Organic Syntheses

Facile Reduction of Amides Using Nickel Catalysis: Reduction of 12-Aminododecanolactam

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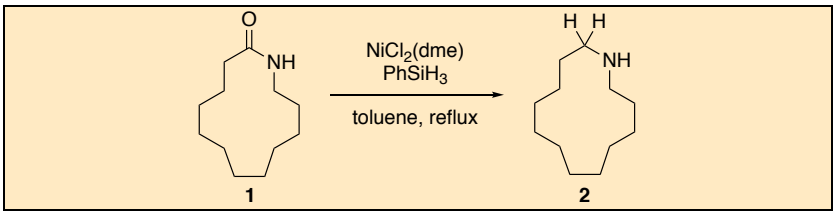

Procedure (Note 1)

A. *Azacyclotridecane* (**2**). A 300-mL, three-necked round-bottomed flask (29/32 central neck, 15/25 side necks) is equipped with a Teflon-coated magnetic stir bar (octagon, 2.4 x 0.8 cm) (Notes 1 and 2). The side necks are fitted with 15/25 rubber septa and the central neck is equipped with a connecting adapter (29/32 upper outer joint, 15/25 lower inner joint) and a water-jacketed reflux condenser (30.0 cm height, 15/25 joint). The reflux condenser is topped with a 15/25 glass adapter connected to a Schlenk line (Figure 1). All glassware junctures are sealed with Teflon tape. The flask is charged with nickel (II) chloride ethylene glycol dimethyl ether complex (1.00 g, 4.56 mmol, 0.100 equiv) and 12-aminododecanolactam (**1**) (9.00 g, 45.6 mmol, 1.00 equiv) (Note 3) through a side neck of the flask. The rubber septa of the side necks are secured and sealed with Teflon tape. The reaction vessel is evacuated for 5 min and backfilled with argon three times. Toluene (46 mL, 1.0 M) (Note 4) is then added to the reaction mixture via syringe and through the 15/25 rubber septum on a side neck of the flask. The reflux condenser is kept at 23 °C with a constant flow of water. The reaction vessel

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is placed in a pre-heated 115 °C oil bath and stirred for 10 min (Figure 2). Phenylsilane (9.87 g, 91.2 mmol, 11.2 ml, 2.00 equiv) (Note 5) is then added dropwise via syringe pump (0.1 mL/min, 11.2 mL, 12.0 mL syringe) through the 15/25 rubber septum on a side neck of the flask (Figure 3). During the addition, the reaction changes color from orange to black with hydrogen gas evolution (Figure 4) (Note 6). Upon complete addition of phenylsilane, the reaction is stirred for 24 h in the 115 °C oil bath. An argon atmosphere is maintained throughout the reaction using an argon manifold system.

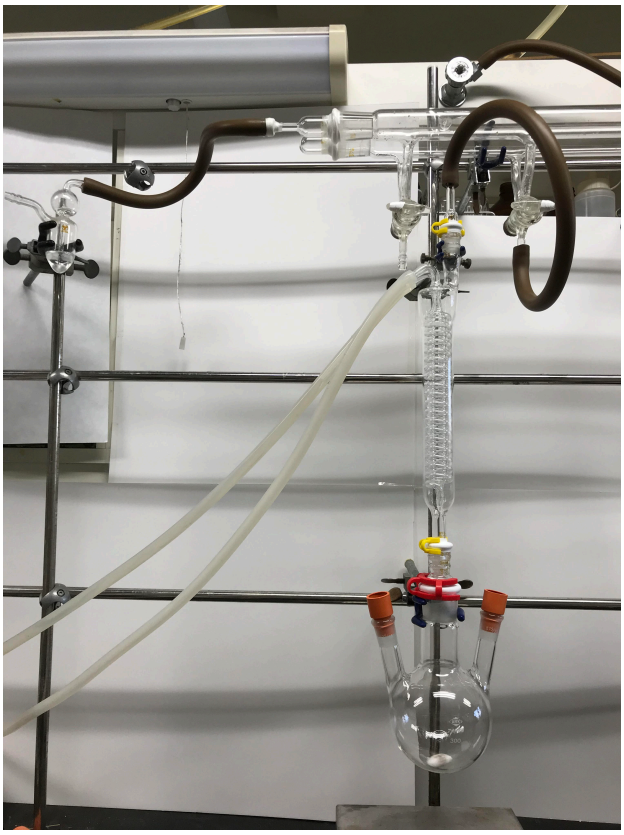


Figure 1. Set-up of glassware for the reaction

(a)

(b)

Figure 2. (a) The reaction mixture before pre-stirring the substrate and Ni catalyst; (b) Pre-stirring of the reaction mixture

Figure 3. Addition of phenylsilane by syringe pump

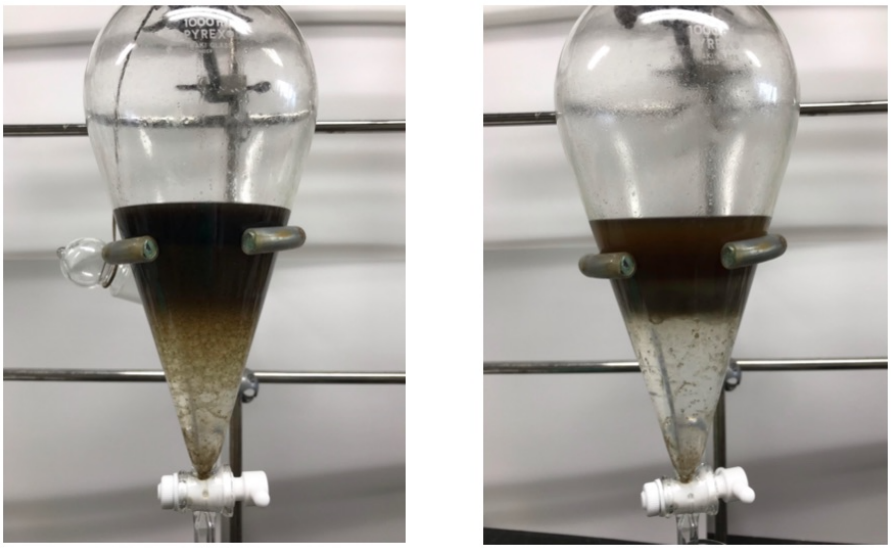
(a) (b)

Figure 4. (a) The reaction mixture before the addition of phenylsilane; (b) The reaction mixture immediately after the complete addition of phenylsilane

After the allotted time, the reaction vessel is removed from the oil bath and cooled to 23 °C over 20 min. Once at 23 °C, the reaction is diluted with EtOAc (50 mL) (Note 7) and stirred at 0 °C for 10 min. A solution of 1.0 M aqueous NaOH (0.5 mL) (Note 8) is added and the reaction is stirred at 0 °C for an additional 5 min. This process is repeated four times (Figure 5) (Note 9). Subsequently, a larger portion of 1.0 M aqueous NaOH (3.0 mL) is added and the resulting mixture is stirred at 0 °C for 5 min. The crude reaction mixture is then transferred to a 1000-mL separatory funnel. The 300-mL round-bottom flask is rinsed with EtOAc (40 mL) and the resulting solution is added to the separatory funnel. Additional 1.0 M aqueous NaOH (3 x 10 mL) is added to the separatory funnel, followed by EtOAc (50 mL) and a saturated aqueous NaCl solution (100 mL) (Figure 6) (Notes 10 and 11). The layers are separated, and the aqueous solution is extracted with EtOAc (3 x 100 mL). The combined organic layers are washed with saturated aqueous NaCl (100 mL), dried for 10 min over anhydrous Na_2SO_4 (150 g) (Note 12), and filtered over a fritted glass funnel (inner diameter: 7.5 cm, height: 6.0 cm) into a 1-L round-bottom flask (Figure 7). The filter cake is

rinsed with EtOAc (4 x 50 mL) and the resulting mixture is concentrated by rotary evaporation (780 to 40 mmHg, 30 °C bath temperature) to give a dark green oil (26.5 g) (Figure 8) (Note 13).

Figure 5. Reaction mixture after quenching with 1.0 M aqueous NaOH



(a) **(b)**

Figure 6. (a) The reaction mixture in separatory funnel after the addition of EtOAc, 1.0 M NaOH, and saturated aqueous sodium chloride (b) The reaction mixture after sitting for 20 min

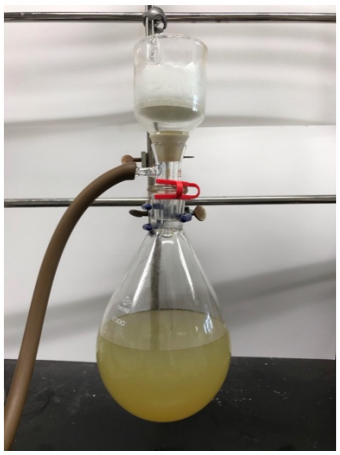


Figure 7. Set-up of reaction filtration

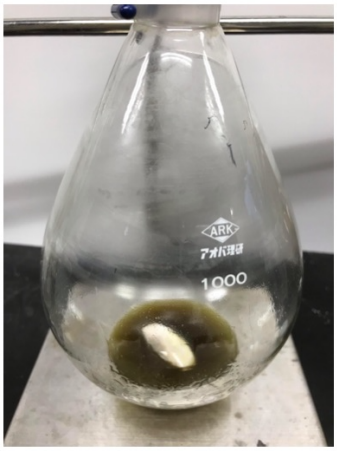


Figure 8. Crude dark green oil

To the round-bottom flask, which contains the crude reaction mixture, is added a Teflon-coated magnetic stir bar (octagon, 4.2 x 1.8 cm) and hexanes (300 mL) (Notes 14 and 15). Next, the mixture is stirred for 2 h at 23 °C (Figure 9). The resulting precipitate is removed via filtration using a fritted glass funnel (inner diameter: 7.5 cm, height: 6.0 cm) packed with celite (20.0 g) (Note 16). The filtrate is collected in a 1-L round-bottom flask (Figure 10), and the filter cake is rinsed with hexanes (200 mL) (Note 17). The volatiles are removed by rotary evaporation (780 to 90 mmHg, 30 °C bath temperature) to afford the crude reaction material as an orange oil (12.2 g) (Figure 11).

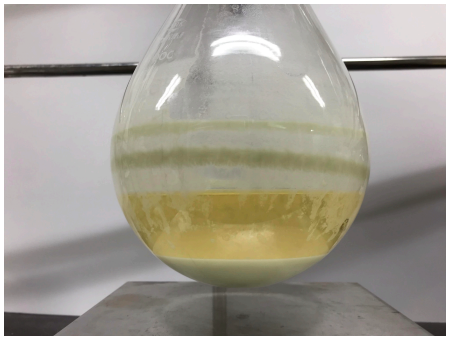


Figure 9. The crude reaction mixture after stirring with hexanes for 2 h

Figure 10. Celite filtration

Figure 11. Crude orange oil

The resulting oil is purified by column chromatography (Note 18) using silica gel (210 g) (Note 19). The fractions containing desired product are concentrated by rotary evaporation (780 to 100 mmHg, 30 °C bath temperature). The purified material is placed under vacuum (2.5 mmHg) for 3 h and then for an additional 1 h (0.5 mmHg) to afford azacyclotridecane (**2**) (7.06 g, 84% yield) as a light green oil (Figure 12) (Notes 20 and 21).

Figure 12. Azacyclotridecane (2). Product collected as a light green oil.

Notes

1. Prior to performing each reaction, a thorough hazard analysis and risk assessment should be carried out with regard to each chemical substance and experimental operation on the scale planned and in the context of the laboratory where the procedures will be carried out. Guidelines for carrying out risk assessments and for analyzing the hazards associated with chemicals can be found in references such as Chapter 4 of "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at https://www.nap.edu/catalog/12654/prudent-practices-in-the-laboratory-handling-and-management-of-chemical. See also "Identifying and Evaluating Hazards in Research Laboratories" (American Chemical Society, 2015) which is available via the associated website "Hazard Assessment in Research Laboratories" at https://www.acs.org/content/acs/en/about/governance/committees/chemicalsafety/hazard-assessment.html. In the case of this procedure, the risk assessment should include (but not necessarily be limited to) an evaluation of the potential hazards associated with nickel (II) chloride ethylene glycol dimethyl ether complex, 12-aminododecanolactam, phenylsilane, toluene, and ethyl acetate, sodium hydroxide, sodium chloride, sodium sulfate, hexane, triethylamine, silica gel, phosphomolybdic acid stain, ceric ammonium molybdate, and dimethyl fumarate, as well as the proper procedures for syringe pump addition and use of a reflux condenser.
2. All glassware was oven-dried prior to reaction set-up.
3. Nickel (II) chloride ethylene glycol dimethyl ether complex (98%) and 12-aminododecanolactam (98%) were purchased from Sigma-Aldrich and used as received (checkers). Nickel (II) chloride ethylene glycol dimethyl ether complex and 12-aminododecanolactam were purchased from Sigma-Aldrich and used as received (submitters).
4. Anhydrous and degassed toluene (99.5%) was purchased from FUJIFILM Wako Pure Chemical Corporation. The solvent: was dried and degassed prior to use on a Glass Contour solvent dispensing system (Nikko Hansen & Co. Ltd.) (checkers). Toluene was purchased from Fisher Scientific and freshly distilled over sodium metal. The solvent was placed through three freeze-pump-thaw cycles before use (submitters).

Submitters also noted that drying and degassing the toluene prior to use was found to be crucial for obtaining reproducibly high yields.

5. Phenylsilane (97%) was purchased from Sigma-Aldrich and used as received (checkers). Phenylsilane was purchased from Oakwood Chemical and used as received (submitters).
6. Slow addition of the phenylsilane was necessary to avoid an excess of hydrogen gas evolution.
7. Ethyl acetate (99.0%) was purchased from Kanto Chemical Co. Ltd. and used as received.
8. Sodium hydroxide (>97%) was purchased from Kanto Chemical Co. Ltd. and used as received.
9. Due to the evolution of hydrogen gas from quenching the reaction, slow addition of 1.0 M aqueous NaOH was necessary.
10. Sodium chloride (99.5%) was purchased from FUJIFILM Wako Pure Chemical Corporation and used as received.
11. The layers slowly separated in the separatory funnel over a time period of approximately 20 min.
12. Anhydrous Na_2SO_4 (99%) was purchased from FUJIFILM Wako Pure Chemical Corporation and used as received.
13. This crude mixture was dried under a higher vacuum for 1 h (1 mmHg) by submitters. Checkers omitted this process due to volatile nature of azacyclotridecane (**2**).
14. Hexane (95%) was purchased from Kanto Chemical Co. Ltd. and used as received.
15. When hexane was added to the crude reaction mixture, a pale green solid was formed. To ensure adequate mixing, a spatula was used to break apart the solid.
16. Celite was purchased from FUJIFILM Wako Pure Chemical Corporation and used as received.
17. TLC analysis of the mixture is shown below. The R_f value of the product and 12-aminododecanolactam (**1**) in hexane/ethyl acetate = 1/1 containing 2% triethylamine (v/v) was 0.23 and 0.35, respectively (Figure 13). The thin-layer chromatography plate (TLC silica gel 60 F_{254} plates, purchased from Merck KGaA) was then visualized using ceric ammonium molybdate stain.

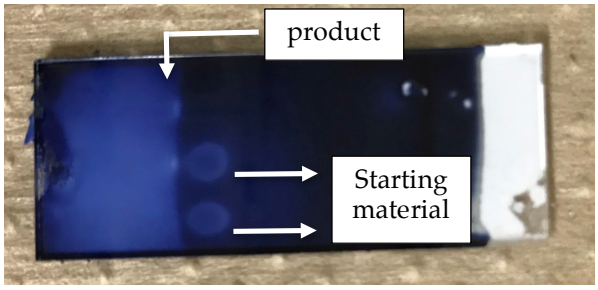


Figure 13. TLC analysis of the crude mixture

18. The column is wet packed in a 5.5 cm diameter x 35 cm height column using hexane. Then, the crude oil dissolved in hexane containing 5% triethylamine (v/v, 3.0 mL) (Note 22) is loaded onto the column. At that point, fraction collection (50-mL fractions, 28 x 195 mm) is begun and the column is eluted with hexane containing 5% triethylamine (v/v). The desired product is obtained in fractions No. 21 through 28 and transferred to a 500 mL round-bottomed flask with hexane (ca. 5 mL per fraction) (Note 23).
19. Silica gel (Silica gel 60N, spherical and neutral, 0.040-0.050 mm) was purchased from Kanto Chemical Co. Ltd. and used as received.
20. When the reaction was carried out on a half-scale, 3.37 g (83%) of the product was obtained.
21. Azacyclotridecane (**2**) exhibits the following physiochemical properties: TLC (hexane/EtOAc = 1/1, 2% triethylamine (v/v)), R_f = 0.25; IR (film): 2925, 2854, 2808, 1454, 1345, 1132 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ : 1.35–1.50 (m, 20H), 2.64 (app. t, J = 6.0 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ : 24.5, 25.3, 25.9, 26.5, 27.7, 47.8; HRMS (ESI) m/z calcd for $C_{12}H_{25}N$ $[M+H]^+$ 184.2060, found 184.2064; The purity of the sample was determined by ^1H qNMR using 17.0 mg of dimethyl fumarate (Note 24) as an internal standard and 17.3 mg of azacyclotridecane (**2**). Azacyclotridecane (**2**) was found to be 98% purity.
22. Triethylamine (99%) was purchased from Nacalai Tesque, Inc. and used as received.
23. The product was visualized by thin-layer chromatography using hexane/EtOAc = 1/1, 2% triethylamine (v/v). The thin-layer chromatography plate (TLC silica gel 60 F_{254} plates, purchased from Merck KGaA) was then visualized using phosphomolybdic acid stain. Once the TLC plate was stained using phophomolybdic acid, it was left

at ambient temperature (23 °C) for 30 min before visualizing the spot of the product.

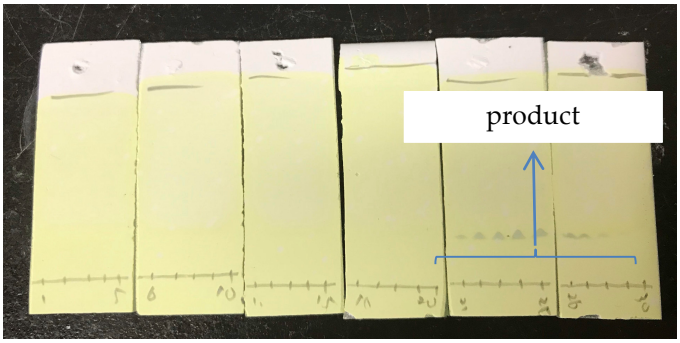


Figure 14. TLC analysis of column fractions

24. Dimethyl fumarate (>99%) was purchased from FUJIFILM Wako Pure Chemical Corporation and used as received.

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

Discussion

A rapidly growing area of research involves the manipulation of amides using nickel catalysis.[2,3,4,5] These transformations are attractive due to nickel's high abundance, low cost, and minimal CO_2 footprint.[6] The protocol described herein focuses on the nickel-catalyzed reduction of amides. This type of reduction often requires the use of Raney nickel, high temperatures, and high pressures of H_2 gas.[7,8] More general approaches have been made by Beller (Fe or Ru, 2° or 3° amides; Zn, 3° amides, Cu 2° amides),[9a,9b,9e,9f,9g] Nagahsima (Pt or Fe, 3° amides),[9c,9k] and Adolfsson (Mo, 3° amides).[9d] The procedure we report utilizes a simple nickel catalyst system.

A variety of amides, both secondary and tertiary, can be reduced to give the corresponding amine products (**1–13**, Figure 15). Amides with electron-donating and –withdrawing groups on the aromatic ring (**1** and **2**) and various heteroaromatic substrates (**3–5**) are well tolerated under these conditions. Aliphatic amides also undergo reduction as seen by amine products (**6–10**). It is noteworthy that significant steric bulk and various heteroatoms do not hinder catalysis. Other amides with various *N*-substituents can also be used in these reactions. For example, the *n*-octyl group can be used in place of the benzyl group shown by the formation of **11**. Tertiary amides including those with heterocycles give rise to amines **12** and **13**.

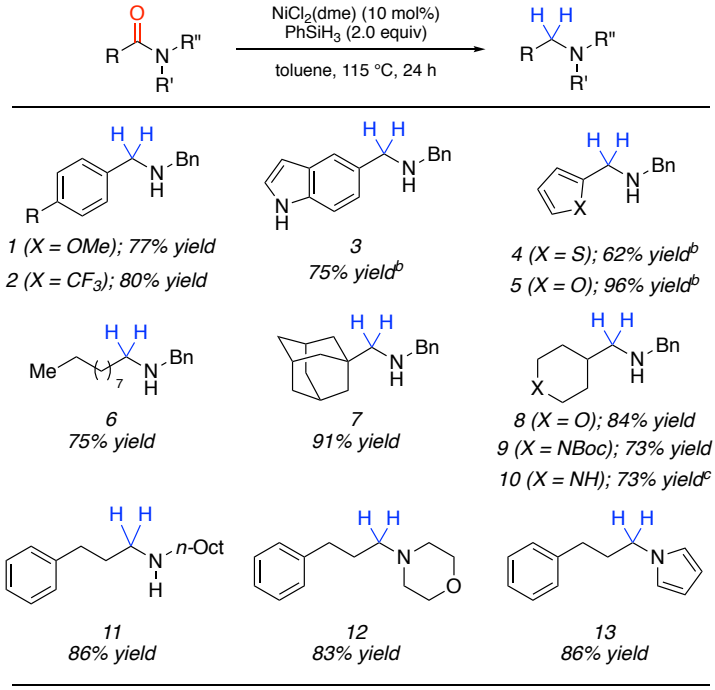
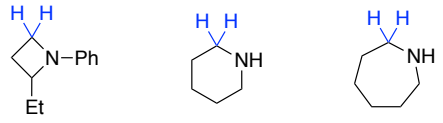


Figure 15. Reduction of secondary and tertiary amides. [a]Conditions unless otherwise stated: $NiCl_2$(dme) (10 mol%), substrate (1.0 equiv, 0.2 mmol), $PhSiH_3$ (2.0 equiv), and toluene (1.0 M) at 115 °C for 24 h in a sealed vial. Yields shown reflect the average of two isolation experiments. [b]$PhSiH_3$ (4.0 equiv) was used. [c]Yield determined by ^1H NMR analysis using hexamethylbenzene as an internal standard.

This chemistry can also be used to reduce lactam substrates as shown in Figure 16 by the formation of amines **14–16**. Thus, the method offers a simple and relatively mild alternative to conventional lactam reduction methods.[10]



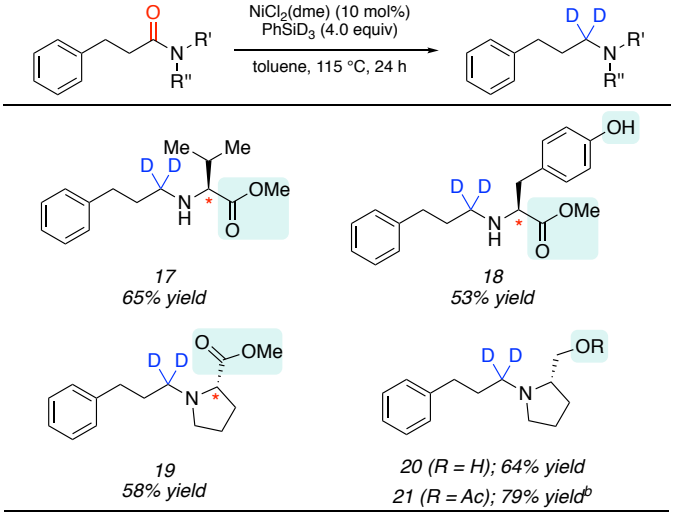
14
64% yield[b]

15
58% yield

16
83% yield

Figure 16. Cyclic amines prepared by reduction of the corresponding lactams. [a]Conditions unless otherwise stated: $NiCl_2$(dme) (10 mol%), substrate (1.0 equiv, 0.2 mmol), $PhSiH_3$ (2.0 equiv), and toluene (1.0 M) at 115 °C for 24 h in a sealed vial. Yield determined by ^1H NMR analysis using hexamethylbenzene as an internal standard due to product volatility. [b]Yield shown reflects the average of two isolation experiments.

A variety of optically enriched amino acid derivatives can be reduced using $PhSiD_3$ to give the corresponding α-deuteroamines (**17–21**, Figure 17). Deuteroamines are less prone to undergo metabolism compared to their nondeutero counterparts and are therefore sought after in drug discovery.[11,12] In these examples, the ester remains intact and epimerization is not observed.



17
65% yield

18
53% yield

19
58% yield

20 (R = H); 64% yield
21 (R = Ac); 79% yield[b]

Figure 17. Reduction of amino acid derivatives for the synthesis of α- deuteroamines. [a]Conditions unless otherwise stated: $NiCl_2$(dme) (10 mol%), substrate (1.0 equiv, 0.1 mmol), $PhSiD_3$ (4.0 equiv), and toluene (1.0 M) at 115 °C for 24 h in a sealed vial. Yields shown reflect the average of two isolation experiments. [b] $PhSiD_3$ (2.0 equiv) was used.

References

1. Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095, United States. E-mail: neilgarg@chem.ucla.edu. ORCID: 0000-0002-7793-2629. The authors are grateful to the University of California, Los Angeles, the UCLA Cota Robles Fellowship Program (M.R.), NIGMS (M.R., Diversity Supplement for R01 GM117016), and the NSF (B.J.S., DGE-1144087). These studies were also supported by shared instrumentation grants from the NSF (CHE-1048804) and the National Center for Research Resources (S10RR025631).
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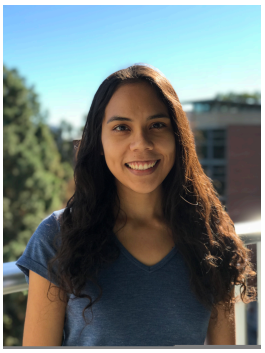
Appendix

Chemical Abstracts Nomenclature (Registry Number)

12-aminododecanolactam; (947-04-6)
Azacyclotridecane; (295-03-4)
Nickel (II) chloride ethylene glycol dimethyl ether complex (29046-78-4)
Phenylsilane (694-53-1)

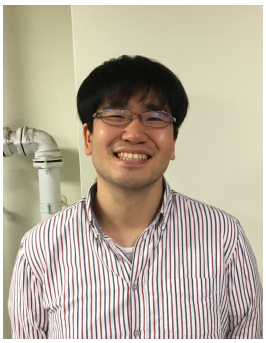
Bryan J. Simmons was born and raised in Los Angeles, CA and received his B.S. degree in chemistry at California Lutheran University. In 2014, he began his doctoral studies at the University of California, Los Angeles under the supervision of Prof. Neil K. Garg. His research interests lie in method development and total synthesis.



Melissa Ramirez was born in Los Angeles, CA and raised in Pasadena, CA. She received her B. A. in chemistry from the University of Pennsylvania (UPenn) in 2016. At UPenn, she performed research in the laboratory of Prof. Gary Molander. She began her doctoral studies at the University of California, Los Angeles in 2016 under the supervision of Prof. Neil K. Garg and Prof. Kendall N. Houk. Her research focuses on the study of strained, cyclic intermediates via a combination of experiments and computations.

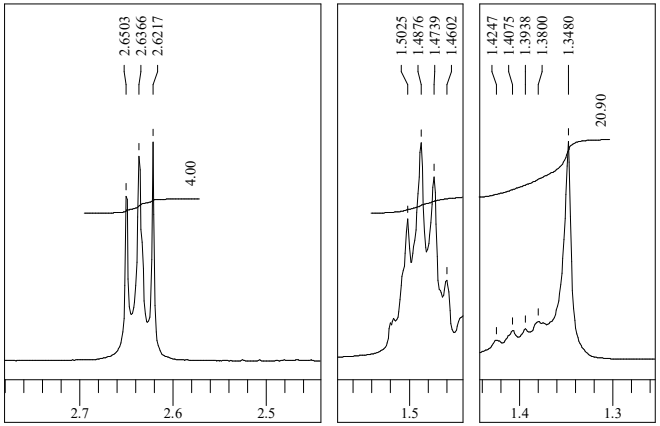
Neil Garg is a Professor of Chemistry and the Kenneth N. Trueblood Endowed Chair at the University of California, Los Angeles. His laboratory develops novel synthetic strategies and methodologies to enable the total synthesis of complex bioactive molecules.

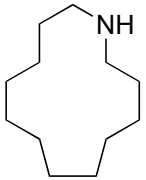
Tsukasa Shimakawa was born in Hyogo, Japan. He graduated from the University of Tokyo in 2017 with B.S. in Pharmaceutical Sciences. He is continuing his graduate studies at the University of Tokyo under the supervision of Prof. Masayuki Inoue. His research interests are in the area of the total synthesis of complex natural products.



Koichi Hagiwara was born in Kanagawa, Japan, in 1989. He received his B.Sc. (2013) and M.S. (2015) degrees in Pharmaceutical Sciences from the University of Tokyo under the supervision of Prof. Masayuki Inoue. After dropping out his Ph.D. course studies, he was appointed as an assistant professor in the Graduate School of Pharmaceutical Sciences at the University of Tokyo. His research interests include the total synthesis of bioactive and highly complex natural products.

Azacyclotridecane (**2**)

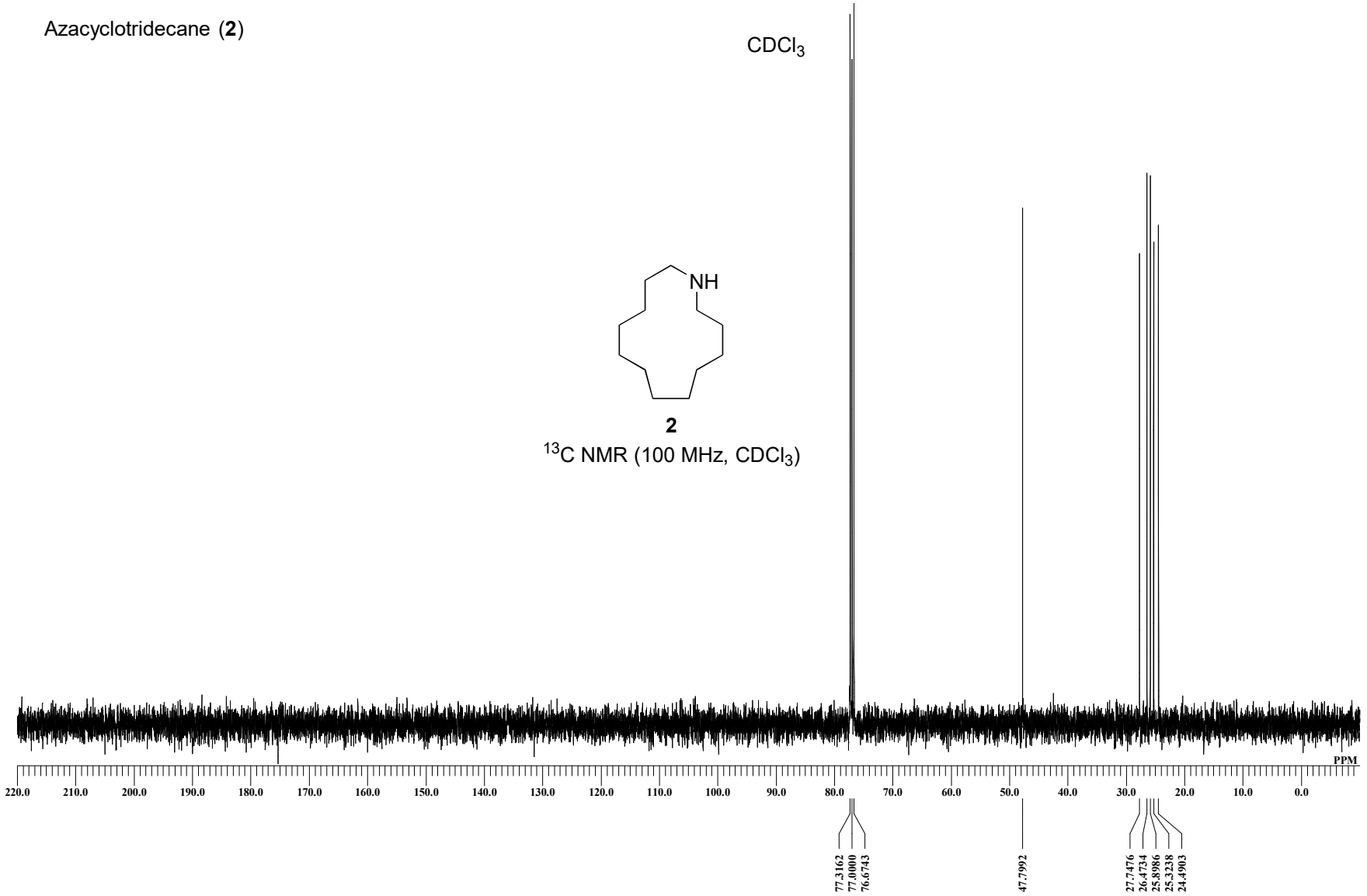




2

^{1}H NMR (400 MHz, $CDCl_3$)

Azacyclotridecane (**2**)



2

^{13}C NMR (100 MHz, $CDCl_3$)

^{1}H qNMR for Azacyclotridecane (**2**) with dimethyl fumarate

purity of Azacyclotridecane (**2**): 98%

	product (**2**)	internal standard (dimethyl fumarate)
Molecular Weight	183.34	144.13
amount	17.3 mg	17.0 mg
proton	4H	2H
area	3.17	2.00