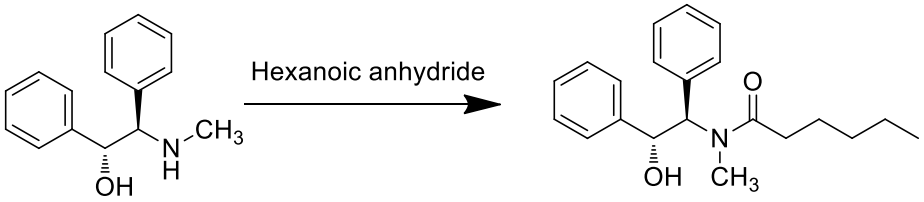
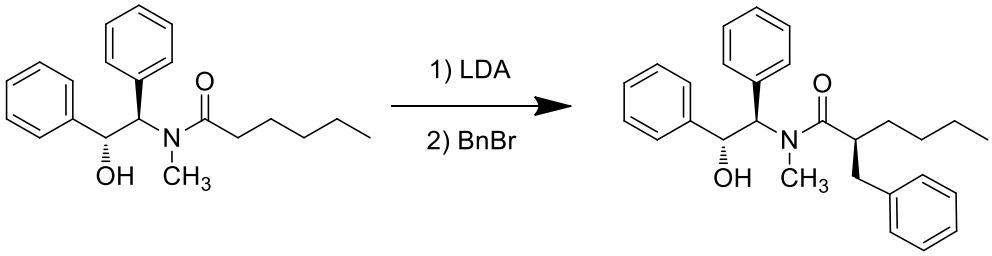
# CHEM 135: EXPERIMENTAL SYNTHETIC CHEMISTRY
# SPRING 2015

## EXPERIMENT 3:
WEEKS 9-11
(3/24/2015 – 4/11/2015)

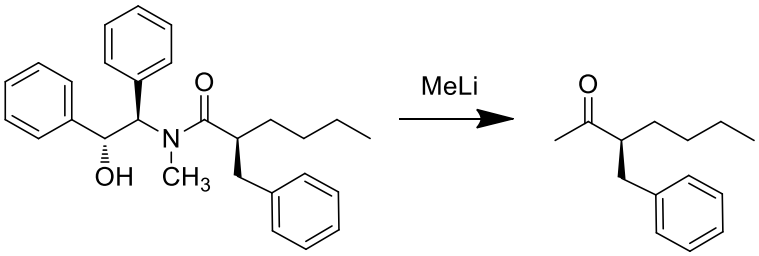
### *(1) SYNTHESIS OF AMIDE DERIVATIVES OF PSEUDOEPHENAMINE*



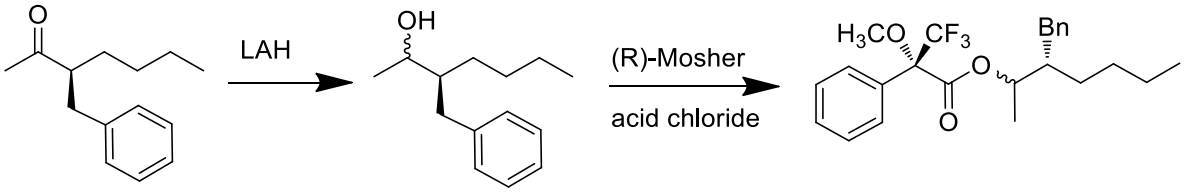

### *(2) DIASTEREOSELECTIVE ALKYLATION OF PSEUDOEPHENAMINE AMIDE*




### *(3) KETONE SYNTHESIS FROM ALKYLATED PSEUDOEPHENAMINE AMIDE*




### *(4) MOSHER ESTER ANALYSIS*



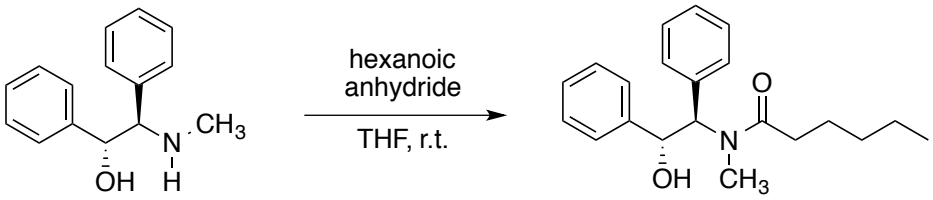

Morales, M.R.; Mellem, K.T.; Myers, A.G. *Angew. Chem. Int. Ed.* **2012**, *51*, 4568-4571.

NOTE: While working in the lab you are required to wear lab coats and safety glasses at all times! Furthermore, you will have to complete a short online safety quiz before starting an experiment. The teaching staff will evaluate your answers and based on your result you will either receive permission to start your experiment or you will have to go back and consult the instructions again.

*developed by Eugene E. Kwan and Andreas Roetheli*

# SYNTHESIS OF AMIDE DERIVATIVES OF PSEUDOEPHENAMINE

*Reaction scheme*




*Procedure*

Reaction: ca. 2 h

Hexanoic anhydride (1.73 mL, 7.50 mmol, 1.07 eq.) was added to a solution of (1*R*,2*R*)-pseudoephenamine (1.59 g, 7.00 mmol, 1.00 eq.) in anhydrous tetrahydrofuran (15 mL) under nitrogen. The reaction mixture was stirred for 1.5 h at room temperature. The reaction was monitored by TLC (60% ethyl acetate/hexanes).

Work-up: ca. 1 h

Excess hexanoic anhydride was quenched by the addition of saturated aqueous sodium bicarbonate solution (9 mL). The resulting biphasic mixture was then partitioned between ethyl acetate (45 mL) and water (32 mL), and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 x 40 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. This material can be stored in the fridge overnight.

Recryst.: ca. 1 h

The mixture was recrystallized from a solution of 8:1 hexanes/dichloromethane at 70 ºC. The system was allowed to cool undisturbed to room temperature over two hours or over night, during which pure hexanamide precipitated as a white solid (mp = 88–90 ºC).

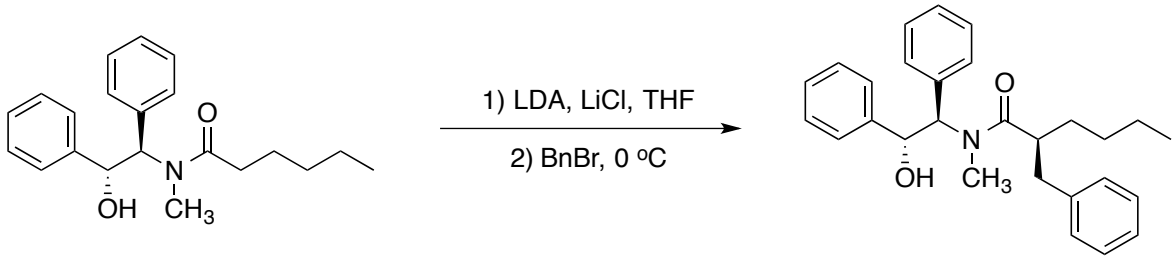
*Safety Remarks & Tips*

• Perform the recrystallization inside a fume hood. Heating can be performed with a heating block or a heat gun. If a heat gun is used, keep all other combustible materials clear. If solvent vapors contact the heating element, there is a significant fire hazard. For more details, please see: http://web.princeton.edu/sites/ehs/labsafetymanual/HeatGunAdvisory.htm

• The recrystallization process can be left to proceed in the fume hood overnight.

# DIASTEREOSELECTIVE ALKYLATION OF PSEUDOEPHENAMINE AMIDE

*Reaction scheme*




*Procedure*

Reaction:
ca. 4 h

*Have the stir bar stirring while you flame dry.*

*You will need to titrate the* n-*BuLi prior to the beginning the experiment, and calculate the volume to be added.*

*Benzyl bromide is a strong lachrymator and skin irritant; it should never be handled outside of a fume hood.*

A 50 mL round-bottom flask was charged with a stir bar and lithium chloride (0.781 g, 18.9 mmol, 6.00 equiv), evacuated, flame dried, cooled to room temperature, and back-filled with nitrogen. The flask was evacuated and back-filled with $N_2$ two additional times. Anhydrous tetrahydrofuran (6.6 mL) was added by syringe, followed by *N*,*N*-diisopropylamine (0.97 mL, 6.95 mmol, 2.26 equiv). The resulting slurry was cooled to –78 ºC in a dry ice/acetone bath. A freshly titrated solution of *n*-butyllithium in hexanes (2.21 equiv) was added by syringe. The reaction mixture was warmed briefly to 0 ºC (5 min) before cooling to –78 ºC. An ice-cooled solution of amide (1.00 g, 3.07 mmol, 1 equiv) in anhydrous tetrahydrofuran (6 mL with 2 mL rinse) in a conical flask was added via cannula. The reaction mixture was stirred for 1 h at –78 ºC, for 15 min at 0 ºC, and for 5 min at 23 ºC, then was cooled to -78 ºC, whereupon benzyl bromide (0.55 mL, 4.61 mmol, 1.50 equiv) was added dropwise. The dry ice/acetone bath was replaced by an ice bath, and the reaction was monitored by TLC (40% ethyl acetate/hexanes), and should take ~1.5 hours.

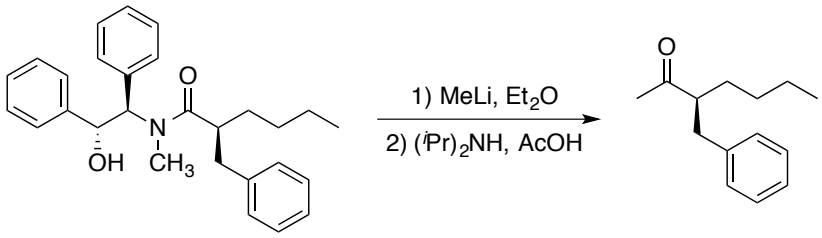
Work-up:
ca. 1 h

After the reaction was complete, saturated aqueous ammonium chloride solution (1 mL) was added to the ice-cold product mixture. The resulting biphasic mixture was partitioned between ethyl acetate (30 mL) and a 1:1 mixture of saturated aqueous sodium chloride and 1 N aqueous hydrochloric acid (total volume: 33 mL). The layers were separated. The aqueous layer was extracted with two 20 mL portions of ethyl acetate. The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. This crude material may be stored in the fridge overnight.

| | |
|---|---|
| Recrystallization: ca. 2 h | The mixture was recrystallized from ~10 mL of hot 20% ethyl acetate/hexanes to yield the desired hexanamide as a white solid (mp = 112–114 ºC). If desired, a second crop of crystals may be obtained. |
| *Safety Remarks & Tips* | • Your TF will instruct you in the proper method of titration for *n*-BuLi. Do not perform this experiment without titrating this reagent!<br>• It is advisable to keep samples of the starting material for TLC comparisons. |

# *KETONE SYNTHESIS FROM ALKYLATED PSEUDOEPHENAMINE AMIDE*

*Reaction scheme*




*Procedure*

Reaction: ca. 1 h

*You will need to titrate the MeLi and calculate the appropriate volume.*

A 50 mL round-bottom flask containing a stir bar was flame dried, placed under nitrogen, then charged with the amide (432 mg, 1.04 mmol, 1 equiv), flushed with nitrogen, and dry diethyl ether (11 mL) was added. The flask was cooled to –78 ºC in a dry ice/acetone bath. A freshly titrated solution of methyllithium in diethyl ether (3.00 equiv) was added by syringe, and the mixture was stirred for 30 min at 0 ºC and for 10 min at 23 ºC.

Work-up: ca. 2 h

*Addition of acetic acid is highly exothermic.*

*Test the pH of both the organic and aqueous layers to ensure pH 4.*

Excess methyllithium was quenched at 0 ºC by the addition of *N*,*N*-diisopropylamine (0.146 mL, 1.04 mmol, 1 equiv). After 15 min, a solution of acetic acid in ether (10% v/v, 22 mL) was *slowly* added to reach pH 4. The mixture was partitioned between ethyl acetate (80 mL) and water (100 mL). The layers were separated. The organic layer was washed sequentially with saturated aqueous sodium bicarbonate (50 mL), water (50 mL), and brine (50 mL). The washed organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The aqueous layer from the first separation was cooled to 0 °C, basified with 1.0 *M* NaOH to pH 14, then extracted with dichloromethane (3 × 50 mL); the combined DCM extracts were washed with brine (100 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo* to recover the pseudoephenamine auxiliary.

Purification: ca. 4 h

The product residue was purified by flash column chromatography (gradient elution: 1-5% ethyl acetate/hexanes) to afford the desired ketone as a colorless oil. Note: if your product looks easily separable by TLC, consult your TF, and a silica plug may be sufficient purification.

*Safety Remarks & Tips*

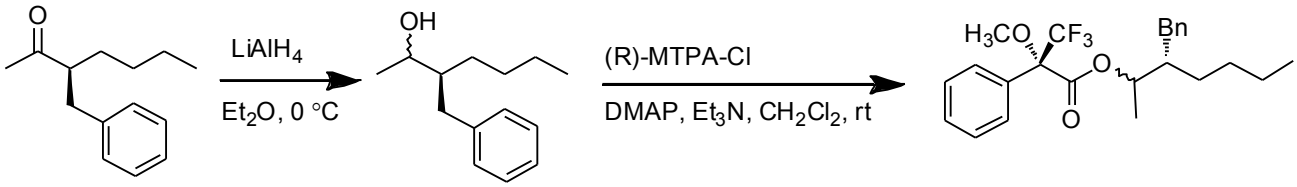
- Methyllithium is pyrophoric. Quench residual methyllithium with dichloromethane/acetone.
- Diethyl ether vapors are highly flammable and heavier than air.

# *MOSHER ESTER ANALYSIS*

*Introduction*

This part of the procedure verifies that the ketone has been formed in high enantiomeric purity. Unselective hydride reduction of the ketone could, in principle, afford four possible stereoisomers. Two correspond to the two alcohol epimers derived from the desired S alkylation product; the other two correspond to the R. Derivatization with Mosher's reagent converts the enantiomeric relationship between the pairs of diasteromers into a diasteromeric one. This is necessary because enantiomers are indistinguishable by NMR.

*Reaction scheme*




*Procedure*

Reaction:
ca. 1 h

*LAH reacts violently with water! Weigh it out in a glass vial.*

Solid lithium aluminum hydride ("LAH," 30 mg, 0.75 mmol, 1.50 equiv) was added to a solution of ketone (102 mg, 0.5 mmol, 1 equiv) in diethyl ether (2.5 mL) under nitrogen at 0 ºC, and the reaction was stirred for 30 min.

Work-up:
ca. 2 h

*These volumes are important, and should be accurately measured with a 100 µL syringe.*

Excess hydride was quenched by sequential, dropwise addition of water (30 µL), 2 N aqueous sodium hydroxide solution (60 µL), and water (90 µL). Saturated aqueous sodium chloride (3 mL) was added to the slurry. The layers were separated. The aqueous layer was extracted with two 10 mL portions of diethyl ether. The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford the desired mixture of alcohols.

Mosher Ester:
ca. 1 h

*Follow the reaction by TLC.*

The mixture of diastereomeric alcohols (10.0 mg, 0.048 mmol, 1 equiv) was exposed to (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (27.1 µL, 0.145 mmol, 3.00 equiv) in the presence of 4-(dimethylamino)-pyridine ("DMAP," 29.6 mg, 0.242 mmol, 5.00 equiv) and triethylamine (34.0 µL, 0.242 mmol, 5.00 equiv) in dichloromethane (1.5 mL) at 23 ºC. The reaction was allowed to proceed overnight (but only requires an hour or so). TLC (10% ethyl acetate/hexanes) confirmed complete consumption of starting material. The mixture was concentrated. $^{1}$H and $^{19}$F NMR analysis of the crude Mosher esters established the %de.

*What to Hand In* Please hand in a typed report that contains:

(1) A copy of all relevant lab notebook pages, including drawings of TLC plates and calculations of relevant $R_f$ values.

(2) A written experimental procedure for the N-acylation reaction in *JOC* format.

(3) For the acylated product: $^{1}H$ and $^{13}C$ NMR spectra and data in ACS format, with all peaks assigned and *J* values calculated when possible.

(4) A written experimental procedure for the alkylation reaction in *JOC* format.

(5) For the alkylated product: $^{1}H$ and $^{13}C$ NMR spectra and data in ACS format, with all peaks assigned and *J* values calculated when possible; and an ESI mass spectrum.

(6) A written experimental procedure for the ketone formation in *JOC* format, including the %ee determined from the Mosher ester analysis.

(7) For the ketone product: $^{1}H$, $^{13}C$ NMR, and IR spectra and data in ACS format, with all peaks assigned and *J* values calculated when possible; and an ESI mass spectrum. Additionally, provide a $^{1}H$ NMR spectrum of the recovered auxiliary.

(8) A written experimental procedure for the Mosher ester formation in *JOC* format.

(9) For the Mosher ester: $^{1}H$ and $^{19}F$ NMR spectra and data in ACS format, with all peaks assigned and *J* values calculated when possible. Annotate the spectra to show the peaks that allow you to determine the diastereomeric ratio.

(10) Answers to the following questions:

a. What affects the error in your %ee determination? How large is the error?

b. What is the relationship between the enantiomeric purity of the ketone and selectivity in the alkylation?

c. How could you determine the selectivity of the alkylation step independently?

d. What are the synthetic advantages and disadvantages of this alkylation method?

*Grading Scheme* total: 23% of course grade

*Laboratory Component*
- complete 1st attempt (+3)
- complete 2nd attempt (+1)
- obtain >1.1 g acylated auxiliary (+1)
- obtain >700 mg benzylated product (+2)
- obtain >115 mg methyl ketone (+3)
- perform a successful Mosher ester derivatization (+1)

*Written Component*
- lab notebook (+2)
- experimental procedures (+2)
- characterization data (+4)
- lab questions (+2)
- lab stewardship (+2)

*Acknowledgements:* This lab was developed in cooperation with Dr. Kevin Mellem, Professor Andrew Myers and Dr. Meiling Li.