Synthesis of Cyclobutanes by Lewis Acid-Promoted Ketene-Alkene [2+2] Cycloadditions

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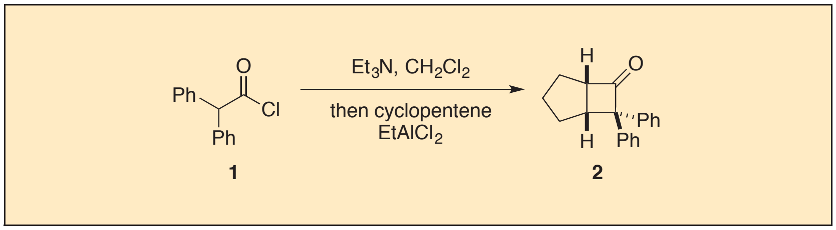

Procedure

A. *7,7-Diphenylbicyclo[3.2.0]heptan-6-one* (**2**). A two-necked, 500 mL round-bottomed flask equipped with a magnetic stir bar (1.9 x 5.0 cm, Teflon-coated, egg-shaped) is flame-dried under vacuum and then allowed to cool. The flask is backfilled with nitrogen and diphenylacetyl chloride (**1**, 9.68 g, 37.8 mmol, 1.00 equiv, 90% technical grade), is weighed out on the benchtop, and added (Note 1). The flask is evacuated and backfilled with nitrogen three times, and then fitted with a rubber septum and Schlenk nitrogen line. Dry dichloromethane (38.0 mL) and triethylamine (5.4 mL, 38.7 mmol, 1.02 equiv) are added by syringe through the septum and the mixture became yellow and heterogeneous (Figure 1) within minutes (Notes 2, 3, and 4). The reaction is stirred at room temperature for 30 min. The flask

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Figure 1. Reaction Mixture after Addition of Triethylamine

is placed in a dry ice/acetone bath (-78 °C) and cyclopentene (7.0 mL, 79.2 mmol, 2.1 equiv) is added down the walls of the flask by syringe through the septum (Note 5). The rubber septum is then quickly replaced with a 250 mL addition funnel equipped with a rubber septum that had been oven-dried and flushed with nitrogen. Ethylaluminum dichloride (95.0 mL, 95.0 mmol, 2.51 equiv, 1 M in hexanes) is added by syringe through the septum to the addition funnel (Notes 6 and 7). The solution of ethylaluminum dichloride is added dropwise to the flask over 50 min with continuous stirring and cooling (Notes 8, 9, and 10). After the addition, the reaction is stirred for 1 h at –78 °C (Figure 2).

Figure 2. Reaction Mixture after Addition of Ethylaluminum Dichloride

The addition funnel is removed and triethylamine (5 mL) is added down the walls of the flask over 5 min to quench the reaction. Deionized water (20 mL) is added directly to the reaction dropwise over 15 min. The flask is removed from the dry ice/acetone bath and the reaction is stirred until it reached room temperature (Note 11). As the solution warmed the color changed from brown to a light yellow. When the reaction reaches room temperature (~30 min) diethyl ether (100 mL) is added to the flask followed by 1 mL portion-wise addition of 1M HCl (100 mL) over 10 minutes with pipette (Notes 12 and 13) (Figure 3). The mixture stirred until it became mostly homogenous (~15 min). The biphasic mixture is then transferred to a 1000 mL separatory funnel. Diethyl ether (10 mL) and 1M HCl (10 mL) are used to rinse the round-bottomed flask and are then added to the separatory funnel. The aqueous layer is separated from the organic layer. The aqueous layer is washed with diethyl ether (100 mL). The layers are separated again; the organic phases are combined, and then are washed with 1M sodium hydroxide (100 mL) (Note 14). The separated organic layer is dried with sodium sulfate (50 g) over 10 min, gravity filtered through filter paper into a 500 mL round-bottomed flask and concentrated via rotary evaporator (ca. 20 mmHg, water bath temperature 30 °C) (Note 15).

Figure 3. Reaction Mixture after Addition of HCl

The crude residue is purified by a combination of silica gel flash column chromatography and recrystallization. Column chromatography using EtOAc and hexanes as eluent (Notes 16, 17 and 18) yielded the title compound as an air and moisture stable, light yellow amorphous solid, containing a small amount of impurities.

The chromatographed mixture of product and impurities is purified by recrystallization using hexanes and diethyl ether. To the crude solid in a 250 mL round-bottomed flask is added hexanes (50 mL) and diethyl ether (10 mL), and the resulting solution is swirled vigorously and gently warmed with a heat gun until all solids dissolved. The flask is loosely capped and left to sit at room temperature for 24 h while white needles form (Note 19). The mother liquor is decanted away into a 100 mL round-bottomed flask and the crystals are collected via vacuum filtration on a fritted Büchner funnel. The resulting crystals are transferred to a pre-weighed 250 mL round-bottomed flask and dried at 0.1 mmHg for 3 h to yield **2** (5.29 g, 20.16 mmol, 53%) as air and moisture stable white needles (Note 20) (Figure 4).

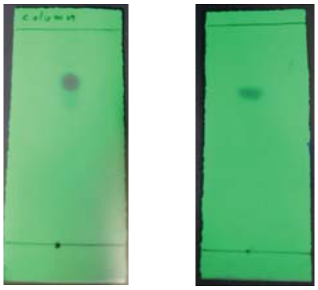
Figure 4. White Crystalline Product

An additional crop of crystals could be obtained by a second recrystallization. The mother liquor is concentrated in a 100 mL round-bottomed flask via rotary evaporator (ca. 20 mmHg, water bath temperature 30 °C) to yield a white solid. To the crude solid is added hexanes (15 mL) and diethyl ether (3 mL) and the resulting solution is swirled vigorously and gently heated with a heat gun until all solids dissolved. The flask is loosely capped and left to sit at room temperature for 24 h while white needles form. The mother liquor is decanted away and the crystals are collected via vacuum filtration on a fritted Büchner funnel. The resulting crystals are transferred to a pre-weighed 100 mL round-bottomed flask and dried at 0.1 mmHg for 3 h to yield **2** (1.09 g, 4.15 mmol, 11%, total of 64% yield) (Notes 20 and 21).

Notes

1. Diphenylacetyl chloride (90% technical grade) is purchased from Sigma Aldrich and used as received.
2. Dichloromethane was collected in an oven-dried (140 ºC for 24 h) 250 mL Schlenk flask, which had been purged with argon atmosphere by three evacuation-backfill cycles from a dry solvent system (Innovative Technology).

3. Triethylamine (>99.5%) was purchased from Sigma Aldrich and used as received.
4. Upon the addition of triethylamine the solution becomes a canary yellow color and a white solid forms within minutes.
5. Cyclopentene (97%) was purchased from Alfa Aesar and used as received.
6. Ethylaluminum dichloride (1 M in hexane) was purchased from Sigma Aldrich and used as received.
7. Excess ethylaluminum dichloride (>1 equiv) is necessary due to product inhibition and reaction with Et_3NHCl. For details see Ref 3a.
8. Transfer and addition of ethylaluminum dichloride should be performed carefully, in small portions, since it reacts violently with water. The transfer of ethylaluminum dichloride to the addition funnel typically requires ~15 min.
9. The rate of the addition was held at approximately one drop every two seconds.
10. During the addition, the reaction smokes and the mixture becomes a dark red/black color.
11. After the bath is removed, vigorous stirring is maintained to prevent excess bubbling/bumping.
12. The quenching process must be completed very slowly to avoid excessive bubbling and bumping.
13. Hydrogen chloride (12 M aqueous) was purchased from Merck and was used as received.
14. Sodium hydroxide was purchased from Honeywell and was used as received.
15. Sodium sulfate was purchased from Merck and was used as received.
16. Thin layer chromatograph was performed on silica gel 60 F_{254} TLC plate (Merck TLC Silica Gel 60 Glass Plates, with 20% EtOAc in hexanes as eluent. The following R_f value was observed (visualized under 254 nm UV light and $KMnO_4$): R_f (product): 0.68 Picture of TLC plate is shown below (A: mixture after column chromatography; B: product after recrystallization (Figure 5).



A **B**

Figure 5. TLC Analysis of A) Product Mixture after Column and B) Product after Recrystallization

17. Silica gel (pore size 60 Å, 230-400 mesh particle size, 40-63 μm particle size) was purchased from Sigma Aldrich (catalog number: 60737) and used as received.
18. Dichloromethane (10 mL) was added to the crude mixture. The solution of crude product was loaded onto a column packed with silica gel slurry in hexanes. Column is 9 cm in diameter, height of silica gel is 20 cm. Gradient elution using hexanes (50 mL), 5% EtOAc in hexanes (100 mL), 10% EtOAc in hexanes (200 mL), 15% EtOAc in hexanes (240 mL), 30% EtOAc in hexanes (580 mL), 40% EtOAc in hexanes (320 mL), and 50% EtOAc in hexanes (800 mL) were collected in 65 mL fractions. All fractions containing product (including mixed fractions) were collected.
19. Crystals typically appeared within 1 h.
20. The product was isolated as a white needles and had the following characteristics: mp = 90–92 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.21–1.36 (m, 1H), 1.51–1.70 (m, 3H), 1.77–1.87 (m, 1H), 2.15 (dd, *J* = 11.2, 6.3 Hz, 1H), 3.70–3.75 (m, 2H), 7.18–7.21 (m, 2H), 7.26–7.30 (m, 4H), 7.32–7.35 (m, 2H), 7.44–7.47 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 26.4, 29.4, 29.5, 41.6, 61.88, 75.9, 126.5, 126.8, 127.0, 128.4, 128.7, 140.1, 141.7, 214.4. IR (neat): 2950, 2932, 2864, 1760, 1490, 1445, 1148, 1079, 1031, 834, 743, 695, 662, 604, 567, 529, 512, 473 cm^{-1}. HRMS (MM: EI): *m*/*z* calcd for $C_{19} H_{19} O_{1}$ $[M]^+$: 263.1430. Found: 263.1432. Anal. Calcd for $C_{19} H_{18} O_{1}$: C, 86.99; H, 6.92; Found: C, 87.08; H, 6.87.
21. A reaction performed on half-scale provided 3.30 g (67%) of the desired product.

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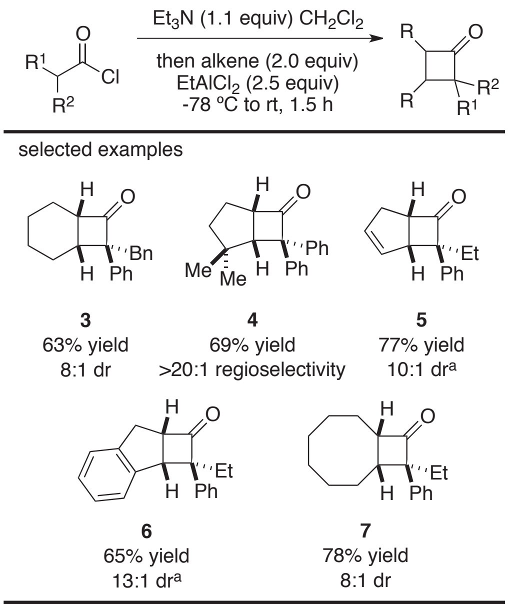
Discussion

Ketene-alkene [2+2] cycloadditions represent a useful method to construct cyclobutanones, a valuable functionality in organic synthesis.[2] These reactions have predominately relied on the inherent reactivity of each coupling partner. Recently, we disclosed Lewis acid-promoted [2+2] ketene-alkene cycloadditions.[3] These reactions demonstrated improved reactivity, stereo- and regioselectivity compared to the thermal cycloadditions. This method is exemplified by the above procedure and is applicable for a variety of alkenes and ketenes (Table 1 **3**-**7**).

Table 1. Representative Scope of Lewis acid-promoted ketene-alkene [2+2] cycloadditions



3
63% yield
8:1 dr

4
69% yield
>20:1 regioselectivity

5
77% yield
10:1 dr[a]

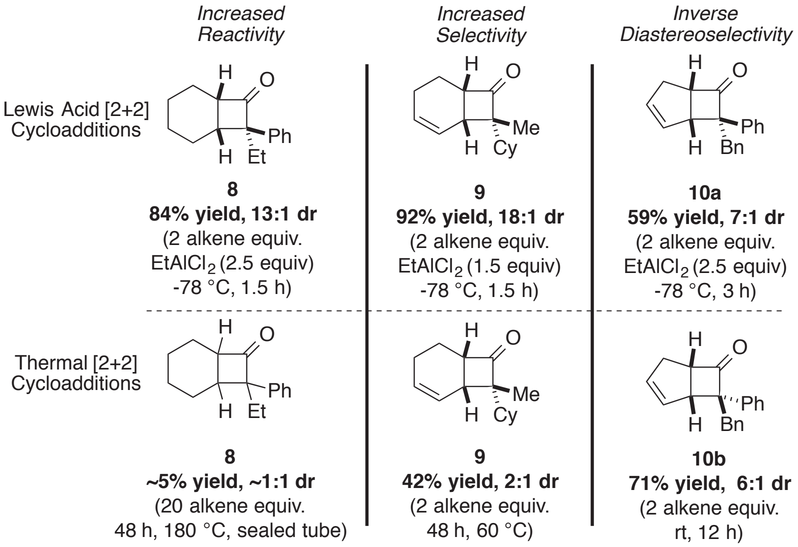
6
65% yield
13:1 dr[a]

7
78% yield
8:1 dr

[a] Reaction was performed at –78 °C for 3 h.

Several points regarding the Lewis acid-promoted cycloadditions are noteworthy (Table 2). (1) When compared to thermally-induced reactions, Lewis acid-promoted variants give rise to increased yields for unactivated alkenes. For example, Lewis acid-promoted conditions yield cycloadduct **8** in 84% yield and 13:1 dr. The corresponding thermally-induced cycloaddition requires forcing conditions that yield cyclobutanone **8** in only 5% yield and 1:1 dr. (2) Increased selectivity is also observed. Lewis acid-promoted cycloaddition yields **9** in 18:1 dr while the thermal cycloaddition yields **9** in 40% in 2:1 dr. (3) Perhaps the most intriguing feature, is the reversal in diastereoselectivity for aryl/alkyl ketene cycloadditions under Lewis acid conditions. Lewis acid-promoted cycloaddition yields **10a** in 59% yield and 7:1 dr. The corresponding thermal cycloaddition, however, yields the opposite diastereomer, **10b**, as major in 71% yield and 6:1 dr.

Table 2. Comparison of thermal and Lewis acid-promoted ketene-alkene [2+2] cycloadditions



References

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3. (a) Rasik, C. M.; Brown, M. K. *J. Am. Chem. Soc.* **2013**, *135*, 1673. (b) Rasik, C.; Brown, M. K. *Synlett* **2014**, *25*, 760. (c) Rasik, C. M.; Hong, Y. J.; Tantillo, D. J.; Brown, M. K. *Org. Lett.* **2014**, *16*, 5168.

Appendix
Chemical Abstracts Nomenclature (Registry Number)

Diphenylacetyl chloride: Benzeneacetyl chloride, α-phenyl- (1871-76-7)
Dichloromethane: Methane, dichloro-; (75-09-2)
Triethylamine: Ethanamine, N,N-diethyl-; (121-44-8)
Cyclopentene: cyclopentene; (142-29-0)
Ethylaluminum dichloride: Aluminum, dichloroethyl- ; (563-43-9)

Christopher M. Rasik was born in Swanton, Ohio. He obtained his B.A. at The Ohio State University and began his graduate work under the tutelage of Prof. M. Kevin Brown at Indiana University in 2011.

Eleni M. Salyers was born in Indianapolis, Indiana. She is currently an undergraduate student at Indiana University studying biochemistry.

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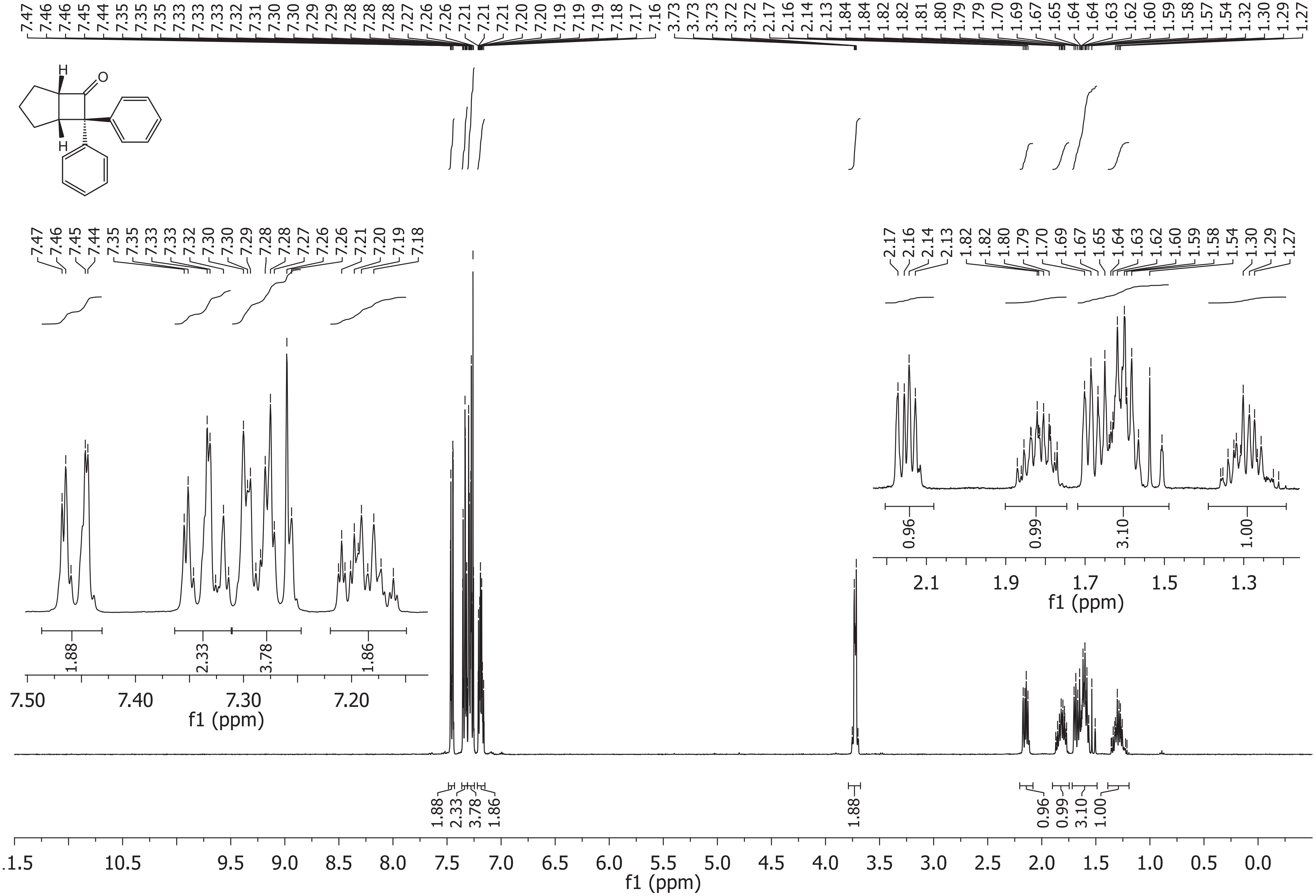
Charel Prost graduated wth a degree in Chemistry from the University of Zurich in 2015. He is currently a Masters student in the group of Prof. Cristina Nevado at the University of Zurich.

Estíbaliz Merino obtained her Ph.D. degree from the Autónoma University (Madrid-Spain). After a postdoctoral stay with Prof. Magnus Rueping at Goethe University Frankfurt and RWTH-Aachen University in Germany, she worked with Prof. Avelino Corma in Instituto de Tecnología Química-CSIC (Valencia) and Prof. Félix Sánchez in Instituto de Química Orgánica General-CSIC (Madrid) in Spain. At present, she is research associate in Prof. Cristina Nevado´s group in University of Zürich. She is interested in the synthesis of natural products using catalytic tools and in the development of new materials with application in heterogeneous catalysis.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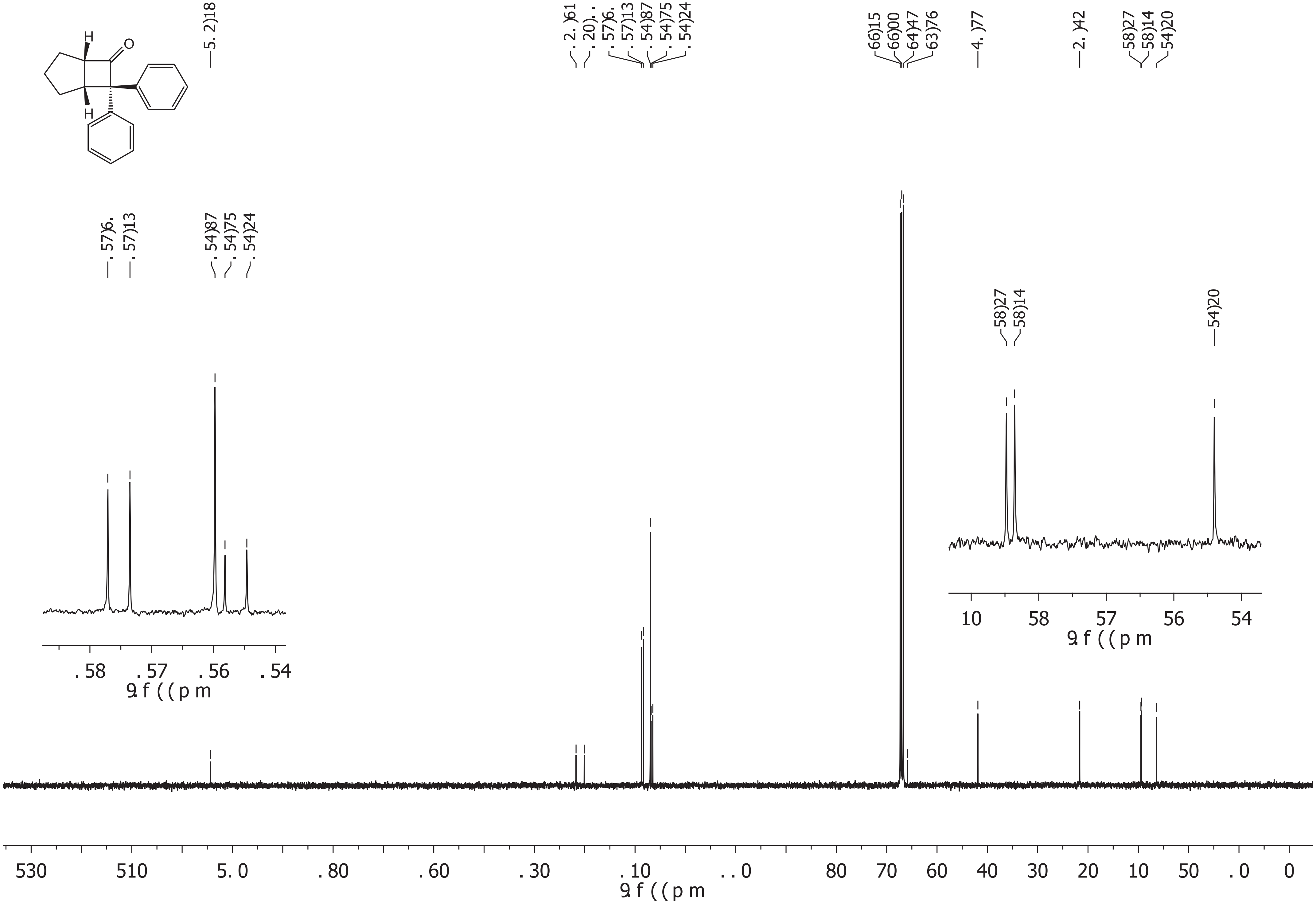
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