Tandem Reactions of Dienes Generated by Enyne Metathesis

Author: Jason Gavenonis

Boston College

The Graduate School of Arts and Sciences

Department of Chemistry

TANDEM REACTIONS OF DIENES GENERATED BY ENYNE METATHESIS

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by

JASON GAVENONIS

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JASON GAVENONIS

Thesis Advisor: Marc L. Snapper

Abstract

A catalyst of notoriety

Decomposes with great variety.

Transformations after metathesis

Facilitate tandem catalysis.

This reaction has a proclivity

For new regioselectivity

With methanolic modification:

Tandem enyne hydrovinylation.

From a diene protonation event,

Unexpected reaction with solvent,

During catalyst optimization:

One-pot enyne hydroarylation.

To my family

”Perhaps the most valuable result of all education is the ability to make yourself do the thing you have to do, when it ought to be done, whether you like it or not; it is the first lesson that ought to be learned; and, however early a man's training begins, it is probably the last lesson that he learns thoroughly.”

--Thomas Henry Huxley, “Technical Education”

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List of Equations, Figures, Schemes, and Tables

General Experimental Details

Starting materials and reagents were purchased from commercial suppliers and used without further purification, except the following: tetrahydrofuran, benzene, and toluene were dried on alumina columns using a solvent dispensing system;[1] benzene and toluene were subsequently degassed by repeated freeze-pump-thaw cycles. Methanol was distilled over magnesium methoxide and degassed by repeated freeze-pump-thaw cycles. Allyl bromide was passed through a short plug of basic alumina immediately prior to use. Hexanes used in chromatography were distilled prior to use. All reactions were conducted in oven (160 °C) or flame-dried glassware under an inert atmosphere of dry nitrogen, unless otherwise noted. Infrared (FTIR) spectra were recorded on a Mattson Galaxy Series FTIR 5000. Bands are characterized as broad (br), very strong (vs), strong (s), medium (m) and weak (w). ^{1}H NMR spectra were recorded on a Varian Unity 300 (300 MHz), Varian Gemini 400 (400 MHz), or a Varian Gemini-500 instrument (500 MHz). Chemical shifts are reported in ppm downfield from tetramethylsilane with the solvent reference as the internal standard ($CHCl_3$: δ 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m =

[1] Pangborn, A.B.; Giardello, M.A.; Grubbs, R.H.; Rosen, R.K.; Timmers, F.J *Organometallics* **1996**, *15*, 1518-1520.

multiplet), coupling constants (Hz), and integration. ^{13}C NMR spectra were recorded on either a Varian Gemini-400 instrument (100 MHz), or a Varian Gemini-500 instrument (125 MHz) with complete proton decoupling. Chemical shifts (δ) are reported in ppm downfield from tetramethylsilane with the solvent as the internal reference ($CDCl_3$: δ 77.23 ppm). High-resolution mass spectral analyses (HRMS) were performed by the Center for Mass Spectrometry, Boston College or the Mass Spectrometry Laboratory at the University of Illinois at Urbana-Champaign.

Acknowledgements

When I was a kid, I wanted to be an architect. I always liked building things, but couldn't really draw a straight line. I guess that's what I ended up doing, just on a much smaller scale, and as anyone who has seen one of my chalk-talk group meetings can attest, I still can't draw a straight line. As I went through school, I quickly became attracted to science, partly because it is a good match for the way I think, but mostly because of some excellent teachers along the way, especially Ms. Barbara Yuscavage and Mr. Fred Frey at Wyoming Valley West High School, who taught me chemistry and biology, respectively. At University of Pennsylvania, I was quite grateful to Professor Patrick J. Walsh for taking a chance on a freshman who wanted to do research. I learned quite a bit more in those three years than I had initially thought possible, and that research experience solidified my decision to go to graduate school. His mentorship will undoubtedly affect the way I approach my independent career.

At Boston College, there are numerous people I need to thank. Professors Amir Hoveyeda and Scott Miller delivered a number of captivating lectures in my first-year organic chemistry classes, and along with Ken Metz, with whom I taught for more than a few semesters, were largely responsible for developing my teaching style. Rich Pijar was instrumental in bringing new life to old lab

equipment. Deb Lynch was great at keeping the Snapper group running smoothly and providing interesting conversation and, more importantly, ample free lunches. Marek Domin provided fast turn-around on mass spec, and John Boylan was immensely helpful with some tricky NMR experiments.

I cannot thank my research advisor, Marc Snapper, enough. He provided the independent atmosphere I wanted for my graduate research, but was always available when I got stuck, which seemed to be more often than not, and helpfully reminded me that negative results still mean something. The diversity of research projects going on the Snapper group provided an excellent atmosphere for learning, and certainly helped put chemistry in a broader context.

The Snapper group was a great place to work, and I want to thank all of you for making my time at BC both intellectually stimulating and immensely entertaining: Brian for showing me the benefits of sitting next to Marc at group meetings, Dr. Scholte for being himself, J3 for time spent turning coffee into ideas, Ben for setting the bar, Dave for sharing his "breath" of knowledge about random topics, Ace for keeping the music going, Murelli for setting the tone of the middle lab, especially on Wednesday afternoons, Krista for feeding us by feeding her baking addiction, Dr. Chicharro for numerous impromptu Spanish lessons, Dr. Kim for some really great science, Traverse for some great discussions in the few months we overlapped, Yu for doing some great science,

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Finally, I would like to think my parents, John and June, my grandparents, Zelino and Minnie Vici, and my uncle Paul Vici for their love and support, both financial and otherwise, throughout the entirety of my education. A special thanks goes to my brother John—not everyone has the chance to talk about their science with family members while in graduate school.

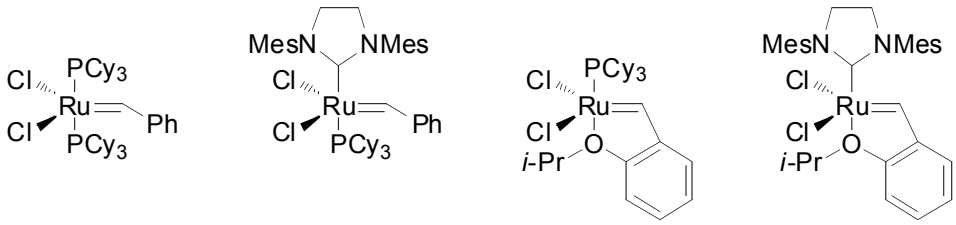
Finally, and I mean it this time, I would like to thank my wife, Catie, for her patience, love, support, and patience throughout this whole process.

Chapter 1

The Organometallic Chemistry of Ruthenium Alkylidene-Based Olefin Metathesis Catalysts

1.1 Introduction

Ruthenium-catalyzed olefin metathesis is a versatile and selective carbon-carbon bond-forming process that has been the subject of much academic study. These air- and moisture-stable transition metal complexes have found broad applications in organic chemistry.[2] Due to the utility and ubiquity of these ruthenium-catalyzed transformations, the decomposition chemistry of the precatalysts has received much attention. Many of these nominative decomposition reactions result in the formation of new, catalytically relevant ruthenium complexes. This review will focus on organometallic transformations of these ruthenium-based olefin metathesis catalysts (Figure 1.1).



C823 **C848** **C601** **C627**

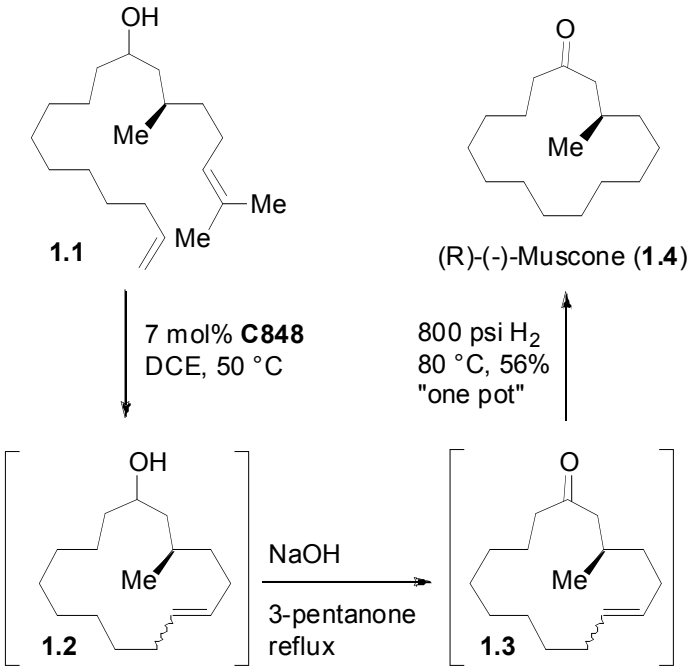
Figure 1.1 - Common ruthenium-based olefin metathesis catalysts

[2] a) P. Schwab, M. B. France, J. W. Ziller, R. H. Grubbs, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2039-2041 doi:10.1002/anie.199520391; b) A. Furstner, *Angew. Chem. Int. Ed.* **2000**, *39*, 3012-3043 doi:10.1002/1521-3773(20000901)39:17<3012::AID-ANIE3012>3.0.CO;2-G; c) R. H. Grubbs, T. M. Trnka, *Acc. Chem. Res.* **2001**, *34*, 18-29 doi:10.1021/ar000114f. For non-metathetic activities of Ru alkylidenes, see: d) B. Alcaide, P. Almendros, A. Luna, *Chem. Rev.* **2009**, *109*, 3817-3858 doi:10.1021/cr9001512.

The degenerate nature of olefin metathesis has led to the development of a number of concurrent, domino, and cascade processes in which simple, acyclic precursors can be converted into complex polycyclic structures in a rapid and efficient manner.[3] While early examples generally feature iterative olefin metathesis, Grubbs reported a three-reaction tandem metathesis sequence[4] in which catalyst **C848** promoted sequential ring-closing metathesis, alcohol oxidation, and olefin hydrogenation (Scheme 1.1).

[3] For reviews on tandem processes, see: a) L. F. Tietze, N. Rackelmann, *Pure Appl. Chem.* **2004**, *76*, 1967-1983 doi:10.1351/pac200476111967; b) J.-C. Wasilke, S. J. Obrey, R. T. Baker, G. C. Bazan, *Chem. Rev.* **2005**, *105*, 1001-1020 doi:10.1021/cr020018n; c) A. Ajamian, J. L. Gleason, *Angew. Chem. Int. Ed.* **2004**, *43*, 3754-3760 doi:10.1002/anie.200301727; d) D. E. Fogg, E. N. dos Santos, *Coord. Chem. Rev.* **2004**, *248*, 2365-2779 doi:10.1016/j.ccr.2004.05.012; e) V. Dragutan, I. Dragutan, *J. Organomet. Chem.* **2006**, *691*, 5129-5147 doi:10.1016/j.jorganchem.2006.08.012.

[4] J. Louie, C. W. Bielawski, R. H. Grubbs, *J. Am. Chem. Soc.* **2001**, *123*, 11312-11313 doi:10.1021/ja016431e.



Scheme 1.1 - Synthesis of (R)-(-)-Muscone via tandem metathesis

With careful study of the aforementioned decomposition chemistry, the possibility for the development of new tandem[5] catalytic processes, in which a second reaction proceeds by a distinct catalytic mechanism, as well as a broader understanding of relevant catalytic intermediates involved in existing tandem processes, should be readily apparent. This review will focus on three classes of transformations: reactions involving hydrogenolysis of the alkylidene, ligand-

[5] Tandem catalysis is defined somewhat inconsistently from review to review (*q.v.* ref. 2). Hereafter, "tandem" will refer to a process in which a single precatalyst promotes multiple, sequential, mechanistically distinct organic transformations in a single reaction vessel, a definition most closely corresponding to that of reference 2d.

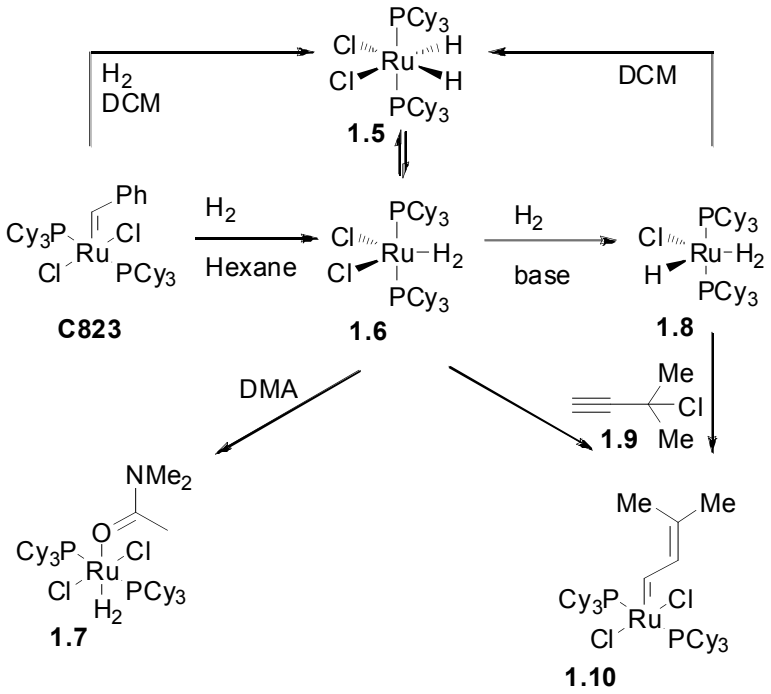
induced catalyst decomposition, and reactions forming carbide or carbyne complexes.

1.2 Hydrogenolysis of the ruthenium alkylidene

Many early examples of tandem metathesis involved a terminal hydrogenation. In 1997, for example, Brookhart published a tandem, homogeneous ROMP/hydrogenation process,[6] and Watson and Wagener reported a tandem ROMP/hydrogenation[7] in which the addition of silica gel created a heterogeneous hydrogenation catalyst. In neither example did the authors determine the identity of the catalyst responsible for the hydrogenation step. In the year 2000, Fogg reported a detailed study on the factors allowing **C823**-promoted hydrogenation to proceed under a hydrogen atmosphere.[8] Hydrogenolysis of a solution of **C823** in DCM or hexane resulted in the formation of dihydride complex **1.5** and dihydrogen complex **1.6**, respectively, which are tautomeric in solution. The DMA adduct **1.7** of complex **1.6** was isolated and characterized by x-ray crystallography, and treatment of the mixture of dichloro complexes **1.5** and **1.6** with base and dihydrogen led to hydridochloro

[6] S. J. McLain, E. F. McCord, S. D. Arthur, A. E. Hauptman, J. Feldman, W. A. Nugent, L. K. Johnson, S. Mecking, M. Brookhart, *Proc. Am. Chem. Soc.; Div. Polym. Mater. Sci. Eng.* **1997**, *76*, 246.
[7] M. D. Watson, K. B. Wagener, *Macromolecules* **2000**, *33*, 3196-3201 doi:10.1021/ma991595p.
[8] S. D. Drouin, G. P. A. Yap, D. E. Fogg, *Inorg. Chem.* **2000**, *39*, 5412-5414 doi:10.1021/ic000102q.

complex **1.8**. Subsequently, Fogg reported that, upon exposure to propargyl chloride **1.9**, both the **1.5**-**1.6** mixture and hydridochloro complex **1.8** generated metathesis-active alkylidene **1.10** (Scheme 1.2). This catalyst "cycling" allowed the preparation of saturated/unsaturated polymer blends via tandem ROMP-hydrogenation-ROMP.[9]

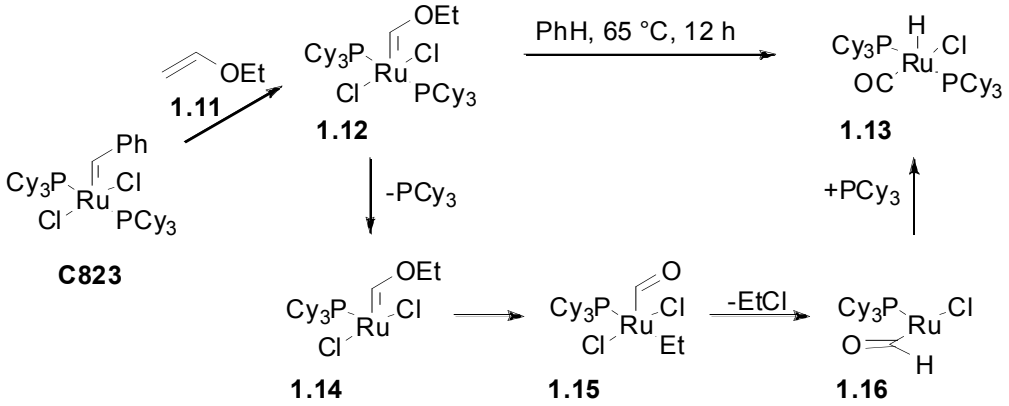


Scheme 1.2 - Alkylidene hydrogenolysis and regeneration

As part of a larger study on Fischer-type carbene complexes of ruthenium,[10] Grubbs found that hydridochlorocarbonyl complex **1.13** was accessible in a two-step protocol from **C823**. Metathesis with ethyl vinyl ether

[9] S. D. Drouin, F. Zamanian, D. E. Fogg, *Organometallics* **2001**, *20*, 5495-5497 doi:10.1021/om010747d.
[10] J. Louie, R. H. Grubbs, *Organometallics* **2002**, *21*, 2153-2164 doi:10.1021/om011037a.

1.11, a compound frequently used to quench metathesis reactions, led to formation of Fischer-type carbene complex **1.12** in 66% yield. Thermolysis of **1.12** (65 °C, benzene, 12 h) resulted in formation of **1.13** in 69% yield. Grubbs had previously reported[11] a plausible decomposition pathway from similar Fischer-type carbene complexes to hydridochlorocarbonyl complexes (Scheme 1.3). After initial loss of a phosphine ligand, direct β-alkyl elimination from **1.14** would form ethyl-formyl Ru(IV) complex **1.15**, which could then undergo reductive elimination of ethyl chloride to form Ru(II) complex **1.16**. Subsequent α-hydride elimination and re-coordination of tricyclohexylphosphine would lead to **1.13**.

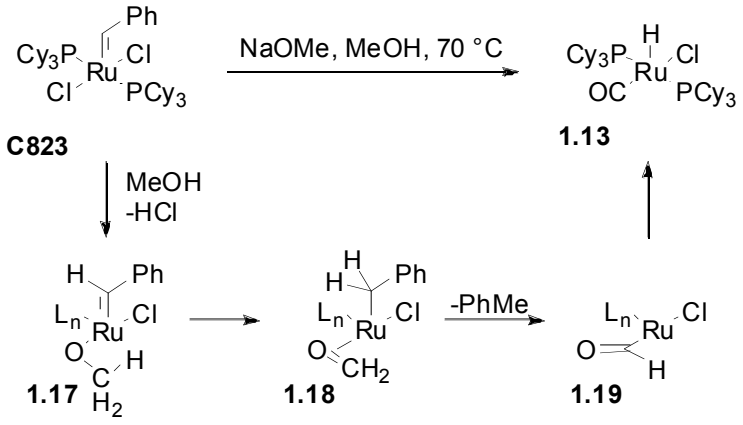


Scheme 1.3 - Ruthenium hydride complexes via Fischer carbene intermediates

Mol later reported[12] this same transformation in a single step. Upon treatment of **C823** with methanol[13] at 70 °C, **1.13** began to form over the course of

[11] Z. Wu, S. T. Nguyen, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1995**, *117*, 5503-5511 doi:10.1021/ja00125a010.
[12] M. B. Dinger, J. C. Mol, *Organometallics* **2003**, *22*, 1089-1095 doi:10.1021om0208218.

two days. Addition of a base,[14] such as sodium methoxide, accelerated this process, with 50% conversion being observed after 15 minutes. Mol proposed the following mechanism (Scheme 1.4). Ligand exchange between methanol and a chloride would produce HCl and ruthenium methoxide complex **1.17**. Subsequent hydride abstraction, or elimination/insertion, would lead to complex **1.18**. C-H insertion and reductive elimination of toluene would provide **1.19**, which could then undergo α-hydride elimination to produce **1.13**.



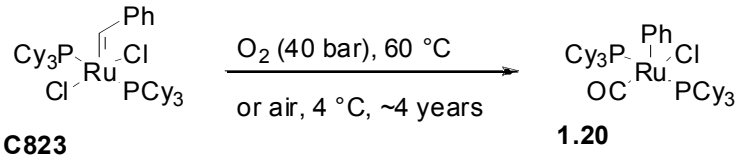
Scheme 1.4 - Degradation of Grubbs' catalyst with methanol

This mechanism was supported by extensive isotopic labeling studies. Treatment of **C823** with $CH_3{}^{13}CH_2OH$, for example, led to formation of $(PCy_3)_2(^{13}CO)Ru(H)(Cl)$, suggesting that the alcohol was the source of the carbonyl carbon. Furthermore, use of CH_3OD resulted in only minimal

[13] Water and primary alcohols such as ethanol and 1-propanol were also effective; 2-propanol was not.

[14] Potassium carbonate, sodium hydroxide, and triethylamine also accelerated this transformation.

formation of $(PCy_3)_2(CO)Ru(D)(Cl)$, a compound also observed when **1.13** was treated with CH_3OD. Finally, decomposition of $(PCy_3)_2Ru(=CDPh)(Cl)_2$ did not result in the formation of **D-1.13**.



C823 **1.20**

Scheme 1.5 - Degradation of Grubbs' catalyst with dioxygen

In addition to hydride complex **1.13**, Mol also observed the formation of phenyl complex **1.20** from oxidative decomposition of solid **C823** (Scheme 1.5), upon treatment with dry dioxygen (40 bar) at 60 °C overnight (75% yield), or air at 4 °C for 4 years[15] (25% conversion).

In an attempted ligand exchange on first-generation Grubbs' catalyst, Fürstner observed[16] formation of a ruthenium hydride byproduct. Treatment of **C823** with Arduengo carbene precursor **1.21** produced a mixture of the expected carbene complex **1.22** and the putative[17] dihydride complex **1.5**, which was characterized by x-ray crystallography (Scheme 1.6).

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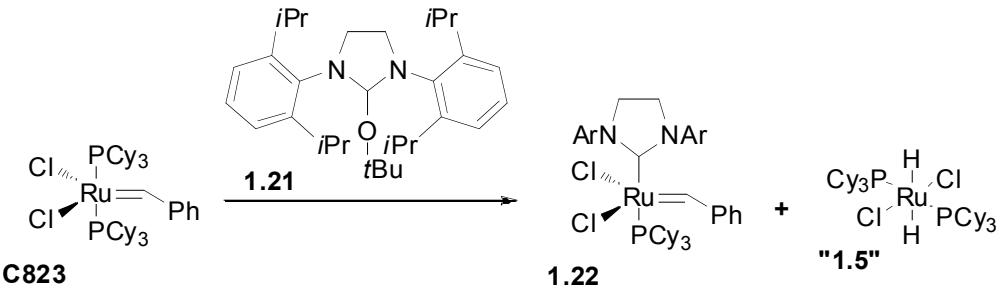
[15] approximately

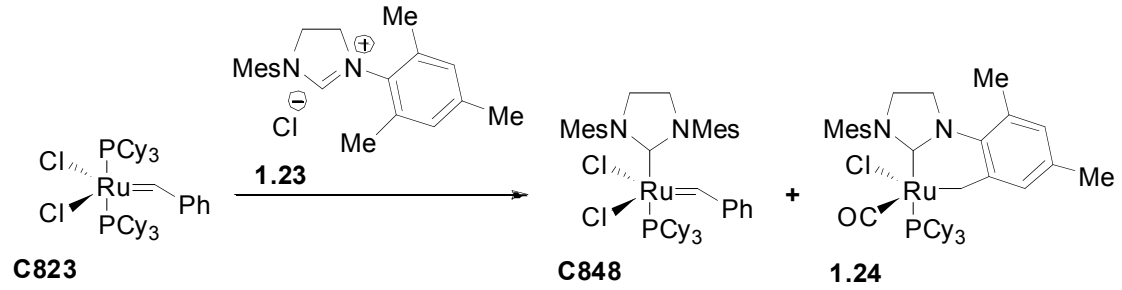
[16] A. Fürstner, L. Ackermann, B. Gabor, R. Goddard, C. W. Lehmann, R. Mynott, F. Stelzer, O. R. Thiel, *Chem. Eur. J.* **2001**, *7*, 3236-3253 doi:10.1002/1521-3765(20010803)7:15<3236::AID-CHEM3236>3.0.CO;2-S.

[17] Grubbs later suggested (*q.v.* ref. 18) that this complex may in fact have been **1.13**, based on the use of methanol in the reaction, matching unit cell parameters, anomalously large and elongated chloride ellipsoids, disorder about the Cl-Ru-CO axis common in compounds of that nature, a very similar hydride resonance in the ^1H NMR (δ -24.4 ppm, t, J_{HP} = 17 Hz), and a characteristic



Scheme 1.6 - Putative dihydride byproduct from ligand exchange

Grubbs also observed[18] that treatment of **C823** with carbene precursor **1.23** without proper air-free conditions resulted in formation of complex **1.24** (Scheme 1.7).



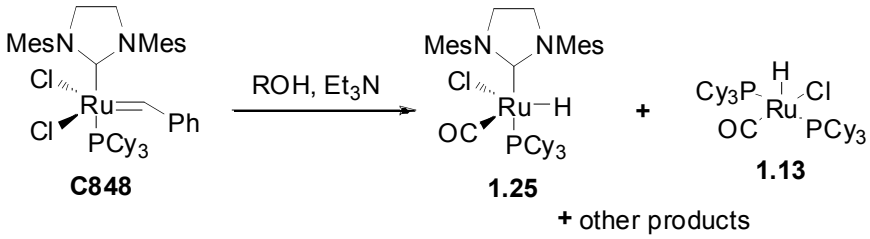
Scheme 1.7 - Oxidative decomposition in second-generation catalyst synthesis

Performing the reaction in a Schlenk tube resulted in clean formation of **C848**. When using a round-bottom flask fitted with a reflux condenser under a slow flow of argon, however, the *ortho*-metalated complex predominated. Complex **1.24** was air-stable in both the solid state and solution.

ν_{CO} of 1905 cm^{-1}. The identity of **1.5** as produced by Fogg, in the absence of methanol, appears not to have changed.

[18] T. M. Trnka, J. P. Morgan, M. S. Sanford, T. E. Wilhelm, M. Scholl, T.-L. Choi, S. Ding, M. W. Day, R. H. Grubbs, *J. Am. Chem. Soc.* **2003**, *125*, 2546-2558 doi:10.1021/ja021146w.

Attempts to expand controlled hydride synthesis to Arduengo carbene-based metathesis catalysts such as **C848** were initially only moderately successful.[19] The reaction of **C848** with methanol and triethylamine produced a complex mixture containing multiple metal hydride complexes (Scheme 1.8). Hydride complex **1.25**[20] appeared to be the major product by NMR (30-40%), but could not be crystallized except at -78 °C, and was not characterized by x-ray crystallography. Complex **1.13** (25-30%) was also observed, along with two other unidentifiable complexes. Use of 1-nonanol instead of methanol resulted in a more favorable ratio of **1.25**:**1.13** (85:15), with concomitant suppression of the other products.

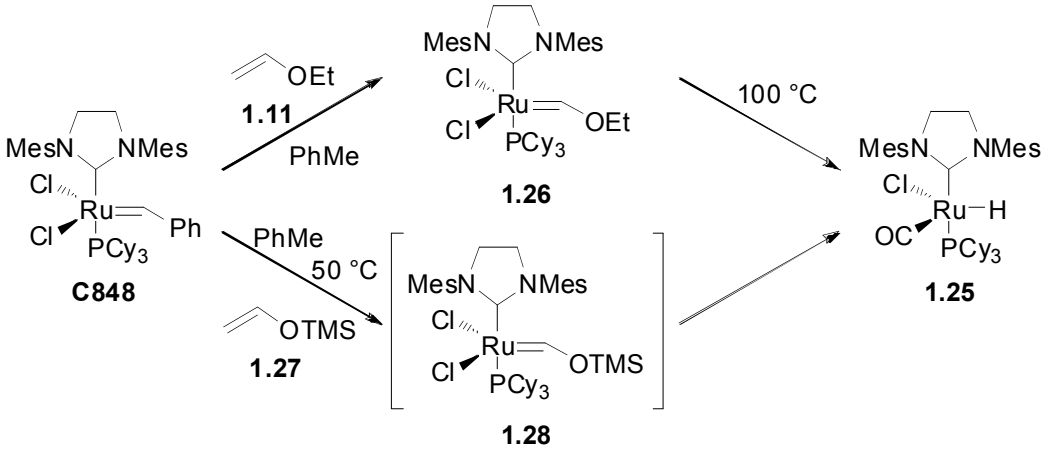


Scheme 1.8 - Degradation of second-generation metathesis catalyst

Nishida later proposed a direct, clean approach from **C848** to **1.25**.[21] Treatment of **C848** with ethyl vinyl ether (**1.11**) in toluene, followed by heating to 100 °C for one hour resulted in clean and quantitative formation of **1.25**, via

[19] M. B. Dinger, J. C. Mol, *Eur. J. Inorg. Chem.* **2003**, 2827-2833 doi:10.1002/ejic.200200702.
[20] A similar complex may also be prepared by a ligand exchange reaction of **1.13** with a free Arduengo carbene: H. M. Lee, D. C. Smith, Jr., Z. He, E. D. Stevens, C. S. Yi, S. P. Nolan, *Organometallics* **2001**, *20*, 794-797 doi:10.1021/om000882a.
[21] M. Arisawa, Y. Terada, K. Takahashi, M. Nakagawa, A. Nishida, *J. Org. Chem.* **2006**, *71*, 4255-4261 doi:10.1021/jo060308u.

isolable intermediate **1.26**.[22] Similarly, a reaction between vinyloxytrimethylsilane (**1.27**) and **C848** at 50 °C produced **1.25**, purportedly through unstable intermediate **1.28** (Scheme 1.9). This transformation likely proceeds through a mechanism similar to that outlined in Scheme 1.3.



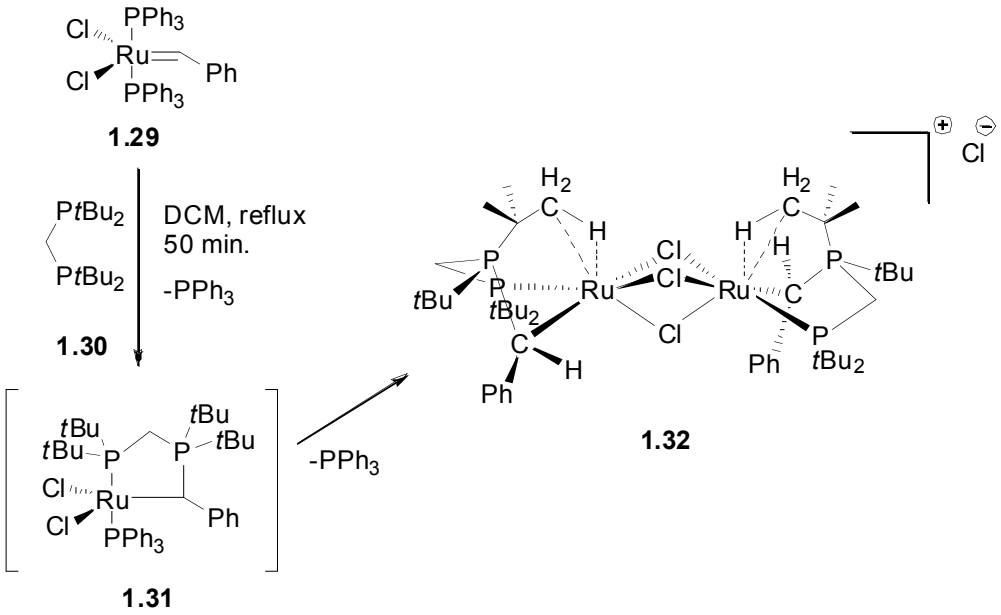
Scheme 1.9 - Optimized second-generation hydride synthesis

1.3 Ligand-induced catalyst decomposition pathways

Using the bis(triphenylphosphine) analog of **C823** (**1.29**), Hofmann observed a novel decomposition pathway upon coordination of bis(di-*tert*-butylphosphanyl)-methane (dtbpm, **1.30**).[23] After initial ligand exchange and attack of the pendent phosphine on the benzylidene carbon, leading to putative

[22] This complex was previously reported by Grubbs, who had not commented on its thermal stability or lack thereof (*q.v.* ref. 10).
[23] S. M. Hansen, F. Rominger, M. Metz, P. Hofmann, *Chem. Eur. J.* **1999**, *5*, 557-566 doi:10.1002/(SICI)1521-3765(19990201)5:2<557::AID-CHEM557>3.0.CO;2-A.

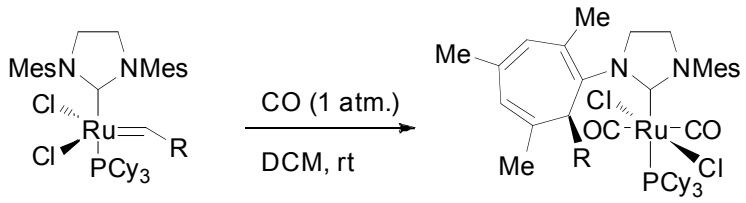
intermediate **1.31**, triphenylphosphine is then lost, leading to triply chloro-bridged, dimeric, cationic complex **1.32** (Scheme 1.10).



Scheme 1.10 - Diphosphine ligand-initiated catalyst decomposition

While using CO to quench metathesis reactions for kinetic studies, Diver observed a novel decomposition pathway for **C848**.[24] Coordination of CO promoted an intramolecular cyclopropanation of one of the mesityl rings on the N-heterocyclic carbene, followed by a 6π electrocyclic rearrangement of the resultant norcaradiene to form a cycloheptatriene (Scheme 1.11).

[24] B. R. Galan, M. Gembicky, P. M. Dominiak, J. B. Keister, S. T. Diver, *J. Am. Chem. Soc.* **2005**, *127*, 15702-15703 doi:10.1021/ja0545618.



C848 R = Ph
1.34 R = H

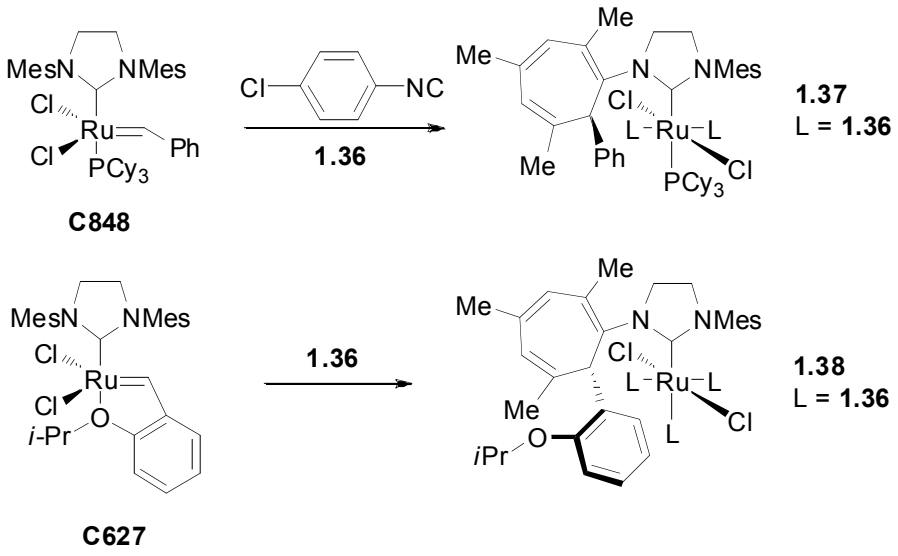
1.33 R = Ph
1.35 R = H

Scheme 1.11 - Büchner reaction of pendent mesityl group

Complex **1.33** was presumed to be the kinetic product of this rearrangement, as the carbonyl ligands are oriented in the less stable *trans* geometry. The migrated phenyl group is *anti* to the metal on an sp^3 carbon, presumably due to steric concerns, and both carbonyl ligands are coplanar with the backbone of the Arduengo carbene ligand. Rearrangement of methylidene complex **1.34** under the same conditions produced complex **1.35**.

Diver also reported that isonitriles promoted this unexpected carbene insertion. Reaction of **C848** with *p*-chlorophenyl isocyanide (**1.36**) produced bis-isonitrile complex **1.37** in 79% yield (Scheme 1.12).[25] Using isonitriles also proved effective for promoting this rearrangement for phosphine-free metathesis catalysts such as **C627**, forming *mer*-tris-isonitrile complex **1.38** in 86% yield, with the aryl group *syn* to the metal. In solution, rotamers about the C-N bond of **1.38** were observed, but orientation of the *o*-isopropoxy phenyl group was invariant.

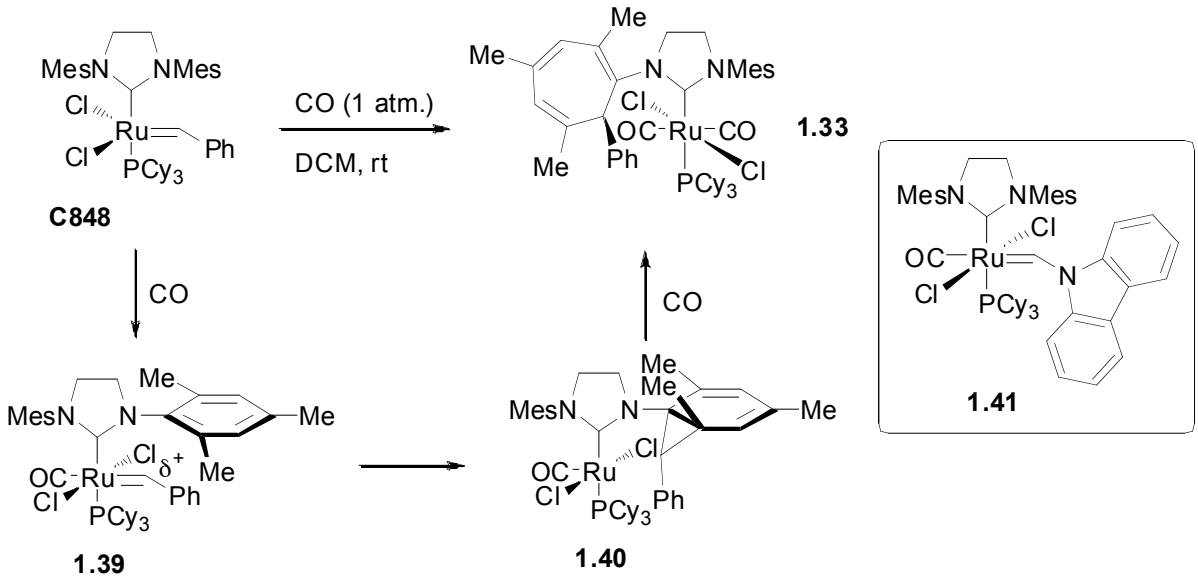
[25] B. R. Galan, M. Pitak, M. Gembicky, J. B. Keister, S. T. Diver, *J. Am. Chem. Soc.* **2009**, *131*, 6822-6832 doi:10.1021/ja809984k.



Scheme 1.12 - Isonitrile-promoted carbene migration

The mechanism proposed by Diver involves initial coordination of CO *trans* to the benzylidene, generating 18 e^- complex **1.39**. In this complex, the π-Lewis acidic CO weakens the Ru-benzylidene π-bond, facilitating electrophilic intramolecular carbene transfer to generate norcaradiene **1.40**. Subsequent electrocyclic rearrangement reveals the open coordination site, allowing addition of the second CO ligand and forming **1.33** (Scheme 1.13). The absence of observable stilbene byproducts or regioisomers of the benzylidene-migration product support a concerted migration in the coordination sphere of the metal, rather than intermediacy of a free carbene. Furthermore, isolation of carbonyl adducts of Fischer carbene complexes such as **1.41**, in which donation from the heteroatom stabilizes the partial positive charge on the alkylidene carbon, thus

inhibiting intramolecular cyclopropanation, augment the plausibility of **1.39** as an intermediate.

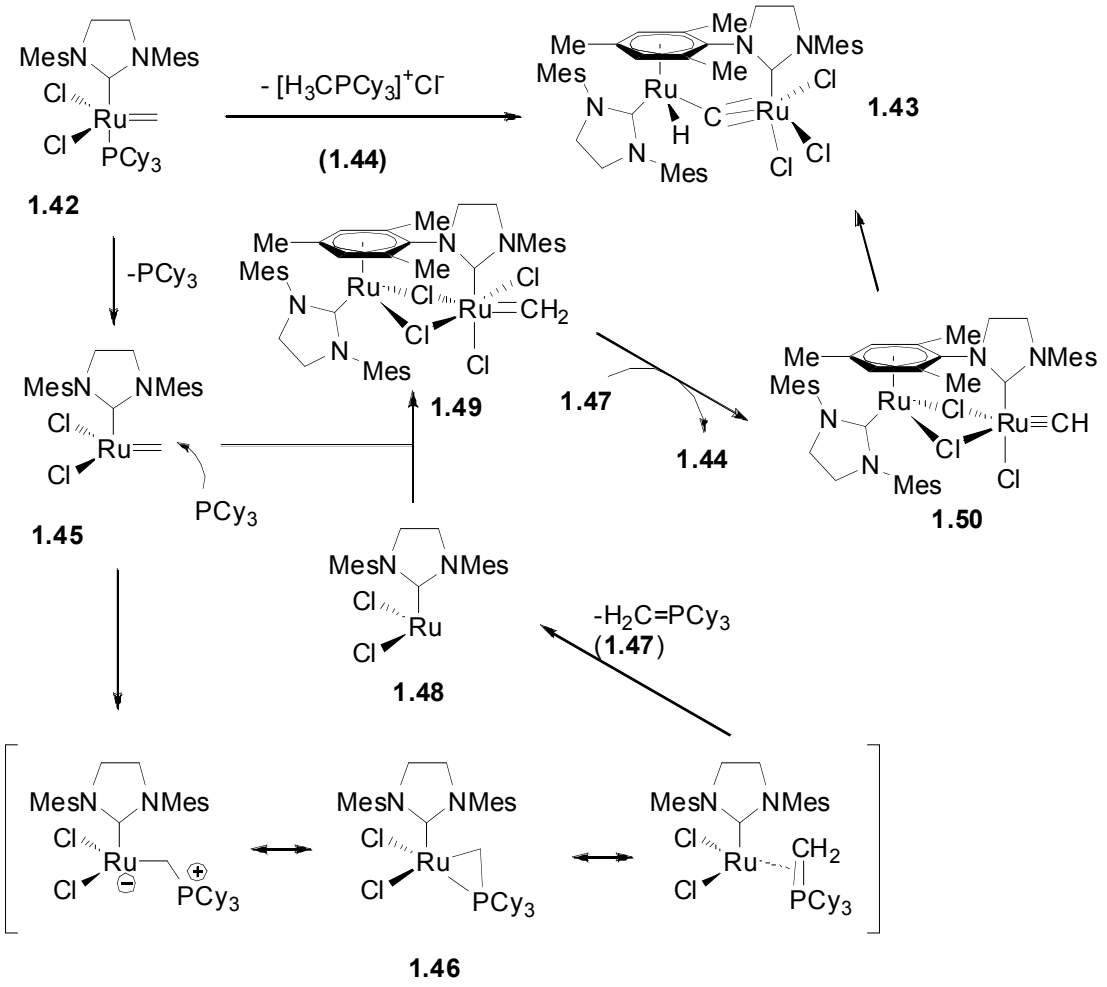


Scheme 1.13 - Proposed mechanism for intramolecular carbene transfer

In 2007, Grubbs reported a comprehensive study of *in situ* catalyst decomposition under simulated reaction conditions. Synthesis of the methylidene analogs and use of ethylene as a model substrate provided a means of replicating the intermediates involved in typical olefin metathesis reactions.[26] In all cases, phosphonium salts formed, presumably via attack of the dissociated phosphine on the methylidene. As detailed in an earlier communication,[27]

[26] S. H. Hong, A. G. Wenzel, T. T. Salguero, M. W. Day, R. H. Grubbs, *J. Am. Chem. Soc.* **2007**, *129*, 7961-7968 doi:10.1021/ja0713577.
[27] S. H. Hong, M. W. Day, R. H. Grubbs, *J. Am. Chem. Soc.* **2004**, *126*, 7414-7415 doi:10.0121/ja0488380.

methylidene **1.42** decomposed to bimetallic hydride complex **1.43** and phosphonium salt **1.44** (Scheme 1.14).

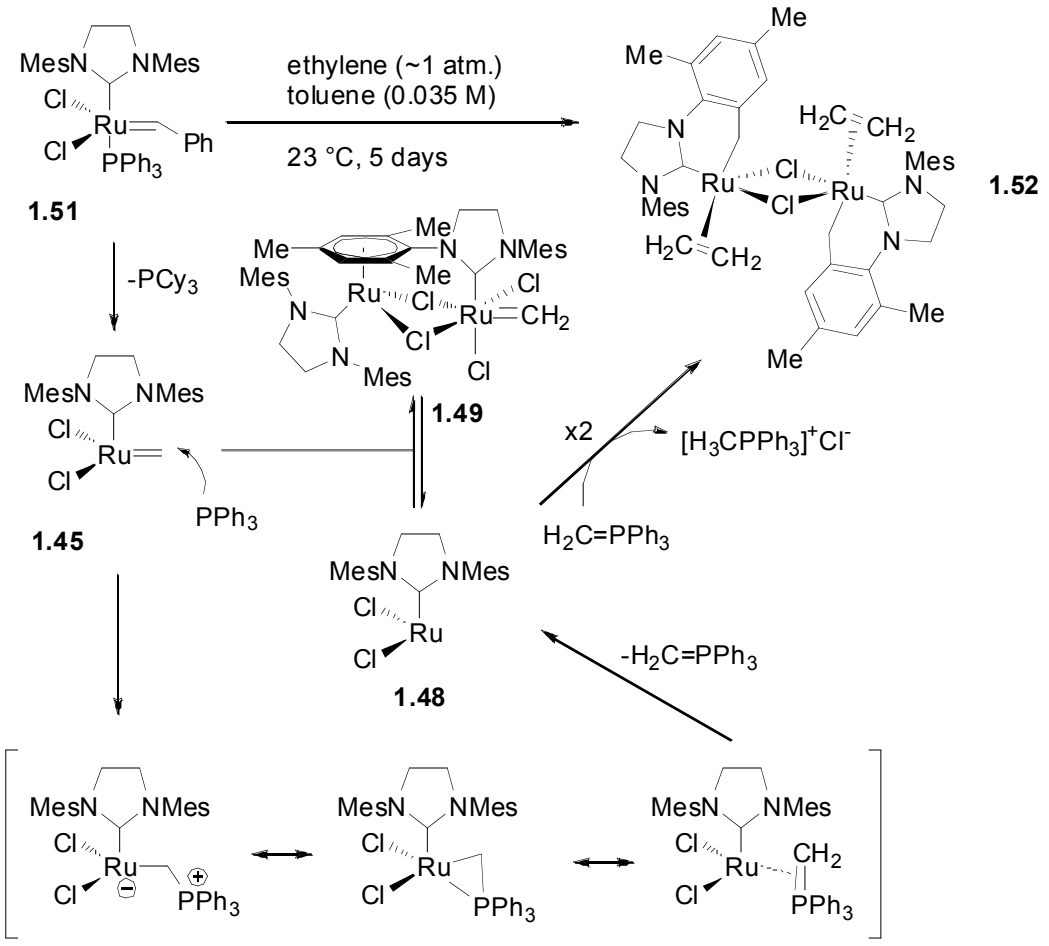


Scheme 1.14 - Decomposition of second-generation methylidene complex

Initial dissociation of the phosphine ligand from **1.42** leads to 14 e^- complex **1.45**. Attack of the liberated phosphine on the methylidene forms metallaphosphorane **1.46**. Upon dissociation of phosphonium ylide **1.47**, 12 e^- complex **1.48** may react with another molecule of **1.45**, forming bimetallic complex **1.49**. Abstraction of

HCl from **1.49** by **1.47**, forming phosphonium salt **1.44**, could lead to formation of bimetallic alkylidyne complex **1.50** which, upon subsequent C-H insertion, could rearrange to **1.43**.

Ethenolysis of the triphenylphosphine analog of **C848** (**1.51**) also produced a bimetallic complex, the C_2-symmetric, *ortho*-metalated dimer **1.52**. Complex **1.49** was observable by mass spectrometry during the reaction, leading Grubbs to hypothesize that **1.52** was formed directly from **1.48** (Scheme 1.15). The diverging reaction pathways leading to **1.43** and **1.52** were attributed to the comparative basicity and steric profile of the phosphine ligands, and, of course, the presence of ethylene. At -40 °C, a metallacyclobutane was observed, indicating that the presence of ethylene may shift the equilibrium from **1.49** to **1.45**. Also, complex **1.52** was unstable in solution in the absence of ethylene.

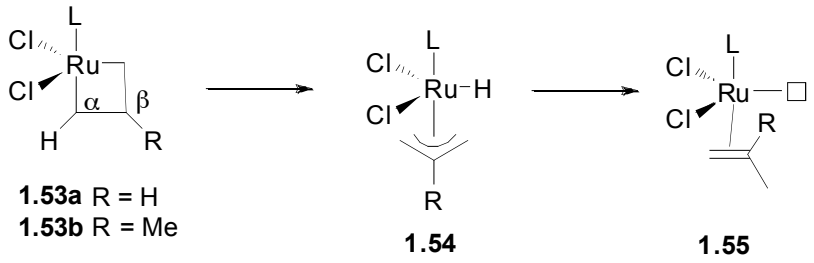


Scheme 1.15 - Ethenolysis of second-generation catalyst

Ethylene-induced catalyst decomposition was also studied both theoretically and experimentally by van Rensburg.[28] Thermolysis of benzene solutions of (40 °C, 16 h) **C823** and **C848** saturated with ethylene produced a mixture of organic products, primarily propene and 1-butene (ca. 3:1 for **C823**),

[28] a) W. J. van Rensburg, P. J. Steynberg, W. H. Meyer, M. M. Kirk, G. S. Forman, *J. Am. Chem. Soc.* **2004**, *126*, 14332-14333 doi:10.1021/ja0453174. b) Other carbenoid decomposition pathways had previously been examined: M. J. Szabo, H. Berke, T. Weiss, T. Ziegler, *Organometallics* **2003**, *22*, 3671-3677 doi:10.1021/om0302995.

with observable, but minor, amounts of 2-butene, cyclopropane, and isobutene. Activation barriers ($\Delta G^{\ddagger}_{298}$) for β-hydride elimination from metallacyclobutane **1.53a** were calculated to be 16.9 kcal/mol and 24.3 kcal/mol for **C823** and **C848**, respectively (Scheme 1.16).



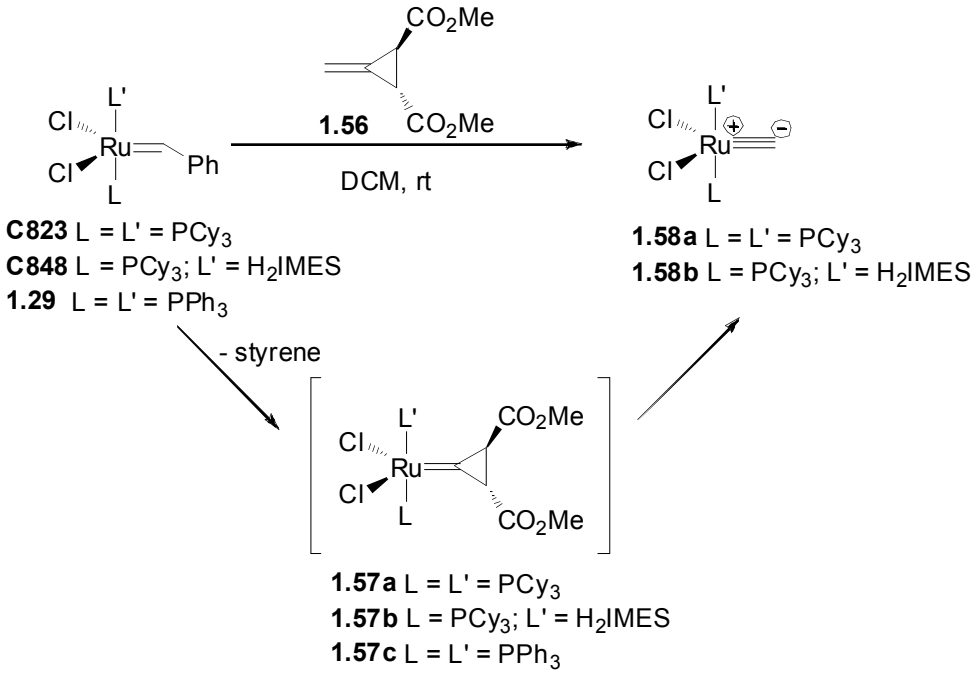
Scheme 1.16 - Thermal ethenolysis of first- and second-generation catalysts

This elimination would produce allyl-hydride complex **1.54**, which could produce propene through reductive elimination. Alternately, direct reductive elimination would lead to cyclopropane. Reaction of propene with remaining methylidene would lead to complex **1.53b**, which, accounts for the formation of isobutene. Production of 2-butene is plausible via self-metathesis of propene, while α-hydride elimination of **1.53a** and subsequent metathesis with ethylene could produce 1-butene.

1.4 Synthesis of ruthenium carbide complexes

In addition to the bridging carbide complex **1.43** mentioned above, a number of terminal carbide complexes have been synthesized from ruthenium alkylidene precursors. Heppert reported formation of carbide complexes **1.58a-b** when either **C823** or **C848** was reacted with methylenecyclopropane **1.56**.[29] GC/MS and NMR analysis of the crude reaction mixtures indicated the presence of both styrene and dimethyl fumarate, and in the ^{13}C NMR there was a characteristic carbide resonance at δ 471.5 ppm (Scheme 1.17).

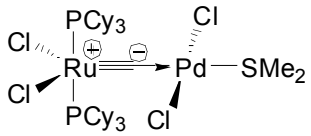
[29] R. G. Carlson, M. A. Gile, J. A. Heppert, M. H. Mason, D. R. Powell, D. Vander Velde, J. M. Vilain, *J. Am. Chem. Soc.* **2002**, *124*, 1580-1581 doi:10.1021/ja017088g.



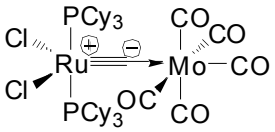
Scheme 1.17 - Carbide complex synthesis via fumarate extrusion

Grubbs had previously isolated[30] intermediate **1.57c**, which, upon treatment with PCy_3,[31] can rearrange to form **1.58a**. Heppert hypothesized that the greater σ-donor ability of PCy_3 and H_2IMES stabilizes the incipient triple bond of the carbide, explaining the stability of **1.57c**. These carbide complexes may also serve as donor ligands for other transition metal complexes. Monomeric complexes with palladium (**1.59**) and molybdenum (**1.60**) have been reported (Figure 1.2).

[30] Z. Wu, S. T. Nguyen, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1995**, *117*, 5503-5511 doi:10.1021/ja00125a010.
[31] A. Hejl, T. M. Trnka, M. W. Day, R. H. Grubbs, *Chem. Commun*. **2002**, 2524-2525 doi:10.1039/b207903h.



1.59



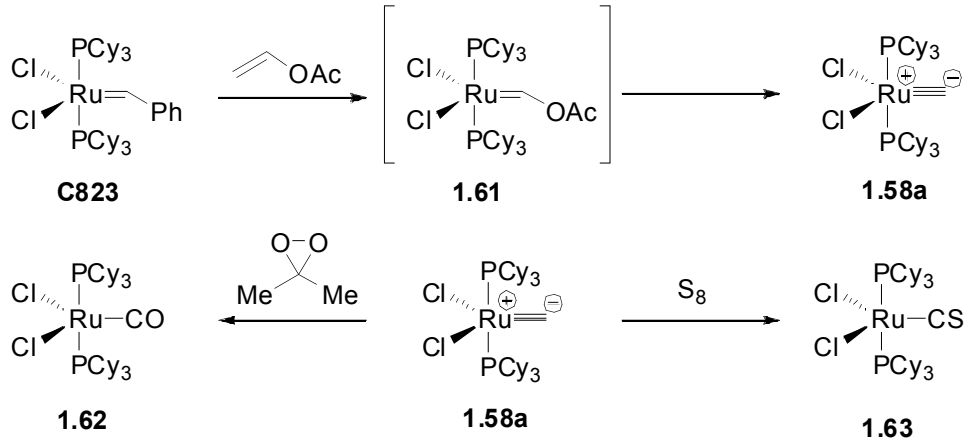
1.60

Figure 1.2 - Monomeric, bimetallic complexes of ruthenium carbides

Johnson later reported a variety of approaches to ruthenium carbide complexes from alkylidene precursors. Treatment of **C823** with vinyl acetate (1 equiv.) for 90 minutes at room temperature resulted in formation of **1.58a** via intermediate **1.61**. The latter could be observed[32] by ^{1}H NMR early in the reaction.[33] Despite the production of acetic acid in the reaction, the addition of amine bases attenuated the selectivity of the transformation. Treatment of **1.58a** with either S_8 or DMDO produced carbonyl complex **1.62** or thiocarbonyl complex **1.63**, respectively (Scheme 1.18).

[32] S. R. Caskey, M. H. Stewart, J. E. Kivela, J. R. Sootsman, M. J. A. Johnson, J. W. Kampf, *J. Am. Chem. Soc.* **2005**, *127*, 16750-16751 doi:10.1021/ja0453735.

[33] Complex **1.58** was not observed under the optimized conditions (20 equiv. vinyl acetate, 15 minutes).



Scheme 1.18 - Synthesis and derivitization of carbide complex **1.58a**

In addition to carbide complexes such as **1.58a**, Johnson documented a variety approaches to aryl carbyne complexes such as **1.64**. Dehydrohalogenation[34] of **C823** with :Ge(CH(TMS)$_2$)$_2$ formed **1.64** directly. This complex was also accessible via a two-step protocol involving treatment with an aryloxide base to form square-planar intermediate **1.65**.[35] Subsequent treatment with $SnCl_2$ yielded complex **1.64**. Inhibition of the reaction by addition of excess phosphine and observation of free phosphine by ^{31}P NMR during the reaction support a mechanism that involves initial phosphine dissociation (Scheme 1.19). The chloride in **1.64** is displaced readily by a number of other halides and *pseudo*-halides.

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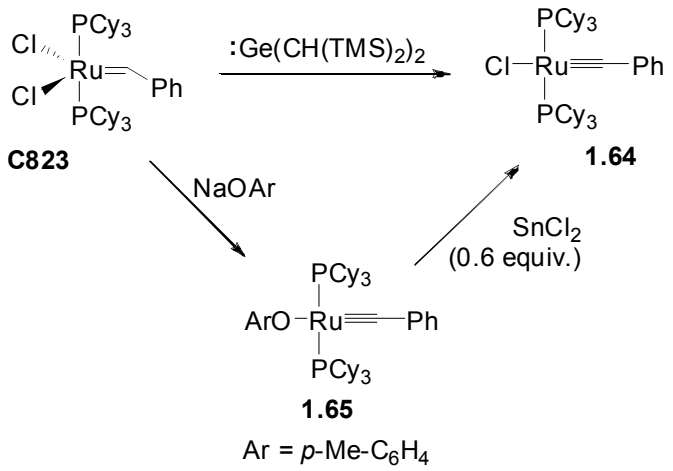
[34] S. R. Caskey, M. H. Stewart, Y. J. Ahn, M. J. A. Johnson, J. W. Kampf, *Organometallics* **2005**, *24*, 6074-6076 doi:10.1021/om0508482.

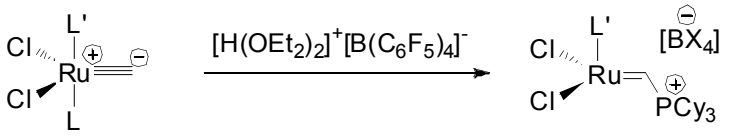
[35] Caulton had previously reported a similar transformation, with excess sodium phenoxide, in a study on the isomerization of vinylidene complexes: J. N. Coalter, III, J. C. Bollinger, O. Eisenstein, K. G. Caulton, *New. J. Chem*. **2000**, *24*, 925-927 doi:10.1039/b006971j.



Scheme 1.19 - Dehydrohalogenation approach to aryl carbynes

Piers found that protonation of **1.58** with Jutzi's acid[36] converted the nucleophilic carbide into an electrophilic carbyne.[37] Upon protonation, **1.58b** is attacked at the carbyne carbon by a phosphine ligand, producing the formally Ru(IV) complex **1.66**, with a dicarbanionic ylide ligand (Scheme 1.20). This complex has subsequently found use as a rapidly initiating olefin metathesis catalyst.

[36] P. Jutzi, C. Muller, A. Stammler, H.-G. Stammler, *Organometallics* **2000**, *19*, 1442-1444 doi:10.1021/om990612w. The non-coordinating anion, tetrakis(perfluorophenyl)borate, is colloquially called BF20.
[37] a) P. E. Romero, W. E. Piers, R. McDonald, *Angew. Chem. Int. Ed.* **2004**, *43*, 6161-6165 doi:10.1002/anie.200461374. b) E. M. Leitao, E. F. van der Eide, P. E. Romero, W. E. Piers, R. McDonald, *J. Am. Chem. Soc.* **2010**, *132*, 2784-2794 doi:10.1021/ja910112m.



1.58a L = L' = PCy_3
1.58b L = PCy_3; L' = H_2IMES

1.66a L' = PCy_3
1.66b L' = H_2IMES

Scheme 1.20 - Protonation of carbide complexes

1.5 Conclusion

Ruthenium-based olefin metathesis catalysts undergo a variety of organometallic transformations. In many cases, decomposition of these complexes produces other catalytically relevant species, such as ruthenium hydrides. Understanding and controlling this decomposition chemistry is essential for both avoiding unexpected and undesired side reactions and for the development of new tandem catalytic processes. Knowledge of these decomposition pathways may also facilitate the development of new olefin metathesis catalysts with increased stability and efficiency.

Chapter 2

Ruthenium-Catalyzed Tandem Enyne Metathesis-Hydrovinylation

"Someone said 'butadiene,' and I heard beauty dying...."

--Thomas Pynchon, *Gravity's Rainbow*

Reproduced in part with permission from J. Gavenonis, R. V. Arroyo, and M. L. Snapper, *Chem. Commun.*, **2010**, 5692-5694, doi:10.1039/c0cc00008f.

2.1 Introduction

Ruthenium-catalyzed olefin metathesis is a versatile and selective carbon-carbon bond-forming process that has been utilized extensively in the synthesis of complex organic molecules.[1] Concurrent, tandem, or domino (cascade) processes that can convert the resultant alkene into different functionalities via an additional ruthenium-catalyzed reaction, allowing simple and rapid generation of molecular complexity with reduced time, cost, and waste, are of particular interest.[2] While there are numerous examples of tandem olefin metatheses involving hydrogenation,[3,38] isomerization,[39] or oxidation[40] of the olefin, there are relatively few processes in which the tandem reaction forms an additional carbon-carbon bond after olefin metathesis. With the recent development of tandem ring-closing metathesis-Kharasch addition,[41] tandem enyne metathesis-cyclopropanation,[42] and tandem ring-closing metathesis *hetero-*

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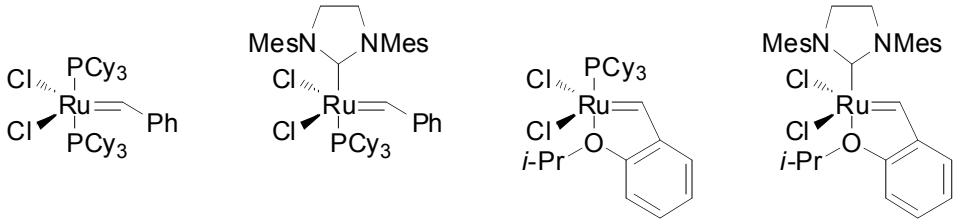
[38] B. Schmidt, M. Pohler, *Org. Biomol. Chem.* **2003**, *1*, 2512-2517 doi:10.1039/b303441k.
[39] a) A. E. Sutton, B. A. Seigal, D. F. Finnegan, M. L. Snapper, *J. Am. Chem. Soc.* **2002**, *124*, 13390-13391 doi:10.1021/ja028044q. b) B. Schmidt, *Eur. J. Org. Chem.* **2003**, *5*, 816-819 doi:10.1002/ejoc.200390124. c) D. F. Finnegan, B.A. Seigal, M. L. Snapper, *Org. Lett.* **2006**, *8*, 2603-2606 doi:10.1021/ol060918g.
[40] a) S. Beligny, S. Eibauer, S. Maechling, S. Blechert, *Angew. Chem. Int. Ed.* **2006**, *45*, 1900-1903 doi:10.1002/anie.200503552. b) A. A. Scholte, M. H. An, M. L. Snapper, *Org. Lett.* **2006**, *8*, 4759-4762 doi:10.1021/ol061837n.
[41] a) B. A. Seigal, C. Fajardo, M. L. Snapper, *J. Am. Chem. Soc.* **2005**, *127*, 16329-16332 doi:10.1021/ja055806j. b) B. Schmidt, M. Pohler, *J. Organomet. Chem.* **2005**, *690*, 5552-5555 doi:10.1016/j.jorganchem.2005.06.042.
[42] a) B. G. Kim, M. L. Snapper, *J. Am. Chem. Soc.* **2006**, *128*, 52-53 doi:10.1021/ja055993l. b) R. P. Murelli, S. Catalán, M. P. Gannon, M. L. Snapper, *Tetrahedron Lett.* **2008**, *49*, 5714-5717 doi:10.1016/j.tetlet.2008.07.119.

Pauson-Khand[43] protocols, the development of new processes that can generate multiple carbon-carbon bonds in a single reaction vessel remains highly desirable as a means of streamlining synthetic sequences.

While all the above tandem reactions rapidly produce significant molecular complexity from simple precursors, in no case does a structurally well-defined ruthenium complex promote the second reaction in the tandem sequence. Given the panoply of organometallic transformations outlined in Chapter 1, there should be numerous opportunities for the development of new tandem reactions that feature an *in situ* conversion of the ruthenium alkylidene (Figure 2.1) used for metathesis into a second, catalytically relevant complex.



C823 **C848** **C601** **C627**

Figure 2.1 - Common ruthenium-based olefin metathesis catalysts

[43] D. F. Finnegan, *Tandem Reactions Involving Ruthenium Alkylidenes*, Ph.D. dissertation, Boston College, United States -- Massachusetts.

2.2 Hydrovinylation Background

While hydrovinylation is traditionally a nickel(II)-catalyzed process,[44] a number of Ru(II) complexes, such as $(PCy_3)_2(CO)Ru(H)(Cl)$ (**2.1**), also mediate the addition of ethylene to olefins and 1,3-dienes. Yi has recently published several examples[45] of ruthenium-catalyzed hydrovinylation of alkenes and 1,3-dienes (Scheme 2.1) in yields of 57-90%. A mixture of **2.1** and $HBF_4 \bullet OEt_2$[46] was found to promote this reaction effectively. For α-olefins such as styrene (**2.2**), the reaction was rapid and selective, producing Markovnikov hydrovinylation product **2.3** in 98% yield after 6 h at ambient temperature. Internal olefins reacted more sluggishly, with methyl cinnamate (**2.4**) requiring higher catalyst loading, time, and temperature to produce an isomeric mixture of product **2.5**. For more reactive 1,3-dienes, substoichiometric amounts of acid could be used. Diene **2.6** was readily converted to 1,4-diene **2.7** in 67% yield, using 1 mol % catalyst and 1 mol % acid over 20 h.

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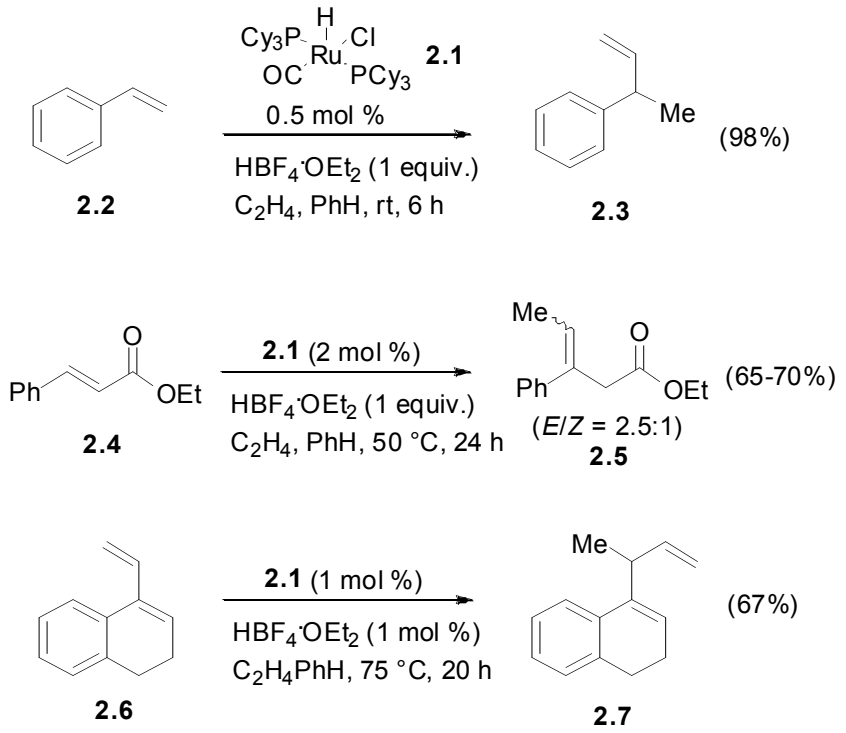
[44] a) B. Bogdanovic, B. Henc, B. Meister, H. Pauling, G. Wilke, *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 1023-1024 doi:10.1002/anie.197210231. b) N. Nomura, J. Jin, H. Park, T. V. RajanBabu *J. Am. Chem. Soc.* **1998**, *120*, 459-460 doi:10.1021/ja973548n. c) A. Zhang, T. V. RajanBabu *J. Am. Chem. Soc.* **2006**, *128*, 54-55 doi:10.1021/ja0561338. d) T. V. RajanBabu, *Chem. Rev.* **2003**, *103*, 2845-2860 doi:10.1021/cr020040g. e) T. V. RajanBabu *Synlett* **2009**, 853-885 doi:10.1055/s-0028-1088213.

[45] a) C. S. Yi, D. W. Lee, Y. Chen, *Organometallics* **1999**, *18*, 2043-2045 doi:10.1021/om990129l. b) C. S. Yi, Z. He, D. W. Lee, *Organometallics* **2001**, *20*, 802-804 doi:10.1021/om000881i. c) Z. He, C. S. Yi, W. A. Donaldson, *Org. Lett.* **2003**, *5*, 1567-1569 doi:10.1021/ol030031+. d) Z. He, C. S. Yi, W. A. Donaldson, *Syntlett* **2004**, 1312-1314 doi:10.1055/s-2004-825605.

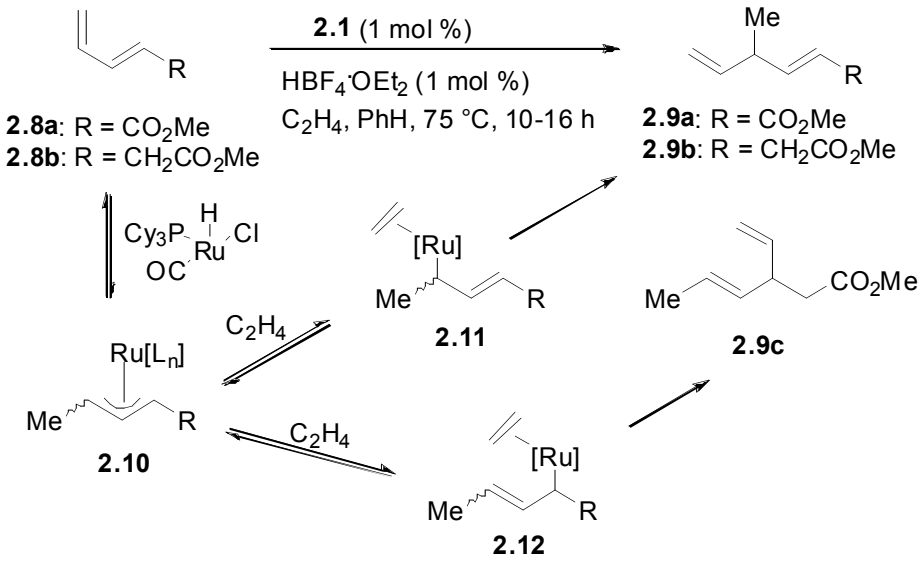
[46] Protonation of a phosphine ligand, sequestering it from coordination to the metal, is thought to generate a more active catalyst (*q.v.* ref. 45a, note 15).



Scheme 2.1 - Known ruthenium-catalyzed hydrovinylations

When the diene moiety was moved out of conjugation with other functional groups, regioisomeric adducts were observed. While hydrovinylation of dienoic ester **2.8a** produced only **2.9a**, **2.8b** produced a mixture of 1,2- and 1,4-hydrovinylation products **2.9b-c** in a 2:1 ratio (Scheme 2.2). Yi hypothesized that the regioisomeric products arise from different σ-allyl intermediates stabilized by conjugation with the ester. Insertion of **2.8** into the Ru-H bond of **2.1** produces π-allyl complex **2.10**, which can freely interconvert to σ-allyl complexes **2.11** and **2.12**. Subsequent migratory insertion of ethylene and β-hydride elimination then yield compounds **2.9a-c**. Due to conjugation between

the ester and the olefin, σ-allyl complex **2.11a** (R = CO_2Me), should be more stable than **2.12a**. In the case of **2.11b** and **2.12b**, however, there is no stabilization through conjugation, and thus a mixture of the 1,2- and 1,4-hydrovinylation products.[47]



Scheme 2.2 - Regiosiomeric adducts in hydrovinylation of dieneoates

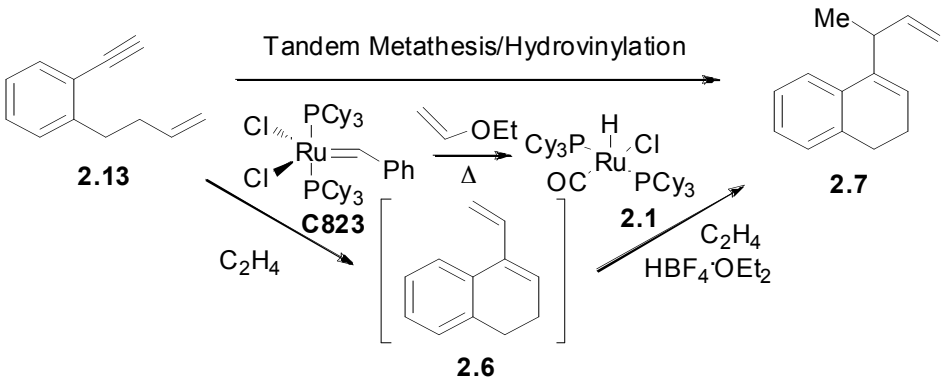
Overall, this reaction was performed on eight 1,3 dienes, with yields varying from 56% to 90%. Of particular interest for the development of a tandem process was diene **2.6**, which was reported[48] to be accessible from enyne **2.13** in 60% yield, although other dienes readily accessible[49] via enyne metathesis would

[47] Formation of 1,4-adducts is not unique to ruthenium-catalyzed hydrovinylations (*q.v.* section 2.5 *infra*)

[48] M. Rosillo, G. Dominguez, L. Casarrubios, U. Amador, J. Perez-Castells, *J. Org. Chem.* **2004**, *69*, 2084-2093 doi:10.1021/jo0356311.

[49] a) M. Mori, N. Sakakibara, A. Kinoshita, *J. Org. Chem.* **1998**, *63*, 6082-6083 doi:10.1021/jo980896e. b) for a recent review on enyne metathesis see: S. T. Diver, A. J. Giessert *Chem. Rev.* **2004**, *104*, 1317-1382 doi:10.1021/cr020009e.

certainly be examined.[50] With complex **2.1** available under a variety of conditions[51] from **C823**, a tandem process as outlined in Scheme 2.3 was envisioned.



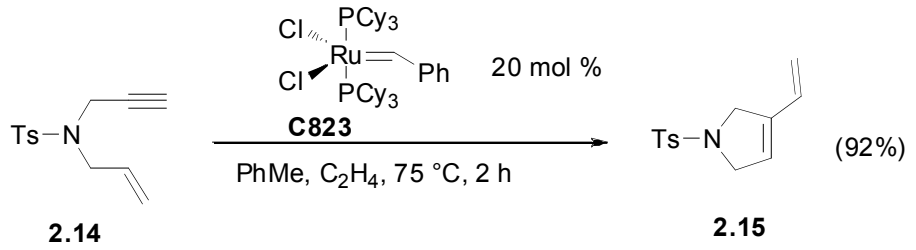
Scheme 2.3 - Planned tandem enyne metathesis-hydrovinylation

Enyne metathesis of **2.13** with **C823** should proceed rapidly under an atmosphere of ethylene to yield diene **2.6**. Addition of ethyl vinyl ether to the reaction should quench the metathesis and convert **C823** (or its methylidene congener) to **2.1**. Addition of $HBF_4 \bullet OEt_2$ and reaction with excess ethylene should then produce **2.7** in a "one-pot" process from **2.13**.

[50] Methyl cinnamate (**2.4**) is also accessible via cross metathesis of styrene and methyl acrylate, although the astute reader will likely have drawn an inference about its suitability for a tandem process from the title of the chapter. A further discussion may be found in section 2.4 (*vide infra*).
[51] See schemes 1.3 and 1.4 for more details on the synthesis of ruthenium hydride complex **2.1** from **C823**.

2.3 Optimization of hydrovinlyation conditions

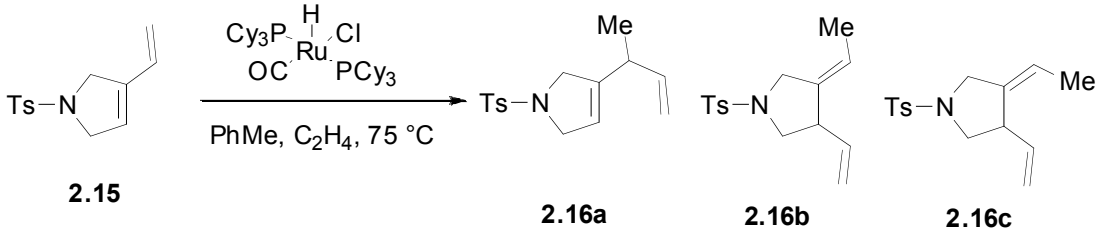
Before developing a tandem process, it was necessary to examine the efficiency of the individual reactions. Diene **2.15** was chosen for initial optimization of the ruthenium-catalyzed hydrovinylation.[52] Treatment of enyne **2.14** with 20 mol % **C823** produces **2.15** in 92% yield (Scheme 2.4).



Scheme 2.4 - Enyne metathesis to generate diene for optimization studies

Hydrovinylation of **2.15** produces a mixture of products, depending upon conditions (Scheme 2.5). Initial attempts at hydrovinylation of **2.15** with Yi's optimized conditions were less than optimal (Table 2.1). With 1 mol % catalyst (entry 1), even with elevated temperature (entry 2), conversion remained low. Somewhat surprisingly, the expected 1,2-hydrovinylation product **2.16a** was not observed. Instead, the major product is a mixture of olefin stereoisomers of the 1,4-hydrovinylation product (**2.16b-c**).

[52] While **2.6** was used in Yi's chemistry, it is an oil that is decomposes upon concentration, and is also somewhat unstable in solution, while **2.15** is an indefinitely stable white, crystalline solid.



2.15 **2.16a** **2.16b** **2.16c**

Scheme 2.5 - Initial optimization of hydrovinylation reaction

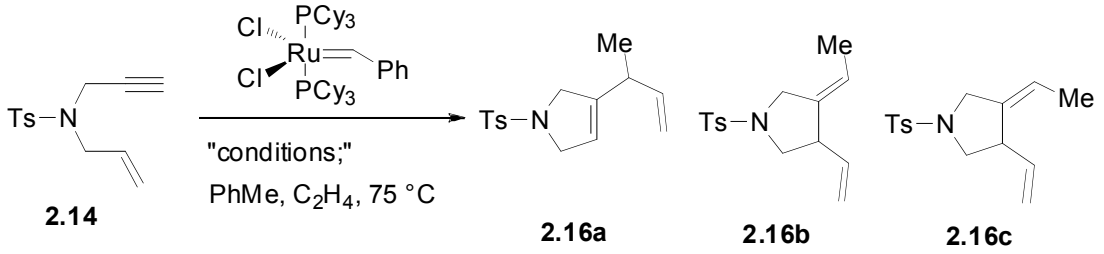
Table 2.1 – Initial optimization of hydrovinylation reaction

Entry	mol % Ru	mol % HBF_4	Time (h)	Temp. (°C)	Conv. (%)	a:b:c	Yield (%) (product)
1	1	1	20	75	9	0:4:5	--
2	1	1	20	100	41	0:3:4	15 (**b**)
3	3	10	18	75	89	0:7:12	21 (**b**)
4	20	40	18	75	89	3:4:2	14 (**a**), 36 (**b**)
5	20*	0	1	75	64	0:0:1	22 (**c**)
*__2.1__ generated *in situ* from **C823** using NaOMe/MeOH							

Only with elevated amounts of catalyst (20 mol %) and $HBF_4 \bullet OEt_2$ (40 mol %) did **2.16a** begin to form (Entry 4). Finally, when **2.1** was generated *in situ* via treatment of **C823** with sodium methoxide in methanol, **2.16c** was the only product of a much more rapid reaction (Entry 5).

The rapidity and selectivity of the reaction promoted by *in situ*-generated **2.1** prompted an examination of the efficiency of other conditions for catalyst modification. These investigations indicated that a 1,2-selective hydrovinylation of **2.15** was increasingly unlikely, as a variety of conditions for generation of ruthenium hydrides produced, in the absence of methanol, generally non-selective product distributions (Table 2.2). In the presence of methanol, however,

improved selectivity for the 1,4-hydrovinylation products, particularly **2.16c**, was observed.



2.14 **2.16a** **2.16b** **2.16c**

Scheme 2.6 - Examination of conditions for *in situ* generation of **2.1**

Table 2.2 – Examination of conditions for *in situ* generation of **2.1**

Entry	t_{met}	Cat. Mod.	t_{mod}	HBF_4 (mol %)	t_{vin} (h)	Conv. (%)	a:b:c	Yield (%) (product)
1	4 h	H_2C=CHOEt, 65 °C	21 h	20	6	69	3:2:2	--
2	4 h	H_2C=CHOEt, 65 °C	18 h	--	6	14	0:7:6	--
3	4 h	95:5 N_2:H_2, MeOH	5 min	--	16	82	1:8:2	36 (**b**)
4	4 h	95:5 N_2:H_2, MeOH	5 min	10	16	>99	0:1:2*	--
5	4 h	95:5 N_2:H_2, MeOH	5 min	10	16	10	0:1:1	--
6	3 h	95:5 N_2:H_2, MeOH	5 min	--	5	89	1:14:2	56 (**b**)
7	3 h	MeOH	5 min	--	6	0	--	--
8	10 min.	NaOMe, MeOH	10 min	--	1.5	74	0:1:7	--
*oligomers also observed by GC/MS								

Use of ethyl vinyl ether to form **2.1**, followed by the addition of $HBF_4 \bullet OEt_2$ duplicated the lack of selectivity observed in previous control reactions (Entry 1). In the absence of acid, hydrovinylation was substantially retarded, and the 1,2 product was no longer observed (Entry 2). A similar lack of selectivity manifested when forming gas[53] was used to generate a ruthenium hydride,[54]

[53] Dilute dihydrogen in dinitrogen, typically 5% v/v.

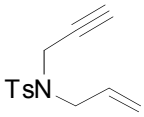
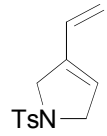
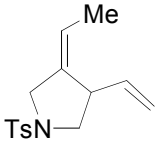
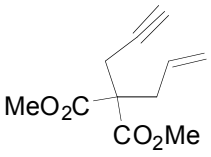
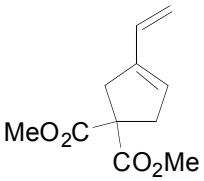
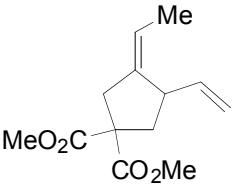
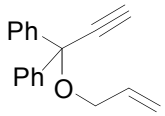
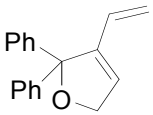
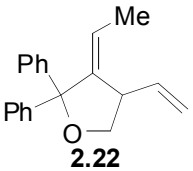
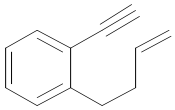
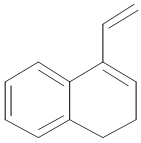
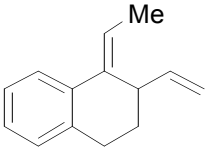
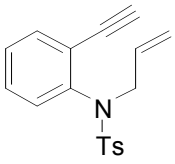
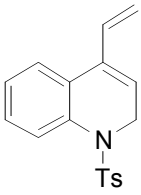
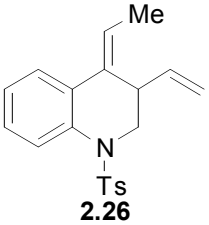
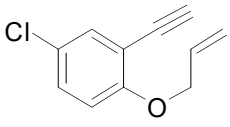
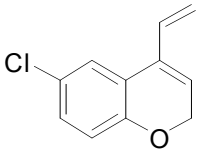
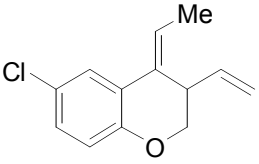
[54] This complex is not necessarily **2.1**, but treatment of ruthenium alkylidenes with forming gas results in the formation of a putative hydride complex, displaying both the characteristic canary-yellow color and activity for olefin isomerization (*q.v.* ref. 39a and ref. 43, chapter 3).

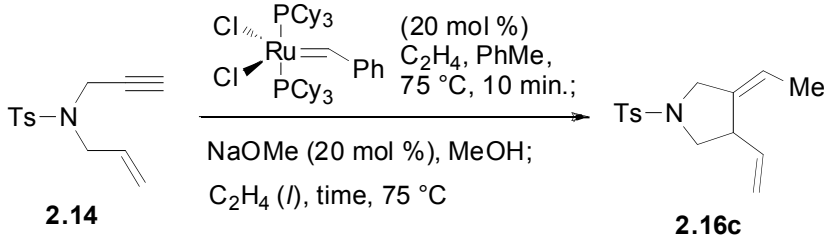
although in the presence of methanol and absence of $HBF_4 \bullet OEt_2$, increased selectivity for the 1,4 products was observed (Entries 3-6). Treatment of the reaction with just methanol (Entry 7) resulted in no hydrovinylation. Finally, use of NaOMe (20 mol%) in methanol to generate **2.1** resulted in a more rapid and selective reaction, generating predominantly **2.16c** in only 90 minutes (Entry 8).

2.4 Scope, selectivity, and limitations of the tandem process

Having determined optimal conditions for the tandem enyne metathesis hydrovinylation of model substrate **2.14** (Scheme 2.7), the generality of this process was then examined (Table 2.3). Malonate-tethered enyne **2.17** produces 1,4-diene **2.19** in 57% yield as a single olefin isomer. Similarly, *gem*-diphenyl enyne **2.20** yields diene **2.22** (64%), with the reaction requiring 5.5 h for completion, likely due to the increased steric bulk adjacent to the alkyne. The tandem reaction also proceeds selectively and efficiently for aromatic compounds **2.13**, **2.24**, and **2.27**, yielding **2.23** (71%), **2.26** (67%), and **2.29** (49%).

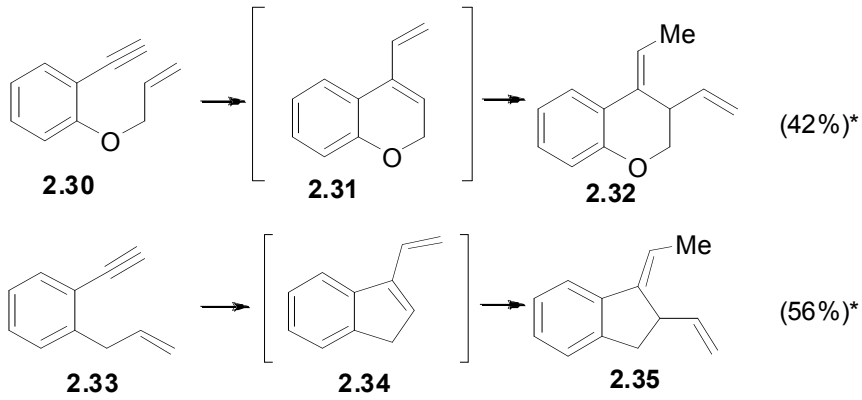
Table 2.3 – Generality of tandem enyne metathesis-hydrovinylation

Entry	Enyne	Diene	$t_{vinylation}$	Product	Yield
1	 **2.14**	 **2.15**	90 min.	 **2.16c**	56%
2	 **2.17**	 **2.18**	90 min.	 **2.19**	57%
3	 **2.20**	 **2.20**	5.5 h	 **2.22**	64%
4	 **2.13**	 **2.6**	80 min.	 **2.23**	71%
5	 **2.24**	 **2.25**	80 min.	 **2.26**	67%
6	 **2.27**	 **2.28**	80 min.	 **2.29**	49%



Scheme 2.7 - Optimized tandem enyne metathesis-hydrovinylation conditions

Several other enynes produced less-than-optimal results in the tandem metathesis-hydrovinylation for a variety of reasons (Scheme 2.8). Reaction of *ortho*-allyloxy phenylacetylene **2.30** produces **2.32** in moderate yield (42%) and marginal purity.[55] Considering the electon-rich aromatic ring, trisubstituted olefin, and relative stabilities of **2.23**, **2.26**, and **2.29**, oxidative decomposition would appear to be responsible for attenuated yields of **2.32**.

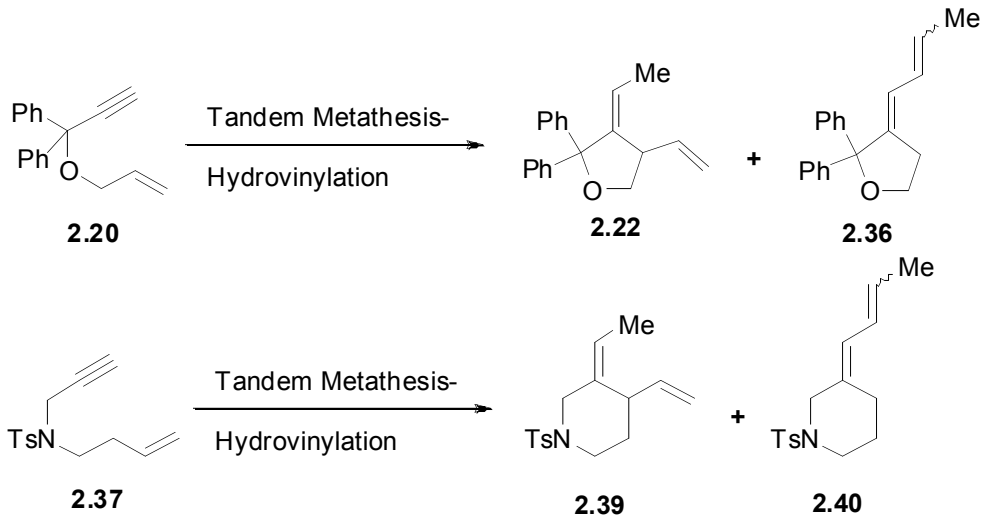


Scheme 2.8 - Problematic enynes for hydrovinylation reaction

[55] Three triplets of varying intensities that increase over time appear in the ^{1}H NMR between δ 3.0 and 2.6 ppm. This impurity is inseparable by standard chromatographic techniques, and apparently non-volatile, as GC/MS analysis indicates only the presence of **2.32**. It is the author's opinion that this is a shortcoming of compound **2.32** rather than the methodology.

Tandem metathesis-hydrovinylation of *ortho*-allyl phenylacetylene **2.33** produces 1,4-diene **2.35** (56% yield by GC/MS), which, due to unexpected volatility, could not be isolated in appreciable quantities nor characterized fully.

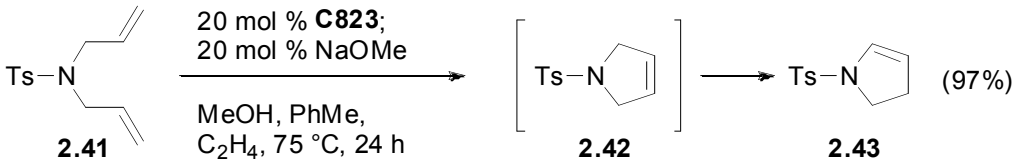
In many cases, tandem enyne metathesis-hydrovinylation produces a mixture of 1,4- and 4,1-hydrovinylation products (Scheme 2.9). The reaction of enyne **2.20** produces a mixture of **2.22** (64%) and small amounts of **2.36** (10%), which are easily separable. Sulfonamide **2.37**, however, produces an intractable mixture of **2.39** and **2.40**.



Scheme 2.9 - Formation of 1,4- and 4,1-hydrovinylation products

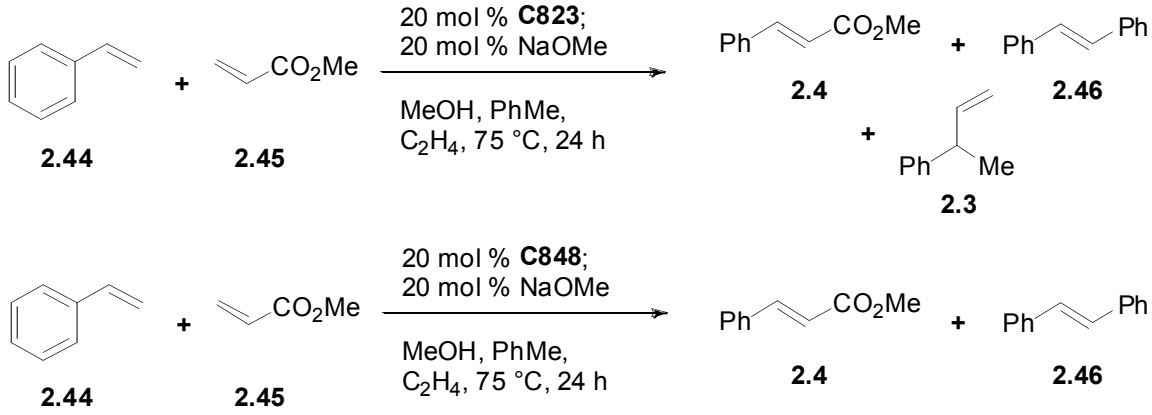
Metathesis-hydrovinylation conditions were also applied to a number of diene substrates. Attempted metathesis-hydrovinylation of N,N-diallyl sulfonamide **2.41** produces only in the olefin isomerization product **2.43** (97% yield) of the metathesis product **2.42**. Even with more forcing conditions, such as

the addition of 40 mol % $HBF_4 \bullet OEt_2$, methanol-free conditions, and extended reaction times, no hydrovinylation is observed (Scheme 2.10).



Scheme 2.10 - Isomerization, not hydrovinylation, of N-tosyl dihydropyrrole

Cross metathesis of styrene (**2.44**) and methyl acrylate (**2.45**) followed by hydrovinylation conditions produces a mixture of products (Scheme 2.11). Methyl cinnamate (**2.4**) is the major product (87% yield). Unreacted styrene and *trans*-stilbene (**2.46**) are also observed, and the only hydrovinylation product present is 2-phenyl-3-butene **2.3**. The same reaction with **C848** produces only methyl cinnamate and *trans*-stilbene. Hydrovinylation of *trans*-stilbene does not proceed even in the presence of 40 mol % $HBF_4 \bullet OEt_2$.



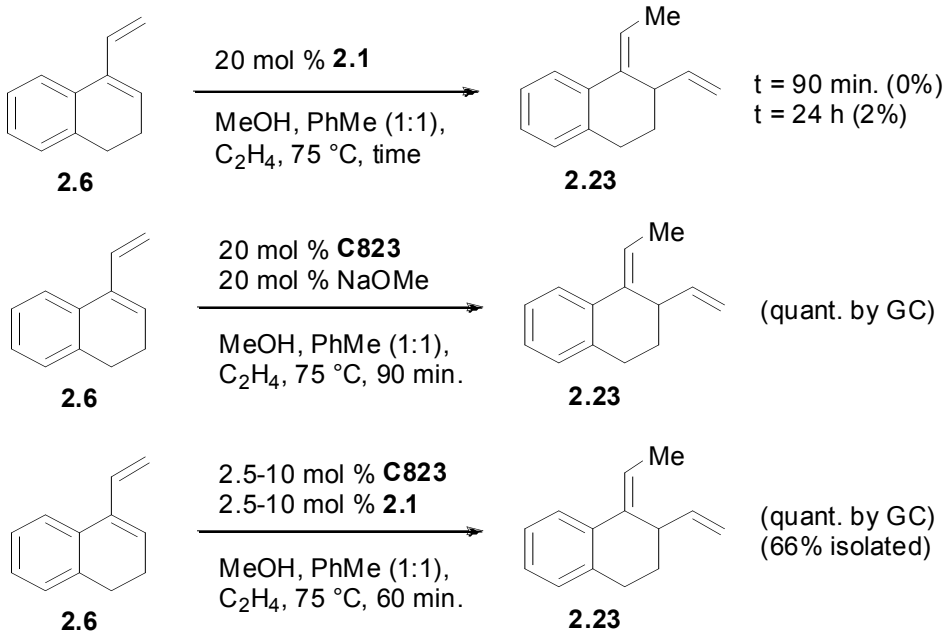
Scheme 2.11 - Attempted cross metathesis-hydrovinylation

2.5 Insight into the mechanism of the hydrovinylation step

Considering both the mechanism proposed by Yi (Scheme 2.2, *vide supra*) and the modifications in reaction conditions for the hydrovinylation, it was initially assumed that a similar mechanism was in operation. In the absence of $HBF_4 \bullet OEt_2$, both phosphines should be available for ligation to the metal. Furthermore, with methanol as a co-solvent, ethylene coordination could be retarded, allowing ample time for interconversion between the relevant σ-allyl intermediates prior to the irreversible insertion of ethylene.

A simple control experiment, however, indicated that a different mechanism was likely responsible for this reactivity. Hydrovinylation of diene **2.6** with 20 mol % **2.1** in toluene/methanol (1:1) produces no detectable amounts of **2.23** after 90 minutes, whereas the tandem process was complete in that time. Even after 24 hours, only 2% conversion from **2.6** to **2.23** is observed (Scheme 2.12). Use of ruthenium hydride **2.1** generated *in situ* from the reaction of **C823** and NaOMe produces **2.23** in efficiency similar to the tandem reaction. Somewhat perplexingly, when a 1:1 mixutre of **2.1** and **C823** is used as a precatalyst, even with as little as 5 mol % ruthenium, the reactivity and selectivity of the tandem process are duplicated. Analysis of the crude reaction mixture by ^{1}H and ^{31}P NMR indicated that both **2.1** and free PCy_3 are present at

the conclusion of the reaction, as well as Cy_3PMeCl. This reaction does not proceed in the absence of hydride **2.1** or NaOMe (i.e. **C823** in MeOH/PhMe).[56] While a mechanism involving a bimetallic catalyst cannot be ruled out, it seems unlikely given that bimetallic decomposition products have only been observed from NHC-based metathesis catalysts.[26-7]

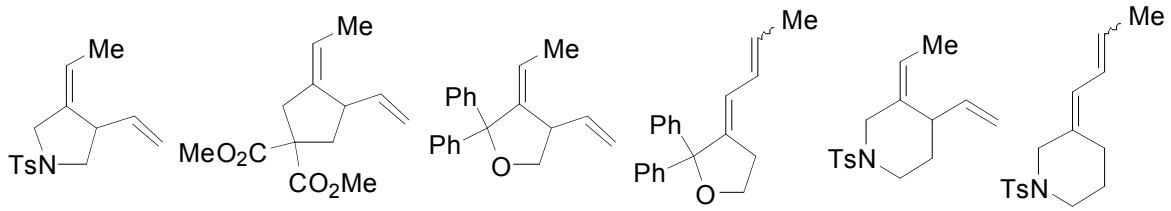


Scheme 2.12 - Initial mechanistic control experiments

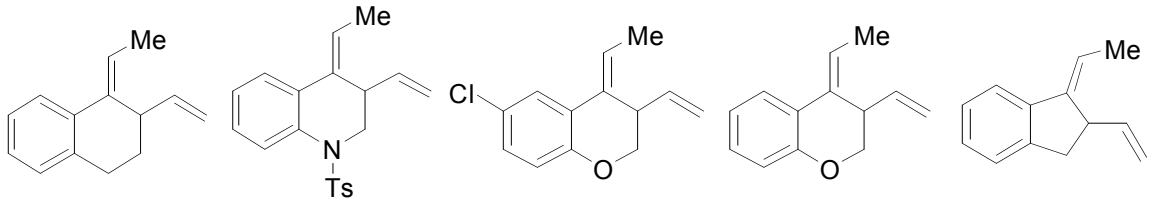
Furthermore, it is noteworthy that all 1-4 (and 4,1) hydrovinylation products share the same stereochemistry on the trisubstituted olefin (Figure 2.2). If Yi's mechanism were responsible for the formation of 1,4-hydrovinylation products in this reaction, olefin stereoisomers would likely have been observed,

[56] *Q.v.* table 2.2, entry 7 (*supra*).

since the σ-allyl complexes could freely interconvert prior to rate-determining insertion of ethylene. Indeed, the observation of 4,1-hydrovinylation products supports the direct reaction of the 1,3-diene's s-*cis* conformation with the metal.



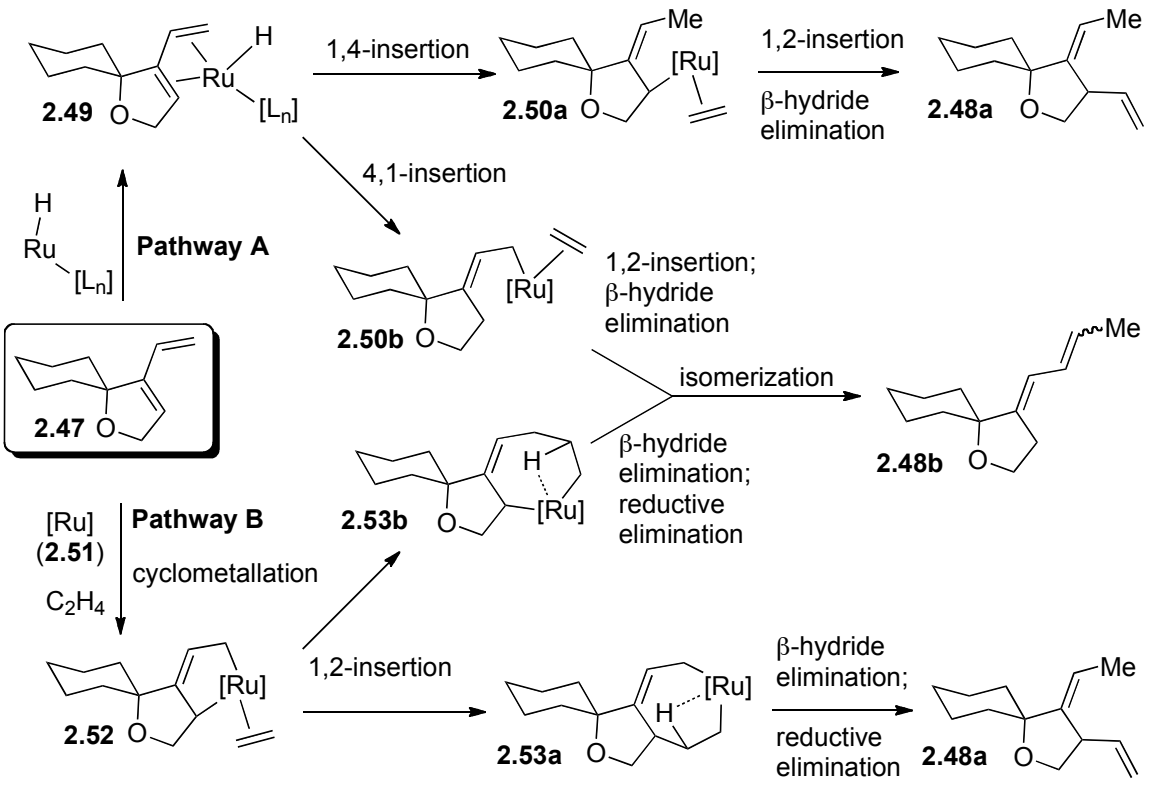
2.16c **2.19** **2.22** **2.36** **2.39** **2.40**



2.23 **2.26** **2.29** **2.32** **2.35**

Figure 2.2 - Stereochemical similarity of tandem metathesis-hydrovinylation products

Two plausible mechanistic scenarios are outlined in Scheme 2.13 and illustrated with diene **2.47**, which produces a mixture of 1,4- and 4,1-hydrovinylation products in the tandem process. In pathway A, a ruthenium hydride coordinates to the 1,3-diene in its s-*cis* conformation (**2.49**). Subsequent direct 1,4-insertion produces a mixture of σ-allyl complexes **2.50a** and **2.50b**, which, upon insertion of ethylene and subsequent eliminations, lead to 1,4- and 4,1-hydrovinylation products **2.48a** and **2.48b**, respectively.

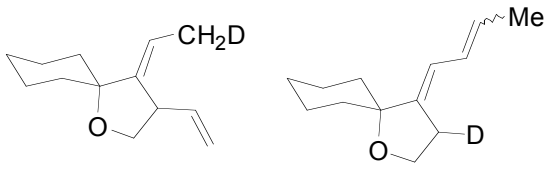


Scheme 2.13 - Plausibile mechanisms for 1,4-selective hydrovinylation

In pathway B, a non-hydridic complex (**2.51**) may undergo cyclometallation, producing ruthenacyclopentene **2.52**. Migratory insertion of ethylene could expand the ring in either direction, producing ruthenacycloheptenes **2.53a** and **2.53b**. Subsequent β-hydride and reductive eliminations would then produce organic products **2.48a** and **2.48b**.

It was anticipated that deuterium labeling studies could provide additional insight into the mechanism of the hydrovinylation step (Figure 2.3). In pathway A, for example, a ruthenium deuteride would be expected to

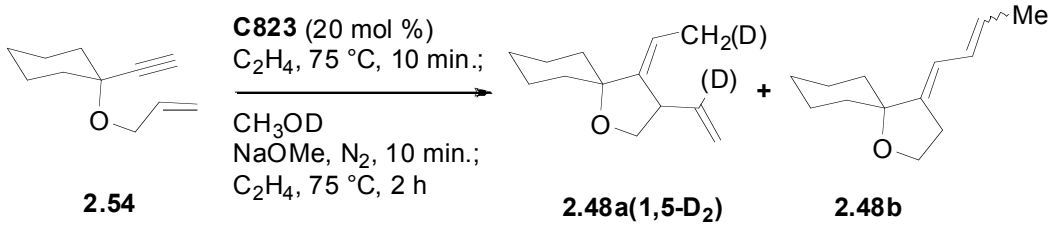
produce **2.48a-1D** and **2.48b-4D**. This ruthenium deuteride could be generated through reaction of **C823** with CD_3OD, or simple H/D exchange with **2.1** and CH_3OD. If pathway B, which does not invoke an exogenous ruthenium hydride, were active, then **2.48a-1D** and **2.48b-4D** should not be observed.



2.48a-1D **2.48b-4D**

Figure 2.3 - Expected deuterated products

Mol had reported that H/D exchange[57] was facile for complex **2.1**, so CH_3OD was initially examined in the tandem process. Tandem metathesis-hydrovinylation of enyne **2.54** results in minimal deuterium incorporation (Scheme 2.14) when CH_3OD is used for hydride generation. The ^{2}H-NMR of the reaction mixture features resonances at δ 1.66 and δ 5.79, with the former corresponding to the allylic methyl group, the latter the terminal vinyl group.



2.54 **2.48a(1,5-D_2)** **2.48b**

Scheme 2.14 - Deuterium labeling experiments

[57] Mol reported only the facility of this exchange, not the relative rate (*q.v.* ref. 12 *supra*).

Deuteration of the allylic methyl group is consistent with both Yi's original mechanism and pathway A, and deuteration of the terminal vinyl group could readily occur via either 1,2-insertion/β-hydride elimination or hydrovinylation with D_1-ethylene generated prior to formation of the carbon-carbon bond. While the ^{2}H-NMR shows some deuterium incorporation, the ^{1}H-NMR does not appear different from that of a reaction run in methanol. This minimal incorporation of deuterium suggests that the H/D exchange on ruthenium occurs at a rate comparable to, but not substantially faster than, hydrovinylation. Furthermore, no incorporation of deuterium into the 4,1-hydrovinylation product is observed, however, suggesting that the 4,1-products might be formed via pathway B.

It was expected that by using CD_3OD to generate a ruthenium deuteride, greater amounts (as much as 20 mol %) of deuterated product could be observed. As in the reaction with CH_3OD, however, minimal deuteration is observed. In addition to the previously observed ^{2}H peaks, a resonance is also observed at δ 3.44-3.36, corresponding to the doubly allylic proton illustrated in Figure 2.4. Deuteration at this position is likely a result of rapid equilibration of σ-allyl intermediates such as **2.50a** and **2.50b** (Scheme 2.13, pathway A), through a common π-allyl intermediate, prior to 1,2-insertion of ethylene. Once again, no deuterium resonances corresponding to 4,1-hydrovinylation products are observed, suggesting pathway B produces these products. Given the contrasting

results of the deuterium labeling studies, it is unlikely that a single mechanism is responsible for formation of both the 1,4- and 4,1-hydrovinylation products.

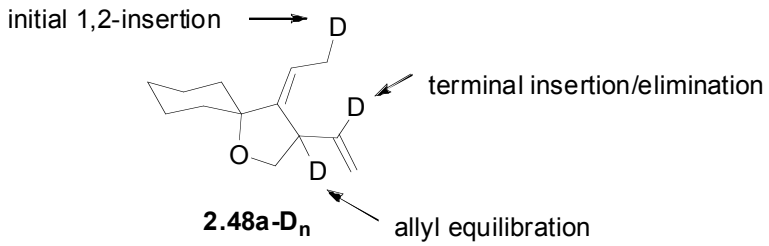
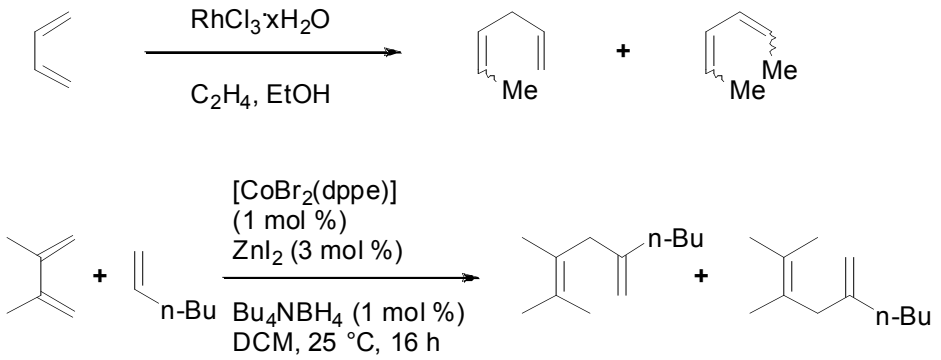


Figure 2.4 - Sites of deuterium incorporation (CD_3OD)

While there are multiple reports of 1,4-selective hydrovinylation, discussion of the mechanism has received comparatively little attention. Although Yi proposed a mechanism for the formation of 1,4-hydrovinylation byproducts,[58] RajanBabu,[59] in a process that otherwise delivered "exquisite regioselectivity," made no such mechanistic hypotheses. Hydrovinylation with complete 1,4-selectivity has been reported for a variety of metals (Scheme 2.15). In the DuPont hexadiene process,[60] 1,4-selectivity was observed in the rhodium(III) chloride-catalyzed addition of ethylene to butadiene.

[58] *Q.v.* scheme 2.2, *supra*.
[59] A. Zhang, T. V. RajanBabu, *J. Am. Chem. Soc.* **2006**, *128*, 54-55 doi:10.1021/ja0561338.
[60] T. Alderson, E. L. Jenner, R. V. Lindsey Jr., *J. Am. Chem. Soc.* **1965**, *87*, 5638-5645 doi:10.1021/ja00952a022.



Scheme 2.15 - Other 1,4-selective hydrovinylations

Hilt reported that a cobalt(I) catalyst previously used for Diels-Alder[61] reactions with alkynes also promotes 1,4-selective hydrovinylation of 1,3-dienes with a variety of α-olefins.[62] It has been suggested that the low-valent metal-catalyzed Diels-Alder process proceeds through stepwise additions in the metal coordination sphere,[63] and that the alternate hydrovinylation pathway occurs when the dienophile possesses accessible β-hydrides. This mechanism is analgous to pathway B proposed above.[64] Based on the lack of deuterium incorporation in labeling studies, it is likely that this mechanism, and thus a

[61] G. Hilt, F.-X. du Mesnil *Tetrahedron Lett.* **2000**, *41*, 6757-6761 doi:10.1016/S0040-4039(00)01163-1.
[62] a) G. Hilt, F.-X. du Mesnil, S. Lüers, *Angew. Chem. Int. Ed.* **2001**, *40*, 387-389 doi:10.1002/1521-3773(20010119)40:2<387::AID-ANIE387>3.0.CO;2-7. b) G. Hilt, S. Lüers, *Synthesis*, **2002**, 609-618 doi:10.1055/s-2002-23549. c) G. Hilt, S. Lüers, F. Schmidt, *Synthesis*, **2004**, 634-638 doi:10.1055/s-2003-44373.
[63] a) M. Lautens, W. Tam, J. C. Lautens, L. G. Edwards, C. M. Crudden, A. C. Smith, *J. Am. Chem. Soc.* **1995**, *117*, 6863-6879 doi:10.1021/ja00131a008. b) Y. Chen, R. Kiattansakul, B. Ma, J. K. Snyder, *J. Org. Chem.* **2001**, *66*, 6932-6942 doi:10.1021/jo010268o.
[64] A similar mechanism, supported by deuterium-labeling studies, has been proposed for a 1,4-hydrovinylation promoted by low-valent iron-iminopyridine complexes: B. Moreau, J. Y. Wu, T. Ritter, *Org. Lett.* **2009**, *11*, 337-339 doi:10.1021/ol802524r.

reduced metal species, is responsible for the formation of 4,1-hydrovinylation byproducts.

2.6 Conclusion

Tandem enyne metathesis-hydrovinylation allows access to a variety of cyclic 1,4-dienes from readily available acyclic precursors. This process proceeds with regioselectivity that has not been previously observed for a ruthenium-catalyzed process. Mechanistic investigations, while not definitive, indicate that this reaction may proceed through a mechanism other than that initially proposed for the ruthenium-catalyzed formation of 1,4-hydrivinylation adducts.

2.7 Experimental Details

Unless otherwise noted, enynes and dienes were prepared by following literature procedures. Enynes **2.14**,[65] **2.17**,[66] **2.20**,[67] **2.33**,[68] **2.30**, **2.37**[71] and **2.13**[69]

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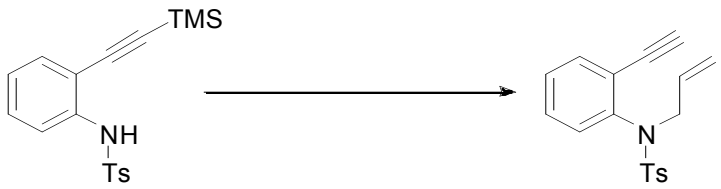
[65] M. C. Patel, T. Livinghouse, B. L. Pagenkopf, *Organic Syntheses*, **2003**, *80*, 93-103.
[66] K. Miura, H. Saito, N. Fujisawa, A. Hosomi, *J. Org. Chem.* **2000**, *65*, 8119-8122 doi:10.1021/jo005567c.
[67] R. Castarlenas, M. Eckert, P. H. Dixneuf, *Angew. Chem. Int. Ed.* **2005**, *44*, 2576-2579 doi:10.1002/anie.200462865.
[68] L. Brandsma, H. Hommes, H. D. Verkruijsse, R. L. P. De Jong, *Recl. Trav. Chim. Pays-Bas* **1985**, *104*, 226-230.

and dienes **2.6**,[70] **2.15**,[71] **2.31**, **2.18**,[66] **2.34**,[72] **2.20**,[5] **2.38**[73] and **2.47**[74] were identified by comparison of their spectral data with published values. Olefin metathesis catalysts were provided by Materia, and used without further purification. Complex **2.1** was prepared directly from **C823**.[75]

Synthesis of Enyne 2.24



2.24

To a rapidly stirred suspension of KH (65.0 mg, 1.65 mmol) and dry THF (20 mL) in a three-necked flask fitted with a reflux condenser and cooled in an ice-water bath was added dropwise, under a nitrogen atmosphere, 4-methyl-*N*-(2-((trimethylsilyl)ethynyl)phenyl) benzenesulfonamide[76] (511 mg, 1.49 mmol) as a solution in 6 mL dry THF. The reaction mixture was allowed to warm to

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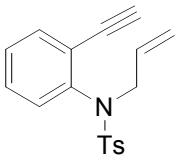
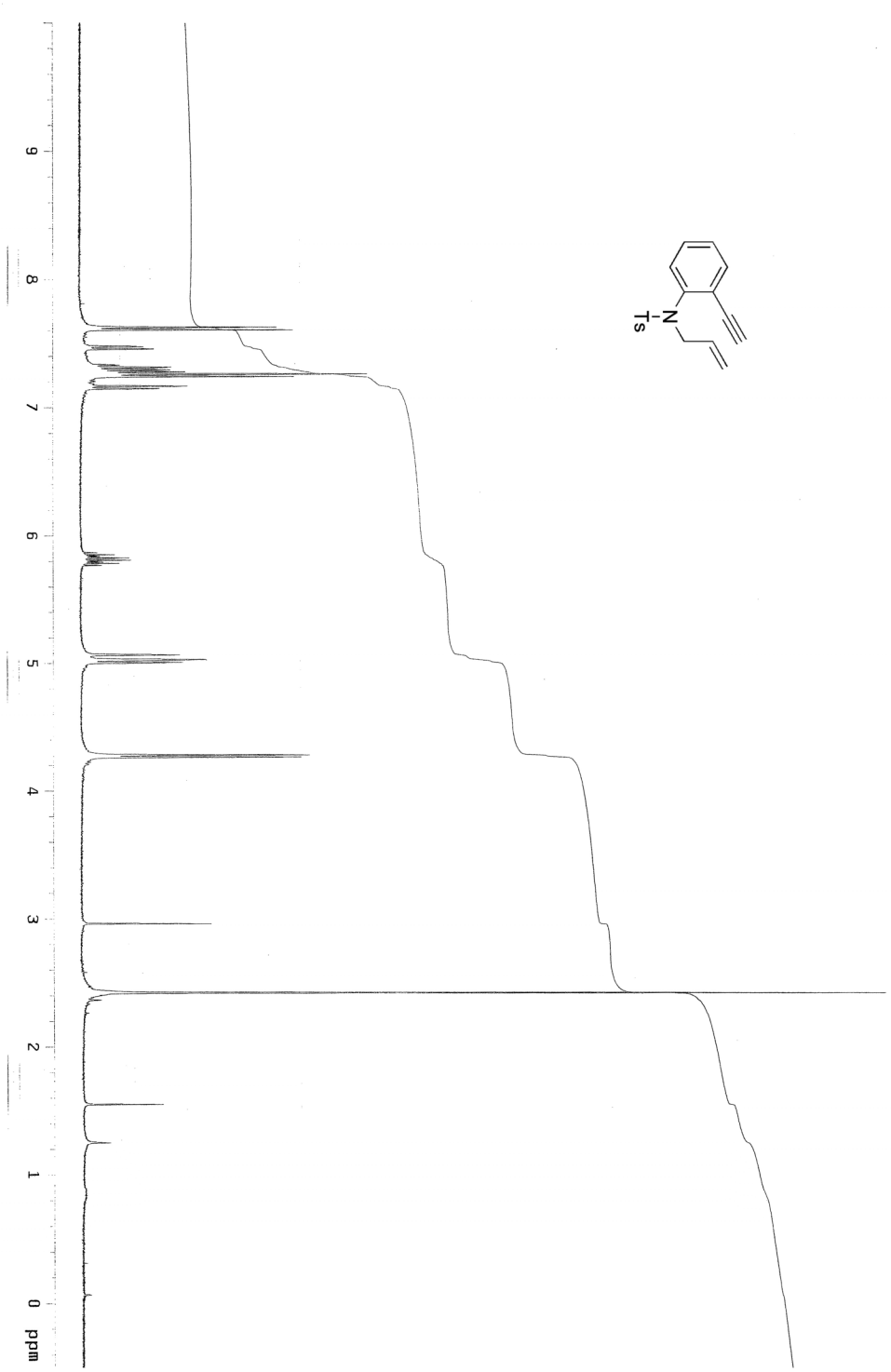
[69] M. Rosillo, G. Dominguez, L. Casarrubios, U. Amador, J. Perez-Castells, *J. Org. Chem.* **2004**, *69*, 2084-2093 doi:10.1021/jo0356311.
[70] D. Bentz, S. Laschat, *Synthesis* **2000**, *12*, 1766-1773 doi:10.1055/s-2000-8211.
[71] C. González-Rodríguez, J. A. Varela, L. Castedo, C. Carlos Saá, *J. Am. Chem. Soc.*, **2007**, *129*, 12916–1291 doi:10.1021/ja0752888.
[72] H.-M. Yin, B. R. Heazlewood, N. P. J. Stamford, K. Nauta, G. B. Backsay, S. H. Kable, T. W. Schmidt, *J. Phys. Chem. A*, **2007**, *111*, 3306-3312 doi:10.1021/jp068844d.
[73] M. Mori, N. Sakakibara, A. Kinoshita, *J. Org. Chem.* **1998**, *63*, 6082-6083 doi:10.1021/jo980896e.
[74] And its enyne precursor: L. Ackermann, C. Bruneau, P. H. Dixneuf, *Synlett*, **2001**, 397-399 doi:10.1055/s-2001-11394.
[75] *Q.v.* ref. 12, *supra*.
[76] M. Hatano, K. Mikami, *J. Am. Chem. Soc.* **2003**, *125*, 4704-4705 doi:10.1021/ja0292748.

ambient temperature and subsequently heated to reflux for fifteen minutes, during which the evolution of gas was observed. Allyl bromide (154 μL, 1.79 mmol) was then added, and the reaction mixture was allowed to reflux overnight, over the course of which a white precipitate formed. The reaction mixture was allowed to return to ambient temperature, then K_2CO_3 (2.00 g, 14.5 mmol) and methanol (25 mL) were added, and the reaction mixture was allowed to stir at ambient temperature for 24 h. The reaction mixture was filtered, concentrated *in vacuo*, and then purified by column chromatography on silica gel with hexanes/dichloromethane (20:1) as the eluent, producing compound **2.24** in 86% yield.



***N*-Allyl-*N*-(2-ethynylphenyl)-4-methylbenzenesulfonamide (2.24):** ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.62 (d, *J* = 8.4 Hz, 2H), 7.47 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.32 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.29 (dd, *J* = 6.0, 2.0 Hz, 1H), 7.25 (d, *J* = 8.8 Hz, 2H), 7.16 (dd, *J* = 8.0, 1.2 Hz, 1H), 5.82 (ddt, *J* = 17.2, 10.4, 6.4 Hz, 1H), 5.05 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.02 (dd, *J* = 10.4, 1.2 Hz, 1H), 4.27 (d, *J* = 6.4 Hz, 2H), 2.96 (s, 1H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 143.4, 140.7, 137.0, 134.2, 133.2, 131.8, 129.5, 129.4, 128.2, 128.0, 123.5, 118.9, 82.1, 80.5, 53.8, 21.9; IR (NaCl, thin film): 3066 (w), 3038 (vs), 3018 (w), 2926 (w), 2361 (w), 2342 (w), 1460 (w), 1346 (w), 1161 (m), 1091 (m), 913 (m), 865 (m),

738 (m), 668 (w), 582 (w), 532 (w), 426 (vs), 412 (vs) cm^{-1}; HRMS (ES+): calculated for $C_{18}H_{17}NO_2SNa^+$: *m/z* 334.0878, found 334.0890.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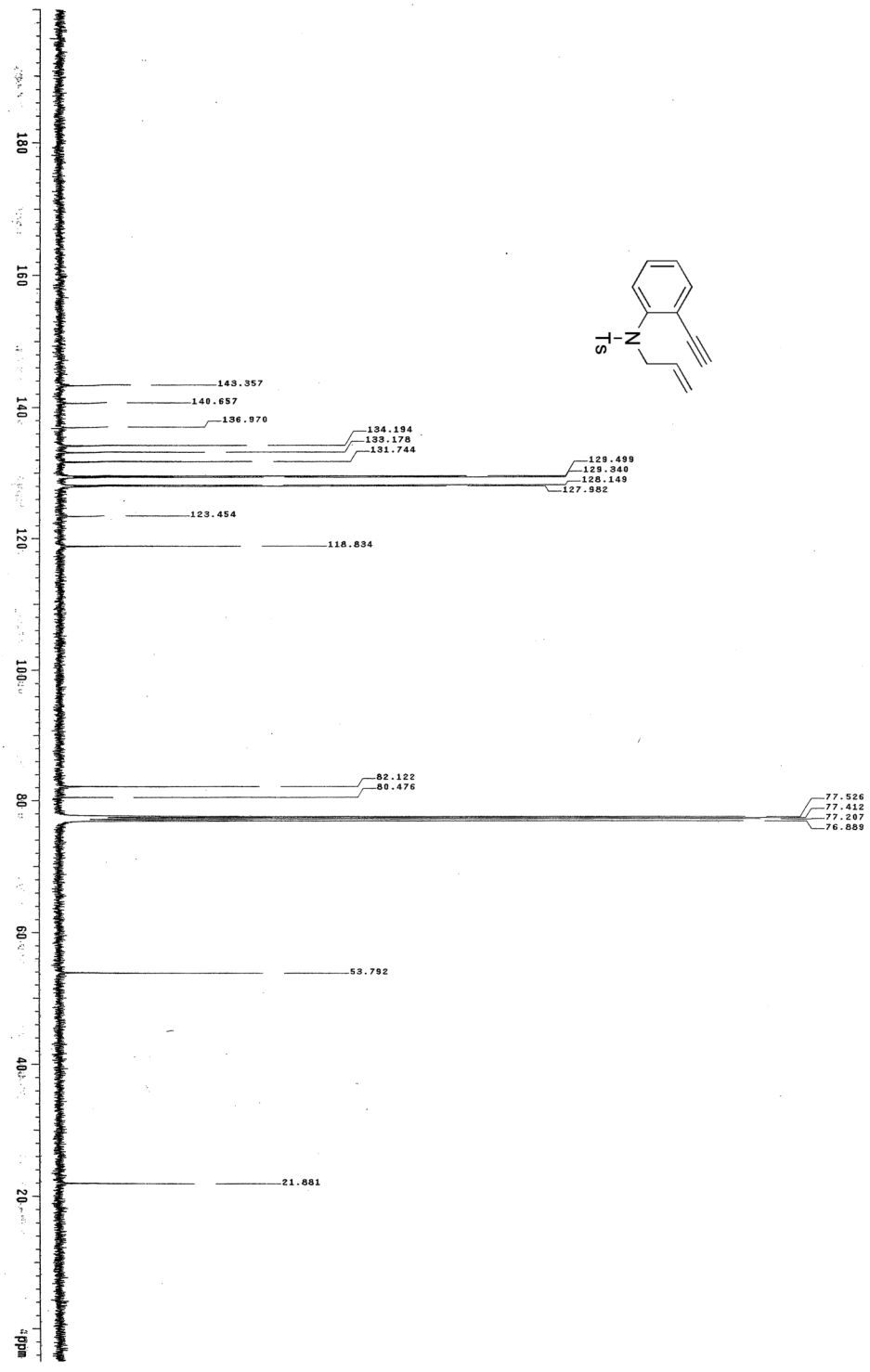
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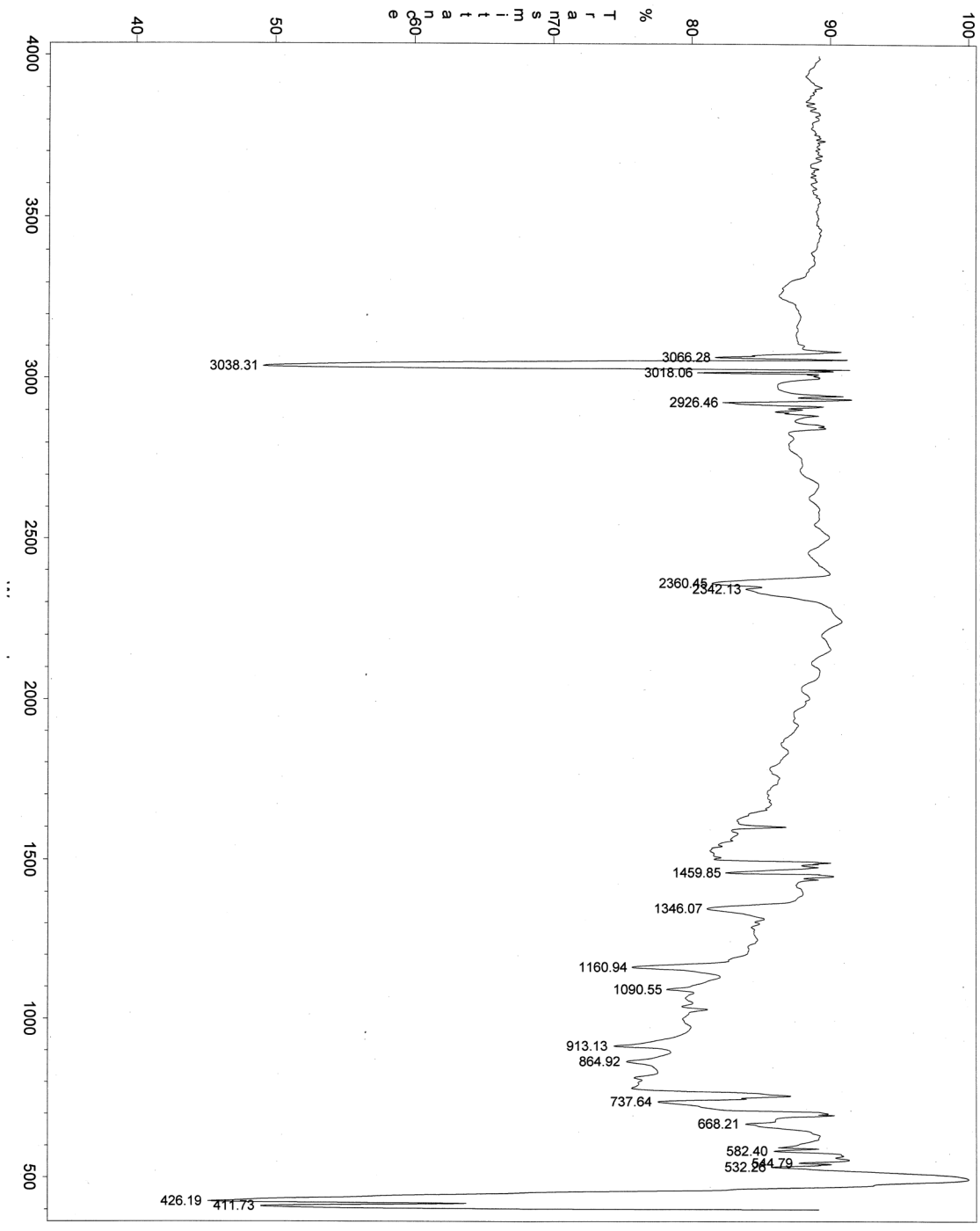
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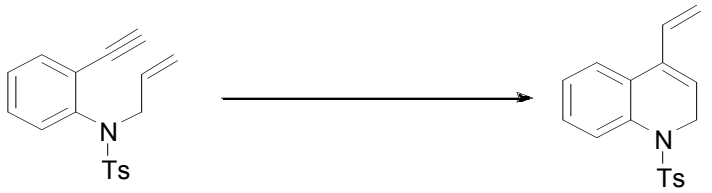
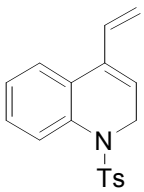
Thu Jun 29 14:23:48:80 2006

Synthesis of Diene 2.25



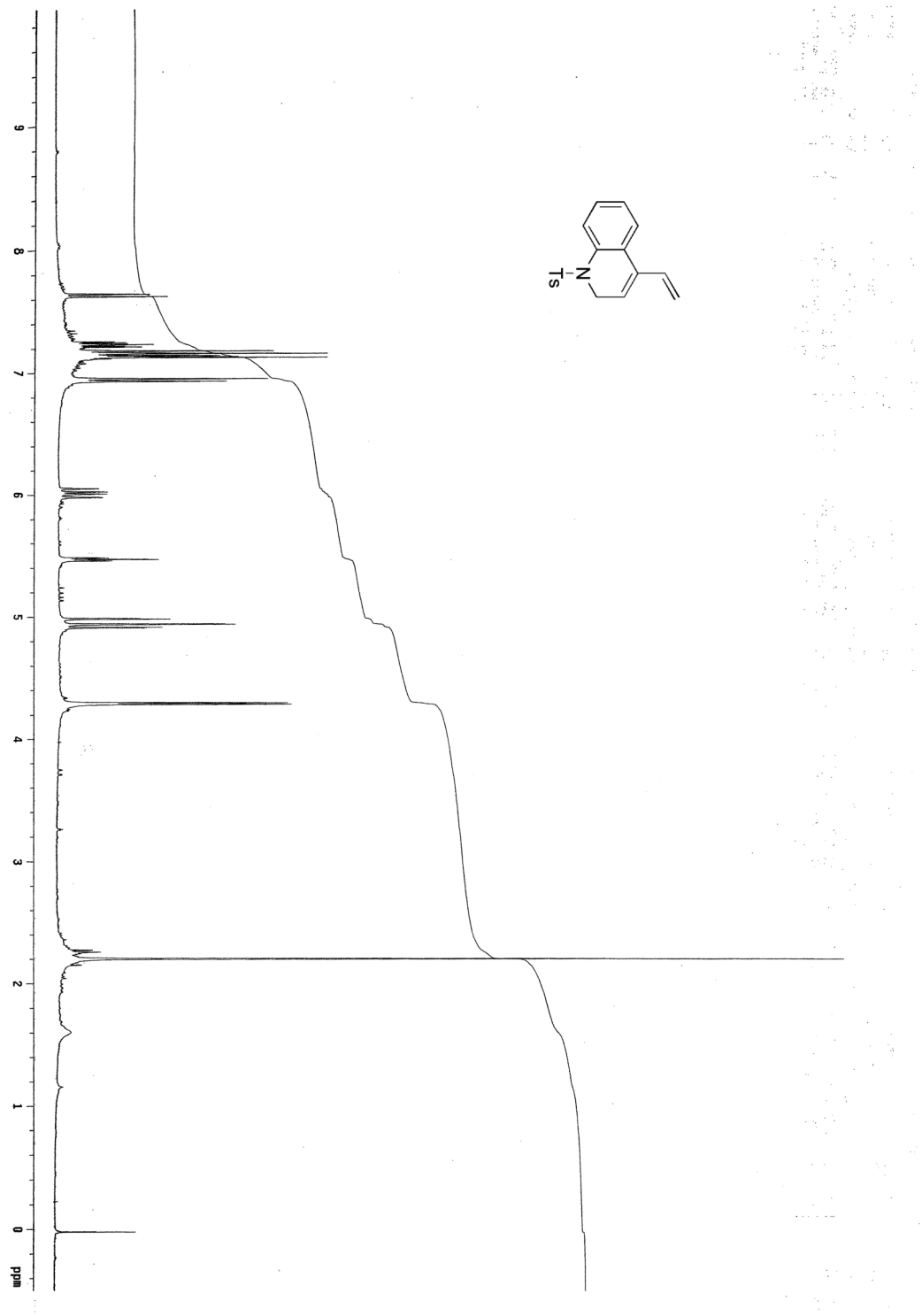
2.24 **2.25**

In a N_2 atmosphere glove box, enyne **2.24** (0.20 mmol) and $(PCy_3)_2Cl_2Ru$=CHPh (33 mg, 40 μmol) were placed in a 25 mL Schlenk tube (or medium-walled pyrolysis tube) and then dissolved in dry, degassed toluene (1.0 mL). After removal from the glove box, the reaction mixture was heated to 75 °C under an atmosphere of ethylene until metathesis was complete as monitored by GC/MS. The residue was then concentrated *in vacuo* and purified by column chromatography on silica gel with hexanes/dichloromethane (20:1) as the eluent, producing compound **2.25** in 68-80% yield.



1-Tosyl-4-vinyl-1,2-dihydroquinoline (2.25): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65 (d, *J* = 8.4 Hz, 1H), 7.27 (dd, *J* = 6.0, 2.4 Hz, 1H), 7.25 (d, *J* = 6.4, 2.8 Hz, 1H), 7.20-7.15 (m, 3H), 6.96 (d, *J* = 8.4 Hz, 2H), 6.04 (dd, *J* = 17.6, 11.2 Hz, 1H), 5.49 (t, *J* = 4.4 Hz, 1H), 4.98 (d, *J* = 17.6 Hz, 1H), 4.95 (d, *J* = 11.2 Hz, 1H), 4.31 (d, *J* = 4.8 Hz, 2H), 2.22 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 143.3, 136.2, 135.6, 135.3, 132.9, 130.0, 129.1, 128.2, 127.7, 127.4, 126.8,

124.4, 120.6, 116.8, 45.5, 21.7; IR (NaCl, thin film): 3584 (w), 3083(w), 3060 (m), 3028 (vs), 2926 (vs), 2909 (vs), 2850 (m), 1492 (m), 1447 (m), 1352 (m), 1164 (s), 814 (w), 752 (s) cm^{-1}; HRMS (ES+): calculated for $C_{18}H_{17}NO_2SNa^+$: *m/z* 334.0878, found 334.0867.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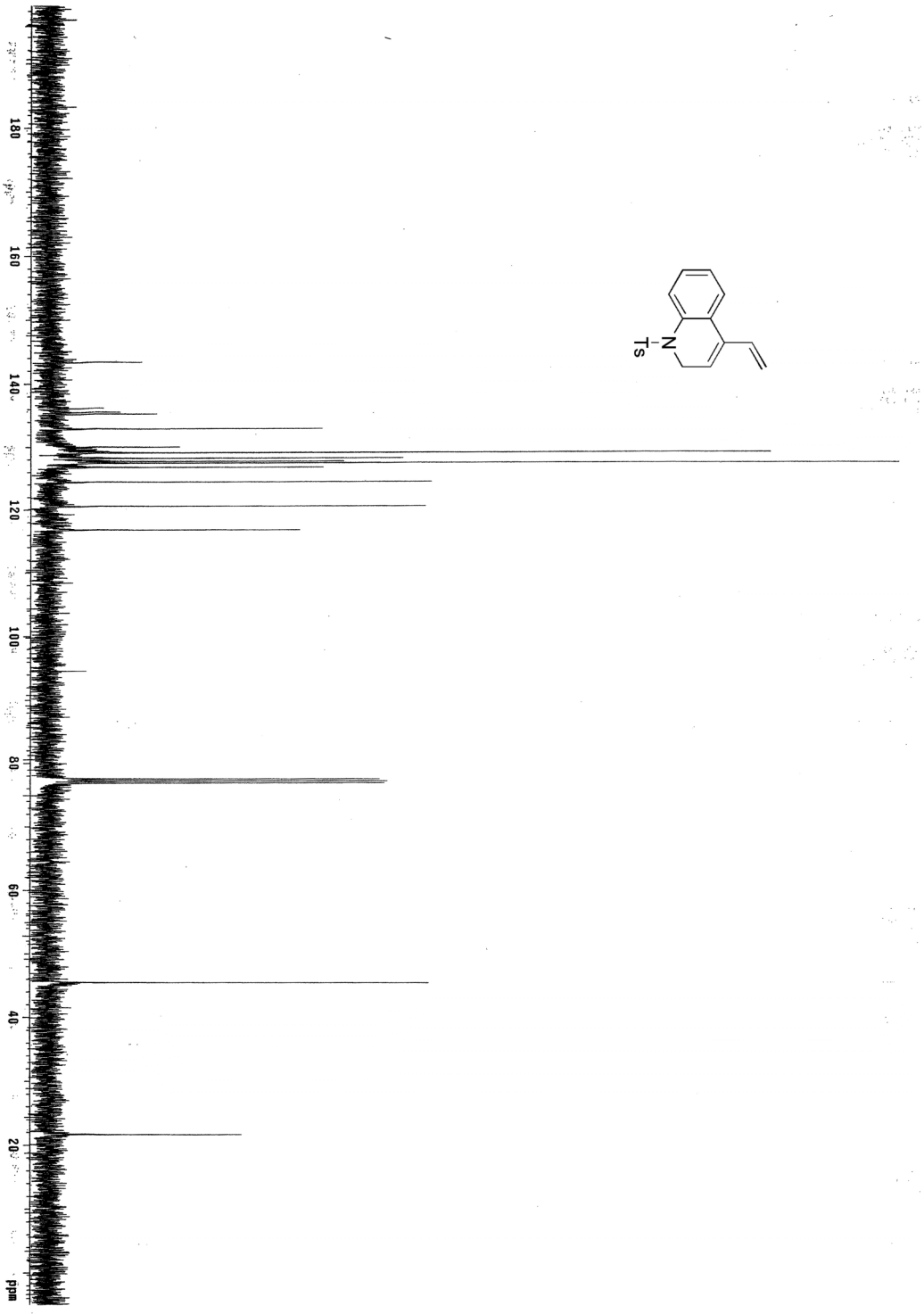
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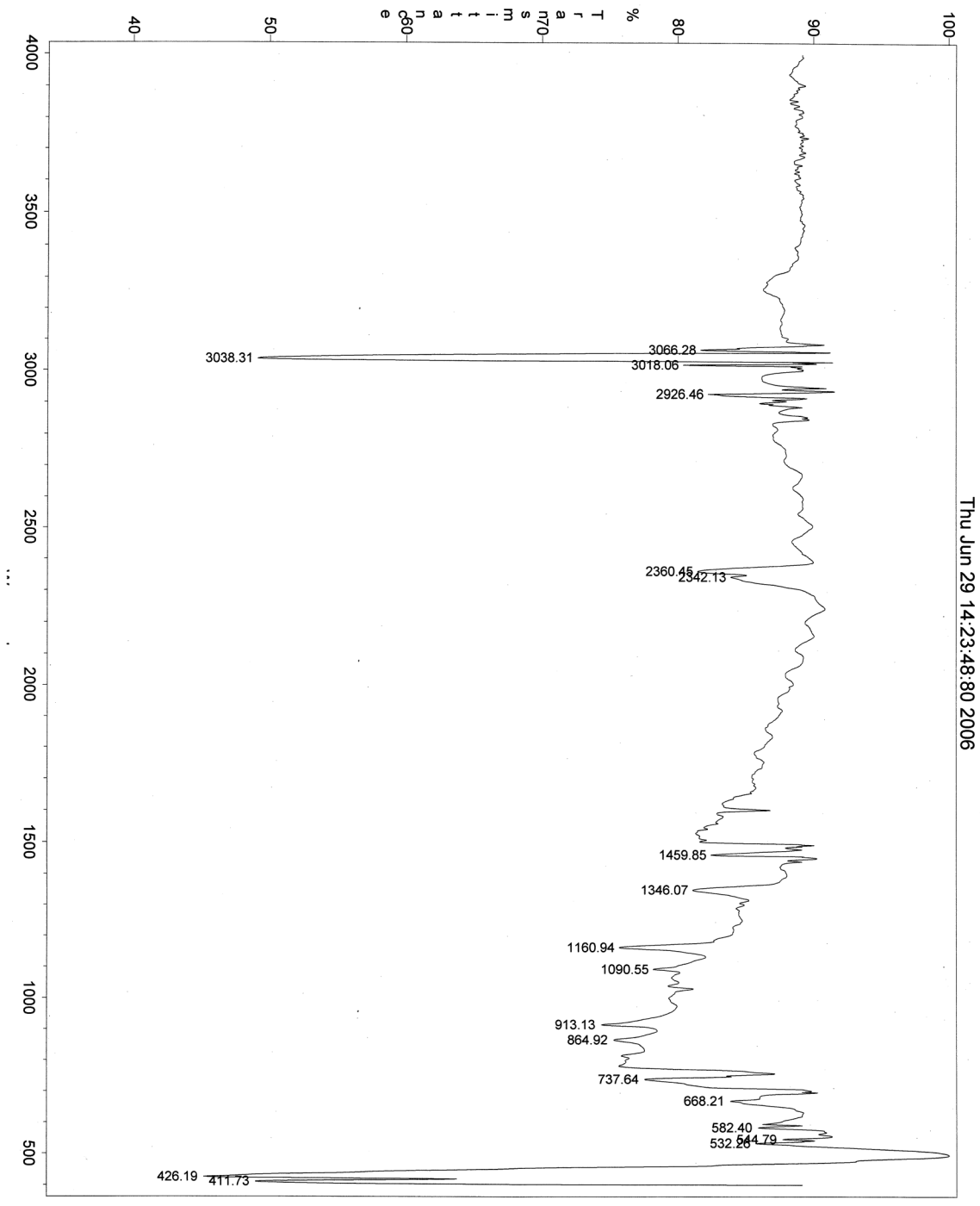
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1346.07
1160.94
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913.13
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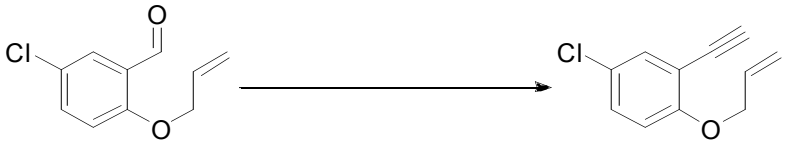
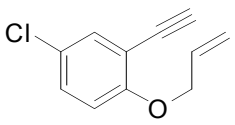
Thu Jun 29 14:23:48:80 2006

Synthesis of Enyne 2.27



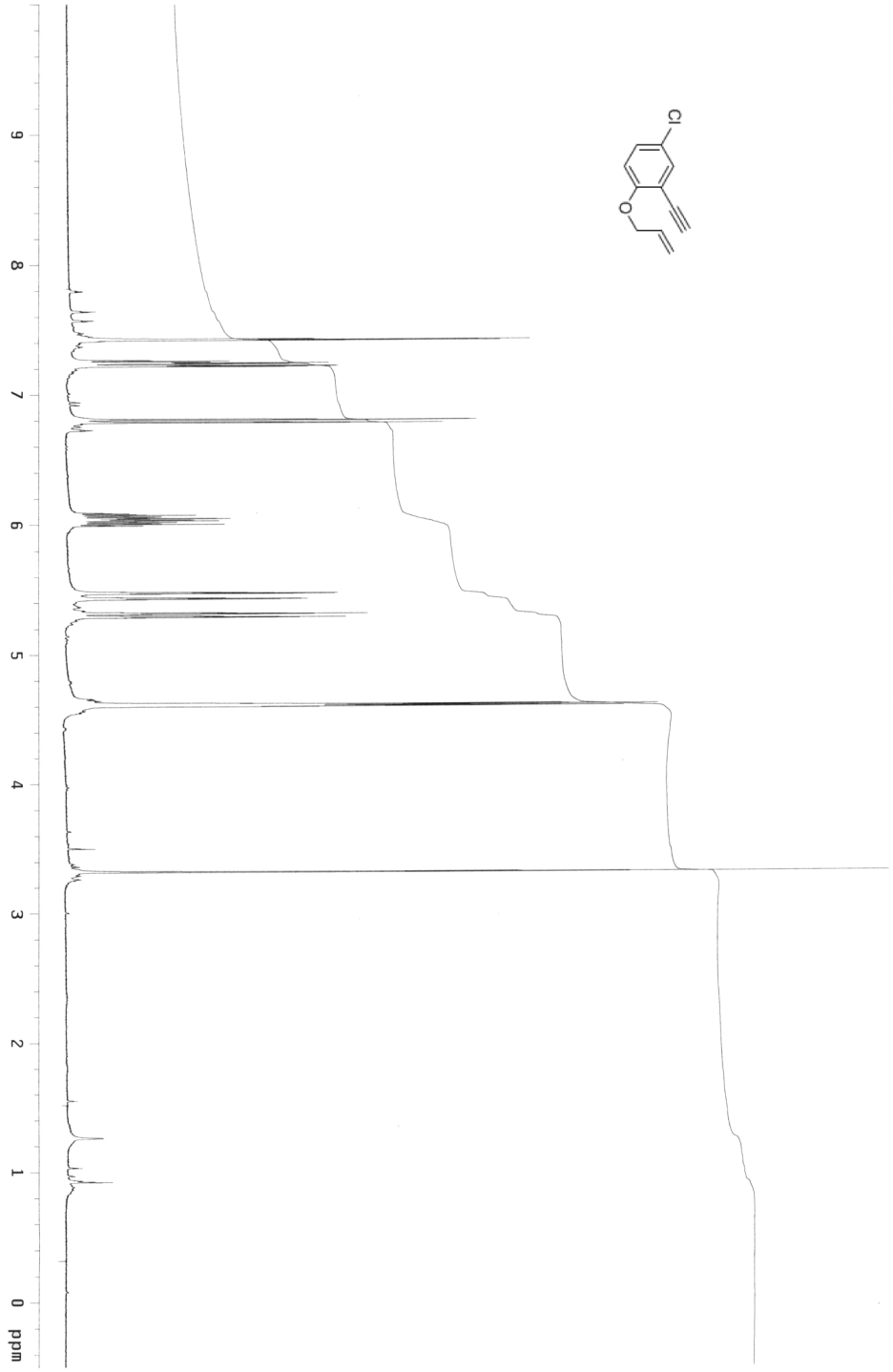
2.27

To a rapidly stirred suspension of potassium carbonate (719 mg, 5.20 mmol) in methanol (50 mL) in a round-bottom flask cooled with an ice-water bath were added sequentially 2-(allyloxy)-5-chlorobenzaldehyde (1.04 g, 5.31 mmol) and dimethyl-1-diazo-2-oxopropylphosphonate (1.02 g, 5.31 mmol). The reaction mixture was allowed to stir under nitrogen and return to ambient temperature overnight. The mixture was then filtered and concentrated *in vacuo* and purified by column chromatography with hexanes as the eluent, producing **2.27**, a pale yellow oil, in 90% yield.



1-(Allyloxy)-4-chloro-2-ethynylbenzene (2.27): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42 (t, *J* = 2.4 Hz, 1H), 7.23 (dt, *J* = 9.2, 2.4 Hz, 1H), 6.80 (dd, *J* = 9.2, 2.4 Hz, 1H), 6.09-5.99 (m, 2H), 5.49-5.43 (m, 1H), 5.33-5.28 (m, 1H), 4.62-4.60 (m, 2H), 3.22 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 158.5, 133.7, 132.7, 130.1, 125.5, 118.0, 113.8, 113.6, 82.6, 78.9, 69.9; IR (NaCl, thin film): 3298 (vs), 3076 (w), 2988 (m), 2953 (m), 2869 (m), 1593 (m), 1484

(vs), 1460 (s), 1424 (m), 1395 (s), 1284 (vs), 1266 (vs), 1254 (vs), 1234 (s), 1181 (w), 1133 (vs), 1014 (m), 997 (s), 930 (m), 808 (s) cm^{-1}; HRMS (ES+): calculated for formula $C_{11}H_{10}ClO^{+}$: *m/z* 193.0420, found 193.0416.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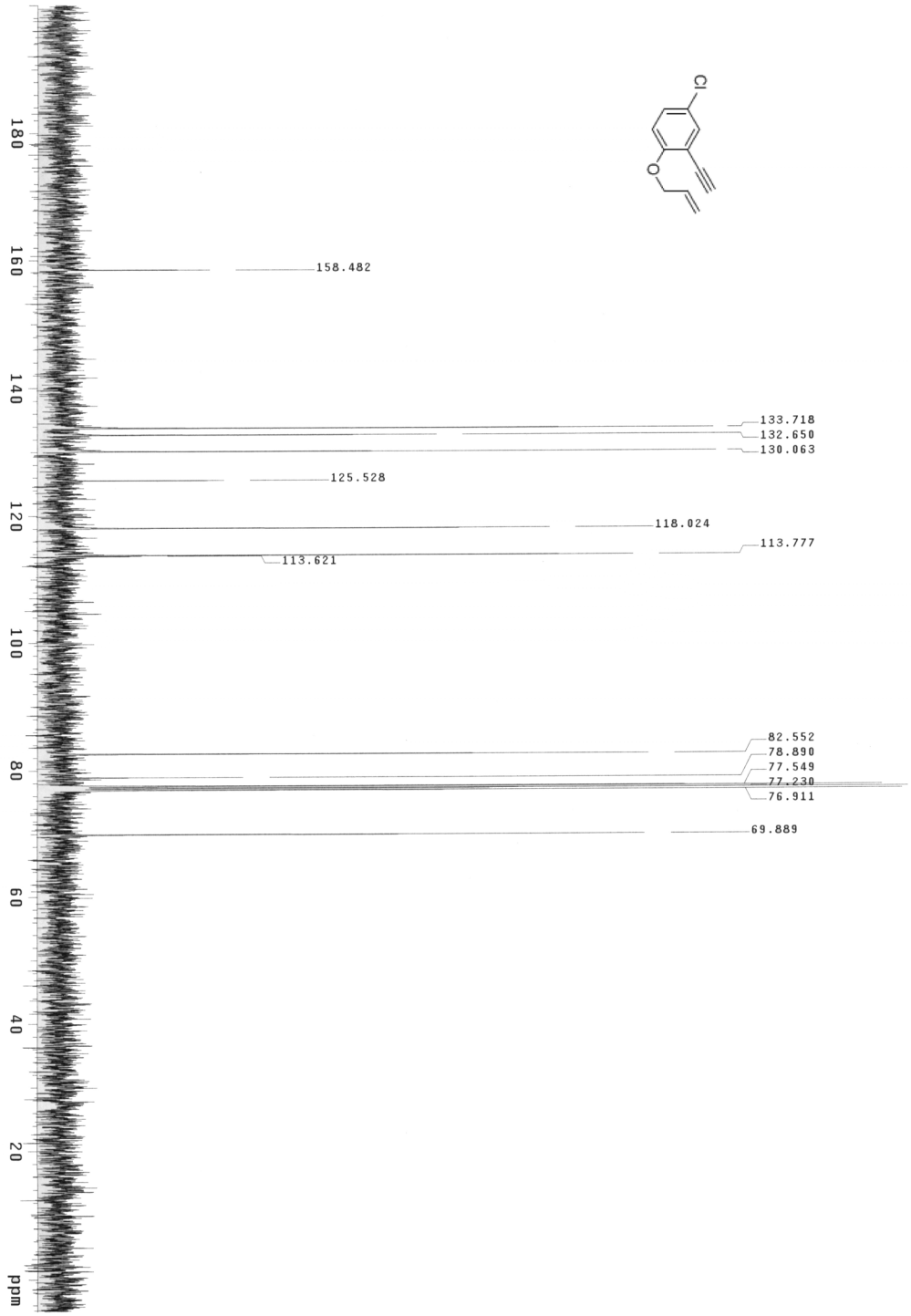
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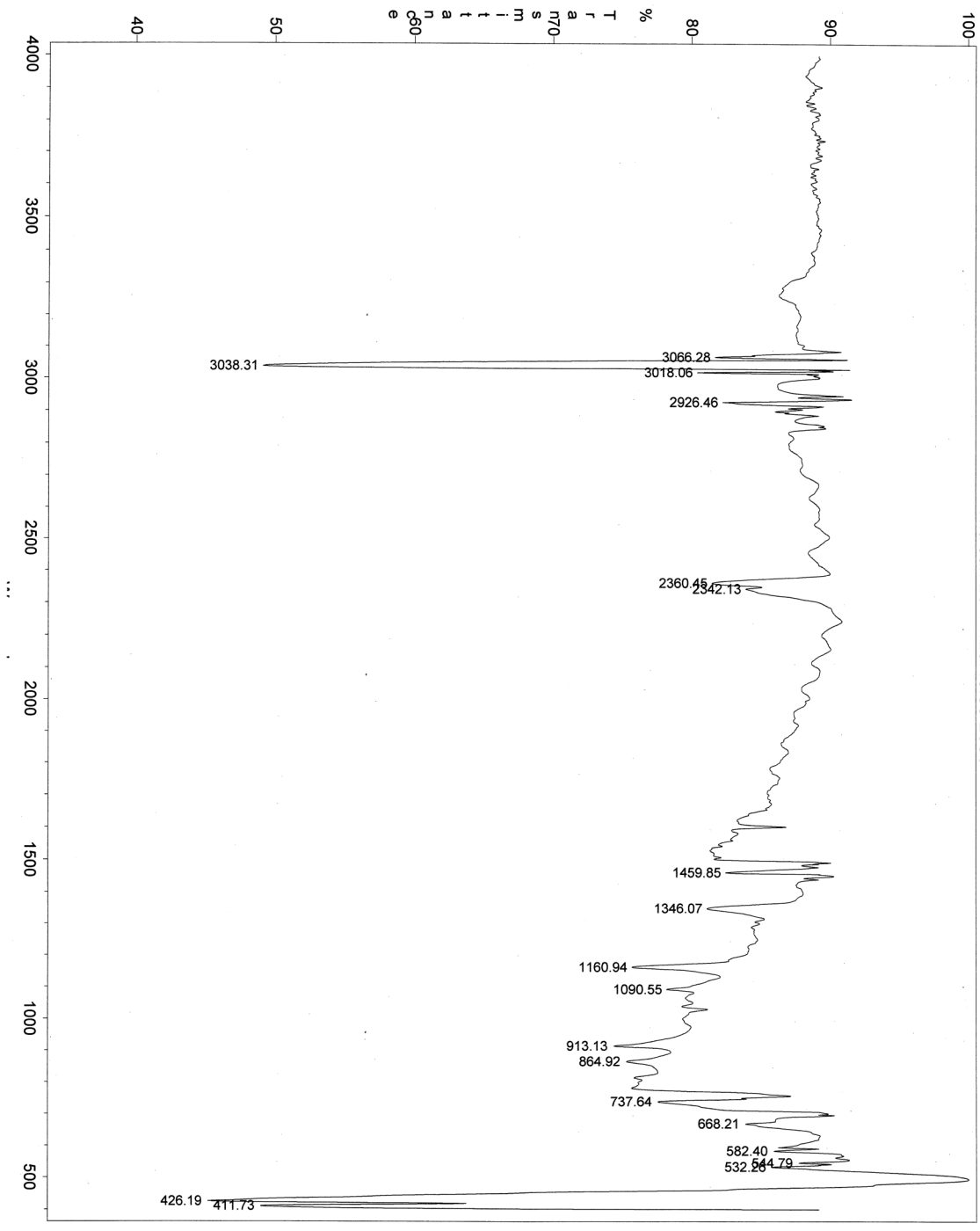
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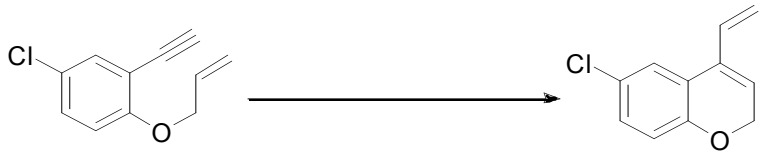
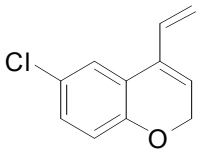
90
100
4000
3500
3000
2500
2000
1500
1000
500
3038.31
3066.28
3018.06
2926.46
2360.45
2342.13
1459.85
1346.07
1160.94
1090.55
913.13
864.92
737.64
668.21
582.40
544.79
532.26
426.19
411.73
Thu Jun 29 14:23:48:80 2006

Synthesis of Diene 2.28



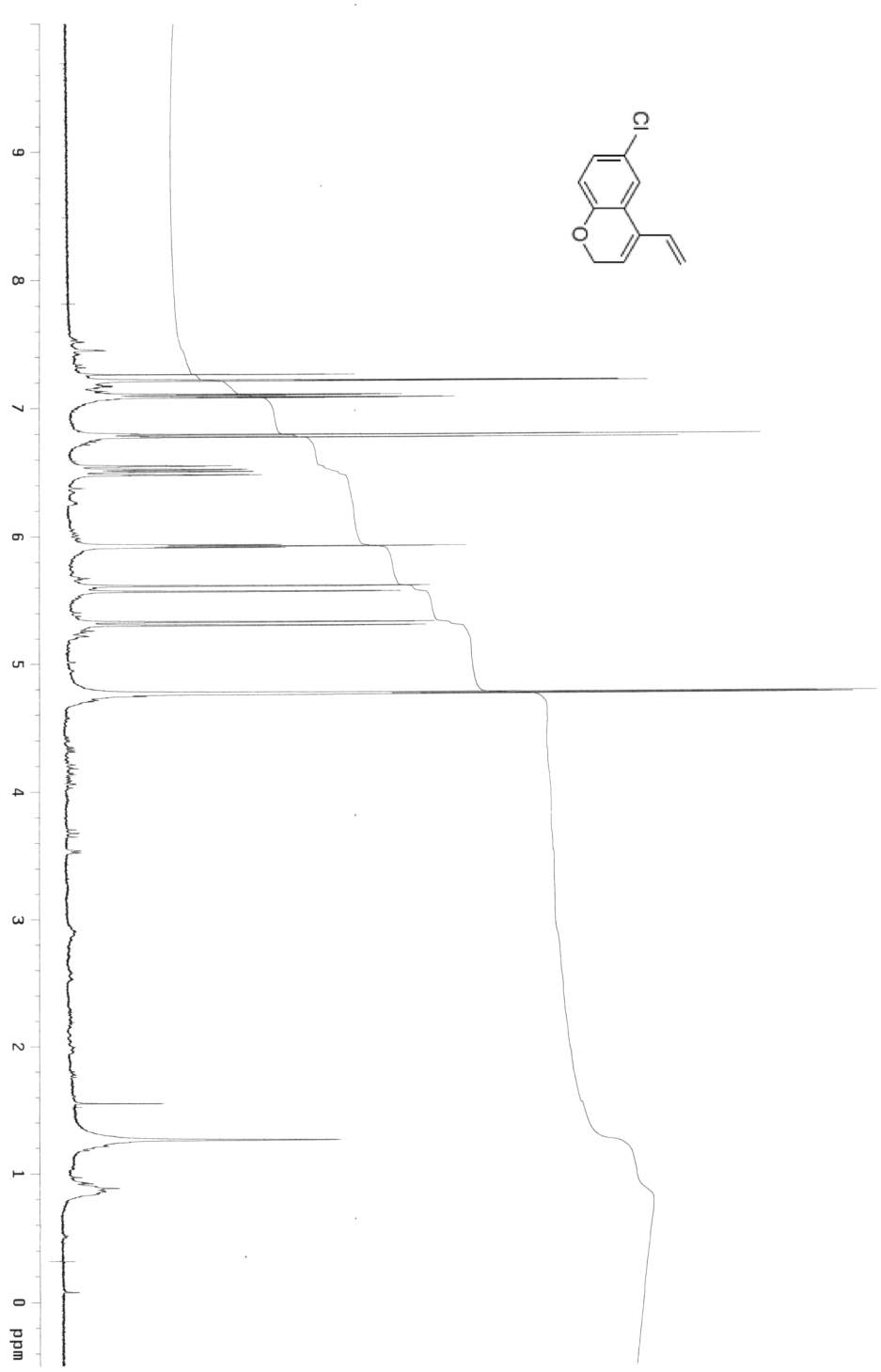
2.27 **2.28**

In a N_2 atmosphere glove box, enyne **2.27** (0.20 mmol) and $(PCy_3)_2Cl_2Ru$=CHPh (33 mg, 40 μmol) were placed in a 25 mL Schlenk tube (or medium-walled pyrolysis tube) and then dissolved in dry, degassed toluene (1.0 mL). After removal from the glove box, the reaction mixture was heated to 75 °C under an atmosphere of ethylene until metathesis was complete as monitored by GC/MS. The residue was then concentrated *in vacuo* and purified by column chromatography on silica gel with hexanes as the eluent, producing diene **2.28** in 73% yield as a pale yellow oil.



6-Chloro-4-vinyl-2H-chromene (2.28): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.21 (d, *J* = 2.8 Hz, 1H), 7.09 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 6.51 (ddd, *J* = 17.2, 10.8, 1.2 Hz, 1H), 5.92 (t, *J* = 4.0 Hz, 1H), 5.59 (d, *J* = 17.2 Hz, 1H), 5.32 (d, *J* = 10.8 Hz, 1H), 4.76 (d, *J* = 4.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 153.0, 133.2, 132.6, 128.9, 126.4, 124.4, 124.2, 119.4, 117.9, 117.7, 65.5; IR (NaCl, thin film): 3060 (m), 3027 (s), 2939 (w), 2916 (s), 2853 (w), 1481 (m), 1453 (m), 1419 (w), 1260 (w), 1222 (m), 1096 (w), 1026 (w), 988 (w),

934 (w), 876 (w), 845 (w), 813 (m), 760 (s), 704 (m) cm^{-1}; HRMS (ES+): calculated for formula $C_{11}H_{10}ClO^+$: *m/z* 193.0420, found 193.0425.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O
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6
5
4
3
2
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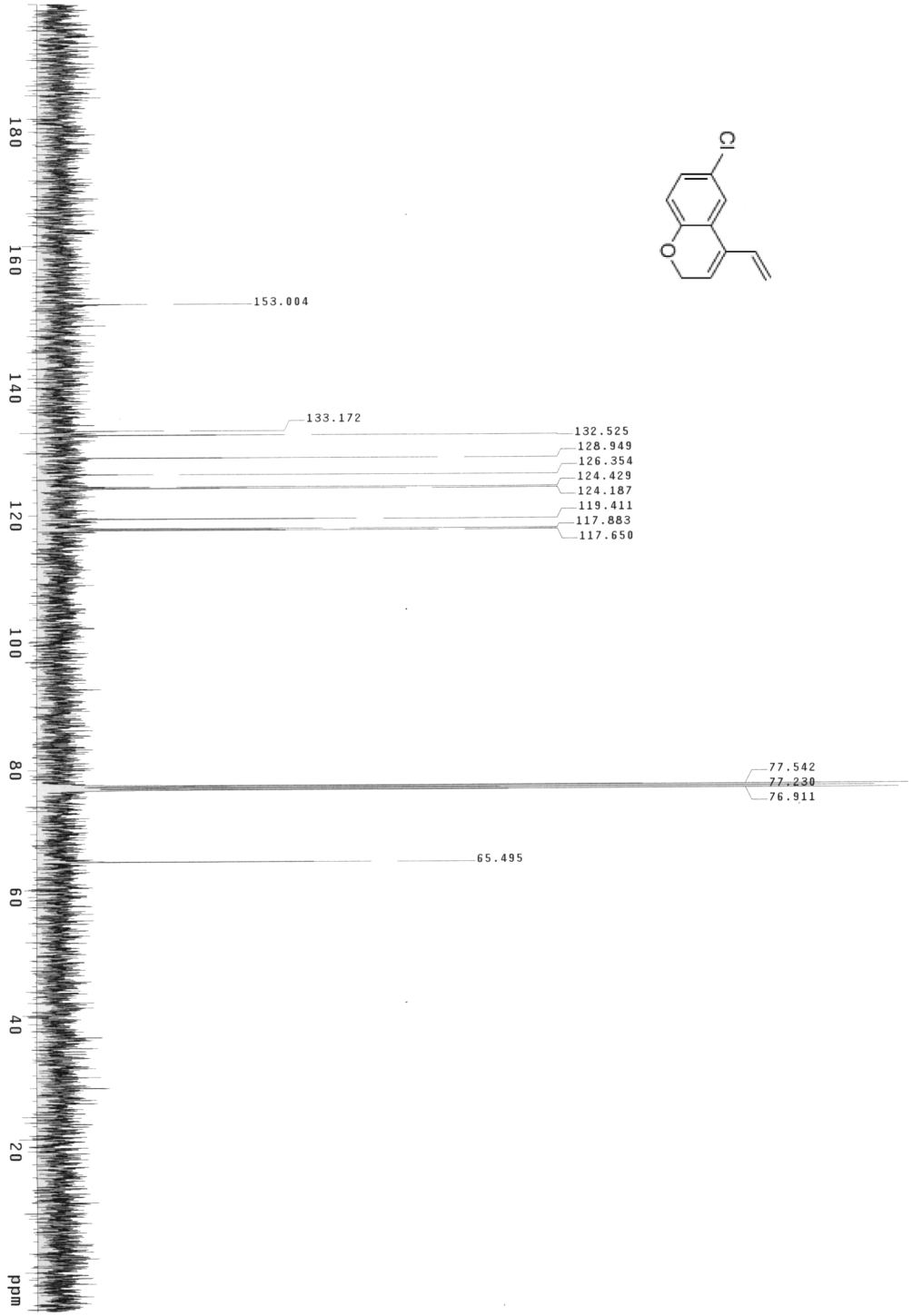
0
ppm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140
120
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60
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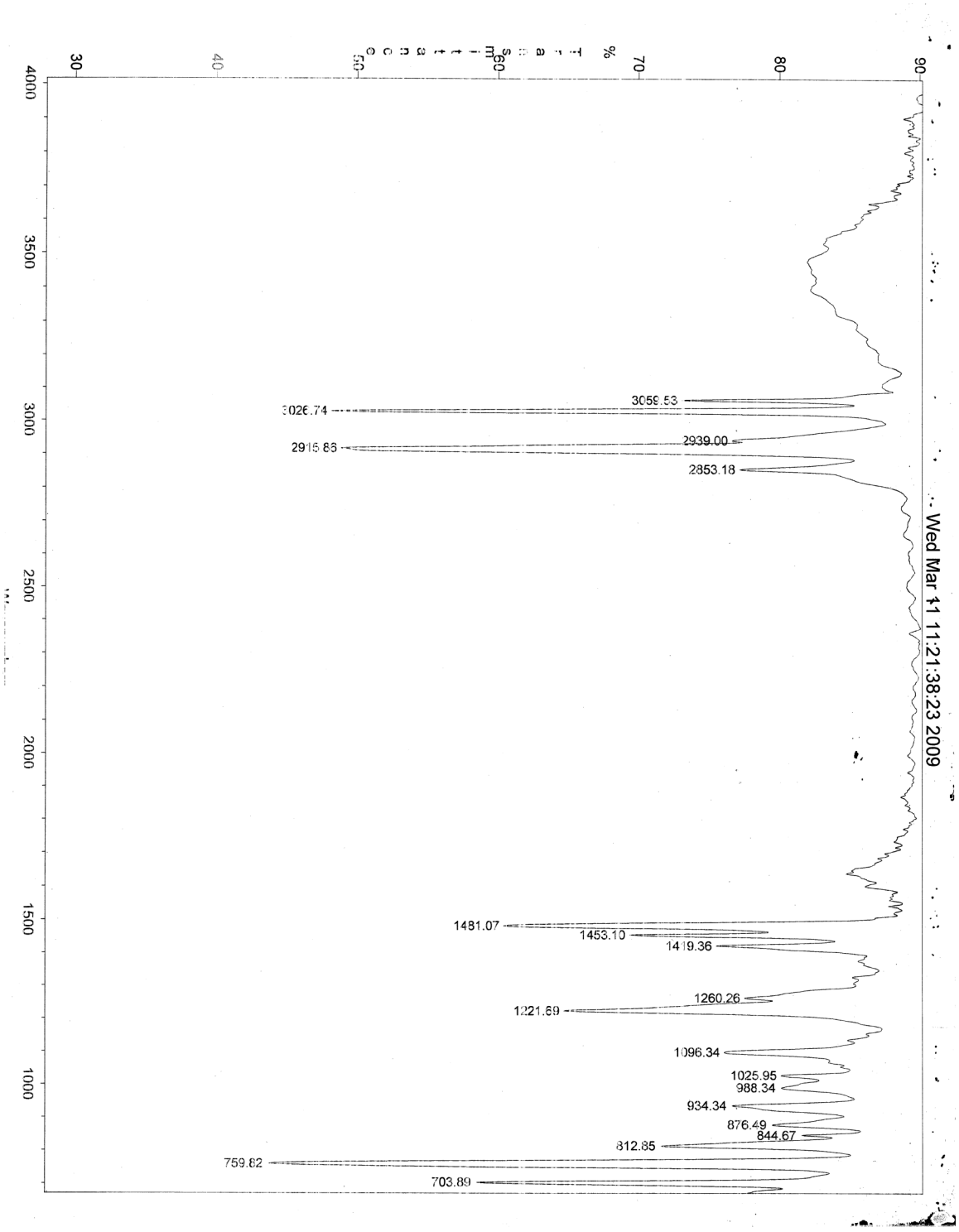
20
ppm


Wed Mar 11 11:21:38:23 2009
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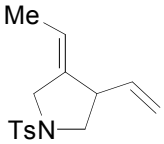
2939.00
2916.86
2853.18
1481.07
1453.10
1419.36
1260.26
1221.69
1096.34
1025.95
988.34
934.34
876.49
844.67
812.85
759.62
703.89

General procedure for Tandem Enyne Metathesis-Hydrovinylation

In a N_2 atmosphere glove box, the enyne (0.20 mmol) and $(PCy_3)_2Cl_2Ru{=}CHPh$ (33 mg, 40 μmol) were placed in a 25 mL Schlenk tube (or medium-walled pyrolysis tube) and then dissolved in dry, degassed toluene (1.0 mL). After removal from the glove box, the reaction mixture was heated to 75 °C under an atmosphere of ethylene until completion of metathesis as evaluated by GC/MS (typically 10-15 min.). The reaction mixture was removed from the heat source and, under a constant stream of dry N_2, 1.0 mL of NaOMe in MeOH solution (40 mM) was added, and then the tube re-sealed. After stirring at 75 °C for 10 minutes, over the course of which the solution color changed from a deep, opaque purple to a clear, dark orange-yellow, the reaction mixture was then placed in a liquid nitrogen bath, and ethylene (ca. 1.0 mL, ca. 20 mmol) was allowed to condense. The vessel was again sealed, and the reaction mixture was allowed to return to ambient temperature over the course of 5 minutes (**CAUTION**: these reactions occur at elevated pressure, and were carried out behind a polycarbonate safety shield). The reaction mixture was then allowed to stir at 75 °C until there was near-complete consumption of the intermediate 1,3-diene (typically 90 minutes as monitored by GC/MS) then, after cooling to ambient temperature, slowly cooled in a liquid nitrogen bath. The reaction

mixture was opened to the atmosphere and slowly returned to ambient temperature, allowing the evaporation of excess ethylene. The reaction mixture was then concentrated *in vacuo*, and the residue purified by column chromatography on silica gel.

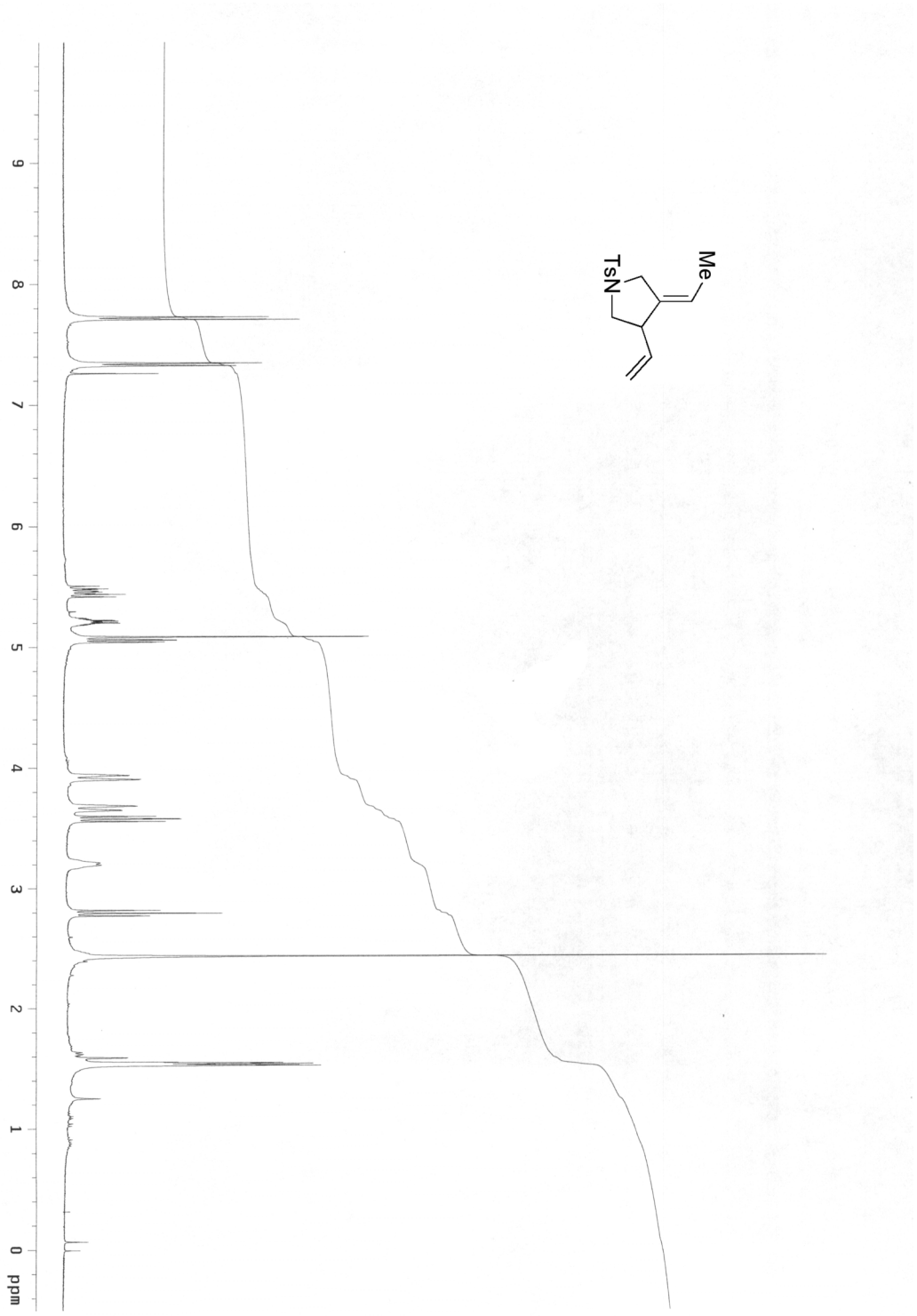
3-Ethylidene-1-tosyl-4-vinylpyrrolidine (2.16) was purified by column chromatography on silica gel with hexanes/ethyl acetate (9:1) as the eluent. **(*E*)-2.16** was identified by comparison of its spectral data with literature values,[77] and olefin stereochemistry assigned by comparison of chemical shifts with those reported for compound **2.19**, for which olefin stereochemistry has been established by NOESY.[78]



(*Z*)-2.16: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72 (d, *J* = 8.1 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 5.46 (ddd, *J* = 16.4, 10.8, 8.4 Hz, 1H), 5.21 (qq, *J* = 6.8, 2.4 Hz, 1H), 5.09-5.04 (m, 2H), 3.92 (d, *J* = 14.4 Hz, 1H), 3.66 (d, *J* = 14.4 Hz, 1H), 3.58 (dd, *J* = 9.2, 7.6 Hz, 1H), 3.21 (br d, *J* = 7.6 Hz, 1H), 2.79 (t, *J* = 9.2 Hz, 1H), 2.44 (s, 3H), 1.54 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 143.7, 138.0, 136.5, 132.9, 129.8, 128.0, 118.6, 117.6, 53.4, 49.8, 47.9, 21.9, 14.9; IR (NaCl,

[77] S. Ikeda, H. Miyashita, Y. Sato, *Organometallics* **1998**, *17*, 4316-4318 doi:10.1021/om980277w.
[78] J. T. Metza, R. A. Terzian, T. Minehan, *Tetrahedron Lett.* **2006**, *47*, 8905-8910 doi:10.1016/j.tetlet.2006.10.043.

thin film): 3026 (s), 2963 (br s), 2942 (w), 2938 (w), 2925 (s), 2920 (s), 2901 (m), 2872 (m), 1500 (w), 1488 (w), 1347 (m), 1163 (vs), 1095 (w), 911 (w) cm^{-1}; HRMS (ES+): calculated for $C_{15}H_{19}NO_2SH^+$: *m/z* 278.1215, found 278.1226.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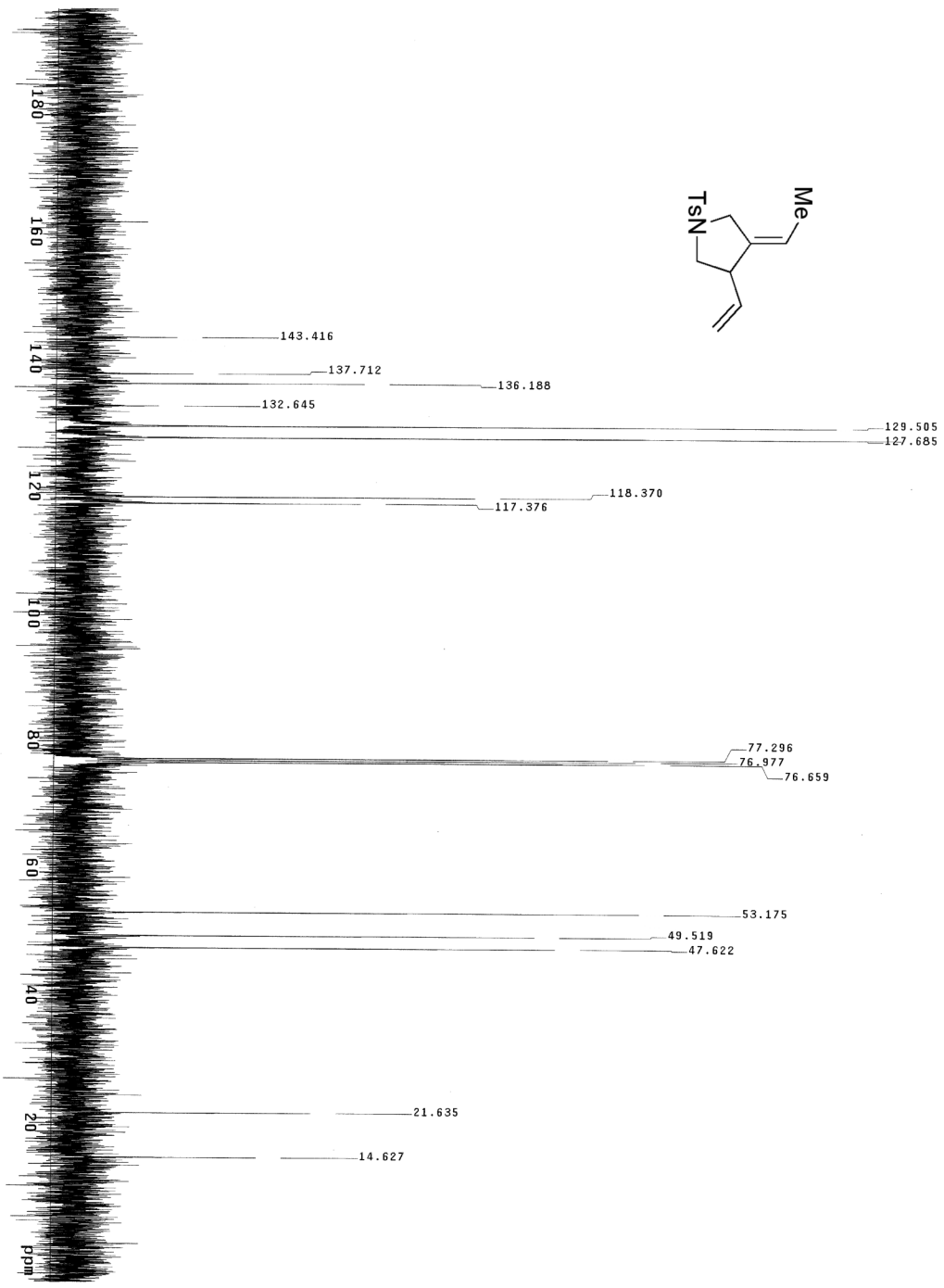
3
2
1
0
ppm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136.188
132.645
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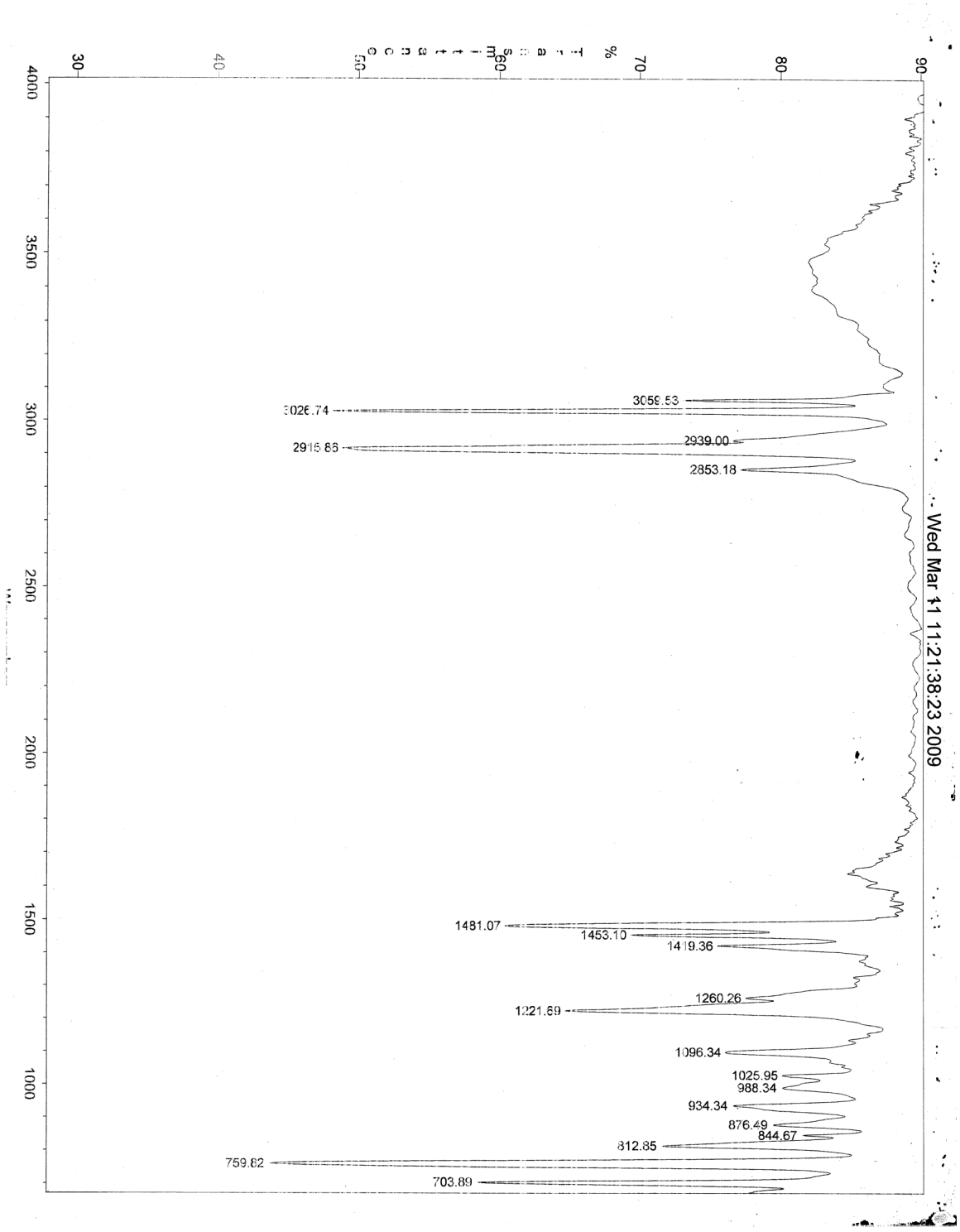
ppm


Wed Mar 11 11:21:38:23 2009
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3026.74
2939.00
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2853.18
1481.07
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1419.36
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876.49
844.67
812.85
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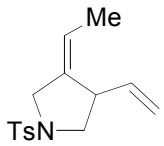
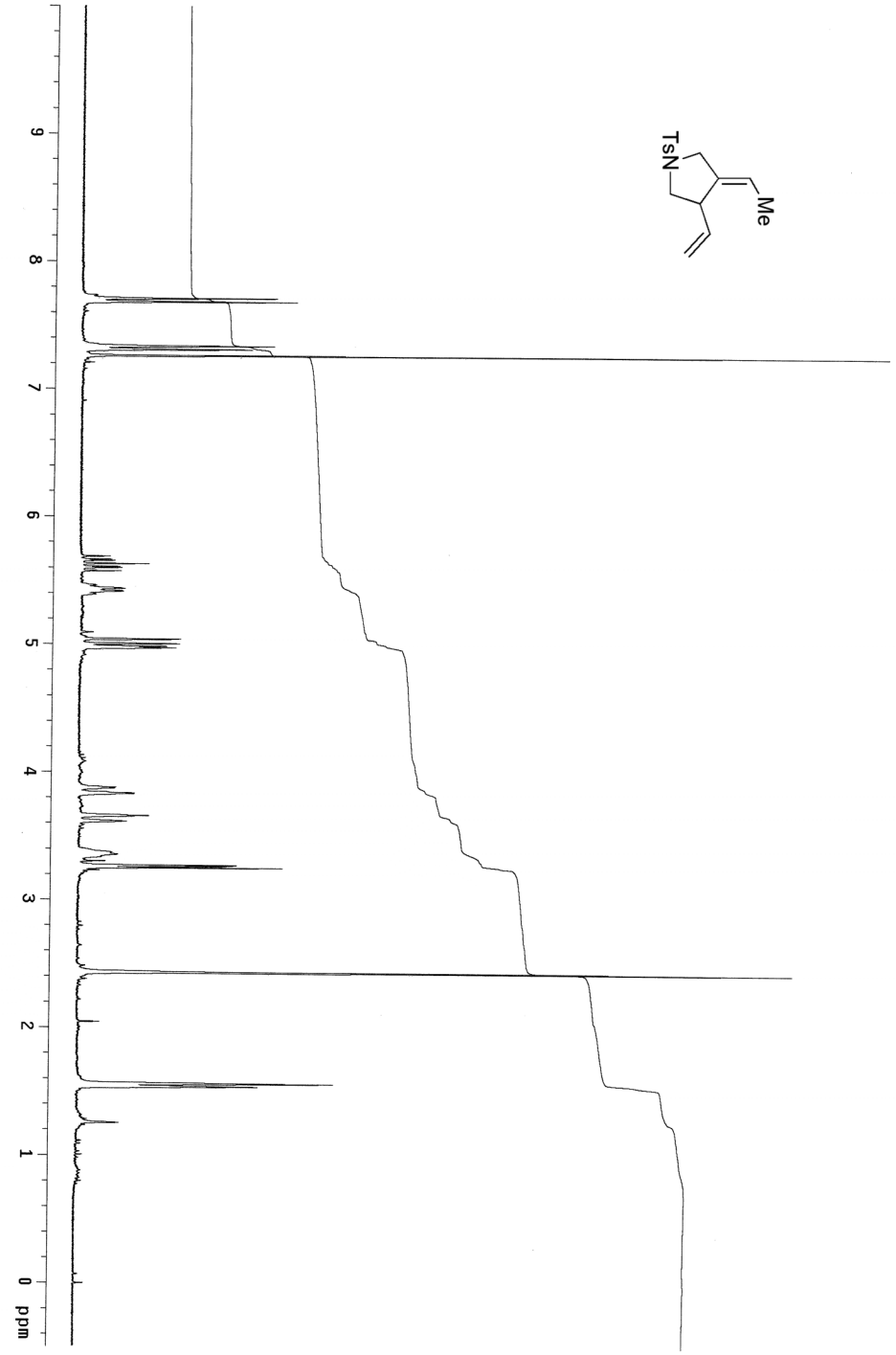
703.89



(*E*)-2.16: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.70 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.1Hz, 2H), 5.63 (ddd, *J* = 17.4, 10.2, 7.5 Hz, 1H), 5.43 (qd, *J* = 6.9, 1.8 Hz, 1H), 5.04-4.97 (m, 2H), 3.86 (dq, *J* = 13.5, 1,8 Hz, 1H), 3.64 (d, *J* = 13.5 Hz, 1H), 3.36 (br, 1H), 3.27-3.23 (m, 2H), 2.43 (s, 3H), 1.55 (d, *J* = 6.9 Hz, 3H). The NMR data are identical to those previously reported for this compound (reference 77, *vide supra*).


TsN
Me
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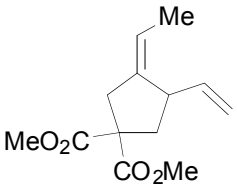
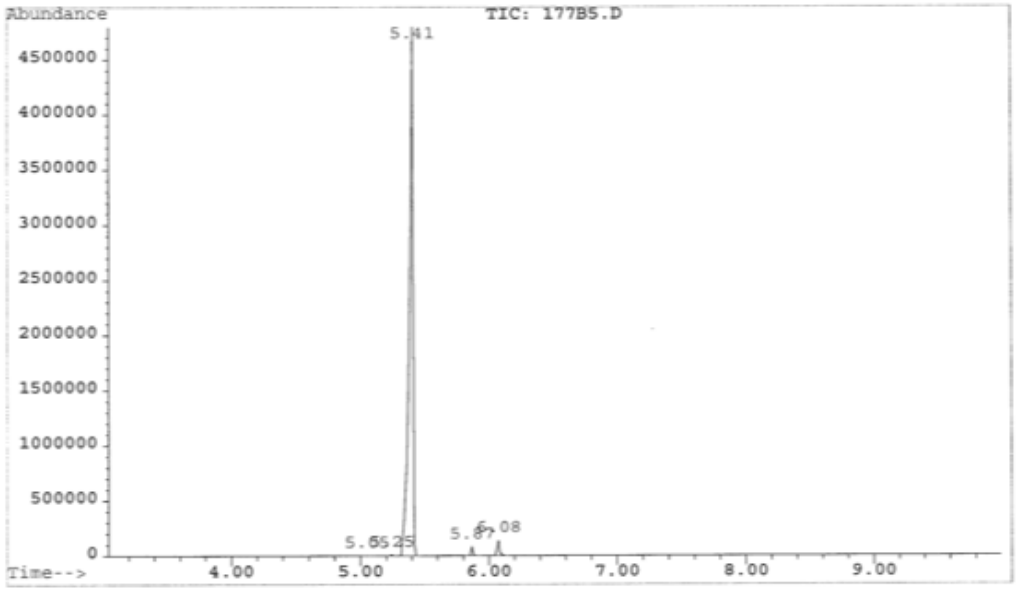
0
ppm



(*Z*)-Dimethyl 3-ethylidene-4-vinylcyclopentane-1,1-dicarboxylate (2.19) was purified by column chromatography on silica gel with hexanes/ethyl acetate (19:1) as the eluent and isolated as a colorless oil in 57% yield, with purity determined to be 97% by GC/MS. 2.**19** was identified by comparison of its spectral data with literature values: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.68 (ddd, *J* = 17.2, 10.0, 7.2 Hz, 1H), 5.48 (q, *J* = 6.8 Hz, 1H), 5.04-4.96 (m, 2H), 3.75-3.66 (br m, 6H), 3.36 (q, *J* = 7.2 Hz, 1H), 3.0 (dq, *J* = 15.6, 2.4 Hz, 1H), 2.79 (d, *J* = 15.6 Hz, 1H), 2.71 (ddd, *J* = 13.2, 8.4, 2.0 Hz, 1H), 2.01 (dd, *J* = 13.2, 6.8 Hz, 1H), 1.54 (d, *J* = 6.8 Hz, 3H).



Retention Time	Area	Area %	Ratio %
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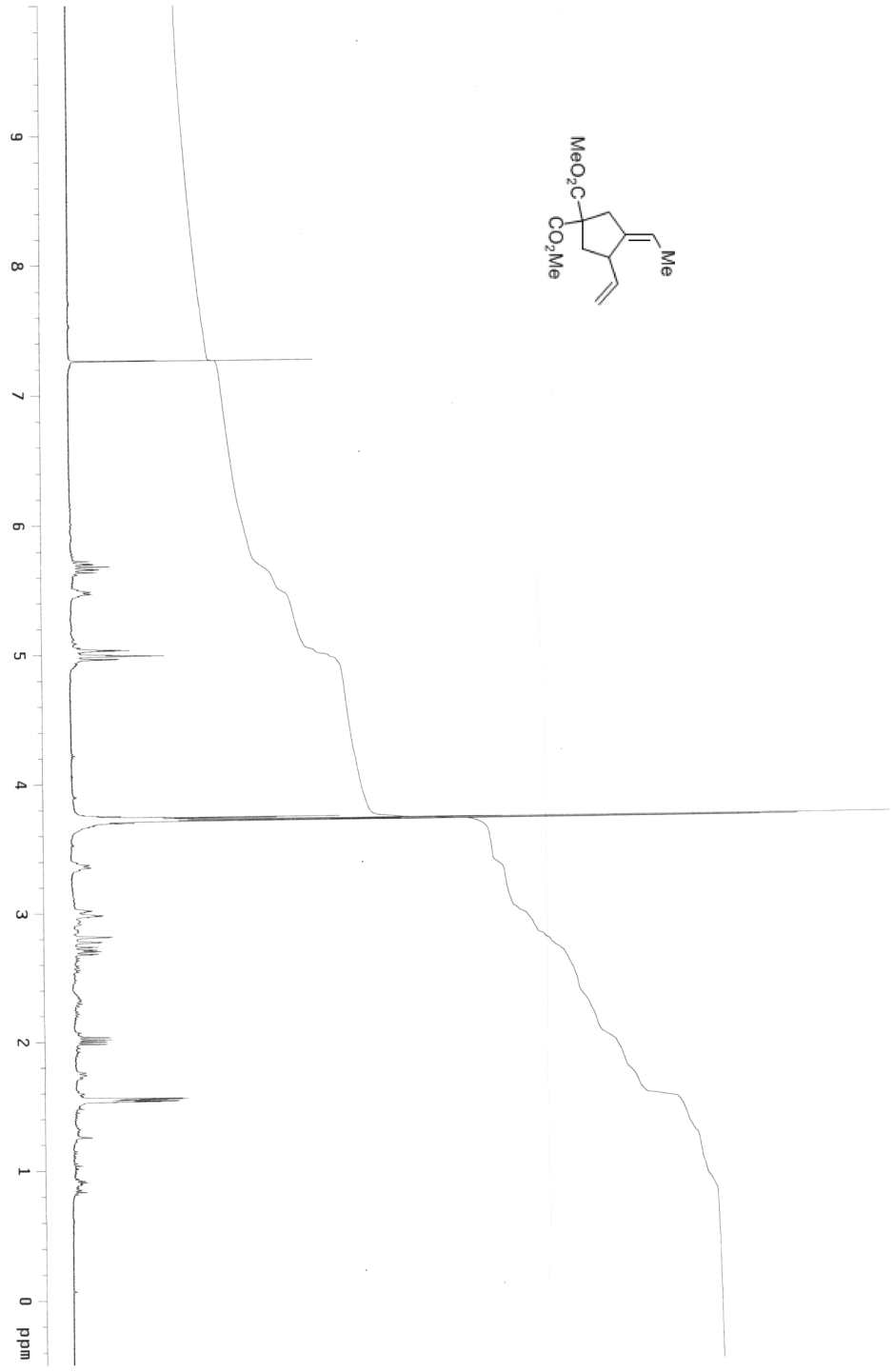
5.871	773692	0.799	0.822
6.078	1736921	1.794	1.844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CO2Me
Me
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7
6
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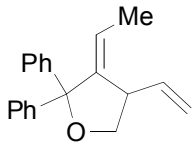
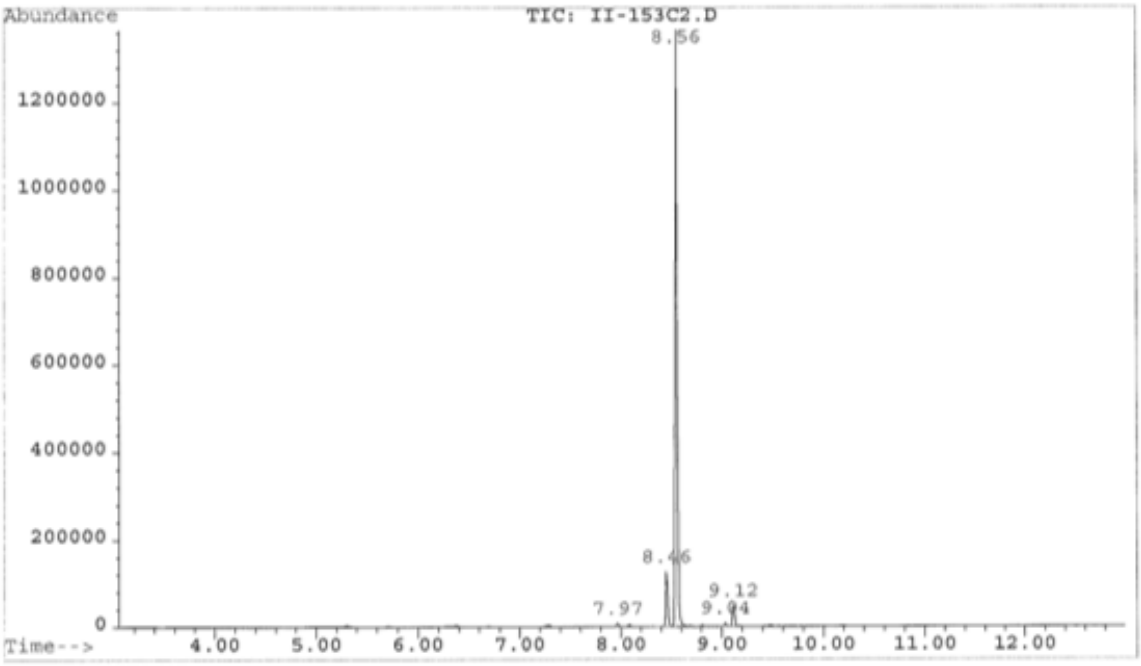
3
2
1
0
ppm



(*E*)-3-Ethylidene-2,2-diphenyl-4-vinyltetrahydrofuran (2.22) was purified by column chromatography on silica gel with n-pentane/diethyl ether (29:1) as the eluent, and olefin stereochemistry was assigned by NOESY. Purity was determined to be 87% by GC/MS, giving a corrected yield of 64%. ^{1}H NMR ($(CD_3)_2CO$ 400 MHz): δ 7.42-7.21 (m, 10H), 5.66-5.57 (m, 1H), 5.24 (qd, *J* = 6.8, 2.4 Hz, 1H), 5.10 (d, *J* = 16.8 Hz, 1H), 5.01 (d, *J* = 8.4 Hz, 1H), 4.09 (dd, *J* = 8.8, 7.6 Hz, 1H), 3.71-3.67 (m, 1H), 3.54 (dd, *J* = 8.8, 5.6 Hz, 1H), 1.70 (d, *J* = 6.8 Hz, 3H),; ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 146.0, 144.7, 143.7, 138.0, 128.0, 128.0, 128.0, 127.8, 127.2, 127.1, 123.0, 115.5, 91.1, 70.5, 47.2, 14.7; IR (NaCl, thin film): 3082 (m), 3060 (s), 3028 (s), 2935 (m), 2925 (m), 1635 (w), 1602 (m), 1491 (w), 1453 (m), 1313 (w), 758 (vs), 696 (vs) cm^{-1}; HRMS (ES+): calculated for $C_{20}H_{21}O^{+}$: *m/z* 277.1592, found 277.1603.



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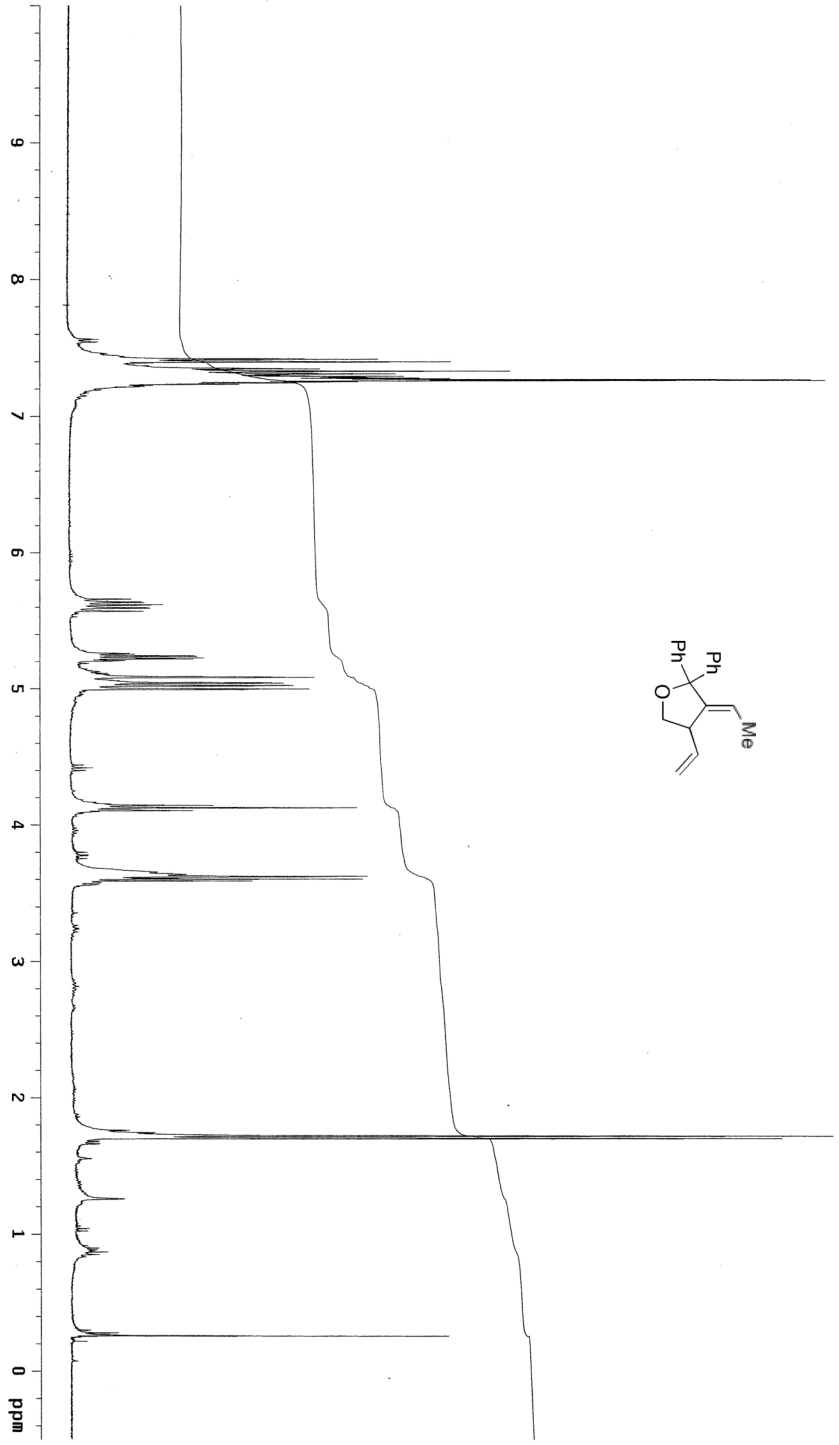
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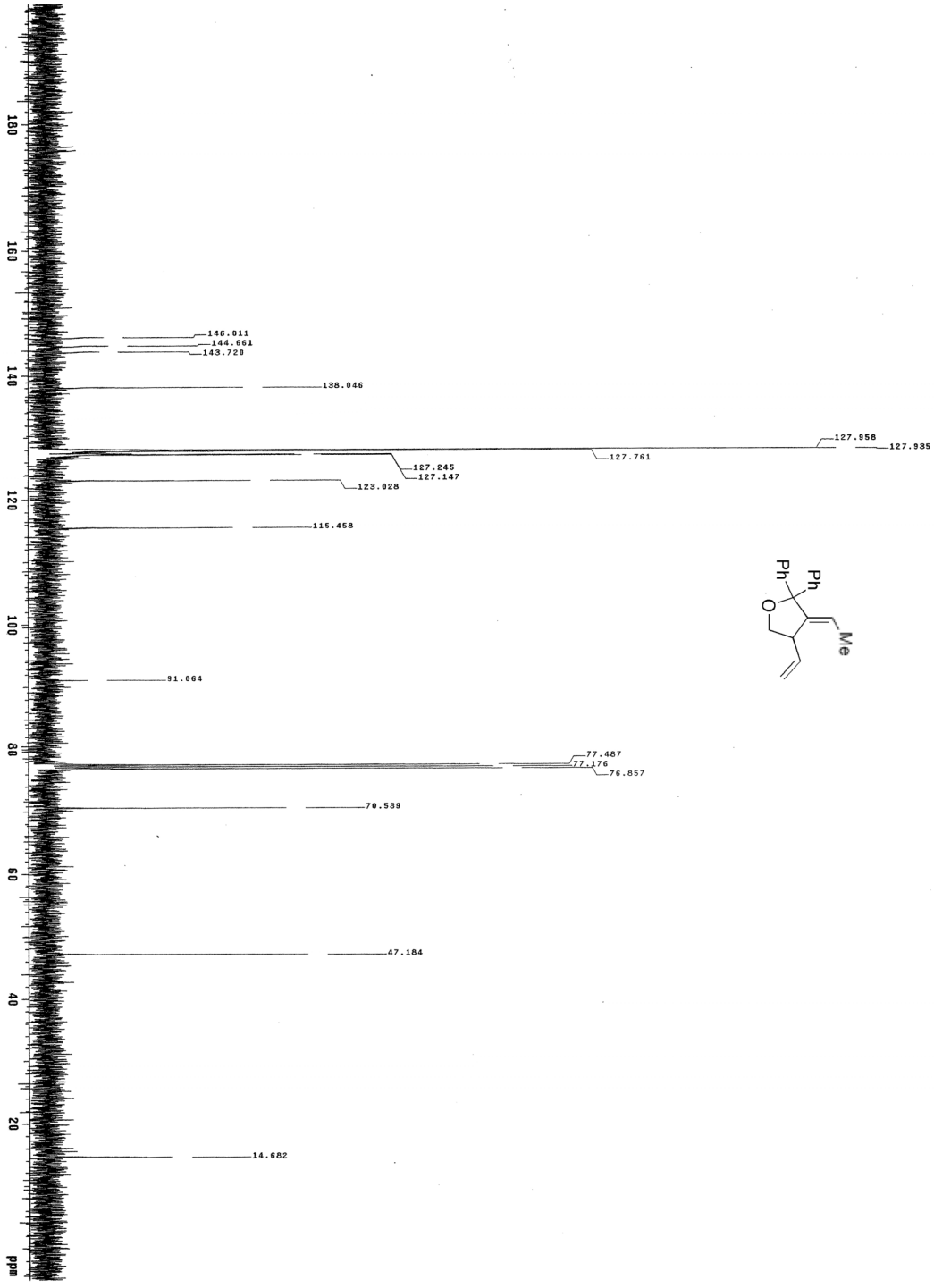
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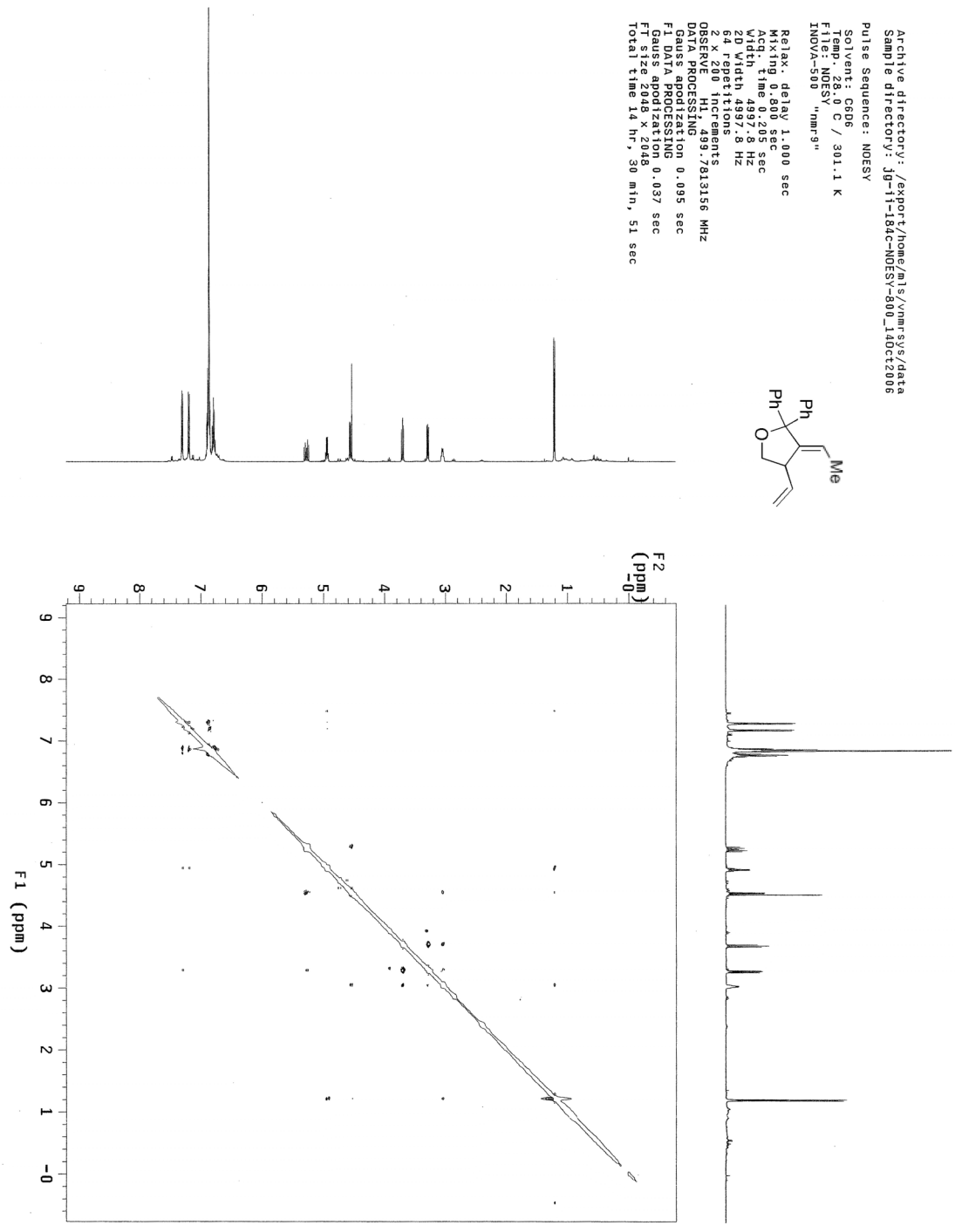
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Sample directory: jg-11-184c-NOESY-600_14Oct2006
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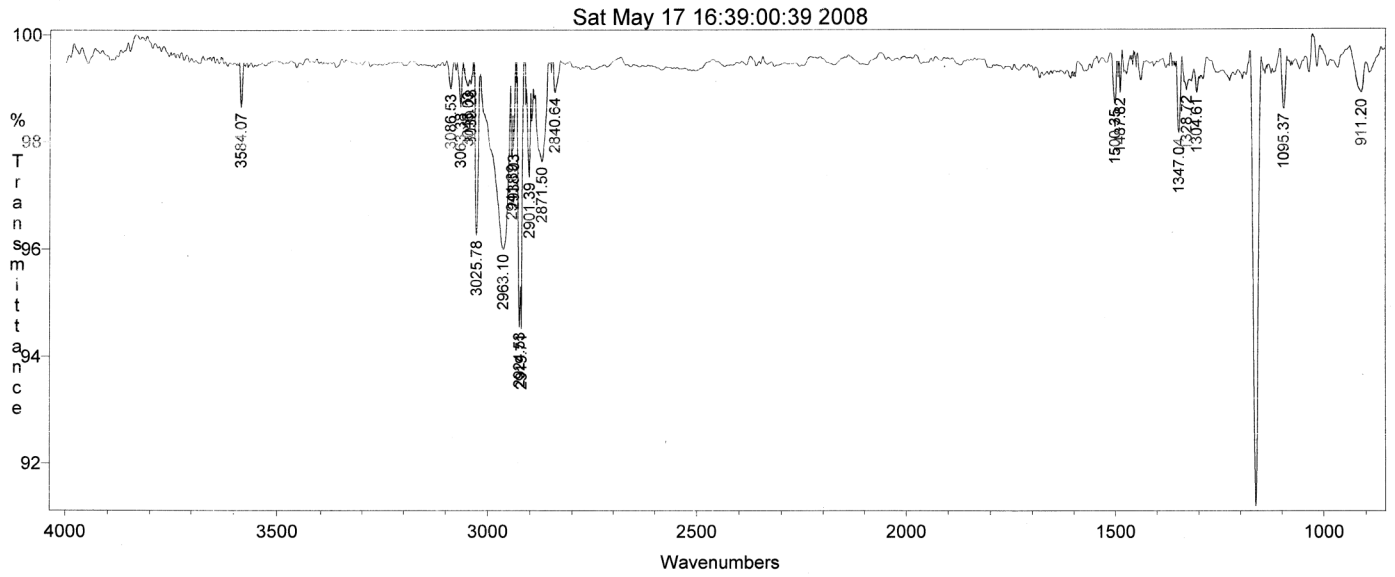
Temp. 28.0 C / 301.1 K
File: NOESY "nmr9"
INOVA-500
Relax. delay 1.000 sec
Mixing 0.800 sec
Acq. time 0.205 sec
width 4997.8 Hz
2D Width 4997.8 Hz
64 repetitions
2 x 200 increments
OBSERVE H1, 499.7813156 MHz
DATA PROCESSING
Gauss apodization 0.095 sec
F1 DATA PROCESSING
Gauss apodization 0.037 sec
FT size 2048 x 2048
Total time 14 hr, 30 min, 51 sec
Ph
Ph
O
Me
F2 (ppm)
F1 (ppm)



Peak Report
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Title: Sat May 17 16:39:00:39 2008
Filter: None

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1304.61	98.9016	1328.72	98.9486	1347.04	98.1462
1487.82	98.9070	1500.35	98.6942	2840.64	98.9224
2871.50	97.6234	2901.39	97.3372	2919.71	94.5198
2924.53	94.5526	2938.03	97.8674	2941.89	97.6763
2963.10	96.0025	3025.78	96.2630	3039.28	99.0839
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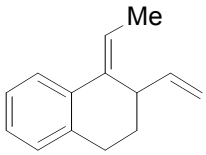
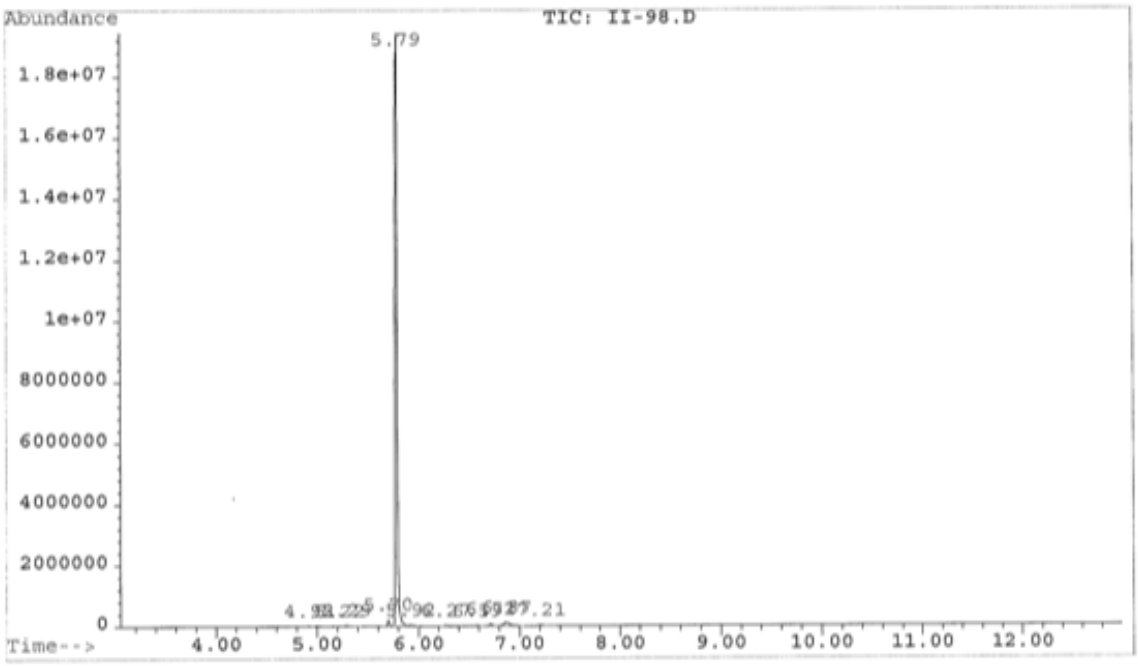
3584.07	98.6435				



(*E*)-1-Ethylidene-2-vinyl-1,2,3,4-tetrahydronaphthalene (2.23) was purified by column chromatography on silica gel with hexanes as the eluent, and olefin stereochemistry was assigned by NOESY. Purity was determined to be 95% by GC/MS, giving a corrected yield of 71%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.59 (d, 1H), 7.09 (m, 3H), 6.24 (q, *J* = 6.8 Hz, 1H), 5.81 (ddd, *J* = 17.2, 10.4, 5.6 Hz, 1H), 4.97 (m, 2H), 3.63 (m, 1H), 2.87-2.75 (m, 1H), 2.63 (dt, *J* = 16.0, 4.4 Hz, 1H), 1.99-1.84 (m, 2H), 1.78 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 138.9, 136.5, 135.8, 135.6, 128.8, 126.4, 126.1, 123.9, 120.5, 115.0, 39.0, 28.9, 26.8, 14.1; IR (NaCl, thin film): 3059 (m), 3028 (s), 2936 (s), 2930 (s), 2920 (vs), 2910 (s), 2858 (m), 1633 (w), 1600 (w), 1486 (m), 1448 (w), 1435 (w), 933 (m), 914 (m), 761 (m), 744 (m), cm^{-1}; HRMS (EI+): calculated for formula $C_{14}H_{16}$: *m/z* 184.1252, found 184.1253.



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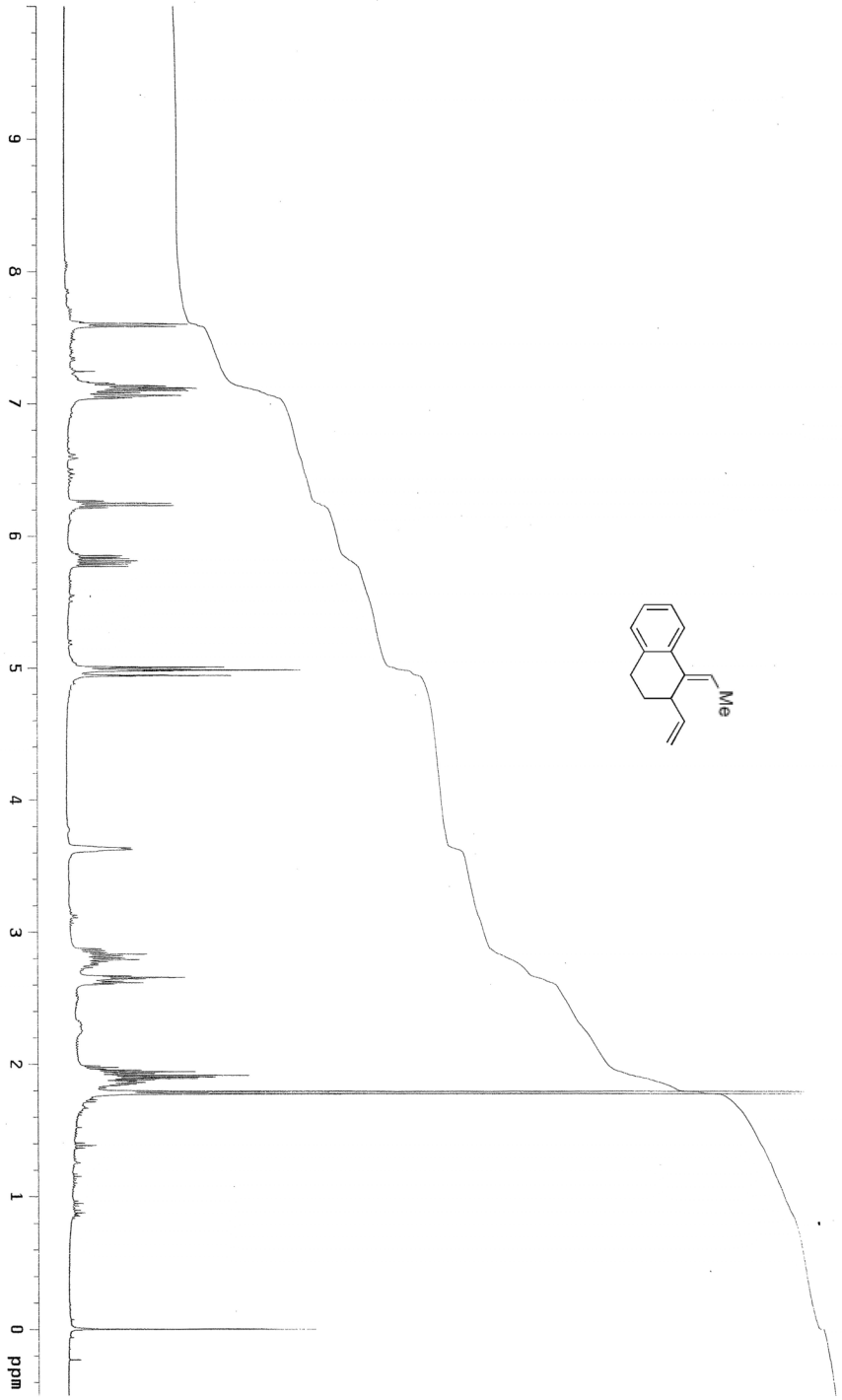
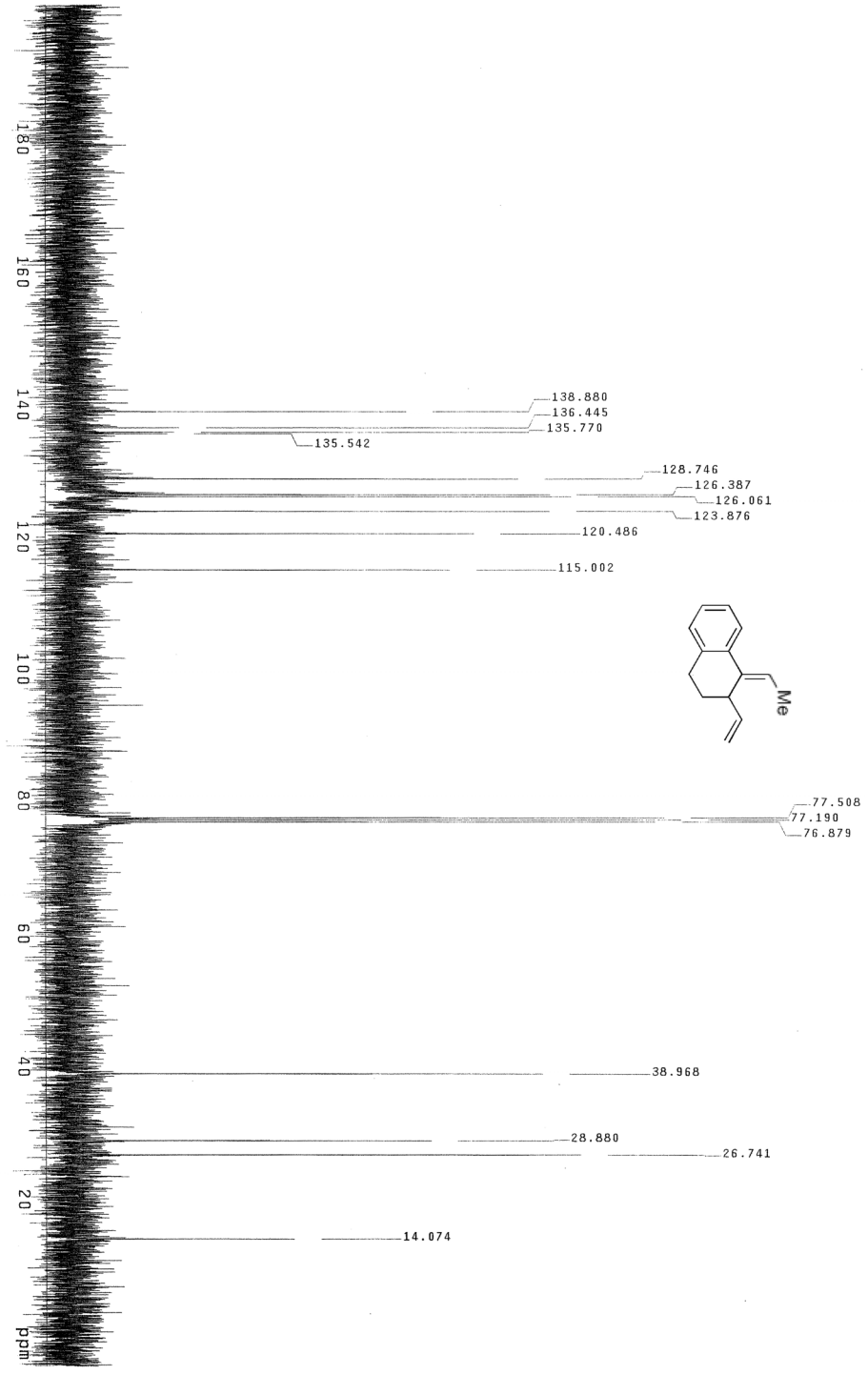
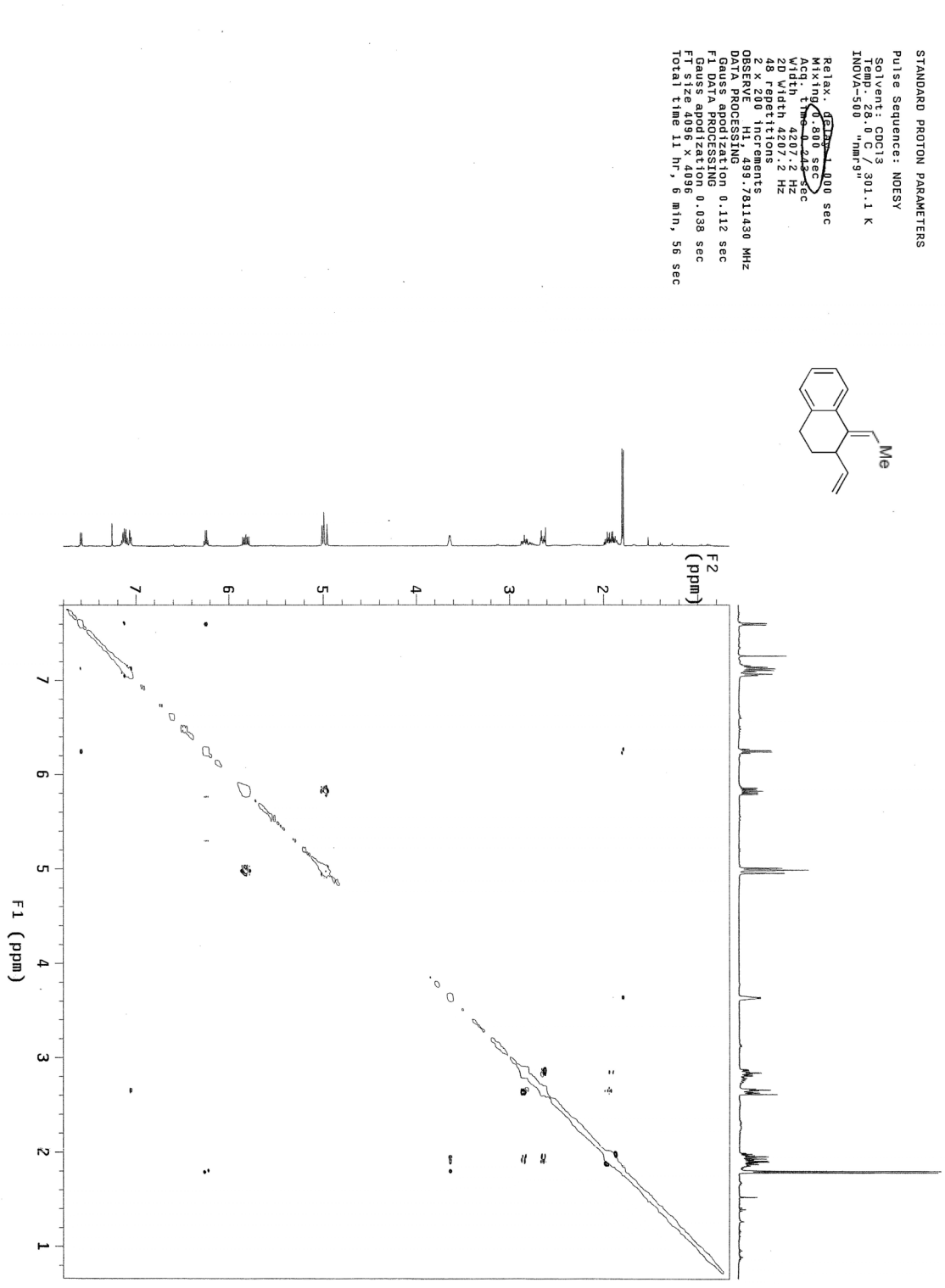
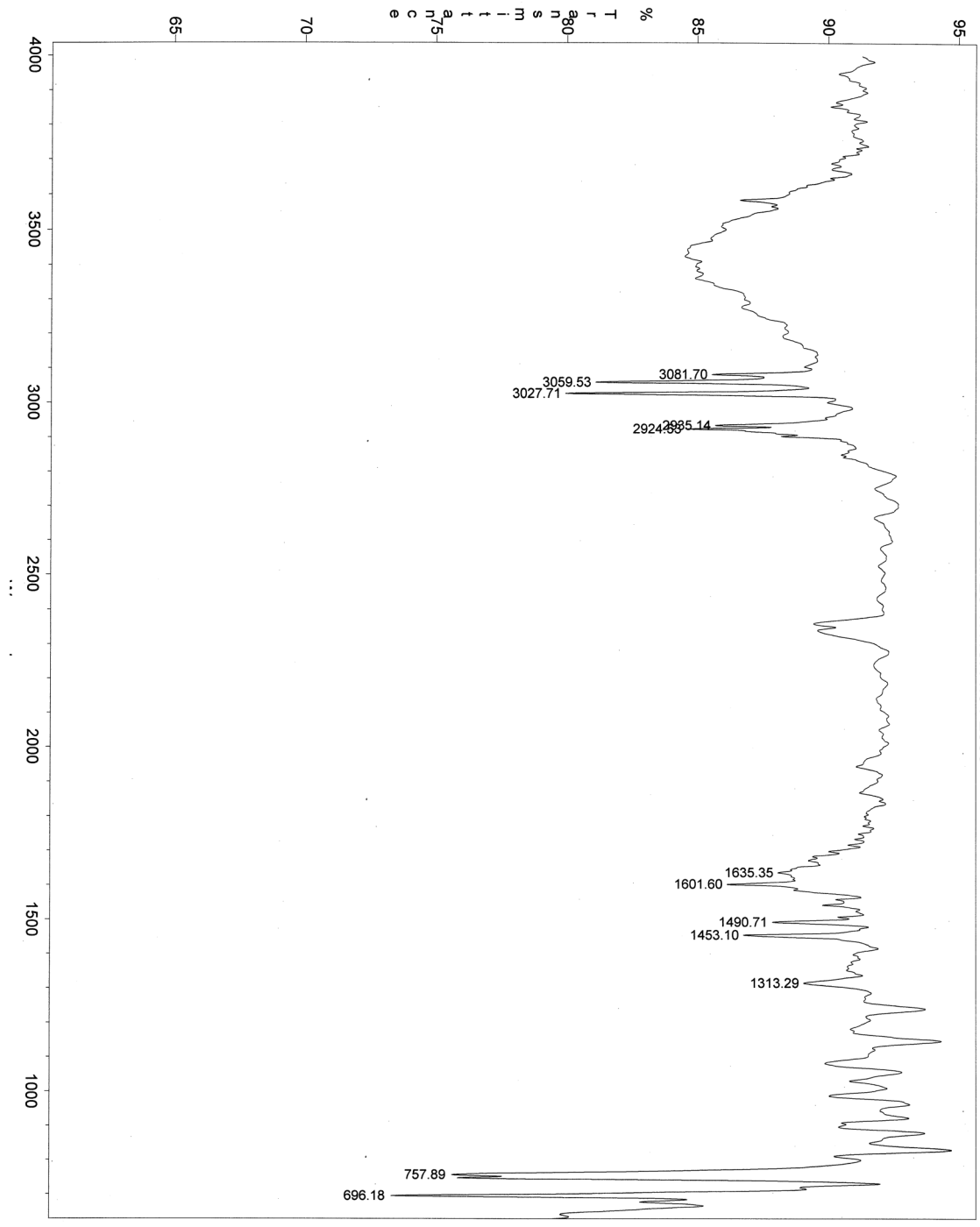
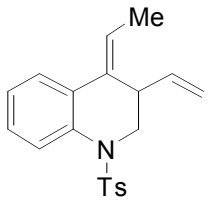
5.705	2660023	0.872	0.918
5.791	289836280	95.014	100.000
5.924	1404676	0.460	0.485
6.271	536022	0.176	0.185
6.585	437713	0.143	0.151
6.718	1507409	0.494	0.520
6.871	5472133	1.794	1.888
7.214	1106611	0.363	0.382


9
8
7
6
5
4
3
2
1
0
ppm
Me

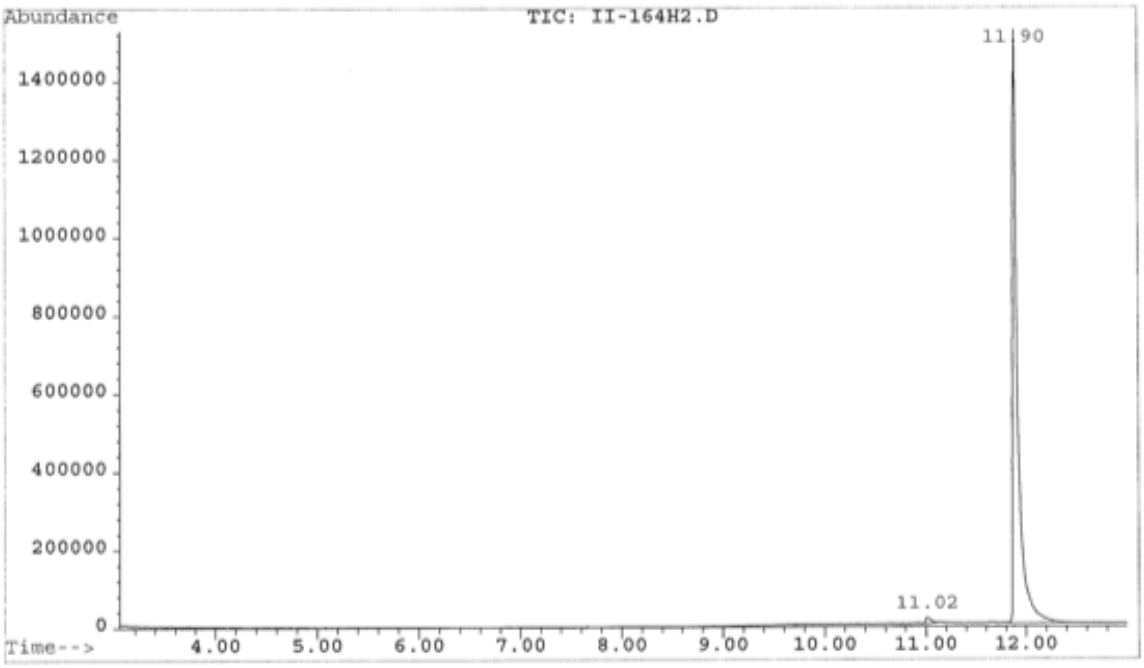

180
160
140
120
100
80
60
40
20
ppm
138.880
136.445
135.770
135.542
128.746
126.387
126.061
123.876
120.486
115.002
Me
77.508
77.190
76.879
38.968
28.880
26.741
14.074


STANDARD PROTON PARAMETERS
Pulse Sequence: NOESY
Solvent: CDCl3
Temp. 28.0 C / 301.1 K
INOVA-500 "nmrf9"
Relax. delay 1.000 sec
Mixing time 0.800 sec
Acq. time 0.242 sec
width 4207.2 Hz
2D width 4207.2 Hz
48 repetitions
2 x 200 increments
OBSERVE H1, 499.7811430 MHz
DATA PROCESSING
Gauss apodization 0.112 sec
F1 DATA PROCESSING
Gauss apodization 0.038 sec
FT size 4096 x 4096
Total time 11 hr, 6 min, 56 sec
Me
F2 (ppm)
F1 (ppm)


Transmittance %
65
70
75
80
85
90
95
4000
3500
3000
2500
2000
1500
1000
3081.70
3059.53
3027.71
2924.55
2885.14
1635.35
1601.60
1490.71
1453.10
1313.29
757.89
696.18
Mon Jun 26 17:10:44:91 2006



(*E*)-4-Ethylidene-1-tosyl-3-vinyl-1,2,3,4-tetrahydroquinoline (2.26) was purified by column chromatography on silica gel with hexanes/ethyl acetate (25:1) as the eluent, producing compound **2.26** in 67% yield. Olefin stereochemistry was assigned by comparison with compound **2.23**. Purity was determined to be 99% by GC/MS. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.55 (d, *J* = 7.6 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.31 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.22 (td, *J* = 7.6, 1.6 Hz, 1H), 7.16 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 2H), 5.61 (q, *J* = 7.2 Hz, 1H), 5.51 (ddd, *J* = 17.2, 10.0, 7.2 Hz, 1H), 5.03 (d, *J* = 9.6 Hz, 1H), 4.99 (d, *J* = 17.2 Hz, 1H), 4.20 (dd, *J* = 14.0, 6.4 Hz, 1H), 3.46 (m, 1H), 3.36 (dd, *J* = 13.6, 9.6 Hz, 1H), 2.36 (s, 3H), 1.38 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 143.4, 137.4, 136.6, 136.3, 133.4, 132.6, 129.5, 127.4, 126.6, 125.5, 125.0, 124.8, 116.3, 51.4, 41.9, 21.8, 14.4; IR (NaCl, thin film): 3061 (s), 3028 (m), 2914 (vs), 1598 (m), 1485 (m), 1459 (m), 1349 (vs), 1306 (m), 1292 (m), 1184 (m), 1165 (vs), 1090 (s), 1061 (m), 919 (m), 815 (m), 750 (m), 732 (m) cm^{-1}; HRMS (ES+): calculated for formula $C_{20}H_{21}NO_2SNa^+$: *m/z* 362.1191, found 362.1196.



Retention Time	Area	Area %	Ratio %
Total Ion Chromatogram			
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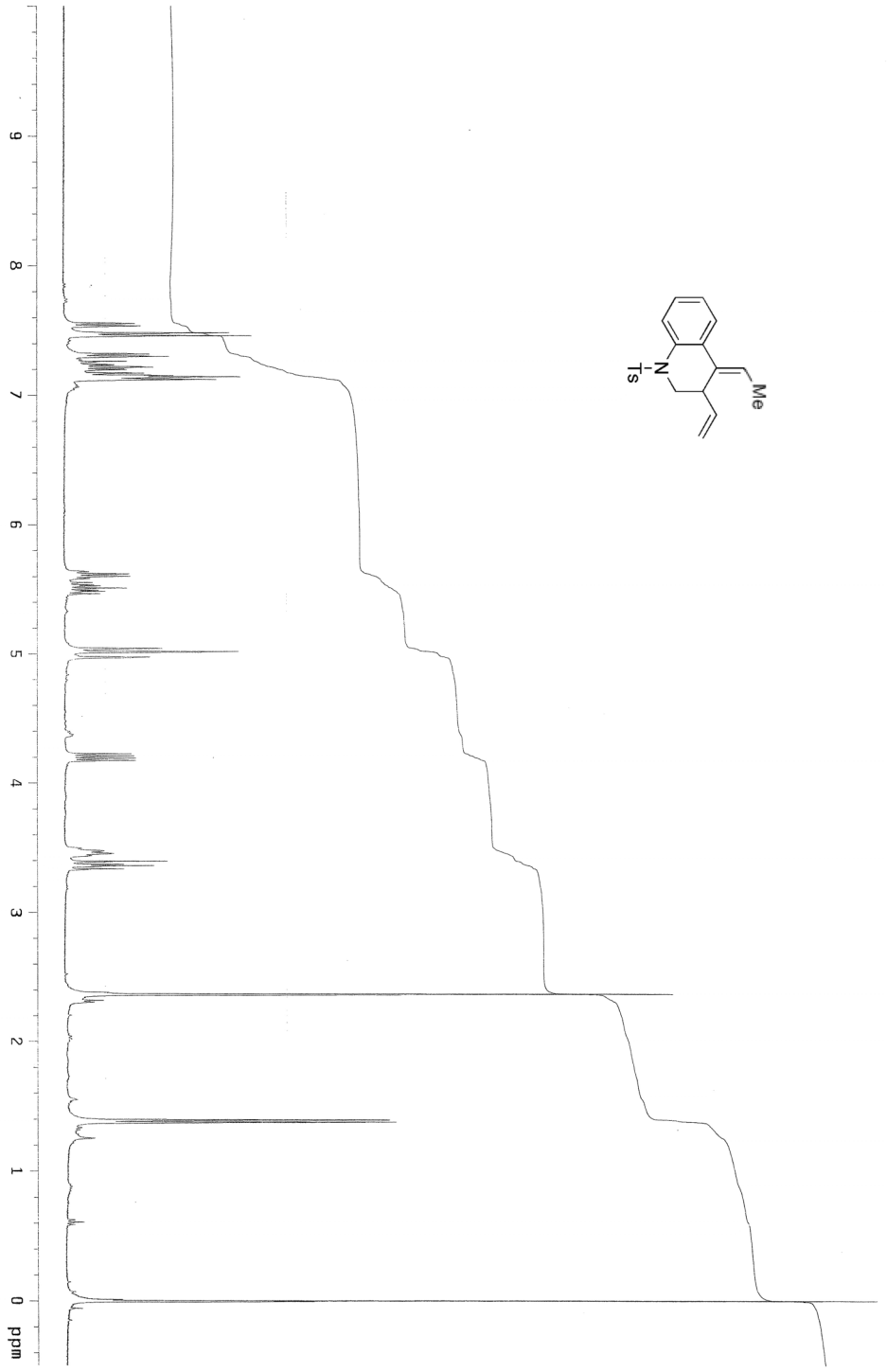
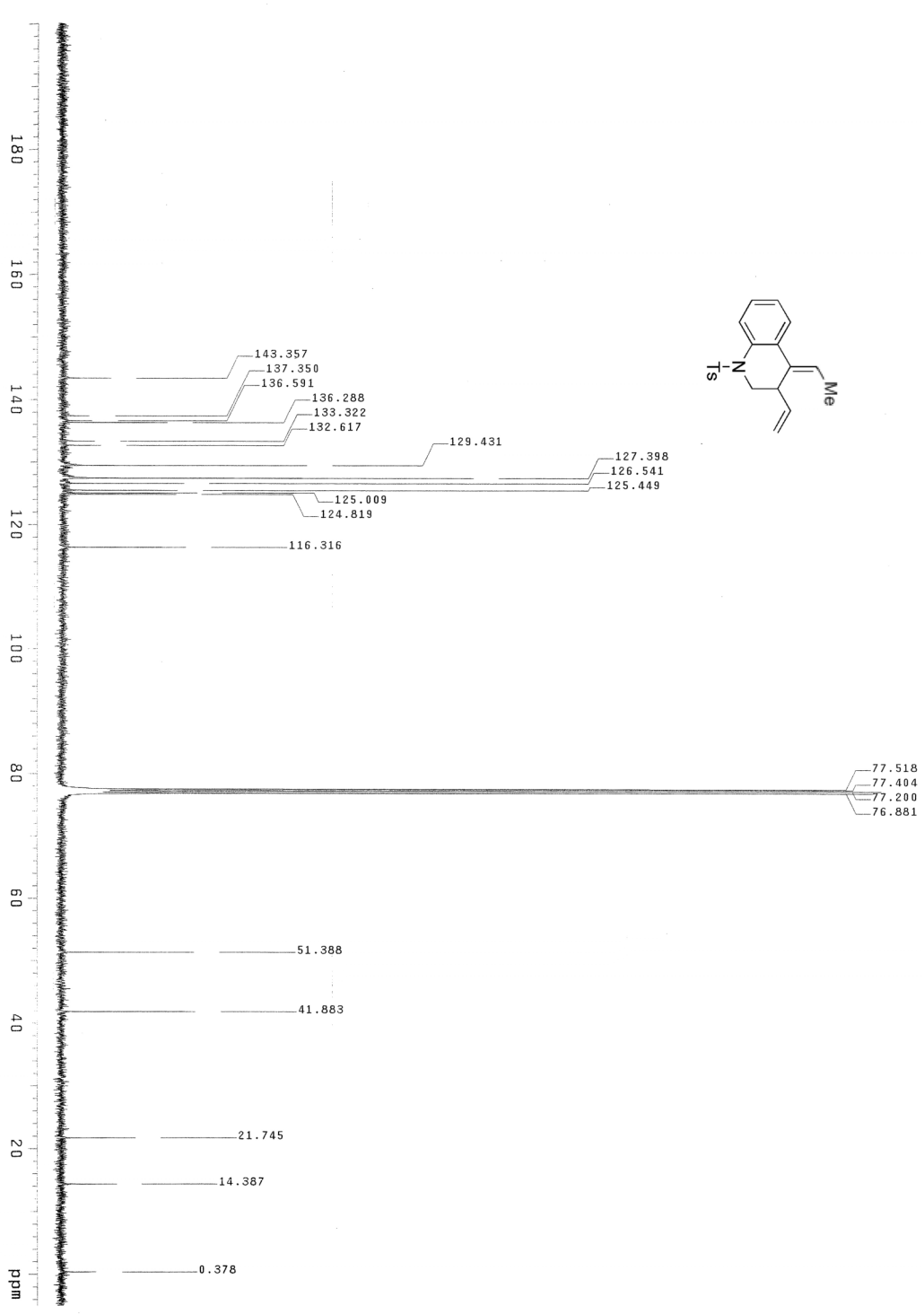
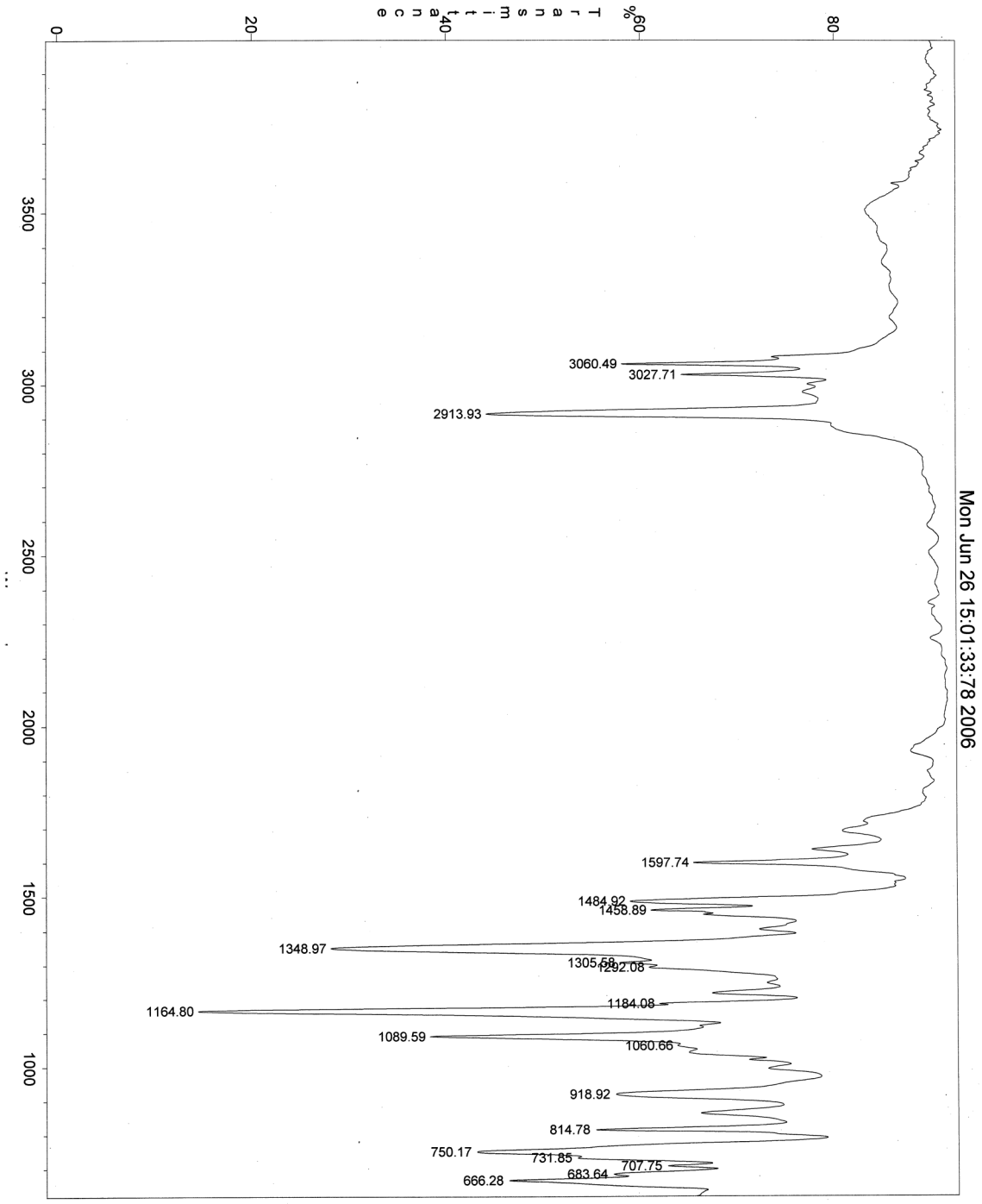
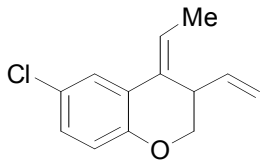
11.895	51814645	98.988	100.000

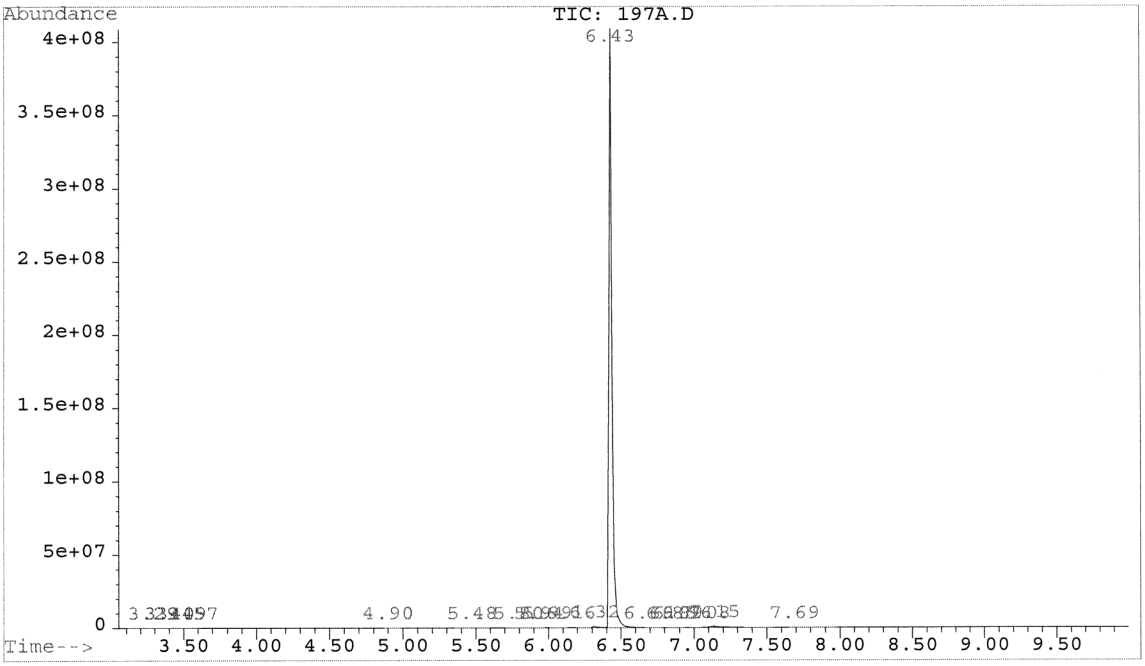

9
8
7
6
5
4
3
2
1
0
ppm
N
Ts
Me


143.357
137.350
136.591
136.288
133.322
132.617
129.431
127.398
126.541
125.449
125.009
124.819
116.316
77.518
77.404
77.200
76.881
51.388
41.883
21.745
14.387
0.378
ppm
Ts
N
Me

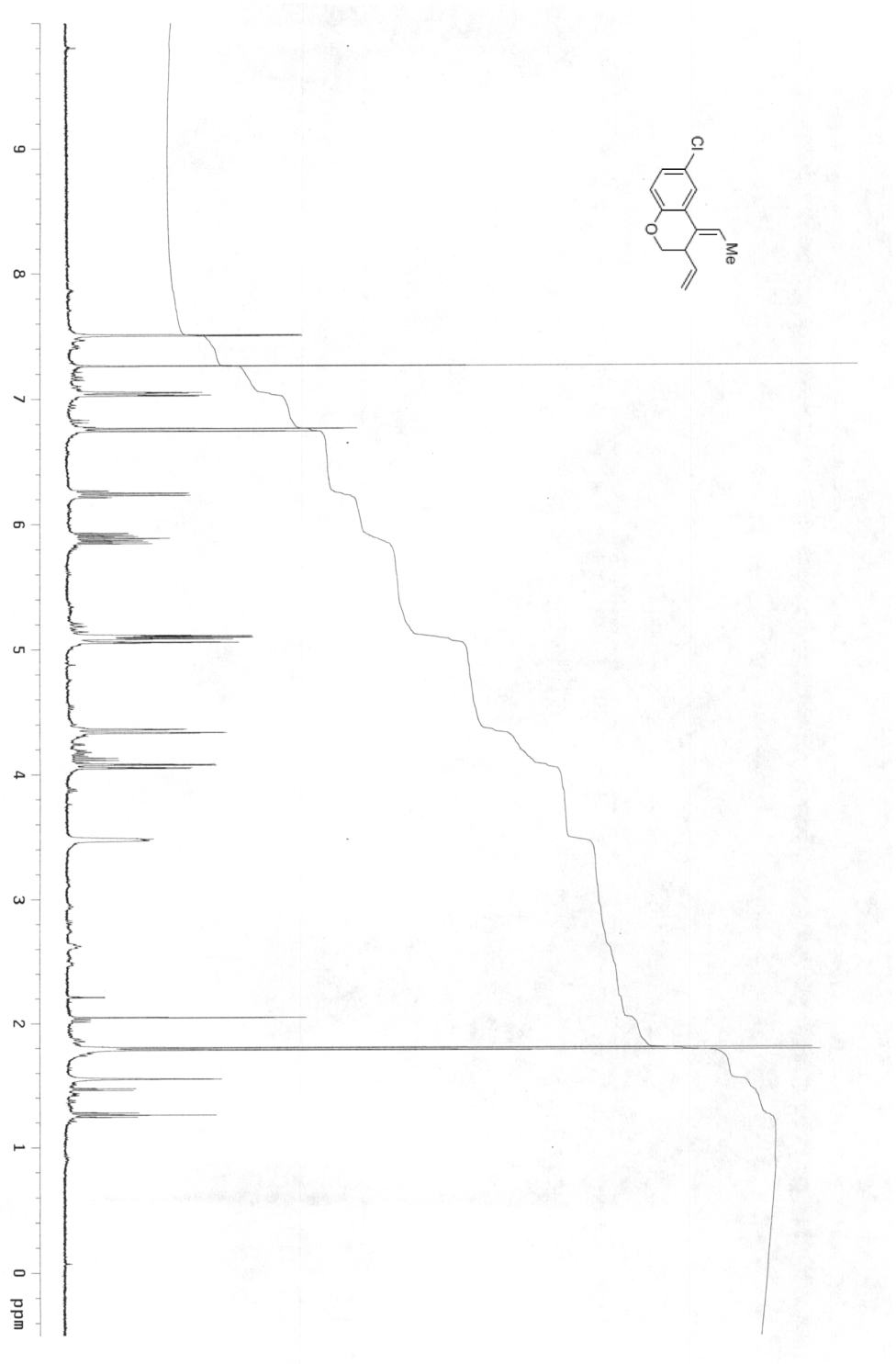

Transmittance %
0
20
40
60
80
3500
3000
2500
2000
1500
1000
3060.49
3027.71
2913.93
1597.74
1484.92
1458.89
1348.97
1305.58
1292.08
1184.08
1164.80
1089.59
1060.66
918.92
814.78
750.17
731.85
707.75
683.64
666.28
Mon Jun 26 15:01:33:78 2006

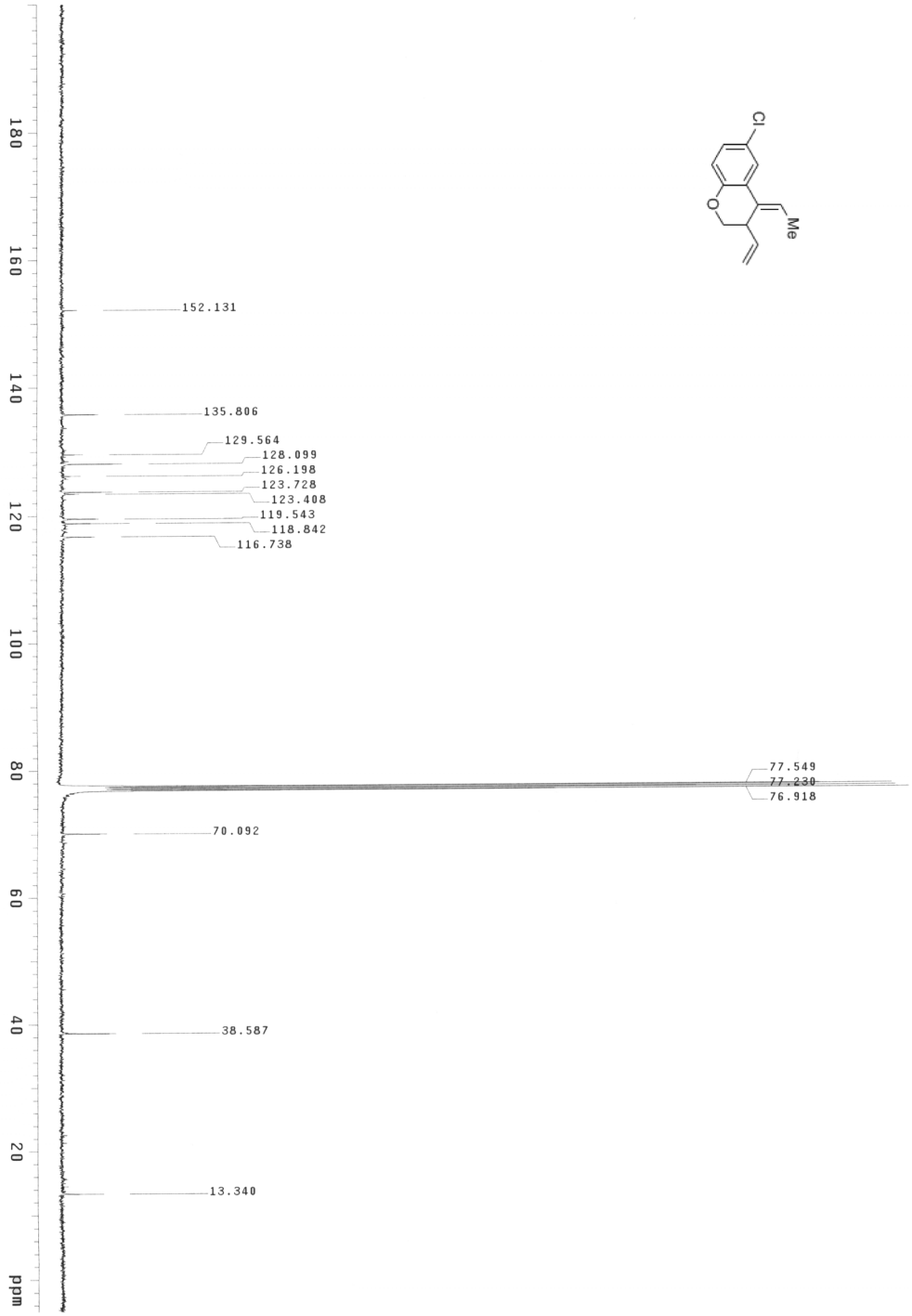


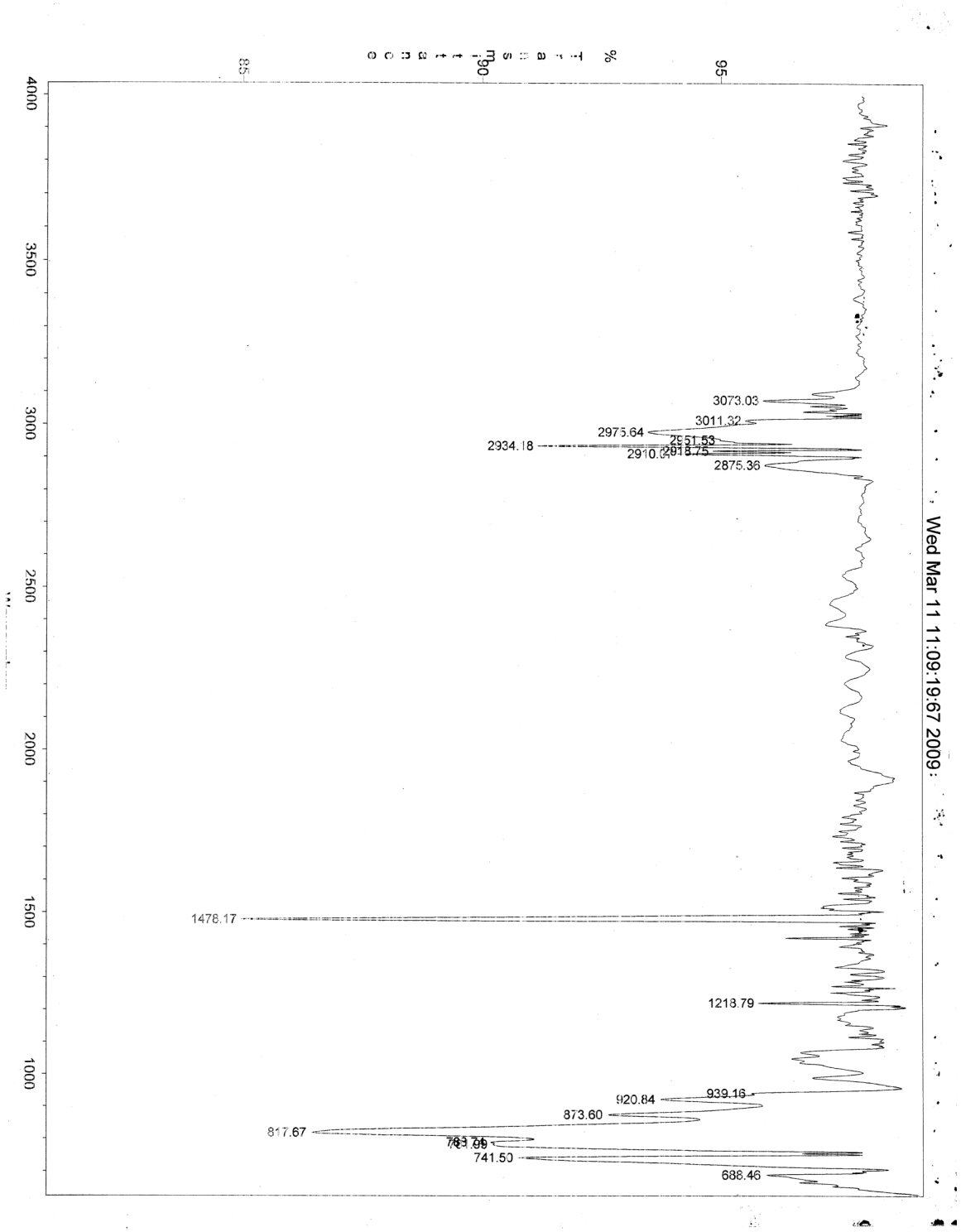
(*E*)-6-Chloro-4-ethylidene-3-vinylchromane (2.29) was purified by column chromatography on silica gel with hexanes as the eluent, producing compound **2.29** in 49% yield. Olefin stereochemistry was assigned by comparison with compound **2.23**. Purity was determined to be 98% by GC/MS. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.50 (d, *J* = 2.8 Hz, 1H), 7.04 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.75 (d, *J* = 8.8 Hz, 1H), 6.24 (q, *J* = 6.8 Hz, 1H), 5.89 (ddd, *J* = 16.0, 10.4, 5.6 Hz, 1H), 5.11-5.05 (m, 2H), 4.35 (dd, *J* = 10.8, 1.2 Hz, 1H), 4.06 (dd, *J* = 10.4, 2.8 Hz, 1H), 3.48 (m, 1H), 1.79 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (C_6D_6, 100.6 MHz) δ 152.1, 135.8, 129.6, 128.1, 126.2, 123.7, 123.4, 119.5, 118.8, 116.7, 70.1, 38.6, 13.3; IR (NaCl, thin film): 3073 (w) 3011 (w), 2976 (br m), 2952 (w), 2934 (m), 2919 (w), 2910 (w), 2875 (br w), 1478 (s), 1219 (w), 939 (w), 921 (m), 874 (m), 818 (s), 789 (m), 782 (m), 742 (m), 688 (w) cm^{-1}; HRMS (ES+): calculated for formula $C_{13}H_{14}ClO^{+}$: *m/z* 221.0733, found 221.0735.

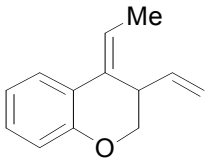


Retention Time	Area	Area %	Ratio %
Total Ion Chromatogram			
3.287	566393	0.009	0.009
3.403	972133	0.016	0.016
3.488	564833	0.009	0.009
3.567	165214	0.003	0.003
4.902	489645	0.008	0.008
5.477	773359	0.013	0.013
5.795	995961	0.016	0.017
5.938	549070	0.009	0.009
5.994	7722526	0.126	0.128
6.158	9201701	0.150	0.153
6.319	25690871	0.418	0.427
6.433	6009757872	97.871	100.000
6.692	5549300	0.090	0.092
6.847	1531289	0.025	0.025
6.894	1784218	0.029	0.030
6.958	6780275	0.110	0.113
7.079	4517282	0.074	0.075
7.146	58328163	0.950	0.971
7.689	4545927	0.074	0.076

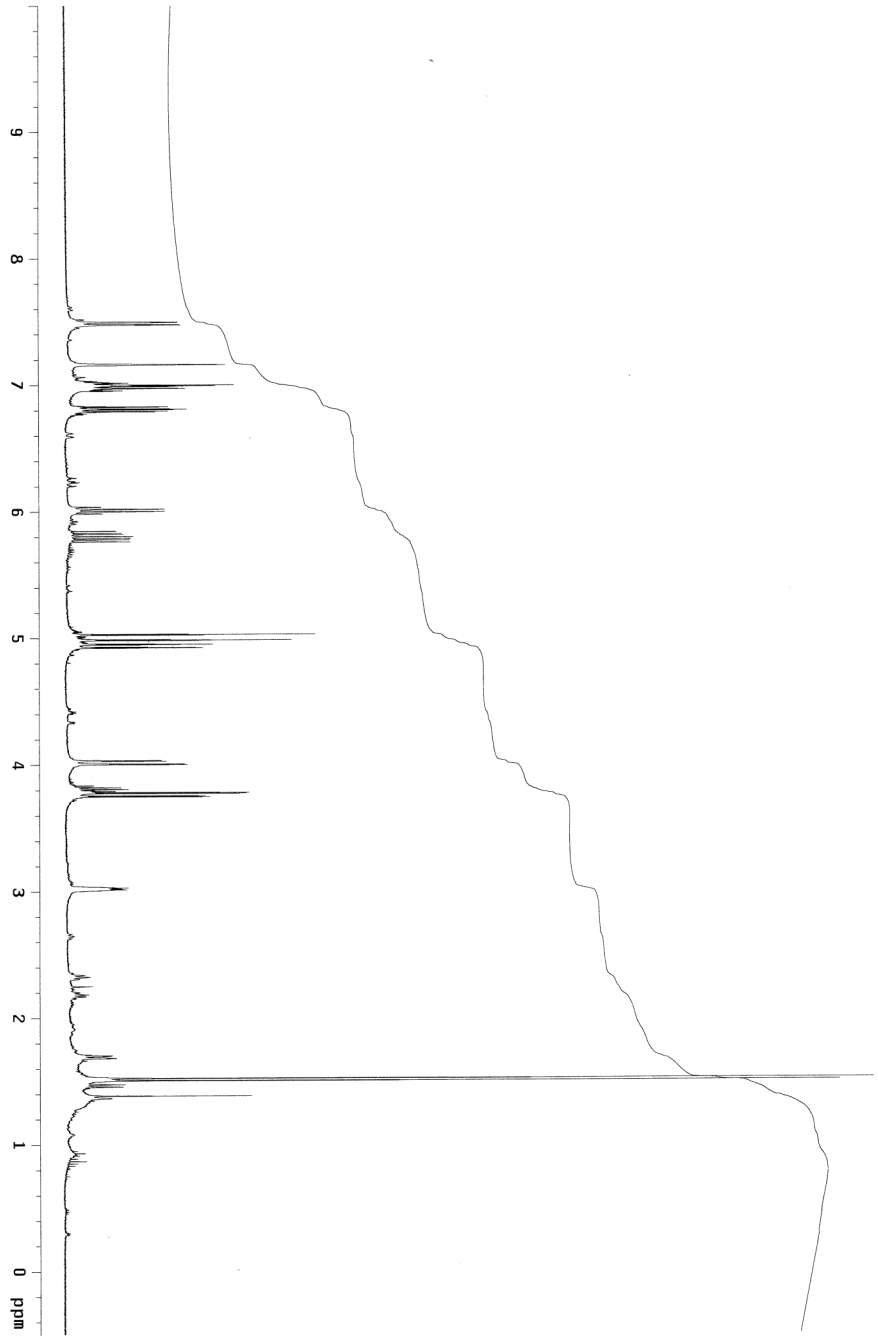

Cl
O
Me
9
8
7
6
5
4
3
2
1
0
ppm

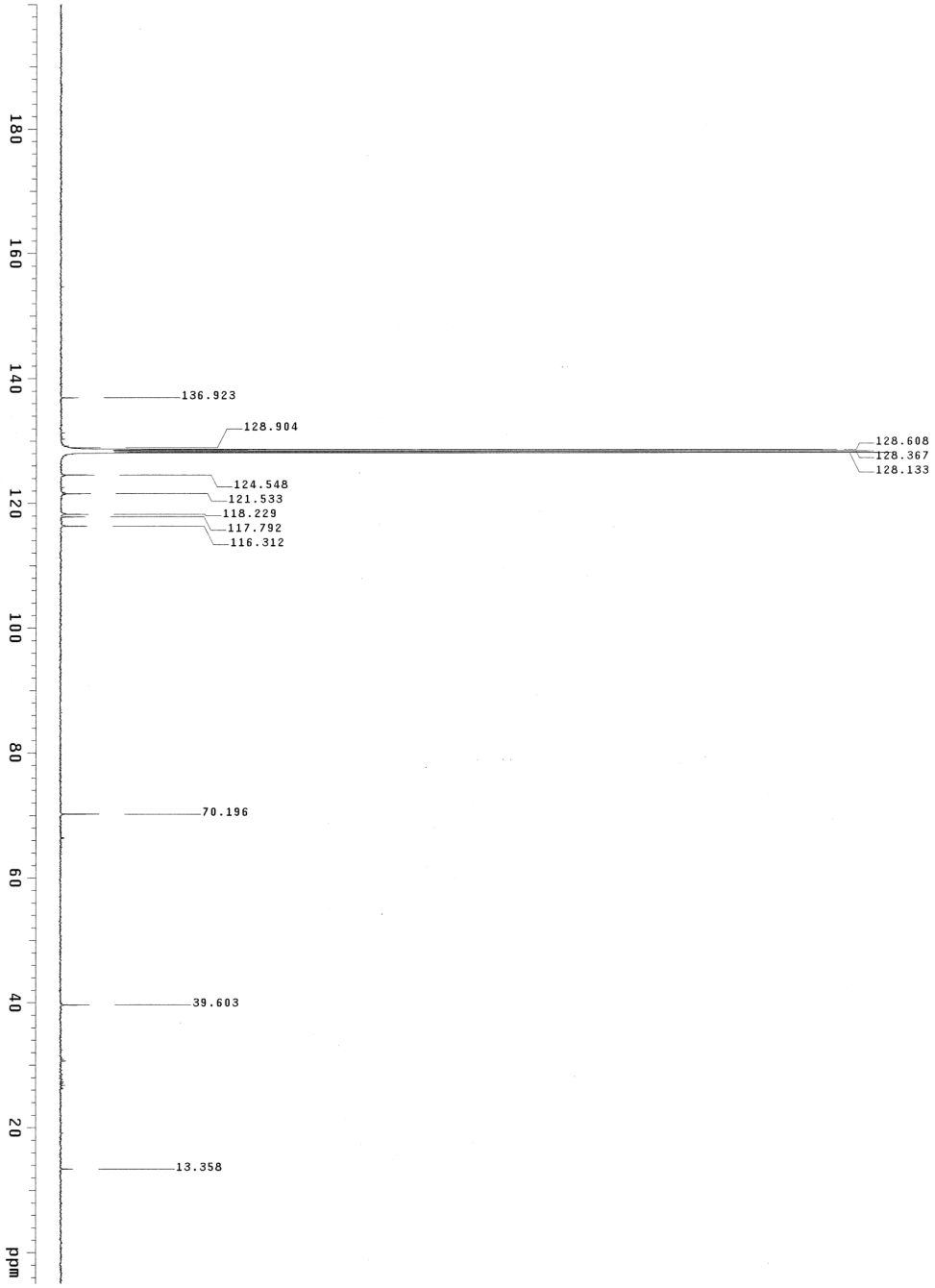

Cl
O
Me
152.131
135.806
129.564
128.099
126.198
123.728
123.408
119.543
118.842
116.738
77.549
77.230
76.918
70.092
38.587
13.340
180
160
140
120
100
80
60
40
20
ppm

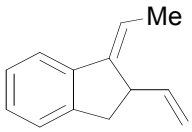

%
95
90
85
4000
3500
3000
2500
2000
1500
1000
3073.03
3011.32
2975.64
2934.18
2875.36
1478.17
1218.79
939.16
920.84
873.60
817.67
741.50
688.46
Wed Mar 11 11:09:19:67 2009



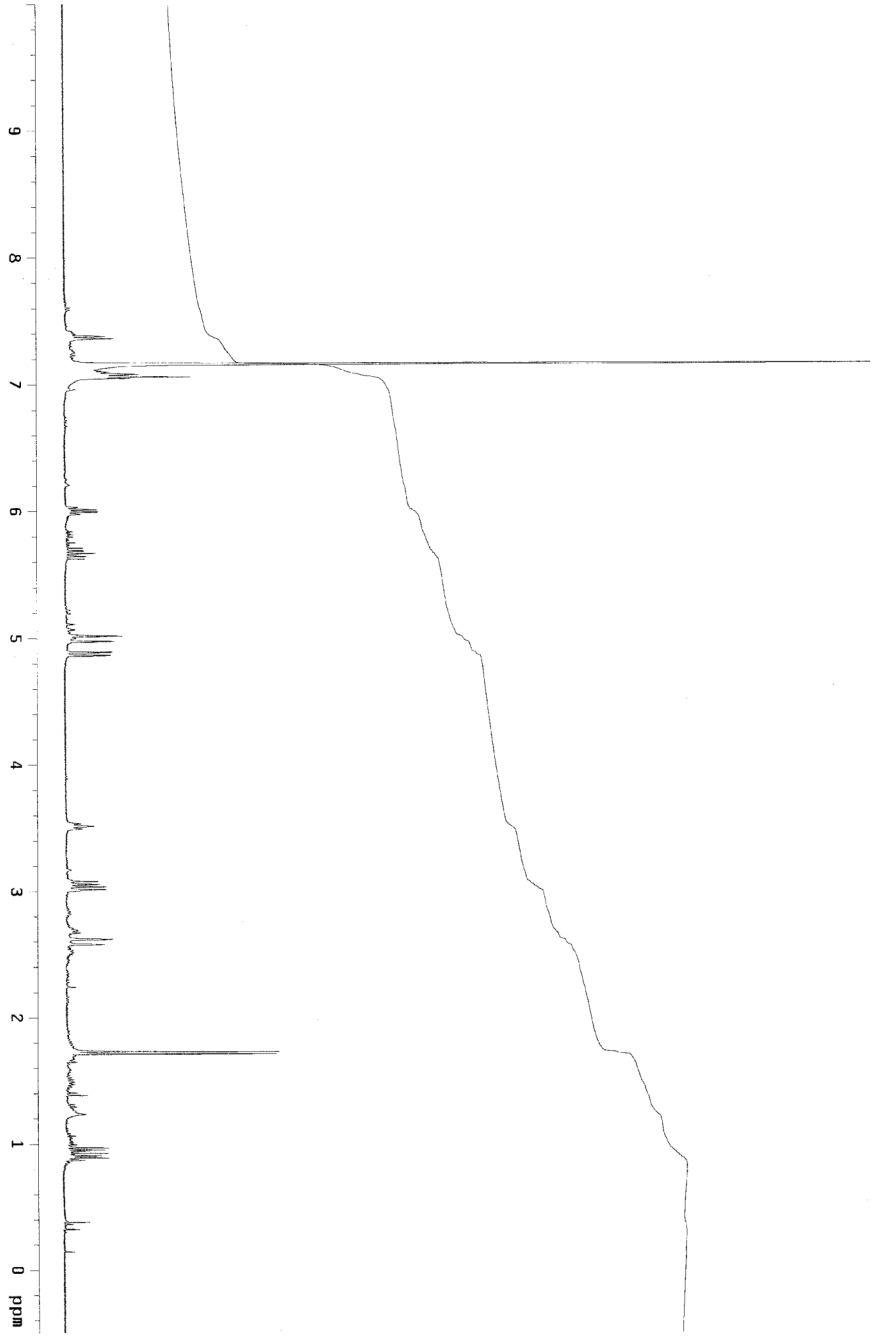
(*E*)-4-ethylidene-3-vinylchromane (2.32) was "purified" by column chromatography on silica gel with hexanes as the eluent, in 42% yield with a number of unidentifiable and intractable impurities. Olefin stereochemistry was assigned by comparison with compound **2.23**. ^{1}H NMR (C_6D_6, 400 MHz): δ 7.49 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.03-6.95 (m, 2H), 6.81 (ddd, *J* = 8.0, 6.8, 2.0 Hz, 1H), 6.01 (q, *J* = 6.8 Hz, 1H), 5.80 (ddd, *J* = 17.2, 10.4, 6.4 Hz, 1H), 4.99 (dt, *J* = 17.2, 1.6 Hz, 1H), 4.93 (dt, *J* = 10.4, 1.6 Hz, 1H), 4.02 (dd, *J* = 6.8, 2.0 Hz, 1H), 3.77 (dd, *J* = 10.8, 2.8 Hz, 1H), 3.02 (br m, 1H), 1.51 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (C_6D_6, 100.6 MHz) δ 136.9, 128.9, 124.5, 121.5, 118.2, 117.8, 116.3, 70.2, 39.6, 13.4 (one carbon presumed obscured by solvent peak); HRMS (ESI+) failed.

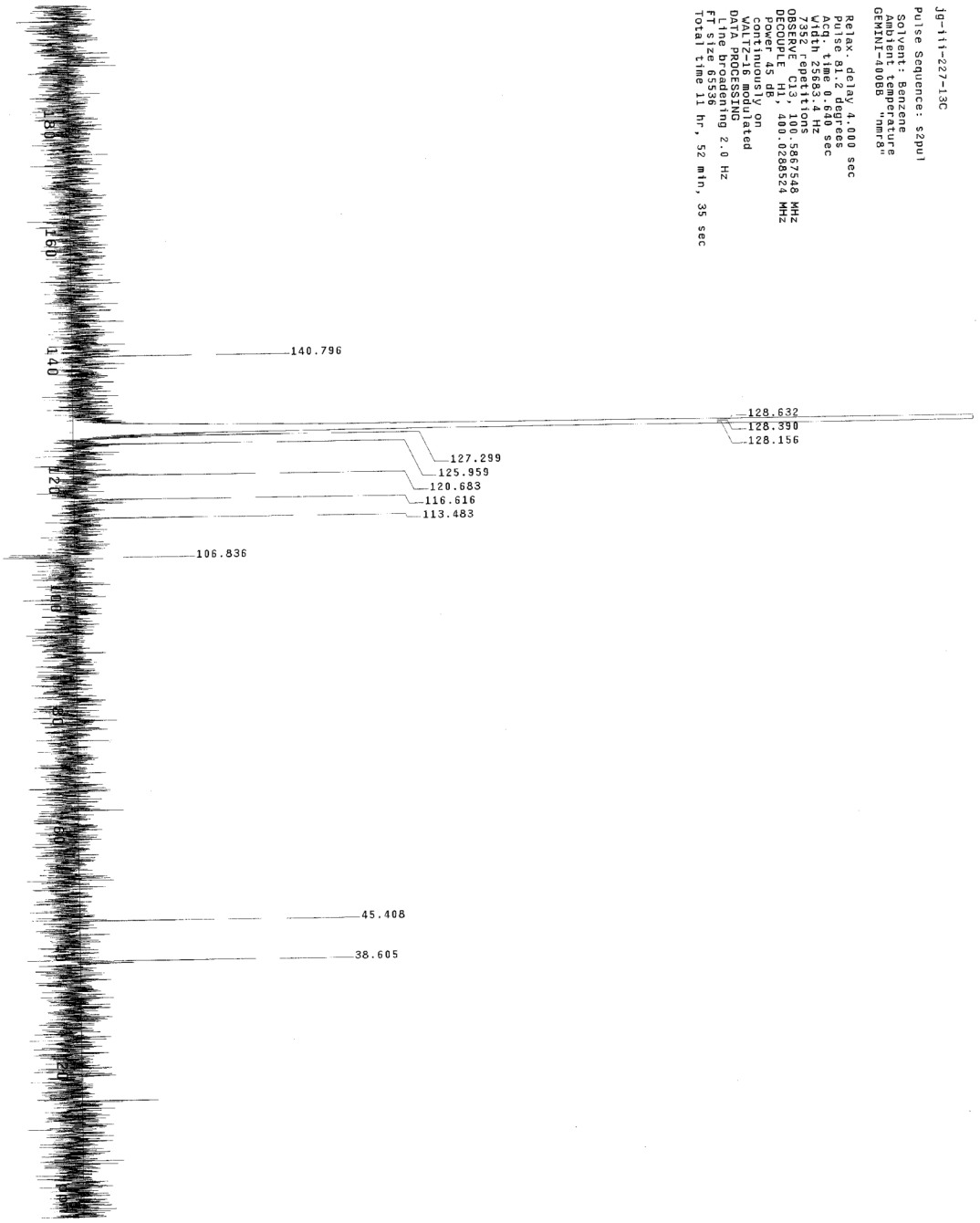

9
8
7
6
5
4
3
2
1
0
ppm


180
160
140
120
100
80
60
40
20
ppm
136.923
128.904
128.608
128.367
128.133
124.548
121.533
118.229
117.792
116.312
70.196
39.603
13.358



(*E*)-1-ethylidene-2-vinyl-2,3-dihydro-1H-indene (2.35) was purified by column chromatography on neutral alumina with pentane as the eluent, and isolated in 56% yield. Olefin stereochemistry was assigned by comparison with compound **2.23**. ^{1}H NMR (C_6D_6, 400 MHz): δ 7.40-7.05 (m, 4H), 6.01 (qd, *J* = 7.2, 2.0 Hz, 1H), 5.67 (ddd, *J* = 17.2, 10.0, 7.6 Hz, 1H), 5.02-4.97 (m, 1H), 4.89-4.86 (m, 1H), 3.54-3.49 (m, 1H), 3.04 (dd, *J* = 16.4, 8.8 Hz, 2H), 2.60 (dd, *J* = 16.4, 2.0 Hz, 2H), 1.72 (2, *J* = 7.2 Hz, 3H); ^{13}C NMR (C_6D_6, 100.6 MHz) δ 140.8, 127.3, 126.0, 120.7, 116.6, 113.5, 106.8, 45.4, 38.6, 14.9 (quaternary carbons not resolved).


9
8
7
6
5
4
3
2
1
0
ppm


jg-iii-227-13C
Pulse Sequence: s2pul
Solvent: Benzene
Ambient temperature
GEMINI-400BB "nmr8"
Relax. delay 4.000 sec
Pulse 81.2 degrees
Acq. time 0.640 sec
Width 25881.4 Hz
72 repetitions
OBSERVE C13, 100.5867548 MHz
DECOUPLE H1, 400.0288524 MHz
Power 45 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 11 hr, 52 min, 35 sec
140.796
128.632
128.390
128.156
127.299
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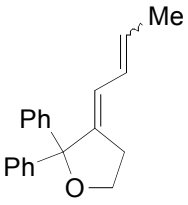
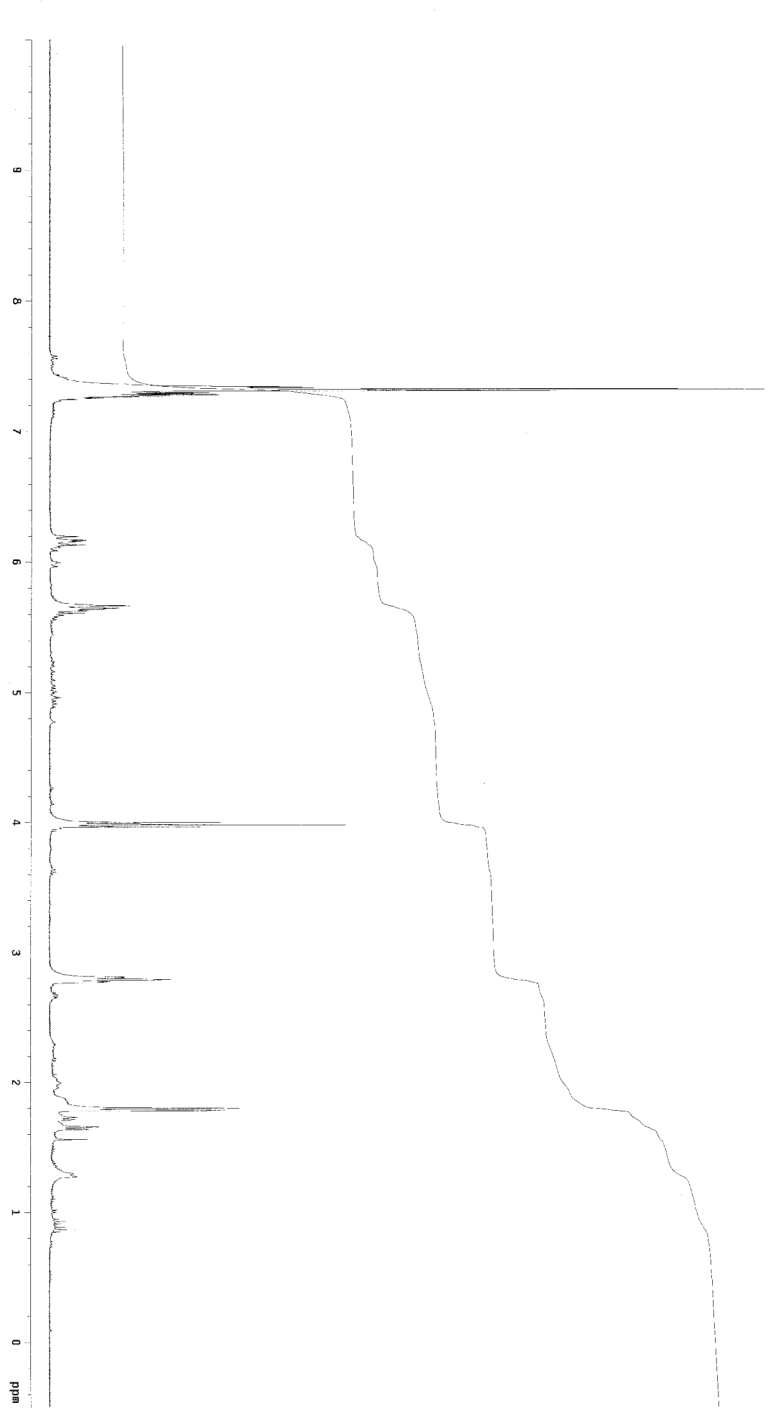
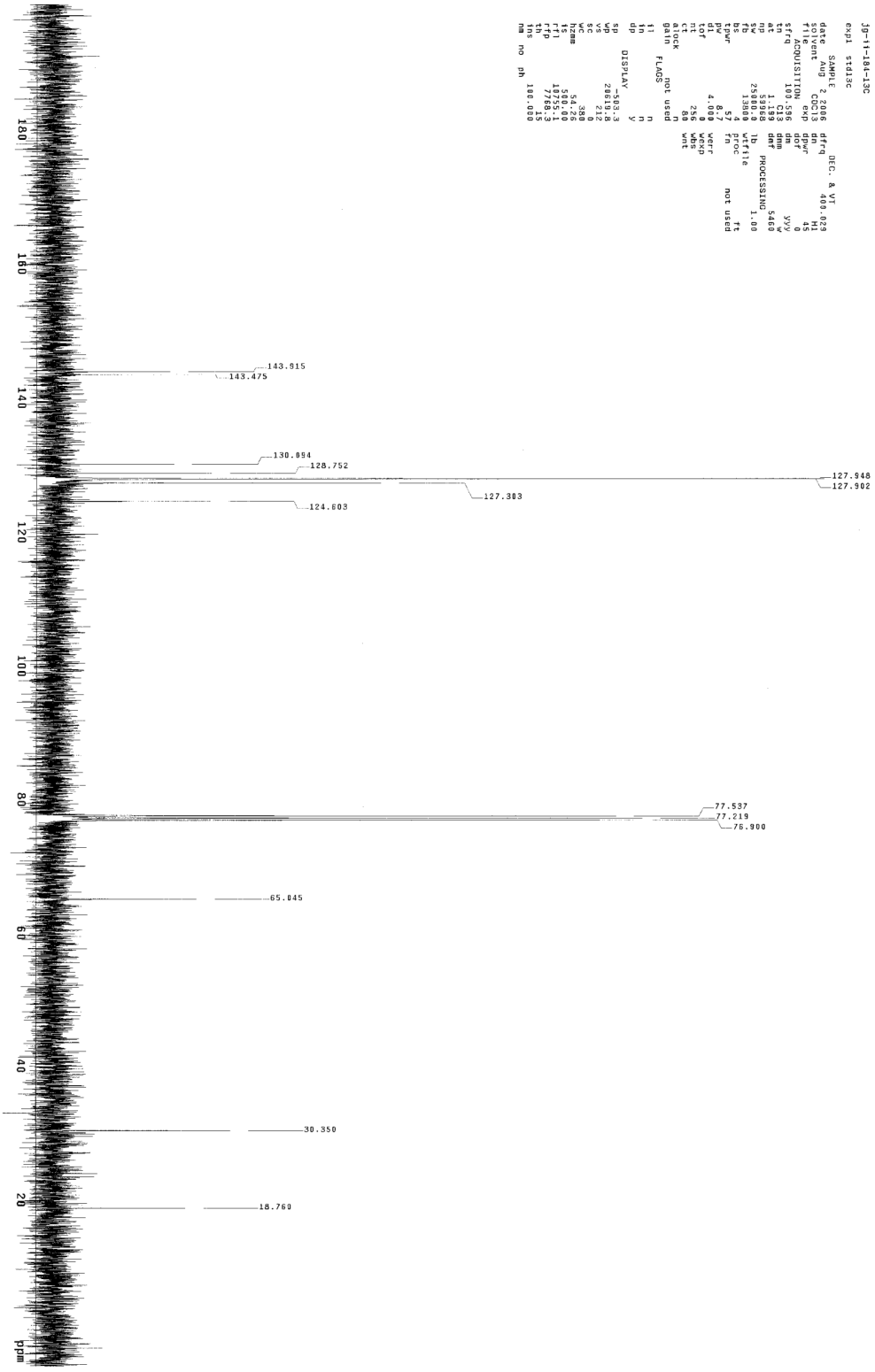
116.616
113.483
106.836
45.408
38.605



(3*E*)-3-(but-2-en-1-ylidene)-2,2-diphenyltetrahydrofuran (2.36) was purified by column chromatography on silica gel with n-pentane/diethyl ether (29:1) as the eluent, producing the compound in 10% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.31-7.22 (m, 10H), 6.20-6.13 (m, 1H), 5.68-5.59 (m, 2H), 3.98 (td, *J* = 18.0, 5.0 Hz, 2H), 2.79 (td, *J* = 18.0, 6.0 Hz, 2H), 1.79 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 143.9, 143.5, 130.1, 128.8, 128.0, 127.9, 127.3, 124.6, 65.0, 30.4, 18.8; .


9
8
7
6
5
4
3
2
1
0
ppm


jg-11-184-13C
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143.475
130.094
128.752
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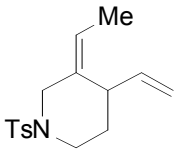
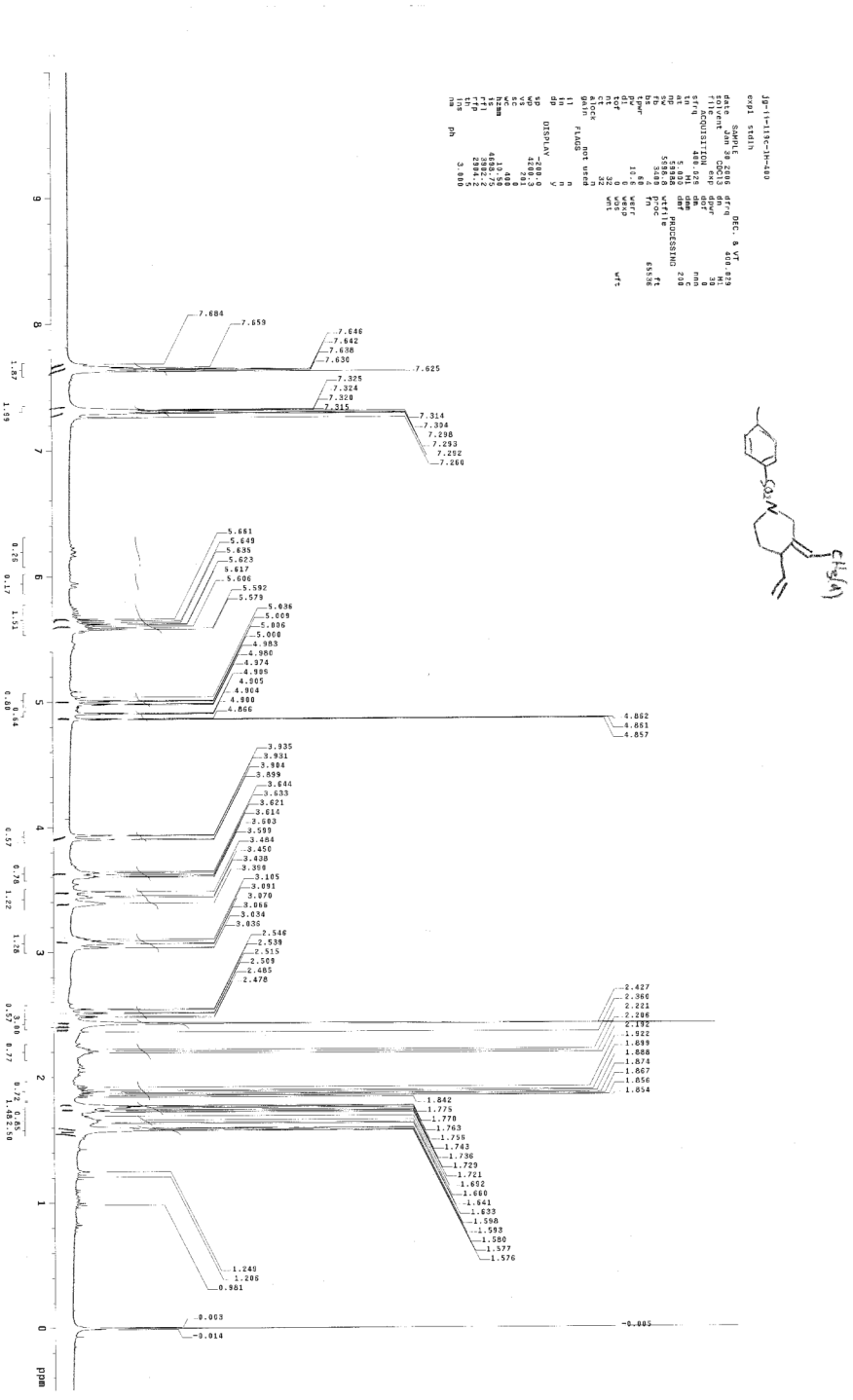
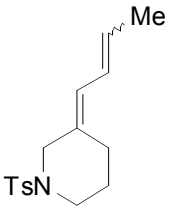
127.902
127.303
124.603
77.537
77.219
76.900
65.045
30.350
18.760
ppm

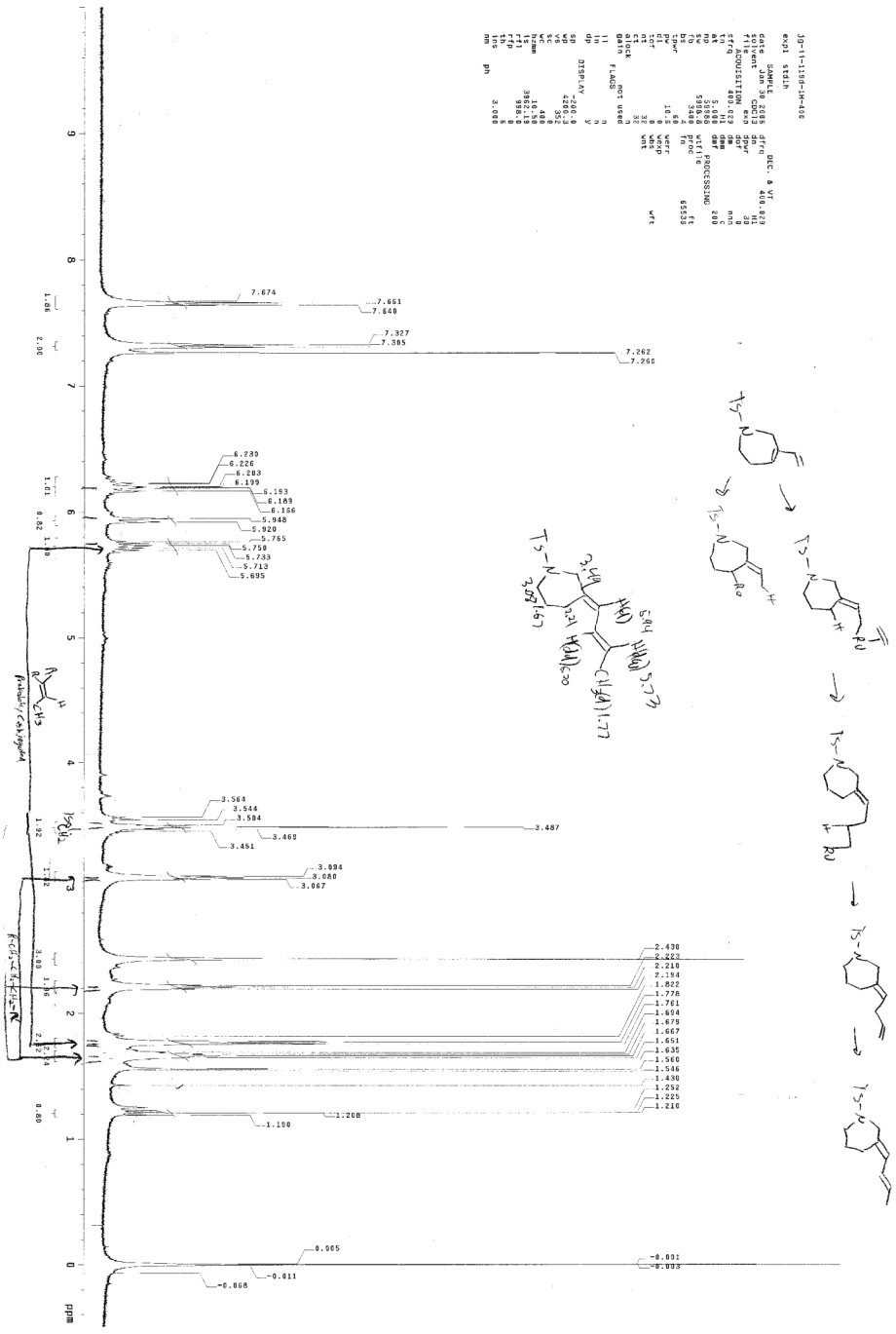


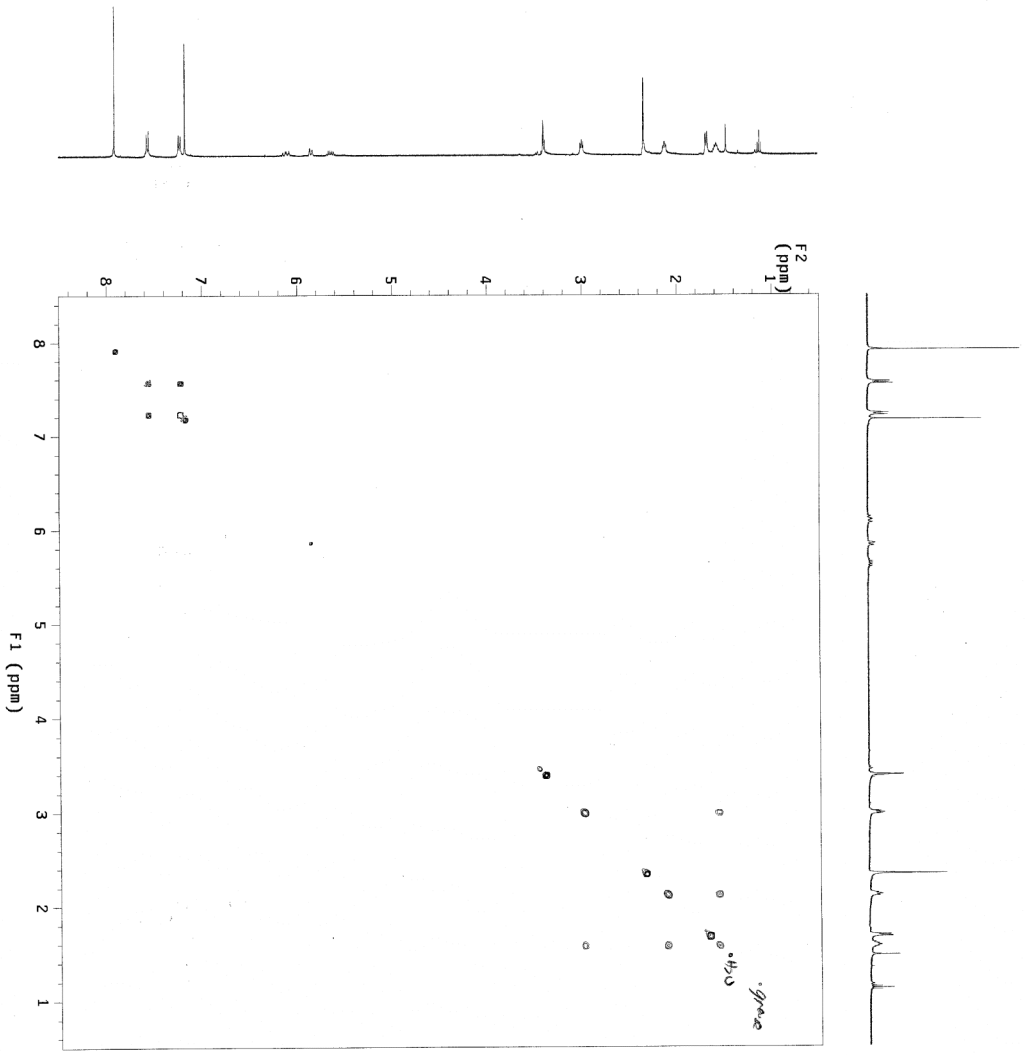
(*E*)-3-ethylidene-1-tosyl-4-vinylpiperidine (2.39) was purified by column chromatography on silica gel with n-pentane/diethyl ether (29:1) as the eluent. The presence of **2.40** in all fractions containing **2.39** precluded full characterization of the latter. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64 (m, 2H), 7.30 (m, 2H), 5.66-5.58 (m, 1H), 5.04-4.97 (m, 1H), 4.91-4.86 (m, 1H), 3.92 (dd, *J* = 12.8, 1.6 Hz, 1H), 3.61 (dt, *J* = 12.0, 4.4 Hz 1H), 3.39 (m, 1H), 2.43 (s, 3H), 1.75 (m, 2H), 1.58 (m, 3H);

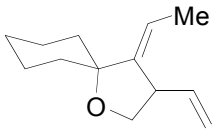




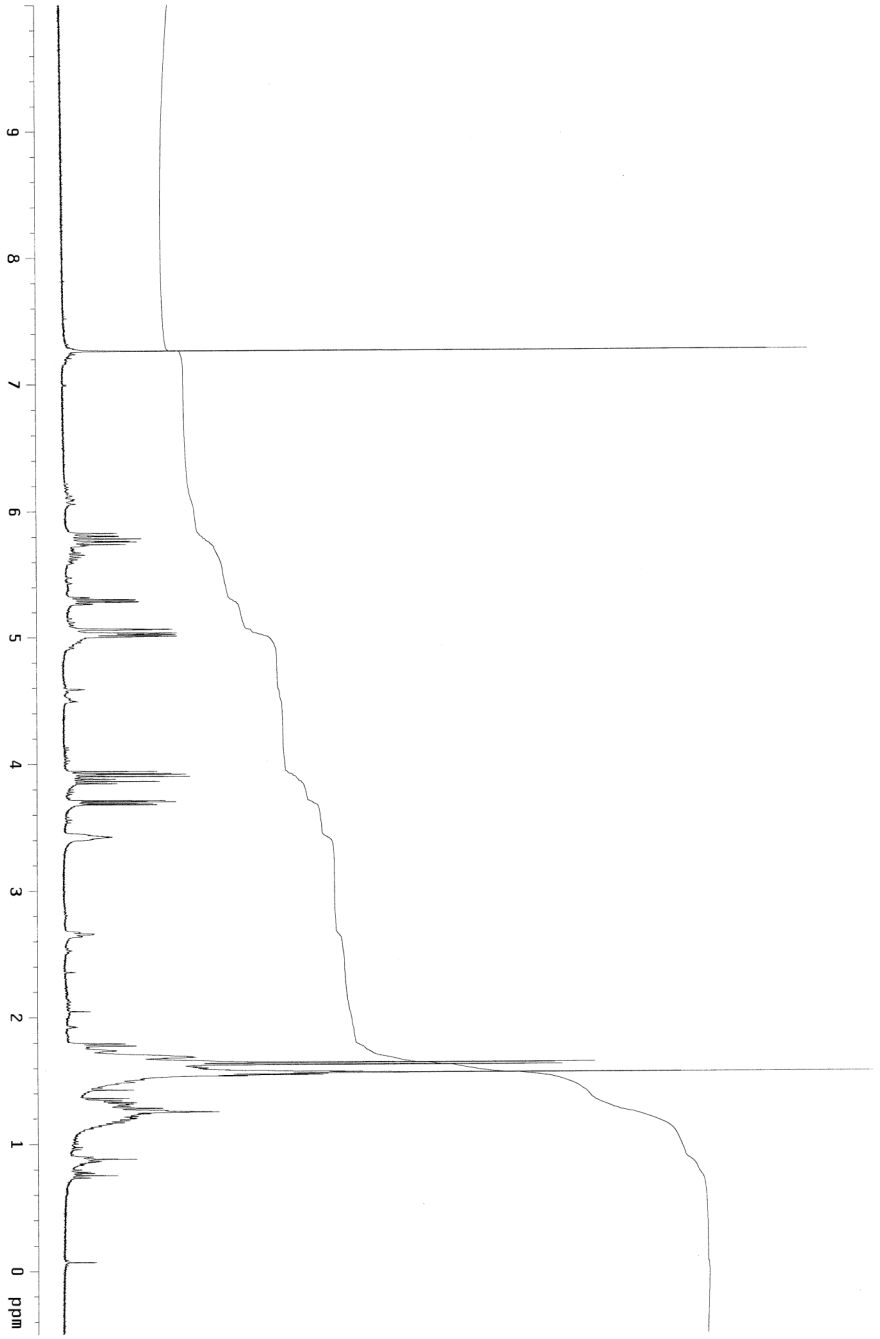
(3*E*)-3-(but-2-en-1-ylidene)-1-tosylpiperidine (2.40) was purified by column chromatography on silica gel with n-pentane/diethyl ether (29:1) as the eluent. Poor separation, as mentioned above, prevented full characterization. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.8 Hz, 2H), 6.20 (dd, *J* = 14.8, 10.8 Hz, 1H), 5.93 (d, *J* = 11.2 Hz, 1H), 5.73 (dq *J* = 15.2, 6.8 Hz, 1H), 3.49 (s, 2H), 3.08 (t, *J* = 5.6 Hz, 2H), 2.43 (s, 3H), 2.21 (t, *J* = 5.6 Hz, 2H), 1.77 (d, *J* = 6.8 Hz, 3H), 1.67 (m, 2H);




F2 (ppm)
F1 (ppm)



(*E*)-4-ethylidene-3-vinyl-1-oxaspiro[4.5]decane (2.48a) was purified by column chromatography on a Biotage ® Si 12+M column with hexanes/ethyl acetate (99:1) as the eluent. Yields varied from 33% to 47%. Complete separation from **2.48b** was not achieved, preventing full characterization. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.78 (ddd, *J* = 17.6, 10.0, 7.6 Hz, 1H), 5.29 (qd, *J* = 6.8, 2.0 Hz, 1H), 5.06-5.00 (m, 2H), 3.92 (dd, *J* = 8.8, 6.8 Hz, 1H), 3.69 (dd, *J* = 8.8, 3.2 Hz, 1H), 3.42 (br m, 1H), 1.73-1.20 (br m, 10 H) 1.63 (dd, *J* = 6.8, 1.2 Hz, 3H).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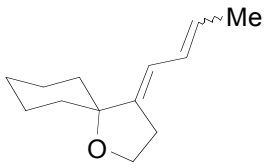
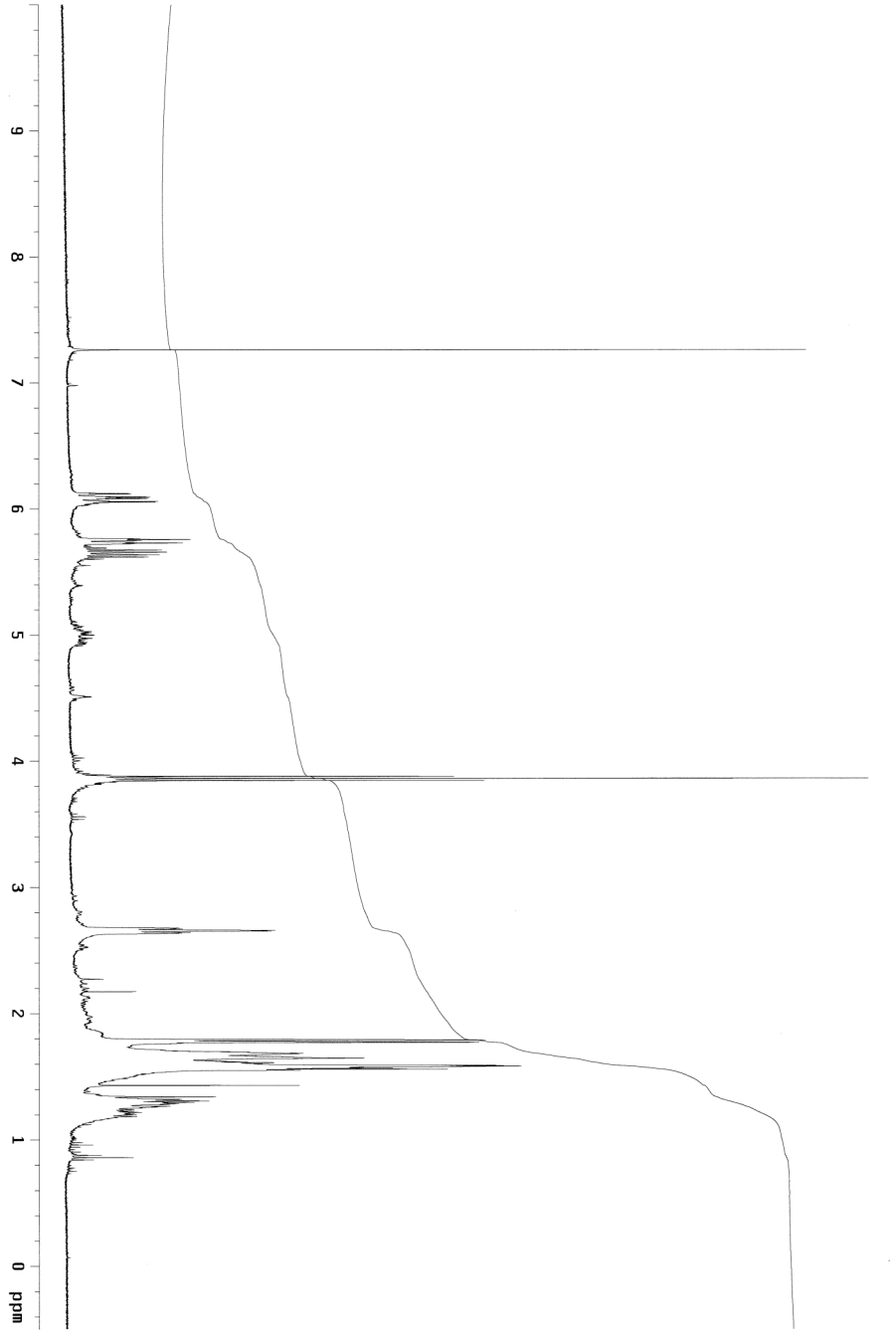


(4*E*)-4-(but-2-en-1-ylidene)-3-methyl-1-oxaspiro[4.5] decane (2.48b) was purified by preparatory thin-layer chromatography on silica gel with hexanes/ethyl acetate (99:1) as the eluent, and, despite the conspicuous lack of a chromophore, the "band" with an Rf of 0.5 produced **2.48b** in 29% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.13-6.03 (m, 1H), 5.74 (dt, *J* = 10.8, 2.4 Hz, 1H), 5.69-5.60 (m, 1H) 3.86 (t, *J* = 6.8 Hz, 2H), 2.65 (td, *J* = 6.8, 2.4 Hz, 2H), 1.78 (d, *J* = 7.2 Hz, 3H), 1.71-1.55 (br m, 8H) 1.32-1.24 (m, 2H).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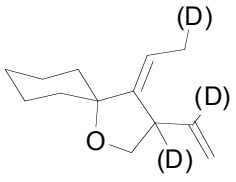
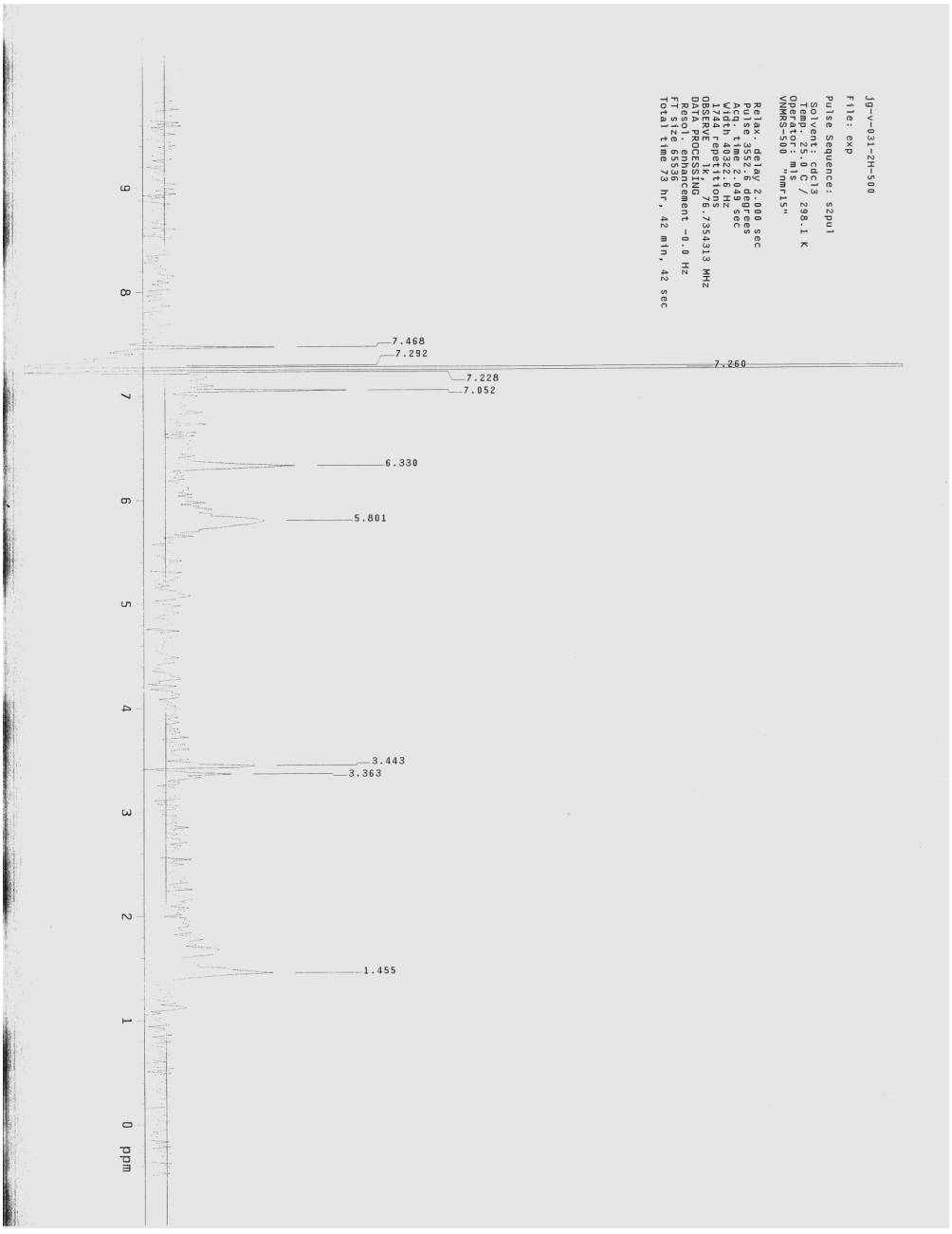


^{2}H NMR ($CDCl_3$, 500 MHz): δ 6.33, 5.73, 3.43, 3.36, 1.64, 1.46.



Chapter 3

Acid-Catalyzed Friedel-Crafts Hydroarylation of 1,3-Dienes

"It's essentially a matter of physics. It isn't a matter of money. It isn't a matter... of desire. It's a matter of production and capability of doing it."

--Donald Rumsfeld

3.1 Introduction

Friedel-Crafts alkylation and acylation are perhaps the most well established methods for the introduction of carbon-containing functionalities onto an aromatic ring. These processes, however, are often complicated by the need for elevated temperatures, lack of regioselectivity, and copious amounts of salt byproducts. While the direct reaction of olefins with arenes[79] obviates the latter drawback, most Friedel-Crafts reactions with olefins still require the use of a strong mineral acid catalyst,[80] elevated temperatures,[81] or intramolecular direction.[82]

Friedel-Crafts chemistry has enjoyed a recent renaissance, with reported additions of simple olefins[81] α,β-unsaturated carbonyls,[83] and 1,3-dienes[84] to a variety of electron-rich aromatic compounds. The latter is particularly

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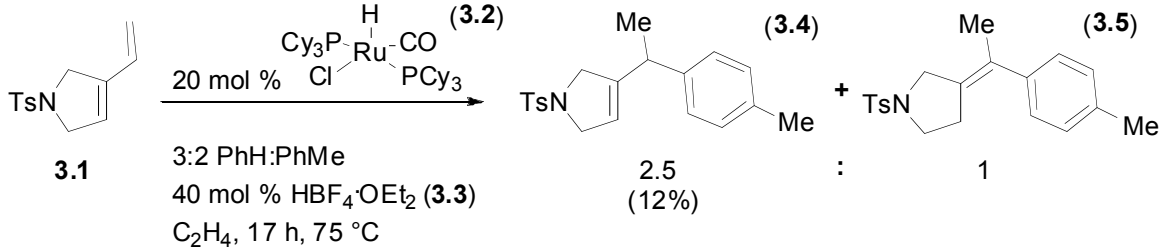
[79] First reported only two years after the initial work of Friedel and Crafts: M. Balsohn, *Bull. Soc. Chim.* **1879**, *[2]31*, 539.
[80] W. T. Smith, J. T. Sellas, *Org. Syn.* **1952**, *32*, 90.
[81] a) D. Karshtedt, A. T. Bell, T. D. Tilley *Organometallics* **2004**, *23*, 4169-4171 doi:10.1021/om0495325. b) D. Karshtedt, J. L. McBee, A. T. Bell. T. D. Tilley *Organometallics*, **2006**, *25*, 1801-1811 doi:10.1021/om0600902. c) M. Rueping, B. J. Nachtsheim, T. Scheidt, *Org. Lett.* **2006**, *8*, 3717-3719 doi:10.1021/ol0612962.
[82] M. Bandini, E. Emer, S. Tommasi, A. Umani-Ronchi, *Eur. J. Org. Chem.* **2006**, 3527-3544 doi:10.1002/ejoc.200500995.
[83] Examples of this reaction, particularly with indoles, are too numerous to list individually. For reviews of catalytic, asymmetric Friedel-Crafts reactions with indoles, see: a) M. Bandini, A. Melloni, A. Umani-Ronchi, *Angew. Chem., Int. Ed.* **2004**, *43*, 550□556. b) K. A. Jørgensen, *Synthesis* **2003**, 1117□1125. For hydroarylation of cinnamic acids by phenols see c) K. Li, L. N. Forsee, J. A. Tunge *J. Org. Chem.* **2005**, *70*, 2881-2883 doi:10.1021/jo0477650.
[84] *Q.v.* refs. 86-87 (*infra*).

advantageous, since the second olefin of the diene stabilizes the carbocation intermediate, preventing unexpected or undesired skeletal rearrangements prior to carbon-carbon bond formation.

3.2 Hydroarylation byproducts from hydrovinylation reactions

In the course of studying the ruthenium-catalyzed hydrovinylation of 1,3-dienes, some unanticipated byproducts were observed. Attempted hydrovinylation of diene **3.1** with ruthenium-hydride catalyst **3.2** and tetrafluoroboric acid (**3.3**) produced, in addition to the expected mixture of hydrovinylation products,[85] small but isolable amounts of 1,2-hydroarylation product **3.4** and its olefin-isomerized congener **3.5** (Scheme 3.1)

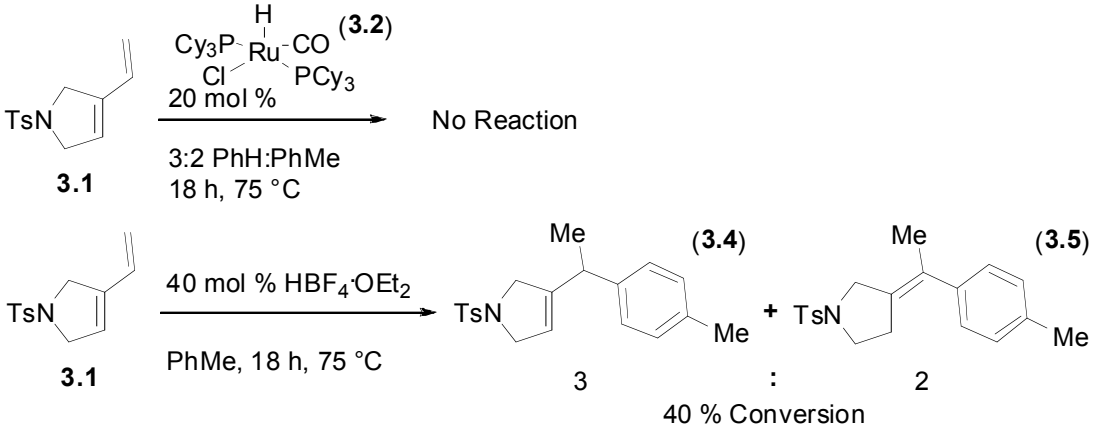


Scheme 3.1 - Observation of hydroarylation byproducts

Control reactions (Scheme 3.2) indicated that complex **3.2** was catalytically irrelevant in this hydroarylation reaction. Diene **3.1** is recovered unchanged

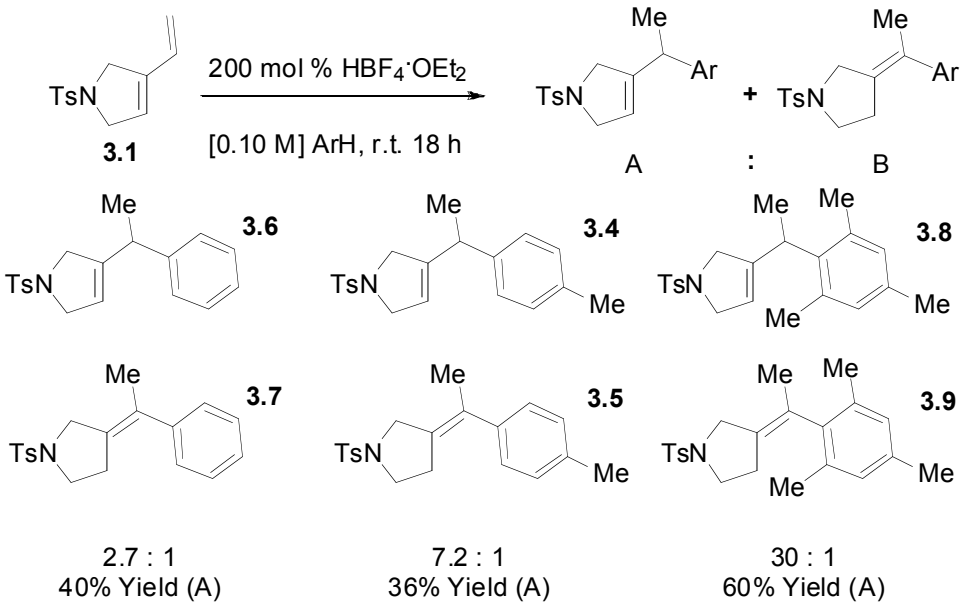
[85] *Q.v.* table 2.1, entry 4 (*supra*).

from the reaction in the absence of HBF_4. Furthermore, the reaction fails to turn over, producing no more than one catalyst equivalent of hydroarylation product.



Scheme 3.2 - Complex **3.2** is not a C-H activation catalyst

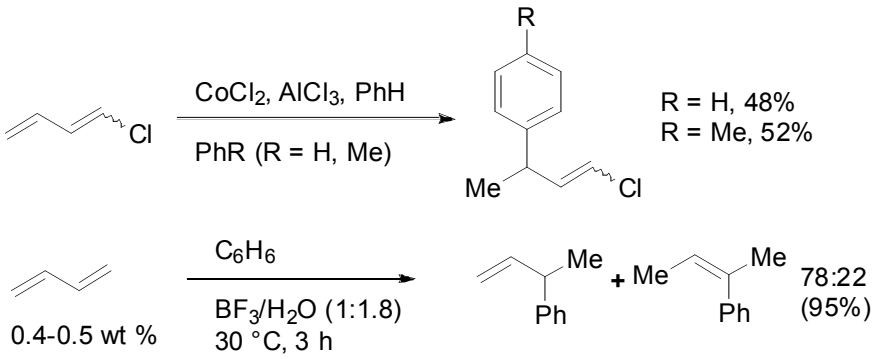
Increasing the amount of tetrafluoroboric acid used allows for the hydroarylation of **3.1** at ambient temperatures. With 200 mol % acid, hydroarylation with benzene, toluene, and mesitylene produces **3.6** (40% yield) and **3.7** (2.7:1), **3.4** (36%) and **3.5** (7.2:1), and **3.8** (60%) and **3.9** (30:1), respectively (Scheme 3.3).



Scheme 3.3 - Optimized Bronsted acid-catalyzed hydroarylation

This reaction has been previously reported for a very limited range of dienes. In 1975, a group of Soviet chemists reported that a cobalt bis-arene complex generated from cobalt (II) chloride, aluminium (III) chloride, and benzene promoted the hydroarylation of 1-chlorobutadiene with toluene or benzene in moderate yield.[86] In 1988, a Japanese group[87] reported that aqueous BF_3 promotes the hydroarylation of butadiene with benzene, producing an isomeric mixture in excellent yield (Scheme 3.4).

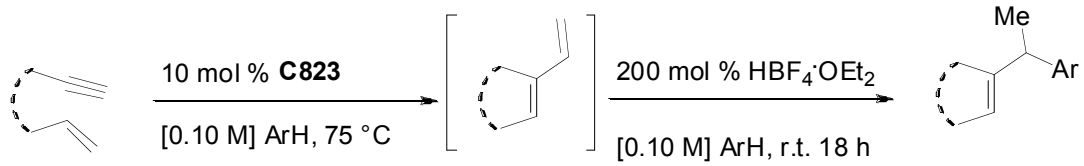
[86] G. T. Martirosyran, G. A. Chukhadzhyan, Zh. G. Gegelyan, A. A. Galechyan, *Arm. Khim. Zh.* **1975**, *28*, 343-344.
[87] H. Takai, Y. Okumura, C. Imai, (Jpn. Kokai Tokkyo Koho, Japan), *Boron trifluoride hydrate catalysts for manufacture of arylalkenes*, Japan patent 63057537, March 12, 1988.



Scheme 3.4 - Known diene hydroarylations

3.3 – One-pot enyne metathesis-hydroarylation

The optimized conditions for the acid-catalyzed hydroarylation of **3.1** were then adapted into a one-pot multicatalytic process with enyne metathesis, to allow more rapid assessment of the scope of dienes and arenes allowed by this reaction. Enyne metathesis with 10 mol % of Grubbs's first-generation catalyst will lead to quantitative formation of the intermediate 1,3-diene. Subsequent addition of 2 equivalents of tetrafluoroboric acid will then allow facile hydroarylation with the aromatic solvent.



Scheme 3.5 - Planned one-pot enyne metathesis-hydroarylation

The results of this one-pot transformation are illustrated in Table 3.1. Reactions with benzene had been sluggish and plagued by isomerization, so more electron-rich arenes such as toluene, *m*-xylene, and mesitylene were examined in this study. In all cases, substitution occurs at a single position in the aromatic ring.

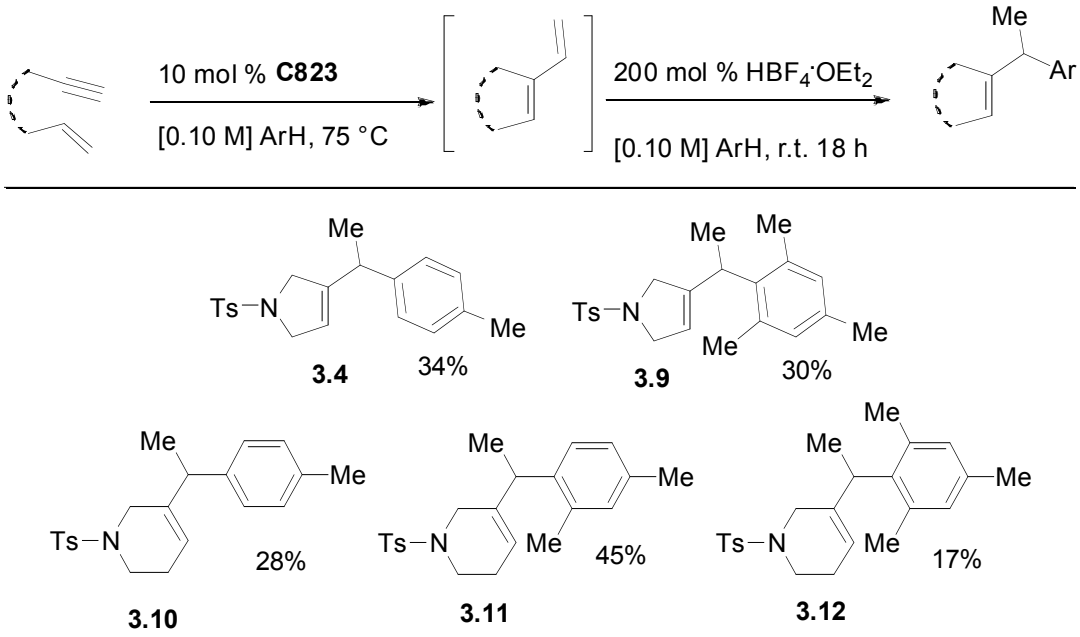
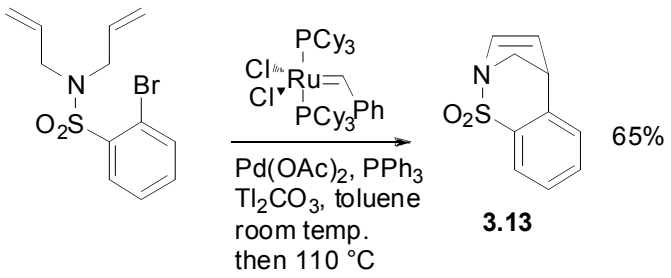


Table 3.1 - One-pot enyne metathesis-hydroarylation (yields unoptimized)

This one-pot enyne metathesis-hydroarylation is complementary to a reported "cascade" ring-closing metathesis-intramolecular Heck reaction that produces bridged, bicyclic compound **3.13** (equation 3.1).[88] This RCM-Heck

[88] R. Grigg, M. York *Tetrahedron Lett.* **2000**, *41*, 7255-7258 doi:10.1016/S0040-4039(00)01250-8.

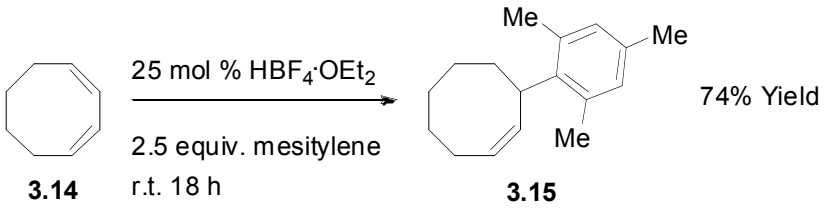
process is limited by several constraints. The reaction is only productive on intramolecular substrates that form five-membered rings, the multicatalytic process was less efficient than the sequential reactions, the presence of ruthenium inhibited the Heck reaction, and phosphine-based Heck catalysts inhibited the metathesis. Ultimately, moderate yields were achieved by using a polymer-bound palladium catalyst that would only swell at elevated temperatures.



Equation 3.1 - One-pot, multicatalytic ring-closing metathesis-Heck reaction

3.4 – Lewis acid-catalyzed hydroarylation of dienes

While hydroarylation of dienes such as **3.1** requires superstoichiometric amounts of Bronsted acid catalyst, the same reaction with a hydrocarbon such as 1,3-cyclooctadiene (**3.14**) proceeds with only 25 mol % HBF_4 to produce hydroarylation product **3.15** in 74% yield (Scheme 3.6), but with substantial formation of the olefin-isomerized congener.



Scheme 3.6 - Optimized Bronsted acid-catalyzed hydroarylation

Since hydroarylation of 1,3-dienes has rarely been observed,[86-7] there are numerous reports of Lewis-acid catalyzed hydroarylation of simple olefins and alkynes,[81c] and Lewis acids have previously shown great utility in catalyzing hydroamination reactions of 1,3-dienes,[89] we sought to develop a more efficient and general catalyst for diene hydroarylation.

Initial screening of Lewis-acid catalysts showed that indium (III) chloride[90] and bismuth (III) triflate both resulted in formation of trace amounts of hydroarylation product at ambient temperature (Table 3.1, entries 1-2).

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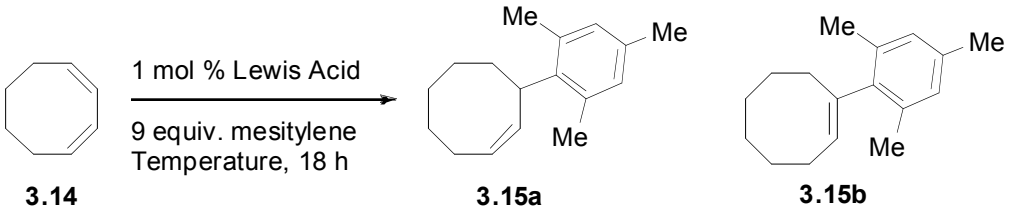
[89] a) H. Wei, G. Quian, Y. Xia, K. Li, Y. Li, W. Li *Eur. J. Org. Chem.* **2007**, *27*, 4471-4474 doi:10.1002/ejoc.200700483. b) J. Michaux, V. Terrasson, S. Marque, J. Wehbe, D. Prim, J.-M. Campagne *Eur. J. Org. Chem.* **2007**, *27*, 2601-2603 doi:10.1002/ejoc.200700023. c) H. Qin, N. Yamagiwa, S. Matsunaga, M. Shibasaki *J. Am. Chem. Soc.* **2006**, *128*, 1611-1614 doi:10.1021/ja056112d. Bronsted acids such as triflic acid also promote similar transformations d) Z. Li, J. Zhang. C. Brouwer, C.-G. Yang, N. W. Reich, C. He *Org. Lett.* **2006**, *8*, 4175-4178 doi:10.1021/ol0610035. e) D. C. Rosenfeld, S. Shekhar, A., Takemiya, M. Utsunomiya, J. F. Hartwig *Org. Lett.* **2006**, *8*, 4179-4182 doi:10.1021/ol061174+. Indium (III) triflate also promotes a thiol-ene reaction of camphene M. Weïwer, X. Chaminade, J. C. Bayón, E. Duñach *Eur. J. Org. Chem.* **2006**, *26*, 2464-2469 doi:10.1002/ejoc.200601112.

[90] Indium (III) Chloride has seen increased use as a mild catalyst for Friedel-Crafts reactions: a) M. J. Earle, U. Hakala, C. Hardacre, J. Karkkainen, B. J. McAuley, D. W. Rooney, K. R. Seddon, J. M. Thompson, K. Wähälä *Chem. Commun.* **2005**, 903-905 doi:10.1039/b413132k. b) K. K. Chauhan, J. P. Hartley, M. Krakowski, C. G. Frost *Lett. Org. Chem.* **2006**, *3*, 228-230. c) R. Hayashi, G. R. Cook *Org. Lett.* **2007**, 9 1311-1314 doi:10.1021/ol070235g.



3.14 **3.15a** **3.15b**

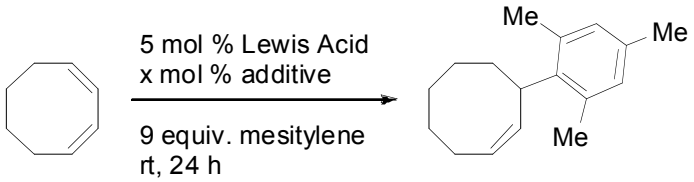
Table 3.1 – Initial Lewis acid screen

Entry	Catalyst	Temperature (°C)	Conversion (%)	Ratio (A:B)
1	$Bi(OTf)_3$	23	<5	1:0
2	$InCl_3$	23	<5	1:0
3	$Bi(OTf)_3$	75	>99	1:3
4	$InCl_3$	75	8	1:0

At 75 °C, however, use of the bismuth catalyst resulted primarily in formation of the isomerized product (entry 3), while $InCl_3$ led to slower, but more selective formation of **3.15a** (entry 4).

Addition of increasing amounts of silver (I) triflate[91] or tetrafluoroborate led to a more rapid reaction without undesired isomerization activity (Table 3.2), with the most efficient catalyst being a 1:3 mixture of $InCl_3$ and AgOTf (entry 6).

[91] Salts of silver with a variety of non-coordinating anions have been reported to accelerate Friedel-Crafts catalysis. a) T. Mukaiyama, T. Ohno, T. Nishimura, S. Suda, S. Kobayashi *Chem. Lett*. **1991**, 1059-1062. b) T. Mukaiyama, K. Suzuki, J. S. Han, S. Kobayashi *Chem. Lett.* **1992**, 435-438. c) A. Kawada, S. Mitamura, S. Kobayashi *Chem. Commun*. **1996**, 183-184. d) C. J. Chapman, C. G. Frost, J. P. Hartley, A. J. Whittle *Tetrahedron Lett.* **2001**, *42*, 773-775. e) C. G. Frost, J. P. Hartley, D. Griffin *Tetrahedron Lett.* **2002**, *43*, 4789-4791.

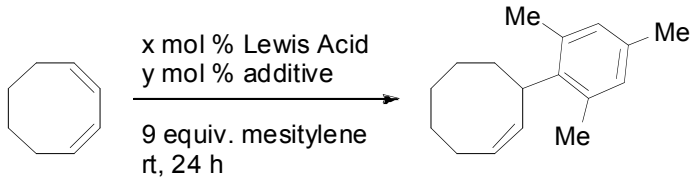


3.14 **3.15**

Table 3.2 – Acceleration of reaction by addition of silver salts

Entry	Lewis Acid	Silver Salt	Yield
1	$InCl_3$	5 mol % $AgBF_4$	NR
2	$InCl_3$	10 mol % $AgBF_4$	>5%
3	$InCl_3$	15 mol % $AgBF_4$	26%
4	$InCl_3$	5 mol % AgOTf	13%
5	$InCl_3$	10 mol % AgOTf	39%
6	$InCl_3$	15 mol % AgOTf	65%

Curiously, $In(OTf)_3$ is not an effective catalyst for this process. Indeed, of all the possible permutations of indium, silver, chloride, and triflate, the only effective catalyst at ambient temperature remained the mixture of $InCl_3$ and AgOTf (Table 3.3). Indium (III) chloride or indium (III) triflate alone (entries 1 and 3, respectively) failed to promote this reaction. Indium (III) triflate in the presence of 30 mol % silver (I) chloride, the expected product of a reaction between indium (III) chloride and silver (I) triflate, did not promote this reaction (Entry 4). Silver (I) triflate alone, a possible source of triflic acid in the presence of adventitious water, did not promote this reaction (Entry 5). Finally, a mixture of indium (III) chloride and indium (III) triflate was also not an effective catalyst for this reaction (Entry 6).

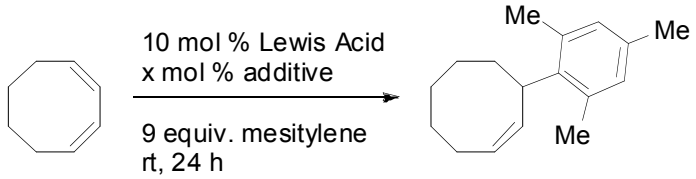


3.14 **3.15**

Table 3.3 – Determining the role of silver triflate

Entry	Lewis Acid (mol %)	Additive (mol %)	Yield
1	$InCl_3$ (10)	---	NR
2	$InCl_3$ (10)	AgOTf (30)	92% (GC)
3	$In(OTf)_3$ (10)	---	NR
4	$In(OTf)_3$ (10)	AgCl (30)	NR
5	---	AgOTf (30)	NR
6	$InCl_3$ (10)	$In(OTf)_3$ (10)	NR

To further rule out the possibility of a reaction catalyzed by triflic acid formed in the presence of adventitious water, possibly from the indium, the reaction was examined in the presence of a number of metal triflates (Table 3.4).



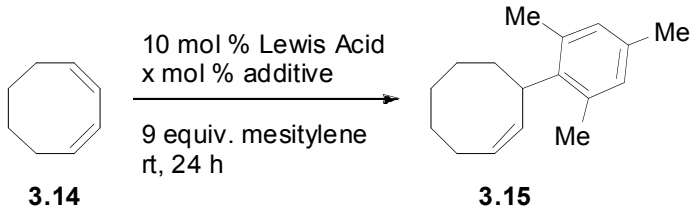
3.14 **3.15**

Table 3.4 – Ruling out adventitious water

Entry	Lewis Acid	Additive	Conversion
1	$InCl_3$	30 mol % AgOTf	96%
2	$InCl_3$	30 mol % CuOTf	0%
3	$InCl_3$	10 mol % $Sc(OTf)_3$	0%
4	$InCl_3$	15 mol % $Zn(OTf)_2$	0%
5	$InCl_3$	10 mol % $Yb(OTf)_3$	0%
6	$InCl_3$	10 mol % $In(OTf)_3$	0%
7	$InCl_3$	30 mol % $LiClO_4$	0%
8	$InCl_3$	30 mol % KPF_6	0%
9	$InCl_3$	30 mol % $NaBF_4$	0%

As shown in entries 2-8, no other metal triflates, perchlorates, hexafluorophosphates, or tetrafluoroborates promote this reaction in the presence of indium (III) chloride. Furthermore, silver (I) triflate from multiple different suppliers (Strem, Aldrich, and Fluka) promoted the reaction with similar efficiency. Similarly, the addition of 10 mol % triethylsilane failed to inhibit this reaction.

To further probe the factors affecting the reactivity of this system, a number of other silver (I) salts were examined (Table 3.5).



3.14 **3.15**

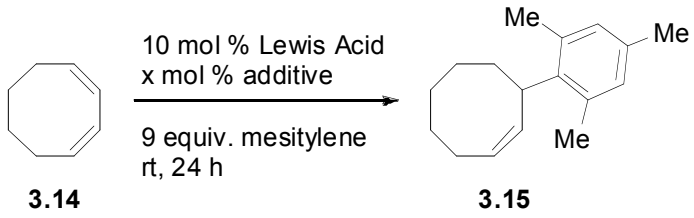
Table 3.5 – Examination of other silver (I) salts

Entry	Lewis Acid	Additive	Yield (GC)
1	$InCl_3$	30 mol % AgOTf	96%
2	$InCl_3$	30 mol % AgOBz	0%
3	$InCl_3$	30 mol % AgF	0%
4	$InCl_3$	30 mol % $AgBF_4$	93%
5	$InCl_3$	30 mol % $AgSbF_6$	58%
6	$InCl_3$	30 mol % $AgClO_4$	98%
7	$InCl_3$	30 mol % AgCl	0%

As shown previously, silver (I) triflate effectively promotes this reaction, producing **3.15** in 96% yield by GC (entry 1). Neither silver benzoate (entry 2) nor silver (I) fluoride (entry 3) promote this reaction. Silver (I) tetrafluoroborate

(entry 4), hexafluoroantimonate (entry 5), and perchlorate (entry 6), however, are all effective additives for this reaction, producing **3.15** in 93%, 58%, and 98% yields, respectively. Finally, silver (I) chloride does not promote this reaction. From these data it can be concluded that the indium (III) chloride-catalyzed hydroarylation of 1,3-dienes is only accelerated by silver salts with non-coordinating anions.

After finding the optimal additive to accelerate this reaction, a number of other Lewis acids were reexamined in the newly optimized reaction (Table 3.6).



3.14 **3.15**

Table 3.6 – Reexamination of Lewis acid catalysts

Entry	Lewis Acid	Additive	GC Yield
1	$InCl_3$	30 mol % $AgClO_4$	98%
2	$AlCl_3$	30 mol % $AgClO_4$	91% *
3	$GaCl_3$	30 mol % $AgClO_4$	79% *
4	$BF_3{\cdot}OEt_2$	30 mol % $AgClO_4$	65%
5	$FeCl_3$	30 mol % $AgClO_4$	85% *
6	$Bi(OTf)_3$	30 mol % AgOTf	>99% *
7	30 mol % HCl	30 mol % $AgClO_4$	23%
8	30 mol % HCl	---	NR
*substantial isomerization of product observed by GC			

While a myriad of other acids promote this reaction, most other Lewis acids result in significant isomerization fo **3.15a** to **3.15b**, with the exception of boron

trifluoride etherate (65% yield, entry 4). Notably, dry HCl in dioxane is a much less effective catalyst than indium (III) chloride (entry 7), and in the absence of silver (I) perchlorate, does not promote product formation, seemingly ruling out simple Bronsted-acid catalysis as the operative mechanism for this reaction.

To further elaborate the mechanistic possibilities of this reaction, all possible permutations of the reactants and catalysts were examined by NMR. The results of this study are summarized in Tables 3.7 and 3.8. First, there is no change in the NMR spectra when 1,3-cyclooctadiene is treated with a Lewis acid, nor the spectra of mesitylene when a cationic silver salt is added.

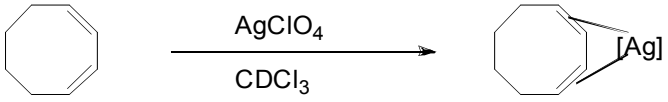


Table 3.7 – Cyclooctadiene and silver (I) perchlorate

^{1}H NMR		^{13}C NMR	
(cod)	(cod) + Ag^{+}	(cod)	(cod) + Ag^{+}
5.81	5.87	131.4	131.3
5.65-5.59	5.70-5.64	126.1	125.6
2.18	2.21	28.3	28.4
1.52-1.50	1.53-1.51	23.4	23.4

In the presence of silver (I) perchlorate, the ^{1}H NMR of 1,3-cyclooctadiene is noticeably shifted, with the olefin C-H resonances shifted downfield by 0.05 to 0.06 ppm and the allylic resonances shifted 0.03 ppm downfield, suggesting an interaction between the π-system and the metal. In the ^{13}C NMR, the sp^2 carbons

are similarly shifted. In the presence of aluminium (III) chloride, the ^{13}C NMR of mesitylene is desymmetrized (Table 3.8).

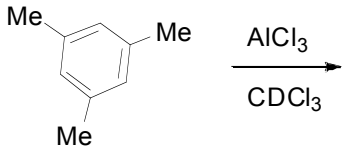


Table 3.8 – $AlCl_3$ and Mesitylene

^{13}C NMR	
mesitlyene	mixture
137.9	162.2
127.0	151.2
	133.6
21.4	24.1
	22.2

The compound formed by mixing silver (I) perchlorate and 1,3-cyclooctadiene was an amorphous white solid, eluding elucidation of the structure by x-ray crystallography. Similarly, reaction of mesitylene with aluminum (III) chloride produces a red oil. When the (cod)$AgClO_4$ compound (**3.16**) is dissolved in mesitylene and nitromethane, however, translucent crystals slowly precipitate from the solution.

Single-crystal x-ray diffraction indicates that a coordination polymer of mesitylene and silver (I) perchlorate is formed (Figure 3.1). Notably, the carbon-carbon bond lengths are unchanged,[92] and ^1H-NMR analysis of the solid

[92] Section 3.6 contains a complete listing of bond lengths and angles determined from the crystal structure of **3.16**.

indicates that the chemical shifts of mesitylene are unshifted. Similar charge-transfer complexes of aromatic hydrocarbons have been reported, but not characterized by x-ray crystallography.[93] Formation of a coordination polymer of silver (I) perchlorate with *trans*,*trans*-1,4-diphenyl-1,3-butadiene, in which the silver atom appears to interact with a single carbon from aromatic rings of separate molecules, has previously been reported.[94]

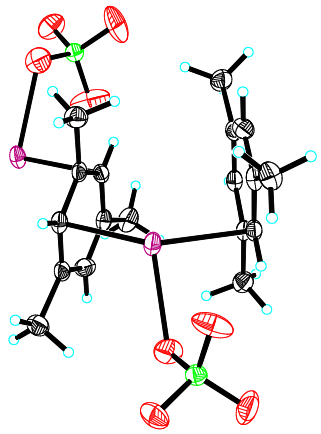
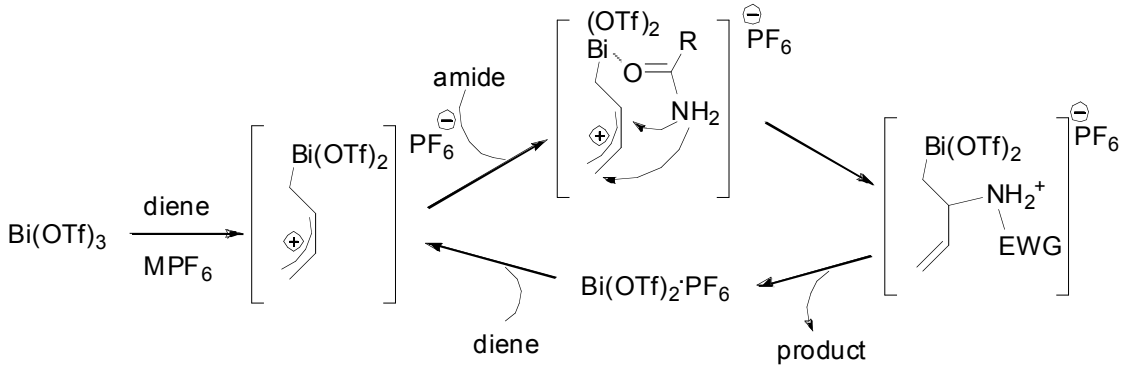


Figure 3.1 – ORTEP of complex **3.16**

While complex **3.16** is certainly interesting, and its formation unexpected, it adds no insight to the mechanism of the hydroarylation reaction. Shibasaki[95] proposed a reasonable mechanism for the activation of 1,3-dienes by bismuth (III) triflate for a hydroamination reaction. This mechanism is illustrated in

[93] B. G. Torre-Mori, D. Janjic, B. P Susz *Helv. Chim. Acta* **1964**, *128*, 1172-1181.
[94] J. C. Zhoing, M. Munakata, M. Maekawa, T. Kuroda-Sowa, Y. Suenaga, H. Konaka *Inorg. Chim. Acta* **2003**, *342*, 202-208.
[95] *Q.v.* ref. 88c (*supra*)

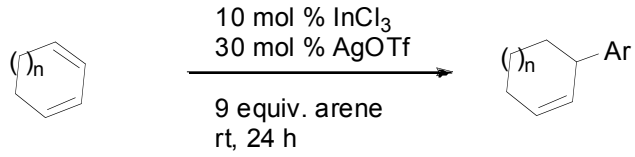
scheme 3.7. Notably, this mechanism accounts for the acceleration of the reaction by addition of an exogenous non-coordinating anion, in this case $Cu(CH_3CN)_4PF_6$. Shibasaki's hypothesis is that the addition of the non-coordinating anion frees a coordination site on the Lewis acid, facilitating interaction with the reaction partner, and thus accelerating the bond-forming event. While activation of the diene-Lewis acid complex may be occurring during the hydroarylation reaction, pre-coordination of the arene prior to bond-forming cannot be either substantiated or ruled out.

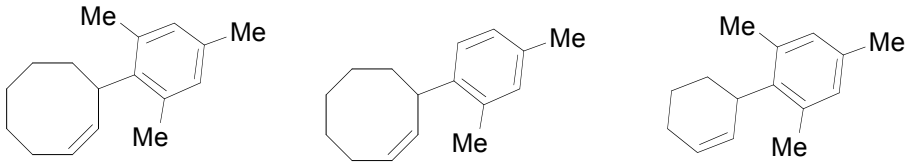


Scheme 3.7 - Shibasaki's proposed hydroamination mechanism

The optimized conditions were then applied to a number of 1,3-dienes and electron-rich aromatic compounds (Table 3.9). Notably, diene **3.1** is unreactive in the Lewis acid-catalyzed system. More electron-rich arenes, such

as anisole, rapidly form di- and tri-substituted adducts, and simple olefins such as 1-octene and neohexene form intractable isomeric mixtures.

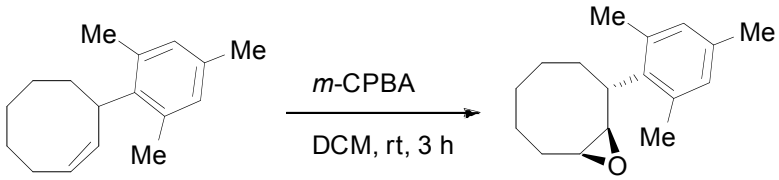




3.15 (65%) **3.17** (60%) **3.18** (44%)

Table 3.9 - Optimized Lewis acid-catalyzed hydroarylation

Part of the impetus for developing a Lewis acid-catalyzed process was to examine the possibility of asymmetric catalysis in this system. Unfortunately, the racemate **3.15** was not readily separated with any chromatographic techniques at our disposal. Epoxidation (Scheme 3.10) of **3.15** produces a single diasteromer of compound **3.19**, which is, unfortunately, also not amenable to chiral chromatography.



3.15 **3.19** (quant. >20:1 dr)

Scheme 3.10 - Epoxidation of hydroarylation product

3.5 – Conclusion

Treatment of 1,3-dienes with Bronsted or Lewis acids in aromatic solvents results in selective and efficient hydroarylation. Using tetrafluoroboric acid, this process may be run in tandem with enyne metathesis. When catalyzed by a mixture of indium (III) chloride and silver perchlorate, isomeric impurities are minimized.

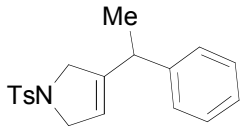
3.6 – Experimental Details

General procedure for acid-catalyzed hydroarylation

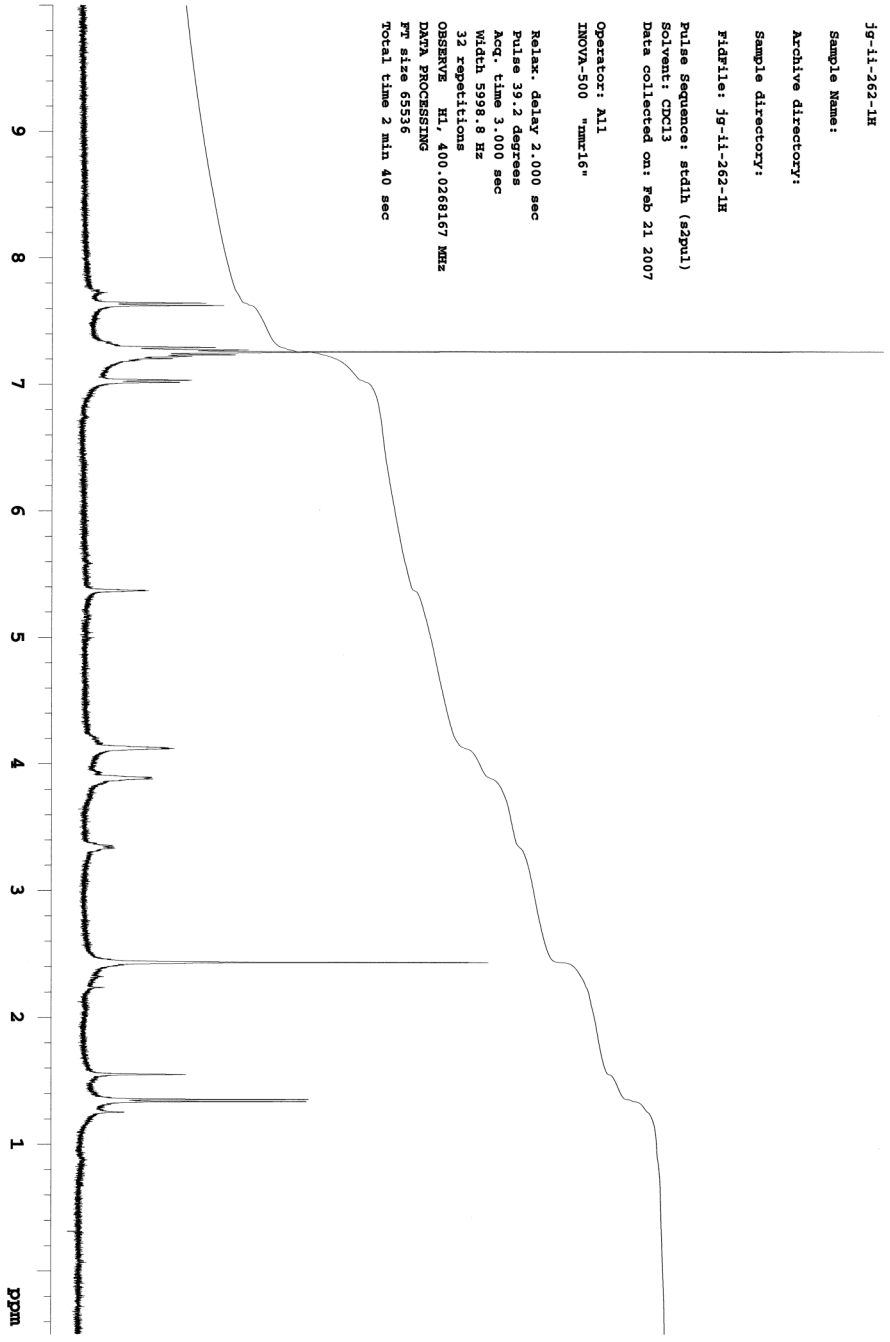
To a flame-dried one-dram vial charged with a magnetic stirbar were added sequentially a 1,3-diene (0.10 M stock solution in aromatic solvent) and tetrafluoroboric acid (2 equiv.) or a Lewis acid (10 mol %) and silver salt (30 mol %). The reaction mixture was allowed to stir at ambient temperature for 18-24 h under nitrogen, and then quenched with an equal volume of saturated, aqueous sodium bicarbonate. The aqueous layer was extracted three times with toluene, and the combined organic fractions dried over sodium sulfate, filtered, and concentrated *in vacuo*.

General procedure for one-pot enyne metathesis-hydroarylation

To a flame-dried one-dram vial charged with a magnetic stirbar were added sequentially an enyne (1 mL, 0.10 M stock solution in an aromatic solvent) and Grubbs's first-generation catalyst (8 mg, 10 μmol, 10 mol %). The solution was briefly sparged with ethylene, and then the reaction mixture was heated to 75 °C for 30 min. The reaction mixture was allowed to return to ambient temperature, and then tetrafluoroboric acid (30 μL, 0.20 mmol 2 equiv.) was added, and the reaction mixture was allowed to stir for 18 h at ambient temperature, and then worked up as above.



3-(1-phenylethyl)-1-tosyl-2,5-dihydro-1H-pyrrole (3.6) was purified by column chromatography on silica gel with hexanes / ethyl acetate (9:1) as the eluent. Due to extensive isomerization of the double bond, the yield (40%) of **3.6a** is adjusted for the presence of **3.6b** as determined by GC/MS, which prevented full characterization. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.63 (d, *J* = 8.4 Hz, 2H), 7.29-7.20 (m, 5 H), 7.03 (d, *J* = 6.4 Hz, 2H), 5.37 (m, 1H), 4.12 (m, 2H), 3.89 (m, 2H), 3.33 (m, 1H), 2.43 (s, 3H), 1.34 (d, *J* = 7.2 Hz, 3H); HRMS (ES+): calculated for formula $C_{19}H_{21}NO_2NaS^+$: *m/z* 350.1191, found 350.1182.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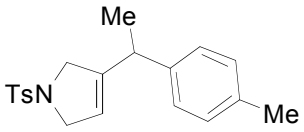
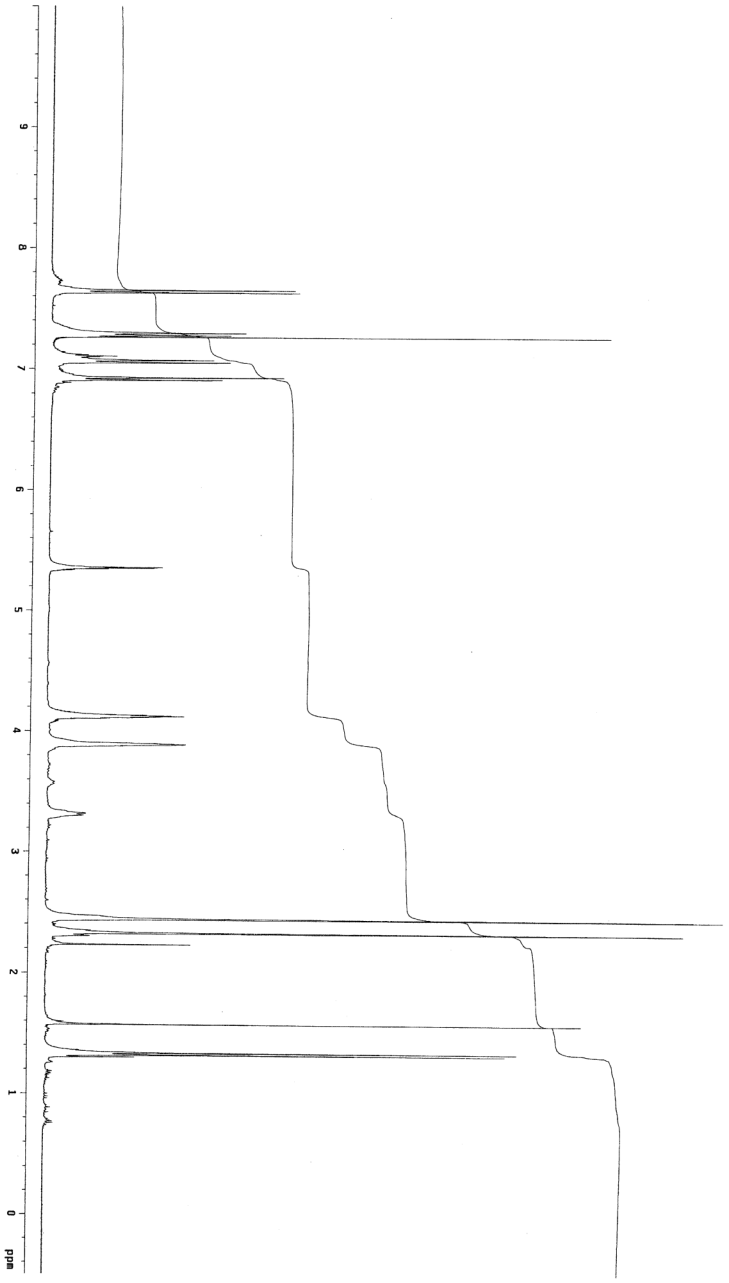


3-(1-(p-tolyl)ethyl)-1-tosyl-2,5-dihydro-1H-pyrrole (3.4) was purified by column chromatography on silica gel with hexanes / ethyl acetate (9:1) as the eluent, producing the named compound in 34% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 7.6 Hz, 2H) 7.06 (d, *J* = 8.0 Hz, 2 H), 6.92 (d, *J* = 7.6 Hz, 2H), 5.35 (s, 1H), 4.12 (s, 2H), 3.89 (s, 2H), 3.31 (m, 1H), 2.44 (s, 3H), 2.32 (s, 3H), 1.32 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (C_6D_6, 100.6 MHz) δ 143.9, 143.3, 140.3, 136.3, 129.8, 129.4, 127.5, 127.0, 118.7, 118.2, 56.1, 55.4, 39.4, 21.9, 21.4, 20.6; IR (NaCl, thin film): 3059 (w), 3028 (w), 2966 (w), 2926 (s), 2917 (m), 2907 (m), 1724 (m), 1460 (w) 1365 (m), 1344 (m), 1170 (s), 1103 (m), 1063 (m), 816 (m), 753 (m) 697 (s), 673 (s) cm^{-1}; HRMS (ES+): calculated for formula $C_{20}H_{23}NO_2NaS^+$: *m/z* 364.1347, found 364.1331.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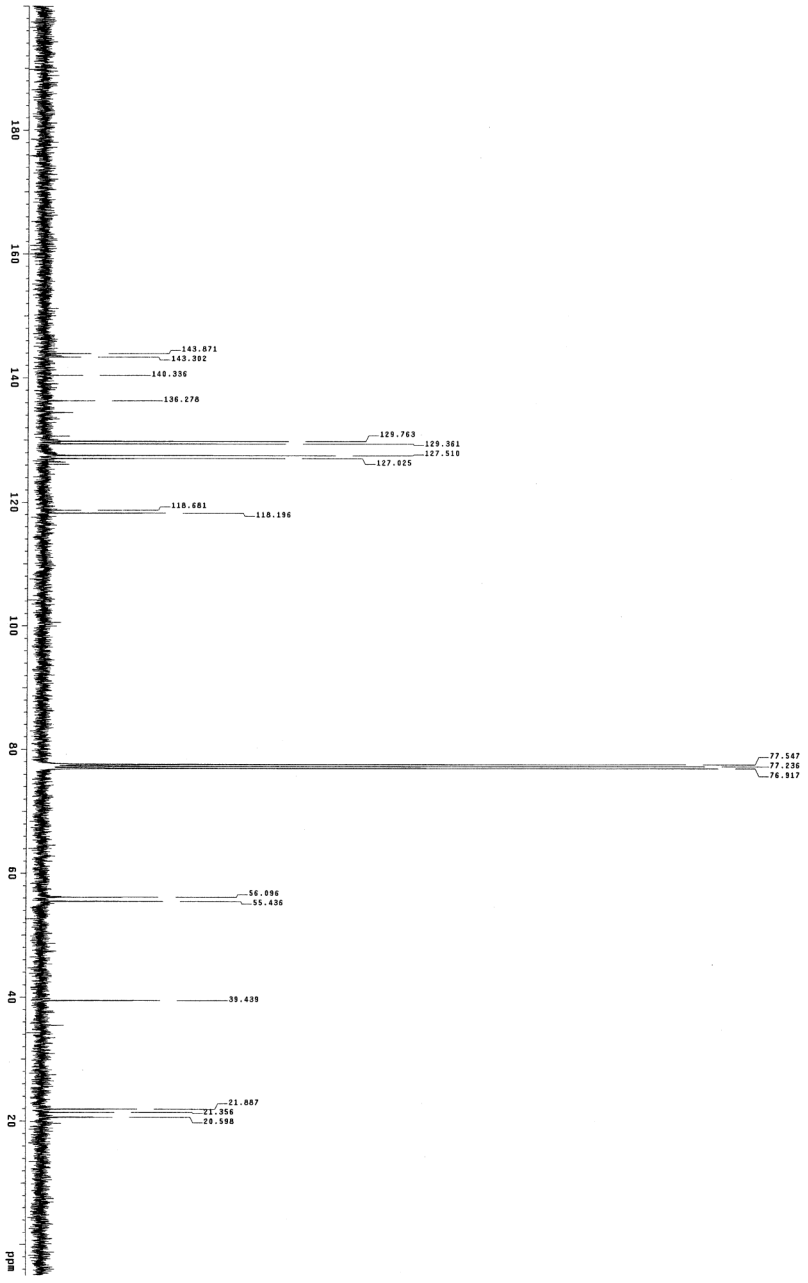
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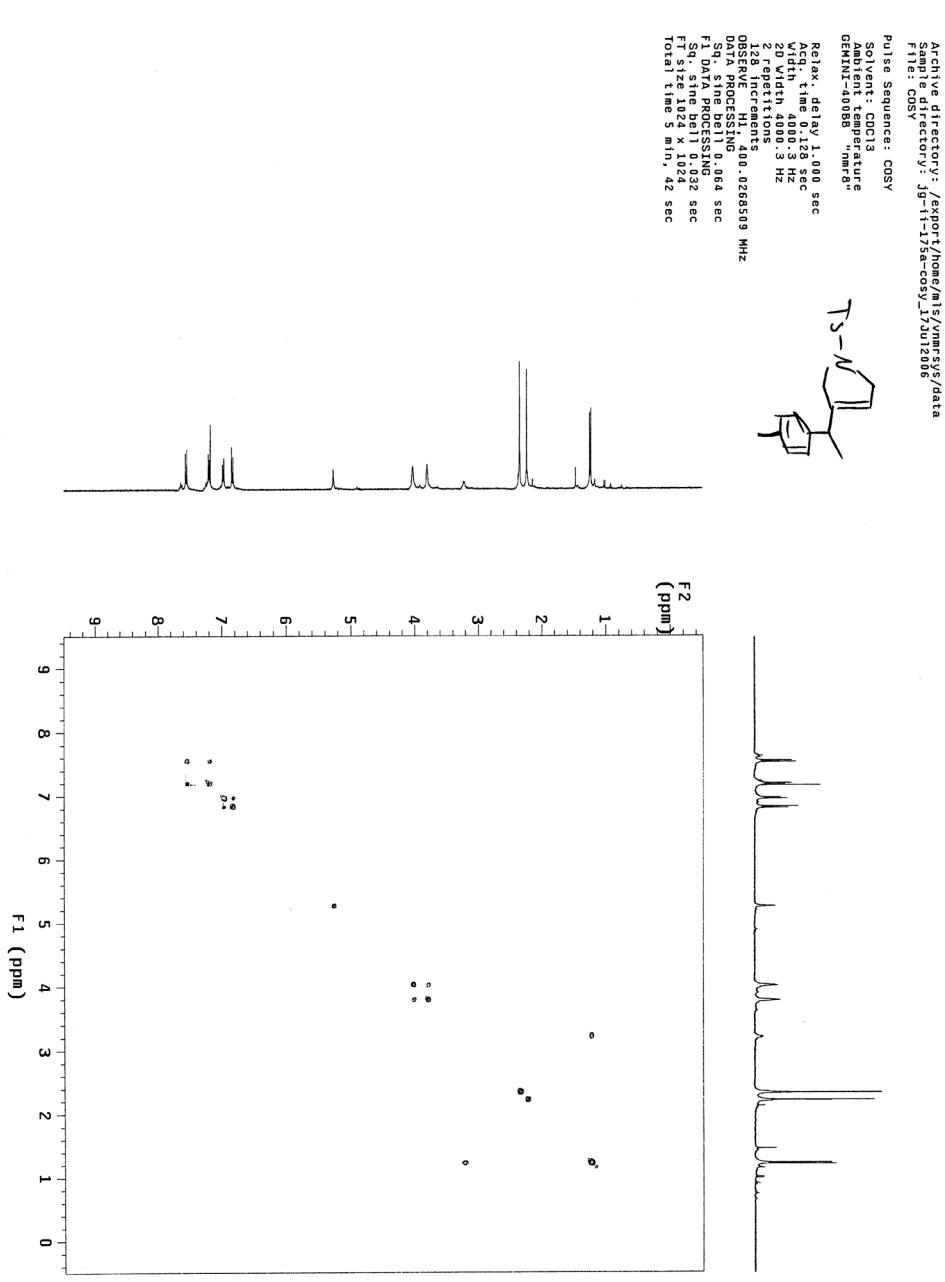
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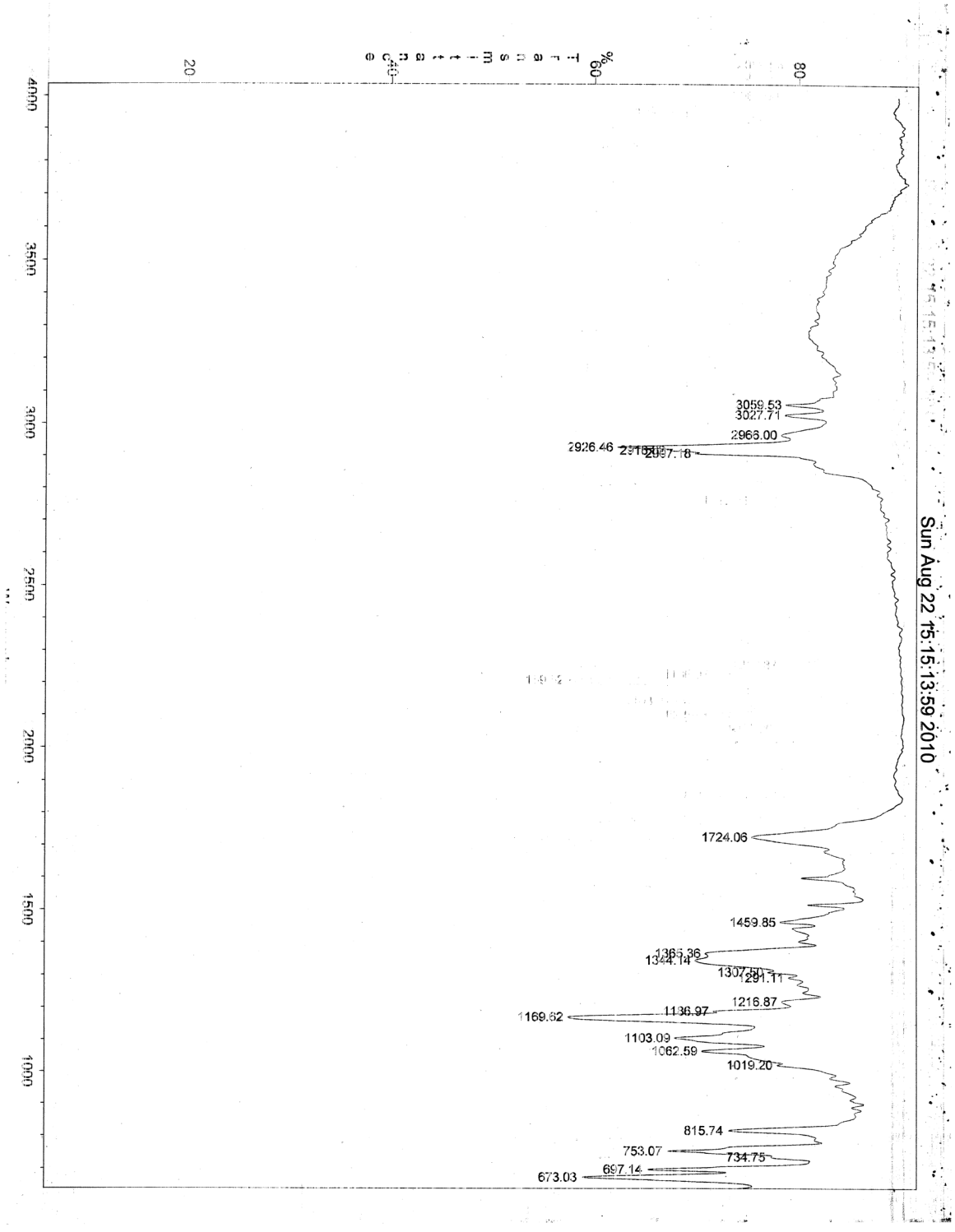
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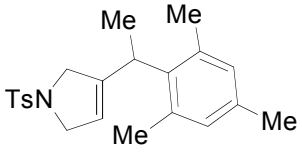
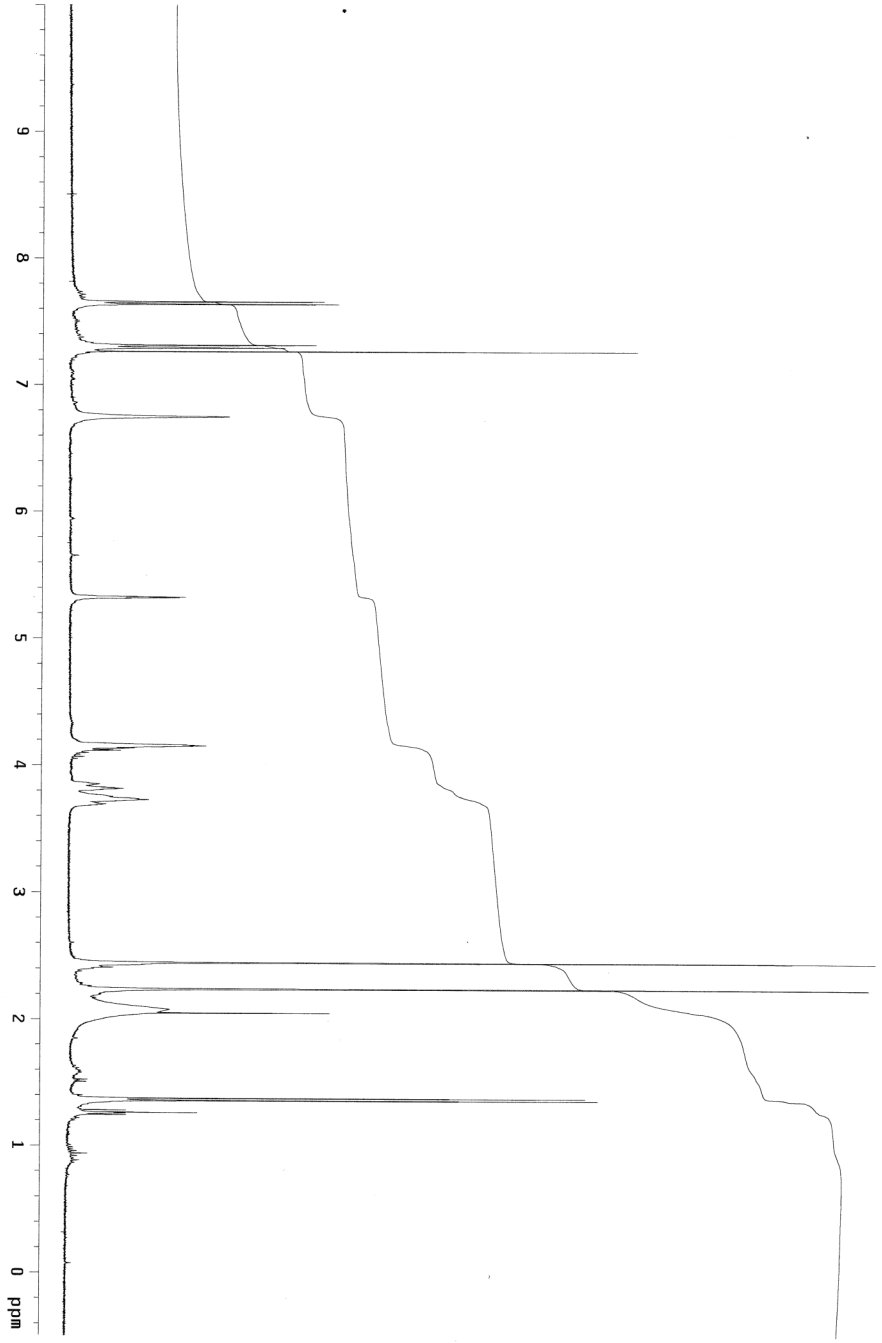


3-(1-mesitylethyl)-1-tosyl-2,5-dihydro-1H-pyrrole (3.9) was purified by column chromatography on silica gel with hexanes / ethyl acetate (9:1) as the eluent, producing the named compound in 30% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H) 6.74 (s, 2H), 5.32 (q, *J* = 2.0 Hz, 1H), 4.16 (m, 2H), 3.85-3.69 (br m, 3H), 2.46 (s, 3H), 2.24 (s, 3H), 2.08-2.05 (br s, 6H), 1.36 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (C_6D_6, 100.6 MHz) δ 143.6, 143.5, 136.3, 136.0, 135.9, 134.2, 130.3, 129.9, 127.6, 117.5, 117.4, 56.9, 55.6, 34.6, 21.8, 20.9, 20.6, 16.8; IR (NaCl, thin film): 3070 (w), 3039 (w), 2966 (w), 2929 (s), 2911 (m), 2865 (m), 2255 (w), 1724 (m), 1476 (m), 1460 (m), 1345 (s), 1164 (s), 1103 (s), 1054 (m), 815 (m), 732 (m) cm^{-1}; HRMS (ES+): calculated for formula $C_{20}H_{27}NO_2NaS^+$: *m/z* 392.1660, found 392.1649.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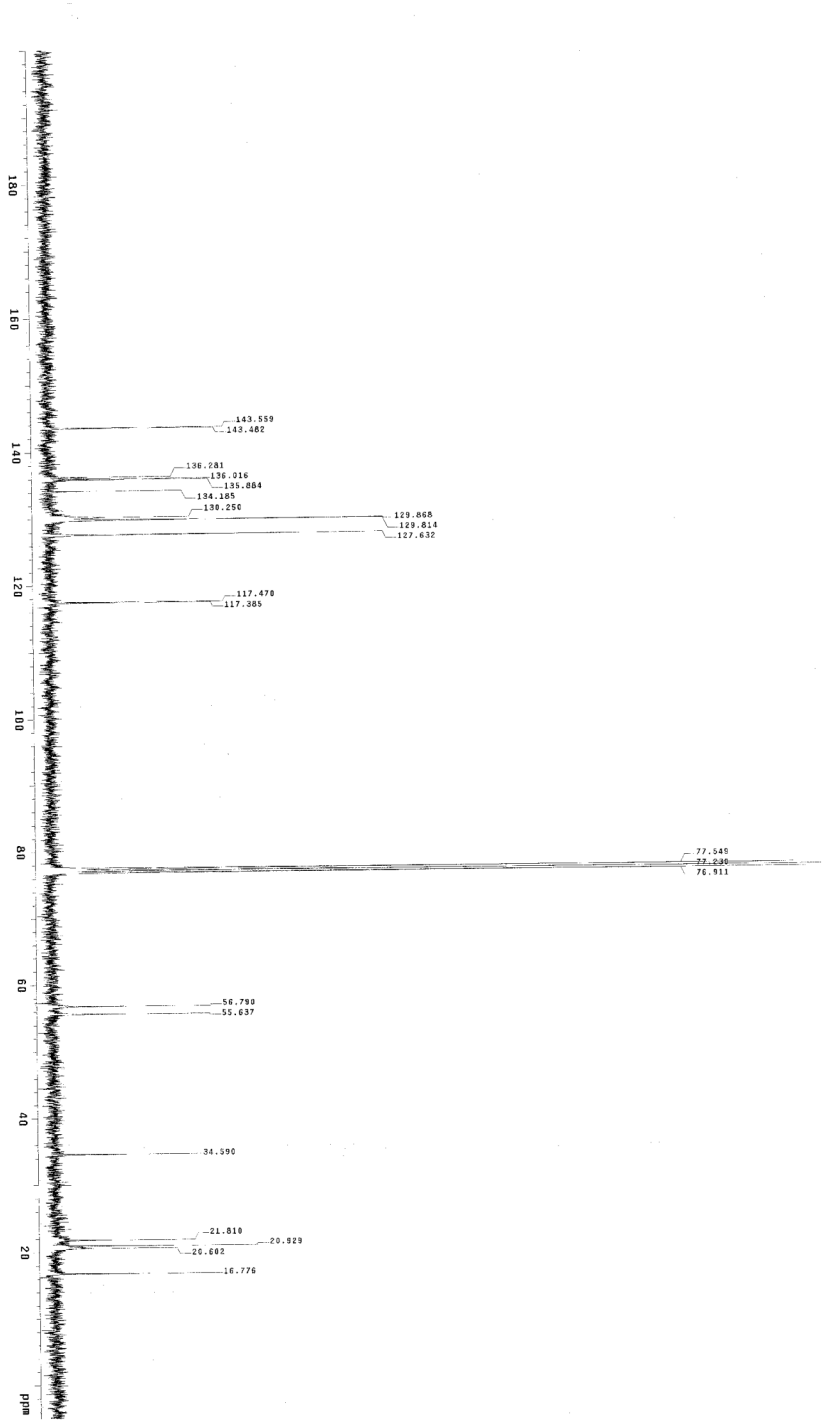
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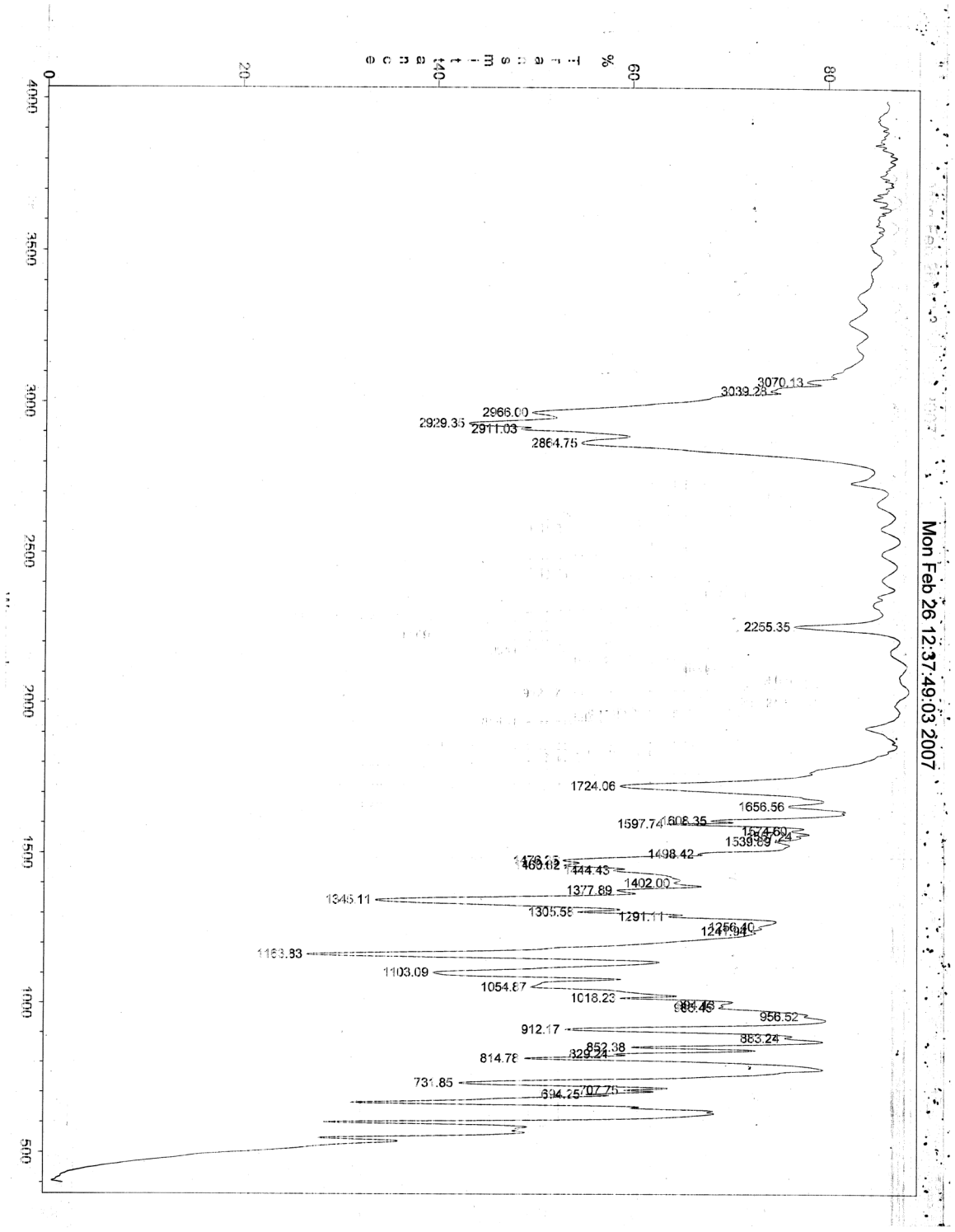
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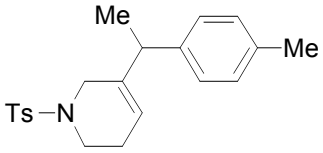
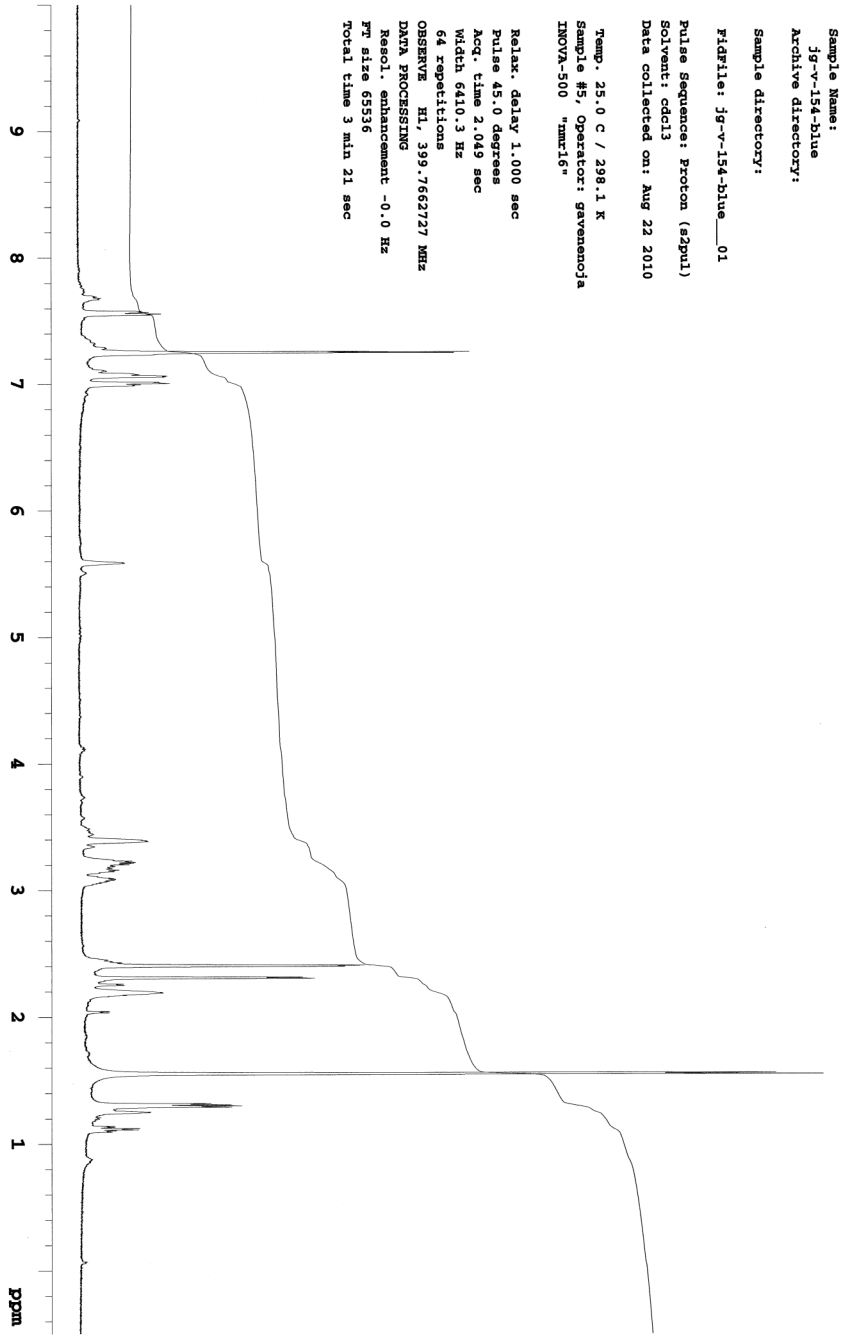


5-(1-(p-tolyl)ethyl)-1-tosyl-1,2,3,6-tetrahydropyridine (3.10) was purified by column chromatography on silica gel with hexanes / ethyl acetate (9:1) as the eluent, producing the named compound in 28% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.56 (m, 2H), 7.26 (m, 2H), 7.07 (m, 2H), 7.00 (m, 2H), 5.59 (s, 1H), 3.39 (br m, 2H), 3.23-3.15 (br m, 2H), 3.10-3.06 (br m, 2H), 2.42 (s, 3H), 2.31 (s, 3H), 2.20 (br m, 2H), 1.31 (d, J = 7.2 Hz, 3 H); ^{13}C NMR (C_6D_6, 100.6 MHz) δ 143.5, 141.3, 138.1, 136.1, 129.7, 129.4, 127.8, 127.4, 118.9, 46.7, 43.8, 42.9, 25.2, 21.7, 21.2, 20.2; IR (NaCl, thin film) 3081 (w), 3059 (m), 3027 (s), 3001 (w), 2962 (w), 2926 (m), 2897 (w), 2852 (w), 1493 (w) 1343 (m), 1164 (m), 1094 (w), 815 (w), 751 (w) cm^{-1}; HRMS (ES+): calculated for formula $C_{21}H_{26}NO_2S^+$: *m/z* 356.1684, found 356.1690.


jg-v-154-blue
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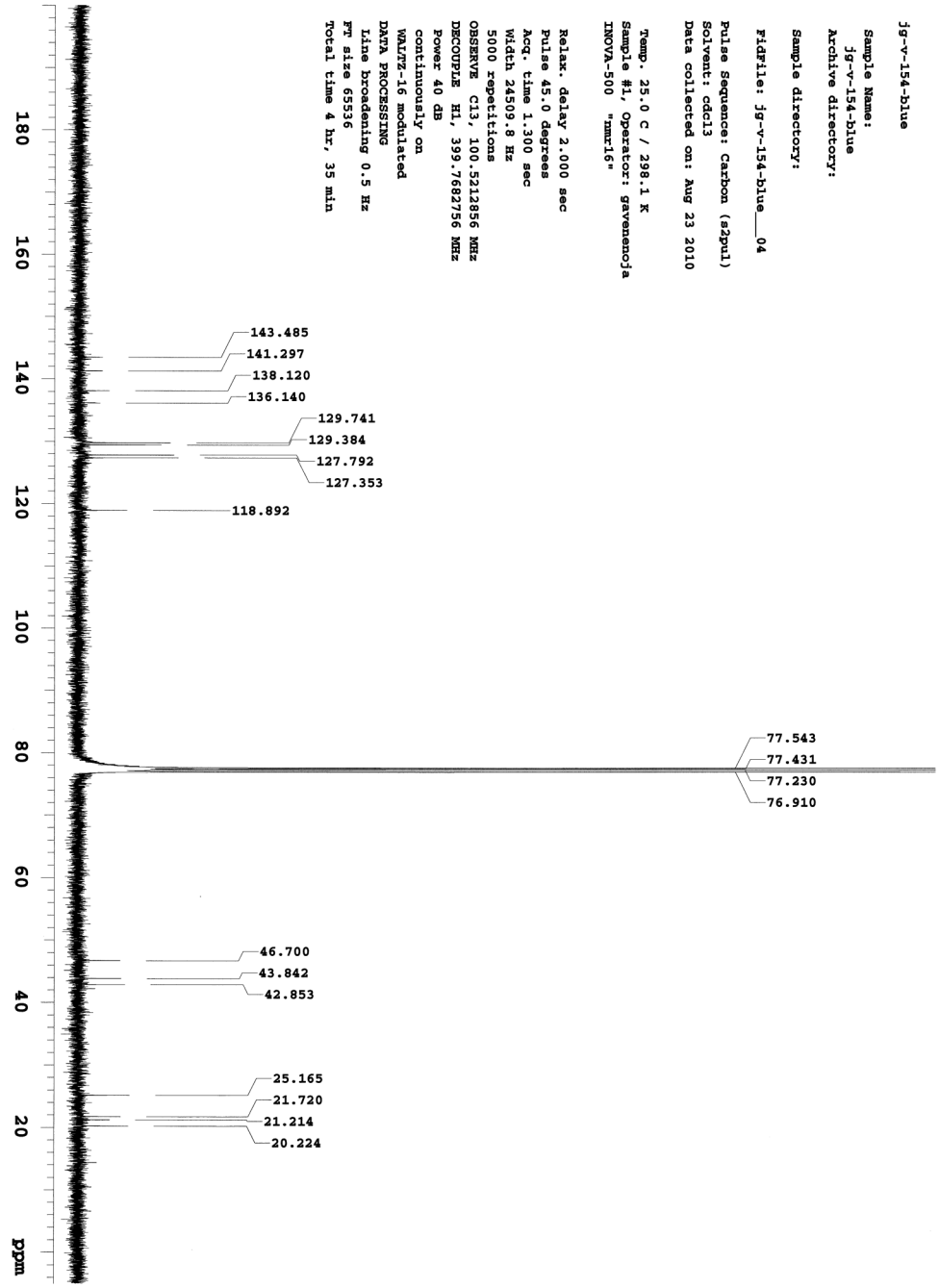
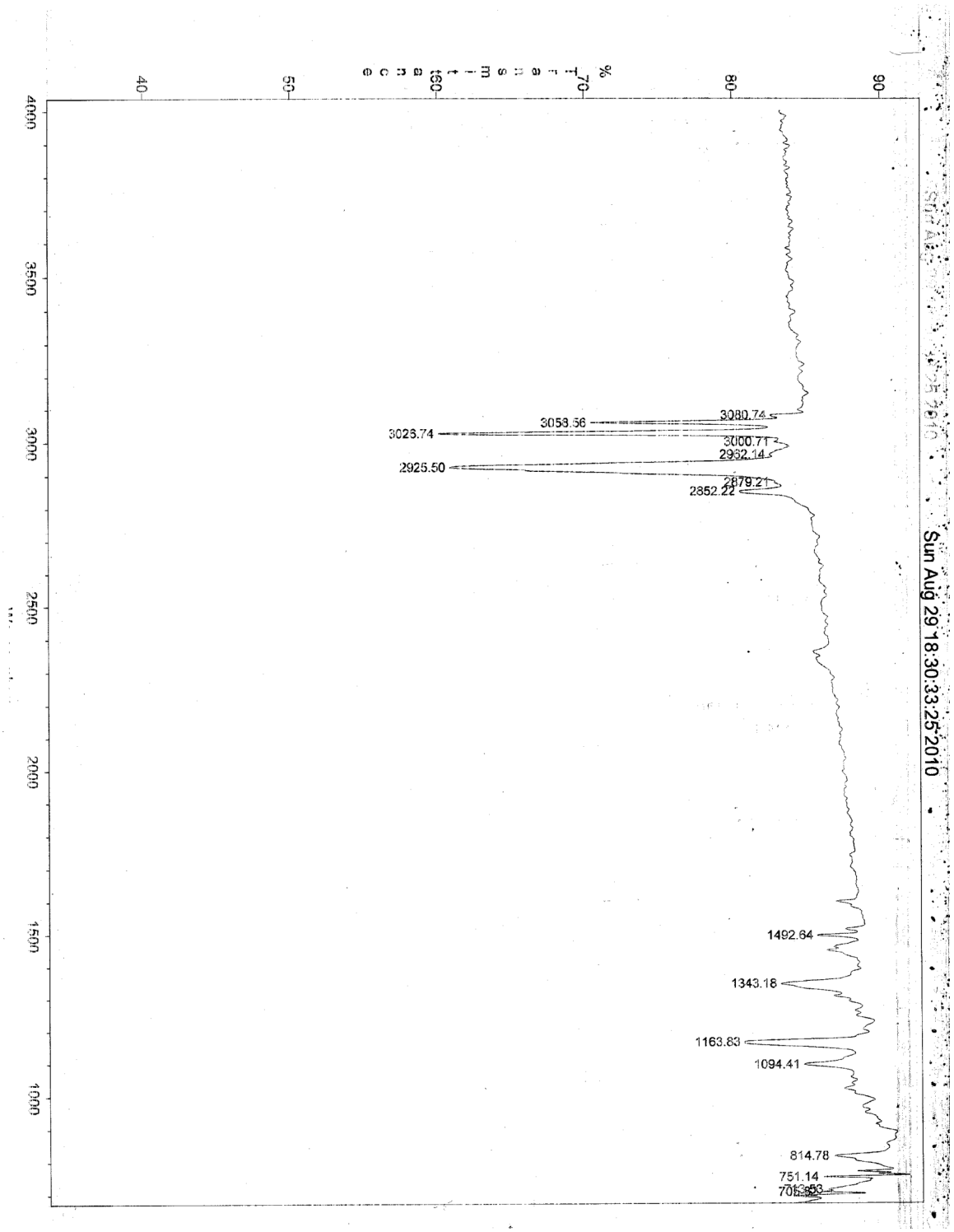
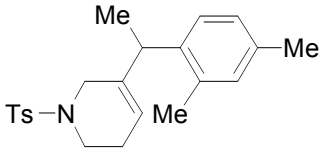
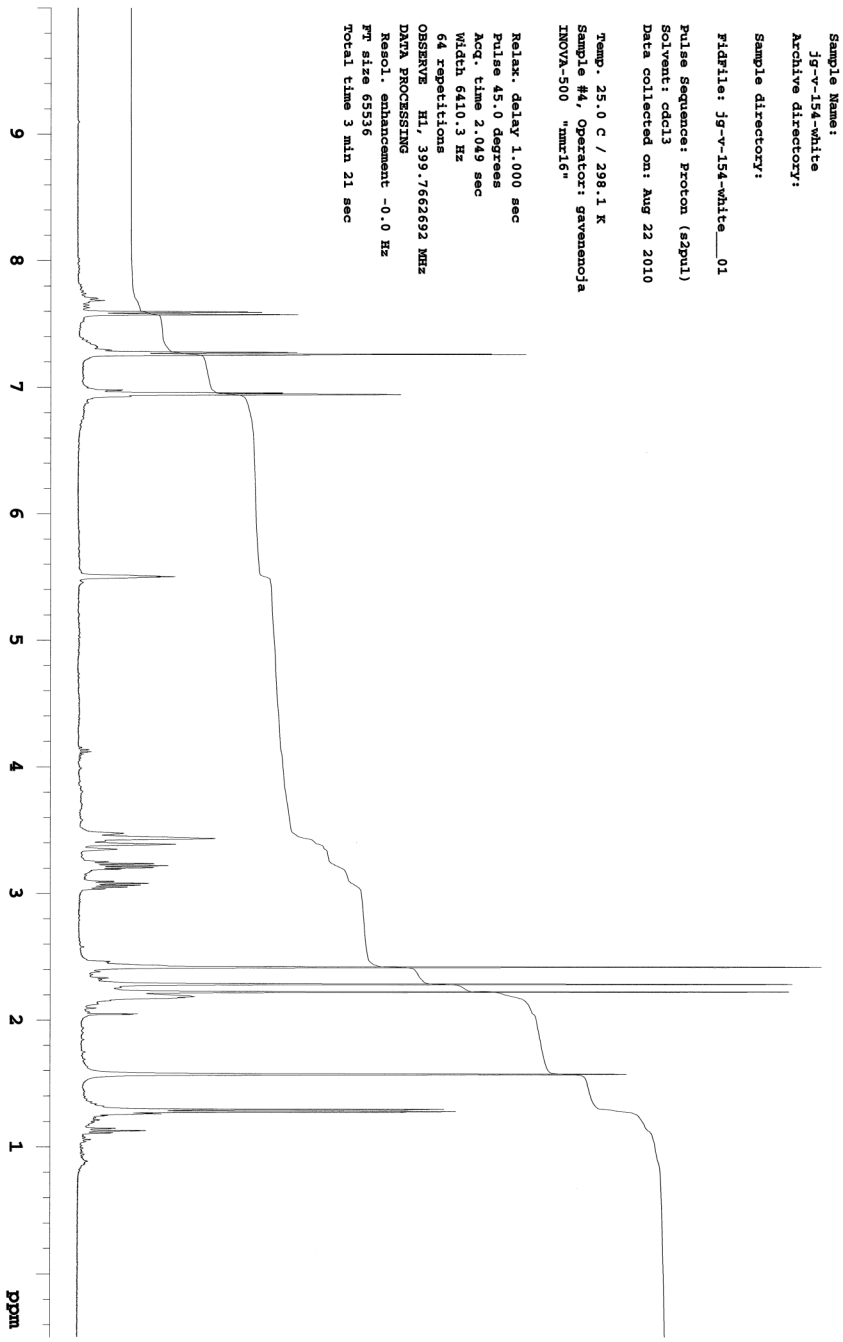
jg-v-154-blue
Archive directory:
Sample directory:
FidFile: jg-v-154-blue__01
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Aug 22 2010
Temp. 25.0 C / 298.1 K
Sample #5, Operator: gavenenoja
INOVA-500 "nmr16"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 6410.3 Hz
64 repetitions
OBSERVE H1, 399.7662727 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 3 min 21 sec
9
8
7
6
5
4
3
2
1
ppm


jg-v-154-blue
Sample Name:
jg-v-154-blue
Archive directory:
Sample directory:
FidFile: jg-v-154-blue___04
Pulse Sequence: Carbon (s2pul)
Solvent: cdcl3
Data collected on: Aug 23 2010
Temp. 25.0 C / 298.1 K
Sample #1, Operator: gavenenoja
INOVA-500 "nmr16"
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
5000 repetitions
OBSERVE C13, 100.5212856 MHz
DECOUPLE H1, 399.7682756 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 4 hr, 35 min
143.485
141.297
138.120
136.140
129.741
129.384
127.792
127.353
118.892
77.543
77.431
77.230
76.910
46.700
43.842
42.853
25.165
21.720
21.214
20.224
180
160
140
120
100
80
60
40
20
ppm


%
Transmittance
40
50
60
70
80
90
4000
3500
3000
2500
2000
1500
1000
3080.74
3058.56
3026.74
3000.71
2962.14
2925.50
2879.21
2852.22
1492.64
1343.18
1163.83
1094.41
814.78
751.14
Sun Aug 29 18:30:33 2010



5-(1-(2,4-dimethylphenyl)ethyl)-1-tosyl-1,2,3,6-tetrahydropyridine (3.11) was purified by column chromatography on silica gel with hexanes / ethyl acetate (9:1) as the eluent, producing the named compound in 45% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.59 (d, *J* = 8.0 Hz, 2H), 7.26 (m, 2H), 6.95 (m, 3H), 5.50 (m, 1H), 3.48-3.35 (m, 3H) 3.22 (m, 2H), 3.07 (m, 2H), 2.42 (s, 3H), 2.29 (s, 3H), 2.23 (s, 3H), 1.28 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (C_6D_6, 100.6 MHz) δ 143.5, 139.1, 137.9, 135.9, 135.8, 134.2, 131.5, 129.7, 127.8, 127.1, 126.3, 119.2, 46.9, 42.9, 39.5, 25.2, 21.7, 21.1, 19.7, 19.6; IR (NaCl, thin film) 3081 (w), 3059 (m), 3027 (m), 2932 (s), 2924 (s), 2849 (w), 1493 (w), 1162 (w), 705 (w) cm^{-1}; HRMS (ES+): calculated for formula $C_{22}H_{28}NO_2S^+$: *m/z* 370.1841, found 370.1846.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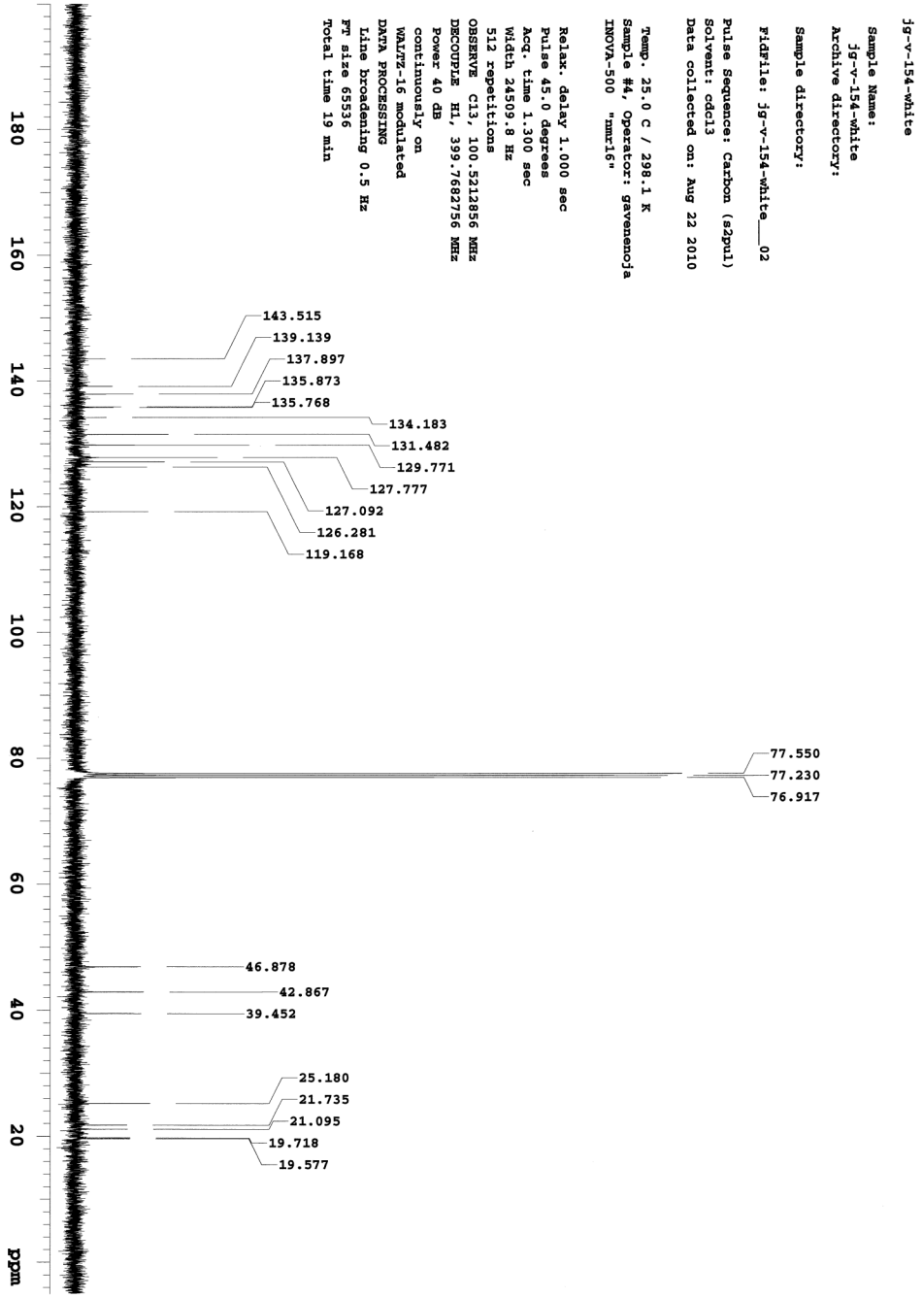
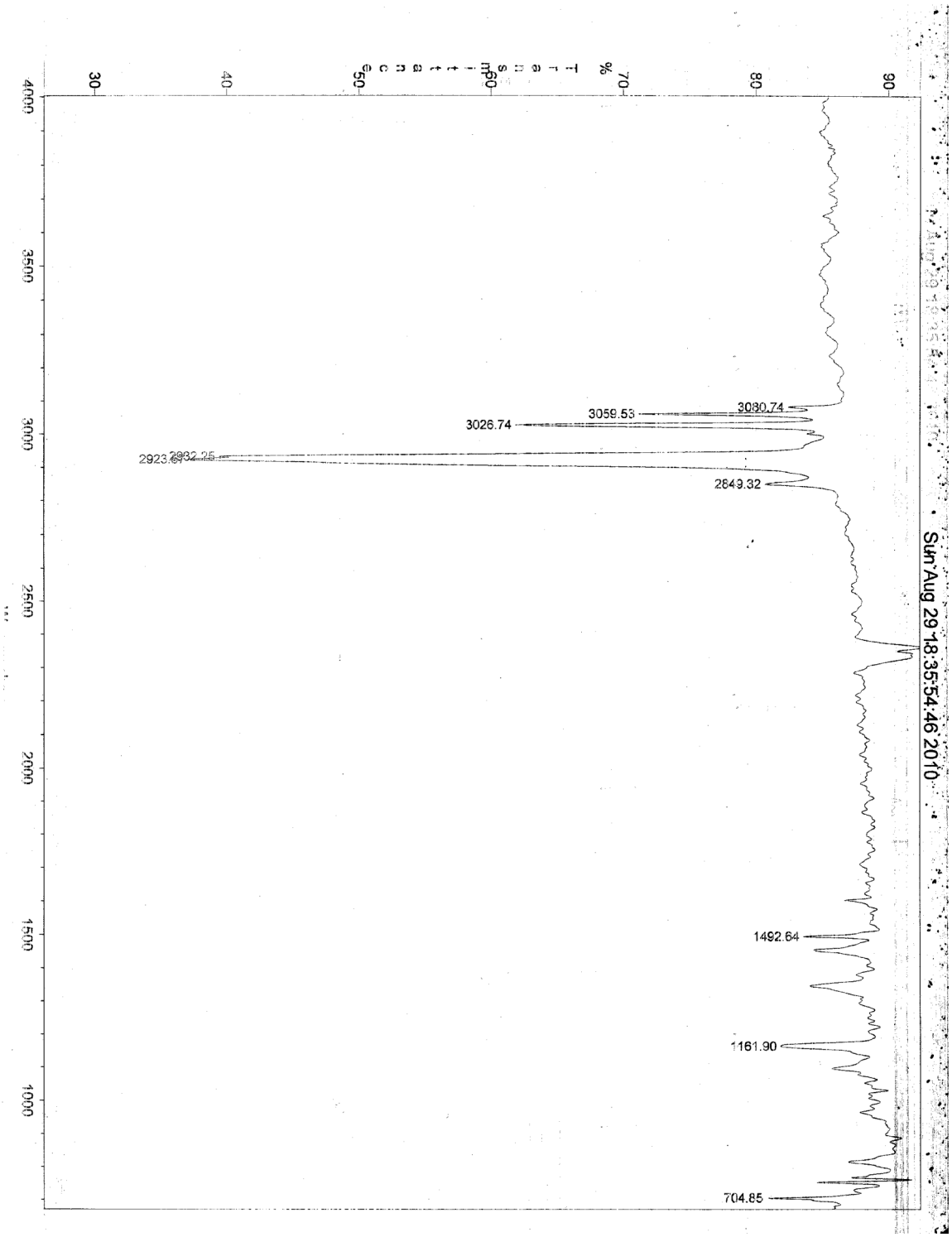
jg-v-154-white
Archive directory:
Sample directory:
FidFile: jg-v-154-white___01
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Aug 22 2010
Temp. 25.0 C / 298.1 K
Sample #4, Operator: gavenenoja
INOVA-500 "nmr16"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 6410.3 Hz
64 repetitions
OBSERVE H1, 399.7662692 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 3 min 21 sec
9
8
7
6
5
4
3
2
1
ppm


jg-v-154-white
Sample Name:
jg-v-154-white
Archive directory:
Sample directory:
FidFile: jg-v-154-white___02
Pulse Sequence: Carbon (s2pul)
Solvent: cdcl3
Data collected on: Aug 22 2010
Temp. 25.0 C / 298.1 K
Sample #4, Operator: gavenenoja
INOVA-500 "nmr16"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
512 repetitions
OBSERVE C13, 100.5212856 MHz
DECOUPLE H1, 399.7682756 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 19 min
143.515
139.139
137.897
135.873
135.768
134.183
131.482
129.771
127.777
127.092
126.281
119.168
77.550
77.230
76.917
46.878
42.867
39.452
25.180
21.735
21.095
19.718
19.577
180
160
140
120
100
80
60
40
20
ppm


%Transmittance
30
40
50
60
70
80
90
4000
3500
3000
2500
2000
1500
1000
3080.74
3059.53
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2923.69
2892.25
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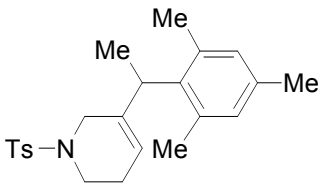
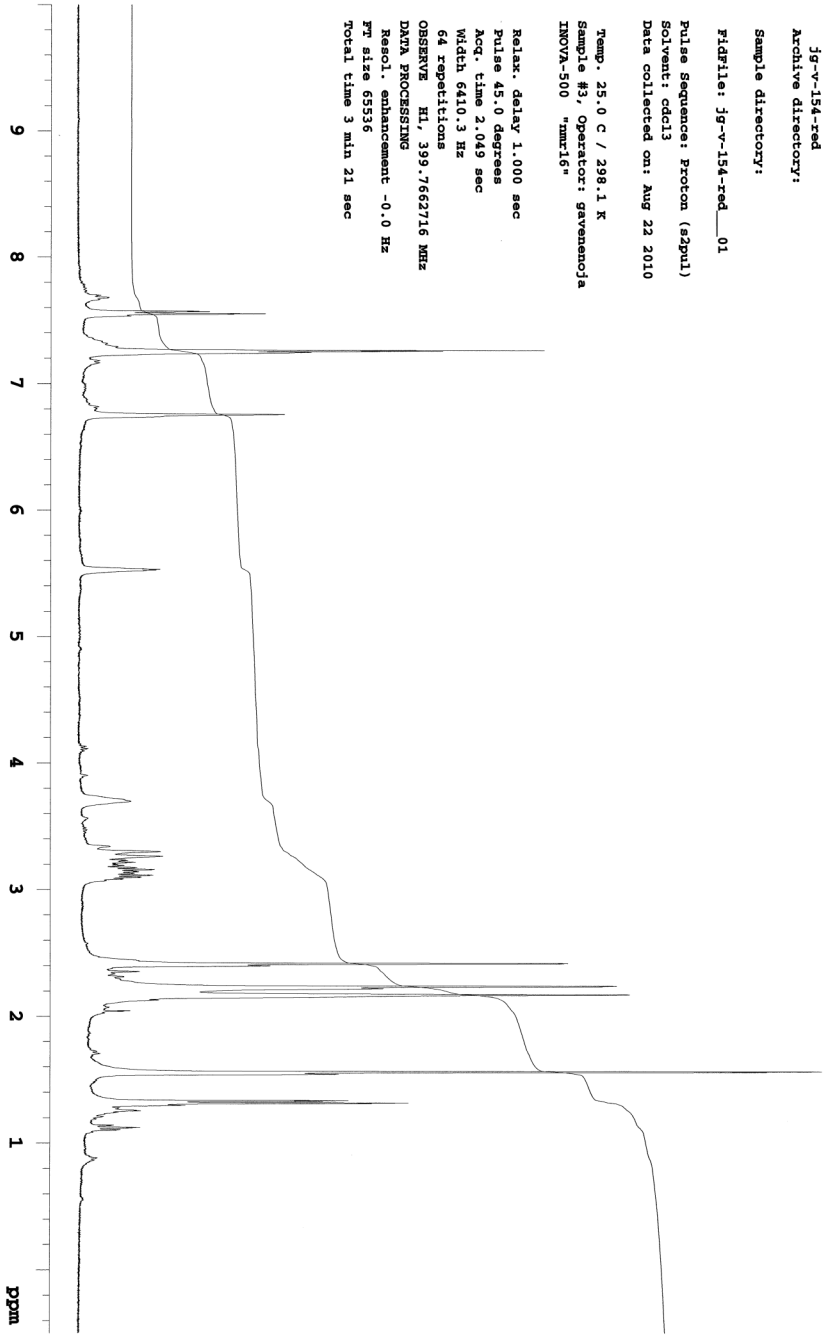
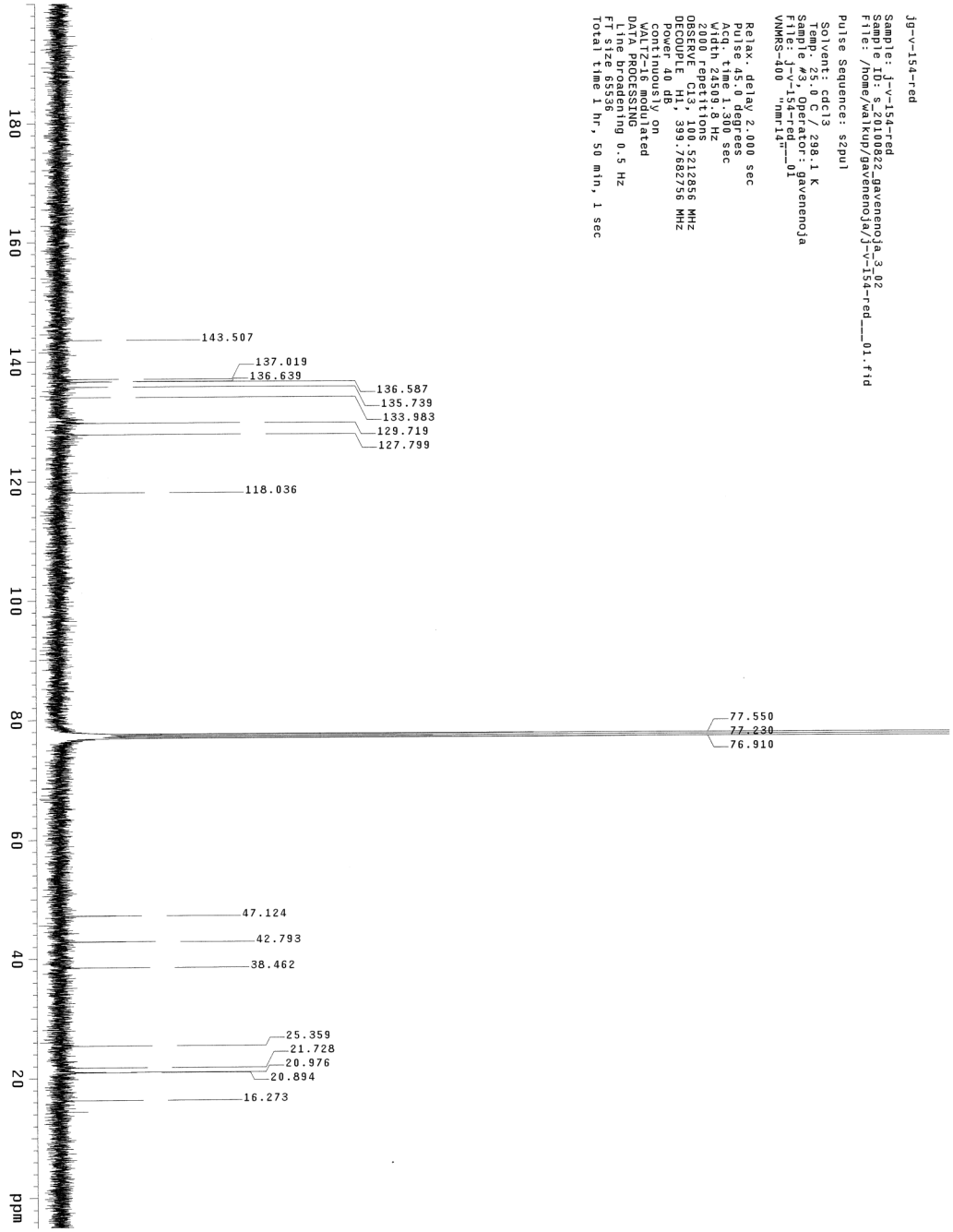
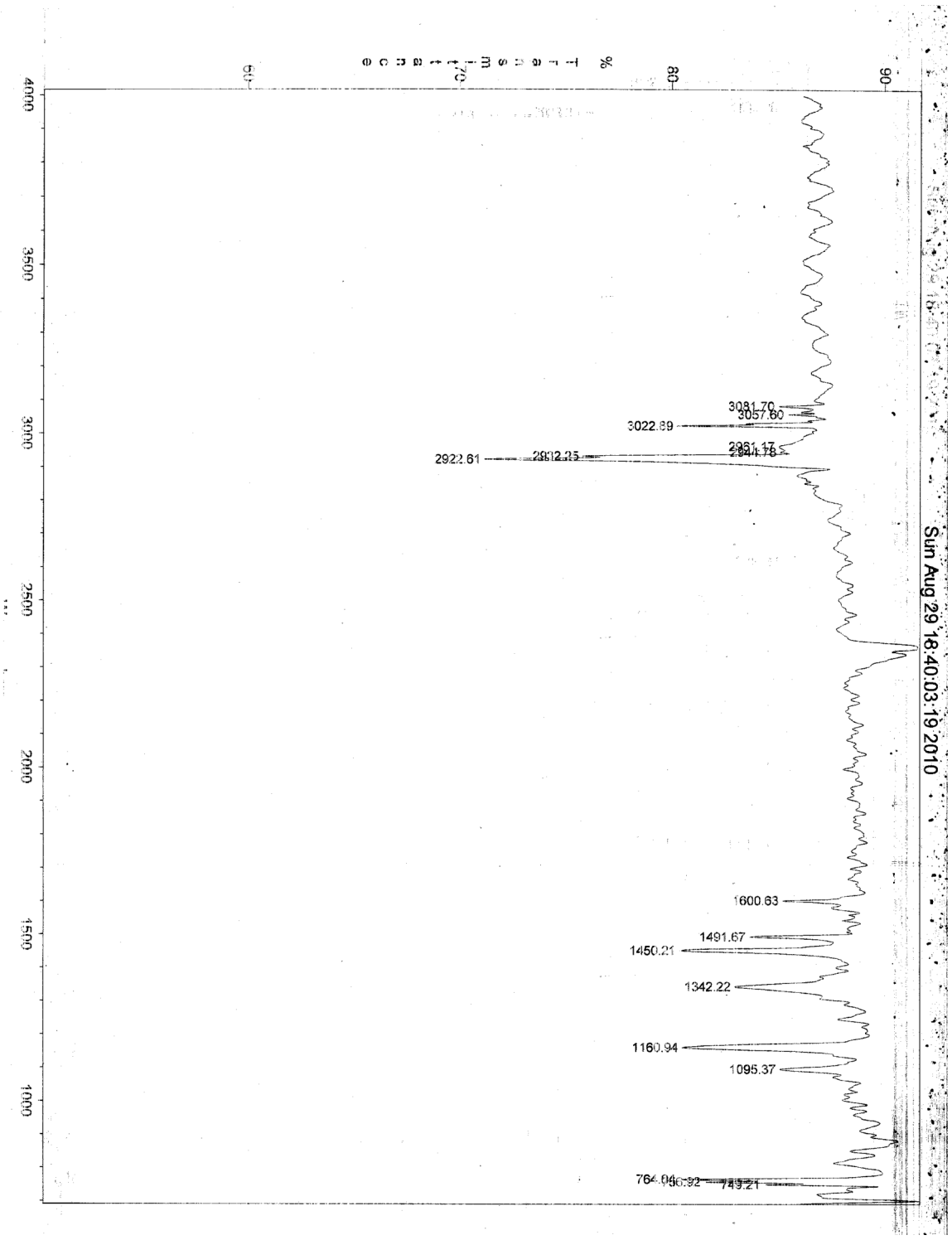
1492.64
1161.90
704.85
Sun Aug 29 18:35:54:46 2010

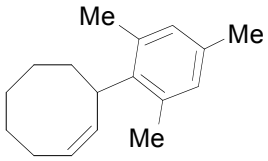


5-(1-mesitylethyl)-1-tosyl-1,2,3,6-tetrahydropyridine (3.12) was purified by column chromatography on silica gel with hexanes / ethyl acetate (9:1) as the eluent, producing the named compound in 17% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.57 (d, *J* = 8.4 Hz, 2H), 7.26 (m, 2H), 6.76 (br m, 2H), 5.53 (m, 1H), 3.70 (s, 1H), 3.34-3.01 (m, 4H), 2.42 (s, 3H), 2.24-2.17 (m, 9H), 1.32 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (C_6D_6, 100.6 MHz) δ 143.5, 137.0, 136.64, 136.59, 135.7, 134.0, 129.7, 127.8, 118.0, 47.1, 42.8, 38.5, 25.4, 21.7, 21.0, 20.9, 16.3; IR (NaCl, thin film) 3082 (w), 3058 (w), 3023 (m), 2961 (w), 2945 (w), 2932 (s), 2923 (s), 1601 (w), 1492 (w), 1450 (m), 1342 (m), 1161 (m), 1095 (w) cm^{-1}; HRMS (ES+): calculated for formula $C_{23}H_{30}NO_2S^+$: *m/z* 384.1997, found 384.1998.

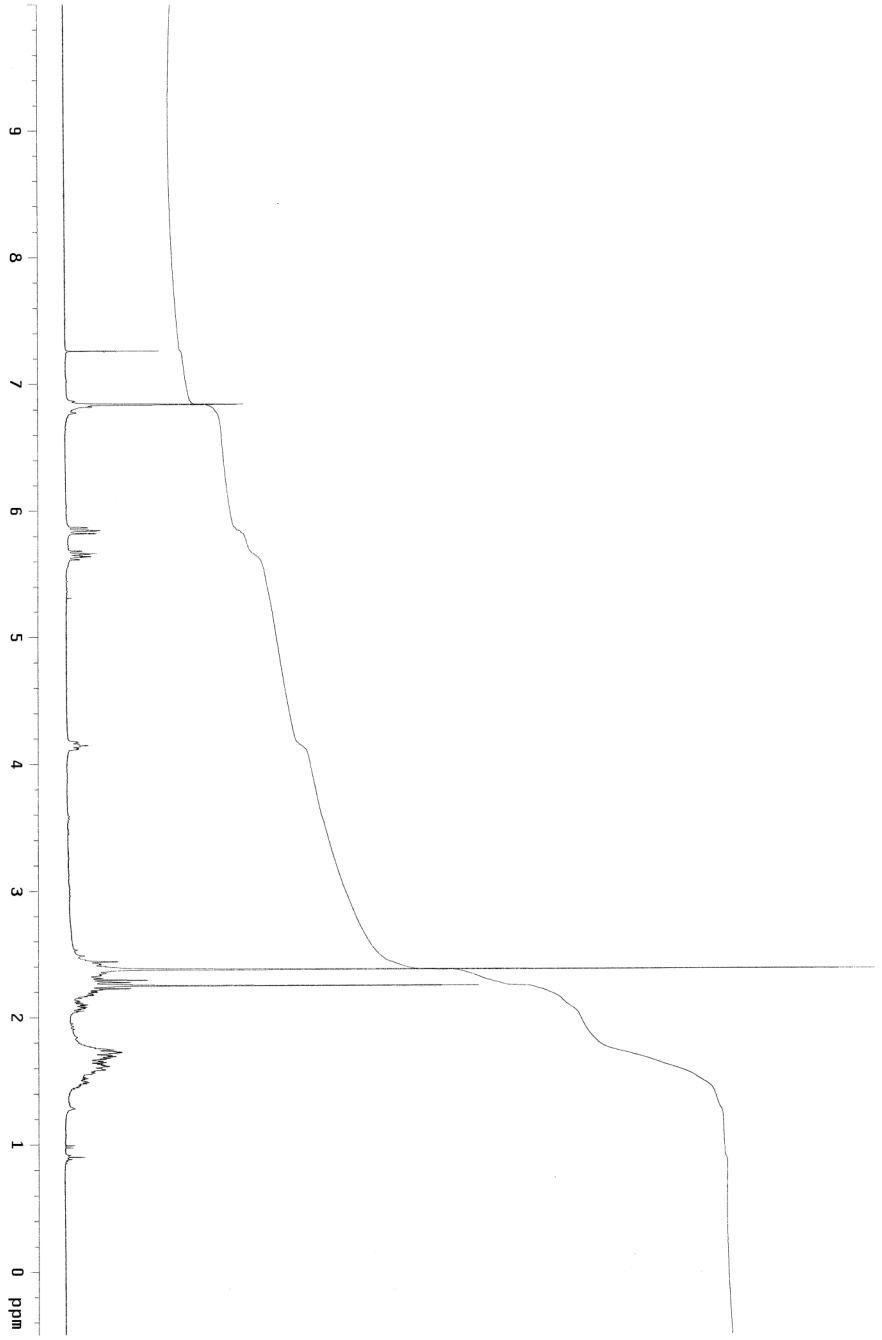

jg-v-154-red
Sample Name:
jg-v-154-red
Archive directory:
Sample directory:
Fidfile: jg-v-154-red___01
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Aug 22 2010
Temp. 25.0 C / 298.1 K
Sample #3, Operator: gavenenoja
INOVA-500 "nmr16"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 6410.3 Hz
64 repetitions
OBSERVE H1, 399.7662716 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 3 min 21 sec
9
8
7
6
5
4
3
2
1
ppm

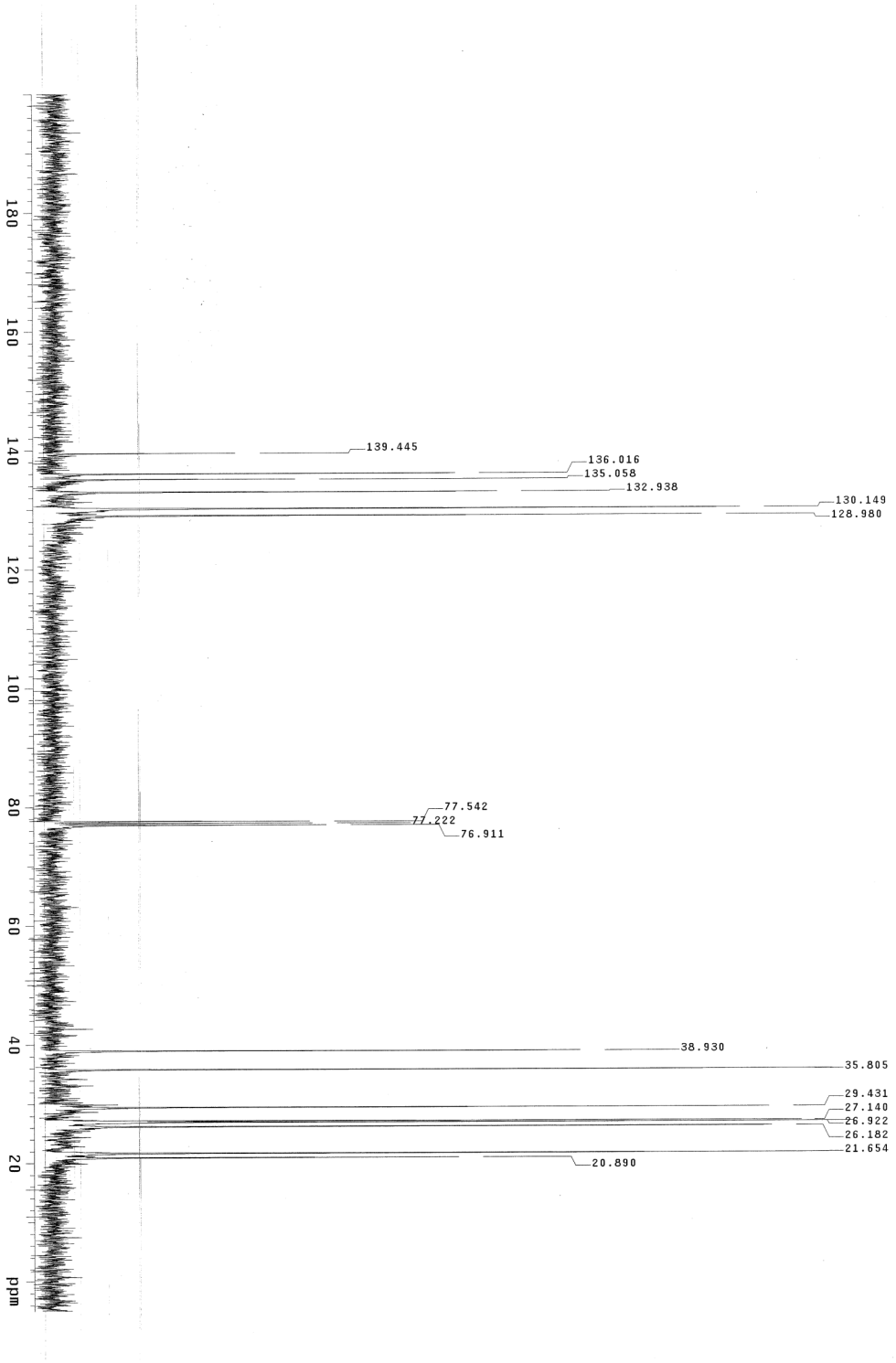

jg-v-154-red
Sample: j-v-154-red
Sample ID: s_20100822_gavenenoja_3_02
File: /home/walkup/gavenenoja/j-v-154-red___01.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #3, Operator: gavenenoja
File: j-v-154-red___01
vNMRS-400 "nmr14"
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 4.300 sec
Width 25641.0 Hz
2000 repetitions
OBSERVE C13, 100.5212856 MHz
DECOUPLE H1, 399.7682756 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 1 hr, 50 min, 1 sec
143.507
137.019
136.639
136.587
135.739
133.983
129.719
127.799
118.036
77.550
77.230
76.910
47.124
42.793
38.462
25.359
21.728
20.976
20.894
16.273
180
160
140
120
100
80
60
40
20
ppm


Sun Aug 29 18:40:03 2010
3081.70
3057.60
3022.89
2922.61
1600.63
1491.67
1450.21
1342.22
1160.94
1095.37
764.04
749.21



(*Z*)-3-mesitylcyclooct-1-ene (3.15) was isolated in 65% yield after removal of excess reactants under high vacuum**:** ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.84 (s, 2H), 5.85 (dd, *J* = 9.2, 7.2 Hz, 1H), 5.65 (m, 1H), 4.15 (m, 1H), 2.38-2.05 (m, 12H), 1.77-1.45 (m, 7H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 139.4, 136.0, 135.1, 132.9, 130.1, 129.0, 38.9, 35.8, 29.4, 27.1, 26.9, 26.2, 21.7, 20.9; IR (NaCl, thin film): 3066 (w), 3038 (vs), 3018 (w), 2926 (w), 2361 (w), 2342 (w), 1460 (w), 1346 (w), 1161 (m), 1091 (m), 913 (m), 865 (m), 738 (m), 668 (w), 582 (w), 532 (w), 426 (vs), 412 (vs) cm^{-1}; HRMS (ES+): calculated for $C_{17}H_{25}^{+}$: *m/z* 229.1956, found 229.1951.


9
8
7
6
5
4
3
2
1
0
ppm


180
160
140
120
100
80
60
40
20
ppm
139.445
136.016
135.058
132.938
130.149
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76.911
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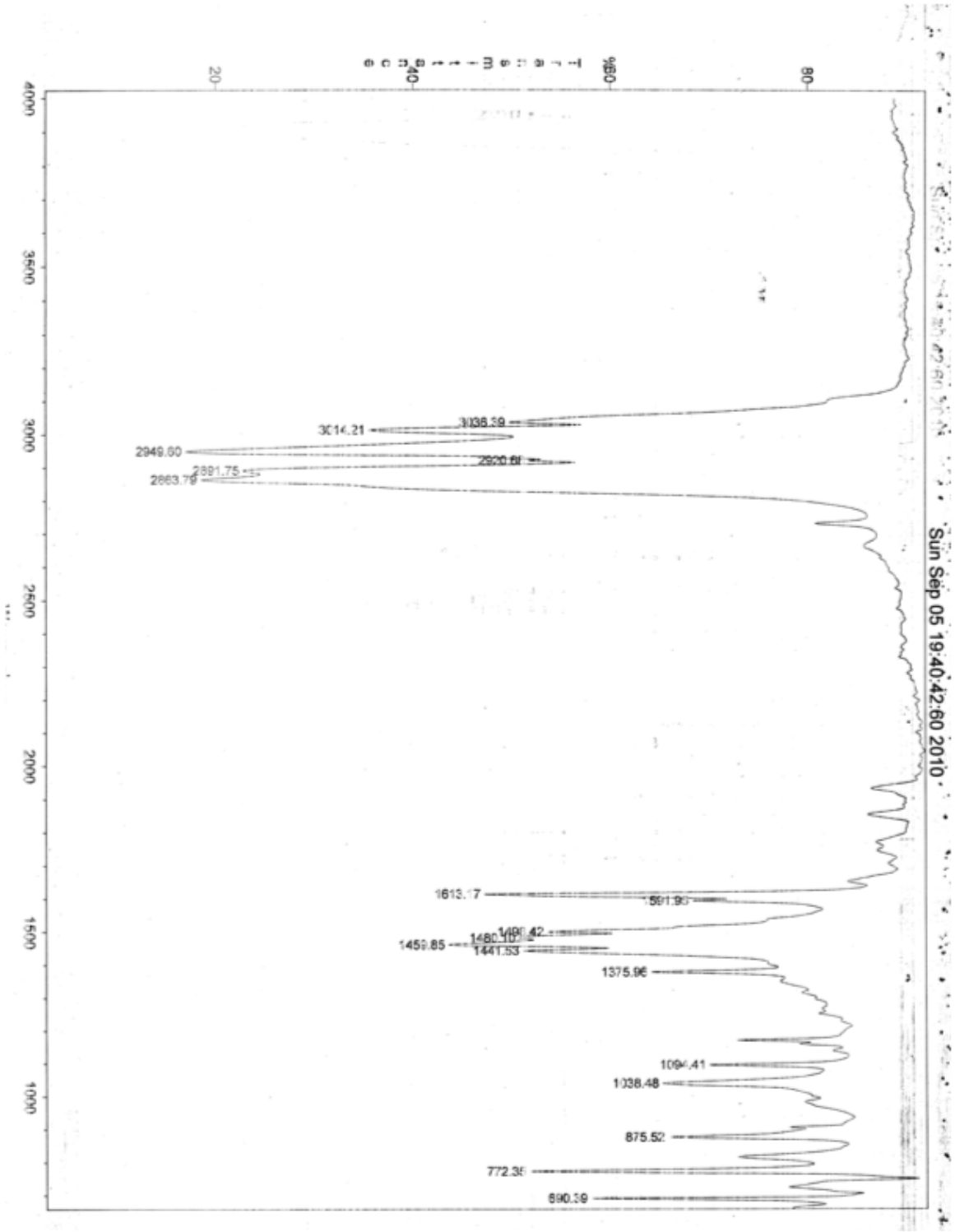
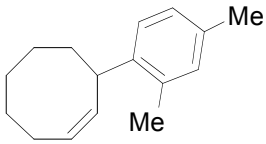
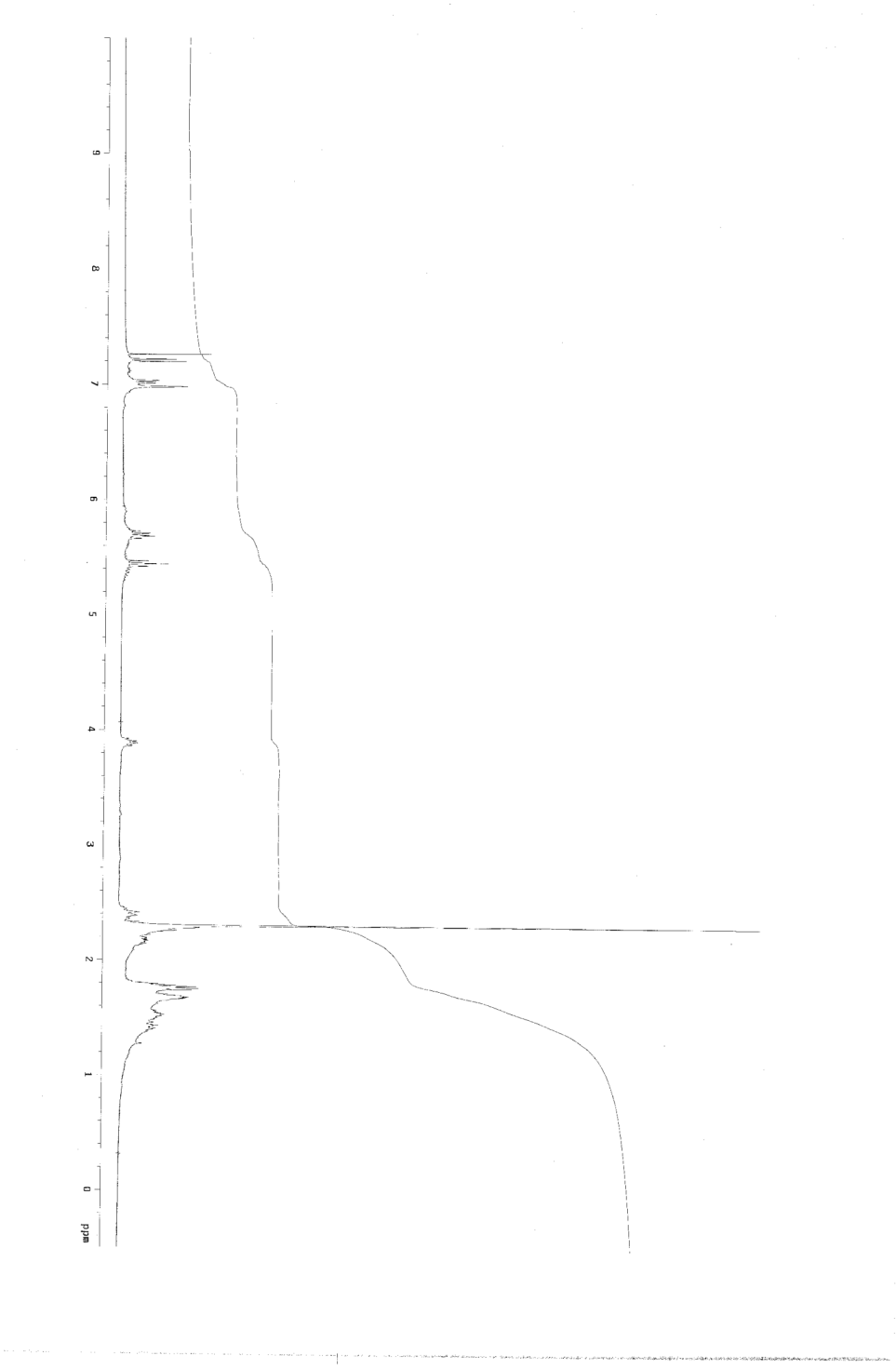
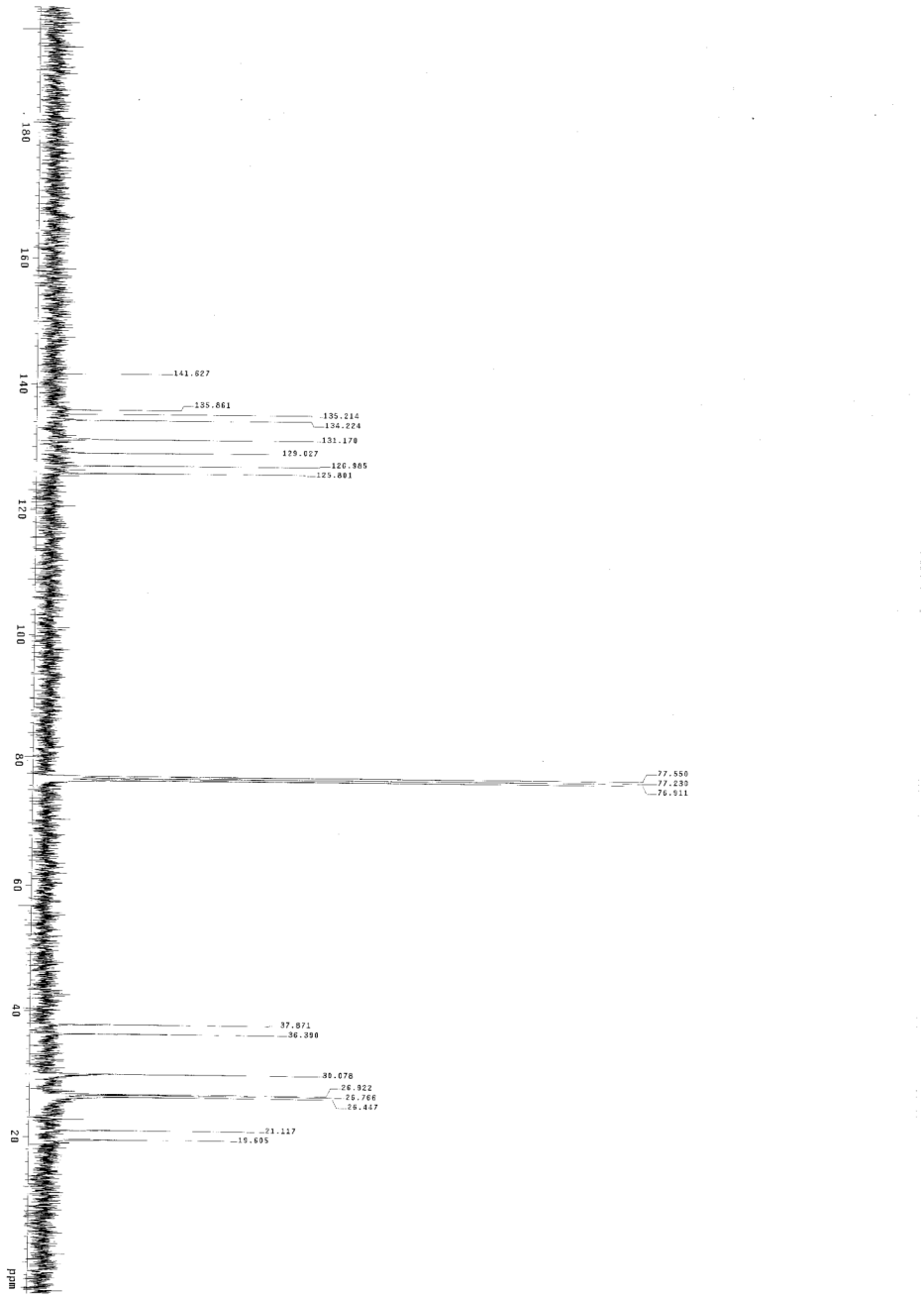
35.805
29.431
27.140
26.922
26.182
21.654
20.890

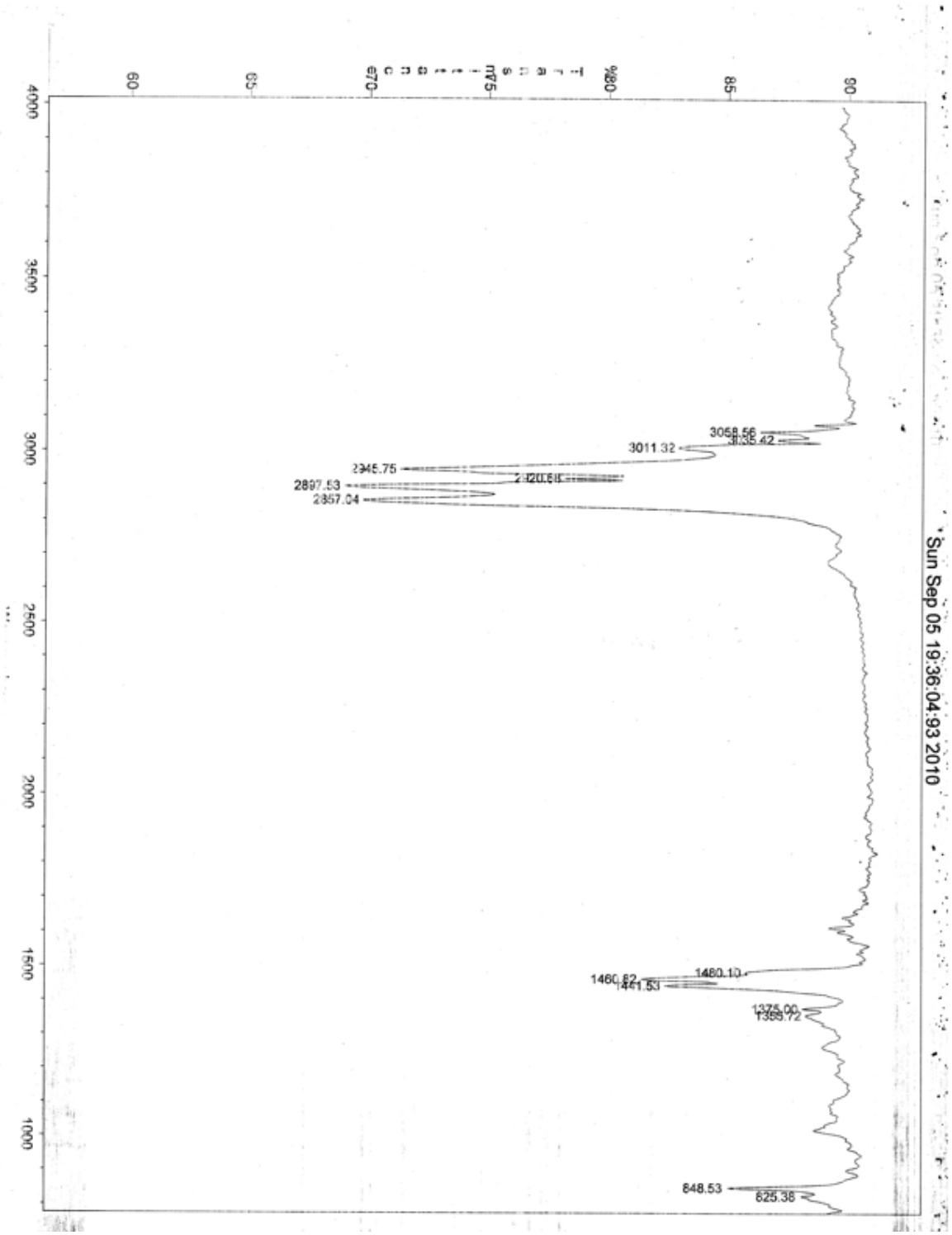

Sun Sep 05 19:40:42:60 2010
2949.60
2863.79
1459.85
1375.96
1038.48
875.52
890.39



(*Z*)-3-(2,4-dimethylphenyl)cyclooct-1-ene (3.17) was isolated in 60% yield as a colorless oil after removal of excess reactants under high vacuum: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.21 (d, *J* = 8.0 Hz, 1H), 7.02 (d, *J* = 7.9 Hz, 1H), 6.98 (s, 1H), 5.71 (m, 1H), 5.44 (t, *J* = 9.2 Hz, 1H), 3.89 (m, 1H), 2.42-2.09 (m, 8H), 1.80-1.38 (m, 8H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 141.6, 135.9, 135.2, 134.2, 131.2, 129.0, 127.0, 125.8, 37.9, 36.4, 30.1, 26.9, 26.8, 26.4, 21.1, 19.6; IR (NaCl, thin film): 3058 (w), 3032 (m), 3013 (s), 2947 (s), 2920 (m), 2895 (s), 2858 (s), 1613 (m), 1499 (m), 1461 (s), 1441 (m), 1376 (w), 875 (w), 809 (m), 771 (m) cm^{-1}.


9
8
7
6
5
4
3
2
1
0
ppm


141.627
135.861
135.214
134.224
131.170
129.027
126.985
125.801
77.550
77.230
76.911
37.871
36.390
30.078
26.922
26.766
26.447
21.117
19.605
ppm


Sun Sep 05 19:36:04:93 2010
3058.56
3035.42
3011.32
2945.75
2897.53
2857.04
1480.10
1460.82
1461.53
1375.00
1355.72
848.53
825.38

Crystallographic data for Compound 3.16 (mesitylene·$AgClO_4$)

Table 1. Crystal data and structure refinement for JG04t.

Identification code	jg04t	
Empirical formula	C12 H16 Ag1.33 Cl1.33 O5.33	
Formula weight	436.67	
Temperature	193(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 7.9350(13) Å	a= 87.770(3)°.
	b = 9.0369(15) Å	b= 83.537(2)°.
	c = 15.409(3) Å	g = 79.094(2)°.
Volume	1077.9(3) $Å^3$	
Z	3	
Density (calculated)	2.018 Mg/m^3	
Absorption coefficient	2.107 mm^{-1}	
F(000)	648	
Crystal size	0.12 x 0.10 x 0.02 mm^3	
Theta range for data collection	1.33 to 28.35°.	
Index ranges	-10<=h<=10, -12<=k<=11, -20<=l<=9	
Reflections collected	7989	
Independent reflections	5319 [R(int) = 0.0424]	
Completeness to theta = 28.35°	98.5 %	
Absorption correction	None	
Max. and min. transmission	0.9591 and 0.7861	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5319 / 0 / 277	
Goodness-of-fit on F^2	0.974	
Final R indices [I>2sigma(I)]	R1 = 0.0351, wR2 = 0.0851	
R indices (all data)	R1 = 0.0486, wR2 = 0.0915	
Largest diff. peak and hole	1.696 and -0.512 e.$Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for JG04t. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Ag(1)	4995(1)	1435(1)	3611(1)	32(1)
Ag(2)	16(1)	3658(1)	1380(1)	33(1)
Cl(1)	7065(1)	-1759(1)	4397(1)	29(1)
Cl(2)	954(1)	6879(1)	610(1)	30(1)
C(3)	7886(4)	1894(4)	3156(2)	28(1)
C(4)	6682(4)	4580(4)	2270(2)	28(1)
C(5)	7481(4)	3244(4)	3610(2)	29(1)
C(6)	2283(4)	3262(4)	2778(2)	26(1)
C(7)	2887(4)	3264(4)	1887(2)	27(1)
C(8)	3290(4)	1936(4)	1407(2)	29(1)
C(9)	7712(4)	1848(4)	2255(2)	27(1)
C(10)	2458(4)	529(4)	2713(2)	30(1)
C(11)	3067(4)	582(4)	1833(2)	34(1)
C(12)	5965(4)	6020(4)	1810(3)	41(1)
C(13)	4042(5)	1952(5)	468(2)	42(1)
C(15)	7114(4)	3218(4)	1824(2)	28(1)
C(16)	2152(5)	-928(4)	3141(3)	42(1)
C(19)	8134(5)	384(4)	1772(2)	38(1)
C(20)	6870(4)	4571(4)	3159(2)	33(1)
C(31)	7775(5)	3300(4)	4549(2)	39(1)
C(32)	1859(5)	4697(4)	3277(2)	38(1)
O(4)	6186(4)	-1344(3)	3635(2)	47(1)
O(1)	7130(5)	-418(3)	4847(2)	61(1)
O(5)	-39(4)	6481(3)	1384(2)	56(1)
O(8)	-130(4)	7751(3)	28(2)	56(1)
O(6)	1797(5)	5529(3)	182(2)	78(1)
O(7)	2152(4)	7709(4)	832(2)	83(1)

C(42)	2082(4)	1870(4)	3179(2)	28(1)
O(2)	6135(4)	-2690(3)	4971(2)	47(1)
O(3)	8736(3)	-2562(4)	4152(2)	66(1)

Table 3. Bond lengths [Å] and angles [°] for JG04t.

Ag(1)-O(2)#1	2.496(3)
Ag(2)-C(15)#2	2.429(3)
Ag(2)-O(8)#3	2.543(3)
Cl(1)-O(3)	1.404(3)
Cl(1)-O(1)	1.431(3)
Cl(1)-O(4)	1.434(2)
Cl(1)-O(2)	1.437(2)
Cl(2)-O(7)	1.395(3)
Cl(2)-O(6)	1.423(3)
Cl(2)-O(8)	1.424(3)
Cl(2)-O(5)	1.427(3)
C(3)-C(5)	1.396(5)
C(3)-C(9)	1.413(4)
C(3)-H(3)	0.9500
C(4)-C(20)	1.395(5)
C(4)-C(15)	1.399(4)
C(4)-C(12)	1.502(4)
C(5)-C(20)	1.395(5)
C(5)-C(31)	1.495(4)
C(6)-C(7)	1.402(4)
C(6)-C(42)	1.408(4)
C(6)-C(32)	1.496(5)
C(7)-C(8)	1.400(4)
C(7)-H(7)	0.9500
C(8)-C(11)	1.398(5)
C(8)-C(13)	1.502(5)
C(9)-C(15)	1.409(4)
C(9)-C(19)	1.506(5)
C(10)-C(11)	1.388(5)
C(10)-C(42)	1.399(5)

C(10)-C(16)	1.499(4)
C(11)-H(11)	0.9500
C(12)-H(12A)	0.9800
C(12)-H(12B)	0.9800
C(12)-H(12C)	0.9800
C(13)-H(13A)	0.9800
C(13)-H(13B)	0.9800
C(13)-H(13C)	0.9800
C(15)-Ag(2)#4	2.429(3)
C(15)-H(15)	0.9500
C(16)-H(16A)	0.9800
C(16)-H(16B)	0.9800
C(16)-H(16C)	0.9800
C(19)-H(19A)	0.9801
C(19)-H(19B)	0.9801
C(19)-H(19C)	0.9801
C(20)-H(20)	0.9500
C(31)-H(31A)	0.9800
C(31)-H(31B)	0.9800
C(31)-H(31C)	0.9800
C(32)-H(32A)	0.9800
C(32)-H(32B)	0.9800
C(32)-H(32C)	0.9800
O(8)-Ag(2)#3	2.543(3)
C(42)-H(42)	0.9500
O(2)-Ag(1)#1	2.496(3)
C(15)#2-Ag(2)-O(8)#3	90.65(11)
O(3)-Cl(1)-O(1)	110.7(2)
O(3)-Cl(1)-O(4)	109.81(19)
O(1)-Cl(1)-O(4)	108.66(17)
O(3)-Cl(1)-O(2)	109.14(19)
O(1)-Cl(1)-O(2)	108.60(17)

O(4)-Cl(1)-O(2)	109.91(17)
O(7)-Cl(2)-O(6)	110.9(2)
O(7)-Cl(2)-O(8)	109.4(2)
O(6)-Cl(2)-O(8)	108.09(19)
O(7)-Cl(2)-O(5)	109.4(2)
O(6)-Cl(2)-O(5)	108.30(19)
O(8)-Cl(2)-O(5)	110.78(18)
C(5)-C(3)-C(9)	121.7(3)
C(5)-C(3)-H(3)	119.2
C(9)-C(3)-H(3)	119.2
C(20)-C(4)-C(15)	118.7(3)
C(20)-C(4)-C(12)	120.4(3)
C(15)-C(4)-C(12)	120.9(3)
C(20)-C(5)-C(3)	118.6(3)
C(20)-C(5)-C(31)	119.9(3)
C(3)-C(5)-C(31)	121.4(3)
C(7)-C(6)-C(42)	117.6(3)
C(7)-C(6)-C(32)	120.7(3)
C(42)-C(6)-C(32)	121.6(3)
C(8)-C(7)-C(6)	121.8(3)
C(8)-C(7)-H(7)	119.1
C(6)-C(7)-H(7)	119.1
C(11)-C(8)-C(7)	118.5(3)
C(11)-C(8)-C(13)	120.7(3)
C(7)-C(8)-C(13)	120.8(3)
C(15)-C(9)-C(3)	117.7(3)
C(15)-C(9)-C(19)	121.0(3)
C(3)-C(9)-C(19)	121.3(3)
C(11)-C(10)-C(42)	118.6(3)
C(11)-C(10)-C(16)	120.4(3)
C(42)-C(10)-C(16)	120.9(3)
C(10)-C(11)-C(8)	121.7(3)

C(10)-C(11)-H(11)	119.1
C(8)-C(11)-H(11)	119.1
C(4)-C(12)-H(12A)	109.5
C(4)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	109.5
C(4)-C(12)-H(12C)	109.5
H(12A)-C(12)-H(12C)	109.5
H(12B)-C(12)-H(12C)	109.5
C(8)-C(13)-H(13A)	109.5
C(8)-C(13)-H(13B)	109.5
H(13A)-C(13)-H(13B)	109.5
C(8)-C(13)-H(13C)	109.5
H(13A)-C(13)-H(13C)	109.5
H(13B)-C(13)-H(13C)	109.5
C(4)-C(15)-C(9)	121.5(3)
C(4)-C(15)-Ag(2)#4	91.30(19)
C(9)-C(15)-Ag(2)#4	93.00(18)
C(4)-C(15)-H(15)	119.2
C(9)-C(15)-H(15)	119.2
Ag(2)#4-C(15)-H(15)	85.6
C(10)-C(16)-H(16A)	109.5
C(10)-C(16)-H(16B)	109.5
H(16A)-C(16)-H(16B)	109.5
C(10)-C(16)-H(16C)	109.5
H(16A)-C(16)-H(16C)	109.5
H(16B)-C(16)-H(16C)	109.5
C(9)-C(19)-H(19A)	109.5
C(9)-C(19)-H(19B)	109.5
H(19A)-C(19)-H(19B)	109.5
C(9)-C(19)-H(19C)	109.5
H(19A)-C(19)-H(19C)	109.5
H(19B)-C(19)-H(19C)	109.5

C(4)-C(20)-C(5)	121.7(3)
C(4)-C(20)-H(20)	119.2
C(5)-C(20)-H(20)	119.1
C(5)-C(31)-H(31A)	109.5
C(5)-C(31)-H(31B)	109.5
H(31A)-C(31)-H(31B)	109.5
C(5)-C(31)-H(31C)	109.5
H(31A)-C(31)-H(31C)	109.5
H(31B)-C(31)-H(31C)	109.5
C(6)-C(32)-H(32A)	109.5
C(6)-C(32)-H(32B)	109.5
H(32A)-C(32)-H(32B)	109.5
C(6)-C(32)-H(32C)	109.5
H(32A)-C(32)-H(32C)	109.5
H(32B)-C(32)-H(32C)	109.5
Cl(2)-O(8)-Ag(2)#3	110.42(16)
C(10)-C(42)-C(6)	121.8(3)
C(10)-C(42)-H(42)	119.1
C(6)-C(42)-H(42)	119.1
Cl(1)-O(2)-Ag(1)#1	111.61(15)

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,-y,-z+1 #2 x-1,y,z #3 -x,-y+1,-z

#4 x+1,y,z

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for JG04t. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Ag(1)	21(1)	40(1)	33(1)	9(1)	-4(1)	-6(1)
Ag(2)	25(1)	43(1)	33(1)	9(1)	-8(1)	-13(1)
Cl(1)	31(1)	30(1)	28(1)	4(1)	-4(1)	-7(1)
Cl(2)	31(1)	31(1)	27(1)	3(1)	-5(1)	-6(1)
C(3)	20(1)	33(2)	33(2)	7(1)	-4(1)	-8(1)
C(4)	22(1)	30(2)	32(2)	6(1)	-3(1)	-9(1)
C(5)	22(1)	40(2)	27(2)	2(1)	-4(1)	-12(1)
C(6)	16(1)	31(2)	31(2)	0(1)	-5(1)	-5(1)
C(7)	22(1)	29(2)	33(2)	9(1)	-6(1)	-8(1)
C(8)	20(1)	39(2)	28(2)	1(1)	-5(1)	-5(1)
C(9)	18(1)	33(2)	30(2)	1(1)	-3(1)	-6(1)
C(10)	20(1)	32(2)	39(2)	9(1)	-9(1)	-7(1)
C(11)	35(2)	28(2)	39(2)	-2(1)	-9(2)	-2(1)
C(12)	36(2)	37(2)	47(2)	10(2)	-6(2)	-4(2)
C(13)	36(2)	57(2)	30(2)	3(2)	-2(2)	-2(2)
C(15)	21(1)	36(2)	27(2)	4(1)	-3(1)	-8(1)
C(16)	39(2)	35(2)	55(2)	13(2)	-12(2)	-12(2)
C(19)	33(2)	38(2)	41(2)	-4(2)	-3(2)	-4(1)
C(20)	36(2)	32(2)	35(2)	-3(1)	-2(2)	-10(1)
C(31)	40(2)	50(2)	30(2)	3(2)	-7(2)	-17(2)
C(32)	41(2)	34(2)	39(2)	-3(2)	-4(2)	-7(2)
O(4)	59(2)	45(2)	41(2)	8(1)	-25(1)	-9(1)
O(1)	116(3)	39(2)	35(2)	3(1)	-18(2)	-31(2)
O(5)	60(2)	56(2)	44(2)	12(1)	17(1)	-7(1)
O(8)	57(2)	60(2)	46(2)	12(1)	-19(1)	8(1)
O(6)	131(3)	44(2)	38(2)	4(1)	9(2)	24(2)
O(7)	70(2)	115(3)	84(3)	13(2)	-32(2)	-60(2)

C(42)	21(1)	37(2)	27(2)	6(1)	-4(1)	-7(1)
O(2)	57(2)	45(2)	41(2)	9(1)	7(1)	-23(1)
O(3)	26(1)	82(2)	82(2)	10(2)	4(1)	2(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for JG04t.

	x	y	z	U(eq)
H(3)	8288	984	3460	34
H(7)	3026	4191	1602	33
H(11)	3339	-325	1513	41
H(12A)	4737	6328	2013	61
H(12B)	6103	5861	1178	61
H(12C)	6588	6810	1939	61
H(13A)	5237	1403	416	63
H(13B)	4018	2996	265	63
H(13C)	3361	1468	112	63
H(15)	7002	3217	1217	33
H(16A)	1473	-1413	2783	63
H(16B)	1520	-730	3721	63
H(16C)	3263	-1595	3199	63
H(19A)	7091	-53	1787	56
H(19B)	9020	-318	2052	56
H(19C)	8565	572	1165	56
H(20)	6575	5492	3466	40
H(31A)	8736	3822	4596	58
H(31B)	8052	2272	4786	58
H(31C)	6728	3845	4879	58
H(32A)	2888	5158	3248	57
H(32B)	1478	4480	3888	57
H(32C)	935	5393	3020	57
H(42)	1681	1841	3783	34

Table 6. Torsion angles [°] for JG04t.

C(9)-C(3)-C(5)-C(20)	0.8(4)
C(9)-C(3)-C(5)-C(31)	-176.0(3)
C(42)-C(6)-C(7)-C(8)	-0.4(4)
C(32)-C(6)-C(7)-C(8)	-179.9(3)
C(6)-C(7)-C(8)-C(11)	0.5(4)
C(6)-C(7)-C(8)-C(13)	-176.0(3)
C(5)-C(3)-C(9)-C(15)	0.1(4)
C(5)-C(3)-C(9)-C(19)	-179.4(3)
C(42)-C(10)-C(11)-C(8)	-0.8(5)
C(16)-C(10)-C(11)-C(8)	177.1(3)
C(7)-C(8)-C(11)-C(10)	0.1(5)
C(13)-C(8)-C(11)-C(10)	176.6(3)
C(20)-C(4)-C(15)-C(9)	0.7(4)
C(12)-C(4)-C(15)-C(9)	-177.0(3)
C(20)-C(4)-C(15)-Ag(2)#4	-93.6(3)
C(12)-C(4)-C(15)-Ag(2)#4	88.7(3)
C(3)-C(9)-C(15)-C(4)	-0.8(4)
C(19)-C(9)-C(15)-C(4)	178.6(3)
C(3)-C(9)-C(15)-Ag(2)#4	92.5(2)
C(19)-C(9)-C(15)-Ag(2)#4	-88.0(3)
C(15)-C(4)-C(20)-C(5)	0.2(5)
C(12)-C(4)-C(20)-C(5)	178.0(3)
C(3)-C(5)-C(20)-C(4)	-1.0(5)
C(31)-C(5)-C(20)-C(4)	175.9(3)
O(7)-Cl(2)-O(8)-Ag(2)#3	123.4(2)
O(6)-Cl(2)-O(8)-Ag(2)#3	2.5(2)
O(5)-Cl(2)-O(8)-Ag(2)#3	-115.98(18)
C(11)-C(10)-C(42)-C(6)	0.9(4)
C(16)-C(10)-C(42)-C(6)	-176.9(3)
C(7)-C(6)-C(42)-C(10)	-0.3(4)

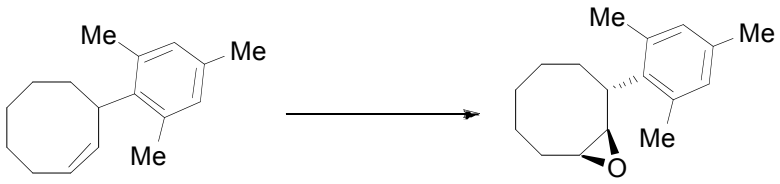
C(32)-C(6)-C(42)-C(10)	179.2(3)
O(3)-Cl(1)-O(2)-Ag(1)#1	123.94(19)
O(1)-Cl(1)-O(2)-Ag(1)#1	3.2(2)
O(4)-Cl(1)-O(2)-Ag(1)#1	-115.58(16)

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,-y,-z+1 #2 x-1,y,z #3 -x,-y+1,-z

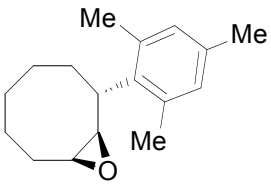
#4 x+1,y,z

Epoxidation of Hydroarylation product:

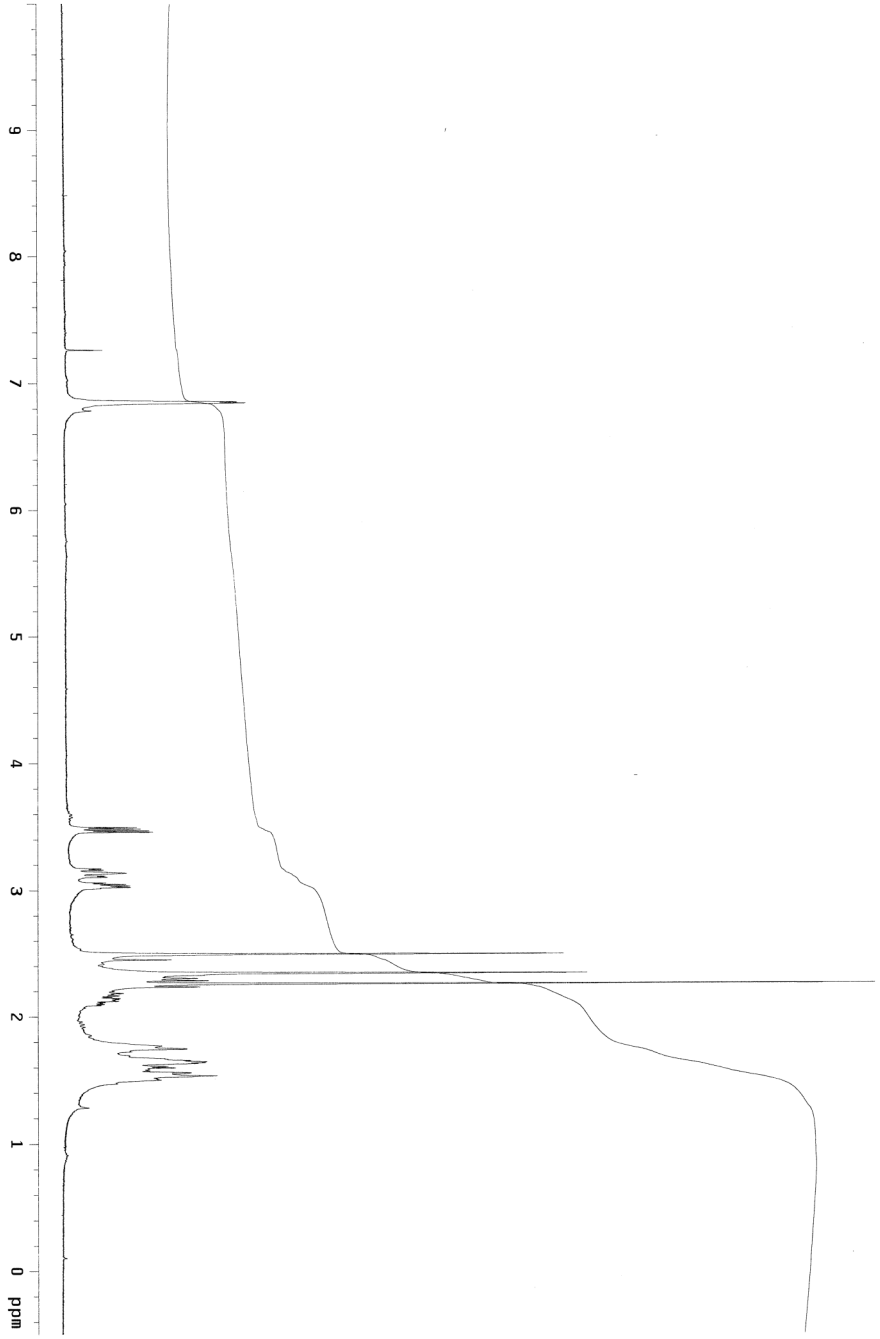


3.15 **3.19**

To an oven dried round-bottomed flask charged with a magnetic stirbar were added sequentially **3.15** (47 mg, 0.21 mmol), dichloromethane (2mL), and *m*-chloroperbenzoic acid (39.3 mg, 0.23 mmol, 1.1 equiv.). The reaction mixture was allowed to stir under nitrogen for three hours, and then quenched by the addition of 2 mL saturated aqueous sodium thiosulfate and 2 mL saturated aqueous sodium bicarbonate. The aqueous layer was then extracted with dichloromethane (3 x 3 mL), dried over sodium sulfate, and concentrated *in vacuo*, producing compound **3.19** in quantitative yield.



2-mesityl-9-oxabicyclo[6.1.0]nonane (3.19): ^{1}H NMR ($CDCl_3$, 400 MHz): d 6.85 (s, 1H), 6.84 (s, 1H), 3.48 (dd, *J* = 10.0, 4.0 Hz, 1H), 3.14 (m, 1H), 3.04 (m, 1H), 2.50 (s, 3H), 2.34 (s, 3H), 2.26 (s, 3H), 1.76-1.50 (m, 10 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) d 137.1, 136.5, 136.1, 135.6, 131.3, 129.5, 129.0, 57.4, 56.7, 39.1, 32.8, 27.6, 27.3, 27.2, 25.8, 22.2, 21.9, 20.9; HRMS (ES+): calculated for $C_{17}H_{25}O^{+}$: *m/z* 245.1905, found 245.1907.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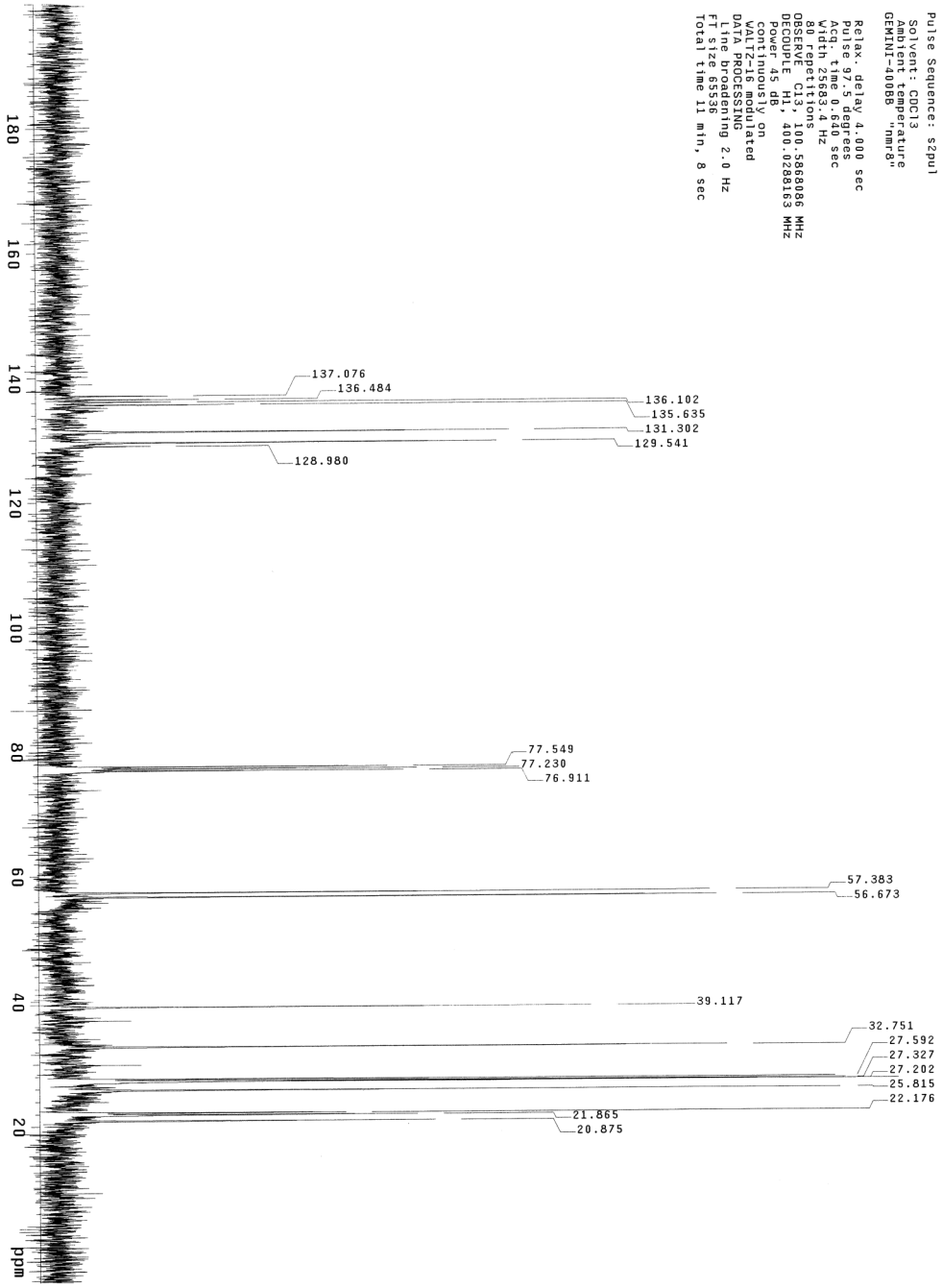
8
7
6
5
4
3
2
1
0
ppm


jg-1v-060-13C
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-400BB "nmr8"
Relax. delay 4.000 sec
Pulse 97.5 degrees
Acq. time 0.640 sec
Width 25683.4 Hz
8 repetitions
OBSERVE C13, 100.5868086 MHz
DECOUPLE H1, 400.0288163 MHz
Power 45 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 11 min, 8 sec
137.076
136.484
136.102
135.635
131.302
129.541
128.980
77.549
77.230
76.911
57.383
56.673
39.117
32.751
27.592
27.327
27.202
25.815
22.176
21.865
20.875
180
160
140
120
100
80
60
40
20
ppm

Appendix A

Tandem Enyne Metathesis-Reductive Coupling

"Nature does not ask your permission, she has nothing to do with your wishes, and whether you like her laws or dislike them, you are bound to accept her as she is, and consequently all her conclusions."

--Fyodor Dostoyevsky, *Notes From the Underground*

A.1 – Introduction

The successful development of a tandem enyne metathesis-hydrovinylation reaction inspired a search for new tandem processes that may be enabled by the *in situ* transformation of first-generation Grubbs' catalyst **C823** to $(Cy_3P)_2Ru(CO)HCl$ (**A.1**). The reductive coupling of 1,3-dienes and carbonyls, catalyzed by $(Ph_3P)_3Ru(CO)HCl$ (**A.2**) and reported by Krische[96] and Ryu,[97] presented a particularly attractive target for a new tandem methodology, since similarly-substituted dienes are accessible *via* enyne metathesis[98] and the reaction is promoted by a catalyst similar to **A.1**. In this process, illustrated in Scheme A.1, both homoallylic alcohols and β,γ-unsaturated ketones are accessible from either benzylic alcohols or benzaldehydes. When the reaction is run in THF with added phosphine ligand, acetone, and *m*-nitrobenzoic acid, the homoallylic alcohol is isolated; in the presence of catalytic trifluoroacetic acid in toluene, the corresponding ketone is observed.

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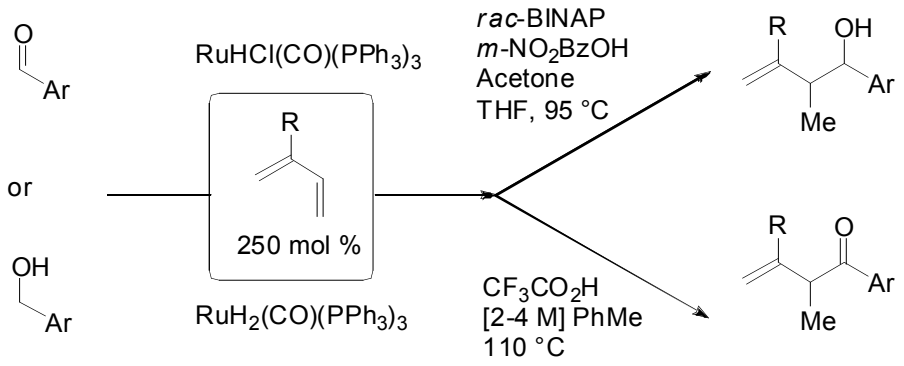
[96] a) F.. Shibahara, J. F. Bower, M. J. Krische *J. Am. Chem. Soc.* **2008**, *130*, 6338-6339 doi:10.1021/ja801213x. b) F. Shibahara, F., J. F. Bower, M. J. Krische, *J. Am. Chem. Soc.* **2008**, *130*, 14120-14122 doi:10.1021/ja805356j. c) T. Smejkal, H. Han, B. Breit, M. J. Krische *J. Am. Chem. Soc.* **2009**, *131*, 10366-10367 doi:10.1021/ja904124b.

[97] S. Omura, T. Fukuyama, J. Horiguchi, Y. Murakami, I. Ryu, *J. Am. Chem. Soc.* **2008**, *130*, 14094-14095 doi:10.1021/ja806929y.

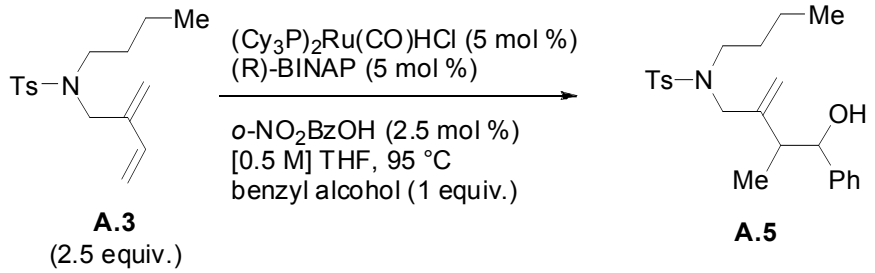
[98] a) J. A. Smulik, S. T. Diver *J. Org. Chem.* **2000**, *65*, 1788-1792 doi:10.1021/jo9916941. b) J. A. Smulik, S. T. Diver, *Org. Lett.* **2000**, *2*, 2271-2274 doi:10.1021/ol006035l.



Scheme A.1 - Reductive coupling of 1,3-dienes with alcohols and aldehydes

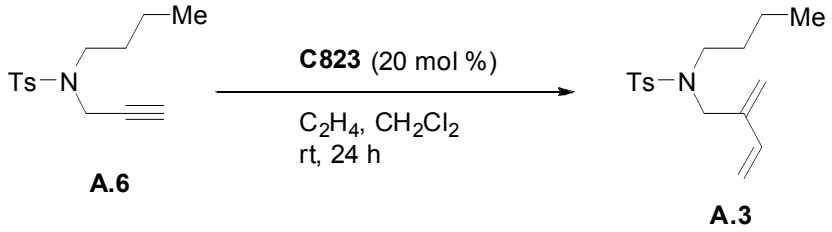
A.2 – Preliminary Results

Initial experiments were designed to determine both whether $(Cy_3P)_2Ru(CO)HCl$ would be catalytically similar to $(Ph_3P)_3Ru(CO)HCl$ or $(Ph_3P)_3Ru(CO)H_2$ and whether dienes generated by enyne metathesis would react in a manner similar to reported substrates for this process, 1,3-butadiene, isoprene and myrcene (Scheme A.2).



Scheme A.2 - Control experiment with $(PCy_3)_2Ru(CO)HCl$

As illustrated in Scheme A.2, catalyst **A.1** promotes this intermolecular reductive allylation with efficiency similar to that of **A.2**. Furthermore, diene **A.3** may be readily generated by metathesis of alkyne **A.6** in ethylene. While some reports suggested that only NHC-based catalyst **C848** would promote this metathesis, the effectiveness of **C823** had been previously disclosed (Scheme A.3).[99]

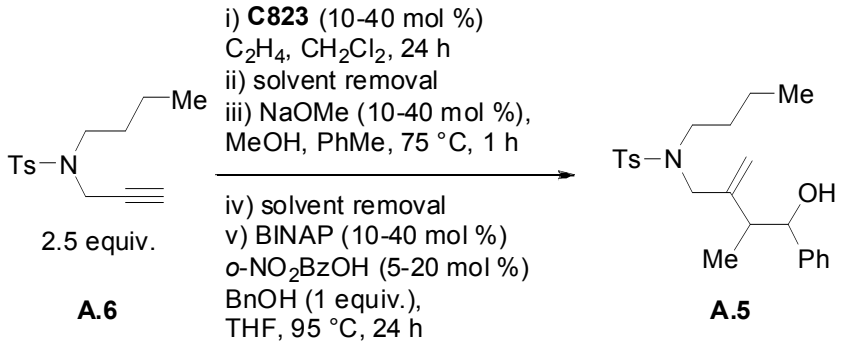


A.6 **A.3**

Scheme A.3 - Enyne metathesis of propargyl sulfonamide with ethylene

Having demonstrated the efficiency of both reactions separately, a tandem process was envisioned as outlined in Scheme A.4. Enyne metathesis of alkyne **A.6**, with catalyst **C823** in dichloromethane saturated with ethylene will produce diene **A.3**. Removal of solvent *in vacuo*, addition of NaOMe in methanol/toluene, and brief heating to 75 °C will convert **C823** to **A.1**. Finally, after evaporation of solvent, redissoultion in THF, and addition of BINAP, *m*-nitrobenzoic acid, and alcohol **A.4**, heating for 24 h should effect the conversion of diene **A.3** to homoallylic alcohol **A.5**.

[99] A. Kinoshita, N. Sakakibara, M. Mori, *Tetrahedron*, **1999**, *55*, 8155-8167 doi:10.1016/S0040(99)00297-5.



Scheme A.4 - Tandem enyne methathesis-reductive coupling

While two solvent-removal steps would not be ideal for an efficient tandem process, the metathesis does not proceed in toluene, elevated temperatures are required for the complete conversion of **C823** to **A.1**, and, while toluene is an effective solvent for the reductive coupling, the potential effect of residual methanol is unknown.

Unfortunately, the isolated yield of **A.5** does not exceed the amount of ruthenium catalyst used (Table A.1). At intermediate catalyst loadings between 5 and 40 mol %, the reaction does not turn over. With 5 mol % catalyst, only trace amounts of **A.5** are observed (entry 1). Increasing the catalyst loading to 15 mol % improves the yield to 12%. The reaction proceeds with NHC-based catalyst **C848**, but with no better yield (entry 3). Addition of freshly prepared $(Cy_3P)_2Ru(CO)HCl$ does not improve the efficiency of the reaction (entry 4). Finally, use of 40 mol % catalyst produces **A.5** in 35% yield.

Table A.1 – Tandem enyne metathesis-reductive coupling

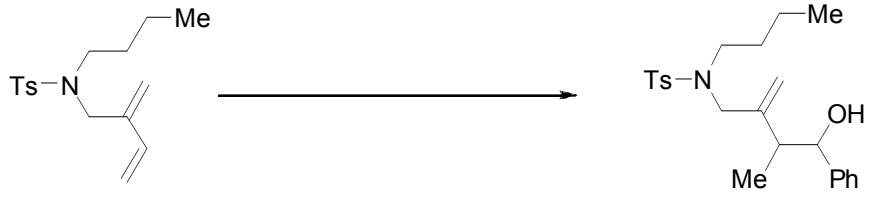
Entry	mol % C823	mol % NaOMe	mol % BINAP	mol % *o*-NO_2BzOH	Yield (%)
1	5	5	5	2.5	trace
2	15	15	15	7.5	12
3	15*	*	15	7.5	10
4	15	**	15	7.5	10
5	40	40	40	20	35
***C848** modified with 20 catalyst equiv. vinyloxytrimethylsilane					
****15 mol % **A.1** added in lieu of catalyst modification; 1:1 ratio of alkyne to alcohol					

A.3 – Conclusion

$(Cy_3P)_2Ru(CO)HCl$ generated *in situ* after enyne metathesis promotes the reductive coupling of a diene and aldehyde. While the expected product may be isolated cleanly, the yield fails to exceed the quantity of catalyst used. It is anticipated that further optimization of this reaction or design of an appropriate substrate for an intramolecular coupling may overcome this shortcoming.

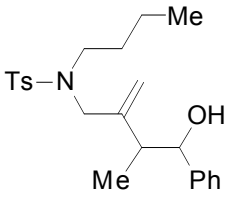
A.4 – Experimental Details

Procedure for reductive coupling

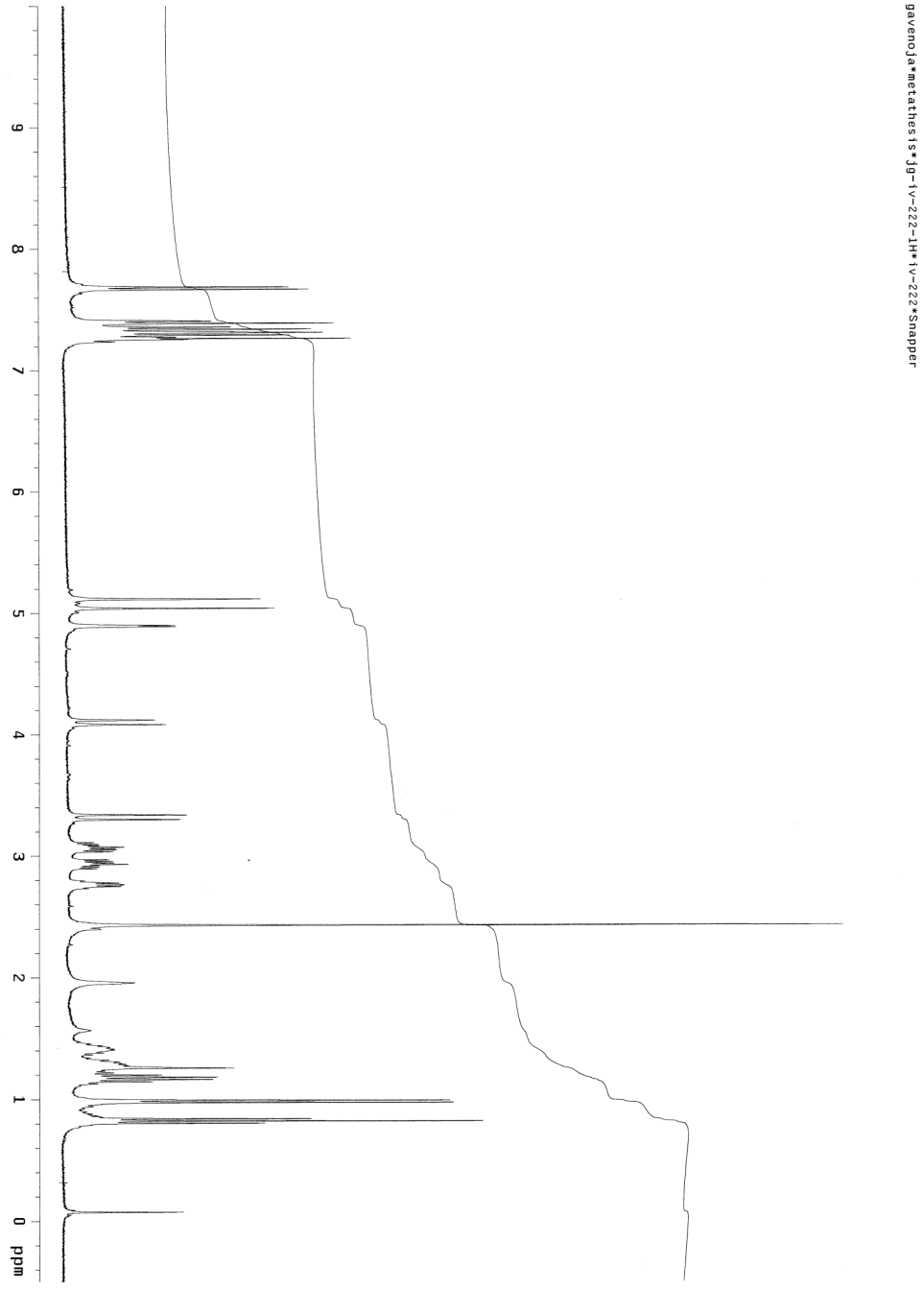


A.3 **A.5**

In an inert-atmosphere glove box, N-butyl-4-methyl-N-(2-methylenebut-3-en-1-yl)benzenesulfonamide (39 mg, 130 μmol, 2.5 equiv.), benzyl alcohol (5.5 μL, 53 μmol, 1.0 equiv.), $(Cy_3P)_2Ru(CO)HCl$ (2.5 mg, 2.7 μmol, 5 mol %), (R)-BINAP (1.7 mg, 2.7 μmol, 5 mol %), *ortho*-nitrobenzoic acid (0.2 mg, 1 μmol, 3 mol %), and THF (250 μL) were added sequentially to a flame-dried, 1 mL conical vial charged with a triangular magnetic spin-vane. The vial was then capped, sealed with electrical tape, removed from the glove box, immersed in a 105 °C oil bath, and allowed to stir for 18 hours. The crude reaction mixture was adsorbed directly on a preparatory thin-layer chromatography plate, and then eluted with hexanes/ethyl acetate (4:1). The band at rf = 0.3 produced 11 mg of compound **A.5** (52% yield) as a single diastereomer.



N-butyl-N-(4-hydroxy-3-methyl-2-methylene-4-phenylbutyl)-4-methylbenzenesulfonamide (A.5): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.68 (d, *J* = 7.6 Hz, 2H), 7.41-7.24 (m, 7H), 5.12 (s, 1H), 5.04 (s, 1H), 4.90 (d, *J* = 4.4 Hz, 1H), 4.10 (d, *J* = 14.8 Hz, 1H), 3.20 (d, *J* = 14.8 Hz, 1H), 3.07 (ddd *J* = 14.4, 9.6, 5.6 Hz, 1H), 2.93 (ddd *J* = 15.2, 10.0, 5.2 Hz, 1H), 2.77 (qd, *J* = 7.2, 4.4 Hz, 1H), 2.43 (s, 3H), 1.96 (br s, 1H), 150-1.21 (m, 2H), 1.17 (q, *J* = 7.2 Hz, 2H), 0.98 (d, *J* = 7.2 Hz, 3H), 0.82 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (C_6D_6, 100.6 MHz) δ 147.2, 143.3, 142.7, 137.1, 129.8, 128.2, 127.32, 127.28, 126.5, 115.1, 75.0, 53.9, 48.4, 42.7, 30.4, 27.8, 20.3, 13.9, 13.2; IR (NaCl, thin film) 3082 (m), 3060 (m), 3028 (m), 2933 (m), 2923 (m), 2913 (m), 1601 (w), 1447 (w), 1026 (w), 1026 (w), 771 (m), 763 (m), 757 (m) cm^{-1}; HRMS (ES+): calculated for formula $C_{23}H_{30}NO_2S^+$.(M+H – H_2O): *m/z* 384.1998, found 384.1988.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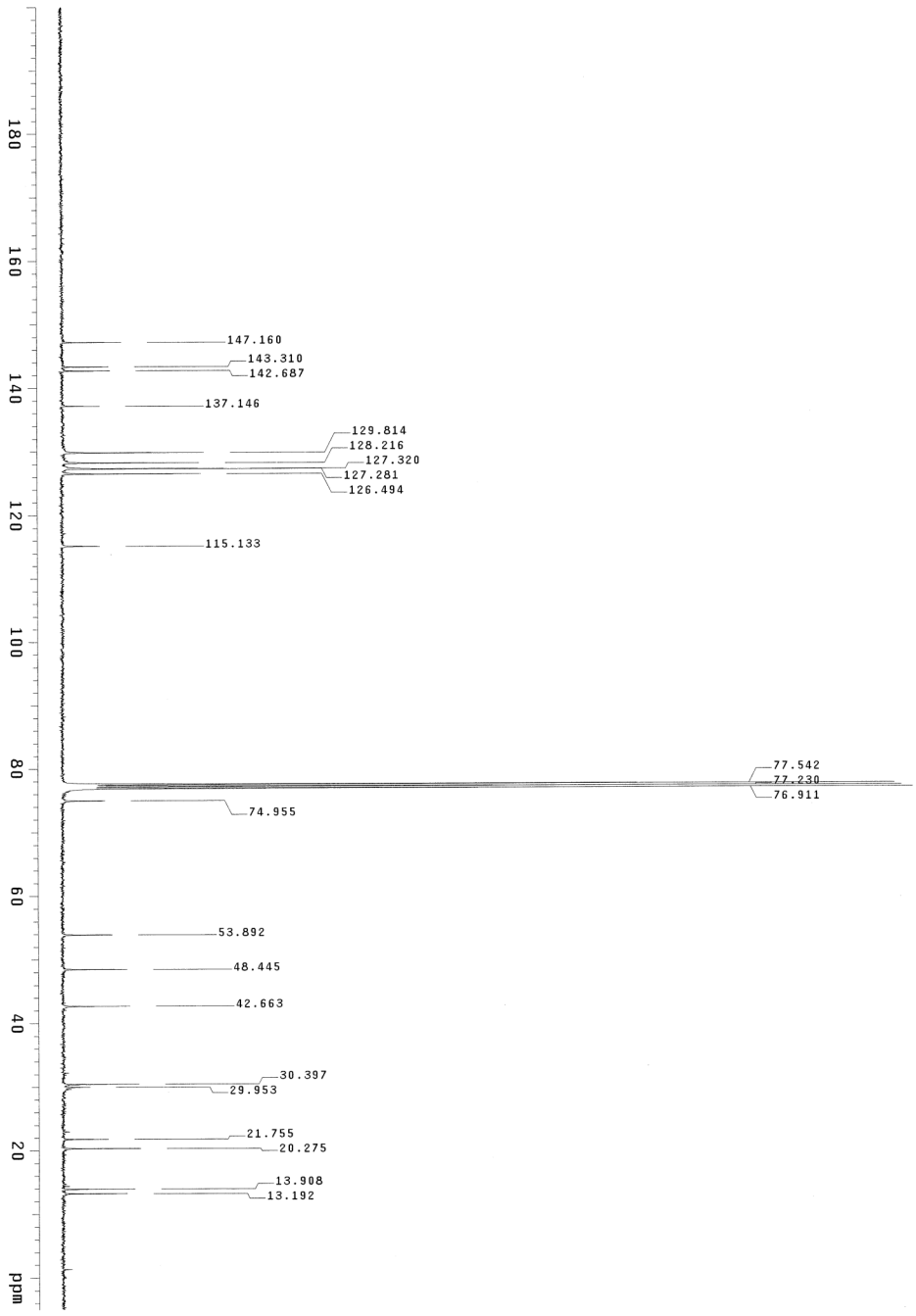
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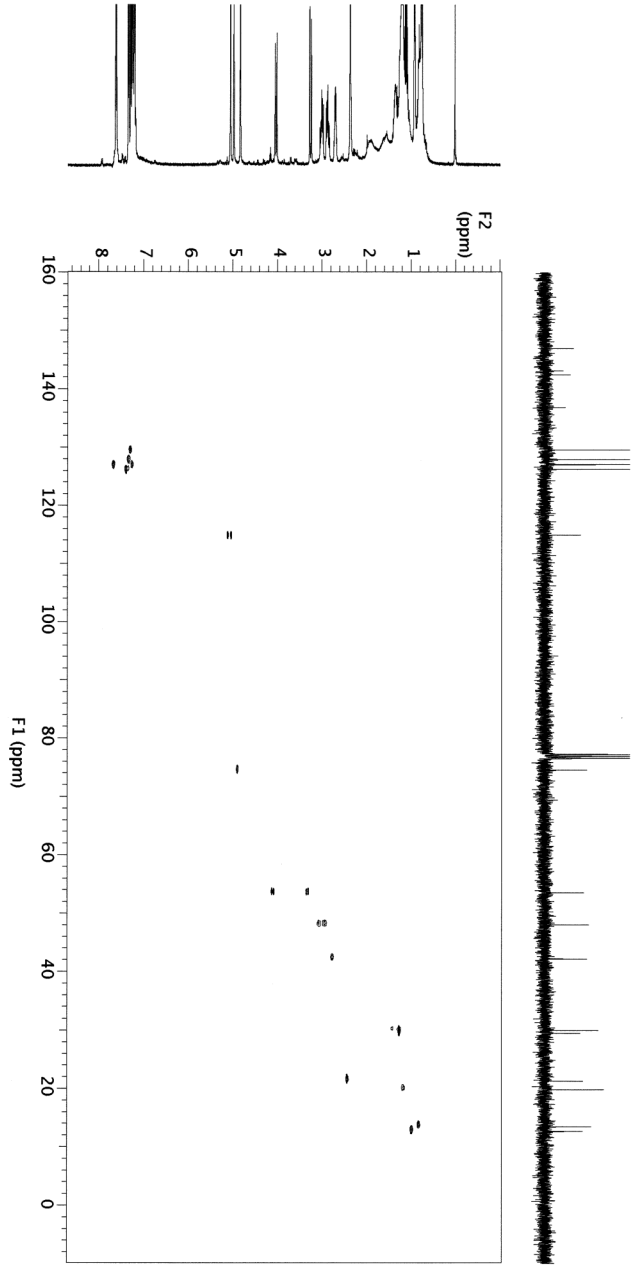
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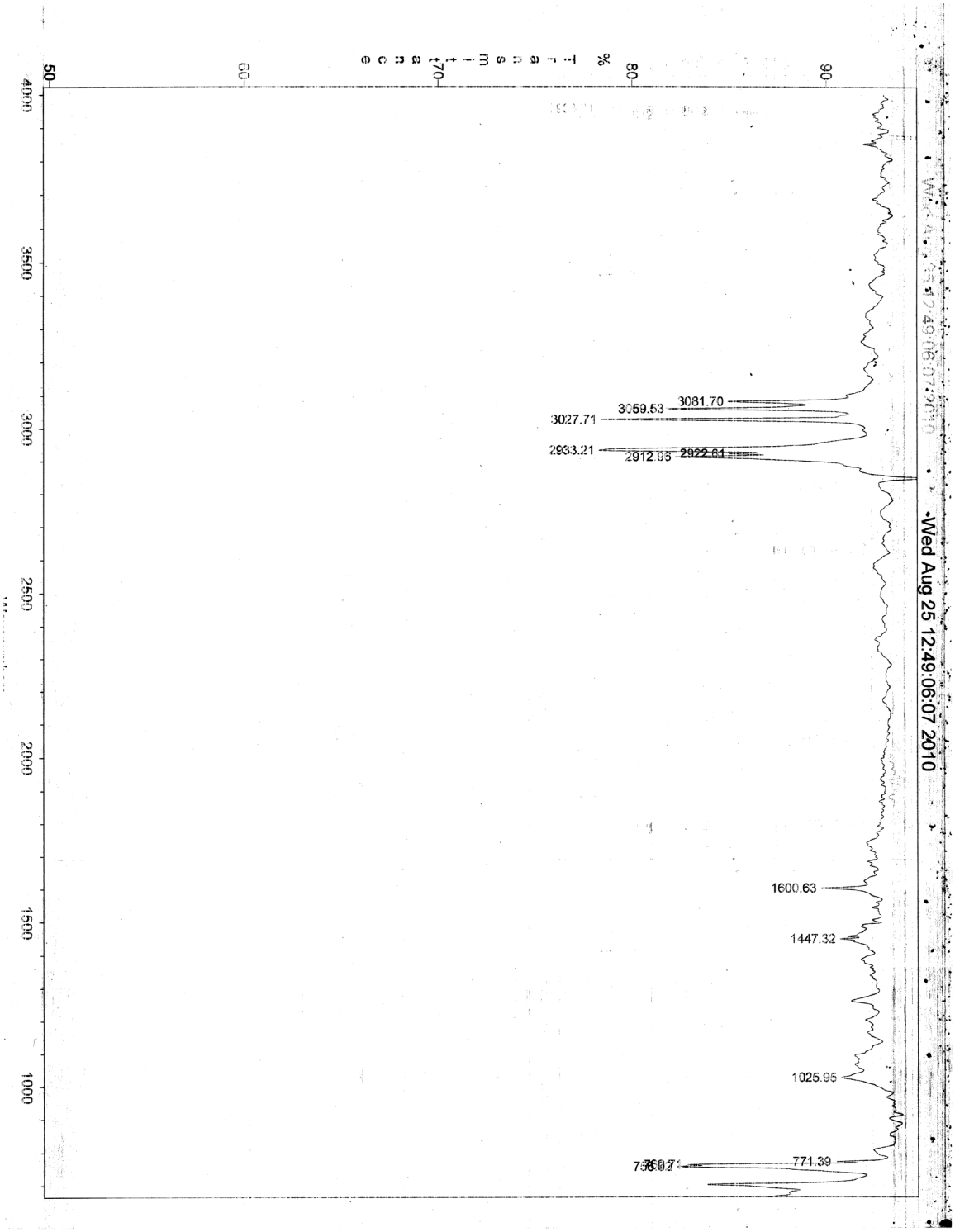
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%
Transmittance
4000
3500
3000
2500
2000
1500
1000
50
60
70
80
90

Procedure for tandem enyne metathesis-reductive coupling

A.6 **A.5**

In an inert-atmosphere glove box, N-butyl-4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide (112 mg, 420 μmol, 2.5 equiv.) and **C823** (53 mg, 64 μmol, 40 mol %) were dissolved in dicholormethane (15 mL) in a Schlenk tube. After removal of the sealed tube from the glove box, the reaction mixture was sparged with ethylene for 5 minutes, the tube was sealed, and the reaction allowed to stir at ambient temperature for 22 h. Solvent was then carefully removed under reduced pressure with vigorous stirring, and toluene (1.6 mL) and sodium methoxide in methanol (64 μmol, 1.6 mL of 0.04 M solution) were then added. The reaction mixture was then heated to 75 °C for 1 hour, and the solvent again removed *in vacuo*. The reaction vessel was returned to the glove box, and (R)-BINAP (40 mg, 64 μmol, 40 mol %), *o*-nitrobenzoic acid (5.3 mg, 32 μmol, 20 mol %), benzyl alcohol (18 mg, 168 μmol, 1 equiv.), and THF (1mL) were added sequentially. The tube was sealed, removed from the glove box, and heated to 100 °C for 24 h. Compound **A.5** (35% yield) was then purified as above.