Breaking Amide C–N Bonds in an Undergraduate Organic Chemistry Laboratory

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Materials and Methods

Unless stated otherwise, all commercially obtained reagents were used as received. Wax capsules containing $Ni(cod)_2$ and SIPr were purchased from TCI America (Product #: B5418). Benzoyl chloride (**SI-1**, CAS: 98-88-4) and *N*-methylaniline (**SI-2**, CAS: 100-61-8) were obtained from TCI America. Triethylamine (CAS: 121-44-8) and dichloromethane (CAS: 75-09-2) were passed through activated alumina columns prior to use. Menthol (ReagentPlus, 99%, CAS: 2216-51-5) was obtained from Sigma Aldrich. Toluene (ACS, 99.5%, CAS: 108-88-3) was purchased from Alfa Aesar. Thin-layer chromatography (TLC) was conducted with J.T. Baker Baker-flex Silica Gel IB2-F pre-coated plates (0.25 mm) and visualized using UV detection. Silicycle Siliaflash P60 (particle size 0.040–0.063 mm) was used for flash column chromatography. ^{1}H NMR spectra were recorded on a Bruker spectrometer (at 400 MHz) and are reported relative to deuterated solvent signals (7.26 ppm for $CDCl_3$). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration.

Should the cost of purchasing wax capsules from TCI be prohibitive, instructors may consider generating the capsules themselves according to the previously published procedure, available *here*:[1]

https://pubsdc3.acs.org/doi/suppl/10.1021/acs.orglett.6b01758/suppl_file/ol6b01758_si_001.pdf.

[1] Dander, J. E.; Weires, N. A.; Garg, N. K. *Org. Lett.* **2016**, *18*, 3934–3936.

Equipment and Supplies

Reaction Set-up

Wax capsules containing $Ni(cod)_2$ and SIPr
Toluene
Amide substrate (synthesized according to the procedure outlined on page S4)
Starting Materials: Benzoylchloride, *N*-methylaniline, NEt_3, Dichloromethane
(–)-Menthol
Wax weighing paper
Spatulas
(VWR) Borosilicate glass vials, 1-dram, 15 x 45 mm
Magnetic stirring bars for 1-dram vials
Solid green Melamine caps with PTFE liner (size 13-425)
Septa caps for 1-dram vials
Heavy Duty Teflon Tape
Compressed N_2 gas
Stirring hotplates
Aluminum heating block (alternatively, oil bath can be used)

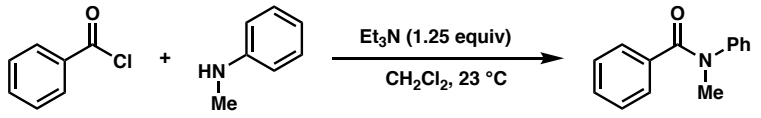
Work-up and Purification

Rotary evaporator(s)
Pasteur pipettes and pipette bulbs
Celite
Ethyl acetate
Hexanes
Dichloromethane
1.5 x 30 cm glass flash chromatography columns (1 per student)
Adapter for air flow through column
Silica gel for column
Test tubes (13 x 100 mm)
Test tube rack (1 per student)
250 mL borosilicate glass round-bottom flasks (1 per student)
Parafilm M

Reaction Analysis

Copper Wire or thin spatula (TLC)
Acetone (TLC)
TLC spotters
TLC plates (5 per student)
TLC development chambers
Hotplates (TLC development)
UV-Vis lamps (TLC visualization)
N-methylaniline (TLC co-spotting)
NMR tubes (1 per student)
NMR caps (1 per student)
$CDCl_3$, 99.8% (CAS: 865-49-6); obtained from Cambridge Isotope Laboratories, Inc.

Synthesis of the Amide Substrate



SI-1 ***SI-2*** **(quantitative yield)** ***1***

A 250-mL round bottom flask equipped with a magnetic stir bar was flame-dried under reduced pressure and cooled under N_2. The flask was then charged with **SI-1** (3.0 g, 21.3 mmol, 1.0 equiv) and dichloromethane (40.0 mL). To the resulting solution was added dropwise a mixture of **SI-2** (2.54 mL, 23.5 mmol, 1.1 equiv) and triethylamine (3.72 mL, 26.7 mmol, 1.25 equiv) over 1 min. The reaction mixture was stirred at 23 °C for 19.5 h before being quenched with 1.0 M HCl (40 mL), diluted with dichloromethane (50 mL), and transferred to a separatory funnel. The layers were separated and the organic layer was filtered over a pad of silica gel (10 g) using 1:1 Hexanes:EtOAc (200 mL) as eluent. The volatiles were removed under reduced pressure and the resulting crude residue was purified by flash chromatography (10:1 Hexanes:EtOAc → 5:1 Hexanes:EtOAc) to yield amide **1** (4.49 g, quantitative yield) as a white solid. Spectral data match those previously reported.[1]

[1] Li, Y.; Jia, F.; Li, Z. *Chem. Eur. J.* **2013**, *19*, 82–86.

Student Handout

A. Objectives

In this lab, you will learn about two modern areas of research: the activation of amide C–N bonds and transition metal-catalyzed cross-coupling reactions. You will perform an esterification of an amide substrate using nickel catalysis (Figure 1). The catalyst is air-sensitive, but by using a wax-encapsulated catalyst system, the reaction can be performed in a straightforward manner. The experiment will involve reaction setup, TLC analysis, workup procedures, including chromatography, and spectroscopic analysis.

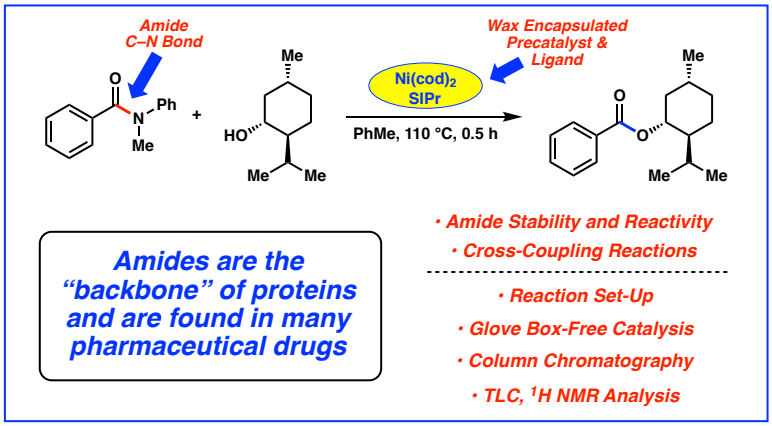


Figure 1. Catalytic activation of amide C–N bonds for the conversion of amides to esters described in this experiment.

Note: This experiment is derived from the protocols described by the Garg Laboratory at UCLA; see: Dander et al. *Org. Lett.* **2016**, *18*, 3934–3936 and Hie et al. *Nature* **2015**, *524*, 79–83.

B. Introduction

Amides in Biology and Synthetic Organic Chemistry

The amide is a common functional group studied in organic chemistry. Amides serve as the primary structural unit of proteins and other peptides and are also encountered in a variety of medicines. If you have studied amides (and we hope you have!), you likely learned that amides are pretty stable. This is because of a resonance effect (Figure 2), which leads to partial double bond character between the amide carbon and nitrogen atoms.[1]

Fun fact: Two-time Nobel Prize winner Linus Pauling took home the Nobel Prize in Chemistry in 1954, in part, for his understanding of this resonance effect. The understanding of amide bond geometry led to insight into protein structure and the model of the alpha helix.[1]

Because of the pronounced stability of the amide C–N bond, there are relatively few ways to manipulate amides in chemical synthesis. They are generally unreactive to acids and bases, redox processes, and common catalytic reactions. However, there are some common ways

chemists use to break amide bonds. Two examples, although beyond the scope of this class, are the conversion of so-called Weinreb amides to ketones[2] and the reduction of amides to aldehydes using the Schwartz reagent.[3]

One last example, which is more relevant to the laboratory experiment you will perform, is the conversion of amides to carboxylic acids or esters. Such reactions have modest synthetic utility because they typically require harshly basic or acidic reaction conditions, a large excess of a suitable nucleophile, high temperatures, or a combination thereof.[1a]

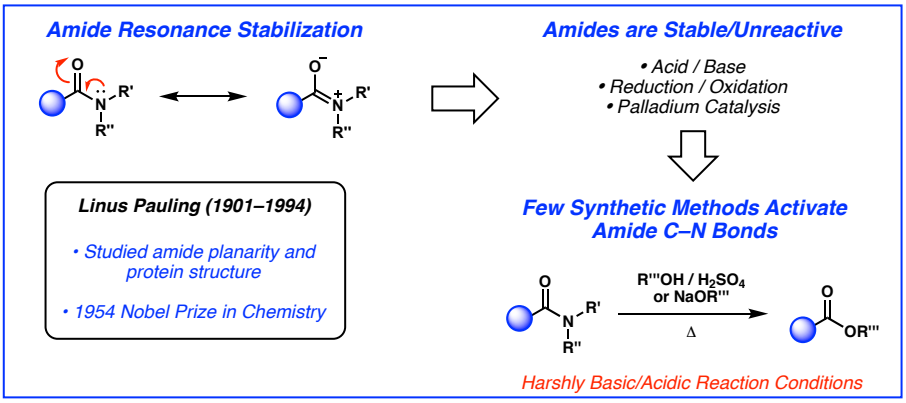


Figure 2. Amide C–N bond stability and synthetic limitations.

Cross-Coupling Reactions and Advances in Nickel Catalysis

One central aspect of scientific research is to question conventional ways of thinking. Many researchers have recently asked, "*The amide is known to be stable, but could one discover mild methods to break amide C–N bonds?"*

To answer this question, researchers turned to the field of catalysis and, specifically, to reactions known as transition metal-catalyzed cross-couplings.[4] Such reactions have allowed chemists to break traditionally 'inert' bonds (such as aryl halide C–X bonds and strong C–O bonds), while constructing new C–C or C–heteroatom bonds. Several key cross-coupling reactions are summarized in Figure 3. They typically require catalysts composed of palladium as the metal.[5]

Cross-coupling reactions are now widely used in academia and industry. In fact, their importance was recognized by the 2010 Nobel Prize in Chemistry.[5]

The last thing you need to know about cross-couplings (for now) is that nickel is the new palladium.[6] Nickel and palladium have similar electronic structures and often display comparable reactivity. However, palladium is not nearly as earth abundant and is considered a precious metal. Consequently, nickel is 3000x cheaper,[7] "greener",[8] and is also less toxic.[9] It also turns out that nickel is pretty reactive and has been shown to easily break bonds that are less reactive to palladium.[6,10]

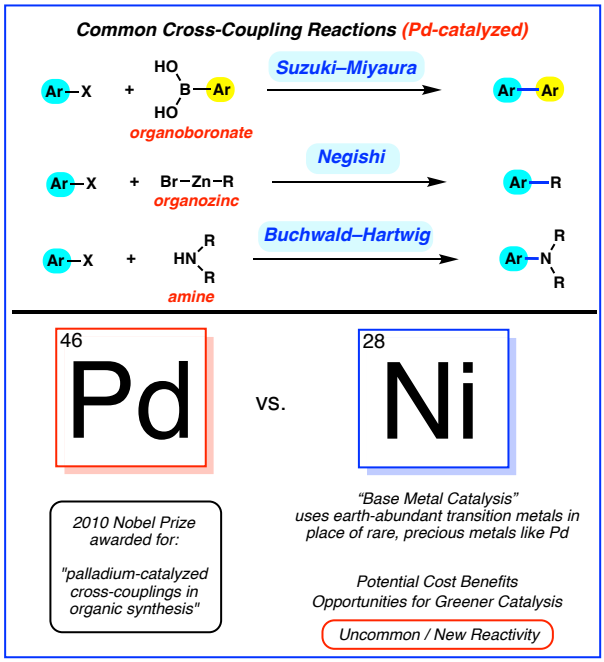


Figure 3. Pd and Ni comparisons and common cross-coupling reactions.

Nickel-Catalyzed Amide C–N Bond Activation

Let's add up what we have learned so far:

Amide C–N bonds are strong, but…
Cross-couplings are useful and lead to Noble Prizes
+ Nickel is good (low cost, reactive alternative to Pd)

= Break amide C–N bonds using Ni cross-couplings?

Using this logic, the Garg laboratory at UCLA discovered the conversion of amides to esters using nickel catalysis.[11] Figure 4 shows an example of this reaction, which is also the experiment you will perform in this laboratory. The amide is reacted with a suitable alcohol, in this case menthol, in the presence of $Ni(cod)_2$ and SIPr. $Ni(cod)_2$ is the precatalyst and SIPr is the ligand (see Figure 5 for their structures).

The presumed mechanism for the transformation you will perform is shown in Figure 4. Here is how it goes:

Step 1: Oxidative addition - the Ni(0) complex reacts with the amide to break the amide C–N bond and form a Ni(II) intermediate. *Hint: this is analogous to the formation of a Grignard reagent.*

Step 2: Ligand exchange – the alcohol displaces the amine from the Ni(II) complex.

Step 3: Reductive elimination – the C–O bond forms with regeneration of Ni(0), which can then re-enter the catalytic cycle.

As you will see from the post-lab questions, the cross-coupling of amides has greatly expanded since its initial discovery. In addition to C–O bonds, chemists have uncovered how to make new C–C and C–N bonds from amides using either nickel or palladium catalysis.[12] More than 50 publications describing the catalytic activation of amide C–N bonds have surfaced from researchers around the world since 2015.

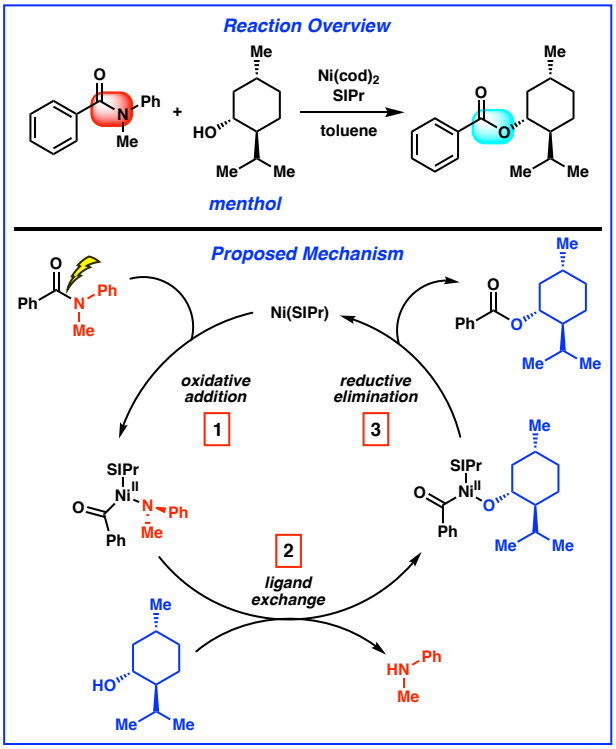


Figure 4. Overview of reaction and proposed catalytic cycle for the nickel-catalyzed esterification of amides performed in this laboratory experiment.

Making the Experiment More Practical

The methodology to break amides and make esters using nickel catalysis represents an important advance in synthetic chemistry. However, we have been hiding something important from you. The nickel precatalyst used, $Ni(cod)_2$, and the ligand, SIPr, are both unstable to oxygen and cannot be handled on the benchtop.[13] Instead, these chemicals must be handled in an inert atmosphere called a glovebox, which is cumbersome and not available in all research laboratories.

To combat this limitation, chemists have sought ways to handle sensitive chemicals on the benchtop. One solution is to encapsulate the necessary reagents in wax.[14] If you have ever

wondered how to encapsulate a reagent in wax, the process is summarized in Figure 5. Luckily, Tokyo Chemical Industry Co., Ltd. (TCI) has commercialized this process and sells the capsules you will need that contain the $Ni(cod)_2$ and SIPr.[15]

Once the wax capsule is sealed, the reagents are protected from air and moisture. Upon heating, the wax melts and the chemicals are released into your reaction.[13]

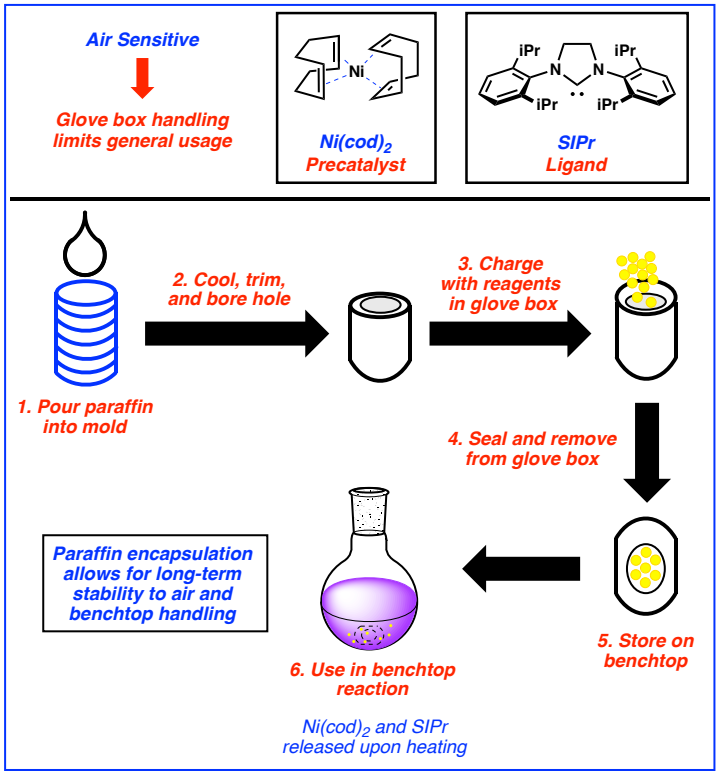


Figure 5. Structures of $Ni(cod)_2$ and SIPr and paraffin encapsulation procedure.

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[15] http://www.tcichemicals.com/en/us/product/professor-product-portal/Garg-research-group.html

C. Experimental Procedures & Record of Observations

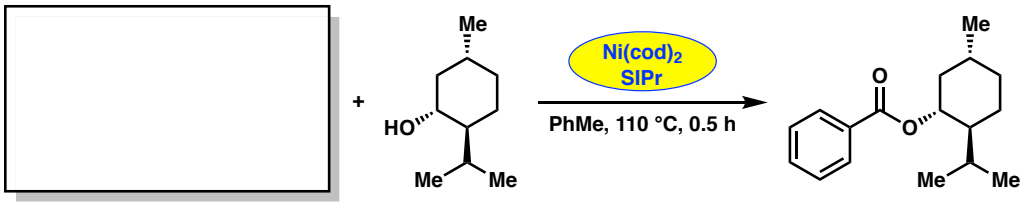
Safety Hazards and Considerations

Closed-toed shoes, long pants covering the ankles, safety glasses, gloves, and flame-resistant laboratory coats should be worn at all times. All hazardous materials should be handled and disposed of in accordance with the recommendation of the materials' safety data sheet and EH&S. The **amide substrate** and **menthol** are irritants. Detailed hazards for the **ester product** have not been described, therefore students should assume it is an irritant and should be handled with care. The **wax capsule** containing **Ni(cod)$_2$** and **SIPr** is an irritant, a flammable solid, and may cause cancer. **Toluene** is flammable, an irritant, and a reproductive toxin. ***N*-methylaniline** is flammable, an irritant, and an acute toxin. **Dichloromethane** is an acute toxin, an irritant, and a regulated carcinogen. **Ethyl acetate** and **hexanes** are flammable and volatile organic solvents. The ***n*-hexane** in hexanes is a neurotoxin and as such, all aspects of the experimental procedure that utilize hexanes must be performed in a ventilated chemical fume hood or using a rotary evaporator that is ventilated to a fume hood. **Deuterated chloroform** is a cancer suspect agent and mutagen. Hot plates should be used inside the fume hood and kept away from flammable solvents. The size of the reaction vessel, the volume of reaction media, and temperature of the heating block should be strictly adhered to in order to avoid pressure buildup in the reaction vessel.

Students will perform this experiment individually.

Reaction Scheme and Stoichiometry

Complete the following scheme and stoichiometry table before your lab period.



N*-methyl-*N*-phenylbenzamide** ***(–)-menthol ***L*-menthylbenzoate**

Reagent Name	MW (g/mol)	Mass	Density	Volume	mmol	equiv	Quality
N-methyl-*N*-phenylbenzamide		42.3 mg	N/A	N/A		1	N/A
(–)-menthol			N/A	N/A		1.2	N/A
Ni(cod)$_2$ - paraffin encapsulated	275.1	5.5 mg	N/A	N/A		0.1	N/A
SIPr - paraffin encapsulated	390.6	7.8 mg	N/A	N/A			N/A
Toluene (PhMe)	N/A	N/A	0.86 g/mL	200 μL	N/A	1.0 M	N/A
L-menthylbenzoate			N/A	N/A			N/A

Experimental Procedures: Day 1

Reaction Set-up

1. Place a dram-vial-sized aluminum block on a hotplate with the thermocouple submerged in oil or sand. Set the temperature to 110 °C and begin heating.
2. Separately, add a small magnetic stir bar to a one-dram vial (4 mL vial); this will serve as your reaction vessel.
3. To the vial, add the following: a) the amide starting material (42.2 mg); b) menthol (37.5 mg); c) one wax capsule containing $Ni(cod)_2$ and SIPr (see table for amounts); d) toluene (0.2 mL).
4. Fit the vial with a red septum cap. Place the vial securely into a test tube rack.
5. "Purge" the reaction vial with N_2 for five minutes *(your TAs will show you exactly how to do this)*. To purge, insert one needle as a N_2 inlet then add a second needle open to air. This creates a positive flow of N_2 through the vial that eventually replaces all air in the vial with N_2. Neither of the needles should come in contact with the solvent.
6. After five minutes, rapidly replace the red, open-top cap with a green Teflon-lined cap under a stream of N_2 and close the vial tightly. Seal the neck of the vial with Teflon tape, and place the vial in the preheated aluminum block. *The heating block should be kept at 110 °C in order to avoid excess pressure buildup in the reaction vessel.*

Record any observations (color changes, fuming, etc.):

Reaction Analysis by TLC

1. After 30 minutes of heating and stirring at 110 °C, carefully remove the reaction vial from the heat source with tweezers, and allow it to cool for 1 minute. (Take care not to overcool the sample, as the paraffin wax will solidify, and the mixture will require re-heating for TLC analysis.)
2. While your reaction is cooling, obtain another clean dram vial. Using a pipette, add 1–2 drop of acetone to the clean dram vial.
3. While the reaction is still warm, dip a thin spatula into the reaction, and immediately submerge the spatula tip in the acetone. Rapidly twirl the spatula to break up any wax

that solidifies. A small amount of product should dissolve in the acetone, allowing for reaction monitoring by TLC.

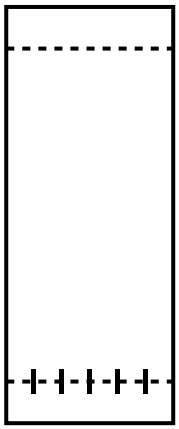
4. Fit the reaction vial with a green cap, and place it back in the aluminum block while you complete the rest of the TLC protocol.
5. Place 5 spots on your TLC plate as follows:

Left lane = amide substrate
Second from left lane = co-spot of amide substrate and reaction mixture
Middle lane = reaction mixture
Second from right lane = co-spot of N-*methylaniline and reaction mixture*
Right lane = N-*methylaniline*

Develop the TLC plate with 5:1 hexanes/ethyl acetate. Visualize the TLC plate using a UV lamp.

Record any observations (TLC results over time, color changes, etc.):

T = 30 min



Identify which spot presumably corresponds to your product.

Reaction Work-up

1. Add 1.0 g of Celite to a 250-mL round-bottom flask.
2. Carefully remove your vial from the aluminum block, and allow it to cool for 1 minute.
3. After 1 minute, pipet ~1 mL hexanes into the reaction vial. Immediately transfer everything in the reaction vial to the 250-mL round-bottom flask containing Celite.
4. Rinse the reaction vial with ~2 mL dichloromethane, and transfer it to the 250-mL round-bottom flask.
5. Rinse the reaction vial with ~2 mL hexanes, and transfer it to the 250-mL round-bottom flask.
6. Pipet ~ 5 mL hexanes into the 250-mL round-bottom flask. Rinse the sides of the round-bottom flask during this pipetting.

7. Pipet ~ 5 mL dichloromethane into the 250-mL round-bottom flask. Rinse the sides of the round-bottom flask during this pipetting.
8. ***Slowly*** remove the solvent using rotary evaporation (rotovap). Be sure to use a clean bump trap! Start at approximately 500 mbar and maintain a moderate rotation rate (5–6 setting), then slowly decrease the pressure by increments of ~50 mbar, holding for 2–3 minutes at each pressure to avoid bumping. Upon **complete** removal of solvent, rotovap at full strength for 10 minutes or until you have a fine powder.
9. Cap and parafilm the round-bottom flask; store underneath your hood until the next lab period.

Record any observations (any interesting appearances, colors, etc.):

Experimental Procedures: Day 2

Purification by Column Chromatography

1. Inspect your column and make sure that the column is dry, clean, and not broken or chipped. Otherwise, notify your TA.
2. *Caution: silica is a serious inhalation hazard and must be handled inside the hood at all times.* In a big Erlenmeyer flask, mix silica and hexanes. Swirl thoroughly to create a slurry of silica.
3. Start carefully pouring the slurry into the column (keep swirling the Erlenmeyer flask to stop the slurry from separating into layers). Touch the mouth of the column with the opening of the Erlenmeyer flask so that the slurry rolls gently down to the bottom.
4. Add more hexanes to the remaining silica in your Erlenmeyer flask. Swirl to create slurry. Add slurry to the column. Repeat this step until almost all the silica has been poured into the column.
5. Open the valve and drain solvent from the column into a large Erlenmeyer flask, until the solvent level drops to just below the silica (you may accelerate this step by pushing the solvent level down with air). Close the valve to stop the column. You should ideally end up with ~12–15 cm of silica gel.
6. Place a glass filter funnel on top of the column. Pour your product (i.e. the dry mixture of your product with Celite) through the funnel onto the top of the silica gel.
7. Use a spatula to scrape off any remaining product from the round-bottom flask and transfer it onto the silica gel.
8. Gently shake or pat the column from the side to make sure that the product/Celite mixture is packed evenly.

9. Add a layer of sand on top of the product/Celite mixture (this is to create a buffer that shields the silica from impact when you add the eluent later).
10. Wet the sand layer by adding ~5 mL of hexanes.
11. Prepare a rack of test tubes. Mark the starting test tube with a sharpie or label.
12. Add 200 mL of 99:1 hexanes/ethyl acetate to the column.
13. Begin running the column and collecting fractions in test tubes. Use the air adaptor to speed up the flow as necessary.
14. TLC the fractions to determine which fractions have your product in them. Develop TLC plates using 5:1 hexanes/ethyl acetate.
15. Combine the fractions that contain your product into a 250-mL round-bottom flask.
16. Remove solvent on a rotary evaporator (rotovap).
17. Tare a 20-mL scintillation vial (record weight: _____ g).
18. Add 0.5 mL diethyl ether to the round-bottomed flask containing your product. Swirl the flask to dissolve your product in the diethyl ether. Transfer this solution to the tared scintillation vial.
19. Use another 2 x 1.0 mL diethyl ether to rinse the flask. Transfer the washings likewise to the vial.
20. Remove the diethyl ether on a rotary evaporator.
21. Weigh the dried product with the vial (record weight: _____ g)
22. Calculate the mass of your isolated product: _____ mg.

What happened to the wax capsule? *Note that the wax melted during the reaction performed on Day 1 of this experiment and was adsorbed onto Celite along with the other chemical components of the crude reaction mixture. Throughout the course of the purification performed on Day 2, the paraffin and catalytic components of the capsule are eluted from the column and disposed of with the rest of the organic waste.*

Record any observations (any difficulties running the column, any other compounds that elute off the column, etc.) and your reaction yield:

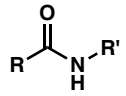
Spectroscopic Analysis/Preparing the NMR Sample

- Transfer ~10 mg of your isolated product to a scintillation vial. Dissolve it in ~0.2 mL deuterated chloroform ($CDCl_3$), and transfer the solution to a clean NMR tube.
- Rinse the vial with further small portions of $CDCl_3$, and transfer the washings likewise to the NMR tube until a total volume of 0.6–0.7 mL has been reached (~2 inches in depth)
- Cap the NMR tube, turn it over a few times to allow the contents to thoroughly mix and become homogeneous.

With a sharpie, clearly write down your initials and section number on the upper part of the NMR sample (do not write on the cap). Hand it in to your TA, who will run the NMR for you.

Pre-Lab Assignment

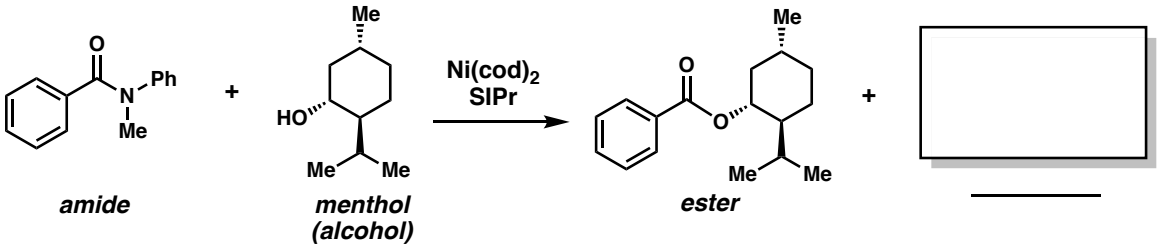
1. Using resonance structures, briefly explain why amides are the least reactive and most stable of carboxylic acid derivatives (=acyl chlorides, anhydrides, esters, amides).



2. Describe two safety concerns you have about performing this particular experiment and any precautions you will take to meet these concerns.

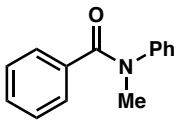
3. Based on the scheme of our reaction given below, answer questions (a)–(c).

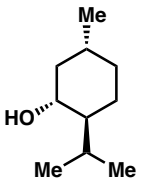
(a) On the scheme, indicate the bonds that are being broken in this reaction using asterisks (*).

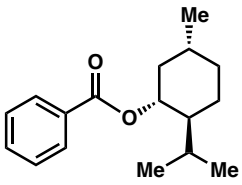


(b) In the box, draw the structure of the expected side product of this reaction. What class of compounds does this side product belong to? Write the name of the functional group on the line below the box.

(c) Based on the ranking of Rf values that we discussed in class earlier in the course, rank the four compounds in this scheme from eluting <u>earliest</u> to <u>latest</u> on normal-phase chromatography.







_____ _____ _____ _____

4. State the roles for each of the following in this experiment.

$Ni(cod)_2$:
(you can practice drawing
the structure for fun!)

SIPr:
(you can practice drawing
the structure for fun!)

Paraffin wax:

5. Draw the step of the catalytic cycle that leads to cleavage of the amide C–N bond. What is the name of this step?

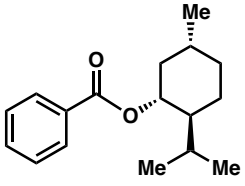
6. What is the purpose of purging the reaction vial with nitrogen after adding all of the reagents?

7. Look up the structure of paraffin wax online. Predict the following properties of paraffin wax (*and think about what this means for our TLC and chromatography!*).

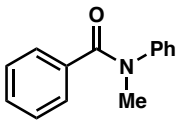
UV active?

Polar or non-polar?

8. Throughout this course, you have utilized a variety of analytical techniques (^{1}H NMR, ^{13}C NMR, 2D NMR, IR, GC-MS, TLC, polarimetry, etc.). Using your accumulated knowledge, list three techniques which you can use to distinguish your product from your starting material (amide). Describe 1–2 diagnostic features you expect to see for each technique.



product



starting material

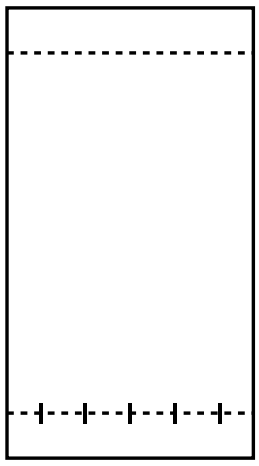
Technique 1:
Diagnostic features:

Technique 2:
Diagnostic features:

Technique 3:
Diagnostic features:

Post-Lab Assignment

1. Provide a sketch of your TLC plate when the reaction was complete and indicate how you visualized compounds on the plate. Be sure to indicate the solvent system you used for TLC and identify all of the spots which you see on the TLC plate.



2. Attach the referenced, integrated and peak-picked ^{1}H NMR spectrum of your purified product.

a) On the spectrum, draw a scheme of your reaction, clearly indicating reaction conditions (catalyst, stoichiometry, solvent, temperature, length of reaction);

b) If the following residual solvents/impurities are present in your spectrum, clearly mark the peaks that correspond to them: i) water; ii) acetone; iii) ethyl acetate; iv) hexanes; v) diethyl ether; vi) toluene; vii) dichloromethane.

c) Based on the ^{1}H NMR spectrum, what conclusions can you draw about the identity and purity of your product?

3. Calculate the percent yield for the amide product you obtained. If the yield is less than 100%, what do you think could have caused the loss in yield?

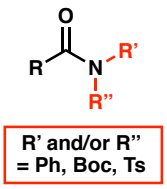
4. You can measure catalyst efficiency by calculating the catalyst turnover number (TON), which is defined as the amount of reactant (in moles) divided by the amount of catalyst (in moles) times **XX** (**XX** being the % yield of product; do not include the % sign in your calculation!). A large TON (typically 10^3 or greater) indicates a stable, long-lived catalyst. Based on your experimental yield, calculate the corresponding TON for the nickel catalyst used.

5. Describe why the reaction you performed is considered a milder method for the conversion of amides to esters compared to more traditional methods.

6. Researchers have used Pd and Ni catalysis to convert amides to other functional groups besides esters. Use online search engines to find one other example of a transition metal-catalyzed reaction of amides. Provide a scheme of the reaction, a mechanism, and list the literature reference. (*Hint: You may look up the research performed by the independent laboratories of Garg and Szostak, amongst others*)

7. Although not as common as their palladium counterparts, nickel-catalyzed cross-coupling reactions have been used in industrial settings for several decades. Using online search engines, identify one nickel-catalyzed reaction utilized in industry to produce something valuable on large scale. Show the reaction below and describe its importance.

8. The currently known transition metal-catalyzed reactions of amides have a limitation: there has to be at least one electron-withdrawing group (i.e., Ph, Boc, Ts) on the amide nitrogen. Provide an explanation for the role of the electron-withdrawing group in allowing the metal-catalyzed couplings of amides to proceed.



10. While wax capsules have been used on reactions up to 1-gram scale, chemists in industry often perform reaction on over 1 kg scale. A different technology called "SecuBags" can be used to deliver air- and moisture-sensitive reagents outside the glovebox on this scale. Using online search engines, identify a reagent commonly delivered with a "SecuBag". Describe a key difference between the "SecuBag" technology and the paraffin encapsulation strategy utilized in this laboratory experiment.

11. Provide us with feedback about this lab! (What did you like? What did you not like? What were the most challenging aspects? What could we have explained better? How can we improve this lab for future students?)

Notes for Instructors

- Instructors of advanced organic chemistry courses may wish to have students propose mechanisms for the reaction performed in this experiment. If so, it is recommended that instructors omit the mechanistic information provided in the "student handout" introduction.
- Instructors may wish to make this laboratory experiment inquiry-focused. Rather than telling students the product that they should make, students could predict or discover the product made through discussion and spectroscopic analysis. Alternatively, instructors could adapt the procedure such that students employ different amide substrates or alcohol nucleophiles to generate variable ester products. The substrates/nucleophiles could be sterically and/or electronically differentiated, which would allow the students to draw relationships between these effects and the reactivity of the substrates. In either case, the "student handout" could be adapted by omitting mentions and depictions of the ester product and instructors would likely need to adjust the pre- and post-lab questions.
- Although menthol was selected as the alcohol nucleophile in the studies described herein because of its commercial availability, low cost, ease of handling (crystalline), and the presence of complex splitting patterns in the ^{1}H NMR of corresponding ester product, other alcohols can be employed in this experiment. Instructors looking to employ alternate alcohols should consult the following reference: Hie, L.; Fine Nathel, N. F.; Shah, T. K.; Baker, E. L.; Hong, X.; Yang, Y.-F.; Liu, P.; Houk, K. N.; Garg, N. K. *Nature* **2015**, *524*, 79−83.
- If the cost of the TCI capsules is an impediment to implementation, instructors may consider generating their own capsules according to the procedure cited and hyperlinked

in the "Materials and Methods" section. Furthermore, costs incurred from purchasing capsules can be limited by having students perform the described experiment in pairs or larger groups.

- The toluene employed in this laboratory should be new, otherwise, instructors may wish to sparge the toluene with N_2 for > 20 min to degas the solvent and keep the reaction rigorously clear of oxygen contamination.
- UCLA laboratory support personnel prepared the amide substrate used in these studies. Instructors may consider synthesizing the staring material themselves or asking students to prepare their own starting materials according to the procedure outlined herein (S4). Additionally, the amide substrate will soon be available for purchase through TCI.
- UCLA laboratory support personnel also prepared reaction "kits" for each student containing a 1-dram vial, a septa cap, a PTFE-lined plastic screw cap, a magnetic stir bar, a 18 ga. needle (inlet for N_2 purging), a 20 ga needle (outlet for N_2 purging), and a ~6" piece of copper wire (TLC), which facilitated students performing the experiment in a reasonable time frame.
- It is possible to run this reaction on a larger scale employing multiple catalyst capsules and a round bottom flask as the reaction vessel so long as oxygen is rigorously excluded from the reaction and corresponding adjustments are made to the dry-loading and purification procedures.
- Assessing "satisfactory completion" of the pre-lab assignment by students was left to the discretion of the teaching assistants. We instruct them to ensure that students are well-prepared to perform the experiment comfortably and safely.

- As the nickel pre-catalyst is extremely sensitive to oxygen, it is highly recommended that a strong nitrogen flow be maintained throughout the purging stage of the experimental set-up. Purging for 10 minutes or more was found to be beneficial.
- All steps of the experimental protocol should be performed mindful of accidental introduction of oxygen. **Accidental introduction of oxygen typically occurs at the cap-switching step, and is the most common cause of failure in this experiment**. It is strongly recommended to have teaching personnel (1) demonstrate the switching technique beforehand, (2) have students practice the technique on an empty vial, prior to performing it on their reaction vial, and (3) supervise students as they perform the cap switching. If students leave too much of a gap between caps, they should be advised to re-purge the vial for another 5–10 minutes, then perform the cap switching again.
- Instructors may wish to emphasize to students to not place vials in the aluminum heating blocks before the vials are fully purged and sealed. Heating the vial with oxygen present causes the wax capsule to melt prematurely and decomposes the air-sensitive catalyst.
- Should rotary evaporators not be available for student use, instructors may consider having students monitor/analyze the reaction by TLC. Other means of reaction monitoring/analysis (i.e. GC/MS or IR) may be complicated by the presence of the paraffin.
- While not included in the present study, other means of analysis, such as IR, may be employed to characterize products or analyze spectroscopic differences between the amide starting material and the ester product following purification away from the wax (i.e. C=O stretching frequencies). **Amide (1):** 3060, 2937, 1641, 1360, and 695 cm^{-1} **Ester (3):** 2953, 1713, 1450, 1270, and 1112 cm^{-1}

- While carrying out the TLC protocol, instructors should advise students to visualize the spotted material under UV light before developing the TLC plate. If no UV active spot is visible, the student should further spot the plate until a spot is visible.
- Mixtures of Celite and organic solvent have a tendency to bump upon rotary evaporation. To avoid contamination of bump traps, it is highly recommended that bump traps be stuffed with cotton to prevent Celite from entering the rotovap.
- The Celite should be "free-flowing" after a successful dry-loading of the crude reaction mixture. Some students benefited from adding additional Celite beyond the recommended 1.5 g.
- Instructors should advise students to not leave chromatography solvent mixtures open to the air. Evaporation of hexanes leads to a more polar solvent mixture, which in turn, leads to undesired co-elution of compounds during chromatography.
- Instructors wishing to avoid the use of hexanes in chromatography may utilize heptane instead. Using a 5:1 ratio of heptanes to ethyl acetate, R_f values were found as follows: 0.13 amide substrate, 0.43 HNMePh, and 0.6 ester product. All are very similar to the corresponding R_f values compared to when hexanes is used in place of heptane.

Student Outcomes

As noted in the manuscript, 37 out of 65 students who performed this reaction reported obtaining the desired product. Most students who did not isolate product attributed this problem to poor technique with regards to switching caps after the N_2 purge step during reaction setup. In some ^{1}H NMR spectra, residual solvent dominated the spectra. In addition, we conducted student

evaluations to help us improve and adapt the experiment moving forward. Student comments from those evaluations pertaining to the experiment are as follows:

- "I found the wax capsule creation process to be cool and interesting."
- "Cool lab. The demonstrations really helped with this lab."
- "It was very cool to experience working with this new capsule technique. Although I was able to eventually visualize product on my TLC, it was a little worrisome/frustrating when we ran the TLC on the first day and only saw starting material because so little product was formed. I think my reaction was exposed to air during the cap transfer, which likely killed the catalyst before the reaction started. In the future, practicing the cap transfer technique prior to the actual experiment may be beneficial!"
- "I loved this lab! I found it especially interesting because transition metal catalysis is one of my greatest research interests."
- "The pace was excellent, very relaxed. Although, the recommended amount of Celite turned out to be too little (1.5 g) and most people ended up using 4.5–5 g."
- "I liked the fact that this lab was done over two lab periods and it was doable in the time provided. Everything was perfect with this lab and there is no need for improvement."
- "I thought the concept was cool initially, but the wax capsule just became obnoxious: 1) it kept hardening while transferring my reaction to the round bottom, 2) wax kept clogging TLC tubes, 3) wax got stuck at the bottom of my column."
- "The wax was difficult to manage in the reaction. Air free transfer would've made the procedure and clean up easier."
- "There should've been a product we could've spotted on the TC plates we ran during our column so we can know what to look for in our elutes."

- "This lab was really cool because it incorporated new techniques developed here at UCLA. It could be improved by figuring out a way to increase the % yield, as it seems many people did not get much product."
- "It was really difficult to visualize which fractions contained product after running the column. I would have enjoyed the lab more if the product was less dilute/more visible on TLC."
- "The wax capsule concept is pretty cool! However, I had no product, a problem shared with some of my classmates."
- "Cool all around though I think my reaction went wrong immediately without any way to salvage it which was fairly frustrating."
- "Some students (including me) had problems with packing/loading the Celite/product mixture into our columns. Perhaps some troubleshooting can be done for future labs."
- "Most challenging aspect: spotting the TLC plate on the 1st day because nothing would show up because my spot was too faint. Other than that, no complaints."
- "Multiple spots very close in elution time to product (too much Celite used) and could not collect pure fractions (several spots appeared very close to product)."
- "If there were better strategies to use in order for most students to get the product that for sure could be recommended. However, it was fun performing our last lab on something/chemistry that was developed at UCLA."
- "Column chromatography was not exactly fun."
- "I liked not having to deal with the air- and water-free transfer. I think the column can be improved to get better separation – I had a mixture of three things in the fractions I pulled. Maybe try a gradient?"

- "I liked using the wax capsules; challenging to isolate product on column due to minimal separation between product, impurities, and byproducts."
- "Wax is horrible to deal with. Why not Secubag? Won't even need dry-load for the column or deal with wax everywhere…"
- "It is amazing to see an UCLA professor who creates this wax encapsulated pre catalysts and ligand. I was hoping to see product in my reaction but due to my horrible lab skills, I probably exposed the catalyst to air. So hopefully, we can come up with a different idea to ensure product in the reaction next time."
- "This lab is very interesting."
- "Cool experiment!"
- "I thought it was cool! I even ended up getting 20% yield after heating up the reaction, on accident, before performing the Indian Jones switch."
- "I did struggle with the cap replacement due to the positioning of the needle. I found the wax capsule creation process to be cool and interesting."
- "I liked the ease of using the capsule and the whole kit. The wax made the later part of the experiment a little difficult later on, but that's okay."
- "I liked how we were able to perform a fairly new experiment."
- "I really liked doing a lab that was developed at UCLA, especially a recently developed one."
- "This was an interesting lab that exposed me to a new way to deal with air- and water-sensitive reagents. The most challenging aspects were keeping out air and water which I don't think I was able to do effectively."
- "Purification process was confusing due to multiple compounds being UV active."

- "I thought this lab was fine; a good way to practice "running" a column. I found the TLC portion of the lab to be difficult since it took me many spots to show up on UV. Overall a decent lab compared to others."
- "Lots of side/unknown product was made – wish we knew what to look for in product (i.e. description); we should have high-vac in lab; interesting in theory, in the end however, the lab was underwhelming."
- "I found it challenging to do the cap switch and keeping everything completely air free. This was still a valuable learning experience for me. It was even more challenging for me to correctly identify the product through TLC because the wax also eluted in my fractions and it was UV active."
- "The wax capsule was pretty cool. I wasn't quite sure if I got my product before NMR, any way to make it more visible or something? I liked the chromatography setup. The solvent mixture was great for purifying it from the wax, though some people weren't able to? Is there a stain or something to make the wax show up?"
- "This was a nice wrap-up for the quarter in terms of lab techniques and overview of new skills. It would have been nice to have more lecture time dedicated, though."
- "I love the theory behind this lab! I wish I had gotten product."
- "I liked using the wax, although it felt incredibly tedious to use. Otherwise, this lab was good practice using another type of metal catalyst. It needs no alterations."
- "This lab was good overall but there was a lot of searching for the post-lab. I didn't think it would be so difficult to find any information on Secubags."
- "The column was not sufficient for separating wax from product. That makes calculating catalyst efficiency difficult. Otherwise, fun lab. I love me a finicky catalyst."

- "It was interesting to learn that there is such a convenient way to handle air/water sensitive metals."
- "I very much enjoyed the use of the capsule-enclosed catalyst. This felt like an interesting and new technique in the field of chemistry and made the procedure stimulating. The wax in the reaction mixture was annoying to deal with during purification, so I would have preferred some step in the workup to remove wax from the mix, but I totally understand if there is no such procedure to be done. Additionally, I think the solvent mixture for the TLC analysis should be changed to something more polar to spread the spots out more. Overall though I enjoyed being part of ongoing research in the Garg Lab."
- "It was hard to deal with wax during the final rotovap. I had a problem, wax kept forming in my sample. This makes it harder to get pure product."
- "Fun lab."
- "I liked learning the mechanism of this reaction, as well as how air- and water-sensitive materials are handled in different ways in the laboratory setting. However, I did not like the use of wax in this lab, as it made the manipulation of the reaction mixture, and other samples very difficult. I thought the experiment was explained very well and I don't feel as if this lab needs to be improved for students."
- "I really liked that we got individual kits to work with and got to be Indiana Jones when we made the cap transfers. It's just kind of sad that reaction yields were so low."
- "This lab was a solid okay. Doing the Indiana Jones thing was pretty fun, but working up my disastrous reaction full of wax was kind of awful. Definitely a cool lab in theory but not fun in practice."

- "It is interesting that we're performing a reaction that was fairly recently discovered (and at UCLA) and that our class labs are contributing data to research about this."
- "It would be great if there were some way to keep the wax out of our NMR. Maybe teach next quarter's students to troubleshoot by asking them how they might solve this problem."
- "This lab was pretty cool since we got to perform really up-to-date chemistry. I did not like how messy the lab was between the silica, Celite, and melted wax. The challenging parts of this lab was making sure the reaction was not exposed to air and getting as much product as possible while keeping the wax melted. Since this lab is notorious for not getting any product, maybe change the format or change the topic of the lab."
- "This lab was so cool, like we got PRE-PACKAGED reaction kits. I didn't like that I bumped my reaction so much (I am sorry for the wax getting everywhere)."
- "This lab wasn't as interactive as I would have liked but the chemistry was interesting!"
- "A bit clunky, but still fun."
- "Although I got no product out, I appreciated the concept and the fact that the reaction was done here at UCLA. I heard not many people got yields so perhaps it was a problem with our air- and moisture-free technique. Maybe next quarter the TAs could provide more stringent supervision in between steps during this lab period. Otherwise, great stuff."
- "The paraffin was hard to exclude from this lab. Maybe the whole class could view the reaction in a glovebox instead of using the encapsulated paraffin starting materials."

- "New exposure to less labor-intensive air-free methods was welcome experience. Adjusting the lab procedure to include (and accurately describe) dry-loading column chromatography would be a great help."
- "This lab was my least favorite because of how messy the wax was. I do enjoy the concept and the procedures, but it was too difficult to execute."
- "I totally liked using techniques developed by the Garg lab – it makes UCLA seem super awesome. I would have liked more explanation about the paraffin wax capsule (molecular composition, etc.). It was also frustrating trying to TLC the reaction as the wax made it nearly impossible."
- "This is a very complicated lab experiment, but interesting because I am exposed to new lab techniques which might come in handing in the future. There are many challenges including: transferring red to green cap to prevent or minimize exposure to air, extracting or taking some sample from the mixture to run TLC, keeping the wax liquid when doing certain parts of the experiment. I don't know if there is a way to improve the experiment beside using the glovebox, but this equipment might be a bit too expensive."
- "I thought the use of the capsule was very interesting since we were able to use an air/water-sensitive reagent without an inert atmosphere. I did not like how bumpy the Celite was. The most challenging aspect was not bumping. You could have explained the cap switch better."
- "It sucks to not get product."
- "This lab was fun because we got to use something that was UCLA-made! However, I wish there was an easier way for us to separate the wax from the product."

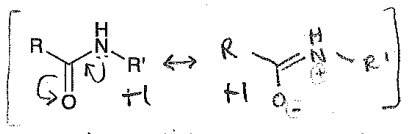
- "It was tragic that my reaction was unsuccessful. I think it'd be nice to review in lab why this might be the case. I liked how in the lab we did a very intense demonstration on how to switch dram lids. I really liked running a column, although it would've been nice to know not to dump all the product in."

"Model" Student Pre-Lab Worksheet

Lab 8 Breaking Amides With a Nickel Capsule **CHEM 30CL**
Name: _____ **Section:** _____

Pre-Lab Assignment 35/35

1. Using resonance structures, briefly explain why amides are the least reactive and most stable of carboxylic acid derivatives (=acyl chlorides, anhydrides, esters, amides).



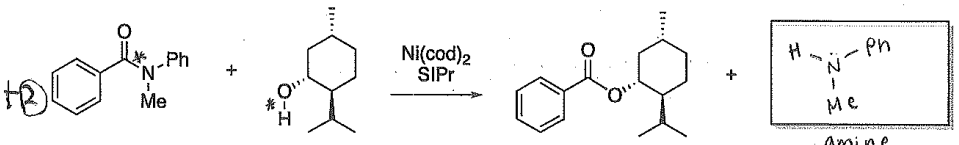
(4) Partial double bond character of the C-N bond makes amides relatively stable when compared to other carboxylic acid derivatives, which don't have double bond character. Double bonds are more difficult to break and thus, to manipulate during chemical processes. +2

2. Describe two safety concerns you have about performing this particular experiment and any precautions you will take to meet these concerns.

(4) One concern I have is that toluene is flammable and an irritant. To address these concerns, I won't handle toluene around any open flames and I will always wear my proper PPE to avoid skin and eye irritation. Another concern I have is that the wax capsule may cause cancer and is also an irritant. To address this concern, I will take extra care when handling the wax capsule so it isn't exposed to mine or my classmates skin.

3. Based on the scheme of our reaction given below, answer questions (a)–(c).

(a) On the scheme, indicate the bonds that are being broken in this reaction using asterisks (*).



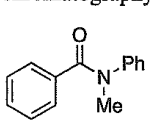
+2 amide | menthol (alcohol) | ester | amine

Lab 8 Breaking Amides With a Nickel Capsule **CHEM 30CL**
Name _____ **Section:** _____

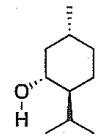
(2) (b) In the box, draw the structure of the expected side product of this reaction. What class of compounds does this side product belong to? Write the name of the functional group on the line below the box.

(c) Based on the ranking of Rf values that we discussed in class earlier in the course, rank the four compounds in this scheme from eluting earliest to latest on normal-phase chromatography.

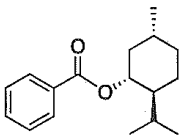
(4)



latest



Second latest



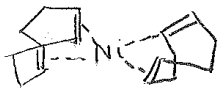
earliest

second earliest

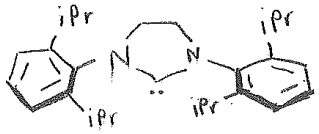
4. State the roles for each of the following in this experiment.

(3)

Ni(cod)$_2$: pre-catalyst
(you can practice drawing the structure for fun!)



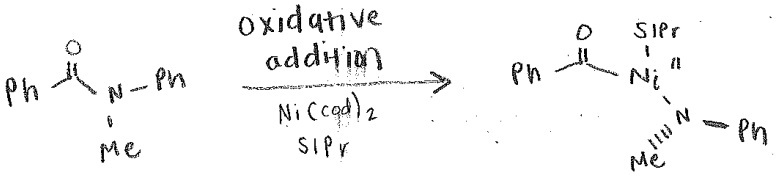
SIPr: ligand
(you can practice drawing the structure for fun!)



Paraffin wax: capsule for enclosing air and water sensitive reagents (Ni(cod)$_2$ and SIPr)

5. Draw the step of the catalytic cycle that leads to cleavage of the amide C–N bond. What is the name of this step?

+(3)



This step is called oxidative addition

Lab 8 Breaking Amides With a Nickel Capsule **CHEM 30CL**
Name: _____ **Section:** _____

6. What is the purpose of purging the reaction vial with nitrogen after adding all of the reagents?

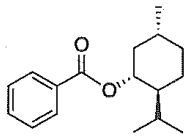
(2) This serves to keep the air and water-sensitive reagents from reacting with air in the vial after the wax melts and the reagents are released.

7. Look up the structure of paraffin wax online. Predict the following properties of paraffin wax (*and think about what this means for our TLC and chromatography!*).

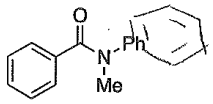
(2) *UV active?*
No

Polar or non-polar? +2
non-polar

8. Throughout this course, you have utilized a variety of analytical techniques (^{1}H NMR, ^{13}C NMR, 2D NMR, IR, GC-MS, TLC, polarimetry, etc.). Using your accumulated knowledge, list three techniques which you can use to distinguish your product from your starting material (amide). Describe 1–2 diagnostic features you expect to see for each technique.



product



starting material

Technique 1: ^{13}C-NMR
Diagnostic features: (3) Product will have C-C peaks in the 0-50 ppm range but the starting material will not.

Technique 2: TLC
Diagnostic features: (3) the starting material will elute last (lower on the plate), but starting material will elute sooner (higher on the plate).

Technique 3: GC-MS
Diagnostic features: (3) The product should elute before the starting material because the product is less polar.

"Model" Student Post-Lab Worksheet

34/35

Lab 8 Breaking Amides With a Nickel Capsule **CHEM 30CL**
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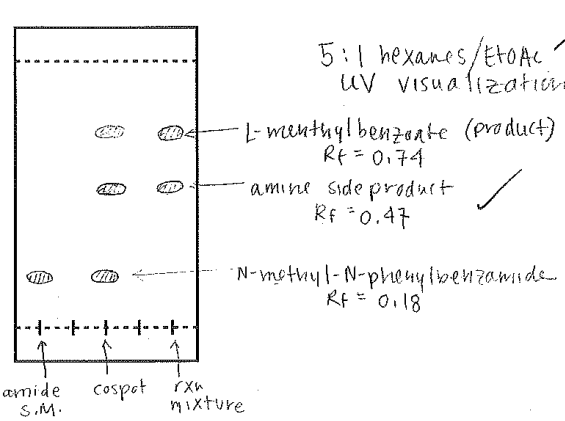
Post-Lab Assignment

1. Provide a sketch of your TLC plate when the reaction was complete and indicate how you visualized compounds on the plate. Be sure to indicate the solvent system you used for TLC and identify all of the spots which you see on the TLC plate.



+4

2. Attach the referenced, integrated and peak-picked ^{1}H NMR spectrum of your purified product.

a) On the spectrum, draw a scheme of your reaction, clearly indicating reaction conditions (catalyst, stoichiometry, solvent, temperature, length of reaction);

b) If the following residual solvents/impurities are present in your spectrum, clearly mark the peaks that correspond to them: i) water; ii) acetone; iii) ethyl acetate; iv) hexanes; v) diethyl ether; vi) toluene; vii) dichloromethane.

+6

c) Based on the ^{1}H NMR spectrum, what conclusions can you draw about the identity and purity of your product?

Product is the desired L-menthyl benzoate (no starting material peaks seen besides unknown TCI impurity). Mostly pure (still has n-hexanes)

3. Calculate the percent yield for the amide product you obtained. If the yield is less than 100%, what do you think could have caused the loss in yield?

$$0.200\ \text{mmol S.M.} \left|\frac{1\ \text{mmol prod}}{1\ \text{mmol S.M.}}\right| \left|\frac{1\ \text{mol}}{1000\ \text{mmol}}\right| \left|\frac{260.38\ \text{g}}{1\ \text{mol prod}}\right| \left|\frac{1000\ \text{mg}}{1\ \text{g}}\right| = 52.1\ \text{mg}$$

expected

$$\text{yield} = \frac{\text{actual mass}}{\text{expected mass}} \times 100 = \frac{40.8\ \text{mg}}{52.1\ \text{mg}} \times 100 = 78.3\%$$

+4

Loss in yield due to: ① presence of impurities in fractions also containing product meant we couldn't isolate all the product from the column ② residual amts of air in reaction could've reacted w/ some catalyst

4. You can measure catalyst efficiency by calculating the catalyst turnover number (TON), which is defined as the amount of reactant (in moles) divided by the amount of catalyst (in

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moles) times **XX** (**XX** being the % yield of product; do not include the % sign in your calculation!). A large TON (typically 10^3 or greater) indicates a stable, long-lived catalyst. Based on your experimental yield, calculate the corresponding TON for the nickel catalyst used.

$\frac{0.00020 \text{ mol reactant}}{0.000020 \text{ mol catalyst}}(78) = 780$

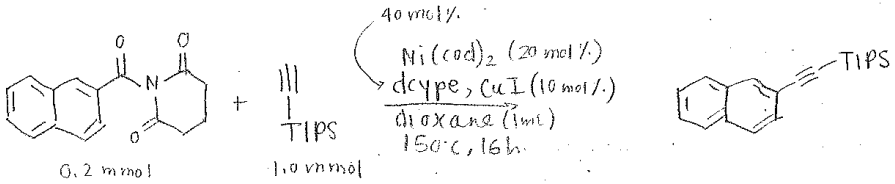
+4

5. Describe why the reaction you performed is considered a milder method for the conversion of amides to esters compared to more traditional methods.

Traditional methods require extreme conditions since the amide bond is so stable & hard to break (such as very basic or acidic conditions or extreme heating). Our reaction required heating, but could be performed at near neutral pH outside of a glove box (the $Ni(cod)_2$ & SiPr typically require a glove box to prevent exposure to air).

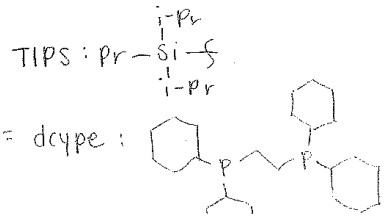
+3

6. Researchers have used Pd and Ni catalysis to convert amides to other functional groups besides esters. Use online search engines to find one other example of a transition metal-catalyzed reaction of amides. Provide a scheme of the reaction, and list the literature reference. (*Hint: You may look up the research performed by the independent laboratories of Garg and Szostak, amongst others*)



+3

Amide to Alkyne conversion
Org. Lett. 2017, 19, 3091-3094



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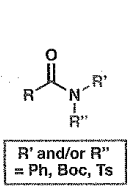
7. Although not as common as their palladium counterparts, nickel-catalyzed cross-coupling reactions have been used in industrial settings for several decades. Using online search engines, identify one nickel-catalyzed reaction utilized in industry to produce something valuable on large scale. Show the reaction below and describe its importance.

$R'-X + R-MgX \xrightarrow{Ni(dppb)Cl_2} R'-R$ (kumada coupling)

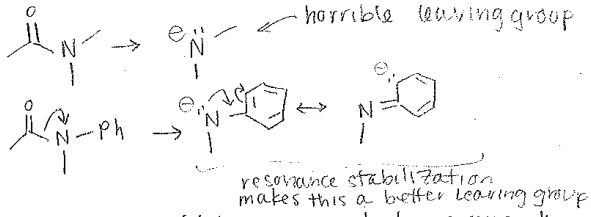
R' = aryl/vinyl
R = aryl/vinyl/alkyl
X = Cl > Br > I

+3 Industrial-scale production of styrene derivatives & synthesis of unsymmetrical biaryls. Avoids additional rxn steps like converting Grignard to zinc for Negishi coupling.

8. The currently known transition metal-catalyzed reactions of amides have a limitation: there has to be at least one electron-withdrawing group (i.e., Ph, Boc, Ts) on the amide nitrogen. Provide an explanation for the role of the electron-withdrawing group in allowing the metal-catalyzed couplings of amides to proceed.



+4



Facilitates the oxidative addition step which requires the C–N bond to be broken as the Ni inserts itself into the C–N bond.

10. While wax capsules have been used on reactions up to 1-gram scale, chemists in industry often perform reaction on over 1 kg scale. A different technology called "SecuBags" can be used to deliver air- and moisture-sensitive reagents outside the glovebox on this scale. Using online search engines, identify a reagent commonly delivered with a "SecuBag". Describe a key difference between the "SecuBag" technology and the paraffin encapsulation strategy utilized in this laboratory experiment.

+3
- NaH commonly delivered via SecuBags
- SecuBags suspend the reagent in 60% mineral oil & use a styrene-butadiene-styrene copolymer bag while the wax capsules suspend the reagent in solid paraffin
  - ↳ SecuBags solvent soluble (immediately dissolve @ RT in Toluene, THF, MeTHF, etc.)
  - ↳ wax capsules heated to dissolve/melt

Lab 8 Breaking Amides With a Nickel Capsule **CHEM 30CL**

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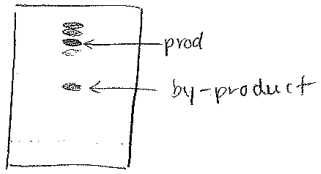
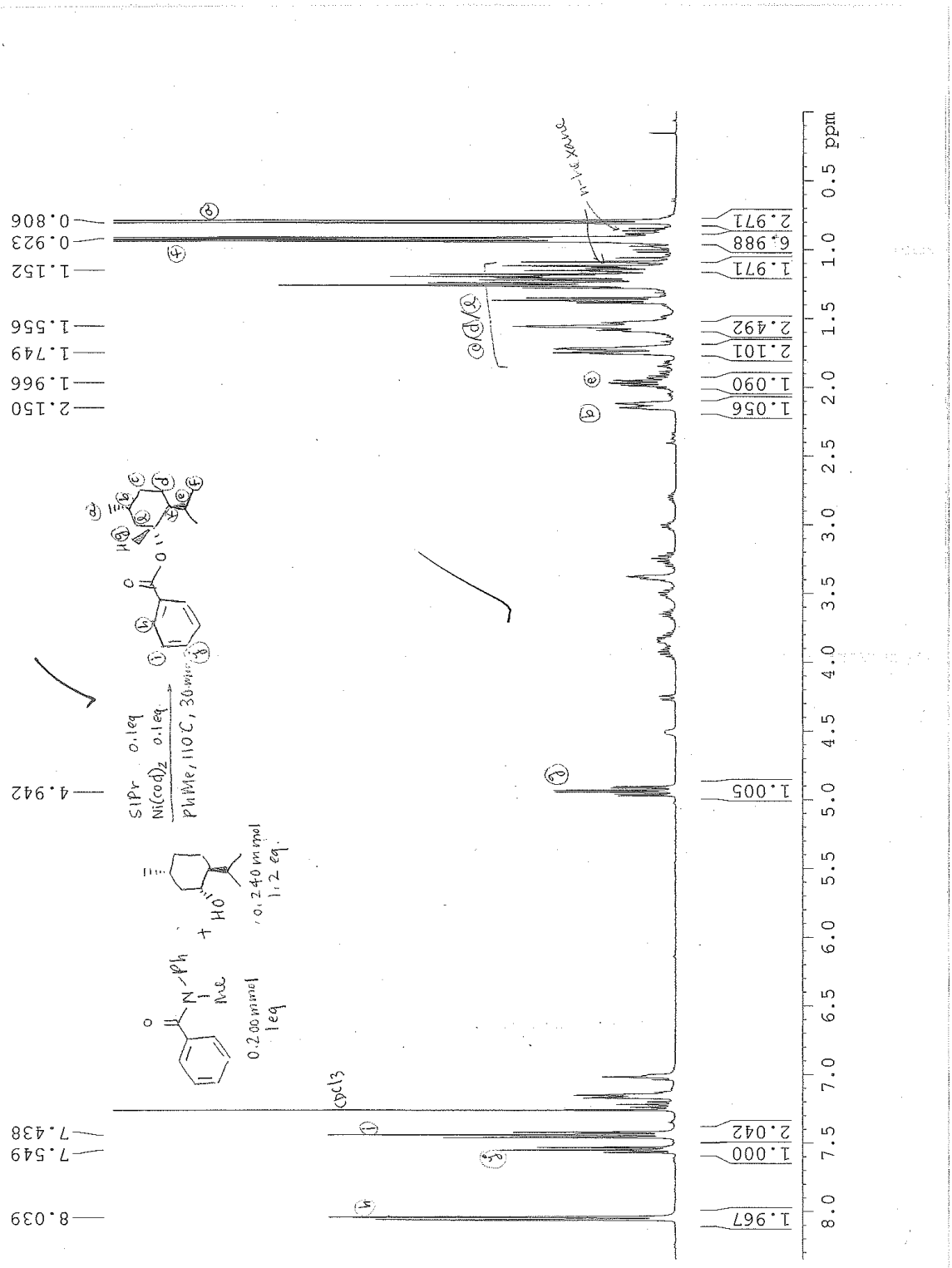
11. Provide us with feedback about this lab! (What did you like? What did you not like? What were the most challenging aspects? What could we have explained better? How can we improve this lab for future students?)

- multiple spots very close in elution time to product (too much celite used)
- could not collect pure fraction b/c several spots appeared very close to prod)

4

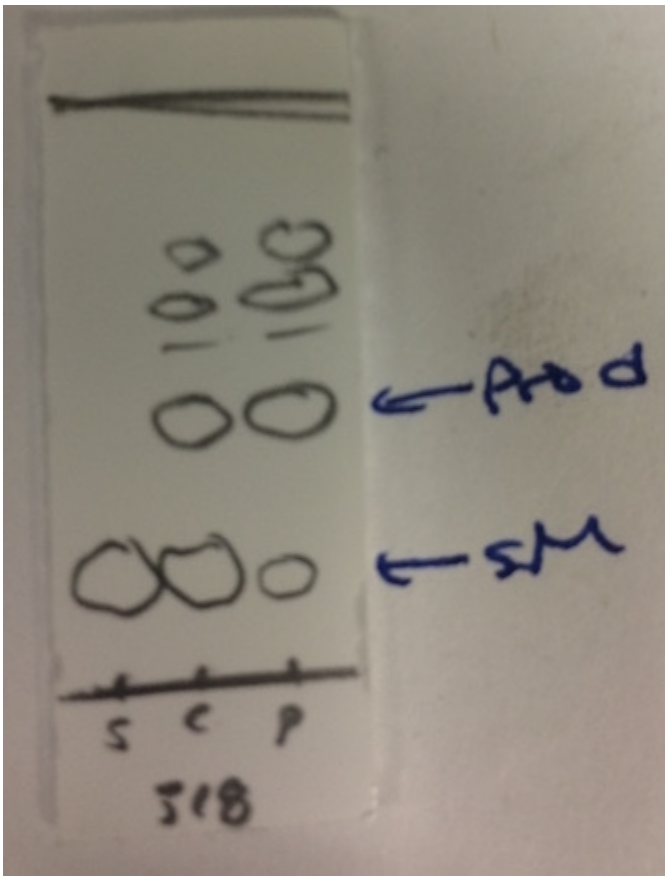



8.039
7.549
7.438
4.942
2.150
1.966
1.749
1.556
1.152
0.923
0.806
1.967
1.000
2.042
1.005
1.056
1.090
2.101
2.492
1.971
6.988
2.971
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
CDCl3
n-hexane
SIPr 0.1eq
Ni(cod)2 0.1eq
PhMe, 110°C, 36hours
0.200 mmol
1eq
0.240 mmol
1.2 eq.

Representative Reaction TLC

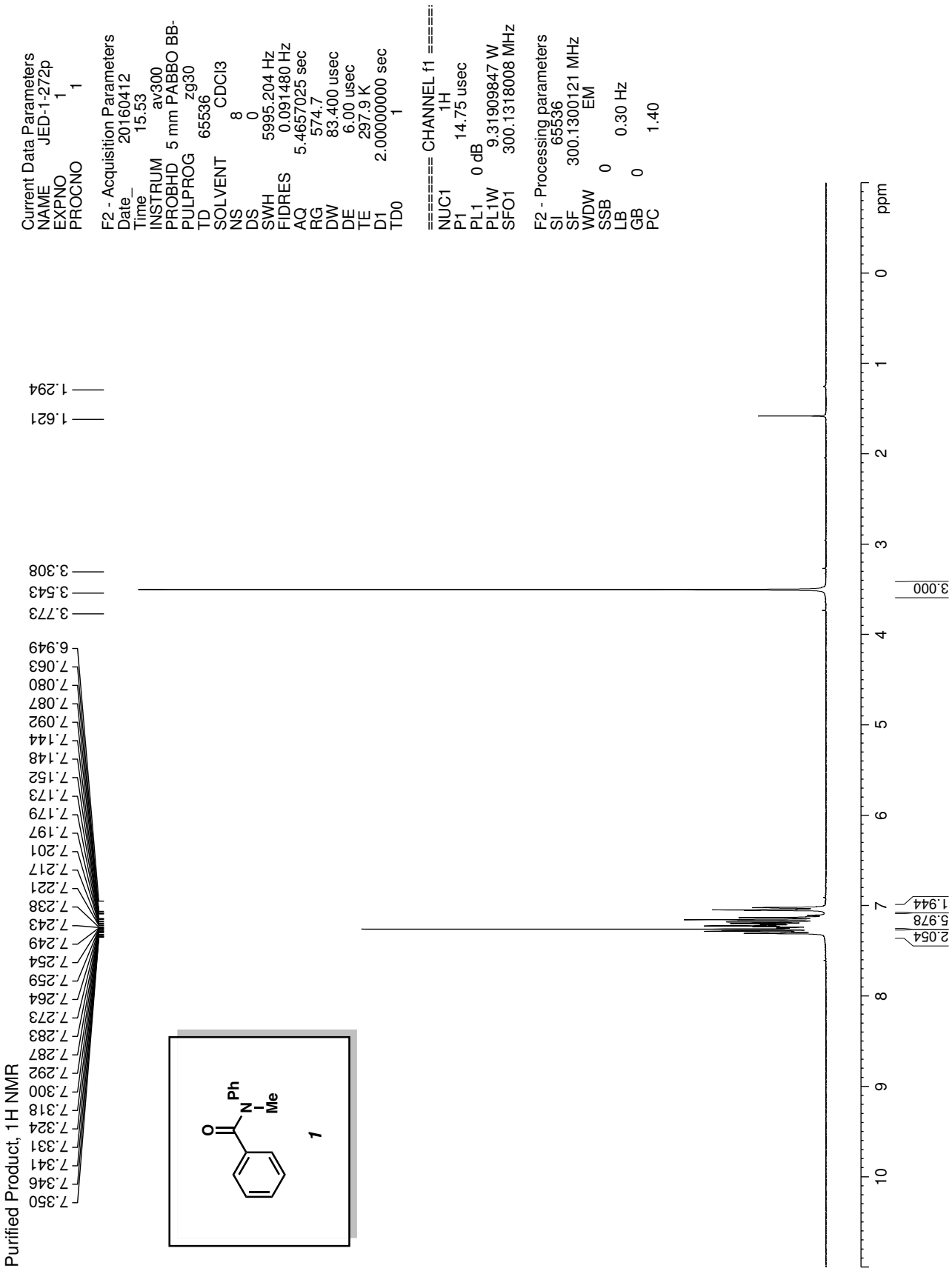
Amide (**1**) Substrate R_f 0.23 (5:1 – hexanes:EtOAc)

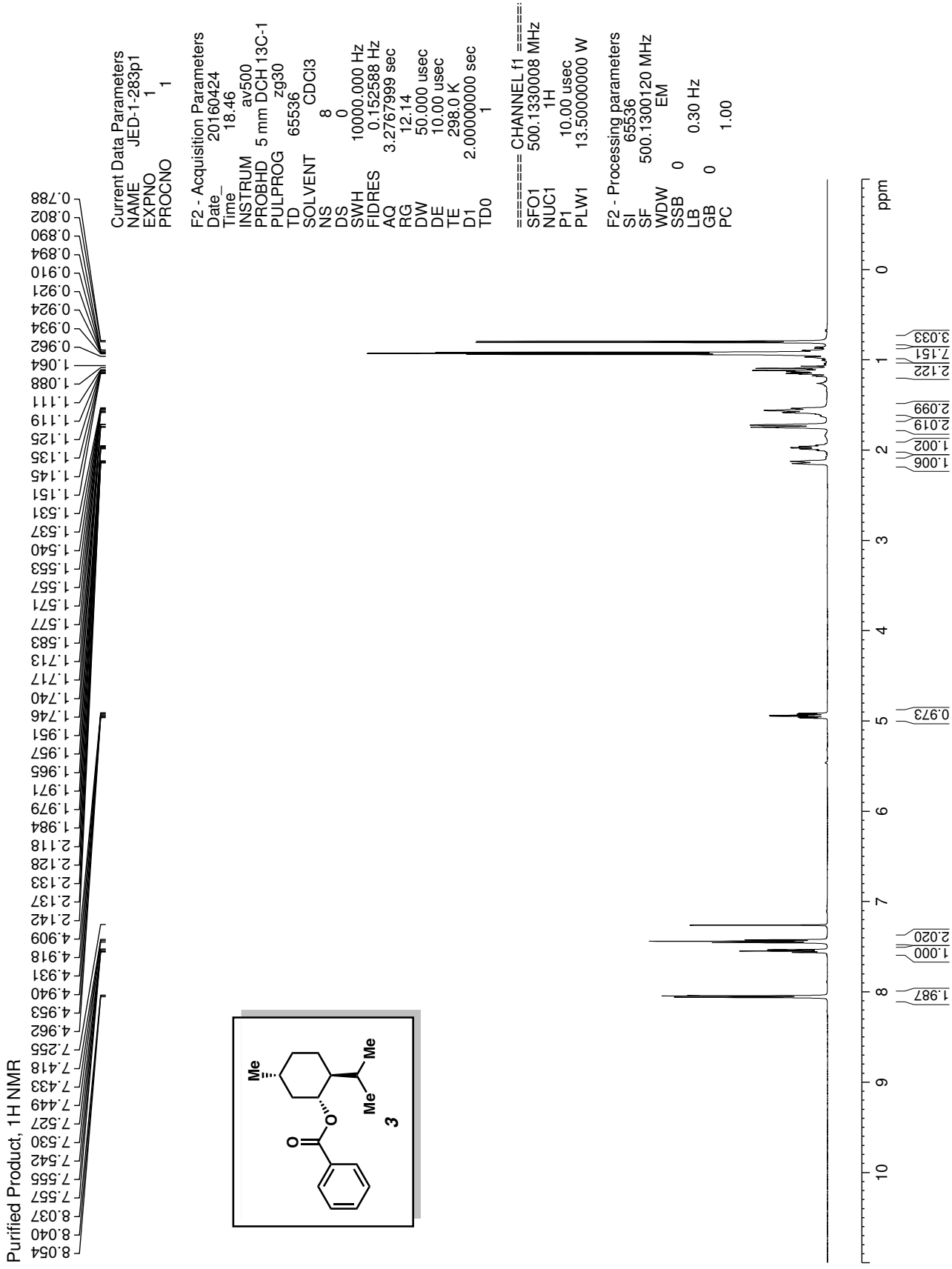
Ester (**3**) Product R_f 0.58 (5:1 – hexanes:EtOAc)



^{1}H NMR Spectra

A. Spectra of the Pure Amide Substrate (1) and Ester Product (3)




Purified Product, 1H NMR
Current Data Parameters
NAME JED-1-283p1
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160424
Time 18.46
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 0
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2767999 sec
RG 12.14
DW 50.000 usec
DE 10.00 usec
TE 298.0 K
D1 2.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 500.1330008 MHz
NUC1 1H
P1 10.00 usec
PLW1 13.50000000 W
F2 - Processing parameters
SI 65536
SF 500.1300120 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
Me
Me
Me
O
O
3
ppm

B. Representative Student ^{1}H NMR Spectrum of 3