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(3S,7aS)-3-(Trichloromethyl)tetrahydropyrrolo[1,2-c]oxazol-1(3H)-one: An Air and Moisture Stable Reagent for the Synthesis of Optically Active α-Branched Prolines

Checked by Gregory L. Aaron, Matthew M. Davis, and Kay M. Brummond.

1. Procedure

A. (3S,7aS)-3-(Trichloromethyl)tetrahydropyrrolo[1,2-c]oxazol-1(3H)-one. To a suspension of L(-)-proline (11.55 g, 100.3 mmol) (Note 1) in chloroform (500 mL) (Note 2) in a 1000-mL, single-necked, round-bottomed flask equipped with a magnetic stirring bar is added 2,2,2-trichloro-1-ethoxyethanol (23.27 g, 120.3 mmol) (Note 3 and 4). A 25-mL Dean-Stark trap topped with a reflux condenser, fitted with an argon adapter, is attached to the reaction vessel and the reaction mixture is heated at reflux using a heating mantle until L(-)-proline is no longer visibly suspended and consumption is observed by reverse phase TLC (Note 5). Heating is
discontinued and the volatile organics are removed under reduced pressure on a rotary evaporator (40 °C, 20–25 mmHg). The resulting brown, crystalline solid is recrystallized from ethanol. Boiling ethanol (30 mL) is added to the crude residue in the reaction flask warmed to 50 °C (bath temperature). The resultant mixture is stirred magnetically with heating on a hot plate until the mixture becomes homogenous. The solution is quickly poured into a 125-mL Erlenmeyer flask. The flask is fitted loosely with a septa and cooled slowly to room temperature then in an ice/water bath for 1 h. The resulting crystals are collected by suction filtration on a Büchner funnel and washed with 15 mL of ice-cold ethanol. The crystals are then transferred to a round-bottomed flask and dried overnight at 0.06 mmHg to provide (3R,7aS)-3-(trichloromethyl)tetrahydropyrrolo[1,2-c]oxazol-1(3H)-one (15.19–15.96 g, 62–65%) as colorless to light brown crystals (Note 6, 7, 8).

B. (3R,7aR)-7a- Allyl-3-(trichloromethyl)tetrahydropyrrolo[1,2-c]oxazol-1(3H)-one. A flame-dried, 500-mL, single-necked, round-bottomed flask equipped with a magnetic stirring bar and an adaptor with an argon inlet, is charged with N,N-diisopropylamine (10.0 mL, 71.4 mmol) (Note 9) and tetrahydrofuran (THF, 140 mL) (Note 10). The reaction vessel is cooled to −78 °C before n-butyllithium in hexane (1.6M, 46.0 mL, 73.6 mmol) (Note 11) is added via syringe. The reaction mixture is stirred for an additional 30 min at −78 °C. In a separate 250-mL single-necked, round-bottomed flask equipped with a magnetic stirbar under argon, (3R,7aS)-3-(trichloromethyl)tetrahydropyrrolo[1,2-c]oxazol-1(3H)-one (12.2 g, 49.9 mmol) is dissolved in THF (100 mL). This solution is cooled to 0 °C and stirred for 10 min. A cannula is used to rapidly deliver this THF solution to the LDA solution at −78 °C under argon over 5 min (Note 12). The resulting solution is stirred for an additional 30 min at −78 °C before the addition of allyl bromide (7.8 mL, 90 mmol) (Note 13) via syringe in a single portion. The reaction mixture is placed in a CO₂/CH₃CN bath to warm to −40 °C, where it is maintained for an additional 30 min (Note 14). The reaction mixture is then poured into a 1-L separatory funnel containing 300 mL of water. The aqueous solution is extracted with chloroform (3 x 300 mL). The combined organic extracts are dried over Na₂SO₄ and concentrated using a rotary evaporator (40 °C, 20–25 mm Hg) to afford (3R,7aR)-7a-allyl-3-(trichloromethyl)tetrahydropyrrolo[1,2-c]oxazol-1(3H)-one (11.34–11.92 g, 80–82%) as a brown oil (Note 15).
C. (R)-Methyl 2-allylpyrrolidine-2-carboxylate hydrochloride. A 500-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, a reflux condenser fitted with an argon inlet, a 300-mL pressure-equalizing additional funnel fitted with a rubber septum, and a glass stopper. The glass stopper is removed and the flask is charged with (3R,7aR)-7a-allyl-3-(trichloromethyl)tetrahydropyrrolo[1,2-c]oxazol-1(3H)-one (8.20 g, 29.0 mmol) and methanol (100 mL) (Note 16). Sodium metal (420 mg, 18.3 mmol) (Note 17) is added slowly (~1 piece every 2 min) over 30 min by removal of the glass stopper. The reaction mixture is stirred for an additional 30 min until sodium pieces are no longer visible (Note 18). The reaction vessel is cooled in an ice/water bath and the pressure-equalizing addition funnel is charged with acetyl chloride (40 mL, 563 mmol) (Note 19), which is added dropwise into the reaction mixture over 1 h (Note 20). The funnel is removed and replaced with a glass stopper and both stoppers are secured using Keck® clips. The resulting milky brown solution is heated to reflux until only baseline material is evident by thin layer chromatography (Note 21). The volatile organics are then removed using a rotary evaporator (40 °C, 20–25 mm Hg). The resulting oily solid is diluted with methylene chloride (50 mL). The precipitated sodium chloride is removed via filtration through a Büchner funnel washing with additional methylene chloride (10 mL). The filtrate is concentrated under reduced pressure by rotary evaporation (40 °C, 20–25 mm Hg). This process is repeated two additional times to afford (R)-methyl 2-allylpyrrolidine-2-carboxylate hydrochloride as an oil. Purification of the crude hydrochloride salt is achieved using flash silica gel chromatography eluting with a gradient of 95:5→90:10 CH₂Cl₂:MeOH (Note 22) to afford (R)-methyl 2-allylpyrrolidine-2-carboxylate hydrochloride (4.16–4.44 g, 71–74%) as an oil, which solidifies under reduced pressure (Note 23). An enantiomeric excess of >99% for the desired product was determined through synthesis of the Mosher amide under Schotten-Baumann conditions followed by NMR spectroscopy and HPLC analysis (Note 24).

2. Notes

1. L(-)-Proline (99+%) was used as received from Acros Organics.
2. Chloroform (ACS grade) was used without further purification from Fisher Scientific.
The original procedure reported by Germanas employed trichloroacetaldehyde or chloral. However, this reagent is regulated and difficult to obtain. The submitters have found that commercially available 2,2,2-trichloro-1-ethoxyethanol can be used as a masked form of chloral.

2,2,2-Trichloro-1-ethoxyethanol (98%) was used as commercially available and was obtained from Alfa Aesar.

Disappearance of L(-)-Proline (R$_f$ = 0.89) and formation of (3R,7aS)-3-(trichloromethyl)tetrahydropyrrolo[1,2-c]oxazol-1(3H)-one (R$_f$ = 0.26) was observed via reverse phase thin layer chromatography performed on Partisi® KC18 Silica Gel 60Å (200 µm thickness) on glass backed plates (1:1 H$_2$O/CH$_3$CN) visualizing with KMnO$_4$ TLC Stain (yellow spots). The reaction requires 15–19 h to reach completion, during which time a color change from a milky opaque to an orange solution is observed.

(3R,7aS)-3-(Trichloromethyl)tetrahydropyrrolo[1,2-c]oxazol-1(3H)-one$^{2,3}$ displays the following physical and spectral characteristics: mp 108–109 °C (lit.$^3$ 107–109 °C); optical rotation: [α]$_D$ = +34.0 (c 2, C$_6$H$_6$), lit.$^3$ [α]$_D$ = +33 (c 2, C$_6$H$_6$); $^1$H NMR (500 MHz, CDCl$_3$) δ: 1.70–1.79 (m, 1 H), 1.90–1.97 (m, 1 H), 2.08–2.14 (m, 1 H), 2.19–2.27 (m, 1 H), 3.11–3.15 (m, 1 H), 3.42 (ddd, J = 11, 7.5, 6 Hz, 1 H), 4.12 (dd, J = 9, 4.5 Hz, 1 H), 5.17 (s, 1 H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 25.3, 29.9, 57.9, 62.4, 100.6, 103.6, 175.5; IR (thin film) 2978, 2962, 2899, 2871, 1782, 1327, 1178, 1009, 959, 815, 791, 744 cm$^{-1}$; Anal. Calcd for C$_7$H$_8$Cl$_3$NO$_2$: C, 34.39; H, 3.30; N, 5.73. Found: C, 34.47; H, 3.28; N, 5.65.

Unlike the Seebach pivaldehyde/proline condensate, this product is air- and moisture-stable and can be stored upon the bench top with no decomposition by NMR spectroscopy after more than 30 days.

Following the submission of this procedure, (3R,7aS)-3-(trichloromethyl)tetrahydropyrrolo[1,2-c]oxazol-1(3H)-one is now commercially produced by AK Scientific, California, USA.

N,N-Diisopropylamine (99%) was purchased from Fisher Scientific and was freshly distilled from CaCl$_2$ prior to use.

Tetrahydrofuran (THF, 99.5%) was purchased from Sigma-Aldrich and was purified via a Sol-Tek ST-002 solvent purification system.

1.6 M $n$-Butyllithium in hexanes was purchased from Sigma-Aldrich and freshly titrated using the method developed by Love and Jones.$^4$

A color change is apparent as the enolate is formed. The LDA solution changes from light yellow, to dark red, to dark brown upon the addition of the oxazolinone.
13. Allyl bromide (98%) was used as received from Alfa Aesar.

14. Thin layer chromatography (TLC) on silica gel F254 (200 µm thickness) glass backed plates was used to monitor the alkylation. Developing the plate in 1:7 EtOAc:hexanes separates the product ($R_f = 0.44$) from the starting material ($R_f = 0.27$). Both the product and starting material can be visualized with KMnO4 TLC stain (yellow spots).

15. The allylated product is of sufficient purity to be used in the next step. However, an analytical sample was obtained by purifying 145 mg of the crude material via flash silica gel chromatography (Column inner diameter 1 cm; packed length 12.5 cm) eluting 1:7 EtOAc/hexanes to afford 111 mg of alkylated product. (3R,7aR)-7a- Allyl-3-(trichloromethyl)-tetrahydropyrrolo[1,2-c]oxazol-1(3H)-one displays the following physical and spectral characteristics: pale yellow oil, which slowly crystallizes upon standing at -10 °C; optical rotation: $[\alpha]_D = +44$ (c 2, CHCl3), $[\alpha]_D = +60$ (c 2, C6H6), lit.3 $[\alpha]_D = +44.6$ (c 2, CHCl3); $^1$H NMR (500 MHz, CDCl3) $\delta$: 1.60–1.70 (m, 1 H), 1.86–1.93 (m, 1 H), 2.02 (ddd, $J = 13.5, 10.0, 7.0$ Hz, 1 H), 2.13 (ddd, $J = 13.0, 8.0, 3.0$ Hz, 1 H), 2.55 (ddd, $J = 14.0, 8.5$ Hz, 1 H), 2.62 (dd, $J = 14.0, 6.5$ Hz, 1 H), 3.14–3.24 (m, 2 H), 4.98 (s, 1H), 5.17 (d, $J = 6.0$ Hz, 1 H), 5.20 (s, 1 H), 5.85–5.93 (m, 1 H); $^{13}$C NMR (100 MHz, CDCl3) $\delta$: 25.2, 35.2, 41.5, 58.3, 71.3, 100.4, 102.3, 119.9, 131.9, 176.2; IR (thin film) 3079, 2976, 2897, 1801, 1640, 1457, 1438, 1355, 1324, 1192, 1129, 1104, 1020, 922, 838, 803, 746 cm$^{-1}$; Anal. Calcd for C10H12Cl3NO2: C, 42.21; H, 4.25; N, 4.92. Found: C, 42.51; H, 4.31; N, 4.84.

16. Methanol (MeOH, ACS grade) was used as received and obtained from Fischer Scientific. Anhydrous MeOH can be employed, but the yield was unchanged as observed by the submitters.

17. Sodium metal cubes (99.95%) in mineral oil were supplied by Sigma-Aldrich. The sodium metal was cut into small pieces using a razor blade and weighed into a tared beaker containing hexanes to remove residual mineral oil prior to addition.

18. The deprotection was monitored by TLC using silica gel F254 (200 µm thickness) glass backed plates, 1:5 EtOAc:hexanes, KMnO4 TLC stain (yellow spots) observing consumption of the starting material ($R_f = 0.57$) and formation of the $N$-formyl ester intermediate ($R_f = 0.11$). It was observed that a full equivalent of sodium methoxide is not necessary for the opening of the lactone to the $N$-formyl ester intermediate.

19. Acetyl chloride (98%) was used as received from Sigma-Aldrich.
20. The addition of acetyl chloride must be conducted at a slow rate to avoid an exothermic reaction and loss of HCl gas. The submitters observed that if the addition is too fast, an additional quantity of acetyl chloride (~20 mL) generally has to be added to the reaction mixture once the solution is brought to reflux.

21. The reaction was monitored by TLC using silica gel F$_{254}$ (200 µm thickness) glass backed plates, 1:1 EtOAc:hexanes, KMnO$_4$ TLC stain, (yellow spots) for the disappearance of the intermediate $N$-formyl ester ($R_f = 0.25$), and other intermediate compounds until only the hydrochloride salt ($R_f = 0.00$) remains.

22. Flash silica gel chromatography of the final product employed a column with specifications of: inner diameter: 2.5 inches; packed length: 6 inches. Fractions of ~27 mL were collected in 16 x 150 mm test tubes. Fractions containing the desired product ($R_f = 0.47$) were determined by TLC (90:10 CH$_2$Cl$_2$:MeOH) with KMnO$_4$ TLC staining. These fractions were combined and concentrated under reduced pressure (40 °C, 20–25 mm Hg).

23. (R)-Methyl 2-allylpyrrolidine-2-carboxylate hydrochloride displays the following physical and spectral characteristics: brown oil that slowly solidifies to a brown solid (99 % $ee$); optical rotation: $[\alpha]_D = -83$ (c 2, CH$_2$Cl$_2$); $^1$H NMR (700 MHz, CDCl$_3$) $\delta$: 1.93 (bs, 1 H), 2.14 (bs, 2 H), 2.45 (bs, 1 H), 2.83–2.90 (m, 1 H), 3.03–3.10 (m, 1 H), 3.54 (bs, 1 H), 3.62 (bs, 1 H), 5.22 (d, $J = 9.8$ Hz, 1 H), 5.32 (d, $J = 16.8$ Hz, 1 H), 5.83-5.92 (m, 1 H), 9.55 (bs, 1 H), 10.64 (bs, 1 H); $^{13}$C NMR (176 MHz, CDCl$_3$) $\delta$: 22.4, 34.5, 39.2, 45.6, 53.7, 72.5, 121.4, 130.2, 170.0; IR (thin film) 3404, 2956, 2719, 2491, 1745, 1642, 1452, 1236 cm$^{-1}$; Anal. Calcd for C$_9$H$_{16}$ClNO$_2$: C, 52.56; H, 7.84; N, 6.81; Found: C: 52.24; H: 7.69; N: 6.66.

24. The $ee$ of the final product was determined via conversion of the final product to the Mosher amide using commercially available (S)-(+)-$\alpha$-methoxy-$\alpha$-trifloromethylphenylacetyl chloride (Note 25) under Schotten-Baumann conditions: In a 5-mL round-bottomed flask with a magnetic stir bar, (R)-methyl 2-allylpyrrolidine-2-carboxylate hydrochloride (26 mg, 0.15 mmol) was partitioned between CH$_2$Cl$_2$ (0.75 mL) and water (0.75 mL). NaOH (30 mg, 0.75 mmol) was added followed by commercially available (S)-(+)-$\alpha$-methoxy-$\alpha$-trifloromethylphenylacetyl chloride (0.03 mL, 0.16 mmol). The reaction mixture was stirred open to the air for 1 h before being transferred to a 30-mL separatory funnel using CH$_2$Cl$_2$ (20 mL) and diluted with H$_2$O. The aqueous layer was separated and the resulting organic layer
was washed with saturated NaHCO₃ (10 mL), 2 M HCl (10 mL), and brine (10 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated \textit{in vacuo}. The resulting crude product (47 mg) was analyzed by NMR spectroscopy and HPLC. \(^1\)H NMR spectroscopy of the crude material observed a single amide rotamer at room temperature. An analytical sample was obtained by purifying the crude material via flash silica gel chromatography (Inner diameter 1 cm; Packed Length 11.5 cm) eluting 2.5:97.5 to 10:90 EtOAc/hexanes to afford 25 mg of the Mosher amide. \(^1\)H NMR (700 MHz, CDCl₃) δ: 1.59–1.71 (m, 2 H), 1.88 (ddd, \(J = 13.3, 7.0, 4.9\) Hz, 1 H), 2.03 (ddd, \(J = 13.3, 9.8, 7.0\) Hz, 1 H), 2.83 (dd, \(J = 14.0, 7.0\) Hz, 1 H), 3.07 (ddd, \(J = 11.2, 7.0, 4.2\) Hz, 1 H), 3.18 (dd, \(J = 14.0, 7.7\) Hz, 1 H), 3.32 (ddd, \(J = 11.2, 8.4, 6.3\) Hz, 1 H), 3.71 (s, 3 H), 3.79 (s, 3 H), 3.18 (dd, \(J = 9.8, 0.7\) Hz, 1 H), 5.20 (d, \(J = 16.8\) Hz, 1 H), 5.81 (ddt, \(J = 17.5, 9.8, 7.0\) Hz, 1 H), 7.40–7.41 (m, 3 H), 7.58–7.60 (m, 2 H); \(^13\)C NMR (176 MHz, CDCl₃) δ: 24.0, 34.1, 37.8, 48.7, 52.2, 55.4, 69.7, 84.5 (q, \(J = 25.0\) Hz), 119.7, 123.5 (q, \(J = 290.4\) Hz), 127.3, 127.9, 129.3, 132.8, 132.9, 164.4, 173.5; \(^19\)F NMR (376 MHz, CDCl₃) δ: –69.8; HPLC purity of the amide was determined by dissolving a sample in CH₃CN and passing it through a Phenomenex Luna 3 micron particle size C18 column (Length 100 mm; Diameter 4.6 mm) using a 60:40 solution of 0.1 % TFA in H₂O and 0.01% TFA in CH₃CN at 1 mL/min over 70 min. The desired product was observed as a single peak at 42.48 min (>99% pure) that was compared to a mixture of both Mosher amide diastereomers (Note 26). See attached chromatograph below.
25. (S)-(+)‐α‐Methoxy‐α‐trifloromethylphenylacetyl chloride (>99.5% ee) was purchased from Aldrich and used without further purification.

26. The amine L-proline methyl ester hydrochloride was protected as the tert-butyloxycarbamate using di-tert-butyl dicarbonate and triethylamine. Subsequent alkylation and epimerization was accomplished by deprotonating with lithium diisopropylamide followed by addition of allyl bromide. The amine was liberated by treatment with trifluoroacetic acid. The amine was converted to the Mosher amide under Schotten-Baumann conditions.

**Waste Disposal Information**

All toxic materials were disposed of in accordance with “Prudent Practices in the Laboratory”; National Academy Press; Washington, DC, 1995.

3. Discussion

The synthesis of optically active amino acids and derivatives continues to be an important area of research for academic laboratories and the pharmaceutical industry. In 1995, Seebach reported an *Organic Syntheses* procedure for the synthesis of a proline/pivaldehyde condensate.
(3), which could be employed for the synthesis of optically active α-branched proline amino acids (cf. 4). However, difficulties are often encountered during the preparation of 3. The condensation of proline (1) and pivaldehyde (2) requires long reaction times in a low boiling solvent, which systematically needs to be replaced over 3-7 days. Since product 3 is extremely sensitive to air and moisture, rigorously anhydrous conditions are required to ensure that no moisture enters the system. In addition, pivaldehyde (2) is required in large excess (~6-7 equivalents) making this procedure economically prohibitive due to its high cost.

Scheme 1

Interestingly, Germanas and Wang reported an alternative to the Seebach oxazolinone, (3R, 7aS)-3-(trichloromethyl)tetrahydropyrrolo[1,2-c]oxazol-1(3H)-one (6), to generate optically active α-branched proline derivatives in good yields (cf. 7). Unlike the Seebach compound 3, the trichloro oxazolinone 6 is an air- and moisture-stable crystalline solid, which can be stored on the bench top for greater than 1 month with no decomposition or observed loss of optical purity. Furthermore, the preparation of 6 requires only a small excess of a choral (5) or choral hydrate.

Scheme 2

Despite the advantages of the trichloro oxazolinone 6 over the Seebach compound 3, it has seen little use in synthesis. Choral (5) is a regulated substance greatly limiting its commercially availability even for small (10–20 g) quantities. Secondly, the cleavage of the trichloro auxiliary from 7, though reported by Germanas to proceed in high yield is generally
reported by other groups to require >24h and proceeds in moderate to low yields.

As such, we have found that 2,2,2-trichloro-1-ethoxyethanol, which is commercially available, can be used as a chloral synthon resulting in a scalable procedure for the synthesis of the oxazolinone 6. In addition, we have discovered that the initial opening of the lactone to the N-formyl methyl ester intermediate is slow when using refluxing HCl in methanol. By employing the one-pot procedure described, exposure of the alkylated product (cf. 7) to sodium methoxide results in rapid conversion to the N-formyl methyl ester at room temperature. This compound is much more amenable to cleavage of the N-formyl group under refluxing HCl in methanol to reproducibly afford the desired R-allyl prolinate hydrochloride salt on a multigram scale.
1. Department of Chemistry, Colorado State University, Fort Collins, CO 80523-1872.


Appendix

Chemical Abstracts Nomenclature (Registry Number)

(S)-Proline; (147-85-3)
2,2,2-Trichloro-1-ethoxyethanol; (515-83-3)
(3R,7aS)-3-(Trichloromethyl)tetrahydropyrrolo[1,2-c]oxazol-1(3H)-one; (97538-67-5)
n-Butyllithium; (109-72-8)
N,N-Diisopropylamine; (108-18-9)
Allyl bromide; (106-95-6)
(3R,7aR)-7a- Allyl-3-(trichloromethyl)tetrahydropyrrolo[1,2-c]oxazol-1(3H)-one; (220200-87-3)
Sodium; (7440-23-5)
Acetyl chloride; (75-36-5)
(R)-Methyl 2-allylpyrrolidine-2-carboxylate hydrochloride (112348-46-6)
Robert M. Williams was born in New York in 1953 and attended Syracuse University where he received the B.A. degree in Chemistry in 1975. He obtained the Ph.D. degree in 1979 at MIT (W.H. Rastetter) and was a post-doctoral fellow at Harvard (1979-1980; R.B. Woodward/Yoshito Kishi). He joined Colorado State University in 1980 and was named a University Distinguished Professor in 2002. His interdisciplinary research program (over 250 publications) at the chemistry-biology interface is focused on the total synthesis of biomedically significant natural products, biosynthesis of secondary metabolites, studies on antitumor drug-DNA interactions, HDAC inhibitors, amino acids and peptides.

Gerald Artman III was born in Michigan in 1978. He received his B.Sc. in Chemistry from Eastern Michigan University in 1999. Gerald moved to the Pennsylvania State University at University Park for his graduate studies. Under the guidance of Professor Steven Weinreb, he explored new methodology development and alkaloid total synthesis. As a NIH Postdoctoral Fellow in the lab of Professor Robert M. Williams, Gerald completed the total synthesis of the stephacidin alkaloids. Since 2007, he has been employed at the Novartis Institutes for BioMedical Research in Cambridge, MA.

Ryan J. Rafferty was born in Denver, CO in 1976. He received his B.Sc. in Chemistry (Biochemistry Emphasis) from the University of Northern Colorado in 2000, where he remained to receive this B.Sc. in Biology and M.Sc. in Biochemistry under the supervision of Prof. Richard Hyslop. His master's degree focused on the toxicology and kinetic studies and development of metabolite assays of 6-thiopurine and its analogs. He is currently pursuing his Ph.D. at Colorado State University under the supervision of Prof. Robert M. Williams. His research is focused on the total synthesis of the antifungal alkaloid ambiguous family.
Gregory Aaron was born in 1985 in Franklin, Pennsylvania. In 2008 he received his B.S. degree in chemistry from the University of Pittsburgh. While pursuing his undergraduate degree he carried out research on a number of projects under the supervision of Prof. Kay Brummond.

Matthew Davis was born in 1981 in Park Forest, Illinois. In 2004 he received his B.S. degree in chemistry from Hope College in Holland, Michigan. He is currently pursuing graduate studies at the University of Pittsburgh, under the guidance of Prof. Kay Brummond. His research currently focuses on expanding the scope of the Rh(I)-catalyzed cyclocarbonylation reaction of allene-ynes.