid obtained was purified by flash chromatography on silica gel eluting with cyclohexane:EtOAc: triethylamine (9:1:0.2) to afford 364 mg (63%) of the homoallylic alcohol as a white solid.

Reference: Bejjani, J.; Chemla, F.; Audouin, M. *J. Org. Chem.* **2003,** *68*, 9747–9752.

5.1.23.2 Denmark's Version Using a Chiral Bis-phosphoramide

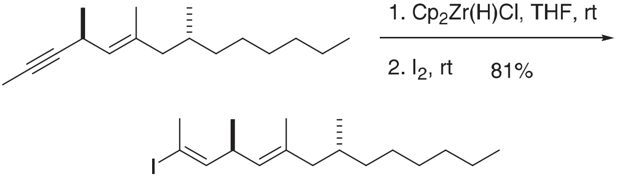


To a solution of the bis-phosphoramide catalyst (59 mg, 0.1 mmol) in CH_2Cl_2 (1 mL) and diisopropylethylamine (1.0 mL) under N_2 at −78 °C was added allyltrichlorosilane (580 μL, 4.0 mmol). The solution was stirred at −78 °C for 10 min before benzaldehyde (200 mL, 2.0 mmol) was added. The resulting mixture was stirred at this temperature for 8 h whereupon the cold solution was poured in to a mixture of saturated aqueous $NaHCO_3$ (10 mL) and saturated aqueous KF (10 mL) at 0 °C with vigorous stirring. The mixture was stirred for 2 h at room temperature and then filtered through Celite. The layers were then separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The oily residue was purified by column chromatography (silica gel) eluting with CH_2Cl_2:pentane (3:1) followed by CH_2Cl_2 to give 254 mg (85%) of the benzylic alcohol in 87% *ee*.

Reference: Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2001,** *123*, 9488–9489.

5.1.24 Schwartz's Reagent

Schwartz hydrozirconation works on both alkenes and alkynes even at room temperature. It works significantly better in ether solvents than hydrocarbon solvents. In addition, the reaction intermediate can be transmetallated into other organometallics that can be used in palladium-catalyzed reactions or trapped with electrophiles. Review: Schwartz, J.; Labinger, J. A. *Angew. Chem. Int. Ed.* **1976,** *15*, 333–340.

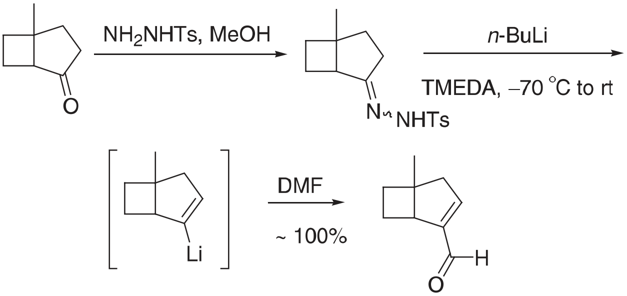


To a stirred suspension of Schwartz's reagent, $Cp_2Zr(H)Cl$ (1.36 g, 5.26 mmol) in THF (15 mL) at room temperature was added a solution of the alkyne (0.585 g, 2.50 mmol) in THF (15 mL). The mixture was stirred for 24 h and then cooled to 0 °C whereupon a solution of iodine (1.27 g, 5.0 mmol) in THF (8 mL) was added dropwise. The resulting reaction mixture was stirred at room temperature for 30 min and then quenched with a dilute solution of sodium thiosulfate. The mixture was extracted with ether (3 ×), and the combined organic extracts were washed successively with a dilute solution of sodium thiosulfate and brine. After drying over anhydrous magnesium sulfate, the suspension was filtered, and the solvent was removed in vacuo to give a semi-solid residue that was extracted with pentane (3×). After removal of the pentane in vacuo, the crude product was chromatographed on silica gel eluting with pentane to give 0.732 g (81%) of the vinyl iodide as a yellow oil.

Reference: Organ, M. G.; Wang, J. *J. Org. Chem.* **2003,** *68*, 5568–5574.

5.1.25 Shapiro Reaction

The Shapiro reaction is the conversion of a ketone to an alkene via a tosylhydrazone. The tosylhydrazone is treated with two equivalents of strong base, typically *n*-BuLi or MeLi, to afford an alkenyllithium species that is quenched with an electrophile to form an alkene. See also section 4.6.6 Shapiro reaction. Reviews: (a) Chamberlin, A. R.; Bloom, S. H. *Org. React.* **1990,** *39*, 1–83. (b) Shapiro, R.H. *Org. React.,* **1976,** *23*, 405.



Tosylhydrazine (3.53g, 18.9 mmol) was added to 60% aqueous MeOH (46 mL) and then heated to 60 °C. The heptanone (2.33 g, 18.8 mmol) was then added dropwise to the clear solution. The reaction was then immediately stored at 5 °C for 15 h. The resultant white crystals were filtered, washed with 60% aqueous methanol, and air dried for 10 min. The hydrazone was obtained as white crystals (4.91 g, 89%).

A suspension of the tosylhydrazone (1.04 g, 3.59 mmol) and TMEDA (15 mL) was cooled to −78 °C under a nitrogen atmosphere. A solution of *n*-BuLi (2.3 M, 4.6 mL, 10.58 mmol) was added dropwise to the frozen suspension, and the resulting solution was kept at −78 °C for 15 min and then allowed to warm to ambient temperature whereupon it turned a dark red color. (*Caution: nitrogen is produced in this reaction and proper ventilation of the gas is required. Do not use a sealed system!*) This solution was stirred for a further 5 h. It was cooled to 0 °C, DMF (0.4 mL, 5.18 mmol) was added, and the solution stirred at ambient temperature overnight. It was then poured into a solution of hydrochloric acid (7.5%, 60 mL) and extracted with CH_2Cl_2 (4 × 40 mL). The combined organic phases were washed with saturated sodium chloride (40 mL) and dried. The solvent was then removed in vacuo to give ~2 g (~100%) of aldehyde.

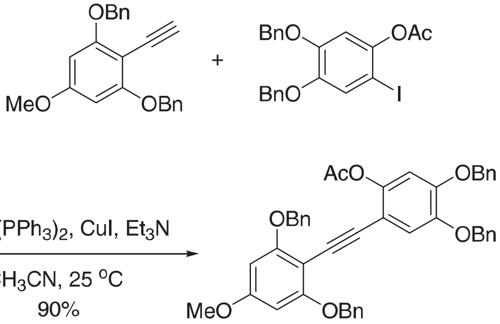
Reference: Hamon, D. P. G.; Tuck, K. L. *J. Org. Chem.* **2000,** *65*, 7839–7846.

5.1.26 Sonogashira Coupling

The palladium catalyzed reaction between a terminal alkyne and an unsaturated organohalide or organotriflate in the presence of CuI and a tertiary organic amine is the

Sonogashira reaction. Unsaturated organic species include arylhalides (X = I, Br, Cl), aryltriflates, vinylhalides, and vinyltriflates. This is a reaction that also tolerates a large number of functional groups. Aryliodides typically react with terminal alkynes under Sonogashira conditions at room temperature; however, less reactive coupling partners such as arylbromides require elevated temperatures. Additives such as tetrabutylammonium bromide and potassium iodide accelerate the Songoashira reaction of less reactive coupling partners. Also, a significant amount of work has been conducted to identify ligands.

Review: Sonogashira, K. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.; deMeijere, A., Eds; Wiley-Interscience: New York, **2002,** Chapter III.2.8: Palladium-Catalyzed Alkynylation, pp. 493–535.



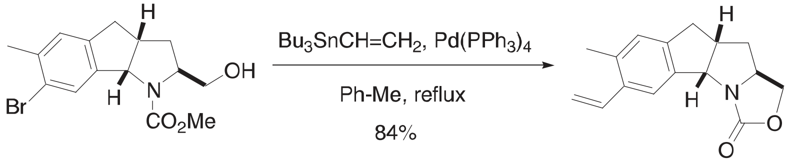
To a nitrogen degassed solution of triethylamine (3.1 mL, 22.2 mmol) in CH_3CN (50 mL) were added the alkyne (2.6 g, 7.5 mmol), the aryl iodide (3.5 g, 7.4 mmol), $PdCl_2(PPh_3)_2$ (61.6 mg, 0.088 mmol), and CuI (16.8 mg, 0.088 mmol), and the mixture was stirred at 25 °C for 12 h. After removal of the solvent, the residue was filtered, concentrated, and purified by flash chromatography on silica gel eluting with petroleum ether:EtOAc (10:1) to give 4.48 g (90%) of the alkyne as a white solid.

Reference: Li, C. C.; Xie, Z. X.; Zhang, Y. D.; Chen, J. H.; Yang, Z. *J. Org. Chem.* **2003,** *68*, 8500–8504.

5.1.27 Stille Reaction

The palladium catalyzed coupling between an organostannane and organohalide or organotriflate is referred to as the Stille reaction. This reaction is tolerant of a variety of functional groups with a plethora of intra- and intermolecular reactions reported in the past 20 years. Consequently, an assortment of simple and multifunctionalized alkynyl, vinyl, aryl, allyl, benzyl, and alkylorganotin reagents have been synthesized. Also, a large number of diverse coupling partners, including acid chlorides, benzyl halides, allyl halides, allyl acetates, aryl halides, heteroaryl halides, aryltriflates, heteroaryltriflates, alkenyl halides, alkeynyl triflates, alkynyl halides, and alkyl halides have been used. The Sn reagents can be synthesized by a host of protocols; however, three of the most popular include palladium coupling between an organohalide (or triflate) and tetramethyltin, metal–halogen exchange of an organohalide followed by quenching of the resulting organolithium with trimethyltin chloride, and Pd-coupling of an organohalide (or triflate) with $Me_3SnSnMe_3$. Pd(0) and Pd (II) catalysts have been utilized for the Stille reaction, including $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$, $BnPd(PPh_3)_2Cl$,

$PdCl_2(MeCN)_2$, $Pd(OAc)_2$, $Pd(dba)_2$, $Pd_2(dba)_3/P(2\text{-furyl})_3$, and $Pd(OAc)_2/P(o\text{-tol})_3$. Typically, the coupling is done in hot or refluxing solvent. Some solvents include THF, benzene, toluene, DMF, CH_3CN, dioxane, and NMP. The major disadvantage of the Stille reaction, compared with other organometallic palladium couplings, is the toxicity of the stannane reagents. Great care should be exercised in preventing exposure of the tin reagent via inhalation or skin absorption. In addition, proper disposal of the tin waste is pertinent. Removal of excess reagent during the workup and purification can also present difficulties. Reviews: (a) Fouquet, E.; Herve, A. In *Handbook of Functionalized Organometallics*. Knochel, P., Ed.; Wiley-VCH: Weinheim, 2005; Vol. 1, Chapter 6: Polyfunctional Tin Organometallics for Organic Synthesis, pp. 203–215. (b) Espinet, P. Echavarren, A. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 4704–4734. (c) Fugami, K.; Kosugi, M. In *Topics in Current Chemitry: Cross-coupling Reactions A Practical Guide.* Miyaura, N., Ed.; Springer-Verlag: Berlin, 2002; Vol. 219, Organotin Compounds, pp. 87–130. (d) Kosug, M.; Fugami, K. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.; deMeijere, A., Eds.; Wiley-Interscience: New York, 2002; Chapter III. 2.3: Overview of the Stille Protocal with Sn, pp. 263–283. (e) Farina, V.; Krishnamurthy, V.; Scott, W. *J. Org. React.* **1997,** 50, 1-652. (f) Stille, J. K. *Angew. Chem. Int. Ed.* **1986***, 25,* 508-524.



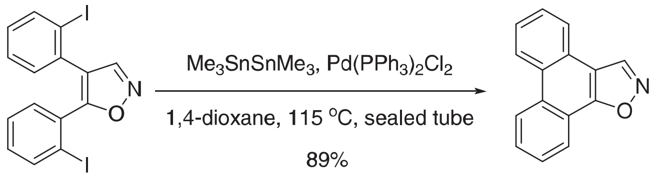
To a stirred suspension of the bromoindene (500 mg, 1.47 mmol) in toluene (20 mL) were added tetrakis(triphenylphosphine)palladium (150 mg, 0.09 equivalents) and then tributyl(vinyl)tin (0.5 mL, 1.15 equivalents), and the mixture was stirred and refluxed for 24 h. The reaction mixture was then cooled to room temperature, diluted with CH_2Cl_2 (20 mL), filtered through a pad of Celite, and evaporated to dryness. The resulting crude product was taken up in CH_2Cl_2 (100 mL), and aqueous saturated potassium fluoride solution (150 mL) was added. The mixture was then stirred vigorously overnight. The organic phase was then separated, and the aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic layers were dried over sodium sulfate, filtered, and evaporated to dryness. The crude product was dissolved in chloroform and purified by flash chromatography eluting with hexanes:EtOAc (7:3) to afford 314 mg (84%) of the 7-vinylindene as a white solid.

(*Note on workup: if the final product is soluble in acetonitrile but lacks solubility in hexanes, a solution of the crude product in acetonitrile can be washed several times with hexanes to extract the tin residues.*)

Reference: Hanessian, S.; Papeo, G.; Angiolini, M.; Fettis, K.; Beretta, M.; Munro, A. *J. Org. Chem.* **2003,** *68*, 7204–7218.

5.1.28 Stille–Kelly Reaction

The Stille–Kelly reaction is a variant of the Stille coupling where an organodihalide undergoes an intramolecular reaction in the presence of hexamethylditin and a palladium catalyst.



A heavy wall-pressure tube was charged with the diarylisoxazole (418 mg, 0.89 mmol), $Pd(PPh_3)_2Cl_2$ (19.3 mg, 0.027 mmol), and degassed dioxane (19 mL) under nitrogen. A solution of Me_6Sn_2 (440 mg, 1.33 mmol) in degassed 1,4-dioxane (7.4 mL) was added dropwise to the resulting suspension, and after flushing with nitrogen at room temperature for 15 min, the mixture was heated at 115 °C in an autoclave for 50 min. After cooling, the resulting black suspension was centrifuged and the deposited black palladium was washed with CH_2Cl_2 (1 × 3 mL). The combined organic layers were washed with saturated potassium fluoride solution (1 × 7 mL), dried (Na_2SO_4), and the solvent was evaporated in vacuo. The resulting yellow residue was purified by flash chromatography eluting with hexane:EtOAc (30:70) providing a colorless oil which was crystallized from methanol to deliver 0.173 g (89%) of the phenanthro[1,2]oxazole as a colorless powder.

Reference: Olivera, R.; SanMartin, R.; Tellitu, I.; Domínguez, E. *Tetrahedron* **2002,** *58*, 3021–3037.

5.1.29 Suzuki Coupling (Suzuki–Miyaura)

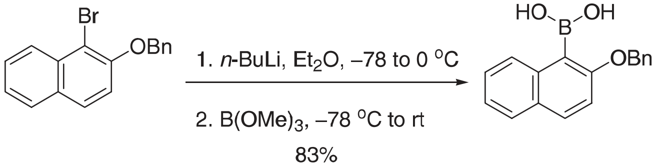
The Pd catalyzed reaction between an organoboronic acid or organic boronic ester and an organohalide in the presence of a base is referred as the Suzuki or Suzuki–Miyaura reaction. The Suzuki reaction has become one of the most powerful carbon–carbon bond forming reactions in organic synthesis because of its tolerance of functionality, lack of toxicity associated with boronic acids, the relative ease of synthesizing boronic acids or boronic esters, and the large number of commercially available boronic acids. Despite these advantages, boronic acids are often contaminated with varying amounts of boronic anhydrides and base sensitive functionality might be compromised in the presence of the required Lewis base. In the traditional Suzuki reaction, a number of catalysts have been used, including $Pd(PPh_3)_4$, $Pd(dppf)Cl_2$, $Pd(PPh_3)_2Cl_2$, $Pd(dba)_2$/dppf, $Pd(OAc)_2$, $Pd(OAc)_2$/dppf, and $Pd(OAc)_2/PPh_3$. Over the years, much development has also been done on other ligands, including $AsPh_3$, $P(o\text{-tol})_3$ and $P(t\text{-Bu})_3$. However, the reader is encouraged to consult the reviews as the ligands are vast. In addition, nickel catalysts such as $NiCl_2(PPh_3)_2$ have been successful involving arylchlorides. Common bases include KF, CsF, $NaHCO_3$, Na_2CO_3, K_2CO_3, Cs_2CO_3, K_3PO_4, NaOH, $Ba(OH)_2$, NaOH, Tl_2CO_3 (*toxic*), TlOH (*toxic*), and triethylamine. Typically, the reactions are run above 70 °C in solvent systems that include THF/water, 1,4-dioxane/water, toluene/EtOH/H_2O, 1,2-dimethoxyethane (DME)/water, and DMF (anhydrous conditions).

Reviews: (a) Knochel, P.; Ila, H.; Korn, T. J.; Baron. O. Functionalized Organoborane Derivatives in Organic Synthesis. In *Handbook of Functionalized Organometallics*. Knochel, P. Ed.; Wiley-VCH: Weinheim, 2005; Vol. 1,, pp. 45–108. (b) Bai, L.; Wang, J.-X. *Curr. Org. Chem.* **2005***, 9,* 535-553. (c) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419-2440. (d) Kotha, S.; Lahiri, K.; Kashinath, D.

Tetrahedron **2002**, *58*, 9633-9695. (e) Knochel, P.; Ila, H.; Korn, T. J.; Baron, O. In *Handbook of Functionalized Organometallics*. Knochel, P. Ed.; Wiley-VCH: Weinheim, 2005; Chapter 3: Functionalized Organoborane Derivatives in Organic Synthesis, pp. 45–108. (f) Miyaura, N. In *Topics in Current Chemistry: Cross-coupling Reactions A Practical Guide.* Miyaura, N., ed.; Springer-Verlag: Berlin, 2002; Vol. 219, Organoboron Compounds, pp. 11–59. (g) Suzuki, A. *Handbook of Organopalladium Chemistry for Organic Synthesis*. Wiley-Interscience: New York, 2002; Vol 1, Chapter III.2.2: Overview of the Suzuki Protocal with B, pp. 249–262. (h) Chemler, S. R. Trauner, D; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2001**, *40*, 4544-4568. (i) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995,** *95*, 2457–2483. (j) Suzuki, A. *Acc. Chem. Res.* **1982**, *15,* 178-184.

5.1.29.1 Via Boronic Acids

5.1.29.1.1 Formation of the Boronic Acid

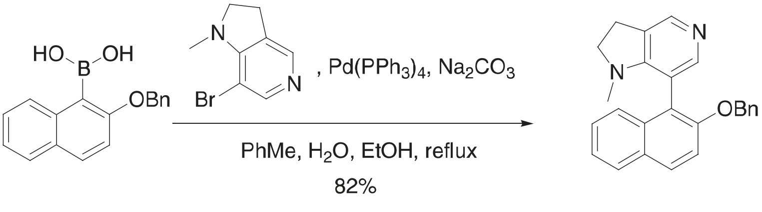


To a suspension of the aryl bromide (6.26 g, 20.0 mmol) in ether (75 mL) at –78 °C was added *n*-BuLi (2.5 M in hexanes, 8.0 mL, 20 mmol), and the mixture was stirred at 0 °C for 1 h. (*Note: typically the halogen metal exchange is done at –78 °C or lower to reduce the chance of side reactions while generating the organolithium. In this case, butyl bromide is produced which could react with the generated aryllithium. See chapter 1 for Wurtz coupling*.) After re-cooling to –78 °C, the mixture was treated with trimethyl borate (2.5 mL, 22 mmol) and allowed to warm to room temperature overnight. The resulting mixture was quenched with 1 M HCl (50 mL) and stirred at room temperature for 45 min. The phases were separated, and the extraction was completed with CH_2Cl_2. The combined organic extracts were dried (magnesium sulfate), filtered, and evaporated in vacuo to give 4.62 g (83%) of the boronic acid as a white powder.

Reference: Spivey, A. C.; Fekner, T.; Spey, S. E.; Adams, H. *J. Org. Chem.* **1999,** *64*, 9430–9443.

5.1.29.1.2 Standard Suzuki

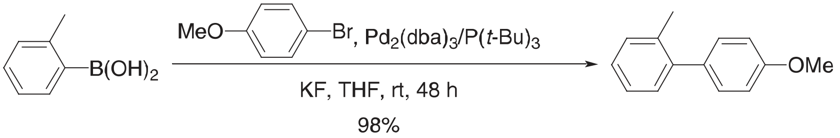
$Pd(PPh_3)_4$ can be an unreliable catalyst because it is air, light, and moisture sensitive; however, $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ and $Pd(PPh_3)_2Cl_2$ enjoy greater stability and are excellent alternatives. All three catalysts are commercially available.



To a solution of aryl bromide (1.49 g, 7.00 mmol) in toluene (28 mL) and ethanol (5 mL) was added an aqueous solution of sodium carbonate (2 M, 28 mL) followed by tetrakis-(triphenylphosphine) palladium (243 mg, 0.210 mmol) and aryl boronic acid (2.53 g, 9.1 mmol). The reaction mixture was then brought to reflux. *Note: degassing of the reaction mixture is usually recommended; however, it is not always necessary*. Additional portions of the boronic acid (680 mg, 2.44 mmol) and tetrakis(triphenylphosphine)palladium (81 mg, 0.070 mmol) were added at 90 min and 4.5 h. The reaction mixture was heated at reflux for a total of 24 h. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by flash chromatography eluting with EtOAc to EtOAc:triethylamine (98:2) to give 2.09 g (82%) of the naphthalene as a white crystalline solid.

Reference: Spivey, A. C.; Fekner, T.; Spey, S. E.; Adams, H. *J. Org. Chem.* **1999,** *64*, 9430–9443.

5.1.29.1.3 Fu Modification



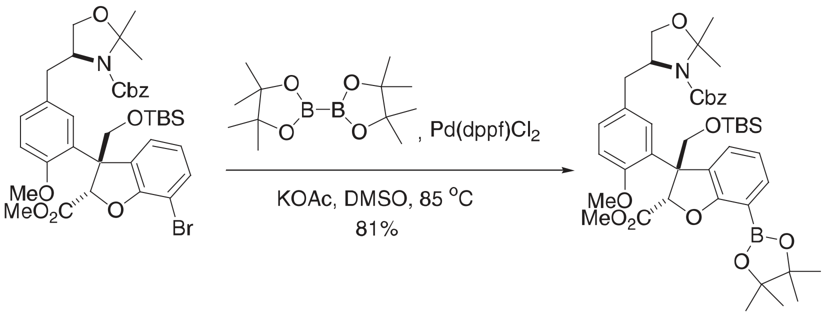
Open to the atmosphere, 4-bromoanisole (1.87 g, 10 mmol), *o*-tolylboronic acid (1.50 g, 11 mmol), KF (spray dried, dried in an oven overnight prior to use, 1.92 g, 33 mmol), and THF (10 mL) were added to a 100-ml round-bottomed Schlenk flask equipped with a stir bar. The reaction system was flushed with argon for about 5 min. $P(t\text{-}Bu)_3$ (1.9×10^{-4} M stock solution in THF; 2.31 mL, 5.0×10^{-5} mmol) and $Pd_2(dba)_3$ (2.16×10^{-5} M stock solution in THF; 2.31 mL, 5.0×10^{-5} mmol) in THF were added sequentially. After 48 h at room temperature, the reaction mixture was diluted with ether or EtOAc, filtered through a pad of silica gel with copious washings, and then concentrated. The crude product was then purified via column chromatography eluting with 5% ether in hexane to yield 1.94 g (98%) of 4-methoxy-2′-methyl-biphenyl as a colorless liquid.

Reference: Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000,** *122*, 4020-4028.

5.1.29.2 Via Pinacolatoboronic Ester

5.1.29.2.1a Formation of a Boronic Ester: Miyaura Protocol

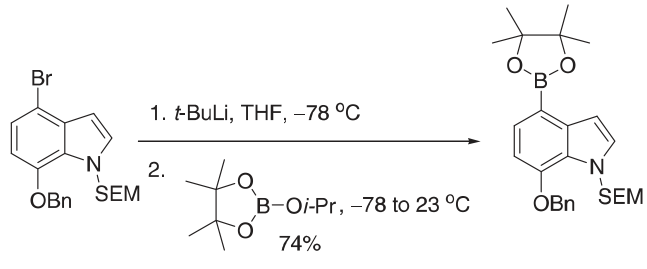
Useful solvents for the formation of the boronate ester include THF, 2-Methyltetrahydrofuran, 1,4-dioxane, dimethylformamide, and dimethylsulfoxide (DMSO). $Pd(dppf)Cl_2$ and potassium acetate are typically used for the formation of the pinacolatoboronic ester. Often after workup, the crude boronate is used for the subsequent Suzuki reaction. As can be seen with the example below, various functional groups tolerate this transformation.



Bispinacolatodiboron (0.855 g, 3.37 mmol), Pd(dppf)$Cl_2 \cdot CH_2Cl_2$ (0.500 g, 0.611 mmol), and potassium acetate (0.900 g, 9.18 mmol) were all added to a flask containing the bromide (2.31 g, 3.06 mmol). This vessel was then equipped with an air condenser, and degassed DMSO (20 mL, prepared by three iterations of the freeze–thaw method) was added at 25 °C. The reaction contents were then warmed to 85 °C and stirred for 6 h. On completion, the reaction mixture was diluted with EtOAc (50 mL), filtered through a short plug of silica, and extracted with EtOAc (3 × 50 mL). The combined organic layers were then washed with water (2 × 50 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated. The resultant yellow–green residue was purified by flash chromatography (silica gel) eluting with EtOAc:hexanes (1:2 to 1:1) to give 1.99 g (81%) of boronic ester as a light yellow foam.

Reference: Nicolaou, K. C.; Snyder, S. A.; Giuseppone, N.; Huang, X.; Bella, M.; Reddy, M. V.; Rao, P. B.; Koumbis, A. E.; Giannakakou, P.; O'Brate, A. *J. Am. Chem. Soc.* **2004,** *126*, 10174–10182.

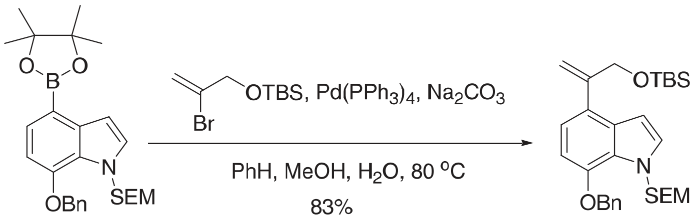
5.1.29.2.1 Formation of a Boronic Ester: Halogen–Lithium Exchange



To a solution of 5-bromoindole (3.81 g, 8.0 mmol) in THF (147 mL) at −78 °C was added *t*-BuLi (1.7 M in pentane, 11.4 mL, 19.4 mmol). Following the addition, the reaction mixture was stirred for 15 min at −78 °C and then the boronate (3.6 mL, 17.6 mmol) was added. The mixture was stirred at −78 °C for 1.5 h, allowed to warm to 23 °C, and then quenched with saturated aqueous ammonium chloride (75 mL). The combined organic layers were washed with brine (100 mL), briefly dried over magnesium sulfate, and evaporated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes:EtOAc (14:1) to give 3.11 g (74%) of the boronic ester as a yellow oil.

Reference: Garg, N. K.; Sarpong, R.; Stoltz, B. M. *J. Am. Chem. Soc.* **2002,** *124*, 13179–13184.

5.1.29.2.2 Standard Suzuki–Miyaura



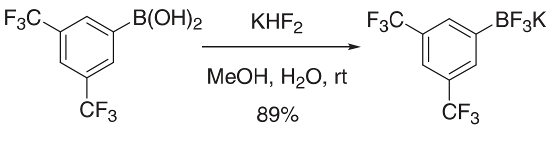
A solution containing the boronic ester (3.17 g, 6.62 mmol) and the bromide (3.32 g, 13.2 mmol) in benzene (130 mL) and methanol (30 mL), and aqueous sodium carbonate (2 M, 11 mL) was deoxygenated by bubbling a stream of argon through the reaction mixture for 5 min. Tetrakis(triphenylphosphine) palladium(0) (1.15 g, 0.99 mmol) was then added and the flask was equipped with a reflux condenser. The mixture was heated to 80 °C for 2 h and allowed to cool to 23 °C. To the reaction vessel was added sodium sulfate (10 g), which was allowed to stand for 30 min. After filtration over a pad of silica gel (CH_2Cl_2 eluent), the filtrate was concentrated to dryness under reduced pressure. The resulting residue was purified by flash chromatography eluting with CH_2Cl_2:hexane (1:1) to provide 2.87 g (83%) of the olefin as a yellow oil.

Reference: Garg, N. K.; Sarpong, R.; Stoltz, B. M. *J. Am. Chem. Soc.* **2002,** *124*, 13179–13184.

5.1.29.3 Potassium Organotrifluoroborates

Potassium organotrifluorborates are monomeric species that are prepared in one step from their corresponding boronic acids. Also, these compounds exhibit excellent stability in air and may be stored indefinitely. Typically, aryltrifluoroborates couple well to aryl bromides and iodides under ligandless conditions; however, electron deficient coupling partners require the use of $Pd(dppf)Cl_2$. The coupling between aryl- and heteroaryltriflates with trifluoroborates also requires a ligand such as PCy_3. Review: Molander, G. A.; Figueroa, R. *Aldrichimica Acta* **2005,** *38*, 49–56.

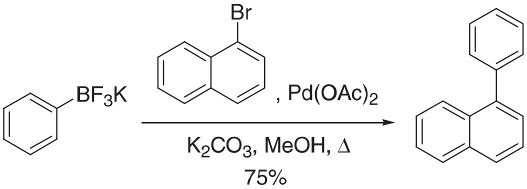
5.1.29.3.1 Formation of an Organotrifluoroborate



A solution of 3,5-bis(trifluoromethyl)phenylboronic acid (10 g, 38.8 mmol) in methanol (15 mL) was added to an aqueous solution of KHF_2 (4.5 M, 26 mL, 117 mmol) at room temperature. A heavy precipitate was deposited. The resulting suspension was stirred for 1 h at room temperature, and the precipitated product was collected and washed with methanol. Recrystallization from a minimum amount of acetone produced 11 g (89%) of potassium 3,5-bis(trifluoromethyl)phenyltrifluoroborate.

Reference: Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003,** *68*, 4302–4314.

5.1.29.3.2 Standard Suzuki

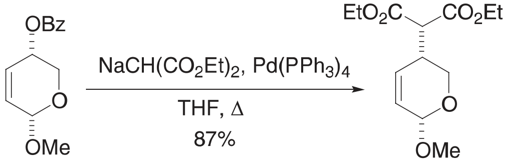


To a suspension of potassium phenyltrifluoroborate (92.3 mg, 0.5 mmol), 1-bromonapthalene (103.5 mg, 0.5 mmol), and K_2CO_3 (204.5 mg, 1. 5 mmol) in MeOH (0.75 mL) was added $Pd(OAc)_2$ in methanol (1.25 mL, 2×10^{-3} M) and then the reaction mixture was stirred and heated at reflux for 2 h. The mixture was cooled to room temperature and diluted with water (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 4 mL). The combined organic extracts were washed with brine (10 mL) and dried ($MgSO_4$). The crude product was then purified via chromatography (silica gel) eluting with hexane to deliver 76.1 mg (75%) of 1-phenylnaphthalene.

Reference: Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003,** *68*, 4302–4314.

5.1.30 Tsuji–Trost Reaction

Leaving groups in the Tsuji–Trost reaction include acetates, halides, ethers, carbonates, sulfones, carbamates, epoxides, and phosphates. Reviews: (a) Tsuji, J. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.; deMeijere, A., Eds.; Wiley-Interscience: New York, 2002; Vol II, Palladium-Catalyzed Nucleophilc Substitution Involving Allyl Palladium, Propargyl-palladium and Related Derivatives, pp. 1669–1687. (b) Frost C. G.; Howarth, J.; Williams, J. M. J. *Tetrahedron Asymmetry* **1992,** *3*, 1089–1122.



Sodium hydride (60% oil dispersion, 0.15 g, 0.38 mmol) was washed with hexane (2 × 2 mL) and THF (1 × 2 mL). (*Note: exercise great care with NaH, particularly after the hexane wash; the NaH should be kept under nitrogen or argon.*) To a suspension of oil-free sodium hydride in THF (5mL) was added diethylmalonate (0.770 mL, 0.38 mmol). After 15 min of stirring, the resulting diethyl malonate anion solution was added via a cannula to a solution of the allylic benzoate (131 mg, 0.56 mmol), $Pd(PPh_3)_4$ (45 mg, 0.039 mmol), and triphenylphosphine (100 mg, 0.39 mmol) in THF (5 mL). The resulting orange mixture was heated at 66 °C for 48 h. The reaction mixture was then separated between water (10 mL) and ether (10 mL). The aqueous layer was extracted with ether (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the residue by flash chromatography gave 133 mg (87%) of the diester as a colorless oil.

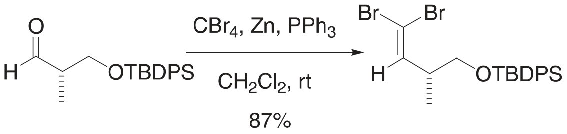
Reference: Brescia, M.-R.; Shimshock, Y. C.; DeShong, P. *J. Org. Chem.* **1997,** *62*, 1257–1263.

5.2 Carbon–Carbon Double Bonds (Olefin Formation)

5.2.1 Corey–Fuchs Reaction

Treatment of a dibromoolefin with two equivalents of *n*-BuLi will give the corresponding terminal alkyne. Alternatively, the intermediate, lithium acetylide, may be used to trap electrophiles.

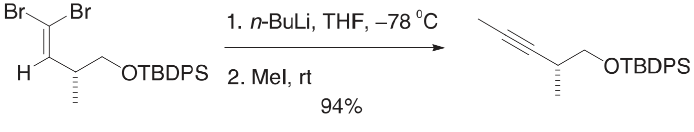
5.2.1.1 Formation of a Dibromoalkene



A solution of the aldehyde (10.5 g, 32.2 mmol) in dry CH_2Cl_2 (400 mL) was treated at room temperature with carbon tetrabromide (42.6 g, 128 mmol) and zinc dust (8.41 g, 128 mmol), followed by triphenylphosphine (33.7g, 128 mmol) in portions to keep the reaction temperature at 25 °C for another 1 h, diluted with hexanes (300 mL), filtered through a thin pad of silica gel, and washed with pentane and ether. The combined organic layers were concentrated in vacuo. The crude product was purified by chromatography (silica gel) eluting with hexanes/EtOAc (10:1) to yield 13.5 g (87%) of the dibromoolefin as a colorless oil.

Reference: Wipf, P.; Xiao, J. *Org. Lett.* **2005,** *7*, 103–106.

5.2.1.2 Formation of a Methylalkyne

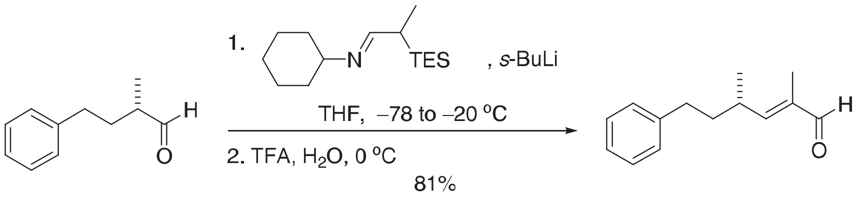


A solution of the dibromoolefin (810 mg, 1.68 mmol) in dry THF (20.0 mL) was treated with a solution of *n*-BuLi (1.6 M in hexanes, 2.20 mL, 3.52 mmol). The reaction mixture was stirred at –78 °C for 1 h and at room temperature for another 1 h, cooled to –78 °C, and treated dropwise with methyl iodide (1.05 mL, 16.8 mmol). The resulting mixture was allowed to warm to room temperature and stirred overnight, quenched with water, and extracted with ether. The combined organic layers were dried ($MgSO_4$), concentrated in vacuo, and purified by chromatography on SiO_2 eluting with hexanes:EtOAc (15:1) to yield 529 mg (94%) of the methylalkyne as a colorless oil.

Reference: Wipf, P.; Xiao, J. *Org. Lett.* **2005,** *7*, 103–106.

5.2.2 Corey–Peterson Olefination

The Corey–Peterson olefination is a version of the Peterson olefination that produces trisubstituted (*E*)-methyl alkenes with high diastereoselectivity via a two-step process.



To a stirred solution of *N*-cyclohexyl-(2-triethylsilylpropylidine)amine (5.13 g, 20.2 mmol) in THF (29 mL) was added *sec*-BuLi (1.4 M in cyclohexane, 13.3 mL, 18.7 mmol). The resulting red–orange mixture was stirred at −78 °C for 30 min and treated with the butyrladehyde (2.52g, 15.6 mmol) in THF (14 mL). The red–orange mixture was immediately warmed to −20 °C and stirred for 1 h and then quenched with water (28 mL). The mixture was then extracted with ether, washed with brine, and dried over $MgSO_4$. The organic layers thus obtained were concentrated and dried under vacuum to give an orange oil (~ 7.35 g). The oil was dissolved in THF (70 mL), cooled to 0 °C, and then treated with trifluoroacetic acid (1.44 mL, 18.7 mmol). The resulting mixture was stirred at 0 °C for 1 h and water (28 mL) was added. This reaction mixture was stirred for 12 h at 0 °C and then carefully quenched with saturated aqueous sodium bicarbonate and extracted with ether. The organic layer was washed with brine, dried of magnesium sulfate, and concentrated. Distillation under reduced pressure gave 2.55 g (81%) of the (*E*)-α,β-unsaturated aldehyde as a clear oil.

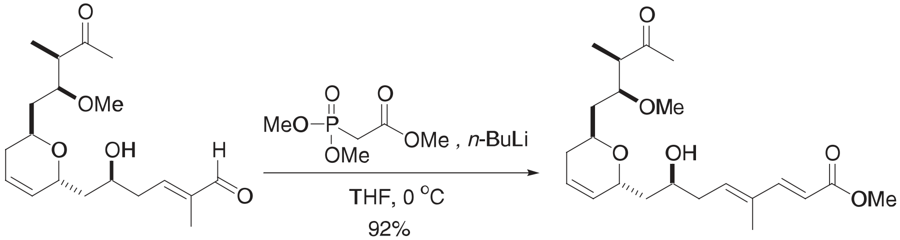
Reference: Zeng, X.; Zeng, F.; Negishi, E. *Org. Lett.* **2004,** *6*, 3245–3248.

5.2.3 Horner–Wadsworth–Emmons Reaction

The Horner–Wadsworth–Emmons (HWE) reaction involves the addition of a stabilized phosphonate anion to an aldehyde or ketone to afford an intermediate which undergoes an elimination reaction to form predominately the (*E*)-alkene. The HWE reaction has been applied inter- and intramolecularly to simple as well as highly functionalized systems.

Reviews: (a) Kelly, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 1, Chapter 3.1: Alkene Synthesis, pp. 761–782. (b) Maryanoff. B. E.; Reitz, A. B. *Chem. Rev.* **1989,** *89*, 863–927. (c) Boutagy, J.; Thomas, R. *Chem. Rev.* **1974,** *24*, 87–99.

5.2.3.1 Standard Horner–Wadsworth–Emmons

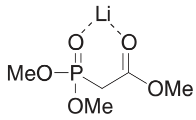


To a solution of trimethylphosphonate (2.35mL, 14.5 mmol) in THF (26 mL) was added a solution of *n*-BuLi (1.57 M in hexane, 6.94 mL, 10.9 mmol) at 0 °C. The mixture was stirred at room temperature for 15 min, cooled again to 0 °C to which the aldehyde (1.23 g, 3.63 mmol) in THF (10 mL) was added, and the mixture was stirred at 0 °C for 1 h. The reaction was quenched with a pH 7 buffer solution, and the mixture was extracted with EtOAc (6×). The combined organic extracts were washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The crude oil was purified by silica gel chromatography eluting with EtOAc/hexane (40:60 then 50:50) to give 1.32 g (92%) of the ester as a colorless oil.

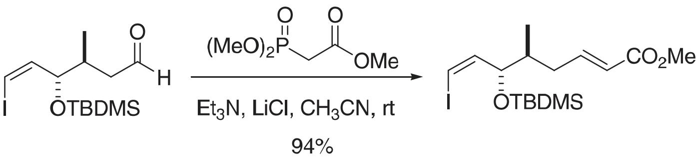
Reference: Nakamura, R.; Tanino, K.; Miyashita, M. *Org. Lett.* **2003,** *5*, 3579–3582.

5.2.3.2 Masamune–Roush Modification of the Horner–Wadsworth–Emmons Reaction

The Masamune–Roush modification of the HWE is a very mild variant that does not require the use of a strong base (i.e., NaH or *n*-BuLi) to generate the phosphonate anion. Instead, in the presence of LiCl, a lithium chelate forms which enhances the acidity of the α-protons. Hence, DBU is sufficiently basic to carry out the deprotonation of the phosphonate.



Since the original paper, milder bases have been used, including triethylamine and disopropylethylamine (Hunigs' base). Again, there is strong preference for the formation of the (*E*)-alkene when the coupling partner is an aldehyde.

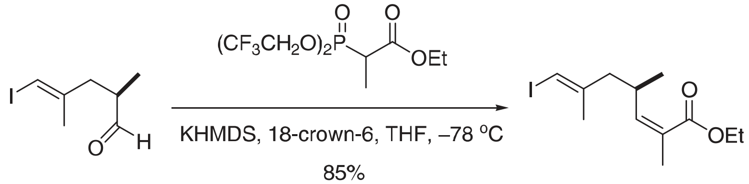


To a suspension of LiCl (160 mg, 3.74 mmol) in CH_3CN (10 mL) was added trimethyl phosphonoacetate (0.76 mL, 4.68 mmol), and the resulting mixture was stirred for 5 min. Et_3N (0.52 mL, 3.74 mmol) was added, followed by 10 min of stirring. A solution of the aldehyde (1.15 g, 3.12 mmol) in CH_3CN (5 mL) was added to the reaction mixture which was then stirred overnight. Ether (20 mL) and a saturated solution of ammonium chloride (30 mL) were added, and the layers were separated. The aqueous layer was extracted with ether (3 × 20 mL), and the combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. Purification of the crude product was accomplished via chromatography on SiO_2 (10% ether/hexane) to give 1.24 g (94%) of the α,β-unsaturated ester as a clear oil.

Reference: Dineen, T. A.; Roush, W. R. *Org. Lett.* **2004,** *6*, 2043–2046.

5.2.3.3 Still–Gennari Modification of the Horner–Wadsworth–Emmons Reaction

The Still–Gennari modification of the HWE reaction was a major achievement, because this modification allowed access to (*Z*)-olefins with high stereoselectivity using a phosphonate. In this version of the HWE, strong preference for Z-alkenes is achieved with the phosphonate bearing electron withdrawing groups under ionic dissociating conditions (crown-ether).

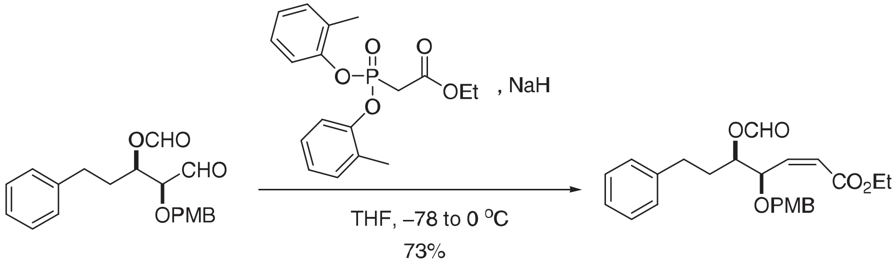


18-Crown-6 (3.51 g, 13.28 mmol) was taken in 30 mL of THF, and the flask was cooled to −78 °C before addition of the phosphonate (2.90, 8.38 mmol) followed by dropwise addition of potassium hexamethyldisilazide (KHMDS 0.5 M in toluene, 16.0 mL, 8.38 mmol). After 10 min, the aldehyde (1.59 g, 6.68 mmol) was added in THF (10 mL). The reaction was quenched after 5 min with $NaHCO_3$ solution. Extractive workup with methyl *tert*-butyl ether followed. The organic layer was then dried over $MgSO_4$ and filtered. The solvent was evaporated in vacuo, and the crude product was chromatographed (hexane/EtOAc, 3:1) to give 1.73 g (85%) of the (*Z*)-α,β-unsaturated ethyl ester.

Reference: Bhatt, U; Christmann, M.; Quitschalle, M.; Claus, E.; Kalesse, M. *J. Org. Chem.* **2001,** *66*, 1885–1893.

5.2.3.4 Ando Modification of the Horner–Wadsworth–Emmons Reaction

The Ando modification of the HWE reaction is yet another major contribution to the formation of (*Z*)-alkenes via phosphonates. In this version of the HWE, diarylphosphonates are utilized. Review: Ando, K. *J. Org. Chem.* **1998,** *63*, 8411–8416.

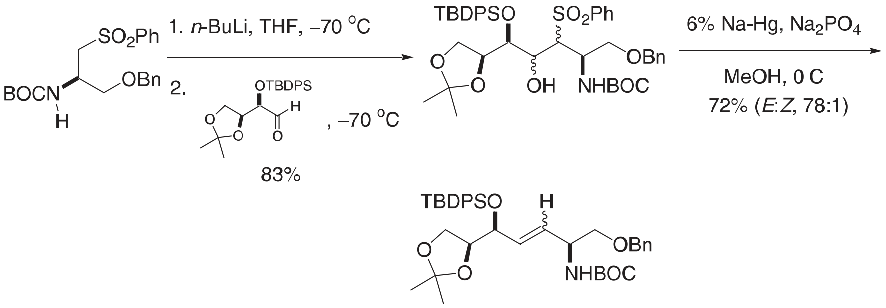


To a suspension of NaH (65 mg, 60% dispersion in oil, 2.7 mmol) in anhydrous THF (4.5 mL) was slowly added a solution of the phosphonate (480 mg, 1 mmol) in anhydrous THF (1.5 mL) at −78 °C under argon atmosphere. The reaction mixture was stirred for 15 min at the same temperature. Then, a solution of the aldehyde (492 mg, 1.44 mmol) in THF (1.5 mL) was slowly added, and the reaction mixture was stirred at −78 °C for 40 min. It was brought to −35 °C and quenched with aqueous ammonium chloride. The reaction mixture was extracted with CH_2Cl_2. The organic layer was washed with water and brine. It was dried over sodium sulfate and concentrated. The crude residue was chromatographed over silica gel to give 420 mg (73%) of the (*Z*)-α,β-unsaturated ester as an oil.

Reference: Singh, R. P.; Singh, V. K. *J. Org. Chem.* **2004,** *69*, 3425–3430.

5.2.4 Julia Coupling

The Julia coupling sequence is a reliable two-step method for affording (*E*)-disubstituted olefins from a phenyl sulfone, bearing two α-hydrogens, and an aldehyde. The reaction sequence opens with a condensation reaction to furnish an aldol-like product followed by a reductive–elimination process to afford the alkene. The Julia coupling has been applied to the formation of tri- and tetrasubstituted olefins where the coupling partner is a ketone, and a sulfone bears two α-hydrogens or a ketone and sulfone with one α-hydrogen. However, the stereoselectivity is less defined. Reviews: (a) Dumeunier, R.; Markó, I. E. In *Modern Carbonyl Olefination-Methods and Applications*: Takeda, T. Ed.; Wiley-VCH: Weinheim, 2004; Chapter 3: The Julia Reaction, pp. 104–150. (b) Kelly, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 1, Chapter 3.1: Alkene Synthesis, pp. 743–746. (c) Kocienski, P. *Phosphorus Sulfur* **1985,** *24*, 97–127.



To a solution of the sulfone (4.85 g, 11.98 mmol) in THF (110 mL) at −70 °C was added dropwise *n*-BuLi (1.6 M in hexane, 16.5 mL, 26.36 mmol). After the mixture was stirred for 30 min, a solution of the aldehyde (6.20 g, 15.58 mmol) in THF (10 mL) was added dropwise. The reaction was stirred at the same temperature for 4 h. Saturated ammonium chloride solution was added. The mixture was then extracted with EtOAc multiple times. The combined organic extracts were washed with brine, dried, and evaporated. The crude product was then purified via flash chromatography (silica gel) eluting with heptane/EtOAc (8:1 then 6:1) to afford 7.98 g (83%) of the β-hydroxysulfone as a mixture of two diastereomers.

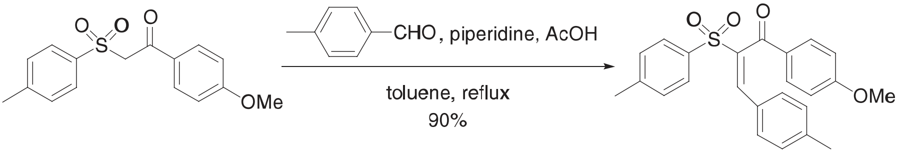
To a solution of the β-hydroxysulfone diastereomers (13.31 g, 16.58 mmol) in methanol (330 mL) at 0 °C were added Na_2PO_4 (28.24 g, 198.9 mmol) and 6% Na–Hg (57.20 g, 149.2 mmol). The reaction mixture was stirred at 0 °C for 2 h. Methanol was evaporated, and the residue was separated in water and EtOAc. The aqueous layer was extracted with EtOAc. (*Note: the aqueous layer must be properly disposed as mercury is present.*) The combined organic layers were washed with brine, dried, and evaporated. The crude product was purified via flash chromatography (silica gel) eluting with heptane:EtOAc (10:1) to afford 7.69 g (72%) of the *E* and *Z*-olefinic isomers as a 78:1 mixture.

Reference: Wang, Q.; Sasaki, A. *J. Org. Chem.* **2004,** *69*, 4767–4773.

5.2.5 Knoevenagel Condensation

The Knoevenagel reaction is the condensation of malonic esters or acetoacetic esters (an active methylene) with aldehydes or ketones. The catalysts are mostly organoamines.

Review: Tietze, L. F.; Beifuss, U. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, U. K., 1991; Vol. 2, Chapter 1.11: The Knoevenagel Reaction, pp. 341–394.

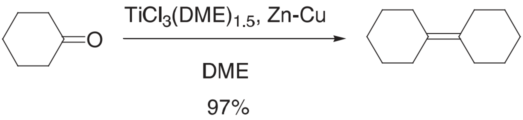


A mixture of the keto-sulfoxide (4.6 g, 15 mmol), *p*-tolualdehyde (2.0 g, 16.5 mmol), piperidine (0.18 g, 2 mmol), and acetic acid in toluene (40 mL) was heated at reflux for 2 h with azeotropic removal of water using a Dean–Stark trap. The mixture was cooled to room temperature and concentrated in vacuo. The residue was purified by flash chromatography eluting with a hexane:EtOAc:toluene (3:1:1) mixture to give 5.5 g (90%) of the olefin as a solid.

Reference: Swenson, R. E.; Sowin, T. J.; Zhang, H. Q. *J. Org. Chem.* **2002,** *67*, 9182–9185.

5.2.6 McMurry Coupling

The McMurray coupling is the reductive coupling between two carbonyl containing compounds, typically aldehydes and ketones, in the presence of $TiCl_3$ or $TiCl_4$. The reaction has been applied inter- and intramolecularly. Reviews: (a) Ephritikhine, M.; Villiers, C. In *Modern Carbonyl Olefination-Methods and Applications*: Takeda, T. Ed.; Wiley-VCH: Weinheim, 2004; Chapter 6: The McMurry Coupling and Related Reactions, pp. 223–285. (b) Ephritikhine, M. *Chem. Commun.* **1998,** *23*, 2549–2554. (c) Fürstner, A; Bogdanović, B. *Angew. Chem. Int. Ed.* **1996,** *35*, 2442–2469. (d) Robertson, G. M. *Comp. Org. Syn.* **1991,** *3*, 583–595; (e) McMurry, J. E. *Chem. Rev.* **1989,** *89*, 1513–1524. (f) McMurray, J. E. *Acc. Chem. Res.* **1983,** *16*, 405–411. (g) Lai, Y.-H. *Org. Prep. Proceed.* **1980,** *12*, 361–391.



Preparation of TiCl$_3$(DME)$_{1.5}$

TiCl$_3$ (25.0g, 0.162 mol) was suspended in dry DME (350 mL), and the mixture was refluxed for 2 days under argon. After the mixture was cooled to room temperature, it was filtered under argon, washed with pentane, and dried under vacuum to give 32.0 g (80%) of the fluffy blue crystalline TiCl$_3$(DME)$_{1.5}$.

Preparation of Zinc–Copper Couple

Zinc dust (9.8 g, 150 mmol) was added to nitrogen purged water (40 mL). The resulting slurry was then purged with nitrogen for 15 min. CuSO4 (0.75g, 4.7 mmol) was then added. The black slurry was filtered under nitrogen, washed with deoxygenated (nitrogen purged) water, acetone, and ether, and dried under vacuum. The couple can be stored indefinitely in a Schlenk tube under nitrogen.

Cyclohexylidenecyclohexane

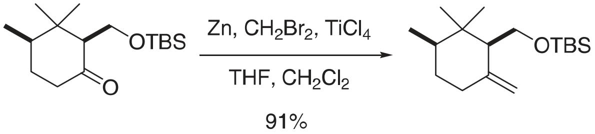
TiCl$_3$(DME)$_{1.5}$ (5.2 g, 17.9 mmol) and Zn–Cu (4.9g, 69 mmol) were transferred under argon to a flask containing DME (100 mL), and the resulting mixture was refluxed for 2 h to yield a black suspension. Cyclohexanone (0.44 g, 4.5 mmol) in DME (10 mL) was added, and the mixture was refluxed for 8 h. After being cooled to room temperature, the reaction mixture was diluted with pentane (100 mL), filtered through a pad of Florisil, and concentrated to yield 0.36 g (97%) of cyclohexylidenecyclohexane as white crystals. The authors noted that if a 3:1 ratio of TiCl$_3$(DME)$_{1.5}$ to cyclohexanone was used, the yield decreased to 94%. Also, the yield further decreased to 75% when a 2:1 ratio of TiCl$_3$(DME)$_{1.5}$ to cyclohexanone was used.

Reference: McMurry, J. E.; Lectka, T.; Rico, J. G. *J. Org. Chem.* **1989,** *54*, 3748–3749.

5.2.7 Methylenation Reagents

5.2.7.1 Lombardo–Takai

The Lombardo–Takai olefination is a mild method for converting ketones, particularly enolizable ones, to terminal olefins. Esters are also converted to olefins in the presence of TMEDA. In order for these methylenation conditions to be reproducible, great care must be given during the preparation of the active reagent. The methylenating reagent is formed with zinc powder, a dihalomethane, and titanium chloride. Lombardo reported in the early 1980s that an "ageing" period of 3 days is required prior to use. This simply entails stirring the reagents at 0 °C for 3 days. Reviews: (a) Matsubara, S.; Oshima, K. In *Modern Carbonyl Olefination-Methods and Applications*: Takeda, T., Ed.; Wiley-VCH: Weinheim, 2004; Chapter 5: Olefination of Carbonyl Compounds by Zinc and Chromium Reagents, pp.203–208. (b) Pine, S. H. *Org. React.*, **1993,** *43*, 1–91.



To a suspension of zinc dust (2.87 g, 44 mmol) and CH_2Br_2 (1.01 mL, 14.4 mmol) in THF (25 mL), stirred under argon atmosphere at −40 °C was added dropwise neat titanium tetrachloride (1.13 mL, 10.3 mmol). The mixture was then allowed to warm to 5 ºC and was stirred for 3 days at this temperature to produce a thick gray slurry of the active reagent.

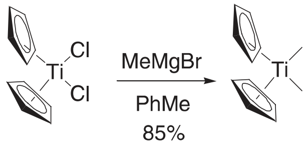
To a solution of the ketone (300 mg, 1.05 mmol) stirred at 5 °C under argon was added the methylenation reagent (2.5 equivalents). After being stirred for 4 h at this temperature, the reaction was diluted with CH_2Cl_2 and then poured into a cold saturated aqueous solution of sodium bicarbonate. The mixture was extracted with ether. The combined organic extracts were washed with brine, dried, filtered, and concentrated. The residue was subjected to column chromatography to afford 270 mg (91%) of the terminal olefin as an oil.

Reference: Laval, G.; Audran, G.; Galano, J.-M.; Monti, H. *J. Org. Chem.* **2000,** *65*, 3551–3554.

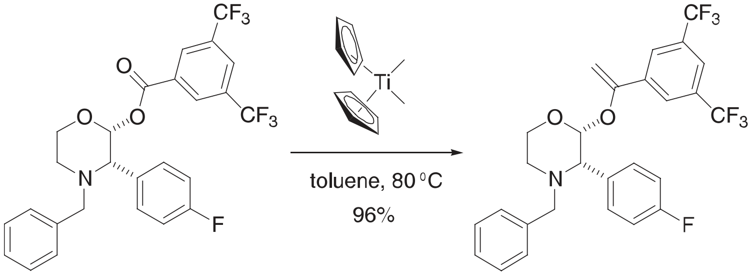
5.2.7.2 Petasis Reagent

The Petasis reagent reacts with aldehydes, ketones, and esters to afford terminal olefins. In addition, this reagent enjoys greater air stability than the Tebbe reagent.

Preparation of dimethyltitanocene



A 1-L, three-necked, round-bottomed flask, equipped for mechanical stirring, and outfitted with a 250-mL, pressure equalizing addition funnel, a Claisen adapter bearing a thermometer, and a nitrogen inlet/outlet vented through a mineral oil bubbler, was placed under a nitrogen atmosphere and charged with titanocene dichloride (41.5 g, 0.167 mol) and dry toluene (450 mL). The slurry was efficiently stirred and chilled to an internal temperature of −5°C in a ice–methanol bath; 126 mL of a 3 M solution (0.38 mol) of methylmagnesium chloride in THF was then added dropwise via the addition funnel over 1 h at a rate of addition adjusted to maintain an internal temperature below +8 °C. The resulting orange slurry was mechanically stirred at an internal temperature of 0 to +5 °C for 1 h or until the insoluble purple titanocene dichloride was no longer seen in the suspension. The addition funnel was removed and replaced by a rubber septum, and the reaction was assayed by ^1H NMR. While the reaction was aging at 0° to +5°C, a 2-L, three-necked, round-bottomed flask, equipped for mechanical stirring, and outfitted with a rubber septum, a Claisen adapter bearing a thermometer, and a nitrogen inlet/outlet vented through a mineral oil bubbler, was placed under a nitrogen atmosphere and charged with 117 mL of 6% aqueous ammonium chloride (7.0 g diluted to 117 mL). The solution was chilled to 1–2 °C, with efficient mechanical stirring. When the formation of dimethyltitanocene was judged to be complete, the toluene/THF reaction mixture was quenched into the well-stirred aqueous ammonium chloride solution via a cannula over a period of 1 h, maintaining an internal temperature of 0° to +5°C in both flasks. Toluene (30 mL) was used to rinse the reaction flask. The biphasic mixture was then poured into a 2-L separatory funnel, with another 30 mL of toluene rinse, and the aqueous phase was separated. The organic layer was washed sequentially with 3 portions of cold water (100 mL each) and brine (100 mL) and then dried over anhydrous sodium sulfate (Na_2SO_4, 35 g). The organic layer was filtered and carefully concentrated under reduced pressure on a rotary evaporator at a bath temperature of no more than 35°C to a weight of 150 g. The resulting orange solution was assayed by ^1H NMR to be 20 weight% dimethyltitanocene (29.55 g, 85.0%). If the solution is stored for more than a week, the reagent should be diluted with 160 mL of dry THF, which has a stabilizing effect on the labile reagent. The solution was stored at 0–10°C under nitrogen in a rubber septum-sealed, round-bottomed flask.

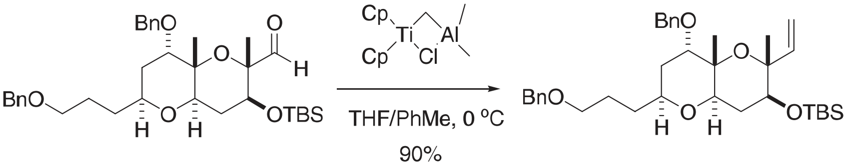


A 50-mL, nitrogen-purged, round-bottomed flask was charged with *cis*-ester 1 ((2R-*cis*)-3-(4-fluorophenyl)-4-benzyl-2-morpholinyl 3,5-bis(trifluoromethyl)benzoate) (2.41 g, 4.57 mmol), dimethyltitanocene in toluene (12 mL of a 20% w/w solution in toluene), and titanocene dichloride (71 mg, 0.28 mmol). The red–orange mixture was heated to 80°C and aged in the dark for 5.5 h, and then cooled to ambient temperature. Sodium bicarbonate (0.60 g), methanol (9.6 mL), and water (0.36 mL) were added, and the mixture was heated to 40°C for 14h. (The hot aqueous methanol treatment was done to decompose the titanium residues into an insoluble solid. The decomposition was judged to be complete when gas evolution ceased.) The green mixture was cooled to ambient temperature and the titanium residues were removed by filtration. The solution was evaporated under reduced pressure and flushed with methanol. The crude material was recrystallized by dissolving in hot (60 °C) methanol (24 mL), cooling to ambient temperature, and then adding water (7.2 mL) over 2 h. The material was stirred for 18 h and then isolated via filtration at ambient temperature. The filter cake was washed with 25% aqueous methanol (6 mL), and the solid was dried at ambient temperature under nitrogen. Vinyl ether 2 ((2R-cis)-2-[[1-[3,5-bis(trifluoromethyl)phenyl]ethenyl]oxy]-3-(4-fluorophenyl)-4-benzylmorpholine) (2.31 g, 96%) was isolated as a pale yellow solid.

Reference: Payack, J. F.; Hughes, D. L.; Cai, D.; Cottrell, I. F.; Verhoeven, T. R. *Org. Syn.* **2004,** *Coll. Vol. 10*, 355–357.

5.2.7.3 Tebbe Reagent

The Tebbe reagent offers distinct advantages over the traditional Wittig reaction. First, aldehydes (to a limited extent), ketones, and esters can be converted to terminal olefins. In addition, the low basicity of this commercially available titanocene–methylidine reagent allows for smooth conversion of enolizable ketones to olefins without compromising an α-stereogenic center. Reviews: (a) Takeda, T.; Tsubouchi, A. In *Modern Carbonyl Olefination-Methods and Applications*: Takeda, T. Ed.; Wiley-VCH: Weinheim, 2004; Chapter 4: Carbonyl Olefination Utilizing Metal Carbene Complexes, pp.151–199. (b) Pines, S. H. *Org. React.* **1993,** *43*, 1–91. (c) Kelly, S. E. *Comp. Org. Syn.* **1991,** *1*, 743–746. (d) Kociensky, P. J. *Phos. Sulfur* **1985,** *24*, 97. (e) Brown-Wensley, K. A.; Buchwald, S. L.; Cannizzo, L.; Clawson, L.; Ho, S.; Meinhardt, D.; Stille, J. R.; Straus, D.; Grubbs, R. H. *Pure Appl. Chem.* **1983,** *55*, 1733–1744.

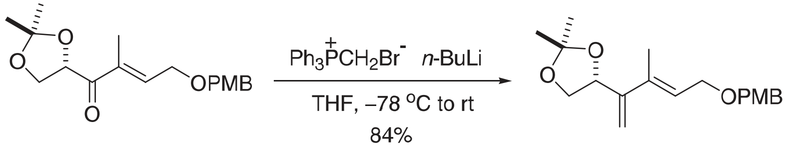


To a solution of the aldehyde (2.56 g, 4.40 mmol) in THF (50 mL) cooled to 0 °C was added the Tebbe reagent (0.5 M, 13.2 mL, 6.60 mmol). After being stirred at 0 °C for 30 min, the reaction mixture was treated with 0.1 M aqueous NaOH (30 mL) and diluted with ether. The resulting mixture was stirred at room temperature for 30 min, filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 10% EtOAc/hexanes) to give 2.30 g (90%) of the terminal olefin as a colorless oil.

Reference: Fuwa, H.; Kainuma, N.; Tachibana, K.; Sasaki, M. *J. Am. Chem. Soc.* **2002,** *124*, 14983–14992.

5.2.7.4 Wittig

The unstabilized ylide, derived from triphenylphosphonium methyl bromide, is a reagent for introducing terminal olefins. Homologues of the methyl derivative deliver Z-alkenes. See section 5.2.11 for the Wittig reaction.

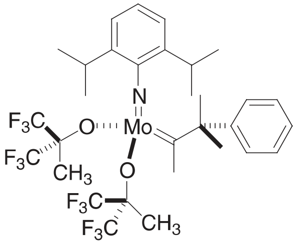


To a suspension of methyltriphenylphosponium bromide (7.84 g, 21.6 mmol) in dry THF (10 mL) at −78 °C under argon was added *n*-BuLi (10.45 mL of 1.98 M solution in hexanes, 20.7 mmol). The mixture was warmed to 0 °C and stirred for 1 h. The mixture was then re-cooled to −78 °C, and a solution of the ketone (6.30 g, 19.77 mmol) in THF (90 mL) was added slowly. The resulting reaction mixture was allowed to warm to 0 °C and stirred for 5 h. The reaction was quenched by addition of aqueous ammonium chloride, and the mixture was diluted with ether. (*Note: the quenching should be done at 0 °C.*) The phases were separated, and the aqueous phase extracted with ether. The organic phases were washed with brine, dried over sodium sulfate, and concentrated in vacuo. The resulting residue was purified via flash chromatography (hexane:EtOAc, 10:1) to afford 5.25 g (84%) of the diene.

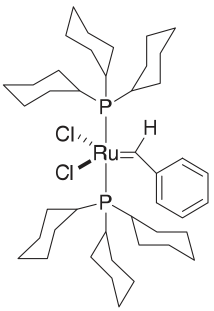
Reference: White, J. D.; Wang, G.; Quaranta, L. *Org. Lett.* **2003,** *5*, 4983–4986.

5.2.8 Olefin Metathesis

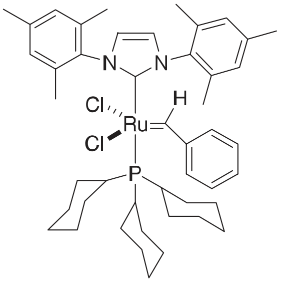
Although olefin metathesis found its genesis in the 1960s, it was not until the 1990s with the advent of Schrock's molydbedum and Grubbs ruthenium catalysts that the utility of this transformation become apparent.



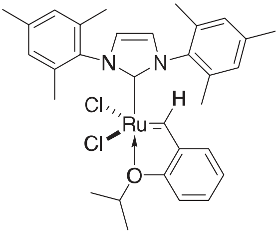
Schrock's catalyst



1st Generation Grubbs' catalyst



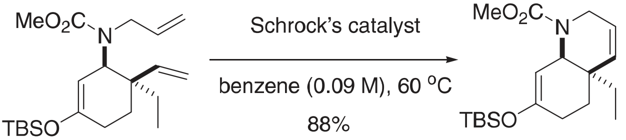
2nd Generation Grubbs' catalyst



Hoveyda-Grubbs' catalyst

In general, olefin metathesis is the exchange of alkylidine groups of alkenes. The four major types of olefin metathesis include ring-closing metathesis (RCM), cross-metathesis (CM), ring-opening metathesis (ROM), and acyclic diene metathesis polymerization (ADMET). For this section, RCM will be the focus along with a procedure for CM using the Hoveyda–Grubbs catalyst. The Schrock and Grubbs catalysts have been extremely successful for RCMs in natural product synthesis for the formation of five, six, seven, eight, nine, ten-membered and higher ring systems. Although both the Mo and Ru catalysts have enjoyed success, the Grubbs catalysts have seen more extensive use because they are easier to handle in the laboratory. They are stable to moisture and air. In contrast, the Schrock catalyst requires manipulation in a glove box. Moreover, the Grubbs' catalysts tolerate a wider range of functional groups in complex oxygenated and alkaloidal molecules. Functional groups include ketones, esters, amides, epoxides, acetals, unprotected alcohols, silyl ethers, amines, and sulfides. In addition to the cyclization dienes to form mono-olefins, RCM has been utilized for enynes to deliver dienes. Reviews: (a) Brenneman, J. B.; Martin, S. F. *Curr. Org. Chem.* **2005,** *9*, 1535–1549. (b) Dieters, A.; Martin, S. F. *Chem Rev.* **2004,** *104*, 2199–2238; (c) McReynolds, M. D.; Dougherty, J. M.; Hanson, P. R. *Chem Rev.* **2004,** *104*, 2239–2258. (d) Grubbs, R. H. *Tetrahedron* **2004,** *60*, 7117–7140. (e) In *Handbook of Metathesis*; Grubbs, R., Ed.;Wiley-VCH: Weinheim, 2003; Vol. 2, pp.1–510. (f) Walters, M. A. Recent Advances in the Synthesis of Heterocycles via RCM. In *Progress in Heterocyclic Chemistry*; Gribble, G. W.; Jouele, J. A., Eds.; Pergamon: Elmsford, NY, 2003; Vol. 15, pp. 1–36. (g) Connon, S. J.; Blechert, S. *Angew. Chem. Int. Ed.* **2003,** *42*, 1900–1923. (h) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001,** *34*, 18–29. (i) Fürstner, A. *Angew. Chem. Int. Ed.* **2000,** *39*, 3012. (j) Wright, D. L. *Curr. Org. Chem.* **1999,** *3*, 211–240. (k) In *Alkene Metathesis in Organic Synthesis.*; Fürstner, A., Ed. Springer: Berlin, 1998. (l) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998,** *54*, 4413–4450. (m) Boger, D. L.; Chai, W. *Tetrahedron* **1998,** *54*,, 3955–3970. (n) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995,** *28*, 446–452.

5.2.8.1 Schrock's Catalyst for Ring Closing Metathesis

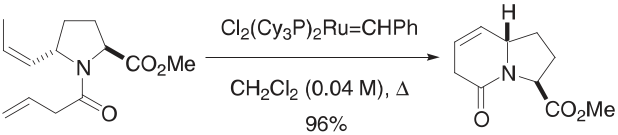


To a degassed solution of the diene (130 mg, 0.34 mmol) in benzene (4.0 mL) under nitrogen atmosphere at 20 °C was added Schrock's molybdenum catalyst in benzene (0.13 mL of 100 mg of catalyst in 1.0 mL of benzene, 0.02 mmol). (*Note: it is recommended that this catalyst is handled in a glove box or glove bag under an inert atmosphere.*) The solution was heated to 60 °C for 1 h, at which point TLC analysis indicated that the reaction was complete. The reaction mixture was concentrated. The crude product was purified via chromatography eluting with 20% ether in hexanes to afford 105 mg (88%) of the *bis*-olefin as a colorless oil.

Reference: Kozmin, S. A.; Iwama, T.; Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002,** *124*, 4628–4641.

5.2.8.2 Grubbs' Catalysts for Ring Closing Metathesis

5.2.8.2.1 First Generation Grubbs'catalyst

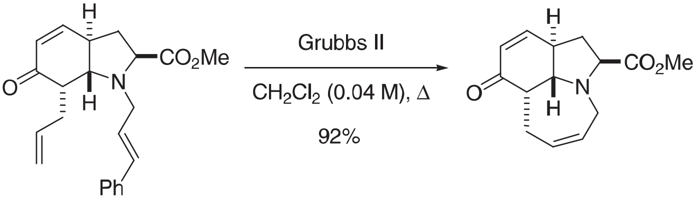


To a solution of the diene (2.70 g, 11.4 mmol) in CH_2Cl_2 (300 mL) at reflux under argon was added bis(tricyclohexylphosphine)benzylidene ruthenium (IV) dichloride

(468 mg, 0.57 mmol), portionwise over a period of 4 h. The mixture was stirred under an air atmosphere for 5 h before being filtered through a 10-cm pad of Florisil/silica. The pad was washed with CH_2Cl_2 (2 × 50 mL), and the solvent was removed by evaporation. The residue was purified by column chromatography (EtOAc:hexanes, 90:10) to yield 2.14 g (96%) of the olefin as transparent colorless needles.

Reference: Hanessian, S.; Sailes, H.; Munro, A.; Therrien, E. *J. Org. Chem.* **2003,** *68*, 7219–7233.

5.2.8.2.2a Second Generation Grubbs' Catalyst: Monoalkene Formation from a Diene

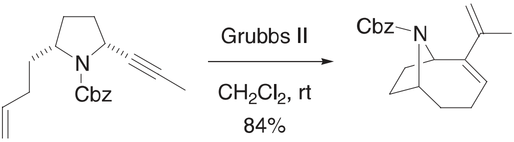


Catalyst	eq. of catalyst	Time	Yield
1st generation	20 mol% (5X4 mol%)	52 h	46%
2nd generation	5 mol%	2 h	92%

To a solution of the diene (220 mg, 0.62 mmol) in CH_2Cl_2 (16 mL) was added the second generation ruthenium catalyst (28 mg, 0.032 mmol). The reaction was heated at reflux for 2 h. After cooling to room temperature, the reaction mixture was filtered through a pad of SiO_2 eluting with EtOAc. The filtrate was concentrated in vacuo, and the crude product was purified on SiO_2 eluting with hexanes:EtOAc (4:1 to 2:1) to give 140 mg (92%) of the olefin as a tan solid.

Reference: Wipf, P.; Spencer, S. R. *J. Am. Chem. Soc.* **2005,** *127*, 225–235.

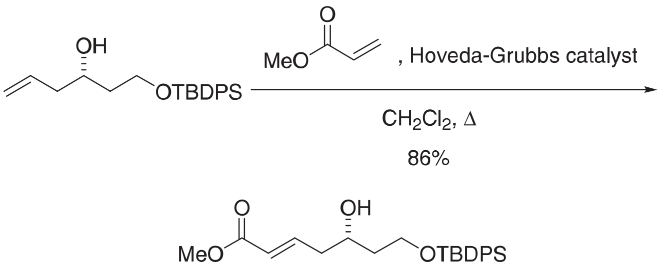
5.2.8.2.2b Second Generation Grubbs' Catalyst: Diene Formation from an Enyne



To a degassed solution of Grubbs II (212 mg, 0.250 mmol) in methylene chloride (500 mL) was added a solution of enyne (744 mg, 2.50 mmol) in degassed methylene chloride (30 mL). The mixture was stirred under a blanket of argon for 16 h, and then DMSO (0.89 mL) was added to decompose the catalyst. The mixture was stirred for an additional 23 h, whereupon the solvent was removed under reduced pressure, and the resulting residue was purified by flash chromatography (SiO_2) eluting with ether/pentane (1:2) to afford 623 mg (84%) of the diene as a yellow oil.

Reference: Brenneman, J. B.; Machauer, R.; Martin, S. F. *Tetrahedron* **2004,** *60*, 7301–7314.

5.2.8.3 Hoyveda–Grubbs' Catalyst (Intermolecular Reaction)

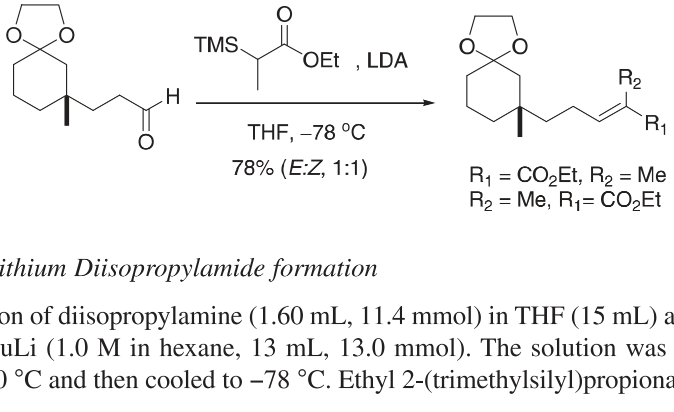


To a stirred solution of the homoallylic alcohol (14.5 g, 40.9 mmol) in CH_2Cl_2 (100 mL) was added methyl acrylate (11.0 mL, 123 mmol) followed by the catalyst (0.26 g, 0.41 mmol). The resulting mixture was heated to reflux for 5 h, after which another portion of the catalyst was added, and the mixture was heated to reflux for an additional 2 h. The solvent was evaporated and the crude product purified by chromatography on SiO_2 (EtOAc:hexanes, 1:3) to give 14.6 g (86%) of the enone as a slightly yellowish oil.

Reference: Dineen, T. A.; Roush, W. R. *Org. Lett.* **2004,** *6*, 2043–2046.

5.2.9 Peterson Olefination

The Peterson olefination is a two-step process for the formation of alkenes from an α-silylcarbanion and an aldehyde or ketone. The first step is an addition reaction that affords both *syn* and *anti* β-hydroxysilanes. The stereochemistry is then controlled during the elimination step by using either an acid or a base. Reviews: Kano, N.; Kawashima, T. In *Modern Carbonyl Olefination-Methods and Applications*: Takeda, T. Ed.; Wiley-VCH: Weinheim, 2004; Chapter 2: The Peterson and Related Reactions, pp. 18–103. (b) Kelly, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 1, Chapter 3.1: Alkene Synthesis, pp. 731–737. (c) Ager, D. J. *Org. React.* **1990,** *38*, 1–223. (d) Ager, D. J. *Synthesis* **1984,** 384–398.



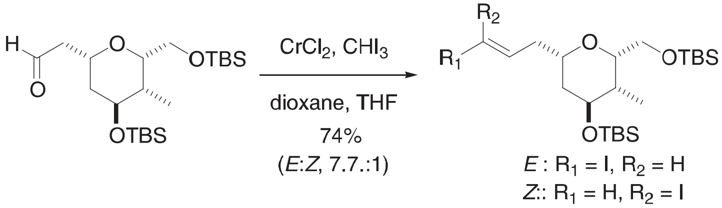
Lithium Diisopropylamide formation

To a solution of diisopropylamine (1.60 mL, 11.4 mmol) in THF (15 mL) at 0 °C was added *n*-BuLi (1.0 M in hexane, 13 mL, 13.0 mmol). The solution was stirred for 15 min at 0 °C and then cooled to −78 °C. Ethyl 2-(trimethylsilyl)propionate (2.00 g, 11.5 mmol) in THF (20 mL) was added dropwise via an addition funnel, and the mixture was stirred for 1 h. The aldehyde (1.97 g, 9.27 mmol) in THF (12 mL) was added dropwise via an addition funnel over a 35-min period, and the mixture was stirred at −78 °C for 3 h, followed by an additional 18 h during which the temperature was slowly raised to room temperature. The reaction was quenched with saturated NH_4Cl (12 mL), and the solution was diluted with ether (150 mL). The organic phase was washed with brine (2 × 15 mL), and the combined aqueous washes were extracted with ether (2 × 10 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed over 50 g of silica gel eluting with petroleum ether:EtOAc 99:1 to afford 2.14 g (78%) of (*E*)- and (*Z*)-olefins as a 1:1 mixture. (*Note*: *the authors reported an 8:1 mixture of E:Z when the corresponding stabilized ylide was used*).

Reference: Guevel, A.-C.; Hart, D. J. *J. Org. Chem.* **1996,** *61*, 465–472.

5.2.10 Takai Olefination

Review: Matsubara, S.; Oshima, K. In *Modern Carbonyl Olefination-Methods and Applications*: Takeda, T., Ed.; Wiley-VCH: Weinheim, 2004; Chapter 5: Olefination of Carbonyl Compounds by Zinc and Chromium Reagents, pp. 214–220.



To a slurry of flame-dried chromium (II) chloride (10.42 g, 84.8 mmol) in THF (20 mL) and dioxane (60 mL) was added the aldehyde (4.71 g, 11.3 mmol) and iodoform (8.90 g, 22.6 mmol) in dioxane (60 mL). The resulting brown suspension was stirred at room temperature for 10 h, diluted with ether (300 mL), and poured into water (300 mL). The aqueous layer was separated and washed with saturated sodium chloride. The aqueous layer thus afforded was extracted with ether (500 mL). The combined organic extracts were washed with brine (200 mL), dried over magnesium sulfate, filtered, and concentrated. Flash chromatography (hexanes: CH_2Cl_2, 7:1 to 6:1) provided 4.0 g (65.5%) of the *E*-olefin and 0.52 g (8.5%) of the *Z*-olefin.

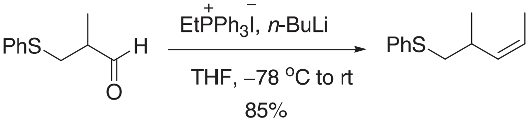
Reference: Song, H. Y.; Joo, J. M.; Kang, J. W.; Kim, D.-S.; Jung, C.-K.; Kwak, H. S.; Park, J. H.; Lee, E.; Hong, C. Y.; Jeong, S.; Jeon, K.; Park, J. H. *J. Org. Chem.* **2003,** *68*, 8080–8087.

5.2.11 Wittig Olefination

The Witttig olefination and its variants have been one of the most indispensable reactions to the synthetic organic chemist in the past 50 years for the generation of olefins from aldehydes and ketones. In addition, the stereochemistry of the olefin is often well predicted, and a chemical handle is often introduced which provides for homologation or functional group manipulation. The basic Wittig reaction is between an ylide ($Ph_3P{=}CR_1R_2 \leftrightarrow PPh_3P^+{-}^-CR_1R_2$) and an aldehyde or ketone. Ylides are relatively stable species which may be generated from the corresponding triphenylphosphonium salts and a base (i.e., *n*-BuLi, NaH, LiHMDS, *etc*.). In general, unstabilized ylides deliver the (*Z*)-alkene while stabilized ylides give the (*E*)-alkene. Examples of unstabilized and stabilized ylides are given in the subsequent procedures. Reviews: (a) Edmonds, M.; Abell, A. In *Modern Carbonyl Olefination-Methods and Applications*: Takeda, T. Ed.; Wiley-VCH: Weinheim, 2004; Chapter 1: The Wittig Reaction, pp. 1–17. (b) Kolodiazhny, O. I. In *Phosphorous Ylides Chemistry and Application in Organic Synthesis*; Wiley-VCH: Weinheim, 1999; pp. 360–538. (c) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev*. **1989,** *89*, 863–927. (d) Bestmann, H. J.; Vostrowsky, O. *Top. Curr. Chem*. **1983,** *109*, 85–163. (e) Gosney, I.; Rowley, A. G. In *Organophosphorus Reagents in Organic Synthesis*, Cadogan J. I. G., Ed.; Academic Press: New York, 1979; pp 17–153; (f) Wadsworth, W. S., Jr., *Org. React*. **1977,** *25*, 73–253. (g) Vollhardt, K. P. C. *Synthesis* **1975,** 765–780. (g) Maercker, A. *Org. React*. **1965,** *14*, 270–490.

5.2.11.1 Unstabilized Ylides

Unstabilized ylides deliver the (Z)-alkene.

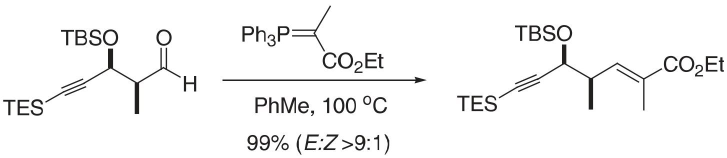


To a suspension of ethylphosphonium iodide (4.1 g, 11 mmol) in dry THF (40 mL) at 0 °C was added a solution of *n*-BuLi (1 M, 11 mL, 11 mmol). The mixture was stirred for 30 min at 0 °C. It was then cooled to –78 °C, and a solution of the aldehyde (1.8 g, 10 mmol) in dry THF (22 mL) was added dropwise. The reaction mixture was stirred for 4 h while allowing to gradually reach room temperature. It was cooled to 0 °C and quenched by the addition of saturated aqueous ammonium chloride. The layers were separated, and the aqueous layer extracted with ether. The combined organic layers were washed successively with water and brine, and dried over sodium sulfate. The organic extracts were concentrated, and the resulting crude product was purified by column chromatography eluting with petroleum ether/EtOAc (95:5) to afford 1.63 g (85%) of the *cis*-olefin as a liquid.

Reference: Raghavan, S.; Reddy, S. R.; Tony, K. A.; Kumar, C. N.; Varma, A. K., Nangia, A. *J. Org. Chem.* **2002,** *67*, 5838–5841.

5.2.11.2 Stabilized Ylides

Stabilized ylides give predominately the (*E*)-olefin.



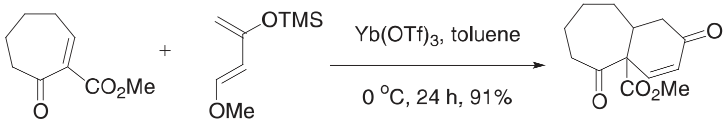
The acetylenic aldehyde (3.4 g, 10.0 mmol) was dissolved in toluene (200 mL). (Carbethoxymethylene)triphenylphosphorane (18.1 g, 50.0 mmol) was added in 1 portion. The stirred mixture was warmed to 100 °C and kept at this temperature for 12 h. The homogeneous solution was cooled to room temperature and washed sequentially with water (50 mL) and brine (50 mL). The organic phase was dried over sodium sulfate, filtered, concentrated, and the crude mixture purified by chromatography (silica gel, hexanes:EtOAc, 98:2) to afford 4.2 g (99%, *E:Z* > 9:1) of the *E*-olefin.

Reference: Nicolaou, K. C.; Fylaktakidou, K. C.; Monenschein, H.; Li, Y.; Weyershausen, B.; Mitchell, H. J.; Wei, H.-X. Guntupalli, P.; Hepworth, G.; Sugita, K. *J. Am. Chem. Soc.* **2003,** *125*, 15433–15442.

5.3 Reactions that Form Multiple Carbon–Carbon Bonds

5.3.1 Diels–Alder Reaction Using Danishefsky's Diene

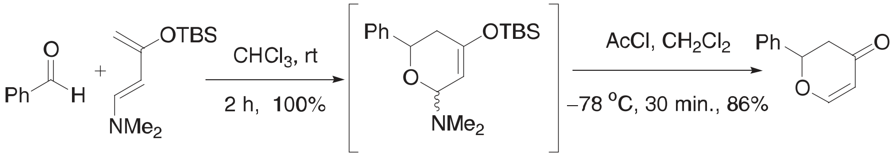
The Danishefsky's diene reacts readily with dienophiles, including alkenes, alkynes, aldehydes, and imines. Reviews: (a) Oppolzer, W. In *Comprehensive Organic Synthesis;* Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, Chapter 4.1: Intermolecular Diels-Alder Reactions, pp. 315–399. (b) Boger, D. L. In *Comprehensive Organic Synthesis;* Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, Chapter 4.3: Heterodiene Additions, pp. 451–512. (c) Weinreb, S. M. In *Comprehensive Organic Synthesis;* Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, Chapter 4.2: Heterodienophile additions to Dienes, pp. 401–499. (d) Mehta, G.; Uma, R. *Acc. Chem. Res.* **2000,** *33*, 278. (e) Jorgensen, K. A. *Eur. J. Org. Chem.* **2002,** 2093. (f) Corey, E. J. *Angew. Chem., Int. Ed.* **2002,** *41*, 1650.



To a cooled solution of the enone (2 mmol) and Danishefsky's diene (480 mg, 2.6 mmol) in toluene (18 mL) was added Yb(OTf)$_3$ (31 mg, 0.05 mmol) at 0 °C. The mixture was stirred at the same temperature for 24 h. The reaction mixture was washed with 2 M K_2CO_3 and dried ($MgSO_4$). After filtration and concentration of the filtrate, the residue was purified via flash chromatography using silica gel eluting with EtOAc/hexanes (20–30%) to give 428 mg (91%) of the adduct.

Reference: Inokuchi, T.; Okano, M.; Miyamoto, T.; Madon, H. B.; Takagi, M. *Synlett* **2000,** 1549–1552.

5.3.2 Hetero-Diels-Alder Reaction Using Rawal's Diene

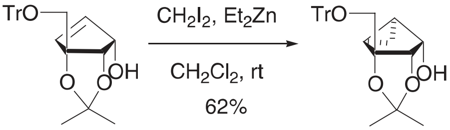


To a 25-mL flame-dried flask under a nitrogen atmosphere were added freshly distilled Rawal's diene (227 mg, 1 mmol, 1.0 equivalents) and 2 mL of $CHCl_3$. Benzaldehyde (1.5 mmol, 1.5 equivalents) was added dropwise via a gas-tight syringe. The reaction mixture was stirred at room temperature for 2 h and then diluted with 15 mL of CH_2Cl_2. The yellow solution was cooled to −78 °C and treated with 142 μL acetyl chloride (2 mmol, 2 equivalents). After stirring for about 30 min, saturated Na_2CO_3 was added. The organic layer was separated and the water phase was diluted with 15 mL of water and extracted twice with CH_2Cl_2. The combined organic phase was dried with $MgSO_4$, filtered, and concentrated to give a yellow oil, which was subjected to flash chromatography to afford the desired dihydropyrone in 86% overall yield.

Reference: Huang, Y.; Rawal, V. H. *Org. Lett.* **2000,** *2*, 3321–3322.

5.3.3 Simmons–Smith Reaction

The Simmons–Smith cyclopropanation converts olefins to the corresponding cyclopropanes stereospecifically. Reviews: (a) Charette, A. B.; Beauchemin, A. *Org. React.* **2001,** *58*, 1–415. (b) For enantioselective cyclopropanations see Davies, H. M. L.; Antoulinakis, E. G. *Org. React.* **2001,** *57*, 1–326.



To a stirred solution of the cyclopentenol (2.14g, 4.99 mmol) in CH_2Cl_2 (40 mL) was added diethylzinc (1.0 M in hexane, 25 mL, 25.00 mL) at 0 °C, and the reaction mixture was stirred at the same temperature for 15 min. Diiodomethane (4.0 mL, 50.21 mmol) was added to the reaction mixture at 0 °C, and the resulting mixture was stirred at room temperature overnight. After aqueous ammonium chloride solution (10 mL) was added, the reaction mixture was partitioned between ethyl acetate and water. The layers were separated, and the organic layer was dried ($MgSO_4$), filtered, and evaporated in vacuo. The residue was purified by silica gel column chromatography using hexane and ethyl acetate (2.5:1) as the eluent to give 1.38 g (62%) of the cyclopropane as a white solid.

Reference: Lee, J. A.; Moon, H. R.; Kim, H. O.; Kim, K, R.; Lee, K. M.; Kim, B. T.; Hwang, K. J.; Chun, M. W.; Jacobson, K. A.; Jeong, L. S. *J. Org. Chem.* **2005,** *70*, 5006–5013.