ABSTRACT

Title of Dissertation:	Oxidative C-H and C=C Bond Functionalization Catalyzed by Dirhodium Caprolactamate
	Arthur J. Catino, Doctor of Philosophy, 2006
Dissertation directed by:	Dr. Michael P. Doyle Professor Department of Chemistry and Biochemistry

Dirhodium tetrakis[ε-caprolactamate], $Rh_2(cap)_4$, was found to be an effective catalyst for allylic oxidation in combination with *tert*-butyl hydroperoxide (*t*-BuOOH). Substituted cyclic olefins were converted to enones and enediones with 0.1 – 1.0 mol% catalyst loading. $Rh_2(cap)_4$ was also found to be an effective catalyst for benzylic oxidation in combination with *t*-BuOOH. Benzylic carbonyl compounds were obtained across a range of substrates including those that contained nitrogen and acid-labile functionality. A formal synthesis of palmarumycin CP_2 was achieved using this methodology. Spectroscopically, it was determined that $Rh_2(cap)_4$ (Rh_2^{4+}) undergoes a 1-electron oxidation upon treatment with *t*-BuOOH to give a higher valent dirhodium(II,III) complex (Rh_2^{5+}).

A mild, efficient, and selective aziridination catalyzed by $Rh_2(cap)_4$ was discovered. Using *p*-toluenesulfonamide ($TsNH_2$), *N*-bromosuccinimide (NBS), and potassium carbonate (K_2CO_3), aziridines were obtained with as little as 0.01 mol% $Rh_2(cap)_4$. Aziridine formation occurred through a Rh_2^{5+}-catalyzed amidobromination and subsequent base-induced ring closure. An

X-ray crystal structure of a Rh_2^{5+} halide complex, formed from the oxidation of $Rh_2(cap)_4$ with *N*-chlorosuccinimide, was obtained.

Finally, $Rh_2(cap)_4$ was found to be a catalyst for C-H oxidation of tertiary amines using *t*-BuOOH. An oxidative Mannich reaction was realized when the C-H oxidation was conducted in the presence of 2-siloxyfurans as nucleophiles. Reactions were performed efficiently (as low as 0.1 mol% loading) in MeOH using 70% *t*-BuOOH in H_2O (T-HYDRO). Synthetically useful aminoalkyl butenolides were obtained.

OXIDATIVE C-H AND C=C BOND FUNCTIONALIZATION CATALYZED BY DIRHODIUM CAPROLACTAMATE

BY

ARTHUR J. CATINO

Dissertation submitted to the Faculty of the Graduate School of the University of Maryland at College Park in partial fulfillment of the requirements for the degree of Doctor of Philosophy
2006

Advisory Committee:

Professor	Michael P. Doyle, Chairman/Advisor
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Professor	Russell Dickerson

DEDICATION

TO MY PARENTS

Arthur and Maria Catino

“Happy the man who bears within him a divinity,

an ideal of beauty and obeys it;

an ideal of art,

an ideal of science,

an ideal of country,

an ideal of the virtues of the Gospel.”

Louis Pasteur (1822 – 1895)

ACKNOWLEDGEMENTS

I would like to thank Professor Michael Doyle for his support throughout my graduate studies. It has been an honor and a privilege to be a member of the Doyle Research Group. Also, I would like to thank Mike for all of the opportunities that he gave to me over years, especially the invitation to come to the University of Maryland and the independence to pursue my own direction in his group. I am truly gratefully for his support, guidance, patience, and kindness over the years.

I would like to thank my undergraduate research advisors Professor Phyllis Leber and Professor Scott Van Arman at Franklin & Marshall College (Lancaster, PA) for their guidance during my undergraduate years. Both were incredible mentors and I consider myself lucky to have worked under their direction.

I would like to thank my high school chemistry teacher Mr. Daniel Welker at Our Lady of Lourdes Regional High School (Coal Township, PA). It was honors chemistry with “ole DW” that ignited my passion for science. I fondly recall our weekly labs, in particular the preparation of copper sulfide. I will never forget the entire school smelling like rotten eggs (next time I’ll use the right amount of sulfur).

I would like to thank Jason Nichols for collaborating with me on several projects during the course of my graduate studies. I am utterly impressed by his ability to dissect problems, especially at the mechanistic level. I would also like to thank Dr. Raymond Forslud, Dr. Hojae Choi, Rishi Sidhu, Sidhartha Gottipamula, Brian Nettles, James Myslinski, and Catt Edgley for their contributions. It has been a pleasure working with all of you.

I would like to thank Professor Lyle Isaacs, Professor Dan Falvey, and Professor Larry Sita, and Professor Russell Dickerson for serving on my defense committee. In particular, thank you to Professor Isaacs for all of the advice during my time at Maryland.

I would like to acknowledge the American Chemical Society Division of Organic for a graduate fellowship in memory of the late Emmanuil Troyankşky.

The University of Maryland has been an excellent place to conduct research due to the dedication of an amazing support staff. I would like thank Yui-Fai Lam and Gene Mazzola for NMR support, Noel Whittaker for MS data, Bob Harper for computer support, Linda Zappasodi, Tayrn Faulkner, and Cathy Clark for office support.

I have been blessed with caring and supportive friends during my graduate studies that have made a positive impact in my life. I would sincerely like to thank Jason Nichols and Darren Bykowski. I cannot even begin to imagine what graduate school would be like without both of you. I only hope that someday I can inspire someone as you have inspired me. I would also like to thank Doyle Group members Tom Weathers, Kousik Kunda, Marcela Valenzuela, John Colyer, Christine Hedberg, Jim Cain, Dr. Raymond Forslud, Dr. Hojae Choi, Dr. Albert Russell, Dr. J.P. Morgan, and Dr. Penglin Huang, Rishi Sidhu, Sidhartha Gottipamula, Brian Nettles, Catt Edgley, Sara Saba, Jon Brekan, Ben Von Hoenstoffen, and Randy Binder. It has been a pleasure working along side of each of you.

I would like to thank Chris Long for his friendship and the good times while at the University of Arizona, especially all the evenings spent at Nancy's

Fort Lowell Pub. I would also like to thank Dave Sisk for making me feel welcomed when I first moved to Arizona.

I would like to thank Adrienne Sochia for her friendship over the years. I will always cherish all of the good times. Thank you also to Matt Crowe, Margaret Royall, Robert Brewer, Sunny John, Shirin Shinde, Micheal “Hick” Reinard, Faycal Falaky, TJ Unger, Trishul Shah, and Kristen Price.

I would like to thank Father William Byrne (Campus Chaplian), Father George Wilkinson (Holy Redeemer Parish, College Park), and Father John McKay (St. Mark the Evangelist Church, Hyattsville). The Archdiocese of Washington DC has been a wonderful place to call my home for the last three years.

I would like to thank Tom Cole for his advice and support going back to my days in high school. I would also like to thank Alfonsus Caser whose knowledge of science and spirituality inspire me (thank you for the many books, in particular, the writings of Saint Alfonsus de Liguori).

I would like to thank my family, my parents Arthur and Maria Catino and my sisters Loriann and Thalia, who have always been there for me. I love you all very much and I thank you for your patience and support over the years.

Finally, I would like to thank God. All glory and honor forever belong to Him.

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LIST OF ABBREVIATIONS

Ac	Acetyl
AIBN	2,2'-Azobis(2-methylpropionitrile)
Boc	*tertiary*-Butylcarbamate
Bn	Benzyl
Bu	Butyl
n-BuLi	*normal*-Butyllithium
CAN	Ceric ammonium nitrate
cat*	Catalyst
conv.	Conversion
DCE	1,2-Dichloroethane
de	Diastereomeric excess
DIAD	Diisopropyl azodicarboxylate
DMA	*N*,*N*-Dimethylaniline
DMAP	Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
Et_3N	Triethylamine
EtOAc	Ethyl acetate
equiv	Equivalent
h	Hour
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
MS	Molecular sieves
MsCl	Methanesulfonyl chloride

NCS	*N*-Chlorosuccinimide
NBS	*N*-Bromosuccinimide
Ns	Nitrosulfonyl
Ph	Phenyl
$Rh_2(cap)_4$	Dirhodium tetrakis[ε-caprolactamate]
rt	Room temperature
T-HYDRO	70% *tertiary*-Butylhydroperoxide in water
TBS	*tertiary*-Butyldimethylsilyl
TBHP	*tertiary*-Butylhydroperoxide
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMS	Trimethylsilyl
Ts	*para*-Toluenesulfonyl

CHAPTER 1

ALLYLIC AND BENZYLIC OXIDATION CATALYZED BY DIRHODIUM CAPROLACTAMATE

I. BACKGROUND AND SIGNIFICANCE

The chemo-, regio-, and stereoselective functionalization of allylic and benzylic C-H bonds with oxygen is fundamentally important in organic synthesis and has far-reaching implications.[1] Yielding a myriad of synthetically useful products, allylic and benzylic oxidations enjoy widespread use in both academia and industry. Several methods have been developed for oxidative functionalization ranging from stoichiometric reagents to catalytic processes, but drawbacks such as poor selectivity, toxic reagents/byproducts, and limited scalability continue to fuel research and development. This overview will specifically highlight chemoselecitve oxidation of allylic and benzylic C-H bonds, i.e. C-H → C=O, using both stoichiometric and catalytic methods.

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[1] For reviews see: (a) Bulman Page, P. C.; McCarthy, T. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, UK, 1991; Vol. 7, 83. (b) Sheldon, R. A. In *Fine Chemicals through Heterogeneous Catalysis*; Sheldon, R. A., van Bekkum, H., Eds.; Wiley: Weinheim, 2001, p 519. (c) Olah, G. A.; Molnár, Á. In *Hydrocarbon Chemistry*, 2[nd] ed; Wiley: Hoboken; 2003; p 427.

Allylic Oxidation (Stoichiometric Methods). Riley and coworkers in 1932 reported that selenium(IV) dioxide (SeO_2) is an effective reagent for the oxidation of methylene groups adjacent to olefins.[2] Subsequently, Guillemont[3] and others[4] observed that oxidations mediated by SeO_2 occur with predictable selectivity: 1) oxidation tends to occur on the most substituted end of an alkene, 2) the preference for oxidation tends to be CH_2 > CH_3 > CH, 3) the oxidation of an endocyclic alkene tends to occur α to the more substituted end of the double bond, and 4) *gem*-dimethyl alkenes tend to oxidized to afford the *E* alkene geometry. Allylic oxidations mediated by SeO_2 and selectivity trends have been extensively reviewed.[5]

Sharpless and coworkers in 1973 proposed that the mechanism of allylic oxidation with SeO_2 proceeds via an initial ene reaction followed by a [2,3]-sigmatropic rearrangement to give selenoxylic ester **1** (Figure 1.1).[6] Solvolysis of **1** (with H_2O) gives the corresponding allylic alcohol, or with prolonged reaction time, the corresponding α,β-unsaturated enone. Thus, chemoselectivity can usually be controlled by work-up; however, mixtures of alcohol and enone are observed. The mechanism for allylic oxidation

[2] (a) Riley, H. L.; Morley, J. F.; Friend, N. A. C. *J. Chem. Soc.* **1932**, 1875. (b) Riley, H. L.; Friend, N. A. C. *J. Chem. Soc.* **1932**, 2342.

[3] (a) Guillemont, A. *Ann. Chim*. **1939**, *11*, 14. (b) Fieser, L. F.; Fieser, M. In *Reagents for Organic Synthesis*; Wiley: New York, 1967, Vol. 1, p 992.

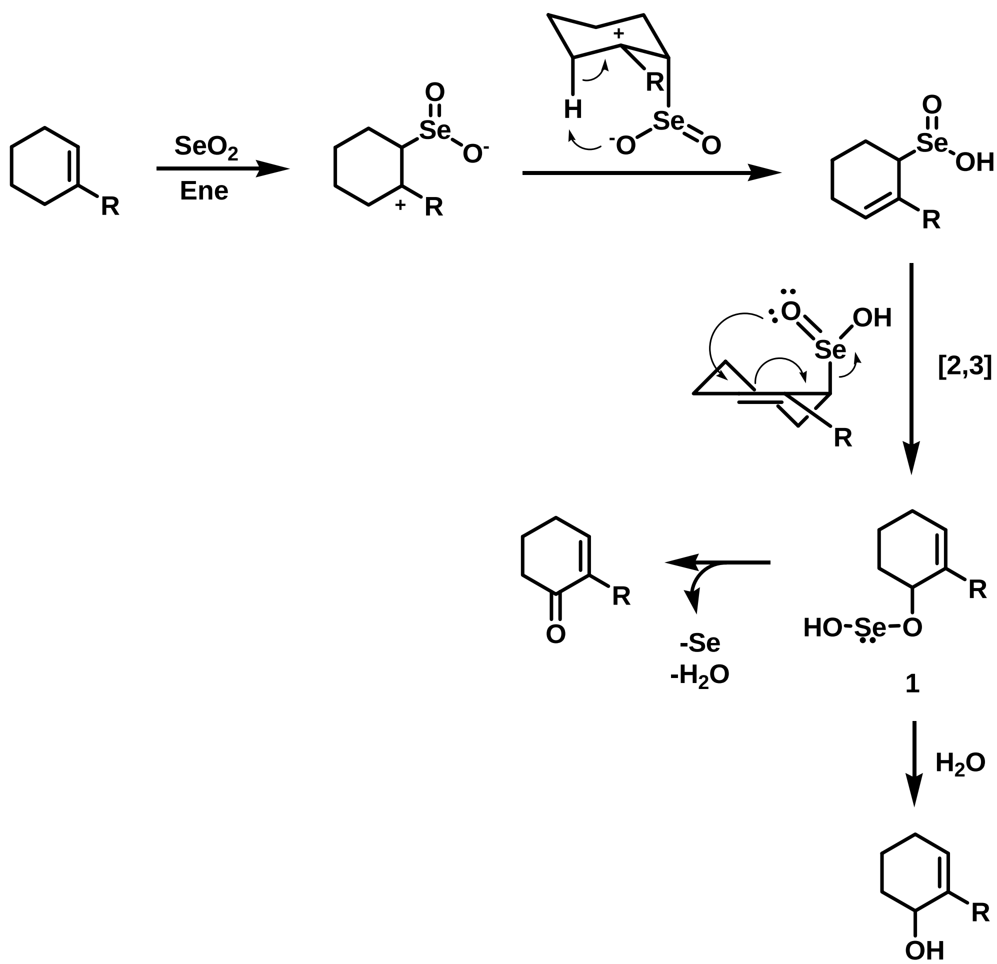
[4] (a) Bhalerao, U. T.; Rapoport, H. *J. Am. Chem. Soc.* **1971**, *93*, 4835. (b) Trachtenberg, E. N.; Carver, J. R. *J. Org. Chem.* **1970**, *35*, 1646.

[5] For reviews see: (a) Waitkins, G. R.; Clark, C. W. *Chem. Rev.* **1945**, *36*, 235. (b) Rabjohn, N. *Org. React.* **1949**, *5*, 331. (c) Rabjohn, N. *Org. React.* **1976**, *24*, 261. (d) Hoekstra, W. J. In *EROS*; Paquette, L. A., Ed.; Wiley: Chicester, UK, 1995; Vol. 6, p 4437.

[6] (a) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1972**, *94*, 7154. (b) Arigoni, D.; Vasella, A.; Sharpless, K. B.; Jensen, H. P. *J. Am. Chem. Soc.* **1973**, *95*, 7917.

advanced by Sharpless was recently supported computationally by Singleton and coworkers in 2000.[7]

Figure 1.1. Mechanistic Proposal for Allylic Oxidation with SeO_2.



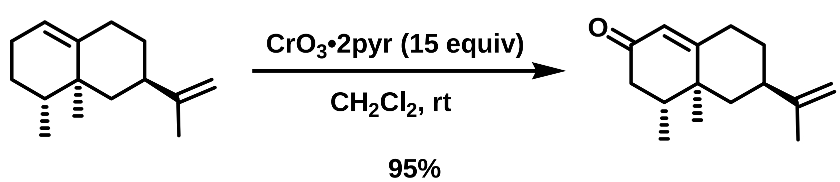
Mechanistically, allylic oxidations using chromium(VI) reagents are less understood than those that use SeO_2. However, it is generally agreed that chromium-based oxidations proceed through an initial hydride or

[7] Singleton, D. A.; Hang, C. *J. Org. Chem.* **2000**, *65*, 7554.

hydrogen atom abstraction to produce an allylic cation or radical, respectively, followed by oxygen transfer to generate an α,β-unsaturated ketone.[8,9]

Dauben and coworkers in 1969 developed a methodology for allylic oxidation using $CrO_3 \cdot 2pyr$ (Collin's reagent[10]) in CH_2Cl_2 at room temperature.[11] The oxidation of several substituted cyclohexenes and steroids were reported to give enones in 48-95% yield. For example, valencene was oxidized to nootkatone in 98% yield at room temperature in 25 hours using $CrO_3 \cdot 2pyr$ (15 equiv) (Scheme 1.1). The authors noted that optimal yields for allylic oxidation were obtained by isolating $CrO_3 \cdot 2pyr$ as opposed to preparing it *in situ.*

Scheme 1.1.



Salmond and coworkers in 1978 at Upjohn found that chromium trioxide-3,5-dimethylpyrazole complex ($CrO_3 \cdot 3,5$-DMP[12]) was superior to

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[8] For reviews see: (a) Cainelli, G.; Cardillo, G. *Chromium Oxidations in Organic Chemistry*; Springer: Berlin, 1984. (b) Muzart, J. *Chem. Rev.* **1992**, *92*, 113.

[9] Wiberg, K. B.; Nielsen, S. D. *J. Org. Chem.* **1964**, *29*, 3353.

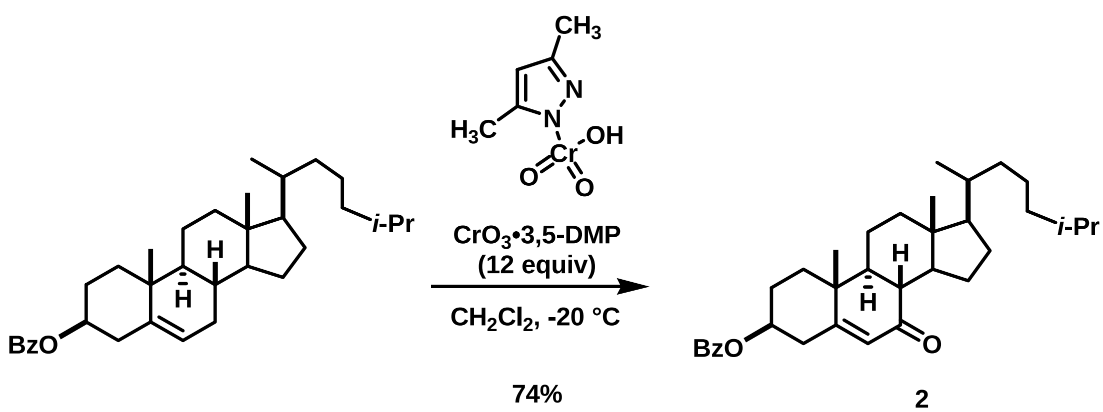
[10] Collins, J. C.; Hess, W. M.; Frank, F. J. *Tetrahedron Lett.* **1968**, 3363.

[11] Dauben, W. G.; Lorber, M.; Fullerton, D. S. *J. Org. Chem.* **1969**, *34*, 3587.

[12] Corey, E. J.; Fleet, G. W. J. *Tetrahedron Lett.* **1973**, 4499.

CrO_3·2pyr for allylic oxidation because it could be prepared in situ and used at or below room temperature.[13] For example, cholesterol benzoate was converted to enone **2** in 74% yield in 4 hours using CrO_3·3,5-DMP (12 equiv). The authors observed a substantial rate enhancement over CrO_3·2pyr that they attributed to the increased solubility of CrO_3·3,5-DMP and the basicity of the proximal nitrogen in the pyrazole nucleus for intramolecular hydrogen abstraction. The limitation is that a large excess of CrO_3·3,5-DMP must typically be used for allylic oxidation. For example, CrO_3·3,5-DMP (20 equiv, 80 g) was used by Shing and coworkers in 2005 to oxidize **3** to **4** on a 10 g scale in 60% yield (Scheme 1.3).[14]

Scheme 1.2.



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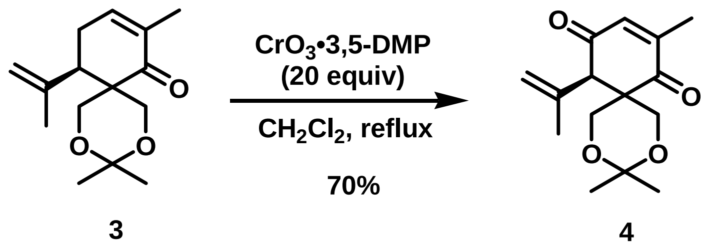
[13] Salmond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem.* **1978**, *43*, 2057.

[14] Shing, T. K. M.; Yeung, Y. Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 7981.

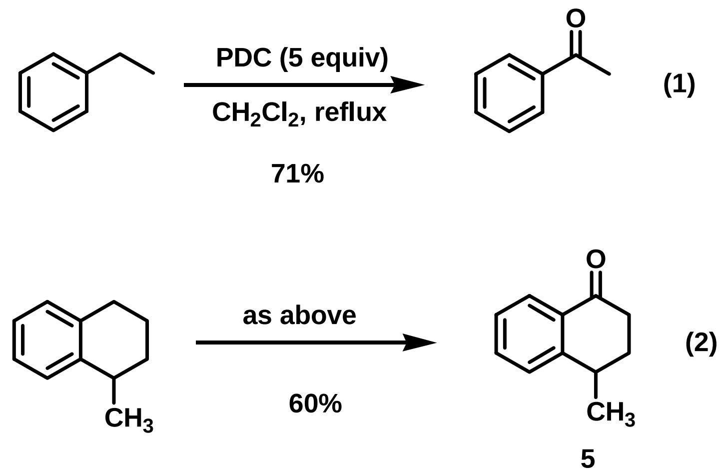
Scheme 1.3.



Benzylic Oxidation (Stoichiometric Methods). Chandrasekaren and coworkers in 1986 reported a procedure for benzylic oxidation using an excess of pyridinium chlorochromtate (PCC) in refluxing CH_2Cl_2.[15] For example, PCC (5 equiv) was used to oxidize ethylbenzene to acetophenone in 71% yield in 15 hours (Scheme 1.4, eq 1). The oxidation of 1-methyl-1,2,3,4-tetrahydronaphthalene gave exclusively 4-methyl-1-tetralone (**5**) in 60% yield in refluxing CH_2Cl_2 for 15 hours (Scheme 1.4, eq 2). No mechanistic information was reported by the authors.

[15] Rathore, R.; Saxena, N.; Chandrasekaran, S. *Synth. Commun.* **1986**, *16*, 1493. For a modification of this procedure, see: Chidambaram, N.; Chandrasekaran, S. *J. Org. Chem.* **1987**, *52*, 5048.

Scheme 1.4.

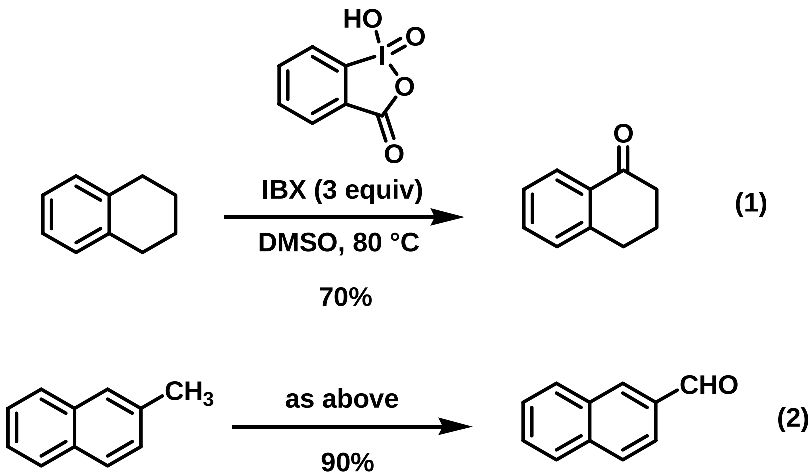


Nicolaou and coworkers in 2001 reported a general method for benzylic oxidation using stoichiometric *o*-iodoxy benzoic acid (IBX).[16] The reaction gave good to excellent yields over 20 examples. For example, using IBX (3.0 equiv) in DMSO at 80 °C, 1,2,3,4-tetrahydronapthalene (tetralin) was converted to α-tetralone in 70% yield after 12 hours (Scheme 1.5, eq 1). The methodology was also amenable to primary benzylic oxidation for the preparation of aldehydes without over-oxidation to the corresponding carboxylic acid (Scheme 1.5, eq 2). The authors proposed that, in the presence of IBX, substrates undergo singe electron transfer (SET) and deprotonation to form a benzylic carbocation. Trapping of the benzylic carbocation with oxygen from DMSO or IBX and subsequent elimination give

[16] (a) Nicolaou, K. C.; Baran, P. S.; Zhong, Y. L. *J. Am. Chem. Soc.* **2001**, *123*, 3183. (b) Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y. L. *J. Am. Chem. Soc.* **2002**, *124*, 2245.

the carbonyl product. This mechanistic proposal was supported by failure of electron-deficient substrates to undergo oxidation.[17]

Scheme 1.5.



Allylic Oxidation (Catalytic Methods). Sharpless and Umbreit in 1977 reported an allylic oxidation catalyzed by SeO_2 (2-50 mol%) in conjunction with *tert*-butyl hydroperoxide (*t*-BuOOH) as a stoichiometric oxidant.[18] Under these conditions, reduced forms of selenium were reoxidized by *t*-BuOOH. The authors noted that reactions using catalytic SeO_2 generally proceed under much milder conditions, give higher yields, and contain less organoselenium by-products. However, milder conditions generally give rise to allylic alcohols as opposed to α,β-unsaturated enones.

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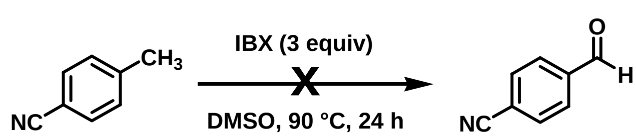
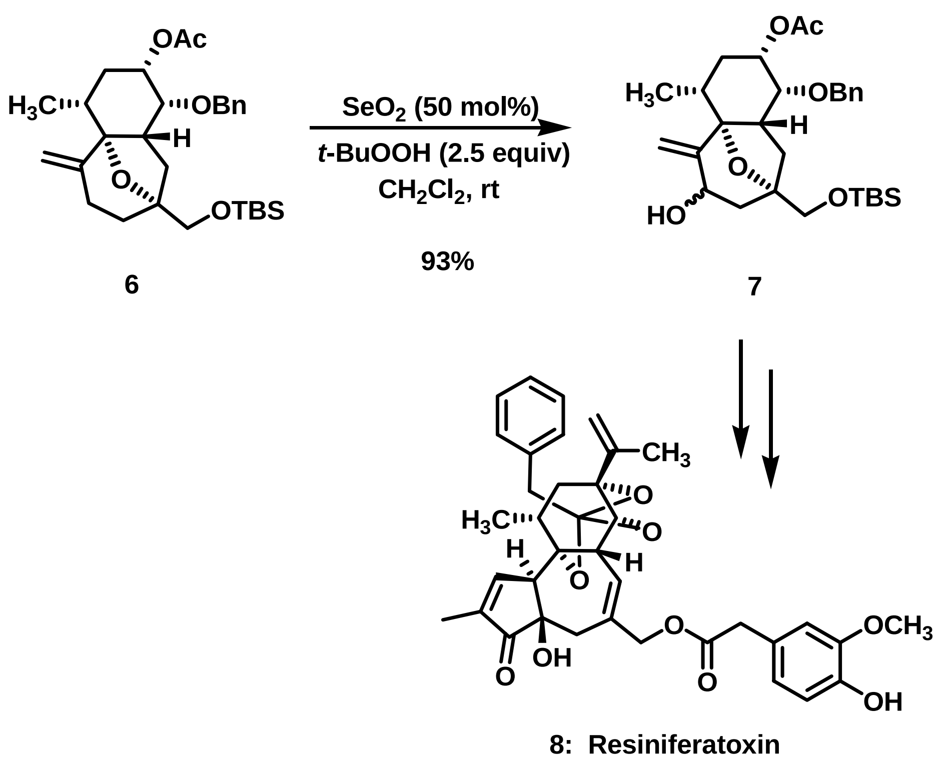
[17] Electron-deficient substrates do not undergo oxidation with IBX:



[18] Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526.

Conditions reported by Sharpless in 1977 have virtually replaced older conditions that required stoichiometric amounts of SeO_2 that are both toxic and malodorous.[19] Catalytic SeO_2 in conjunction with *t*-BuOOH has been used in natural product synthesis. For example, Wender and coworkers in 1997 used a SeO_2-catalyzed allylic oxidation *en route* to resiniferatoxin (**8**), a well-known daphnane diterpene.[20] Oxidation of exocyclic alkene **6** gave allylic alcohol **7** in 93% yield after 9 hours (Scheme 1.6).

Scheme 1.6.

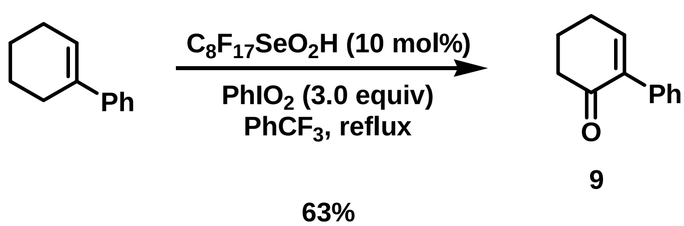


[19] Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63.

[20] Wender, P. A.; Jesudason, C. D.; Nakahira, H.; Tamura, N.; Tebbe, A. L.; Ueno, Y. *J. Am. Chem. Soc.* **1997**, *119*, 12976.

Crich and Zou in 2004 developed a catalytic recyclable selenium-catalyst, i.e. a fluorous seleninic acid, for allylic oxidation using iodoxybenzene ($PhIO_2$) as a stoichiometric oxidant.[21] The authors pointed out that selenium-based oxidations can be problematic on scale-up due to high catalyst loading and the inherent difficulty in recycling selenium. Thus, using $C_8F_{17}SeO_2H$ (10 mol%) and $PhIO_2$ (3.0 equiv), 1-phenylcyclohexene was oxidized to enone **9** in 63% yield with 88% catalyst recovery (Scheme 1.7). Based on the the observed regioselectivity of **9** (as well as other substrates), Crich and Zou proposed that allylic oxidation with seleninic acids likely proceeds through a mechanism similar to SeO_2.

Scheme 1.7.



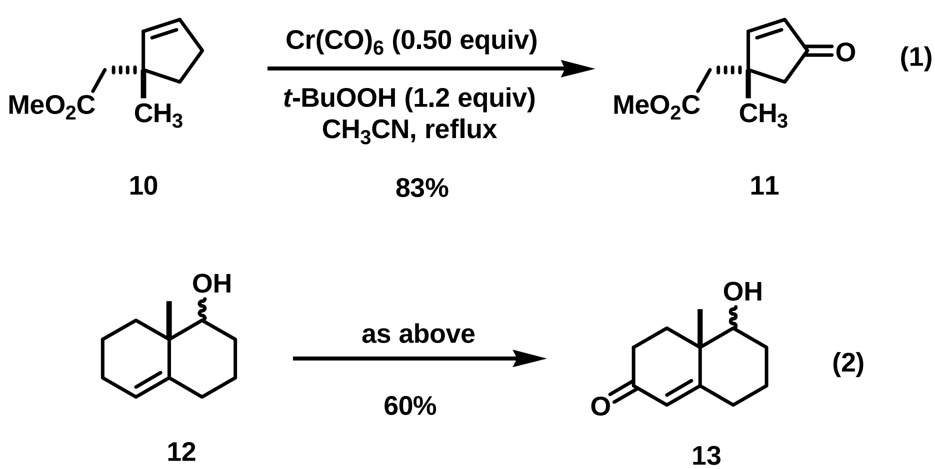
Pearson and coworkers in 1984 serendipitously discovered a catalytic allylic oxidation while screening metal-complexes for the epoxidation of **10** (Scheme 1.8).[22] Catalytic chromium hexacarbonyl [$Cr(CO)_6$, 50 mol%] in refluxing CH_3CN gave enone **11** as the exclusive product after 18 hours (Scheme 1.8, eq 1). Under these conditions, allylic oxidation of **12** to **13** occurred in the presence of a secondary alcohol (Scheme 1.8, eq 2).

[21] Crich, D.; Zou, Y. *Org. Lett.* **2004**, *6*, 775.

[22] Pearson, A. J.; Chen, Y. S.; Hsu, S. Y.; Ray, T. *Tetrahedron Lett.* **1984**, *25*, 1235.

Catalyst loading could be dropped to 5.0 mol%; however, longer reaction times were required (38 hours). Interestingly, the authors reported that mixtures of enone and epoxide were observed when the reaction was conducted in benzene as a solvent. Although no mechanistic rationale was given, the dimunition of chemoselectivity in benzene was attributed to the catalyst. The authors determined spectroscopically that $Cr(CO)_3(CH_3CN)_3$ was formed in situ using CH_3CN as a solvent.

Scheme 1.8.

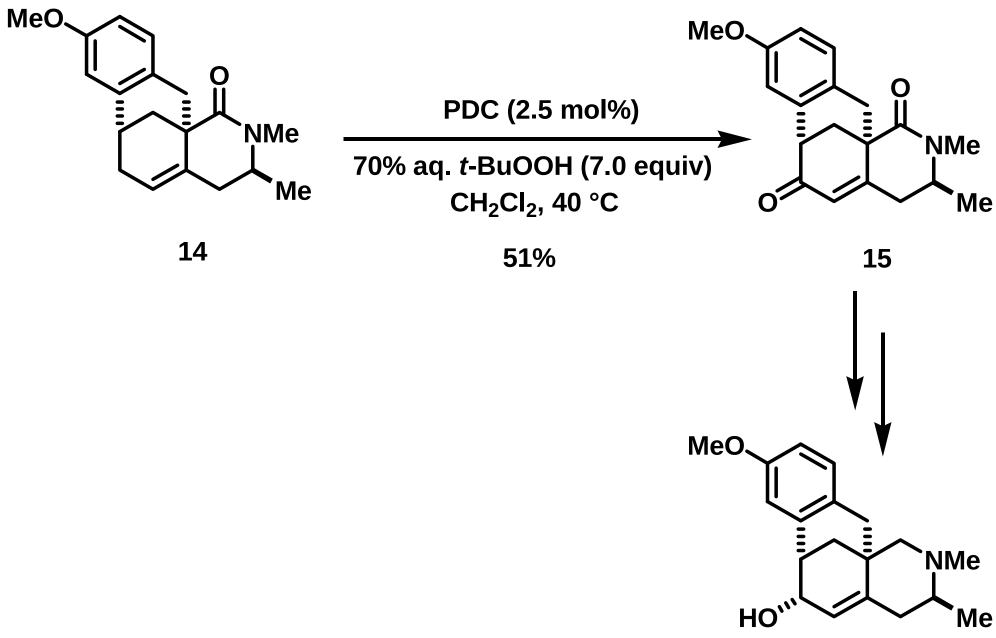


A catalytic allylic oxidation was described by Schultz and coworkers in 1998 for the synthesis of μ-opiod receptor **16** (Scheme 1.9).[23] Olefin **14** was treated with catalytic pyridinium dichromate (2.5 mol%, PDC) and 70% *t*-BuOOH in water (70% aq. *t*-BuOOH) at room temperature to give **15** in 51% yield after 18 hours. Albeit one example, this procedure was noteworthy due

[23] Schultz, A. G.; Guzi, T. J.; Larsson, E.; Rahm, R.; Thakkar, K.; Bidlack, J. M. *J. Org. Chem.* **1998**, *63*, 7795.

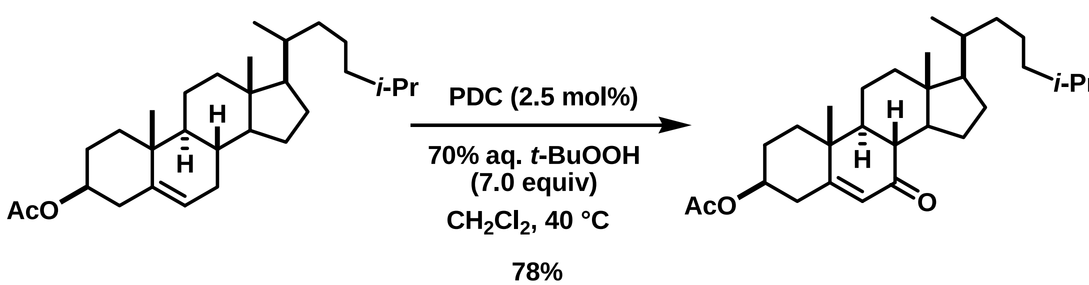
to the mild reaction conditions, low catalyst loading, and use of aqueous *t*-BuOOH. Recently, Muzart and coworkers applied this procedure to the allylic oxidation of Δ^5-steroids (Scheme 1.10).[24]

Scheme 1.9.



14 **15** **16**

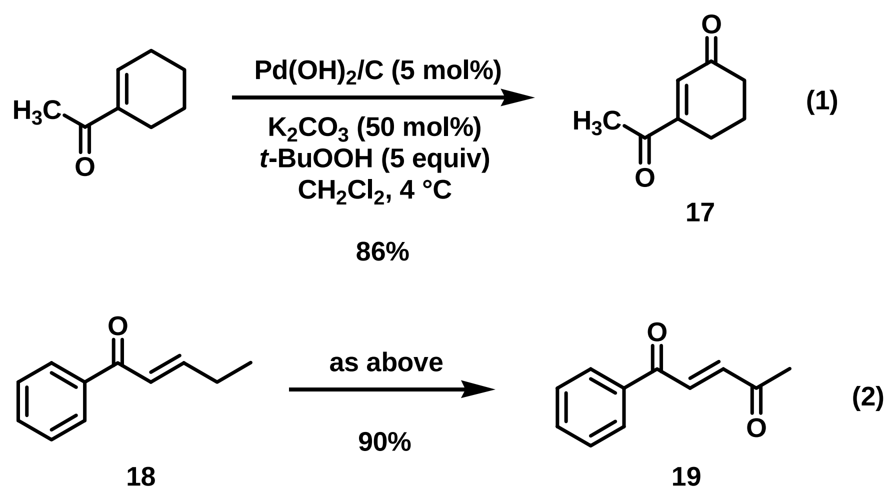
Scheme 1.10.



[24] Fousteris, M. A.; Koutsourea, A. I.; Nikolaropoulos, S. S.; Riahi, A.; Muzart, J. *J. Mol. Cat. A* **2006**, *250*, 70.

Corey and Yu in 2003 described a catalytic allylic oxidation for the conversion of α,β-enones into 1,4-enediones using 5 mol% $Pd(OH)_2$ on carbon (Pearlman's catalyst[25]), K_2CO_3, and anhydrous *t*-BuOOH.[26] For example, 1-acetylcyclohexene was converted to enedione **17** in 86% yield after 36 hours at 4 °C (Scheme 1.11, eq 1). Acyclic enone **18**, under the same conditions, was converted to enedione **19** in 90% yield (Scheme 1.11, eq 2). Subsequent applications using palladium-catalyzed allylic oxidation were reported.[27,28,29]

Scheme 1.11.



[25] Pearlman, W. M. *Tetrahedron Lett.* **1967**, 1663.

[26] (a) Yu, J.-Q.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 3232. (b) Yu, J. Q.; Wu, H. C.; Corey, E. J. *Org. Lett.* **2005**, *7*, 1415.

[27] In the synthesis guanacastepene A, see: Chiu, P.; Li, S. L. *Org. Lett.* **2004**, *6*, 613.

[28] In the synthesis of (±)-1,2-anhydromethyl rocaglate, see: Magnus, P.; Stent, M. A. H. *Org. Lett.* **2005**, *7*, 3853.

[29] For an example where Pd-catalyzed allylic oxidation failed, see: Manzano, F. L.; Guerra, F. M.; Moreno-Dorado, F. J.; Jorge, Z. D.; Massanet, G. M. *Org. Lett.* **2006**, *8*, 2879.

Mechanistically, Corey and Yu proposed that allylic oxidation occurs through an uncommon Pd^{2+}/Pd^{1+} catalytic cycle (Figure 1.2). Specifically, they proposed that treatment of $Pd^{II}(OH)_2$ with *t*-BuOOH generates a $Pd^{II}(OO^tBu)_2$ species (not shown) which can homolytically dissociate to form $Pd^{I}(OO^tBu)$ and *tert*-butyl peroxy radical (*t*-BuOO·).[30] Hydrogen atom abstraction of **20** with *t*-BuOO· gives carbon-centered radical **21**. The authors then proposed that transfer of *tert*-butyl peroxide from species **22** gives mixed peroxide **23**[31] followed by K_2CO_3-induced peroxide elimination[32] to give enedione **24**. Alternatively, it was also noted that **21** could undergo capture with O_2 followed by hydroperoxide elimination to give enedione **24**. To complete the cycle, the authors suggest that the lower valent palladium(I) species **25** is oxidized in the presence of the *t*-BuOOH to regenerate the

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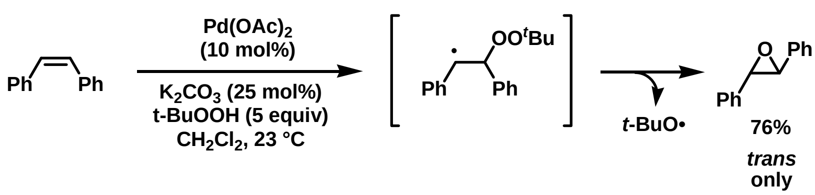
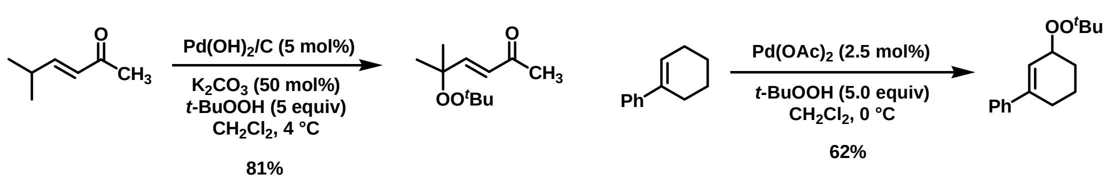
[30] Corey and Yu in 2002 reported that $Pd(OAc)_2$ is converted to $Pd(OOtBu)_2$ in the presence of *t*-BuOOH (5 equiv) as determined by ^{1}H NMR and mass spectral analysis. They noted that at room temperature the mixture liberates O_2 which is indicative of *t*-BuOO·. Moreover, the authors reported the epoxidation of various olefins and further implicated the presence of free *t*-BuOO· in the reaction, see: Yu, J.-Q.; Corey, E. J. *Org. Lett.* **2002**, *4*, 2727.



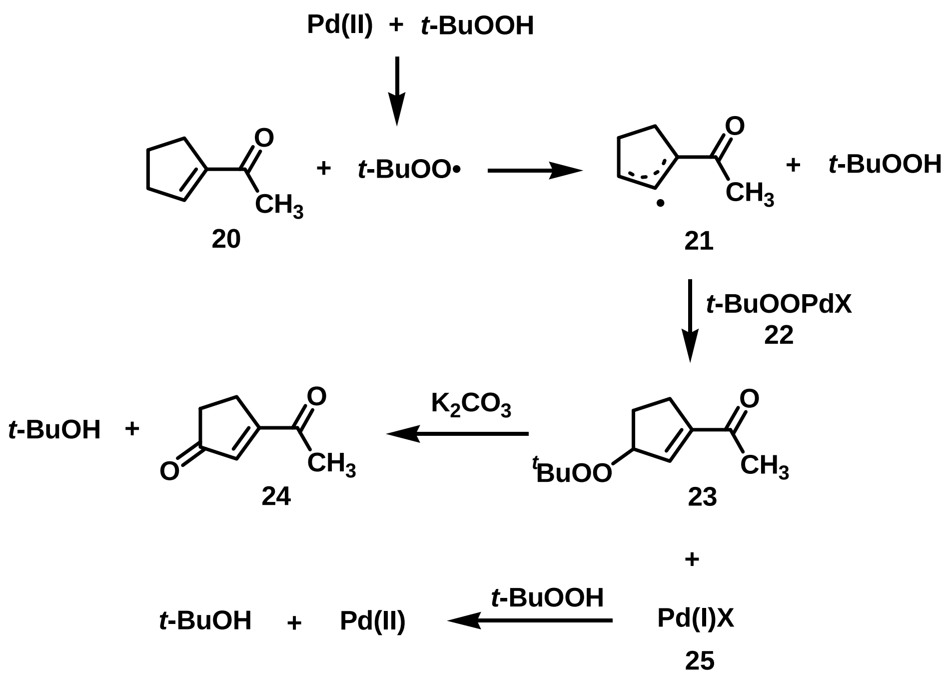
[31] The intermediacy of mixed peroxides was supported using an α,β-enone that contained only one γ-hydrogen (left equation). Additionally, the authors showed that mixed peroxides were obtained using $Pd(OAc)_2$ as a catalyst, see ref. 30 (right equation).



[32] For base induced elimination of mixed peroxides, see: Kornblum, N.; DeLaMare, H. E. *J. Am. Chem. Soc.* **1951**, *73*, 880.

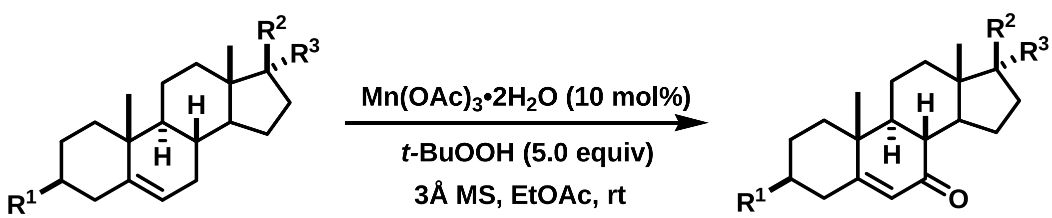
palladium(II) catalyst. (Note: The authors did not identify the ligand "X" on palladium intermediates **22** and **25**.)

Figure 1.2. Mechanistic Proposal for Palladium Catalyzed Allylic Oxidation.



Shing and coworkers in 2006 reported that manganese(III) acetate [$Mn(OAc)_3 \cdot 2H_2O$] in conjunction with anhydrous *t*-BuOOH catalyzed the allylic oxidation of several Δ^5-steroids and simple alkenes.[33,34] The authors reported 17 examples in which Δ^5-steroids were converted to Δ^5-en-7-ones using $Mn(OAc)_3$ (10 mol%) and *t*-BuOOH (5.0 equiv) ranging from good to excellent yield (Scheme 1.12). These conditions were then extended to simple alkenes and demonstrated both chemo- and regioselectivity (Scheme 1.13). The reaction time required for oxidation was generally 48 hours. The authors note that molecular sieves (3Å MS) were essential to remove water from the reaction (water was shown to cause disproportionation of $Mn(OAc)_3$).

Scheme 1.12.



17 examples
68-99%

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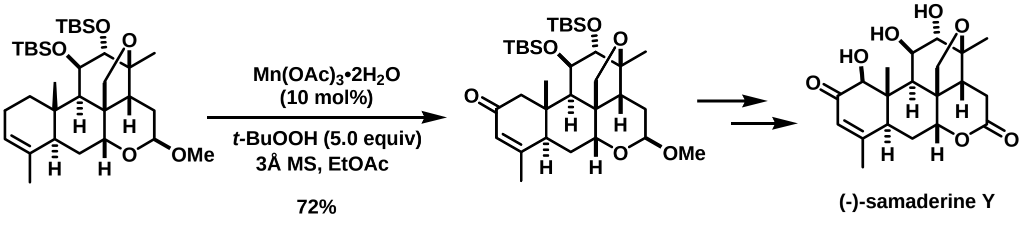
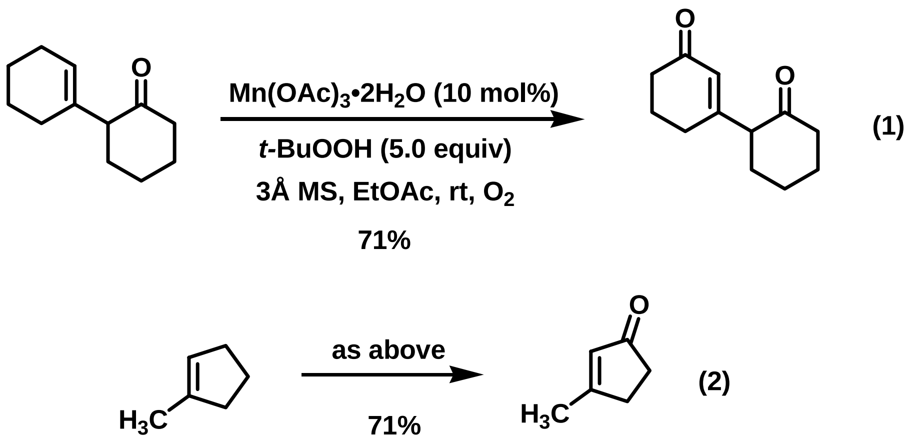
[33] Shing, T. K. M.; Yeung, Y.-Y.; Su, P. L. *Org. Lett.* **2006**, *8*, 3149.

[34] Allylic oxidation catalyzed by $Mn(OAc)_3$ was originally reported in 2005 during the total synthesis of (-)-samaderine Y, see footnote 14.



Scheme 1.13.



Shing and coworkers proposed a mechanism similar to Corey's allylic oxidation catalyzed by $Pd(OH)_2$ (Figure 1.3). $Mn(OAc)_3$ has a trinuclear structure represented as $Mn_3O(OAc)_9$ (**26**) which, in the presence to *t*-BuOOH, undergoes loss of AcOH to give *t*-$BuOOMn_3O(OAc)_8$ (**27**) (as determined by ^{1}H NMR analysis). The authors speculated that **27** transfers *t*-BuOO· to carbon-centered radical **28** to give mixed peroxide **29**.[35] They then proposed that manganese complex **30** undergoes turnover by reaction with *t*-BuOOH to generate *tert*-butoxy radical (*t*-BuO·)[36] and manganese-hydroxyl

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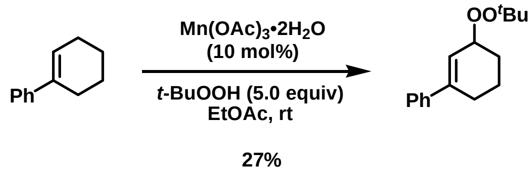
[35] For the oxidation of 1-phenylcyclohexene under the reaction conditions, the corresponding mixed peroxide was isolated in 27% yield from the reaction. The mixed peroxide was resubmitted to the reaction and gave the corresponding enone in 90% yield.

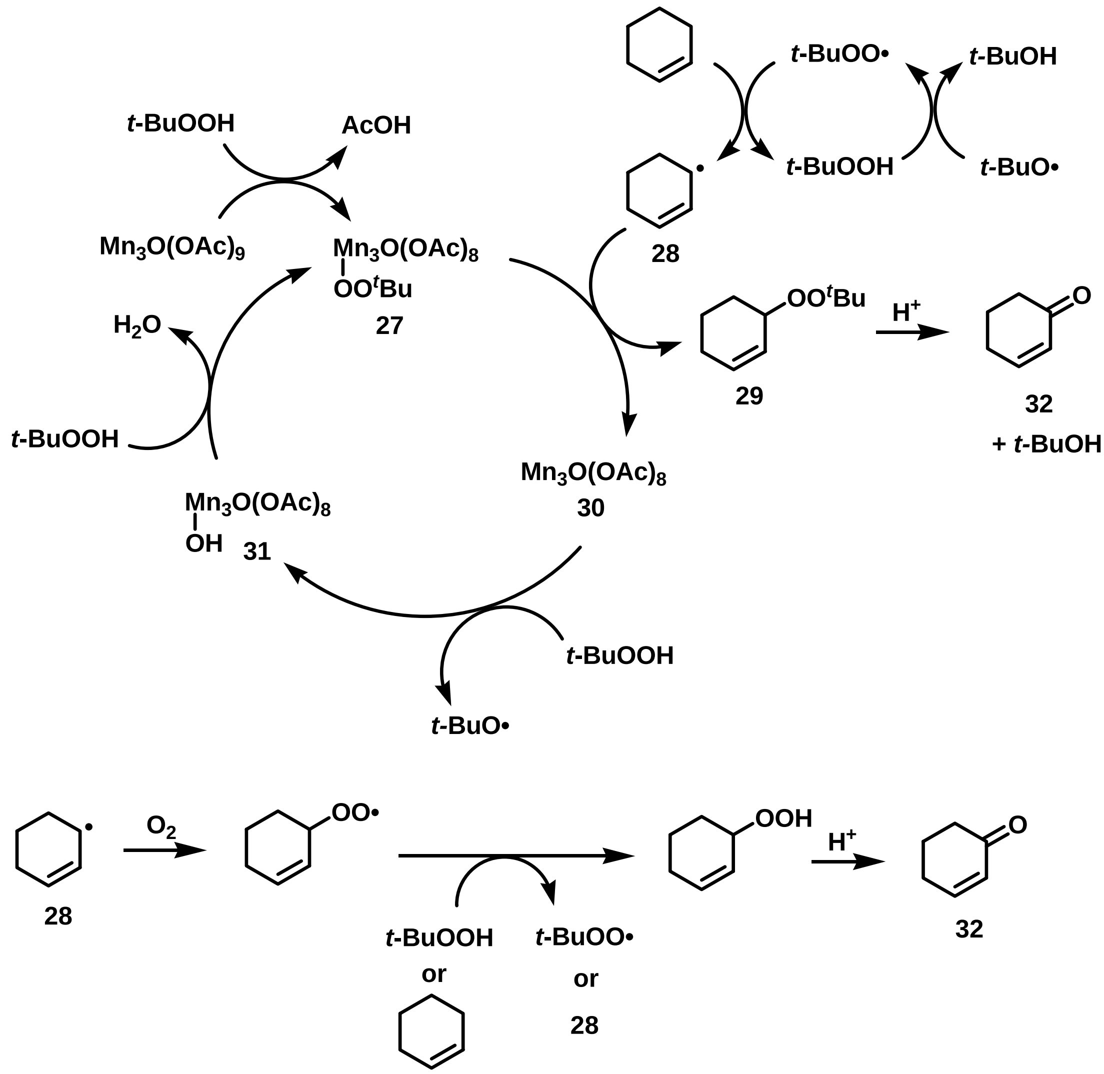


[36] As shown in Figure 1.3, *t*-BuO· reacts with *t*-BuOOH to give *t*-BuOO·. Evidence for *t*-BuOO· included O_2 evolution and detection by electron paramagnetic resonance (EPR) spectroscopy.

complex **31**, which in turn undergoes another reaction with *t*-BuOOH to liberate water and regenerate **27**. Alternatively, the authors noted that carbon-centered radical **28** could undergo capture with molecular oxygen followed by elimination of the corresponding hydroperoxide to give enone product **32**. Finally, the authors proposed that mixed peroxide **29** is decomposed in the presence of acid (H^+) to give enone **32**.[37]

[37] The authors suggest an acid-mediated decomposition of mixed peroxide **29** due to the acidity of the reaction mixture measured after 36 h (pH = 4).

Figure 1.3. Mechanistic Proposal for $Mn(OAc)_3$ Catalyzed Allylic Oxidation.



Benzylic Oxidation (Catalytic Methods). Unlike their allylic counterpart, catalytic methods for benzylic oxidation are extremely limited. Metal-catalyzed processes have been reported for benzylic oxidation using selenium,[38] chromium-,[39] cobalt-,[40] ruthenium-,[41] and manganese[42] in conjunction with *t*-BuOOH. However, these protocols are limited in regard to substrate scope. For example, Pearson and Han in 1985 developed a catalytic method for benzylic oxidation using $Cr(CO)_6$; however, the procedure was applied to only a few substrates as shown in Scheme 1.14.[39(a)] A general catalytic protocol capable of oxidizing a wide range of substrates has not yet been achieved.

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[38] Campos, O.; Cook, J. M. *Tetrahedron Lett.* **1979**, 1025.

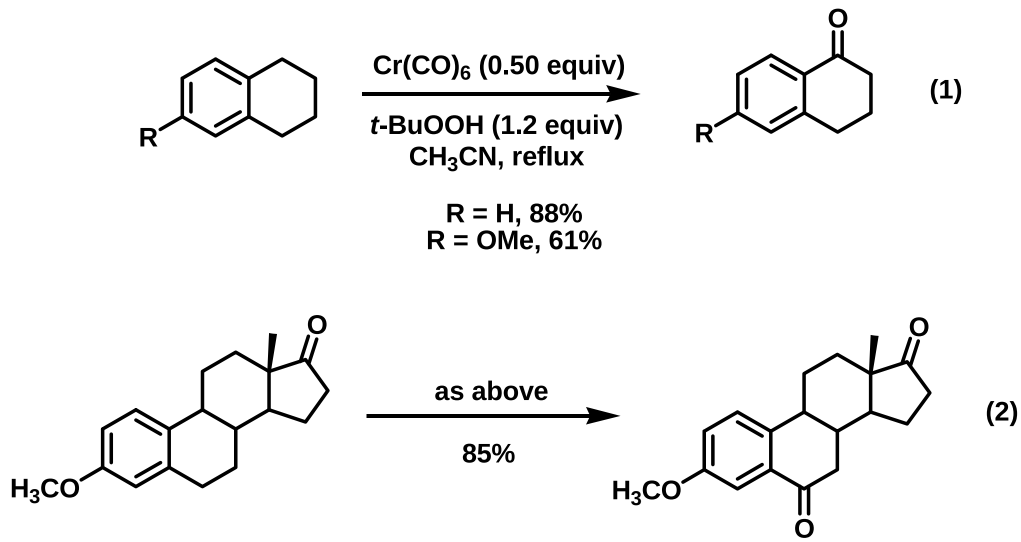
[39] For Cr-catalyzed procedures see: (a) Pearson, A. J.; Han, G. R. *J. Org. Chem.* **1985**, *50*, 2791. (b) Muzart, J. *Tetrahedron Lett.* **1986**, *27*, 3139. (e) Rathore, R.; Saxena, N.; Chandrasekaran, S. *Synth. Commun.* **1986**, *16*, 1493. (c) Muzart, J. *Tetrahedron Lett.* **1987**, *28*, 2131. (d) Muzart, J.; Ajjou, A. N. A. *J. Mol. Catal.* **1991**, *66*, 155. (e) Choudary, B. M.; Prasad, A. D.; Bhuma, V.; Swapna, V. *J. Org. Chem.* **1992**, *57*, 5841. (f) Das, T. K.; Chaudhari, K.; Nandanan, E.; Chandwadkar, A. J.; Sudalai, A.; Ravindranathan, T.; Sivasanker, S. *Tetrahedron Lett.* **1997**, *38*, 3631. (g) Rothenberg, G.; Wiener, H.; Sasson, Y. *J. Mol. Catal. A: Chemical* **1998**, *136*, 253.

[40] For Co-catalyzed procedures see: (a) Modica, E.; Bombieri, G.; Colombo, D.; Marchini, N.; Ronchetti, F.; Scala, A.; Toma, L. *Eur. J. Org. Chem.* **2003**, 2964. (b) Jurado-Gonzalez, M.; Sullivan, A. C.; Wilson, J. R. H. *Tetrahedron Lett*. **2003**, *44*, 4283.

[41] For Ru-catalyzed procedures see: (a) Murahashi, S.; Oda, Y.; Naota, T.; Kuwabara, T. *Tetrahedron Lett.* **1993**, *34*, 1299. (b) Nikalje, M. D.; Sudalai, A. *Tetrahedron* **1999**, *55*, 5903.

[42] For Mn-catalyzed procedures see: (a) Blay, G.; Fernández, I.; Giménez, T.; Pedro, J. R.; Ruiz, R.; Pardo, E.; Lloret, F.; Muñoz, M. C. *Chem. Commun.* **2001**, 2102. (b) Pan, J. F.; Chen, K. M. *J. Mol. Catal. A: Chemical* **2001**, *176*, 19. (c) Shing, T. K. M.; Yeung, Y.-Y.; Su, P. L. *Org. Lett.* **2006**, *8*, 3149, see supporting information.

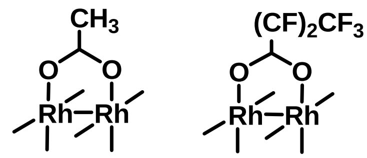
Scheme 1.14.



Summary. Allylic and benzylic oxidation are fundamentally important in organic chemistry. This review highlighted the chemoselective oxidation of allylic and benzylic C-H bonds (C-H → C=O) using stoichiometric and catalytic methods. Stoichiometric methods have historically used SeO_2 or chromium(VI) reagents. Catalytic variants have been developed for several redox-active metals in conjunction with a stoichiometric oxidant. Toward this end, anhydrous *t*-BuOOH appears to be the most widely used stoichiometric oxidant. Finally, despite a variety of allylic oxidations that have been reported, a general and effective catalytic benzylic oxidation has not been reported.

II. RESULTS AND DISCUSSION[43]

Initial Results. Dirhodium(II) carboxylate complexes, e.g. $Rh_2(OAc)_4$ and $Rh_2(pfb)_4$, are stable diamagnetic complexes containing a bimetallic core and four O-C-O dinuclear bridging ligands. Teyssie and coworkers in 1979 reported dirhodium(II) acetate promoted autooxidation reactions.[44] Thus, in the presence of a stoichiometric amount of $Rh_2(OAc)_2$, cyclohexene was converted to a mixture of 2-cyclohexen-1-one and 2-cyclohexen-1-ol (<15% conversion, relative amounts undetermined) with molecular oxygen (1 atm) in benzene at 55 °C.



$Rh_2(OAc)_4$ **$Rh_2(pfb)_4$**

Uemura and Patil in 1982 reported that cyclohexene undergos allylic oxidation catalyzed by $Rh_2(OAc)_4$ (0.5 mol%) in conjunction with 70% aqueous *t*-BuOOH in acetic acid to give a mixture of enone and allylic acetate products after 42 hours (Scheme 1.15).[45] The authors only suggested the possibility of radical intermediates and the formation of a *tert*-butylperoxy-, acetoxy, or hydroxyl-rhodium species in the reaction. Mechanistic studies were not conducted.

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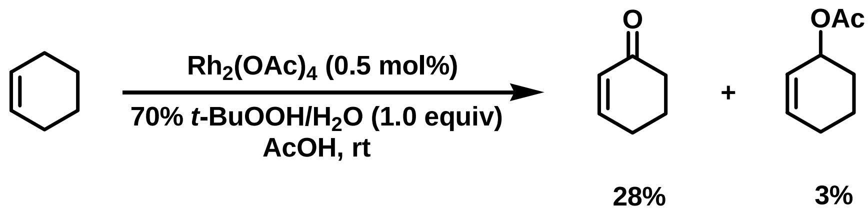
[43] For the disclosure of this work, see: (a) Catino, A. J.; Forslund, R. E.; Doyle, M. P. *J. Am. Chem. Soc.* **2004**, *126*, 13622. (b) Catino, A. J.; Nichols, J. M.; Choi, H.; Gottipamula, S.; Doyle, M. P. *Org. Lett.* **2005**, *7*, 5167.

[44] Noels, A. F.; Hubert, A. J.; Teyssie, P. " *J. Organomet. Chem.* **1979**, *166*, 79.

[45] (a) Uemura, S.; Patil, S. R. *Chem. Lett.* **1982**, 1743. (b) Uemura, S.; Patil, S. R. *Tetrahedron Lett.* **1982**, *23*, 4353.

Scheme 1.15.

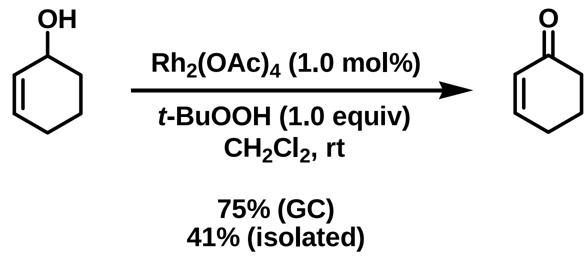


Moody and Palmer in 2002 described the oxidation of secondary allylic and benzylic alcohols using $Rh_2(OAc)_4$ (1.0 mol%) and anhydrous *t*-BuOOH (1.0 equiv).[46] As a representative example, 2-cyclohexen-1-ol was converted to 2-cyclohexen-1-one in 75% yield after 31 hours (Scheme 1.16). These results are intriguing considering that Doyle and coworkers in 1984 evaluated the fate of *t*-BuOOH with $Rh_2(OAc)_4$ (0.3 - 0.6 mol%) in CH_2Cl_2 at 25 °C and found complete conversion to *tert*-butyl alcohol and molecular oxygen in 4 to 6 hours.[47] Moody and Palmer pointed out that the rate of oxidation of 2-cylcohexen-1-ol was much slower with dirhodium catalysts containing more strongly electron-withdrawing carboxylate ligands. For example, 2-cyclohexen-1-one was obtained in 55% yield after 20 days using $Rh_2(OCOCF_3)_4$ (1.0 mol%) and *t*-BuOOH (1.0 equiv). Experiments using dirhodium catalysts that contained less electron-withdrawling ligands were overlooked.

[46] Moody, C. J.; Palmer, F. N. *Tetrahedron Lett.* **2002**, *43*, 139.

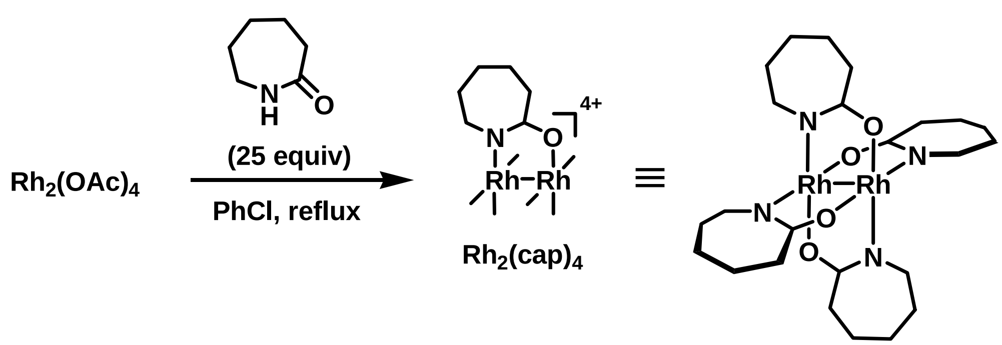
[47] Doyle, M. P.; Terpstra, J. W.; Winter, C. H.; Griffin, J. H. *J. Mol. Catal.* **1984**, *26*, 259.

Scheme 1.16.



As pointed out by Kochi, the most effective catalysts for allylic oxidation are those metals that readily undergo 1-electron redox processes, e.g., $Fe^{2+} \leftrightarrow Fe^{3+}$, $Cu^{1+} \leftrightarrow Cu^{2+}$, and $Co^{2+} \leftrightarrow Co^{3+}$.[48] With this in mind, dirhodium(II) caprolactamate [$Rh_2(cap)_4$] was considered as a catalyst. $Rh_2(cap)_4$ is a bench-stable purple solid readily prepared via ligand exchange from $Rh_2(OAc)_4$ (Scheme 1.17).[49]

Scheme 1.17.



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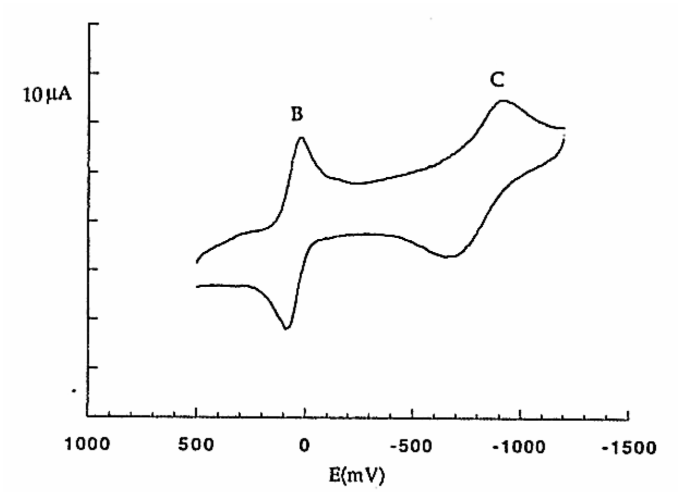
[48] Srinivasan, K.; Perrier, S.; Kochi, J. K. *J. Mol. Catal.* **1986**, *36*, 297.

[49] Doyle, M. P.; Westrum, L. J.; Wolthuis, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958.

Doyle and Ren in 2001 reported that $Rh_2(cap)_4$ undergoes a reversible oxidation at 55 mV (via cyclic voltammetry) that corresponds to the $Rh_2^{4+} \leftrightarrow Rh_2^{5+}$ redox couple (**B**, Figure 1.4).[50] The authors reported that $Rh_2(cap)_4$ readily underwent a 1-electron oxidation ($E_{1/2}$ = 11 mV), compared to $Rh_2(OAc)_4$ and $Rh_2(pfb)_4$ ($E_{1/2}$ = 1170 and >1800 mV, respectively).[51] This data indicates that $Rh_2(cap)_4$ is more electron-rich relative to $Rh_2(OAc)_4$ and $Rh_2(pfb)_4$. Furthermore, the low $E_{1/2}$ of $Rh_2(cap)_4$ suggests that it could access Rh_2^{5+} oxidation state (with an appropriate oxidant) and perhaps participate as a 1-electron redox catalyst.

Figure 1.4. Cyclic Voltammetry Data for $Rh_2(cap)_4$ in CH_3CN (vs Ag/AgCl).

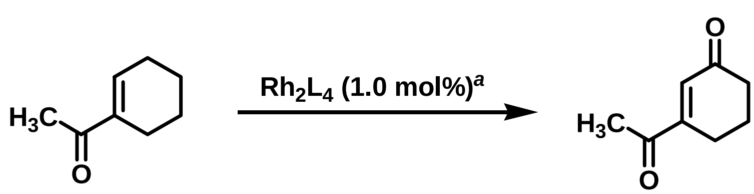


[50] Doyle, M. P.; Ren, T. In *Prog. Inorg. Chem.*; Karlin, K., Ed; Wiley: New York, 2001; Vol. 49, p 113.

[51] (a) Das, K.; Kadish, K. M.; Bear, J. L. *Inorg. Chem.* **1978**, *17*, 930. (b) Zhu, T. P.; Ahsan, M. Q.; Malinski, T.; Kadish, K. M.; Bear, J. L. *Inorg. Chem.* **1984**, *23*, 2.

Allylic Oxidation Catalyzed by $Rh_2(cap)_4$ (Reaction Development).[52] Allylic oxidation was examined using 1-acetylcylcohexene to yield enedione **33** (Scheme 1.9). Enedione **33** is a stable non-volatile solid that has been previously reported. Both $Rh_2(OAc)_4$ and $Rh_2(pfb)_4$ in conjunction with anhydrous *t*-BuOOH (5 equiv) in CH_2Cl_2 yielded only trace amounts of **33** after 12 hours. However, under the same conditions, $Rh_2(cap)_4$ (1.0 mol%) provided **33** in 33% yield. Considering literature precedent by Corey and Yu,[26] K_2CO_3 was examined as an additive for allylic oxidation (Table 1.1). Although the exact role of K_2CO_3 remains unclear, the overall yield of **33** and the apparent rate of reaction improved dramatically. The optimal amount of K_2CO_3 was found to be 50 mol% which gave enedione **33** in 72% yield after 1 hour (Table 1.1). A diminution in yield was observed above and below 50 mol% of K_2CO_3. The amount of *t*-BuOOH was also examined from 1 to 5 equivalents relative to substrate (Table 1.2). The optimal amount of *t*-BuOOH appears to be 5 equivalents; however, three equivalents of *t*-BuOOH were viable.

Scheme 1.18.



33

Rh_2L_4 = $Rh_2(OAc)_4$ trace
= $Rh_2(pfb)_4$ trace
= $Rh_2(cap)_4$ 33%

[a]Conditions: Rh_2L_4 (1.0 mol%), *t*-BuOOH (5.0 equiv), CH_2Cl_2, rt, 12 h

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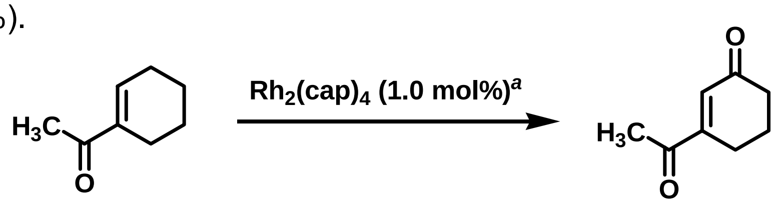
[52] Dr. Raymond E. Forslund, University of Maryland, conducted the optimization experiments for allylic oxidation catalyzed by $Rh_2(cap)_4$.

Table 1.1. Yield (%) of 3-Acetylcyclohex-2-en-1-one (**33**) as a Function of K_2CO_3 (mol%).

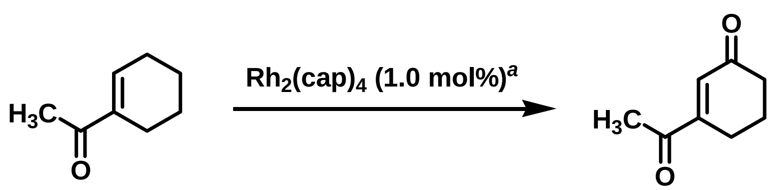


33

K_2CO_3 (mol%)	Yield **33** (%)
10	14
20	35
30	47
40	65
50	72
60	46
70	43
80	40
90	34
100	32

[a]Conditions: $Rh_2(cap)_4$ (1.0 mol%), *t*-BuOOH (3.0 equiv), K_2CO_3 (x mol%), CH_2Cl_2, rt, 1 h; [b]Isolated yield after chromatography.

Table 1.2. Yield (%) of 3-Acetylcyclohex-2-en-1-one (**33**) as a Function of *t*-BuOOH (equiv).



33

t-BuOOH (equiv)	yield **33** (%)[b]
1.0	18
2.0	34
3.0	72
4.0	77
5.0	80

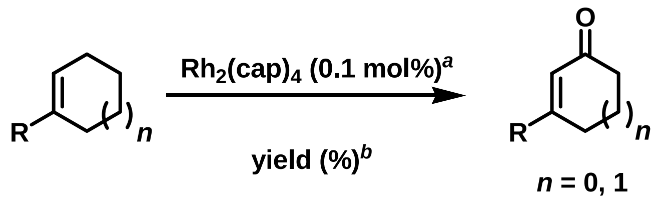
[a]Conditions: $Rh_2(cap)_4$ (1.0 mol%), *t*-BuOOH (x equiv), K_2CO_3 (50 mol%), CH_2Cl_2, rt, 1 h; [b]Isolated yield after chromatography.

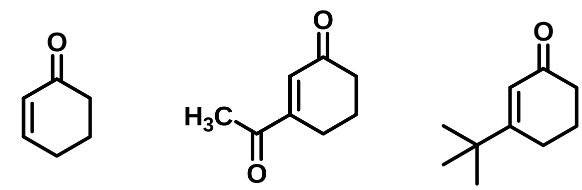
Substrate Scope. During the course of optimization, analysis by thin-layer chromatography (tlc) indicated that reactions conducted with 1.0 mol% $Rh_2(cap)_4$ proceeded rapidly in a few minutes and probably did not require one hour. Based on this observation, catalyst loading was reduced to 0.1 mol% $Rh_2(cap)_4$. Oxygen evolution and a mild exotherm were observed. Reaction vessels were capped with a septum and equipped with an empty balloon (through a needle) to allow out-gassing while keeping the O_2 in the system.[53]

It was found that several cyclic alkenes underwent allylic oxidation to the corresponding enones or enediones at 0.1 mol% loading in one hour (Table 1.3). Work-up involved filtering the reaction mixture over a short plug of silica to remove the dirhodium catalyst, evaporation of the CH_2Cl_2, and column chromatography.

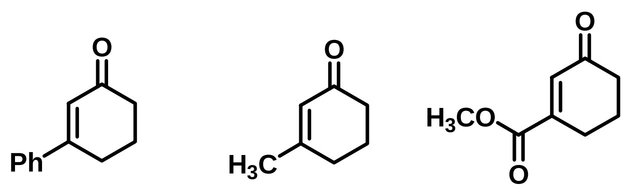
[53] It was later determined that O_2 is consumed during the reaction, Mr. Jason M. Nichols, University of Maryland, Candidacy Report, 2005.

Table 1.3. Allylic Oxidation of Substituted Cycloalkenes Catalyzed by 0.1 mol% of $Rh_2(cap)_4$.

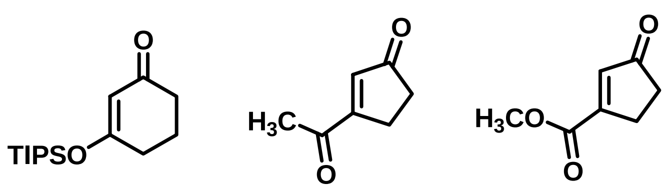




34, 60%[c] 33, 78% 35, 94%



36, 77% 37, 89%[d] 38, 92%

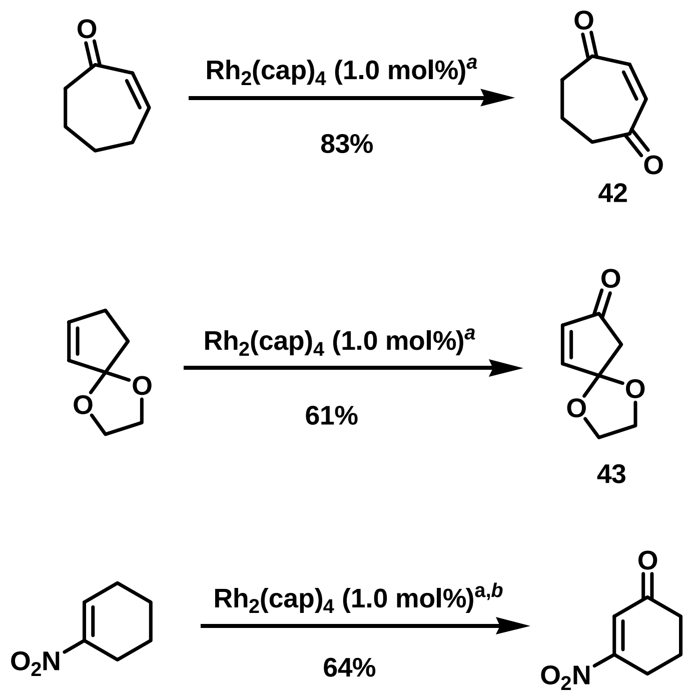


39, 81% 40, 86% 41, 79%

[a]Conditions: olefin (1.0 equiv), *t*-BuOOH (5.0 equiv), $Rh_2(cap)_4$ (0.1 mol%), CH_2Cl_2, rt, 1 h; [b]Isolated yield after column chromatography. [c]Diminished yield due to product volatility. [d]Reaction time was 0.3 h.

Olefins listed in Scheme 1.19 were reluctant to oxidize at 0.1 and 1.0 mol% loading at room temperature (<20% yield observed). However, it was found that a combination of heat (40 °C), additional *t*-BuOOH, and increased reaction time gave useful yields. It is presently unclear why 2-cyclohepten-1-one and 2-cyclopenten-1-one ethylene ketal were reluctant to oxidize. Corey and Yu also noted a similar lack of reactivity with these substrates. The reluctance of 1-nitrocyclohexene to undergo allylic oxidation is presumably due to the strong electron-withdrawing nature of the nitro group relative to other groups.

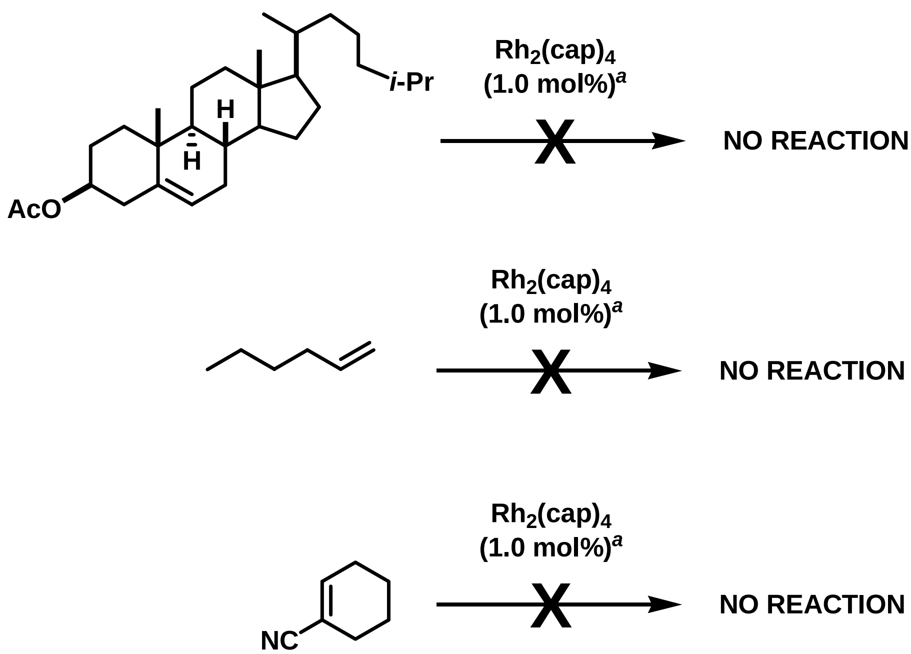
Scheme 1.19.



[a]Conditions: $Rh_2(cap)_4$ (1 mol%) added in two portions (0.5 mol% catalyst and 5 equiv of *t*-BuOOH at the start and another 0.5 mol% catalyst and 5 equiv of *t*-BuOOH after 1.5 h), olefin (1 equiv), K_2CO_3 (50 mol%) in CH_2Cl_2 at 40 °C for 3 h. [b]Reaction time was 24 h and catalyst (1.0 mol%) was added in two portions (0.5 mol% catalyst and 5 equiv of *t*-BuOOH at the start, and another 0.5 mol% catalyst and 5 equiv of *t*-BuOOH after 12 h).

Finally, three substrates showed no reactivity using $Rh_2(cap)_4$ (1.0 mol%) at room temperature (Scheme 1.20). It remains unclear why cholesterol acetate and 1-hexene failed to undergo oxidation. However, it is likely that 1-cyclohexene-1-carbonitrile failed to undergo allylic oxidation due to the electron-withdrawing nature of the cyanide and substrate coordination to the catalyst.

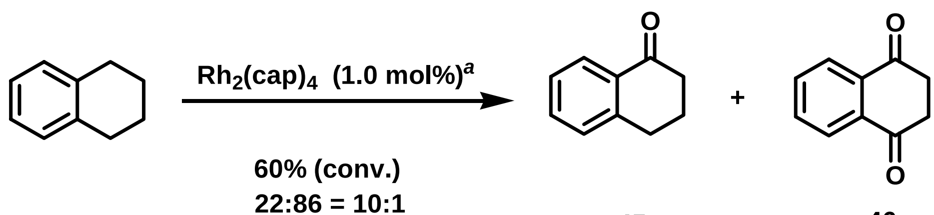
Scheme 1.20.



[a]Conditions: $Rh_2(cap)_4$ (1.0 mol%), *t*-BuOOH (5.0 equiv), K_2CO_3 (50 mol%), CH_2Cl_2, rt, 12 h

Benzylic Oxidation Catalyzed by $Rh_2(cap)_4$ (Reaction Development). Benzylic oxidation was examined next using 1,2,3,4-tetrahydronapthalene (tetralin) as a substrate. Treatment of tetralin with $Rh_2(cap)_4$ (1.0 mol%), *t*-BuOOH, and K_2CO_3 in CH_2Cl_2 gave 60% conversion after one hour (Scheme 1.21). Catalyst decomposition was noted at this time by a color change from red to orange/yellow. Additionally, no further conversion was observed after one hour. Analysis of the crude reaction mixture by ^{1}H NMR revealed a 10:1 mixture of α-tetralone (**45**) and dione **46**. Moreover, despite the formation of dione **46**, its aromatic tautomer (1,4-napthalenediol) was not observed.

Scheme 1.21.



45 **46**

[a]Conditions: $Rh_2(cap)_4$ (1.0 mol%), *t*-BuOOH (5.0 equiv), K_2CO_3 (50 mol%), CH_2Cl_2, rt, 1 h

Seeking to overcome low substrate conversion, a parallel screening of additives was undertaken (Figure 1.5).[54] Parallel screening involves running several reactions simultaneously to determine the most optimal additive. Notably in benzylic oxidation catalyzed by $Rh_2(cap)_4$, K_2CO_3 was inferior to other bases examined. Both $(NH_4)_2CO_3$ and NH_4OAc showed promising results for the conversion of tetralin after 16 hours, but they caused substrate decomposition when applied to compounds containing acid-labile groups. Sodium bicarbonate ($NaHCO_3$), however, was not detrimental to acid-labile groups. Furthermore, the reaction efficiency was not compromised using 1,2-

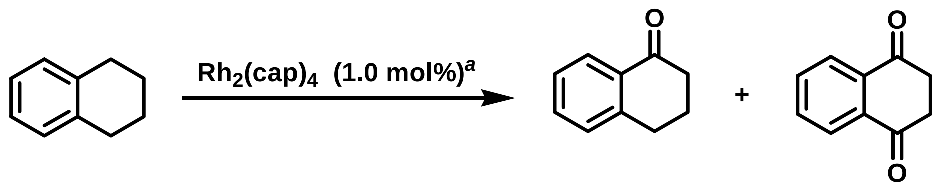
[54] Parallel screening was performed by GC analysis, see Experimental for details.

dichloroethane (DCE) as a replacement for CH_2Cl_2 (DCE allows access to higher reaction temperatures).

In addition to conversion of tetralin, oxygen evolution was also evaluated as a function of additive. Dramatically less oxygen evolution was observed in reactions using $NaHCO_3$ as opposed to K_2CO_3. Oxygen evolution indicates the presence of *tert*-butylperoxy radical (*t*-BuOO·) which can undergo dimerization to di-*tert*-butyltetraoxide and decomposition to release O_2.[55] However, the role of base and its relationship to O_2 formation remain unclear.

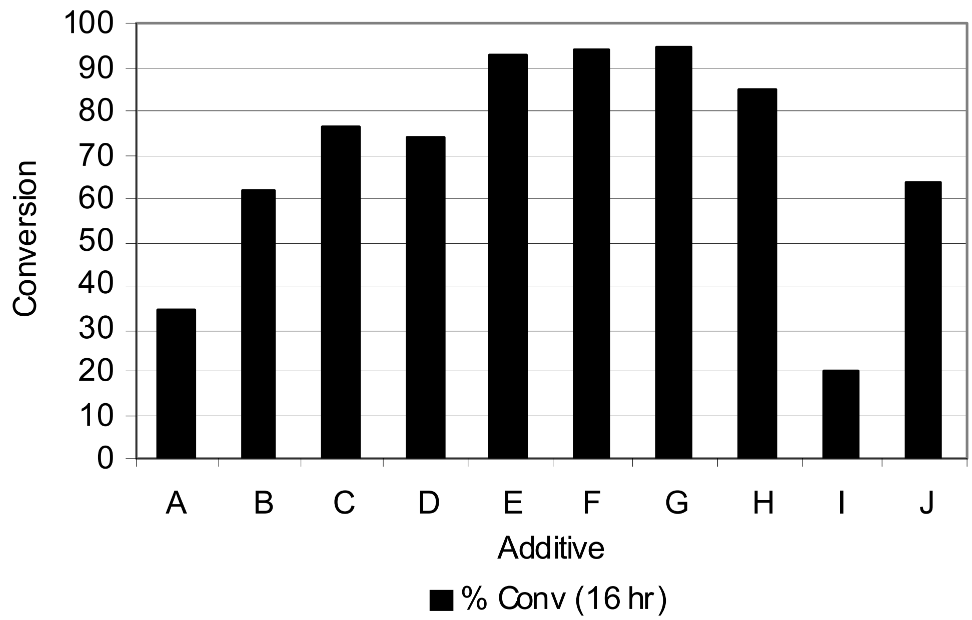
[55] (a) Bartlett, P. D.; Gunther, P. *J. Am. Chem. Soc.* **1966**, *88*, 3288. (b) Bartlett, P. D.; Guaraldi, G. *J. Am. Chem. Soc.* **1967**, *89*, 4799.

Figure 1.5. Parallel Screening of Additives for Benzylic Oxidation.



45 46

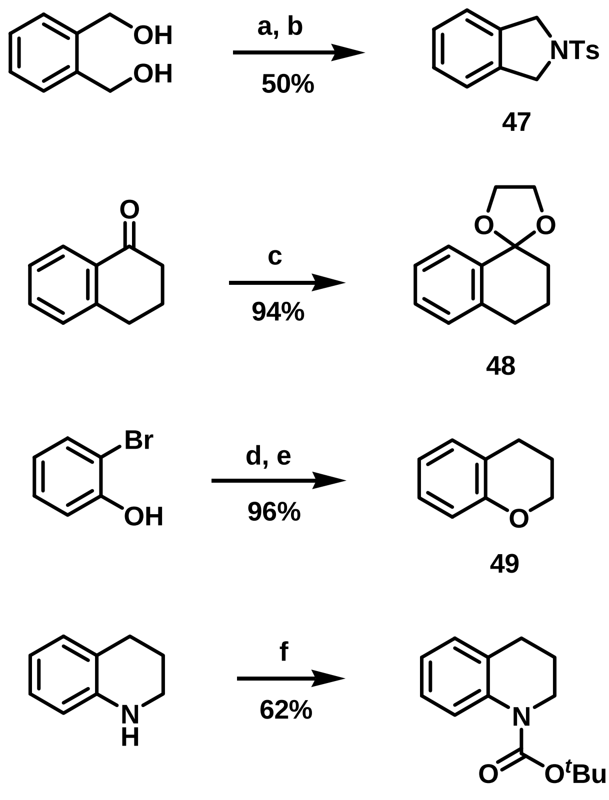
[a]**Conditions: $Rh_2(cap)_4$ (1.0 mol%), *t*-BuOOH (5.0 equiv), additive (50 mol%), CH_2Cl_2, rt, 16 h**



A = no additive, B = K_2CO_3, C = Cs_2CO_3, D = Na_2CO_3, E = $(NH_4)_2CO_3$, F = $NaHCO_3$, G = NH_4OAc, H = $K_2PO_4 \cdot 3H_2O$, I = $NaHSO_4$, J = H_2KPO_4

Substrate Preparation. Several substrates containing benzylic C-H functionality are commercially available; however, additional substrates were prepared. Representative examples are shown in Scheme 1.22. Isoindoline **47** was prepared by treating benzene dimethanol with methansulfonyl chloride followed by displacement with *p*-toluenesulfonamide anion. Ethylene ketal **48** was prepared according to the procedure of Patel and coworkers by treating α-tetralone with catalytic tetrabutylammonium tribromide ($Bu_4N^+Br_3^-$) in ethylene glycol.[56] Chroman (**49**) was prepared in two steps by an intermolecular Mitsunobu reaction and subsequent intramolecular cyclization.[57] Finally, treatment of 1,2,3,4-tetrahydroquinoine with di-*tert*-butyldicarbonate (Boc_2O) gave the *N*-Boc protected amine **50**.

Scheme 1.22.



a) MsCl, Et_3N, THF, 0 °C, 1 h; b) NaH, DMF, $TsNH_2$, rt, overnight; c) 1,2-ethanediol, $(EtO)_3CH$, $Bu_4N^+Br_3^-$ (1.0 mol%), rt, 1 h; d) Ph_3P, DIAD, $HOCH_2CH_2Cl$, THF, 0 °C; e) *n*-BuLi, THF, -78 °C, 1.5 h; f) Boc_2O, DMAP, THF, rt, overnight

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[56] Gopinath, R.; Haque, S. J.; Patel, B. K. *J. Org. Chem.* **2002**, *67*, 5842.

[57] Dandapani, S.; Curran, D. P. *Tetrahedron* **2002**, *58*, 2855.

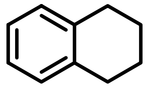
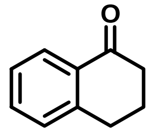
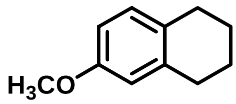
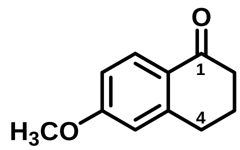
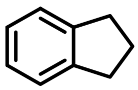
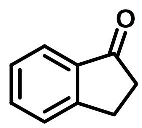
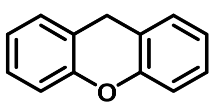
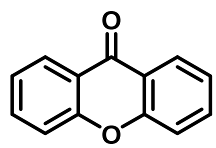
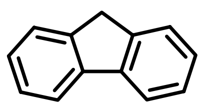
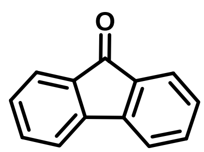
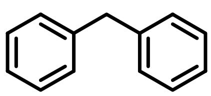
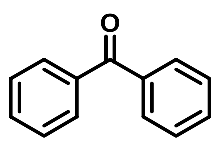
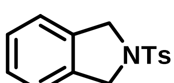
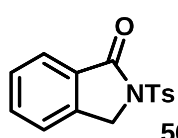
Substrate Scope. The oxidation of various hydrocarbons containing benzylic methylene groups was examined using $Rh_2(cap)_4$ (1.0 mol%), $NaHCO_3$ (50 mol%), and *t*-BuOOH (5.0 equiv) in DCE at room temperature (Table 1.4). Excellent conversion (>95%) was observed for most substrates (determined by ^{1}H NMR analysis of the crude reaction mixture prior to purification). The oxidation of 6-methoxytetralin gave a 1:1 mixture of C1:C4 tetralone isomers (entry 2, Table 1.4) which indicated that selectivity was not influenced by electronic factors. Interestingly, the oxidation of fluorene (entry 5, Table 1.4) proceeded in excellent conversion (> 95%); however, under identical conditions diphenylmethane (entry 6, Table 1.5) gave only 57% conversion to benzophenone. The oxidation of *N*-tosylisoindoline **47** proceeded rapidly to give amide **56** in 69% yield (longer reaction times led to an intractable mixture of products).

$Rh_2(cap)_4$ (1.0 mol%) in combination with $NaHCO_3$ and *t*-BuOOH (10 equiv) at 40 °C were required for substrates that contained electron-withdrawing groups and substrates that were acyclic (Table 1.5). The oxidation of α-tetralone ethylene ketal **58** proceeded smoothly to give **57** in 84% yield; however, the oxidation of 1-indanone ethylene ketal **58** gave **59** in only 32% yield (entries 1 and 2, Table 1.5). *N*-Protected tetrahydroquinolines (entries 3 and 4, Table 1.5) underwent oxidation to the corresponding keto-derivatives. Chroman (**49**), notoriously difficult to oxidize due to poor regioselectivity,[58] underwent smooth oxidation to give chromanone **63** exclusively in 92% isolated yield (entry 5, Table 1.5). Regioselectivity was also observed with 1-acetoxytetrahydronapthalene **64** (entry 6, Table 1.5) to give the C-4 tetralone **65** in 88% yield. Finally, acyclic substrates (entries 7-9,

[58] Hodgetts, K. J. *Tetrahedron Lett.* **2001**, *42*, 3763., and references therein.

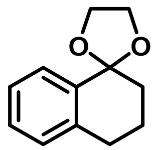
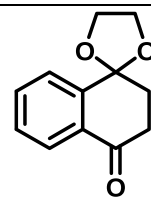
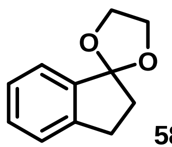
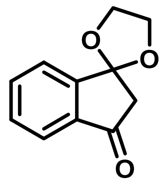
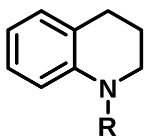
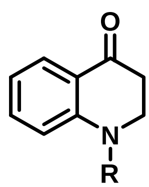
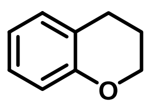
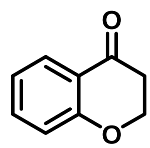
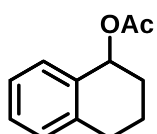
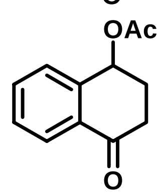
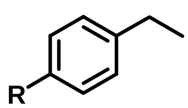
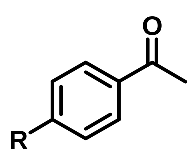
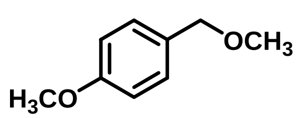
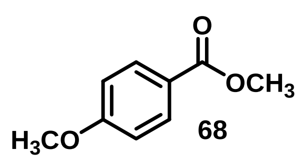
Table 1.5) were viable participants for benzylic oxidation. Yields for these substrates increased to 84% with increasing substitution by electron-donating groups.

Table 1.4. Benzylic Oxidation Catalyzed by $Rh_2(cap)_4$ at Room Temperature.[a]

entry	substrate	product	conv. (%)[b]	yield (%)[c]
1		 **45**	>95	60[d]
2		 **51**	>95	60[e,f]
3		 **52**	>95	84[g]
4		 **53**	>95	79
5		 **54**	>95	99
6		 **55**	57	55
7	 **47**	 **56**	>95	69[h]

[a]Reactions were performed using $Rh_2(cap)_4$ (1 mol%), substrate (1 equiv), $NaHCO_3$ (50 mol%), and *t*-BuOOH (5.0 equiv) in DCE at rt for 16 h unless otherwise noted. [b]Conversion determined by ^1H NMR analysis of the crude reaction mixture prior to purification. [c]Isolated yield after column chromatography. [d]Dione **46** was isolated in 27% from the reaction. [e]Isolated as a mixture of C1/C4 isomers (1:1). [f]Dione **69** was isolated in 29% from the reaction. [g]$(NH_4)_2CO_3$ (50 mol%) was used. [h]Reaction was complete in 4 h.

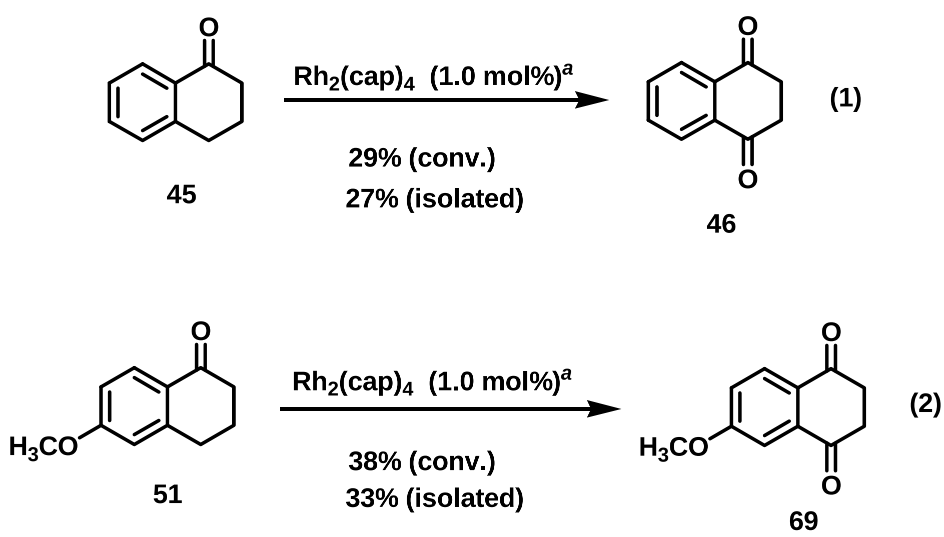
Table 1.5. Benzylic Oxidation Catalyzed by $Rh_2(cap)_4$ at 40 °C.[a]

entry	substrate	product	conv. (%)[b]	yield (%)[c]
1	 **48**	 **57**	>95	84
2	 **58**	 **59**	48	32
3	 **50: R = Boc**	 **60: R = Boc**	>95	82
4	**61: R = Ts**	**62: R = Ts**	>95	84
5	 **49**	 **63**	>95	92
6	 **64**	 **65**	>95	88
7		 **66: R = H**	42[d]	20
8		**67: R = OMe**	90	75
9		 **68**	>95	84

[a]Reactions were performed using $Rh_2(cap)_4$ (1 mol%) added in two portions (0.5 mol% catalyst and 5 equiv of *t*-BuOOH at the start and another 0.5 mol% catalyst and 5 equiv of *t*-BuOOH after 3 h), substrate (1 equiv), $NaHCO_3$ (0.50 equiv) in DCE at 40 °C for 16 h. [b]Conversion determined by ^1H NMR analysis of the crude reaction mixture prior to purification. [c]Isolated yield after column chromatography. [d]Conversion determined by GC analysis (area %) of the crude reaction mixture due to the volatility of ethylbenzene.

Moderate isolated yields for entries 1 and 2 in Table 1.4 are reflective of product oxidation resulting in dione formation. The origin of these products was confirmed by submitting commercial α-tetralone and 6-methoxy-1-tetralone to the reaction conditions used in Table 1.4 to give diones **46** and **69**, respectively (Scheme 1.23). The observed yields of dione correspond directly to the amount of dione observed in the oxidation reactions of the parent hydrocarbons.

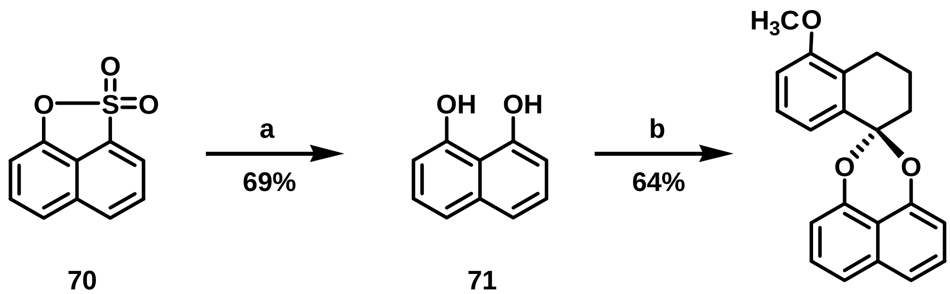
Scheme 1.23.



[a]**Conditions: $Rh_2(cap)_4$ (1.0 mol%), *t*-BuOOH (5.0 equiv), $NaHCO_3$ (50 mol%), DCE, rt, 16 h (same conditions as used in Table 1.4).**

Formal Synthesis of Palmarumycin CP_2. The utility of $Rh_2(cap)_4$ as a catalyst for benzylic oxidation was demonstrated in a short formal synthesis of Palmarumycin CP_2 (**74**). Acetal **72** was prepared in two steps as shown in Scheme 1.24. Nucleophilic aromatic substitution of 1,8-naphthosultone (**70**) in molten KOH/NaOH gave 1,8-hydroxynapthalene (**71**) in 69% according to the procedure of Wuest and coworkers.[59] Acetalization of 5-methoxy-1-tetralone and **71** catalyzed by H_2SO_4 gave acetal **72** in 64% according to the procedure of Taylor and coworkers (Scheme 1.25).[60]

Scheme 1.24.



a) KOH/NaOH, melt, ~200 - 260 °C, b) H_2SO_4 (0.2 equiv), 5-methoxy-1-tetralone, toluene, reflux, 72 h

Isolated in 1994 by Singh and coworkers, palmarumycin CP_2 (**74**, Scheme 1.25) is a biosynthetic precursor to the preussomerin class of natural products that exhibit a wide range of biological activity (e.g., antifungal, antibacterial, antitumor, and herbicidal activity).[61] Chromium-catalyzed procedures (catalyst loadings from 10 mol% to 250 mol% chromium) in combination with *t*-BuOOH (16 to 30 equiv) have offered the only reported

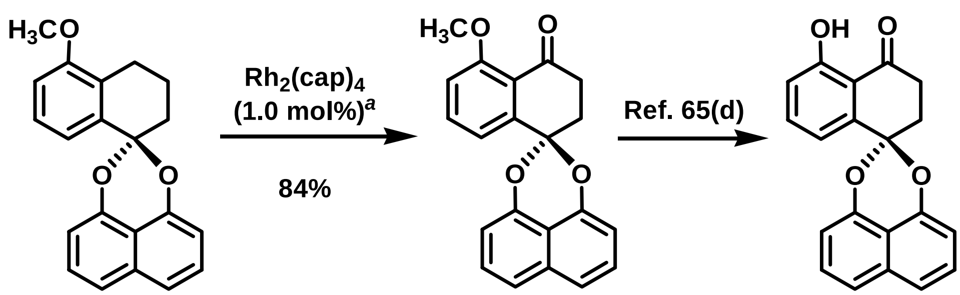
[59] Poirier, M.; Simard, M.; Wuest, J. D. *Organometallics* **1996**, *15*, 1296.

[60] Ragot, J. P.; Alcaraz, M.-L.; Taylor, R. J. K. *Tetrahedron Lett*. **1998**, *39*, 4921.

[61] Singh, S. B.; Zink, D. L.; Liesch, J. M.; Ball, R. G.; Goetz, M. A.; Bolessa, E. A.; Giacobbe, R. A.; Silverman, K. C.; Bills, G. F.; Pelaez, F.; Cascales, C.; Gibbs, J. B.; Lingham, R. B. *J. Org. Chem.* **1994**, *59*, 6296.

means of accessing ketone **73** from **72** in moderate yields.[62] It was also noted by Barrett and coworkers that IBX-mediated oxidation was not effective for **72**.[62(a)] However, using Rh_2(cap)$_4$ (1.0 mol%), **72** was oxidized to ketone **73** in 84% isolated yield.

Scheme 1.25.



72 **73** **74: Palmarumycin CP$_2$**

[a]Conditions: Rh_2(cap)$_4$ (1.0 mol%), *t*-BuOOH (10.0 equiv), $NaHCO_3$ (50 mol%), DCE, 40 °C, 16 h (same conditions as used in Table 1.5).

A few substrates were not amenable to oxidation catalyzed by Rh_2(cap)$_4$ and include **75**, **76** and **77** (Scheme 1.26). Failure of **75** to undergo benzylic oxidation is likely the result of amine coordination to the catalyst. Substrate **76**, containing an acetate group, did not undergo benzylic oxidation for reasons that are not clear. The lack of reaction with butyl benzene (**77**) is also difficult to rationalize being that ethylbenzene underwent oxidation, albeit in low yield.

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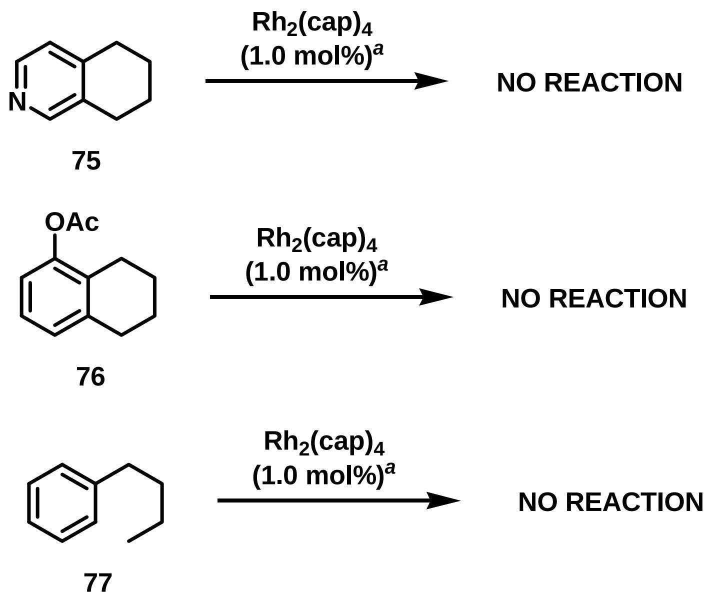
[62] For the oxidation of **72** to **73**, see: (a) Barrett, A. G. M.; Hamprecht, D.; Meyer, T. *Chem. Commun.* **1998**, 809. (b) Ragot, J. P.; Alcaraz, M. L.; Taylor, R. J. K. *Tetrahedron Lett.* **1998**, *39*, 4921. (c) Ragot, J. P.; Steeneck, C.; Alcaraz, M. L.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1073. (d) Barrett, A. G. M.; Blaney, F.; Campbell, A. D.; Hamprecht, D.; Meyer, T.; White, A. J. P.; Witty, D.; Williams, D. J. *J. Org. Chem.* **2002**, *67*, 2735.

Scheme 1.26.

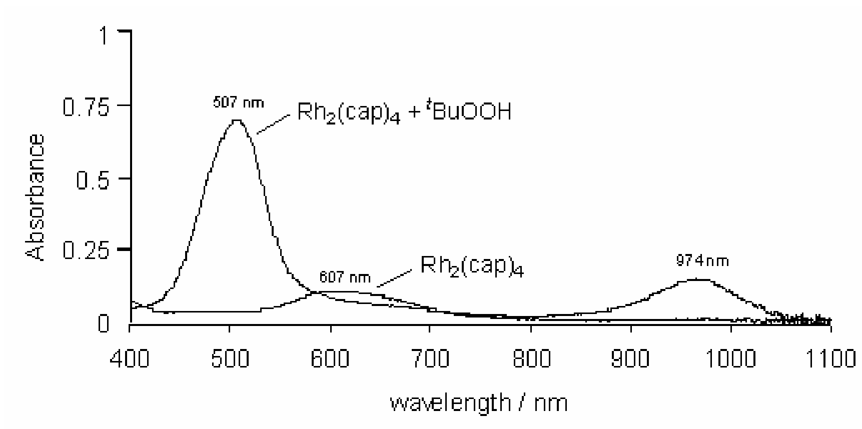


[a]Conditions: $Rh_2(cap)_4$ (1.0 mol%), *t*-BuOOH (10.0 equiv), $NaHCO_3$ (50 mol%), DCE, 40 °C, 16 h (same conditions as used in Table 1.5).

Mechanistic Discussion. $Rh_2(cap)_4$ undergoes a one-electron oxidation in the presence of *t*-BuOOH to form a paramagnetic (NMR-silent) dirhodium(II,III) species (Rh_2^{5+}). Evidence for this oxidative transformation included a dramatic color change from light blue to deep red in CH_2Cl_2. The UV-visible spectrum of the catalyst upon addition of *t*-BuOOH revealed a low energy adsorption at 974 nm (δ-δ* transitions) consistent with a mixed-valent dinuclear metal species (Figure 1.6).[63]

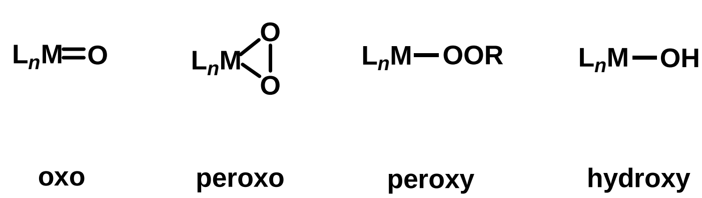
[63] (a) Cotton, F. A.; Walton, R. A. *Multiple Bonds Between Metal Atoms*, Wiley: New York, 1982; p 390. (b) Cotton, F.A.; Walton, R. A. *Multiple Bonds Between Metal Atoms*, 2nd ed.; Oxford: New York, 1993; p 475.

Figure 1.6. UV-Visible Spectrum of $Rh_2(cap)_4$ upon Addition of *t*-BuOOH.



The observed chemoselectivity, specifically allylic oxidation opposed to epoxide formation, indicates that reactions catalyzed by $Rh_2(cap)_4$ do not proceed via an oxo or peroxo species (Figure 1.7).[64] Furthermore, $Rh_2(cap)_4$ only contains one open coordination site per metal atom which further removes metallo oxo and peroxo species from consideration. This suggests that the newly formed Rh_2^{5+} species by treatment with *t*-BuOOH could be either a metallo-peroxy complex or a metallo-hydroxy complex (vide infra).

Figure 1.7. Various Metallo-oxy Intermediates in Oxidation Chemistry.



[64] Metallo-oxo and metallo-peroxo species have a long-standing history in catalytic epoxidations, see: Adam, W.; Malisch, W.; Roschmann, K. J.; Saha-Möller, C. R.; Schenk, W. A. *J. Organomet. Chem.* **2002**, *661*, 3.

The observed regioselectivity for allylic oxidation catalyzed by $Rh_2(cap)_4$ (i.e., α to the less substituted end of a double bond in a endocyclic alkene) is consistent with a radical or carbocation process, but it is not consistent with oxidations mediated by SeO_2 that tend to give oxidation α to the more substituted end of a double bond of an endocyclic alkene. A similar regiochemical preference was observed using other metal catalysts in conjunction with *t*-BuOOH.[26,33]

Mixed peroxides from *t*-BuOOH were obtained as minor products in both allylic and benzylic oxidation catalyzed by $Rh_2(cap)_4$ (Scheme 1.27). The oxidation of phenylcyclohexene catalyzed by $Rh_2(cap)_4$ with K_2CO_3 (0.05 equiv) and *t*-BuOOH (5.0 equiv) gave a 35% yield of mixed peroxide **78** (Scheme 1.27, eq 1).[65,66] Mixed peroxide **78** was resubmitted to the reaction conditions shown in Table 1.3 and gave the corresponding enone **36** (>95% conv.).[65,67] The oxidation of isochroman using conditions described in Table 1.4 gave mixed peroxide **79** in 7% yield and the expected isochomanone (**80**, not shown) in 70% yield (Scheme 1.27, eq 3).[68]

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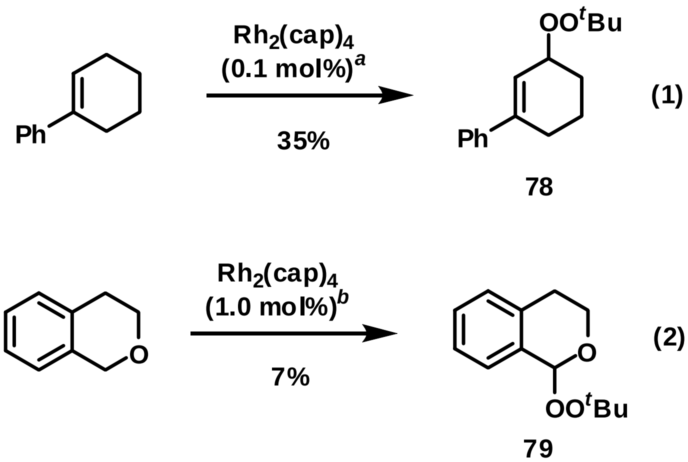
[65] Dr. Raymond E. Forslund, University of Maryland.

[66] The oxidation of 1-phenylcyclohexene to **78** was also reported using palladium and manganese catalysis, see ref. 26 and ref. 33, respectively.

[67] The formation of ketones from mixed peroxided with *t*-BuOOH under metal-catalyzed conditions has been reported: Muzart, J.; Ajjou, A. N. *J. Mol. Catal.* **1994**, *92*, 141.

[68] Mr. Jason M. Nichols, University of Maryland.

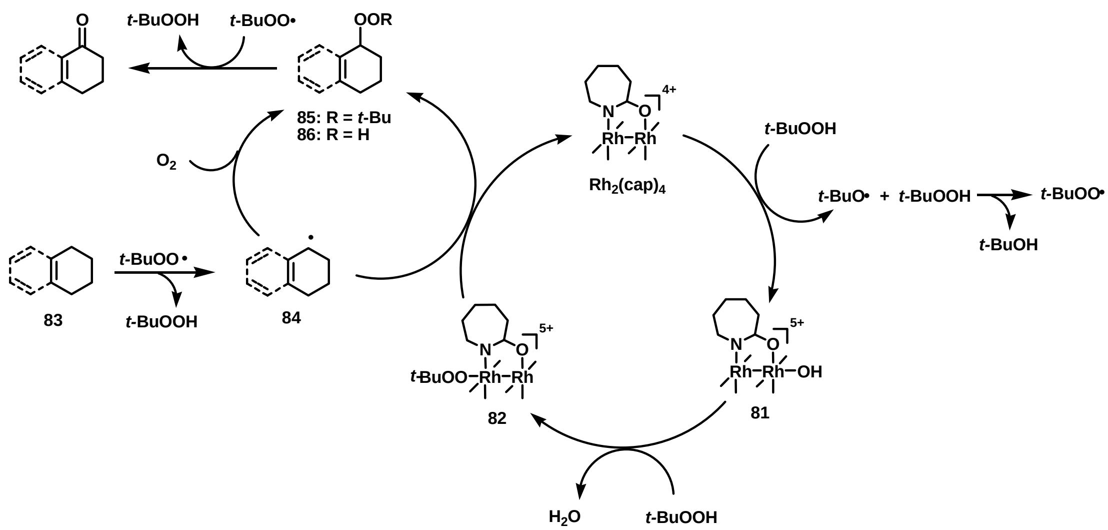
Scheme 1.27.



[a]Conditions: $Rh_2(cap)_4$ (0.1 mol%), K_2CO_3 (0.05 equiv), *t*-BuOOH (5.0 equiv), rt, 1 h
[b]Conditions: $Rh_2(cap)_4$ (1.0 mol%), $NaHCO_3$ (0.50 equiv), *t*-BuOOH (5.0 equiv), rt, 16 h

Proposed Catalytic Cycle. Based on the formation of a Rh_2^{5+} complex spectroscopically, the observed chemo- and regioselectivity, the implicated presence of *t*-BuOO·, the formation of mixed peroxides *en route* to keto-products, and precedent from other metal-catalyzed oxidations,[26,33] a mechanistic proposal can be advanced (Figure 1.8). It is proposed that $Rh_2(cap)_4$ undergoes a 1-electron oxidation in the presence of *t*-BuOOH to form a Rh_2^{5+} species tentatively assigned as dirhodium(II,III) hydroxy complex **81**, which could be converted under the reaction conditions to dirhodium peroxy complex **82** by ligand transfer. Hydrogen atom abstraction of **83** with tBuOO· can give carbon-centered radical **84**. Either transfer of *tert*-butyl peroxy radical from **82** or capture with molecular oxygen can give **85** or **86**, respectively. Radical catalyzed carbonyl-forming elimination of **85** and/or **86** can yield the keto product.[69,70]

Figure 1.8. Mechanistic Proposal for Allylic and Benzylic Oxidation Catalyzed by $Rh_2(cap)_4$.



[69] Courtneidge, J. L.; Bush, M.; Loh, L. S. *Tetrahedron* **1992**, *48*, 3835.

[70] A base-induced carbonyl-forming elimination (ref. 32) was ruled out. Mixed peroxides **78** and **79** failed to give carbonyl products upon treatment with K_2CO_3 (50 mol%) and $NaHCO_3$ (50 mol%) in CH_2Cl_2 (0.27M/[mixed peroxide]) at room temperature.

III. CONCLUSION

Allylic and benzylic oxidations are fundamentally important in organic chemistry. However, a general and effective method for oxidizing a wide variety of substrates containing allylic and benzylic C-H bonds has not be forthcoming. Described herein, $Rh_2(cap)_4$ is an effective catalyst for allylic oxidation in combination with *t*-BuOOH. A variety of substituted cyclic alkenes were converted to enones and enediones with only 0.1 – 1.0 mol% catalyst loading. $Rh_2(cap)_4$ was then found to be an effective catalyst for benzylic oxidation with *t*-BuOOH. From parallel screening, sodium bicarbonate was determined to be the most optimal base additive for substrate conversion. Benzylic carbonyl compounds were obtained in high isolated yield across a range of substrates including those containing nitrogen and acid-labile protecting groups. A formal synthesis of palmarumycin CP_2 was also described using this methodology. From spectroscopic measurements, $Rh_2(cap)_4$ undergoes a 1-electron oxidation upon treatment with *t*-BuOOH to give a higher valent dirhodium(II,III) complex (Rh_2^{5+}). This reaction was consistent with the low oxidation potential of $Rh_2(cap)_4$ as measured by cyclic voltammetry. A mechanistic proposal for allylic and benzylic oxidation was advanced.

IV. EXPERIMENTAL

General. All reactions were performed under an air atmosphere unless otherwise noted. Moisture sensitive reactions were performed using oven-dried glassware under a dried nitrogen atmosphere. All reagents were obtained from commercial sources and used without purification unless otherwise noted. 1-Triisopropylsiloxycyclohexene,[26(b)] 3',4'-dihydro-2'*H*-spiro[1,3-dioxolane-2,1'-naphthalene] (**48**), 2',3'-dihydrospiro[1,3-dioxolane-2,1'-indene] (**58**), 1-[(4-methylphenyl)sulfonyl]-1,2,3,4-tetrahydroquinoline (**61**),[71] chromane (**49**), 1,2,3,4-tetrahydronaphthalen-1-yl acetate (**64**),[72] 4-methoxybenzylmethyl ether,[73] 1,8-naphthalenediol (**71**), (2*H*)-5-methoxy-2,3-dihydrospiro[naphthalene-1(4*H*),2'-naphtho-[1,8-*de*][1,3]dioxine] (**73**) were prepared according to literature methods. Anhydrous CH_2Cl_2 and THF were purified prior to use by nitrogen forced-flow over activated alumina.[74] Chlorobenzene was treated with activated 3Å molecular sieves prior to use.[75]

Yields reported are for isolated yields unless otherwise noted. Preparative chromatographic purification was performed using SiliCycle (60 Å, 40-63 mesh) silica gel according to the method of Still.[76] Thin layer

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[71] Togo, H.; Hoshina, Y.; Muraki, T.; Nakayama, H.; Yokoyama, M. *J. Org. Chem.* **1998**, *63*, 5193.

[72] Ouedraogo, A.; Viet, M. T. P.; Saunders, J. K.; Lessard, J. *Can. J. Chem.* **1987**, *65*, 1761.

[73] Branchi, B.; Bietti, M.; Ercolani, G.; Izquierdo, M. A.; Miranda, M. A.; Stella, L. *J. Org. Chem.* **2004**, *69*, 8874.

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

[75] Armarego, W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemicals*; 5th ed., Elsevier Science: New York, 2003.

[76] Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978**, *43*, 2923.

chromatography (TLC) was performed on Merck 0.25 mm silica gel 60 F_{254} plates with visualization by aqueous $KMnO_4$ or fluorescence quenching.

^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were obtained on a Bruker DRX-400 NMR spectrometer as solutions in $CDCl_3$ containing 0.01% v/v Me_4Si (TMS). Chemical shifts are reported in parts per million (ppm) δ downfield from TMS; coupling constants are reported in Hertz (Hz). Infrared (IR) spectra were obtained on a JASCO FT/IR-4100 instrument with band assignments reported in units of cm^{-1}. Mass spectra were obtained on a JEOL SX102 magnetic sector mass spectrometer. Melting points were recorded using an Electrothermal Mel-Temp apparatus and were reported uncorrected.

Dirhodium(II) tetrakis[ε-caprolactamate] Acetonitrile Solvate [$Rh_2(cap)_4 \cdot 2CH_3CN$]. To an oven-dried 250 mL flask was added rhodium(II) acetate (2.00 g, 4.18 mmol), ε-caprolactam (11.84 g, 104.6 mmol), and chlorobenzene (110 mL). The flask was fitted with a Soxhlet extraction apparatus to which was placed a thimble containing oven-dried Na_2CO_3 and sand in a 3:1 ratio. An additional portion of chlorobenzene (50 mL) was added to partially fill the Soxhlet apparatus. The mixture was placed in an oil bath and refluxed under an atmosphere of nitrogen for 12 h during which time the color turned from green to dark blue. The mixture was cooled to room temperature and concentrated *in vacuo* to give a blue, glass-like residue. To the flask was added acetone (100 mL) and a purple solid formed upon trituration with a metal spatula. The acetone was evaporated *in vacuo*. An additional portion of acetone (100 mL) was added to the flask, the resultant solid was triturated with a metal spatula, and the acetone was evaporated *in* *vacuo*. Finally, acetone (100 mL) was added, the resultant purple solid was gravity-filtered over a course glass-fritted funnel, and washed with acetone (50 mL). The solid was scraped from the funnel to give 3.52 g of a light purple powder. The solid was recrystallized from boiling CH_3CN/MeOH (110 mL, 10:1 CH_3CN/MeOH) to give 2.95 g (96%) of $Rh_2(cap)_4{\cdot}2CH_3CN$ as dark purple crystals. Data for $Rh_2(cap)_4{\cdot}2CH_3CN$: ^1H NMR (400 MHz, $CDCl_3$) δ 3.37 - 3.24 (comp, 8H), 2.44 - 2.31 (comp, 8H), 2.07 (bs, 9H), 1.67 - 1.39 (comp, 24H); ^{13}C NMR (100 MHz) δ 185.67, 115.60, 53.55, 36.69, 30.61, 28.87, 24.13, 2.34 ppm; HRMS (FAB) calcd for $C_{24}H_{40}N_4O_4Rh_2$ 654.1160, found 654.1180 (M+); Anal. calcd for $C_{28}H_{46}N_6O_4Rh_2$: C, 45.66; H, 6.30; N, 11.41; Found: C, 45.65; H, 6.44; N, 11.90.

General Procedure for Allylic Oxidation Catalyzed by $Rh_2(cap)_4$ (Table 1.3). To a stirring solution of olefin (1.0 equiv), K_2CO_3 (0.50 equiv), and $Rh_2(cap)_4$ (0.1 mol%) in CH_2Cl_2 (0.27 M/[olefin]) was added anhydrous *t*-BuOOH (5.5 M in decane, 5.0 equiv) in one portion. The flask was immediately sealed with a septum, and an empty balloon was added to capture oxygen generated during the course of the reaction. After 1 h, the reaction mixture was filtered through a short plug of silica to remove the catalyst; and the filtrate was concentrated *in vacuo*. Column chromatography on silica gel yielded the analytically pure compound.

3-Acetylcyclohex-2-en-1-one (33).[26(a)] The general procedure for allylic oxidation catalyzed by $Rh_2(cap)_4$ was followed using 1-acetylcyclohexene. Purified by chromatography on silica gel (3:1 hexanes/EtOAc), yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.52 (s, 1H), 2.45 (dd, *J* = 6.0, 1.6 Hz, 2H), 2.41 (t, *J* = 6.0 Hz, 2H), 2.35 (s, 3H), 1.98 (tt, *J* = 6.0, 6.0 Hz, 2H).

2-Cyclohexene-1-one (34). The general procedure for allylic oxidation catalyzed by $Rh_2(cap)_4$ was followed using cyclohexene. Purified by chromatography on silica gel (3:1 hexanes/Et_2O), yellow liquid, 60% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (dt, *J* = 10.0, 4.0 Hz, 1H), 6.03 (dt, *J* = 10.0, 2.0 Hz, 1H), 2.45 - 2.42 (comp, 2H), 2.38 - 2.34 (comp, 2H), 2.03 (tt, *J* = 2.4, 2.4 Hz, 2H).

3-*tert*-Butyl-2-cyclohexen-1-one (35). The general procedure for allylic oxidation catalyzed by $Rh_2(cap)_4$ was followed using 1-*tert*-butylcyclohexene. Purified by chromatography on silica gel (3:1 hexanes/Et_2O), yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96 (s, 1H), 2.38 - 2.34 (comp, 4H), 1.97 (tt, *J* = 6.8, 6.8 Hz, 2H), 1.13 (s, 9H).

3-Phenyl-2-cyclohexen-1-one (36). The general procedure for allylic oxidation catalyzed by $Rh_2(cap)_4$ was followed using 1-phenylcyclohexene. Purified by chromatography on silica gel (4:1 hexanes/EtOAc), yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 - 7.37 (comp, 5H), 6.43 (s, 1H), 3.89 - 3.87

(comp, 2H), 2.78 (t, J = 6.8 Hz, 2H), 2.49 (t, J = 6.8 Hz, 2H), 2.16 (tt, J = 6.8, 6.8 Hz, 2H).

3-Methyl-2-cyclohexene-1-one (37).[77] The general procedure for allylic oxidation catalyzed by $Rh_2(cap)_4$ was followed using 1-methylcyclohexene. Purified by chromatography on silica gel (3:1 hexanes/Et_2O), yellow liquid; ^1H NMR (400 MHz, $CDCl_3$) δ 5.88 (s, 1H), 2.36 - 2.27 (comp, 4H), 2.03 - 1.96 (comp, 5H).

Methyl 3-oxocyclohex-1-ene-1-carboxylate (38).[26(a)] The general procedure for allylic oxidation catalyzed by $Rh_2(cap)_4$ was followed using methyl-1-cyclohexene carboxylate. Purified by chromatography on silica gel (4:1 hexanes/EtOAc), yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 6.77 (t, J = 2.0 Hz, 1H), 3.86 (s, 3H), 2.62 (ddd, J = 12.0, 6.0, 2.0 Hz, 2H), 2.50 - 2.46 (comp, 2H), 2.12 - 2.07 (comp, 2H).

3-Oxo-1-(triisopropylsiloxy)cyclohexene (38).[26(b)] The general procedure for allylic oxidation catalyzed by $Rh_2(cap)_4$ was followed using 1-triisopropylsiloxycyclohexene. Purified by chromatography on silica gel (4:1 hexanes/EtOAc), yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 5.43 (s, 1H), 2.41 (t,

[77] Murray, R. W.; Singh, M.; Williams, B. L.; Moncrieff, H. M. *J. Org. Chem.* **1996**, *61*, 1830.

J = 6.4 Hz, 2H), 2.33 (t, *J* = 6.4 Hz, 2H), 1.98 (tt, *J* = 6.4, 6.4 Hz, 2H), 1.30 – 0.98 (comp, 21H).

3-Acetylcyclopent-2-en-1-one (40).[26(a)] The general procedure for allylic oxidation catalyzed by $Rh_2(cap)_4$ was followed using 1-acetylcyclopentenone. Purified by chromatography on silica gel (3:1 hexanes/EtOAc), yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.64 (t, *J* = 2.0 Hz, 1H), 2.81 (ddd, *J* = 10.0, 7.2, 2.0 Hz, 2H), 2.53 (ddd, *J* = 10.0, 4.8, 2.0 Hz, 2H), 2.50 (s, 3H).

Methyl 3-oxocyclopent-1-ene-1-carboxylate (41).[26(a)] The general procedure for allylic oxidation catalyzed by $Rh_2(cap)_4$ was followed using methyl-1-cyclopentene carboxylate. Purified by chromatography on silica gel (4:1 hexanes/EtOAc), yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (t, *J* = 2.0 Hz, 1H), 3.88 (s, 3H), 2.87 (dt, *J* = 7.6, 2.0 Hz, 2H), 2.56 - 2.54 (comp, 2H).

Cyclohept-2-ene-1,4-dione (42).[26(a)] To a stirring solution of 2-cyclohepten-1-one (0.060 g, 0.543 mmol), K_2CO_3 (0.038 g, 0.272 mmol), and $Rh_2(cap)_4$ (2.0 mg, 0.0027 mmol) in CH_2Cl_2 (2.0 mL) was added anhydrous *t*-BuOOH (5.5 M in decane, 0.493 mL, 2.72 mmol) at which time the color of the solution immediately turned from light blue to red. The flask was equipped with a reflux condenser. The reflux condenser was fitted with a septum and an empty balloon to capture any oxygen generated during the course of the reaction. The flask was placed in a preheated oil bath at 40 °C. After 1.5 hours, $Rh_2(cap)_4$ (2.0 mg, 0.0027 mmol) and anhydrous *t*-BuOOH (0.493 mL, 2.72 mmol) were added and the mixture was stirred for an additional 1.5 h at 40 °C. The reaction mixture was cooled to room temperature, filtered through a short plug of silica to remove the catalyst, and evaporated *in vacuo*. Purification by column chromatography on silica gel (3:1 hexanes/EtOAc) gave 0.056 g (83%) of **42** as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.45 (s, 2H), 2.82 - 2.78 (comp, 4H), 2.12 - 2.06 (comp, 2H).

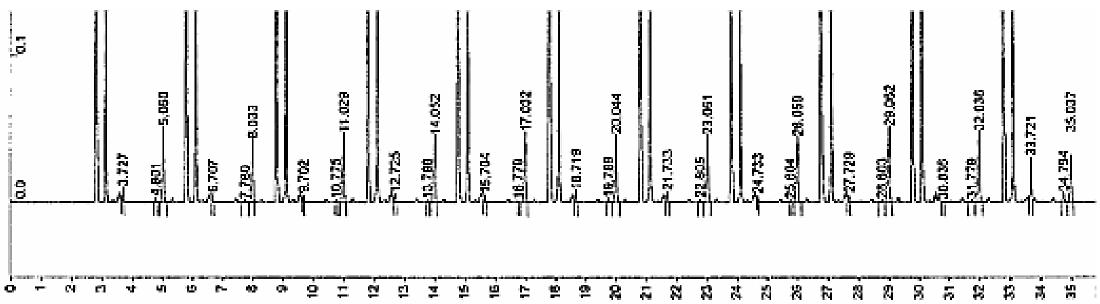
1,4-Dioxaspiro[4.4]non-8-en-7-one (43).[26(a)] The procedure for the preparation of cyclohept-2-ene-1,4-dione (**43**) was followed using 2-cyclopenten-1-one ethylene ketal. Purified by chromatography on silica gel (3:1 hexanes/Et_2O), clear liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 5.8 Hz, 1H), 6.23 (d, *J* = 5.8 Hz, 1H), 4.11 - 4.03 (comp, 4H), 2.63 (s, 2H).

3-Nitro-2-cyclohexen-1-one (44). To a stirring solution of 1-nitrocyclohexene (0.069 g, 0.543 mmol), K_2CO_3 (0.038 g, 0.272 mmol), and $Rh_2(cap)_4$ (2.0 mg, 0.0027 mmol) in CH_2Cl_2 (2.0 mL) was added anhydrous *t*-BuOOH (5.5 M in decane, 0.493 mL, 2.72 mmol) at which time the color of the solution immediately turned from light blue to red. The flask was equipped with a reflux condenser and was fitted with a septum and an empty balloon to capture any oxygen generated during the course of the reaction. The flask was placed in a preheated oil bath at 40 °C. After 12 hours, $Rh_2(cap)_4$ (2.0 mg, 0.0027 mmol) and anhydrous *t*-BuOOH (0.493 mL, 2.72 mmol) were added, and the mixture was stirred for an additional 12 h at 40 °C. The reaction mixture was cooled to room temperature, filtered through a short plug of silica to remove the catalyst, and the solvent evaporated *in vacuo*. Purification by column chromatography on silica gel (3:1 hexanes/EtOAc) gave 0.061 g (64%) of **44** as a yellow oil. TLC R_f = 0.30 (3:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (s, 1H), 2.92 (dd, *J* = 6.0, 1.6 Hz, 2H), 2.54 - 2.51 (comp, 2H), 2.19 (p, *J* = 6.0 Hz, 2H); ^{13}C NMR (100 MHz) δ 198.2, 164.0, 125.7, 37.0, 24.4, 20.9; IR (neat) 1699 (C=O), 1536 (N=O), 1340 (N-O) cm^{-1}; HRMS (EI) calcd for $C_6H_7NO_3$ 141.0426, found 141.0429 (M+).

Benzylic Oxidation Catalyzed by $Rh_2(cap)_4$ (Parallel Screening Procedure, Figure 1.5). To an oven-dried 1-dram vial equipped with a stirbar was added 1,2,3,4-tetrahydronaphthalene (0.036 mg, 0.272 mmol), $Rh_2(cap)_4$ (2.0 mg, 0.0027 mmol), additive (0.50 equiv), and CH_2Cl_2 (1.0 mL). To the mixture was added anhydrous *t*-BuOOH (5.5 M in decane, 1.36 mmol). The loss of 1,2,3,4-tetrahydronaphthalene was measured by removing 1 μL aliquots from the reaction. The samples were injected on a Hewlett-Packard 5890 gas chromatograph equipped with a SPB-5 column (30 m, 0.25 mm) at

180 °C (isothermal). Data was obtained via continuous acquisition (injections at 3 minute intervals) for each reaction in the screen (Figure 1.9). Retention times: 1,2,3,4-tetrahydronaphthalene (3.727 min), 2,3-dihydronaphthalene-1,4-dione (**46**) (4.801 min), α-tetralone (**45**) (5.060 min).

Figure 1.9. Representative GC Trace by Continuous Acquisition.



2-[(4-Methylphenyl)sulfonyl]isoindoline (47).[78] To a solution of 1,2-benzenedimethanol (2.0 g, 14.5 mmol) in THF (50 mL) was added triethylamine (4.23 mL, 30.4 mmol). The solution was cooled to 0 °C and methanesulfonyl chloride (2.30 mL, 29.7 mmol) was added dropwise via syringe over 10 minutes. The solution was stirred for an additional 1 h at 0 °C. The THF was removed *in vacuo* and the remaining white solid was taken up in ether (100 mL) and filtered over a plug of silica/Celite (1:1). The filtrate was evaporated *in vacuo* to give a light yellow oil (4.26 g, 14.5 mmol) which was dissolved in anhydrous DMF (100 mL). The solution was cooled to 0 °C

[78] Bottino, F.; Digrazia, M.; Finocchiaro, P.; Fronczek, F. R.; Mamo, A.; Pappalardo, S. *J. Org. Chem.* **1988**, *53*, 3521.

to which was added *p*-toluenesulfonamide (2.73 g, 15.9 mmol) and sodium hydride (60% mineral oil dispersion, 1.27 g, 31.8 mmol). The mixture was allowed to warm to room temperature and stirred overnight. Water (100 mL) was carefully added and the mixture was extracted with EtOAc (2 x 75 mL). The combined organic extracts were washed with brine (2 x 150 mL), dried over anhydrous $MgSO_4$, and evaporated *in vacuo* to give a yellow residue that was recrystallized from toluene/hexanes (10:1) to give 1.98 g (50%) of **47** as a white solid, mp = 175 – 176 °C (lit. = 178 – 179 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.26 - 718 (comp, 4H), 4.62 (s, 4H), 2.40 (s, 3H).

***tert*-Butyl-3,4-dihydroquinoline-1(2*H*)-carboxylate (50)**.[79] To a stirring solution of 1,2,3,4-tetrahydroquinoline (2.09 g, 15.7 mmol) in THF (30 mL) was added DMAP (0.192 g, 1.57 mmol) and di-*tert*-butyl dicarbonate (4.45 g, 20.4 mmol) and stirred overnight. The solvent was evaporated; and the residual oil was dissolved in ether (30 mL) and washed with saturated NH_4Cl (3 x 30 mL) and brine (30 mL). The solution was dried over anhydrous $MgSO_4$ and the ether was evaporated *in vacuo*. Column chromatography (9:1 hexanes/EtOAc) on silica gel yielded 2.26 g (62%) of **50** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 - 7.06 (comp, 4H), 3.79 (t, *J* = 6.6 Hz, 2H), 2.79 (t, *J* = 6.6 Hz, 2H), 2.04 - 1.97 (comp, 2H), 1.52 (s, 9H).

[79] Padwa, A.; Brodney, M. A.; Liu, B.; Satake, K.; Wu, T. *J. Org. Chem.* **1999**, *64*, 3595.

General Procedure for Benzylic Oxidation Catalyzed by $Rh_2(cap)_4$ at Room Temperature (Table 1.4). To a stirring solution of substrate (1.0 equiv), $NaHCO_3$ (0.50 equiv), and $Rh_2(cap)_4$ (1.0 mol%) in DCE at room temperature was added anhydrous *t*-BuOOH (5.5 M in decane, 5.0 equiv) at which time the color of the solution immediately turned from light blue to red. The flask was sealed with a septum allowing inclusion of air and an empty balloon was added to capture any oxygen generated during the course of the reaction. After stirring for 16 h, the mixture was filtered through a short plug of silica to remove the catalyst, and the solvent was evaporated *in vacuo*. Column chromatography on silica gel yielded the analytically pure compound.

α-Tetralone (45).[80] The general procedure for benzylic oxidation catalyzed by $Rh_2(cap)_4$ at room temperature was followed using 1,2,3,4-tetrahydronaphthalene as the substrate. Purified by chromatography on silica gel (3:1 hexanes/EtOAc), yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 7.9 Hz, 1H), 7.47 (t, J = 7.9 Hz, 1H), 7.32 – 7.24 (comp, 2H), 2.97 (t, J = 6.0 Hz, 2H), 2.66 (t, J = 6.0 Hz, 2H), 2.14 (tt, J = 6.0, 6.0 Hz, 2H).

6-Methoxy-1-tetralone and 7-Methoxy-1-tetralone (1:1) (54).[81] The general procedure for benzylic oxidation catalyzed by $Rh_2(cap)_4$ at room temperature was followed using 6-methoxy-1,2,3,4-tetrahydronaphthalene as the substrate. Purified by chromatography on silica gel (5:1 hexanes/EtOAc),

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[80] Ozaki, S.; Adachi, M.; Sekiya, S.; Kamikawa, R. *J. Org. Chem.* **2003**, *68*, 4586.

[81] (a) Gogoi, P.; Sarmah, G. K.; Konwar, D. *J. Org. Chem.* **2004**, *69*, 5153. (b) Chang, H. M.; Cheng, K. P.; Choang, T. F.; Chow, H. F.; Chui, K. Y.; Hon, P. M.; Tan, F. W. L.; Yang, Y.; Zhong, Z. P.; Lee, C. M.; Sham, H. L.; Chan, C. F.; Cui, Y. X.; Wong, H. N. C. *J. Org. Chem.* **1990**, *55*, 3537.

yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 – 8.00 (comp, 2H), 7.45 (d, *J* = 2.4 Hz, 1H), 7.23 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.82 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.70 (d, *J* = 2.4 Hz, 1H), 3.86 (s, 3H), 3.73 (s, 3H), 2.93 (t, *J* = 6.0 Hz, 4H), 2.61 (t, *J* = 6.4 Hz, 4H), 2.12 (p, *J* = 6.4 Hz, 4H). A 1:1 mixture of products was determined by ^{1}H NMR (integration of -OC**H**$_3$ signals) prior to purification.

1-Indanone (52).[82] The general procedure for benzylic oxidation catalyzed by $Rh_2(cap)_4$ at room temperature was followed using $(NH_4)_2CO_3$ (50 mol%) and indan as the substrate. Purified by chromatography on silica gel (5:1 hexanes/EtOAc), colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.0 Hz, 1H), 7.56 – 7.54 (m, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.36 (t, *J* = 8.0 Hz, 1H), 3.15 (t, *J* = 6.1 Hz, 2H), 2.70 (t, *J* = 6.1 Hz, 2H).

Xanthone (53).[83] The general procedure for benzylic oxidation catalyzed by $Rh_2(cap)_4$ at room temperature was followed using xanthane as the substrate. Purified by chromatography on silica gel (3:1 hexanes/EtOAc), white solid (mp = 175 – 176 °C, lit. = 178 – 180 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.0 Hz, 2H), 7.62 (t, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.28 (t, *J* = 8.0 Hz, 2H).

Fluorenone (54).[Error! Bookmark not defined.] The general procedure for benzylic oxidation catalyzed by $Rh_2(cap)_4$ at room temperature was followed using fluorene as a substrate. Purified by chromatography on silica gel (3:1

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[82] Shaabani, A.; Mirzaei, P.; Naderi, S.; Lee, D. G. *Tetrahedron* **2004**, *60*, 11415.

[83] (a) Zhao, J.; Larock, R. C. *Org. Lett.* **2005**, *7*, 4273. (b) Xu, F.; Cao, X.; Cao, Z.; Zou, L. *Tetrahedron Lett.* **2000**, *41*, 10257.

hexanes/EtOAc), yellow solid (mp = 79 – 80 °C, lit. = 81 – 82 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 7.6 Hz, 2H), 7.35 – 7.34 (comp, 4H), 7.19 – 7.15 (comp, 2H).

Benzophenone (55). The general procedure for benzylic oxidation catalyzed by $Rh_2(cap)_4$ at room temperature was followed using diphenylmethane as the substrate. Purified by chromatography on silica gel (5:1 hexanes/EtOAc), white solid (mp = 47 – 48 °C, lit.[84] = 50 – 51 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.6 Hz, 4H), 7.56 (t, *J* = 7.6 Hz, 2H), 7.45 (t, *J* = 7.6 Hz, 2H).

2-[(4-Methylphenyl)sulfonyl]isoindolin-1-one (56).[85] The general procedure for benzylic oxidation catalyzed by $Rh_2(cap)_4$ at room temperature was followed using 2-[(4-methylphenyl)sulfonyl]isoindoline (**47**) as the substrate. Reaction time was 4 h. Purified by chromatography on silica gel (3:1 hexanes/EtOAc), white solid (mp = 214 - 216 °C, lit. = 216 - 218 °C); ^{1}H NMR (400 MHz, $CDCl_3$) 8.03 (d, *J* = 8.0 Hz, 2H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.64 (t, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 4.91 (s, 2H), 2.42 (s, 3H).

2,3-Dihydronaphthalene-1,4-dione (46).[86] The general procedure for benzylic oxidation catalyzed by $Rh_2(cap)_4$ at room temperature was followed using α-tetralone as the substrate. Purified by chromatography on silica gel

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[84] Levine, R.; Karten, M. J. *J. Org. Chem.* **1976**, *41*, 1176.

[85] Morimoto, T.; Fujioka, M.; Fuji, K.; Tsutsumi, K.; Kakiuchi, K. *Chem. Lett.* **2003**, *32*, 154.

[86] Tsuji, T.; Okuyama, M.; Ohkita, M.; Kawai, H.; Suzuki, T. *J. Am. Chem. Soc.* **2003**, *125*, 951.

(5:1 hexanes/EtOAc), white solid (mp = 87 – 89 °C, lit. = not reported); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 - 8.03 (comp, 2H), 7.76 - 7.73 (comp, 2H), 3.09 (s, 4H).

6-Methoxy-2,3-dihydronaphthalene-1,4-dione (69). The general procedure for benzylic oxidation catalyzed by $Rh_2(cap)_4$ at room temperature was followed using 6-methoxy-1-tetralone as the substrate. Purified by chromatography on silica gel (5:1 hexanes/EtOAc), bright yellow solid (mp = 80 – 83 °C): TLC R_f = 0.29 (3:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.8 Hz, 1H), 7.43 (d, J = 2.8 Hz, 1H), 7.21 (dd, J = 8.8, 2.8 Hz, 1H), 3.94 (s, 3H), 3.10 - 3.01 (comp, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.2, 194.7, 164.2, 137.2, 129.1, 128.8, 121.5, 108.8, 55.8, 37.6, 37.1; IR (neat) 1682 (C=O), 1595 (C=O) cm^{-1}; HRMS (EI) calcd for $C_{11}H_{10}O_3$ 190.0630, found 190.0625 (M+).

General Procedure for Benzylic Oxidation Catalyzed by $Rh_2(cap)_4$ at 40 °C (Table 1.5). To a stirring solution of substrate (1.0 equiv), $NaHCO_3$ (0.50 equiv), and $Rh_2(cap)_4$ (0.5 mol%) in DCE was added anhydrous *t*-BuOOH (5.5 M in decane, 5.0 equiv) at which time the color of the solution immediately turned from light blue to red. The flask was sealed with a septum and an empty balloon was added to capture any oxygen generated during the course of the reaction. The flask was placed in a preheated oil bath at 40 °C. After 3 hours, $Rh_2(cap)_4$ (0.5 mol%) and *t*-BuOOH (5.0 equiv) were added and the solution was stirred for an additional 13 h at 40 °C. The solution was cooled to room temperature, filtered through a short plug of silica to remove the catalyst, and evaporated *in vacuo*. Column chromatography on silica gel yielded the analytically pure compound.

2',3'-Dihydro-4'*H*-spiro[1,3-dioxolane-2,1'-naphthalen]-4'-one (57). The general procedure for benzylic oxidation catalyzed by $Rh_2(cap)_4$ at 40 °C was followed using 3',4'-dihydro-2'*H*-spiro[1,3-dioxolane-2,1'-naphthalene] (**48**) as the substrate. Purified by chromatography on silica gel (4:1 hexanes/EtOAc); clear oil: TLC R_f = 0.34 (3:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 - 8.01 (m, 1H), 7.64 - 7.57 (comp, 2H), 7.49 - 7.45 (m, 1H), 4.26 - 4.13 (comp, 4H), 2.90 (t, *J* = 6.9 Hz, 2H), 2.35 (t, *J* = 6.9 Hz, 2H); ^{13}C NMR (100 MHz) δ 197.0, 142.8, 133.9, 132.0, 129.2, 126.9, 124.9, 105.7, 65.5, 35.8, 33.5; IR (neat) 1693 (C=O) cm^{-1}; HRMS (EI) calcd for $C_{12}H_{12}O_3$ 204.0786, found 204.0779 (M+).

Spiro[1,3-dioxolane-2,1'-inden]-3'(2'*H*)-one (59). The general procedure for benzylic oxidation catalyzed by $Rh_2(cap)_4$ at 40 °C was followed using 2',3'-dihydrospiro[1,3-dioxolane-2,1'-indene] (**58**) as the substrate. Purified by chromatography on silica gel (4:1 hexanes/EtOAc), clear oil, TLC R_f = 0.32 (3:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 - 7.64 (comp, 3H), 7.58 - 7.54 (m, 1H), 4.31 - 4.25 (comp, 2H), 4.17 - 4.13 (comp, 2H), 2.96 (s, 2H); ^{13}C NMR (100 MHz) δ 200.9, 151.4, 137.3, 135.4, 130.8, 124.3, 122.7, 100.0, 65.8, 49.1; IR (neat) 1716 (C=O) cm^{-1}; HRMS (EI) calcd for $C_{11}H_{10}O_3$ 190.0630, found 190.0633 (M+).

***tert*-Butyl-4-oxo-3,4-dihydroquinoline-1(2*H*)-carboxylate (60)**. The general procedure for benzylic oxidation catalyzed by $Rh_2(cap)_4$ at 40 °C was followed using *tert*-butyl-3,4-dihydroquinoline-1(2*H*)-carboxylate (**50**) as the substrate. Purified by chromatography on silica gel (5:1 hexanes/EtOAc), light yellow oil: TLC R_f = 0.34 (3:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.77 (pseudo s, 1H), 7.60 - 7.55 (m, 1H), 7.30 - 7.26 (m, 1H), 4.23 (t, *J* = 6.4 Hz, 2H), 2.87 (t, *J* = 6.4 Hz, 2H), 1.53 (s, 9H); ^{13}C NMR (100 MHz) δ 192.9, 147.9, 146.6, 142.2, 134.4, 127.6, 125.6, 123.5, 86.1, 45.5, 38.8, 27.4; IR (neat) 1731 (C=O), 1693 (C=O) cm^{-1}; HRMS (EI) calcd for $C_{14}H_{17}NO_3$ 247.1208, found 247.1217 (M+).

1-[(4-Methylphenyl)sulfonyl]-2,3-dihydroquinolin-4(1*H*)-one (62). The general procedure for benzylic oxidation catalyzed by $Rh_2(cap)_4$ at 40 °C was followed using 1-[(4-methylphenyl)sulfonyl]-1,2,3,4-tetrahydroquinoline as the substrate. Purified by chromatography on silica gel (5:1 hexanes/EtOAc), pale yellow solid (mp = 136 – 138 °C): TLC R_f = 0.20 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.6 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.55 – 7.50 (comp, 3H), 7.24 – 7.18 (comp, 3H), 4.19 (t, *J* = 6.4 Hz, 2H), 2.36 – 2.34 (comp, 5H); ^{13}C NMR (100 MHz) δ 192.6, 144.5, 142.2, 136.7, 134.6, 130.0, 127.6, 126.8, 125.6, 125.5, 124.4, 46.1, 36.4, 21.5; IR (neat) 1683 (C=O) cm^{-1}; HRMS (EI) calcd for $C_{16}H_{15}NO_3S$ 301.0772, found 301.0769 (M+).

Chromanone (63).[87] The general procedure for benzylic oxidation catalyzed by $Rh_2(cap)_4$ at 40 °C was followed using chromane (**49**) as the substrate. Purified by chromatography on silica gel (9:1 hexanes/EtOAc),

[87] Hwu, J. R.; Wein, Y. S.; Leu, Y. J. *J. Org. Chem.* **1996**, *61*, 1493.

colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 6.4, 1.6 Hz, 1H), 7.48 (t, *J* = 6.4 Hz, 1H), 7.04 – 6.96 (comp, 2H), 4.54 (t, *J* = 6.4 Hz, 2H), 2.82 (t, *J* = 6.4 Hz, 2H).

4-Oxo-1,2,3,4-tetrahydronaphthalen-1-yl acetate (65).[88] The general procedure for benzylic oxidation catalyzed by $Rh_2(cap)_4$ at 40 °C was followed using 1,2,3,4-tetrahydronaphthalen-1-yl acetate (**64**) as the substrate. Purified by chromatography on silica gel (3:1 hexanes/EtOAc), yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 8.04 (m, 1H), 7.60 – 7.56 (m, 1H), 7.47 – 7.43 (comp, 2H), 6.13 (dd, *J* = 6.0, 3.6 Hz, 1H), 2.98 – 2.90 (m, 1H), 2.71 – 2.64 (m, 1H), 2.42 – 2.28 (comp, 2H), 2.13 (s, 3H).

Acetophenone (66).[Error! Bookmark not defined.] The general procedure for benzylic oxidation catalyzed by $Rh_2(cap)_4$ at 40 °C was followed using ethyl benzene as the substrate. Purified by chromatography on silica gel (5:1 hexanes/EtOAc), colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 – 7.95 (comp, 2H), 7.59 – 7.54 (m, 1H), 7.46 (t, J = 8.0 Hz, 2H), 2.61 (s, 3H).

4-Methoxyacetophenone (67).[89] The general procedure for benzylic oxidation catalyzed by $Rh_2(cap)_4$ at 40 °C was followed using 4-ethylanisole as the substrate. Purified by chromatography on silica gel (5:1 hexanes/EtOAc), light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 3.81 (s, 3H), 2.50 (s, 3H).

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[88] Joly, S.; Nair, M. S. *Tetrahedron: Asymmetry*, **2001**, *12*, 2283.

[89] Huang, Z. Z.; Tang, Y. *J. Org. Chem.* **2002**, *67*, 5320.

4-Methoxybenzoic acid methyl ester (68).[90] The general procedure for benzylic oxidation catalyzed by $Rh_2(cap)_4$ at 40 °C was followed using 4-methoxybenzylmethyl ether as the substrate. Purified by chromatography on silica gel (5:1 hexanes/EtOAc), yellow solid (mp = 44 – 45 °C, lit. = 47 – 48 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 3.80 (s, 3H), 3.76 (s, 3H).

5-Methoxy-2,3-dihydrospiro[naphthalene-1(4H),2'-naphtho[1,8-*de*][1,3]dioxin]-4-one (73).[91] The general procedure for benzylic oxidation catalyzed by $Rh_2(cap)_4$ at 40 °C was followed using (2*H*)-5-methoxy-2,3-dihydrospiro[naphthalene-1(4*H*),2'-naphtho-[1,8-*de*][1,3]dioxine] (**72**) as the substrate. Purified by chromatography on silica gel (3:1 hexanes/EtOAc), orange solid (mp = 121 – 122 °C, lit.[92] = 126 – 128 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.42 (comp, 6H), 7.12 (d, *J* = 8.4 Hz, 1H), 6.96 (d, *J* = 7.6 Hz, 1H), 3.98 (s, 3H), 2.77 (t, *J* = 6.8 Hz, 2H), 2.48 (t, *J* = 6.8 Hz, 2H).

3-*tert*-Butylperoxy-1-phenylcyclohexene (78).[30] The general procedure for allylic oxidation catalyzed by $Rh_2(cap)_4$ was followed using K_2CO_3 (5.0 mol%) and 1-phenylcyclohexene. Purified by chromatography on silica gel (25:1 → 15:1 hexanes/EtOAc), colorless liquid; ^{1}H NMR (400 MHz,

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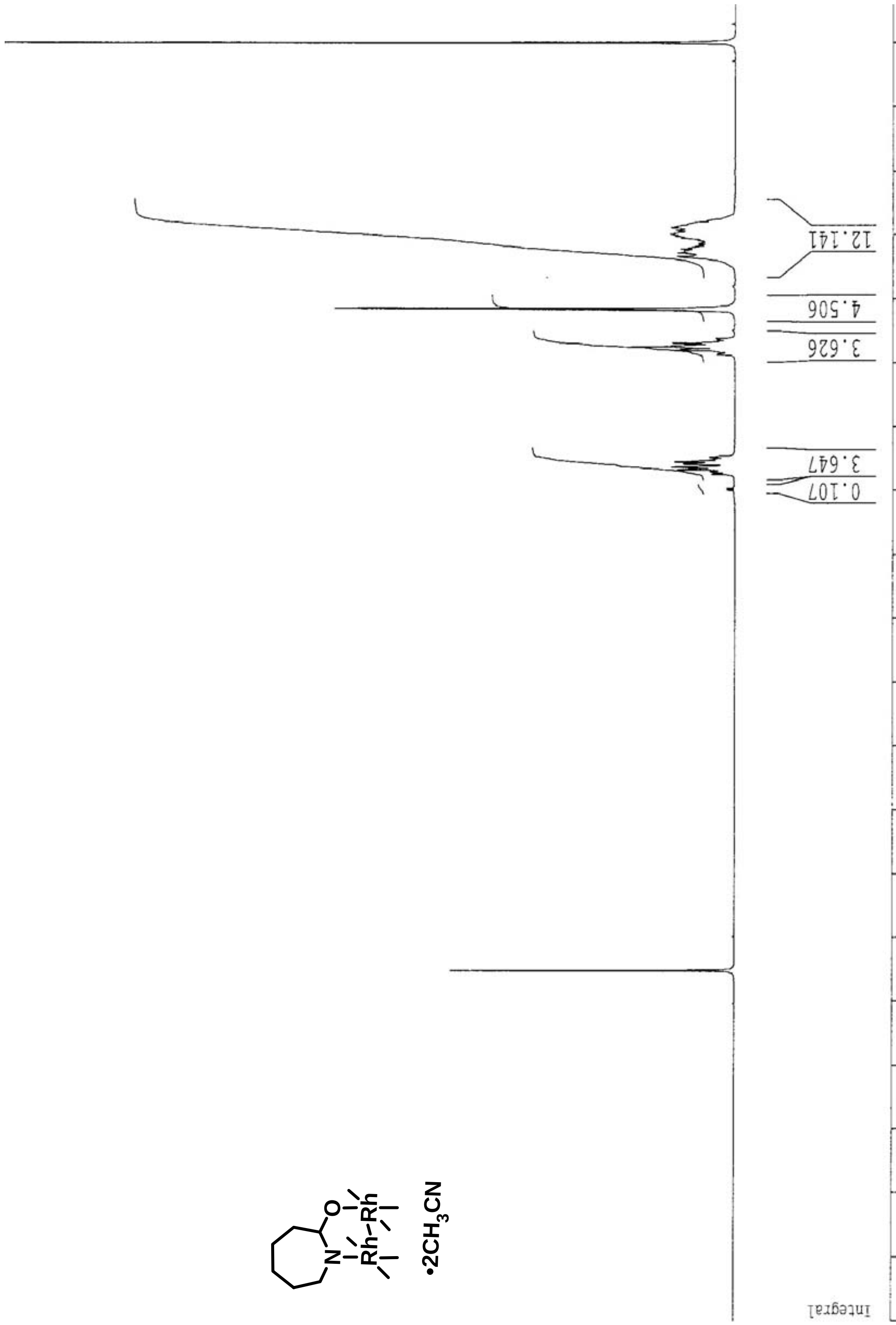
[90] McNulty, J.; Capretta, A.; Laritchev, V.; Dyck, J.; Robertson, A. J. *J. Org. Chem.* **2003**, *68*, 1597.

[91] Barrett, A. G. M.; Blaney, F.; Campbell, A. D.; Hamprecht, D.; Meyer, T.; White, A. J. P.; Witty, D.; Williams, D. J. *J. Org. Chem.* **2002**, *67*, 2735.

[92] Ragot, J. P.; Steeneck, C.; Alcaraz, M. L.; Taylor, R. J. K. *J. Chem. Soc. Perkin Trans. 1* **1999**, 1073.

$CDCl_3$) δ 7.48 (d, *J* = 7.6 Hz, 1H), 7.43 – 7.30 (comp, 4H), 6.14 – 6.13 (m, 1H), 4.63 – 4.60 (m, 1H), 2.52 – 2.44 (m, 1H), 2.39 – 2.39 (m, 1H), 2.15 – 2.09 (m, 1H), 2.02 – 1.96 (m, 1H), 1.82 – 1.69 (comp, 2H).

1-(*tert*-Butylperoxy)-3,4-dihydro-1*H*-isochromene (79). The general procedure for benzylic oxidation catalyzed by $Rh_2(cap)_4$ at room temperature was followed using isochromane as the substrate. Purified by chromatography on silica gel (9:1 pentanes/Et_2O); clear oil: TLC R_f = 0.32 (5:1 hexanes/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 - 7.30 (d, *J* = 8.0 Hz, 1H), 7.25 - 7.17 (comp, 2H), 7.11 - 7.09 (d, *J* = 8.0 Hz, 1H), 6.02 (s, 1H), 4.22 - 4.16 (dt, *J* = 11.8, 3.2 Hz, 1H), 3.99 - 3.94 (dd, *J* = 11.8, 5.2 Hz, 1H), 3.04 - 2.95 (m, 1H), 2.58 - 2.54 (dd, *J* = 16.0, 2.8 Hz, 1H), 1.32 (s, 9H); ^{13}C NMR (100 MHz) δ 135.5, 130.1, 128.7, 128.6, 128.2, 126.1, 99.1, 80.9, 56.0, 27.0, 26.6; IR (neat) 1092 (C-O-O) cm^{-1}; HRMS (FAB) calcd for $C_{13}H_{18}CsO_3$ 355.0310, found 355.0322 (M+Cs).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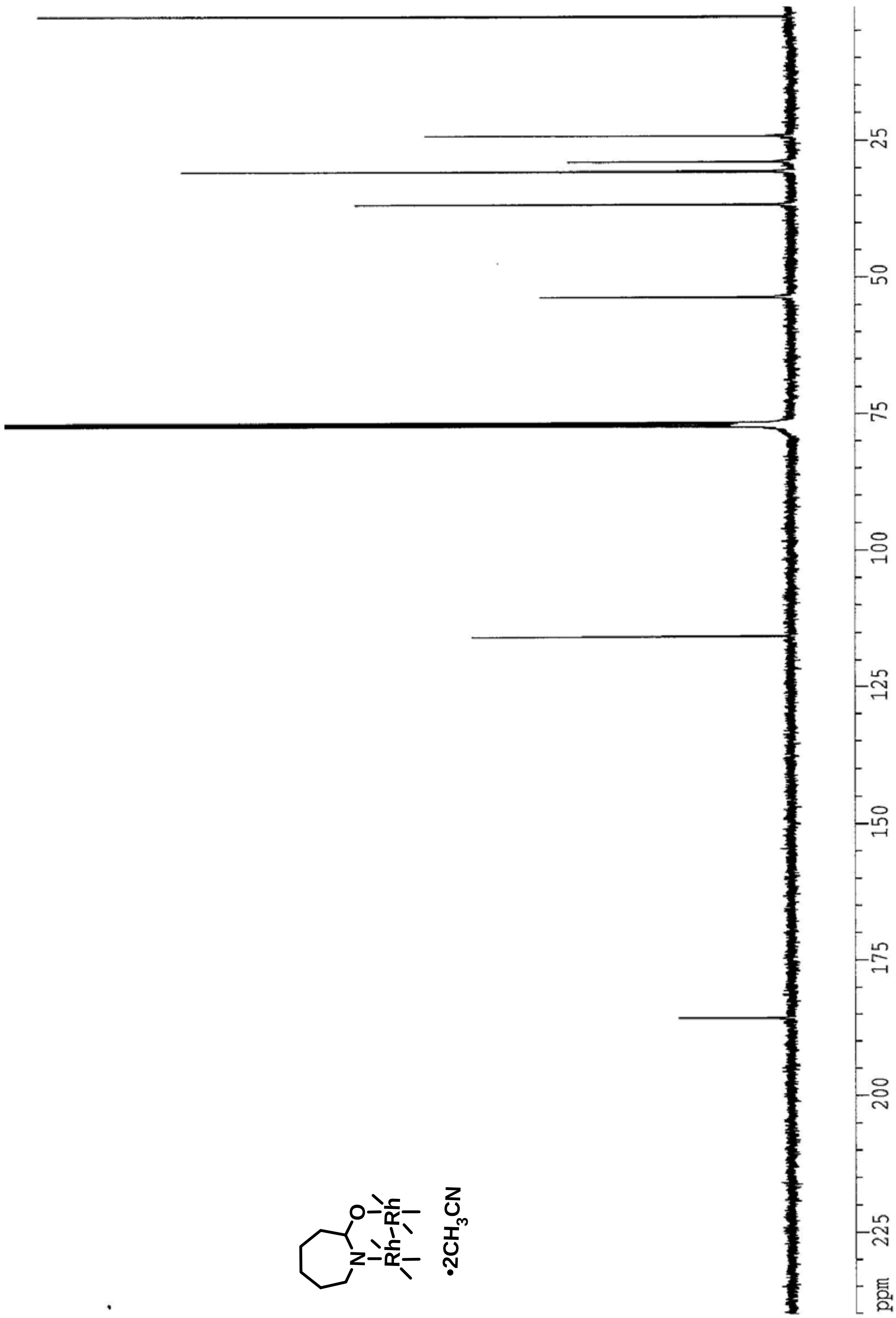

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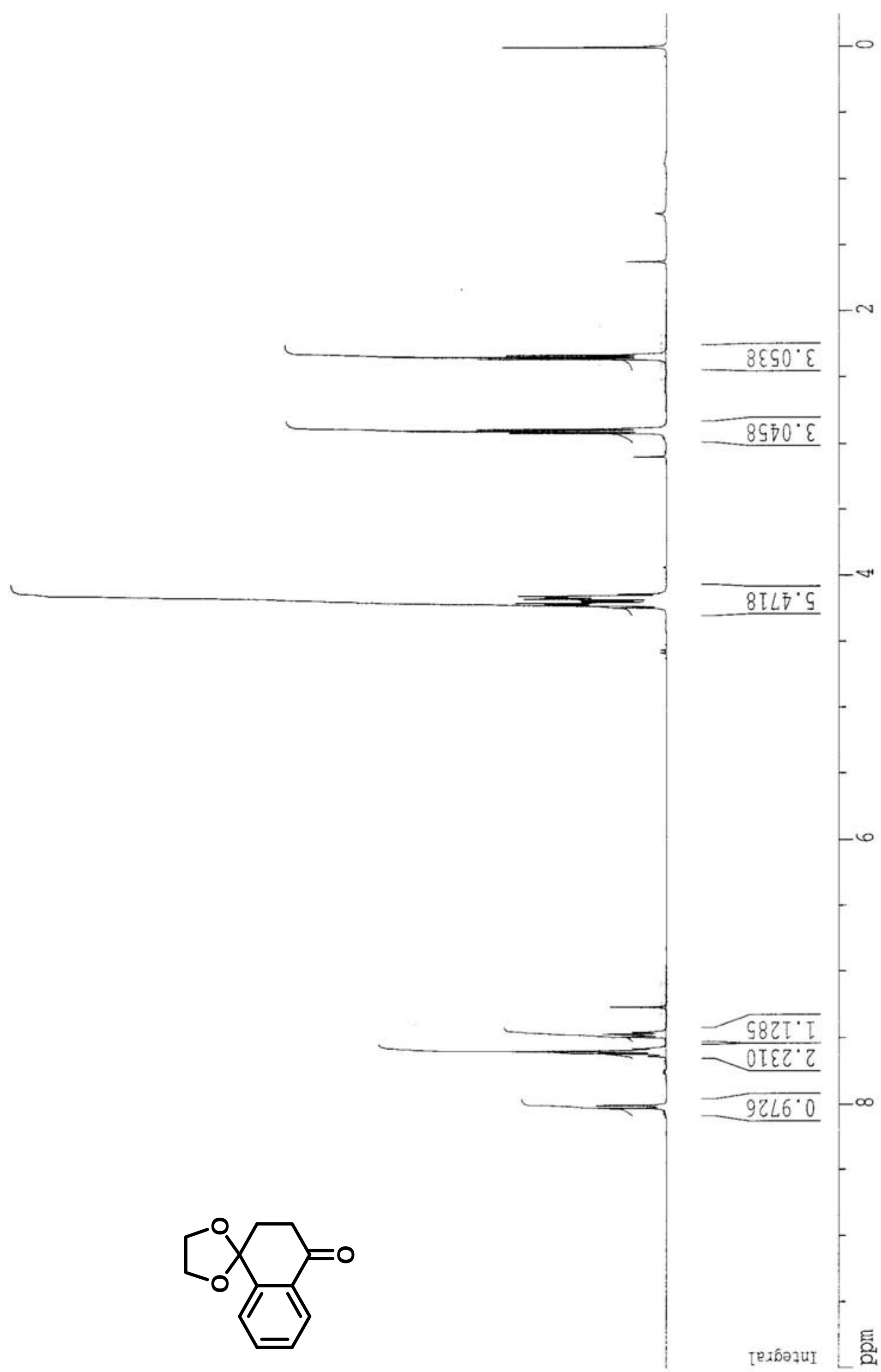

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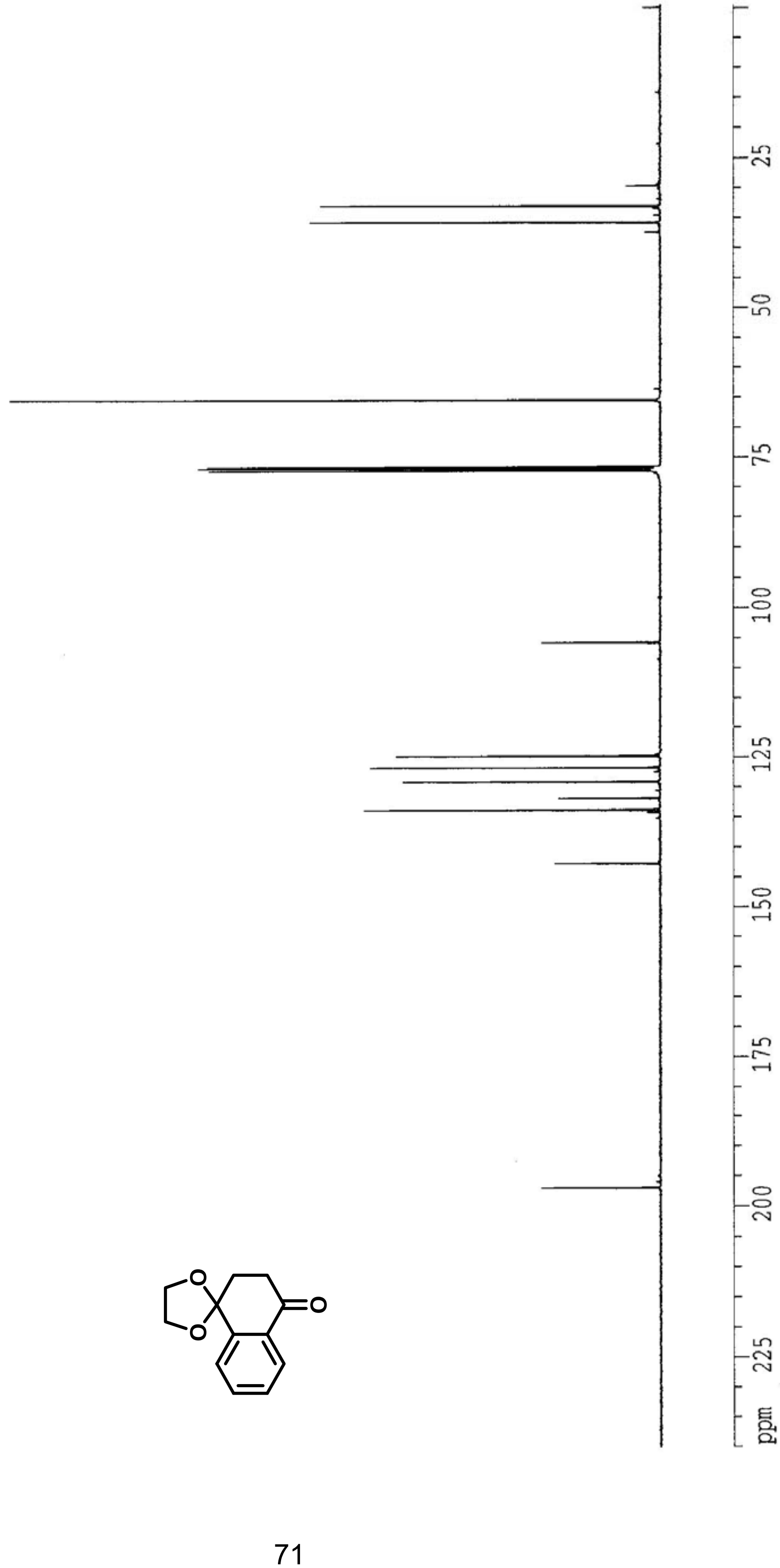

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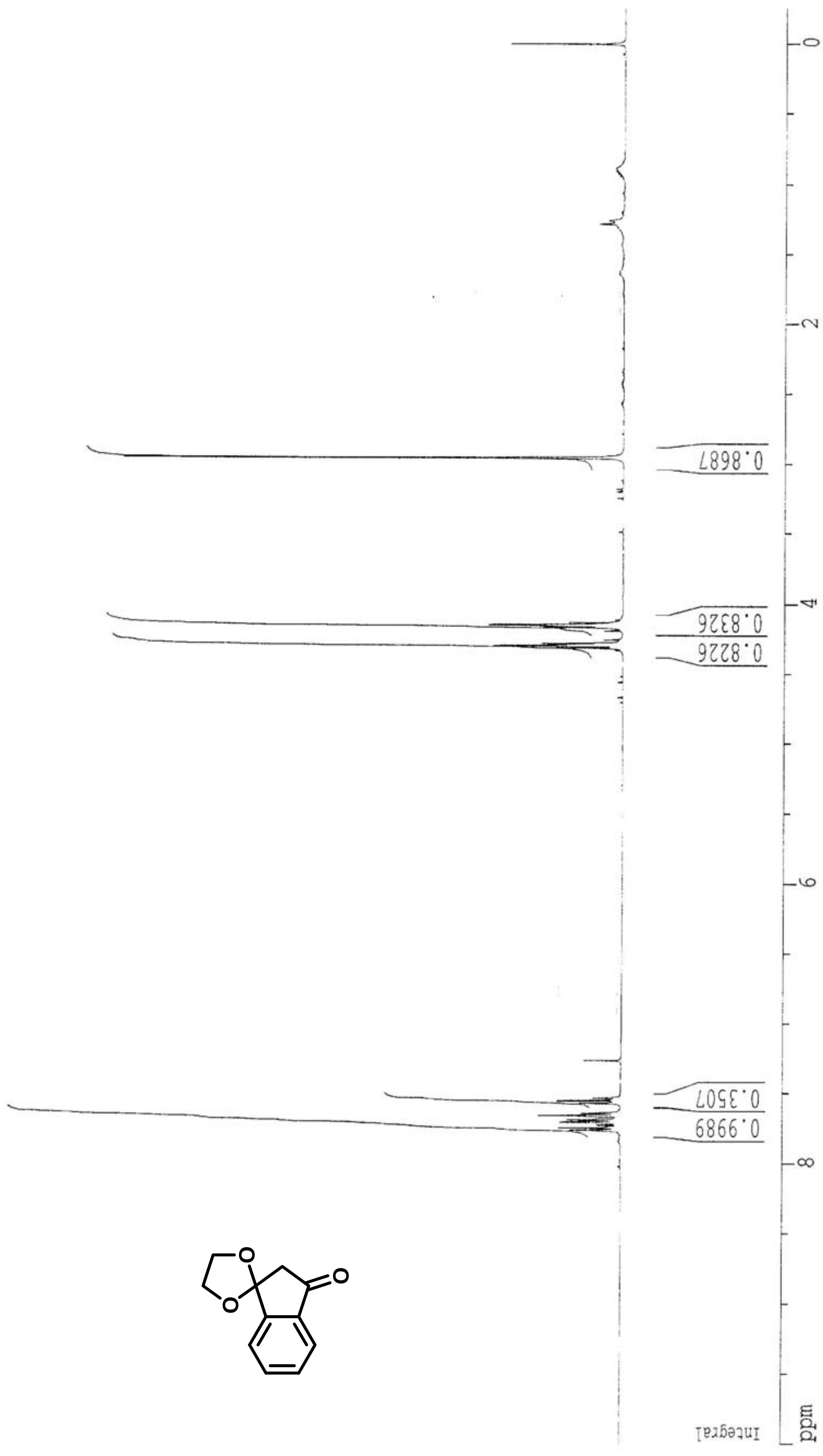
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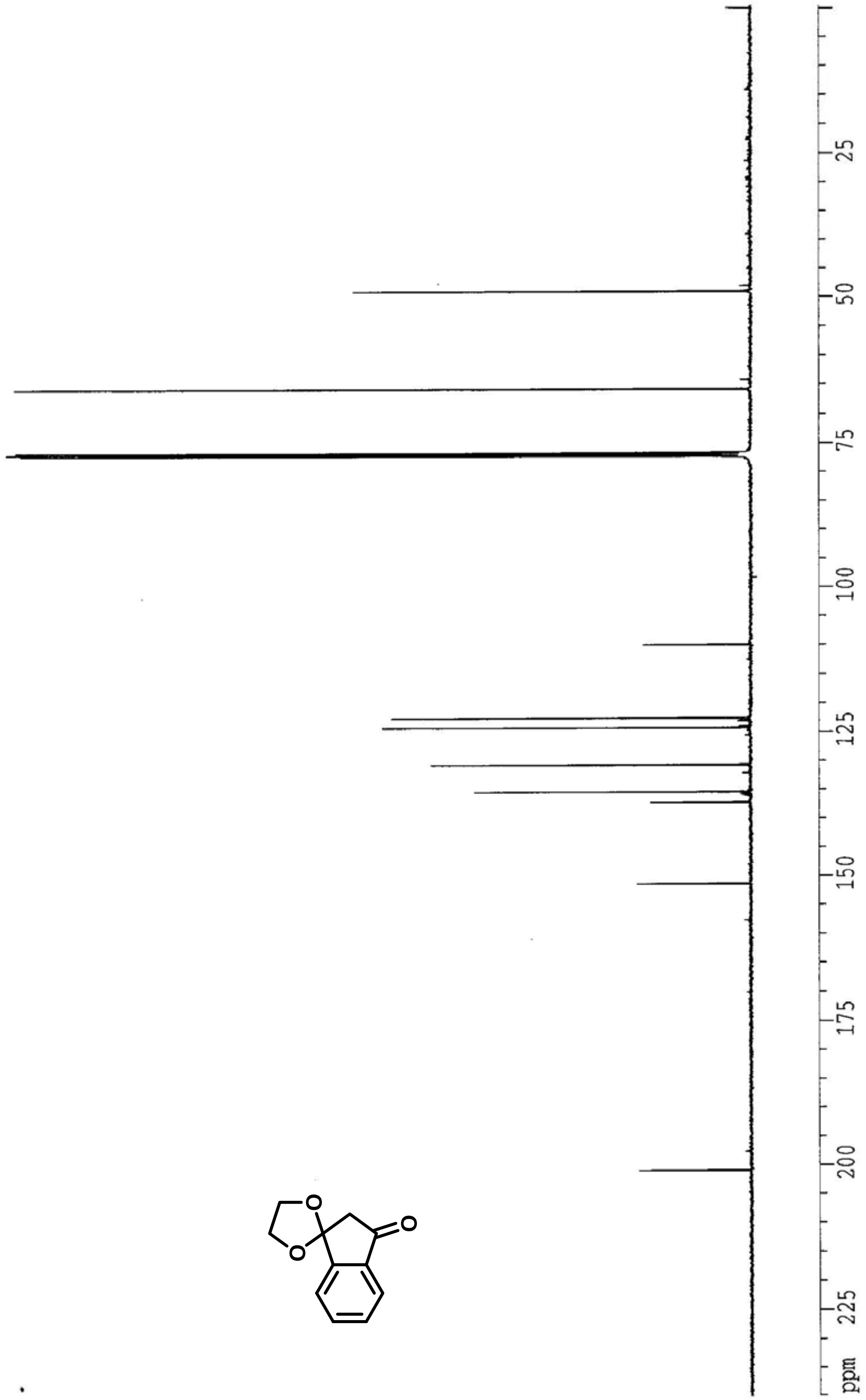
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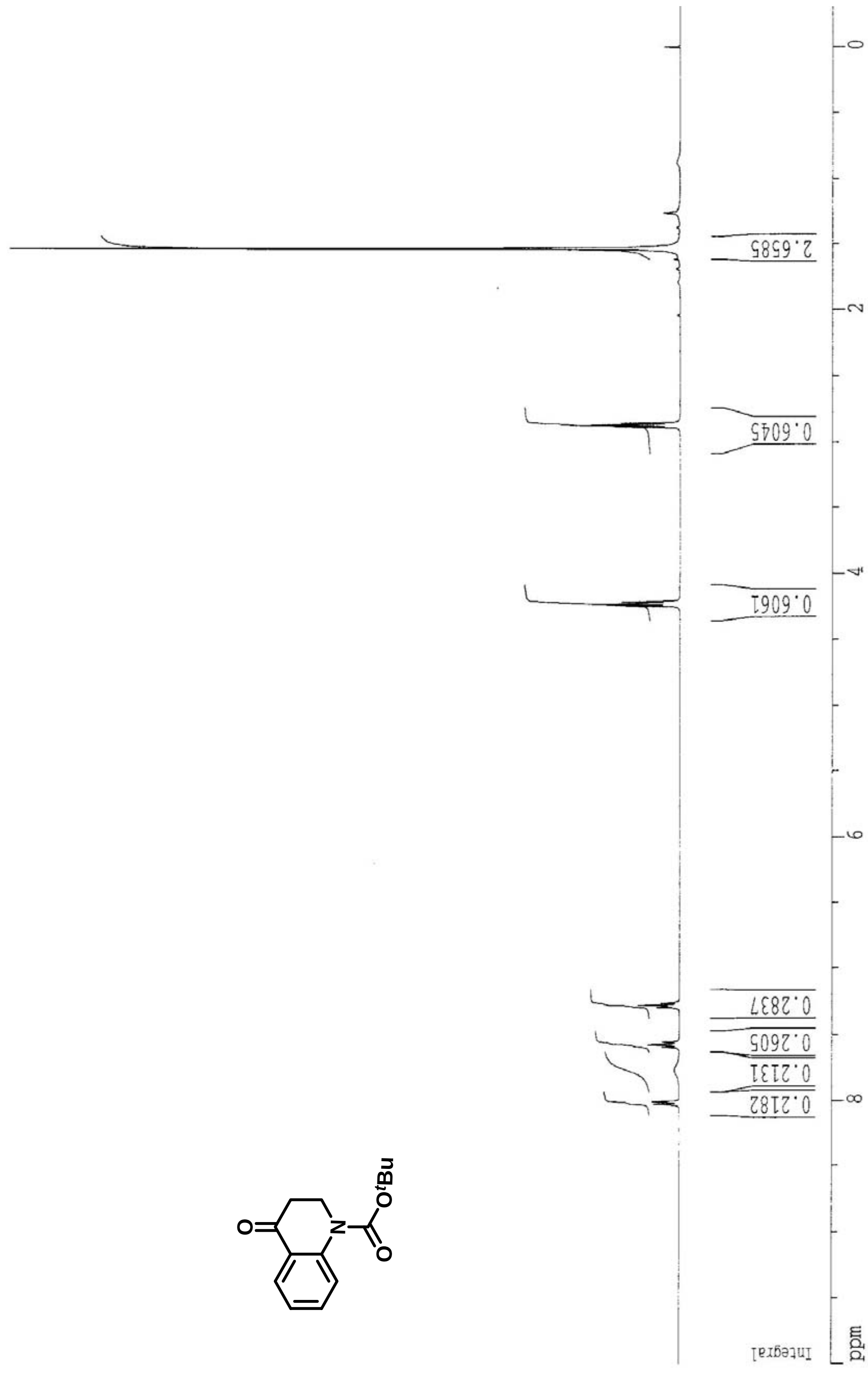

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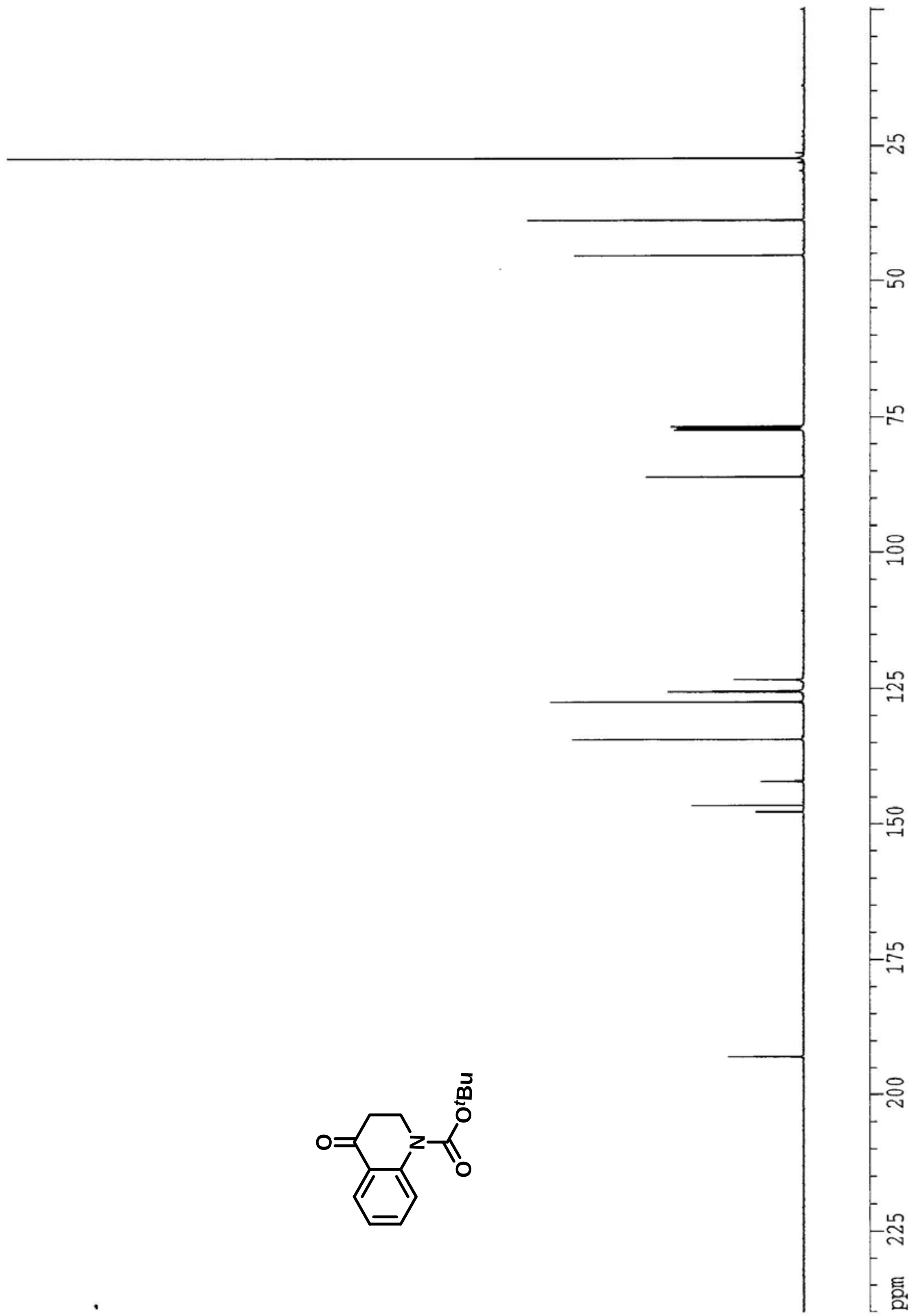
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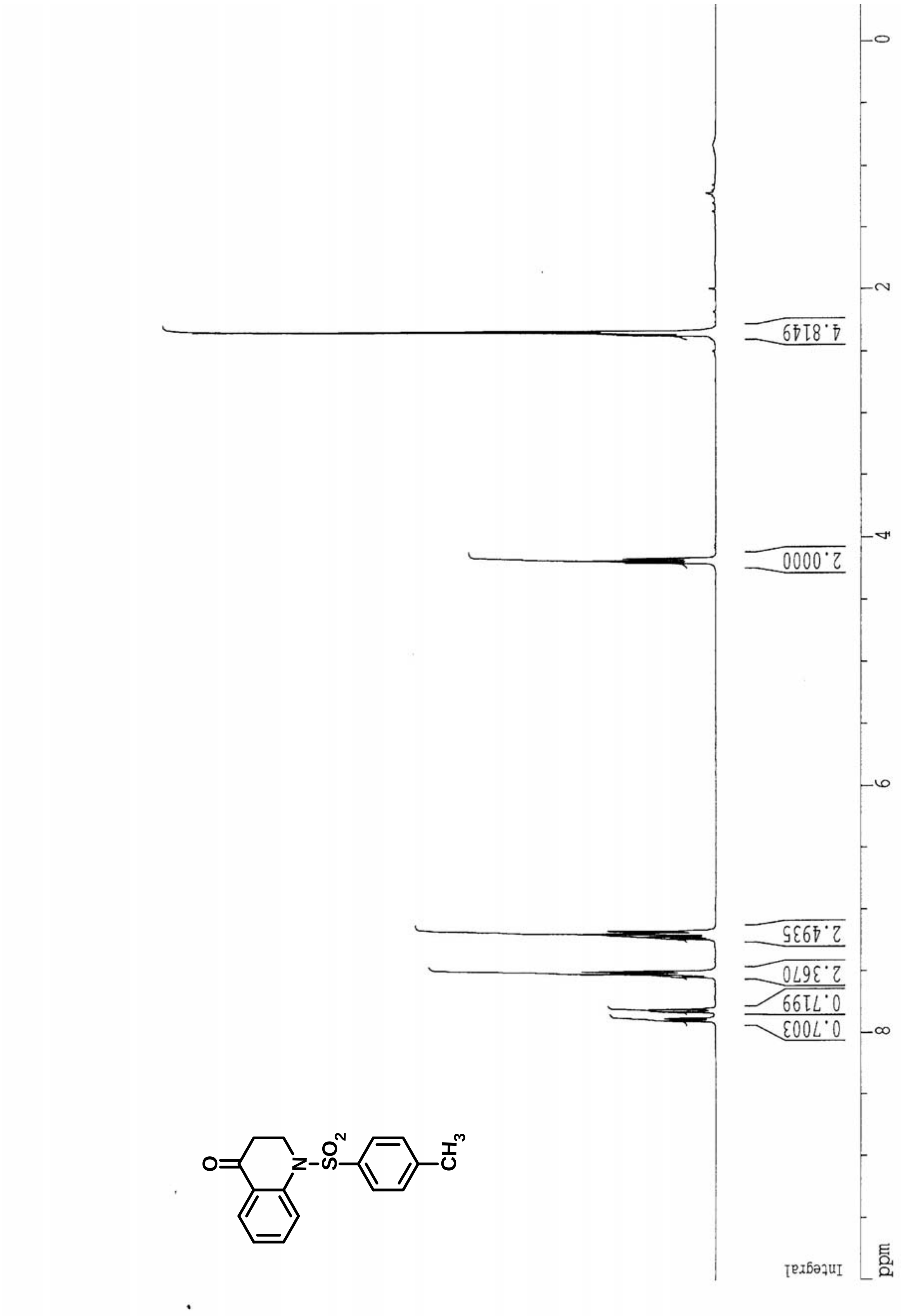

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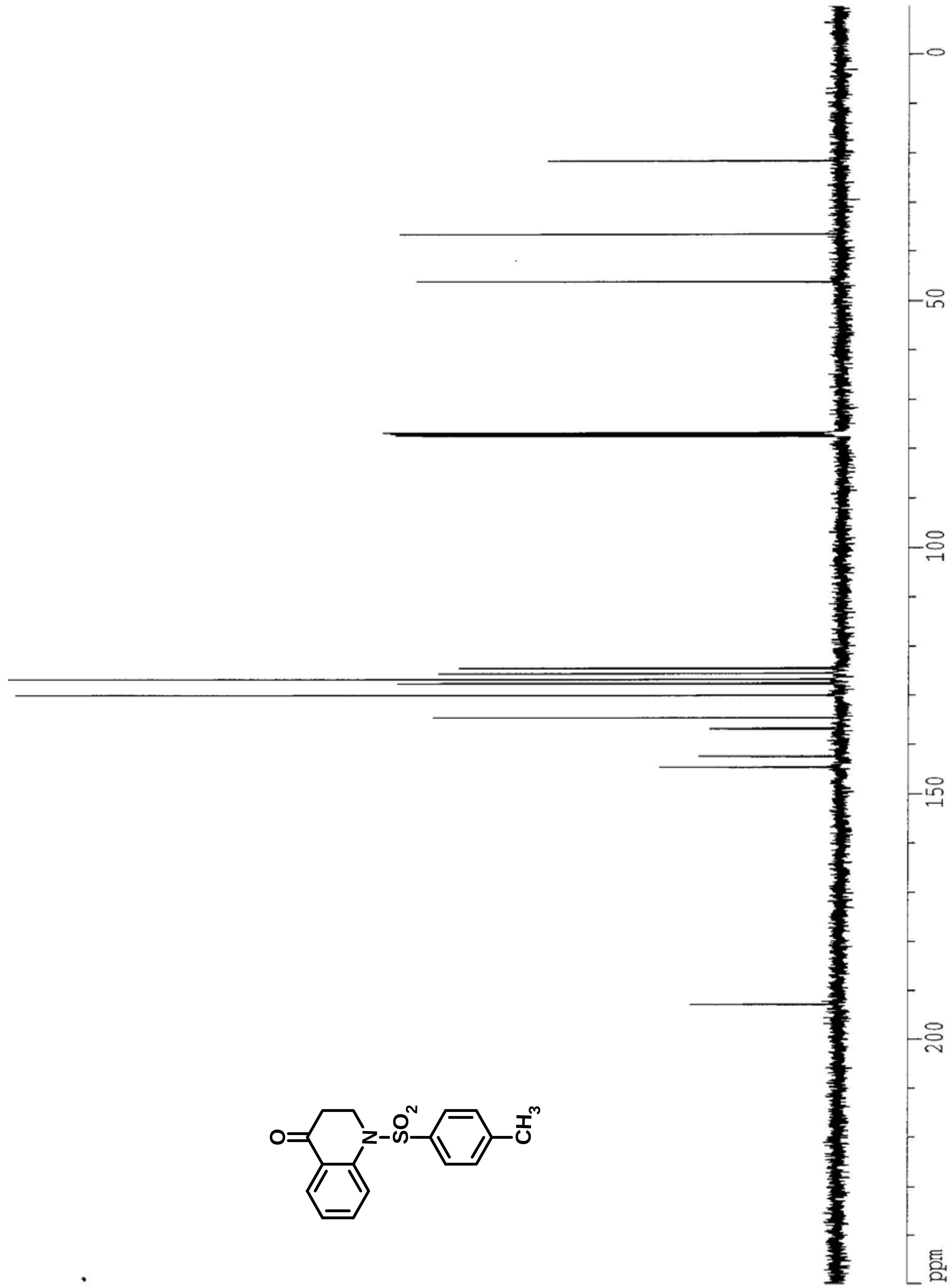

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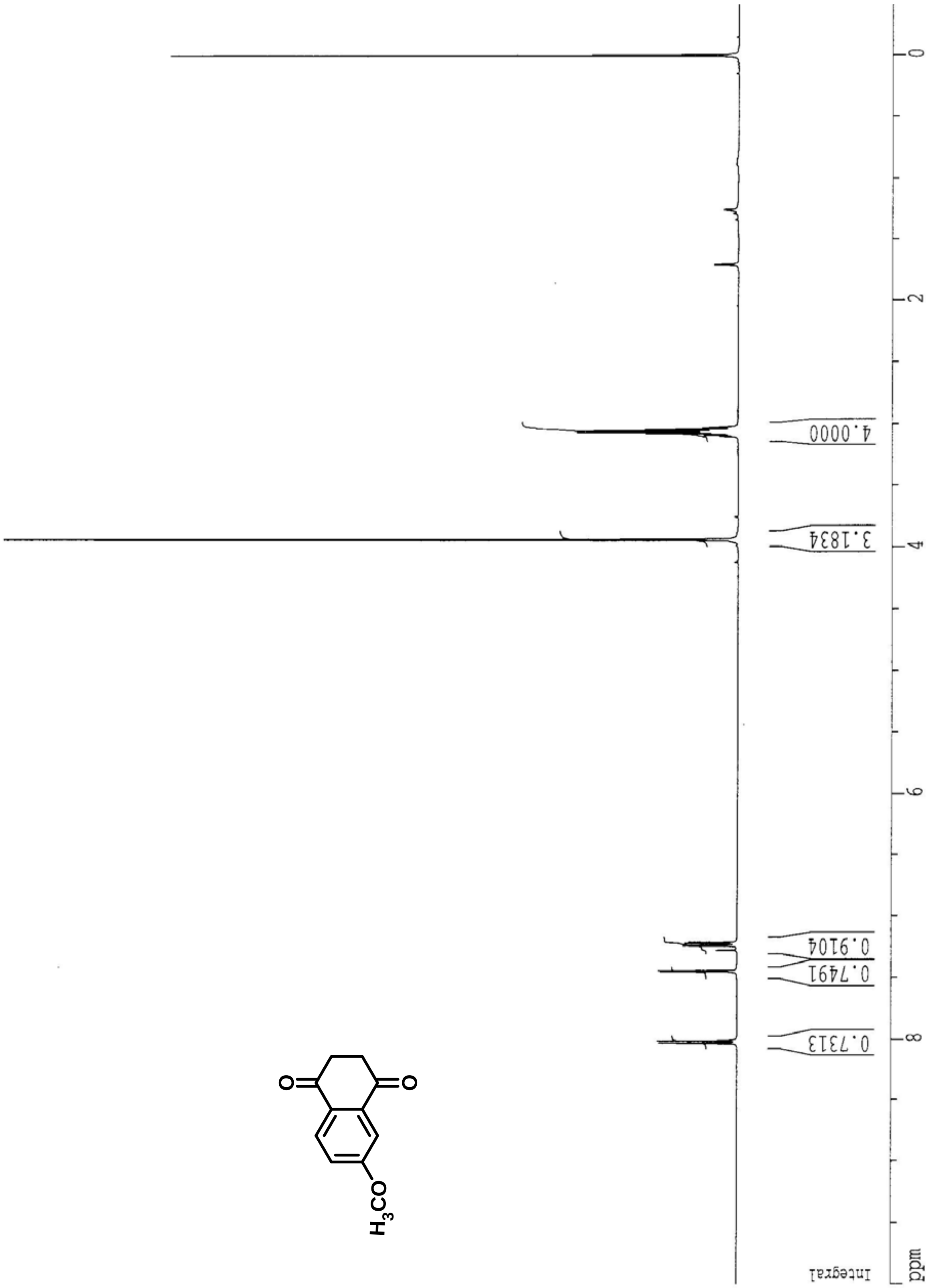

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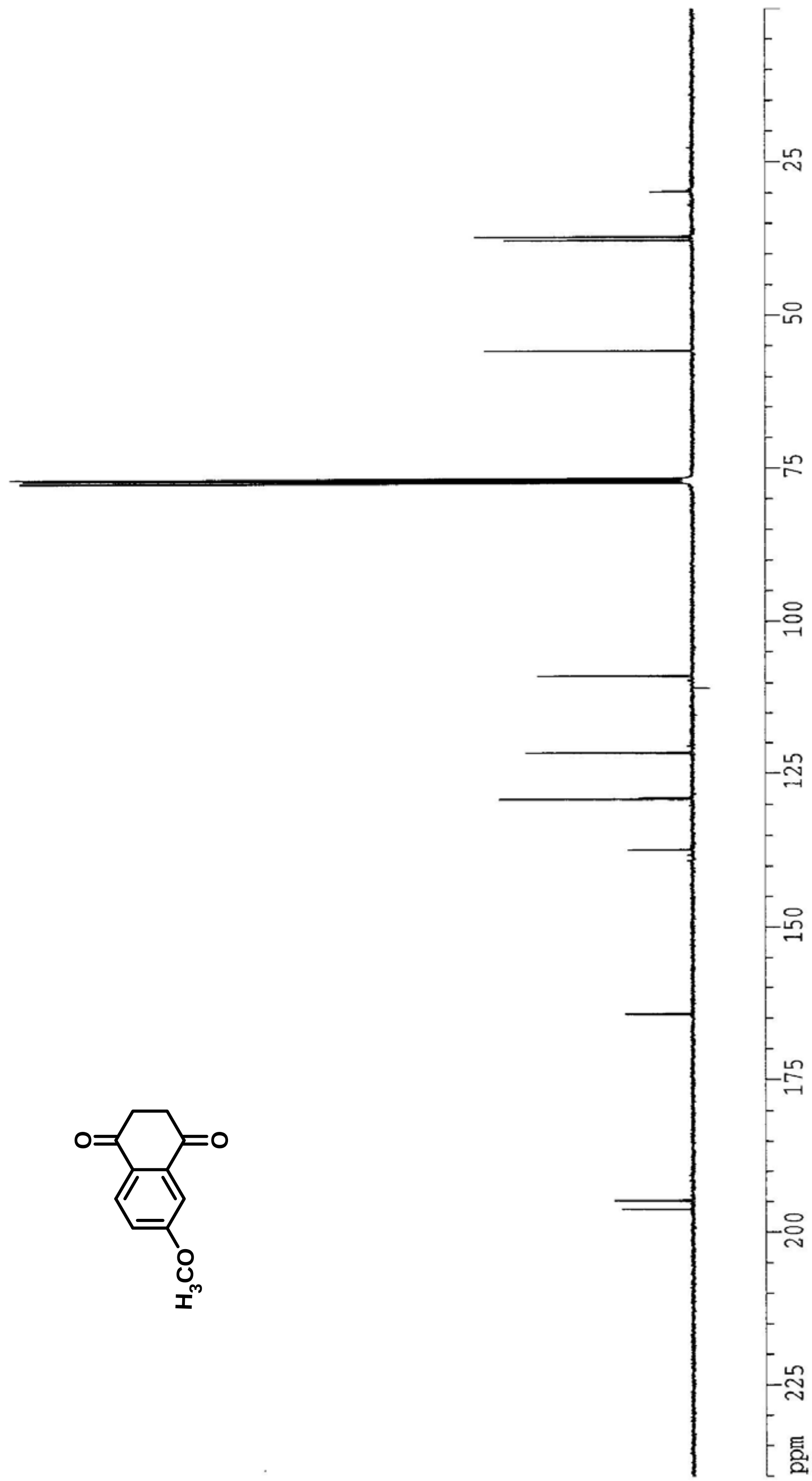

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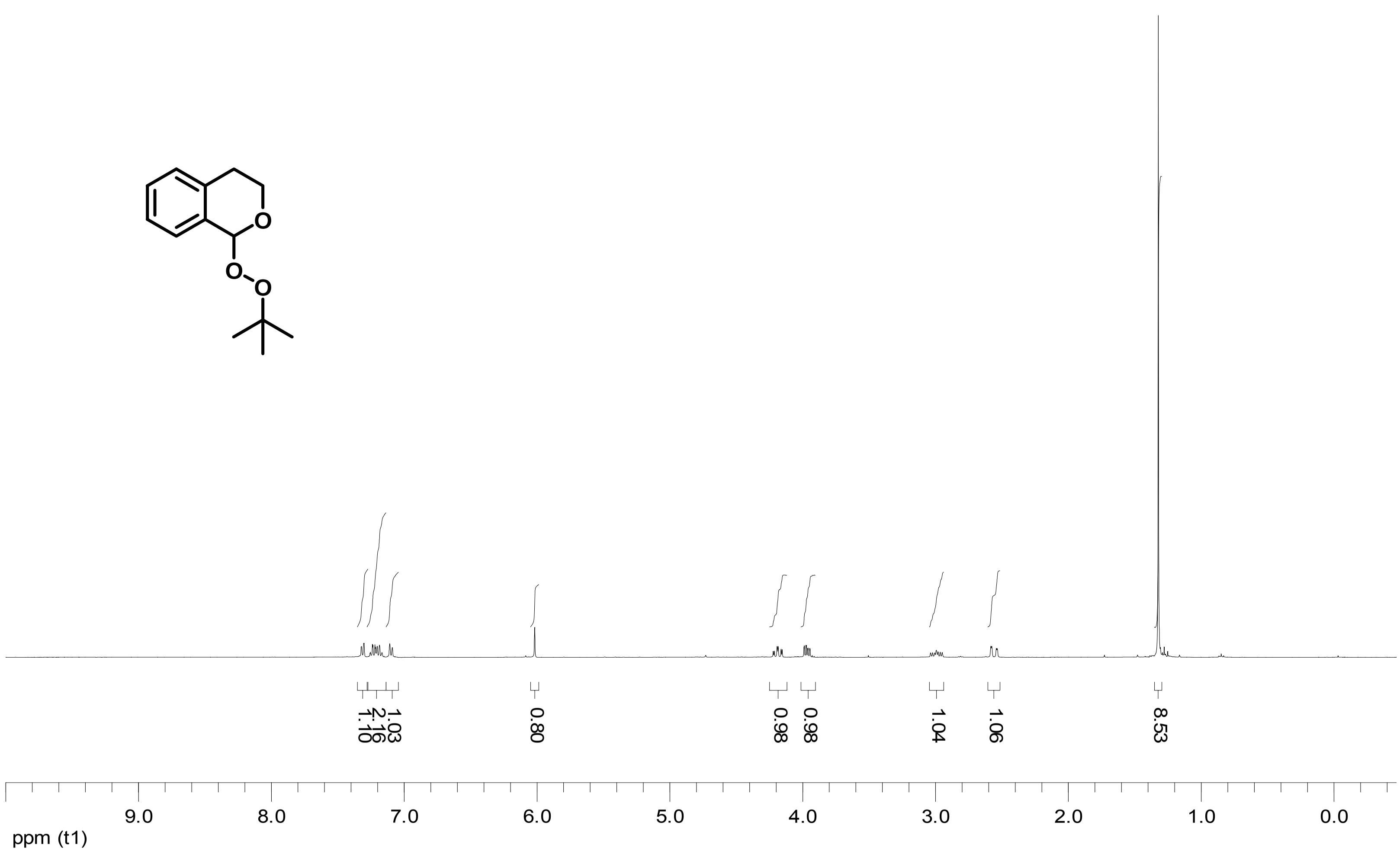

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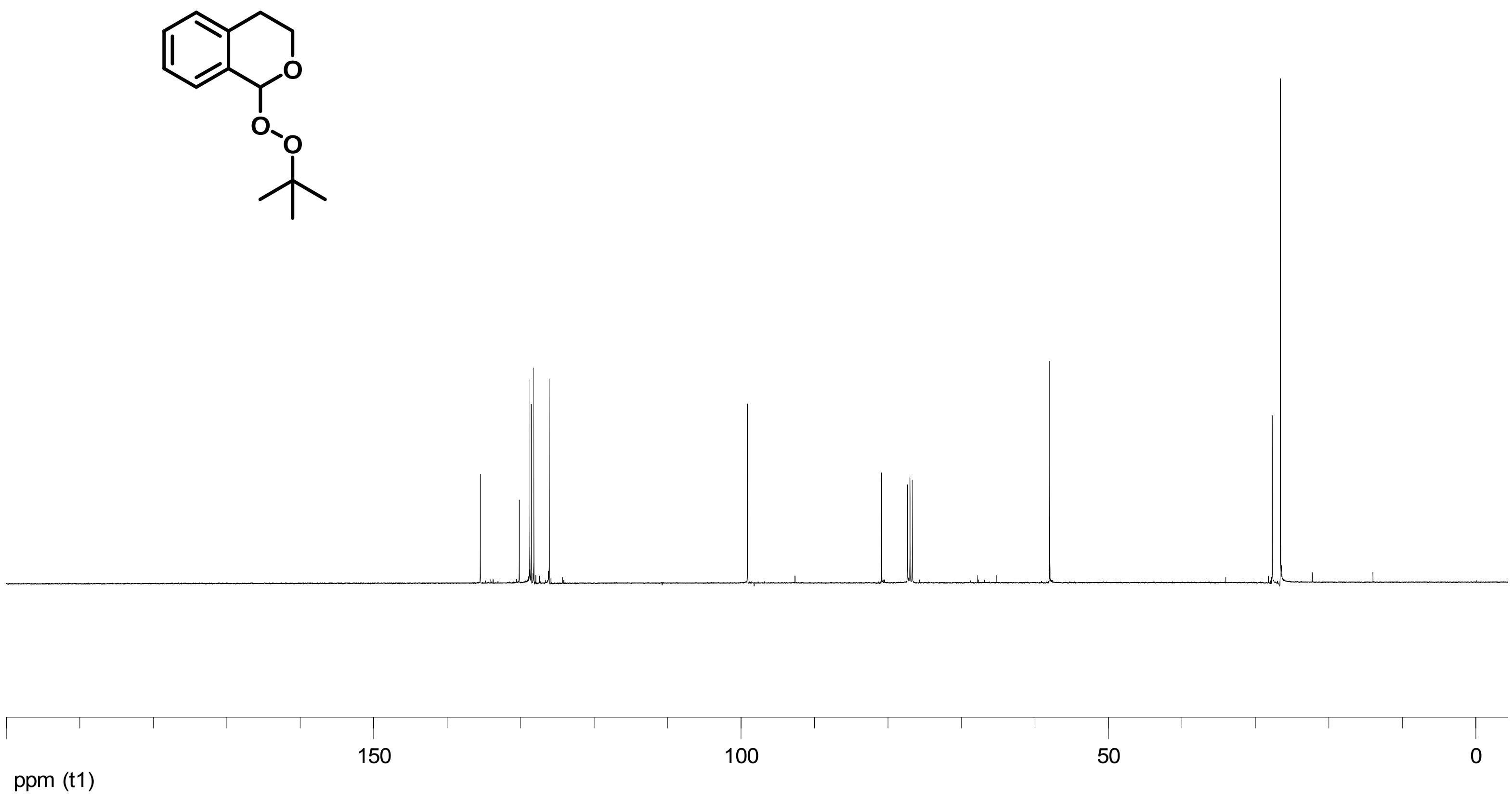

CHAPTER 2

AZIRIDINATION OF OLEFINS CATALYZED BY DIRHODIUM CAPROLACTAMATE

I. BACKGROUND AND SIGNIFICANCE

Olefin aziridination is a powerful approach for the incorporation of nitrogen into organic compounds.[1,2] Largely regarded for their synthetic versatility, aziridines are well suited for ring opening with an assortment of nucleophiles, yielding functionalized amines.[3]

Metal-catalyzed aziridination using stoichiometric iminophenyl-iodinanes, such as [*N*-(*p*-toluenesulfonyl)imino]phenyliodinane (TsN=IPh), has received considerable attention (Scheme 2.1).[4] The preparation of

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[1] For a review of carbon-nitrogen bond formation, see: Kemp, J. E. G. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, UK, 1991; Vol. 7, p 469.

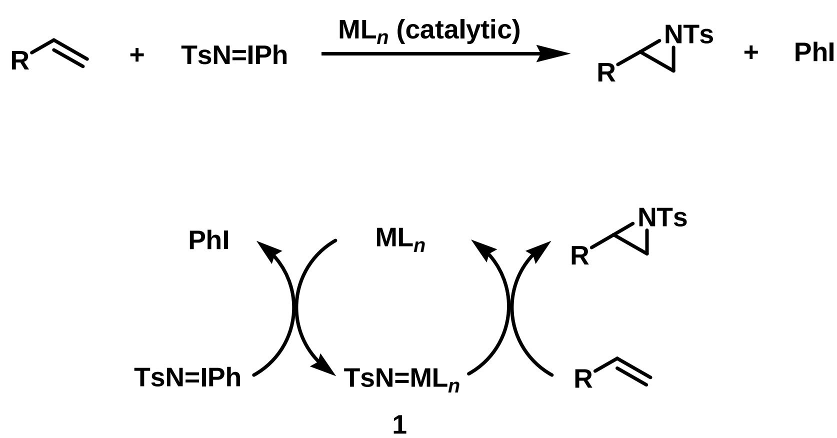
[2] For reviews of olefin aziridination, see: (a) Halfen, J. A. *Curr. Org. Chem.* **2005**, *9*, 657. (b) Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905. (c) Dauban, P.; Dodd, R. H. *Synlett* **2003**, 1571. (d) Jacobsen, E. N. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Phaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 2, p 607. (e) Müller, P. In *Advances in Catalytic Processes*; Doyle, M. P., Ed; JAI Press Inc.: Greenwich, 1997; Vol. 2, p 113.

[3] For a comprehensive review of aziridine ring opening, see: Hu, X. E. *Tetrahedron* **2004**, *60*, 2701.

[4] For representative syntheses using iminophenyliodinanes, see: (a) Dauban, P.; Saniére, L.; Tarrade, A.; Dodd, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 7707. (b) Duran, F.; Leman, L.; Ghini, A.; Burton, G.; Dauban, P.; Dodd, R. H. *Org. Lett.* **2002**, *4*, 2481. (c) Siu, T.; Yudin, A. K. *J. Am. Chem. Soc.* **2002**, *124*, 530.

TsN=IPh was first reported by Yamada and coworkers in 1975 by treatment of *p*-toluenesulfonamide ($TsNH_2$) with iodosobenezene diacetate ($PhI(OAc)_2$) in methanolic KOH.[5] In the presence of a certain metal catalysts (ML_n), it is believed that TsN=IPh undergoes loss of PhI to form metallo-nitrene intermediate **1**.[6] Reaction of **1** with an olefin yields the aziridine and regenerates the metal catalyst.[7]

Scheme 2.1.



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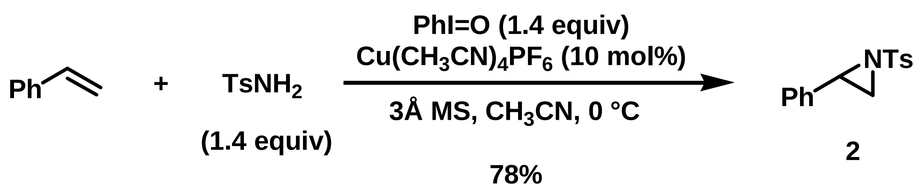
[5] Yamada, Y.; Yamamoto, T. *Chem. Lett.* **1975**, 361.

[6] For mechanistic studies, see: Brandt, P.; Södergren, M. J.; Andersson, P. G.; Norrby, P.-O. *J. Am. Chem. Soc.* **2000**, *122*, 8013.

[7] Due to the proximity of the metal-ligand complex to the reacting nitrogen in **1**, catalytic asymmetric aziridinations have been realized, see: (a) Li, Z.; Conser, K. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 5326. (b) Evans, D. A.; Bilodeau, M. T.; Faul, M. M. *J. Am. Chem. Soc.* **1994**, *116*, 2742. (c) Sanders, C. J.; Gillespie, K. M.; Bell, D.; Scott, P. *J. Am. Chem. Soc.* **2000**, *122*, 7132. (d) Liang, J.-L.; Huang, J.-S.; Yu, X.-Q.; Zhu, N.; Che, C.-M. *Chem. Eur. J.* **2002**, *8*, 1563.

Recently, it was discovered that iminophenyliodinanes can be prepared in situ in metal-catalyzed aziridination reactions. Dauban, Dodd, and coworkers in 2001 reported a copper-catalyzed aziridination using $TsNH_2$ and iodosylbenzene (PhI=O) thereby forming TsN=IPh in situ.[4(a)] The authors also pointed out the long-standing drawbacks/difficulties associated with the direct use of TsN=IPh including its storage, preparation, and isolation.[2(b)] Thus, using tetrakis(acetonitrile) copper(I) hexafluorophosphate (10 mol%), styrene was converted to aziridine **2** in 78% yield after 18 hours (Scheme 2.2).

Scheme 2.2.



2

Dinuclear rhodium complexes (Rh_2^{4+}) have also been shown to be viable catalysts for aziridination in conjunction with iminophenyliodinanes.[8] Although Müller was the first to report dirhodium-catalyzed aziridination with TsN=IPh and related sulfonamide-derived iminophenyliodinanes,[8(b)] it was DuBois and Guthikonda in 2002 who reported the first in situ variant (Scheme 2.3).[8(c)] Thus, following a rigorous screen of sulfonamides, solvents, and

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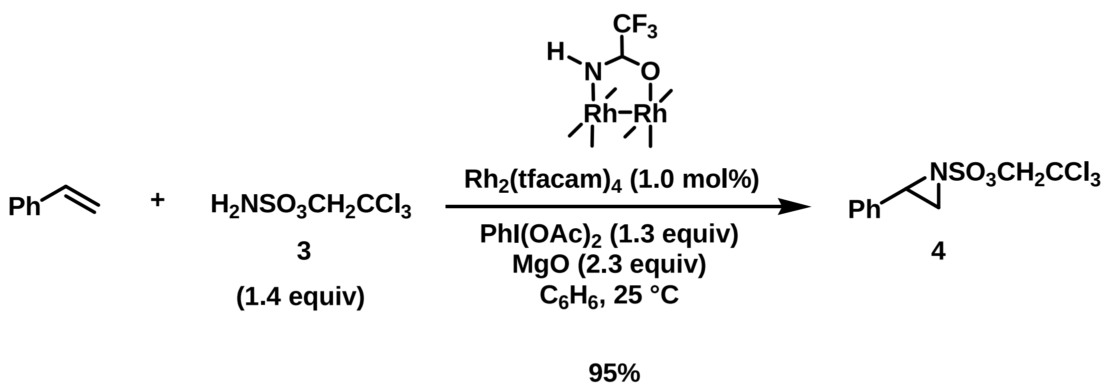
[8] For Rh_2^{4+} catalyzed aziridination, see: (a) Müller, P.; Baud, C.; Jacquier, Y. *Tetrahedron* **1996**, *52*, 1543. (b) Müller, P.; Baud, C.; Jacquier, Y. *Can. J. Chem.* **1998**, *76*, 738. (c) Guthikonda, K.; DuBois, J. *J. Am. Chem. Soc.* **2002**, *124*, 13672. (d) Liang, J.-L.; Yuan, S.-X.; Chan, P. W. H.; Che, C.-M. *Org. Lett.* **2002**, *4*, 4507. (e) Liang, J. L.; Yuan, S. X.; Chan, P. W. H.; Che, C. M. *Tetrahedron Lett.* **2003**, *44*, 5917. (f) Fruit, C.; Müller, P. *Tetrahedron-Asymmetry* **2004**, *15*, 1019.

additives, DuBois and Guthikonda converted styrene to aziridine **4** in 95% yield after 8 hours using trichloroethylsulfamate ester **3**, $PhI(OAc)_2$, and 1.0 mol% $Rh_2(tfacam)_4$ (tfacam = trifluoroacetamidate).

Scheme 2.3.



Sharpless and coworkers in 1998 reported a practical method for olefin aziridination catalyzed by phenyltrimethylammonium tribromide (PTAB = $PhNMe_3^+Br_3^-$).[9,10] For example, styrene was converted to aziridine **2** in 68% yield in 12 hours using PTAB (10 mol%) and stoichiometric chloramine-T (TsNClNa) as a nitrogen source (Scheme 2.4). The authors pointed out that this method is particularly attractive because PTAB and TsNClNa are inexpensive, the aziridine products tend to be crystalline, and the reaction can be run at fairly high concentrations (e.g., 0.5 M/[olefin]). Noted limitations

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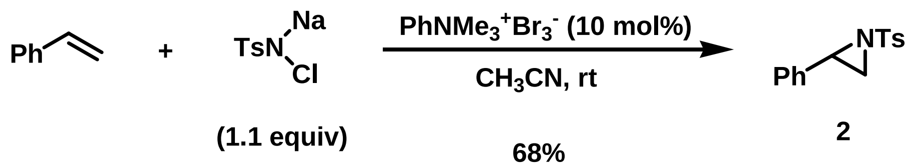
[9] For bromine catalyzed aziridination see: Jeong, J. U.; Tao, B.; Sagasser, I.; Henniges, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 6844.

[10] For related work, see: (a) Ali, S. I.; Nikalje, M. D.; Sudalai, A. *Org. Lett*. **1999**, *1*, 705. (b) Dauban, P.; Dodd, R. H. *Tetrahedron Lett.* **2001**, *42*, 1037. (c) Thakur, V. V.; Sudalai, A. *Tetrahedron Lett.* **2003**, *44*, 989. (d) Jain, S. L.; Sharma, V. B.; Sain, B. *Tetrahedron Lett*. **2004**, *45*, 8731.

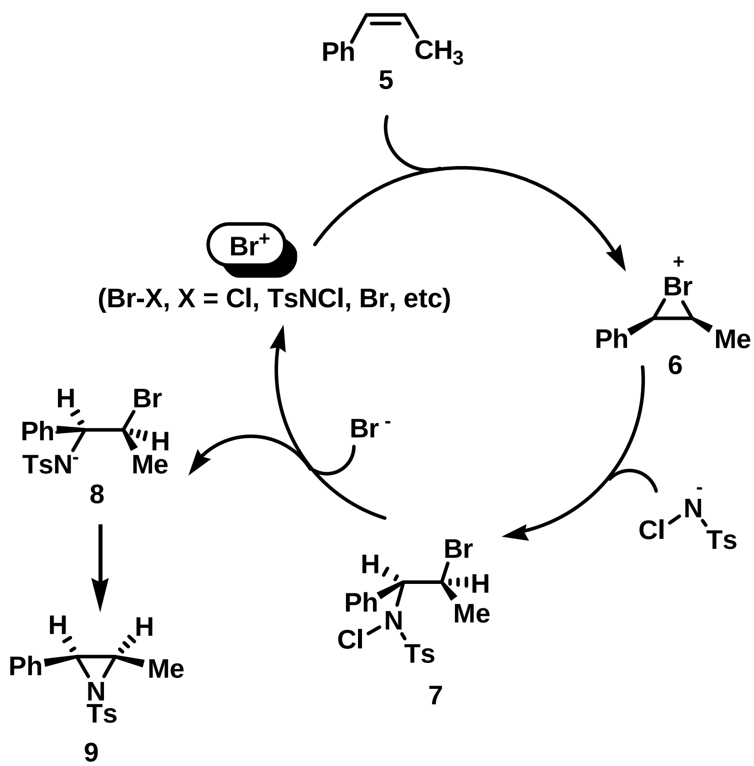
include moderate yield of aziridines and the formation of 1,2-dibromide products.

Scheme 2.4.



Mechanistically, Sharpless proposed a catalytic cycle that involves atom-transfer redox catalysis (Scheme 2.5). Specifically, Sharpless proposed that 1) olefin **5** reacts stereospecifically with a "Br^+ source" to give bromonium ion **6**; 2) bromonium ion **6** undergoes attack with nucleophilic chloramine-T to give *N*-chloro-amidobromide **7**; and 3) in the presence of Br^- or $TsNCl^-$, amidobromide **7** forms anion **8** which reacts intramolecularly to give aziridine **9**.

Figure 2.1. Olefin Aziridination Catalyzed by $PhNMe_3^+Br_3^-$.



In his mechanistic proposal (vide supra), Sharpless implicated the intermediacy of *N*-chloroamidobromide **7** *en route* to aziridine **9**. Interestingly, aziridines can often be obtained from vicinal haloamines by treatment with base to induce cyclization.[1,11] In turn, vicinal haloamines are obtained from aminohalogenation of olefins. Broadly defined, aminohalogenation refers to the incorporation of nitrogen (either as an amine, amide, or sulfonamide) and a halogen (F, Cl, Br, or I) into a molecule.

[11] For a discussion, see: Cardillo, G.; Gentilucci, L.; Tolomelli, A. *Aldrichimica Acta* **2003**, *36*, 39.

Early work in aminohalogenation employed stoichiometric reagents, e.g., *N*-haloamines and *N*,*N*-dihaloamines.[12] Recently, metal-catalyzed amidohalogenation of olefins has emerged as a useful and practical procedure. This overview will highlight metal-catalyzed amidohalogenation of olefins.

Li and coworkers in 1999 reported the first transition metal-catalyzed amidohalogenation in which cinnamic esters were transformed into amidochlorination products.[13] Using *N*,*N*-dichloro-*p*-toluenesulfonamide ($TsNCl_2$) as a chlorine/nitrogen source and catalytic $ZnCl_2$ or $Cu(OTf)_2$ (8 mol%), a variety of cinnamic esters were converted to vicinal haloamides in CH_3CN over 12 hours (Scheme 2.5). To explain the observed regio- and stereoselectivity, Li proposed a copper-bound intermediate (**10**) that leads to aziridinium ion **11** followed by nucleophilic attack with chloride.[14] Moreover, *N*,*N*-dichloro-2-nitrobenzenesulfonamide could be used as a chlorine/ nitrogen source to give products containing the nitrobenzenesulfonyl group that can be readily cleaved with $PhSH/K_2CO_3$ in DMF.[14(a)]

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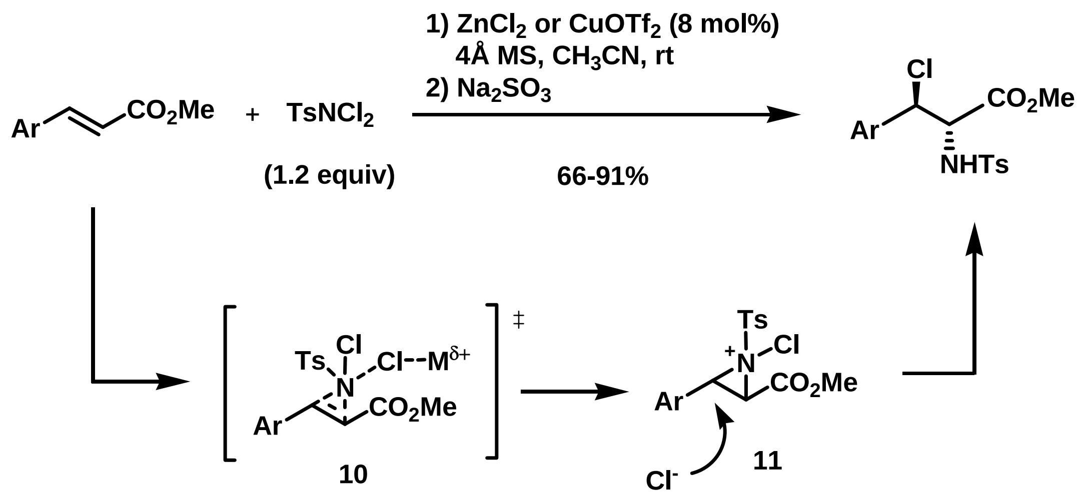
[12] (a) Karasch, M. S.; Priestley, H. M. *J. Am. Chem. Soc*. **1939**, *61*, 469. (b) Danhiher, F. A.; Butler, P. E. *J. Org. Chem*. **1968**, *33*, 4336. (c) Ueno, Y.; Takemura, S.; Ando, Y.; Terauchi, H. *Chem. Pharm. Bull.* **1967**, 15, 1193. (d) Ueno, Y.; Takemura, S.; Ando, Y.; Terauchi, H. *Chem. Pharm. Bull.* **1967**, 15, 1198. (e) Terauchi, H.; Takemura, S.; Ueno, Y. *Chem. Pharm. Bull.* **1975**, 23, 640. (f) Terauchi, H.; Yamasaki, A.; Takemura, S. *Chem. Pharm. Bull.* **1975**, 23, 3162. (g) Zawadzki, S.; Zwierzak, A. *Tetrahedron* **1981**, 37, 2675. (h) Klepacz, A.; Zwierzak, A. *Tetrahedron Lett.* **2001**, 42, 4539. (i) Sliwinska, A.; Zwierzak, A. *Tetrahedron* **2003**, 59, 5927.

[13] Li, G.; Wei, H.-X.; Kim, S. H.; Neighbors, M. *Org.Lett.* **1999**, 1, 395.

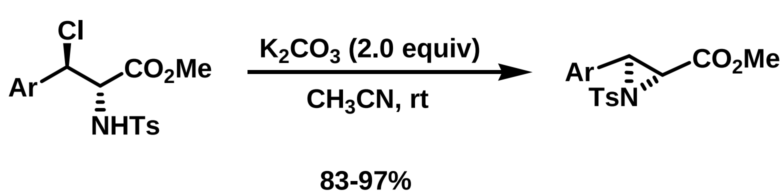
[14] (a) Li, G.; Wei, H.-X.; Kim, S. H. *Org. Lett.* **2000**, 2, 2249. (b) Li, G.; Wei, H. X.; Kim, S. H. *Tetrahedron* **2001**, 57, 8407. (c) Wei, H. X.; Kim, S. H.; Li, G. *Tetrahedron* **2001**, 57, 3869. (d) Chen, D.; Timmons, C.; Chao, S.; Li, G. *Eur. J. Org. Chem.* **2004**, 3097. (e) Li, Q.; Shi, M.; Timmons, C.; Li, G. *Org. Lett.* **2006**, *8*, 625.

Scheme 2.5.



In 2003, Li and coworkers showed that aziridines could be obtained by simply treating these cinnamate-derived halosulfonamides with potassium carbonate (2.0 equiv) in acetonitrile at room temperature for 3 hours (Scheme 2.6).[15]

Scheme 2.6.

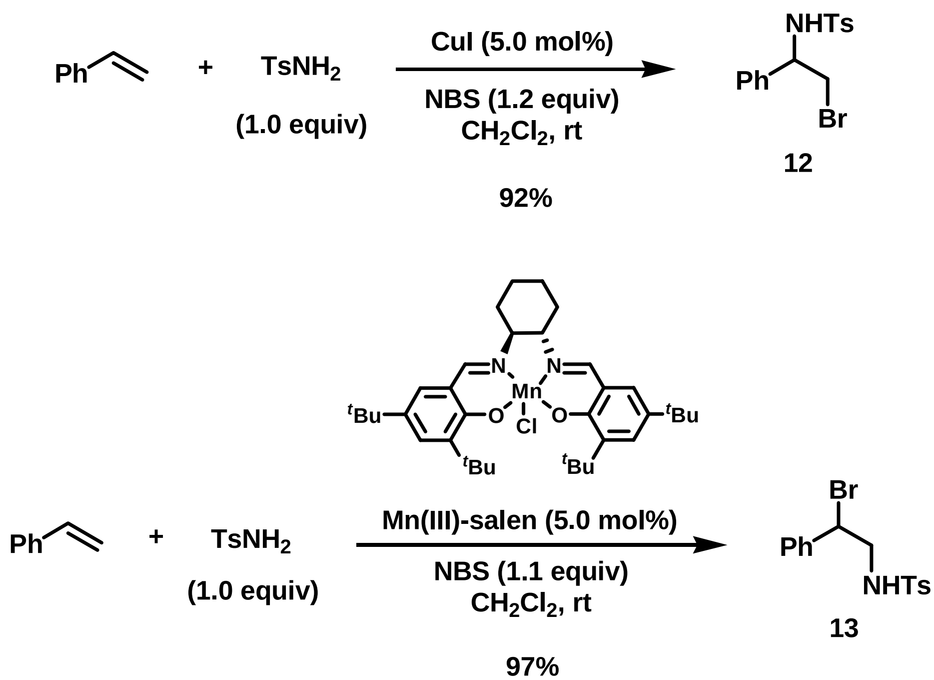


[15] Chen, D.; Kim, S. H.; Hodges, B.; Li, G. *ARKIVOC* **2003**, *12*, 56, and references therein.

Sudalai and coworkers in 2003 reported a metal-catalyzed regio- and stereoselective amidobromination of olefins using $TsNH_2$ and *N*-bromosuccinimide (NBS).[16] This was the first example of a catalytic amidohalogenation reaction that did not require preformed *N*-halo-, or *N*,*N*-dihaloamides. For example, amidobromide **12** was obtained after 2 hours when styrene was treated with catalytic CuI (5.0 mol%) and stoichiometric $TsNH_2$ and NBS in CH_2Cl_2 at 25 °C (Scheme 2.7, eq 1). Both $MnSO_4$ (5 mol%) and V_2O_5 (5 mol%) also gave **12** exclusively and in high yield (>90%) under the reaction conditions (not shown). However, a reversal of regiochemistry was observed using Mn(III)-salen (5 mol%) as a catalyst to give **13** exclusively in 97% yield under identical conditions (Scheme 2.7, eq 2). In the absence of catalyst, styrene gave a 20% yield of amidobromides **12** and **13** in a ratio of 60:40, respectively. The authors proposed that the amidobromide products likely arise from the intermediacy of bromonium ions, although it remains unclear why a reversal of regiochemistry occurs using Mn(III)-salen.

[16] Thakur, V. V.; Talluri, S. K.; Sudalai, A. *Org. Lett.* **2003**, *5*, 861.

Scheme 2.7.



Li and coworkers in 2004 described a diastereoselective amidohalogenation using α,β-unsaturated *N*-acyl 4-oxazolidinones (Scheme 2.9).[17] CuOTf (8 mol%) was found to be the optimal catalyst in conjunction with $TsNCl_2$, and a diastereomeric excess (de) as high as 75% was obtained (best result shown in Scheme 2.8). Li pointed out that the amidohalogenation of α,β-unsaturated *N*-acyl 4-oxazolidinones could *only* be performed in the ionic liquid [Bmim][BF_4][18] and all "normal" organic solvents failed to give any of the desired product for this transformation. The crucial role of the solvent remains unclear.

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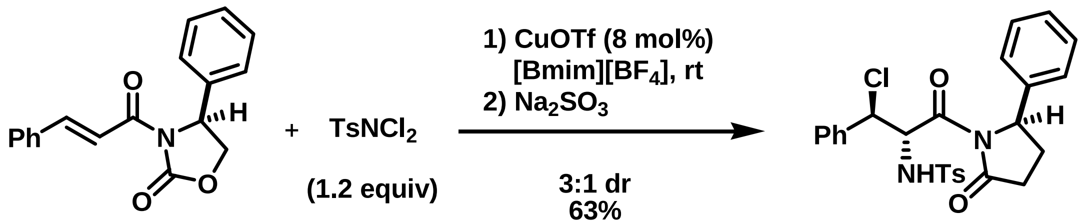
[17] Xu, X.; Kotti, S. R. S. S.; Liu, J.; Cannon, J. F.; Headley, A. D.; Li, G. *Org. Lett.* **2004**, *6*, 4881.

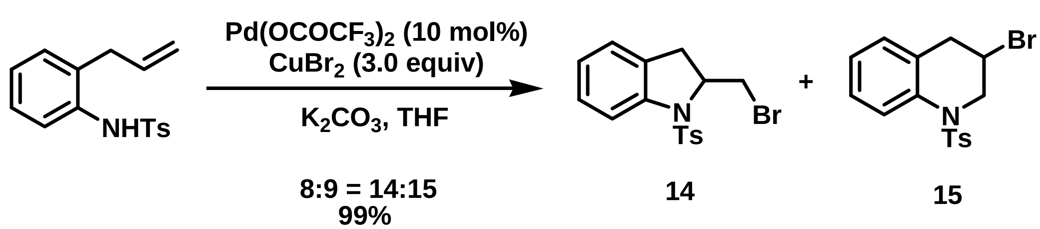
[18] [Bmim][BF_4] = 1-butyl-3-methylimidazolium tetrafluoroborate

Scheme 2.8.



Chemler and coworkers in 2004 reported the first metal-catalyzed *intramolecular* amidobromination of olefins.[19] Using catalytic $Pd(OCOCF_3)_2$ (10 mol%) and stoichiometric $CuBr_2$ (3.0 equiv), *N*-tosyl-*ortho*-allylaniline underwent amidobromination over 24 hours to give a 3:1 mixture of **14** and **15**, respectively, in 99% yield (Scheme 2.9). The degree of regioselectivity for this process was highly dependent on the substrate undergoing cyclization. Although detailed mechanistic studies were not undertaken, Chemler proposed that the reaction proceeds through an amidopalladation and subsequent reductive elimination. However, the exact role of the copper halide salt in the mechanism remains unclear.

Scheme 2.9.



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15

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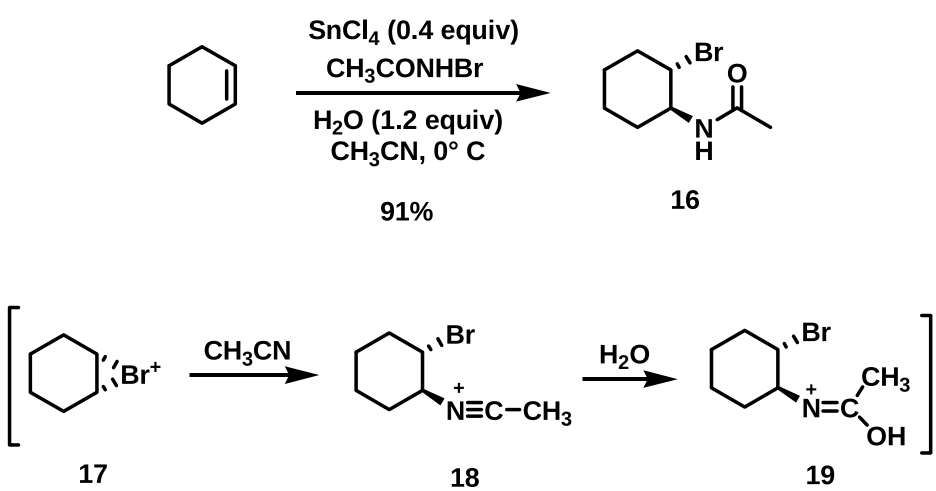
[19] Manzoni, M. R.; Zabawa, T. P.; Kasi, D.; Chemler, S. R. *Organometallics* **2004**, *23*, 5618.

Corey and coworkers in 2006 described a metal-catalyzed amidobromination of olefins using *N*-haloamides (Scheme 2.10).[20] The reaction was extended to over ten substrates with excellent regio- and stereocontrol. For example, cyclohexene was converted to bromoamide **16** in 91% yield after one hour using a catalytic amount of $SnCl_4$ (0.4 equiv) and *N*-bromoacetamide.[21] Mechanistically, the authors proposed that the reaction proceeds through bromonium ion **17**, followed by capture with acetonitrile to give nitrilium ion **18**, which is hydrolyzed by H_2O to give **19**.

Scheme 2.10.

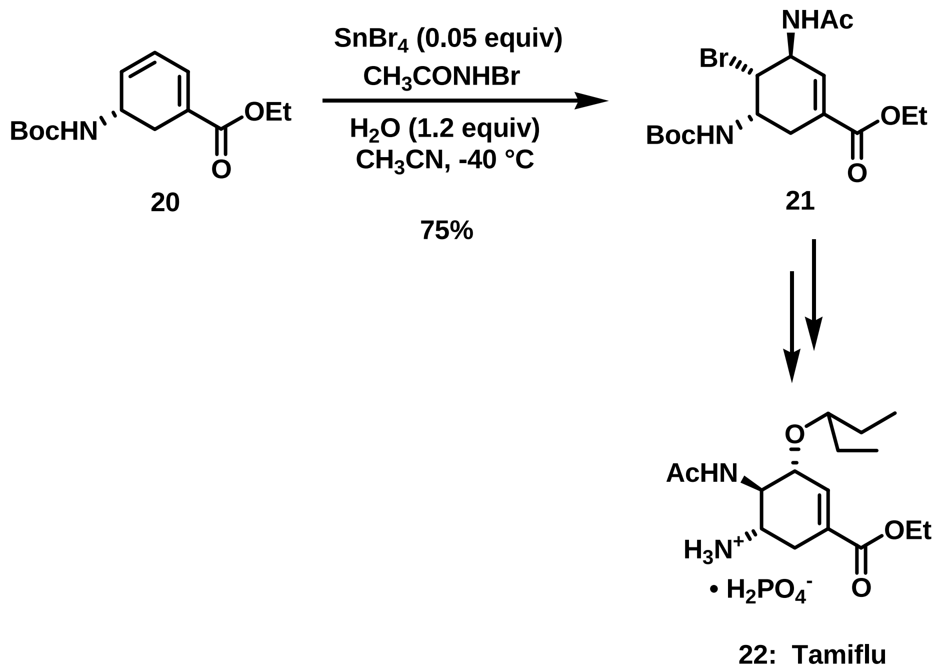


[20] Yeung, Y.-Y.; Gao, X.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 9644.

[21] The authors note that NBS was also a viable in the procedure; however, *N*-bromo-acetimde was preferable due to the solubility of the resultant acetamide in H_2O during work-up.

Corey and coworkers also applied this methodology to a short synthesis of oseltamivir (**22**, Tamifu).[22] Using $SnBr_4$ (0.05 equiv) at -40 °C, diene **20** was converted to bromoamide **21** in 75% yield after 5 hours (Scheme 2.11). The observed regio- and steroselectivity was rationalized by bromonium ion complexation *cis* to the NHBoc group.

Scheme 2.11.



[22] Yeung, Y.-Y.; Hong, S.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 6310.

Summary. The development of methods for the preparation of aziridines is fundamentally important due to their value and utility. Metal-catalyzed aziridination in conjunction with iminophenyliodinanes has provided a route to aziridines for over twenty years. Conversely, metal-catalyzed amidohalogenation of olefins is a relative recent area of development. Vicinal amidohalides can often be transformed into aziridines by treatment with base. More importantly, metal-catalyzed amidohalogenation, despite a limited number of examples, may offer a more practical, efficient, and controlled method for olefin functionalization.

II. RESULTS AND DISCUSSION[23]

Initial Results. As described in Chapter 1, $Rh_2(cap)_4$ is an electron-rich complex that is susceptible to 1-electron oxidation. Moroever, it was shown electrochemically that $Rh_2(cap)_4$ could access other redox states (e.g., Rh_2^{3+}, Rh_2^{4+}, and Rh_2^{5+}) by the addition/removal of electrons.[24]

As previously described, Sharpless and coworkers reported that aziridination could be accomplished using $PhNMe_3^+Br_3^-$ as an atom transfer catalyst. With this information in mind, atom transfer catalysis using dirhodium was considered (Figure 2.2). Assuming that a Rh_2^{5+} halide complex **23** could be generated via 1-electron oxidation of $Rh_2(cap)_4$, it was surmised that treatment with an olefin would yield Rh_2^{3+} complex **24** and halonium ion **25**. Then, in the presence of TsNNaX, **25** would undergo capture to give amidohalide **26**. Finally, dirhodium complex **23** could be regenerated from **26** with concomitant aziridine closure. The proposed catalytic cycle is hypothetical, but mechanistically reasonable. If the catalytic cycle proposed in Figure 2.2 was viable, it might provide promising levels of efficiency (turnover) and offer an entrée to enantioselective aziridination with chiral dirhodium catalysts.

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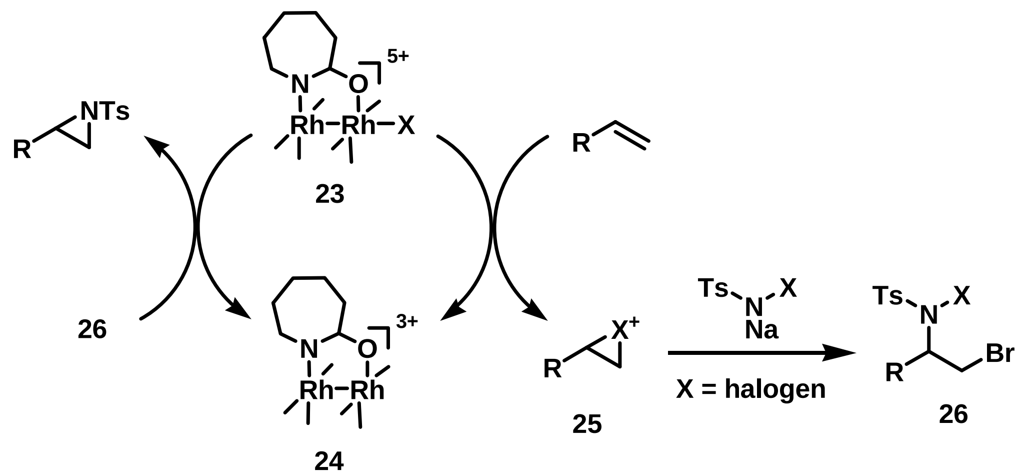
[23] For the disclosure of this work, see: Catino, A. J.; Nichols, J. M.; Forslund, R. E.; Doyle, M. P. *Org. Lett.* **2005**, *7*, 2787.

[24] Doyle, M. P.; Ren, T. *Progress in Inorganic Chem*istry; Karlin, K., Ed; Wiley: New York, 2001; Vol. 49, p 113.

Figure 2.2. Mechanistic Proposal for Atom Transfer Catalyzed by $Rh_2(cap)_4$.



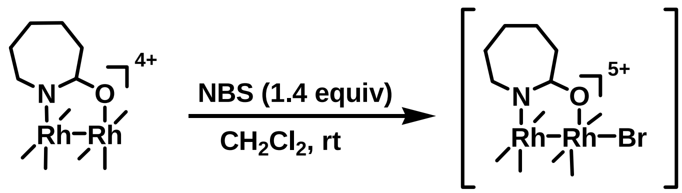
The first objective was to prepare a Rh_2^{5+} halide complex in order to determine if the proposed redox chemistry was viable. Thus, in the presence of stoichiometric *N*-bromosuccinimide (NBS), $Rh_2(cap)_4$ underwent a 1-electron oxidation tentatively assigned as Rh_2^{5+} bromide complex **27** (Scheme 2.12).[25] Several pieces of evidence supported this assignment: 1) A dramatic color change (light blue → deep red) in CH_2Cl_2 was observed upon the addition of NBS, indicating an oxidative reorganization of electrons;[26] 2) the UV/visible spectrum of $Rh_2(cap)_4$ upon addition of NBS contained a low energy absorption (δ-δ* transition) at 971 nm

[25] *N*-Halosuccinimides have been shown to be stoichiometric 1-electron oxidants for cobalt-salen complexes, i.e., Co(II) → Co(III)X, see: Kang, S. H.; Lee, Sung, B. L.; Park, C. M. *J. Amer. Chem. Soc.* **2003**, *125*, 15748, and references therein.

[26] Sheldon, R. A.; Kochi, J. K. *Metal-Catalyzed Oxidations of Organic Compounds*; Academic: New York, 1981.

(ε = 930 $M^{-1}cm^{-1}$) consistent with Rh_2^{5+} species;[27,28] and 3) **27** was NMR silent, which is consistent with an odd electron Rh_2^{5+} complex. This information *only* provided information for the overall charge of the complex. Structural information, particularly the existence of an axially Rh-Br bond, could not be ascertained from this information. Unfortunately, X-ray quality crystals of **27** were not obtained.

Scheme 2.12.



Rh2(cap)4 27

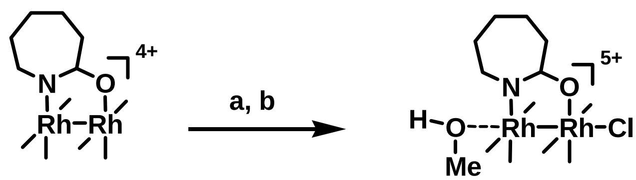
Crystals for X-ray analysis were obtained by replacing NBS with *N*-chlorosuccinimide (NCS) followed by recrystallization from MeOH/hexanes (1:50 v/v) to give the Rh_2^{5+} chloride complex **28** as a deep red solid (Scheme 2.13). X-ray diffraction revealed a dirhodium carboxamidate complex consisting of two rhodium atoms, four bridging carprolactamate ligands arrayed in a *cis*-2,2 configuration, an axially chloride, and an axially-bound methanol (Figure 2.3). The Rh-Rh bond length of **28** is 2.408 Å, which is

[27] (a) Cotton, F. A.; Walton, R. A. *Multiple Bonds Between Metal Atoms*, Wiley: New York, 1982; p 390. (b) Cotton, F.A.; Walton, R. A. *Multiple Bonds Between Metal Atoms*, 2nd ed.; Oxford: New York, 1993; p 475.

[28] Kadish, K. M.; Phan, T. D.; Giribabu, L.; Van Caemelbecke, E.; Bear, J. L., *Inorg. Chem.* **2003,** *42*, 8663.

shortened relative to the Rh-Rh bond of $Rh_2(cap)_4$ (2.422 Å).[29] This structural assignment of **28** provides indirect support for the structure of dirhodium bromide complex **27**.

Scheme 2.13.

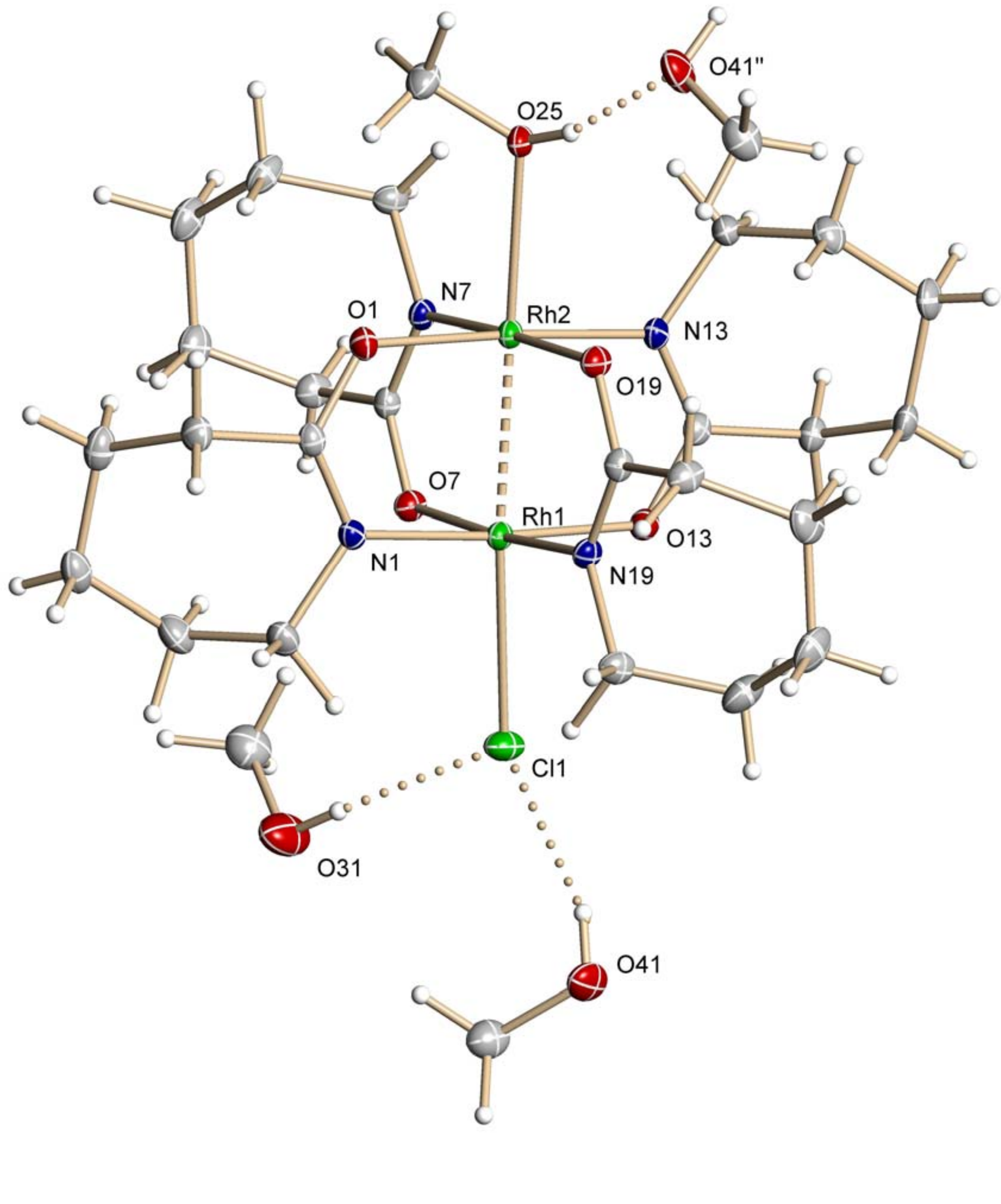


$Rh_2(cap)_4$ **28**

a) NCS (1.4 equiv), CH_2Cl_2, rt, b) MeOH/hexane (1:50 v/v, recrystallize)

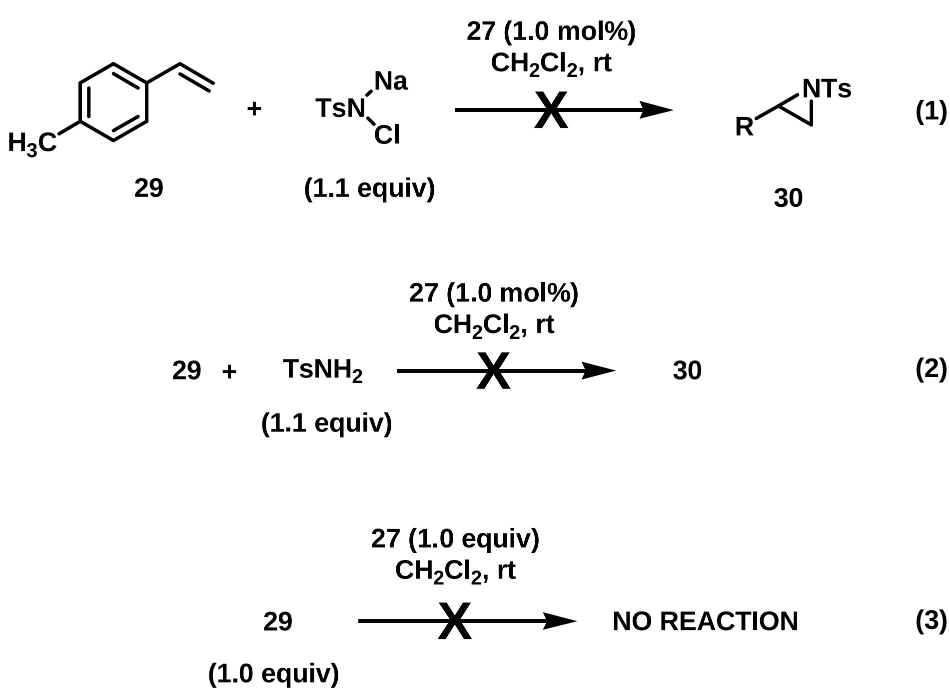
[29] For the X-ray crystal structure of $Rh_2(cap)_4 \cdot 2CH_3CN$, see: Nichols, J. M.; Wolf, J.; Zavalij, P. Y.; Varughese, B.; Doyle, M. P. *Angew. Chem., Int. Ed.* **2006**, manuscript submitted.

Figure 2.3. ORTEP Representation of Dirodium tetrakis[ε-caprolactamate] Chloride Methanol Solvate (**28**). (Atomic displacement ellipsoids for the non-hydrogen atoms are shown at the 30% probability level.)



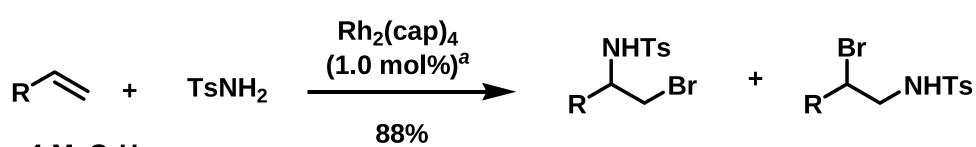
Using chloramine-T (TsNClNa, 1.1 equiv) as a nitrogen source, 4-methylstyrene (**29**, 1.0 equiv), and catalytic **27** (1.0 mol%) in CH_2Cl_2 at room temperature failed to give the corresponding tosyl-aziridine **30** (Scheme 2.14, eq 1). Complete lack of reaction was attributed to catalyst decomposition noted by a color change in solution from red to orange/yellow when **27** was treated with TsNClNa. Next, the feasibility of the less basic $TsNH_2$ was considered; however, aziridine **30** was not observed (no reaction, Scheme 2.14, eq 2). Finally, no reaction was observed when **27** was treated with an equivalent amount of 4-methylstyrene in CH_2Cl_2 which indicated that **27** was not (by itself) a viable source of Br^+ (Scheme 2.14, eq 3). (In contrast, $PhNMe_3^+Br_3^-$ is a source of Br^+ and reacts with olefins to give 1,2-dibromide products.)

Scheme 2.14.



It was clear at this point, that the proposed catalytic cycle in Scheme 2.13 was not viable. However, treating 4-methylstyrene (1.0 equiv) with $TsNH_2$ (1.1 equiv), NBS (1.1 equiv), and 1.0 mol% $Rh_2(cap)_4$ in CH_2Cl_2 at room temperature gave bromosulfonamide **31** in 88% isolated yield after one hour (Scheme 2.15). By ^1H NMR spectroscopy, 70% conversion of starting material was observed in only 3 minutes at 1.0 mol% $Rh_2(cap)_4$. In fact, reducing the catalyst loading to 0.1 mol% $Rh_2(cap)_4$ gave **31** in 95% yield after 1 hour. The regioisomeric preference in each case was >95:5 by ^1H NMR in favor of the branched bromosulfonamide **31**.[30] These results were complimentary to the methodology developed by Sudalai and coworkers in 2003 who observed amidobromination with $TsNH_2$, NBS, and 5.0 mol% of CuI.[16]

Scheme 2.15.



R = 4-MeC$_6$H$_4$

29

31 **32**

31:**32** = >95:5

[a]Conditions: $Rh_2(cap)_4$ (1.0 mol%), 4-methylstyrene (1.0 equiv), $TsNH_2$ (1.1 equiv), NBS (1.1 equiv), CH_2Cl_2, rt, 1 h

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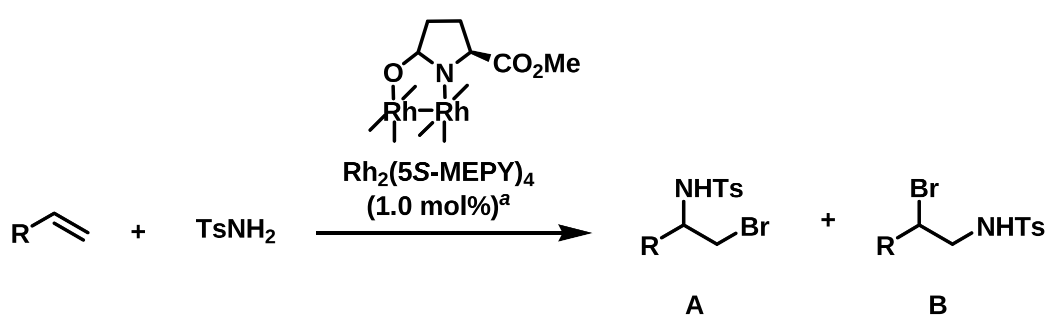
[30] Branched notation refers to the placement of nitrogen on the more substituted carbon of the product. Linear refers to the placement of nitrogen on the less substituted carbon. This notation may also be referred to as Markovnikov and anti-Markovnikov, respectively. For a complete description, see: Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem., Int. Ed*. **2004**, *43*, 3368.

To determine if enantioselectivity could be obtained, the amidobromination of 4-methylstyrene was conducted with Rh_2(5*S*-MEPY)$_4$ under identical conditions as those in Scheme 2.18. An inseparable mixture of regioisomers were obtained in a ratio of 73:27 linear:branched, respectively (Scheme 2.16). A different product distribution was observed for the amidobromination of styrene which gave predominately the linear product (vide infra). However, in each case no optical activity was observed for the product mixture. The change in regioselectivity is dependent on catalyst and substrate, but any further explanation at this time cannot be given. Sudalia and coworkers also observed a reversal of regiochemistry using a chiral catalyst (Scheme 2.7).

Scheme 2.18.

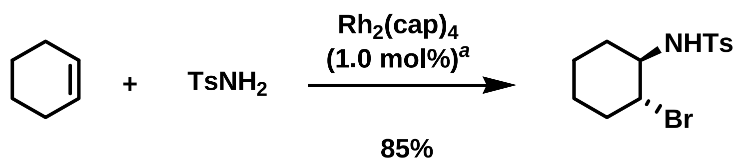


R	yield[b]	A:B[c]
4-MeC_6H_4	98%	73:27
C_6H_5	92%	5:95

[a]Conditions: Rh_2(5*S*-MEPY)$_4$ (1.0 mol%), olefin (1.0 equiv), $TsNH_2$ (1.1 equiv), NBS (1.1 equiv), CH_2Cl_2, rt, 1 h; [b]Isolated yield (A+B) after chromatography; [c]Determined by ^1H NMR.

The amidobromination of cyclohexene catalyzed by $Rh_2(cap)_4$ (1.0 mol%) gave exclusively the *trans*-bromosulfonamide **33** in 85% yield (Scheme 2.17). Spectral data was consistent with the known compound. The *trans* stereochemistry indicates that a bromonium ion is likely involved as an intermediate.

Scheme 2.17.



[a]Conditions: $Rh_2(cap)_4$ (1.0 mol%), cyclohexene (1.0 equiv), $TsNH_2$ (1.1 equiv), NBS (1.1 equiv), CH_2Cl_2, rt, 1 h

To confirm the intermediacy of a bromonium ion and a stepwise process, the amidobromination of *trans*-2-phenyl-1-vinylcyclopropane (**34**) was examined (Scheme 2.18).[40,31] The preparation of **34** is outlined in Scheme 2.19. Reduction of *trans*-2-phenylcyclopropane-1-carboxylic acid (**35**) with $LiAlH_4$ followed by Swern oxidation (95% and 90%, respectively) gave aldehyde **37** according to the procedure of Toste.[32] Wittig olefination of **37** gave vinylcyclopropane **34** in 80% yield according to the procedure of Jacobsen.[33]

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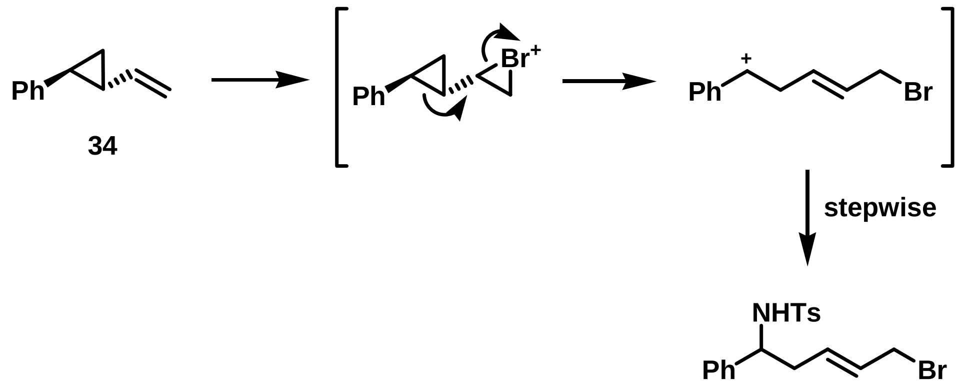
[31] Additionally, **34** has been used as a radical clock, see: Newcomb, M.; Johnson, C. C.; Manek, M. B.; Varick, T. R. *J. Am. Chem. Soc.* **1992**, *114*, 10915.

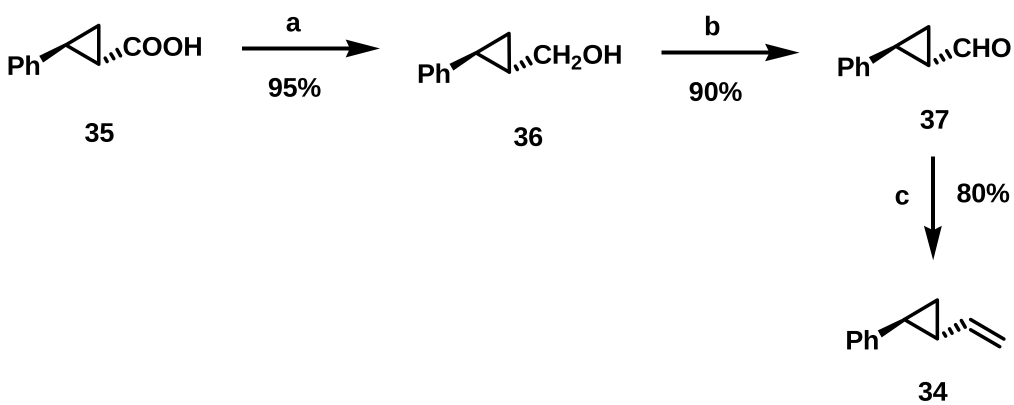
[32] Radosevich, A. T.; Musich, C.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 1090.

[33] Fu, H.; Look, G. C.; Zhang, W.; Jacobsen, E. N.; Wong, C-H. *J. Org. Chem.* **1991**, *56*, 6497.

Scheme 2.18.



Scheme 2.19.

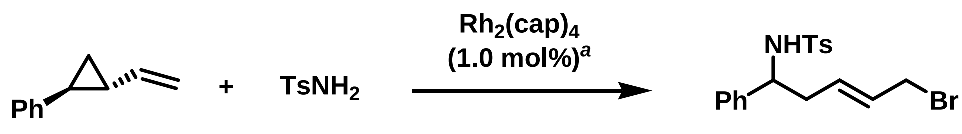


a) $LiAH_4$, Et_2O, 0 °C, 3 h; b) $(COCl)_2$, DMSO, -78 °C, then Et_3N, 1 h; c) Ph_3PCH_2Br, KO^tBu, 0 °C, 10 min

The aminobromination of **34** catalyzed by $Rh_2(cap)_4$ gave exclusively ring-opened product **38** in 62% yield under the reaction conditions along with remaining starting material (Scheme 2.20). This result is consistent with the ring opening of benzylidenecyclopropanes via a bromonium ions reported by

Haung[34] and suggests that bromonium ion intermediates are operative under dirhodium catalysis.

Scheme 2.20.

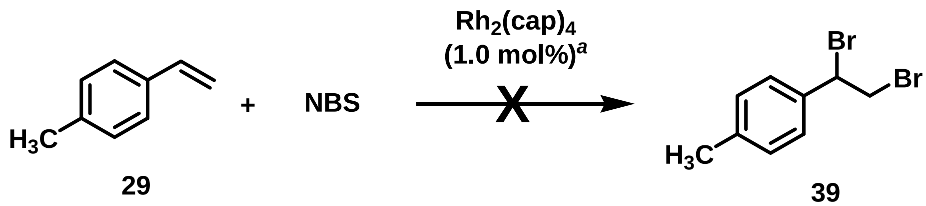


[a]**Conditions: $Rh_2(cap)_4$ (1.0 mol%), 34 (1.0 equiv), $TsNH_2$ (1.1 equiv), NBS (1.1 equiv), CH_2Cl_2, rt, 1 h**

In order to generate a bromonium ion, it is reasonable to assume that a source of Br^+ needs to be present. It was previously noted that **27**, generated in situ, was not a source of Br^+ (see Scheme 2.14, eq 3). In fact, treatment of 4-methylstyrene with NBS (1.1 equiv) and $Rh_2(cap)_4$ in the absence of $TsNH_2$ did not yield dibromide product **39** (Scheme 2.21). These results implicate the involvement of $TsNH_2$ in brominium ion formation. Indeed, both Sudalia and Huang[34] have shown that $TsNH_2$ and NBS react in the absence of catalyst to form TsNHBr in CH_2Cl_2 at room temperature (in each case, the authors isolated and characterized TsNHBr).

[34] Huang, X.; Fu, W.-J. *Synthesis* **2006**, *6*, 1016.

Scheme 2.21.



[a]Conditions: $Rh_2(cap)_4$ (1.0 mol%), 4-methylstyrene (1.0 equiv), NBS (1.1 equiv), CH_2Cl_2, rt, 1 h

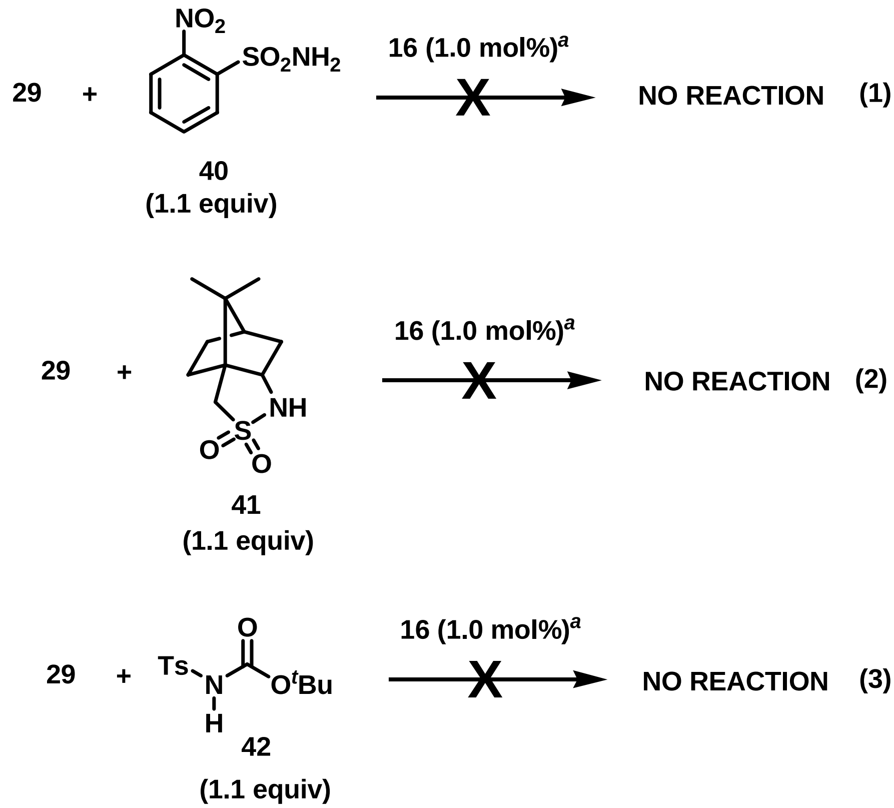
To examine the role of sulfonamide, a few synthetically useful sulfonamides were examined for aminobromination catalyzed by $Rh_2(cap)_4$ (Scheme 2.22). The 2-nitrobenzenesulfonamide (**40**), which can be removed by treatment with PhSH in DMF,[35] failed to react under the reaction conditions (Scheme 2.22, eq 1). Presumably, this is due to the electron withdrawing nature of **40** or to its poor solubility in CH_2Cl_2. The camphor-derived sulfonamide **41** (Oppolzer's sultam[36]), which would provide a mixture of diastereomers, failed to undergo amidobromination under the reaction conditions (Scheme 2.22, eq 2). Finally, *tert*-butoxycarbonylsulfonamide **42**, shown by Weinreb to be useful in the Mitsonobu reaction,[37] failed to undergo reaction (Scheme 2.22, eq 3).

[35] Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373.

[36] Oppolzer, W.; Lienard, P. *Tetrahedron Lett.* **1993**, *34*, 4321.

[37] (a) Weinreb, S. M.; Demko, D. M.; Lessen, T. A,; Demers, J. P. Tetrahedron Lett. **1986**, *27*, 2099. (b) Henry, J. R.; Marcin, L. R.; McIntosh, M. C.; Scola, P. M.; Harris, G. D.; Weinreb, S. M. Tetrahedron Lett. **1989**, *30*, 5709.

Scheme 2.22.



[a]Conditions: $Rh_2(cap)_4$ (1.0 mol%), styrene (1.0 equiv), RNH_2 (1.1 equiv), NBS (1.1 equiv), CH_2Cl_2, rt, 1 h

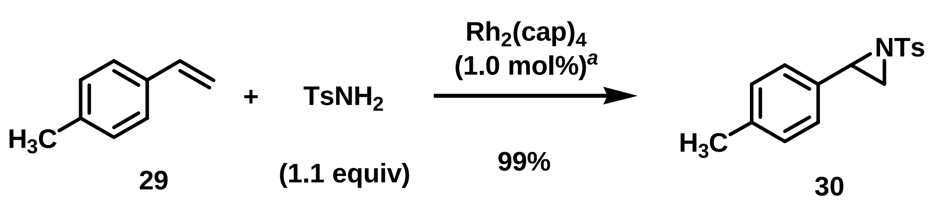
Mechanistic Conclusion. Lewis acids have been shown to "activate" NBS in amidobromination reactions; however, the mechanism/mode of activation presently remains unclear.[16,20] Likewise, $Rh_2(cap)_4$ and the Rh_2^{5+} complex **27** (generated in situ) are both viable Lewis acids[38] that could function in this capacity. Presumably, the catalyst activates NBS or TsNHBr

[38] For dirhodium carboxamidates as Lewis acids, see: (a) Doyle, M. P.; Phillips, I. M.; Hu, W. H. *J. Am. Chem. Soc.* **2001**, 123, 5366. (b) Anada, M.; Washio, T.; Shimada, N.; Kitagaki, S.; Nakajima, M.; Shiro, M.; Hashimoto, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 2665. (c) Doyle, M. P.; Valenzuela, M.; Huang, P. L. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, 101, 5391.

to transfer of Br^+ to an olefin. A bromonium ion was implicated under dirhodium catalysis by the observed *trans*-stereochemistry of **33** and ring opening of **34**. The potential for developing an enantioselective variant of this reaction lies in the understanding of the mode of activation for this process.

Olefin Aziridination. Results obtained from amidobromination were promising, but there was no tactical advantage to use $Rh_2(cap)_4$ over CuI for the amidobromination of olefins as reported by Sudalia. However, the comparative efficiency exhibited by $Rh_2(cap)_4$ at 1.0 and 0.1 mol% catalyst loading was striking. Seeking to convert amidobromide **31** *directly* to aziridine **30**, the addition of base to the reaction mixture was considered.[39] Based on precedent by Li, K_2CO_3 (2.1 equiv) was added to the reaction mixture. Thus, in one pot, treatment of 4-methylstyrene (1.0 equiv) with $TsNH_2$ (1.1 equiv), NBS (1.1 equiv) and K_2CO_3 (2.1 equiv) in CH_2Cl_2 gave aziridine **30**[40] in 99% isolated yield after 12 hours (Scheme 2.23).

Scheme 2.23.



[a]Conditions: $Rh_2(cap)_4$ (1.0 mol%), 4-methylstyrene (1.0 equiv), $TsNH_2$ (1.1 equiv), NBS (1.1 equiv), K_2CO_3 (2.1 equiv), CH_2Cl_2, rt, 12 h

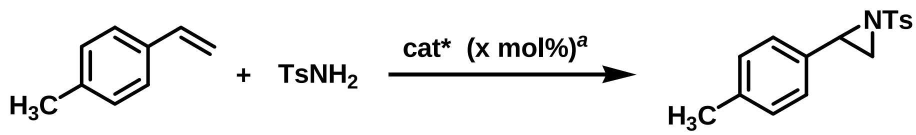
[39] Dr. Raymond E. Forslund, University of Maryland

[40] Spectral data was consistent with the known aziridine, see: Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1994**, *116*, 2742.

The aziridination of 4-methystyrene (**29**) under the reaction condition was examined with other metal catalysts (Table 2.1). In the absence of catalyst, aziridine **30** was obtained in 19% yield (entry 1, Table 2.1) and is consistent with the background reaction observed for amidobromination using $TsNH_2$ and NBS. Catalysts reported by Sudalai, e.g. CuI and Mn(III)salen, gave a moderate enhancement in yield over the background reaction (entries 2-4, Table 2.1). Presumably, this is due to the incompatibility of these catalysts with potassium carbonate under the reaction conditions. Dirhodium(II,II) carboxylates gave moderate yields of aziridine **30** (entries 5 and 6, Table 2.1).[41] Overall, $Rh_2(cap)_4$ was found to be the most effective at 1.0, 0.1, and 0.01 mol% catalyst loading (entries 7-9, Table 2.1).

[41] A color change did not occur when $Rh_2(OAc)_4$ and $Rh_2(pfb)_4$ were treated with NBS which indicates that these complexes do not undergo 1-electron oxidation to Rh_2^{5+} in the reaction.

Table 2.1. Olefin Aziridination of 4-Methylstyrene (**29**) as a Function of Catalyst.



29 **30**

entry	cat*	mol%	yield (%)[b]
1	no catalyst		19
2	CuI	1.0	28
3	CuI	5.0	55
4	Mn(III)-salen[c]	5.0	41
5	$Rh_2(OAc)_4$	1.0	42
6	$Rh_2(pfb)_4$	1.0	49
7	$Rh_2(cap)_4$	1.0	99
8	$Rh_2(cap)_4$	0.1	88
9	$Rh_2(cap)_4$	0.01	73

[a]Reactions were performed using 4-methylstyrene (1.0 equiv), $TsNH_2$ (1.1 equiv), NBS (1.10 equiv), and K_2CO_3 (2.1 equiv) in CH_2Cl_2 at rt for 12 h. [b]Isolated yield after column chromatography. [c]*N*,*N*'-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride.

Aziridination catalyzed by $Rh_2(cap)_4$ was extended to a variety of olefins (Table 2.2). Aziridines were obtained after silica gel chromatography and in all cases were identical to the spectral data of the known compounds.[7(b),42,43,44,45,46] Aryl-substituted alkenes underwent aziridination in good to excellent yield under these conditions (entries 1-6, Table 2.2). The aziridination of diastereomerically pure *trans*-β-methyl styrene gave a 69% yield of a 4:1 trans/cis mixture of aziridines (entries 2, Table 2.2); whereas, *cis*-β-methyl styrene gave 77% yield of a 7:1 cis/trans mixture.[47] The apparent diminution in stereospecificity is likely the result of charged (carbocation) intermediates.[48] Finally, cyclic non-aryl-substituted alkenes, e.g. cyclohexane and cyclooctane, reacted sluggishly; however, yield was improved to a useful level by using a 5-fold excess of substrate (entries 7 and 8, Table 2.2).[49] (Typically, a 5-fold excess has provided useful yields of aziridines in nitrene-transfer processes.[2a])

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[42] Jeong, J. U.; Tao, B.; Sagasser, I.; Henniges, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 6844.

[43] Gao, G.-Y.; Harden, J. D.; Zhang, X. P. *Org. Lett.* **2005**, *7*, 3191.

[44] Chanda, B. M.; Vyas, R.; Bedekar, A. V. *J. Org. Chem.* **2001**, *66*, 30.

[45] Albone, D. P.; Aujla, P. S.; Taylor, P. C.; Challenger, S.; Derrick, A. M. *J. Org. Chem.* **1998**, *63*, 9569.

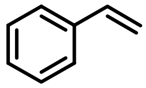
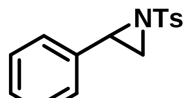
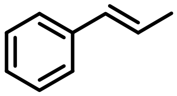
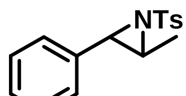
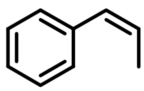
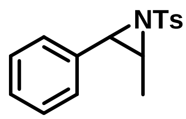
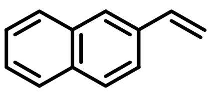
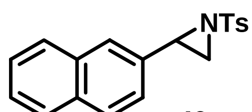
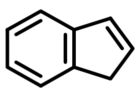
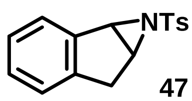
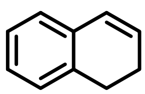
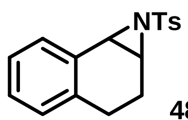
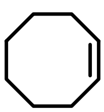
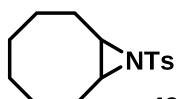
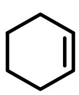
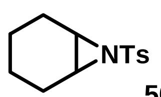
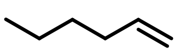
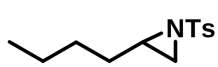
[46] Cui, Y.; He, C. *J. Am. Chem. Soc.* **2003**, *125*, 16202.

[47] Dr. Raymond E. Forslund, University of Maryland.

[48] Benzylic carbocation intermediates have been implicated in the hydroamination and hydroalkoxylation of activated styrenes using NBS, see: Talluri, S. V.; Sudalai, A. *Org. Lett*. **2005**, *7*, 855.

[49] Mr. Jason M. Nichols, University of Maryland.

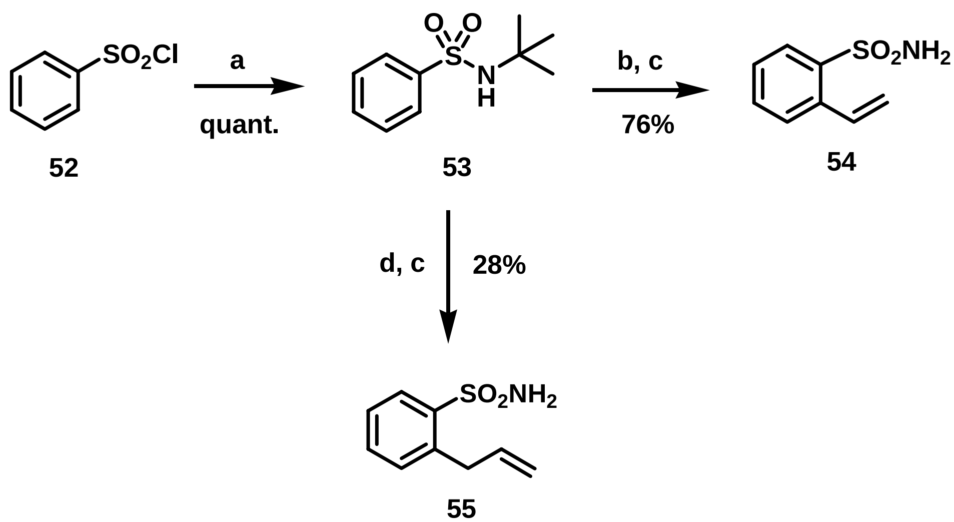
Table 2.2. Olefin Aziridination Catalyzed by $Rh_2(cap)_4$.[a]

entry	substrate	product	$Rh_2(cap)_4$ (mol%)	yield (%)[b]	ref.[f]
1		 **43**	1.0 0.1	77 62	7(b)
2		 **44**	1.0	69[c]	42
3		 **45**	1.0	77[d]	42
4		 **46**	0.1	65	43
5		 **47**	0.1	88	44
6		 **48**	1.0 0.1	95 84	43
7		 **49**	1.0 1.0	47 74[e]	46
8		 **50**	1.0 1.0	49 60[e]	46
9		 **51**	1.0	77	7(b)

[a]Reactions were performed using $Rh_2(cap)_4$, olefin (1.0 equiv), $TsNH_2$ (1.1 equiv), NBS (1.10 equiv), K_2CO_3 (2.10 equiv) in CH_2Cl_2 at rt for 12 h unless otherwise noted. [b]Isolated yield after column chromatography. [c]trans/cis = 4:1 as determined by ^1H NMR prior to purification. [d]cis/trans = 7:1 as determined by ^1H NMR analysis prior to purification. [e]Reaction was performed using 5 equiv of olefin, yield was based on $TsNH_2$ as the limiting reagent. [f]Cited footnote for spectral data of product.

Intramolecular olefin aziridination was examined next. The preparation of sulfonamides **53** and **55** is outlined in Scheme 2.24. Dropwise addition of $^{t}BuNH_2$ to a solution of benzenesulfonyl chloride (**52**) gave sulfonamide **53** in quantitative yield.[50] According to the procedure of Dauban and Dodd, treatment of **53** with *n*-BuLi, quenching with DMF, Wittig olefination, and ^{t}Bu-deprotection with neat CF_3CO_2H (TFA) gave **54** in a combined yield of 76%.[51] Alternatively, treatment of **53** with *n*-BuLi followed by allyl bromide and subsequent TFA-induced deprotection gave **55** in a combined yield of 28%.

Scheme 2.24.



a) $^{t}BuNH_2$**,** CH_2Cl_2**, rt, 12 h; b)** ***n*****-BuLi, THF, -78 °C, 3 h, then DMF, 0 °C, 15 min, then** Ph_3PCH_2Br**, KO**^{t}**Bu, rt, 2 h; c) neat TFA, anisole, 4 °C, 24 h; d)** ***n*****-BuLi, THF, -78 °C, 3 h, then allyl bromide, 4 °C, 12 h.**

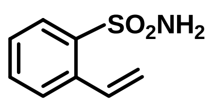
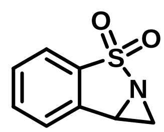
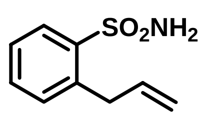
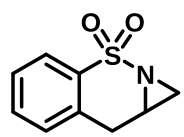
---

[50] Chang, L. L.; Ashton, W. T.; Flanagan, K. L.; Chen, T.-B.; O'Malley, S. S.; Zingaro, G. J.; Kivlighn, S. D.; Siegl, P. K. S.; Lotti, V. J.; et al. *J. Med. Chem.* **1995**, *38*, 3741.

[51] Dauban, P.; Dodd, R. H. *Org. Lett.* **2000**, *2*, 2327.

The intramolecular aziridination of **54** at 0.1 mol% catalyst loading gave aziridine **56** in 86% yield. The aziridination of **55** at 1.0 mol% catalyst loading gave aziridine **57** in 87% yield. (The aziridination of **55** was not conducted at 0.1 mol% loading due to a lack of starting material.)

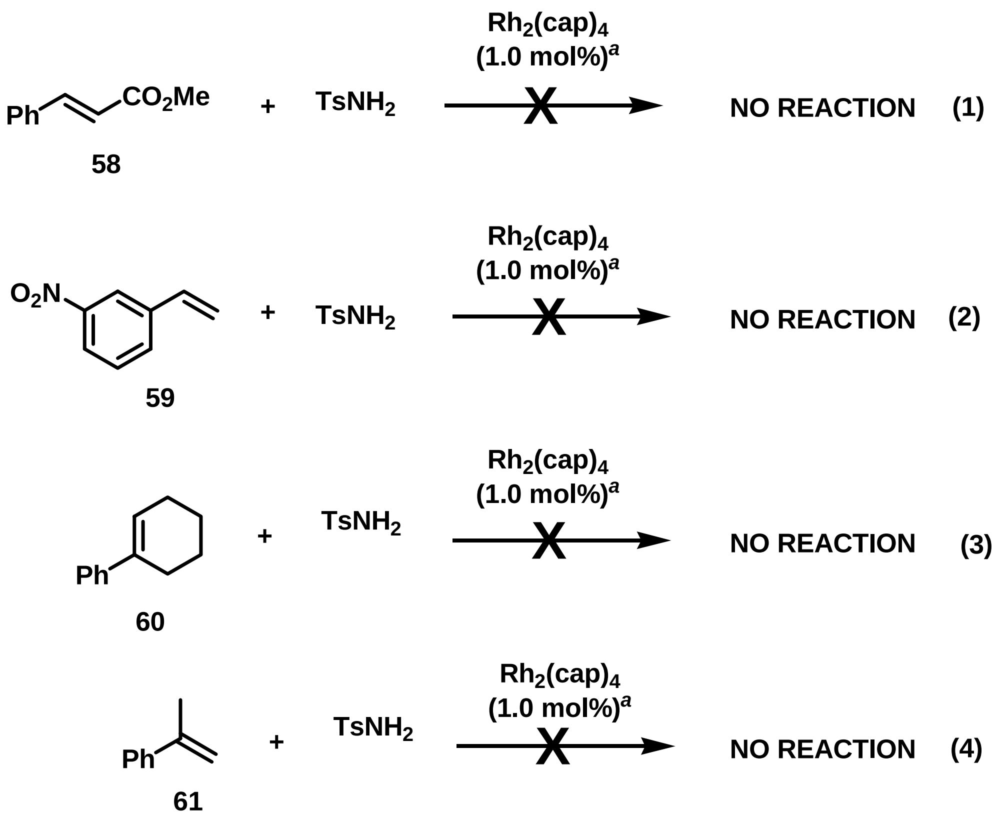
Table 2.3. Intramolecular Olefin Aziridination Catalyzed by $Rh_2(cap)_4$.[a]

entry	substrate	product	$Rh_2(cap)_4$ (mol%)	yield (%)[b]	ref.[c]
1	 **54**	 **56**	0.1	86	51
2	 **55**	 **57**	1.0	87	51

[a]Reactions were performed using $Rh_2(cap)_4$, substrate (1.0 equiv), NBS (1.10 equiv), K_2CO_3 (2.10 equiv) in CH_2Cl_2 at rt for 12 h. [b]Isolated yield after column chromatography. [c]Cited footnote for spectral data of product.

A few olefins were not amenable to aziridination catalyzed by $Rh_2(cap)_4$ (Scheme 2.25). Both methyl *trans*-cinnamate (**58**) and 3-nitrostyrene (**59**) failed to undergo aziridination and remained unchanged after 12 hours (Scheme 2.25, eq 1 and 2). Likewise, 1-phenylcyclohexene (**60**) and α-methylstyrene (**61**) failed to undergo reaction. Lack of reactivity by **58** and **59** can be attributed to the electron deficiency of these alkenes. However, the apparent lack of reactivity of **60** and **61** is difficult to rationalize.

Scheme 2.25.



[a]Conditions: $Rh_2(cap)_4$ (1.0 mol%), olefin (1.0 equiv), $TsNH_2$ (1.1 equiv), NBS (1.1 equiv), K_2CO_3 (2.1 equiv), CH_2Cl_2, rt, 12 h

III. CONCLUSION

The development of methods for the preparation of aziridines is fundamentally important. Aziridines are synthetically useful compounds because they undergo ring opening with an assortment of nucleophiles. Presently, the preparation of aziridines is dominated by methods that use metal catalysts in conjunction with iminophenyliodinanes. Described herein, dirhodium(II) caprolactamate [$Rh_2(cap)_4$] serves as an effective catalyst for olefin aziridination. Using *p*-toluenesulfonamide ($TsNH_2$), *N*-bromosuccinimide (NBS), and potassium carbonate (K_2CO_3), aziridines are obtained at room temperature with as little as 0.01 mol% catalyst. Aziridine formation occurs through Rh_2^{5+} catalyzed amidobromination and subsequent base-induced ring closure. The exact mechanism of activation by dirhodium remains unclear. An X-ray crystal structure of a Rh_2^{5+} chloride complex, generated from the oxidation of $Rh_2(cap)_4$ with *N*-chlorosuccinimide, supports the intermediacy of Rh_2^{5+} in the catalytic cycle.

IV. EXPERIMENTAL

General. All reactions were performed under an air atmosphere unless otherwise noted. Moisture sensitive reactions were performed using oven dried glassware under a dried nitrogen atmosphere. All reagents were obtained from commercial sources and used without purification unless otherwise noted. *N*-Bromosuccinimide (NBS) was recrystallized from water according to the guidelines of Armarego and Chai.[52] Olefins that were liquids were filtered over a plug of alumina and distilled prior to use. Rh_2(5*S*-MEPY)$_4$,[53] *trans*-2-phenylcyclopropane-1-carboxaldehyde (**36**), *trans*-2-phenyl-1-vinyl-cyclopropane (**34**), *N*-*tert*-butylbenzenesulfonamide (**53**), 2-vinylbenzenesulfonamide (**54**), and 2-allylbenzenesulfonamide (**55**) were prepared according to literature methods. Anhydrous CH_2Cl_2 and THF were purified prior to use by nitrogen forced-flow over activated alumina.[54]

Yields reported are for isolated yields unless otherwise noted. Preparative chromatographic purification was performed using SiliCycle (60 Å, 40-63 mesh) silica gel according to the method of Still.[55] Thin layer chromatography (TLC) was performed on Merck 0.25 mm silica gel 60 F_{254} plates with visualization by aqueous $KMnO_4$ or fluorescence quenching.

^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were obtained on a Bruker DRX-400 NMR spectrometer as solutions in $CDCl_3$ containing 0.01%

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

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v/v Me_4Si (TMS). Chemical shifts are reported in parts per million (ppm) δ downfield from TMS; coupling constants are reported in Hertz (Hz). Infrared (IR) spectra were obtained on a JASCO FT/IR-4000 instrument with band assignments reported in units of cm^{-1}. Mass spectra were obtained on a JEOL SX102 magnetic sector mass spectrometer. Melting points were recorded using an Electrothermal Mel-Temp apparatus and were reported uncorrected.

2-Bromo-1-[(4-methylphenyl)sulfonamido]-1-(4-methyphenyl) ethane (31). To a stirring solution of 4-methylstyrene (0.032 g, 0.272 mmol) in CH_2Cl_2 (1 mL) was added $TsNH_2$ (0.051 g, 0.297 mmol) and $Rh_2(cap)_4$ (2.0 mg, 0.0027 mmol). To the solution was added NBS (0.053 g, 0.297 mmol) in one portion at which time the color of the solution immediately turned from light blue to red. The reaction was sealed with a septum and stirred for 1 hour at room temperature. The reaction mixture was filtered over a short plug of silica to remove the catalyst, and the solvent was removed *in vacuo*. The residue was purified by chromatography on silica gel (4:1 hexanes/EtOAc) to give 0.088 g (88%) of **31** as a yellow oil: TLC R_f = 0.25 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.4 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 6.98 – 6.92 (m, 4H), 5.40 (d, *J* = 6.5 Hz, 1H), 4.45 (q, *J* = 6.5 Hz, 1H), 3.55 – 3.46 (comp, 2H), 2.33 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (100 MHz) δ 143.6, 138.2, 136.9, 134.7, 129.6, 129.4, 127.2, 126.7, 58.0, 36.7, 21.6, 21.1; IR (neat) 3260, 1774, 1688, 1593, 1330, 1163 cm^{-1}; HRMS (FAB) calcd for $C_{16}H_{19}BrNO_2S$ 368.0320, found 368.0257 $(M+H)^+$.

2-Bromo-1-[(4-methylphenyl)sulfonamido]-1-phenylethane (12). The procedure for the preparation of 2-bromo-1-[(4-methylphenylsulfon-amido]-1-(4-methyphenyl)ethane (**31**) was followed using styrene. Purified by chromatography on silica gel (5:1 hexanes/EtOAc); white solid (mp = 166 – 168 °C, lit. = 166 – 169 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.4 Hz, 2H), 7.26 – 7.12 (comp, 7H), 5.34 (d, *J* = 6.4 Hz, 1H), 4.57 (q, *J* = 6.4 Hz, 1H), 3.58 (d, *J* = 6.4 Hz, 2H), 2.39 (s, 3H).

1-Bromo-2-[(4-methylphenyl)sulfonamido]-1-phenylethane (13). The procedure for the preparation of 2-bromo-1-[(4-methylphenylsulfon-amido]-1-(4-methyphenyl)ethane (**31**) was followed using styrene and Rh_2(5*S*-MEPY)$_4$ (1.0 mol%). Purified by chromatography on silica gel (5:1 hexanes/EtOAc); light yellow solid (mp = 110 - 112 °C, lit. = 113 - 114); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.4 Hz, 2H), 7.33 – 7.26 (m, 7H), 4.92 – 4.88 (comp, 2H), 3.59 – 3.54 (comp, 2H), 2.44 (s, 3H).

***trans*-2-Bromo-1-[(4-methylphenyl)sulfonamido]cyclohexane (33).**[16] The procedure for the preparation of 2-bromo-1-[(4-methylphenylsulfon-amido]-1-(4-methyphenyl)ethane (**31**) was followed using cyclohexene. Purified by chromatography on silica gel (4:1 hexanes/EtOAc); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 5.43 (d, *J* = 10.3 Hz, 1 H), 3.87 – 3.81 (m, 1H), 3.20 – 3.13 (m, 1H), 2.43 (s, 3H), 2.34 – 2.27 (comp, 2H), 1.84 – 1.74 (comp, 3H), 1.32 – 1.26 (comp, 3H).

N-[(3E)-5-Bromo-1-phenylpent-3-en-1-yl]-4-methylbenzenesulfon-amide (38). The procedure for the preparation of 2-bromo-1-[(4-methylphenylsulfon-amido]-1-(4-methyphenyl)ethane (**31**) was followed using *trans*-2-phenyl-1-vinylcyclopropane (**34**). Purified by chromatography on silica gel (4:1 hexanes/EtOAc); clear oil; TLC R_f = 0.22 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz) δ 7.58 (d, J = 8.0 Hz, 2H), 7.20 - 7.15 (comp, 5H), 7.08 - 7.04 (comp, 2H), 5.66 (dt, J = 15.0, 7.2 Hz, 1H), 5.42 (dt, J = 15.0, 7.2 Hz, 1H), 5.10 (d, J = 7.2 Hz, 1H), 4.35 (q, J = 7.2 Hz, 1H), 3.78 (d, J = 7.6, 2H), 2.53 - 2.43 (comp, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz) δ 143.2, 140.0, 137.4, 130.5, 130.2, 129.4, 128.5, 127.5, 127.1, 126.4, 57.3, 39.9, 32.2, 21.5; HRMS (FAB) calcd for $C_{18}H_{21}BrNO_2S$ 394.0476, found 394.0463 (M+H).

General Procedure for Aziridination of Olefins Catalyzed by $Rh_2(cap)_4$. To a stirring solution of olefin (1.0 equiv) in CH_2Cl_2 (0.27 M/[olefin]) was added $TsNH_2$ (1.1 equiv), K_2CO_3 (2.1 equiv), and $Rh_2(cap)_4$ (1.0 mol%). To the mixture was added NBS (1.10 equiv) in one portion at which time the color of the solution immediately turned from light blue to red. The flask was sealed with a septum and stirred for 12 hours at room temperature during which time the color of the solution gradually turned light brown. The reaction mixture was evaporated onto silica gel and the product was purified by column chromatography.

1-[(4-Methylphenyl)sulfonyl]-2-(4-methylpheny)azridine (30).[7(b)] The general procedure for the aziridination of olefins catalyzed by $Rh_2(cap)_4$ was followed using 4-methylstyrene. Purified by column chromatography on silica gel (4:1 hexanes/EtOAc); white solid (mp = 136 – 137 °C, lit.[7(b)] = 136 – 137 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.0 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.13 (s, 4H), 3.76 (dd, *J* = 7.2, 4.4 Hz, 1H), 2.99 (d, *J* = 7.2 Hz, 1H), 2.46 (s, 3H), 2.40 (d, *J* = 4.4 Hz, 1H), 2.34 (s, 3H).

1-[(4-Methylphenyl)sulfonyl]-2-phenylazridine (43).[7(b)] The general procedure for the aziridination of olefins catalyzed by $Rh_2(cap)_4$ was followed. Purified by chromatography on silica gel (4:1 hexanes/EtOAc); light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.3 Hz, 2H), 7.34 - 7.21 (comp, 7H), 3.78 (dd, *J* = 7.2, 4.5 Hz, 1H), 2.98 (d, *J* = 7.2 Hz, 1H), 2.43 (s, 3H), 2.39 (d, *J* = 4.4 Hz, 1H).

***trans*-2-Methyl-1-[(4-methylphenyl)sulfonyl]-3-phenylazridine (44)**. The general procedure for the aziridination of olefins catalyzed by $Rh_2(cap)_4$ was followed using *trans*-β-methylstyrene. Purified by chromatography on silica gel (5:1 hexanes/EtOAc); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.4 Hz, 2H), 7.30 - 7.24 (comp, 5H), 7.19 - 7.15 (comp, 2H), 3.79 (d, *J* = 4.4 Hz, 1H), 2.94 – 2.88 (m, 1H), 2.39 (s, 3H), 1.84 (d, *J* = 6.0 Hz, 3H).

***cis*-2-Methyl-1-[(4-Methylphenyl)sulfonyl]-3-phenylazridine (45)**. The general procedure for the aziridination of olefins catalyzed by $Rh_2(cap)_4$ was followed using *cis*-β-methylstyrene. Purified by chromatography on silica gel (5:1 hexanes/EtOAc); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.4 Hz, 2H), 7.38 - 7.17 (comp, 5H), 3.92 (d, *J* = 7.6 Hz, 1H), 3.22 – 3.15 (m, 1H), 2.44 (s, 3H), 1.01 (d, *J* = 6.0 Hz, 3H).

1-[(4-Methylphenyl)sulfonyl]-2-(2-naphthyl)aziridine (46). The general procedure for the aziridination of olefins catalyzed by $Rh_2(cap)_4$ was followed using 2-vinylnaphthalene. Purified by chromatography on silica gel (5:1 hexanes/EtOAc); light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.1 Hz, 2H), 7.81 - 7.72 (comp, 4H), 7.48 – 7.45 (comp, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.26 (s, 1H), 3.92 (d, *J* = 7.2, 4.4 Hz, 1H), 3.06 (d, *J* = 7.2 Hz, 1H), 2.49 (d, *J* = 4.4 Hz, 1H), 2.42 (s, 3H).

1,1a,6,6a-Tetrahydroindeno[1,2-*b*]aziren-1-yl-4-methylphenyl-sulfone (47). The general procedure for the aziridination of olefins catalyzed by $Rh_2(cap)_4$ was followed using indene. Purified by chromatography on silica gel (4:1 hexanes/EtOAc); white solid (mp = 152 – 153 °C, lit. = not reported); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.9 Hz, 2H), 7.41 – 7.15 (comp, 7H), 4.30 (d, *J* = 5.2 Hz, 1H), 3.92 – 3.89 (m, 1H), 3.15 – 3.15 (comp, 2H), 2.44 (s, 3H).

***N*-(*p*-Tolylsulfonyl)amino-1,2,3,4-tetrahydronapthalene-1,2-imine (48)**. The general procedure for the aziridination of olefins catalyzed by $Rh_2(cap)_4$ was followed using 1,2-dihydronaphthalene. Purified by chromatography on silica gel (5:1 hexanes/EtOAc), light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.3 Hz, 2H), 7.30 – 7.02 (comp, 6H), 3.80 (d, *J* = 7.2 Hz, 1H), 3.55 (d, *J* = 7.2 Hz, 1H), 2.72 (dt, *J* = 14.7, 5.4 Hz, 1H), 2.52 (dd, *J* = 15.7, 5.4 Hz, 1H), 2.39 (s, 3H), 2.27 – 2.21 (m, 1H), 1.69 – 1.60 (m, 1H).

1-[(4-Methylphenyl)sulfonyl])-9-azabicyclo[6.1.0]nonane (49). The general procedure for the aziridination of olefins catalyzed by $Rh_2(cap)_4$ was followed using *cis*-cyclooctene. Purified by chromatography on silica gel (5:1 hexanes/EtOAc); white solid (mp = 99 – 101 °C, lit = not reported); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 - 7.74 (d, *J* = 8.4 Hz, 2H), 7.26 - 7.24 (d, *J* = 8.4 Hz, 2H), 2.73 - 2.70 (comp, 2H), 2.37 (s, 3H), 1.97 - 1.92 (dd, *J* = 14.0, 3.6 Hz, 2H), 1.46 - 1.53 (comp, 4H), 1.38 - 1.31 (comp, 4H), 1.26 - 1.19 (comp, 2H).

1-[(4-Methylphenyl)sulfonyl])-7-azabicyclo[4.1.0]heptane (50).[46] The general procedure for the aziridination of olefins catalyzed by $Rh_2(cap)_4$ was followed using cyclohexene. Purified by chromatography on silica gel (5:1 hexanes/EtOAc); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 2.94 (s, 2H), 2.41 (s, 3H), 1.76 (t, *J* = 5.2 Hz, 4H), 1.38 – 1.34 (comp, 2H), 1.22 – 1.17 (comp, 2H).

1-[(4-Methylphenyl)sulfonyl]-2-*n*-butylazridine (51).[7(b)] The general procedure for the aziridination of olefins catalyzed by $Rh_2(cap)_4$ was followed using 1-hexene. Purified by chromatography on silica gel (4:1 hexanes/EtOAc); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.3 Hz, 2H), 7.75 (d, *J* = 8.3 Hz, 2H), 2.75 – 2.69 (m, 1H), 2.63 (d, *J* = 7.0 Hz, 1H), 2.45 (s, 3H), 2.06 (d, *J* = 4.6 Hz, 1H), 1.59 – 1.52 (m, 1H), 1.34 – 1.18 (comp, 5H), 0.81 (t, *J* = 6.8 Hz, 1H).

1,1a-Dihydro-6-thia-6a-azacyclopropa[a]indene-6,6-dioxide (56).[51] To a stirring solution of 2-vinylbenzenesulfonamide (**54**) (0.249 g, 1.36 mmol) in CH_2Cl_2 (5 mL) was added K_2CO_3 (0.394 g, 2.85 mmol) and $Rh_2(cap)_4$ (1.0

mg, 0.0014 mmol). To the solution was added NBS (0.266 g, 1.49 mmol) in one portion at which time the color of the solution immediately turned from light blue to red. The flask was sealed with a septum and stirred for 12 h at room temperature during which time the color of the solution gradually turned light brown. The reaction mixture was evaporated onto silica gel and the product was purified by column chromatography (5:1 → 3:1 hexanes/EtOAc) to yield 0.212 mg (86%) of **56** as a white solid (mp = 78 – 80 °C, lit. = 79 – 80 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.1 Hz, 1H), 7.66 – 7.55 (comp, 3H), 4.14 (t, *J* = 4.6 Hz, 1H), 2.89 (dd, *J* = 4.6, 1.1 Hz, 1H), 2.36 (dd, *J* = 3.8, 1.1 Hz, 1H).

1a,2-Dihydro-1*H*-7-thia-7a-azacyclopropa[b]naphthalene 7,7-dioxide (57). To a stirring solution of 2-allylbenzenesulfonamide (**55**) (0.107 g, 0.543 mmol) in CH_2Cl_2 (2 mL) was added K_2CO_3 (0.158 g, 1.14 mmol) and $Rh_2(cap)_4$ (4.0 mg, 0.0054 mmol). To the solution was added NBS (0.106 g, 0.597 mmol) in one portion at which time the color of the solution immediately turned from light blue to red. The flask was sealed with a septum and stirred for 12 hours at room temperature during which time the color of the solution gradually turned light brown. The reaction mixture was evaporated onto silica gel and the product was purified by column chromatography (5:1 → 3:1 hexanes/EtOAc) to yield 0.092 g (87%) of **57** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.59 (dt, *J* = 7.5, 1.5 Hz, 1 H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.29 (d, *J* = 7.5 Hz, 1H), 3.58 (dd, *J* = 16.8, 3.9 Hz), 3.28 - 3.24 (comp, 2H), 2.49 - 2.47 (m, 1H), 1.91 (dd, *J* = 3.9, 1.5 Hz, 1H).

Dirodium tetrakis[ε-caprolactamate] Bromide Methanol Solvate (27) and Reaction with Chloramine-T (Scheme 2.16). To a stirring solution of $Rh_2(cap)_4$ (20.0 mg, 0.031 mmol) in CH_2Cl_2 (5 mL) was added NBS (6.0 mg, 0.034 mmol) at which time the color of the solution immediately turned from light blue to red. The solution was stirred for 1 h, the solvent was removed *in vacuo*, and the residue was submitted to column chromatography on silica gel (6:1 CH_2Cl_2/MeOH) to give 10 mg of a red solid tentatively assigned as **27**. To a stirring solution of 4-methylstyrene (0.032 g, 0.272 mmol) in CH_2Cl_2 (1 mL) at room temperature was added chloramine-T hydrate (0.068 g, 0.300 mmol) followed by **27** (2.0 mg, 0.0027 mmol). The color of the reaction turned red and then gradually to orange over the course of 12 h. The solution was filtered over a short plug of silica gel to remove the catalyst and the solvent was removed *in vacuo*. ^{1}H NMR and TLC analysis indicated that no reaction occurred. The same procedure was followed when chloramine-T hydrate was replaced with $TsNH_2$ (0.051 mg, 0.298 mmol) and gave no reaction.

Dirodium tetrakis[ε-caprolactamate] Chloride Methanol Solvate (28). To a stirring solution of $Rh_2(cap)_4$ (0.010 g, 0.014 mmol) in CH_2Cl_2 (5 mL) at rt was added *N*-chlorosuccinimide (2.7 mg, 0.020 mmol) at which time the color of the solution turned from light blue to red. The solution was stirred for 1 h, the solvent was removed *in vacuo*, and the residue was submitted to column chromatography on silica gel (6:1 CH_2Cl_2/MeOH) to give 0.006 g of a red solid. Crystals were obtained by slow evaporation from MeOH/hexanes (1:50). $C_{27}H_{52}Cl_1N_4O_7Rh_2$, M = 784.99, monoclinic, space group $P2_1$, a = 8.3834(5) Å, b = 18.8291(11) Å, c = 10.2686(6) Å, β = 98.088(1), U = 1604.8(2) Å3, Z = 2, T = 173 K, MoKα (0.71073 Å), 25387 reflection measured, 7344 unique (R_{int} = 0.0318), which were all used in calculations. The final *wR2* was 0.0623 (all data).

X-Ray Crystallographic Data for Dirodium tetrakis[ε-caprolactamate] Chloride Methanol Solvate (28).[56] A reddish-orange plate with approximate orthogonal dimensions 0.306 x 0.124 x 0.018mm^3 was placed and optically centered on the Bruker SMART CCD system at –100 °C. The initial unit cell was indexed using a least-squares analysis of a random set of reflections collected from three series of 0.3° wide ω-scans, 10 seconds per frame, and 25 frames per series that were well distributed in reciprocal space. Data frames were collected [MoKα] with 0.3° wide ω-scans, 40 seconds per frame and 606 frames per series. Five complete series were collected at varying φ angles (φ=0°, 72°, 144°, 216°, 288°). The crystal to detector distance was 4.893cm, thus providing a nearly complete sphere of data to $2\theta_{max}$=55.13°. A total of 25387 reflections were collected and corrected for Lorentz and polarization effects and absorption using Blessing's method as incorporated into the program SADABS[57,58] with 7378 unique.

Structural Determination and Refinement. All crystallographic calculations were performed on a Personal computer (PC) with a Pentium

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[56] Crystallographic data was obtained by James C. Fettinger, Department of Chemistry and Biochemistry, University of Maryland, December 12, 2003. A structural refinement was performed by Peter Y. Zavalig, Department of Chemistry and Biochemistry, University of Maryland, November 21, 2006 (H25 added).

[57] An Empirical Correction for Absorption Anisotropy, Blessing, R. H. (1995). Acta Cryst., A51, 33-38.

[58] Sheldrick, G.M., SADABS 'Siemens Area Detector Absorption Correction' Universität Göttingen: Göttingen, Germany, 1996.

1.80GHz processor and 512MB of extended memory. The SHELXTL[59] program package was implemented to determine the probable space group and set up the initial files. System symmetry, systematic absences and intensity statistics indicated the unique chiral monoclinic space group $P2_1$ (no. 4). The structure was determined by direct methods with the successful location of all the non-hydrogen atoms using the program XS.[60] The structure was refined with XL.[61] The 25387 data collected were merged during least-squares refinement to 7344 unique data [R(int)=0.0318]. Multiple least-squares difference-Fourier cycles were required to locate the remaining non-hydrogen atoms. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were allowed to refine freely (xyzU) but for those attached to the methanol oxygen atoms (U only). The final structure was refined to convergence [$\Delta/\sigma \leq 0.001$] with R(F)=5.91%, wR(F^2)=11.59%, GOF=1.048 for all 12386 unique reflections [R(F)=4.20%, wR(F^2)=10.62% for those 9858 data with Fo > 4σ(Fo)]. The final difference-Fourier map was featureless indicating that the structure is both correct and complete. The absolute structure parameter, Flack(x),[62] was refined and found to be 0.26(2) indicating racemic twinning that was also refined. The function minimized during the full-matrix least-squares refinement was $\Sigma w(Fo^2-Fc^2)$ where $w=1/[\sigma^2(Fo^2)+(0.0382*P)^2 + 0.0*P]$ and $P=(max(Fo^2,0)+2*Fc^2)/3$. An

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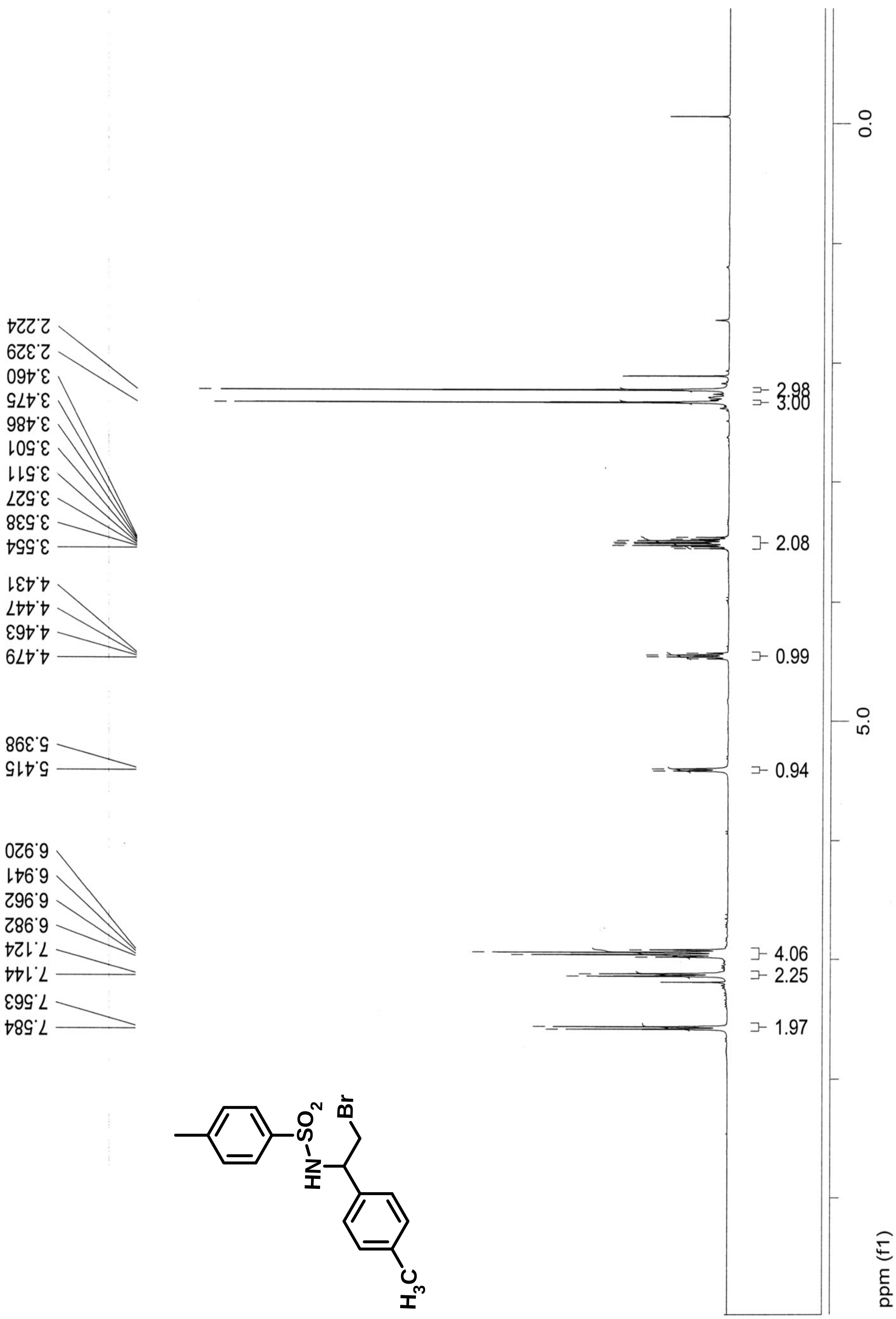
[59] Sheldrick, G.M., (1994). SHELXTL/PC. Version 5.03. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.

[60] Phase Annealing in SHELX-90: Direct Methods for Larger Structures, Sheldrick, G. M., (1990). Acta Cryst. A46, 467-473.

[61] Sheldrick, G.M., (1993). Shelxl93 Program for the Refinement of Crystal Structures. University of Göttingen, Germany.

[62] On Enantiomorph-Polarity Estimation, Flack, H.D. (1983). Acta Cryst., A39, 876-881.

empirical correction for extinction was also attempted but found to be negative and therefore not applied.



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3.460
3.475
3.486
3.501
3.511
3.527
3.538
3.554
4.431
4.447
4.463
4.479
5.398
5.415
6.920
6.941
6.962
6.982
7.124
7.144
7.563
7.584
2.98
3.00
2.08
0.99
0.94
4.06
2.25
1.97
0.0
5.0
ppm (f1)
HN
SO2
Br
H3C


21.141
21.569
36.667
57.984
126.660
127.247
129.355
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138.183
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0
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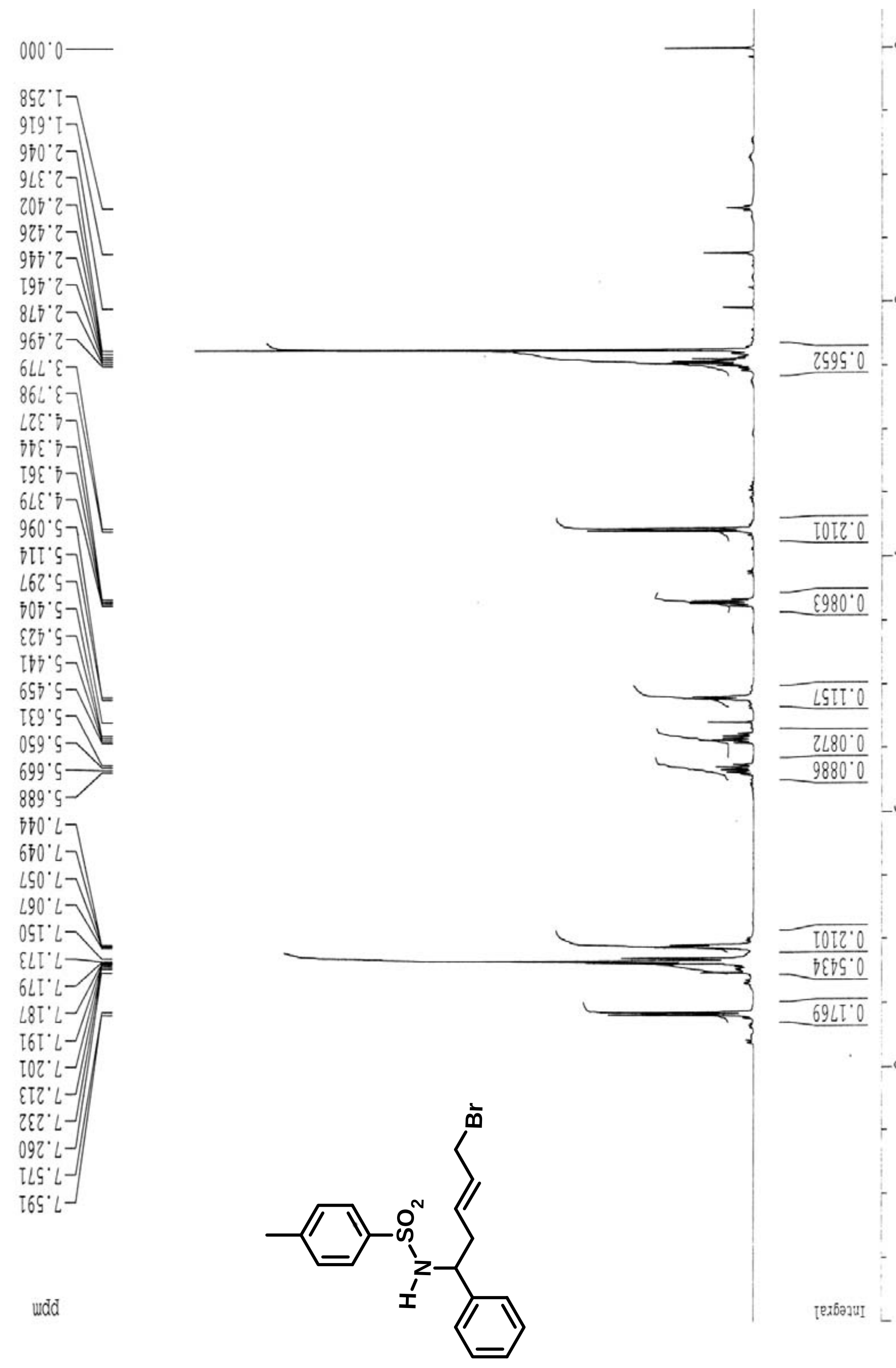
100
150
200
ppm (f1)
HN
SO2
Br
H3C



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1.616
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2.402
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2.446
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2.478
2.496
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3.798
4.327
4.344
4.361
4.379
5.096
5.114
5.297
5.404
5.423
5.441
5.459
5.631
5.650
5.669
5.688
7.044
7.049
7.057
7.067
7.150
7.173
7.179
7.187
7.191
7.201
7.213
7.232
7.260
7.571
7.591
ppm
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0.0863
0.1157
0.0872
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Integral
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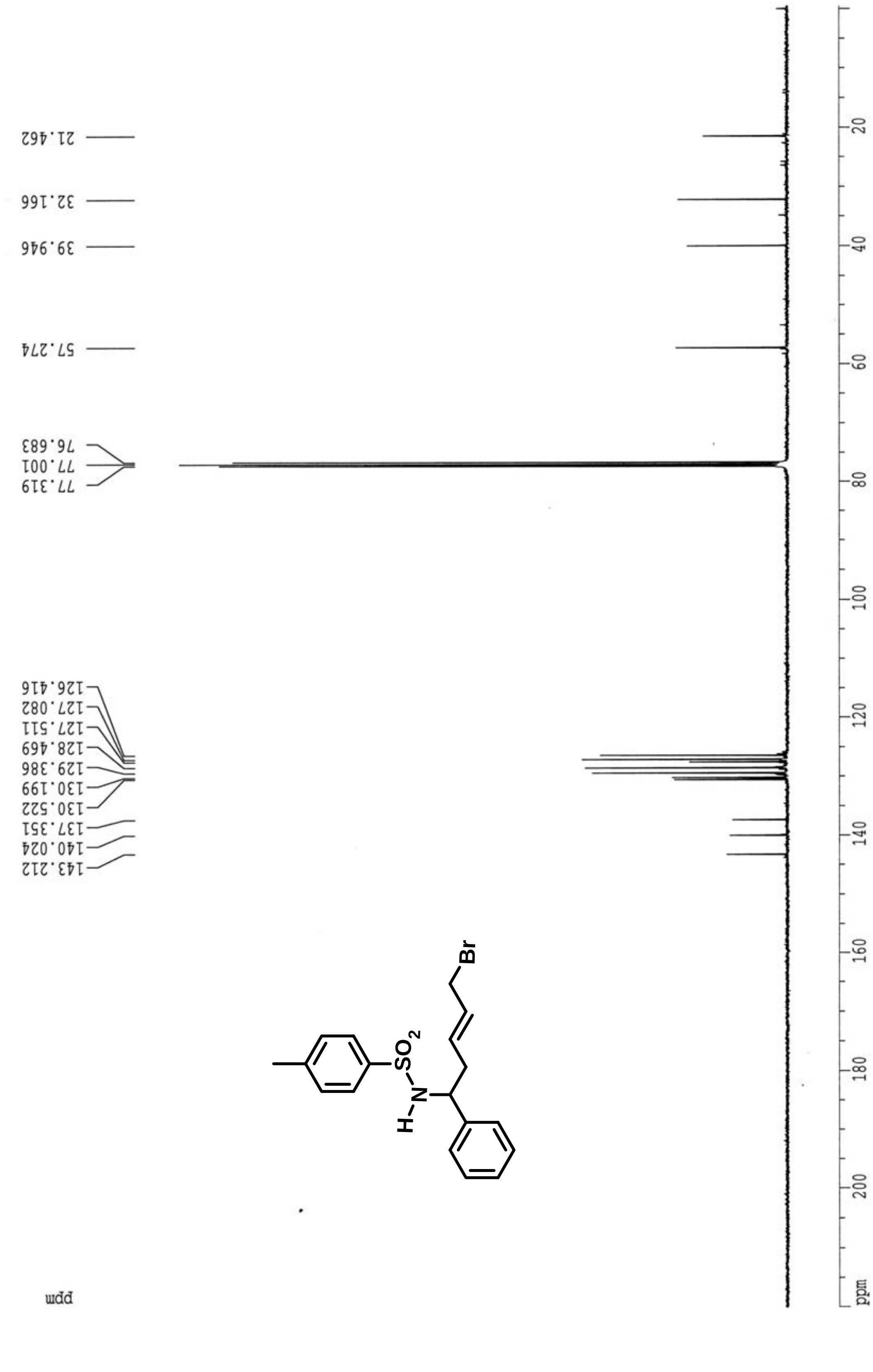
2
4
6
8
ppm
Br
SO2
H–N


21.462
32.166
39.946
57.274
76.683
77.001
77.319
126.416
127.082
127.511
128.469
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130.199
130.522
137.351
140.024
143.212
ppm
20
40
60
80
100
120
140
160
180
200
ppm
Br
SO2
H–N

Table 2.4. Crystal Data and Structure Refinement for Dirodium tetrakis[ε-caprolactamate] Chloride Methanol Solvate (**28**).

Empirical formula	C27 H52 Cl N4 O7 Rh2	
Formula weight	786.00	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal size	0.306 × 0.124 × 0.018 mm^3	
Crystal habit	Orange Plate	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 8.3834(5) Å	α = 90°
	b = 18.8291(11) Å	β = 98.0880(10)°
	c = 10.2686(6) Å	γ = 90°
Volume	1604.79(16) $Å^3$	
Z	2	
Density, ρ_{calc}	1.627 g/cm^3	
Absorption coefficient, μ	1.160 mm^{-1}	
F(000)	810 $\bar{e}$	
Diffractometer	Bruker Smart1000 CCD area detector	
Radiation source	fine-focus sealed tube, MoKα	
Generator power	50 kV, 30 ma	
Detector distance	4.95 cm	
Detector resolution	8.33 pixels/mm	
Total frames	3030	
Frame size	512 pixels	
Frame width	0.3 °	
Exposure per frame	40 sec	
Total measurement time	39.7 hours	
Data collection method	ω scans	
θ range for data collection	2.16 to 27.50°	
Index ranges	$-10 \leq h \leq 10, -24 \leq k \leq 24, -13 \leq l \leq 13$	
Reflections collected	25387	
Independent reflections	7344	
Observed reflection, $I>2\sigma(I)$	6732	
Coverage of independent reflections	99.9 %	
Variation in check reflections	? %	
Absorption correction	Semi-empirical from equivalents SADABS (Sheldrick, 1996)	
Max. and min. transmission	0.979 and 0.764	
Structure solution technique	direct	
Structure solution program	SHELXS-97 (Sheldrick, 1990)	
Refinement technique	Full-matrix least-squares on F^2	
Refinement program	SHELXL-97 (Sheldrick, 1997)	
Function minimized	$\Sigma w(F_o^2 - F_c^2)^2$	
Data / restraints / parameters	7344 / 6 / 542	
Goodness-of-fit on F^2	1.000	
Δ/σ_{max}	0.001	
Final R indices: R_1, $I>2\sigma(I)$	0.0265	
wR_2, all data	0.0598	
R_{int}	0.0318	
R_{sig}	0.0323	
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0028.P)^2 + 1.22P]$, $P = [\max(F_o^2, 0) + 2F_o^2]/3$	
Absolute structure parameter	0.26(2)	
Largest diff. peak and hole	0.896 and -0.756 $\bar{e}/Å^3$	

$R_1 = \Sigma||F_o|-|F_c||/\Sigma|F_o|$, $wR2 = [\Sigma w(F_o^2-F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$

Atomic coordinates and equivalent* isotropic atomic displacement parameters (Å^2).

Atom	*x/a*	*y/b*	*z/c*	U_{eq}
Rh1	0.77705(3)	0.143581(14)	0.37325(2)	0.01984(6)
Rh2	0.88010(3)	0.031328(12)	0.30978(2)	0.01891(6)
Cl1	0.63547(11)	0.25235(5)	0.46032(10)	0.0339(2)
C1	0.8873(4)	0.1421(2)	0.1168(3)	0.0221(6)
N1	0.8236(4)	0.18261(16)	0.1996(3)	0.0220(6)
O1	0.9273(3)	0.07706(13)	0.1411(2)	0.0242(5)
C2	0.9119(5)	0.1679(2)	-0.0191(4)	0.0291(8)
C3	0.7519(5)	0.1769(3)	-0.1093(4)	0.0349(9)
C4	0.6671(6)	0.2461(2)	-0.0879(4)	0.0368(10)
C5	0.6268(5)	0.2565(3)	0.0504(4)	0.0373(9)
C6	0.7712(6)	0.2552(2)	0.1594(4)	0.0313(9)
C7	0.5377(4)	0.05434(19)	0.2255(3)	0.0214(7)
N7	0.6556(4)	0.00819(16)	0.2255(3)	0.0213(6)
O7	0.5570(3)	0.11498(13)	0.2833(2)	0.0242(5)
C8	0.3704(4)	0.0403(2)	0.1543(4)	0.0282(8)
C9	0.3637(5)	0.0388(3)	0.0050(4)	0.0345(9)
C10	0.4232(5)	-0.0295(3)	-0.0497(4)	0.0371(10)
C11	0.5958(5)	-0.0506(3)	0.0060(4)	0.0333(9)
C12	0.6236(5)	-0.0596(2)	0.1556(4)	0.0249(8)
C13	0.7700(4)	0.0322(2)	0.5649(3)	0.0217(6)
N13	0.8341(4)	-0.00816(16)	0.4811(3)	0.0222(6)
O13	0.7290(3)	0.09731(14)	0.5396(2)	0.0239(5)
C14	0.7495(4)	0.0066(2)	0.7004(4)	0.0251(8)
C15	0.9144(5)	0.0011(2)	0.7864(4)	0.0293(8)
C16	1.0012(5)	-0.0681(2)	0.7653(4)	0.0327(9)
C17	1.0387(5)	-0.0798(3)	0.6264(4)	0.0315(9)
C18	0.8884(5)	-0.0802(2)	0.5222(4)	0.0259(8)
C19	1.1220(4)	0.12074(19)	0.4524(3)	0.0231(7)
N19	1.0040(3)	0.16596(15)	0.4565(3)	0.0220(6)
O19	1.1016(3)	0.05974(14)	0.3948(2)	0.0246(5)
C20	1.2927(4)	0.1364(3)	0.5157(4)	0.0294(8)
C21	1.3109(5)	0.1393(3)	0.6668(4)	0.0406(10)
C22	1.2542(6)	0.2091(3)	0.7197(5)	0.0449(12)
C23	1.0798(6)	0.2278(3)	0.6725(4)	0.0398(11)
C24	1.0398(5)	0.2349(2)	0.5236(4)	0.0294(8)
C25	1.0267(5)	-0.0844(2)	0.1143(4)	0.0345(9)
O25	1.0044(3)	-0.07244(14)	0.2471(2)	0.0244(5)
C31	0.2609(6)	0.2594(3)	0.2057(5)	0.0490(12)
O31	0.3469(4)	0.3168(2)	0.2666(4)	0.0625(10)
C41	0.5950(5)	0.4309(2)	0.5406(5)	0.0407(10)
O41	0.7073(3)	0.38876(16)	0.6242(3)	0.0403(7)

* U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

Anisotropic atomic displacement parameters * (Å^2).

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Rh1	0.01859(12)	0.02093(12)	0.01880(12)	-0.00140(10)	-0.00154(9)	0.00052(11)
Rh2	0.01826(11)	0.02091(12)	0.01664(12)	-0.00023(10)	-0.00070(9)	0.00077(10)
Cl1	0.0301(5)	0.0280(5)	0.0418(5)	-0.0086(4)	-0.0019(4)	0.0040(4)
C1	0.0194(15)	0.0251(17)	0.0208(16)	0.0030(17)	-0.0010(12)	-0.0027(18)
N1	0.0230(15)	0.0209(15)	0.0208(15)	0.0003(12)	-0.0019(12)	-0.0006(12)
O1	0.0256(13)	0.0264(14)	0.0206(13)	0.0034(10)	0.0034(10)	0.0009(11)
C2	0.031(2)	0.031(2)	0.026(2)	0.0041(16)	0.0060(16)	-0.0001(17)
C3	0.034(2)	0.044(3)	0.025(2)	0.0024(18)	-0.0019(17)	-0.0116(19)
C4	0.035(2)	0.039(2)	0.033(2)	0.0091(19)	-0.0089(18)	-0.007(2)
C5	0.034(2)	0.033(2)	0.042(2)	0.009(2)	-0.0020(18)	0.006(2)
C6	0.039(2)	0.024(2)	0.030(2)	0.0037(18)	0.0015(18)	-0.0028(19)
C7	0.0213(17)	0.0239(18)	0.0184(16)	0.0017(13)	0.0011(13)	-0.0029(13)
N7	0.0204(15)	0.0230(16)	0.0194(15)	-0.0006(11)	-0.0011(11)	-0.0021(11)
O7	0.0201(12)	0.0254(13)	0.0262(13)	-0.0033(10)	0.0003(10)	0.0006(10)
C8	0.0184(16)	0.032(2)	0.0335(19)	-0.0044(18)	-0.0001(14)	-0.0033(17)
C9	0.0252(18)	0.046(3)	0.0300(19)	0.000(2)	-0.0055(15)	-0.004(2)
C10	0.028(2)	0.054(3)	0.027(2)	-0.0081(19)	-0.0040(16)	-0.0026(19)
C11	0.0234(19)	0.048(3)	0.027(2)	-0.0127(19)	0.0004(16)	-0.0036(18)
C12	0.0207(19)	0.0214(19)	0.032(2)	-0.0050(15)	0.0001(16)	-0.0024(15)
C13	0.0160(14)	0.0270(17)	0.0207(15)	-0.0010(17)	-0.0016(11)	-0.0008(17)
N13	0.0230(15)	0.0242(16)	0.0180(15)	0.0001(12)	-0.0019(12)	0.0001(13)
O13	0.0247(13)	0.0262(14)	0.0208(13)	-0.0012(10)	0.0032(10)	0.0017(11)
C14	0.0241(18)	0.031(2)	0.0193(17)	0.0006(14)	0.0018(14)	-0.0018(15)
C15	0.037(2)	0.034(2)	0.0151(17)	-0.0002(16)	-0.0016(15)	-0.0011(18)
C16	0.031(2)	0.043(3)	0.0214(19)	0.0047(17)	-0.0085(16)	0.0015(19)
C17	0.026(2)	0.035(2)	0.032(2)	0.0051(18)	0.0005(16)	0.0055(18)
C18	0.031(2)	0.0240(19)	0.0217(18)	0.0007(16)	0.0014(15)	0.0044(17)
C19	0.0192(17)	0.0280(19)	0.0218(17)	0.0009(14)	0.0015(13)	-0.0033(13)
N19	0.0202(15)	0.0235(16)	0.0212(15)	-0.0030(11)	-0.0012(12)	-0.0036(11)
O19	0.0204(12)	0.0269(13)	0.0249(13)	-0.0026(10)	-0.0024(10)	0.0005(10)
C20	0.0186(16)	0.035(2)	0.0338(19)	-0.0069(19)	-0.0009(14)	0.0008(18)
C21	0.032(2)	0.047(3)	0.038(2)	0.002(2)	-0.0142(17)	0.002(2)
C22	0.038(2)	0.063(3)	0.030(2)	-0.014(2)	-0.0081(19)	-0.005(2)
C23	0.038(2)	0.047(3)	0.034(2)	-0.018(2)	0.0050(19)	-0.005(2)
C24	0.0232(19)	0.028(2)	0.034(2)	-0.0057(16)	-0.0038(16)	-0.0025(16)
C25	0.034(2)	0.043(2)	0.0268(19)	-0.0044(17)	0.0043(16)	0.0069(18)
O25	0.0258(13)	0.0266(13)	0.0191(12)	-0.0008(10)	-0.0029(10)	0.0047(11)
C31	0.036(2)	0.054(3)	0.056(3)	0.001(2)	0.004(2)	0.004(2)
O31	0.050(2)	0.055(2)	0.075(3)	-0.0091(19)	-0.0168(19)	0.0185(17)
C41	0.030(2)	0.043(2)	0.047(3)	-0.008(2)	-0.0007(18)	0.0021(18)
O41	0.0367(16)	0.0377(17)	0.0415(17)	-0.0104(13)	-0.0116(13)	-0.0026(13)

* The anisotropic atomic displacement factor exponent takes the form: $-2\pi^2$ [$h^2a^{*2}U_{11}$ + ... + $2hka^*b^*U_{12}$]

Hydrogen atom coordinates and isotropic atomic displacement parameters (Å^2).

Atom	*x/a*	*y/b*	*z/c*	U_{iso}
H2A	0.975(5)	0.131(2)	-0.050(3)	0.020(9)
H2B	0.969(6)	0.208(3)	-0.009(5)	0.043(13)
H3A	0.780(5)	0.176(2)	-0.201(4)	0.024(10)
H3B	0.678(4)	0.137(2)	-0.105(3)	0.018(9)
H4A	0.735(5)	0.287(2)	-0.104(4)	0.021(10)
H4B	0.576(8)	0.256(3)	-0.141(6)	0.073(19)
H5A	0.554(5)	0.223(2)	0.075(4)	0.023(11)
H5B	0.593(6)	0.3062(13)	0.053(5)	0.047(14)
H6A	0.851(5)	0.283(2)	0.133(4)	0.026(11)
H6B	0.741(5)	0.280(2)	0.243(4)	0.029(11)
H8A	0.304(6)	0.078(3)	0.176(4)	0.034(12)
H8B	0.326(4)	-0.002(2)	0.181(4)	0.011(8)
H9A	0.257(6)	0.051(2)	-0.032(4)	0.038(12)
H9B	0.419(5)	0.076(2)	-0.031(4)	0.026(11)
H10A	0.413(5)	-0.027(3)	-0.154(5)	0.041(12)
H10B	0.355(6)	-0.070(3)	-0.025(5)	0.041(13)
H11A	0.629(5)	-0.096(2)	-0.034(4)	0.026(10)
H11B	0.676(5)	-0.015(2)	-0.013(4)	0.031(11)
H12A	0.536(4)	-0.082(2)	0.182(3)	0.009(9)
H12B	0.710(5)	-0.089(2)	0.187(4)	0.014(9)
H14A	0.695(4)	-0.039(2)	0.699(3)	0.012(8)
H14B	0.691(4)	0.0409(17)	0.739(3)	0.024(10)
H15A	0.977(4)	0.0428(15)	0.763(4)	0.022(10)
H15B	0.898(6)	0.007(3)	0.872(5)	0.051(15)
H16A	1.088(6)	-0.071(3)	0.826(5)	0.043(13)
H16B	0.943(6)	-0.112(3)	0.788(5)	0.046(14)
H17A	1.092(4)	-0.127(2)	0.624(4)	0.018(9)
H17B	1.110(5)	-0.042(2)	0.601(4)	0.026(11)
H18A	0.904(4)	-0.105(2)	0.443(4)	0.018(9)
H18B	0.805(5)	-0.104(2)	0.554(4)	0.034(12)
H20A	1.328(5)	0.183(3)	0.479(5)	0.038(12)
H20B	1.350(5)	0.099(2)	0.493(4)	0.022(11)
H21A	1.254(6)	0.0976(19)	0.693(5)	0.052(16)
H21B	1.428(5)	0.129(2)	0.697(4)	0.029(11)
H22A	1.267(6)	0.209(3)	0.814(5)	0.044(13)
H22B	1.322(5)	0.247(2)	0.699(4)	0.027(11)
H23A	1.054(6)	0.270(3)	0.710(5)	0.046(14)
H23B	1.020(5)	0.194(3)	0.713(4)	0.033(12)
H24A	0.945(5)	0.270(2)	0.501(4)	0.035(12)
H24B	1.139(6)	0.260(2)	0.489(4)	0.038(12)
H25A	0.9328	-0.1094	0.0683	0.052
H25B	1.1236	-0.1132	0.1119	0.052
H25C	1.0391	-0.0387	0.0710	0.052
H25	1.094(3)	-0.077(3)	0.293(4)	0.052(15)
H31A	0.3267	0.2163	0.2190	0.073
H31B	0.2343	0.2688	0.1113	0.073
H31C	0.1613	0.2528	0.2441	0.073
H31	0.4315	0.3019	0.3120	0.09(2)
H41C	0.6037	0.4202	0.4485	0.061
H41B	0.6183	0.4813	0.5578	0.061
H41A	0.4855	0.4203	0.5580	0.061
H41	0.7022	0.3465	0.5976	0.046(14)

Bond lengths (Å) and angles (°).

Rh1-O13	2.008(3)	Rh1-N1	2.016(3)	Rh1-O7	2.017(2)
Rh1-N19	2.017(3)	Rh1-Rh2	2.4077(4)	Rh1-Cl1	2.5887(10)
Rh2-N13	1.997(3)	Rh2-N7	2.006(3)	Rh2-O19	2.010(2)
Rh2-O1	2.023(2)	Rh2-O25	2.347(3)	C1-O1	1.284(5)
C1-N1	1.312(5)	C1-C2	1.519(5)	N1-C6	1.477(5)
C2-C3	1.528(6)	C3-C4	1.515(7)	C4-C5	1.517(6)
C5-C6	1.529(6)	C7-O7	1.287(4)	C7-N7	1.316(5)
C7-C8	1.511(5)	N7-C12	1.470(5)	C8-C9	1.526(5)
C9-C10	1.517(7)	C10-C11	1.532(6)	C11-C12	1.531(6)
C13-O13	1.291(5)	C13-N13	1.318(5)	C13-C14	1.505(5)
N13-C18	1.473(5)	C14-C15	1.535(5)	C15-C16	1.522(6)
C16-C17	1.519(6)	C17-C18	1.534(6)	C19-O19	1.292(4)
C19-N19	1.311(4)	C19-C20	1.515(5)	N19-C24	1.480(5)
C20-C21	1.539(6)	C21-C22	1.525(8)	C22-C23	1.515(7)
C23-C24	1.524(6)	C25-O25	1.420(4)	C25-H25A	0.9800
C31-O31	1.397(6)	O31-H31	0.8400	C41-O41	1.423(5)
O41-H41	0.8400				
O13-Rh1-N1	175.59(12)	O13-Rh1-O7	89.63(10)	N1-Rh1-O7	88.32(11)
O13-Rh1-N19	91.16(11)	N1-Rh1-N19	90.60(12)	O7-Rh1-N19	175.72(11)
O13-Rh1-Rh2	88.40(7)	N1-Rh1-Rh2	87.66(9)	O7-Rh1-Rh2	88.95(7)
N19-Rh1-Rh2	86.86(8)	O13-Rh1-Cl1	83.84(8)	N1-Rh1-Cl1	99.91(9)
O7-Rh1-Cl1	86.27(7)	N19-Rh1-Cl1	98.00(9)	Rh2-Rh1-Cl1	170.91(3)
N13-Rh2-N7	90.78(12)	N13-Rh2-O19	89.84(11)	N7-Rh2-O19	177.06(12)
N13-Rh2-O1	176.65(12)	N7-Rh2-O1	90.44(11)	O19-Rh2-O1	88.78(10)
N13-Rh2-O25	94.57(11)	N7-Rh2-O25	97.29(11)	O19-Rh2-O25	85.52(9)
O1-Rh2-O25	88.37(9)	N13-Rh2-Rh1	88.13(9)	N7-Rh2-Rh1	87.52(9)
O19-Rh2-Rh1	89.62(7)	O1-Rh2-Rh1	88.80(7)	O25-Rh2-Rh1	174.43(7)
H41-Cl1-H31	100.7	H41-Cl1-Rh1	138.0	H31-Cl1-Rh1	115.0
O1-C1-N1	123.2(3)	O1-C1-C2	114.7(3)	N1-C1-C2	122.0(4)
C1-N1-C6	119.3(3)	C1-N1-Rh1	120.6(3)	C6-N1-Rh1	119.9(2)
C1-O1-Rh2	119.6(2)	C1-C2-C3	111.8(3)	C4-C3-C2	113.4(4)
C3-C4-C5	114.7(4)	C4-C5-C6	115.2(4)	N1-C6-C5	113.2(4)
O7-C7-N7	122.7(3)	O7-C7-C8	115.2(3)	N7-C7-C8	122.0(3)
C7-N7-C12	119.2(3)	C7-N7-Rh2	121.0(2)	C12-N7-Rh2	119.7(2)
C7-O7-Rh1	119.7(2)	C7-C8-C9	112.9(3)	C10-C9-C8	114.8(4)
C9-C10-C11	115.1(3)	C12-C11-C10	113.9(3)	N7-C12-C11	112.7(3)
O13-C13-N13	122.5(3)	O13-C13-C14	115.4(3)	N13-C13-C14	122.0(4)
C13-N13-C18	118.7(3)	C13-N13-Rh2	120.5(3)	C18-N13-Rh2	120.4(2)
C13-O13-Rh1	120.3(2)	C13-C14-C15	110.0(3)	C16-C15-C14	112.7(3)
C17-C16-C15	115.1(4)	C16-C17-C18	113.4(3)	N13-C18-C17	112.7(3)
O19-C19-N19	122.7(3)	O19-C19-C20	115.2(3)	N19-C19-C20	122.1(3)
C19-N19-C24	118.7(3)	C19-N19-Rh1	121.5(2)	C24-N19-Rh1	119.9(2)
C19-O19-Rh2	119.4(2)	C19-C20-C21	113.1(3)	C22-C21-C20	113.4(4)
C23-C22-C21	114.9(4)	C22-C23-C24	114.0(4)	N19-C24-C23	113.0(4)
C25-O25-Rh2	121.2(2)	Rh2-O25-H25	109(4)		

Hydrogen bond information.

D—H···A*	d(D—H)	d(H···A)	d(D···A)	∠(DHA)
O41—H41···Cl1	0.84	2.29	3.083(3)	158.7
O31—H31···Cl1	0.84	2.32	3.151(4)	170.1
O25—H25···O41#1	0.830(10)	1.878(17)	2.688(4)	165(5)

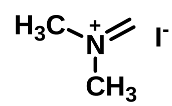
* D - donor atom, H - hydrogen, A - acceptor.
Symmetry transformation codes: #1 -x+2,y-1/2,-z+1

CHAPTER 3

THE OXIDATIVE MANNICH REACTION CATALYZED BY DIRHODIUM CAPROLACTAMATE

I. BACKGROUND AND SIGNIFICANCE

Broadly defined, the Mannich reaction is the addition of a resonance-stabilized carbon nucleophile to an imine or iminium ion.[1] This fundamentally important carbon-carbon bond forming reaction has found widespread use in organic synthesis, especially for the preparation of amine-containing compounds. In this regard, it is the electrophilic character of an iminium ion that allows it to undergo reaction with almost any nucleophile;[1(c),2] whereas, imines often require Lewis- or Brönsted acid activation.[3] Iminium ions are usually prepared in situ because of their electrophilic nature, but a few iminium salts such as **1**



1

[1] (a) Kleinman, E. D. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 2, p 893. (b) Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311. (c) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1045.

[2] For the electrophilicities of iminium ions, see: Mayr, H.; Ofial, A. R. *Tetrahedron Lett*. **1997**, *38*, 3503.

[3] For addition to imines, see: Bloch, R. *Chem. Rev*. **1998**, *98*, 1407.

(Eshenmoser's salt[4]) are stable and can be introduced directly into a reaction.

Iminium ions can be generated in situ via four methods (Figure 3.1).[1(b)] Condensation of primary or secondary amines with a non-enolizable aldehyde (e.g., formaldehyde) under acidic aqueous conditions is a classical method of accessing an iminium ion. α-Fragmentation occurs when an amine containing a proximal leaving group is treated with a Lewis acid. For example, aminals[5] (X = NR_2 or benzotriazole), N,O-acetals[6] (X = OCH_3), and α-haloamines[7] (X = halogen) readily undergo α-fragmentation in the presence of a Lewis acid.[8] Alkylation (or acylation if treated with an acid halide) provides another route for generating an iminium ion, albeit from the imine. Finally, a relatively new approach for the accessing an iminium ion is the C-H oxidation of a tertiary amine. Tertiary amines are among the most easily oxidized neutral organic substances with oxidation potentials (E^o vs SCE) ranging from +0.8 to +0.5 V.[9] The thermodynamic facility at which tertiary amines undergo oxidation has led to the development of a number methods for C-H oxidation.

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[4] Schreiber, J.; Maag, H.; Hashimoto, N.; Eschenmoser, A. E. *Angew. Chem., Int. Ed.* **1971**, *10*, 330.

[5] Katritzky, A. R.; Manju, K.; Singh, S.; Meher, N. K. *Tetrahedron* **2005**, *61*, 2555.

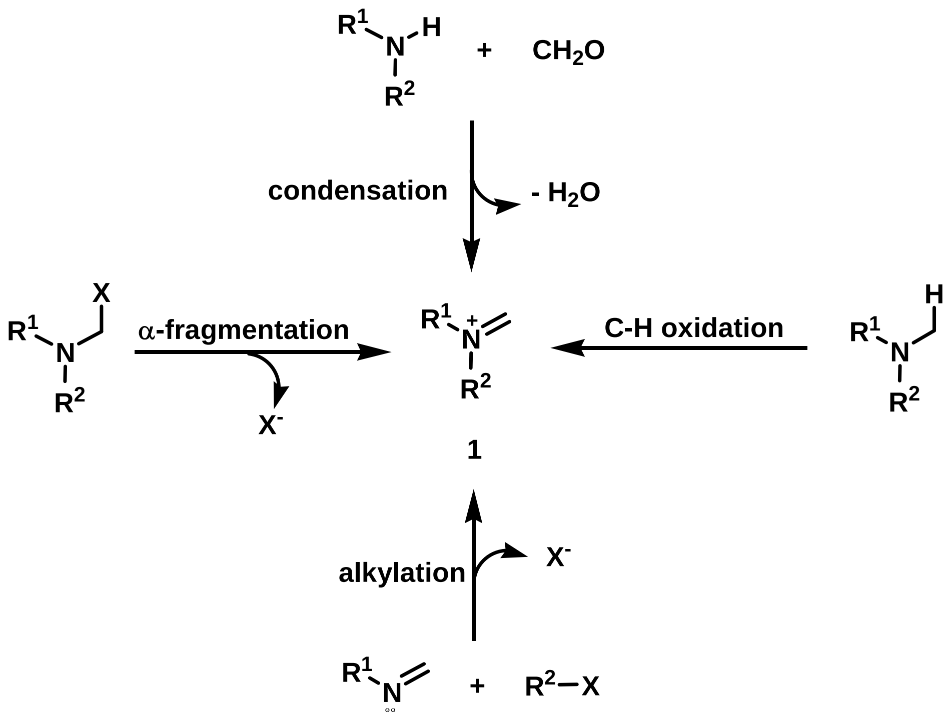
[6] Fiori, K. W.; Fleming, J. J.; Du Bois, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 4349.

[7] (a) Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*, Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991, Vol. 2, p 1047. (b) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817.

[8] Depending on the nature of the leaving group, acylation, silylation, or thermal conditions may be used to induce α-fragmentation.

[9] Sumalekshmy, S.; Gopidas, K. R. *Chem. Phys. Lett.* **2005**, *413*, 294.

Figure 3.1. Representative Methods for Iminium Ion Formation.



The Vinylogous Mannich Reaction. The vinylogous Mannich reaction refers to the addition of a vinylogous nucleophile to an imine or iminium ion.[10] Functioning as α,β-unsaturated butyrolactonic anion equivalents, 2-siloxyfurans have been particularly useful nucleophiles for the vinylogous Mannich reaction in natural product synthesis (Figure 3.2). This is attributed to the occurrence of the γ-butyrolactone moiety in approximately 10% of all natural products.[11]

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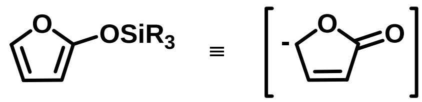
[10] For a review of 2-siloxyfurans and related analogs see: Rassu, G.; Zanardi, F.; Battistini, L.; Casiraghi, G. *Chem. Soc. Rev.* **2000**, *29*, 109.

[11] Seitz, M.; Reiser, O. *Curr. Opin. Cell. Biol.* **2005**, *9*, 285 and references therein.

Figure 3.2. 2-Siloxyfurans as Butyrolactonic Anion Equivalents.

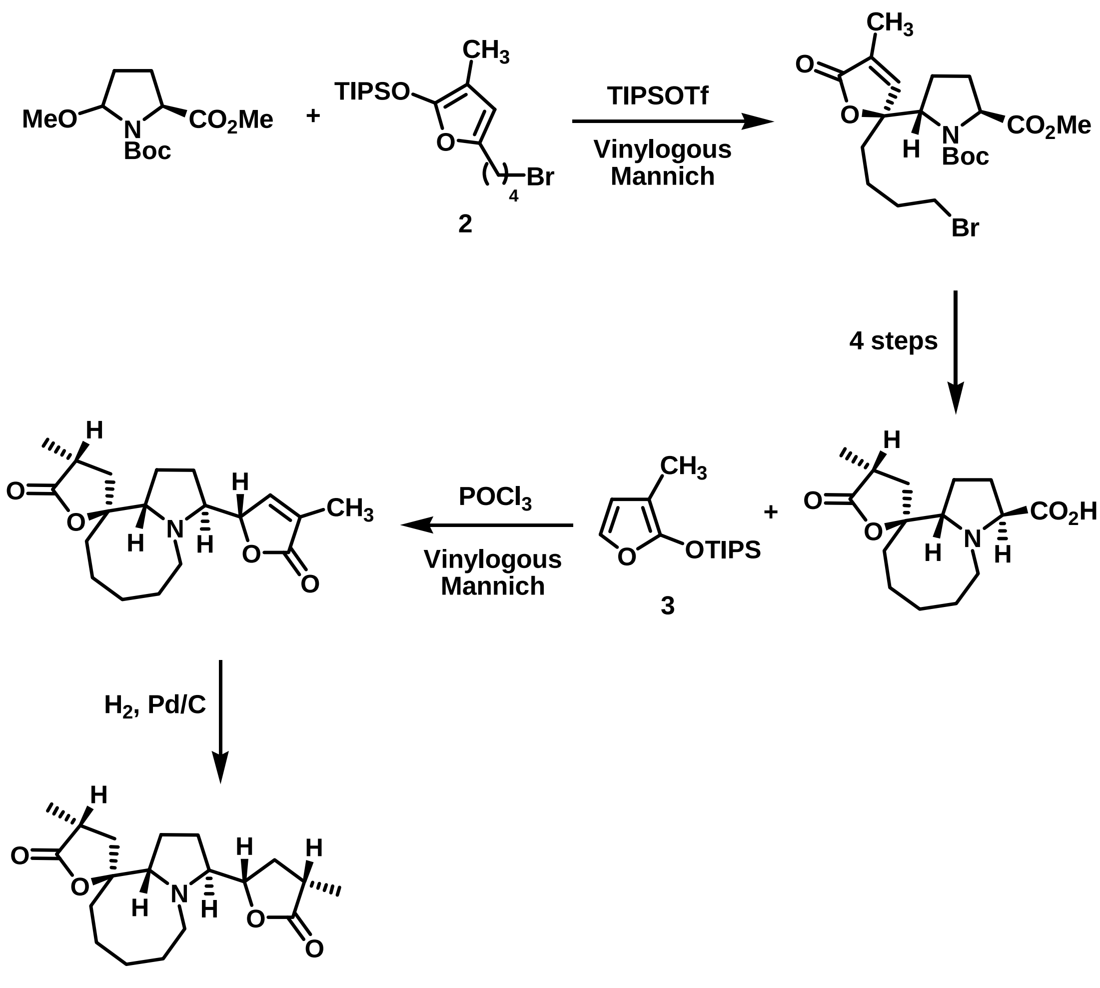


Most notably, Martin and coworkers have used the 2-siloxyfurans in the vinylogous Mannich reaction for the preparation of alkaloid natural products.[12] For example, the enantioselective synthesis of *Stemona* alkaloid (+)-croomine (**4**) was accomplished using two intermolecular vinylogous Mannich reactions with siloxyfurans **2** and **3** (Scheme 3.1).[13] Iminium ion formation in each case was generated via α-fragmentation. The total synthesis of **4** by Martin and coworkers was accomplished in only 11 steps from commercially available materials.

[12] For reviews, see: (a) Martin, S. F. *Acc. Chem. Res.* **2002**, *35*, 895. (b) Bur, S. K.; Martin, S. F. *Tetrahedron* **2001**, *57*, 3221.

[13] Martin, S. F.; Barr, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 3299.

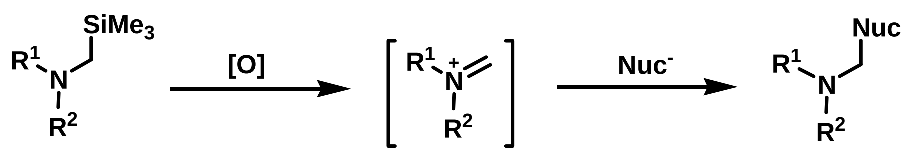
Scheme 3.1.



4: (+)-Croomine

The Oxidative Mannich Reaction. The oxidative Mannich reaction is herein defined as 1) the oxidative formation of an imine or iminium ion, and 2) its subsequent capture with a nucleophile to form a carbon-carbon bond. The term "oxidative Mannich reaction" was first coined by Mariano and coworkers in 1992 to describe the oxidation of α-trimethylsilyl-substituted tertiary amines followed by nucleophilic capture (Scheme 3.2).[14] It will be shown in this section that the oxidative Mannich reaction is broad in scope and predates the notation introduced by Mariano and coworkers.

Scheme 3.2.



The definition of the oxidative Mannich reaction (part 1, vide supra) also applies to the C-H oxidation of tertiary amines (Scheme 3.3). This route is synthetically more direct because it involves the oxidation of readily available amines containing α-C-H bonds as opposed to amines containing an α-C-$SiMe_3$ bond (vide supra).[15]

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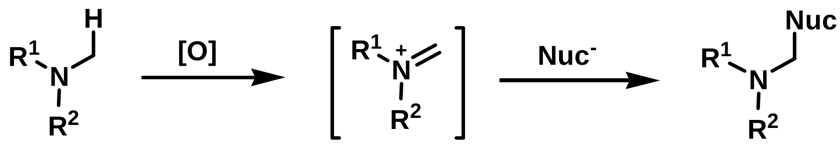
[14] For the oxidative Mannich reaction of α-trimethylsilyl tertiary amines, see: (a) Yoon, U. C.; Mariano, P. S. *Acc. Chem. Res.* **1992**, *25*, 233. (b) Zhang, X.; Jung, Y. S.; Mariano, P. S.; Fox, M. A.; Martin, P. S.; Merkert, J. *Tetrahedron Lett.* **1993**, *34*, 5239. (c) Castro, P.; Overman, L. E.; Zhang, X.; Mariano, P. S. *Tetrahedron Lett.* **1993**, *34*, 5243. (d) Khim, S.-K.; Wu, X.; Mariano, P. S. *Tetrahedron Lett.* **1996**, *37*, 571. (e) Wu, X.-D.; Khim, S.-K.; Zhang, X.; Cederstrom, E. M.; Mariano, P. S. *J. Org. Chem.* **1998**, *63*, 841. (f) Wu, X.-D.; Khim, S.-K.; Zhang, X.; Cederstrom, E. M.; Mariano, P. S. *J. Org. Chem.* **1998**, *63*, 841. (g) Kim, H.-J.; Yoon, U.-C.; Jung, Y.-S.; Park, N. S.; Cederstrom, E. M.; Mariano, P. S. *J. Org. Chem.* **1998**, *63*, 860.

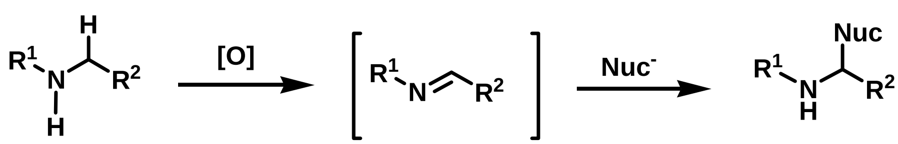
[15] For a discussion of “direct” C-H functionalization, see: Godula, K.; Sames, D. *Science*, **2006**, *312*, 67.

Scheme 3.3.



Finally, the oxidative Mannich reaction includes the oxidation of secondary amines to imines followed by capture with a nucleophile (Scheme 3.4). This type of oxidative Mannich reaction is not widely used because imines are synthetically accessible from primary amines and aldehydes/ketones. However, oxidation has been useful for imines that are derived from aliphatic aldehydes (i.e., aliphatic aldimines, where R^2 = aliphatic) that are difficult to prepare and prone to enamine isomerization.[16]

Scheme 3.4.

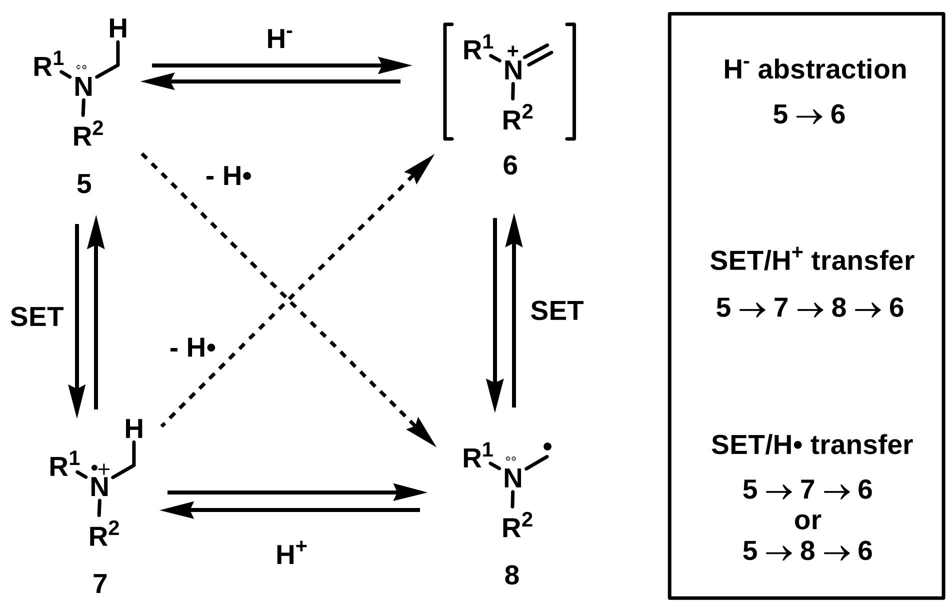


This overview will focus specifically on the oxidative Mannich reaction as it pertains to the C-H oxidation of tertiary amines to iminium ions followed by nucleophilic capture/C-C bond formation.

[16] For selected reactions, see: (a) Ibrahem, I.; Samec, J. S. M.; Bäeckvall, J. E.; Córdova, A. *Tetrahedron Lett.* **2005**, *46*, 3965. (b) Matsuo, J. I.; Tanaki, Y.; Ishibashi, H. *Org. Lett.* **2006**, *8*, 4371.

C-H Oxidation of Tertiary Amines (Mechanistic Overview). Tertiary amines undergo C-H oxidation via three mechanistically distinct pathways (Figure 3.3).[17,18] The first pathway involves hydride (H^-) abstraction (or shift) to generate an iminium ion (**5** → **6**). The second pathway involves two single electron transfer (SET) events coupled with a proton transfer (H^+), i.e., SET/H^+ transfer (**5** → **7** → **8** → **6**). The final pathway to form an iminium ion involves SET coupled with the transfer of a hydrogen atom (H·), i.e., SET/H· transfer (**5** → **7** → **6** or **5** → **8** → **6**).

Figure 3.3. Mechanistic Pathways for Tertiary Amine C-H Oxidation.



[17] For general review of electron-transfer reactions of amines, see: Das, S.; Suresh, V. In *Electron Transfer in Chemistry*; Balzani, V., Ed.; Wiley-VCH: Weinheim, 2001, p 379.

[18] For metal-catalyzed amine oxidation, see: (a) Murahashi, S.-I. *Angew. Chem., Int. Ed.* **1995**, *34*, 2443. (b) Murahashi, S.-I.; Imada, Y. In *Transition Metals for Organic Synthesis*; Beller, M.; Bolm, C., Eds; Wiley-VCH: Weinheim, 2004; Vol. 2, p 497. (c) Murahashi, S.-I.; Komiya, N. In *Modern Oxidation Methods*; Bäckvall, J.-E., Ed.; Wiley-VCH: Weinheim, 2004, p 165.

Pertinent to the following discussion, oxidative Mannich reactions will be assigned a C-H oxidation pathway.[19] The objective of this treatment is twofold: 1) to identify oxidative Mannich reactions and their respective mechanisms within the framework outlined in Figure 3.3, and 2) to demonstrate a pattern of reactivity that exists for these processes. The reader is instructed to refer to the primary references for a more thorough discussion of a particular reaction and/or mechanism.

Oxidative Mannich Reactions via Hydride Shift. Reinhoudt and coworkers in 1984 reported a series of intramolecular oxidative Mannich reactions based on 2-substituted-*N,N*-dialkylanilines.[20,21] For example, dicarbonitrile **9** was transformed into quinoline **10** in 82% yield in 2 hours in refluxing 1-butanol (Scheme 3.5). The authors proposed a thermally-induced concerted 1,5-hydrogen shift to form zwitterion **11** followed by intramolecular iminium ion capture. In support of this pathway, electron-withdrawing CN groups were required to stabilize the "negative end" of the 1,5-dipole, and a polar solvent was required to stabilize intermediate charged species in solution.

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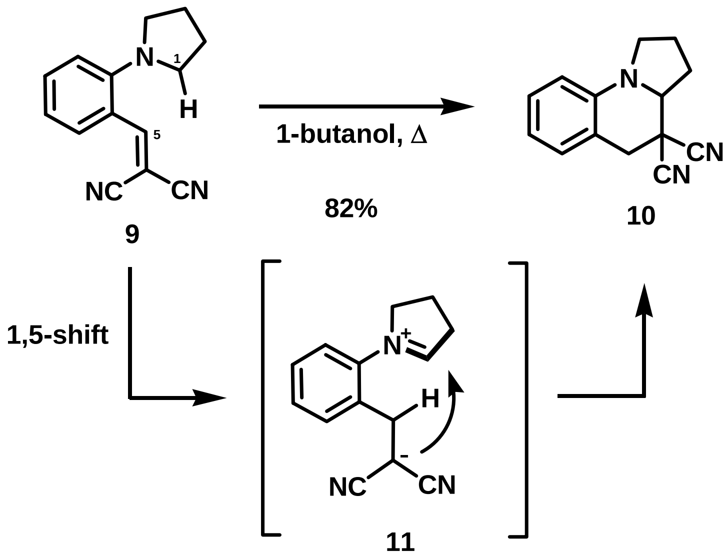
[19] In certain cases, insufficient data is available to determine the mechanistic pathway and therefore will be discussed separately.

[20] (a) Verboon, W.; Reinhoudt, D. N.; Visser, R.; Harkema, S. *J. Org. Chem.* **1984**, *49*, 269. (b) Nijhuis, W. H. N.; Verboom, W.; Reinhoudt, D. N.; Harkema, S. *J. Am. Chem. Soc.* **1987**, *109*, 3136. (c) Nijhuis, W. H. N.; Verboom, W.; Abu El-Fadl, A.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.* **1989**, *54*, 199.

[21] For the preparation of 2-substitued-*N,N*-dialkylanilines, see: Nijhuis, W. H. N.; Verboom, W.; Reinhoudt, D. N. *Synthesis* **1987**, 641

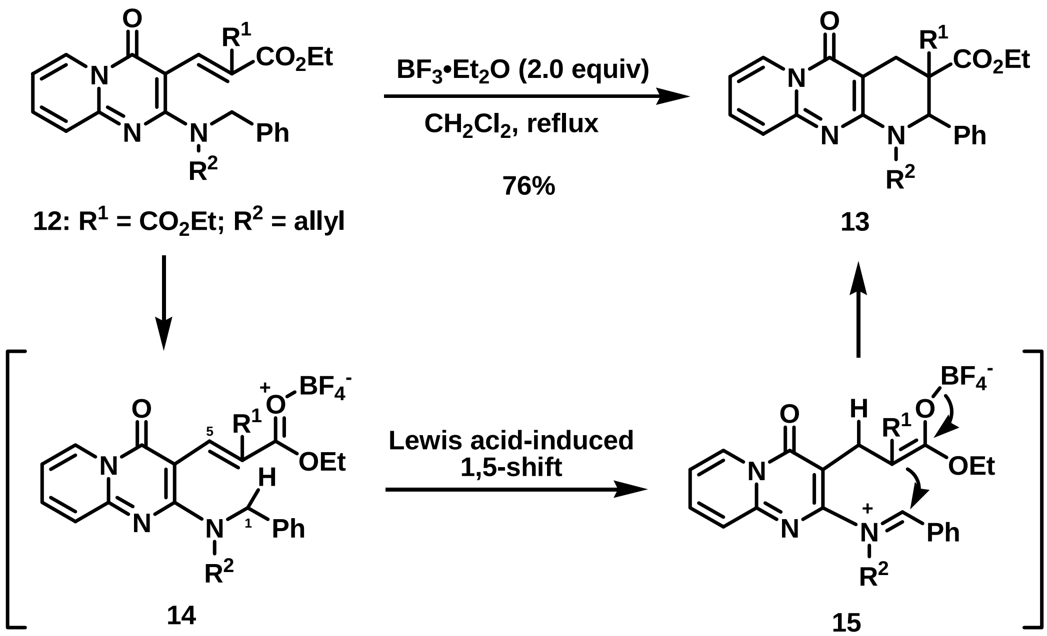
Scheme 3.5.



Noguchi and coworkers in 1998 described a Lewis acid-induced oxidative Mannich reaction.[22] Treatment of **12** with $BF_3 \cdot Et_2O$ (2.0 equiv) in refluxing CH_2Cl_2 over 24 hours gave pyrimidinone **13** in 76% yield (Scheme 3.6). Noguchi rationalized this outcome by proposing a mechanism that involved BF_3 coordination to the ester carbonyl (**14**), 1,5-hydride shift across the π-electron system to generate an iminium ion (**15**), and intramolecular capture by the pendant boron-enolate. This mechanistic hypothesis seems to be reasonable considering research precedent by Reinhoudt (vide supra).

[22] Noguchi, M.; Yamada, H.; Sunagawa, T. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3327.

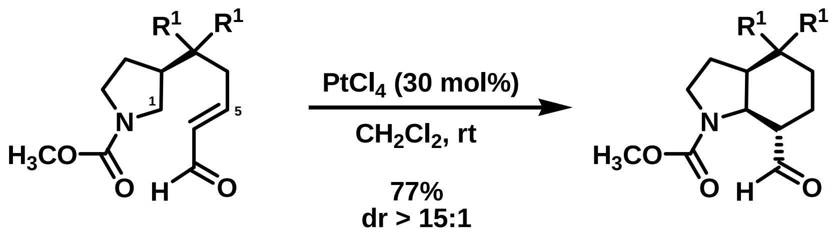
Scheme 3.6.



Sames and coworkers in 2005 reported a Lewis acid-*catalyzed* oxidative Mannich reaction (albeit one example).[23] Treatment of carbamide **16** with $PtCl_4$ (30 mol%) at room temperature for 38 hours gave bicycle **17** in 77% yield (Scheme 3.7). Sames suggested that the reaction likely proceeds via a 1,5-hydride shift. The authors point out that a 1,5-relationship between the electrophilic site and the α-amino C-H bond was an essential requirement (no reaction took place with 1,6-relationship).

[23] Pastine, S. J.; McQuaid, K. M.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 12180. For a related transformation, see: Pastine, S. J.; Sames, D. *Org. Lett.* **2005**, *7*, 5429.

Scheme 3.7.

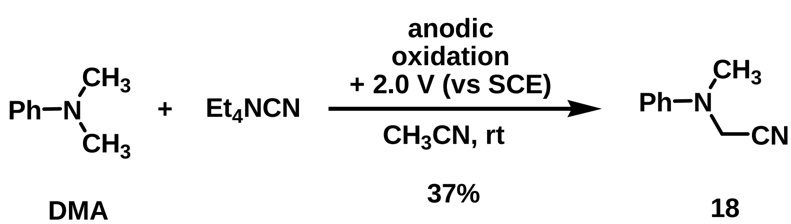


16: $R^1 = CO_2Et$

17

Oxidative Mannich Reactions via Single Electron Transfer/Proton Transfer (SET/H^+). Andreades and Zahnow in 1969 described an oxidative cyanation of tertiary amines that constitutes an oxidative Mannich reaction.[24] Electrochemical oxidation (2.0 V vs SCE) of *N*,*N*-dimethylaniline (DMA) in acetonitrile (CH_3CN) containing tetraethylammonium cyanide (Et_4NCN) gave α-aminonitrile **18** in 37% yield (Scheme 3.8).[25,26] Cyanide was chosen as a nucleophile because of its high oxidation potential relative to DMA.

Scheme 3.8.



DMA

18

[24] Andreade.S; Zahnow, E. W. *J. Am. Chem. Soc.* **1969**, *91*, 4181.

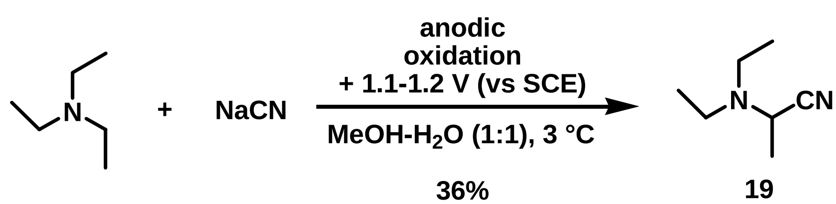
[25] For electrochemical oxidation of organic compounds see, Weinberg, N. L.; Weinberg, H. R. *Chem. Rev.* **1968**, *68*, 449.

[26] For a recent review of the synthetic application of electrochemistry in organic synthesis, see: Moeller, K. D. *Tetrahedron*, **2000**, *56*, 9527.

Electrochemical oxidation of tertiary amines has been shown to proceed via SET/H^+ transfer mechanism according the pathway outlined in Figure 3.3.[27] Thus, the SET of a tertiary amine via anodic oxidation leads to the formation of radical cation (**7**, Figure 3.3). Due to its acidity, radical cations are prone to rapid α-CH deprotonation in the presence of base (or solvent) leading to the formation of an α-aminyl radical (**8**, Figure 3.3). Das and von Sontag in 1986 using pulse radiolysis determined the p*K*a of $Me_3N^{\bullet+}$ to be approximately 8 in H_2O at 25 °C; and moreover, the transfer of H^+ from $Me_3N^{\bullet+}$ to Me_3N occurred at approximately 7×10^8 M^{-1} s^{-1}.[28] Finally, another SET from the α-aminyl radical induced from anodic oxidation gives the iminium ion.

Chiba and Takata in 1977 extended electrochemical cyanation to tertiary *aliphatic* amines.[29] For example, triethylamine was electrochemically oxidized in the presence of NaCN to give α-aminonitrile **19** in 36% yield (Scheme 3.9). Yields were uniformly poor to modest across a range of aliphatic amine substrates.

Scheme 3.9.



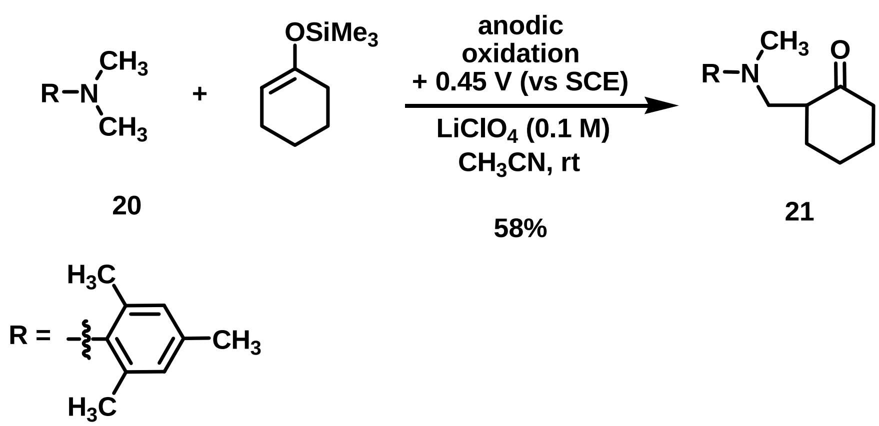
[27] For the mechanism of electrochemical oxidation of tertiary amines, see: (a) Shono, T. *Electroorganic Chemistry as a Tool in Organic Synthesis*; Springer-Verlag: Berlin, 1984. (b) Shono, T. *Top. Curr. Chem.* **1988**, *148*, 131.

[28] Das, S.; von Sonntag, C. Z. *Naturforsch.* **1986**, *416*, 505.

[29] Chiba, T.; Takata, Y. *J. Org. Chem.* **1977**, *42*, 2973.

Renaud and coworkers in 1983 described an oxidative Mannich reaction using silyl enol ethers as nucleophiles.[30] The authors noted that to avoid unwanted oxidation of the nucleophile, the reaction had to be performed using an electron-rich aniline, e.g., *N*,*N*-dimethylmesidine (**20**). Thus, under relatively mild anodic conditions (0.45 V vs SCE), **20** was oxidized in the presence of 1-trimethylsilyloxy-1-cylcohexene to give γ-aminoalkyl-cyclohexanone **21** in 58% yield (Scheme 3.10). Despite the requirement for an electron-rich amine such as **20**, a variety of silyl enol ethers were viable partners that gave Mannich addition products in poor to moderate yield (maximum 58% yield, as shown in Scheme 3.10).

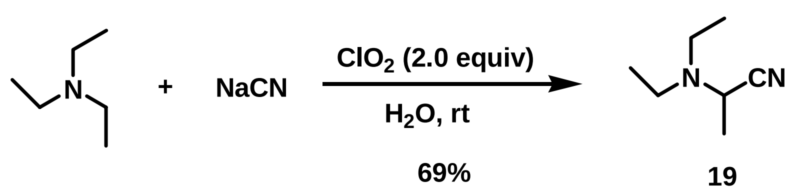
Scheme 3.10.



[30] (a) Renaud, R. N.; Berube, D.; Stephens, C. J. *Can. J. Chem.* **1983**, *61*, 1379. (b) Renaud, R. N.; Stephens, C. J.; Brochu, G. *Can. J. Chem.* **1984**, *62*, 565.

Chen and coworkers in 1988 reported a cyanation of tertiary amines using chlorine dioxide (ClO_2).[31] Triethylamine in the presence of NaCN was converted to α-aminonitrile **19** in 69% yield using ClO_2 (2.0 equiv) in H_2O buffered at pH 12 (Scheme 3.11). Mechanistically, Rosenblatt and coworkers determined that oxidation of tertiary amines with ClO_2 occurs via SET/H^+ transfer similar to electrochemical oxidation.[32] The reaction was limited to cyanide as a nucleophile; however, a short synthesis of the indolizidine alkaloid (±)-elaeocarpidine (**22**) was achieved using this methodology (Scheme 3.12).

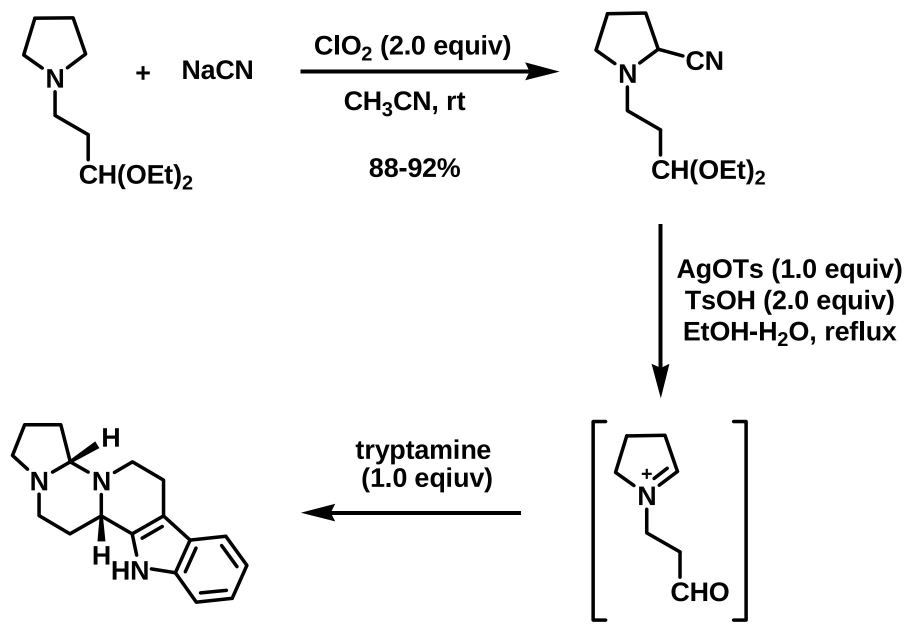
Scheme 3.11.



[31] Chen, C. K.; Hortmann, A. G.; Marzabadi, M. R. *J. Am. Chem. Soc.* **1988**, *110*, 4829.

[32] Hull, L. A.; Davis, G. T.; Rosenblatt, D. H. *J. Am. Chem. Soc.* **1969**, *91*, 6247.

Scheme 3.12.



22: (±)-elaeocarpidine

Yoshida, Suga, and coworkers in 1999 devised an oxidative Mannich reaction that involved the formation of a so-called "cation-pool" using electrochemical oxidation. (Scheme 3.13).[33,34] "Cation-pool" was used to describe the electrochemical formation of iminium ions at low temperature (-78 °C) in a non-polar solvent (CH_2Cl_2) in the absence of a trapping species. Once the cation-pool was generated, the nucleophile was introduced without being oxidized. Several nucleophiles underwent reaction including vinyl

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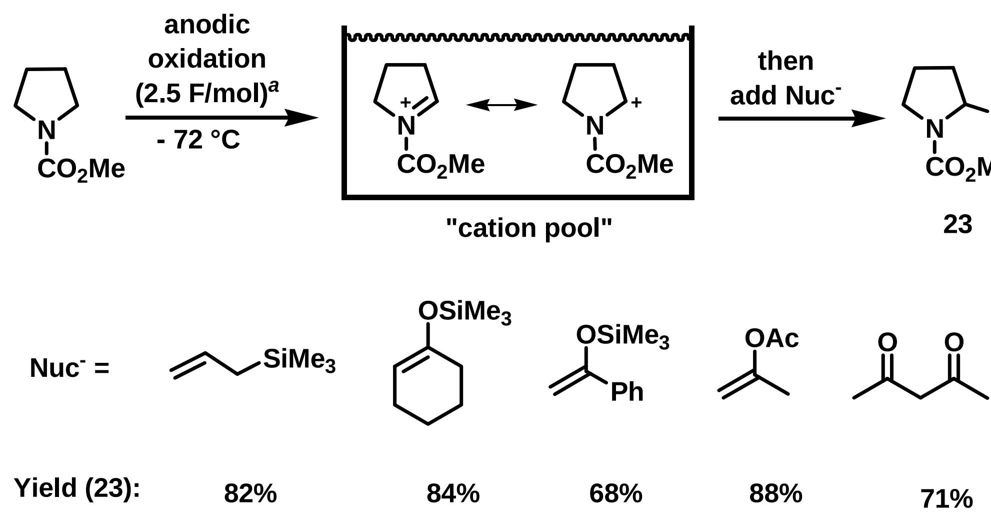
[33] (a) Yoshida, J.-I.; Suga, S.; Suzuki, S.; Kinomura, N.; Yamamoto, A.; Fujiwara, K. *J. Am. Chem. Soc.* **1999**, *121*, 9546. (b) Suga, S.; Okajima, M.; Fujiwara, K.; Yoshida, J.-I. *J. Am. Chem. Soc.* **2001**, *123*, 7941. For a review on the "cation-pool" method, see: Yoshida, J.-I.; Suga, S. *Chem. Eur. J.* **2002**, *8*, 2650.

[34] In Scheme 3.13., 2.5 F/mol = 2.5 moles of electrons per mole of substrate

silanes, silyl enol ethers, electron-rich arenes, and activated methylene compounds.[35]

Scheme 3.13.



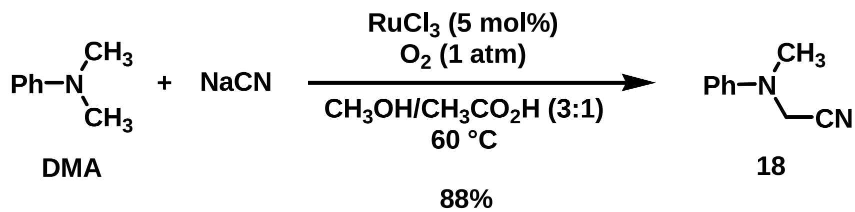
Oxidative Mannich Reactions via Single Electron Transfer/ Hydrogen Atom Transfer (SET/H·). Murahashi and coworkers in 2003 reported an aerobic oxidative Mannich reaction catalyzed by $RuCl_3$ in which tertiary arylamines were converted to α-aminonitriles.[36] For example, DMA was converted into **18** in 88% yield using $RuCl_3$ (5 mol%) and 1 atmosphere of O_2 after 2 hours (Scheme 3.14). The reaction was limited to the use of cyanide as a nucleophile; however, the authors demonstrated that the

[35] Grignard reagents were viable nucleophiles for this process, see: Suga, S.; Okajima, M.; Yoshida, J.-I. *Tetrahedron Lett.* **2001**, *42*, 2173.

[36] Murahashi, S.; Komiya, N.; Terai, H.; Nakae, T. *J. Am. Chem. Soc.* **2003**, *125*, 15312.

α-aminonitrile products could be reduced with $LiAlH_4$ to give more useful vicinal diamines.[37]

Scheme 3.14.



Murahashi proposed a mechanism whereby SET/H· transfer from the amine to ruthenium generates an iminium ion (Figure 3.4). A relative rate study of *para*-substituted *N,N*-dimethylanilines correlated well with the Hammett linear free-energy relationship. A ρ value of -3.35 was obtained which indicates that formation of a cationic intermediate is in the rate-determining step. The intramolecular deuterium isotope effect of *N*-methyl-*N*-(trideuteriomethyl) aniline was found to be 2.4 which indicates that SET likely occurs prior to H· abstraction. SET followed by H· abstraction was further implicated by the chemoselective cyanation of *N*-ethyl-*N*-methylaniline (**24**) under the reaction conditions giving predominately CN capture at the methyl position (Scheme 3.15). Finally, oxygen uptake measurements showed that 1 mmol of oxygen was consumed for every 2 mmol of DMA.

[37] The reduction of **18** with $LiAlH_4$ gave *N*-methyl-*N*-phenylglycine in 87% yield.

Scheme 3.15.

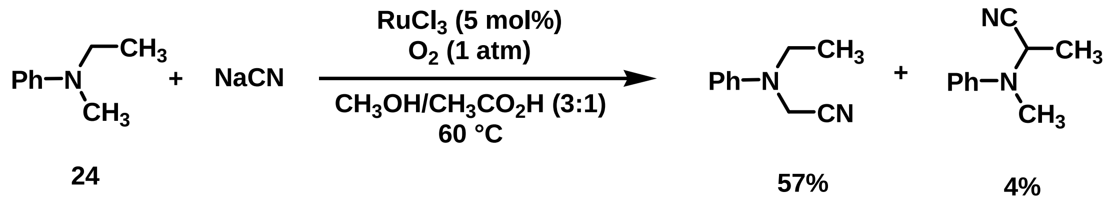
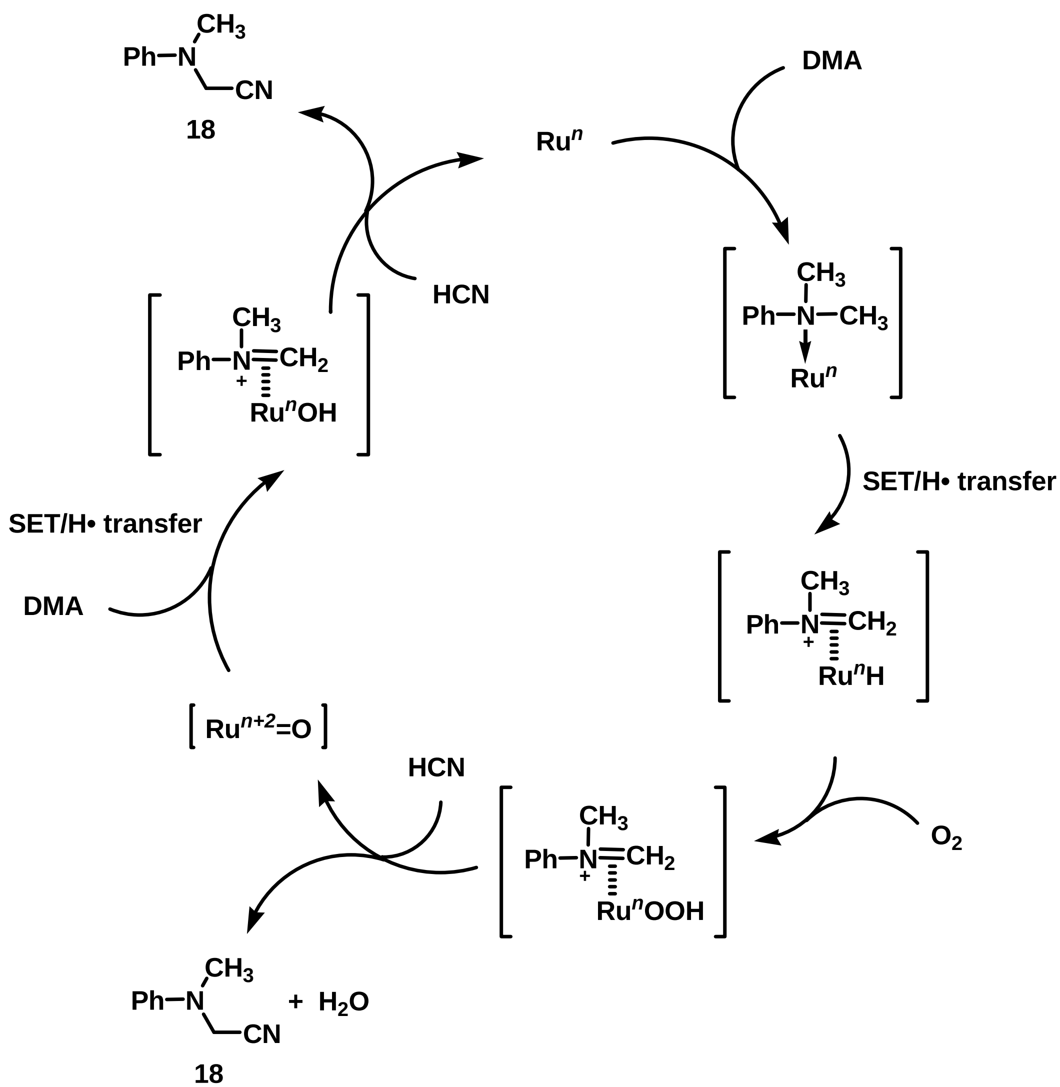
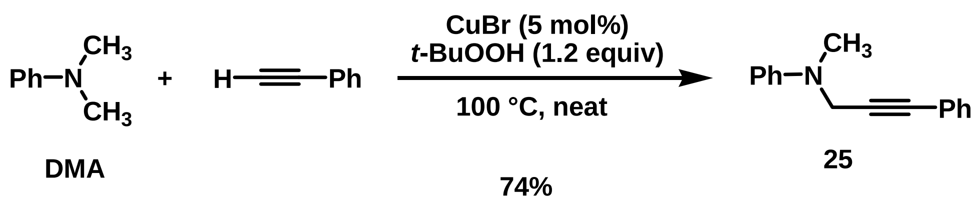


Figure 3.4. Mechanistic Proposal for Oxidative Cyanation.



Li and Li in 2004 described a CuBr-catalyzed alkynylation of tertiary amines.[38] For example, the reaction of DMA and phenylacetylene in presence of CuBr (5 mol%) and *t*-BuOOH (1.0 – 1.2 equiv) neat at 100 °C gave **25** in 74% yield after 3 hours (Scheme 3.16). The reaction was applied to a series of substituted dimethylanilines and aryl acetylenes.

Scheme 3.16.

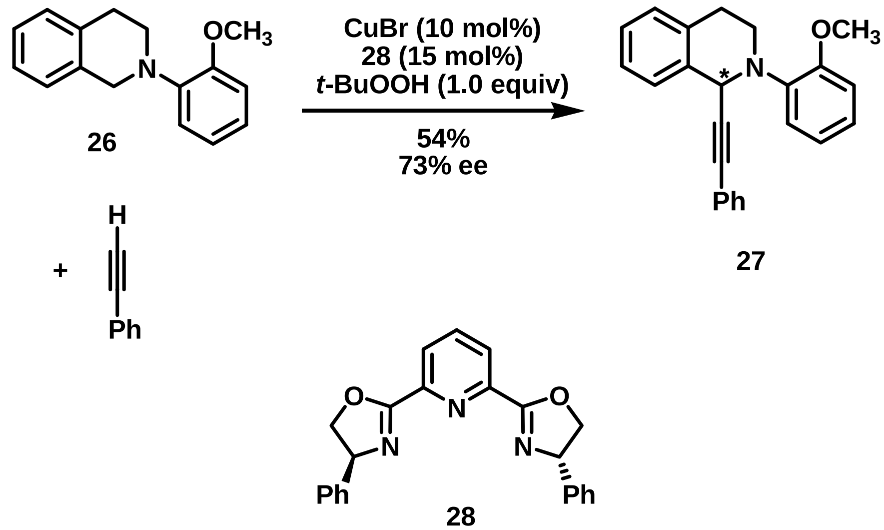


Shortly thereafter, the reaction was rendered enantioselective using a Cu(I)-pybox catalyst (Scheme 3.17).[39] Using CuBr (10 mol%) in conjuction with chiral pybox ligand **28** (15 mol%), modest yields and enantioselectivity were observed for the alkynylation of *N*-aryltetrahydroisoquinoline **26** (best result shown in Scheme 3.17). This reaction was the first report (and only report to date) of a catalytic asymmetric oxidative Mannich reaction.

[38] Li, Z. P.; Li, C. J. *J. Am. Chem. Soc.* **2004**, *126*, 11810.

[39] (a) Li, Z.; Li, C.-J. *Org. Lett.* **2004**, *6*, 4997. (b) Li, Z.; MacLeod, P. D.; Li, C.-J. *Tetrahedron: Asymmetry* **2006**, *17*, 590.

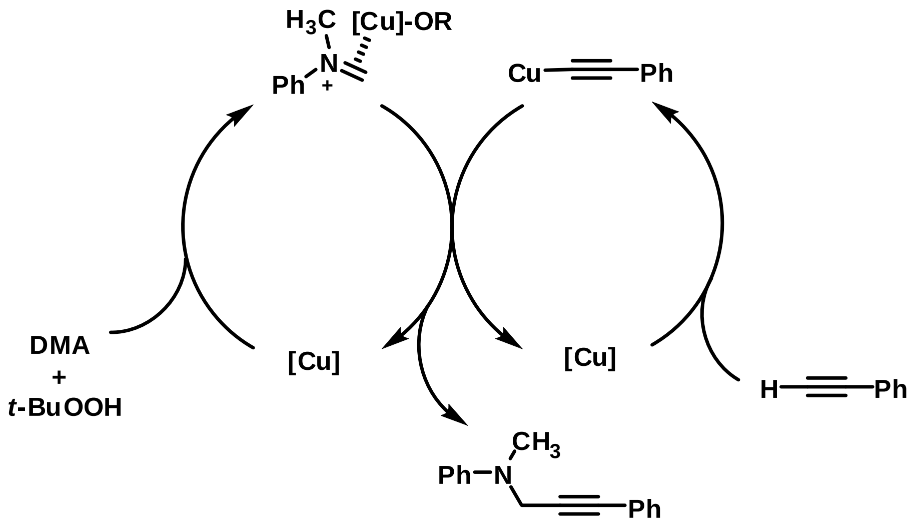
Scheme 3.17.



Li proposed a dual-catalytic cycle for tertiary amine alkynlation whereby the copper salt was responsible for amine oxidation (in combination with *t*-BuOOH) and acetylene activation (Figure 3.5). Unfortunately, the mechanistic proposal outlined in Figure 3.5 only addresses C-C bond formation and falls short of addressing C-H oxidation. Although not discussed by the authors, C-H oxidation probably occurs via SET/H· transfer.[40]

[40] In the presence *t*-BuOOH, it has been shown that Cu(I) is oxidized to Cu(II) with concomitant generation of *tert*-butoxy radicals (*t*-BuO·). It has also been shown that Cu(II) is capable of SET in the presence of DMA, while tBuO· is capable of hydrogen atom abstraction, see: (a) Kochi, J. K. *Tetrahedron* **1962**, *18*, 483. (b) Sumalekshmy, S.; Gopidas, K.R.; *Chem. Phy. Lett.* **2005**, *413*, 294.

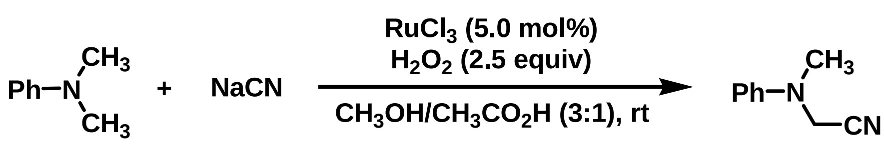
Figure 3.5. Mechanistic Proposal for Copper-Catalyzed Alkynlation.[38]



25

Murahashi and coworkers in 2005 described another oxidative cyanation of tertiary amines using 30% aqueous hydrogen peroxide (H_2O_2) as an oxidant (Scheme 3.18).[41] The authors proposed that C-H oxidation proceeds via SET/H· transfer (Figure 3.6) in a similar fashion to their previously described aerobic cynanation.

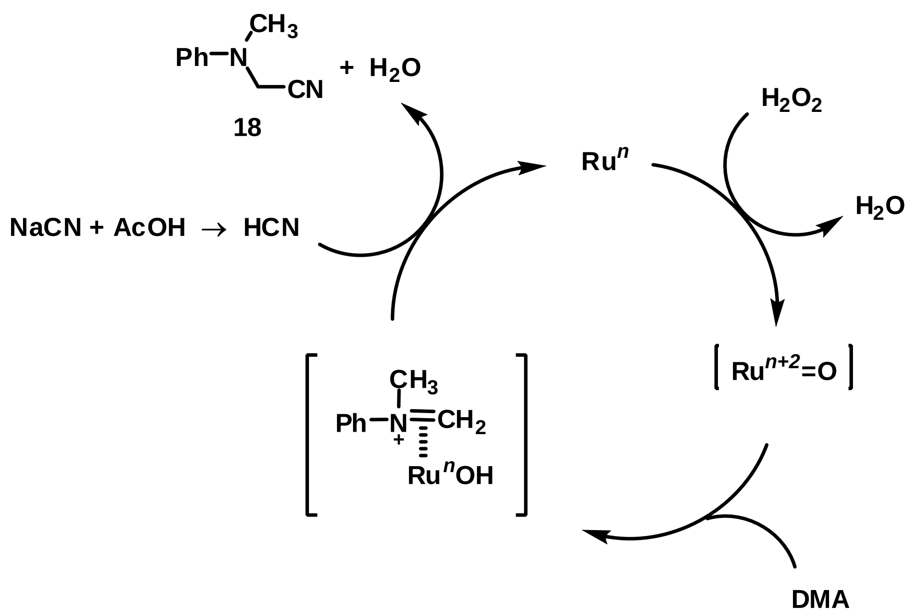
Scheme 3.18.



DMA 80% 18

[41] Murahashi, S.-I.; Komiya, N.; Terai, H. *Angew. Chem. Int. Ed.* **2005**, *44*, 6931.

Figure 3.6. Ruthenium-Catalyzed Oxidative Cyanation with H_2O_2.



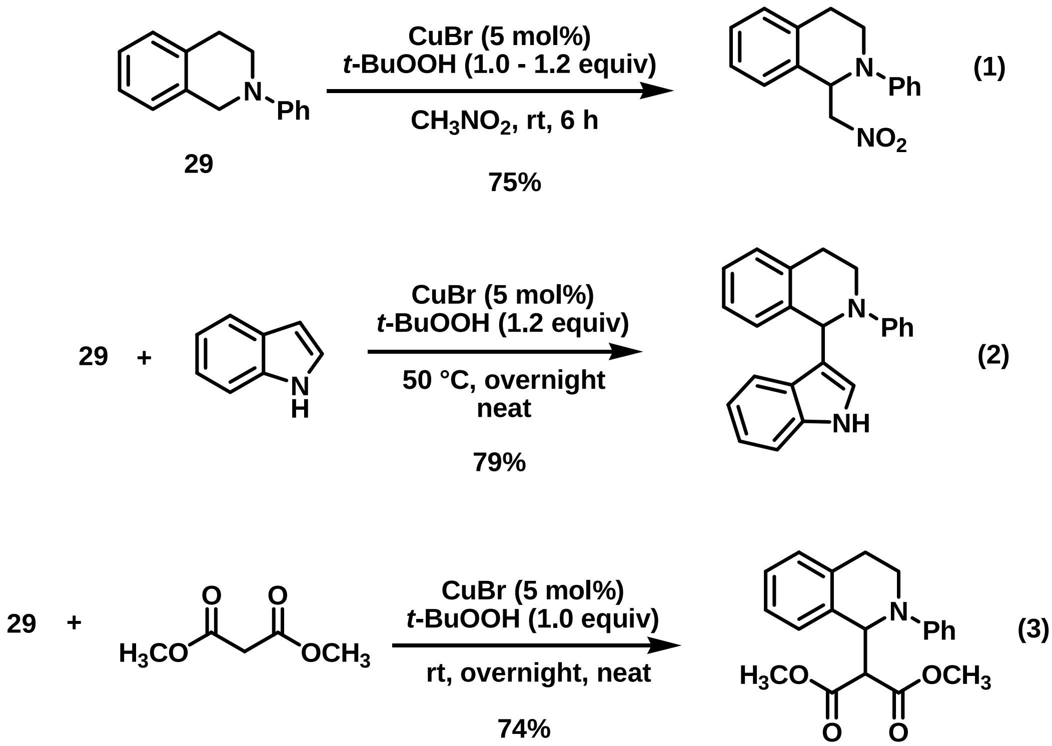
Li in 2005 described a series oxidative Mannich reactions catalyzed by CuBr and stoichiometric *t*-BuOOH (Scheme 3.19). The authors referred to the reactions as "cross-dehydrogenative-couplings" because two different (crossed) C-H bonds were transformed into a C-C bond; however, the reaction simply constitutes an oxidative Mannich reaction. Thus, *N*-phenyltetrahydroisoquinoline **29** was coupled with nitromethane (Scheme 3.19, eq 1),[42] indole (Scheme 3.19, eq 2),[43] and dimethylmalonate (Scheme 3.19, eq 3).[44] The drawback to these methodologies is that the tertiary amine substrate is largely restricted to *N*-phenyltetrahydroisoquinolines (a severe diminution in yield was observed using *N,N*-dimethylaniline as a substrate).

[42] Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 3672.

[43] Li, Z. P.; Li, C. J. *J. Am. Chem. Soc.* **2005**, *127*, 6968.

[44] Li, Z. P.; Li, C. J. *Eur. J. Org. Chem*. **2005**, 3173.

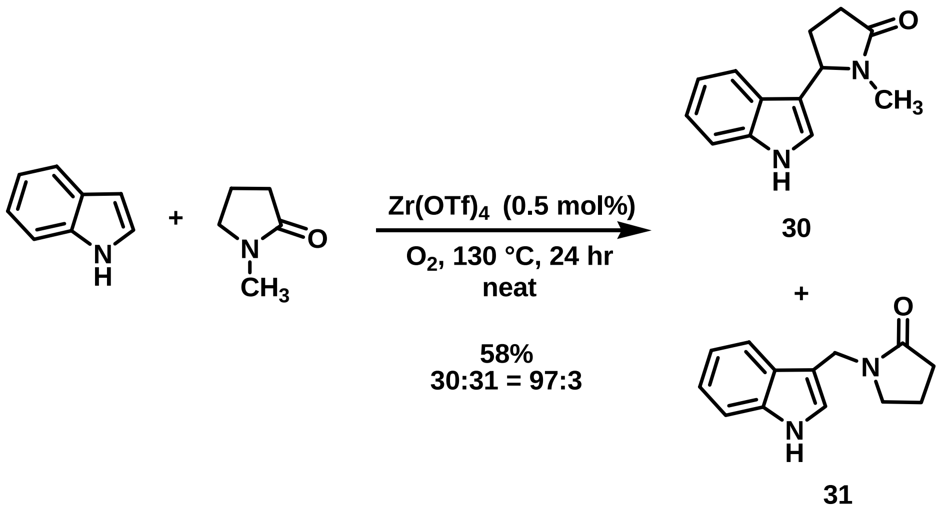
Scheme 3.19.



Oxidative Mannich Reactions (Unknown Mechanism). Tsuchimoto and coworkers in 2004 described a zirconium catalyzed aerobic oxidation of lactams with heterocyclic arenes.[45] *N*-Methylpyrolidinone (NMP) in the presence of indole was treated with $Zr(OTf)_4$ (0.5 mol%) under an O_2 atmosphere to give **30** and **31** in 58% overall yield (Scheme 3.20). Mechanistic studies were not undertaken, however, the authors proposed that an *N*-acyliminium ion was generated in situ followed by capture with indole.

[45] Tsuchimoto, T.; Ozawa, Y.; Negoro, R.; Shirakawa, E.; Kawakami, Y. *Angew. Chem., Int. Ed.* **2004**, *43*, 4231.

Scheme 3.20.

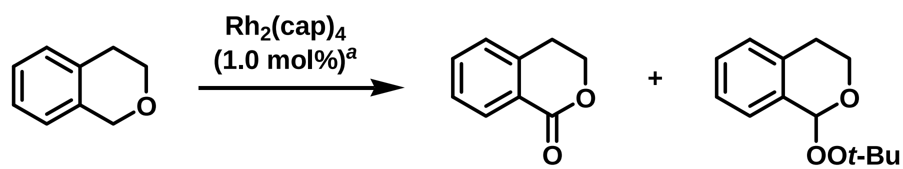


Summary. The C-H oxidation of a tertiary amine to an iminium ion occurs either by H^- abstraction (or shift), SET/H^+ transfer, or SET/H· transfer. When these processes are coupled with nucleophilic capture, the net outcome is an oxidative Mannich reaction. Reported examples where H^- abstraction is operative typically involve substrates that can undergo intramolecular 1,5-hydrogen shift. The oxidative Mannich reaction where C-H oxidation proceeds via SET/H^+ transfer has been localized to the realm of electrochemistry. Oxidative Mannich reactions that proceed via SET/H· transfer are relatively new and are typically catalyzed by a redox active metal in conjunction with a stoichiometric oxidant such as O_2, *t*-BuOOH, or H_2O_2.

II. RESULTS AND DISCUSSION[46]

Initial Results. During the course of investigating benzylic oxidation catalyzed by $Rh_2(cap)_4$, isochroman (**32**) was oxidized predominantly to isochomanone (**33**) and mixed peroxide **34** in 93% conversion using five stoichiometric equivalents of *t*-BuOOH (Scheme 3.21).[47] Changing the amount of *t*-BuOOH from five equivalents to two equivalents increased the amount of mixed peroxide **34** relative to isochomanone (**33**) (vide infra).

Scheme 3.21.



32 **33** **34**

t-BuOOH (equiv)	33:34[b]
5.0	86:14
2.0	60:40

[a]Conditions: $Rh_2(cap)_4$ (1.0 mol%), $NaHCO_3$ (0.50 equiv), *t*-BuOOH, CH_2Cl_2, rt, 16 h; [b]Determined by ^1H NMR.

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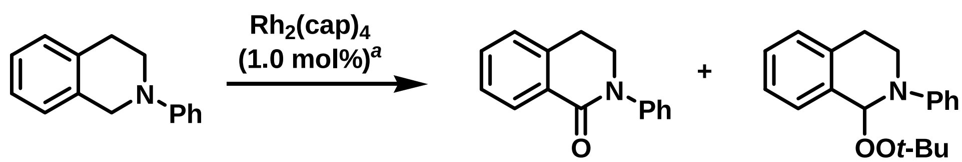
[46] For the disclosure of this work, see: Catino, A. J.; Nichols, J. M.; Nettles, B. J.; Doyle, M. P. *J. Am. Chem. Soc.* **2006**, *128*, 5648.

[47] Catino, A. J.; Nichols, J. M.; Choi, H.; Gottipamula, S.; Doyle, M. P. *Org. Lett.* **2005**, *7*, 5167.

A more dramatic product distribution was observed for the oxidation of 1,2,3,4-tetrahydroisoquinoline (**29**) in the presence of *t*-BuOOH using catalytic $Rh_2(cap)_4$ (Scheme 3.22). When five equivalents of *t*-BuOOH were used, known amide **35**[48] was obtained (>95% conv.) as determined by ^1H NMR analysis. However, when two equivalents of *t*-BuOOH were used, the known mixed peroxide **36**[49] was obtained as the exclusive product in >95% conversion.

Scheme 3.22.



29 **35** **36**

t-BuOOH (equiv)	35:36[b]
5.0	>95:5
2.0	<5:95

[a]Conditions: $Rh_2(cap)_4$ (1.0 mol%), $NaHCO_3$ (0.50 equiv), *t*-BuOOH, CH_2Cl_2, rt, 16 h; [b]Determined by ^1H NMR.

Mixed peroxides have been observed as intermediates en route to carbonyl-containing products in catalytic hydrocarbon oxidations.[50] However,

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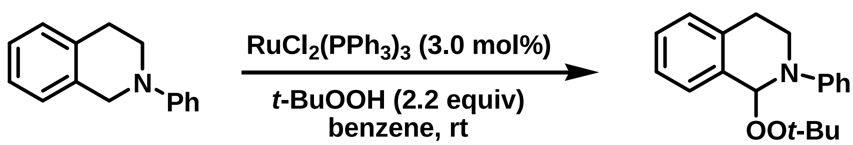
[48] Cheng, C.-Y.; Tsai, H.-B.; Lin, M.-S. *J. Heterocycl. Chem.* **1995**, *32*, 73.

[49] Murahashi, S.; Naota, T.; Yonemura, K. *J. Am. Chem. Soc.* **1988**, *110*, 8256.

[50] See Chapter 1 for a discussion.

little is known about metal-catalyzed α-CH peroxidation of ethers and tertiary amines. Murahashi and coworkers in 1988 reported a metal-catalyzed peroxidation of tertiary amines using *t*-BuOOH. The oxidation of **29** using catalytic $RuCl_2(PPh_3)_3$ (3.0 mol%) and anhydrous *t*-BuOOH (2.2 equiv, dropwise addition, 3 hours) gave mixed peroxide **37** in 65% yield (Scheme 3.23). Murahashi proposed that peroxidation of **29** proceeds via a metal-catalyzed C-H oxidation via SET/H· transfer to give an iminium ion followed by capture with *t*-BuOOH.

Scheme 3.23.



29

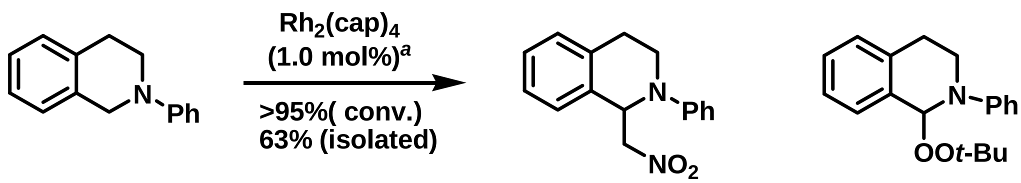
65%

37

The oxidation of **29** catalyzed by $Rh_2(cap)_4$ was conducted in nitromethane (CH_3NO_2) as solvent (Scheme 3.24). The enolization of nitromethane and its subsequent reaction with an imine or iminium ion is referred to as a nitro-Mannich reaction.[51] The reactivity/nucleophilicity of nitromethane is derived from the strong electron withdrawing capability of the nitro group which allows it to undergo facile deprotonation ($CH_3NO_3 \rightarrow {}^{-}CH_2NO_2$, pKa ≈ 10) and subsequent electrophilic trapping (${}^{-}CH_2NO_2 + E^+ \rightarrow E\text{-}CH_2NO_2$). Toward this end, the oxidation of **29** using two equivalents of *t*-BuOOH in nitromethane gave exclusively **38** in 63% isolated yield.

[51] For a discussion of the nitro-Mannich reaction, see: Westermann, B. *Angew. Chem., Int. Ed.* **2003**, *42*, 151.

Scheme 3.24.



29 **38** **37**
not observed

[a]Conditions: $Rh_2(cap)_4$ (1.0 mol%), $NaHCO_3$ (0.50 equiv), anh. *t*-BuOOH, CH_3NO_2, rt, 3 h

Both $Rh_2(cap)_4$ catalyzed peroxidation (Scheme 3.22) and nitromethane capture (Scheme 3.24) of **29** support the intermediacy of an *N*-aryliminium ion generated in situ from C-H oxidation. Unfortunately, products **37** and **38** are notably unstable to storage, silica gel purification, and have limited synthetic utility. At this juncture, 2-siloxyfurans were considered as nucleophiles.

2-Siloxyfurans. 2-Trimethylsiloxyfuran (**40**) was first reported by Takei and coworkers in 1977 (Figure 3.7).[52] The preparation of 2-siloxyfurans containing bulkier silyl groups was later reported. Both 2-*tert*-butyldimethylsiloxyfuran (**41**) and 2-triisopropylsiloxyfuran (**42**) are stable to silica purification and storage in a refrigerator for several months.

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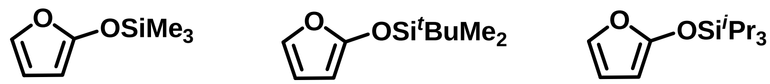
[52] Asaoka, M.; Miyake, K.; Takei, H. *Chem. Lett*. **1977**, 167.

Figure 3.7. Various 2-Siloxyfurans.



40 **41** **42**

The preparation of 2-siloxyfuran **41** and **42** is outlined in Scheme 3.25. Baeyer-Villager oxidation of furfural (**43**) according to the procedure of Nasman using a refluxing solution of performic acid (generated in situ) gave 2-furanone **44** in 54% yield after distillation.[53] Treatment of **44** with a slight molar excess of triethylamine (Et_3N) followed by TBSOTf gave **41** in 70% yield.[54] Similarly, treatment of **44** with Et_3N and TIPSOTf gave **42** in 95% yield.[55]

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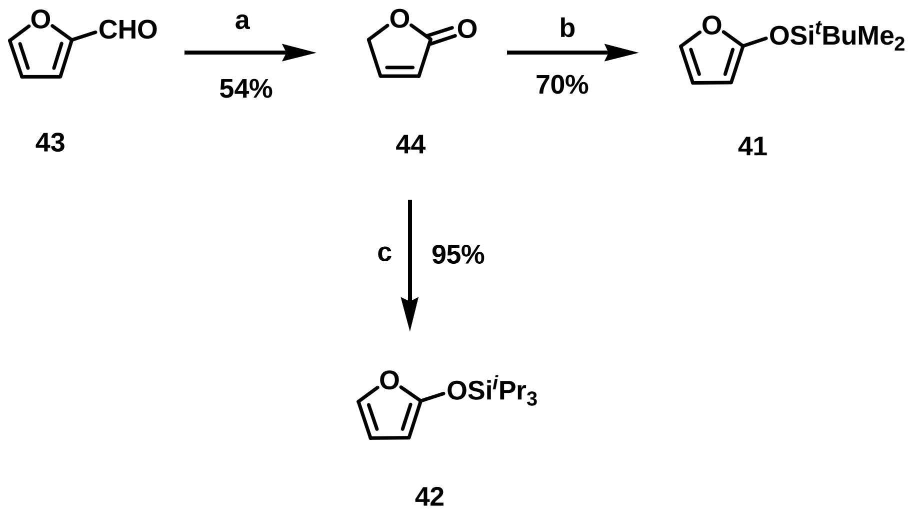
[53] (a) Naesman, J. A. H.; Pensar, K. G. *Synthesis* **1985**, 786. (b) Nasman, J. H. *Org. Synth.* **1990**, *68*, 162.

[54] Rassu, G.; Zanardi, F.; Battistini, L.; Gaetani, E.; Casiraghi, G. *J. Med. Chem.* **1997**, *40*, 168.

[55] Martin, S. F.; Bur, S. K. *Tetrahedron* **1999**, *55*, 8905.

Scheme 3.25.



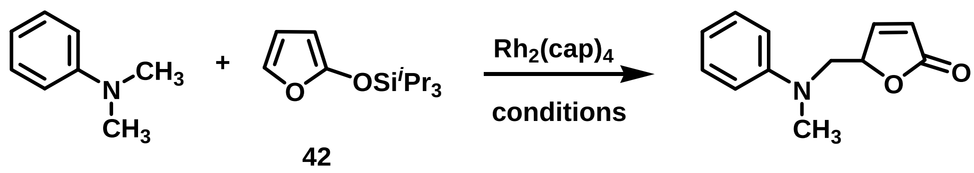
a) H_2O_2, K_2CO_3, CH_2Cl_2, Na_2SO_4, reflux; b) TBSOTf, Et_3N, CH_2Cl_2 rt; c) TIPSOTf, Et_3N, rt

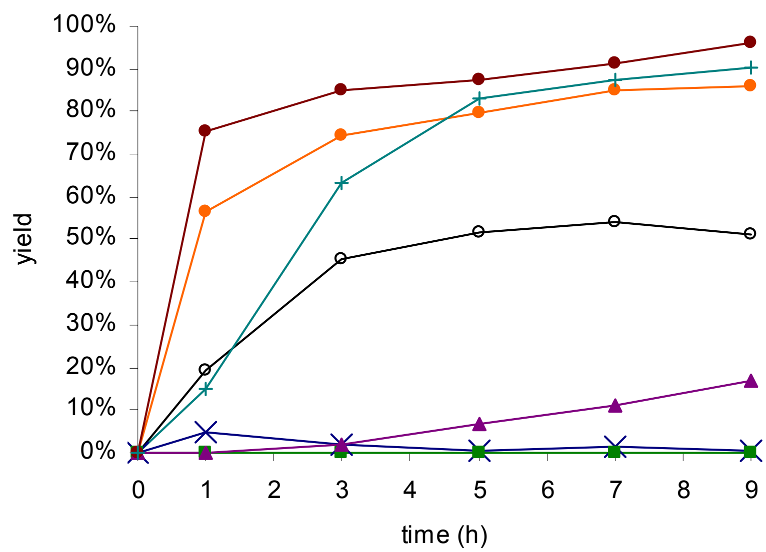
Development of the Oxidative Mannich Catalyzed by $Rh_2(cap)_4$. Although **40** and **41** are competent nucleophiles, 2-triisopropylsiloxyfuran (**42**) was chosen for initial studies due to its stability toward protodesilylation. *N*,*N*-Dimethylaniline (DMA), T-HYDRO (70% *t*-BuOOH in H_2O), and catalytic $Rh_2(cap)_4$ were chosen for the C-H oxidation component of the reaction. Biphenyl was used as an internal standard (^{1}H NMR analysis) to measure product yield as a function of time.

A summary of conditions used to develop the oxidative Mannich reaction catalyzed by $Rh_2(cap)_4$ is described in Table 3.1. Using conditions previously developed for benzylic oxidation (e.g., using $NaHCO_3$ as an additive in CH_2Cl_2) gave only trace amounts of Mannich product **45** (entry 1, Table 3.1). Mindful of iminium ion stabilization, the reaction was conducted in methanol as a solvent. Interestingly, no Mannich reaction was observed in the presence of base additive (entry 2, Table 3.1); however, removal of $NaHCO_3$ from the reaction mixture yielded Mannich product **45** in 17% yield (entry 3, Table 3.1). Heating the solution to 60 °C dramatically increased the yield of **45** to 86% (entry 4, Table 3.1). Ethanol was also suitable for the oxidative Mannich reaction but gave moderate yield of **45** (entry 5, Table 3.1).[56] Finally if was found that modifying the stoichiometry of the reaction (i.e., using a 2-fold excess of DMA relative to **42**) gave the highest yield of **45** (entry **6**, Table 3.1). Under these conditions, the reaction could be performed using only 0.1 mol% catalyst loading (entry 7, Table 3.1).

[56] EtOH is a solvent of choice for green chemistry, see: Taber, G. P.; Pfisterer, D. M.; Colberg, J. C. *Org. Process Res. Dev.* **2004**, *8*, 385.

Table 3.1. Development of the Oxidative Mannich Reaction.



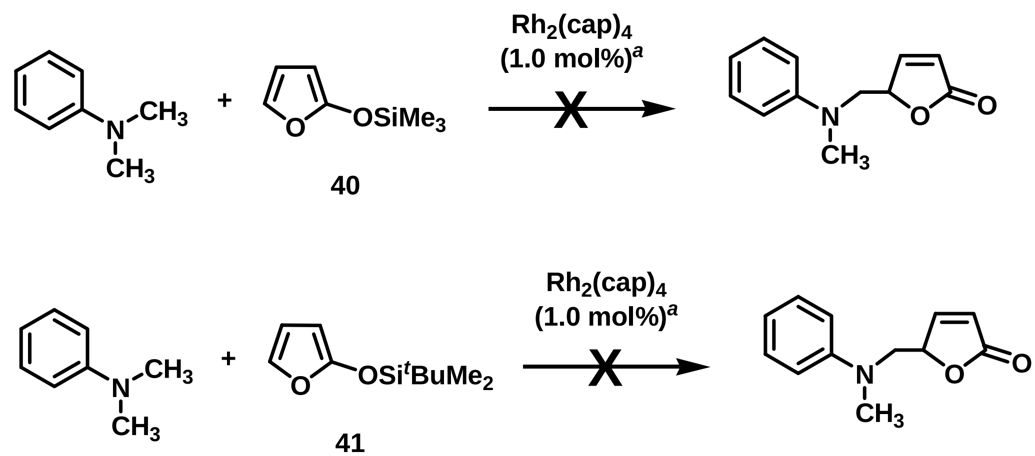


entry	key	conditions[a]	yield[b]
1		$Rh_2(cap)_4$ (1.0 mol%), CH_2Cl_2, $NaHCO_3$ (50 mol%), rt	nr
2		$Rh_2(cap)_4$ (1.0 mol%), MeOH, $NaHCO_3$ (50 mol%), rt	nr
3		$Rh_2(cap)_4$ (1.0 mol%), MeOH, rt	17
4		$Rh_2(cap)_4$ (1.0 mol%), MeOH, 60 °C	86
5		$Rh_2(cap)_4$ (1.0 mol%), EtOH, 60 °C	51
6		$Rh_2(cap)_4$ (1.0 mol%), DMA (2.0 equiv), **42** (1.0 equiv), MeOH, 60 °C	96 (95)[c]
7		$Rh_2(cap)_4$ (0.1 mol%), DMA (2.0 equiv), **42** (1.0 equiv), MeOH, 60 °C	90 (78)[c]

[a]Reactions were performed using DMA (1.0 equiv), **42** (1.5 equiv), T-HYDRO® (1.2 equiv), and solvent (0.27 M/[substrate]) unless otherwise noted. [b]Yield was determined by ^1H NMR using biphenyl as an internal standard. [c]Isolated yield of the analytically pure compound after chromatography (SiO_2).

Replacing **42** with siloxyfurans **40** and **41** gave no Mannich product **45** (Scheme 3.26). Both **40** and **41** underwent protodesilylation under the reaction conditions.

Scheme 3.26.



[a]Conditions: $Rh_2(cap)_4$ (1.0 mol%), amine (2.0 equiv), 2-siloxyfuran (1.0 equiv), T-HYDRO (1.2 equiv), MeOH, 60 °C, 3 h.

Substrate Scope. Several *N*,*N*-dimethylanilines are commercially available; however, those that are not commercially available were readily prepared via reductive amination according to Kim and coworkers.[57] This protocol was applied to the preparation *N*,*N*-dimethyl-3,4-dimethylaniline (**46**) and *N*,*N*-dimethyl-3,4-methylenedioxyaniline (**47**) (Scheme 3.27).

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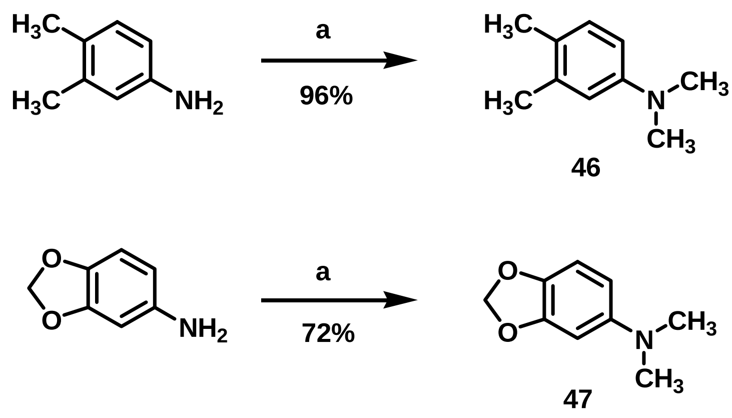
[57] Kim, S.; Oh, C. H.; Ko, J. S.; Ahn, K. H.; Kim, Y. J. *J. Org. Chem*. **1985**, *50*, 1927.

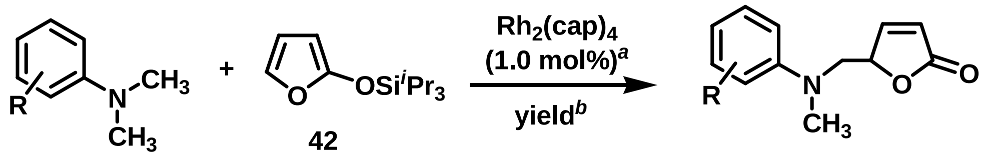
Scheme 3.27.

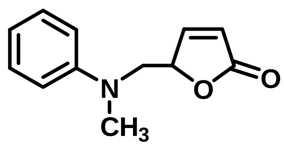


a) CH_2O (37% aqueous), $NaCNBH_3$, $ZnCl_2$, MeOH, rt

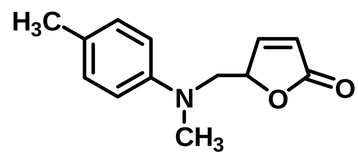
The oxidative Mannich reaction was extended to variety of substituted *N*,*N*-dimethylanilines (Table 3.2). Substrates containing both electron-withdrawing and electron-donating groups underwent reactions to give the corresponding γ-aminoalkyl-butenolides. *N*,*N*-Dimethyl-3,4-methylenedioxy-aniline (**47**) was converted to Mannich product **52** in 45% yield under the reaction conditions; however, the yield was improved to 57% by running the reaction for only 1 hour (product **52** itself may not be oxidatively stable). Isolation of the analytically pure material involved evaporation of the MeOH followed by silica gel chromatography.

Table 3.2. Oxidative Mannich Reaction of Substituted *N*,*N*-Dimethylanilines Catalyzed by 1.0 mol% of $Rh_2(cap)_4$.

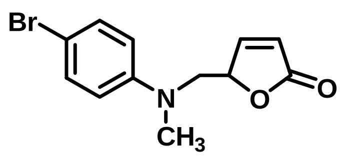




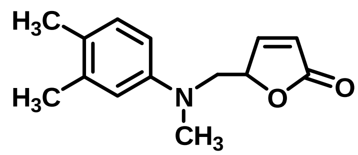
45, 95%



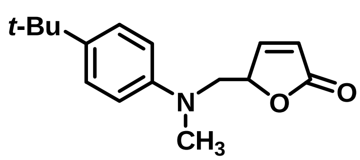
48, 76%



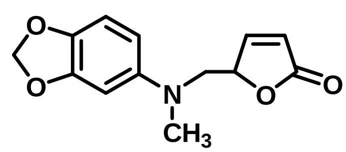
49, 78%



50, 78%



51, 89%

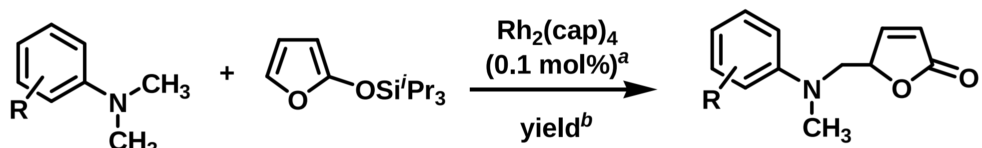


52, 45%[c]

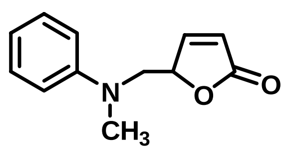
[a]Conditions: $Rh_2(cap)_4$ (1.0 mol%), amine (2.0 equiv), 2-siloxyfuran (1.0 equiv), T-HYDRO (1.2 equiv), MeOH, 60 °C, 3-5 h. [b]Isolated yield after chromatography (SiO_2). [c]57% yield was obtained when the reaction was stopped after 1 h.

The oxidative Mannich reaction was performed with 0.1 mol% catalyst loading using four different amine substrates (Table 3.3). Longer reaction times (16 hours) were required for product formation.

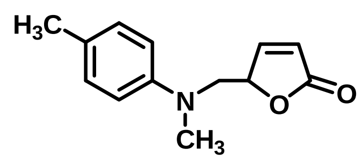
Table 3.3. Oxidative Mannich Reaction of Substituted *N*,*N*-Dimethylanilines Catalyzed by 0.1 mol% of $Rh_2(cap)_4$.



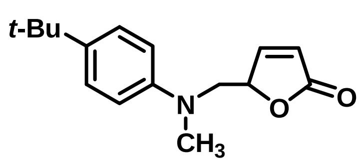
42



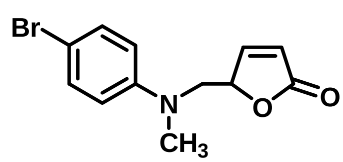
45, 78%



48, 79%



51, 84%

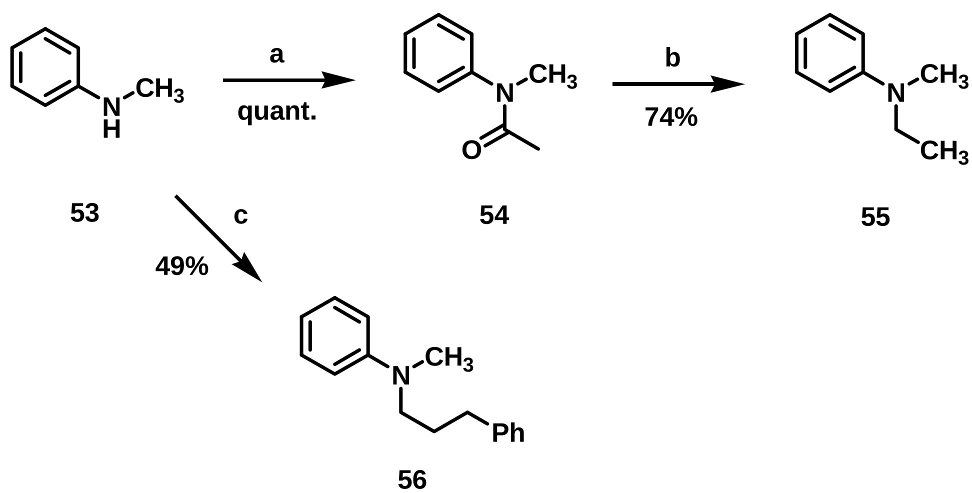


49, 66%

[a]Conditions: $Rh_2(cap)_4$ (0.1 mol%), amine (2.0 equiv), 2-siloxyfuran (1.0 equiv), T-HYDRO (1.2 equiv), MeOH, 60 °C, 16 h. [b]Isolated yield after chromatography (SiO_2).

Unsymmetrical *N*-alkyl-*N*-methylaniles were also examined. *N*-Methylaniline (**53**) was acylated with acetyl chloride and then reduced with $NaBH_4/I_2$ to give *N*-ethyl-*N*-methylaniline (**55**) (Scheme 3.28).[58] *N*-Methyl-*N*-3-phenylpropylaniline (**56**) was prepared via reductive amination using $NaCNBH_3/ZnCl_2$ according to the procedure of Kim.

Scheme 3.28.



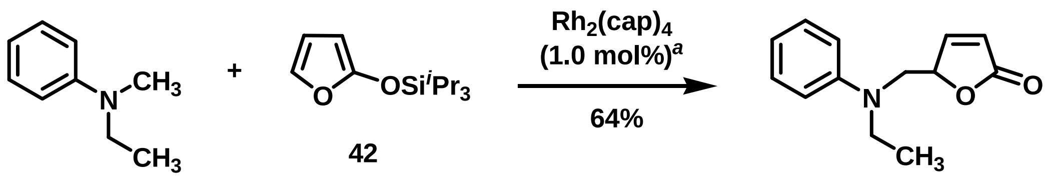
a) CH_3COCl, $NaHCO_3$, EtOAc, H_2O, 0 °C; b) $NaBH_4$, I_2, THF, reflux; c) $Ph(CH_2)_3CHO$, $NaBH_3CN$, $ZnCl_2$, rt

The oxidative Mannich reaction of *N*-ethyl-*N*-methylaniline (**55**) gave Mannich adduct **57** in 64% yield; while *N*-methyl-*N*-3-phenylpropylaniline (**56**) gave adduct **58** in 53% yield (Scheme 3.29). Regioisomeric addition-products

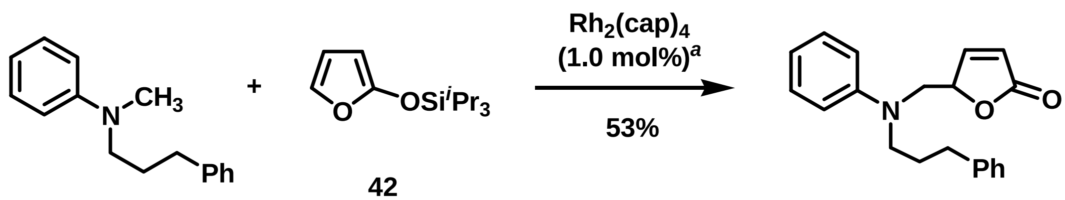
[58] Prasad, A. S. B.; Kanth, J. V. B.; Periasamy, M. *Tetrahedron* **1992**, *48*, 4623.

arising from 2-siloxyfuran attack at the α-methylene position were not observed by ^{1}H NMR.[59]

Scheme 3.29.



55 42 57



56 42 58

[a]Conditions: $Rh_2(cap)_4$ (1.0 mol%), amine (2.0 equiv), 2-siloxyfuran (1.0 equiv), , T-HYDRO (1.2 equiv), MeOH, 60 °C, 3-5 h.

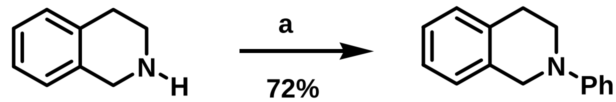
The oxidative Mannich reaction was also amendable to *N*-phenyl-pyrrolidine (**59**) and *N*-phenyl-1,2,3,4-tetrahydroisoquinoline (**29**). Tetrahydroisoquinoline **29** was prepared from **60** in 72% yield using a copper-catalyzed cross coupling procedure developed by Quach and Batey.[60]

---

[59] Similar selectivity was observed for ruthenium catalyzed cyanation and periodation of unsymmetrical amines, see: Ref. 36, 41, and 49.

[60] Quach, T. D.; Batey, R. A. *Org. Lett.* **2003**, *5*, 4397.

Scheme 3.30.

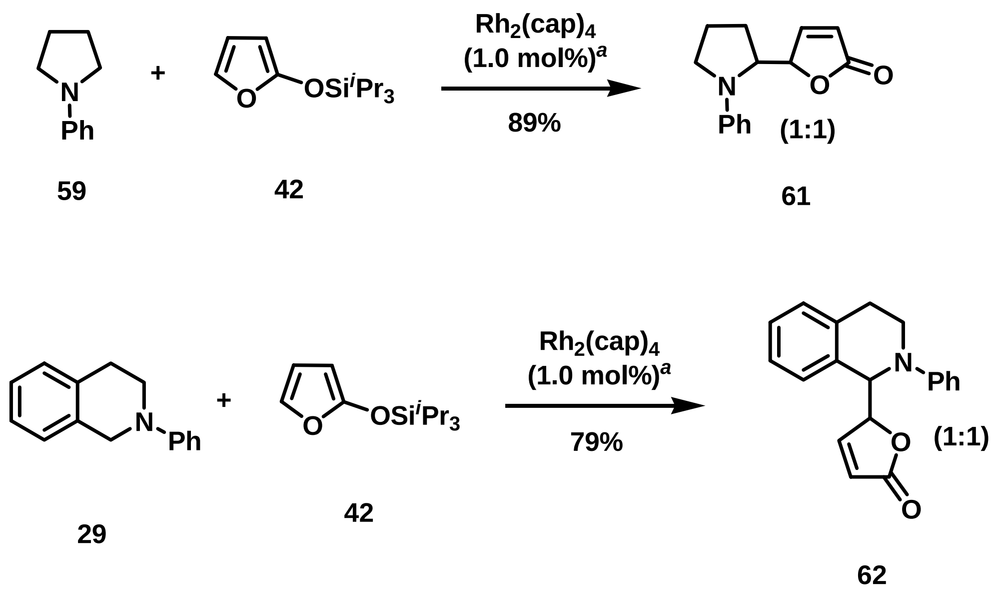


60 **29**

a) $Cu(OAc)_2{\cdot}H_2O$ (10 mol%), $PhB(OH)_2$, 4 Å MS, O_2, rt

The oxidative Mannich reaction of **59** gave **61** in 89% yield as a 1:1 mixture of inseparable diastereomeric butenolides as determined by ^{1}H NMR analysis (Scheme 3.31). The oxidative Mannich reaction of **29** gave **62** in 79% yield and was also a 1:1 diastereomeric mixture of butenolides.

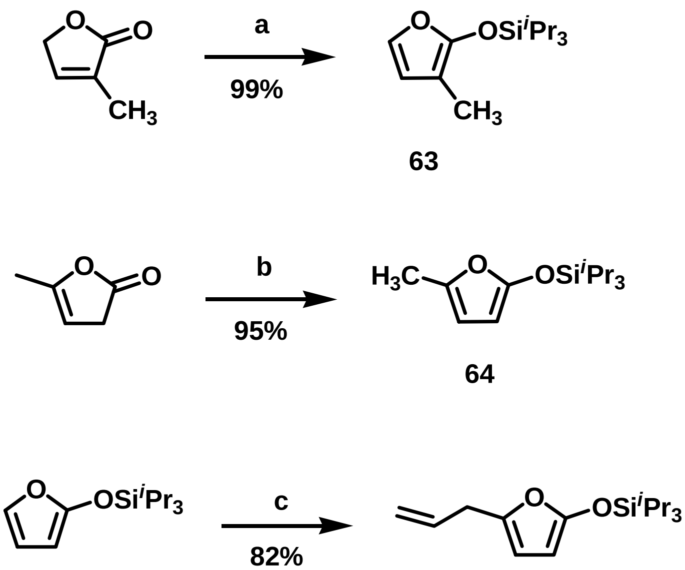
Scheme 3.31.



[a]Conditions: $Rh_2(cap)_4$ (1.0 mol%), amine (2.0 equiv), 2-siloxyfuran (1.0 equiv), T-HYDRO (1.2 equiv), MeOH, 60 °C, 3-5 h. [b]Isolated yield after chromatography (SiO_2).

Siloxyfuran Scope. Substituted 2-siloxyfurans were prepared from readily available precursors (Scheme 3.32). Both 3-methyl- and 5-methyl-2-triisopropylsiloxyfuran (**63** and **64**, respectively) were prepared by standard treatment with Et_3N and TIPSOTf according to the procedure of Martin.[55,61] Lithiation of siloxyfuran **42**, followed by quenching with allyl bromide gave 5-allyl-2-siloxyfuran **65** in 82% yield.[62] The oxidative Mannich reaction using substituted siloxyfurans **63-65** proceeded in good yield under the reaction conditions (Table 3.4).

Scheme 3.32.



a) TIPSOTf, Et_3N, CH_2Cl_2, rt, b) TIPSOTf, Et_3N, CH_2Cl_2, rt, c) *n*-BuLi, TMEDA, heptane, -78 °C

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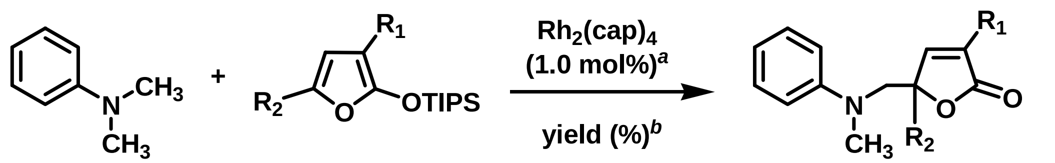
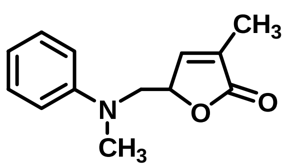
[61] Rosso, G. B.; Pilli, R. A. *Tetrahedron Lett.* **2006**, *47*, 185.

[62] Siloxyfuran **65** was first reported by Liras and coworkers for the synthesis of (±)-securinine, see: Liras, S.; Davoren, J. E.; Bordner, J. *Org. Lett.* **2001**, *3*, 703.

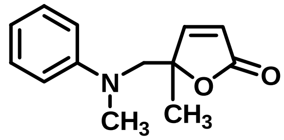
Table 3.4. Oxidative Mannich Reaction of Substituted N,N-Dimethylanilines Catalyzed by 1.0 mol% $Rh_2(cap)_4$.



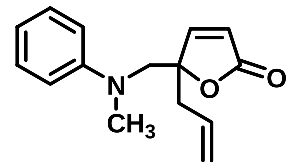
18 **63-63**



66, 86%



67, 72%



68, 75%

[a]Conditions: $Rh_2(cap)_4$ (1.0 mol%), amine (2.0 equiv), 2-siloxyfuran (1.0 equiv), T-HYDRO (1.2 equiv), MeOH, 60 °C, 3-5 h. [b]Isolated yield after chromatography.

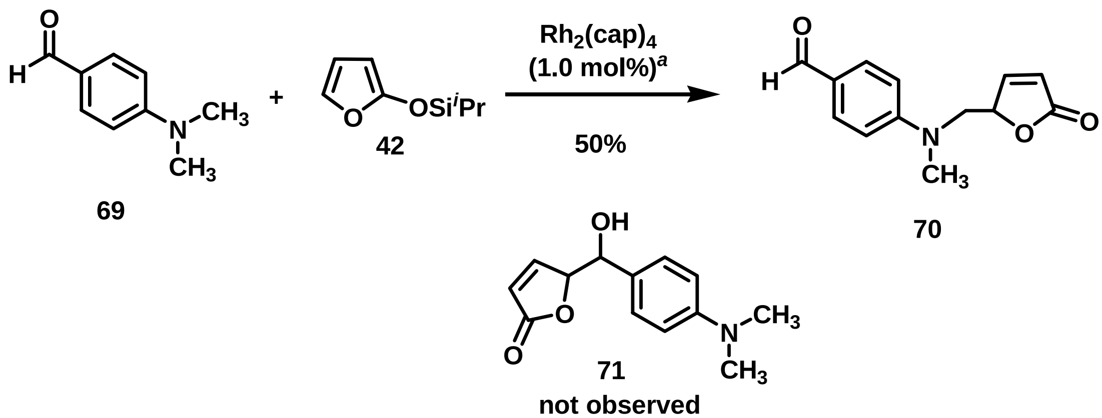
Additional Studies. In the presence of certain Lewis acids, nucleophilic 2-siloxyfurans undergo addition to aldehydes (i.e., the vinylogous Aldol reaction).[63] Dirhodium carboxamides have been shown to be viable Lewis acids.[64] With this in mind, 4-*N*,*N*-dimethylaminobenzaldehyde (**69**) was considered (Scheme 3.33). Under the reaction conditions, Mannich product **70** was obtained in 50% yield and the vinylogous aldol adduct **71** was not

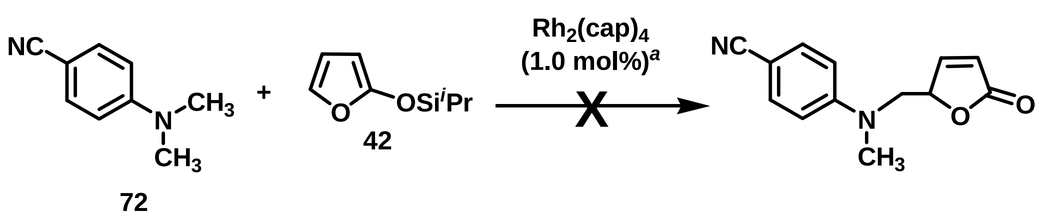
[63] For a review of the vinylogous aldol reaction, see: Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929.

[64] (a) Doyle, M. P.; Phillips, I. M.; Hu, W. H. *J. Am. Chem. Soc.* **2001**, 123, 5366. (b) Anada, M.; Washio, T.; Shimada, N.; Kitagaki, S.; Nakajima, M.; Shiro, M.; Hashimoto, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 2665. (c) Doyle, M. P.; Valenzuela, M.; Huang, P. L. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, 101, 5391.

observed. The low yield in this reaction was likely due to the electron withdrawing nature of the **69**. Indeed, the electron-deficient 4-cyano-*N,N*-dimethylaniline (**72**) failed to give any detectable oxidative Mannich product under the reaction conditions.

Scheme 3.33.



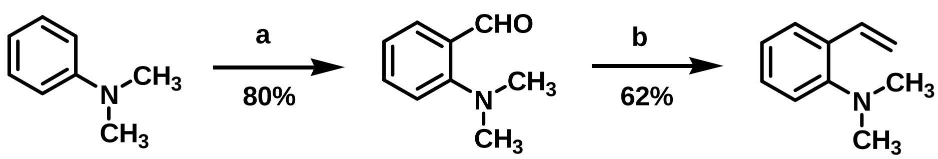


[a]Conditions: $Rh_2(cap)_4$ (1.0 mol%), amine (2.0 equiv), 2-siloxyfuran (1.0 equiv), T-HYDRO (1.2 equiv), MeOH, 60 °C, 3-5 h. [b]Isolated yield after chromatography.

Iminium ions have enjoyed a long history as intermediates in cyclization reactions.[1(b)] With this in mind, *o*-dimethylaminostyrene **74** was prepared (Scheme 3.34). Ortho-lithiation of DMA by treatment with *n*-BuLi in

TMEDA as the solvent gave benzaldehyde **73** in 80% yield.[65] Wittig olefination of **73** gave styrene **74** in 62% yield.

Scheme 3.34.



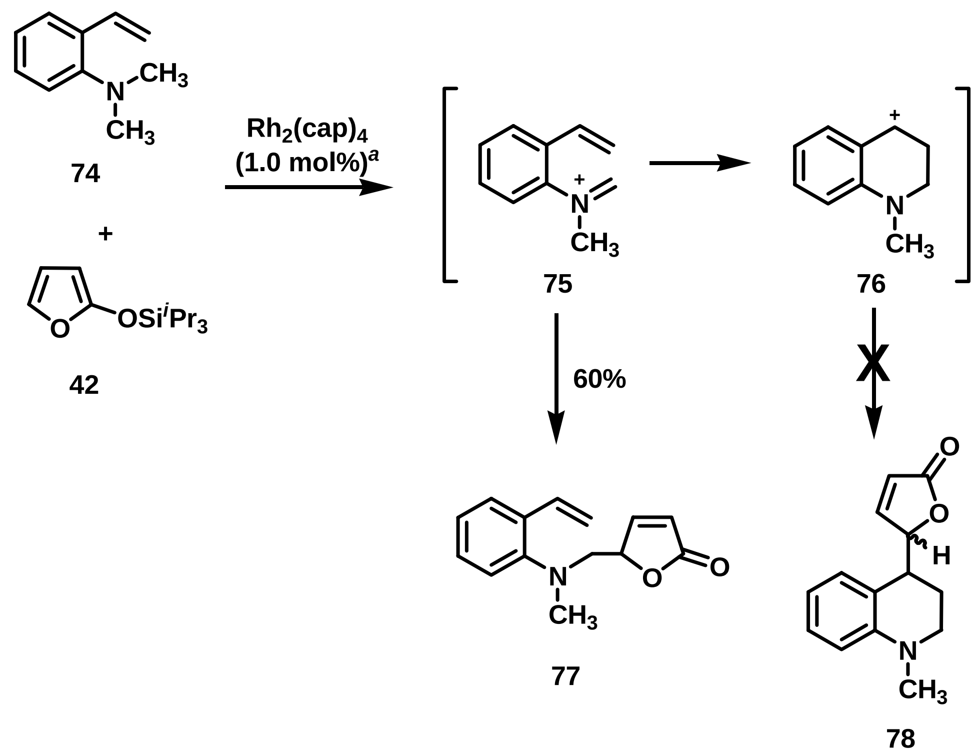
DMA **73** **74**

a) *n*-BuLi, TMEDA, -78 °C, then DMF, 0 °C, rt, b) Ph_3PCH_2Br, KO^tBu, THF, 0 °C.

The rationale for the preparation of **74** was to determine if an electrocyclization of iminium ion **75** would give benzylic carbocation **76** which in turn would undergo capture with the siloxyfuran to give **78** (Scheme 3.35). Toward this end, submitting **74** to the oxidative Mannich reaction failed to give cyclization product **78**. Instead, the Mannich adduct **77** was obtained in 60% yield.

[65] Stanetty, P.; Rodler, I. K.; Krumpak, B. *J. Prakt. Chem.* **1994**, *336*, 333.

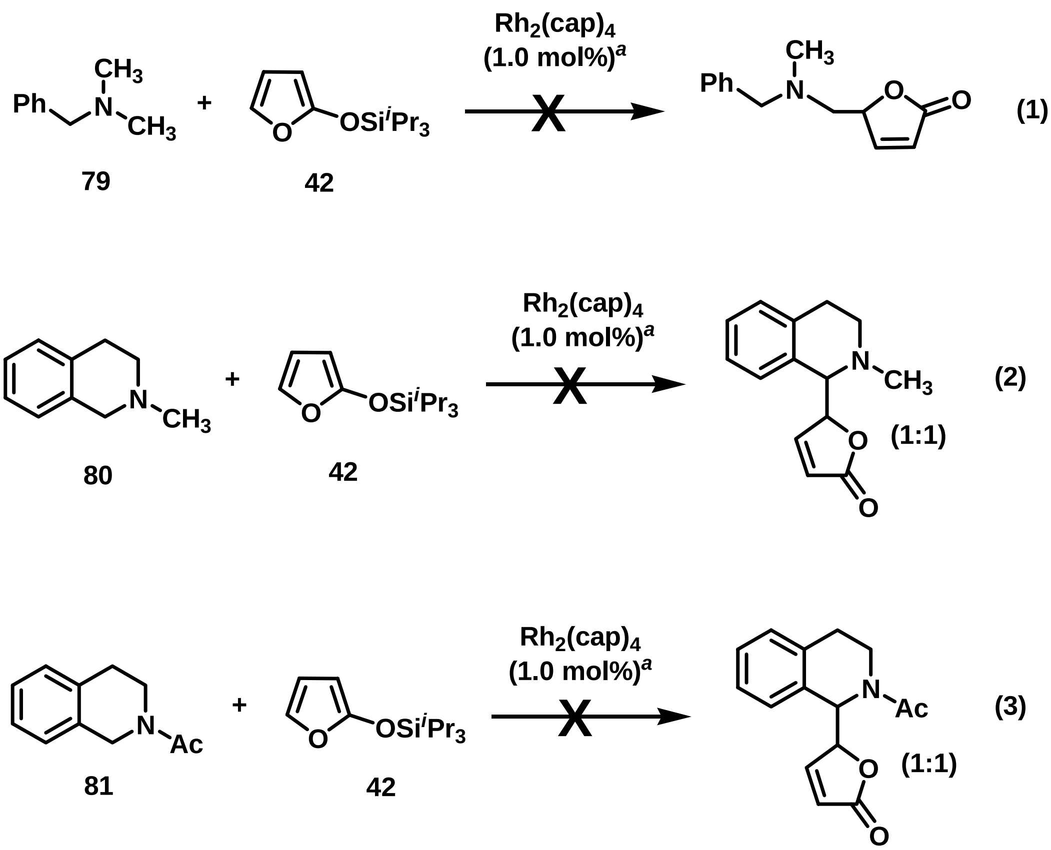
Scheme 3.35.



[a]Conditions: $Rh_2(cap)_4$ (1.0 mol%), amine (2.0 equiv), 2-siloxyfuran (1.0 equiv), T-HYDRO (1.2 equiv), MeOH, 60 °C, 3-5 h. [b]Isolated yield after chromatography.

Tertiary Amine Scope/Variation. Tertiary amines **79-81** were examined in the oxidative Mannich reaction using 2-siloxyfuran **42** under the standard reaction conditions reported in Table 3.2 (Scheme 3.36). Substrates **79** and **80** were aliphatic tertiary amines, whereas substrate **81** was a tertiary amide. In all cases, no products from C-C bond formation were observed. Thus, it appears that the oxidative Mannich reaction catalyzed by $Rh_2(cap)_4$ is limited to tertiary arylamines. However, this is consistent with previously reported oxidative Mannich processes which proceed via SET/H· transfer.[36,38,39]

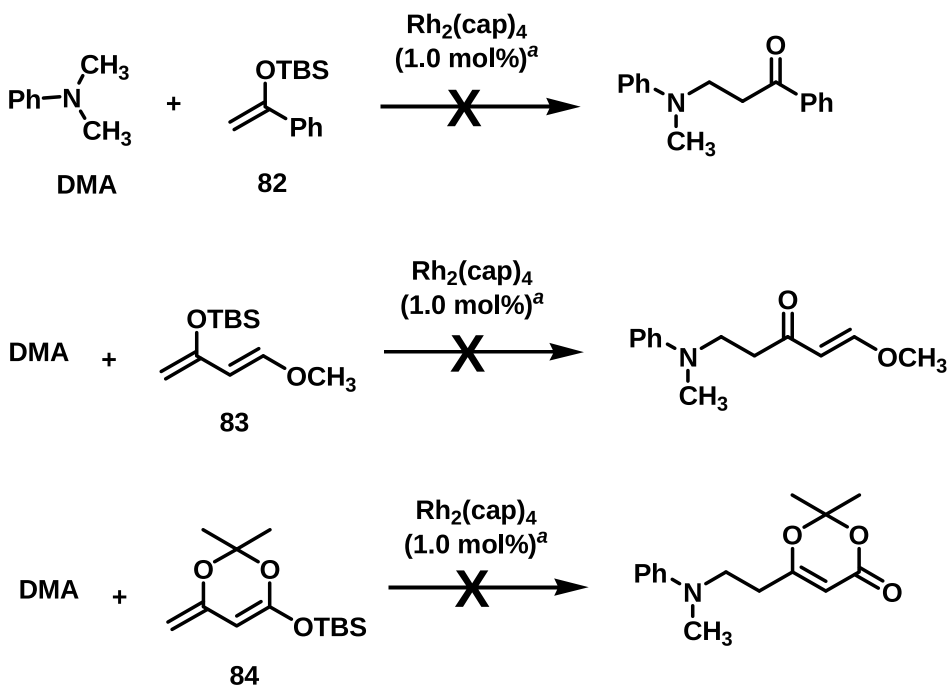
Scheme 3.36.



[a]**Conditions: $Rh_2(cap)_4$ (1.0 mol%), amine (2.0 equiv), 42 (1.0 equiv), T-HYDRO (1.2 equiv), MeOH, 60 °C, 3-5 h.**

Nucleophile Scope/Variation. Nucleophiles **82-84** were examined in the oxidative Mannich reaction using DMA under the reaction standard conditions reported in Table 3.2 (Scheme 3.37). Nucleophiles **82** and **83** were silyl enol ethers, whereas **84** was a silyl ketene acetal. In all cases, no products from C-C bond formation were observed due to proto-desilylation under the reaction conditions.

Scheme 3.37.

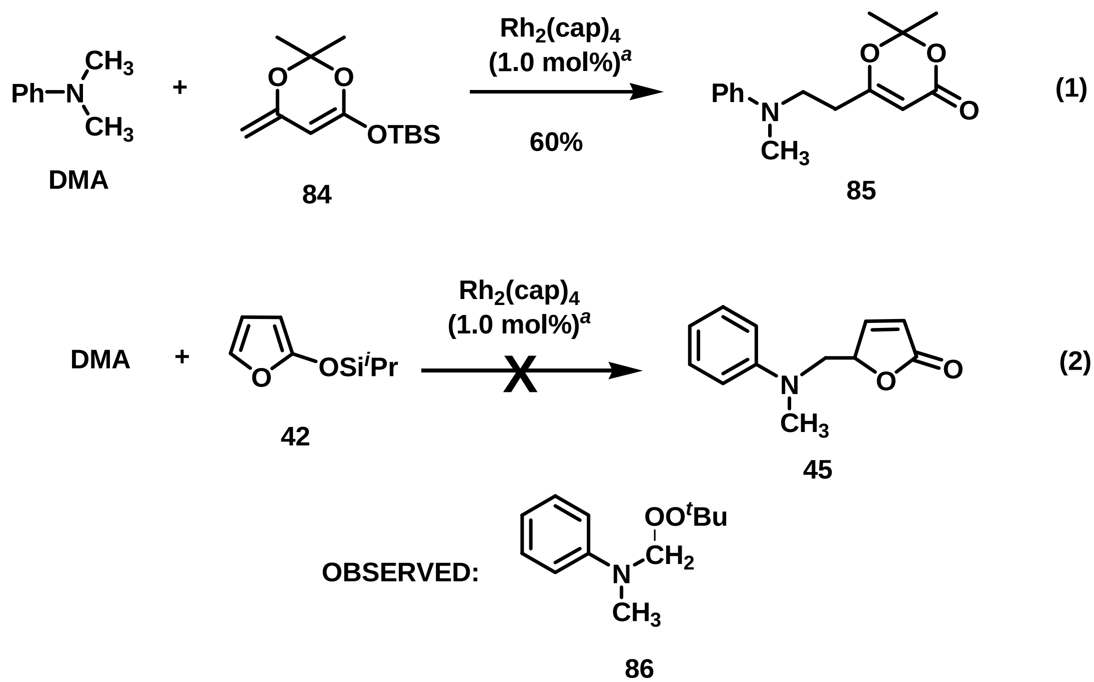


[a]Conditions: $Rh_2(cap)_4$ (1.0 mol%), amine (2.0 equiv), 2-siloxyfuran (1.0 equiv), T-HYDRO (1.2 equiv), MeOH, 60 °C, 3-5 h. [b]Isolated yield after chromatography.

In order to thwart proto-desilylation of the nucleophile, the oxidative Mannich reaction was conducted in CH_3CN as a solvent. Initial results using silyl ketene acetal **84** gave Mannich adduct **85** in 60% yield in one hour at room temperature (Scheme 3.38, eq 1). However, the oxidative Mannich reaction of DMA using siloxyfuran **42** under identical conditions in CH_3CN

failed to give product **45**, but rather gave 60% yield of mixed peroxide **86** (Scheme 3.38, eq 2).

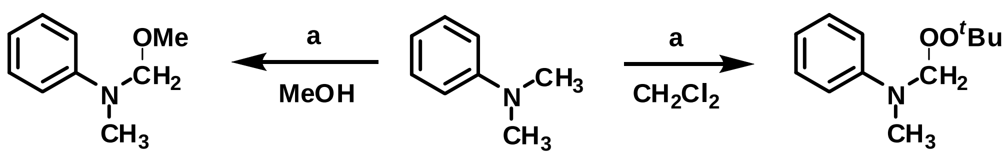
Scheme 3.38.



[a]**Conditions: $Rh_2(cap)_4$ (1.0 mol%), amine (2.0 equiv), nucleophile (1.0 equiv), T-HYDRO (1.2 equiv), CH_3CN, rt, 1 h.**

Curious as to the difference in product outcome using **84** and **42** (vide supra), the oxidative Mannich reaction was performed in the *absence* of nucleophile. In MeOH, the oxidation of DMA yielded α-methoxyamine **87** (62% yield) without evidence of mixed peroxide **86** (Scheme 3.39).[66] Whereas, replacing methanol as the solvent with non-nucleophilic CH_2Cl_2 gave **86** in 60% yield under identical conditions. These results indicate the formation of an iminium ion which can undergo reaction with a variety of nucleophiles under the appropriate set of conditions. Thus, the attractive possibility for future development remains open.

Scheme 3.39.



87 DMA 86

a) $Rh_2(cap)_4$ (1.0 mol%), T-HYDRO (1.2 equiv), solvent, rt, 30 mins.

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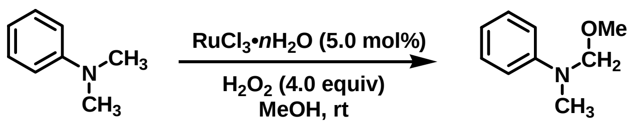
[66] Murahashi and coworkers in 1992 reported a similar transformation using $RuCl_3$ and H_2O_2, see: Murahashi, S.; Naota, T.; Miyaguchi, N.; Nakato, T. *Tetrahedron Lett.* **1992**, *33*, 6991.



DMA 67% 87

III. CONCLUSION

The oxidative Mannich reaction is defined as 1) the oxidative formation of an imine or iminium ion, and 2) the subsequent capture with a nucleophile to form a carbon-carbon bond. An oxidative Mannich reaction catalyzed by $Rh_2(cap)_4$ was developed for the synthesis of γ-aminoalkyl-butenolides. The reaction proceeds via tertiary amine C-H oxidation followed by nucleophilic capture with 2-triisopropylsiloxyfuran in MeOH using T-HYDRO (70% *t*-BuOOH in water) as the stoichiometric oxidant. Considering prior literature precedent and the requirement for tertiary arylamines in the oxidative Mannich reaction, it is reasonable to hypothesize at this juncture that C-H oxidation using $Rh_2(cap)_4$ and *t*-BuOOH proceeds via SET/H· transfer. Finally, results indicate a variety of nucleophiles could be used to trap iminium ions generated from dirhodium catalysis thereby allowing the possibility for future development.

IV. EXPERIMENTAL

General. All reactions were performed under an air atmosphere unless otherwise noted. Moisture sensitive reactions were performed using oven dried glassware under a dried nitrogen atmosphere. All reagents were obtained from commercial sources and used without purification unless otherwise noted. T-HYDRO® (70 wt. % *tert*-butyl hydroperoxide in H_2O) was obtained from Aldrich and used as received. *N*-Pheny-1,2,3-4-tetra-hydroisoquinoline (**29**), *N*-ethyl-*N*-methylaniline (**55**), 2-*N*,*N*-demethyl-aminobenzaldehyde (**73**), 2-triisopropylsiloxyfuran (**42**), 2-*tert*-butyl-dimethylsiloxyfuran (**41**), 3-methyl-2-triisopropylsiloxyfuran (**63**), 5-methyl-2-triisopropylsiloxyfuran (**64**), 5-allyl-2-triisopropylsiloxyfuran (**65**), *tert*-butyl-(2,2-demethyl-6-methylene-6*H*-[1,3]dioxin-4-yloxy)dimethylsilane (**84**)[67] were prepared according to published procedures. Anhydrous CH_2Cl_2 and THF were purified prior to use by nitrogen forced-flow over activated alumina.[68]

Yields reported are for isolated yields unless otherwise noted. Preparative chromatographic purification was performed using SiliCycle (60 Å, 40-63 mesh) silica gel according to the method of Still.[69] Thin layer chromatography (TLC) was performed on Merck 0.25 mm silica gel 60 F_{254} plates with visualization by aqueous $KMnO_4$ or fluorescence quenching.

^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were obtained on a Bruker DRX-400 NMR spectrometer as solutions in $CDCl_3$ containing 0.01%

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[67] Beutner, G. L.; Denmark, S. E. *J. Amer. Chem. Soc.* **2003**, *125*, 7800.

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

[69] Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978**, *43*, 2923.

v/v Me_4Si (TMS). Chemical shifts are reported in parts per million (ppm) δ downfield from TMS; coupling constants are reported in Hertz (Hz). Infrared (IR) spectra were obtained on a JASCO FT/IR-4000 instrument with band assignments reported in units of cm^{-1}. Mass spectra were obtained on a JEOL SX102 magnetic sector mass spectrometer. Melting points were recorded using an Electrothermal Mel-Temp apparatus and were reported uncorrected.

***N*,*N*-Dimethyl-3,4-methylenedioxyaniline (47)**. To a stirring solution of 3,4-dimethylendioxyaniline (2.00 g, 14.6 mmol) and aqueous formaldehyde (37% in H_2O, 3.55 mL, 43.8 mmol) in methanol (15 mL) atroom temperaturewas added a solution of $NaCNBH_3$ (1.10 g, 17.5 mmol) and $ZnCl_2$ (0.994 g, 7.29 mmol) in MeOH (15 mL). The mixture was stirred overnight at room temperature and was treated with 0.1 N NaOH (30 mL). The MeOH was evaporated *in vacuo* and the remaining aqueous solution was extracted with EtOAc (3 x 60 mL). The combined organic extracts were washed with water (150 mL), brine (150 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Bulb-to-bulb distillation (110-112 °C, 0.2 Torr) gave 2.32 g of **47** as a pale yellow oil (96%): TLC R_f = 0.38 (10:1 hexanes/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 6.72 (d, *J* = 8.5 Hz, 1H), 6.42 (d, *J* = 2.4 Hz, 1H), 6.17 (dd, *J* = 8.5 Hz, 2.4 Hz, 1H), 5.87 (s, 2H), 2.86 (s, 6H); ^{13}C NMR (100 MHz) δ 148.2, 147.1, 139.2, 108.1, 105.0, 100.4, 96.3, 41.5; IR (neat) 2897, 2874, 1633m 1493, 1224 cm^{-1}; HRMS (EI) calcd for $C_9H_{11}NO_2$ 165.0790, found 165.0789 (M+).

***N*,*N*-Dimethyl-3,4-dimethylaniline (46)**.[70] Prepared according to the procedure for *N*,*N*-dimethyl-3,4-methylenedioxyaniline (**47**) using 3,4-dimethylaniline. Bulb-to-bulb distillation (120 - 122 °C, 0.2 Torr, lit. = not reported) gave a **46** as a yellow oil (72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, J = 8.0 Hz, 1H), 6.59 – 6.53 (comp, 2H), 2.89 (s, 6H), 2.24 (s, 3H), 2.17 (s, 3H).

***N*-Methyl-*N*-3-phenylpropylaniline (56)**. To a stirring solution of *N*-methylaniline (2.0 g, 18.7 mmol) and 3-phenylpropionaldehyde (3.72 mL, 28.0 mmol) in methanol (15 mL) was added a solution of $NaCNBH_3$ (1.41 g, 22.4 mmol) and $ZnCl_2$ (1.27 g, 9.33 mmol) in MeOH (15 mL). The mixture was stirred overnight at room temperature and was treated with 0.1 N NaOH (30 mL). The MeOH was evaporated and the remaining aqueous solution was extracted with EtOAc (3 x 60 mL). The combined organic extract was washed with water (150 mL), brine (150 mL), dried over anhydrous $MgSO_4$, concentrated *in vacuo*. Purification by column chromatography (SiO_2, 25:1 hexanes/EtOAc) gave 2.06 g of **56** as a yellow oil (49%): TLC R_f = 0.55 (10:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.18 (m, 7H), 6.69 – 6.65 (m, 3H), 3.34 (t, *J* = 7.7 Hz, 2H), 2.92 (s, 3H), 2.65 (t, *J* = 7.7 Hz, 2H), 1.92 (p, *J* = 7.7 Hz, 2H); ^{13}C NMR (100 MHz) δ 149.2, 141.6, 129.0, 128.2, 128.2, 125.7, 115.9, 112.1, 52.0, 38.1, 33.2, 28.0; IR (neat) 3066, 2912, 2823, 1928, 1596 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{19}N$ 225.1517, found 225.1516 (M+).

[70] Al-Omran, F.; Ridd, J. H. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1185.

2-Ethenyl-*N,N*-dimethylaniline (74).[71] To a stirring solution of 2-*N*,*N*-dimethylaminobenzaldehyde (**73**) (0.985 g, 6.60 mmol) and methyltriphenylphosphonium bromide (2.83 g, 7.92 mmol) in anhydrous THF (30 mL) at 0 °C was added KO^{t}Bu (0.889 g, 7.92 mmol) at which time the color of the solution turned bright yellow. The ice bath was removed and the solution was stirred at room temperatureunder under an atmosphere of N_2 until TLC analysis indicated consumption of the starting material (approx. 2 h). The solvent was removed *in vacuo* and replaced with hexane/Et_2O (95:5, 100 mL) at which point a white precipitate formed. The solution was filtered over a plug of Celite and the filtrate was concentrated *in vacuo*. Bulb-to-bulb distillation (172 - 174 °C, 0.2 Torr; lit = not reported) gave 0.604 g of **74** as colorless oil (62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.32 – 7.27 (m, 1H), 7.15 - 7.00 (comp, 3H), 5.55 (dd, *J* = 17.6, 1.6 Hz, 1H), 5.22 (dd, *J* = 10.0, 1.6 Hz, 1H), 2.76 (s, 6H).

General Procedure for the Oxidative Mannich Reaction Catalyzed by Rh_2(cap)$_4$. T-HYDRO® (1.2 equiv) was added in one portion to a stirring solution of amine (2.0 equiv), 2-triisopropoxysilylfuran (1.0 equiv), and Rh_2(cap)$_4$ (1.0 mol%) in MeOH (0.27 M/[siloxyfuran]). The reaction mixture was heated at 60 °C for 3-5 hr (or 16 hr with 0.1 mol % catalyst). The solvent was then evaporated, and the product was purified using silica gel.

5-{[Methyl(phenyl)amino]methyl}furan-2(*5H*)-one (45). The general procedure for the oxidative Mannich reaction catalyzed by Rh_2(cap)$_4$ was followed using *N,N*-dimethylaniline. Purified by chromatography on silica gel

[71] Denmark, S. E.; Butler, C. R. *Org. Lett.* **2006**, *8*, 63.

(5:1 → 1:1 hexanes/EtOAc); orange oil: TLC R_f = 0.30 (1:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 5.8, 1.5 Hz, 1H), 7.25 (t, *J* = 8.0 Hz, 2H), 6.77 (t, *J* = 7.3 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 2H), 6.13 (dd, *J* = 5.8, 2.0 Hz, 1H), 5.27 (tt, *J* = 5.8, 2.0 Hz, 1H), 3.69 (d, *J* = 5.8 Hz, 2H), 3.02 (s, 3H); ^{13}C NMR (100 MHz) δ 172.6, 154.4, 148.2, 129.4, 122.2, 117.4, 112.3, 81.9, 55.0, 39.5; IR (neat) 1755 (C=O) cm^{-1}; HRMS (EI) calcd for $C_{12}H_{14}NO_2$ 204.1025, found 204.1026 (M+H).

5-{[Methyl(4-methylphenyl)amino]methyl}furan-2(*5H*)-one (48). The general procedure for the oxidative Mannich reaction catalyzed by $Rh_2(cap)_4$ was followed using *N,N*-dimethyltoluidine. Purified by chromatography on silica gel (5:1 → 1:1 hexanes/EtOAc); orange oil: TLC R_f = 0.50 (1:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 5.6 Hz, 1H), 7.06 (d, *J* = 7.8 Hz, 2H), 6.64 (d, *J* = 7.8, 2H), 6.11 (d, *J* = 5.6 Hz, 1H), 5.26 – 5.24 (m, 1H), 3.64 (d, *J* = 5.8 Hz, 2H), 2.99 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz) δ 172.6, 154.5, 146.2, 129.9, 126.7, 122.0, 112.6, 82.0, 55.3, 39.6, 20.1; IR (neat) 1751 (C=O) cm^{-1}; HRMS (EI) calcd for $C_{13}H_{15}NO_2$ 218.1181, found 218.1176 (M+H).

5-{[(4-*tert*-Butylphenyl)(methyl)amino]methyl}furan-2(*5H*)-one (51). The general procedure for the oxidative Mannich reaction catalyzed by $Rh_2(cap)_4$ was followed using 4-*tert*-buty-*N,N*-dimethylaniline. Purified by chromatography on silica gel (5:1 → 1:1 hexanes/EtOAc); orange oil: TLC R_f = 0.25 (2:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 5.6 Hz, 1H), 7.26 (d, *J* = 8.7 Hz, 2H), 6.66 (d, *J* = 8.7 Hz, 2H), 6.10 - 6.08 (m, 1H), 5.25 - 5.22 (m, 1H), 3.67 - 3.56 (comp, 2H), 2.97 (s, 3H), 1.28 (s, 9H); ^{13}C

NMR (100 MHz) δ 172.5, 154.6, 145.9, 139.8, 125.9, 121.8, 111.9, 81.9, 55.1, 39.3, 33.5, 31.3; IR (neat) 1756 (C=O) cm^{-1}; HRMS (EI) calcd for $C_{16}H_{22}NO_2$ 260.1651, found 260.1646 (M+H).

5-{[(4-Bromophenyl)(methyl)amino]methyl}furan-2(5*H*)-one (49). The general procedure for the oxidative Mannich reaction catalyzed by $Rh_2(cap)_4$ was followed using 4-bromo-*N,N*-dimethylaniline. Purified by chromatography on silica gel (5:1 → 1:1 hexanes/EtOAc); yellow oil: TLC R_f = 0.22 (2:1 hexanes/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 5.7, 1.3 Hz, 1H), 7.32 (d, *J* = 8.9 Hz, 2H), 6.58 (d, *J* = 8.9 Hz, 2H), 6.14 (dd, *J* = 5.8, 1.9 Hz, 1H), 5.26 – 5.23 (m, 1H), 3.70 (dd, *J* = 15.4, 5.6 Hz, 1H), 3.63 (dd, *J* = 15.4, 6.0 Hz, 1H), 3.00 (s, 3H); ^{13}C NMR (100 MHz) δ 172.4, 153.9, 147.2, 132.0, 122.4, 113.9, 109.3, 81.8, 54.8, 39.6; IR (neat) 1755 (C=O) cm^{-1}; HRMS (EI) calcd for $C_{12}H_{13}BrNO_2$ 282.0130, found 282.0130 (M+H).

5-{[(3,4-Dimethylphenyl)(methyl)amino]methyl}furan-2(5*H*)-one (50). The general procedure for the oxidative Mannich reaction catalyzed by $Rh_2(cap)_4$ was followed using *N*,*N*-dimethyl-3,4-dimethylaniline (**46**). Purified by chromatography on silica gel (5:1 → 1:1 hexanes/EtOAc); orange oil: TLC R_f = 0.14 (3:1 hexanes/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 5.8, 1.6 Hz, 1H), 7.00 (d, *J* = 8.1 Hz, 1H), 6.54 – 6.54 (m, 1H), 6.50 – 6.47 (m, 1H), 6.12 (dd, *J* = 5.8, 1.6 Hz, 1H), 5.25 (tt, *J* = 5.8, 1.6 Hz, 1H), 3.69 – 3.58 (comp, 2H), 2.94 (s, 3H), 2.24 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (100 MHz) δ 172.6, 154.6, 145.6, 137.4, 130.3, 125.5, 121.9, 114.2, 110.1, 82.0, 55.3, 39.6, 20.3, 18.5; IR (neat) 1751 (C=O) cm^{-1}; HRMS (EI) calcd for $C_{14}H_{18}NO_2$ 232.1338, found 232.1331 (M+H).

5-{[1,3-Benzodioxol-5-yl(methyl)amino]methyl}furan-2(5*H*)-one (52). The general procedure for the oxidative Mannich reaction catalyzed by $Rh_2(cap)_4$ was followed using *N*,*N*-dimethyl-3,4-methylenedioxyaniline (**47**). Purified by chromatography on silica gel (5:1 → 1:1 hexanes/EtOAc); orange oil: TLC R_f = 0.36 (1:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 5.6, 1.6 Hz, 1H), 6.72 (d, *J* = 8.3 Hz, 1H), 6.38 (d, *J* = 2.6 Hz, 1H), 6.17 – 6.13 (comp, 2H), 5.89 (s, 2H), 5.24 (tt, *J* = 5.8 Hz, 1.6 Hz, 1H), 3.64 – 3.53 (comp, 2H), 2.95 (s, 3H); ^{13}C NMR (100 MHz) δ 172.6, 154.4, 148.6, 144.6, 139.8, 122.1, 108.5, 105.1, 100.8, 96.2, 81.9, 56.3, 40.3; IR (neat) 1751 (C=O) cm^{-1}; HRMS (EI) calcd for $C_{13}H_{14}NO_4$ 248.0923, found 248.0927 (M+H).

5-{[Methyl(2-vinylphenyl)amino]methyl}furan-2(5*H*)-one (77). The general procedure for the oxidative Mannich reaction catalyzed by $Rh_2(cap)_4$ was followed using 2-ethenyl-*N,N*-dimethylaniline (**74**). Purified by chromatography on silica gel (8:1 → 2:1 hexanes/EtOAc); bright yellow oil: TLC R_f = 0.35 (3:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 17.7, 1.5 Hz, 1H), 7.34 (dd, *J* = 5.7, 1.6 Hz, 1H), 7.28 – 7.24 (m, 1H), 7.14 – 7.01 (m, 3H), 6.07 (dd, *J* = 5.7, 1.6 Hz, 1H) 5.68 (dd, *J* = 17.7, 1.5 Hz, 1H), 5.27 (dd, *J* = 10.9, 1.5 Hz, 1H), 5.11 (tt, *J* = 5.6, 1.6 Hz, 1H), 3.33 (d, *J* = 5.6 Hz, 2H), 2.86 (s, 3H); ^{13}C NMR (100 MHz) δ 172.8, 155.1, 149.5, 134.1, 133.0, 128.6, 127.0, 123.9, 121.7, 120.6, 114.3, 82.2, 58.4, 43.4; IR (neat) 1746 (C=O) cm^{-1}; HRMS (EI) calcd for $C_{14}H_{16}NO_2$ 230.1181, found 230.1187 (M+H).

4-{Methyl[(5-oxo-2,5-dihydrofuran-2-yl)methyl]amino}benzaldehyde (70). The general procedure for the oxidative Mannich reaction catalyzed by Rh_2(cap)$_4$ was followed using 4-*N,N*-dimethyaminobenzaldehyde (**69**). Purified by chromatography on silica gel (2:1 → 1:2 hexanes/EtOAc); yellow oil: TLC R_f = 0.25 (1:2 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (s, 1H), 7.77 (d, *J* = 8.9 Hz, 2H), 7.50 (dd, *J* = 5.8, 1.4 Hz, 1H), 6.76 (d, *J* = 8.9 Hz, 2H), 6.19 (dd, *J* = 5.8, 2.0 Hz, 1H), 5.32 – 5.29 (m, 1H), 3.89 (dd, *J* = 15.5, 5.0 Hz, 1H), 3.74 (dd, *J* = 15.5, 6.2 Hz, 1H), 3.14 (s, 3H); ^{13}C NMR (100 MHz) δ 190.2, 172.1, 153.4, 152.7, 132.0, 126.1, 122.7, 111.2, 81.7, 54.1, 39.8; IR (neat) 1746, 1588 (C=O) cm^{-1}; HRMS (EI) calcd for $C_{13}H_{14}NO_3$ 232.0974, found 232.0974 (M+H).

5-{[Ethyl(phenyl)amino]methyl}furan-2(5*H*)-one (57). The general procedure for the oxidative Mannich reaction catalyzed by Rh_2(cap)$_4$ was followed using *N*-ethyl-*N*-methylaniline (**55**). Purified by chromatography on silica gel (5:1 → 2:1 hexanes/EtOAc); yellow oil: TLC R_f = 0.22 (3:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 5.8 Hz, 1H), 7.27 – 7.23 (comp, 2H), 6.73 – 6.70 (comp, 3H), 6.16 – 6.14 (m, 1H), 5.27 – 5.34 (m, 1H), 3.70 (dd, *J* = 15.2, 5.8 Hz, 1H), 3.57 (dd, *J* = 15.2, 6.4 Hz, 1H), 3.52 – 3.34 (comp, 2H), 1.17 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz) δ 172.6, 154.7, 146.9, 129.5, 122.1, 117.1, 112.5, 81.8, 52.9, 45.8, 11.9; IR (neat) 1751 (C=O) cm^{-1}; HRMS (EI) calcd for $C_{13}H_{16}NO_2$ 218.1181, found 218.1184 (M+H).

5-{[Phenyl(3-phenylpropyl)amino]methyl}furan-2(5*H*)-one (58). The general procedure for the oxidative Mannich reaction catalyzed by Rh_2(cap)$_4$

was followed using *N*-methyl-*N*-3-phenylpropylaniline (**56**). Purified by chromatography on silica gel (6:1 → 3:1 hexanes/EtOAc); yellow oil: TLC R_f = 0.26 (3:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 5.6, 1.4 Hz, 1H), 7.30 – 7.17 (comp, 7H), 6.73 (t, *J* = 7.2 Hz, 1H), 6.63 (d, *J* = 8.1 Hz, 2H), 6.10 (dd, *J* = 5.6, 1.9 Hz, 1H), 5.21 – 5.18 (m, 1H), 3.65 (dd, *J* = 15.2, 6.0 Hz, 1H), 3.56 (dd, *J* = 15.2, 6.2 Hz, 1H), 3.44 - 3.27 (m, 2H), 2.64 (t, *J* = 7.6 Hz, 2H), 1.92 (p, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz) δ 172.5, 154.5, 146.9, 141.2, 129.4, 128.4, 128.2, 126.0, 122.0, 117.2, 112.7, 81.6, 53.5, 51.0, 33.0, 28.1; IR (neat) 1765 (C=O) cm^{-1}; HRMS (EI) calcd for $C_{20}H_{22}NO_2$ 308.1651, found 308.1643 (M+H).

5-(2-Phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)furan-2(5*H*)-one (62). The general procedure for the oxidative Mannich reaction catalyzed by $Rh_2(cap)_4$ was followed using *N*-pheny-1,2,3,4-tetrahydroisoquinoline (**29**). Purified by chromatography on silica gel (5:1 → 1:1 hexanes/EtOAc); orange oil: TLC R_f = 0.26 (3:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 5.8 Hz, 1H), 7.38 (d, *J* = 5.8 Hz, 1H), 7.33 – 7.18 (comp, 6H), 7.00 (d, *J* = 8.3 Hz, 1H), 6.89 (d, *J* = 8.3 Hz, 1H), 6.86 – 6.80 (m, 1H), 6.14 – 6.12 (m, 1H), 5.94 – 5.92 (m, 1H), 5.46 – 5.45 (m, 1H), 5.36 – 5.34 (m, 1H), 5.18 (d, *J* = 4.2 Hz, 1H), 4.91 (d, *J* = 6.2 Hz, 1H), 3.82 – 3.76 (m, 1H), 3.67 – 3.55 (comp, 2H), 3.47 – 3.41 (m, 1H), 3.10 – 2.91 (comp, 4H); ^{13}C NMR (100 MHz) δ 172.5, 172.4, 154.6, 153.6, 148.9, 148.8, 135.7, 135.3, 132.4, 131.9, 129.4, 129.4, 128.6, 128.4, 128.1, 127.8, 127.7, 127.5, 126.3, 125.9, 122.5, 122.2, 118.8, 118.6, 114.5, 114.4, 85.9, 85.4, 61.7, 60.5, 44.0, 43.4, 28.3, 27.2; IR (neat) 1756 (C=O) cm^{-1}; HRMS (EI) calcd for $C_{19}H_{18}NO_2$ 292.1338, found 292.1331 (M+H).

5-(1-Phenylpyrrolidin-2-yl)furan-2(5*H*)-one (61). The general procedure for the oxidative Mannich reaction catalyzed by $Rh_2(cap)_4$ was followed using *N*-phenylpyrrolidine (**59**). Purified by chromatography on silica gel (5:1 → 1:1 hexanes/EtOAc); yellow oil: TLC R_f = 0.22 (3:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.40 (comp, 2H), 7.30 – 7.22 (comp, 4H), 6.80 – 6.72 (comp, 4H), 6.59 (d, *J* = 8.1 Hz, 2H), 6.19 – 6.16 (comp, 2H), 5.40 – 5.39 (m, 1H), 5.03 – 5.02 (m, 1H), 4.40 – 4.37 (m, 1H), 3.86 (t, *J* = 7.2 Hz, 1H), 3.64 – 3.55 (comp, 2H), 3.24 – 3.16 (comp, 2H), 2.17 – 1.68 (comp, 8H); ^{13}C NMR (100 MHz) δ 172.8, 172.7, 155.9, 153.6, 1467.0, 146.8, 129.4, 129.2, 122.7, 121.6, 117.2, 117.0, 112.6, 112.4, 84.0, 82.4, 60.5, 59.1, 49.4, 49.1, 27.8, 25.2, 24.1, 23.2; IR (neat) 1756 (C=O) cm^{-1}; HRMS (EI) calcd for $C_{14}H_{16}NO_2$ 230.1181, found 230.1177 (M+H).

3-Methyl-5-{[methyl(phenyl)amino]methyl}furan-2(5*H*)-one (66). The general procedure for the oxidative Mannich reaction catalyzed by $Rh_2(cap)_4$ was followed using *N,N*-dimethylaniline and 3-methyl-2-triisopropylsiloxyfuran (**63**). Purified by chromatography on silica gel (5:1 → 1:1 hexanes/EtOAc); yellow oil: TLC R_f = 0.27 (3:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (t, *J* = 7.6 Hz, 2H), 7.05 (s, 1H), 6.76 – 6.70 (comp, 3H), 5.12 – 5.09 (m, 1H), 3.65 (dd, *J* = 15.3, 5.3 Hz, 1H), 3.55 (dd, *J* = 15.3, 5.9 Hz, 1H), 3.00 (s, 3H), 1.89 (s, 3H); ^{13}C NMR (100 MHz) δ 173.7, 148.3, 146.7, 130.6, 129.2, 117.1, 112.2, 79.6, 55.3, 39.4, 10.6; IR (neat) 1751 (C=O) cm^{-1}; HRMS (EI) calcd for $C_{13}H_{16}NO_2$ 218.1181, found 218.1181 (M+H).

5-Methyl-5-{[methyl(phenyl)amino]methyl}furan-2(5*H*)-one (67). The general procedure for the oxidative Mannich reaction catalyzed by $Rh_2(cap)_4$ was followed using *N,N*-dimethylaniline and 5-methyl-2-triisopropylsiloxyfuran (**64**). Purified by chromatography on silica gel (5:1 → 1:1 hexanes/EtOAc); light yellow solid (mp = 116 – 117 °C): TLC R_f = 0.44 (3:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 5.6 Hz, 1H), 7.23 – 7.19 (m, 2H), 6.72 (t, *J* = 7.2 Hz, 1H), 6.65 (d, *J* = 8.1 Hz, 2H), 5.92 (d, *J* = 5.6 Hz, 1H), 3.69 (d, *J* = 15.6 Hz, 1H), 3.63 (d, *J* = 15.6 Hz, 1H), 2.97 (s, 3H), 1.51 (s, 3H); ^{13}C NMR (100 MHz) δ 171.9, 157.8, 148.8, 129.1, 121.2, 117.0, 112.0, 90.5, 58.8, 40.0, 21.8; IR (neat) 1751 (C=O) cm^{-1}; HRMS (EI) calcd for $C_{13}H_{16}NO_2$ 218.1181, found 218.1183 (M+H).

5-Allyl-5-{[methyl(phenyl)amino]methyl}furan-2(5*H*)-one (68). The general procedure for the oxidative Mannich reaction catalyzed by $Rh_2(cap)_4$ was followed using *N,N*-dimethylaniline and 5-allyl-2-triisopropylsiloxyfuran (**65**). Purified by chromatography on silica gel (5:1 → 1:1 hexanes/EtOAc); yellow oil: TLC R_f = 0.35 (3:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 5.8 Hz, 1H), 7.21 (t, *J* = 8.3 Hz, 2H), 6.72 (t, *J* = 7.3 Hz, 1H), 6.64 (d, *J* = 8.3 Hz, 2H), 5.95 (d, *J* = 5.8 Hz, 1H), 5.73 – 5.63 (m, 1H), 5.20 – 5.15 (comp, 2H), 3.78 (d, *J* = 15.7 Hz, 1H), 3.66 (d, *J* = 15.7 Hz, 1H), 2.96 (s, 3H), 2.66 – 2.54 (comp, 2H); ^{13}C NMR (100 MHz) δ 171.9, 156.3, 148.8, 130.1, 129.1, 122.3, 120.5, 117.0, 112.0, 92.2, 57.6, 40.1, 39.6; IR (neat) 1756 (C=O) cm^{-1}; HRMS (EI) calcd for $C_{15}H_{18}NO_2$ 244.1338, found 244.1333 (M+H).

_N_-(Methoxymethyl)-_N_-methylaniline (87). The general procedure for the oxidative Mannich reaction catalyzed by $Rh_2(cap)_4$ was followed at room temperature in the absence of 2-triisopropylsiloxyfuran (**42**). Purified by chromatography on silica gel (25:1 hexanes/EtOAc), light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.17 (comp, 3H), 6.89 – 6.71 (comp, 2H), 4.75 (s, 2H), 3.31 (s, 3H), 3.10 (s, 3H).

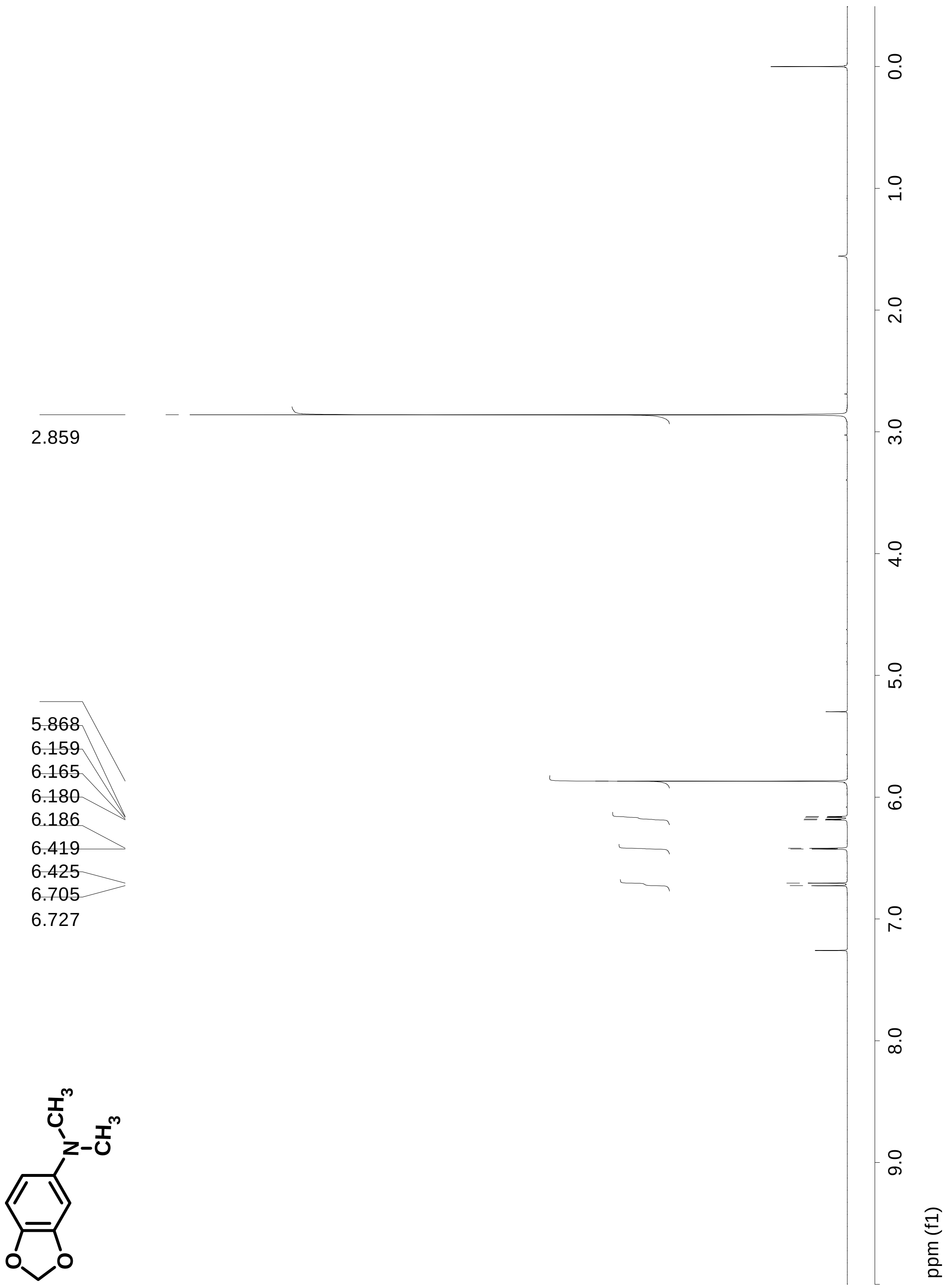
_N_-[(_tert_-Butylperoxy)methyl]-_N_-methylaniline (86). The general procedure for the oxidative Mannich reaction catalyzed by $Rh_2(cap)_4$ was followed using CH_2Cl_2 at room temperature in the absence of 2-triisopropylsiloxyfuran (**42**). Purified by chromatography on silica gel (20:1 hexanes/EtOAc), bright yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.22 (comp, 2H), 6.87 (d, J = 8.0 Hz, 2H), 6.78 (t, J = 7.2 Hz, 1H), 5.15 (s, 2H), 3.14 (s, 3H), 1.20 (s, 9H).

1-_tert_-Butylperoxy-2-phenyl-1,2,3,4-tetrahydroisoquinoline (37). To a stirring solution of _N_-phenyl-1,2,3,4-tetrahydroquinoline (**29**) (0.114 g, 0.543 mmol) in CH_2Cl_2 (2.0 mL) at room temperaturewas added $NaHCO_3$ (0.023 g, 0.272 mmol) and $Rh_2(cap)_4$ (4.0 mg, 0.0054 mmol). Anhydrous _t_-BuOOH (6.3 M in decane, 172 μL, 1.09 mmol) was added in one portion at which time the color of the solution turned from blue to red. The solution was sealed with a septum and stirred for 16 h. The solution was filtered over a short plug of silica to remove the catalyst and the solvent was evaporated _in vacuo_ to yield a yellow oil. ^{1}H NMR analysis indicated >95% conversion of **37** based on starting material. Purification by column chromatography on silica gel (25:1 hexanes/EtOAc) gave 0.077 g (48%) as a yellow oil. ^{1}H NMR (400 MHz,

$CDCl_3$): δ 7.36 (d, *J* = 7.2 Hz, 1H), 7.29 – 7.18 (comp, 7H), 6.83 (t, *J* = 7.2 Hz, 1H), 6.18 (s, 1H), 3.75 – 3.70 (m, 1H), 3.59 – 3.55 (m, 1H), 3.08 – 2.99 (comp, 2H), 1.13 (s, 9H).

1-(Nitromethyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (38). To a stirring solution of *N*-phenyl-1,2,3,4-tetrahydroquinoline (**29**) (0.056 g, 0.272 mmol) in CH_2Cl_2 (1.0 mL) at room temperature was added $NaHCO_3$ (0.011 g, 0.136 mmol) and $Rh_2(cap)_4$ (2.0 mg, 0.0027 mmol). Anhydrous *t*-BuOOH (6.3 M in decane, 74 μL, 0.54 mmol) was added in one portion at which time the color of the solution turned from blue to red. The solution was sealed with a septum and stirred for 3 h. The solution was filtered over a short plug of silica to remove the catalyst and the solvent was evaporated *in vacuo* to yield a bright yellow oil. ^{1}H NMR analysis indicated >95% conversion of **38** based on starting material. Purification by column chromatography on silica gel (7:1 hexanes/EtOAc) gave 0.046 g (63%) of **38** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 – 7.12 (comp, 6H), 6.97 (d, *J* = 8.5 Hz, 2H), 6.85 (t, *J* = 7.2 Hz, 1H), 5.55 (t, *J* = 7.2 Hz, 1H), 4.86 (dd, *J* = 11.9, 7.9 Hz, 1H), 4.55 (dd, *J* = 11.9, 6.6 Hz, 1H), 3.68 – 3.58 (comp, 2H), 3.09 (ddd, *J* = 16.3, 8.5, 5.9 Hz, 1H), 2.79 (dt, *J* = 16.3, 4.8 Hz, 1H).

2,2-Dimethyl-6-{2-[methyl(phenyl)amino]ethyl}-4*H*-1,3-dioxin-4-one (85). To a stirring solution *N*,*N*-dimethylaniline (0.132 g, 1.09 mmol), *tert*-butyl-(2,2-demethyl-6-methylene-6*H*-[1,3]dioxin-4-yloxy)dimethylsilane (**84**) (0.139 g, 0.543 mmol), and $Rh_2(cap)_4$ (4.0 mg, 0.0054 mmol) in CH_3CN at room temperature was added T-HYDRO® (0.093 mL, 0.652 mmol) in one portion. The solution was sealed with a septum and stirred for one hour. The solvent was evaporated *in vacuo*; and the residue was purified by column chromatography on silica gel (3:1 hexanes/EtOAc) to give 0.086 mg (60%) of **85** as a light yellow oil: TLC R_f = 0.26 (3:1 hexanes/EtOAc), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.22 (comp, 2H), 6.75 – 6.70 (comp, 2H), 5.25 (s, 1H), 3.58 (t, *J* = 7.3 Hz, 2H), 2.93 (s, 3H), 2.47 (t, *J* = 7.3 Hz, 2H), 1.67 (s, 6H); ^{13}C NMR (100 MHz) δ 169.6, 160.7, 148.2, 129.2, 116.9, 112.5, 106.4, 94.1, 49.3, 38.1, 30.9, 24.9; IR (neat) 1727 (C=O) cm^{-1}; HRMS (EI) calcd for $C_{15}H_{19}NO_3$ 261.1365, found 261.1370 (M+).



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2.0
3.0
4.0
5.0
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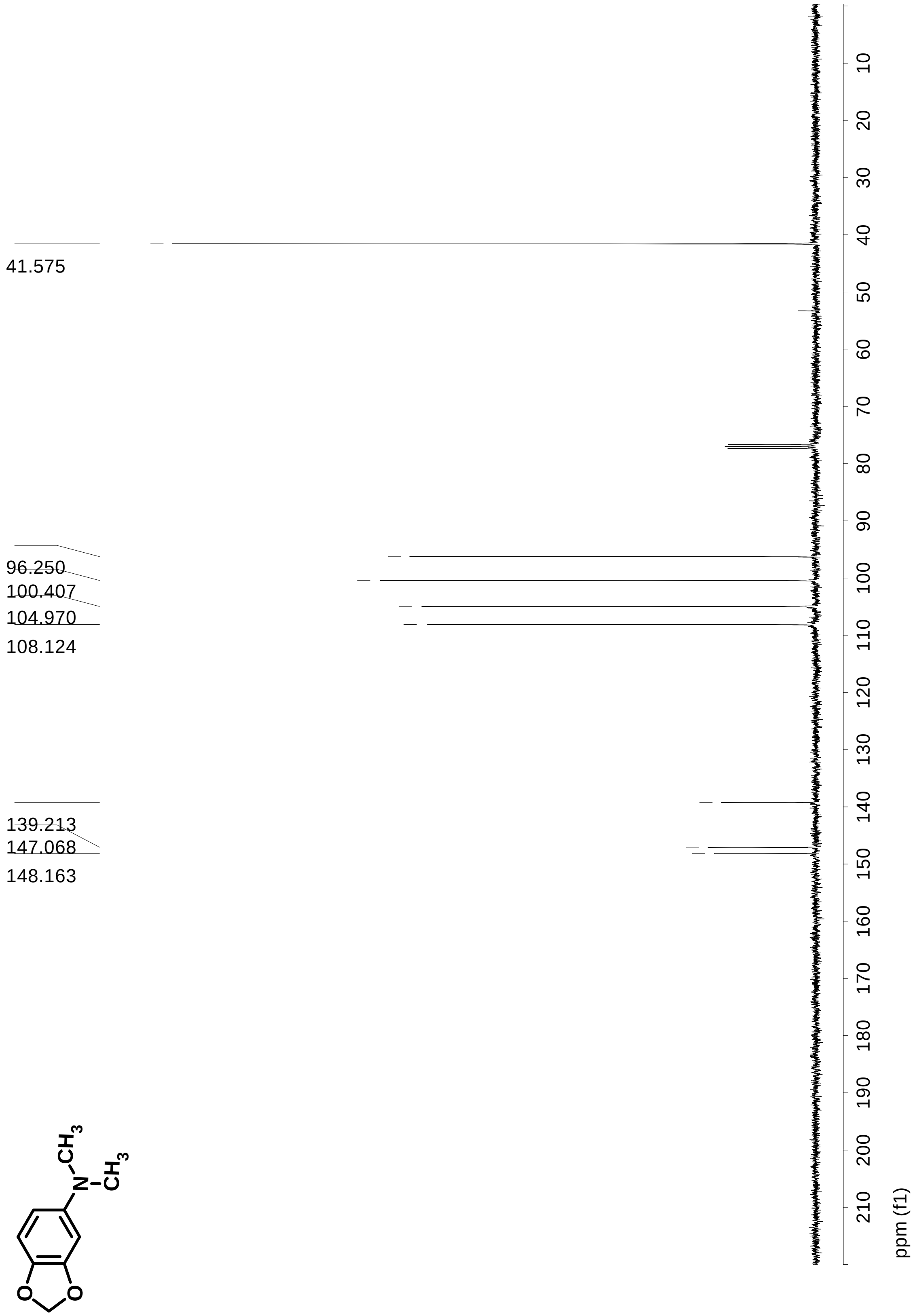
7.0
8.0
9.0
ppm (f1)



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148.163
ppm (f1)
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80
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200
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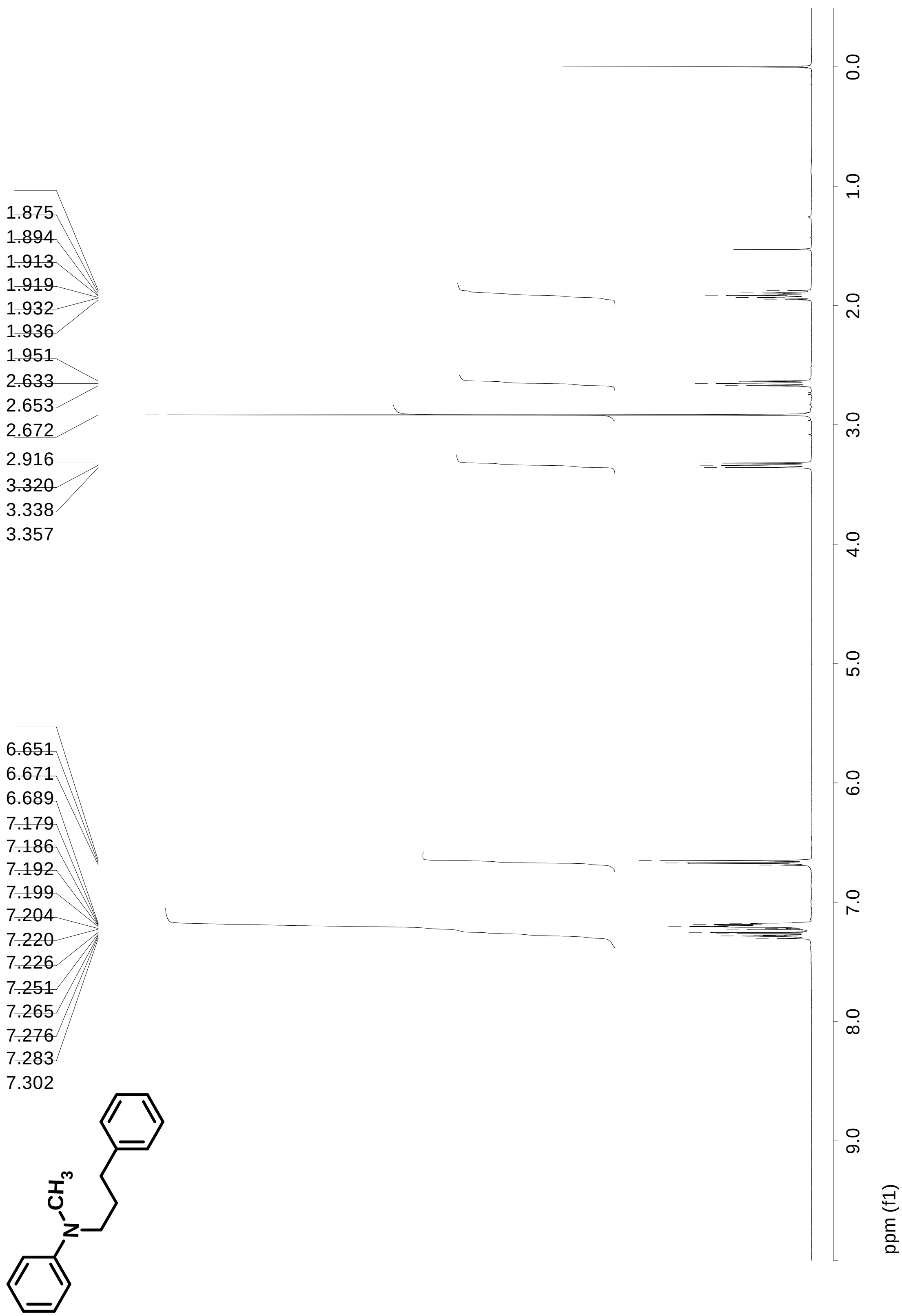
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3.338
3.357
6.651
6.671
6.689
7.179
7.186
7.192
7.199
7.204
7.220
7.226
7.251
7.265
7.276
7.283
7.302
N
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4.0
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7.0
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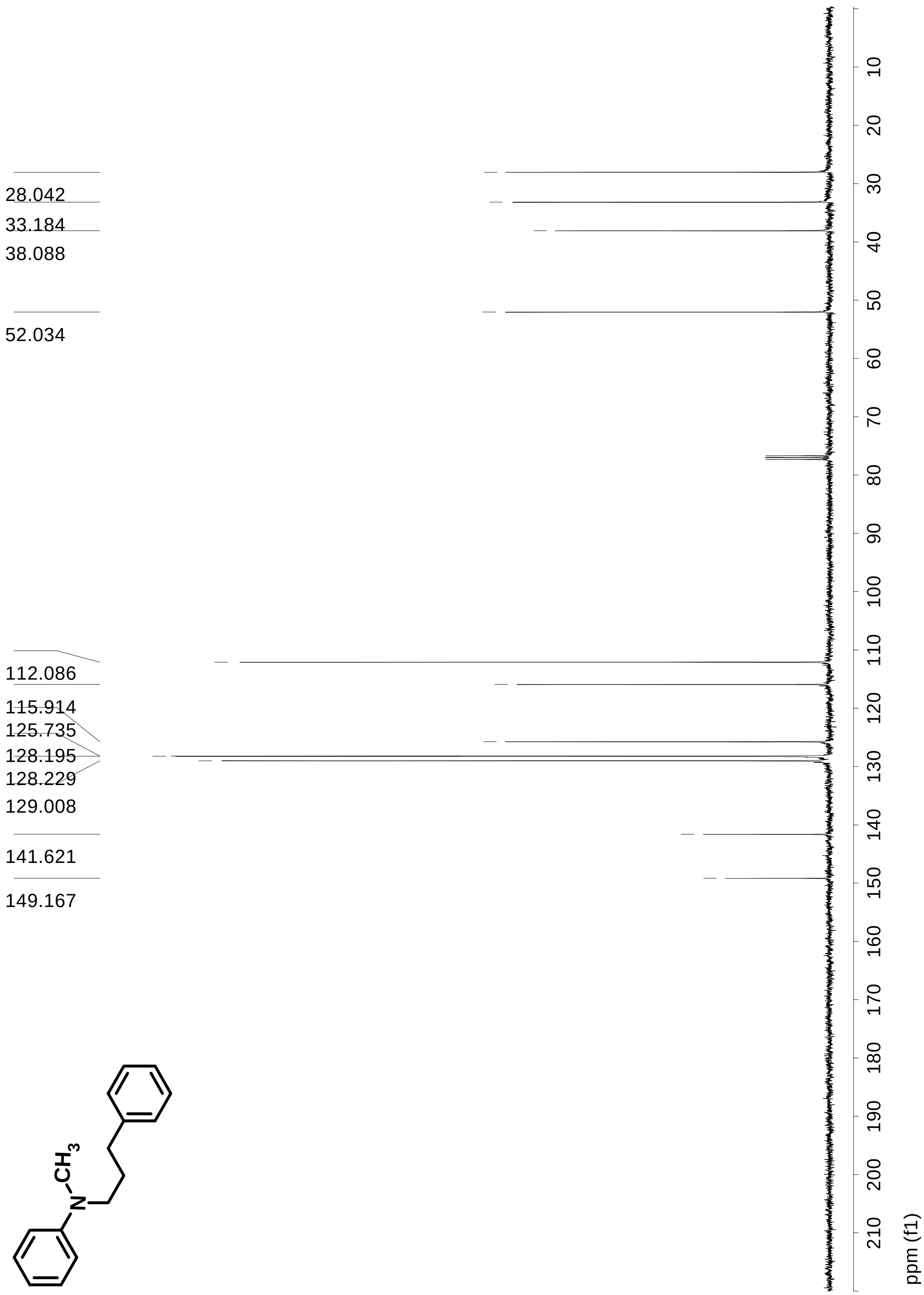
9.0
ppm (f1)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128.229
129.008
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CH3
N
ppm (f1)
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20
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60
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80
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100
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120
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140
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200
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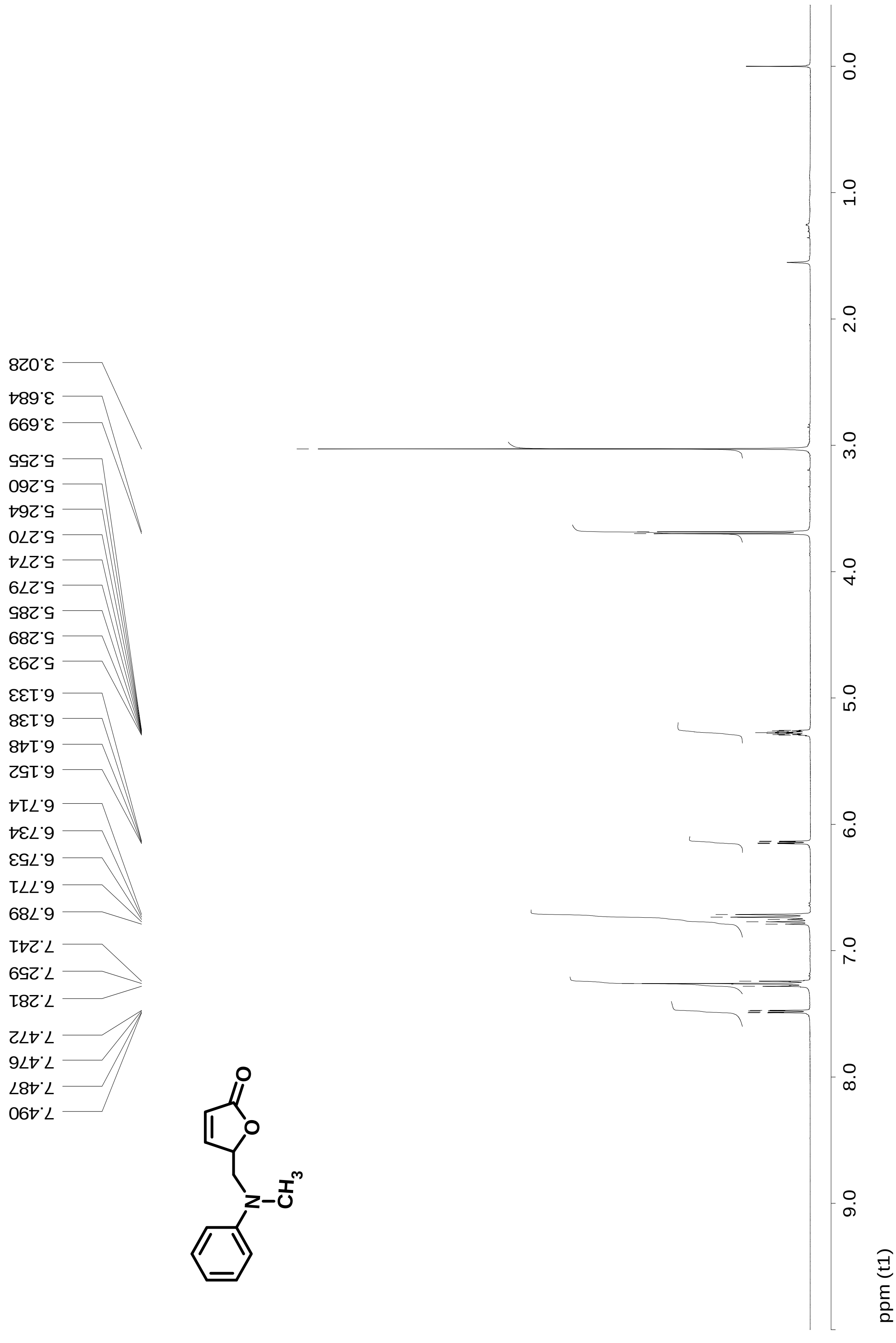

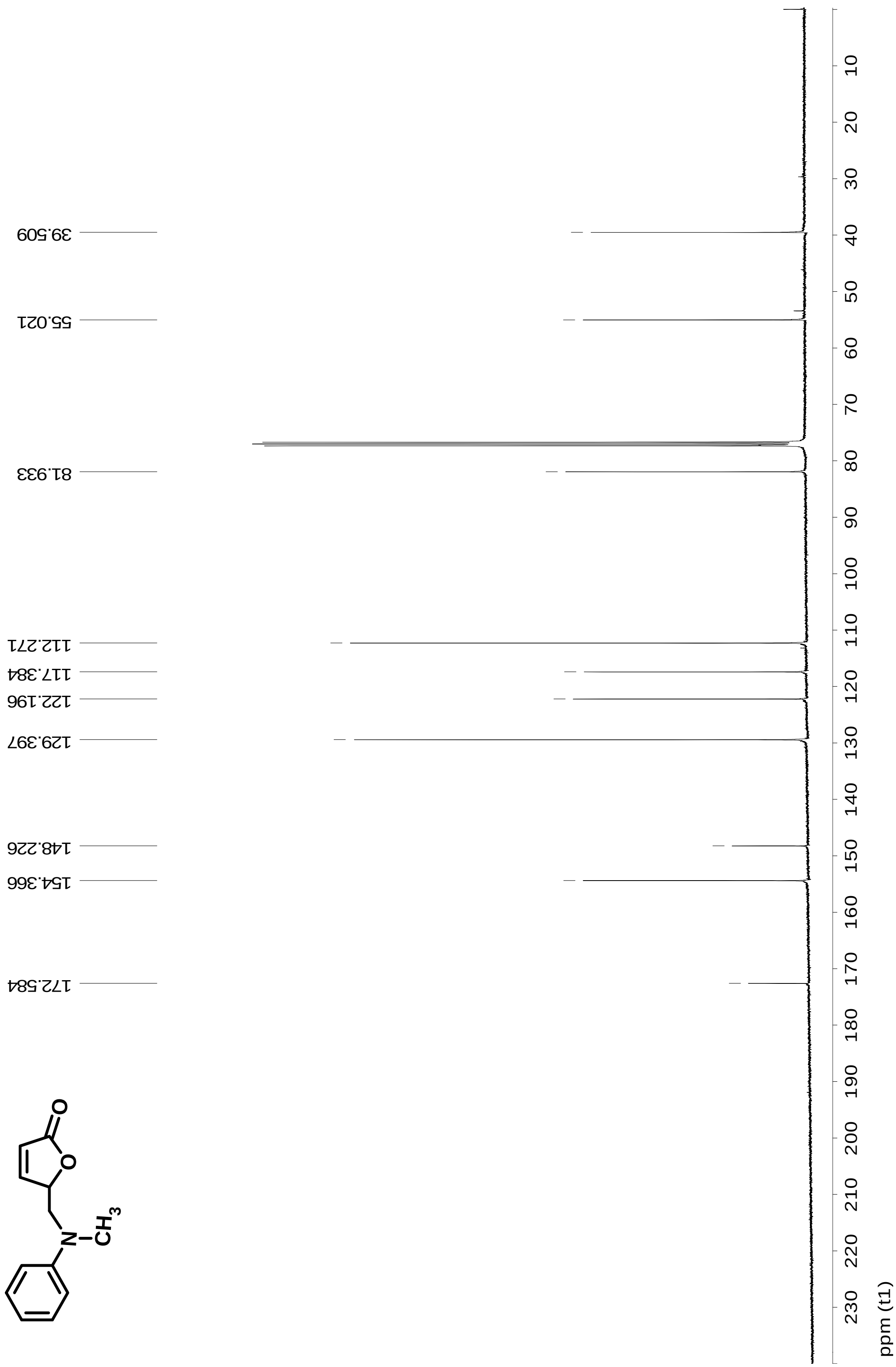
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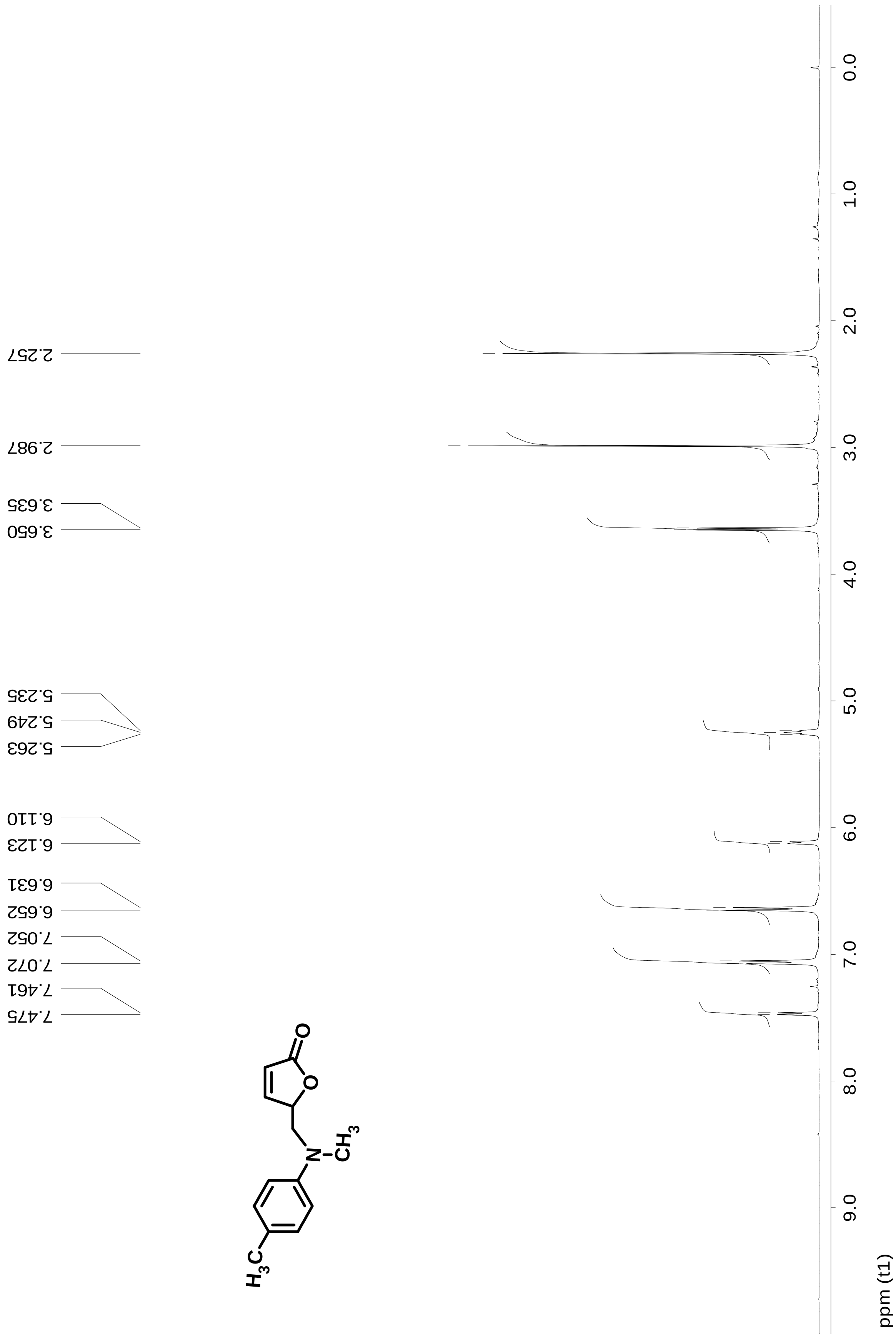
ppm (t1)



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3.650
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6.110
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6.652
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7.072
7.461
7.475
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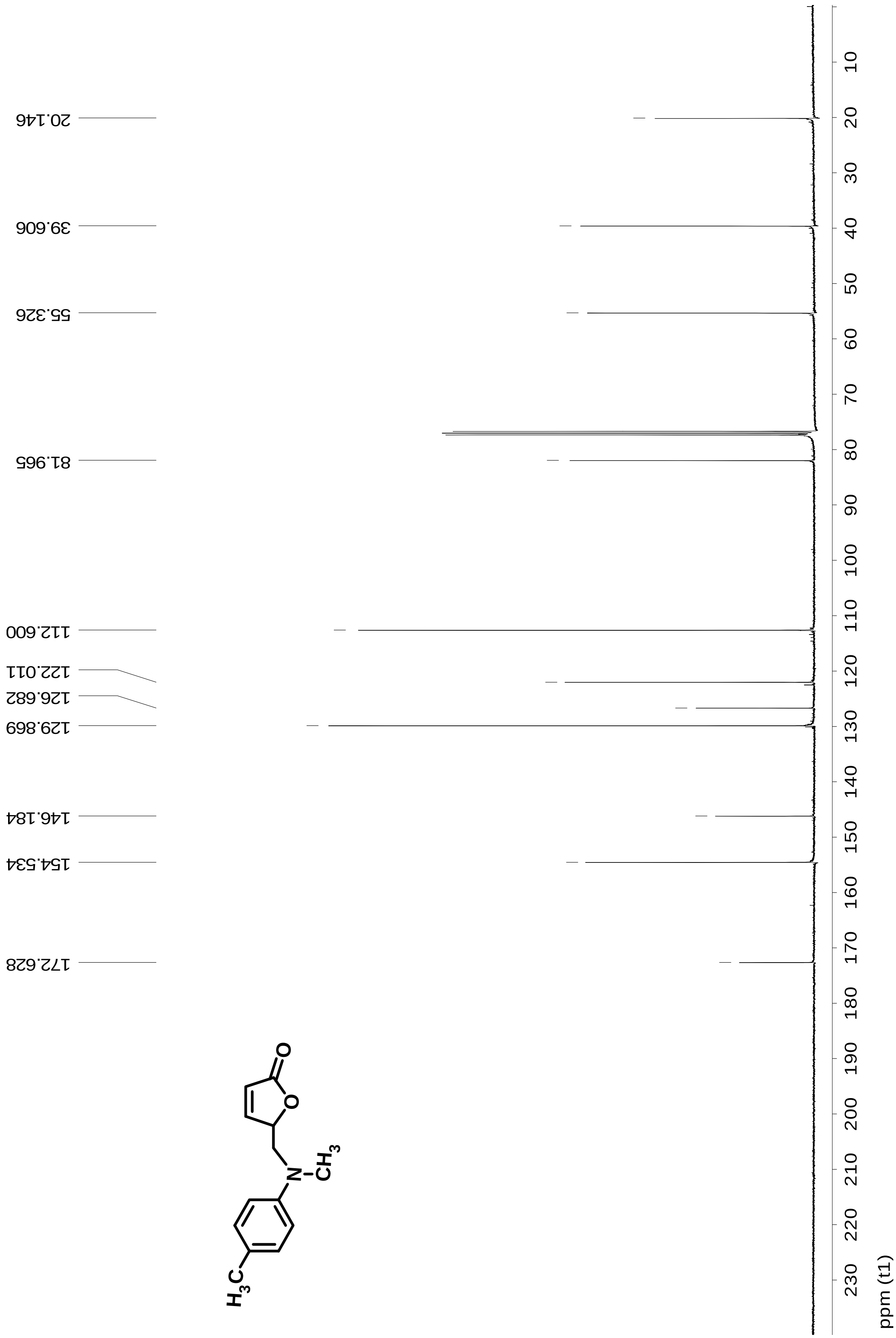
ppm (t1)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30
40
50
60
70
80
90
100
110
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190
200
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220
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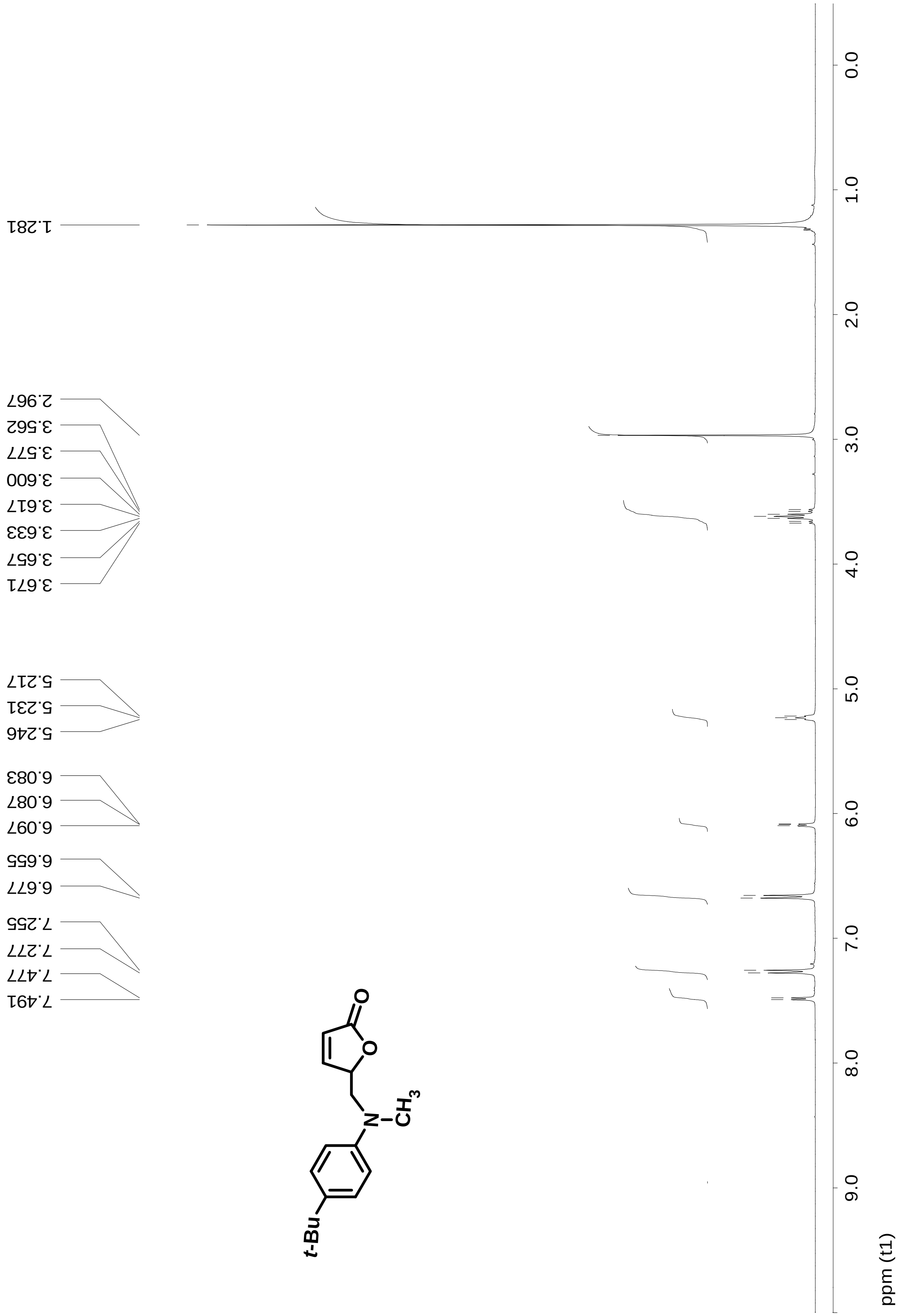
ppm (t1)
O
O
N
CH3
H3C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6.083
6.087
6.097
6.655
6.677
7.255
7.277
7.477
7.491
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1.0
2.0
3.0
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5.0
6.0
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ppm (t1)
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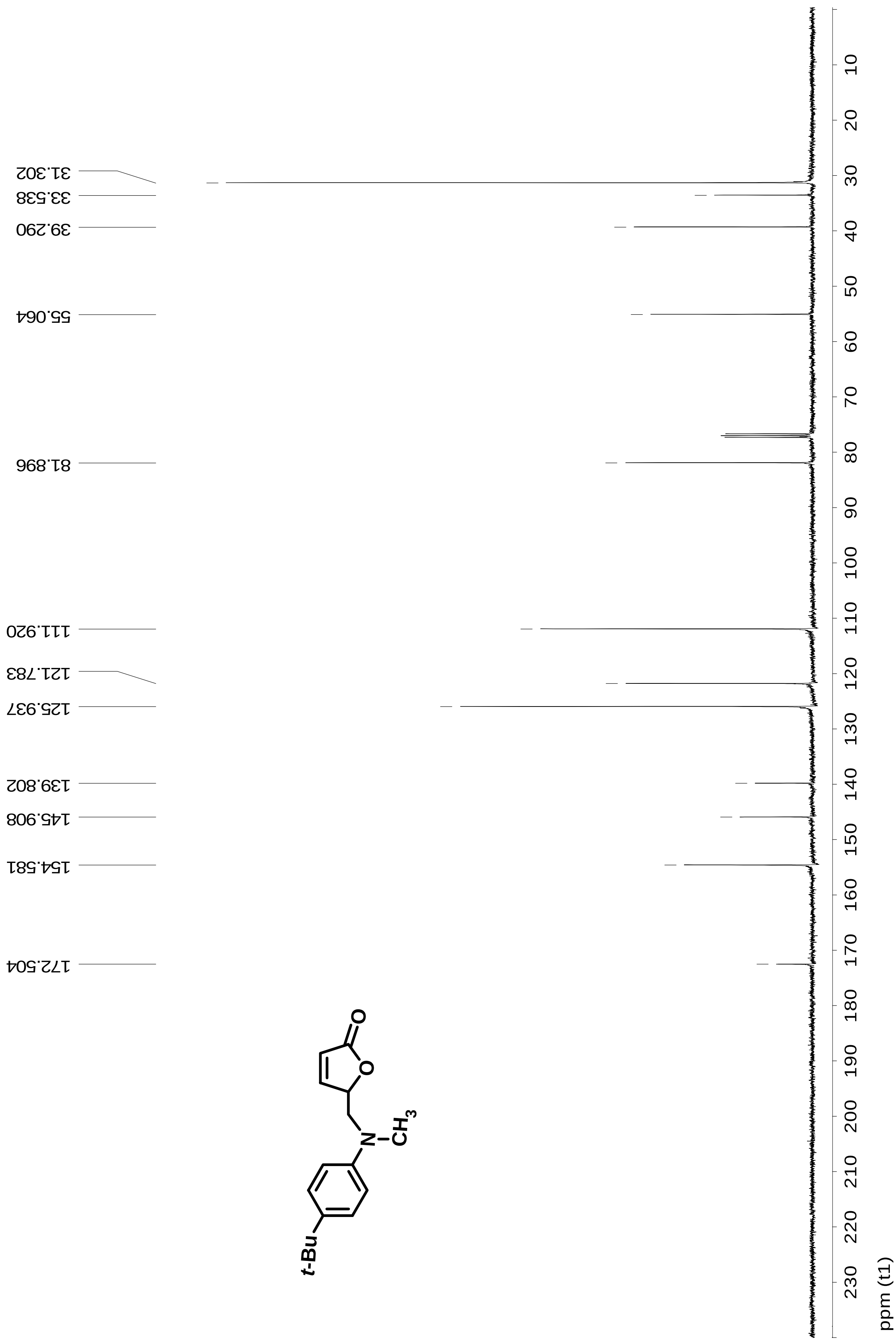
O
N
CH3
t-Bu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t-Bu
N
CH3
O


2.997
3.603
3.617
3.641
3.656
3.675
3.688
3.714
3.727
5.233
5.238
5.247
5.257
5.261
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6.144
6.153
6.158
6.572
6.595
7.309
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7.450
7.453
7.464
7.468
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1.0
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7.0
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ppm (t1)
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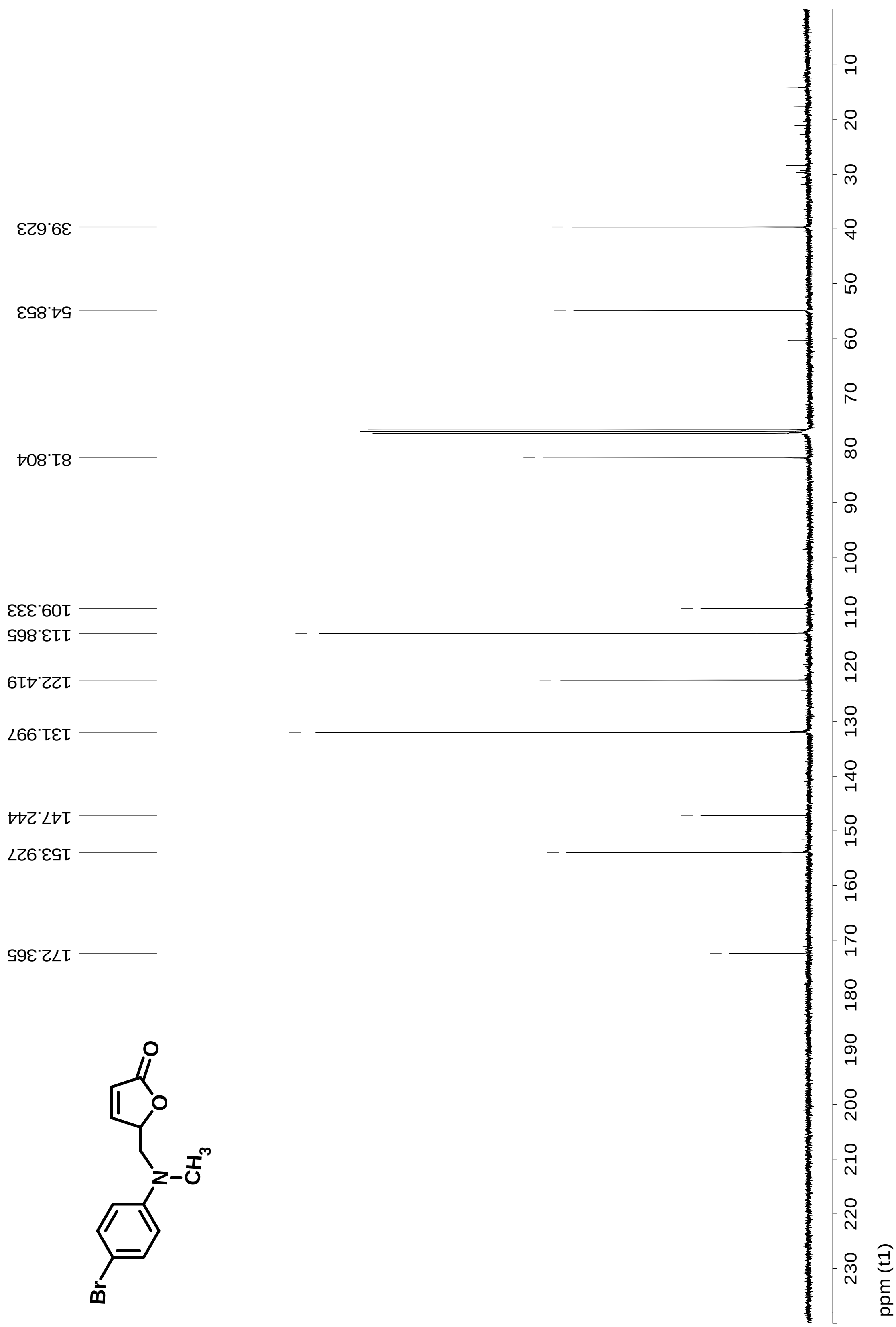
O
N
CH3
Br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50
60
70
80
90
100
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170
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200
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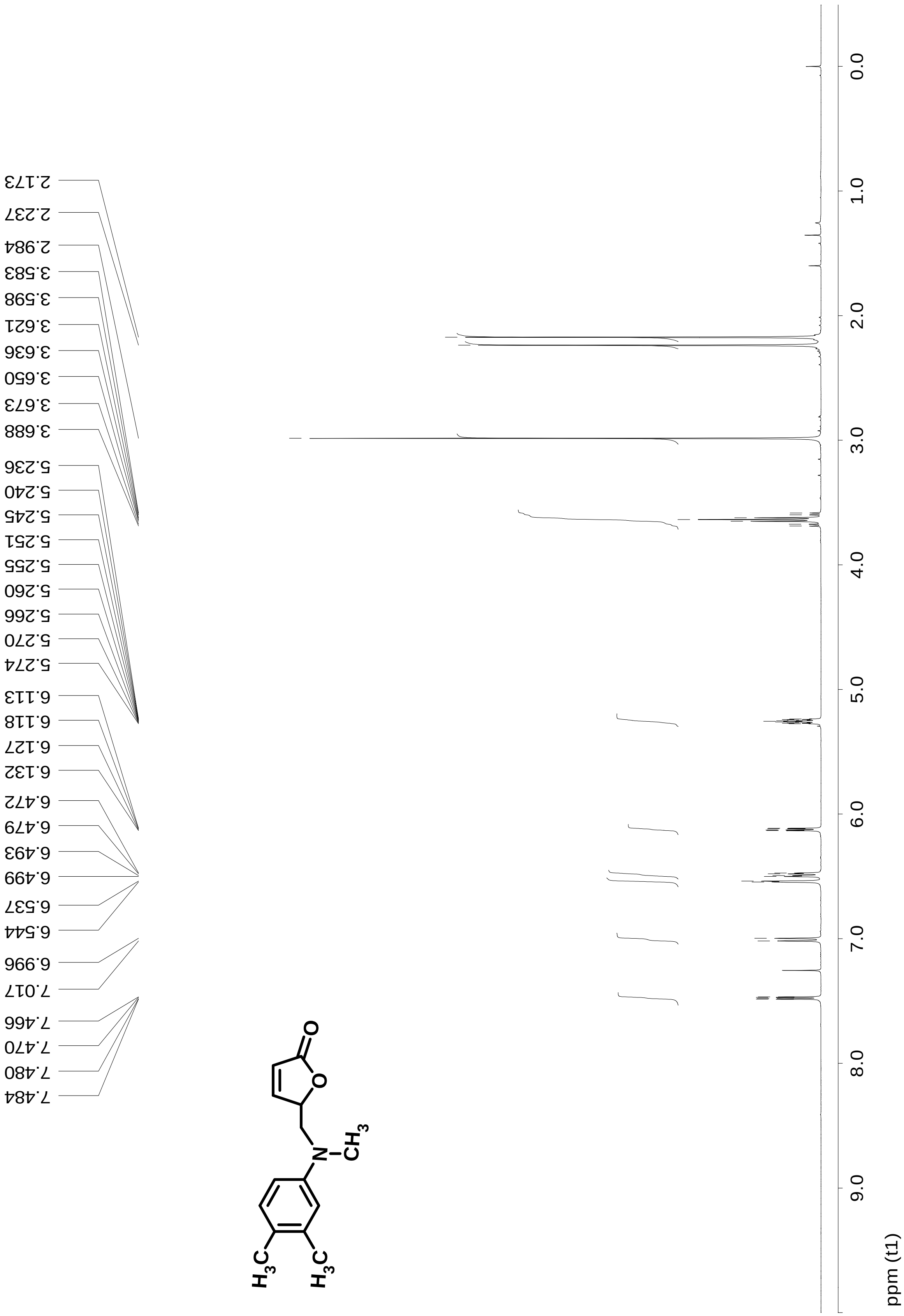
230
ppm (t1)
O
O
N
CH3
Br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5.251
5.255
5.260
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5.270
5.274
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6.118
6.127
6.132
6.472
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6.493
6.499
6.537
6.544
6.996
7.017
7.466
7.470
7.480
7.484
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N
CH3
H3C
H3C
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3.0
4.0
5.0
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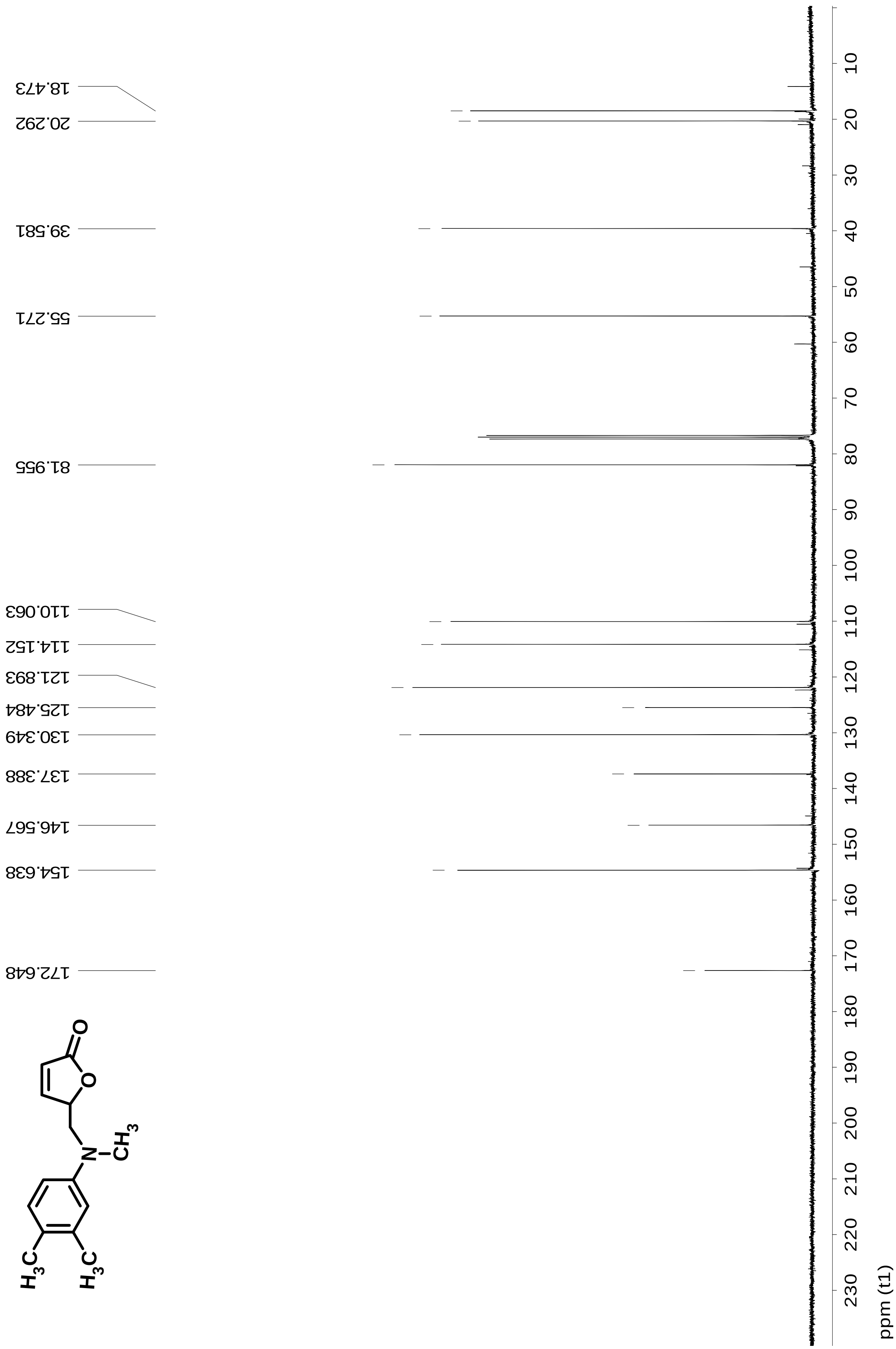
7.0
8.0
9.0
ppm (t1)



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121.893
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130.349
137.388
146.567
154.638
172.648
ppm (t1)


2.954
3.532
3.547
3.570
3.585
3.588
3.602
3.626
3.641
5.222
5.227
5.231
5.237
5.241
5.245
5.251
5.256
5.260
5.889
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6.137
6.144
6.149
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7.461
7.472
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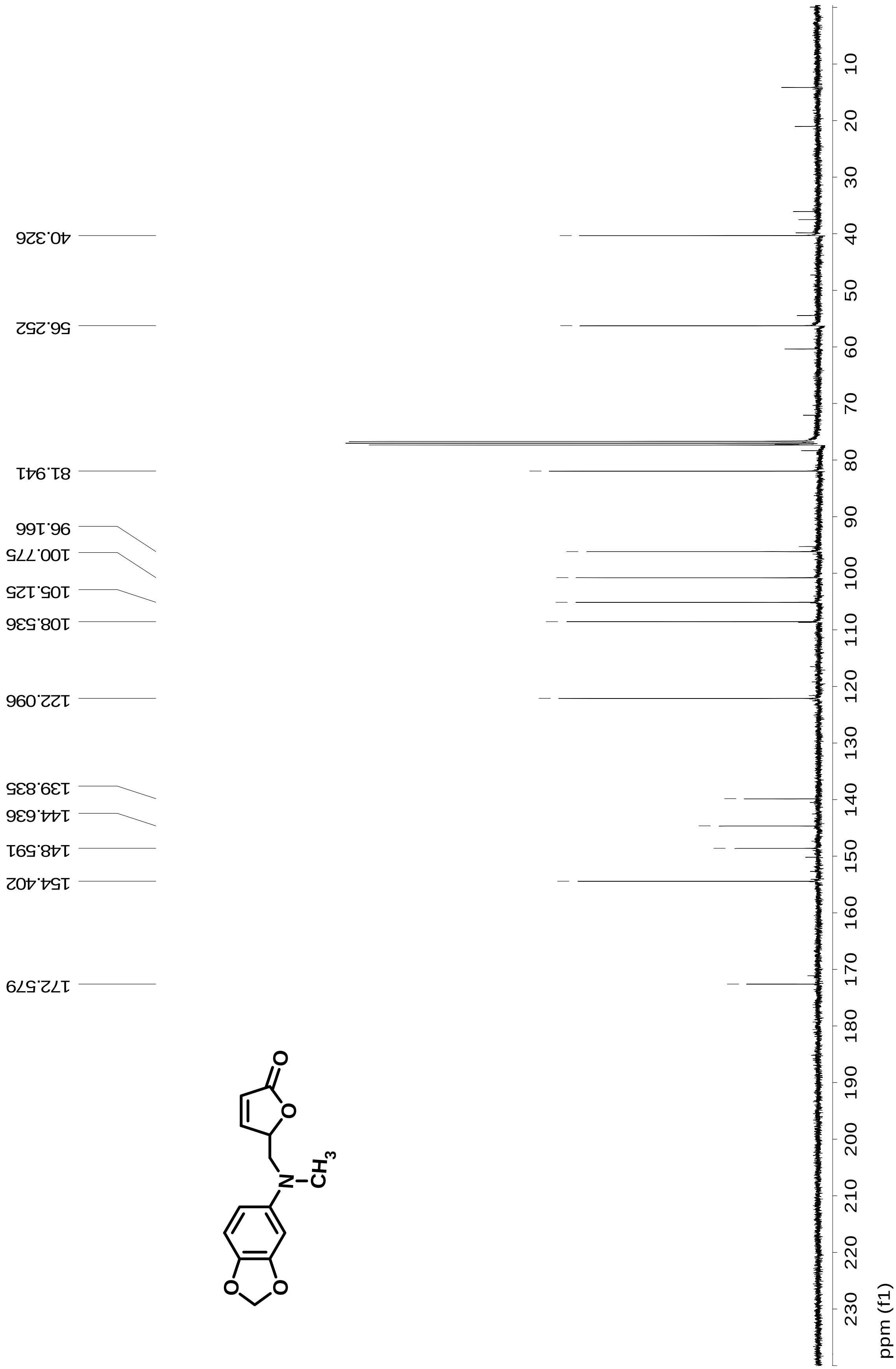
3.0
4.0
5.0
6.0
7.0
8.0
9.0
ppm (f1)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154.402
172.579
ppm (f1)

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3.326
3.341
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5.111
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5.266
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5.655
5.658
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7.357
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7.500
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N
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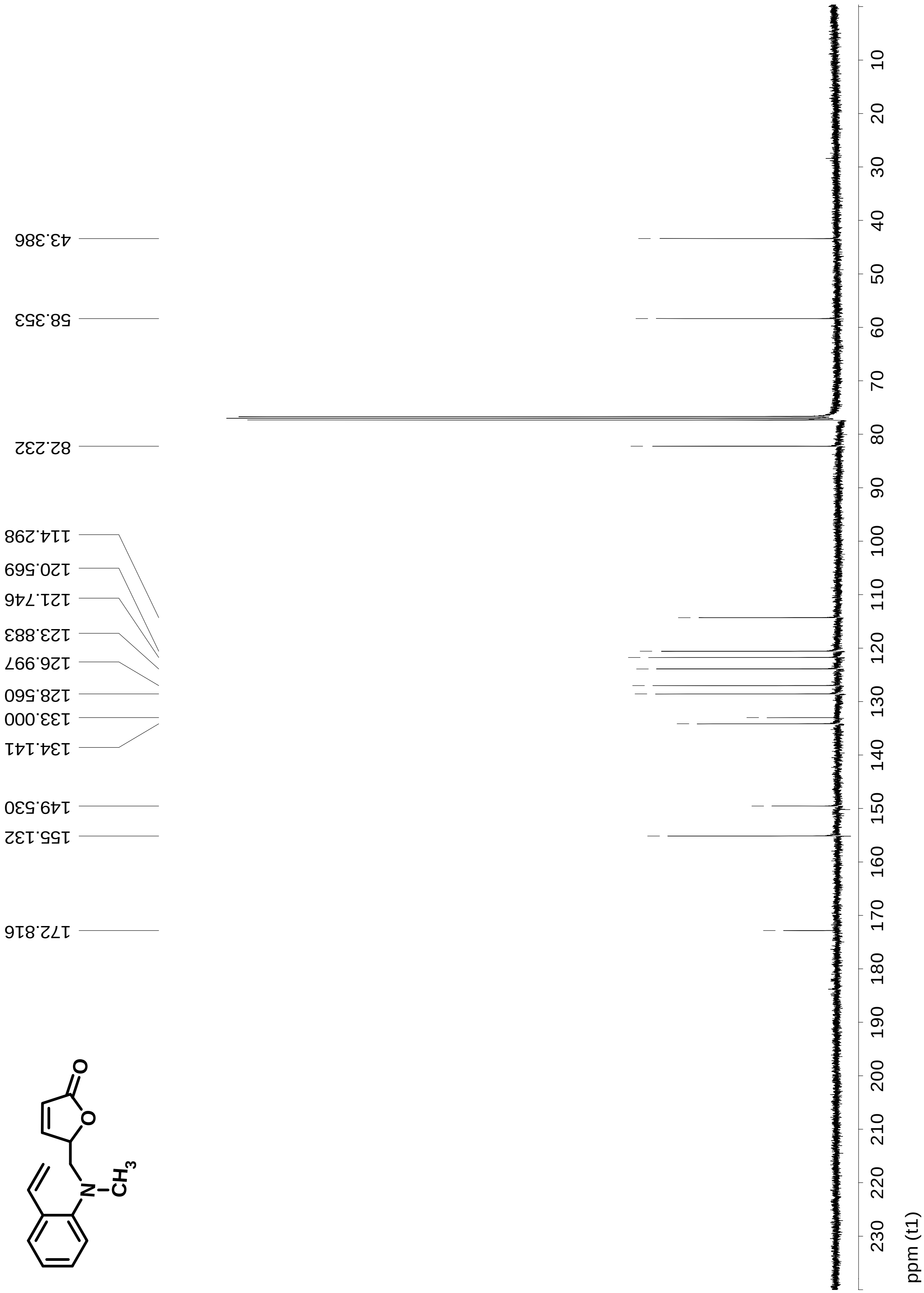
9.0
ppm (t1)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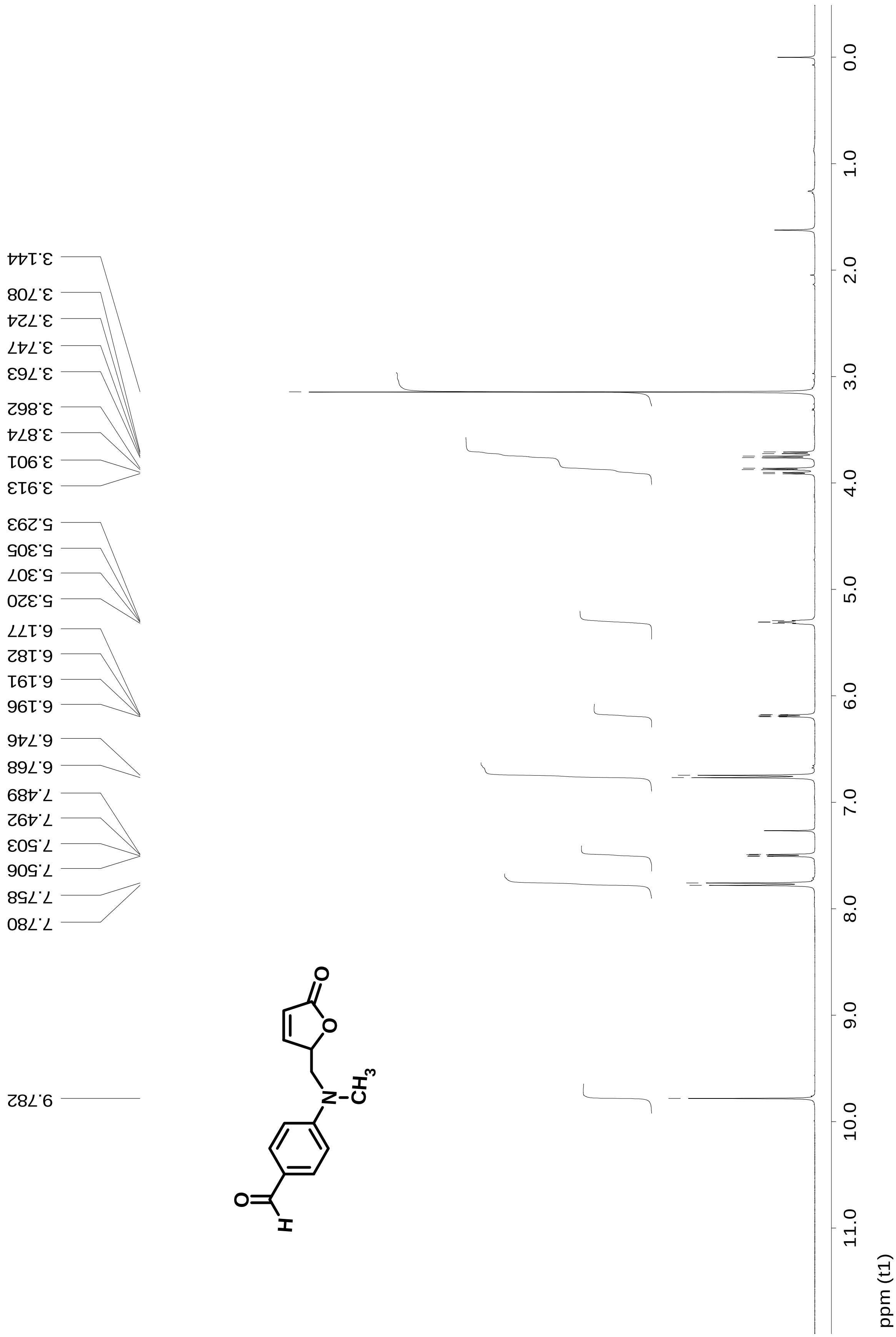
172.816
ppm (t1)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5.307
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6.177
6.182
6.191
6.196
6.746
6.768
7.489
7.492
7.503
7.506
7.758
7.780
9.782
0.0
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6.0
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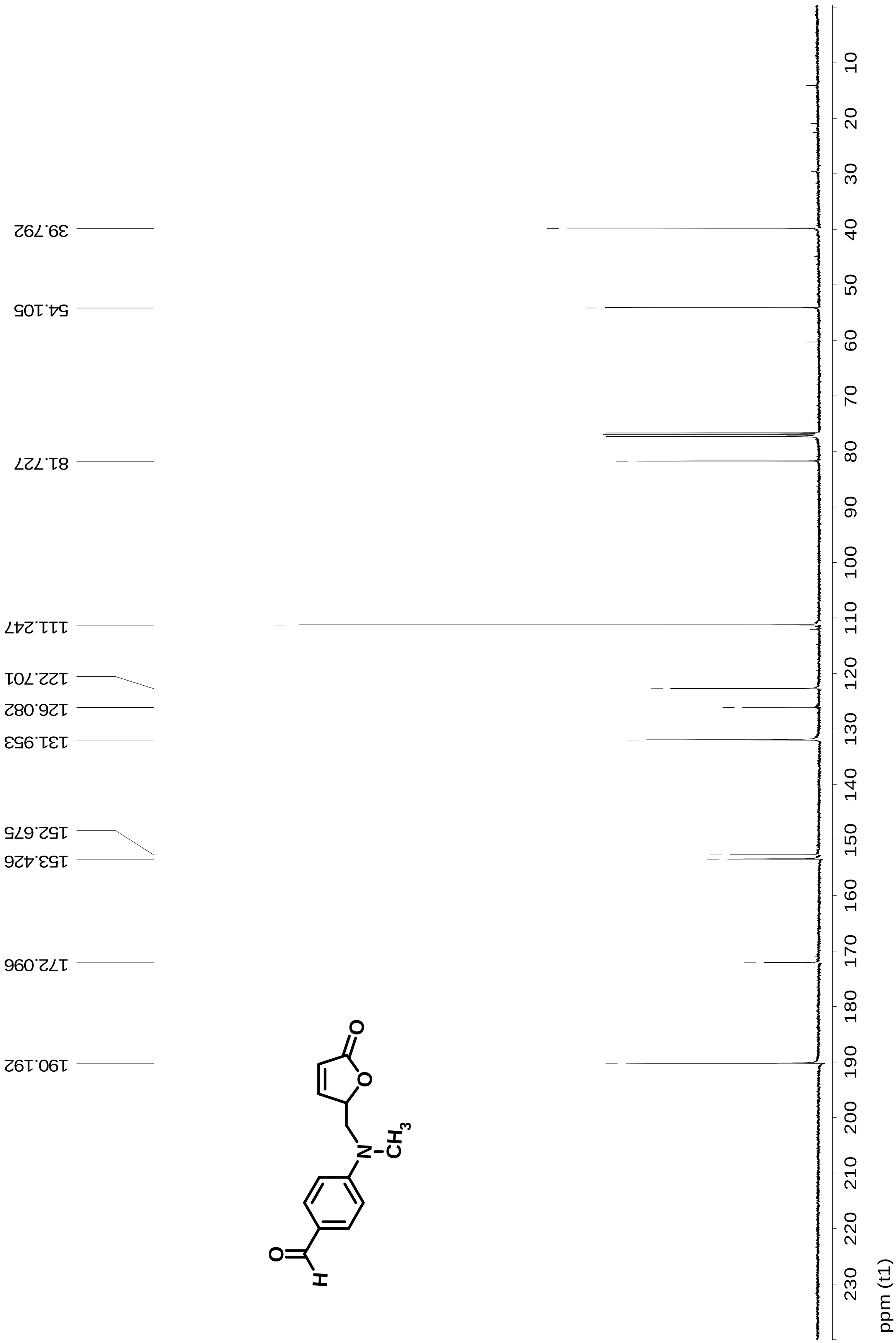
10.0
11.0
ppm (t1)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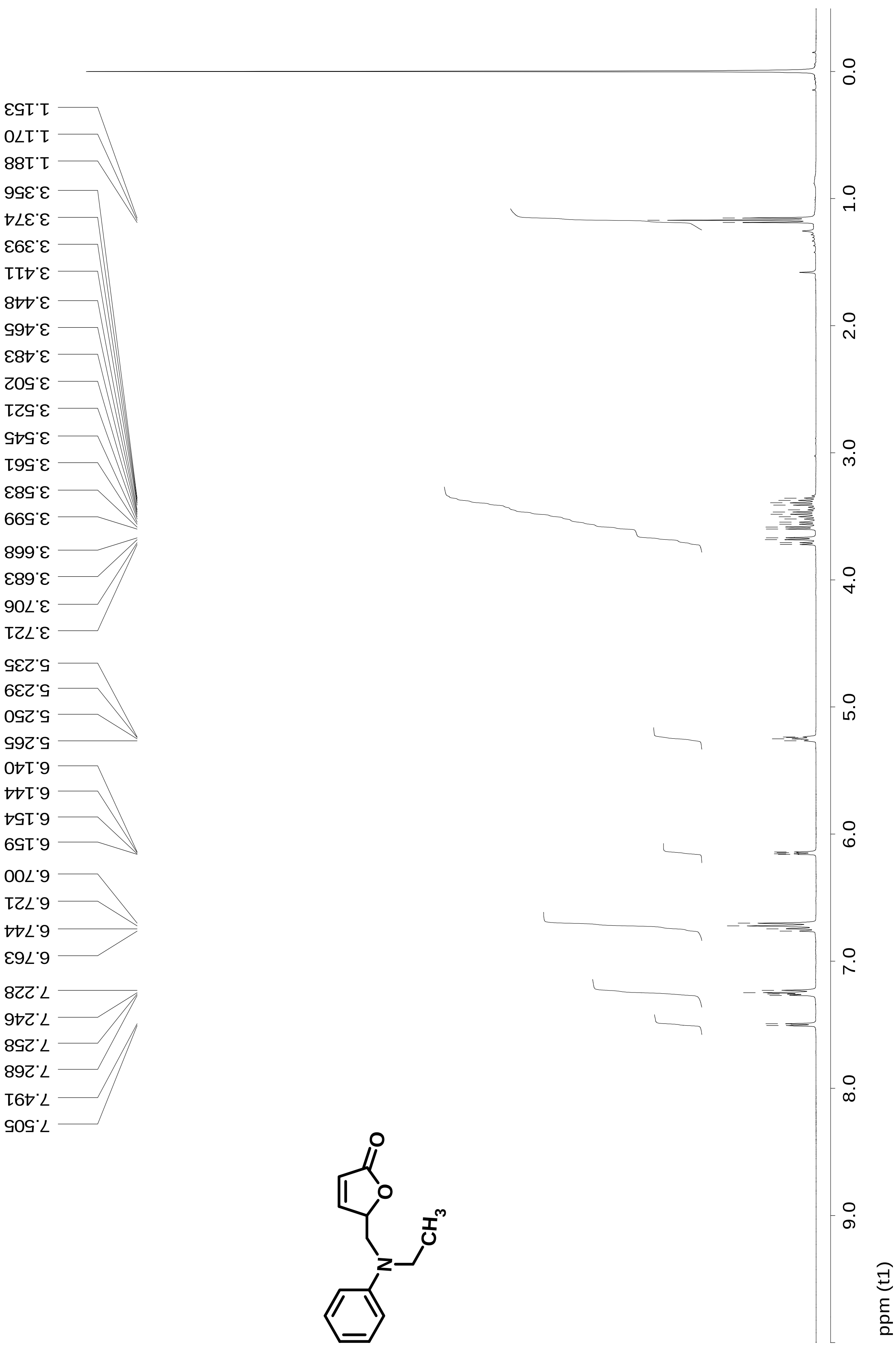
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3.545
3.561
3.583
3.599
3.668
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3.706
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5.250
5.265
6.140
6.144
6.154
6.159
6.700
6.721
6.744
6.763
7.228
7.246
7.258
7.268
7.491
7.505
0.0
1.0
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5.0
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9.0
ppm (t1)
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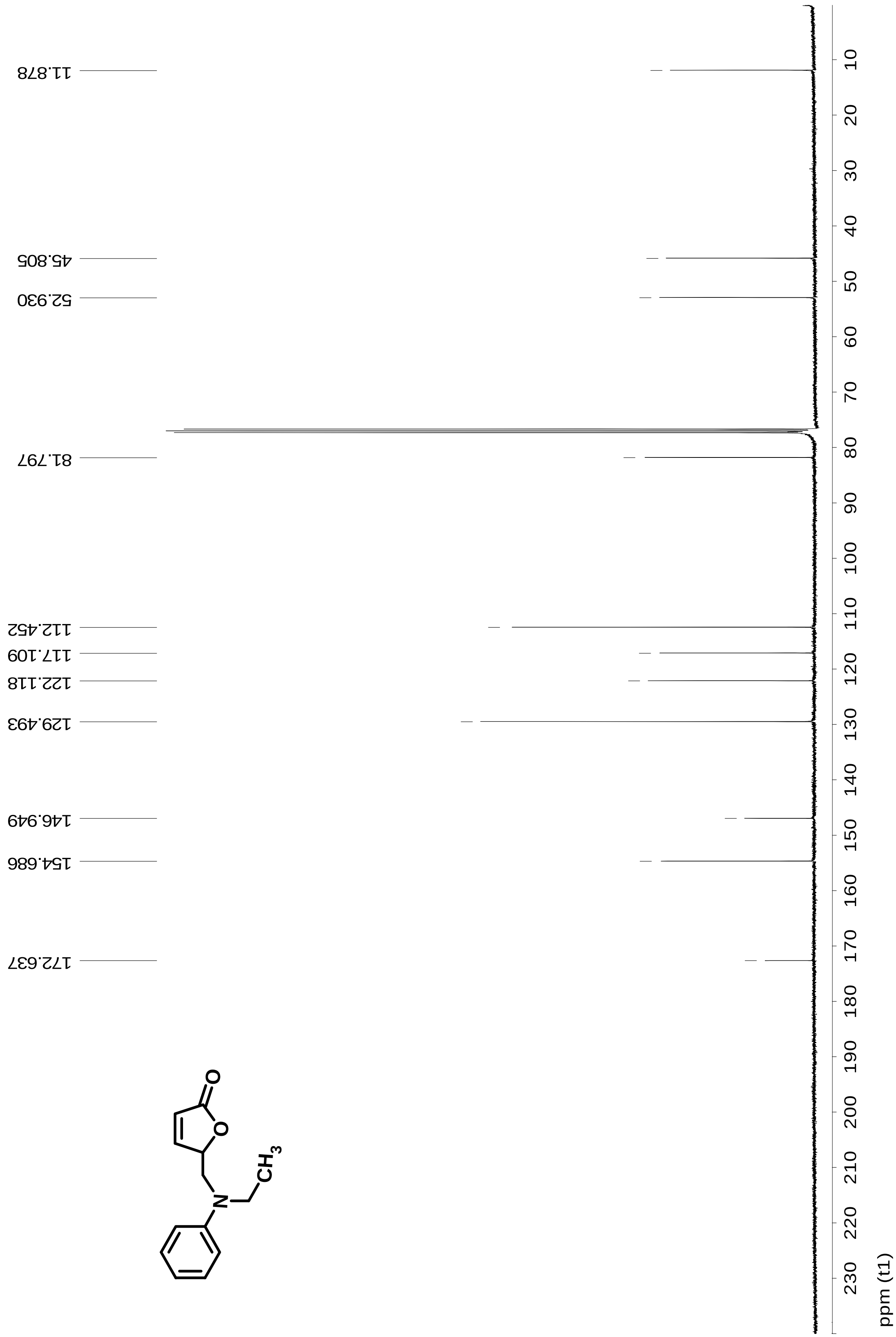
O
N
CH3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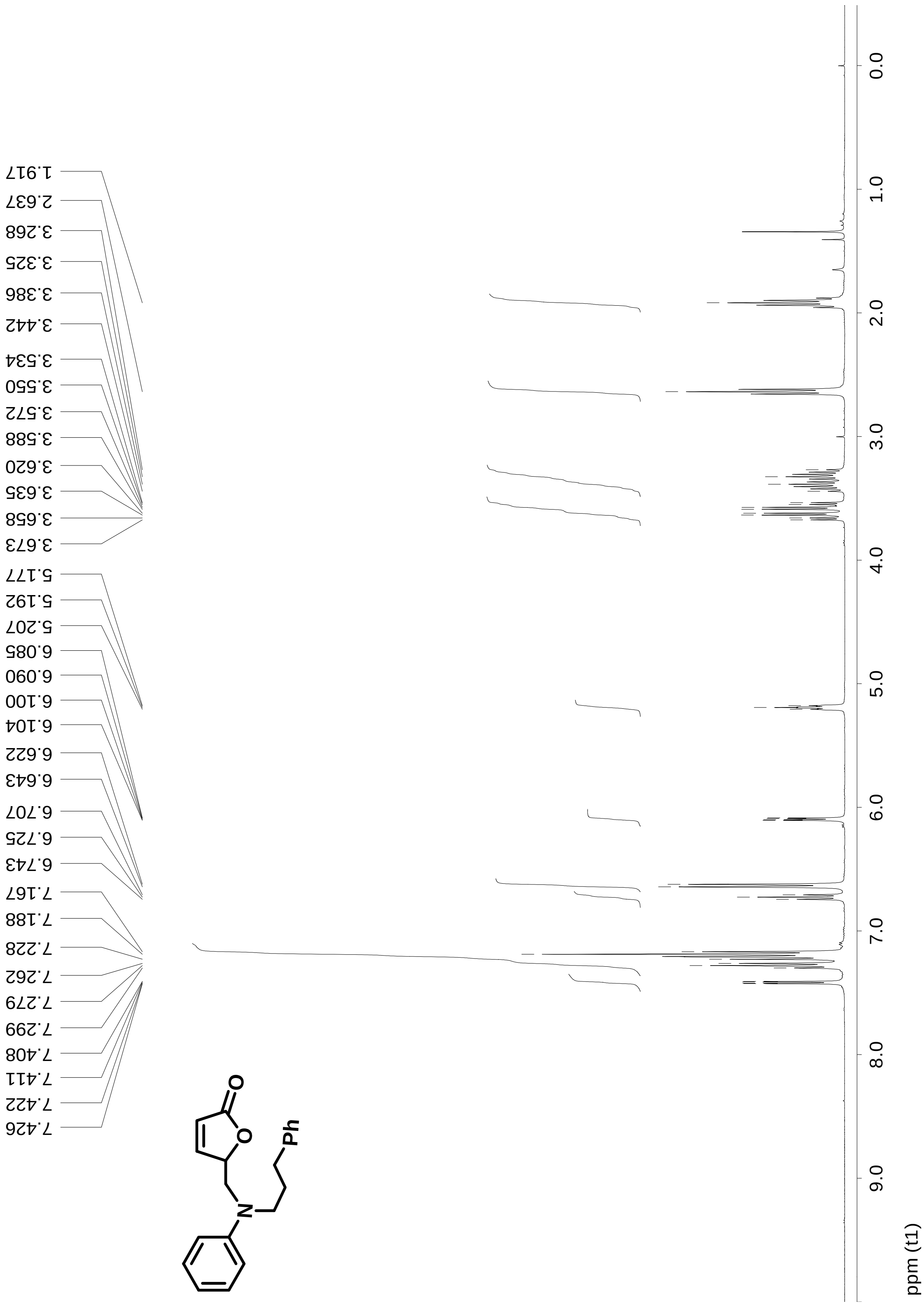
CH3
ppm (t1)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3.658
3.673
5.177
5.192
5.207
6.085
6.090
6.100
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6.622
6.643
6.707
6.725
6.743
7.167
7.188
7.228
7.262
7.279
7.299
7.408
7.411
7.422
7.426
O
O
N
Ph
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3.0
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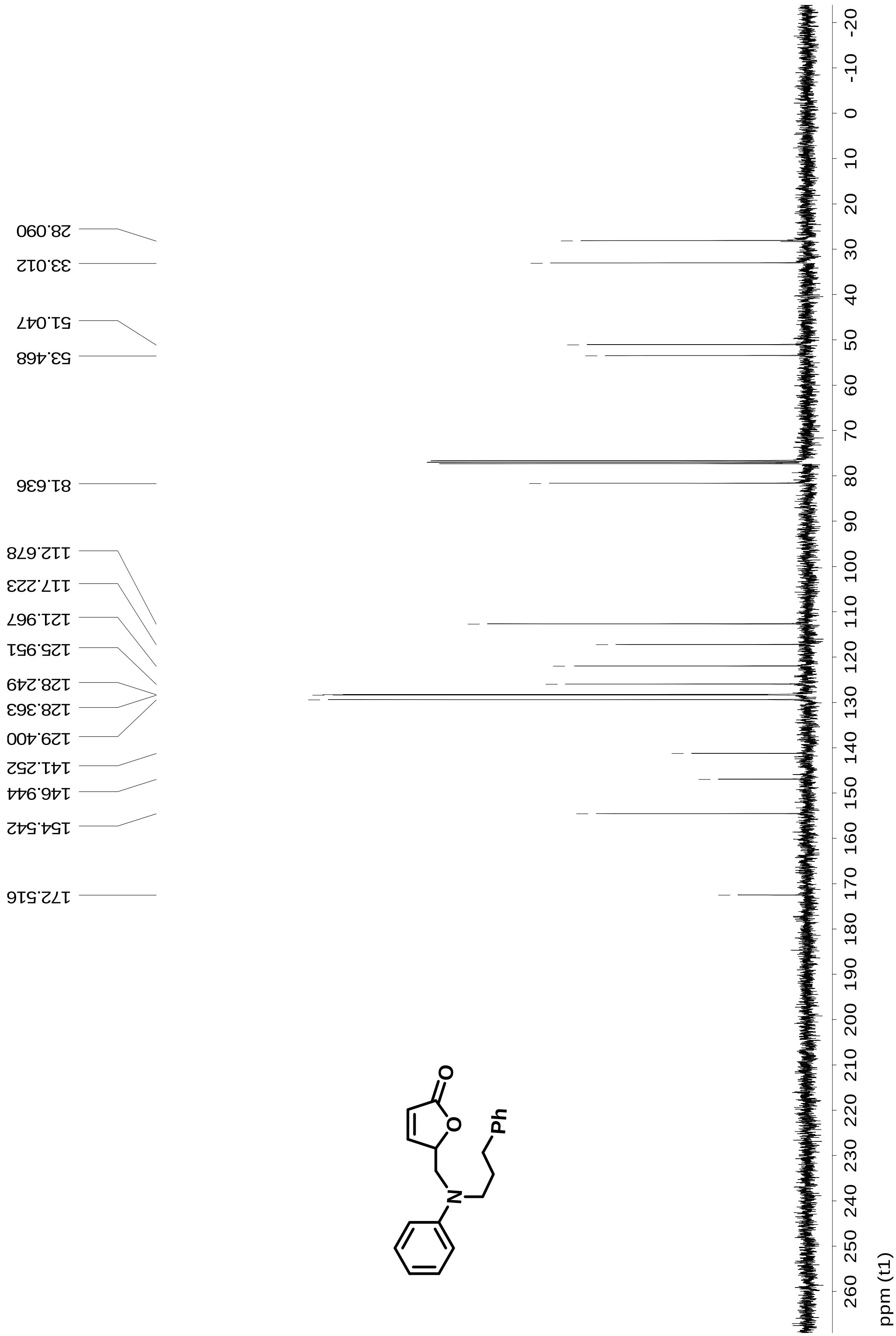
7.0
8.0
9.0
ppm (t1)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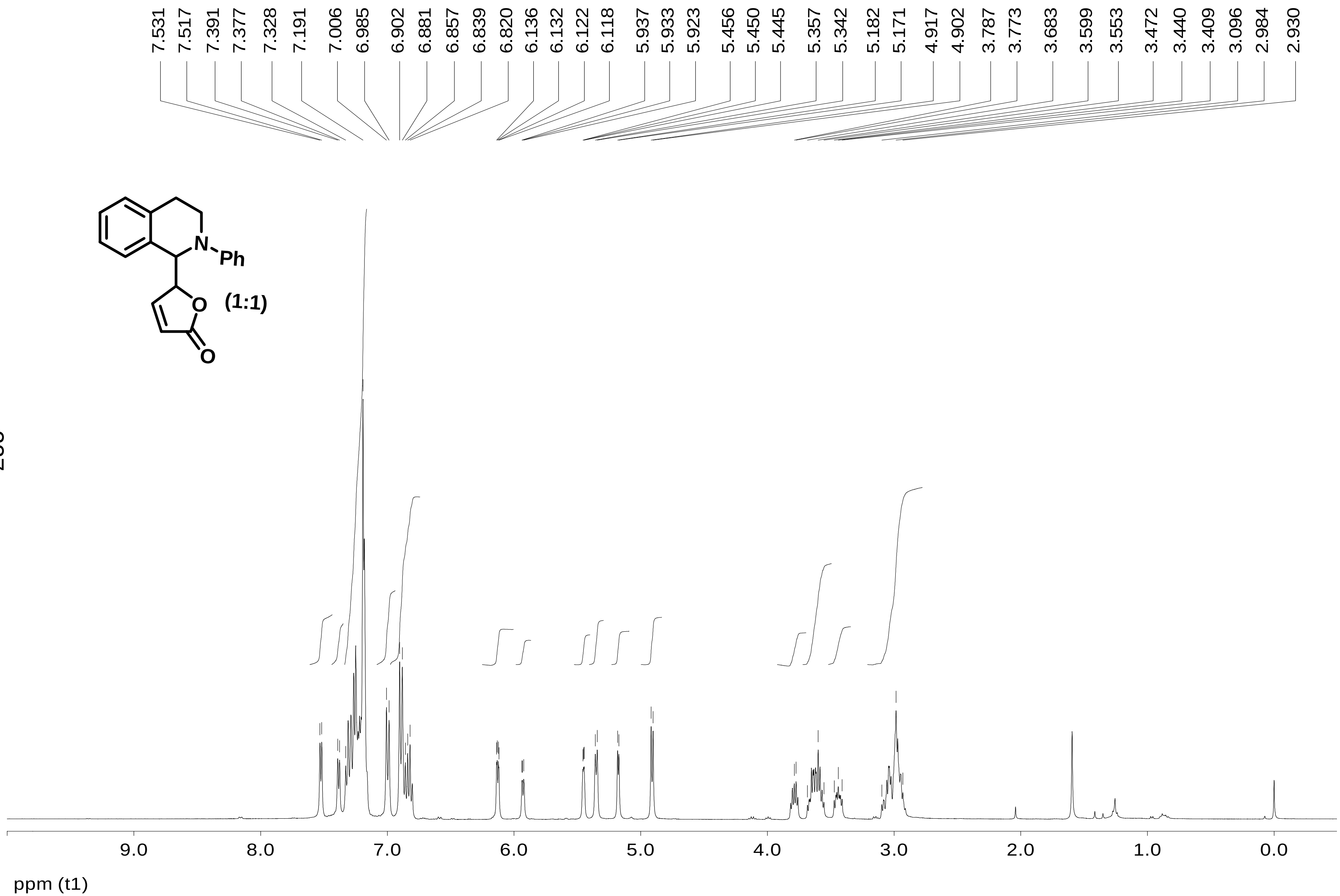
ppm (t1)
O
O
N
Ph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6.820
6.136
6.132
6.122
6.118
5.937
5.933
5.923
5.456
5.450
5.445
5.357
5.342
5.182
5.171
4.917
4.902
3.787
3.773
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Ph
O
O
(1:1)
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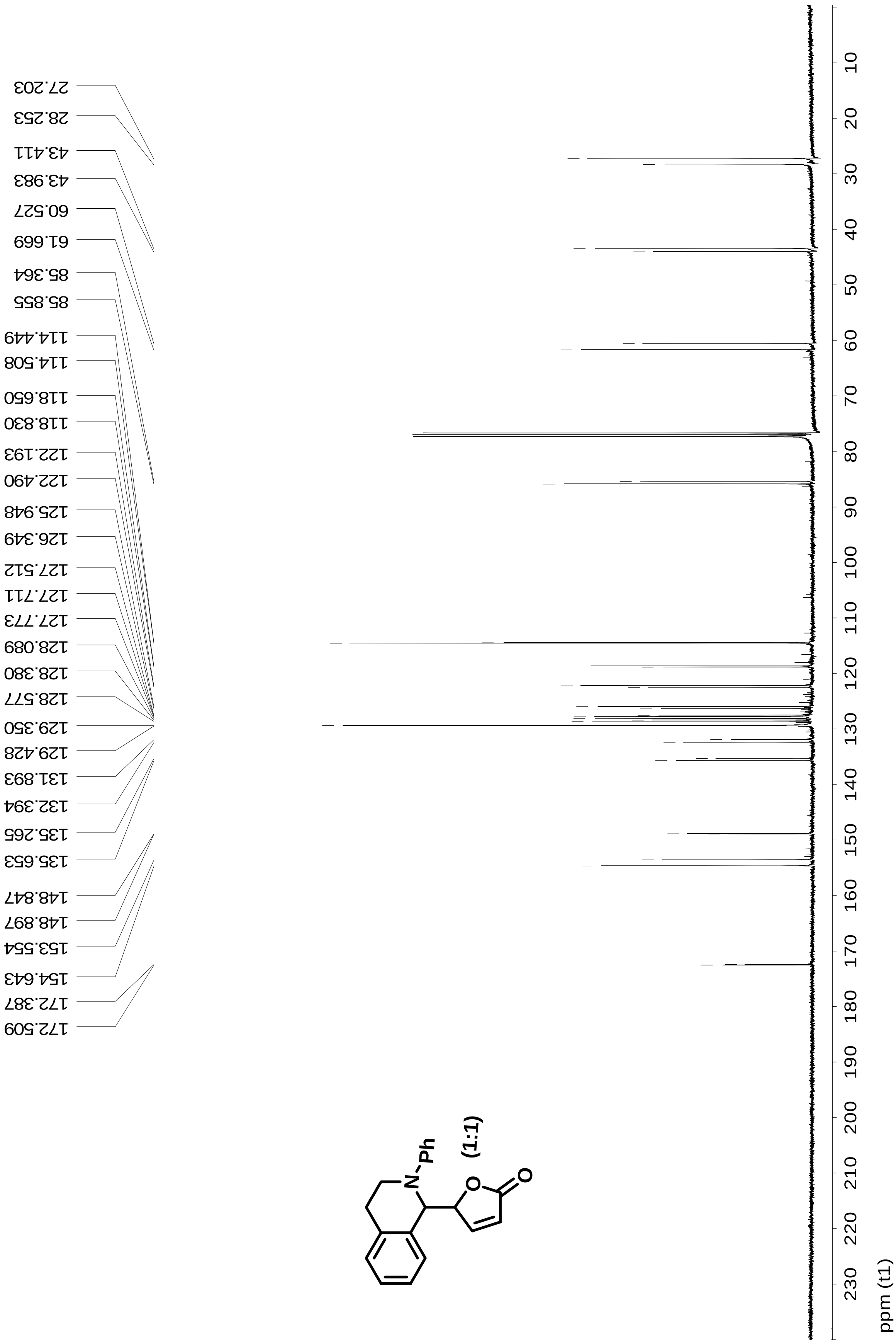
0.0
ppm (t1)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28.253
43.411
43.983
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61.669
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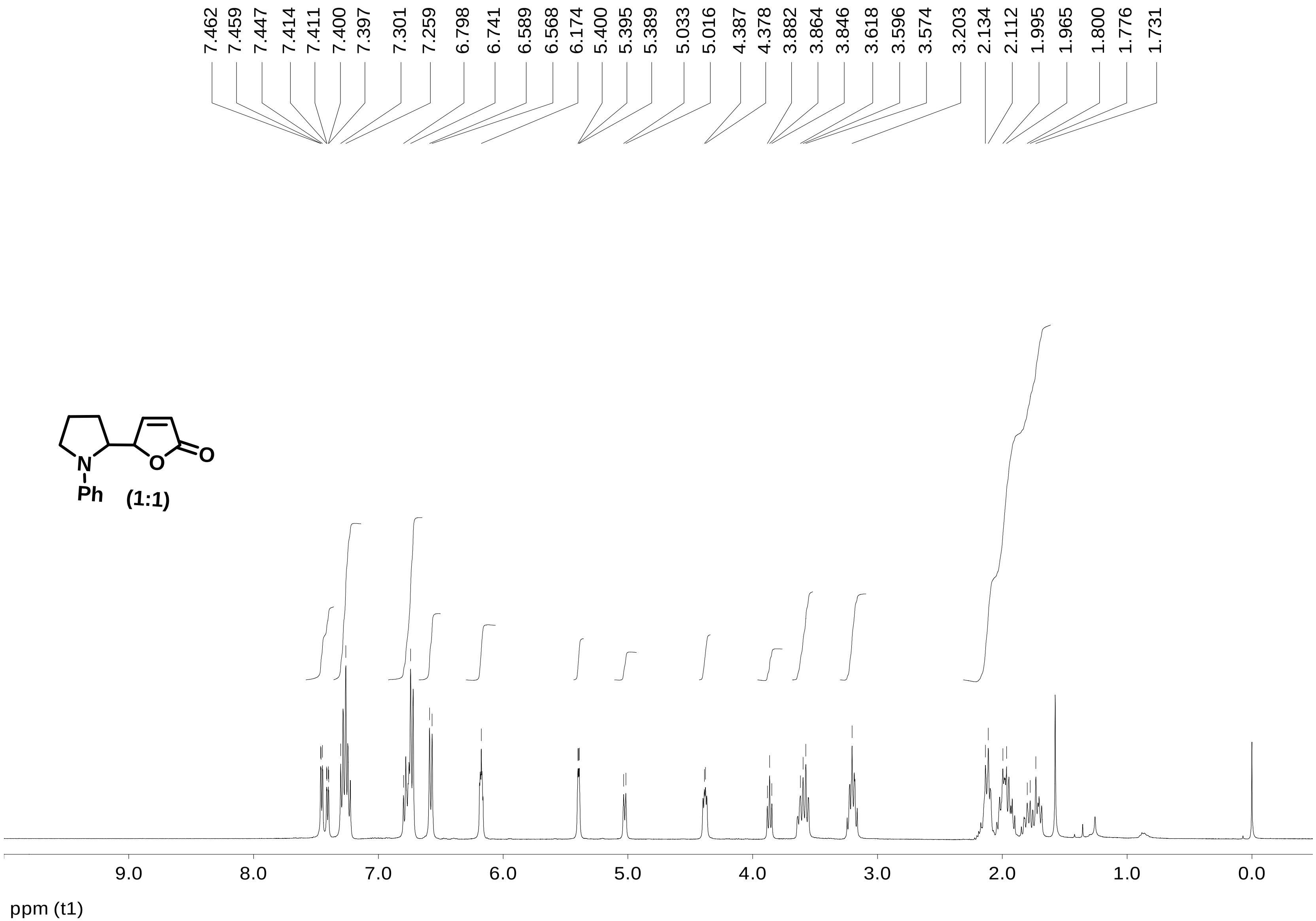
85.855
114.449
114.508
118.650
118.830
122.193
122.490
125.948
126.349
127.512
127.711
127.773
128.089
128.380
128.577
129.350
129.428
131.893
132.394
135.265
135.653
148.847
148.897
153.554
154.643
172.387
172.509
N
Ph
O
O
(1:1)
ppm (t1)



7.462
7.459
7.447
7.414
7.411
7.400
7.397
7.301
7.259
6.798
6.741
6.589
6.568
6.174
5.400
5.395
5.389
5.033
5.016
4.387
4.378
3.882
3.864
3.846
3.618
3.596
3.574
3.203
2.134
2.112
1.995
1.965
1.800
1.776
1.731
N
Ph
O
O
(1:1)
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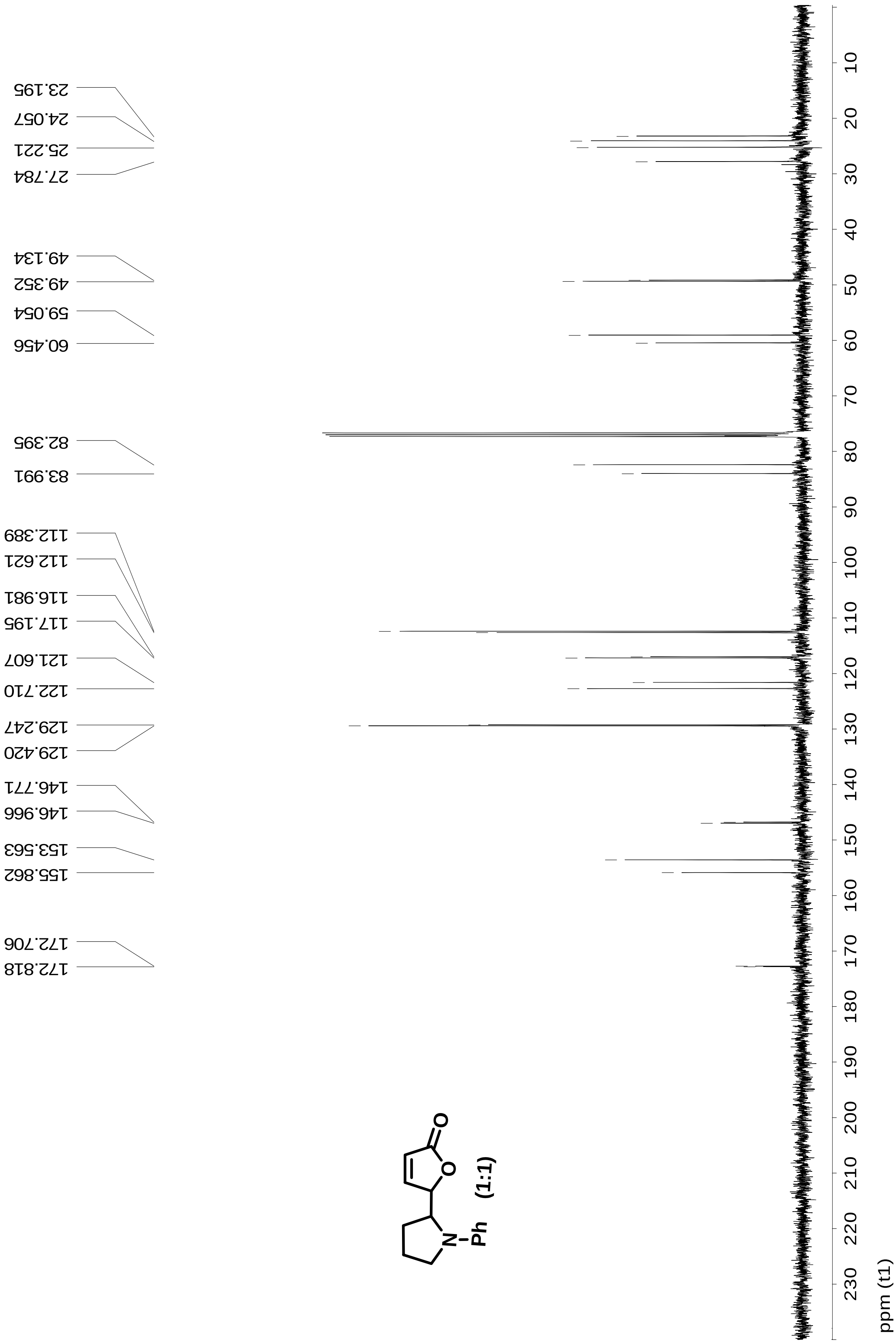
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


23.195
24.057
25.221
27.784
49.134
49.352
59.054
60.456
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83.991
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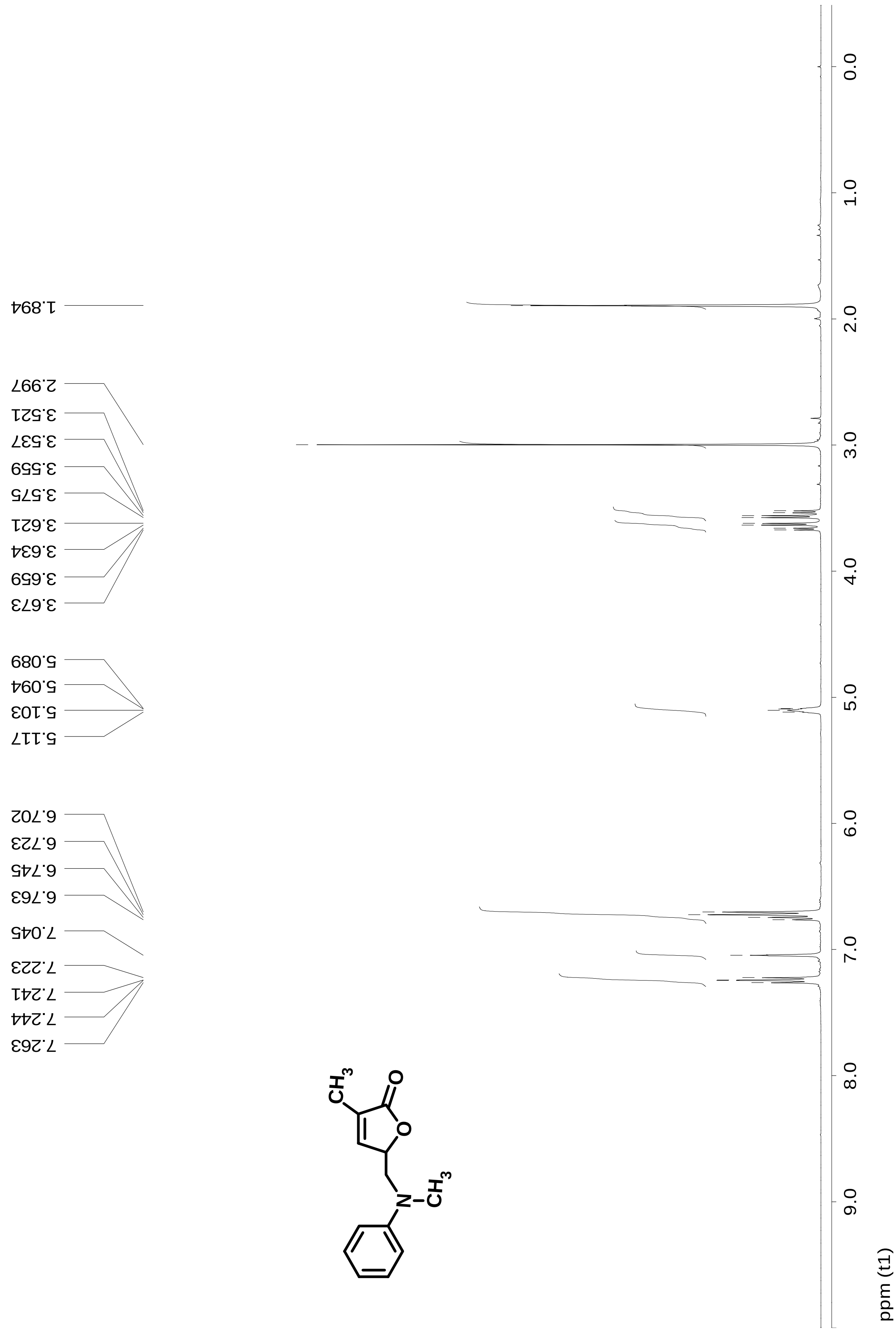
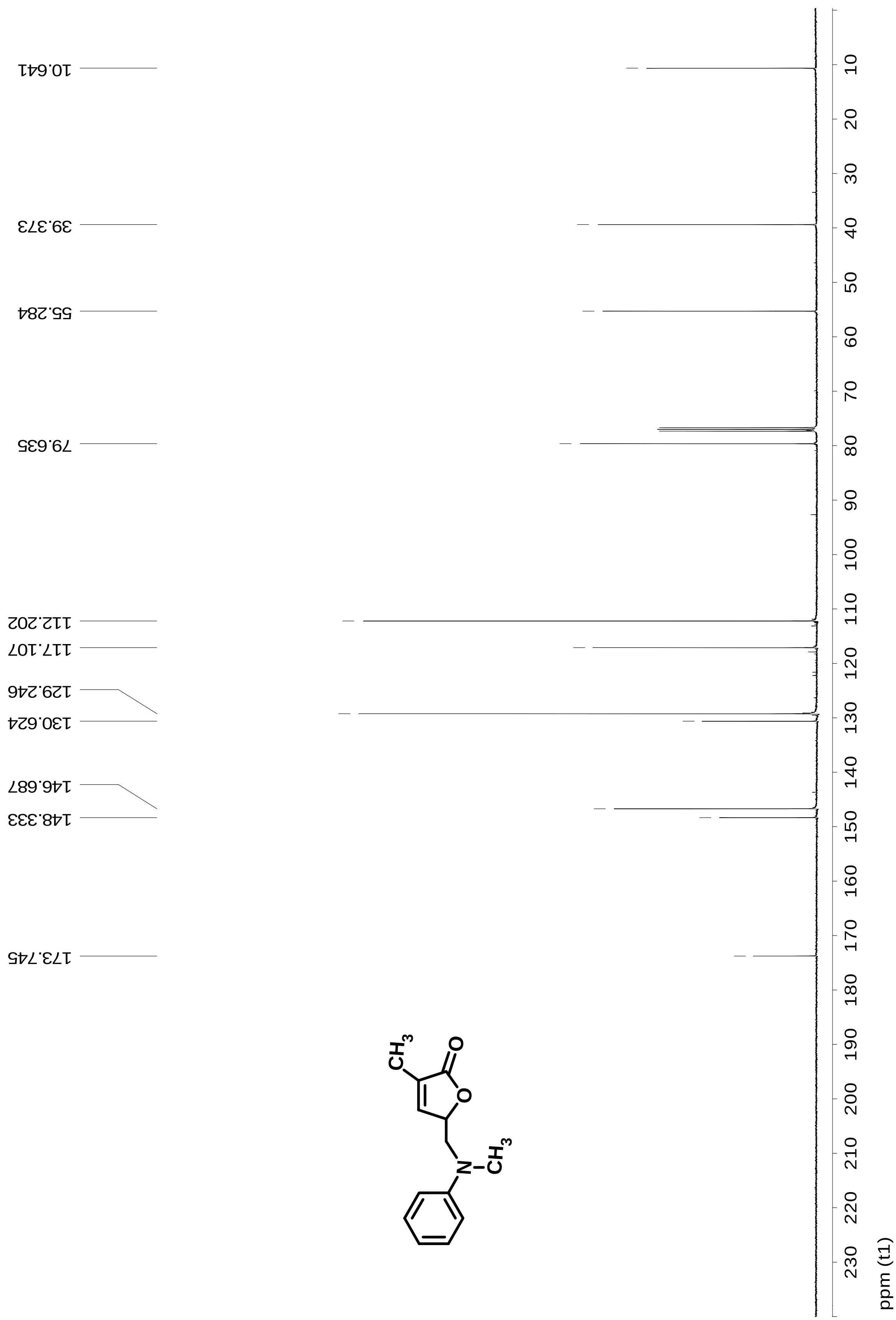
112.621
116.981
117.195
121.607
122.710
129.247
129.420
146.771
146.966
153.563
155.862
172.706
172.818
(1:1)
Ph
ppm (t1)


1.894
2.997
3.521
3.537
3.559
3.575
3.621
3.634
3.659
3.673
5.089
5.094
5.103
5.117
6.702
6.723
6.745
6.763
7.045
7.223
7.241
7.244
7.263
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
ppm (t1)
CH3
O
N
CH3



10.641
39.373
55.284
79.635
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129.246
130.624
146.687
148.333
173.745
CH3
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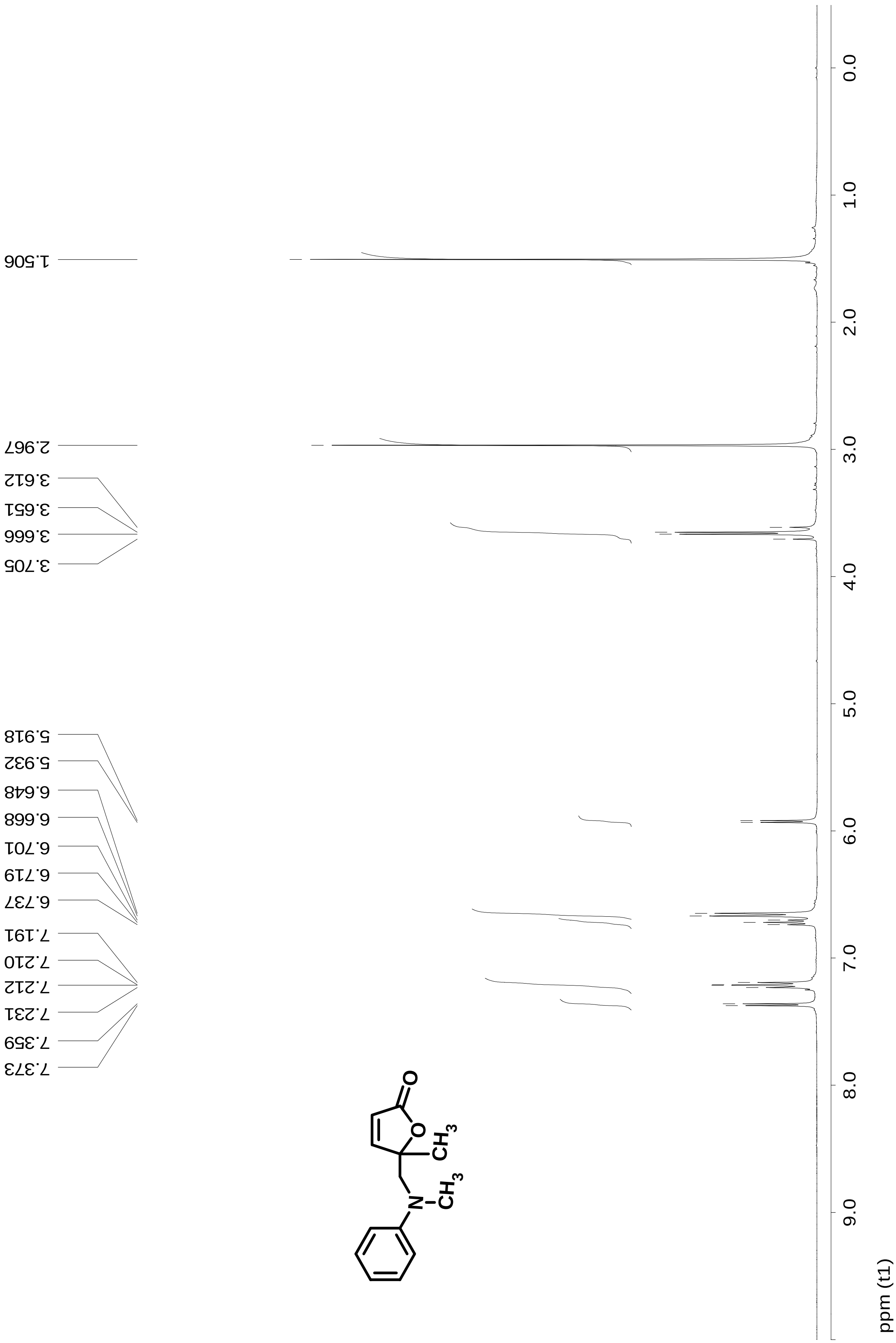
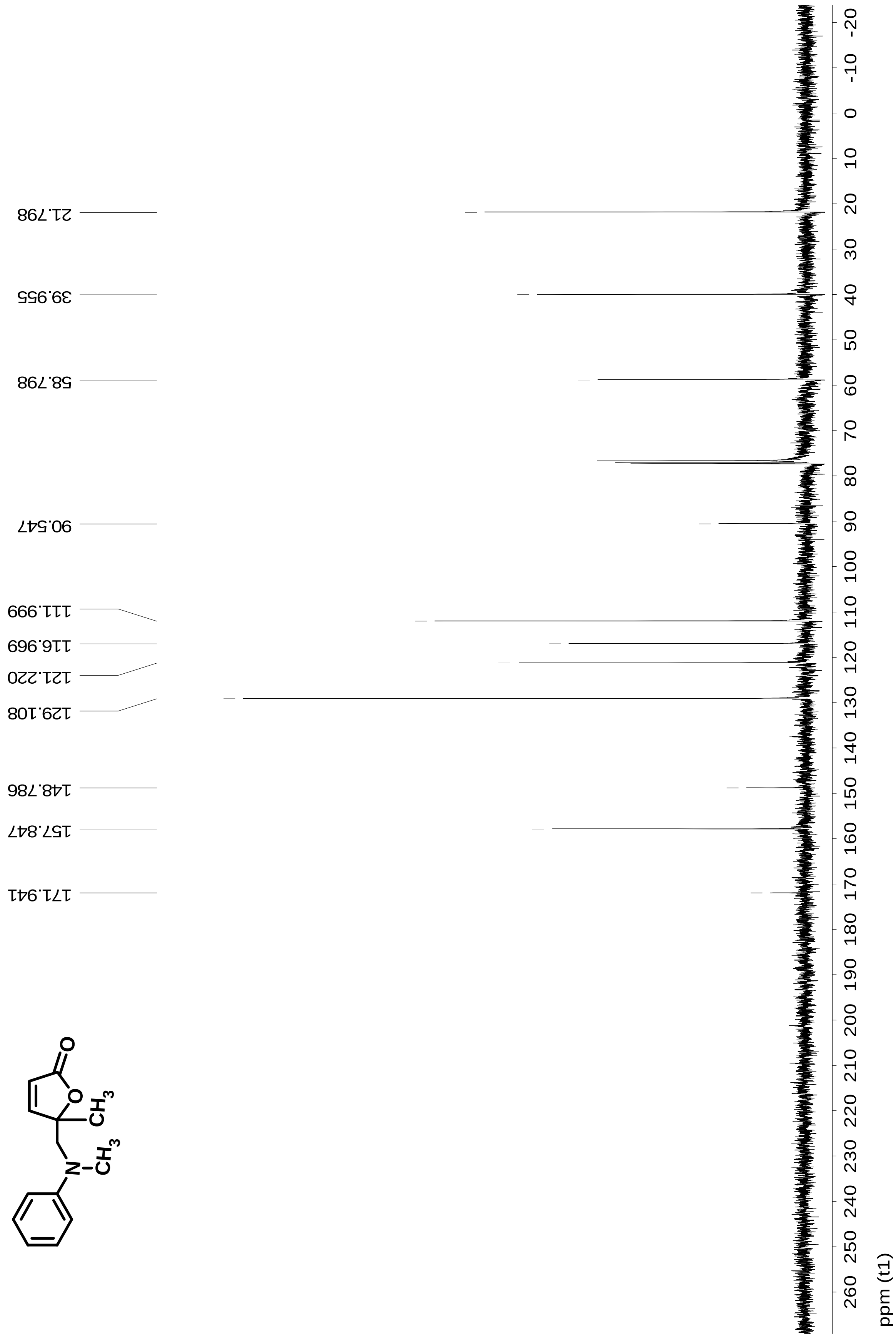
O
N
CH3
ppm (t1)


1.506
2.967
3.612
3.651
3.666
3.705
5.918
5.932
6.648
6.668
6.701
6.719
6.737
7.191
7.210
7.212
7.231
7.359
7.373
O
O
CH3
N
CH3
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
ppm (t1)


21.798
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58.798
90.547
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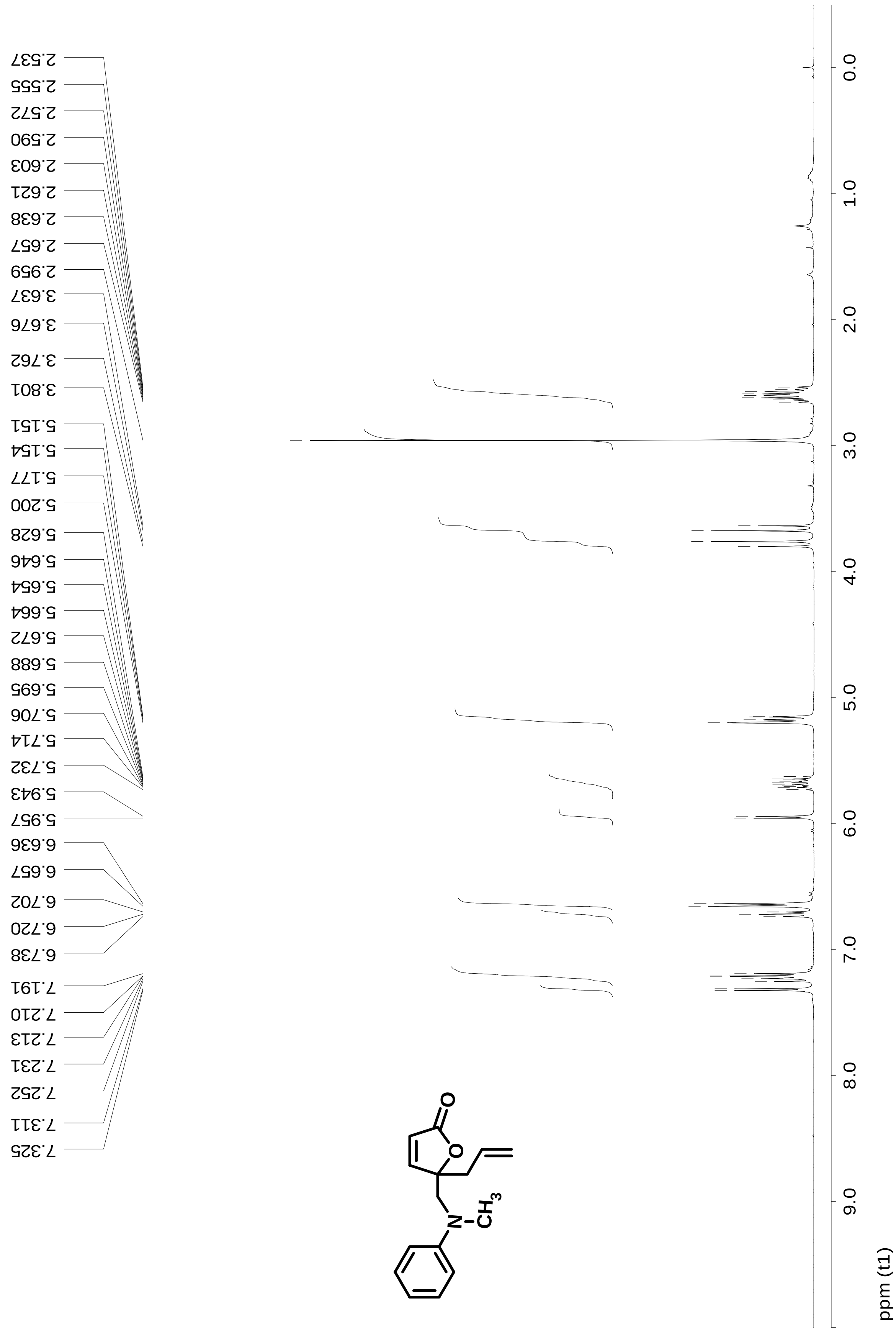
116.969
121.220
129.108
148.786
157.847
171.941
O
O
N
CH3
CH3
ppm (t1)


2.537
2.555
2.572
2.590
2.603
2.621
2.638
2.657
2.959
3.637
3.676
3.762
3.801
5.151
5.154
5.177
5.200
5.628
5.646
5.654
5.664
5.672
5.688
5.695
5.706
5.714
5.732
5.943
5.957
6.636
6.657
6.702
6.720
6.738
7.191
7.210
7.213
7.231
7.252
7.311
7.325
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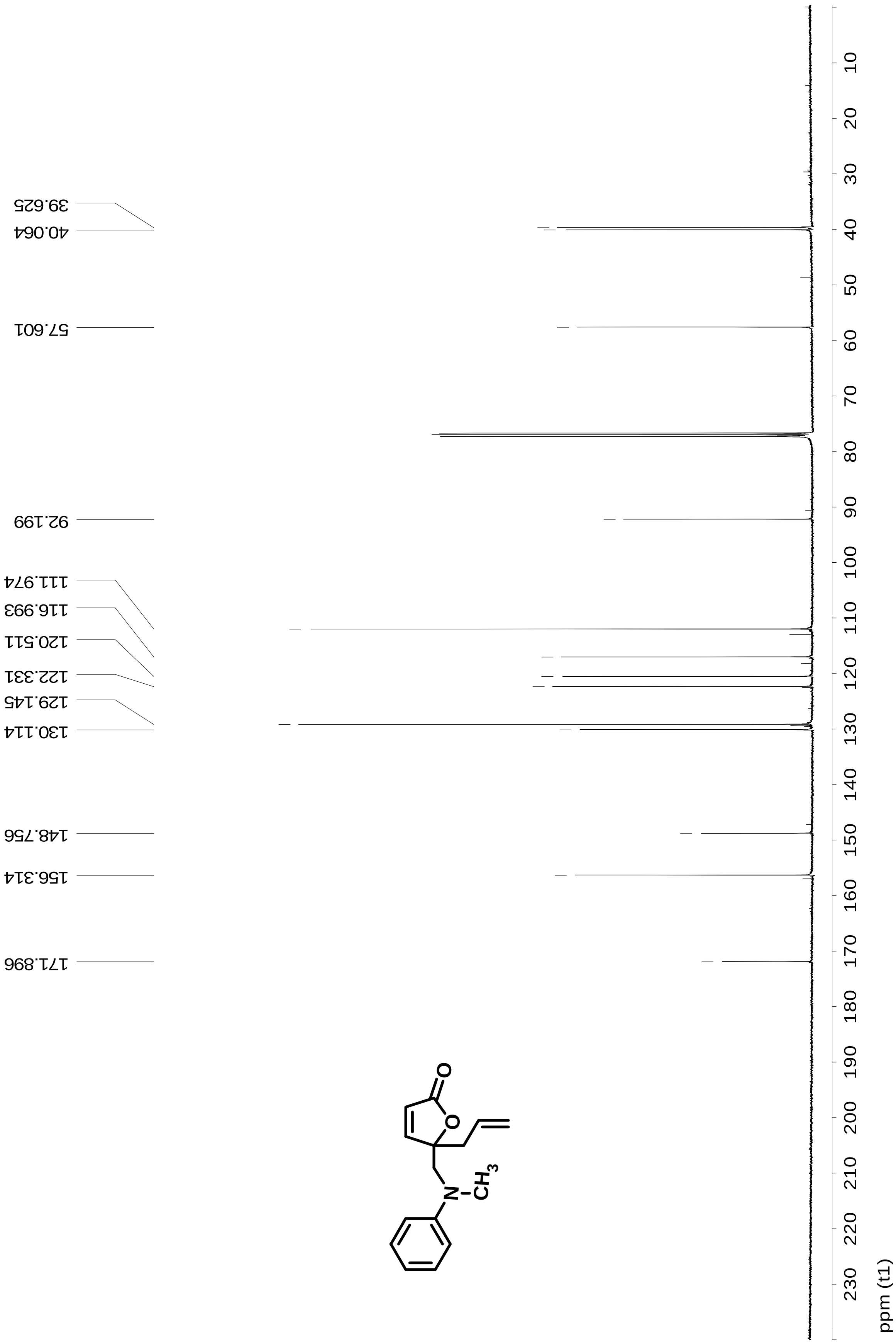
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
ppm (t1)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57.601
92.199
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116.993
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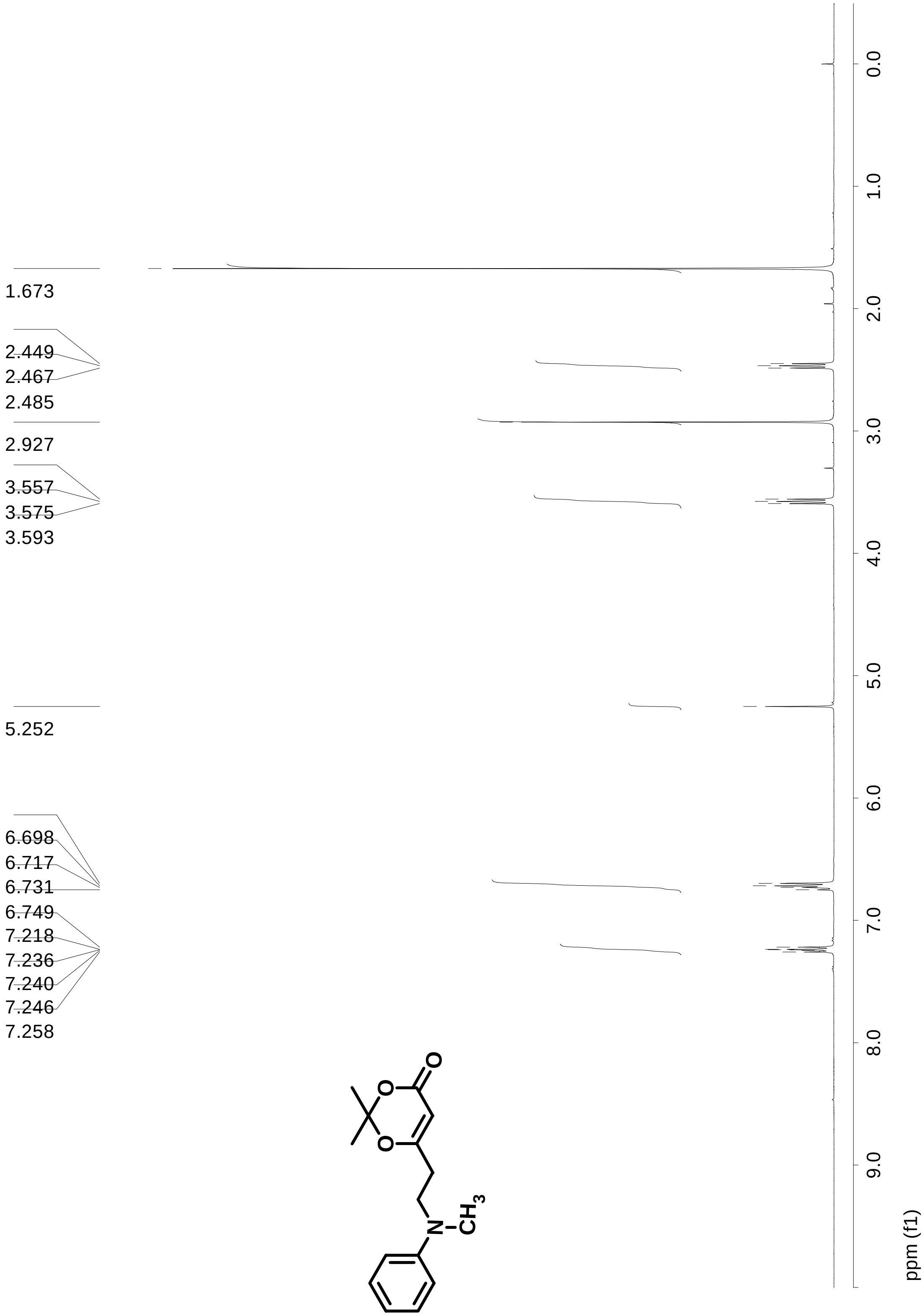
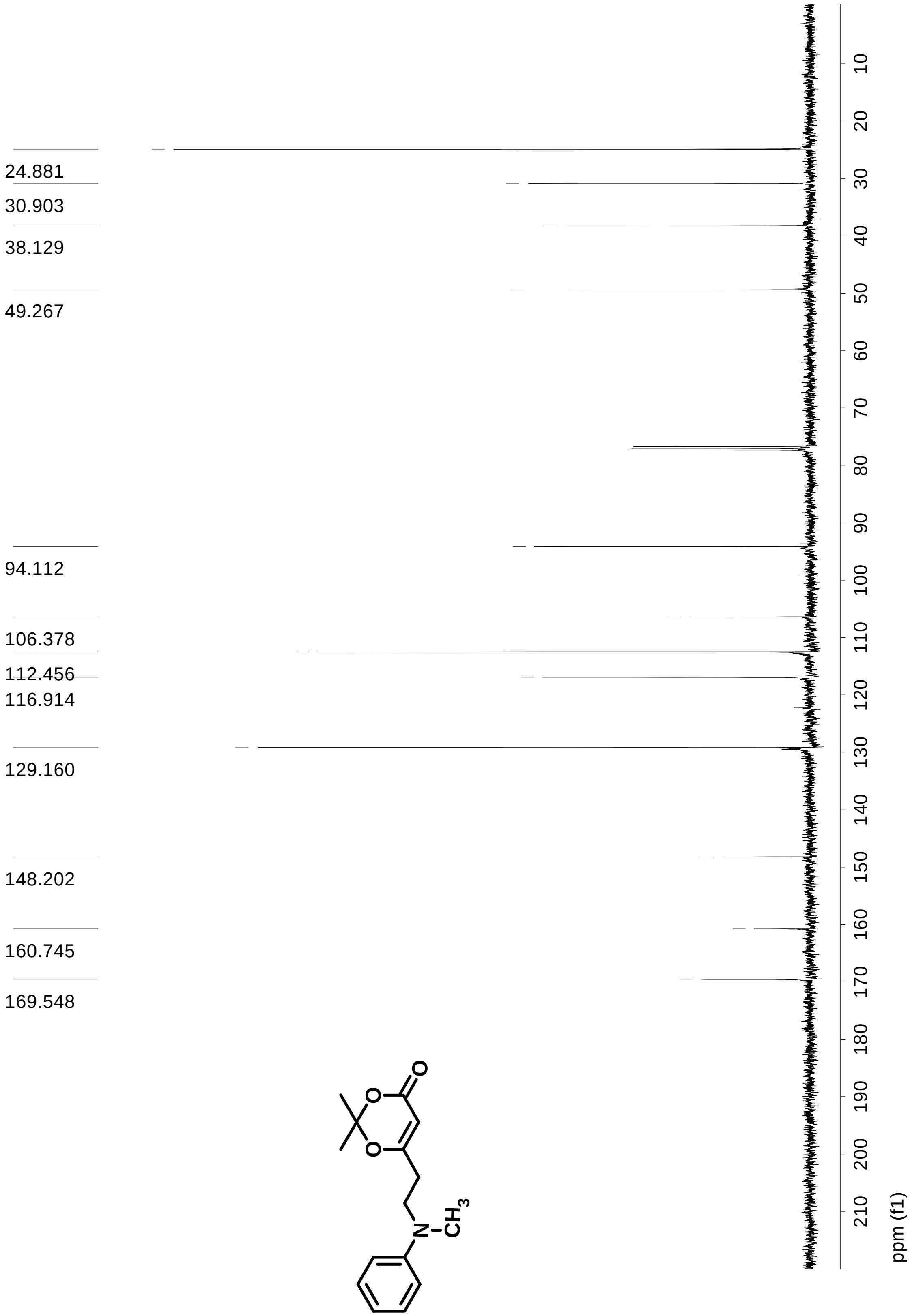
122.331
129.145
130.114
148.756
156.314
171.896
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
230
ppm (t1)
O
O
N
CH3


1.673
2.449
2.467
2.485
2.927
3.557
3.575
3.593
5.252
6.698
6.717
6.731
6.749
7.218
7.236
7.240
7.246
7.258
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
ppm (f1)
O
O
O
N
CH3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49.267
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106.378
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116.914
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148.202
160.745
169.548
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
ppm (f1)
O
O
O
N
CH3

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