2

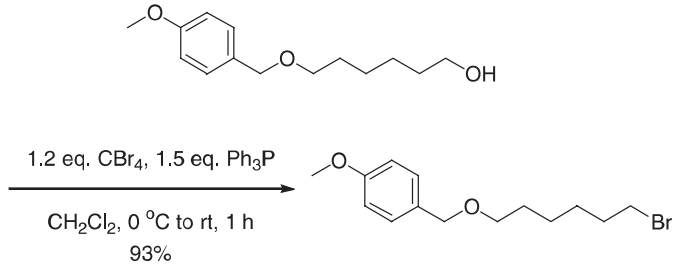
Functional Group Manipulations

2.1 Alcohol Oxidation State

2.1.1 Alcohols

2.1.1.1 Alkyl Alcohol to Alkyl Bromide

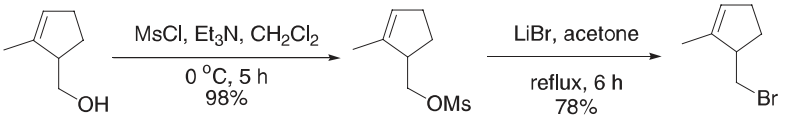
CBr_4–Ph_3P is very straightforward and widely used. Workup and purification can be messy at times because of the by-product, Ph_3PO.



To a mixture of the alcohol (0.800 g, 3.36 mmol) and carbon tetrabromide (1.337 g, 4.03 mmol) in CH_2Cl_2 at 0 ºC was added a solution of PPh_3 (1.319 g, 5.03 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was stirred at room temperature for 1 h, concentrated under reduced pressure, and purified by column chromatography to afford the bromide (0.941 g, 93% yield).

Reference: Hu, T.-S.; Yu, Q.; Wu, Y.-L.; Wu, Y. *J. Org. Chem.* **2001**, *66*, 853–861.

A two-step sequence consisting of mesylate formation followed by treatment with LiBr can also be used. This procedure involves two steps, but workup and purification are very straightforward. The bromide can be carried out to the next step without further purification in many cases.



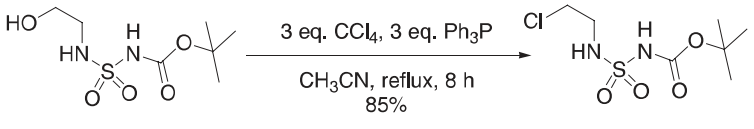
To a solution of 5-hydroxymethyl-1-methylcyclopentene (3.8 g, 34 mmol) in CH_2Cl_2 (50 mL) at 0 ºC was added triethylamine (5.2 mL, 37 mmol) followed by methanesulfonyl chloride (2.9 mL, 37 mmol). The mixture was stirred at 0 ºC for 5 h and then water was added. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure to give 6.4 g (98%) of (2-methylcyclopent-2-enyl)methyl methanesulfonate, which was used in the next step without further purification.

A solution containing the mesylate (6.4 g, 34 mmol) in acetone (70 mL) was treated with lithium bromide (8.89 g, 102 mmol). The mixture was heated at reflux for 6 h, cooled to room temperature, diluted with water, extracted with ether, and the combined ethereal extracts were dried over $MgSO_4$. Removal of the solvent under reduced pressure gave 4.6 g (78%) of 5-bromomethyl-1-methylcyclopentene, which was used in the next step without further purification.

Reference: Padwa, A.; Dimitroff, M.; Liu, B. *Org. Lett*. **2000**, *2*, 3233–3235.

2.1.1.2 Alkyl Alcohol to Alkyl Chloride

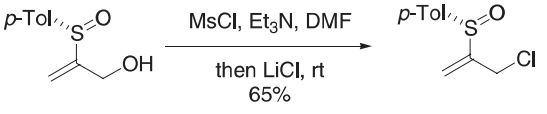
CCl_4–Ph_3P is a straightforward and widely used method for converting alcohols to alkyl chlorides. Workup and purification can be tricky at times because of the by-product, Ph_3PO. An alternative source of Ph_3P is a commercially available triphenylphosphine resin. The advantage of the resin is that the by-product, triphenylphosphine oxide, is bound to the resin, and purification is simplified.



A solution of BOC-sulfamoylaminoalcohol (5.35 mmol), triphenylphosphine (16.05 mmol), and CCl_4 (16.05 mmol) in anhydrous acetonitrile (100 mL) was refluxed for 8 h. After cooling to room temperature, the solution was concentrated in vacuo. The residue was triturated with diethyl ether (3 × 150 mL). Triphenylphosphine oxide, which precipitates in the combined organic layers, was removed by filtration. The filtrate was concentrated and the residue purified on silica gel (CH_2Cl_2) to afford $\boldsymbol{N^1}$-BOC,$\boldsymbol{N^3}$-(2-chloroethyl) sulfamide with 85% yield.

Reference: Regaïnia, Z.; Abdaoui, M.; Aouf, N.-E.; Dewynter, G.; Montero, J.-L. *Tetrahedron* **2000**, *56*, 381–387.

An alternate procedure involves mesylate formation and S_N2 replacement by LiCl. This reaction should be monitored carefully (especially with active alcohols such as allylic and benzylic alcohols) as frequently the chloride by-product will displace the mesylate in situ.

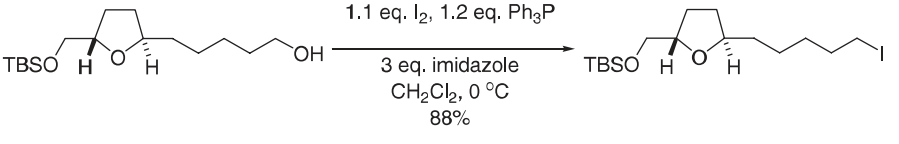


A solution of (S_s)-2-(*p*-tolylsulfinyl)-2-propen-1-ol (1.1 g, 5.6 mmol) in anhydrous dimethylformamide (DMF) (8 mL) under argon was treated at 0 ºC with Et_3N (630 mg, 6.2 mmol) and methanesulfonyl chloride (705 mg, 6.2 mmol). The reaction mixture was allowed to warm to room temperature and monitored by thin layer chromatography (TLC) (CH_2Cl_2/MeOH 97:3) until the starting alcohol was not detected. The mixture was next diluted with additional anhydrous DMF (10 mL), and LiCl (952 mg, 22.4 mmol) was added portion-wise. Stirring at room temperature was continued until TLC monitoring indicated total consumption of the intermediate mesylate. The reaction mixture was then evaporated to dryness, and the oily residue was taken up in ether and washed with brine. Drying of the organic phase (anhydrous Na_2SO_4) and evaporation afforded crude material that was flash-chromatographed (hexanes/EtOAc 85:15) to afford the allylic chloride (0.782 g, 65% yield).

Reference: Márquez, F.; Llebaria, A.; Delgado, A. *Org. Lett*. **2000**, *2*, 547–549.

2.1.1.3 Alkyl Alcohol to Alkyl Iodide

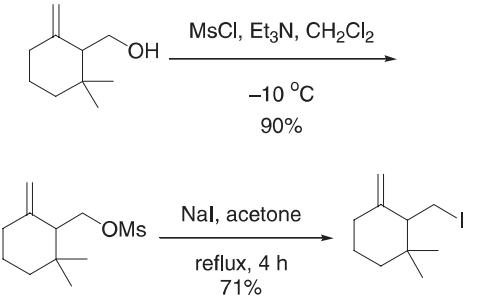
I_2–Ph_3P–Imidazole is a straightforward and widely used method to form alkyl iodides. Workup and purification can be awkward at times because of the by-product, Ph_3PO.



Iodine (536 mg, 2.11 mmol) was added to a solution of imidazole (359 mg, 5.27 mmol) and PPh_3 (509 mg, 1.94 mmol) in CH_2Cl_2 (10 mL) at 0 ºC. The solution was stirred for 5 min, and the alcohol (750 mg, 1.76 mmol), dissolved in CH_2Cl_2 (2 mL), was then added slowly. The reaction mixture was stirred for 4 h with the exclusion of light. It was then quenched by the addition of an aqueous $Na_2S_2O_3$ solution (10 mL). The aqueous layer was extracted with methyl *tert*-butyl ether (MTBE 3 × 20 mL). The combined organic layers were washed with saturated aqueous NaCl (10 mL) and dried with $MgSO_4$. The solvents were removed in vacuo. The crude product was purified by flash column chromatography (20 g silica, petroleum ether/MTBE 20:1) to yield the iodide (836 mg, 1.54 mmol, 88%) as a colorless oil.

Reference: Arndt, S.; Emde, U.; Bäurle, S.; Friedriech, T.; Grubert, L.; Koert, U. *Chem. Eur. J*. **2001**, 993–1005.

Alkyl alcohols can be converted to alkyl iodides via a two-step sequence consisting of mesylate formation followed by treatment with NaI. This procedure involves two steps, but workup and purification are very straightforward. The iodide can be carried on to the next step without further purification in many cases.



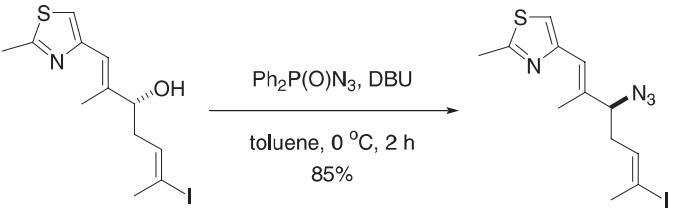
To a solution of freshly distilled triethylamine (1.82 g, 18 mmol) in anhydrous CH_2Cl_2 (35 mL) under argon at –10 ºC, the alcohol (2.0 g, 12 mmol) was added dropwise. After stirring for 10 min, methanesulfonyl chloride (1.60 g, 14 mmol) was added. The reaction mixture was stirred for a further 20 min and then washed with saturated aqueous sodium hydrogen carbonate (20 mL), water (20 mL), and brine (10 mL), dried and concentrated in vacuo. The crude mesylate was chromatographed, eluting with petroleum ether:EtOAc (10:1), to obtain the mesylate (2.68 g, 90%) as an off-white waxy solid. To a solution of sodium iodide (0.525 g, 3.5 mmol) in hot anhydrous acetone (30 mL) under argon, was added dropwise a solution of the mesylate (0.5 g, 2 mmol) in anhydrous acetone (25 mL), and the resulting mixture was heated under reflux for 4 h. The acetone was then removed in vacuo and the residue dissolved in ether. Water was added to dissolve the remaining sodium iodide and the organic layer was separated, washed with water (50 mL) and brine (50 mL), dried, and concentrated in vacuo. The residue was chromatographed, eluting with pentane, yielding the iodide (0.396 g, 71%) as a pale brown oil.

Reference: Crombie, B. S.; Smith, C.; Varnavas, C. Z.; Wallace, T. W. *J. Chem. Soc. Perkin Trans*. **2001**, *1*, 206–215.

2.1.1.4 Alkyl Alcohol to Azide

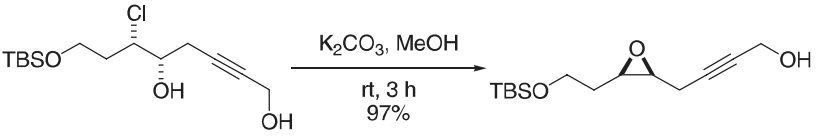
Treatment of an alcohol with diphenylphosphoryl azide is a one-step procedure to make azides. But treatment of a mesylate with NaN_3 is also frequently used for converting an alcohol to the corresponding azide as a two-step procedure.

The alcohol (1.74 g, 4.99 mmol) was dissolved in toluene (30 mL) and cooled to 0 ºC. Diphenylphosphoryl azide (1.65 g, 5.98 mmol) was added followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (0.91 g, 5.98 mmol). The reaction mixture was stirred at 0 ºC for 2 h. The solution was then warmed to 25 ºC followed by the addition of EtOAc (100 mL). The organic layer was washed sequentially with H_2O (1 × 30 mL), saturated $NaHCO_3$ (1 × 50 mL), and brine (1 × 50 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatography on silica gel (7.5% EtOAc/hexanes) provided the azide (1.58 g, 85%) as a light yellow oil.



Reference: Stachel, S. J.; Lee, C. B.; Spassova, M.; Chappell, M. D.; Bornmann, W. G.; Danishefsky, S. J.; Chou, T.-C.; Guan, Y. *J. Org. Chem.* **2001**, *66*, 4369–4378.

2.1.1.5 Alkyl Alcohol (Halohydrin) to Epoxide

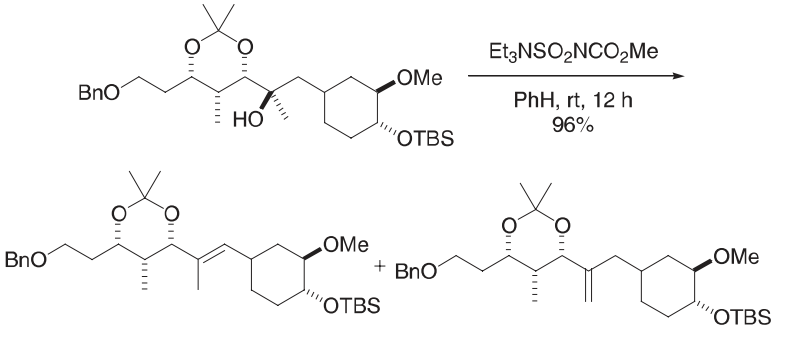


The chlorohydrin (17.61 g, 53.8 mmol) and K_2CO_3 (13.2 g, 88.5 mmol) in MeOH (88 mL) were stirred at room temperature for 3 h. The reaction mixture was diluted with ether (350 mL), washed with water (3 × 80 mL) and brine (100 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash chromatography (SiO_2, 20% EtOAc in hexanes) to yield the epoxide as a colorless oil (14.13 g, 97%).

Reference: Gao, L.-X.; Murai, A. *Heterocycles* **1995**, *42*, 745–774.

2.1.1.6 Alcohol to Olefin via Burgess Dehydrating Reagent

Burgess dehydrating reagent is efficient at generating olefins from secondary and tertiary alcohols. It does notwork with primary alcohols.



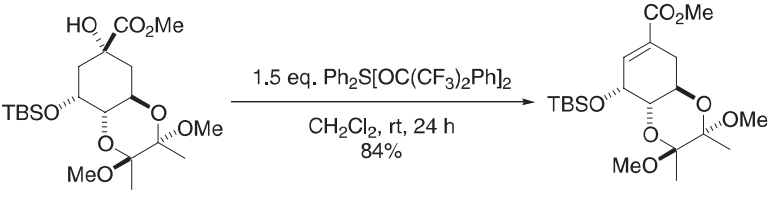
The Burgess reagent (62.0 mg, 0.260 mmol) was added to a solution of the alcohol (19.6 mg, 0.0336 mmol) in 1.2 mL of benzene. The heterogeneous mixture was stirred under nitrogen at ambient temperature for 12 h and then warmed briefly to 50 ºC to complete the elimination. After cooling, the mixture was diluted with 5 mL of ether,

and 0.5 mL of H_2O was added. The organic layer was removed and dried by passage through a magnesium sulfate plug. Flash chromatography (25% ether in hexanes) furnished the olefinic products (18.2 mg, 96%) as an inseparable 3:1 mixture of isomers favoring the desired trisubstituted olefin.

Reference: Nakatsuka, M.; Ragan, J. A.; Sammakia, T.; Smith, D. B.; Uehling, D. E.; Schreiber, S. L. *J. Am. Chem. Soc*. **1990**, *112*, 5583–5601.

2.1.1.7 Alcohol to Olefin via Martin's Sulfurane

Martin's sulfurane dehydrates secondary and tertiary alcohols to give olefins, but forms ethers with primary alcohols.



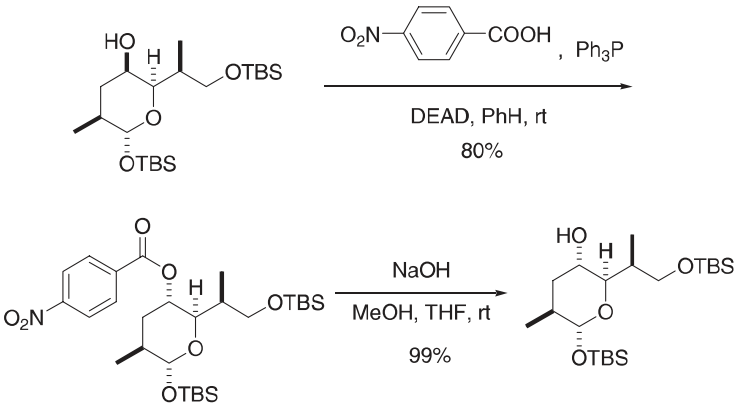
A solution of Martin's sulfurane (0.949 g, 1.41 mmol) in CH_2Cl_2 (5 mL) was slowly added under an atmosphere of nitrogen to a stirred solution of the alcohol (0.41 g, 0.94 mmol) in CH_2Cl_2 (10 mL) at room temperature. The resulting pale yellow solution was stirred for 24 h at which time the solvent was removed in vacuo to yield the crude product as a pale yellow oil. Purification by flash column chromatography [SiO_2; EtOAc:petroleum ether (40:60)] followed by recrystallization (CH_3OH/H_2O) furnished the olefin product as a colorless solid (0.33 g, 84% yield).

Reference: Begum, L.; Box, J. M.; Drew, M. G. B.; Harwood, L. M.; Humphreys, J. L.; Lowes, D. J.; Morris, G. A.; Redon, P. M.; Walker, F. M.; Whitehead, R. C. *Tetrahedron* **2003**, *59*, 4827–4841.

2.1.1.8 Mitsunobu Reaction

The venerable Mitsunobu reaction remains a powerful method for the stereoselective inversion of chiral secondary alcohols. When considering this reaction, the chemist should take into account the solvent, the phosphine, the azodicarboxylate, and the nucleophile. The most common solvents used for the Mitsunobu reaction include tetrahydrofuran (THF), dioxane, CH_2Cl_2, $CHCl_3$, Et_2O, DMF, toluene, and benzene. Also, the two most common azodicarboxylates used are diethylazodicarboxylate (DEAD) and diisopropyldicarboxylate. In terms of the phosphine, most reactions are run in the presence of triphenylphosphine, although removal of the resulting triphenylphosine oxide can be problematic. Moreover, it has been shown that the carboxylic acid nucleophile can play a critical role in this reaction, and therefore some carboxylic acids include formic acid, acetic acid, benzoic acid, 4-nitrobenzoic acid, and 3,5-dinitrobenzoic acid. Finally, in some instances it is advantageous to pre-mix the phosphine with the azodicarboxylate and then add the alcohol. Although the Mitsunobu is most famous for the inversion of chiral alcohols, the scope of this reaction has been expanded to include formation of C–N, C–S, C–halogen, and C–C bonds.

Reviews: (a) Hughes, D. L. *Org. Prep. Proc. Int*. **1996**, *28*, 127–164. (b) Hughes, D. L. *Org. React*. **1992**, *42*, 335–656. (c) Castro, B. R. *Org. React*. **1983**, *29*, 1–162. (d) Mitsunobu, O. Synthesis **1981**, 1–28.

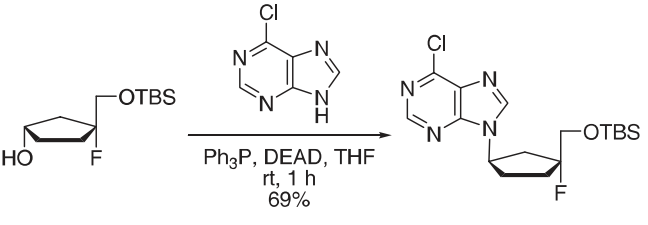


Diethyl azodicarboxylate (11.6 mL, 74.0 mmol) was added dropwise with stirring to a solution of the alcohol (6.20 g, 14.9 mmol), Ph_3P (19.7 g, 75.1 mmol), and 4-nitrobenzoic acid (11.2 g, 67.2 mmol) at room temperature in benzene (300 mL), and the resulting orange solution was stirred for 20 h at room temperature. The solution was concentrated under reduced pressure to give a viscous orange oil that was dissolved in a minimal amount of CH_2Cl_2 and purified twice by flash chromatography; the first column was eluted with 5% ether/hexanes to give the partially purified ester which was resubjected to chromatography eluting with 2% ether/hexanes to give 6.80 g (80%) of 4-nitrobenzoate ester as a white crystalline solid.

The nitrobenzoate ester (6.80 g, 12.0 mmol) in a mixture of THF/MeOH (10 mL:300 mL), containing powdered sodium hydroxide (1.56 g, 39.0 mmol), was stirred at room temperature for 15 min. The reaction was concentrated under reduced pressure, and the residue was partitioned in ether/water (100 mL, 1:1 by volume). The layers were separated, and the aqueous portion was extracted with ether (3 × 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with 5% ether/hexanes to provide 5.00 g (99%) of the inverted alcohol as a clear oil.

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

2.1.1.8.2 Formation of a C–N Bond



A suspension of triphenylphosphine (590 mg, 2.25 mmol) and 6-chloropurine (348 mg, 2.25 mmol) in anhydrous THF (10 mL) was treated with DEAD (355 μL, 2.25 mmol) at room temperature in the dark for 1 h. A solution of the alcohol (140 mg, 0.56 mmol) in anhydrous THF was then added and the mixture was stirred in the dark at room temperature for 6 h. Evaporation of solvent gave a crude product which was purified by flash chromatography (4:1 hexanes/EtOAc) to yield 149 mg (69%) of the product as a white solid.

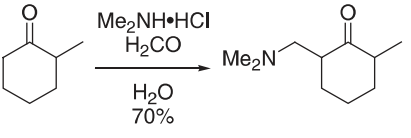
Reference: Chong, Y.; Gumina, G.; Chu, C. K. *Tetrahedron: Asymmetry* **2000**, *11*, 4853–4875.

2.1.2 Amines

2.1.2.1 Mannich Reaction

The Mannich reaction is an aldol reaction with an imine. It has been the subject of many excellent reviews. For example, see Arend, M.; Westerman, B.; Risch, N. *Angew. Chem. Int. Ed*. **1998**, *37*, 1044–1070. Asymmetric variants have also been reported; see, for example, Notz, W.; Tanaka, F.; Barbas, C. F., III; *Acc. Chem. Res*. **2004**, *37*, 580–591.

2.1.2.1.1 Traditional

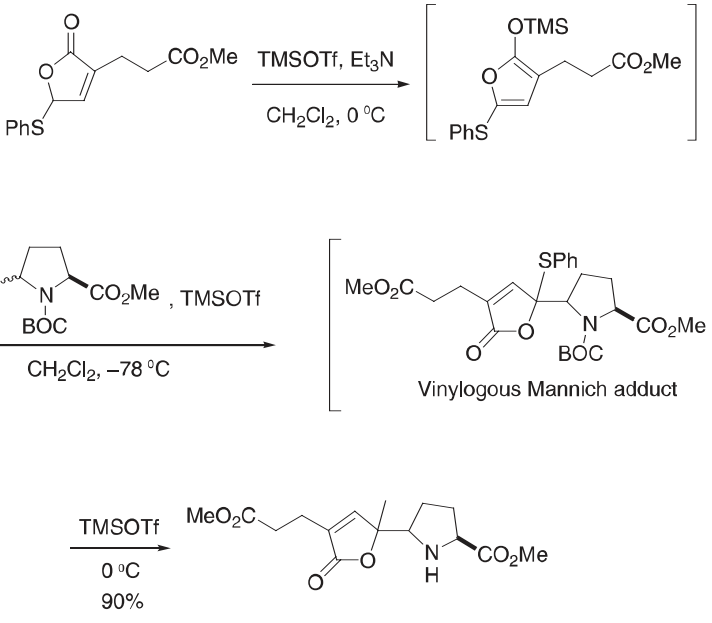


Dimethylamine hydrochloride (1 equivalent) was prepared by evaporation of a mixture of aqueous dimethylamine (45 g, 1.0 mol, as 25% aqueous solution) and excess concentrated hydrochloric acid under reduced pressure. To the solid residue was added an aqueous solution of the cyclohexanone (224 g, 2.0 mol) and formaldehyde (30 g, 1.0 mol, 40% aqueous solution). The two-phase mixture was heated carefully (reaction is exothermic) to boiling under a long reflux condenser, boiled for about 5 min, and then cooled to room temperature. Water (200 mL) was added, the layers separated, the aqueous layer saturated with sodium chloride, washed with ether (4 × 50 mL), and then made basic with 30% aqueous potassium hydroxide (1.3 equivalents). The Mannich base separated as a yellow upper layer with a strong amine odor. The layers were separated, the aqueous layer extracted with ether (5 × 100 mL), the combined organic layer and ether extracts dried over magnesium sulfate, and the solvent was distilled to provide the amino ketone (118 g, 70%).

Reference: Frank, R. L.; Pierle, R. C. *J. Am. Chem. Soc*. **1951**, *73*, 724–730.

2.1.2.1.2 Vinylogous Mannich

Reviews: (a) Bur, S. K.; Martin, S. F. *Tetrahedron* **2001**, *57*, 3221–3242. (b) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev*. **2000**, *100*, 1929–1972.



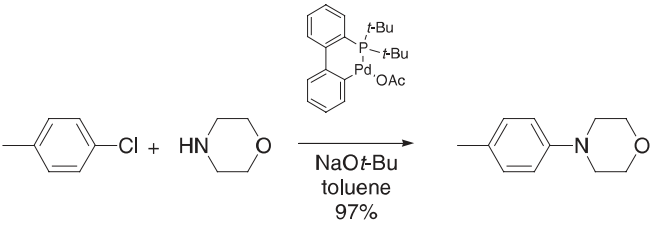
Freshly distilled trimethlysilyl triflate (TMSOTf 461 μL, 2.55 mmol) was added to a mixture of the butenolide (644 mg, 2.31 mmol) and triethylamine (387 μL, 2.78 mmol) in CH_2Cl_2 (23 mL) at 0 ºC. (In situ formation of the siloxyfuran.) The mixture was stirred at 0 ºC for 1 h and then cooled to −78 ºC. A solution of the aminal (660 mg, 2.55 mmol) in CH_2Cl_2 (3 mL) and then TMSOTf (84 μL, 0.463 mmol) were added, and the reaction mixture was stirred at –78 ºC for 1 h. (Formation of the vinylogous Mannich adduct.) Another quantity of TMSOTf (838 μL, 4.63 mmol) was then added. The cooling bath was exchanged for an ice-bath, and the mixture was stirred at 0 ºC for 2 h. (BOC deprotection) The mixture was poured into saturated aqueous sodium bicarbonate (30 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 30 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting yellow oil was purified by flash chromatography eluting with EtOAc/hexanes (2:1) to give 839 mg (90%) of the diastereomeric amino butenolides.

Reference: Reichelt, A.; Bur, S. K.; Martin, S. F. *Tetrahedron* **2002**, *58*, 6323–6328.

2.1.3 Halides

2.1.3.1 Hartwig-Buchwald Aromatic Amination

Although this reaction is relatively new, it has already been the subject of several reviews: Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res*. **1998**, *31*, 805–818; Hartwig, J. F. *Acc. Chem. Res*. **1998**, *31*, 852–860; and Hartwig, J. F. *Angew. Chem. Int. Ed*. **1998**, *37*, 2046–2067. Innumerable conditions have been developed; however, probably the easiest conditions to try for a first pass reaction are shown below.

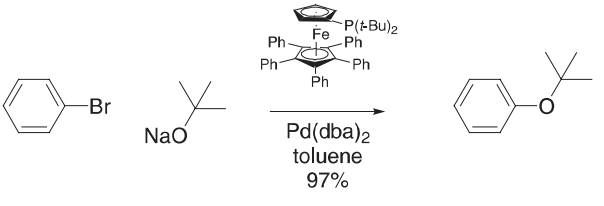


An oven-dried, resealable Schlenk flask was charged with the palladium source (2.3 mg, 0.005 mmol) and NaO*t*-Bu (134 mg, 1.4 mmol). The flask was evacuated, backfilled with argon, and the aryl chloride (126 mg, 1 mmol), toluene (1 mL), and the amine (105 mg, 1.2 mmol) were then added. The flask was sealed with a Teflon screwcap and the mixture was stirred at 80 ºC. After all starting material had been consumed, as judged by gas chromatography (GC), the mixture was allowed to cool to room temperature and was then diluted with ether (40 mL). The resulting suspension was transferred to a separatory funnel and washed with water (10 mL). The organic layer was separated, dried with $MgSO_4$, and concentrated under vacuum. The crude material was purified by flash chromatography to provide the aniline (172 mg, 97%).

Reference: Zim, D.; Buchwald, S. L. *Org. Lett*. **2003**, *5*, 2413–2415.

2.1.3.2 Hartwig-Buchwald Ether Formation

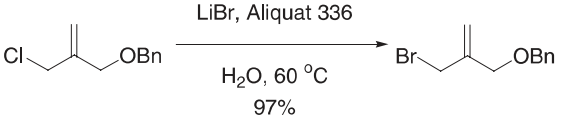
Organometallic conditions to form diaryl ethers and aryl alkyl ethers have been developed. For reviews, see Hartwig, J.F. *Angew. Chem. Int. Ed*. **1998,** *37*, 2046–2067; Muci, A.R.; Buchwald, S.L. Practical Palladium Catalysts for C–N and C–O Bond Formation. In *Topics in Current Chemistry;* Miyaura, N., Ed.; Springer-Verlag: Berlin, **2001**, *Vol. 219*, pp. 131–209.



A 4-mL vial was charged with bromobenzene (63 mg, 0.40 mmol), $Pd(dba)_2$ (11.5 mg, 0.0200 mmol), Ph_5FcP-(*t*-Bu)$_2$ (14.2 mg, 0.0200 mmol), and sodium *tert*-butoxide (47 mg, 0.48 mmol). Anhydrous toluene (2 mL) was added, and the vial was sealed with a cap containing a PTFE septum and removed from the dry box. The reaction mixture was stirred at room temperature for 23 h. The reaction solution was then adsorbed onto silica gel, and the product was isolated by eluting with EtOAc/hexanes (0 to 10% gradient) to give the ether (58 mg, 97%).

Reference: Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem*. **2002**, *67*, 5553–5566.

2.1.3.3 *Finkelstein Reaction*

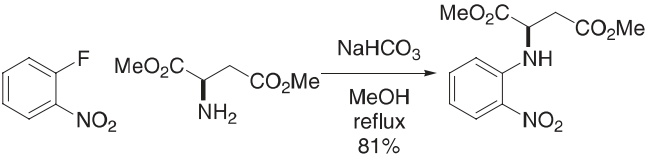


The chloride (7.20 g, 36.64 mmol) and Aliquat 336 (0.7 g, 1.73 mmol) were added to aqueous LiBr (6.38 g, 73.47 mmol). The mixture was heated to 60 ºC for 2 h. After cooling, the mixture was filtered through Florisil to yield the bromide as a pale yellow oil (8.53 g, 97%).

Reference: Chen, B.; Ko, R. Y. Y.; Yuen, M. S. M.; Cheng, K.-F.; Chiu, P. *J. Org. Chem.* **2003**, *68*, 4195–4205.

2.1.3.4 Nucleophilic Aromatic Substitution (S_NAr)

A variety of electron withdrawing groups activate aromatic rings towards nucleophilic aromatic substitution, including nitro, carboxyl, and cyano groups. The leaving group can be ortho or para to the electron withdrawing group. Fluoride is the most common leaving group, but other halogens and sometimes sulfonate esters are also used.



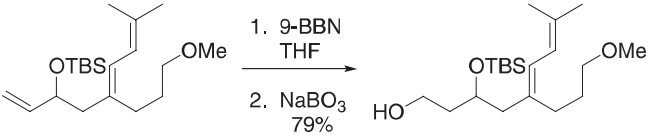
To a solution of dimethyl *D*-aspartate (18 g, 111.7 mmol) in MeOH (500 mL) was added 2-fluoronitrobenzene (17.33 g, 122.86 mmol) and $NaHCO_3$ (9.38 g, 111.7 mmol). The reaction mixture was refluxed under N_2 for approximately 2 days. The solvent was removed under reduced pressure, and the residue was azeotropically dried with benzene (2 × 100 mL). The crude material was then redissolved in MeOH (200 mL), cooled to 0 ºC, and the pH of the reaction mixture was adjusted to 4 with HCl(g). The reaction mixture was stirred overnight at room temperature and concentrated under reduced pressure. The residue was taken up in EtOAc and washed with a saturated $NaHCO_3$/10% Na_2CO_3 solution (9:1, 2 × 500 mL) and brine (300 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated to give dimethyl (2*R*)-2-(2-nitrophenylamino)butanedioate (25.54 g, 81%).

Reference: Su, D.-S.; Markowitz, M. K.; DiPardo, R. M.; Murphy, K. L.; Harrell, C. M.; O'Malley, S. S.; Ransom, R. W.; Chang, R. S. L.; Ha, S.; Hess, F. J.; Pettibone, D. J.; Mason, G. S.; Boyce, S.; Freidinger, R. M.; Bock, M. G. *J. Am. Chem. Soc*. **2003**, *125*, 7516–7517.

2.1.4 Olefins

2.1.4.1 Hydroboration Reaction

There are a wide variety of hydroborating reagents, including BH_3 complexes, pinacolborane, thexyl borane, and catechol borane. The following employs 9-borabicyclo[3.3.1]nonane (9-BBN), which places the boron on the less sterically hindered carbon with high regioselectivity; however, completely removing the cyclooctane by-products can be problematic. The alkylborane can be isolated, but is typically used directly in the next reaction, in this case oxidation to the primary alcohol.

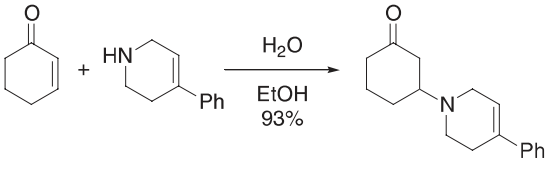


Into a 100-mL round bottomed flask equipped with a nitrogen inlet and a magnetic stir bar was placed the triene (1.09 g, 3.22 mmol) followed by addition of 9-BBN (0.43 M solution in THF, 8.22 mL, 3.54 mmol) via a syringe. After 1 h 20 min of stirring at room temperature, water (8.0 mL) was added, followed by $NaBO_3$ï$4H_2O$ (2.48 g, 16.1 mmol). Moderate heat evolution was observed. The heterogeneous mixture was vigorously stirred for 1 h 10 min, quenched with a saturated aqueous solution of NH_4Cl (30 mL), and extracted with a mixture of 1:1 hexane/MTBE (3 × 50 mL). The combined organic layers were dried ($CaCl_2$), filtered, and concentrated. The colorless oil was purified by chromatography (silica gel (20 g), hexane/EtOAc, gradient 10/1 to 4/1, 20 mm column) to afford the alcohol as a colorless oily material (911 mg, 79%).

Reference: Denmark, S. E.; Baiazitov, R. Y. *Org. Lett*. **2005**, *7*, 5617–5620.

2.1.4.2 Michael Addition

A variety of nucleophiles can be added in a conjugate manner to α,β-unsaturated ketones. The reaction is reversible, so the main difficulty is finding conditions that drive the equilibrium to the right. For catalytic enantioselective Michael reactions, see Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171–196. For intramolecular Michael reactions see: Little, R.D.; Masjedizadeh, M. R.; Wallquist, O.; Mcloughlin, J. I. *Org. React*. **1995**, *47*, 315–552.



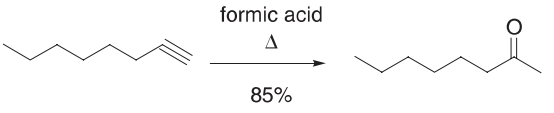
2-Cyclohexenone (9.68 mL, 0.1 mol) and the amine (15.92 g, 0.1 mol) were combined with H_2O (2.5 mL). Within minutes the mixture became warm and turned solid. This solid was dissolved in EtOH (250 mL), and the solution was heated to reflux for 4 h. The reaction mixture was cooled, dried over $MgSO_4$, and concentrated to give the amino ketone as an unstable yellow solid (24.0 g, 93%).

Reference: Wright, J. L.; Caprathe, B. W.; Downing, D. M.; Glase, S. A.; Heffner, T. G.; Jaen, J. C.; Johnson, S. J.; Kesten, S. R.; MacKenzie, R. G.; Meltzer, L. T.; Pugsley, T. A.; Smith, S. J.; Wise, L. D.; Wustrow, D. J. *J. Med. Chem.* **1994**, *37*, 3523–3533.

2.2 Ketone Oxidation State

2.2.1 Alkyne Hydrolysis

The hydrolysis has traditionally been performed with protic acids. Recently, however, transition metals have been used to facilitate the reaction. Frequently, with internal alkynes, a mixture of regioisomeric ketones are formed.

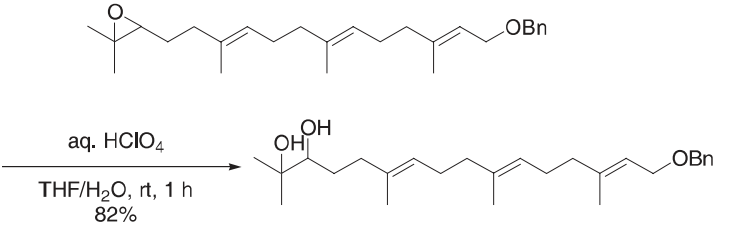


1-Octyne (7.5 g) and formic acid (100 mL) were heated in an oil bath at 100 ºC until all starting material was consumed. The progress of the reaction was monitored by GC analysis of the reaction solution. Quantitative GC analysis at the end of the reaction (6 h) indicated 92% yield of 2-octanone. The cooled reaction mixture was taken up with CH_2Cl_2 (170 mL), and the solution was washed with water, sodium carbonate solution, and water, dried over $MgSO_4$, and evaporated in vacuo. The residue was distilled (bp 171–173 ºC) to give 2-octanone (7.42 g, 85%).

Reference: Menashe, N.; Reshef, D.; Shvo, Y. *J. Org. Chem.* **1991**, *56*, 2912–2914.

2.2.2 Epoxides

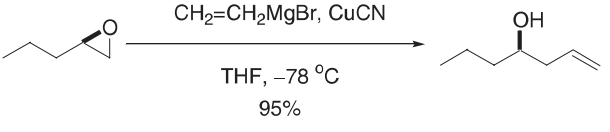
2.2.2.1 Epoxide Ring Opening Reactions, S_N1



Note: *Perchloric acid is an extremely corrosive acid. The proper personal protection equipment must be worn. In addition, perchloric acid must be handled in a hood, preferably in a hood designed for it. Avoid contact with paper, cotton, and wood as these materials may catch fire. If perchloric acid becomes concentrated, a fire or explosion could result. Read its Material Safety Data Sheet for more details.* A suspension of the epoxide (144 mg, 0.36 mmol) in THF (2.5 mL) and H_2O (1.4 mL) at room temperature was added to $HClO_4$ (70% in H_2O, 20 μL, 0.23 mmol). After 50 min at room temperature, $NaHCO_3$ (20 mL, saturated) was added and the aqueous layer was extracted with ether (4 × 20 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (30 mL) and brine (30 mL), dried (Na_2SO_4), and evaporated to give a pale yellow oil (160 mg). The crude product was purified by flash chromatography (SiO_2, 40% EtOAc in hexanes) to give the diol as a colorless oil (124 mg, 82%).

Reference: Jin, Q.; Williams, D. C.; Hezari, M.; Croteau, R.; Coates, R. M. *J. Org. Chem.* **2005**, *70*, 4667–4675.

2.2.2.2 Epoxide Ring Opening Reactions, S_N2



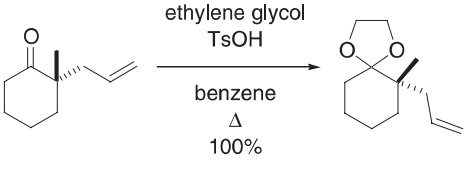
To a stirred solution of the epoxide (3.50 g, 40.6 mmol) and CuCN (364 mg, 4.06 mmol) in dry THF (30 mL) was added a 1 M solution of vinylmagnesium bromide in THF (52.8 mL, 52.8 mmol), over 45 min, dropwise at –78 ºC. The mixture was allowed to warm up to 0 ºC before it was quenched with a saturated aqueous NH_4Cl solution (20 mL). The layers were separated, the aqueous layer extracted with ether (3 × 50 mL), and the combined ethereal extracts were washed with brine (20 mL) and dried ($MgSO_4$). Evaporation of the solvent and chromatographic purification of the crude product (silica, Et_2O:pentane 1:3) gave the alcohol as a pale yellow oil (4.41 g, 95%).

Reference: Holub, N.; Neidhoefer, J.; Blechert, S. *Org. Lett*. **2005**, *7*, 1227–1229.

2.2.3 Ketones

2.2.3.1 Ketal Formation

The most common ketals are dioxolane and dioxane; these form more readily and have fewer problems with enol ether contamination. Sometimes, however, they can be difficult to hydrolyze, particularly when the molecule contains sensitive functional groups. The reaction is acid catalyzed, with some of the more common acids being para-toluenesulfonic, pyridinium para-toluenesulfonic, and camphorsulfonic. The eliminated water can be removed either with an azeotroping solvent (such as toluene or benzene) or by the addition of a dehydrating agent such as trimethylorthoformate.

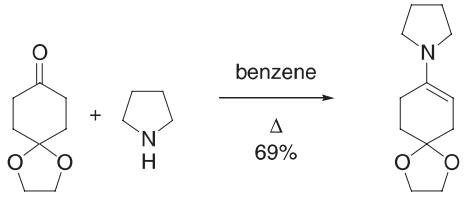


A solution of the ketone (1.23 g, 8.11 mmol), ethylene glycol (1.8 mL, 32 mmol), pyridinium tosylate (0.6 g, 2.4 mmol), and benzene (45 mL) was refluxed for 22 h in a Dean–Stark apparatus. The reaction mixture was cooled, poured into saturated $NaHCO_3$ (50 mL), the aqueous layer extracted with hexanes/Et_2O (1/1, 2 × 20 mL), and washed with brine (2 × 15 mL). The combined organics were dried ($MgSO_4$), concentrated, and chromatographed to give the ketal (1.59 g, 100%).

Reference: Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044–15045.

2.2.3.2 Enamine Formation

As with imines, enamines have varying stability. They are typically used crude without further purification.

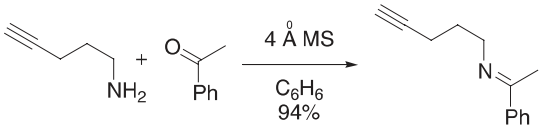


A 250-mL round-bottomed flask equipped with a Dean–Stark trap and reflux condenser was charged with the ketone (5.2 g, 33.3 mmol) and pyrrolidine (2.4 mL, 33.3 mmol) in anhydrous benzene (200 mL). The solution was refluxed for 8 h until no more H_2O was collected in the Dean–Stark trap. The Dean–Stark trap was removed and replaced with a distillation head, and the benzene was removed by distillation. The product was distilled (0.2 torr, 105 ºC) to give the enamine (4.78 g, 69%) as a yellow viscous oil, which was used immediately to avoid decomposition.

Reference: Davis, K. M.; Carpenter, B. K. *J. Org. Chem.* **1996**, *61*, 4617–4622.

2.2.3.3 Imine Formation

Imines display a variety of stabilities—some condensations of anilines with benzaldehydes liberate water before any heat can be applied while some imines cannot survive TLC and, as in this case, must be stored under special conditions to prevent hydrolysis.

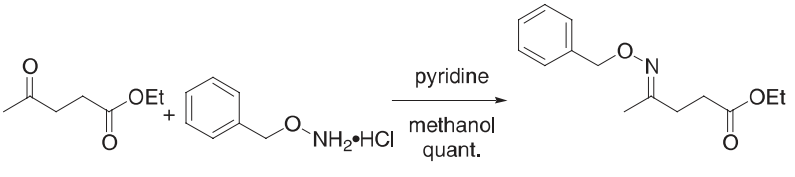


4-Pentynyl-1-amine (0.59 g, 6.7 mmol) was dissolved in dry benzene (15 mL), and 4 Å molecular sieves (~ 4 g) were added to the solution. The mixture was stirred at room temperature and acetophenone (0.78 mL, 6.7 mmol) was added dropwise. The mixture was stirred until ^{1}H NMR spectroscopy revealed complete imine formation (~ 6 h). The reaction mixture was filtered through a plug of dry Celite, and the molecular sieves were washed thoroughly with ether. The solution was concentrated in vacuo to yield the imine (1.2 g, 94%) as a clear oil, which was used without further purification. The imine can be stored frozen in benzene to avoid hydrolysis.

Reference: Prabhakaran, E. N.; Nugent, B. M.; Williams, A. L.; Nailor, K. E.; Johnston, J. *J. Org. Lett*. **2002**, *4*, 4197–4200.

2.2.3.4 Oxime Formation

Oximes are formed in much the same way as imines (condensation with a carbonyl, typically driven by removing the formed water). Oximes are usually much more stable than imines and can be more easily purified.



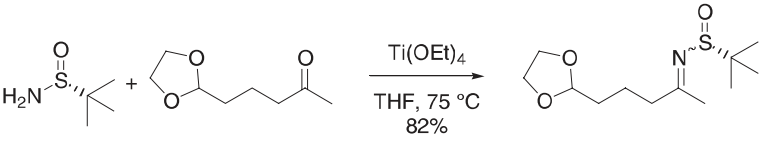
To a solution of the keto-ester (1.44 g, 10 mmol, 1.0) and benzyl-hydroxylamine (1.60 g, 10 mmol, 1.0) in ethanol (30 mL) was added pyridine (5.0 mL, 62 mmol) in 1 portion. The reaction mixture was heated at 55 ºC for 24 h and then concentrated

on a rotary evaporator. The residue was partitioned between ether (150 mL) and water (50 mL). The organic layer was sequentially washed with HCl (0.5 N, 2 × 30 mL) and water (30 mL), and then dried over $MgSO_4$. Concentration in vacuo provided the oxime (2.50 g, 100%) as a 3:1 mixture of *E*:*Z* isomers as a colorless liquid.

Reference: Hart, D. J.; Magomedov, N. A. *J. Am. Chem. Soc*. **2001**, *123*, 5892–5899.

2.2.3.5 Sulfinimine Formation

One of the most effective ways of preparing enantiomerically pure secondary amines is the addition of organometallic reagents to chiral sulfinimines, which are prepared by the condensation of an aldehyde (or ketone) with a sulfinamide. The preparation of *t*-butyl sulfinamide had been problematic, but the synthesis (and supplies) now seems to be more reliable.

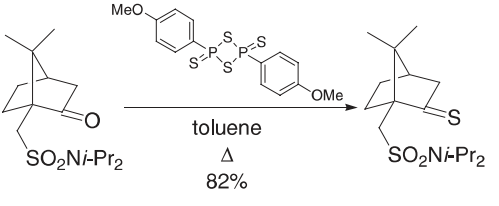


A mixture of *t*-butyl sulfinamide (1.52 g, 12.5 mmol), the ketone (2.37 g, 15.0 mmol), and $Ti(OEt)_4$ (6.0 g, 25.0 mmol) in 25 mL of THF was heated to reflux for 15 h and then was cooled to room temperature. The reaction mixture was poured into 25 mL of brine while rapidly stirring, and the resulting mixture was filtered through a plug of Celite. The filter cake was washed with EtOAc, and the combined filtrate was transferred to a separatory funnel where the organic layer was washed with brine. The brine layer was extracted once with EtOAc, and the combined organic portions were dried over Na_2SO_4, filtered, and concentrated. Column chromatography (4:6 hexanes/EtOAc) afforded the sulfinimine (3.21 g, 82%) as a mixture of *E*/*Z* isomers (8:1 by ^1H NMR in $CDCl_3$).

Reference: Kochi, T.; Tang, T. P.; Ellman J. A. *J. Am. Chem. Soc*. **2003**, *125*, 11276–11282.

2.2.3.6 Thioketone Formation

The two primary reagents for accomplishing this transformation are P_4S_{10} (alternately referred to as P_2S_5) and Lawesson's reagent. The primary advantage of P_4S_{10} is that it is far less expensive and more atom economical. The primary advantage of Lawesson's reagent is that it can be used with only a moderate excess, whereas P_4S_{10} requires a large excess and is easier to handle. Both of these reagents have the stench one might expect from a compound containing multiple sulfur atoms.



The ketone (1.00 g, 3.17 mmol) and 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide (Lawesson's reagent, 3.85 g, 9.52 mmol) were mixed in PhMe (80 mL) and heated at reflux for 12 h. The mixture was allowed to cool to room temperature, filtered through a plug of silica, and concentrated in vacuo. Chromatography (1:3 EtOAc:hexane; R_f 0.27) followed by recrystallization (hexane) gave the thione (0.86 g, 82%) as orange crystals.

Reference: Barrett, A. G. M.; Braddock, D. C.; Christian, P. W. N.; Pilipauskas, D.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **1998**, *63*, 5818–5823.

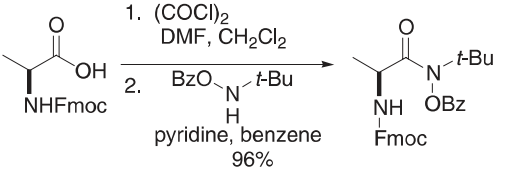
2.3 Acid Oxidation State

2.3.1 Reaction by Reactive Intermediates

Because the intermediates described in this section are reactive and potentially unstable compounds, the procedures describe the preparation of the active intermediate followed by a subsequent reaction rather than just the active intermediate.

2.3.1.1 Acid Chloride Formation by Oxalyl Chloride

One of the most straightforward methods of activating acids via the acid chloride is by reacting the acid with oxalyl chloride and a catalytic amount of DMF. This reaction is fast and liberates a great deal of gas, so it is important that the reaction vessel is adequately vented; it is also moderately exothermic and frequently requires cooling. As the intermediate acid chloride typically hydrolyzes on silica gel, the reaction can be monitored by first dropping an aliquot of the reaction mixture into methanol and then checking by TLC for disappearance of the acid and formation of the methyl ester.

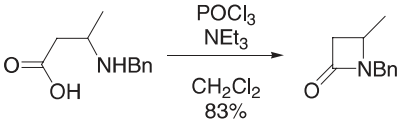


To a room temperature solution of Fmoc-*L*-alanine (1.04 g, 3.35 mmol) in dichloromethane (5 mL) was added DMF (26 μL) followed by oxalyl chloride (584 μL, 6.69 mmol). Once the effervescence had subsided, the yellow solution was heated to reflux for 1.5 h. After cooling, the solution was evaporated in vacuo and the solid residue azeotroped with benzene, before being dissolved in benzene (6 mL). To this yellow solution was added a solution of *N*-*tert*-butyl-*O*-benzoylhydroxylamine (0.71 g, 3.68 mmol) in benzene (5 mL), followed by pyridine (541 μL, 6.69 mmol). The mixture was heated to reflux overnight and then cooled. The colorless suspension was taken up in EtOAc and 10% HCl (aqueous), separated, the organic layer washed with brine, and then dried over $MgSO_4$. Evaporation gave a viscous, colorless oil that was purified by flash chromatography (4:1 Hexane:EtOAc) to give the hydroxamic acid as a colorless oil (1.56 g, 96%).

Reference: Braslau, R.; Axon, J. R.; Lee, B. *Org. Lett.* **2000**, *2*, 1399–1401.

2.3.1.2 Acid Chloride Formation by Phosphorous Oxychloride

An advantage of phosphorous oxychloride in the preparation of acid chlorides is that no gas is evolved. As is demonstrated in the following example, basic nitrogens do not interfere with the reaction.

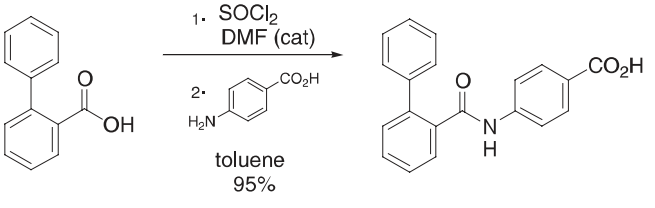


To a cooled solution (0 ºC) of the amino acid (193 mg, 1 mmol) and triethylamine (418 μL, 3 mmol) in CH_2Cl_2 (25 mL) was added $POCl_3$ (460 mg, 3 mmol) dropwise, and the reaction mixture was stirred overnight at room temperature. The resulting solution was washed with saturated aqueous $NaHCO_3$ (25 mL), brine (25 mL), and water (3 × 25 mL). Drying over anhydrous Na_2SO_4 and evaporation of the solvent yielded the β-lactam (145 mg, 83%).

Reference: Sharma, S. D.; Anand, R. D.; Kaur, G. *Synth. Commun*. **2004**, *34*, 1855–1862.

2.3.1.3 Acid Chloride Formation by Thionyl Chloride

Thionyl chloride costs less and liberates less gas than oxalyl chloride.

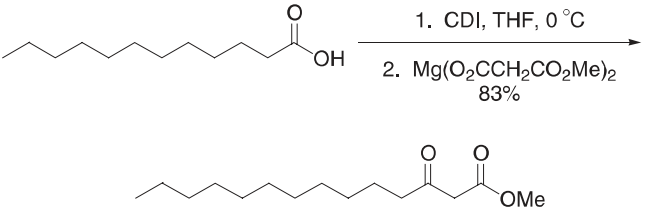


Thionyl chloride (10.4 g, 87.4 mmol) was added to a mixture of biphenyl-2-carboxylic acid (15.0 g, 75.7 mmol) and DMF (0.28 g, 3.83 mmol) in toluene (72 mL) at an internal temperature of 40 ºC. The mixture was stirred at this temperature for approximately 2 h. After completion of the reaction, the mixture was concentrated to dryness at 60 ºC. The resultant residue was then diluted with toluene (36 mL) and concentrated to dryness at 60 ºC, and the process was repeated again to give biphenyl-2-carbonyl chloride as an oil. Acetone (100 mL) was added to the oil, and 4-amino benzoic acid (10.4 g, 75.8 mmol) and *N*,*N*-dimethylaniline (10.1 g, 83.3 mmol) were added to the resultant solution at 25 ºC. The mixture was stirred at this temperature for approximately 2 h. Water (100 mL) was then poured into the mixture, and it was stirred at 25 ºC for more than 1 h. The resultant crystals were collected by filtration and dissolved in DMF (100 mL) at 25 ºC. The solution was then filtered to remove insoluble materials, water (100 mL) was poured into the filtrate, and it was stirred at 25 ºC for approximately 2 h. The resultant crystals were collected by filtration and dried at 40 ºC to give the amide as white crystals (22.7 g, 95%).

Reference: Tsunoda, T.; Yamazaki, A.; Mase, T.; Sakamoto, S. *Org. Process Res. Dev.* **2005**, *9*, 593–598.

2.3.1.4 Carbonyldiimidazole Activation

Acyl imidazolides can be used as activated acids; they are very frequently used to prepare β-keto esters from acids. It has recently been found that carbon dioxide dramatically increases the rate of reaction of the acyl imidazolide with an amine (see Vaidyanathan, R.; Kalthod, V. G.; Ngo, D. P.; Manley, J. M.; Lapekas, S. P.; *J. Org. Chem.* **2004**, *69*, 2565–2568).

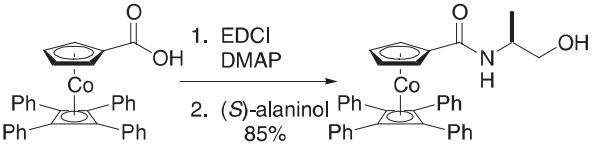


The carboxylic acid (13.8 g, 69 mmol, 1.0 equivalents) was dissolved in dry THF under an inert atmosphere and cooled to 0 ºC. CDI (13.4 g, 83 mmol, 1.2 equivalents) was then added in small portions over several minutes. After 10 min, the reaction was allowed to warm slowly to room temperature and was then stirred for 1 h. In a separate flask, monomethyl malonate (9.8g, 83 mmol, 1.2 equivalents) was dissolved in THF under an inert atmosphere and cooled to −78 ºC. To this solution was added dibutylmagnesium (1.0 M in heptane, 0.6 equivalents). A white solid formed instantly on addition of the base. After 10 min, the reaction was warmed to room temperature and stirred for 1 h. The acylimidazole was then added by cannula to the flask containing the magnesium salt. The resulting slurry was stirred for 3 days. The reaction mixture was then concentrated on a rotary evaporator and the residue redissolved in EtOAc. The resulting solution was washed with 1.2 M HCl, saturated aqueous $NaHCO_3$, and brine. The organic phase was dried over sodium sulfate, filtered, concentrated, and the residue purified by flash chromatography (7:1 hexanes:EtOAc) to give the β-keto ester (14.7g, 83%).

Reference: Durham, T. B.; Miller, M. J. *J. Org. Chem.* **2003**, *68*, 27–34.

2.3.1.5 EDCI Activation

1-Ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDCI), which is frequently used in amino acid couplings, is very mild and results in minimal epimerization. EDCI is shown here as representative of all carbodiimide coupling reagents. The advantage of EDCI is that the urea by-product can be extracted into an aqueous acidic layer, whereas many times complete removal of the urea from the final product can be problematic.

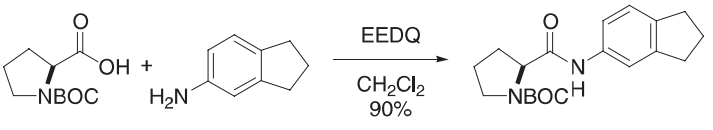


To a solution of the acid (2.00 g, 3.81 mmol) in CH_2Cl_2 (30 mL) under a nitrogen atmosphere were added EDCI (0.880 g, 4.59 mmol), *N,N*-dimethylaminopyridine (DMAP 558 mg, 4.57 mmol), and a solution of (*S*)-alaninol (0.343 g, 4.57 mmol) in CH_2Cl_2 (20 mL), and the resulting mixture stirred for 48 h at room temperature. The reaction was quenched by the addition of 10% aqueous citric acid (20 mL), followed by stirring for 5 min. The mixture was then partitioned and the orange organic fraction dried (Na_2SO_4) and evaporated in vacuo to afford a solid, which was purified by column chromatography (EtOAc) to give the amide as an orange crystalline solid (1.88 g, 85%).

Reference: Prasad, R. S.; Anderson, C. E.; Richards, C. J.; Overman, L. E. *Organometallics* **2005**, *24*, 77–81.

2.3.1.6 EEDQ Activation

2-Ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) activates acids via a mixed anhydride and generates quinoline, ethanol, and carbon dioxide as by-products. As with EDCI, the by-product quinoline of the reaction can be extracted into an aqueous acidic medium.

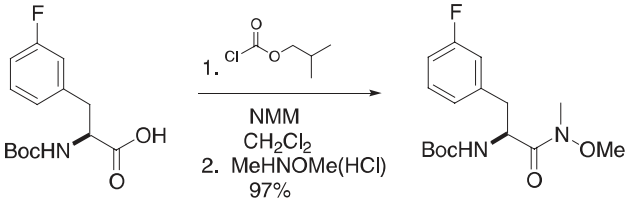


To a solution of *N*-BOC-*L*-proline (85 g, 0.40 mol) and EEDQ (100 g, 0.41 mol) in CH_2Cl_2 (200 mL) was added 5-aminoindan (54 g, 0.41 mol) at 0 ºC. The reaction mixture was stirred at 0 ºC for 2 h and then allowed to react overnight at room temperature. The reaction mixture was diluted with 100 mL of CH_2Cl_2 and washed with 1 M HCl (3 × 50 mL), saturated aqueous $NaHCO_3$ (2 × 50 mL), H_2O (50 mL), and brine (2 × 50 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated to give a viscous oil. The crude product was then redissolved in a 1:1 mixture of CH_2Cl_2/EtOAc. Cooling the mixture to –10 ºC afforded the amide (116 g, 90%) as an off-white crystalline solid.

Reference: Ling, F. H.; Lu, V.; Svec, F.; Frechet, J. M. J. *J. Org. Chem.* **2002**, *67*, 1993–2002.

2.3.1.7 Isobutylchloroformate Activation

The mixed anhydride formed by the reaction of a carboxylic acid with isobutyl chloroformate is frequently more stable than the corresponding acid chloride, so epimerization of an α-stereogenic center is minimized.

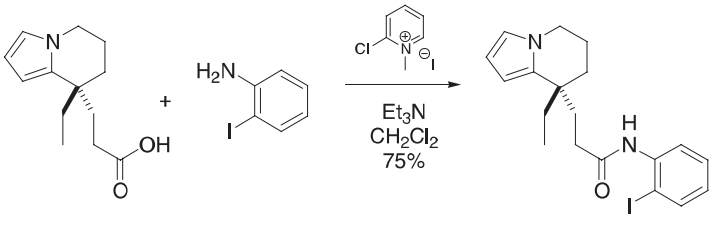


In a 1-L, four-neckedflask equipped with an addition funnel, a low temperature thermometer, an N_2 inlet, and a mechanical stirrer, *N*-BOC-(3-fluorophenyl)alanine (56.6 g, 0.2 mol) was dissolved in CH_2Cl_2 (300 mL). *N*-Methylmorpholine (23.05 mL, 0.2 mol) was added in a slow stream with a slight exotherm of 18–24 ºC. The solution was cooled to –25 ºC, and isobutyl chloroformate (25.27 mL, 0.2 mol) was added over 2–3 min while keeping the temperature between −25 and −20 ºC. A precipitate formed as the reaction mixture was stirred at −20 to −10 ºC for 1 h. In a separate flask, a slurry of *N*,*O*-dimethylhydroxylamine hydrochloride (21.45 g, 0.22 mol) in CH_2Cl_2 (200 mL) was treated with *N*-methylmorpholine (24.15 mL, 0.22 mol) at room temperature. The reaction remained a slurry throughout as *N*-methylmorpholine hydrochloride formed. After 1 h, the hydroxylamine suspension was added over 30 min to the mixed anhydride with the temperature rising to 5 ºC. The mixture was stirred at room temperature over the weekend. (The reaction was probably done on addition.) The reaction was quenched by the addition of a solution of citric acid (50 g) in water (200 mL). The organic layer was separated and washed with water, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated to an oil which was dried under high vacuum to remove residual solvents to provide the hydroxamate ester (61.7 g, 97%).

Reference: Urban, F. J.; Jasys, V. *J. Org. Process Res. Dev.* **2004**, *8*, 169–175.

2.3.1.8 Mukaiyama Esterification

A variety of alkyl pyridinium salts have been used in the Mukaiyama coupling; a representative example is shown below.

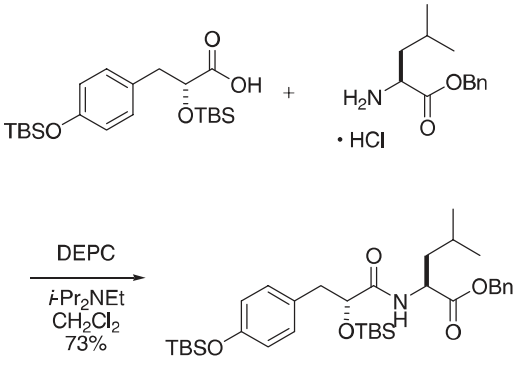


To a solution of the acid (300 mg, 1.1 mmol) in CH_2Cl_2 (5 mL) was added 2-chloro-1-methyl-pyridinium iodide (the Mukaiyama reagent, 330 mg, 1.3 mmol) and the aniline (1.29 g, 5.89 mmol). The mixture was heated at reflux for 1 h and then allowed to cool. Et_3N (0.30 mL, 2.2 mmol) was added, and the mixture was heated at reflux for an additional 20 h, allowed to cool, poured into water (40 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried, filtered, and concentrated. The crude material was purified by column chromatography (25% EtOAc in hexanes) to furnish the amide (387 mg, 75%).

Reference: Bowie, Jr., A. L.; Hughes, C. C.; Trauner, D. *Org. Lett*. **2005**, *7*, 5207–5209.

2.3.1.9 Yamada Coupling

Yamada's coupling reagent (diethylcyanophosphonate, DEPC) is representative of phosphorous based activators, including diphenylphosphoryl azide.

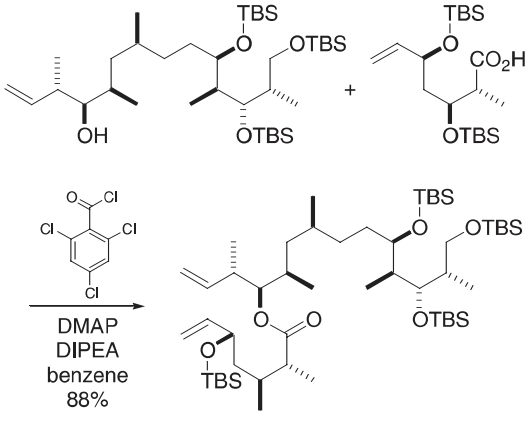


A solution of the acid (168 mg, 0.371 mmol) in CH_2Cl_2 (5 mL) was treated with *i*-Pr_2NEt (400 μL, 2.30 mmol), cooled to −30 ºC, and then DEPC (100 μL, 0.659 mmol) was added. The reaction was warmed to −20 ºC over a 20-min period, a solution of $HCl{\cdot}NH_2$-*L*-Leu-OBn (282 mg, 1.09 mmol) in CH_2Cl_2 (1 mL) was added and stirring was continued for another 2 h. The solution was partitioned between Et_2O and 10% HCl, and the organic layer was washed with 2 N NaOH, water, dried ($MgSO_4$), filtered, and concentrated. Chromatography on SiO_2 (hexanes/EtOAc, 9:1) provided the amide (178 mg, 73%).

Reference: Wipf, P.; Methot, J.-L. *Org. Lett*. **2000**, *2*, 4213–4216.

2.3.1.10 Yamaguchi Esterification

The Yamaguchi esterification (activation of an acid with trichlorobenzoyl chloride) is typically used to make macrolides, indicating its reliability. Unfortunately, these examples are typically done on very small scale, so a different example is shown.



To a stirred solution of the acid (100 mg, 248 μmol) in benzene (2.5 mL) were added *i*-Pr_2NEt (99.8 μL, 573 μmol), $Cl_3C_6H_2COCl$ (85.6 μL, 548 μmol), and DMAP (151 mg, 1.24 mmol). The alcohol (32.1 mg, 124 μmol) was then added in benzene (1.5 mL). The resulting mixture was diluted with benzene (1.5 mL) and stirring continued for 20 h. Benzene (50 mL) and saturated aqueous $NaHCO_3$ (50 mL) were added. The layers

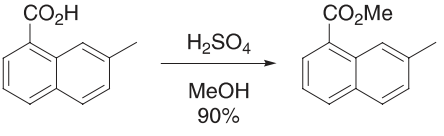
were separated, and the aqueous layer extracted with benzene (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated in vacuo. Flash chromatography (hexane/EtOAc 30:1) yielded the ester (68.0 mg, 85%) as an oil.

Reference: Kangani, C. O.; Brückner, A. M.; Curran, D. P. *Org. Lett.* **2005**, *7*, 379–382.

2.3.2 Acid Reaction Without Prior Activation

2.3.2.1 Fischer Esterification

The Fischer esterification is one of the oldest and most reliable methods of converting an acid to an ester. The reaction requires acid catalysis, elevated temperatures, and frequently the removal of the water by-product. As long as the remainder of the starting acid can withstand these requirements, the Fischer esterification deserves consideration.

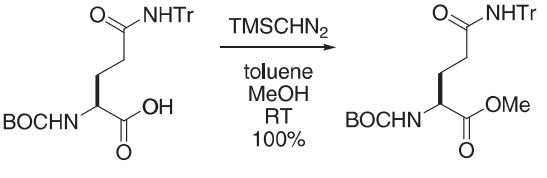


To methanol (80 mL) cooled to 0 ºC (ice/water) was added dropwise concentrated H_2SO_4 (25 mL). To the resulting clear solution was added immediately the carboxylic acid (21 g, 112 mmol), and the mixture was refluxed for 3 h, at which time TLC indicated the reaction to be complete. The resulting yellowish emulsion was cooled to room temperature, and the solvent was evaporated as much as possible. The residue was partitioned between CH_2Cl_2 and water. The collected organic layer was washed with saturated $NaHCO_3$ (aqueous), collected, dried (Na_2SO_4), and decanted. The solvent was concentrated and the resulting brownish oil was subjected to Kugelrohr distillation to afford the ester (20 g, 90%) as a yellowish oil.

Reference: Kolotuchin, S. V.; Meyers, A. I. *J. Org. Chem.* **1999**, *64*, 7921–7928.

2.3.2.2 TMSCHN$_2$ Esterification

Trimethylsilyldiazomethane is a commercially available equivalent to diazomethane. It reliably converts an acid to the methyl ester. Methanol is an essential co-solvent for this esterification.



To a solution of BOC-Gln(Trt)-OH (10.1 g, 20.8 mmol) in toluene:methanol (7:1, 300 mL) was added a solution of $TMSCHN_2$ (12.5 mL, 2.0 M). The mixture was allowed to stir at room temperature until the evolution of N_2 ceased (approximately 6 h). The solvents were removed in vacuo to provide BOC-Gln(Trt)-OMe (10.4 g, 100%).

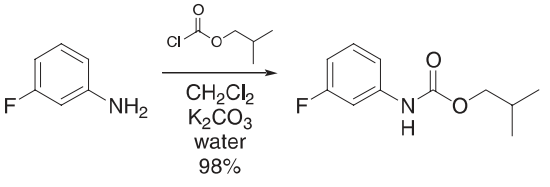
Reference: Brewer, M.; James, C. A.; Rich, D. H. *Org. Lett.* **2004**, *6*, 4779–4782.

2.3.3 Acid Chloride

See also the above section about the reaction of acids, as acid chlorides are frequently not isolated but used immediately after formation.

2.3.3.1 Schotten–Baumann Reaction

The Schotten–Baumann reaction is one of the most effective methods of converting acid chlorides to amides or chloroformates to carbamates. The workup typically involves separating the phases, drying the organic layer, and concentrating.



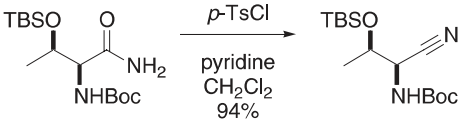
To a solution of 3-fluoroaniline (50.0 g, 450 mmol) in CH_2Cl_2 (200 mL) was added a solution of potassium carbonate (46.9 g, 339 mmol) in water (200 mL) at room temperature. The mixture was warmed to 32 ºC, and isobutyl chloroformate (66.2 g, 485 mmol) was added over 13 min while maintaining the temperature at 30–35 ºC. The mixture was stirred at 30–35 ºC for 2.5 h until complete by GC analysis. Aqueous ammonia (29.3 wt%, 7.2 mL, 111 mmol) was added and the mixture stirred at 30–35 ºC for 15 min. The mixture was cooled to 25 ºC and the pH adjusted from 8.7 to 1.9 with concentrated hydrochloric acid. The phases were separated, and the aqueous layer was washed with CH_2Cl_2 (100 mL). The combined organics were washed with water (200 mL), and the water was back-extracted with CH_2Cl_2 (100 mL). Typically, the crude product was carried into the next step but, if desired, crystallization at this point from heptane at –30 ºC afforded the amide (93.1 g, 98.1%).

Reference: Herrinton, P. M.; Owen, C. E.; Gage, J. R. *Org. Process Res. Dev.* **2001,** *5*, 80–83.

2.3.4 Amide

2.3.4.1 Dehydration to Nitrile

A variety of dehydrating agents can be used, including P_2O_5, TCCA, and tosyl chloride.



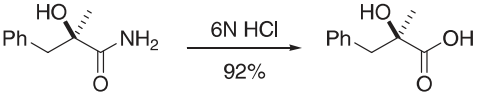
To a solution of the amide (1.15 g, 3.6 mmol) and *para*-toluenesulfonyl chloride (1.91 g, 7.2 mmol) in CH_2Cl_2 (9 mL) was added pyridine (1.46 mL, 18 mmol). After complete reaction, as judged by TLC, saturated aqueous $NaHCO_3$ was carefully added.

The resultant two-phase mixture was stirred vigorously for 2 h before the layers were separated and the organic phase was washed with 1 M aqueous HCl and then another portion of saturated aqueous $NaHCO_3$. The aqueous phases were back-extracted with CH_2Cl_2 and the combined organic phases were dried, filtered, and concentrated to leave a crude product. This crude product was purified by column chromatography to provide the nitrile (1.02g, 94%).

Reference: McLaughlin, M.; Mohareb, R. M.; Rapoport, H. *J. Org. Chem*. **2003**, *68*, 50–54.

2.3.4.2 Hydrolysis to Acid

Amides are much more robust than esters but can be hydrolyzed under vigorous conditions.



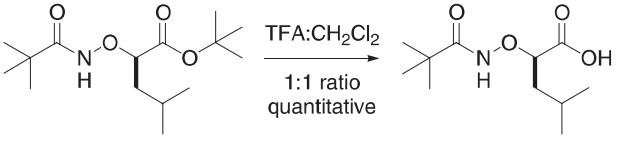
R-(+)-2-Methyl-2-hydroxy-3-phenylpropionamide (179 mg, 1 mmol) was refluxed in hydrochloric acid (6 *N*, 29 ml) for 3 h to give, after extraction with EtOAc and column chromatography using a silica gel column with a mixture of petroleum ether and EtOAc (1:2) as an eluent, *R*-(+)-2-methyl-2-hydroxy-3-phenylpropionic acid as a white solid (166 mg, 92%).

Reference: Wang, M.-X.; Deng, G.; Wang, D.-X.; Zheng Q.-Y. *J. Org. Chem*. **2005**, *70*, 2439–2444.

2.3.5 Ester Hydrolysis

2.3.5.1 Acid Promoted

An acid promoted hydrolysis is usually slower than a similar base promoted hydrolysis. In some cases, as with a *t*-butyl ester, however, acid catalyzed hydrolyses are preferred. With the *t*-butyl ester, sometimes a reducing agent such as formic acid or triethylsilane is added to scavenge the carbocation.

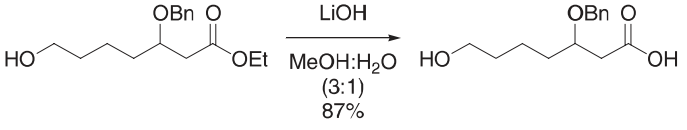


To the solution of the ester (950 mg, 3.31 mmol) in CH_2Cl_2 (10 mL) was carefully added an equal volume of CF_3CO_2H (10 mL) through a syringe at room temperature. After being stirred at room temperature for 3 h, the reaction mixture was concentrated in vacuo. The residue was azeotroped with toluene twice to give the acid in a quantitative yield.

Reference: Yang, D.; Qu, J.; Li, W.; Wang, D.-P.; Ren, Y.; Wu Y.-D. *J. Am. Chem. Soc*. **2003**, *125*, 14452–14457.

2.3.5.2 Base Promoted

Saponification of an ester with base is rapid and reliable. Lithium, sodium, and potassium hydroxide can be used.



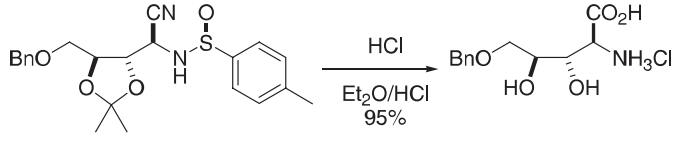
To a cooled (0 ºC) solution of the ester (2.33 g, 8.31 mmol) in 32 mL of MeOH/H_2O (3:1 v/v) was added LiOH·H_2O (0.891 g of hydrate, 56% LiOH, 11.9 mmol of LiOH), and then the solution was warmed to ambient temperature. After 4 h, the reaction mixture was acidified to below pH 2 using 40 mL of 1.0 M HCl; 50 mL of EtOAc and 25 mL of brine were then added to facilitate separation of the layers. The aqueous portion was extracted with 10 mL of EtOAc and the combined organic extracts were washed with 50 mL of brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to afford the acid as a colorless oil (1.825 g, 87%).

Reference: Chamberland S.; Woerpel, K. A. *Org. Lett*. **2004**, *6*, 4739–4741.

2.3.6 Nitrile

2.3.6.1 Acid Promoted Hydrolysis to Acid

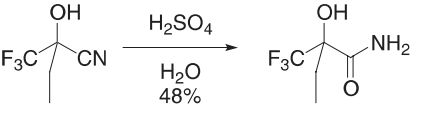
Nitrile hydrolysis to amide is relatively facile; subsequent hydrolysis to the acid requires somewhat more forcing conditions.



In a 25-mL, single-necked, round-bottomed flask equipped with a magnetic stirring bar was placed 0.21 g (0.5 mmol) of the nitrile. Saturated ethereal HCl (20 mL) was added with vigorous stirring, which resulted in the immediate formation of white precipitate. A few drops of H_2O were added, and the reaction mixture was stirred at room temperature for 12 h. At this time the solution was diluted with ether (25 mL), and the precipitated hydrochloride was filtered and dried under vacuum to give the acid as a white solid (0.12g, 95%).

Reference: Davis, F. A.; Prasad, K. R.; Carroll, P. J. *J. Org. Chem.* **2002**, *67*, 7802–7806.

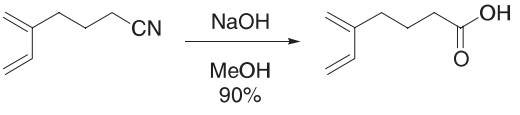
2.3.6.2 *Acid Promoted Hydrolysis to Amide*



2-Hydroxy-2-(trifluoromethyl)butanenitrile (8 g, 52 mmol) was added slowly dropwise to concentrated H_2SO_4 (15.3 g). The mixture was heated to 115 ºC for 15 min, cooled to 8 ºC and 22 g of water added. Diethyl ether (50 mL) was then added, and the organic phase was washed with water (25.0 mL), saturated aqueous $NaHCO_3$ (25.0 mL), and again with water (25.0 mL). The diethyl ether phase was dried over Na_2SO_4, filtered, and evaporated. The resulting oil was treated with *n*-hexane, and the resulting amide (4.27 g, 48%) was collected by filtration.

Reference: Shaw, N. M.; Naughton, A. B. *Tetrahedron* **2004**, *60*, 747–752.

2.3.6.3 Base Promoted Hydrolysis to Acid

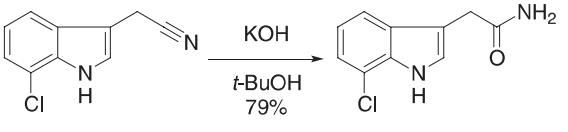


A solution of 5-methylene-6-heptenenitrile (2.0 g, 16.5 mmol) in 25% NaOH (95 mL) and MeOH (300 mL) was heated to reflux for 48 h. The solution was cooled, concentrated to half its original volume, and acidified with concentrated HCl to pH 1. The mixture was extracted with Et_2O (2 × 30 mL), the combined extracts dried ($MgSO_4$), and concentrated in vacuo to afford 2.10 g (90%) of 5-methylene-6-heptenoic acid as a pale yellow oil.

Reference: Sparks, S. M.; Chow, C. P.; Zhu, L.; Shea K. J. *J. Org. Chem.* **2004**, *69*, 3025–3035.

2.3.6.4 Base Promoted Hydrolysis to Amide

The base promoted conversion of nitrile to amide is sometimes catalyzed by addition of hydrogen peroxide. Because of safety concerns with peroxides, a procedure without this additive has been selected.



A solution of the nitrile (2.77 g, 14.5 mmol) and powdered 85% KOH (7.66 g, 116 mmol) in *t*-butyl alcohol (30 mL) was heated at reflux for 1.5 h. The reaction mixture was then cooled to room temperature, diluted with water (30 mL), and acidified with 1 N HCl (116 mL, 116 mmol) to give a slurry that was filtered and rinsed with water and then Et_2O (40 mL). The solid was dried in a vacuum oven at 40 ºC to give 2.39 g (79%) of the amide.

Reference: Faul, M. M.; Winneroski, L. L.; Krumrich, C. A. *J. Org. Chem.* **1999**, *64*, 2465–2470.