A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

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.

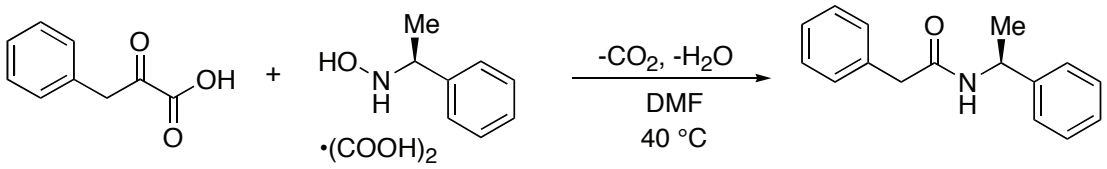
In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior 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.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.087.0218

AMIDE FORMATION BY DECARBOXYLATIVE CONDENSATION OF HYDROXYLAMINES AND α-KETOACIDS: *N*-[(1*S*)-1 PHENYLETHYL]-BENZENEACETAMIDE



Submitted by Lei Ju and Jeffrey W. Bode.[1]
Checked by Tatsuya Toma and Tohru Fukuyama.

1. Procedure

N-[(1S)-1-Phenylethyl]-benzeneacetamide. A 500-mL, single-necked, round-bottomed flask equipped with an 8.0 × 30 mm, octagon-shaped Teflon coated-magnetic stir bar, a reflux condenser, a rubber septum and nitrogen gas inlet is charged with phenylpyruvic acid (4.75 g, 28.9 mmol, 1.0 equiv) (Note 1) and *N*,*N*-dimethylformamide (289 mL) (Note 2). After stirring for 5 min, *N*-hydroxy-(*S*)-1-phenylethylamine oxalate (9.20 g, 40.5 mmol, 1.4 equiv) (Note 3) is added to the homogeneous solution (Note 4) as a solid in one portion at ambient temperature (23 °C). The reaction mixture is warmed to 40 °C in an oil bath and stirred at that temperature under a nitrogen atmosphere until completion (Note 5). The reaction is subsequently concentrated by rotary evaporation (50 °C, 10 mmHg) to approximately 20 mL. The resulting slightly yellow solution is allowed to cool to ambient temperature (23 °C) over the course of 30 min and diluted with ethyl ether (Et_2O) (200 mL) (Note 6). The solution is carefully poured into a 2-L separatory funnel, to which 1 N aqueous hydrochloric acid solution (200 mL) is added. The organic layer is separated and extracted with an additional portion of 1 N aqueous hydrochloric acid solution (200 mL), and the combined aqueous phase is extracted with Et_2O (3 × 200 mL). To the combined organic layers is added saturated sodium bicarbonate ($NaHCO_3$) solution (200 mL) and the mixture is partitioned. The basic aqueous solution is back-extracted with Et_2O (2 × 200 mL). The combined organic phase is washed with brine (400 mL) (Note 7), dried over anhydrous sodium sulfate (Na_2SO_4) (Note 8), and filtered. The filtrate is concentrated on a rotary evaporator (40 °C, 20 mmHg), and dried under reduced pressure (2 mmHg)

Org. Synth. **2010**, *87*, 218-225
Published on the Web 4/1/2010

overnight to afford a yellow, viscous oil (6.55–6.92 g, 95–100%) (Note 9). The resulting crude product is dissolved in dichloromethane (5 mL) and loaded on a column (6.0 cm i.d. × 20 cm) of SiO_2 (280 g) (Note 10, 11). After elution with 400 mL of 30% ethyl acetate in hexanes, the product is obtained by collecting 450 mL (18 × 25 mL fractions) of the eluent (Note 12). The combined fractions are concentrated by rotary evaporation (40 °C, 20 mmHg) followed by high vacuum (2 mmHg) to provide *N*-[(1*S*)-1 phenylethyl]-benzeneacetamide (5.92–5.96 g, 85–86%) as a white solid. The product is dissolved in hot Et_2O (300 mL) (50 °C, at reflux) and cooled to 4 °C overnight. The resulting crystals are collected by filtration on a Büchner funnel and washed with ice-cold Et_2O (50 mL). The crystals are then transferred to a 100-mL round-bottomed flask and dried overnight at 2.0 mmHg to afford a spindle-like solid (5.06–5.08 g, 73%) (Notes 13, 14, and 15).

2. Notes

1. Phenylpyruvic acid (98%) was purchased from Aldrich Chemical Co., Inc and was recrystallized from hot benzene before use. CAUTION: Benzene is carcinogenic, and must be handled with care.

2. *N*,*N*-Dimethylformamide (99.8%), purchased by the submitters from EMD Biosciences, Inc. and by the checkers from Wako Pure Chemical Industries, Ltd., was passed over activated molecular sieves 4A under an argon atmosphere before use.

3. *N*-Hydroxy-(*S*)-1-phenylethylamine oxalate was prepared from (*S*)-1-phenylethylamine following a reported procedure.[2] The oxalate salt of the hydroxylamine was recrystallized from hot ethanol and washed with ethyl ether. The oxalate salt form of the hydroxylamine is bench stable and more efficient in the ligation reaction. CAUTION: Free hydroxylamines may cause explosions under certain conditions. Careful handling is required when they are heated.

4. Phenylpyruvic acid was allowed to dissolve completely in *N*,*N*-dimethylformamide as a 0.1 M solution. White precipitate persisted if phenylpyruvic acid was used without recrystallization.

5. The progress of the reaction was monitored on reverse phase HPLC by following the disappearance of phenylpyruvic acid. Analytical conditions were: Column: Shiseido Capcell Pac C18; Eluent: 0.1% TFA in H_2O/MeCN; Flow rate: 1 mL/min; Detection: 216 nm, 235 nm, 288 nm, 221

nm; Gradient: 0–95% MeCN over 30 min. R_T of phenylpyruvic acid = 19.04 min; R_T of product = 21.56 min. The reaction typically takes 26–30 h to complete, while trace amounts of phenylpyruvic acid could still be observed at 288 nm.

6. Ethyl ether (Et_2O) (99.9%), unstabilized, was purchased by the submitters from EMD Biosciences, Inc. and by the checkers from Wako Pure Chemical Industries, Ltd., and used without further purification.

7. Sodium chloride (NaCl), crystalline, was purchased by the submitters from EMD Biosciences, Inc. and by the checkers from Wako Pure Chemical Industries, Ltd.

8. Sodium sulfate (Na_2SO_4) anhydrous, crystalline, was purchased by the submitters from EMD Biosciences, Inc. and by the checkers from Wako Pure Chemical Industries, Ltd.

9. ^{1}H NMR analysis by the submitters indicated a high purity of the crude product, which was contaminated by 3 wt. % of residual *N*,*N*-dimethylformamide. No residual *N*,*N*-dimethylformamide was detected by the checkers and the crude product was obtained as a yellow solid.

10. The column was packed by the submitters with EMD Silica Gel 60 (230-400 Mesh, Art 7747) and by the checkers with Silica Gel 60 purchased from Kanto Chemical Co, Inc.

11. Thin layer chromatography (TLC) was performed by the submitters on EMD precoated plates (silica gel 60 F_{254}, Art 5715, 0.25 mm) and by the checkers on Merck precoated plates (silica gel 60 F_{254}, 0.25 mm). TLC analysis of the crude product (with elution of 30% EtOAc/Hexanes) was visualized with a 254-nm UV lamp and phosphomolybdic acid stain. The crude mixture contained desired product with R_f = 0.22 (blue), and a trace spot on the baseline.

12. The checkers found that the column chromatographic purification could be omitted. Direct recrystallization from hot Et_2O afforded the ligation product in a similar yield (5.05-5.09 g, 73%).

13. The pure product exhibits the following physical and spectroscopic properties: mp 117.4–118.6 °C; $[\alpha]_D^{20}$ +0.97 (*c* 1.00, $CHCl_3$); IR (KBr, thin film): ν 3306 (s, NH), 3062, 3029, 5975, 1645 (s, C=O, amide), 1541, 1495, 1446, 1413, 1357, 1337, 1247, 1206, 1128, 1018, 760 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.40 (d, *J* = 7.2 Hz, 3 H), 3.58 (s, 2 H), 5.12 (quintet, *J* = 7.2 Hz, 1 H), 5.60 (br s, 1 H), 7.14–7.40 (m, 10 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.8, 43.9, 48.7, 125.9, 127.2, 127.3, 128.6, 129.0, 129.3, 134.8, 143.0, 170.0; HRMS (ESI) *m/z* calcd. for $C_{16}H_{18}NONa$ ($[M+Na]^+$) 262.1208;

found 262.1201; Anal. calcd. for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85; found: C, 80.14; H, 7.16; N, 5.85.

14. When 1.0 equiv of (*S*)-*N*-1-phenylethylhydroxylamine oxalate was used instead of 1.4 equiv relative to phenylpyruvic acid, the yield of the product was reduced to 65% due to decomposition of the hydroxylamine upon heating. The reaction rate was observed by HPLC to be slower when 10:1 DMF:H_2O was used as solvent.

15. The enantiomeric purity was shown by the submitters to be > 99% ee by SFC analysis on a chiral stationary phase. Analytical conditions were: Column: Chiralcel OJ-H; Eluent: MeOH and super critical CO_2; Flow rate: 1 mL/min; Detection: 220 nm, 254 nm; Gradient: 5% MeOH hold 0.1 min, 5–80% MeOH 13 min. R_T of racemic standard = 4.81 min, 5.40 min; R_T of ligation product = 5.40 min. The checker determined the enantiomeric purity by HPLC analysis. Analytical conditions were: Column: Chiralcel OD-H; Eluent: 15% *i*-PrOH/*n*-hexane; Flow rate: 1 mL/min; Detection: 220 nm, 254 nm; R_T of racemic standard = 25.32 min, 26.57 min; R_T of ligation product = 26.57 min.

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

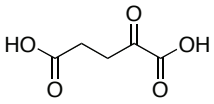
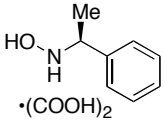
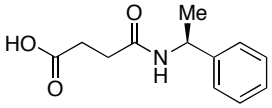
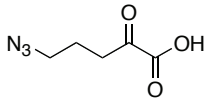
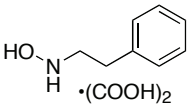
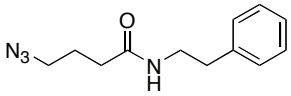
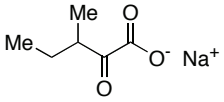
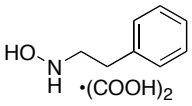
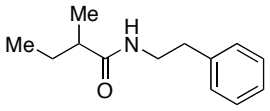
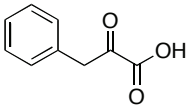
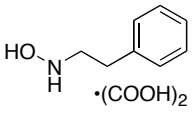
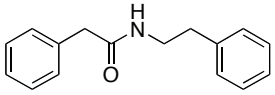
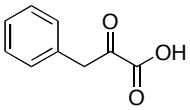
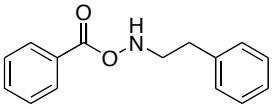
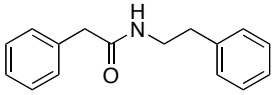
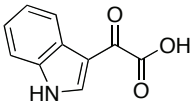
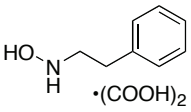
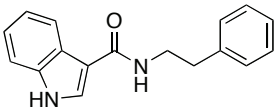
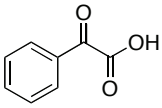
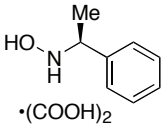
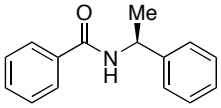
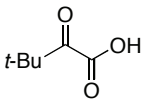
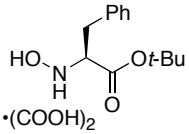
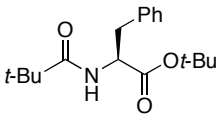
The construction of an amide bond generally involves activation of carboxylic acids as acyl halides, acyl azides, anhydrides, or esters followed by reaction with an amine.[3] Employing common activating reagents complicates the amide formation with racemization, difficult purification, protection of reactive functionalities and deprotection steps. Therefore, chemoselective amide-bond forming reactions are in demand.[4,5] We have developed a novel approach to amide synthesis[6] by decarboxylative condensation of *N*-alkyl hydroxylamines[7] and α-ketoacids.[8]

Decarboxylative condensation of *N*-hydroxy-(*S*)-1-phenylethylamine oxalate and phenylpyruvic acid illustrates the amide bond-forming protocol under mild, simple condition. This method is reagent/catalyst-free, proceeds cleanly by simply mixing the two ligation partners in polar solvents with gentle heating, and produces only innocuous, volatile byproducts. A variety

of functionalities have been demonstrated to be compatible with the ligation conditions including carboxylic acids, azides, amines, alcohols, and heterocyclic substrates (Table 1).[9] Benzoyl-protected hydroxylamine undergoes the ligation reaction with a similar outcome to the use of the free hydroxylamine oxalate salt. The steric environment due to substituents adjacent to the ligation centers affects coupling efficiency. A more hindered junction (Entry 8) gave the ligation product in lower yield even when heated to 60 °C.

The ligation between α-ketoacids and hydroxylamines is a powerful, chemoselective strategy that proceeds in the presence of reactive functional groups without activating reagents or catalysts. This method should find application in circumstances that require convergent synthesis of amides in the presence of unprotected functionalities.

Table 1. Decarboxylative Condensation of α-Ketoacids and *N*-Alkyl Hydroxylamines

Entry	α-Ketoacid	Hydroxylamine	Ligation product	Yield[a] (%)
1				90
2[b]				63[c]
3				81
4				78
5				80
6				56
7				43[d]
8[c]				27

[a] Isolated yield, entries are average of two experiments on a 0.2 mmol scale. [b] 5-azido 2-oxopentanoic acid was prepared from the corresponding phosphorous ylide via DMDO oxidation.[10] [c] Yield was calculated from the starting phosphorous ylide over two steps. [d] *N*-Benzylidene-(*S*)-±-α-methylbenzylamine *N*-oxide was isolated as a major byproduct in 33% yield. [e] Reaction was carried out at 60 °C.

1. Roy and Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, Philadelphia, PA 19104. Current address: Laboratorium für Organische Chemie, ETH-Zürich, CH-8093, Switzerland. Email: bode@org.chem.ethz.ch

2. Tokuyama, H.; Kuboyama, T.; Fukuyama, T. *Org. Synth*. **2003**, *80,* 207-212.
3. Montalbetti, C. A. G. N.; Falque, V. *Tetrahedron* **2005**, *61*, 10827-10852.
4. For other strategies in chemoselective amide-forming ligation reactions see: (a) Dawson, P. E.; Muir, T. W.; Clark-Lewis, I.; Kent, S. B. H. *Science* **1994**, *266*, 776-779. (b) Nilsson, B. L.; Kiessling, L. L.; Raines, R. T. *Org. Lett*. **2001**, *3*, 9-12. (c) Saxon, E.; Armstrong, J. I.; Bertozzi, C. R. *Org. Lett*. **2000**, *2*, 2141-2143. (d) Crich, D.; Sana, K.; Guo, S. *Org. Lett*. **2007**, *9*, 4423-4426.
5. Shangguan, N.; Katukojvala, S.; Greenberg, R.; Williams, L. J. *J. Am. Chem. Soc*. **2003**, *125*, 7754-7755.
6. Bode, J. W.; Fox, R. M.; Baucom, K. D. *Angew. Chem. Int. Ed*. **2006**, *45*, 1248-1252.
7. For a review on hydroxylamines see: Ottenheijm, H. C. J.; Herscheid, J. D. M. *Chem. Rev*. **1986**, *86*, 697-707.
8. For a review on ketoacids see: Cooper, A. J. L.; Ginos, J. Z.; Meister, A. *Chem. Rev*. **1983**, *83*, 321-358.
9. For the application of this reaction to the synthesis of peptides containing unprotected side chains, see (a) Ju, L.; Lippert, A. R.; Bode, J. W. *J. Am. Chem. Soc*. **2008**, *130*, 4253-4255. (b) Ju, L.; Bode, J. W. *Org. Biomol. Chem*. **2009**, *7*, 2259-2264.
10. Wasserman, H. H.; Peterson, A. K. *J. Org. Chem*. **1997**, *62*, 8972-8973.

Appendix
Chemical Abstracts Nomenclature; (Registry Number)

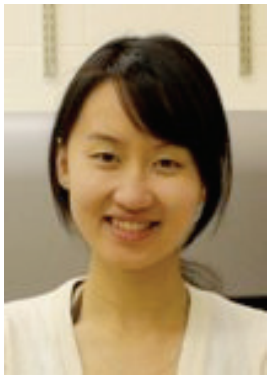
Phenylpyruvic acid: α-Oxobenzenepropanoic acid, 2-Oxo-3-phenylpropionic acid; (156-06-9)

N, N-Dimethylformamide: DMF; (68-12-2)

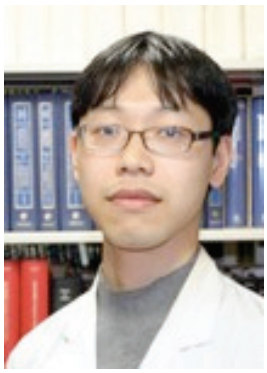
(*S*)-(α-Methylbenzyl)hydroxylamine oxalate salt: (α*R*)-*N*-Hydroxy-α-methyl-benzenemethanamine ethanedioate salt; (78798-33-1)

Benzeneacetamide, *N*-[(1*S*)-1-phenylethyl]-: 2-phenyl-*N*-(1-phenylethyl)acetamide; (17194-90-0)

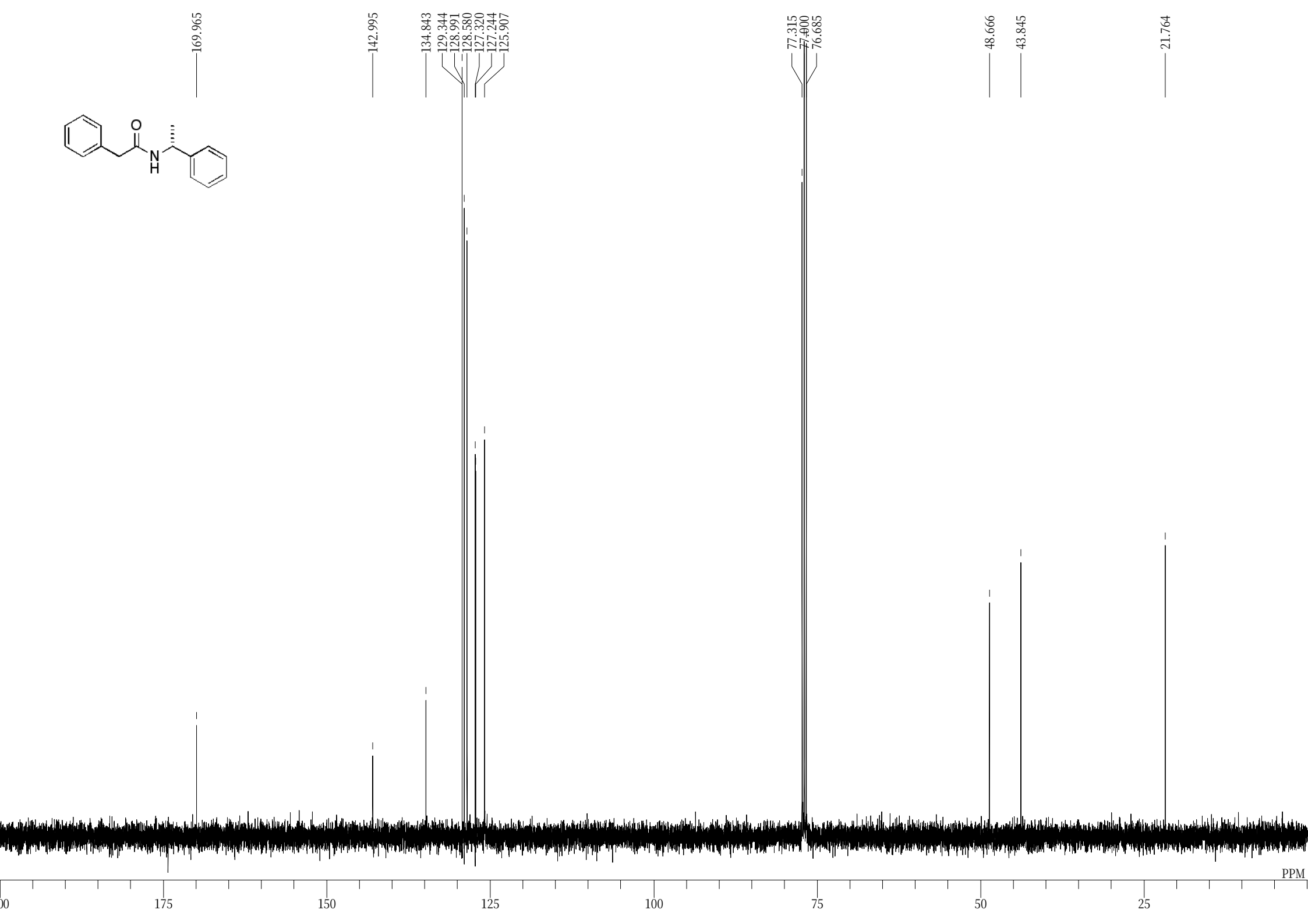
Jeffrey W. Bode was born in California in 1974 and studied chemistry and philosophy at Trinity University in San Antonio, Texas. He received his Dok. Nat. Sci. from the Eidgenössicsche Technische Hochschule (ETH) in Zürich, Switzerland with Prof. Erick M. Carreira in 2001. Following a JSPS Postdoctoral Fellowship with Prof. Keisuke Suzuki at the Tokyo Institution of Technology, he joined the faculty of the University of California, Santa Barbara as an Assistant Professor in 2003. In 2007, he joined the University of Pennsylvania in Philadelphia, Pennsylvania as an Associate Professor of Chemistry and in 2010 returned to ETH-Zürich as Professor of Chemistry. His research interests include the development of new synthetic methods, catalysis, peptide synthesis, and bioorganic chemistry.

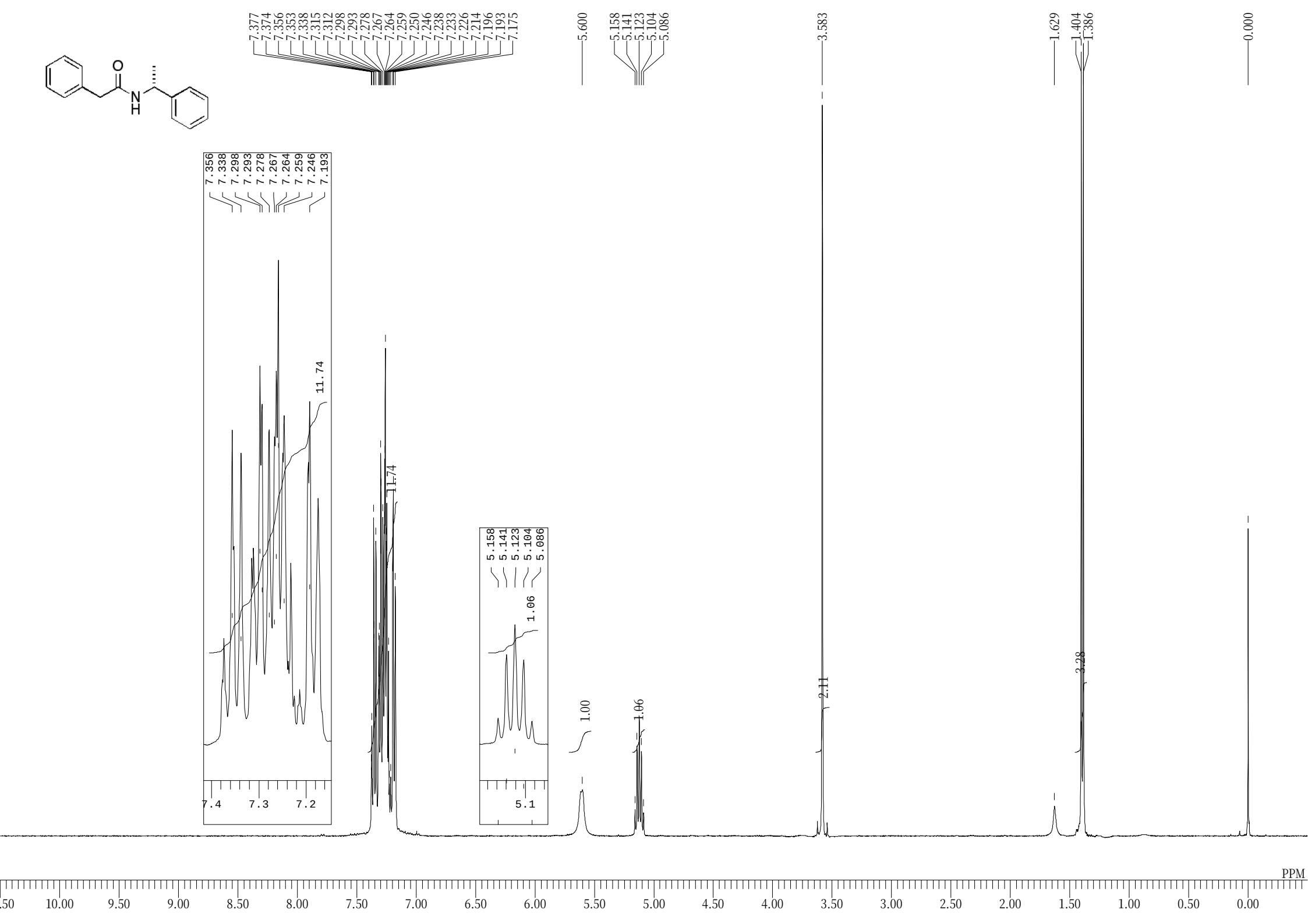


Lei Ju was born in Dandong, China in 1982. In 2005, she received her B.S degree in chemistry/biochemistry from University of California, San Diego, where she conducted research with Yoshihisa Kobayashi. She subsequently started her graduate studies at University of California, Santa Barbara under the supervision of professor Jeffrey W. Bode. Her research efforts focused on the amide bond-forming ligations between a-ketoacids and hydroxylamines. In the summer of 2007, she moved to University of Pennsylvania in Philadelphia, PA to continue with her research.



Tatsuya Toma was born in 1984 in Saitama, Japan. He graduated in 2007 and received his M. S. degree in 2009 from the University of Tokyo. The same year he started his Ph. D. study under the supervision of Professor Tohru Fukuyama. His current interest is enantioselective total synthesis of complex natural products.


169.965
142.995
134.843
129.344
128.991
128.580
127.320
127.244
125.907
77.315
77.000
76.685
48.666
43.845
21.764
O
N
H
PPM
00
175
150
125
100
75
50
25


7.377
7.374
7.356
7.353
7.338
7.315
7.312
7.298
7.293
7.278
7.267
7.264
7.259
7.250
7.246
7.238
7.233
7.226
7.214
7.196
7.193
7.175
5.600
5.158
5.141
5.123
5.104
5.086
3.583
1.629
1.404
1.386
0.000
11.74
1.06
1.00
2.11
3.28
PPM