ABSTRACT

Title of dissertation: SYNTHESIS OF HIGHLY FUNCTIONALIZED DIAZOACETOACETATES AND THEIR SYNTHETIC APPLICATIONS

Kousik Kundu, Doctor of Philosophy, 2006

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I. Catalytic Addition Methods for the Synthesis of Functionalized Diazoacetoacetates

We have developed efficient Mukaiyama aldol and Mannich addition reactions of readily accessible vinyldiazoacetates with aldehydes and imines using low catalytic amounts of commercially available Lewis acids. During the reaction the diazo functionality remained intact. The products are synthetically interesting as they are set to undergo a Rh(II)-catalyzed carbene reactions to form various complex carbocycles with multiple stereogenic centers.

II. Constructing Chiral Diazoacetoacetates by Catalytic Highly Enantioselective Mukaiyama Aldol Addition Reactions

Silver(I)-BINAP catalyzed highly enantioselective Mukaiyama aldol addition methodology has been developed for efficient synthesis of chiral diazoacetoacetates. Furthermore, in order to make this approach more practical as far as product yields and enantioselections are concerned, a novel Sc(III)-mixed ligands (heterochiral) catalyst has been developed.

III. Synthetic Applications of Diazoacetoacetates Prepared by Mukaiyama Aldol Addition Reactions

Diazoacetoacetate addition products from reactions with aromatic aldehydes undergo rhodium(II)-catalyzed ring closure to cyclobutanones with high diastereocontrol. TMS-protected Mukaiyama aldol adducts on the other hand go through similar ylide-derived pathway, but lead to dihydrofurans in excellent chemical yield. Diazoacetoacetates derived from aliphatic aldehydes form cyclopentanone by C—H insertion, but leads to dihydrofurans with TMS-protected adducts.

SYNTHESIS OF HIGHLY FUNCTIONALIZED DIAZOACETOACETATES AND THEIR SYNTHETIC APPLICATIONS

By

Kousik Kundu

Dissertation submitted to the faculty of the Graduate School of the
University of Maryland, College park, in partial fulfillment
of the Requirements for the degree of
Doctor of Philosophy
2006

Advisory Committee:
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DEDICATION

I dedicate this dissertation to the following people who left the most important and long-lasting impact in my personal and professional life.

My parents Professor Sanatan Kundu and Chhaya Kundu

My Teachers Professor Lawrence R. Sita and Professor Andrew T. Morehead Jr.

&

My Wife Priya

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LIST OF ABBREVIATIONS

Ac	Acetyl
AIBN	2,2′-Azobisisobutyronitrile
aq.	Aqueous
app.	Apparent
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
BINOL	Binaphthol
Box	Bis-oxazoline
Bn	Benzyl
BOC	*tert*-Butyloxycarbonyl
bp	Boiling Point
br	Broad
n-Bu	*n*-Butyl
t-Bu	*t*-Butyl
calcd	Calculated
cat.	Catalytic amount
CI	Chemical ionization
comp	Complex
CSA	Camphorsulfonic acid
d	doublet
DCE	Dichloroethane
DCM	Dichloromethane
DMF	*N,N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
dr	Diastereoisomeric ratio
ee	Enantiomeric Excess
EI	Electron impact
equiv	Equivalent
Et	Ethyl

FAB	Fast atom bombardment
H	hour
HMPA	Hexamethylphosphoramide
HPLC	High performance liquid chromatography
HRMS	High-resolution mass spectroscopy
hν	light
Hz	Hertz
IR	Infrared (spectrum)
LA	Lewis acid
LiHMDS	Lithium hexamethyldisilazide
m	Multiplet (or medium)
m	Mass
Me	Methyl
MHz	Megahertz
min	Minute
mol	Mole
mp	Melting point
MS	Molecular Sieve
Ms	Mesyl (methanesulfonyl)
NBS	*N*-Bromosuccinimide
nd	not determined
NMR	nuclear magnetic resonace
nOe	nuclear Overhouser effect
[O]	Oxidation
Ph	Phenyl
PhH	Benzene
PMB	*p*-Methoxybenzyl
ppm	Parts per million
i-Pr	Isopropyl
Py	Pyridine
PYBOX	Pyridinebisoxazoline

R_f	Retention factor
s	Singlet or strong
t	Triplet
TBAF	Tetrabutylammonium fluoride
TBAT	Tetrabutylammonium triphenylfluorosilicate
TBHP	*t*-Butyl hydrogen peroxide
TBDPS	*t*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TEA	Triethylamine
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	*N,N,N′,N′*-tetramethylethyenediamine
TMS	Trimethylsilyl
tol	toluene
tol-BINAP	2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl
Ts	*p*-Toluenesulfonyl (tosyl)
TsOH	*p*-Toluenesulfonic acid
w	Weak
z	Charge
Δ	Heat at reflux

Chapter 1:

Catalytic Addition Method for the Synthesis of Functionalized Diazoacetoacetates

1.1. *Introduction*

1.1.1. Synthetic Applications of Diazoacetoacetates:

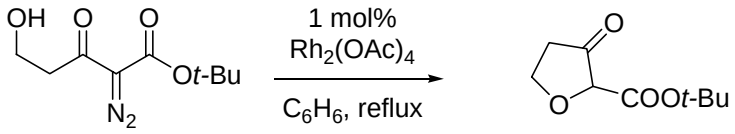
Diazoacetoacetates, widely used in catalytic metal carbene reactions,[1,2] exhibit higher thermal and acid stabilities than their diazoacetate counterparts, and they often offer greater reaction control in transformations following diazo decomposition.[1,3] Catalytic reactions of diazoacetoacetates involving addition, insertion, and association (ylide-derived processes) that produce cyclopropanes, cycloalkanones, lactones, and lactams are well documented.[1,2,4] These processes have been successfully used in the syntheses of several natural products.[5]

1.1.1.1. Synthesis of Tetrahydrofurans by O—H Insertion:

(1) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides;* John Wiley & Sons: New York, **1998.**
(2) Reviews: (a) Merlic, C. A.; Zechman, A. L. *Synthesis* **2003**, 1137-1156. (b) Davies, H. M. L.; Antoulinakis, E. G. *Org. React.* **2001**, *57*, 1-326. (c) Hodgson, D. M.; Pierard, F. Y. T. M.; Stupple, P. A. *Chem. Soc. Rev.* **2001**, *30*, 50-61. (d) Doyle, M. P. In *Catalytic Asymmetric Synthesis, Second Edition,* I. Ojima, Ed., John Wiley & Sons, Inc.: New York, **2000**. (d) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911-935. (d) Khlebnikov, A. F.; Novikov, M. S.; Kostikov, R. R. *Adv. Heterocyclic Chem.* **1996**, *65*, 93-233. (e) Padwa, A.; Austin, D. J. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1797-1815.
(3) Doyle, M. P. In *Comprehensive Organometallic Chemistry II*; Hegedus, L. S., Ed.; Pergammon Press, New York, **1995**; Vol. 12, Chapter 5.2.
(4) (a) Davis, F. A.; Wu, Y.; Xu, H.; Zhang, J. *Org. Lett*. **2004**, *6*, 4523-4525. (b) Davis, F. A.; Fang, T.; Goswami, R. *Org. Lett*. **2002**, *4*, 1599-1602. (c) Taber, D. F.; Malcolm, S. C. *J. Org. Chem.* **2001**, *66*, 944-953. (d) Hughes, C. C.; Kennedy-Smith, J. J.; Trauner, D. *Org. Lett*. **2003**, *5*, 4113-4115.
(5) Examples of uses in natural product syntheses: (a) Corey, E. J.; Wess, J.; Xiang, Y. B.; Singh, A. K. *J. Am. Chem. Soc.* **1987**, 109, 4717-4718. (b) Hughes, C. C.; Kennedy-Smith, J. J.; Trauner, D. *Org. Lett.* **2003**, *5*, 4113-4115. (c) Corey, E. J.; Kamiyana, K. *Tetrahedron Lett*. **1990**, *31*, 3995-3998. (d) Taber, D. F.; Malcolm, S. C. *J. Org. Chem.* **2001**, *66*, 944–953. (e) Pirang, M. C.; Brown, W. L.; Rege, S.; Laughton, P. *J. Am. Chem. Soc*. **1991**, *113*, 8561-8562.

Rapoport and co-workers have reported an efficient Rh(II)-catalyzed intramolecular O—H insertion reaction of α-diazo-β-ketoesters (**1**) that produced tetrahydrofuran **2** in quantitative yield (*Scheme 1.1*).[6]

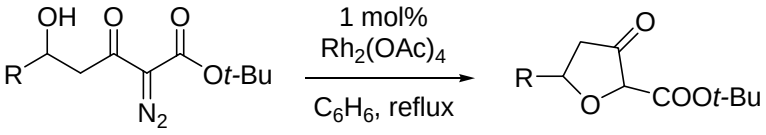
Scheme 1.1:



1 **2**

Calter and co-workers have studied the scope of this O—H insertion reaction. They showed that the reaction is highly chemoselective and gives, exclusively, the O—H insertion reaction products (*Scheme 1.2*).[7]

Scheme 1.2:



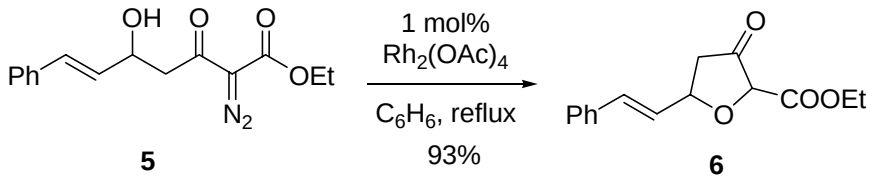
3 **4**

entry	R	yield of **4** [%]
1	Ph	93
2	*i*-Pr	92
3	*t*-Bu	92
4	*n*-pentyl	93

(6) Moyer, M. P.; Feldman, P. L.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 5223.
(7) Calter, M. A.; Sugathapala, P. M.; Zhu, C. *Tet. Lett.* **1997**, *38*, 3837-3840.

Similar chemoselectivity was reported by Wang and co-workers in their Rh(II)-mediated O—H insertion reaction of diazoacetoacetate **5**, where formation of cyclopropane product was not observed (*Scheme 1.3*).[8]

Scheme 1.3:



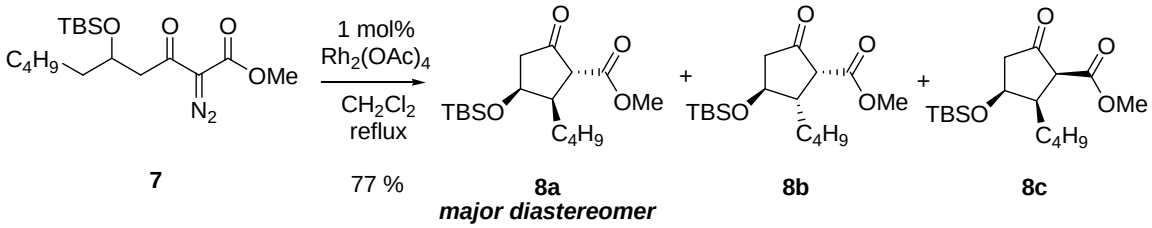
5 **6**

1.1.1.2. Synthesis of Cyclopentanones by C—H Insertion:

The Rh(II)-catalyzed intramolecular C—H insertion reaction is a versatile and efficient method for the formation of cyclopentanones,[9] as five-membered rings are preferentially formed.[10] Ikeda and co-workers have reported the formation of cyclopentanone **8a-c** *via* the C—H insertion reaction of diazoacetoacetate **7**. The cyclopentanone products were formed in overall good yield and moderate diastereoselectivity (3:1:1). Cyclopentanone **8a** was found to be the major diastereoisomer (*Scheme 1.4*).[11]

(8) Deng, G.; Tian, X.; Qu, Z.; Wang, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2773-2776.
(9) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003***, 103*, 2861.
(10) Taber, D. F.; Joshi, P. V. In *Modern Rhodium-Catalyzed Organic Reactions*, Evans, P. A. Ed.; Wiley-VCH, Weinheim, 2005, Chapter 16
(11) Yakura, T.; Yamada, S.; Kunimune, Y.; Ueki, A.; Ikeda, M. *J. Chem. Soc., Perkin Tran. 1,* **1997**, 3643-3649.

Scheme 1.4:

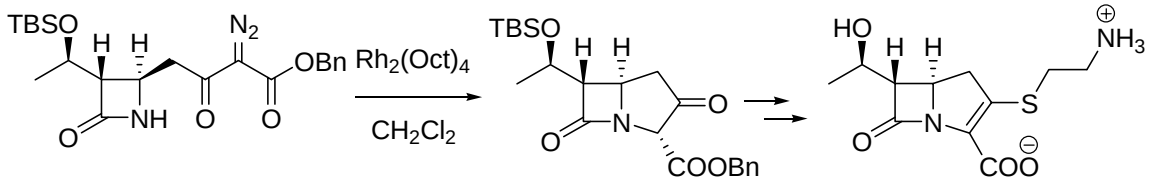


7 **8a** ***major diastereomer*** **8b** **8c**

1.1.1.3. Synthesis of Pyrroles by N—H Insertion:

Karadi and co-workers have utilized Rh(II)-catalyzed N—H insertion of diazoacetoacetate (**9**) in their route to thienamycin (**11**) (*Scheme 1.5*).[12]

Scheme 1.5:



9 **10** **11**

Thienamycin

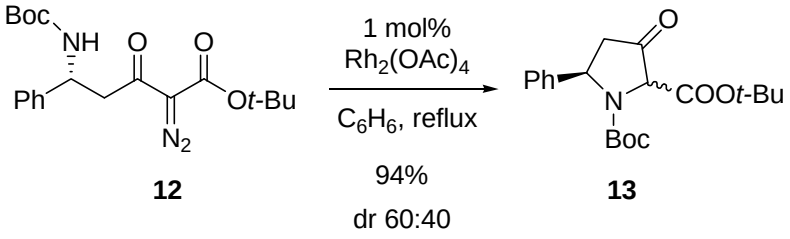
Davis and co-workers have used Rh(II)-catalyzed N—H insertion reactions to convert γ-amino β-ketoesters (**12**) into 5-substituted 3-oxoproline (**13**). The product was formed in high chemical yield, but diastereoselectivity was found to be poor (*Scheme 1.6*).[13]

Scheme 1.6:

---

(12) Karadi, S.; Amato, J. S.; Reamer, R. A.; Weinstock, L. N. *J. Am. Chem. soc*. **1981**, *103*, 6765-6767

(13) Davis, F. A.; Fang, T.; Goswami, R. *Org. Lett.* **2002**, *4*, 1599-1602.

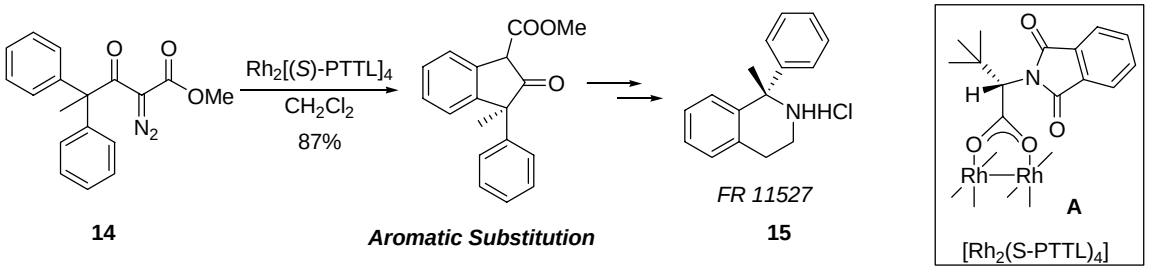


12 **13**

1.1.1.4. Miscellaneous Examples:

Highly functionalized diazoacetoacetates have been used extensively in the synthesis of various natural products.[16] Aromatic substitution using Rh_2[(*S*)-PTTL]$_4$ catalyst with sterically hindered diazoacetoacetate **14** was the key strategic step in the total synthesis of FR-11527 (**15**), reported by the Hashimoto group (*Scheme 1.7*).[14]

Scheme 1.7:

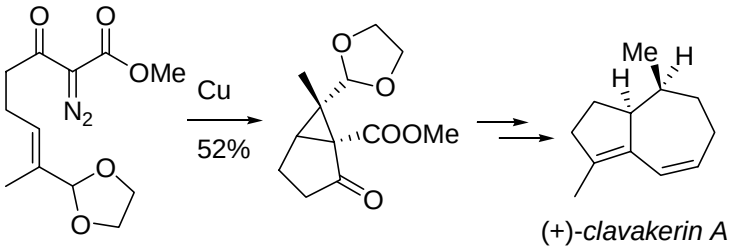


14 ***Aromatic Substitution*** **15**

In the stereoselective synthesis of (±)-clavukerin (**17**)**,** Rh(II)-catalyzed cyclopropanation of diazoacetoacetate **16** was used as the key step (*Scheme 1.8*).[15]

Scheme 1.8:

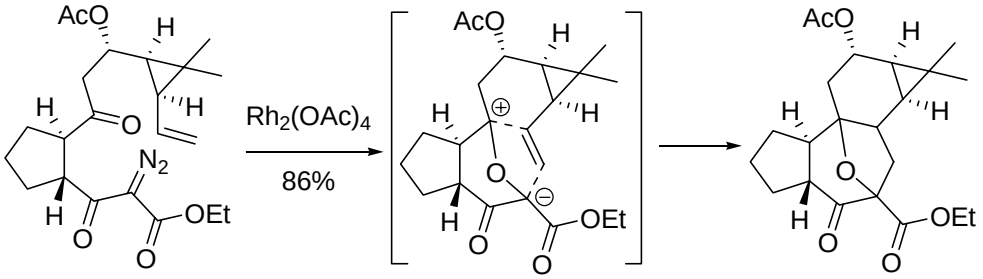
(14) Watanabe, N.; Ogawa, T.; Ohtake, Y.; Ikegami, S.; Hashimoto, S. I. *Synlett*. **1996**, 85-86
(15) Shimizu, I.; Ishikawa, T. *Tetrahedron Lett.* **1994**, *35*, 1905-1908.



16 ***Cyclopropanation*** **17**

An oxonium ylide transformation was the central step in the synthesis of tigliane ring system **18**, reported by Dauben (*Scheme 1.9*).[16]

Scheme 1.9:



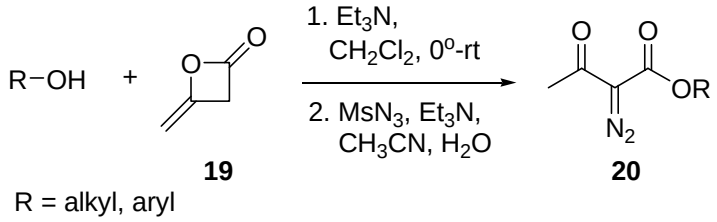
Ylide Transformation **18**

1.1.2. Synthesis of Diazoacetoacetates by Diazo Transfer:

Generally, diazoacetoacetates (**20**) are prepared by condensation of alcohols or phenols with diketene (**19**) or its surrogate,[17,18] followed by diazo transfer (*Scheme 1.10*).[19]

(16) Dauben, W. G.; Dinges, J.; Smith, T. C. *J. Org. Chem.* **1993**, *58*, 7635-7637.
(17) (a) Padwa, A.; Austin, D. J.; Price, A. T.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N.; Winchester, W. R.; Tran. A. *J. Am. Chem. Soc.* **1993**, *115*, 8669-8680. (b) Doyle, M. P.; Westrum, L. J.;

Scheme 1.10:



1.1.3. Diazoacetoacetates by Addition Reactions:

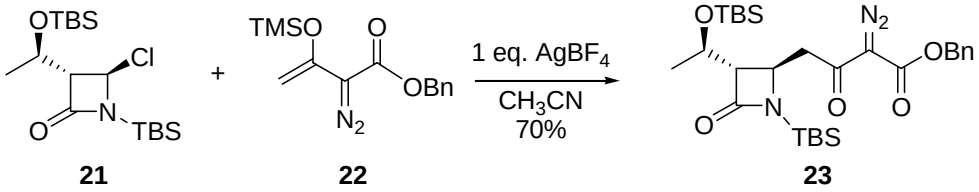
Chemical modifications with diazocarbonyl compounds have been of long-standing interest[1] and both acid and base promoted aldol reactions have been developed for this purpose. However, these reactions generally result in the loss of the diazo functionality.[20] Although earlier studies have shown that condensation of ethyl diazoacetate with aldehydes and ketones can occur with retention of the diazo group,[21,22,23] only recently have methods involving Lewis acids been used to couple diazoacetates with aldehydes.

1.1.3.1. Stoichiometric Ag(I)/Ti(IV) Promoted Addition Reactions by Karadi:

Wolthuis, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958-964.
(18) Clemens, R. J.; Hyatt, J. A. *J. Org. Chem.* **1985**, *50*, 2431-2435.
(19) Regitz, M.; Maas, G. *Diazo Compounds; Properties and Synthesis;* Academic Press, Orlando, FL, **1986**.
(20) Holmquist, C. R.; Roskamp, E. J. *J. Org. Chem*. **1989**, *54*, 3258-3260.
(21) (a) Wenkert, E.; McPherson, C. A. *J. Am. Chem. Soc.* **1972**, *94*, 8084-8090. (b) Sa, M. M.; Silveira, G. P.; Bortoluzzi, A. J.; Padwa, A. *Tetrahedron* **2003**, *59*, 5441-5447. (c) Jiang, N.; Wang, J. *Tetrahedron Lett.* **2002**, *43*, 1285-1287.
(22) Kanemasa, S.; Araki, T.; Kanai, T.; Wada, E. *Tetrahedron Lett*. **1999**, *40*, 5059-5062.
(23) Moody, C. J.; Morfitt, C. N. *Synthesis* **1998**, 1039-1042.

Karadi reported the addition reaction of vinyldiazoacetate **22** to 3-chloro-β-lactam **21** using a stoichiometric amount of silver(I) tetrafluoroborate to give rise to the corresponding diazoacetoacetate **23** in 70% isolated yield (*Scheme 1.11*).[12]

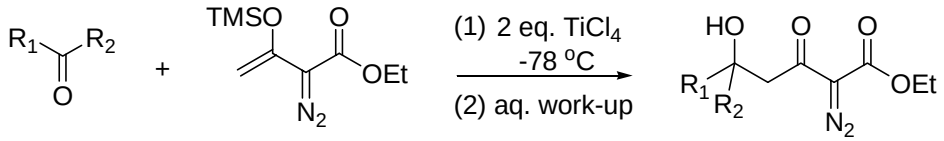
Scheme 1.11:



21 **22** **23**

Karadi and co-workers also reported a Mukaiyama aldol addition of vinyldiazoacetate **22** to aromatic aldehydes (benzaldehyde, 2-pyridyl carboxaldehyde and furfural) and ketones (acetophenone and benzophenone) using stoichiometric $TiCl_4$ (2 eq.). Only moderate (60-80%) isolated yields of the aldol adducts **25** were obtained (*Scheme 1.12*).[24]

Scheme 1.12:



24 **22** **25**

R_1 = Ph, R_2 = H;
R_1 = 2-pyridyl, R_2 = H;
R_1 = 2-furyl, R_2 = H;

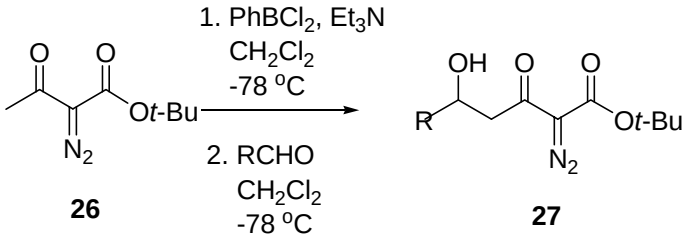
R_1 = Ph, R_2 = Me;
R_1 = Ph, R_2 = Ph;

(24) Karadi, S.; Amato, J. S.; Reamer, R. A.; Weinstock, L. N. *Tet. Lett*. **1996**, *37*, 8277 – 8280

1.1.3.2. Stoichiometric B(III)-Promoted Addition Reaction by Calter:

Calter and co-workers reported $PhBCl_2$ (1.21 eq.) promoted direct aldol addition reactions using diazoketoesters **26** (*Scheme 1.13*).[7] Both aromatic and aliphatic aldehydes undergo this aldol addition reaction. Despite using 1.2 equivalents of Lewis acid, the chemical yields of **27** were found to be moderate (60-70%).

Scheme 1.13:



26 **27**

entry	R	Yield of **27** [%]
1	C_6H_5	63
2	*i*-Pr	72
3	*t*-Bu	70
4	C_5H_{11}	69

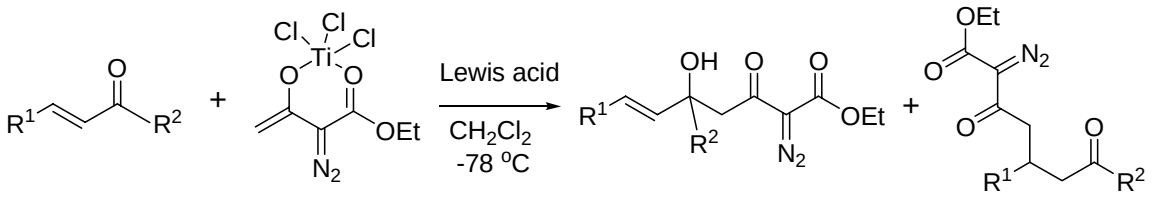
1.1.3.3. Stoichiometric Ti(IV)-Promoted Addition by Wang:

Recently, Wang reported Lewis acid controlled regioselective 1,2- and 1,4-addition reactions of α,β-unsaturated carbonyl compounds (**28**) with titanium-enolate **29** derived from α-diazo β-ketocarbonyl compound **26** (*Scheme 1.14*).[25] These addition

(25) Deng, G.; Tian, X.; Qu, Z.; Wang, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2773-2776.

reactions call for 1.1 equivalents of $TiCl_4$ for making the titanium-enolate and 1.0 equivalent of additional Lewis acid for carbonyl activation.[24]

Scheme 1.14:



28 **29** **30** **31**

Entry	R^1	R^2	Lewis acid	**30:31**	Yield of **30**+**31** [%]
1	Ph	Me	none	60:40	70
2	Ph	Me	$Ti(OiPr)_4$	96:4	78
3	Ph	Me	$TiCl_4$	17:83	63
4	Ph	Ph	none	50:50	71
5.	Ph	Ph	$Ti(OiPr)_4$	76:24	90
6	Ph	Ph	$TiCl_4$	100:0	71

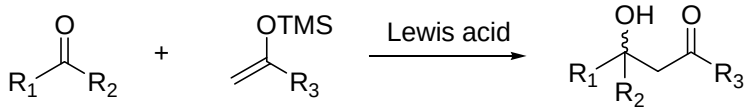
1.1.4. Mukaiyama Aldol Reaction:

1.1.4.1. General:

Construction of functionalized diazoacetoacetates by Lewis acid promoted Mukaiyama aldol addition reaction (*Scheme 1.12*)[9] can be improved by carrying out the reaction in the presence of a catalytic instead of a stoichiometric amount of Lewis acid.

The aldol addition reaction is considered as one of the most important methods for stereocontrolled carbon-carbon bond formation.[26] Powerful variants of this classical reaction have been developed in recent years.[27] One of the most important variants is the Lewis acid mediated addition of enol silanes (**33**) to carbonyl compounds (**32**), popularly known as the Mukaiyama aldol addition reaction (*Scheme 1.15*).[29] Mukaiyama originally developed this methodology using stoichiometric amounts of $TiCl_4$.[28] Lately, a plethora of catalytic versions of this reaction were reported using $BF_3.OEt_2$, $MgBr_2$, $AlCl_3$, $SiCl_4$, $Sc(OTf)_3$, $Ti(OiPr)_4$, $FeCl_3$, $Cu(OTf)_2$, $ZrCl_4$, $RuCl_2$, Rh(COD)Cl, $PdCl_2$, Ag(OTf), $Sn(OTf)_2$, $SnCl_4$, $La(OTf)_3$, Au(OTf) complexes as well as Ar_3C^+ as Lewis acids.[29] The advantages of this approach lie in their chemo-, regio- and stereoselective execution.[30]

Scheme 1.15:



32 **33** **34**

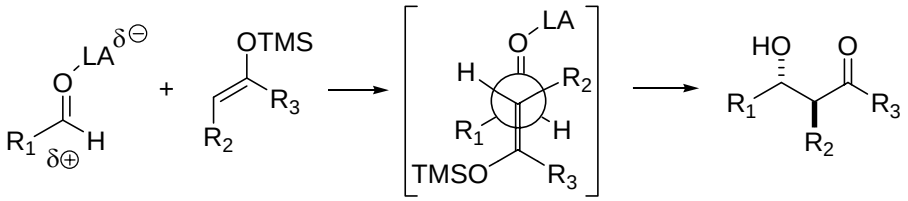
R_1 = aryl, alkyl
R_2 = aryl, alkyl, H
R_3 = aryl, alkyl, OMe, SMe

(26) *Modern Aldol Reactions*, Mahrwald, R. Ed.; Wiley-VCH, Weinheim, Germany, **2004**, *Vol 1&2*
(27) a) Heathcock, C. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1993; Vol. 2, Chapter 1.6. b). Heathcock, C. H. *Science* **1981**, *214*, 395. C) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl*. **1985**, *24*, 1.
(28) (a) Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, 1011-1014. (b) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503-7509.
(29) (a) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095-1120. (b) Palomo, C.; Oiarbide, M.; Garcia, J. M. *Chem. Soc. Rev.* **2004**, *33*, 65-75.
(30) Mukaiyama, T. *Aldrichimica Acta* **1996**, *29*, 59.

1.1.4.2. Mechanism:

The mechanism of Mukaiyama aldol addition depends on several factors including the substrates, reaction conditions and catalysts.[25] The most widely accepted mechanism involves the activation of a carbonyl group by the Lewis acid, followed by attack by the silyl enol ether (*Scheme 1.16*).[31]

Scheme 1.16:



A

The stereochemical outcome of Mukaiyama aldol reaction cannot be explained by the Zimmermann-Traxler model.[32] An "open" or "extended" transition-state model (**A**), provides the best agreement of stereochemical results (anti-diasteromer) in the Mukaiyama aldol-type reaction described in the *Scheme 1.16*.[33]

(31) Gennari, C. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1993; Vol. 2, Chapter 2.4, p 629.
(32) Zimmermann, H. E.; Traxler, M. D. *J. Am. Chem. Soc*. **1957**, *79*, 1920.
(33) (a) Nakamura, E.; Yamago, S.; Machii, D.; Kuwajima, I. *Tetrahedron Lett*. **1988**, *29*, 2207. (b) Denmark, S. E.; Henke, B. R. *J. Am. Chem. Soc*. **1989**, *111*, 8032.

1.1.4.3. Diastereoselection:

Addition of silyl enol ether to a chiral aldehyde can occur selectively to one of the two diastereotopic face, leading to highly diastereoselective addition.[34] The stereochemical outcome of a diastereoselective Mukaiyama aldol addition can be best explained and predicted by the models of Cram,[35] Felkin,[36] or Ahn.[37]

1.1.5. Mannich Addition:

1.1.5.1 General:

The Mannich reaction is a classical method that involves an addition of a nucleophile to an imine producing amines as the product (*Scheme 1.17*).[38] There have been several improvements made to the original direct Mannich reaction, the most important one being the addition of C-nucleophiles (**36**) to imines (**35**) catalyzed by Lewis acids.[39]

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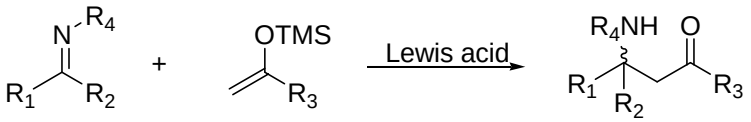
(34) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, D. J., Ed.; Chapter 2, Academic: New York, 1984; Vol. 3, Part. B, p 111.
(35) Cram, D. J.; Abd Elhafez, F. A. *J. Am. Chem. Soc*. **1952**, *74*, 5828.
(36) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett*. **1968**, 2199.
(37) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim*. **1977**, *1*, 61. Anh, N. T. *Top. Curr. Chem*. **1980**, *88*, 145.
(38) For reviews of the Mannich reaction, see: (a) Kleinman, E. D. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 2, p 893. (b) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1045. (c) Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311.
(39) (a) Cordove, A. *Acc. Chem. Res.* **2004**, *37*, 102-112. (b) Kobayashi, S. Ueno, M. *Comprehensive Asymmetric Catalysis, Supplement* **2004**, *1*, 143-150.

Scheme 1.17:



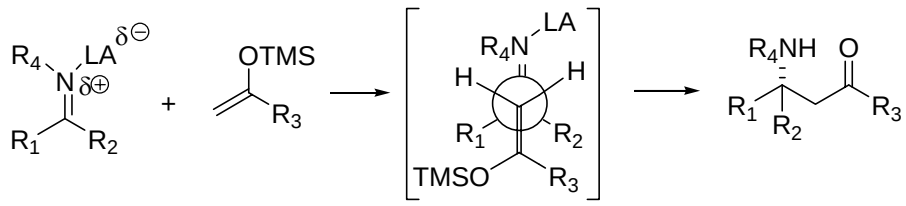
35 **36** **37**

R_1 = aryl, alkyl
R_2 /R_3 = aryl, alkyl, H
R_4= aryl, alkyl, OMe, SMe

1.1.5.2. Mechanism:

The Lewis acid catalyzed Mannich addition of a C-nucleophile to an imine follows a mechanism similar to that for the Mukaiyama aldol addition.[37a] Initial activation of the imine by a Lewis acid catalyst facilitates the concomitant attack by the C-nucleophile, such as an enol silane (*Scheme 1.18*).[43b] The Lewis acid catalyzed Mannich addition reaction sometimes suffers from product inhibition due to the basic nature of the product amine.[38]

Scheme 1.18:



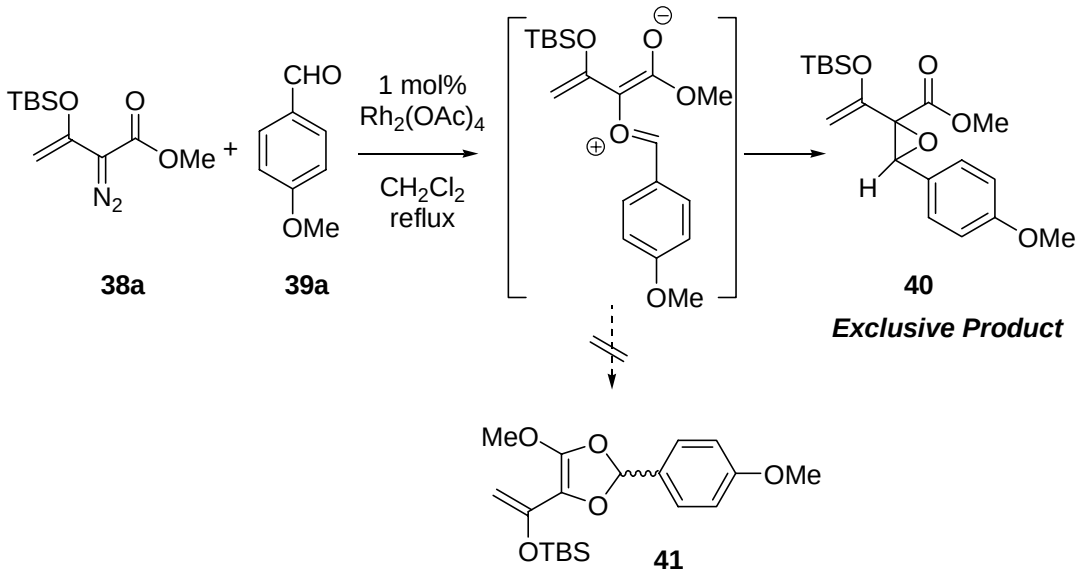
B

1.2. Development of the Catalytic Mukaiyama Aldol Addition of Vinyl Diazoacetates to Aldehydes:

1.2.1. Starting Point:[40]

While studying the divergence of carbonyl ylide reactions (epoxidation and dioxalane) as a function of the diazocarbonyl compound and the substituents on the aldehyde an interesting feature of the reaction was observed. Vinyldiazoacetoacetate **38a** under conditions for diazo decomposition with 1 mol% of $Rh_2(OAc)_4$ in presence of *p*-anisaldehyde **39a** produced epoxide **40** exclusively in modest yield (*Scheme 1.19*).[41]

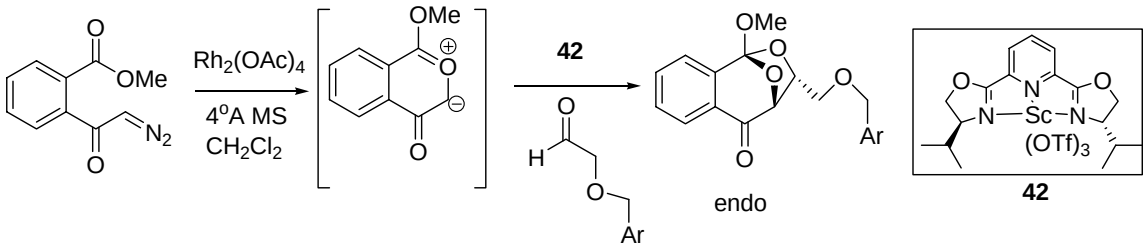
Scheme 1.19:



(40) Experimental work in this section was done by Dr. Albert E. Russell.
(41) Russell, A. E.; Brekan, J.; Gronenberg, L.; Doyle, M. P. *J. Org. Chem.* **2004**, *69*, 5269-5273.

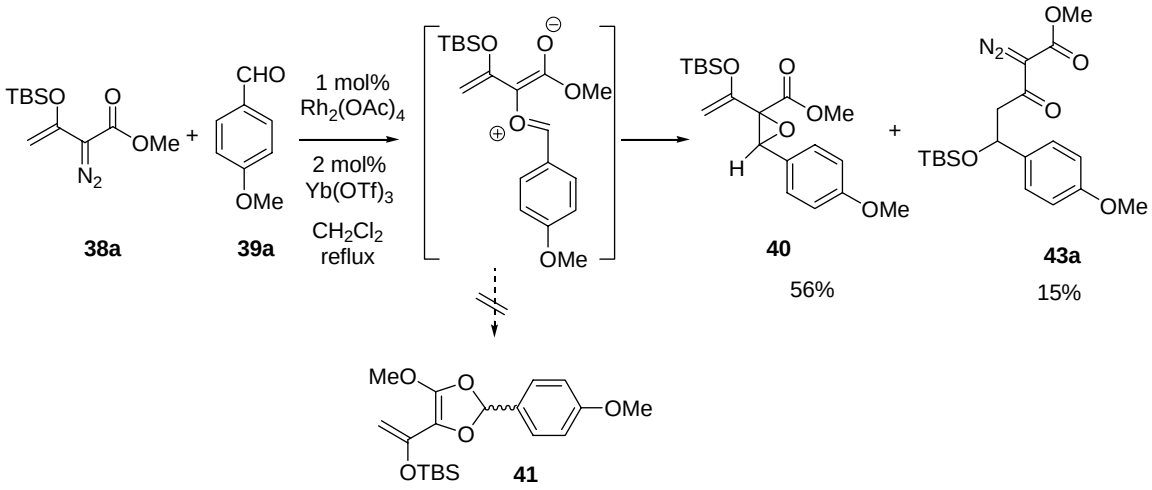
In order to control the chemoselectivity from epoxide **40** to dioxalane **41**, addition of a Lewis acid was thought to be a logical step. Saga and co-workers have reported a [3+2] dipolar cycloaddition of an oxonium ylide to an aldehyde in presence of a Sc(III)-catalyst **42** (*Scheme 1.20*).[42]

Scheme 1.20:



When the reaction was carried out in the presence of 2 mol% of $Yb(OTf)_3$ and 1 mol% of $Rh_2(OAc)_4$ the reaction produced the epoxide **40** as the major product along with 15% Mukaiyama aldol adduct **43** (*Scheme 1.21*).

Scheme 1.21:



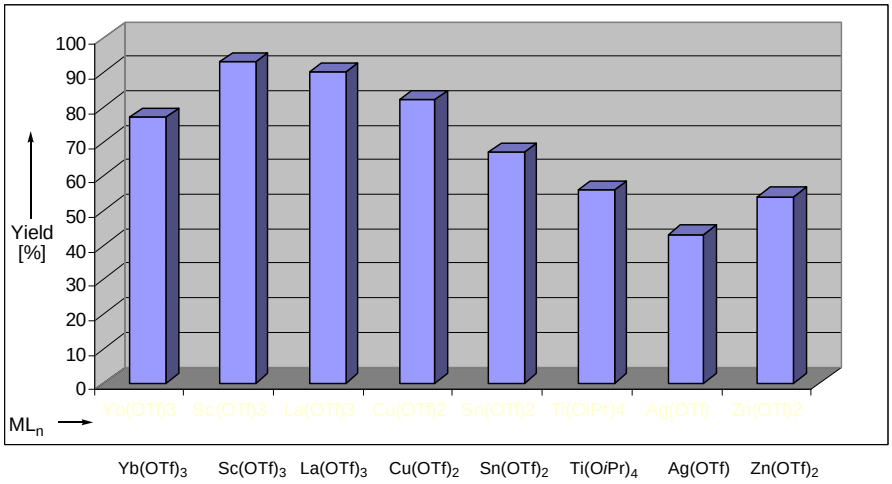
(42) Suga, H.; Inoue, S.; Kaheki, A. *J. Am. Chem. Soc.* **2002,** *124*, 14836-14837.

It was interesting to find out that the Mukaiyama aldol addition reaction of vinyl diazoacetate **38a** to *p*-anisaldehyde **39a** led to the corresponding adduct **43a,** without decomposing the diazo functionality in both **38** and/or **43a**. Efforts were made to develop this lanthanide catalyzed aldol addition reaction as a general methodology for the construction of highly functionalized diazoacetoacetates.

1.2.2. Catalysts:

Catalytic Mukaiyama aldol condensation reactions of aldehydes with silyl enol ethers have been reported using a broad selection of catalysts (*See Section 1.1.4.1*).[43] This formed the basis of early catalyst screening of Lewis acids (*Scheme 1.22*).

Scheme 1.22:



(43) Doyle, M. P.; Kundu, K.; Russell, A. E. *Org. Lett.* **2005**, *7*, 5171-5174.

[a] All the reactions were carried out in same temperature (24.5 ^{o}C), same reaction time (10 h), same catalyst loading (2 mol%) and using same ratio of **39c** and **38a** (1.0:1.5).

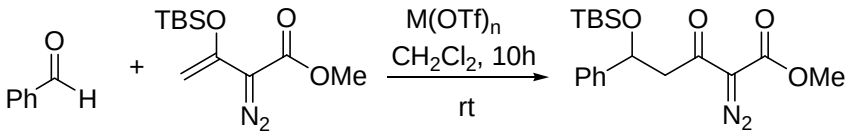
[b] With 2 mol% $Sc(OTf)_3$ only 62% yield of **43c** was isolated when 1:1 ratio of **39c** and **38a** were used

[c]Average yield of two reactions after isolation of **43c** by column chromatography.

This catalyst screening established that scandium(III) triflate is a superior catalyst for the addition reaction as far as the yield of **43c** is concerned. Lanthanum(III) triflate was also found to be a superior catalyst. Ytterbium(III), copper(II) and tin(II) triflates were also effective in catalytic amounts (2 mol %) for condensation reactions performed between **38a** and benzaldehyde **39c** (*Scheme 1.22*). With copper(II) triflate the yield of condensation product **43c** was lower compared to scandium or lanthanum catalysts, due to slow decomposition of the diazo moiety of **38** and/or **43c** even at low temperatures as evident from the crude ^{1}H NMR spectrum. Very clean ^{1}H NMR spectra were obtained while using $Sc(OTf)_3$, $La(OTf)_3$ and $Yb(OTf)_3$ as catalysts. Yields of **43c** were low for $Yb(OTf)_3$, $Sn(OTf)_2$, $Ti(O^{i}Pr)_4$, Ag(OTf) and $Zn(OTf)_2$, but in all these cases the ^{1}H NMR spectra were found to be clean, producing the adduct with unreacted starting materials.

Chemical yields of **43c** for Sc(III), La(III) and Yb(III) can be explained on the basis of ionic radii of M^{+3} and oxophilicity (*Table 1.1.*).

Table 1.1.



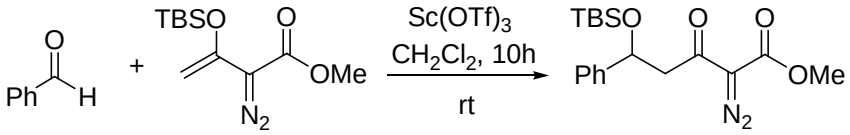
39c **38a** **43c**

Entry	catalyst (2 mol %)	Radius of M^{+3} (^{o}A)	Oxophilicity (kcal/mol) ($D_o \pm 5$ kcal/mol)	yield [%] of **43c**[a]
1	$Sc(OTf)_3$	0.754	165	93
2	$La(OTf)_3$	1.032	190	90
3	$Yb(OTf)_3$	0.868	95	77

[a]Average yield of two reactions after isolation of **43c** by column chromatography

Next catalyst loading was optimized by carrying out the reaction using different amounts of $Sc(OTf)_3$ under the same reaction conditions (ambient temperature and 10h reaction time). 1 mol% scandium (III) triflate gave 90% yield of the adduct **43c**. Reducing the catalyst loading to 0.5% decreased the yield to 67%, and with 0.1 mol% of the catalyst there was only 5% conversion. Increasing catalyst loading to 3 mol% did not improve the yield to any significant extent. Increasing reaction time to 20h with 0.5 mol% $Sc(OTf)_3$ did not improve the yield of **43c** significantly. Therefore, 2 mol% of $Sc(OTf)_3$ was the optimum catalyst loading for this reaction (*Table 1.2*).

Table 1.2.



39c **38a** **43c**

entry	% Mol of $Sc(OTf)_3$	Yield [%][a]
1	0.1	5
2	0.5	67
3	1.0	90
4	2.0	93
5	3.0	94

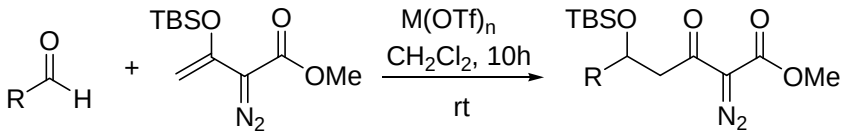
[a]Average yield of two reactions after isolation of **43c** by column chromatography.

1.2.3. Aldehydes:

We then evaluated the potential of this methodology with a selection of Lewis acids and aldehydes (*Table 1.3*). Both aromatic (entries 1 to 7) and aliphatic aldehydes (entries 8 to 11) underwent condensation with very high yields. Electron-rich aldehydes were found to be the most suitable substrates (entries 1 and 2), while very electron-poor aldehydes (e.g., 4-nitrobenzaldehyde, entry 6), did not undergo this reaction. The α,β-unsaturated aromatic aldehyde cinnamaldehyde (entry 7) was also found to be a suitable substrate, providing high yields of the corresponding adduct from reactions catalyzed by

either scandium or lanthanum triflates. Surprisingly, moderately electron poor 4-trifluoromethylbenzaldehyde was found to be a very good substrate for the Mukaiyama aldol addition (entry 5).

Table 1.3 Lewis acid catalyzed Mukaiyama aldol reaction of vinyldiazoacetate[a]



39a-k **38a** **43a-k**

entry	Aldehyde	R	yield [%] of **43a-k**[b]		
			$Sc(OTf)_3$	$La(OTf)_3$	$Cu(OTf)_2$
1	**39a**	4-$MeOC_6H_4$	98	90	82
2	**39b**	4-MeC_6H_4	97	89	77
3	**39c**	Ph	93	90	76
4	**39d**	4-ClC_6H_4	98	91	76
5	**39e**	4-$CF_3C_6H_4$	94	-	-
6	**39f**	4-$NO_2C_6H_4$[c]	0	0	0
7	**39g**	*trans*-β-styryl	89	88	-
8	**39h**	$BnOCH_2$	93	93	72
9	**39i**	COOEt	91	-	-
10	**39j**	*n*-heptyl	94	93	-
11	**39k**	*n*-propyl [d]	92	-	-

[a]Aldehyde **39** (1.5 mmol) was added to a solution of vinyldiazoacetate **38a** (2.2 mmol) and metal triflate (2.0 mol%) in CH_2Cl_2 (3 mL) and stirred at rt for 10 h.

[b] Average yield of two reactions after isolation of **43** by column chromatography.

[c]Unreacted aldehyde **39f** and **38a** were the only materials recovered after 10 h and the reaction was attemped twice.

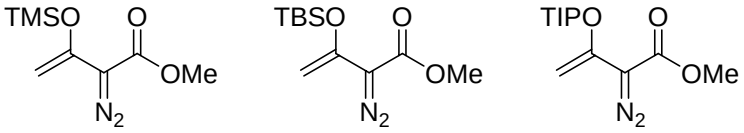
[d]Isolated yield for the deprotected Mukaiyama aldol adduct (see Experimental Section for details).

[e] The reactions were found to be incomplete after 6 h for both benzaldehyde and *p*-anisaldehyde.

1.2.3. Vinyldiazoacetates:

3-*tert*-Butyldimethylsilanyloxy-2-diazobut-3-enoate **38a** was prepared by the method described by Davies.[44] Methyl 3-trimethylsilanyloxy-2-diazobut-3-enoate (**38b**) was prepared according to the procedure reported by Karadi.[19] The TBDMS and TIPS protective groups provided greater stability to **38** and to the condensation products, and they were easier to handle than those with TMS-protection. Both the TBDMS and TIPS enolates were found to be stable at ambient temperature for days.

Scheme 1.23:

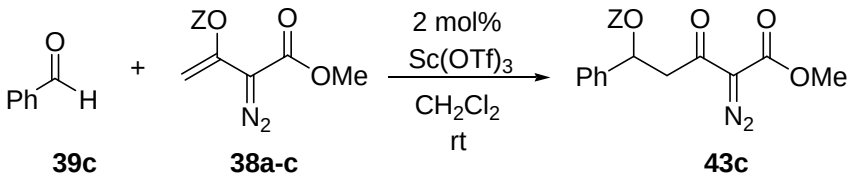


38a **38b** **38c**

The Mukaiyama aldol additions of **38a-c** to **39c** were carried out in presence of 2 mol% of $Sc(OTf)_3$ in dichloromethane under the same reaction conditions. The reaction of TMS-enolether **(38b)** and **39c** in 1:1 ratio was found to be very fast, and a quantitative yield of **43cb** was obtained after 0.5 h. Additional 0.5 equivalent of both **38a** and **38c** are required for good product formation. Reaction with TIPS-enolether **38c** was found to be sluggish, but an 88% yield of **43cc** was obtained after 15 h (*Table 1.4.*).

(44) Davies, H. M. L.; Ahmed, G.; Churchill, M. R. *J. Am. Chem. Soc.* **1996**, *118*, 10774-10780.

Table 1.4. Mukaiyama Aldol Reaction with Various Vinyldiazoacetates.[a]



39c **38a-c** **43c**

Entry	Z	Enolate	t (h)	Yield of **43ca-c** [%][b]
1	TBS	38a	10	90
2	TMS[c]	38b	0.5	Quantitative[d]
3	TIPS	38c	15	88

[a] Aldehyde **39c** (1.5 mmol) was added to a solution of vinyldiazoacetate **38a**/**38c** (2.2 mmol) and metal triflate (2.0 mol%) in CH_2Cl_2 (3 mL) and stirred at rt for 10 h and 15 h respectively. The reaction with **38c** was found to be incomplete after 10 h.

[b]Average yield of two reactions after purification of **43ca** and **43cc** by column chromatography

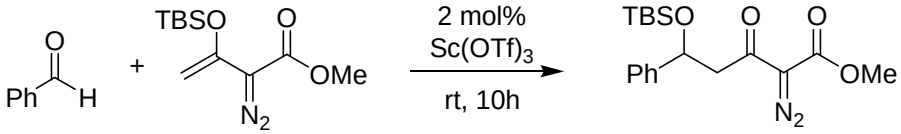
[c] 1:1 ratio of **39a** and **38b** were found to be sufficient for excellent yield of **43cb**

[d] **43cb** was purified by passing the reaction mixture through a small cellite plug with washings of CH_2Cl_2.

1.2.4 Solvent:

The Mukaiyama aldol addition of vinyldiazoacetate **38a** with **39c** was carried out in different solvents in order to determine the effect of solvents on the reaction. Reactions were performed in presence of 2 mol% $Sc(OTf)_3$ under the same reaction conditions (24 ^oC, 10 h and same amount of solvent). Dichloromethane was found to be the solvent of choice for this reaction. The reaction was found to be a little slower in acetonitrile and sluggish in THF.

Table 1.5. Mukaiyama Aldol Reaction in Various Solvents.[a]



39c **38a** **43c**

entry	solvent	yield of **43c** [%][a]
1	CH_2Cl_2	93
2	THF	78
3	CH_3CN	88

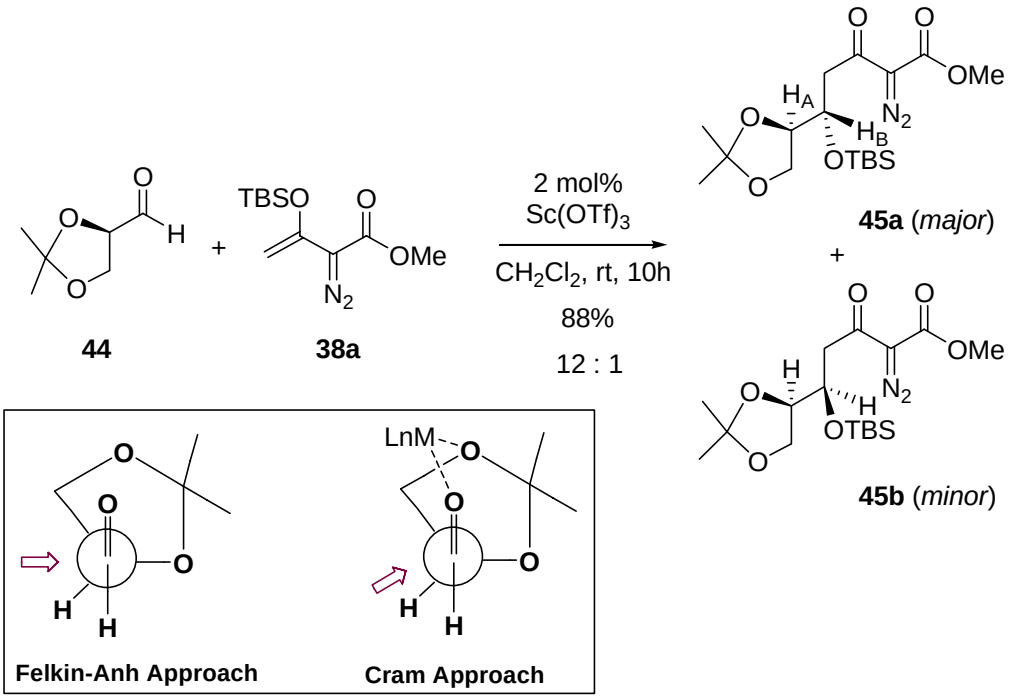
[a] Yield of isolated **43c** following column chromatography.

1.2.5 Diastereoselection:

Lewis acid catalyzed Mukaiyama aldol addition of vinyldiazoacetoacetates (**38a-c**) with chiral aldehydes would lead to enantiomerically enriched diazoacetoacetates. The advantage of this approach is the easy availability of chiral aldehydes, which would lead to a divergent synthesis of chiral diazoacetates. Diastereoselection in the Mukaiyama aldol addition of vinyldiazoacetate **38b** was evaluated using commercially available chiral aldehyde **44**. The reaction was carried out under the standard reaction conditions using 2 mol % $Sc(OTf)_3$ catalyst in dichloromethane at ambient temperature. The reaction proceeded cleanly, giving rise to the mixture of **45a** and **45b** in a 12:1 diastereomeric ratio and 88% isolated yield (*Scheme 1.24*). The relative stereochemistry

of the major product was determined by the coupling constants between H_A and H_B (J = 5.4 Hz) of the newly formed carbinol hydrogen with its neighboring hydrogen and also comparing the relative stereochemistry of a similar reported compound.[45] The observed diastereoselectivity can be explained by the Cram's chelation model[34] as well as the Felkin-Anh model.[35, 36] Both of the models predict **45a** to be the major diastereomer.

Scheme 1.24:



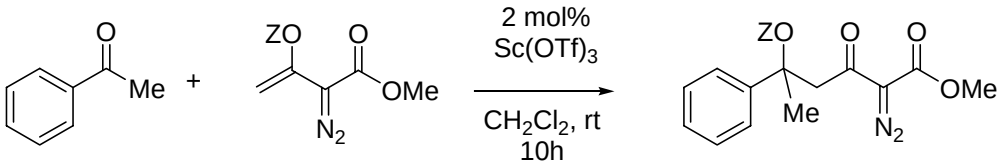
1.2.6. Addition to Acetophenone:

Furthermore, efforts to extend the scope of the addition reaction of vinyldiazoacetate **38b** to acetophenone were made. Unfortunately, under the same

(45) Cho, B. H. *Tetrahedron* **2005**, *61*, 4341-4346.

conditions as used for aldehydes (2 mol% $Sc(OTf)_3$ in CH_2Cl_2 at room temperature for 10 h) acetophenone produced the corresponding adduct in only 18% isolated yield. However, dramatic increase in yield was observed under the same conditions when the TBS group in the vinyldiazoacetate was replaced by labile TMS group. The corresponding Mukaiyama aldol adduct **47b** was isolated in 89% yield (*Scheme 1.25*).

Scheme 1.25:



46 **38a-b** 89% **47a-b**

38a (Z = TBS); 18%

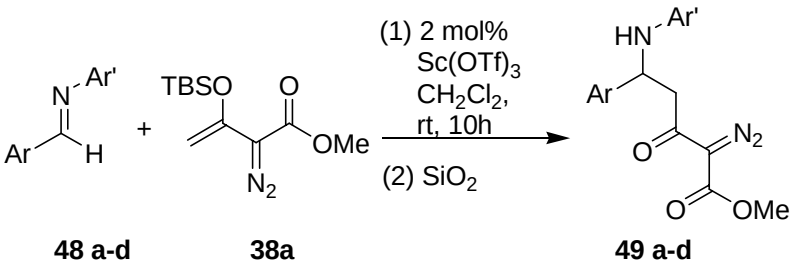
38b (Z = TMS); 89%

1.3. Mannich Addition:

1.3.1. Imines:

Extension of the aldol addition reaction methodology to reactions of **38a** with benzylideneanilines **48a-d** produced the corresponding Mannich addition products **49a-d** reported in *Table 1.6*.

Table 1.6.



48 a-d **38a** **49 a-d**

imine	Ar	Ar′	yield of **49** [%][b]
48a	4-$MeOC_6H_4$	4-$NO_2C_6H_4$	95
48b	4-ClC_6H_4	Ph	90
48c	Ph	4-$NO_2C_6H_4$	93
48d	Ph	Ph	88

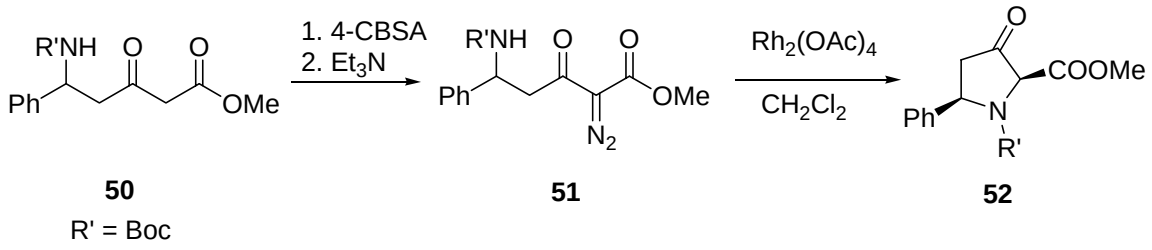
[a] Imine (1.5 mmol) in CH_2Cl_2 (1 mL) was added to a solution of vinyldiazoacetate **38a** (2.2 mmol) and scandium(III) triflate (2.0 mol%) in CH_2Cl_2 (2 mL) then stirred at room temperature for 10 h.

[b]Average yield of two reactions after isolation of **49** by column chromatography.

The diazo functionality was retained in these reactions. The TBDMS protective group comes off nitrogen upon passing the reaction mixture through a short plug of silica

gel to remove catalyst. Curiously, the basic nature of the reactant and product in this transformation does not change the catalytic loading relative to that used for reactions with aldehydes. This previously unreported Mannich-type addition methodology to form substituted diazoacetoacetates directly may be a viable alternative to the approach of effecting diazo transfer to the amine-substituted acetoacetate (*Scheme 1.26*).[7a,b] Davis has reported that analogs of **49** undergo highly selective intramolecular N—H insertion catalyzed by $Rh_2(OAc)_4$.[10]

Scheme 1.26:



50
R' = Boc

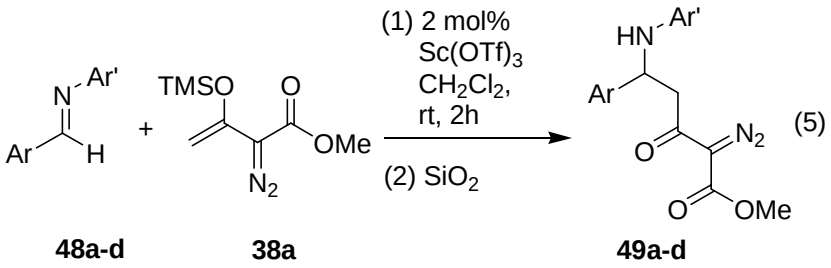
51

52

1.3.2. Vinyldiazoacetoacetates:

Switching from the TBS to the TMS group, as expected, produced the Mannich adducts with almost quantitative conversions. Amines (**49a-d**) were formed after removing the TMS group in higher isolated yields while using same amounts of catalysts with shorter reaction time (*Table 1.7.*).

Table 1.7.



imine	Ar	Ar′	yield of **49** [%][b]
48a	4-$MeOC_6H_4$	4-$NO_2C_6H_4$	99
48b	4-ClC_6H_4	Ph	97
48c	Ph	4-$NO_2C_6H_4$	96
48d	Ph	Ph	93

[a] Imine (1.5 mmol) in CH_2Cl_2 (1 mL) was added to a solution of vinyldiazoacetate **38b** (2.2 mmol) and scandium(III) triflate (2.0 mol%) in CH_2Cl_2 (3 mL) then stirred at room temperarute for 2 h.

[b] Average yield of two reactions after isolation of **49** by column chromatography.

1.4. Conclusion:

In summary, efficient Mukaiyama aldol and Mannich addition reactions of readily accessible vinyldiazoacetates (**38a-b**) with aldehydes or imines have been developed using low catalytic amounts of commercially available Lewis acids. The products are synthetically interesting as they are set to undergo a Rh(II) catalyzed carbene reactions to form various carbocycles or hereocycles with multiple stereogenic centers.

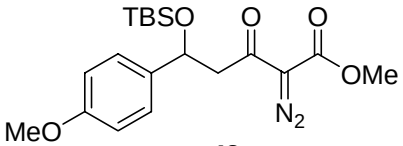
1.5. Experimental Section:

General. Reactions were performed in oven-dried (140 ^{o}C) or flame-dried glassware under an atmosphere of dry N_2. Dichloromethane was passed through a solvent column prior to use and was not distilled. Tetrahydrofuran and diethyl ether were distilled over sodium/benzophenone ketyl. Thin layer chromatography (TLC) was carried out using EM Science silica gel 60 F254 plates. The developed chromatogram was analyzed by UV (254 nm), ethanolate phosphomolybdic acid, potassium permanganate ($KMnO_4$), or cerium ammonium molybdate (CAM). Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated system on silica gel (230-400 mesh). Scandium(III), lanthanum(III), ytterbium(III), and copper(II) triflates were purchased from Aldrich and used as received. 3-*tert*-Butyldimethylsilanyloxy-2-diazobut-3-enoate (**38a**) was prepared by the method described by Davies.[46] Methyl 3-trimethylsilanyloxy-2-diazobut-3-enoate (**38b**) was prepared according to the procedure reported by Karadi.[19]

General Procedure for Mukaiyama Aldol Addition Reactions. To a dry 5-mL round-bottomed flask containing a stir bar and fitted with a septum was added anhydrous scandium(III) triflate (14 mg, 0.030 mmol) and 3 mL of anhydrous dichloromethane. Methyl 3-*t*-butyldimethylsilanyloxy-2-diazobut-3-enoate **38a** (564 mg, 2.20 mmol) was then added drop wise to the above mixture over 5 min from a 1-mL syringe. Finally, benzaldehyde **39c** (152 μL, 1.50 mmol) was added to the reaction mixture using a 100 μL microsyringe. The reaction mixture was stirred at room temperature for 10 h. (The reactions were found to be incomplete after 6 h for both benzaldehyde and *p*-

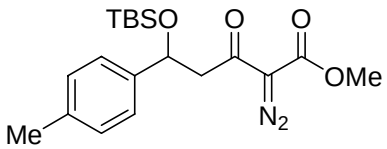
(46) Davies, H. M. L.; Ahmed, G.; Churchill, M. R. *J. Am. Chem. Soc.* **1996**, *118*, 10774-10780.

anisaldehyde.) Over this time the solution changed color from orange to pale yellow at the end. After the reaction was complete, the solution was passed through a silica gel plug to remove the catalyst with washings of dichloromethane (2 mL x 3). After removal of the solvent under reduced pressure, the product was isolated by flash chromatography.



43a

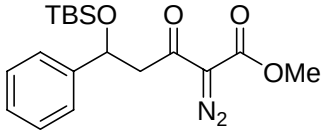
Methyl 5-(*tert*-Butyldimethylsilanoxy)-2-diazo-5-(*p*-anisyl)-3-oxopentanoate (43a). IR (neat): 2955, 2133, 1725, 1659 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.8 Hz, 2H), 6.79 (d, *J* = 8.8 Hz, 2H), 5.13 (dd, *J* = 8.8, 4.0 Hz, 1H), 3.77 (s, 3H), 3.73 (s, 3H), 3.46 (dd, *J* = 14.4, 8.8 Hz, 1H), 2.87 (dd, *J* = 14.4, 4.0 Hz, 1H), 0.77 (s, 9H), -0.07 (s, 3H), -0.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.4, 161.5, 158.8, 136.5, 127.1, 113.5, 71.6, 55.1, 52.1, 50.4, 25.6, 17.9, -4.8, -5.4 (not seen, C=N_2); HRMS (FAB) for $C_{19}H_{28}N_2O_5Si$ $[M+Li]^+$ calcd: 399.1928; found: 399.1909; TLC R_f = 0.26 (9:1 hexanes:ethyl acetate).



43b

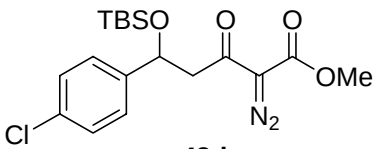
Methyl 5-(*tert*-Butyldimethylsilanoxy)-2-diazo-5-(*p*-tolyl)-3-oxopentanoate (43b). IR (neat): 2955, 2133, 1726, 1661 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.27 (d, *J* = 7.6 Hz,

2H), 7.11 (d, *J* = 7.6 Hz, 2H), 5.18 (dd, *J* = 9.2, 4.0 Hz, 1H), 3.83 (s, 3 H), 3.50 (dd, *J* = 14.8, 9.2 Hz, 1H), 2.91 (dd, *J* = 14.8, 4.0 Hz, 1H), 2.33 (s, 3H), 0.82 (s, 9H), -0.03 (s, 3H), -0.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.4, 161.6, 141.4, 136.9, 128.8, 125.9, 71.9, 52.1, 50.5, 25.6, 21.1, 18.0, -4.8, -5.4 (not seen, C=N_2); HRMS (EI) for $C_{19}H_{28}O_4N_2Si$ $[M+Na]^+$ calcd: 399.1727; found: 399.1716; TLC R_f = 0.27 (9:1 hexanes:ethyl acetate).



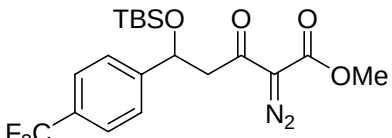
43c

Methyl 5-(*tert*-Butyldimethylsilanoxy)-2-diazo-3-oxo-5-phenylpentanoate (43c). IR (neat): 2955, 2133, 1725, 1658 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.22 (comp, 5H), 5.20 (dd, *J* = 9.2, 4.0 Hz, 1H), 3.81 (s, 3H), 3.50 (dd, *J* = 14.8, 9.2 Hz, 1H), 2.92 (dd, *J* = 14.8, 4.0 Hz, 1H), 0.81 (s, 9H), -0.03 (s, 3H), -0.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.3, 161.6, 144.3, 128.2, 127.4, 126.0, 72.0, 52.2, 50.4, 25.6, 18.0, -4.8, -5.3 (not seen, C=N_2); HRMS (FAB) for $C_{18}H_{26}O_4N_2Si$ $[M+H]^+$ calcd: 363.1740; found: 363.1746; TLC R_f = 0.40 (9:1 hexanes:ethyl acetate).



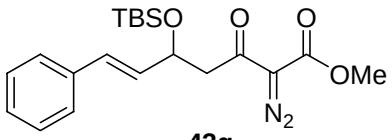
43d

Methyl 5-(*tert*-Butyldimethylsilanoxy)-5-(*p*-chlorophenyl)-2-diazo-3-oxopentanoate (43d). IR (neat): 2928, 2135, 1718, 1653 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.30 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 5.17 (dd, *J* = 8.8, 4.0 Hz, 1H), 3.79 (s, 3H), 3.42 (dd, *J* = 14.8, 8.8 Hz, 1H), 2.91 (dd, *J* = 14.8, 4.0 Hz, 1H), 0.79 (s, 9H), -0.05 (s, 3H), -0.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.0, 161.5, 143.0, 133.0, 128.4, 127.4, 71.2, 52.2, 50.3, 25.6, 18.0, -4.8, -5.3 (not seen, $C=N_2$); HRMS (FAB) for $C_{18}H_{25}ClN_2O_4Si$ $[M+Li]^+$ calcd: 403.1432; found: 403.1425; TLC R_f = 0.40 (9:1 hexanes:ethyl acetate).



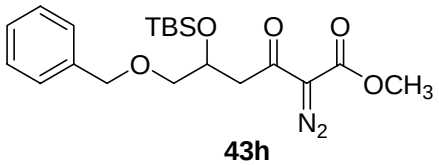
43e

Methyl 5-(*tert*-Butyldimethylsilanoxy)-2-diazo-3-oxo-5-(*p*-trifloromethyl)pentanoate (43e). IR (neat): 2956, 2136, 1725, 1662 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 2H), 5.27 (ddd, *J* = 8.8, 4.4 Hz, 1H), 3.79 (s, 3H), 3.43 (dd, *J* = 15.2, 8.8 Hz, 1H), 2.95 (dd, *J* = 15.2, 4.4 Hz, 1H), 0.81 (s, 9H), -0.02 (s, 3H), -0.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.7, 161.5, 148.5, 126.2, 125.2, 125.1, 71.2, 52.1, 50.3, 25.5, 17.9, -4.9, -5.4 (not seen, $C=N_2$); HRMS (FAB) for $C_{19}H_{26}F_3N_2O_4Si$ $[M+H]^+$ calcd: 431.1607; found: 431.1614; TLC R_f = 0.30 (7:1 hexanes :ethyl acetate).



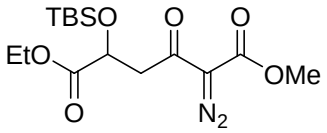
43g

Methyl (*E*)-5-(*tert*-Butyldimethylsilanoxy)-2-diazo-3-oxo-7-phenylhept-6-enoate (43g). IR (neat): 2955, 2134, 1725, 1654 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36-7.27 (comp, 5H), 6.56 (d, *J* = 16 Hz, 1H), 6.22 (dd, *J* = 16.0, 6.8 Hz, 1H), 4.84 (ddd, *J* = 7.6, 6.8, 5.2 Hz, 1H), 3.81 (s, 3H), 3.32 (dd, *J* = 15.2, 7.6 Hz, 1H), 2.98 (dd, *J* = 15.2, 5.2 Hz, 1H), 0.87 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.2, 161.6, 136.8, 132.0, 129.7, 128.5, 127.5, 126.5, 70.5, 52.2, 48.2, 25.7, 18.1, -4.3, -5.1 (not seen, $C=N_2$); HRMS (ESI) for $C_{20}H_{28}N_2O_4Si$ $[M+Na]^+$ calcd: 411.1716; found 411.1707; TLC R_f= 0.37 (9:1 hexanes :ethyl acetate).



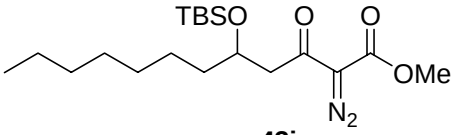
43h

Methyl 6-(Benzyloxy)-5-*tert*-butyldimethylsilanoxy-2-diazo-3-oxohexanoate (43h). IR (neat): 2955, 2856, 2135, 1726, 1654 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.31-7.29 (comp, 5H), 4.5 (s, 2H), 4.42-4.41 (comp, 1H), 3.78 (s, 3H), 3.48 (dd, *J* = 9.6, 5.2 Hz, 1H), 3.40 (dd, *J* = 9.6, 7.2 Hz, 1H), 3.13 (dd, *J* = 15.2, 7.2 Hz, 1H), 3.05 (dd, *J* = 15.2, 5.2 Hz, 1H), 0.83 (s, 9H), 0.05 (s, 3 H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.5, 161.6, 138.3, 128.3, 127.5, 127.5, 74.4, 73.2, 68.3, 52.1, 45.0, 25.7, 18.0, -4.6, -5.1 (not seen, $C=N_2$); HRMS (FAB) for $C_{20}H_{30}N_2O_5Si$ $[M+H]^+$ calcd: 407.2002; found: 407.2002; TLC R_f= 0.33 (9:1 hexanes:ethyl acetate).



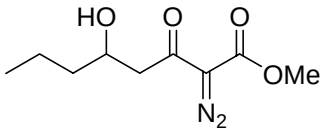
43i

Ethyl 1-Carbomethoxy-4-(*tert*-butyldimethylsilanoxy)-1-diazo-2-oxopentanoate (43i). IR (neat): 2930, 2135, 1729, 1660 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.69 (t, *J* = 6.4 Hz, 1H), 4.20-4.12 (comp, 2H), 3.81 (s, 3H), 3.29 (d, *J* = 6.0 Hz, 2H), 1.25 (t, *J* = 7.2 Hz, 3H), 0.84 (s, 9H), 0.08 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.2, 172.6, 161.5, 68.6, 61.1, 52.2, 44.8, 25.6, 18.1, 14.1, -5.0, -5.5 (not seen, C=N_2); HRMS (FAB) for $C_{20}H_{30}N_2O_5Si$ $[M+H]^+$ calcd: 359.1638; found: 359.1627; TLC R_f = 0.19 (9:1 hexanes:ethyl acetate).



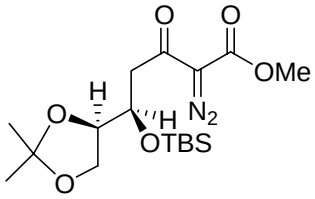
43j

Methyl 5-(*tert*-Butyldimethylsilanoxy)-2-diazo-3-oxododecanoate (43j). IR (neat): 2929, 2856, 2134, 1731, 1653 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.18-4.16 (comp, 1H), 3.79 (s, 3H), 3.12 (dd, *J* = 15.2, 7.6 Hz, 1H), 2.80 (dd, *J* = 15.2, 5.2 Hz, 1H), 1.45-1.42 (comp, 2H), 1.29-1.22 (comp, 10H), 0.84 (t, *J* = 6.8 Hz, 3H), 0.80 (s, 9H), -0.00 (s, 3H), -0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.2, 161.6, 69.2, 52.1, 47.1, 37.9, 31.7, 29.6, 29.2, 25.7, 24.9, 22.6, 17.9, 14.0, -4.7, -4.9 (not seen, C=N_2); HRMS (FAB) for $C_{19}H_{36}N_2O_4Si$ $[M+H]^+$ calcd: 385.2523; found: 385.2527; TLC R_f = 0.46 (9:1 hexanes:ethyl acetate).



43k'

Methyl 2-Diazo-5-hydroxy-3-oxooctanoate (43k′). The TBDMS protecting group was removed by stirring the solution of **3k** (0.10 g, 0.47 mmol) in methanol (2 mL) and silica gel (5 g) for 4 hrs at ambient temperature. IR (neat): 3498, 2959, 2137, 1723, 1657, 1649 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.07-4.01 (m, 1H), 3.79 (s, 3H), 3.02 (dd, *J* = 17.2, 2.8 Hz, 1H), 2.86 (dd, *J* = 17.2, 9.2 Hz, 1H), 1.51-1.30 (comp, 4H), 0.88 (t, 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.9, 161.6, 67.8, 52.2, 46.8, 38.8, 18.6, 13.9 (not seen, $C=N_2$); HRMS (FAB) for $C_9H_{14}N_2O_4$ $[M+H]^+$ calcd: 215.1032; found 215.1025; TLC R_f = 0.31 (4:1 hexanes:ethyl acetate).

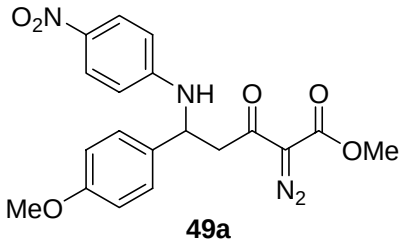


45a (*major*)

Methyl (5*R*)-5-(*tert*-Butylsilanoxy)-2-diazo-3-oxo-6((6*R*)-2,2-dimethyl-[1,3]-dioxolan-4-yl)-pentanoate (45a): IR (neat): 2932, 2134, 1734, 1652 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$*):* δ 4.16 (ddd, *J* = 10.6, 6.4, 5.2 Hz, 1H), 4.06-4.02 (comp, 1H), 3.91-3.90 (comp, 1H), 3.81 (s, 3H), 3.07 (comp, 2H), 1.39 (s, 3H), 1.31 (s, 3H), 0.80 (s, 9H), 0.07 (s, 3H), 0.02 (s, 3H) (not seen, $C=N_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.2, 172.6, 161.5, 68.6,

61.1, 52.2, 44.8, 25.6, 18.1, 14.1, -5.0, -5.5*;* HRMS (FAB) for $C_{17}H_{30}N_2O_6Si$ $[M+H]^+$ calcd: 386.1938; found: 386.1927; TLC R_f= 0.20 (9:1 hexanes:ethyl acetate).

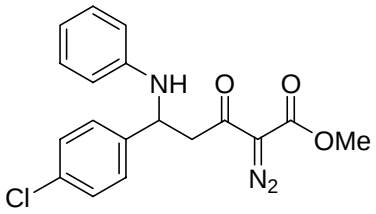
General Procedure for Mannich Addition of 38a to Representative Benzylidene-anilines. To a dry 5-mL round-bottomed flask containing a stir bar and fitted with a septum was added anhydrous scandium(III) triflate (14 mg, 0.030 mmol) and 2 mL of anhydrous dichloromethane. Methyl 3-(*tert*-butyldimethylsilanyloxy)-2-diazo-3-butenoate **38a** (564 mg, 2.20 mmol) was then added dropwise over 5 min *via* a 1-mL syringe. Finally, imine (1.5 mmol) in CH_2Cl_2 (1 mL) was added dropwise over 5 min to the reaction mixture. The reaction mixture was stirred at room temperature for 10 h. (The reaction with **49a** was found to be incomplete after 6 h.). Over this time the solution changed color from orange to bright yellow and was subsequently passed through a silica gel plug with washings of dichloromethane to remove the catalyst. Solvent was removed under reduced pressure. The TBDMS group was deprotected by stirring the solution of the Mannich adduct in methanol (5 mL) and silica gel (5 gm) for 20 min at ambient temperature. Product was isolated by flash column chromatography eluting with 4:1 hexane:ethyl acetate.



49a

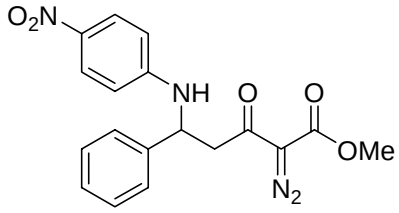
Methyl 2-Diazo-5-(4-methoxyphenyl)-5-(4-nitroanilino)-3-oxopentanoate (49a). IR (neat): 3375, 2953, 2148, 1721, 1643 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, *J* =

8.8 Hz, 2H), 7.28 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.44 (d, *J* = 8.8 Hz, 2H), 4.93-4.90 (m, 1H), 4.12 (bs, 1H), 3.85 (s, 3H), 3.75 (s, 3H), 3.37-3.35 (comp, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.2, 161.9, 159.1, 152.1, 138.3, 132.7, 127.8, 127.2, 114.4, 112.1, 55.2, 54.2, 52.5, 46.9 (not seen, C=N_2); HRMS (EI) for $C_{19}H_{18}N_4O_6$ $[M+H]^+$ calcd: 398.1226; found: 398.1232; TLC R_f = 0.20 (4:1 hexanes:ethyl acetate).



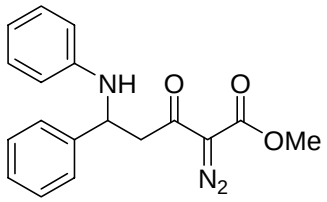
49b

Methyl 2-Diazo-5-(4-chlorophenyl)-5-anilino-3-oxo-pentanoate (49b). IR (neat): 3394, 2917, 2141, 1721, 1647 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.10-6.47 (comp, 5H), 4.85 (dd, *J* = 9.6, 4.0 Hz, 1H), 4.69 (bs, 1H), 3.87 (s, 3H), 3.38 (dd, *J* = 14.4, 4.0 Hz, 1H), 3.20 (dd, *J* = 14.4, 9.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.8, 162.2, 146.9, 141.6, 133.4, 129.6, 129.3, 128.2, 118.3, 114.0, 54.9, 52.9, 47.9 (not seen, C=N_2); HRMS (EI) for $C_{18}H_{16}ClN_3O_3$ $[M+H]^+$ calcd: 357.0880; found: 357.0882; TLC R_f = 0.29 (4:1 hexanes:ethyl acetate).



49c

Methyl 2-Diazo-5-(4-nitrophenylamino)-3-oxo-5-phenylpentanoate (49c). IR (neat): 3353, 2134, 1716, 1652 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, *J* = 8.8 Hz, 2H), 7.38-7.24 (comp, 5H), 6.44 (d, *J* = 8.8 Hz, 2H), 5.67 (bs, 1H), 4.95-4.93 (m, 1H), 3.86 (s, 3H), 3.37-3.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.1, 161.9, 152.0, 140.7, 138.4, 129.0, 127.9, 126.1, 126.0, 112.1, 54.8, 52.5, 46.8 (not seen, C=N_2); HRMS (EI) for $C_{18}H_{16}N_4O_5$ $[M+H]^+$ calcd: 368.1121; found: 368.1112; TLC R_f = 0.30 (4:1 hexanes:ethyl acetate).

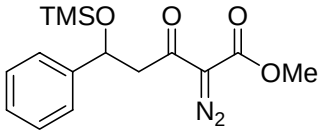


49d

Methyl 2-Diazo-5-anilino-3-oxo-5-phenylpentanoate (49d). IR (neat): 3365, 2132, 1720, 1641 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.42-7.25 (comp, 5H), 7.05-6.49 (comp, 5H), 4.87 (dd, *J* = 9.6, 4.4 Hz, 1H), 4.67 (bs, 1H), 3.82 (s, 3H), 3.37 (dd, 14.4, 4.4 Hz, 1H), 3.23 (dd, 14.4, 9.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.1, 162.3, 147.2, 143.0, 129.5, 129.1, 127.7, 126.7, 118.0, 114.0, 55.4, 52.8, 48.0 (not seen, C=N_2); HRMS (EI) for $C_{18}H_{17}N_3O_3$ $[M+H]^+$ calcd: 323.3521; found: 323.3519; TLC R_f = 0.33 (4:1 hexanes: ethyl acetate).

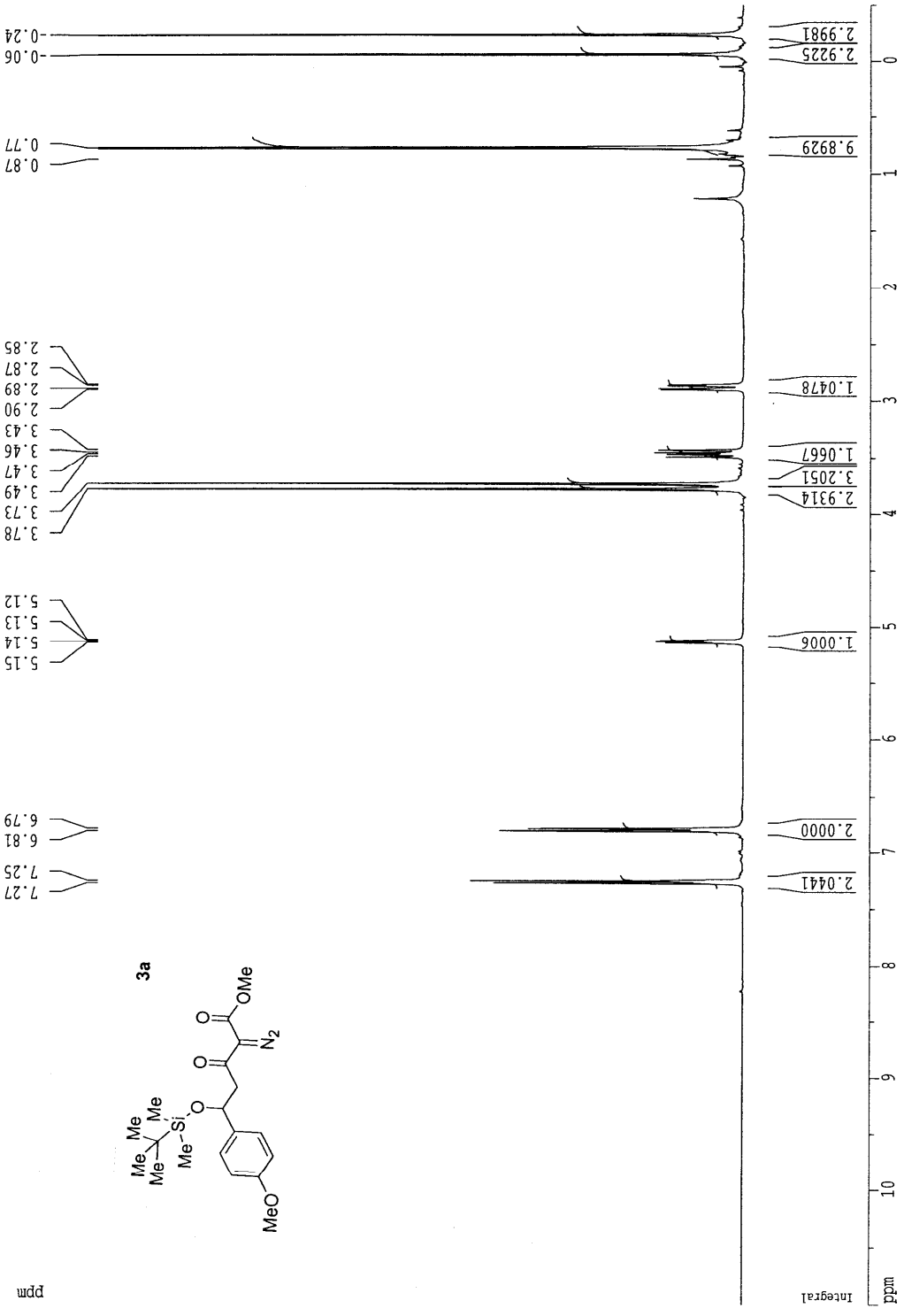
Mukaiyama Aldol Addition Reaction with Methyl 3-trimethylsilanyloxy-2-diazobut-3-enoate 38b and benzaldehyde. To a dry 5-mL round-bottomed flask containing a stir bar and fitted with a septum was added anhydrous scandium(III) triflate (14 mg, 0.030 mmol) and 3 mL of anhydrous dichloromethane. Methyl 3-trimethylsilanyloxy-2-

diazobut-3-enoate **38b** (327 mg, 1.50 mmol) was then added drop wise to the above mixture over 5 min from a 1-mL syringe. Finally, benzaldehyde **39c** (152 μL, 1.50 mmol) was added to the reaction mixture using a 500-μL microsyringe. The reaction mixture was stirred at room temperature for 0.5 h. (The reactions were found to be incomplete after 20 min for both benzaldehyde and *p*-anisaldehyde.) Over this time the solution changed color from orange to pale yellow at the end. After the reaction was complete, the solution was passed through a celite plug to remove the catalyst with washings of dichloromethane (2 mL x 3) and the solvent was removed under reduced pressure.



43c-b

2-Diazo-3-oxo-5-phenyl-5-trimethylsilanyloxy-methylpentanoate (43c-b): IR (neat):3505, 2958, 2141, 1721, 1654; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.18 (comp, 5H), 5.22 (dd, *J* = 9.2, 4.0 Hz 1H), 3.78 (s, 3 H), 3.38 (dd, *J* = 15.2, 9.2 Hz, 1H), 2.99 (dd, *J* = 15.2, 4.0 Hz, 1H), -0.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 190.1, 161.6, 142.7, 128.5, 127.7, 125.7, 69.9, 52.1, 48.2, 1.9 (not seen, C=N_2); HRMS for $C_{15}H_{20}O_4N_2Si$ [M+1] calcd: 320.1240; found 320.1246.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Si
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2.0000
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0.77
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2.87
2.89
2.90
3.43
3.46
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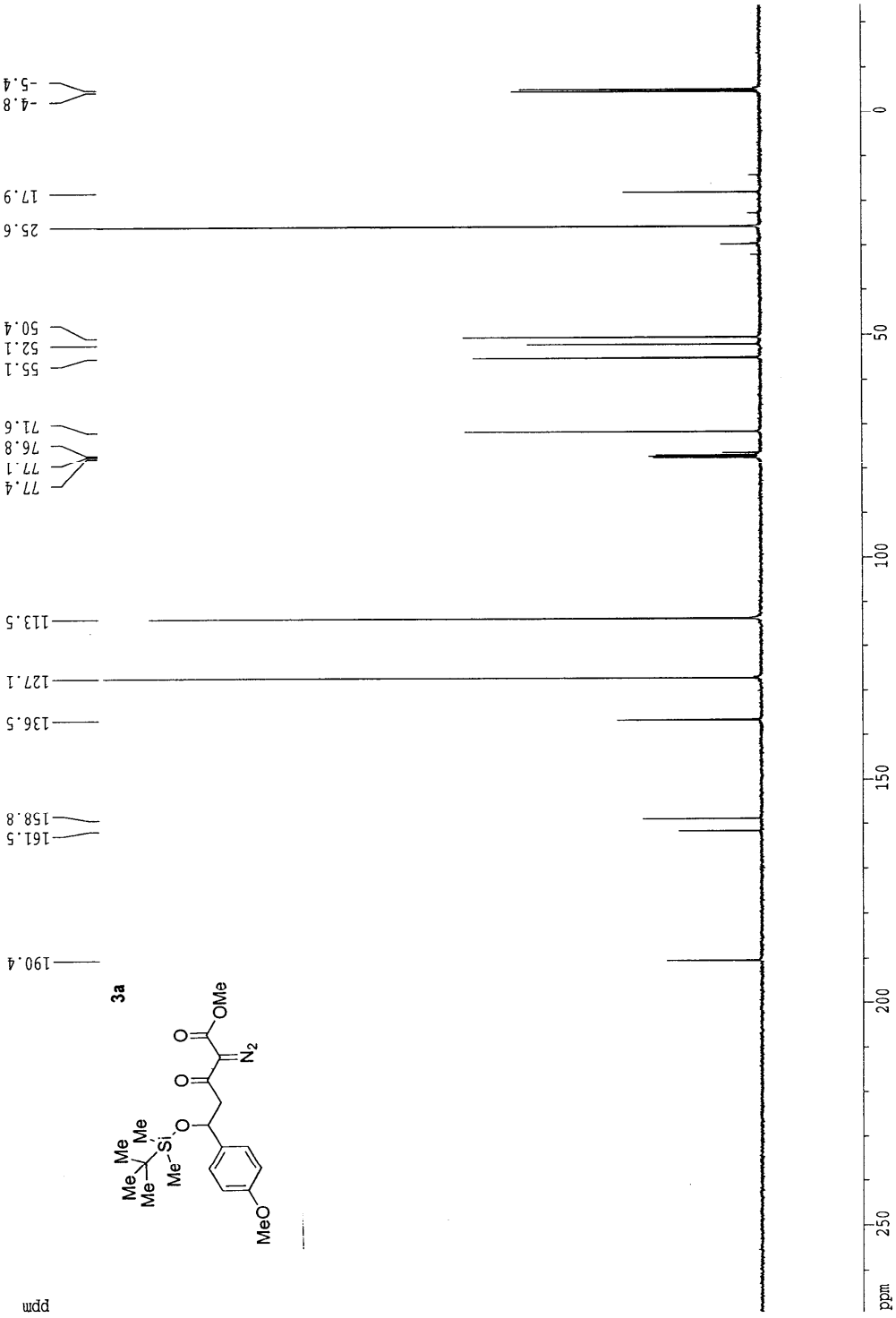
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158.8
161.5
190.4
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Si
Me
Me
Me
Me
MeO
ppm
0
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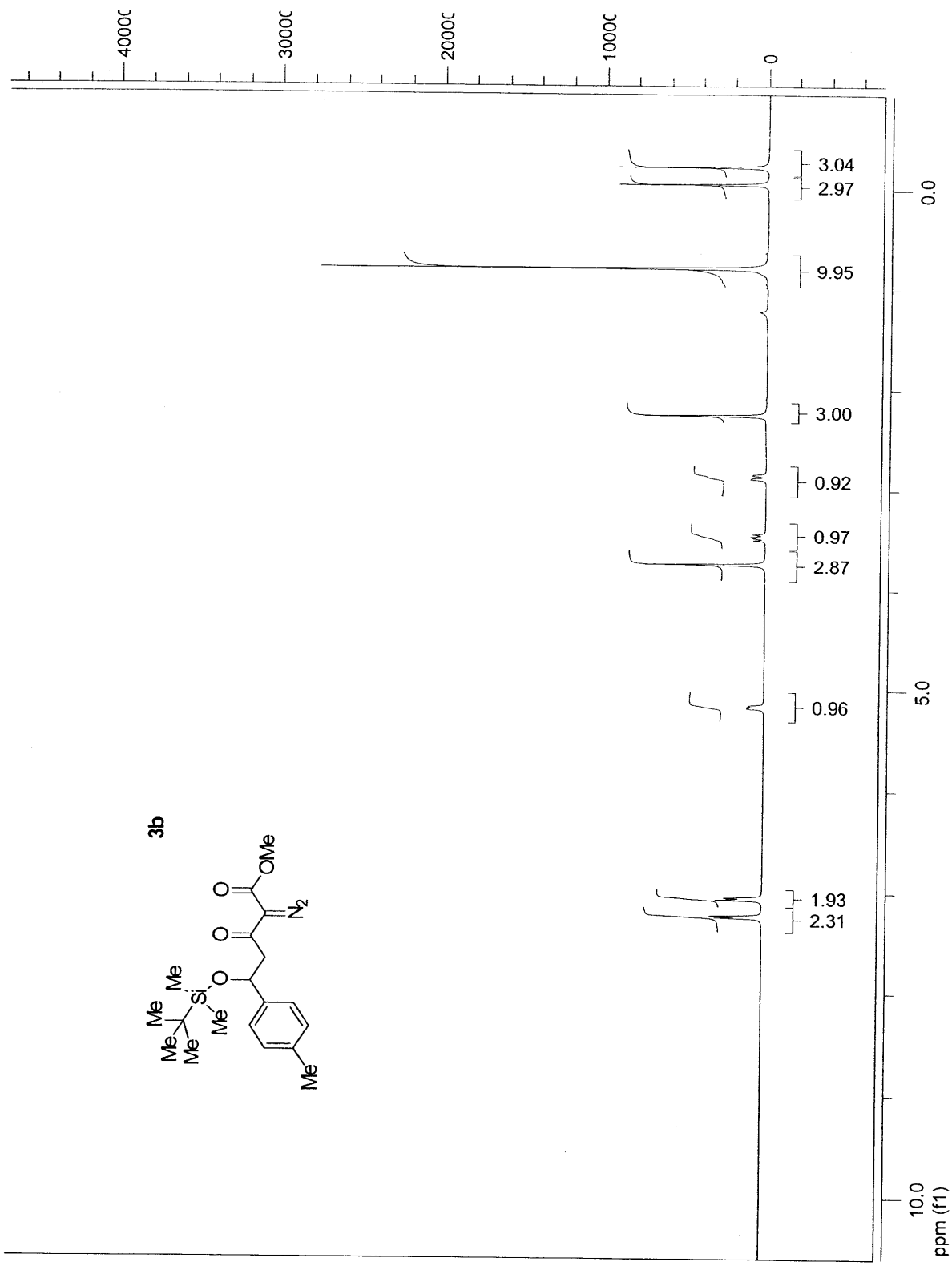
100
150
200
250
ppm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O
Si
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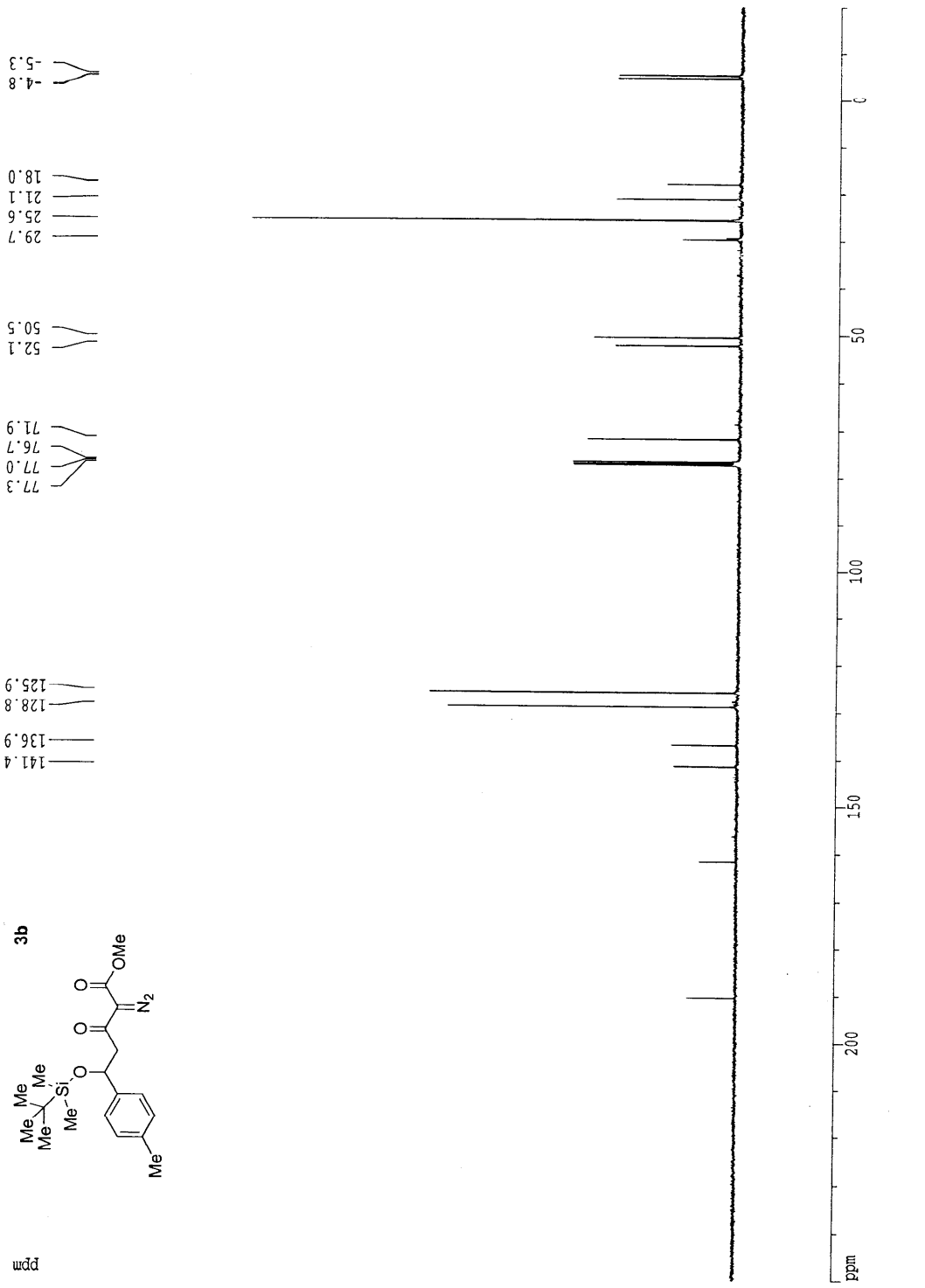
Me
Me
Me
Me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N2
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Me
Me
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Me
O
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52.1
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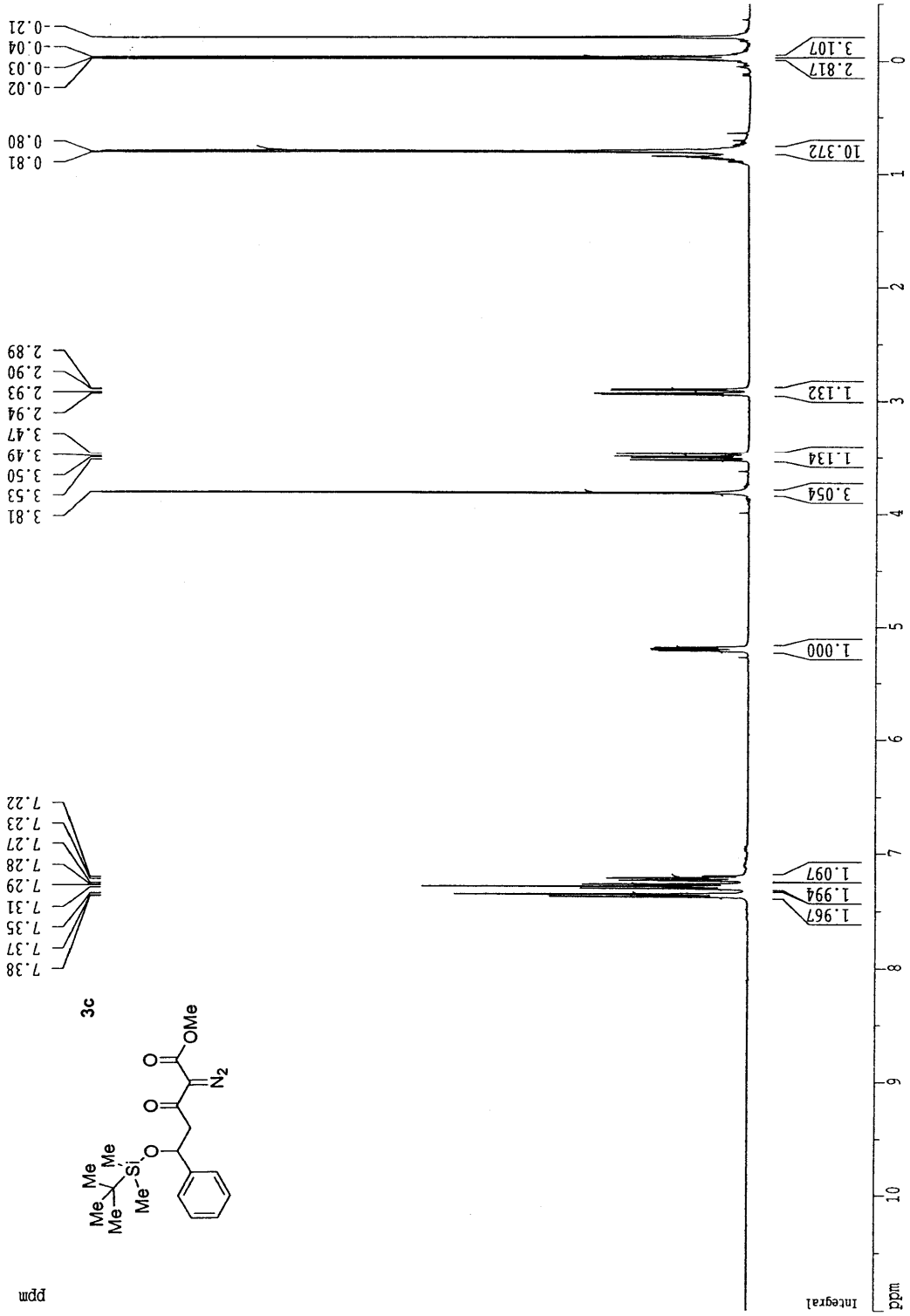
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Si
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3.53
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7.28
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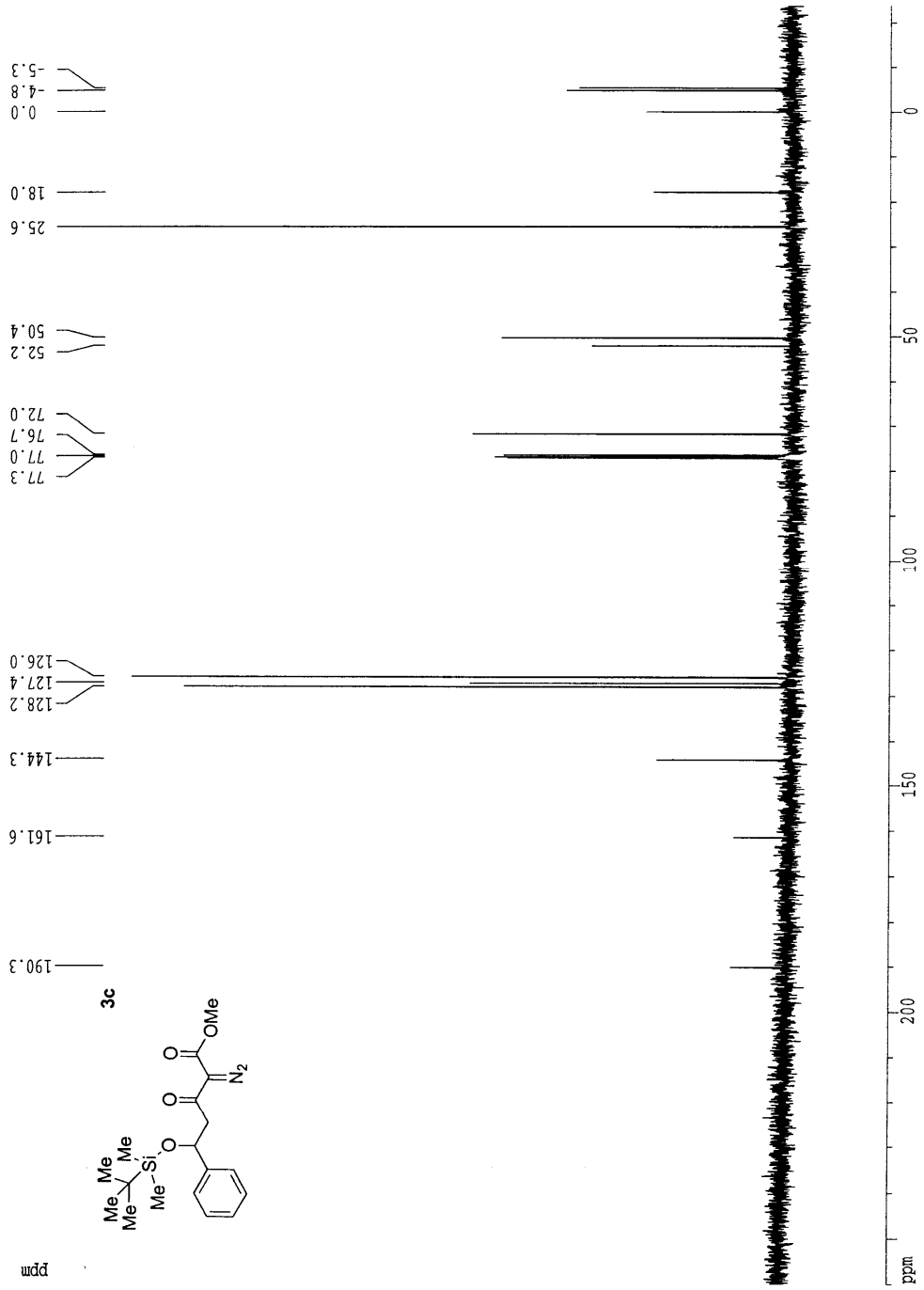
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161.6
190.3
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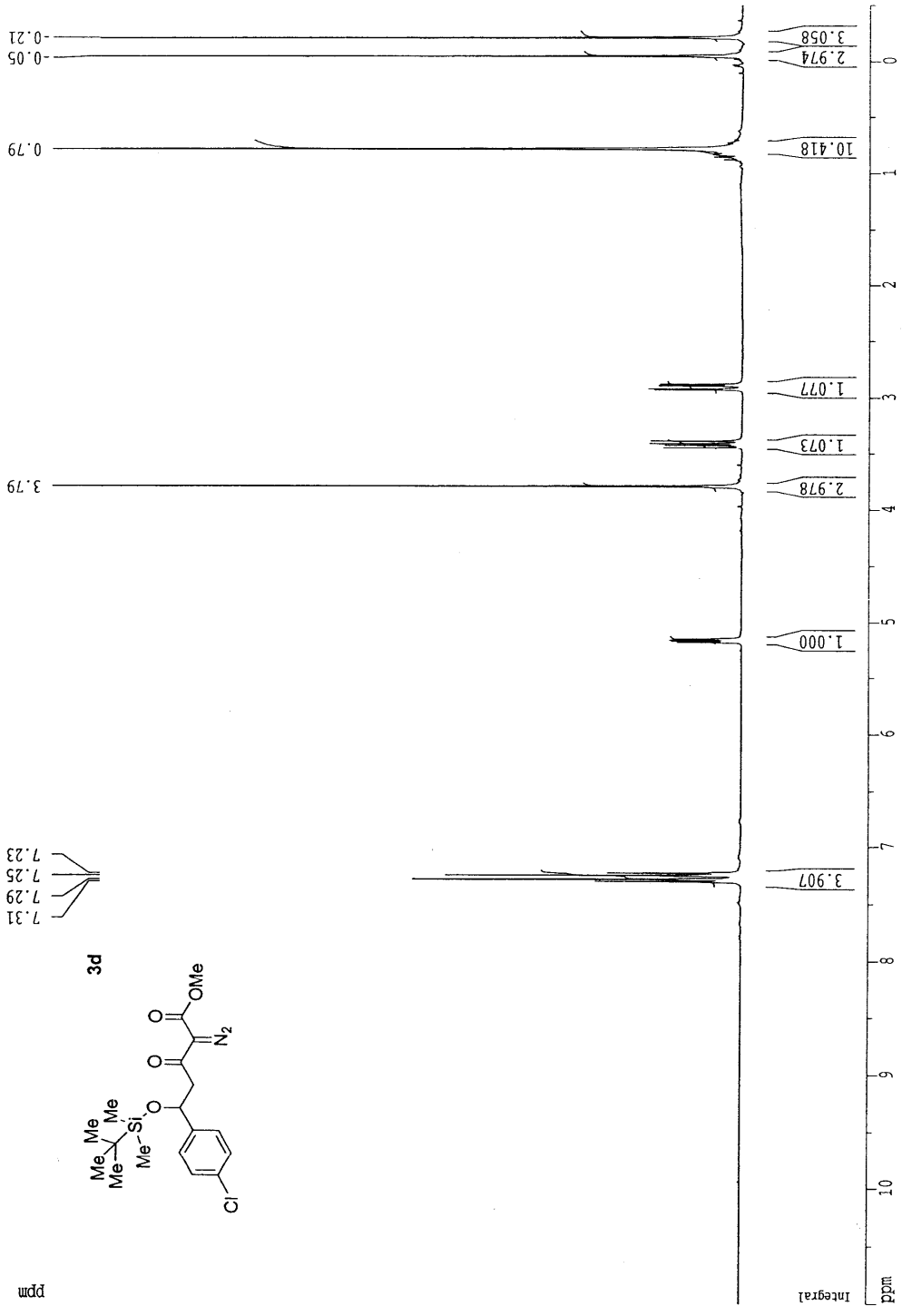
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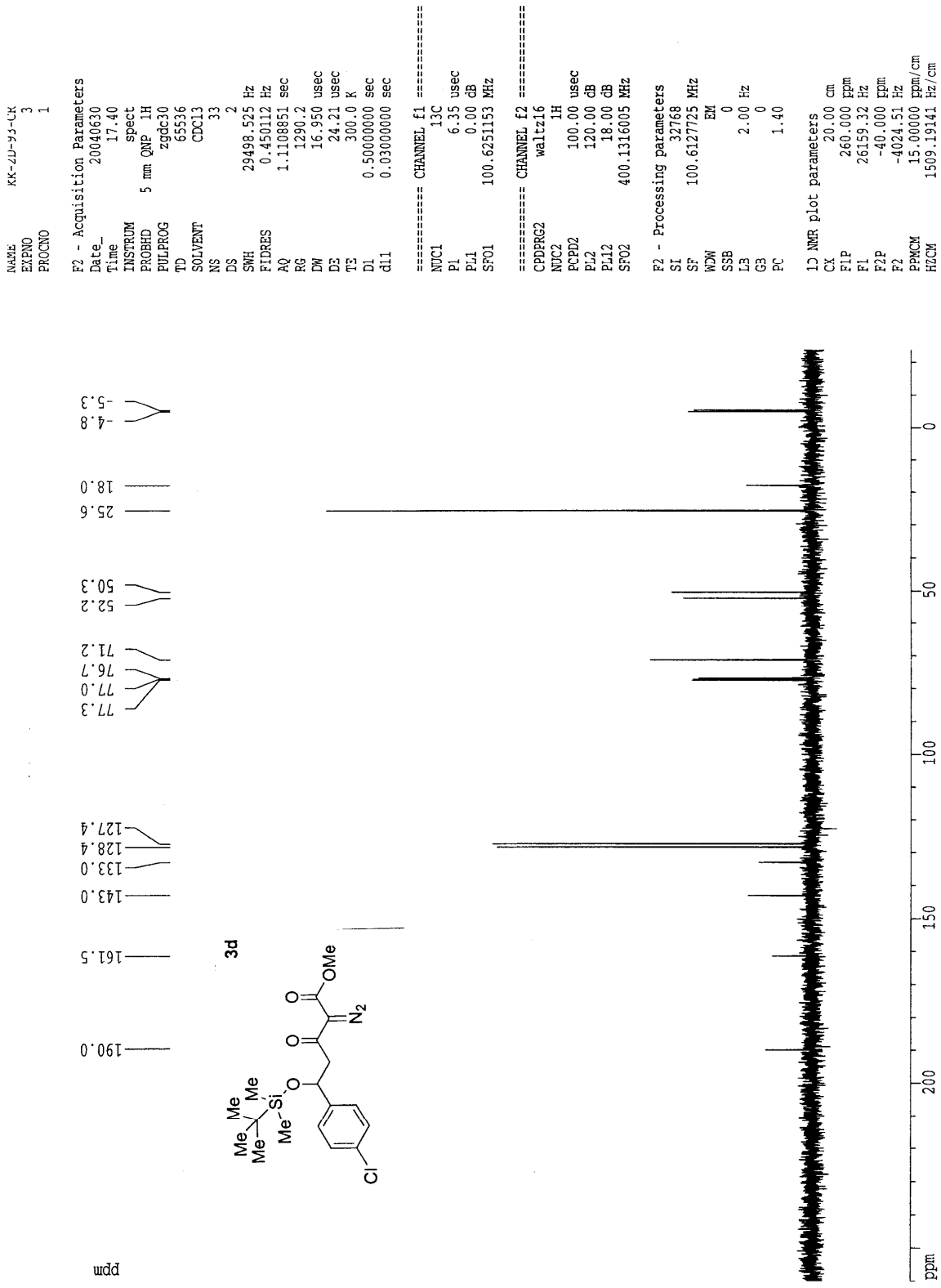
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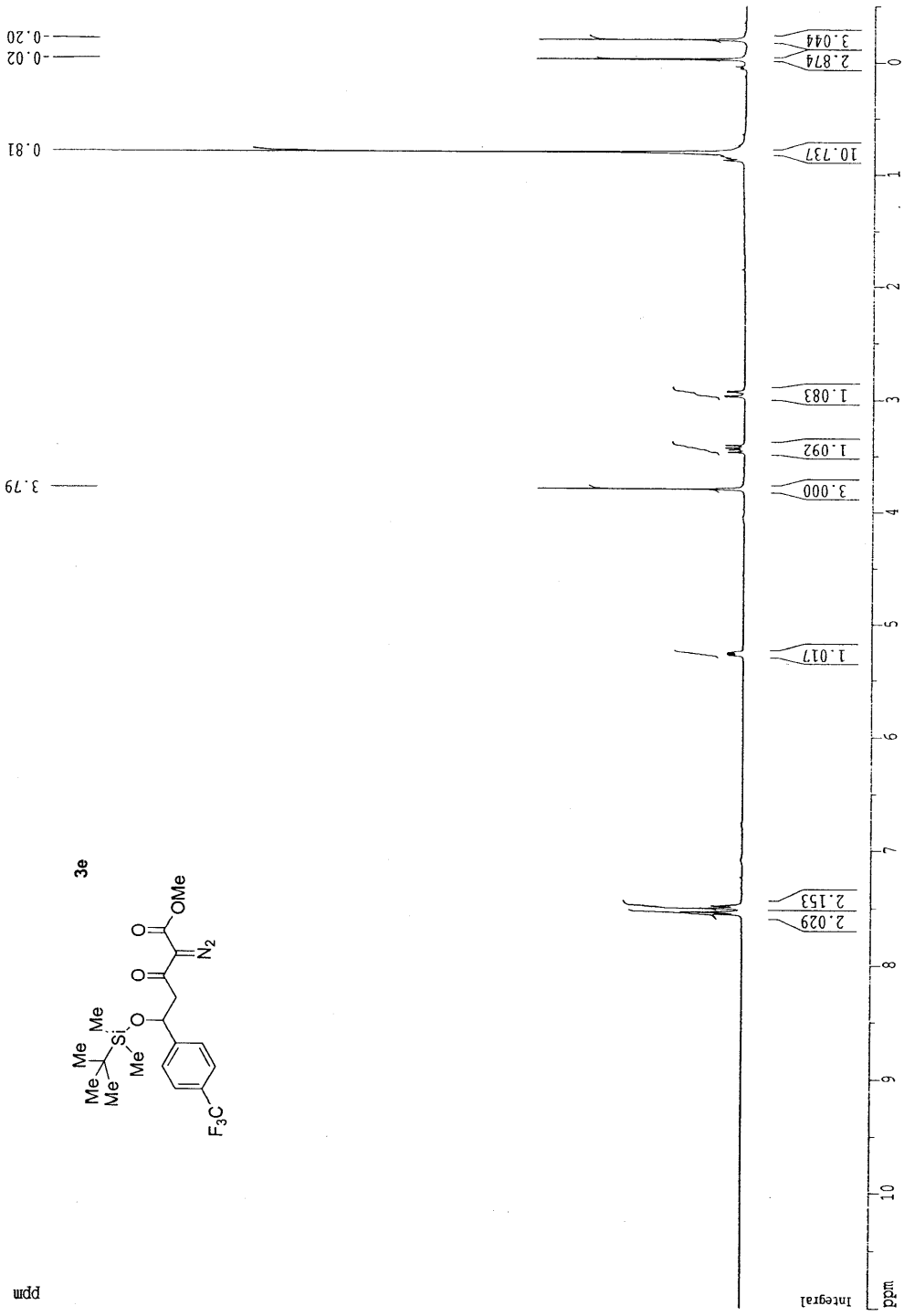
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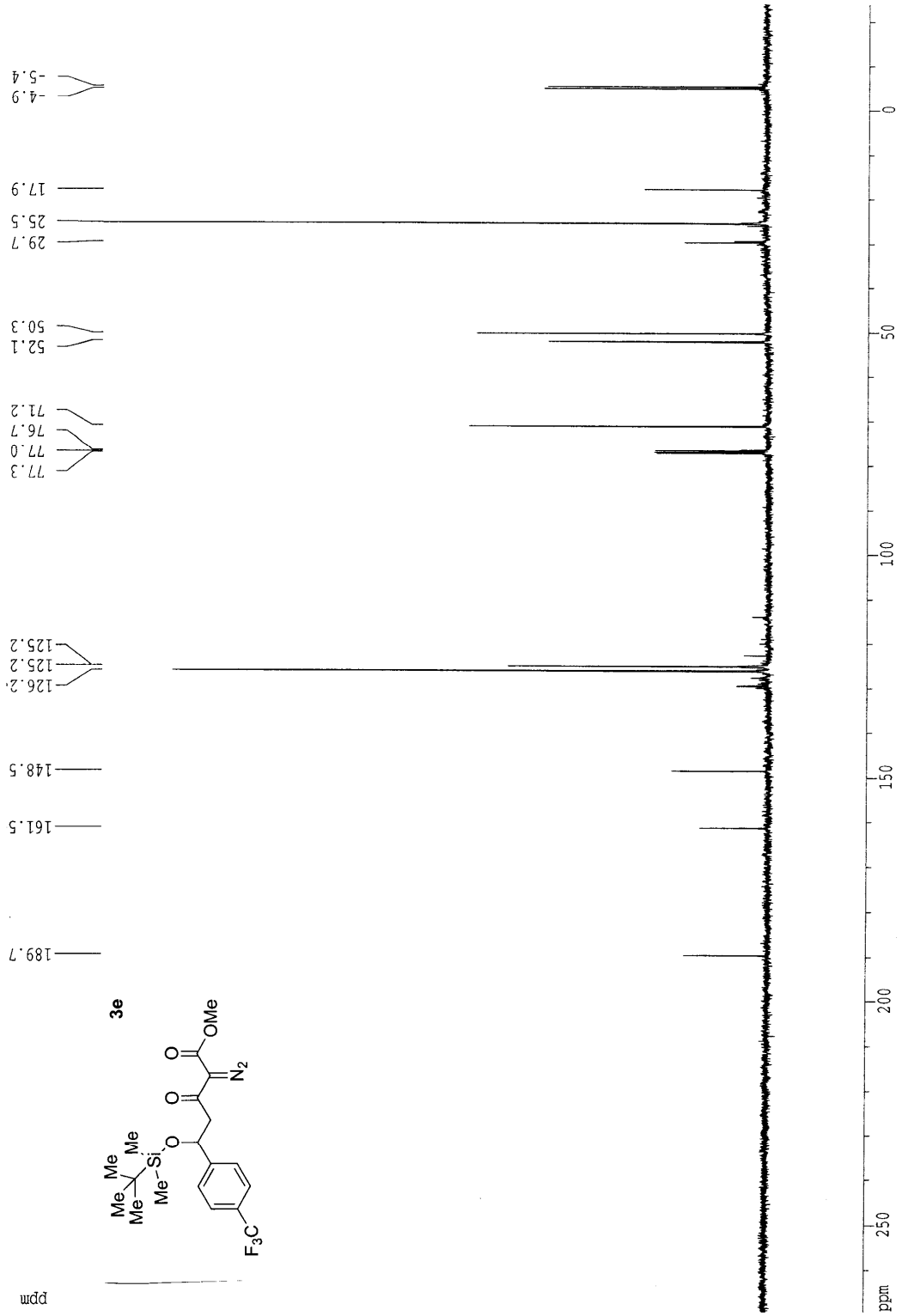
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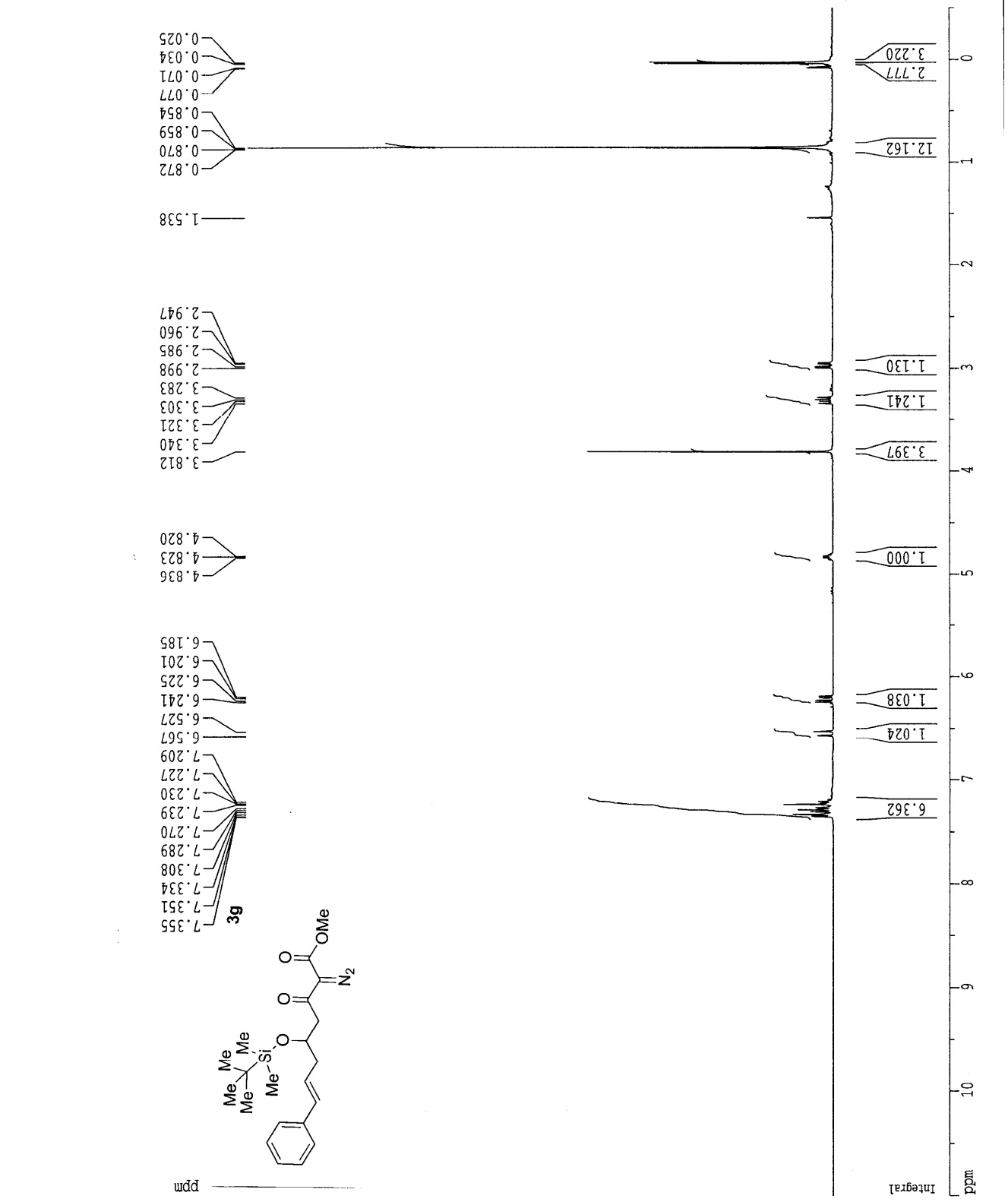
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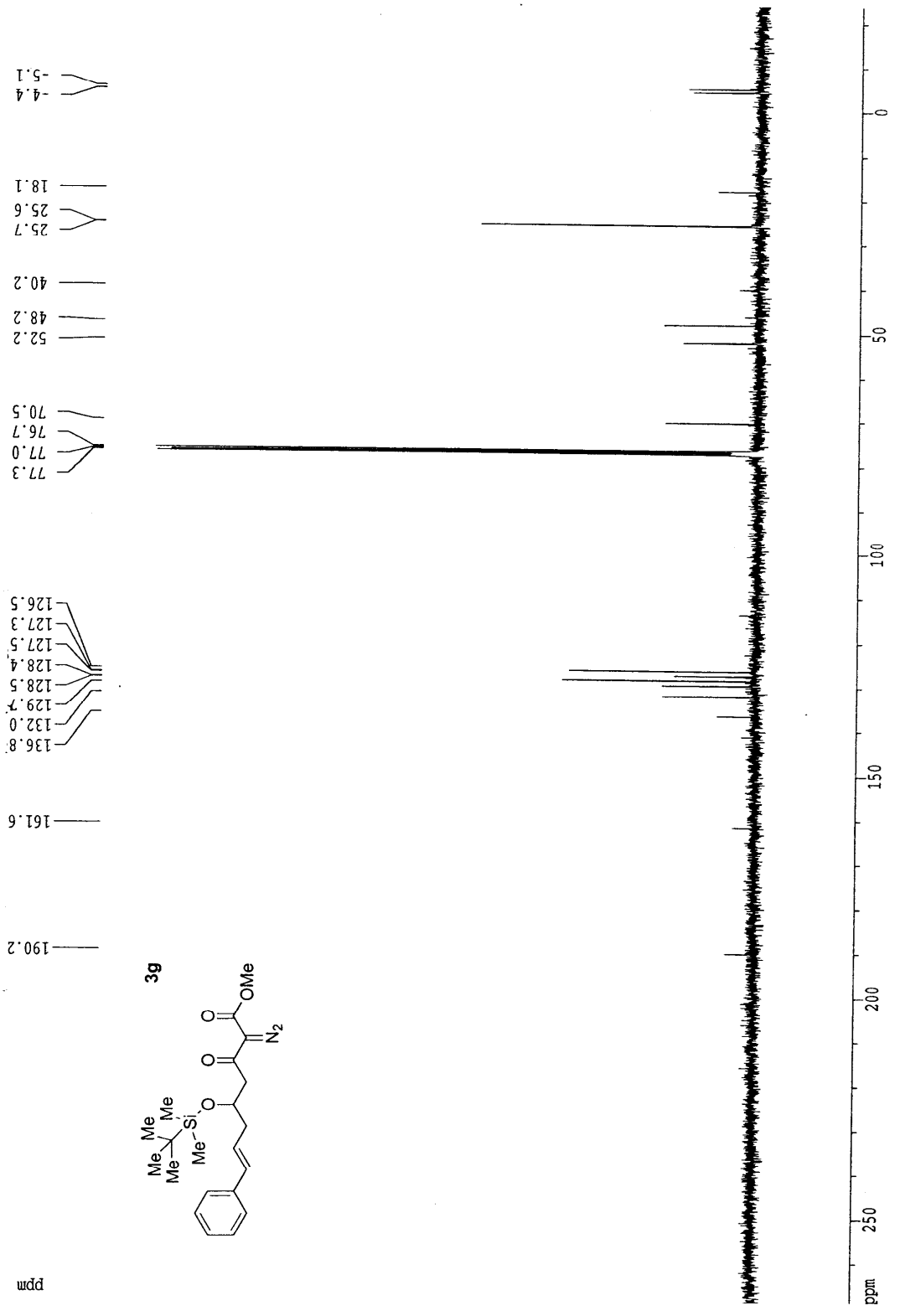
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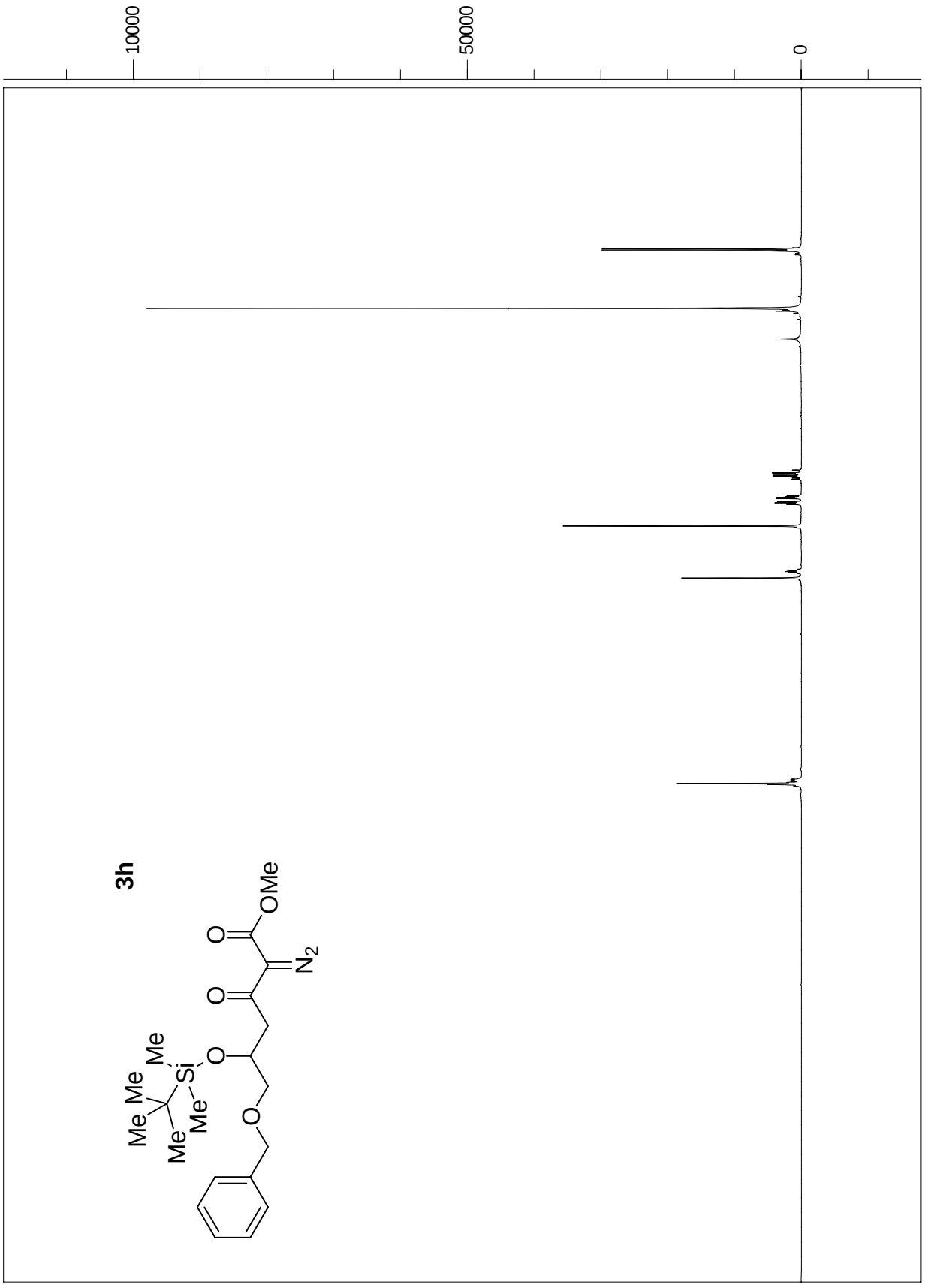
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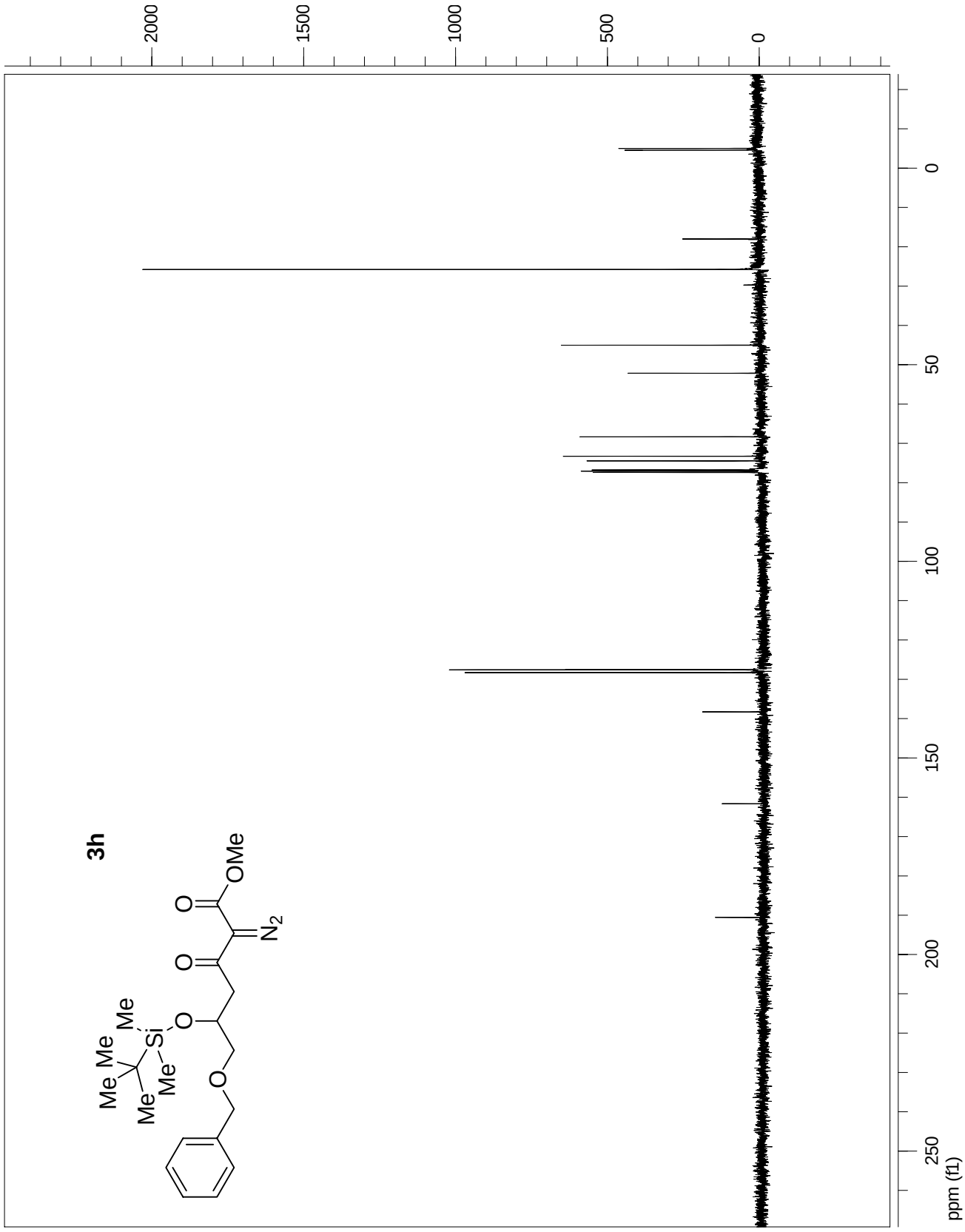
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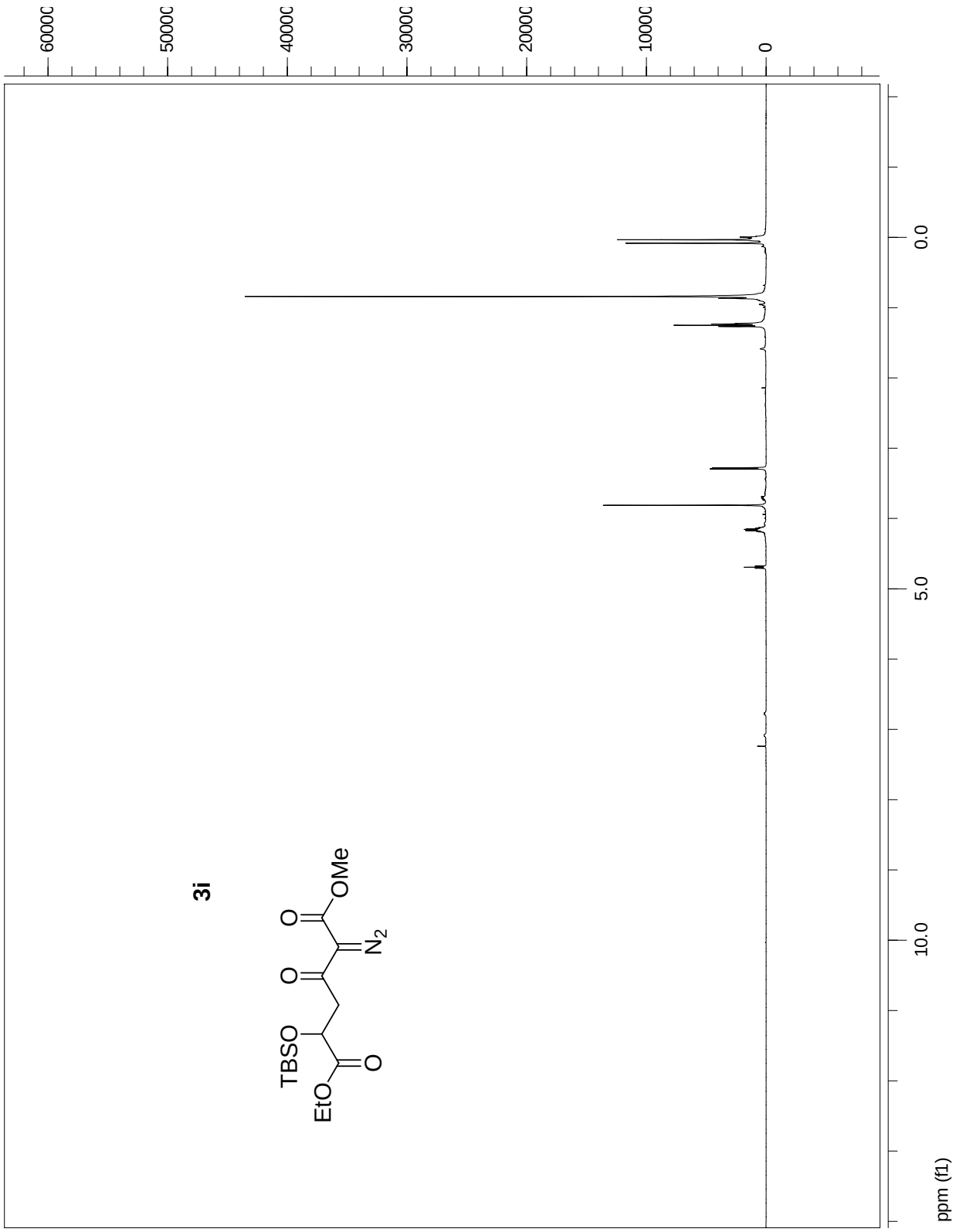
ppm (f1)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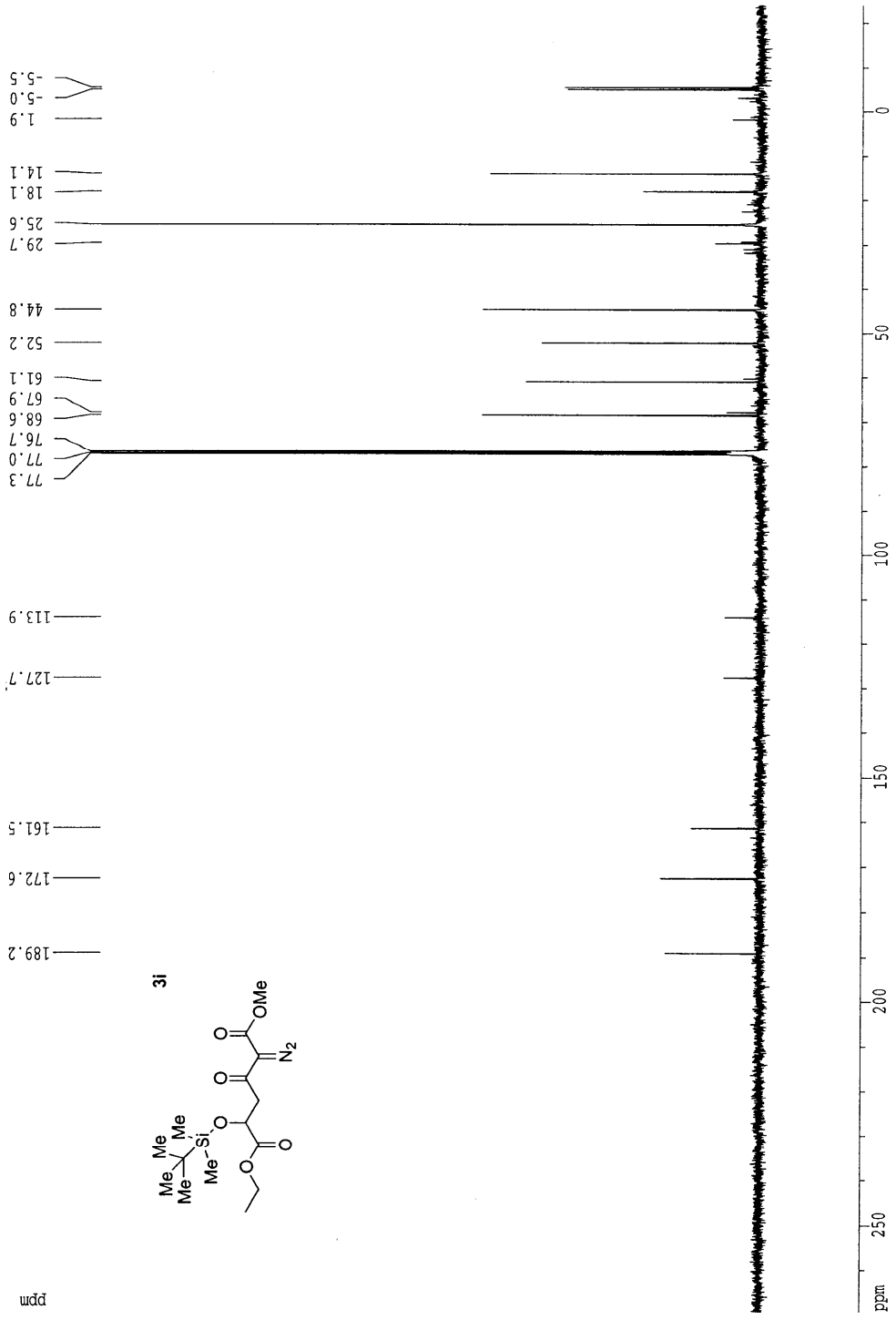
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3i
OMe
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Si
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Me
Me
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ppm
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150
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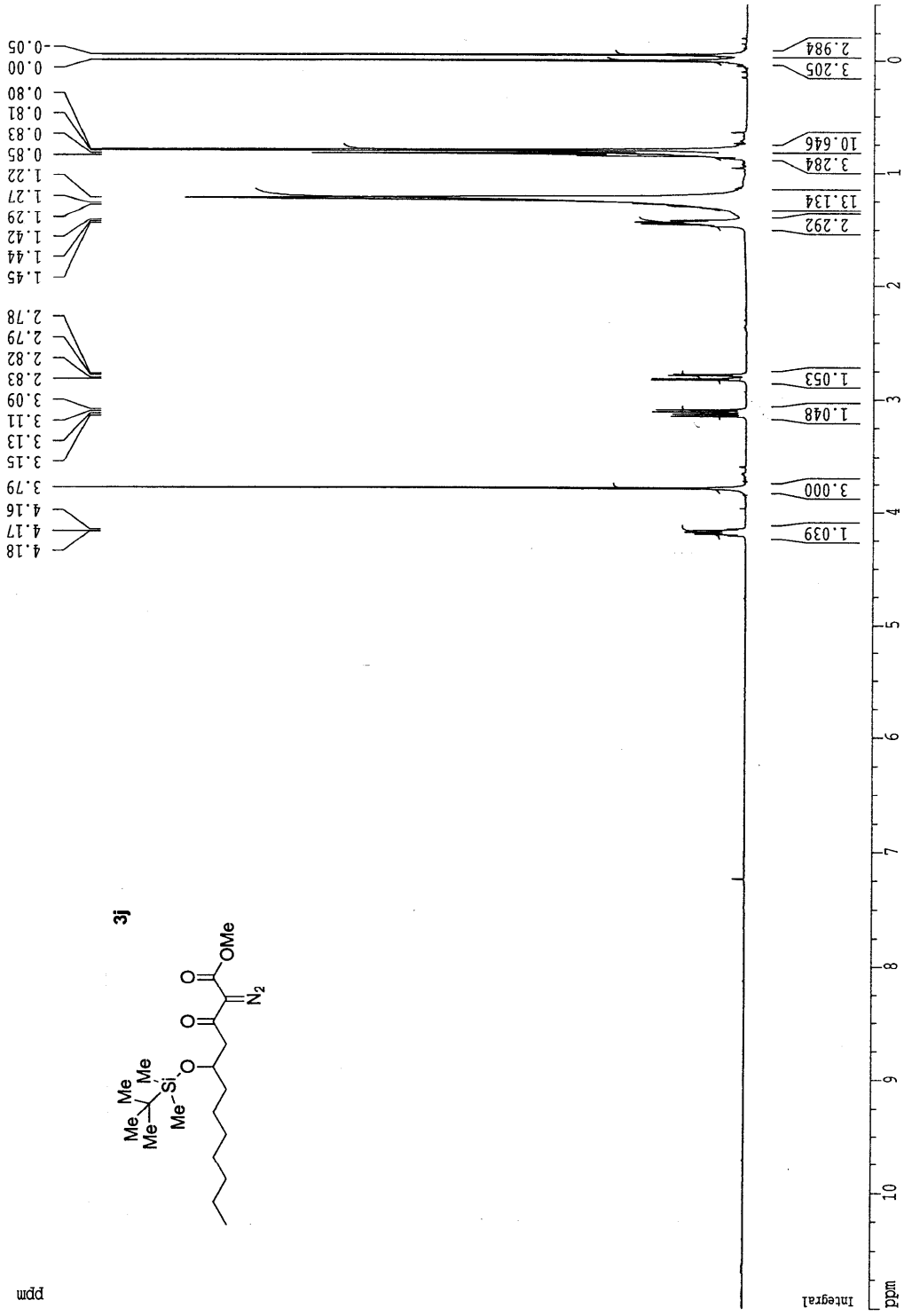
ppm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O
N2
Me
Me
Me
Si
Me
O
ppm
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0.00
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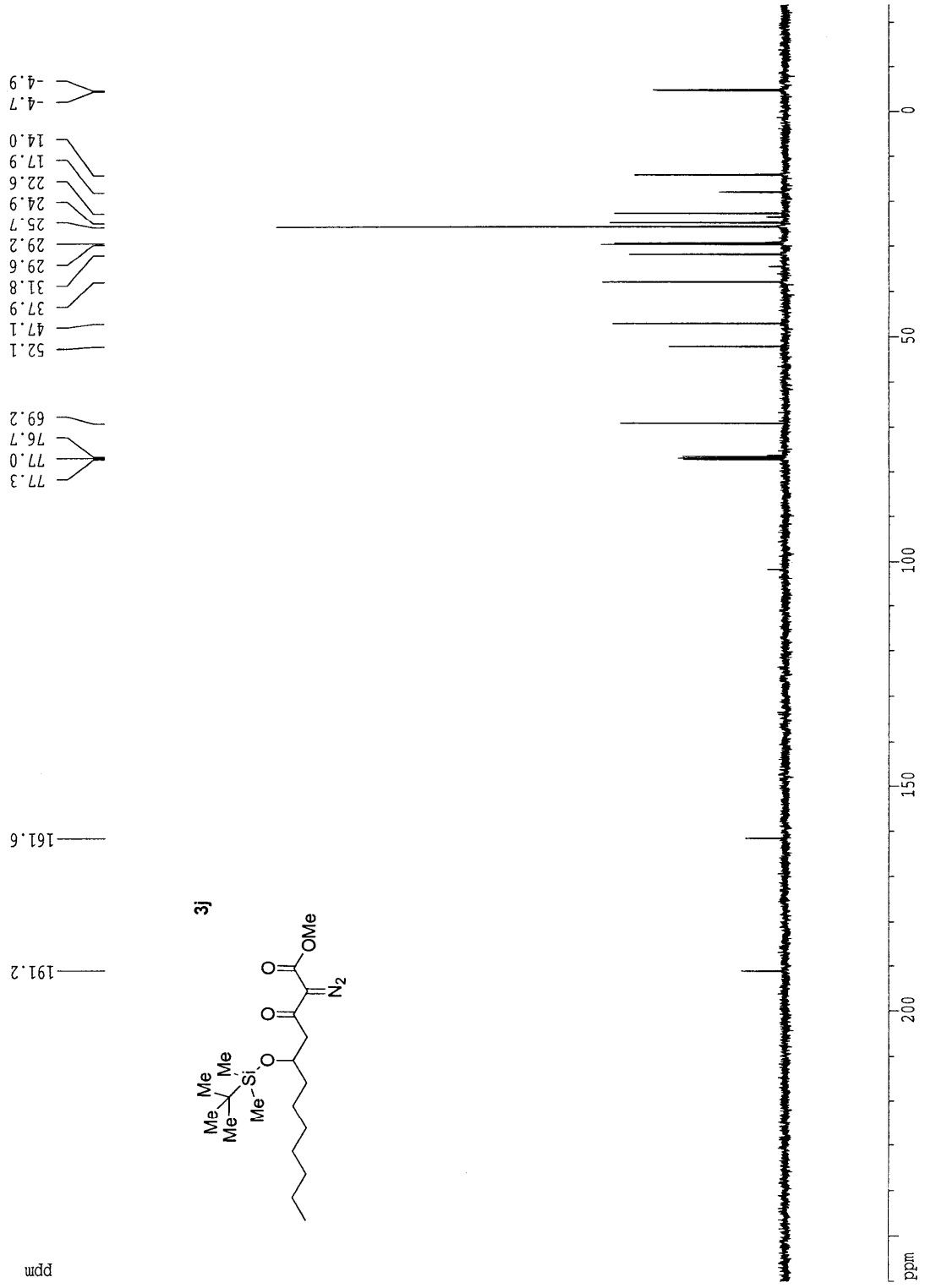
0.81
0.83
0.85
1.22
1.27
1.29
1.42
1.44
1.45
2.78
2.79
2.82
2.83
3.09
3.11
3.13
3.15
3.79
4.16
4.17
4.18
2.984
3.205
10.646
3.284
13.134
2.292
1.053
1.048
3.000
1.039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Si
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Me
Me
Me
ppm
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37.9
31.8
29.6
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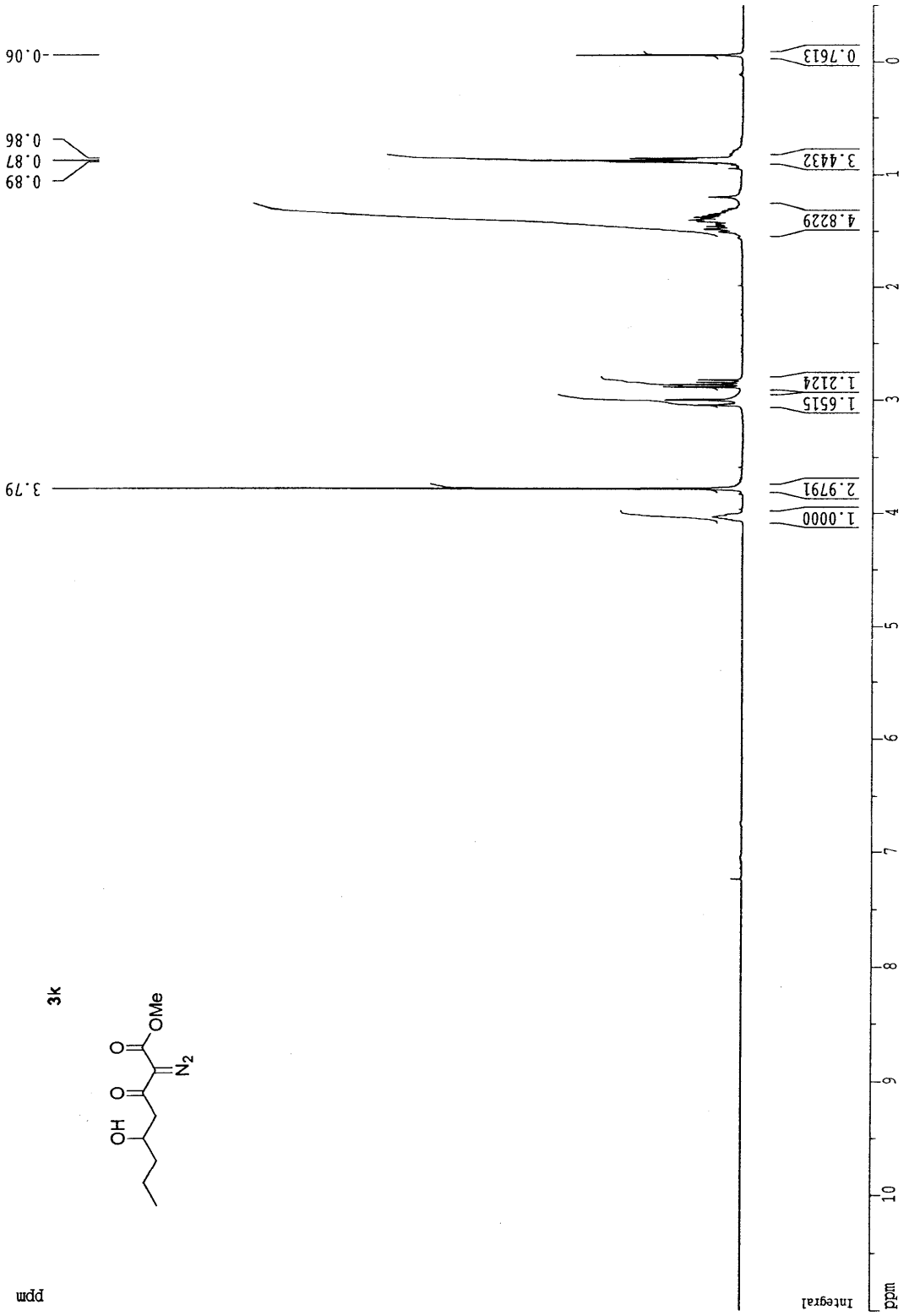
ppm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O
N_2
OH
ppm
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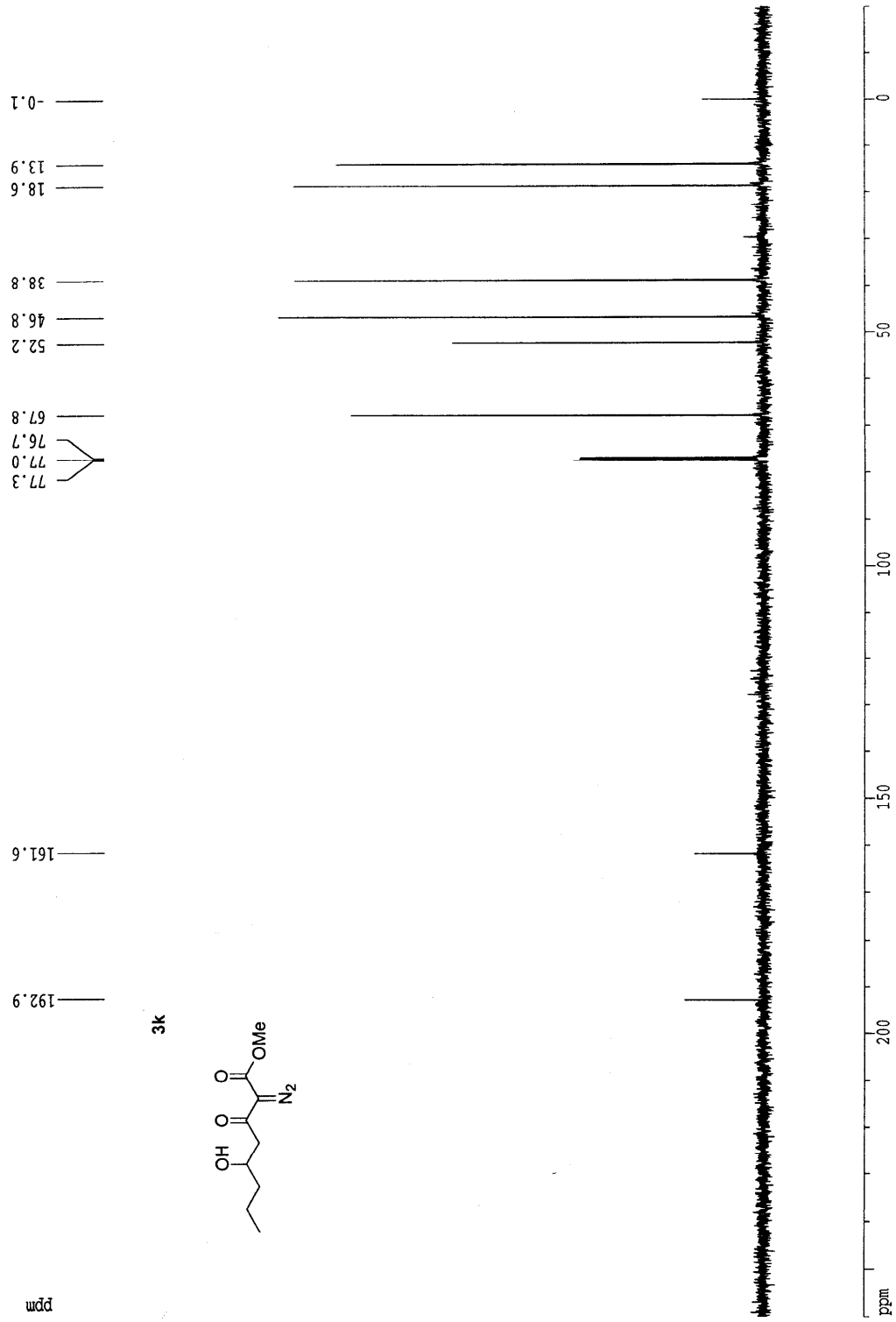
1.2124
1.6515
2.9791
1.0000
3.79
0.89
0.87
0.86
-0.06
0
1
2
3
4
5
6
7
8
9
10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76.7
77.0
77.3
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ppm
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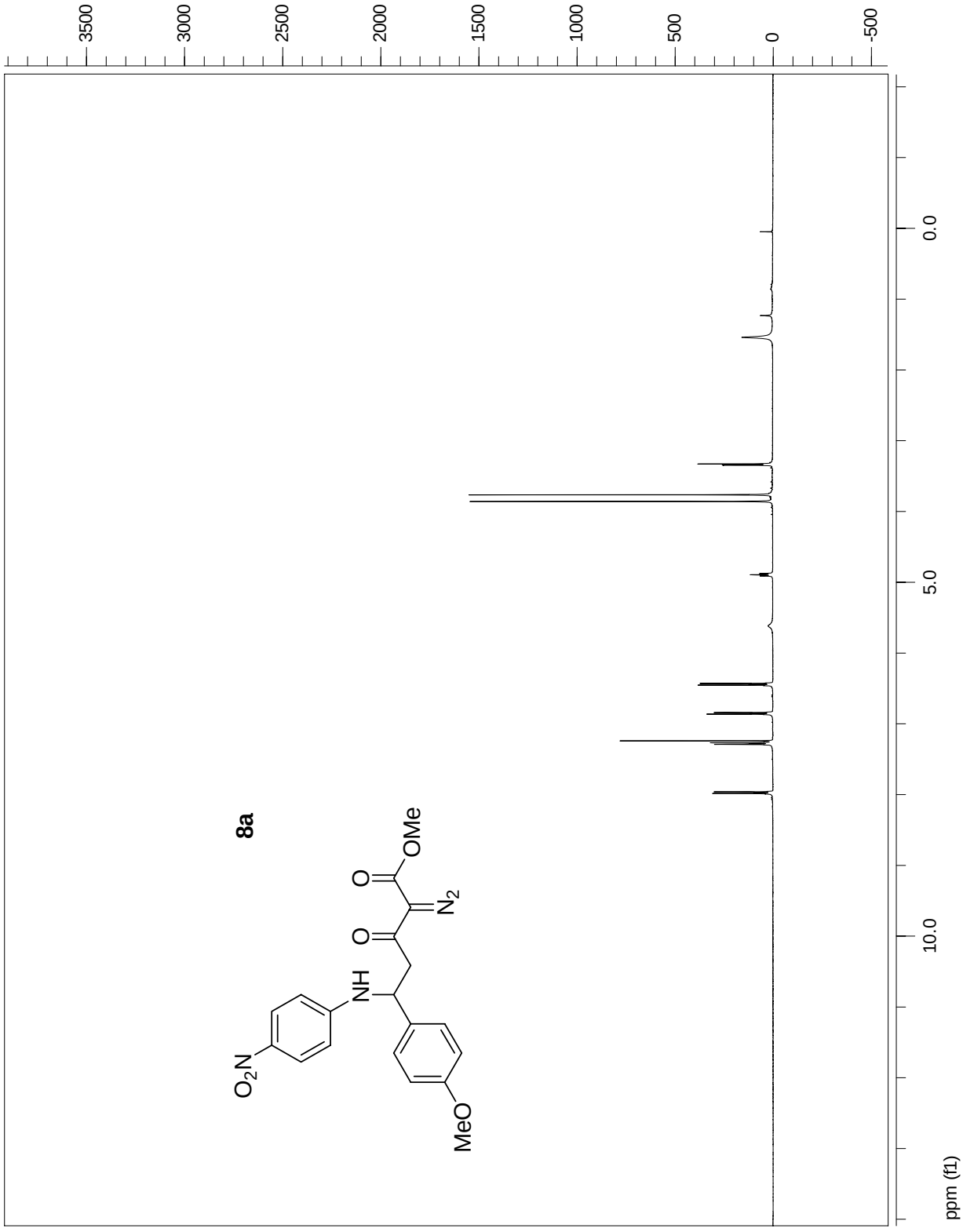
200
ppm


8a
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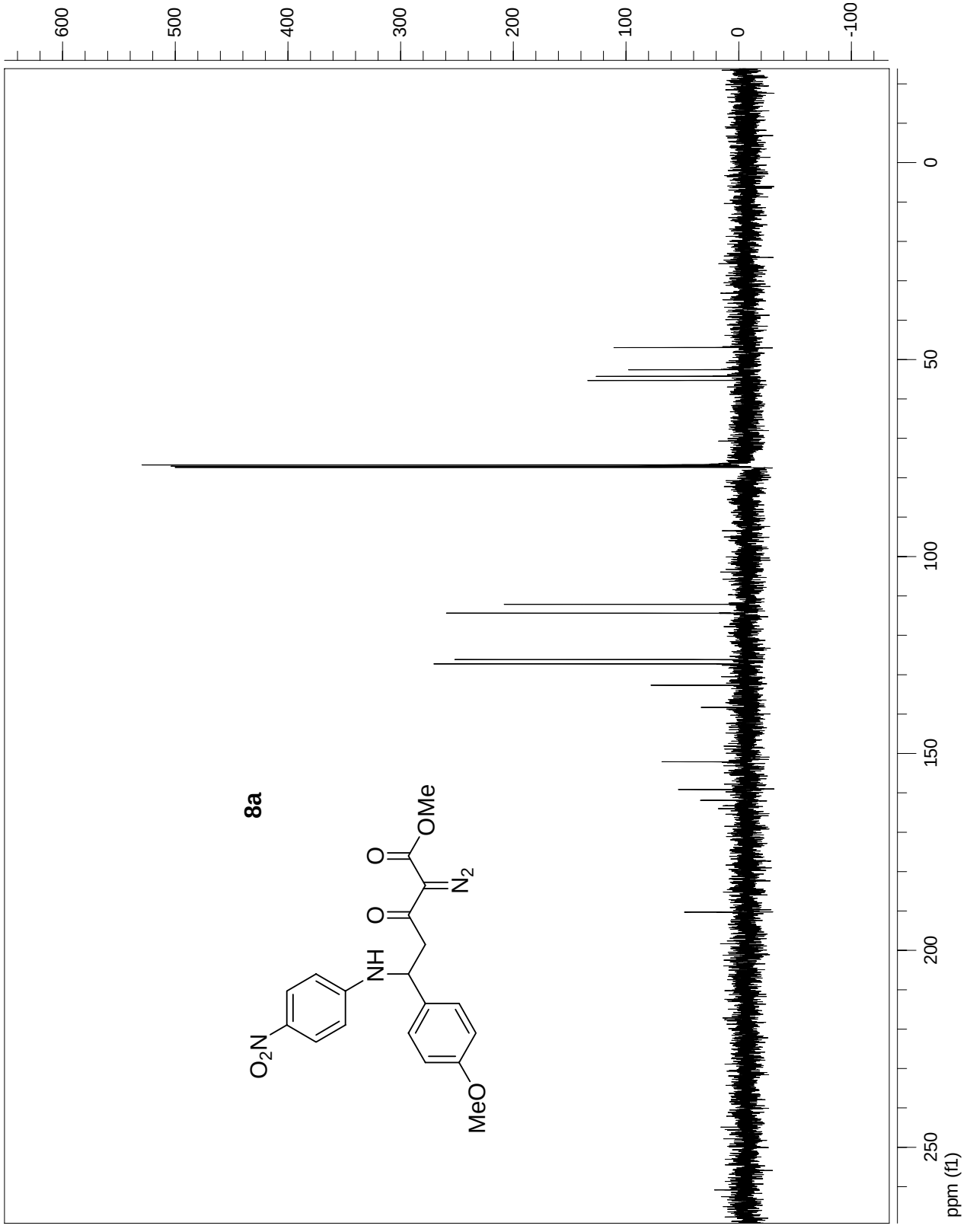
NH
O
O
N2
OMe
MeO
3500
3000
2500
2000
1500
1000
500
0
-500
0.0
5.0
10.0
ppm (f1)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500
400
300
200
100
0
-100
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50
100
150
200
250
ppm (f1)
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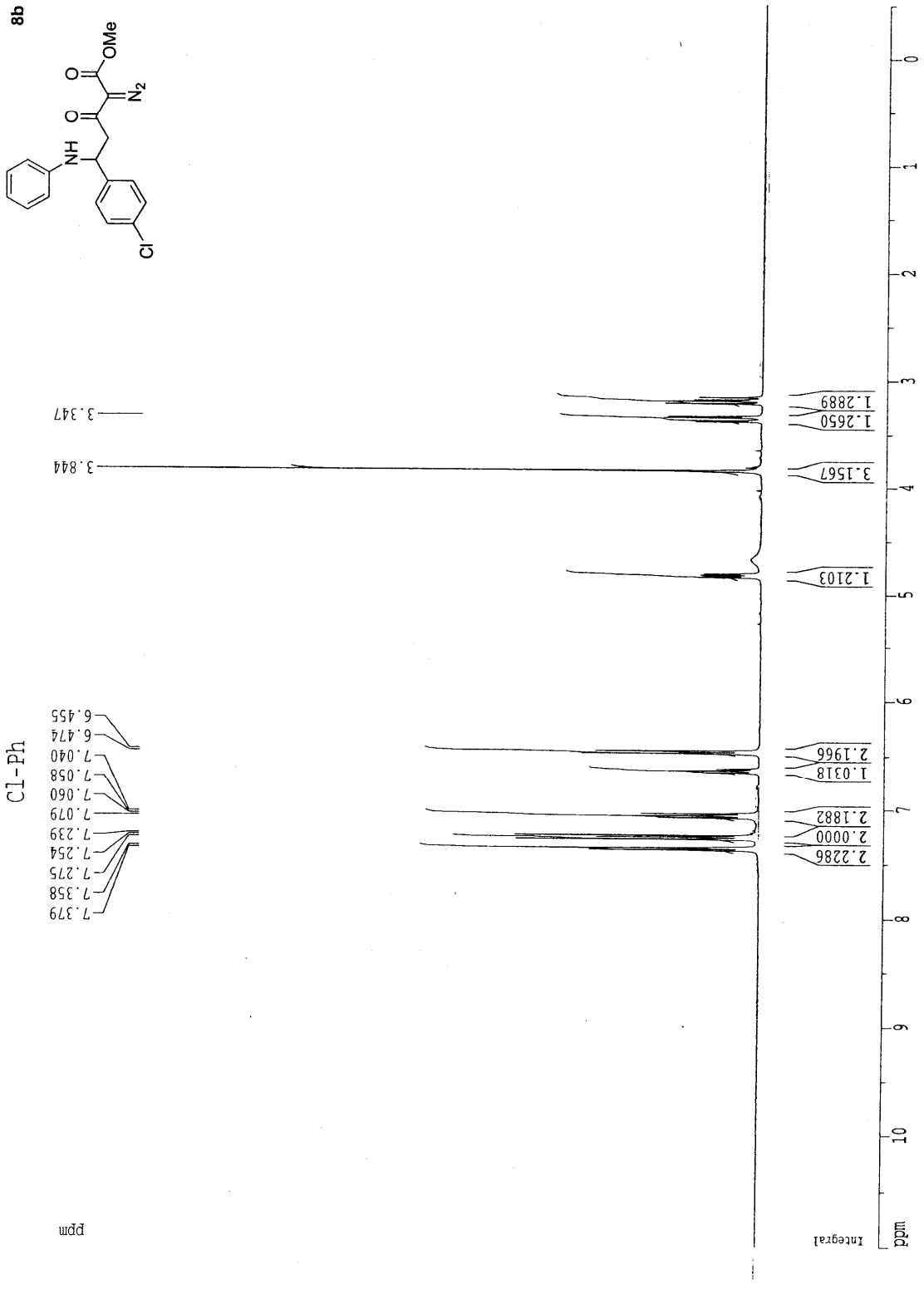
OMe
N2
O
NH
O2N
MeO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N2
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Cl
Cl-Ph
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7.358
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7.239
7.079
7.060
7.058
7.040
6.474
6.455
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2.1882
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2.1966
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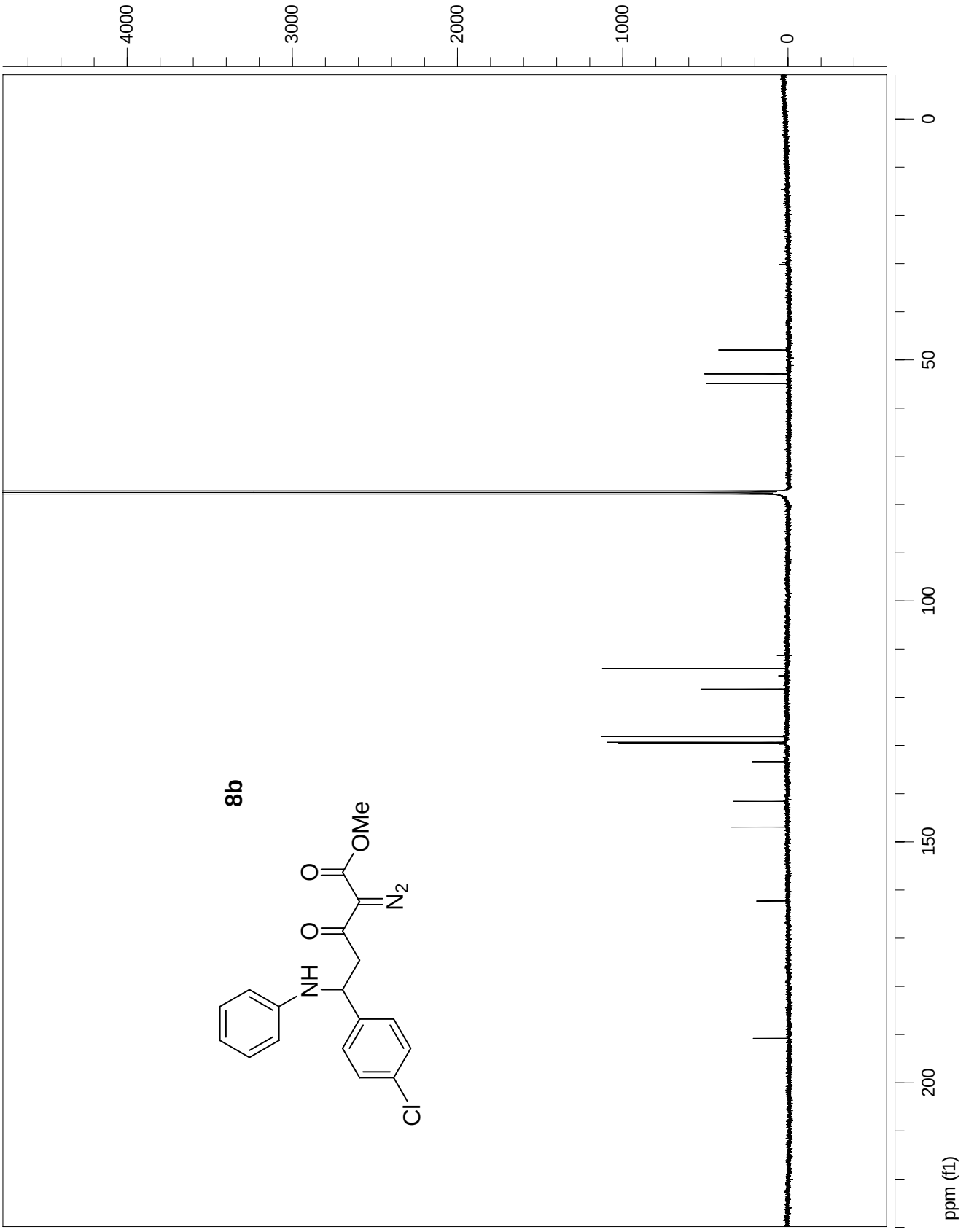
Integral
ppm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100
150
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ppm (f1)
8b
OMe
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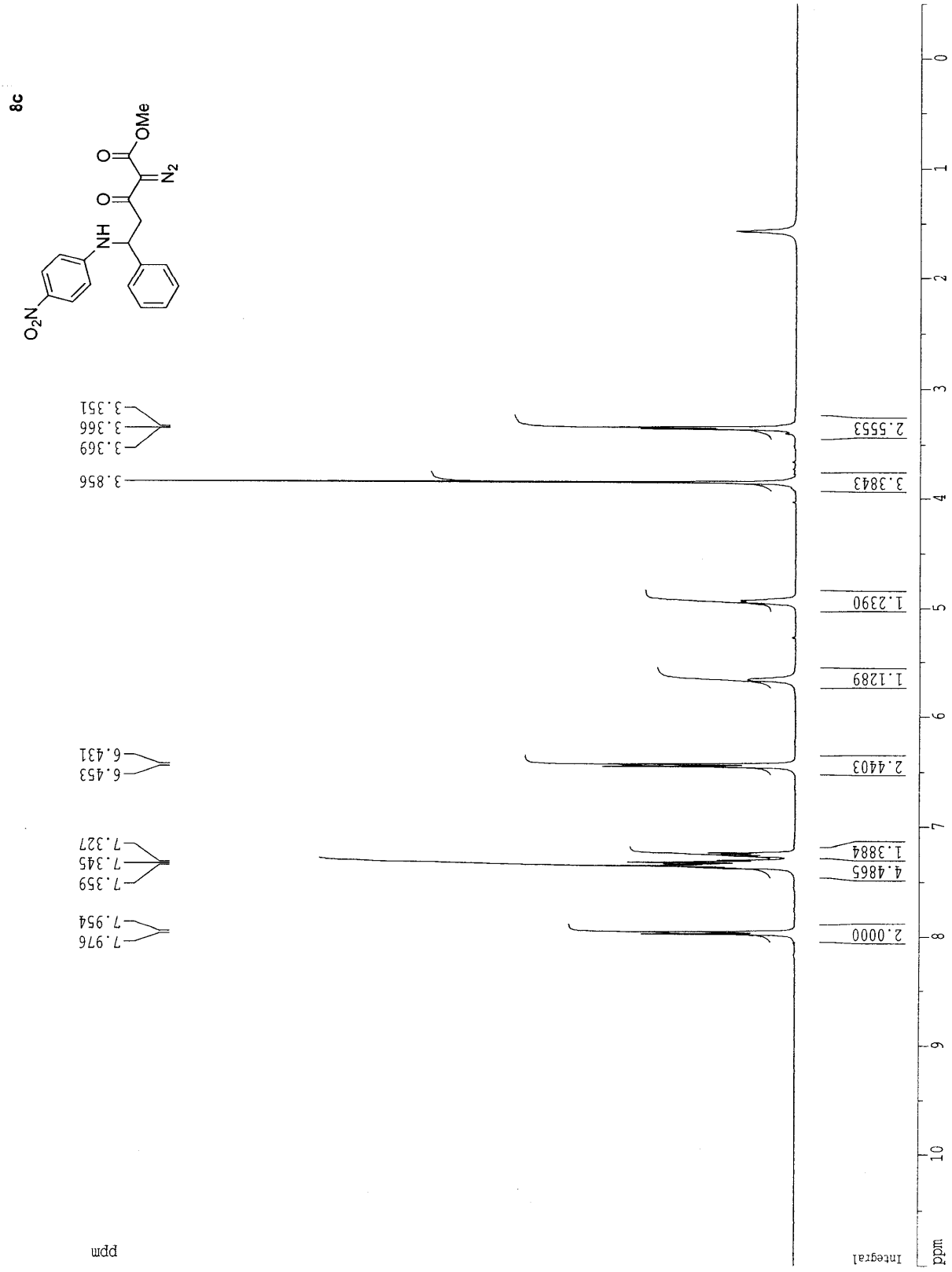
N2
O
NH
Cl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N2
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NH
O2N
ppm
Integral
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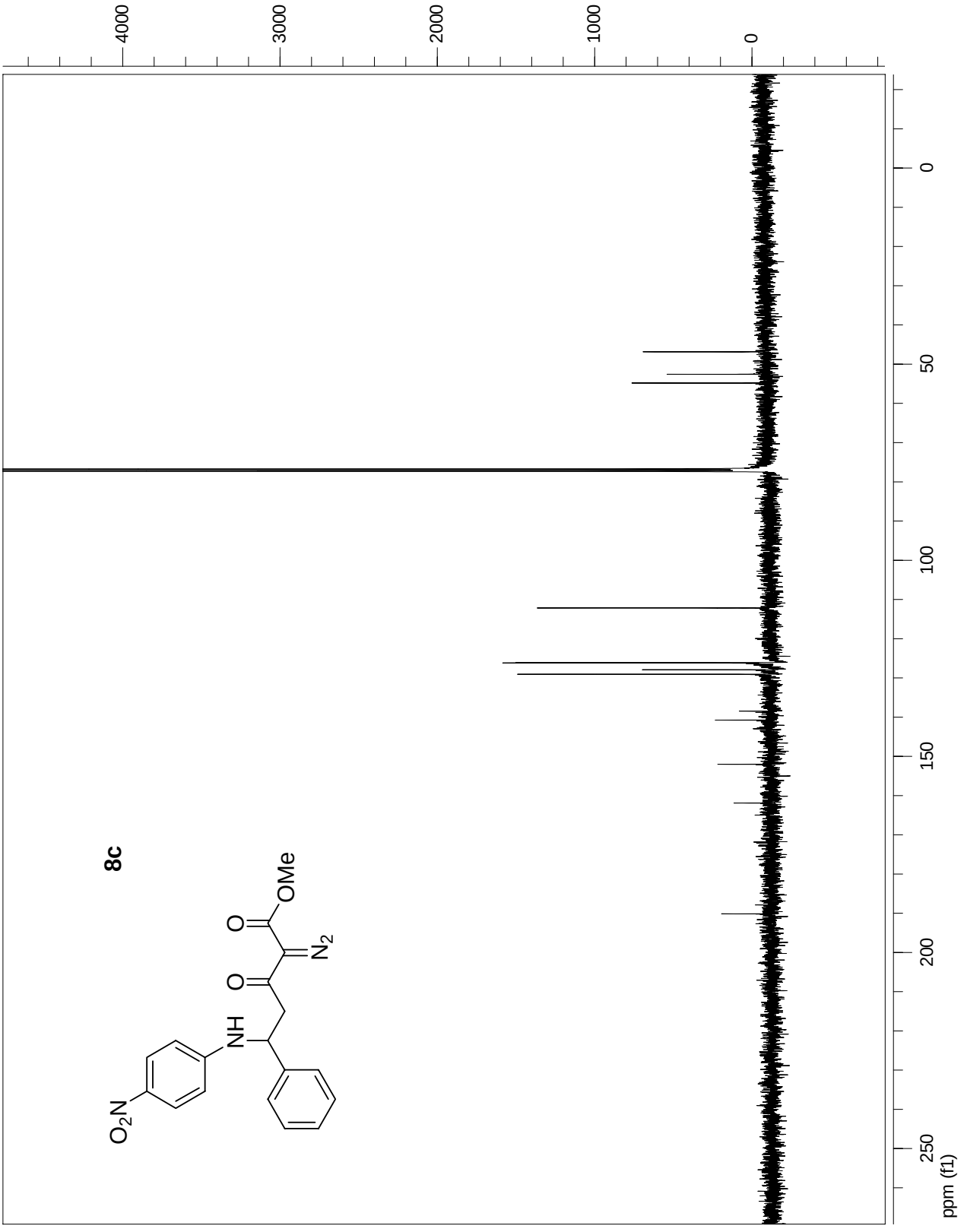
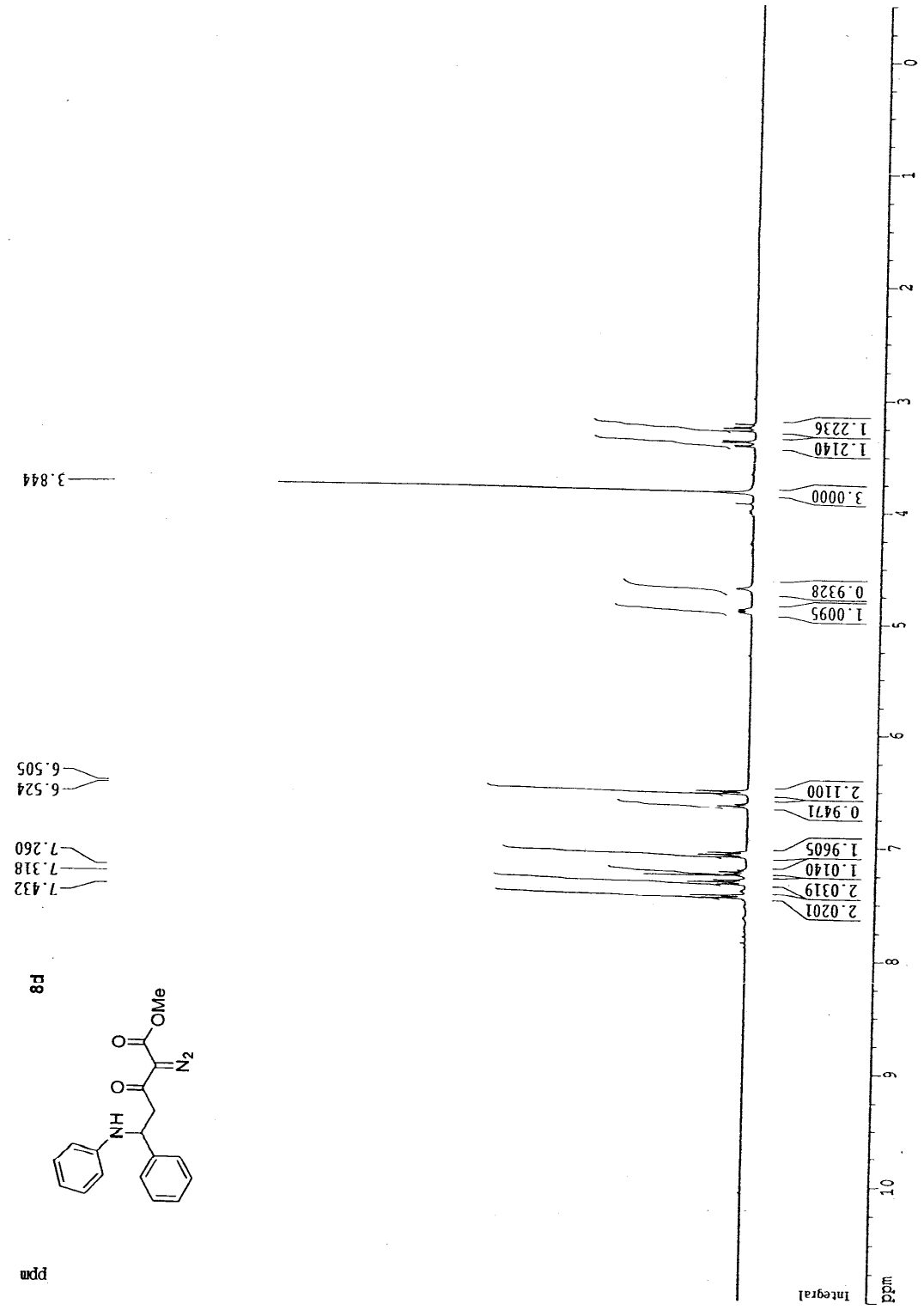
1.3884
2.4403
1.1289
1.2390
3.8443
2.5553
7.976
7.954
7.359
7.345
7.327
6.453
6.431
3.856
3.369
3.366
3.351


8c
OMe
O
N2
O
NH
O2N
4000
3000
2000
1000
0
0
50
100
150
200
250
ppm (f1)


ppm
Integral
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2.0319
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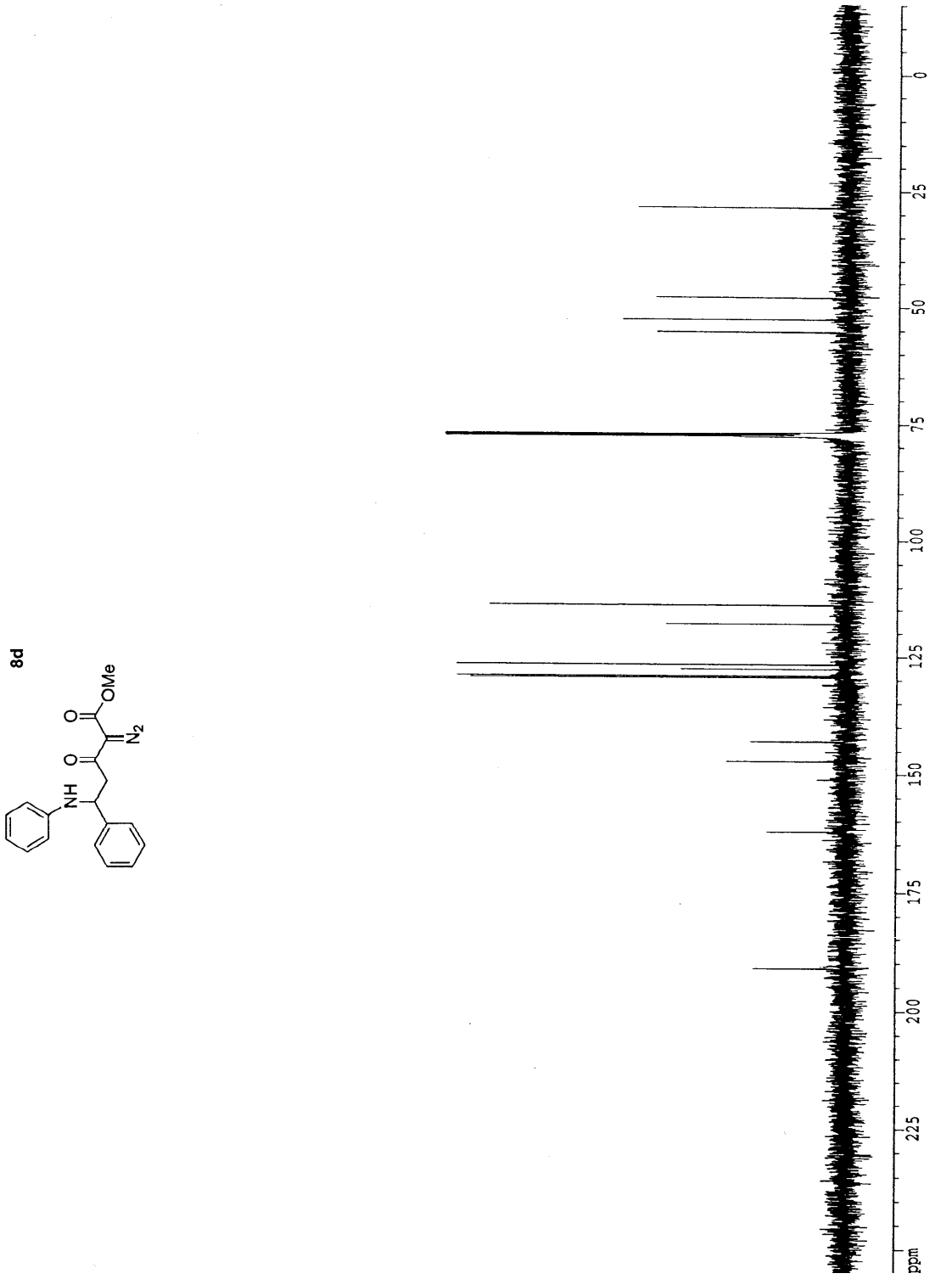
1.9605
0.9471
2.1100
1.0095
0.9328
3.0000
1.2140
1.2236
3.844
6.505
6.524
7.260
7.318
7.432
P8
OMe
O
O
N2
NH


8d
NH
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O
N2
OMe
0
25
50
75
100
125
150
175
200
225
ppm

Chapter 2:

Constructing Chiral Diazoacetoacetates by Highly Enantioselective Catalytic Mukaiyama Aldol Reaction

2.1. *Introduction*

2.1.1 Challenges in Stereoselective Transformations of Diazoacetoacetates:

Diazoacetoacetates are popular precursors for metal carbenes in the synthesis of natural products and compounds of pharmaceutical interest.[47,48] Catalytic reactions involving addition, insertion, and association (ylide-derived processes) that produce cyclopropanes, cycloalkanones, lactones and lactams are well documented.[1-49] However, enantiocontrol from the use of a chiral catalyst with diazoacetoacetates in asymmetric metal carbene transformations has been disappointing. Neither copper nor dirhodium catalysts have provided enantioselectivites beyond 50% ee in reactions with either diazoacetoacetates or diazomalonates.[50] Ikegami and co-workers have investigated

(47) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides;* John Wiley & Sons: New York, **1998.**

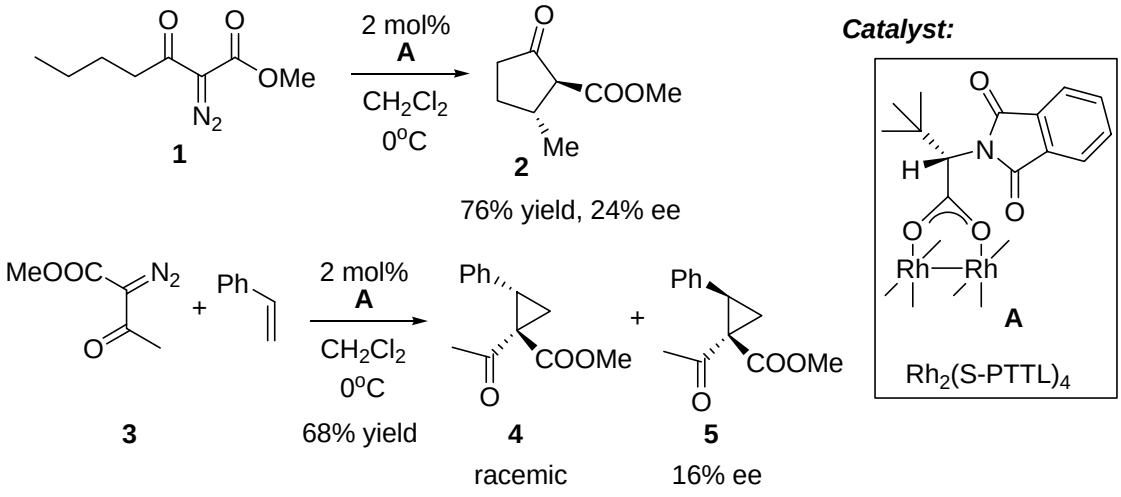
(48) Examples include: (a) Davis, F. A.; Wu, Y.; Xu, H.; Zhang, J. *Org. Lett*. **2004**, *6*, 4523-4525. (b) Hughes, C. C.; Kennedy-Smith, J. J.; Trauner, D. *Org. Lett*. **2003**, *5*, 4113-4115. (c) Davis, F. A.; Fang, T.; Goswami, R. *Org. Lett*. **2002**, *4*, 1599-1602. (d) Taber, D. F.; Malcolm, S. C. *J. Org. Chem.* **2001**, *66*, 944-953.

(49) Reviews: (a) Merlic, C. A.; Zechman, A. L. *Synthesis* **2003**, 1137-1156. (b) Davis, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861-2903. (c) Davies, H. M. L.; Antoulinakis, E. G. *Org. React.* **2001**, *57*, 1-326. (c) Hodgson, D. M.; Pierard, F. Y. T. M.; Stupple, P. A. *Chem. Soc. Rev.* **2001**, *30*, 50-61. (d) Doyle, M. P. In *Catalytic Asymmetric Synthesis, Second Edition,* I. Ojima, Ed., John Wiley & Sons, Inc.: New York, **2000**. (d) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911-935. (d) Khlebnikov, A. F.; Novikov, M. S.; Kostikov, R. R. *Adv. Heterocyclic Chem.* **1996**, *65*, 93-233. (e) Padwa, A.; Austin, D. J. *Angew. Chem. Int .Ed. Engl.* **1994**, *33*, 1797-1815.

(50) (a) Pique, C.; Fahndrich, B.; Pfaltz, A.*Synthetic Lett.* **1995,** 491-492. (b) Ye, T.; Garcia, C. F.; McKervey, M. A. *J. Chem. Soc., Perkin Trans I* **1995**, 1373-1379. (c) Watanabe, N.; Ogawa, T.; Ohtake, Y.; Ikegami, S.; Hashimoto, S. *Synlett* **1996**, 85-86. (d) Pierson, N.; Fernández-Garcia, C.; McKervey, M. A. *Tetrahedron Lett.* **1997**, *38*, 4705-4708. (e) Doyle, M. P.; Davies, S. B.; Hu, W. *Organic Lett.* **2000**, *2*, 1145-1147. (f) Hodgson, D. M.; Stupple, P. A.; Pierard, T. M.; Labande, A. H.; Johnstone, C. *Chem. Eur. J*., **2001**, 7, 4465-4476. (g) Müller, P.; Lacrampe, F.; Bernardinelli, G. *Tetrahedron: Asymmetry* **2003**, *14*, 1503-1510. (h) Hashimoto, S.; Watanabe, N.; Ikegami, S. *Tetrahedron Lett.* **1990**, *31*, 5173-5174. (i)

asymmetric C—H insertion reactions of diazoacetoacetate **1** using a phthalimide-derivatized phenylalaninate dirhodium(II) catalyst [Rh_2(*S*-PTTL)$_4$] (**A**) (*Scheme 2.1*). The cyclopentanone product **2** was obtained in moderate yield and low enantioselectivity.[4h] Müller and co-workers reported their efforts towards asymmetric cyclopropanation of methyl diazoacetoacetate (**3**) with styrene using the same dirhodium(II) catalyst (**A**). The reaction yielded racemic *trans*-isomer **4** and *cis*-isomer **5** (16% ee) in a 1:8 diastereomeric mixture (*Scheme 2.1*).[4i]

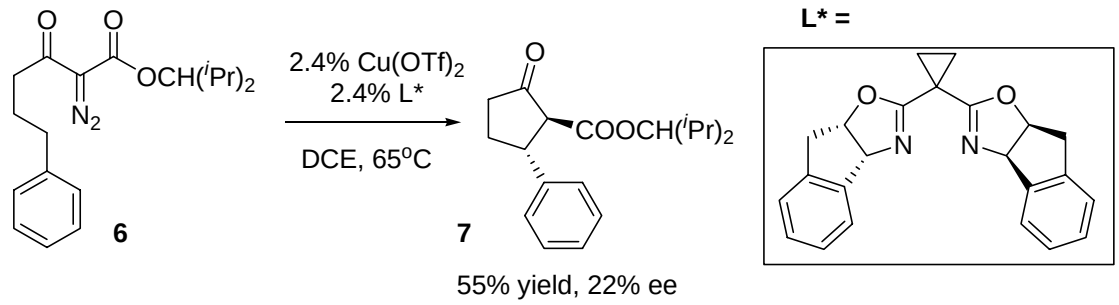
Scheme 2.1:



Müller and co-workers also reported a Cu(I)-catalyzed intramolecular C—H insertion reaction of diazoacetoacetate **6** using a chiral ligand (**L***), where the reaction proceeded in moderate yield but low enantioselectivity (*Scheme 2.2*).[4j]

Müller, P.; Bernardinelli, G.; Allenbach, Y. F.; Ferri, M.; Flack, H. D. *Org. Lett.* **2004**, *6*, 1725-1728. (j) Müller, P.;Bole′a. *Helv. Chim. Acta.* **2002**, *85*, 483-494.

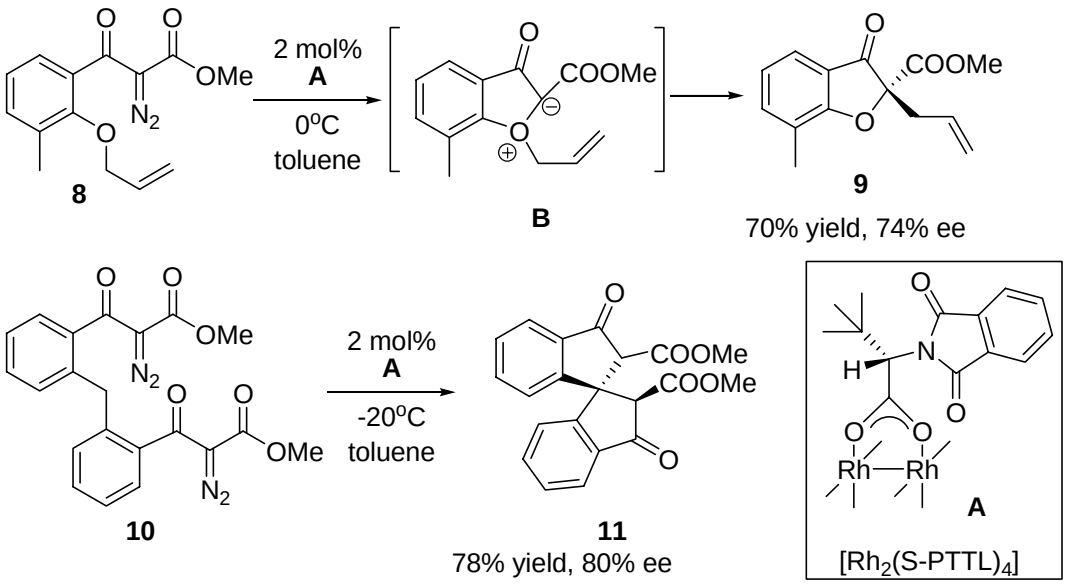
Scheme 2.2



There have only been a few exceptional cases where catalytic metal carbene transformations led to products with high enantioselectivity, but in all these examples highly constrained diazoacetoacetates were used as substrates. Hashimoto and co-workers have reported enantioselectve [2, 3]-sigmatropic rearrangement of the oxonium ylide (**B**) generated from the diazoacetoacetate **8** using chiral dirhodium catalyst **A** (*Scheme 2.3*).[51] The rearranged product was obtained in 70% yield and 74% enantiomeric excess. Using the same catalyst, the Hashimoto group was successful in double cyclization of **10** to form spirobiindanone derivative **11** in 80% ee *via* double C—H insertion (*Scheme 2.3*).

(51) (a) Anada, M.; Hashimoto, S. *Tetrahedron Lett.* **1998**, *39*, 79-82. (b) Anada, M.; Watanabe, N.; Hashimoto, S. *J.Chem.Soc., Chem. Commun.***1998**, 1517-1518. (c) Kitagaki, S.; Yamamoto, Y.; Tsutsui, H.; Anada, M.; Nakajima, M.; Hashimoto, S. *Tetrahedron Lett.* **2001**, *42*, 6361-6364. (d) Takahashi, T.; Tsutsui, H.; Tamara, M.; Kitagaki, S. M.; Nakajima, M.; Hashimoto, S. *J. Chem. Soc., Chem. Commun*., **2001**, 1604-1605.

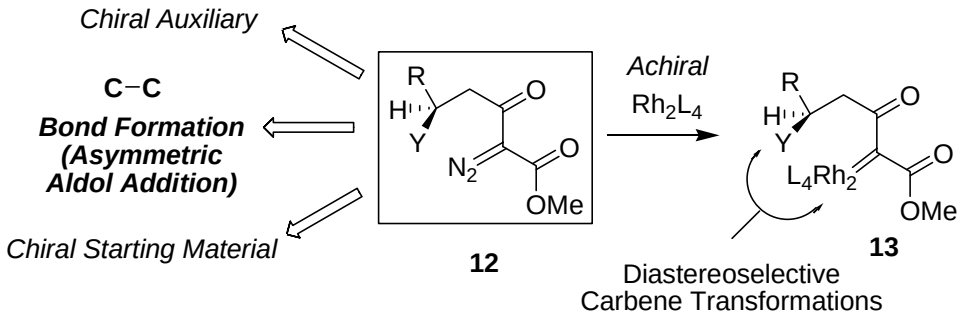
Scheme 2.3:



2.1.2. Chiral Diazoacetoacetates as Important Synthon:

A practical alternative to asymmetric diazo decomposition by a chiral catalyst can be the synthesis of enantiomerically enriched diazoacetoacetates that are amenable to subsequent catalytic reaction (*Scheme 2.4*).

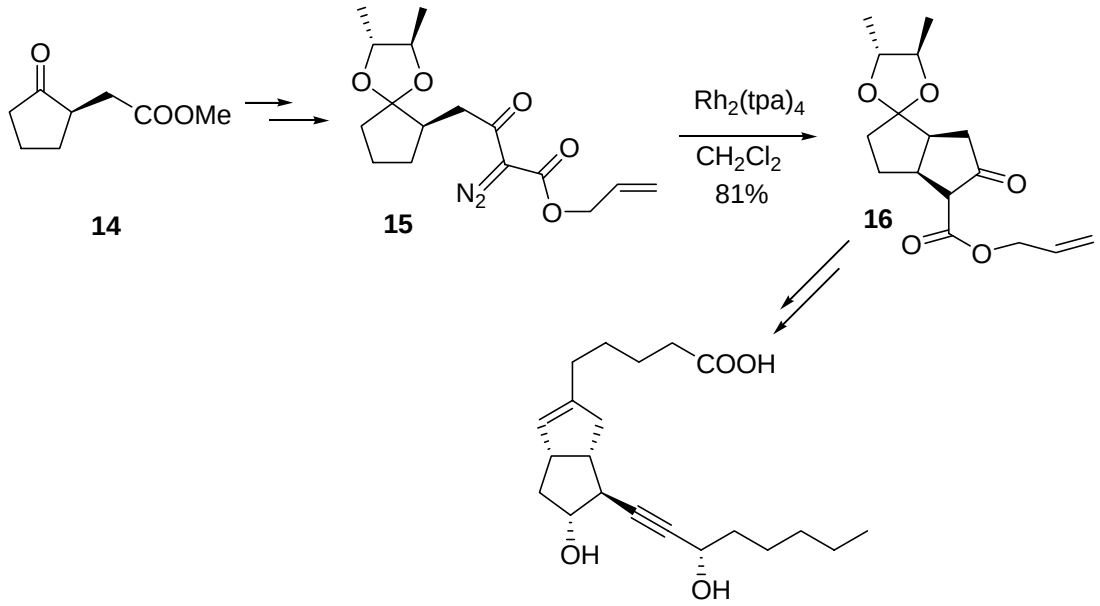
Scheme 2.4:



As depicted in the *Scheme 2.4*, enantiomerically enriched diazoacetoacetates can be obtained by either using reactants from chiral pool that includes either making suitable chiral starting material or using chiral auxiliary.[52] The other possibility can be asymmetric C—C bond formation *via* aldol addition reaction using chiral catalysts. The advantage of aldol addition reaction using a chiral catalyst is the requirement of only catalytic amount of chiral information. On the other hand, the major disadvantage of chiral auxiliary method is the additional synthetic manipulations required in the attachment and removal of the chiral auxiliary, whereas making chiral starting material is very substrate specific. Ikegami and co-workers have described their utilization of chiral diazoacetoacetate **15** starting material in their total synthesis of 13,14-didehydroisocarbacyclin **17** (*Scheme 2.5*).[53] Regio- and diastereocontrolled cyclization through dirhodium(II)-catalyzed C—H insertion of the chiral diazoacetoacetate **15**, derived from methyl (2*R*)-oxocyclopentane-(1*R*)-acetate **14**, was the key step in their synthesis.

(52)Davies, H. M. L.; Ahmed, G.; Calvo, R. L.; Churchill, M. R.; Churchill, D. G. *J. Org. Chem.***1998**, *68*, 2641-2645.
(53) Hashimoto, S.; Miyazaki, Y.; Ikegami, S. *Synlett*, **1996**, 324-326.

Scheme 2.5:



13,14-didehydroisocarbacyclin

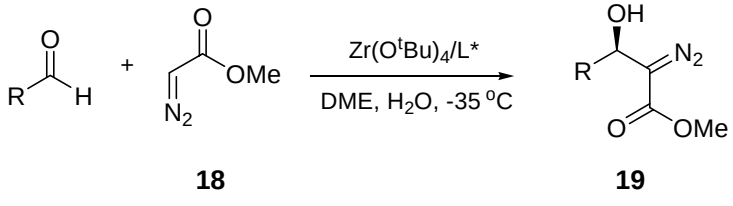
2.1.3. Synthesis of Chiral Diazo Compounds by Catalytic Addition Reaction (Aldol Addition):

Over the last two decades aldol reactions have emerged as one of the most important classes of C—C bond constructing methods with impressive regio, chemo, diastereo and enantiocontrol.[54] Developments of chiral metal complexes as Lewis acid catalysts and discovery of aldol reaction variants such as Mukaiyama aldol addition or Mannich addition have claimed a venerable place in the field of asymmetric synthesis. With these advances of aldol chemistry efforts were made to use aldol technology for efficient construction of diazoacetoacetates. Kardi,[55] Calter[56] and Wang[57] have reported

(54) (a) *Modern Aldol Reactions*, Mahrwald, R. Ed.; Wiley-VCH, Weinheim, Germany, **2004**, *Vol 1&2*. (b) Gröger, H.; Vogl, E. M.; Shibasaki, M. *Chem. Eur. J.* **1998**, *4*, 1137-1141.
(55) Karadi, S.; Amato, J.S.; Reamer, R. A.; Weinstock, L. N. *J. Am. Chem. soc*. **1981**, *103*, 6765-6767

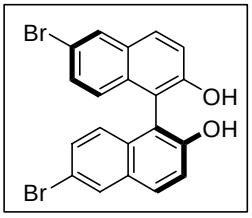
aldol addition method for synthesis of diazoacetoacetates using stoichiometric Lewis acids. But the approach towards the synthesis of chiral diazoacetoacetates *via* catalytic asymmetric aldol addition has not been achieved. Wang and co-workers only recently reported an enantioselective addition method for the synthesis of chiral diazo compounds. Ethyl diazoacetate **18** was added to a selection of aldehydes using a (*S*)-BINOL/Zr(O-^{t}Bu)$_4$ catalyst to give chiral β-hydroxy α-diazo carbonyl compounds in 50-80% chemical yields, and enantiomeric excesses ranging from 53 to 87% were achieved (*Scheme 2.6*).[58] This is the only example of the construction of chiral diazocarbonyl compounds by addition reaction method. But the requirement of high catalyst loading [20 mol% Zr(O-^{t}Bu)$_4$ and 44 mol% ligand] makes this aldol addition reaction method less attractive for practical applications.

Scheme 2.6:



18 **19**

L* =



Catalyst Loading = 20 mol%

Ligand: 44%

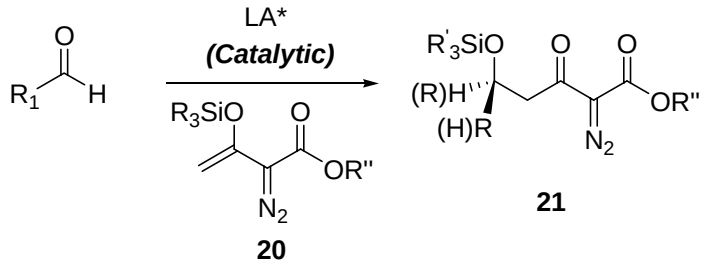
entry	R	Yield [%]	ee[%]
1	Ph	65	87
2	4-ClC_6H_4	59	72
3	(*E*)-C_6H_4CH=CH-	72	79
4	2-furyl	80	86
5	*n*-C_3H_7	82	57

(56) Calter, M. A.; Sugathapala, P. M.; Zhu, C. *Tet. Lett.* **1997**, *38*, 3837-3840.
(57) Deng, G.; Tian, X.; Qu, Z.; Wang, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2773-2776.
(58) Yao, W.; Wang, J. *Org. Lett.* **2003**, *5*, 1527-1530.

2.1.4. General Strategy:

Vinyldiazoacetates like **20** can be used as their corresponding silylenolethers in Lewis acid catalyzed asymmetric Mukaiyama aldol addition reactions for the synthesis of functionalized diazoacetoacetates with sterogenic centers, like **21**. A general strategy for construction of chiral diazoacetoacetates has been depicted in *Scheme 2.7*.

Scheme 2.7:



In order to make this strategy a practical method we aimed to achieve the following objectives:

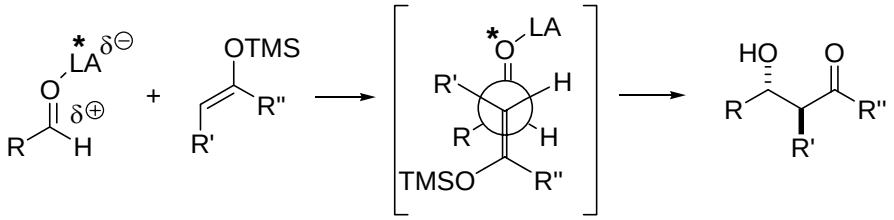
- High chemical yield of the product (> 90% isolated yield)
- High enantiocontrol of the aldol adduct (> 90% ee)
- Low catalyst loading (≤ 5 mol%)
- Easy experimental execution (Not requiring glove-box conditions)
- No decomposition of the diazo functional group

2.1.5. Catalytic Enantioselective Mukaiyama aldol Reaction:

2.1.5.1. General Introduction:

Extensive research efforts have been devoted over the last two decades to the development of efficient catalysts for enantioselective execution of the Mukaiyama aldol addition reaction.[8],[13] Although, various approaches have been made for catalytic enantioselective Mukaiyama aldol addition,[59] the most common approach was activation of a carbonyl group by chiral metal complexes acting as Lewis acids (*Scheme 2.8*).[60]

Scheme 2.8: *Activation of Carbonyl Group by Lewis Acid:*



2.1.5.2. Prior Art

Reetz reported the first catalytic asymmetric Mukaiyama reactions where he used aluminum(III)[61] and rhodium(I)[62] Lewis acids respectively. However, enantiomeric

(59) (a) Mukaiyama, T. *Angew. Chem.* **1977**, *89*, 858-866. (b) Mukaiyama, T. *Aldrichimica Acta* **1996**, *29*, 59-76. (c) Mahrwald, R. *Chem. Rev*. **1999**, *99*, 1095–1120. (d) Carreira, E. M. In *Comprehensive Asymmetric Catalysis* Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. Ed.; Springer-Verlag, Berlin, Germany, **1999**, Chapter 29. (e) Mukaiyama, T. *Angew. Chem. Int. Ed.* **2004**, *43*, 5590-5614. (f) Gröger, H.; Vogl, E. M.; Shibasaki, M. *Chem. Eur. J*. **1998**, *4*, 1137-1141.
(60) (a) Nakamura, E.; Yamago, S.; Machii, D.; Kuwajima, I. *Tetrahedron Lett*. **1988**, *29*, 2207. (b) Denmark, S. E.; Henke, B. R. *J. Am. Chem. Soc*. **1989**, *111*, 8032.
(61) Reetz, M. T.; Voungoukas, A. E. *Tetrahedron Lett.* **1987**, *28*, 793.

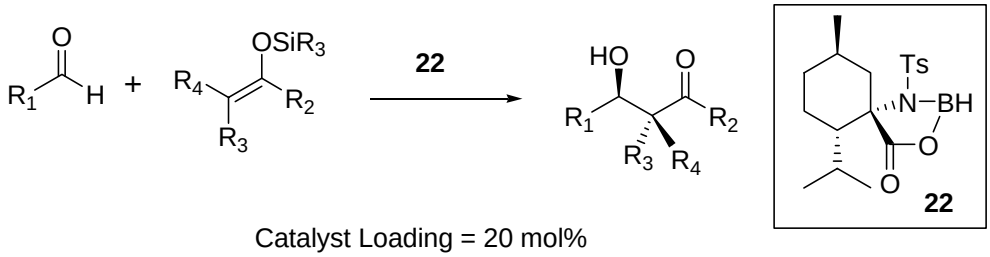
excesses obtained were not high enough for general applications. Since then, several transition metal complexes as well as lanthanide metal complexes with chiral ligands have been successfully used as efficient catalysts for Mukaiyama aldol addition. Several reviews[13a,13b,13c,13e,13f] and book chapters[8,13d,16] were dedicated to asymmetric Mukaiyama aldol addition reaction. But the following part of this section was designed to provide a concise and critical overview on various asymmetric catalysts developed over the years and their major advantages and disadvantages. For comparison purposes, the following scale of catalyst loadings will be followed: very high (≥ 20%), high (≥ 10%), low (≤ 5%) and very low (≤ 1%).

Boron Lewis Acids:

Various boron Lewis acid catalysts for asymmetric Mukaiyama aldol addition reaction have been reported over the past two decades.[63] Masamune and co-workers used a chiral ligand derived from the sulfonamide of α-amino acid (**22)** (*Scheme 2.9*).[64]

Scheme 2.9:

(62) Reetz, M. T.; Kyung, S.-H.; Bol, C. *Chem. Ind*. **1986**, 824.
(63)(a) Deloux, L.; Srebnik, M. *Chem. Rev*. 1993, *93*, 763. (b) Wallbaum, S.; Martens, J. *Tetrahedron: Asymmetry* 1992, *3*, 1475.
(64) (a) Parmee, E. R.; Hong, Y.; Tempkin, O.; Masamune, S. *Tetrahedron Lett.* **1992**, *33*, 1729. (b) Parmee, E. R.; Hong, Y.; Tempkin, O.; Masamune, S. *J. Am. Chem. Soc.* **1991**, *113*, 9365



Catalyst Loading = 20 mol%

entry	R_1	R_2	R_3	R_4	Yield [%]	ee[%]
1	Ph	OEt	Me	Me	83	91
2	C_6H_{11}	OEt	Me	Me	59	96
4	Ph	S^{t}Bu	H	H	98	85

Salient Features:

- Aldehydes: Excellent method for aromatic and alicyclic aldehydes
- Nucleophile: Works well only with ketyl acetals and thioacetals
- Catalyst Loading: Very high (20 mol%)
- Ligand/catalyst: Not commercially available

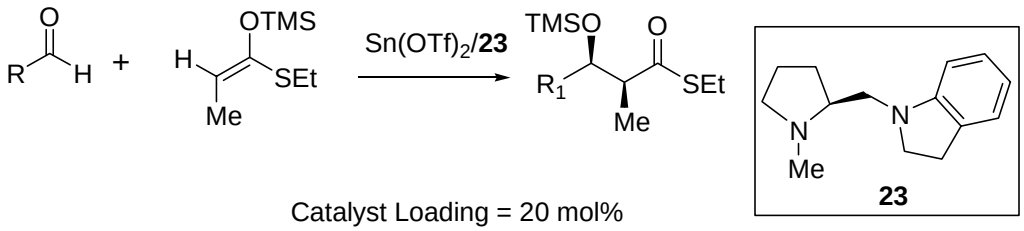
Tin Lewis Acids:

At the beginning of the 1990s, Mukaiyama succeeded in carrying out enantioselective execution of aldol addition reactions of enolsilanes to aldehydes, using stoichiometric amounts of $Sn(OTf)_2$, chiral diamine **23** and Bu_3SnF.[65] Later, Mukaiyama's student Kobayashi reported the diastereo- and enantioselective Mukaiyama

(65) (a) Kobayashi, S.; Fujishita, Y.; Mukaiyama, T. *Chem. Lett*. **1990**, 1453. (b) Kobayashi, S.; Uchiro, H.; Shiina, I.; Mukaiyama, T. *Tetrahedron* **1993**, *49*, 1761

reaction using 20 mol% of tin(II) Lewis acids.[66] Several proline-derived chiral diamines (**23**) were used as ligands (*Scheme 2.10*).

Scheme 2.10:



Catalyst Loading = 20 mol%

entry	R_1	Yield [%]	ee[%]
1	Ph	77	90
2	4-ClC_6H_4	83	90
3	4-MePh	75	91
4	C_7H_{15}	80	>98
5	C_6H_{11}	71	>91

Salient Features:

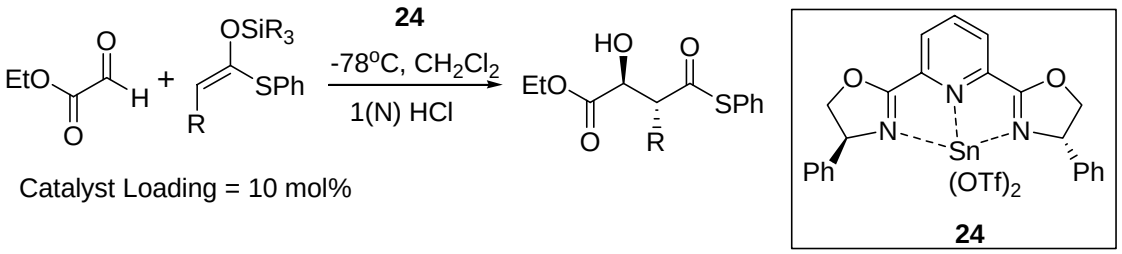
- Aldehydes: Excellent method for aromatic and aliphatic aldehydes
- Nucleophile: Works well only with ketyl thioacetals.
- Catalyst Loading: Very high (20%)
- Ligand/catalyst: Not commercially available

The Evans group described the use of stannous triflate and chiral PYBOX (**24**) complexes (10 mol%) in additions of thioester-derived silyl ketene acetals to glyoxylate and pyruvate esters. Aldol adducts were obtained in high enantiomeric excesses (*Scheme*

(66) (a) Kobayashi, S.; Hayashi, T. *J. Org. Chem*. **1995**, *60*, 1098. (b) Kobayashi, S.; Horibe, M. *Tetrahedron: Asymmetry* **1995**, *6*, 2565.

2.11).[67] This process suffers from narrow substrate scope as enantioselectivity is obtained only for aldehydes with two binding sites (ethyl glyoxalate and benzoxyacetaldehyde).

Scheme 2.11:



Catalyst Loading = 10 mol%

entry	R	Yield [%]	ee[%]
1	H	90	98
2	Me	87	95
3	Et	90	95
4	^{i}Pr	72	95

Salient Features:

- Aldehydes: Works only with ethyl glyoxalate and benzoxyacetaldehyde (narrow substrate scope)
- Nucleophile: Works well only with ketyl thioacetals
- Catalyst Loading: High (10 mol%)
- Ligand/catalyst: Commercially available

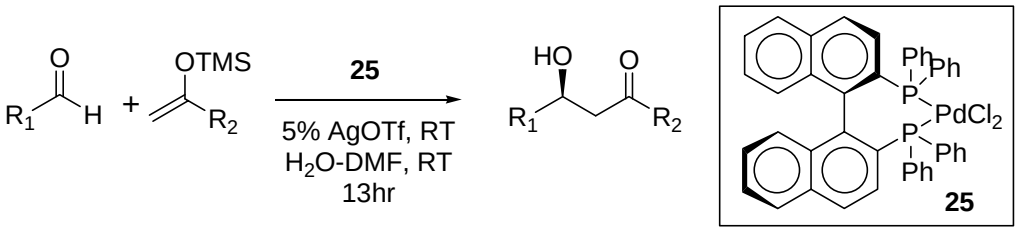
Palladium Lewis Acids:

In the cases described so far, Lewis acid-coordinated aldehydes react with activated carbonyl compounds (e.g., silyl enol ether). Shibasaki et al. showed that one can

(67) Evans, D. A.; McMillan, D. W. C.; Campos, K. R. *J. Am. Chem. Soc*. **1997**, *119,* 10859.

also work in another direction where Lewis acid-coordinated enolates will form and will react with aldehydes *via* a more compact chair-like transition state (*Scheme 2.12*).[68] The disadvantages of this method are that silver salt (AgOTf) along with Pd(II)-Lewis acid is required for in situ generation of catalyst, and products with lower enantiocontrol (~70-75%) relative to those previously discussed are obtained.

Scheme 2.12:



Catalyst Loading = 5 mol%

entry	R_1	R_2	Yield [%]	ee[%]
1	Ph	Ph	96	71
2	Ph	2-Nap	80	73
3	Ph-$(CH_2)_2$-	Ph	86	73

Salient Features:

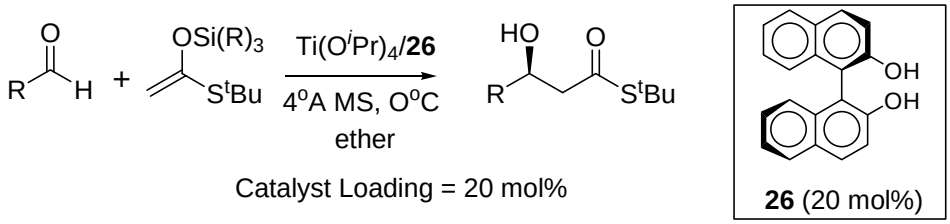
- Aldehydes: Works well with aromatic aldehydes
- Nucleophile: Works well with silyl enol ethers
- Catalyst Loading: Low (5 mol%)
- Ligand/catalyst: Commercially available

(68) (a) Sodeoka, M.; Ohrai, K.; Shibasaki, M. *J. Org. Chem*. **1995**, *60*, 2648. (b) Sodeoka, N.; Tokunoh, R.; Miyazaki, F.; Hagiwara, E.; Shibasaki, M. *Synlett* **1997**, 463

Titanium Lewis Acids:

Mikami and Keck independently developed at the same time a chiral titanium(IV)-BINOL (**26**) based catalyst system for asymmetric Mukaiyama reactions. Keck used $Ti(O^iPr)_4$/BINOL as the catalyst, and for optimum results 20% catalyst was found to be necessary (*Scheme 2.13*).[69] On the other hand, Mikami and co-workers, used $TiCl_2$.(*R*)-BINOL complex as catalyst.[70] 20 mol% of the catalyst is necessary for this reaction in order to achieve satisfactory yields and enantioselectivity.

Scheme 2.13:



entry	R	Yield [%]	ee[%]
1	Ph	90	97
2	Ph-$(CH_2)_2$-	80	97
3	C_7H_{15}	74	98
4	Furyl	88	>98
5	$PhCH_2$=CH_2	76	89

Salient Features:

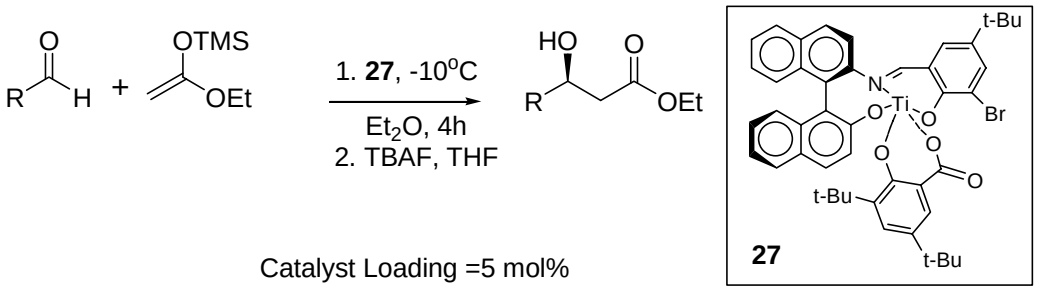
- Aldehydes: Works only with aromatic, aliphatic and alicyclic aldehydes
- Nucleophile: Works well only with ketyl thioacetals

(69) (a). Keck, G. E.; Krishnamurthy, D. *J. Am. Chem. Soc.* **1995**, *117*, 2363.(b) Keck, G. E.; Li, X.-Y.; Krishnamurthy, D. *J. Org. Chem.* **1995**, *60*, 5998.
(70) (a) Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1994**, *116*, 4077. (b) Mikami, K.; Takasaki, T.; Matsukawa, S.; Maruta, M. *Synlett* **1995**, 1057. (c) Matsukawa, S.; Mikami, K. *Tetrahdron: Asymmetry* **1995**, *6*, 2571.

- Catalyst Loading: Very high (20 mol%)
- Ligand/catalyst: Commercially available

The best results using catalytic amounts of titanium Lewis acids were reported by Carreira et al.[71] This group developed a catalyst **27**, consisting of a tridentate ligand, $Ti(O^iPr)_4$ and 3,5-di-*tert*-butylsalicylic acid. Satisfactory results were obtained using only 5 mol% catalyst (*Scheme 2.14*). The illustrated structure of the catalyst **27** is intended to be a composition model only (provided by the authors) as the detailed structure of the active catalyst is unknown. High enantioselctivity were obtained with aromatic aldehydes as well as aliphatic aldehydes.

Scheme 2.14:



Catalyst Loading =5 mol%

entry	R	Yield [%]	ee[%]
1	Ph	98	92
2	Ph-$(CH_2)_2$-	80	89
3	C_6H_{11}	72	94
4	$PhCH_2$=CH_2	92	93
5	$MeCH_2$=CH_2	90	92
6	Me-$(CH_2)_2$-	80	88

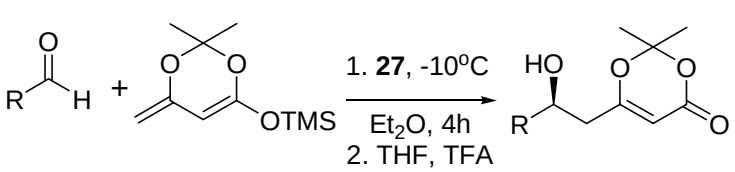
(71) Carreira, E. M.; Singer, R. A.; Lee, W. *J. Am. Chem. Soc.* **1994**, *116*, 8837.

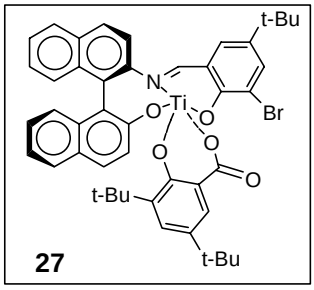
Salient Features:

- Aldehydes: Works well with aromatic and aliphatic aldehydes
- Nucleophile: Works well with ketyl acetals
- Catalyst Loading: Low (5 mol%)
- Ligand/catalyst: Ligand is not commercially available

Later, Carreira et al. used this catalyst system (**27**) in aldol addition reactions of silyl dienolates (*Scheme 2.15*).[72] The addition of *O*-silyl dienolates to aldehydes is catalyzed by 1-3 mol % of the chiral titanium complex and affords the aldol adducts in both good yields and enantioselectivity. The carbinol adduct obtained serves as a versatile precursor for the preparation of optically active γ-hydroxy-β-ketoester, amides, or lactones.

Scheme 2.15:





Catalyst Loading = 3 mol%

entry	R	Yield [%]	ee[%]
1	Ph	83	84
2	Ph-$(CH_2)_2$-	97	80
3	$PhCH_2$=CH_2	88	92
4	Bu_3Sn-CH_2=CH_2	79	92
5	TIPS—≡—	86	91

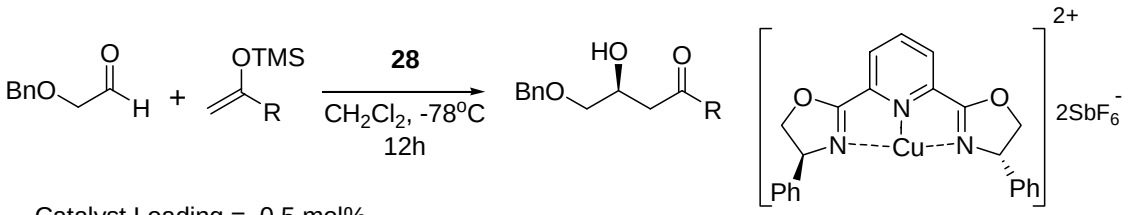
(72) Singer, R. A.; Carreira, E. M. *J. Am. Chem. Soc.* **1995**, *117*, 12360

Copper Lewis Acids:

Evans et al. applied bis(oxazolinyl)pyridine copper(II) complexes (**28**) to the aldol reaction of α-(benzyloxy)acetaldehyde[73] and pyruvate esters[74] with a wide variety of silyl ketene acetals (*Scheme 2.16*). Only 0.5 mol% of this copper catalyst is required for successful execution. These aldehydes were chosen in order to produce an effective catalyst-substrate organization through bidentate chelation. And, indeed, aldol additions of benzaldehyde or dihydrocinnamaldehyde with silyl ketene acetals led to racemic mixtures of products. Interestingly, β-(benzyloxy)propionaldehyde gave racemic products. This indicates a rigid requirement for a five-membered catalyst-aldehyde chelate. The geometry of the applied ketene thioacetals influences the yields of the aldol adducts formed decisively. The major disadvantage of this catalyst system is its very narrow substrate scope as bis-coordination of the aldehyde is important for enantioselectivity.

(73) Evans, D. A.; Murry, J. A.; Kozlowski, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 5814
(74) (a) Evans, D. A.; Kozlowski, M. C.; Burgey, C. S.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **1997**, *119*, 7893. (b) Evans, D. A.; Kozlowski, M. C.; Tedrow, J. C. *Tetrahedron Lett*. **1997**, *42*, 7841.

Scheme 2.16:



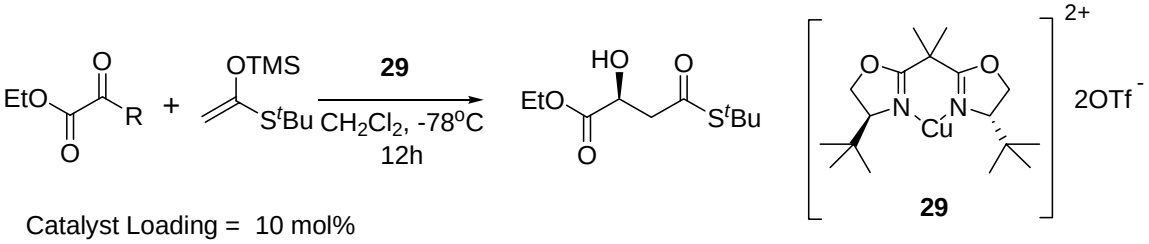
Catalyst Loading = 0.5 mol%

entry	R	Yield [%]	ee[%]
1	S^{t}Bu	100	99
2	SEt	95	98
3	OEt	99	98

Salient Features:

- Aldehydes: Works well only with benzoyloxyacetaldehyde
- Nucleophile: Works well only with ketyl acetals and thioacetals
- Catalyst Loading: Very low (0.5 mol%)
- Ligand/catalyst: Ligand is commercially available

Scheme 2.17:

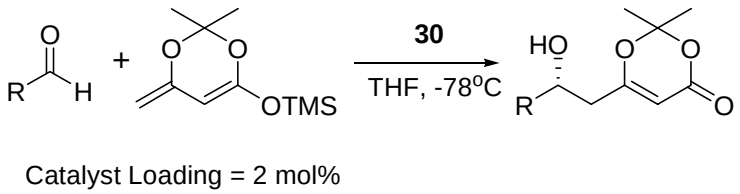


Catalyst Loading = 10 mol%

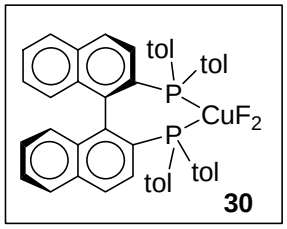
entry	R	Yield [%]	ee[%]
1	Me	96	96
2	Et	94	84
3	^{i}Bu	94	94

Carriera and coworkers have also developed a Cu(II)/tol-BINAP (**30**) based catalyst for Mukaiyama aldol addition (*Scheme 2.18*).[75] Through a detailed mechanistic study they concluded that the addition occurs *via* copper enolate.[76]

Scheme 2.18:



Catalyst Loading = 2 mol%



entry	R	Yield [%]	ee[%]
1	Ph-	92	94
2	2-Nap-	86	93
3	2-furyl-	91	94
4	(*E*)-Ph-CH=CH-	83	85
5	(*E*)-Me-CH=CH-	49	91
6	4-$MeOC_6H_4$	93	94

Salient Features:

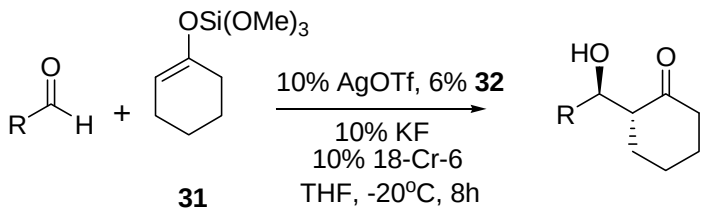
- Aldehydes: Works well only with aromatic aldehydes
- Nucleophile: Works well only with *O*-silyl dienolates
- Catalyst Loading: Low (2.0 mol%)
- Ligand/catalyst: Commercially available

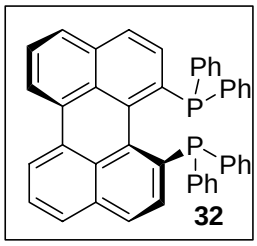
(75) Krgüer,J.; Carreira, E. M. *J. Am. Chem. Soc.***1998**, *120*, 837-838.
(76) Pagenkopf, B. L.; Kruger, J.; Stojanovic, A; Carreira, E. M. *Angew. Chem, Int. Ed.* **1998**, *37*, 3124-3126.

Silver Lewis Acids:

Silver salts are mildly Lewis acidic, and they have been utilized as selective catalysts for enantioselective Mukaiyama aldol addition reactions. In 1997 Yanagisawa, Yamamoto and their colleagues first reported the Ag(I)/BINAP (**32**) complex as an effective catalyst for the asymmetric Mukaiyama aldol addition of silyloxy enol (**31**) ethers to aromatic and α,β-unsaturated aldehydes with impressive enantio- and diastereocontrol.[77] Recently Yamamoto and co-workers have developed a novel method for highly enantioselective Mukaiyama aldol addition of trimethoxysilyl enol ether with aromatic aldehydes using catalytic amounts of AgOTf/BINAP (**32**)/ KF/18-crown-6 ether in THF (*Scheme 2.19*).[78]

Scheme 2.19:





entry	R	Yield [%]	ee [%]
1	Ph	78	93
2	Ph-CH=CH-	68	89
3	1-Nap	70	90
4	4-$MeOC_6H_4$	55	93
6	4-BrC_6H_4	86	95

(77) Yanagisawa, A.; Matsumoto, Y.; Nakashima, H.; Asakawa, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1997**, *119*, 9319–9320.
(78) Wadamoto, M.; Ozasa, N.; Yanagisawa, A.; Yamamoto, H. *J. Org. Chem.* **2003**, 68, 5593–5601.

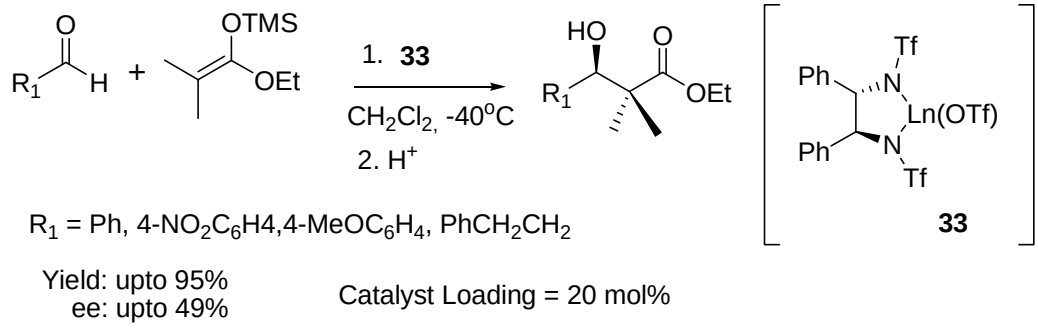
Salient Features:

- Aldehydes: Works well only with aromatic aldehydes
- Nucleophile: Works well with weakly nucleophilic silyloxy and stanyl enol ethers
- Catalyst Loading: High (10 mol%)
- Ligand/catalyst: Commercially available

Lanthanide Lewis Acids:

Triflates of several rare earth metals (La, Eu,[79] Yb[80]) were complexed with the chiral bis(trifyl)amide and were employed in the Mukaiyama aldol addition reaction.[81] Aromatic aldehydes and hydrocinnamaldehyde were reacted with silyl ketene acetals in the presence of 20 mol % of the described chiral lanthanide Lewis acid **33**; however, only poor to moderate enantioselectivities were reported (*Scheme 2.20*).

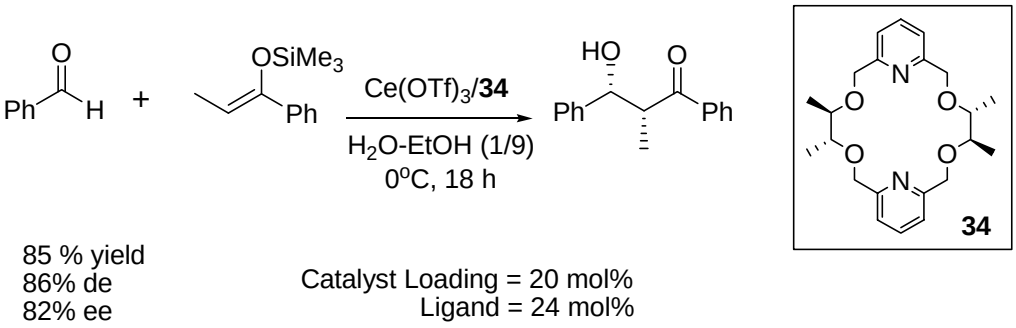
Scheme 2.20:



(79) Bednarski, M.; Maring, C.; Danishefsky, S. J. *Tetrahedron Lett*. **1983**, *24*, 3451-3454.
(80) Gong, L.; Streitweiser, A. *J. Org. Chem.* **1990**, *55*, 6235-6236.
(81) Uotsu, K.; Sasai, H.; Shibasaki, M. *Tetrahedron: Asymmetry* **1995**, *6*, 71-74.

Recently, Kobayashi et al. described the results of Mukaiyama aldol reactions of benzaldehyde in the presence of various lanthanide triflates and chiral ligand **34** in aqueous media. Catalyst derived from 20 mol% cerium triflate and 24 mol% **34** was found to give high enantiocontrol (*Scheme 2.21*).[82]

Scheme 2.21:



Salient Features:

- Aldehydes: Works well only with benzaldehyde
- Nucleophile: Works well with enolsilanes
- Catalyst Loading: Very high (20 mol% metal salt, 24% ligand)
- Ligand/catalyst: Ligand is not commercially available and needs multiple synthetic steps to prepare.

Examples of scandium (III)-catalyzed asymmetric Mukaiyama aldol additions will be discussed in section 2.3.1.2.

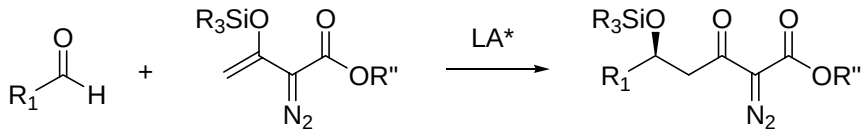
(82) Kobayashi, S.; Hamada, T.; Nagayama, S.; Manabe, K. *Org. Lett.* **2001**, *3*, 165-167

2.2. *Chiral Diazoacetoacetates by Enantioselective Catalytic Mukaiyama Aldol Reaction Catalyzed by Known Catalysts.*

2.2.1. Selection of Catalysts:

A general strategy based on catalytic asymmetric Mukaiyama aldol addition reactions for the construction of chiral diazoacetates is shown below (*Scheme 2.22*).

Scheme 2.22:

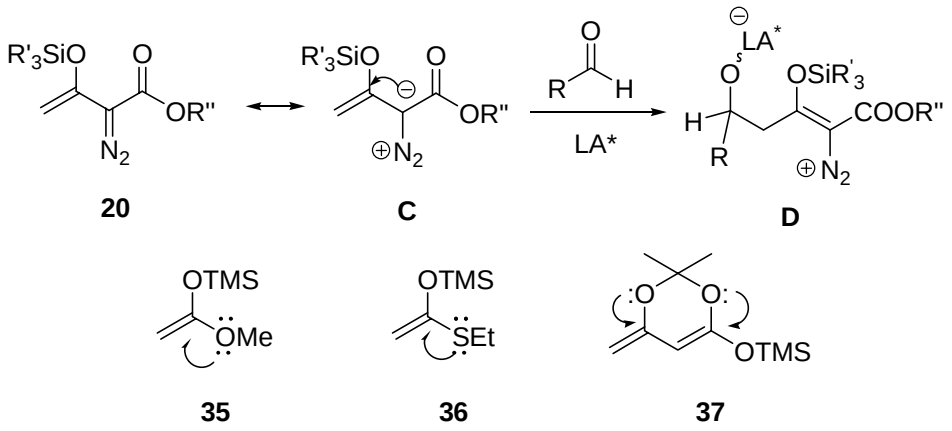


20 **21**

Before selecting the catalysts to be used for screening the above reaction, the nucleophilicity of the vinyldiazoacetate **20** was analyzed. The diazoester functional group as shown in the resonance structure **B** increases the nucleophilicity of the vinyldiazoacetate **20**. This diazoester group can also stabilize the positive charge which builds up during the course of addition to the aldehyde leading to the aldol adduct **C**.[83] Therefore, it can be expected that the silyl enol ether **20** would have similar nucleophilicity as **35** or **36** or **37** (*Scheme 2.23*).[84]

(83) Burfindt, J.; Paltz, M.; Müller, M.; Mayr, H. *J. Am. Chem. Soc.* **1998**, *120*, 3629-3634.
(84) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66-77.

Scheme 2.23:



The following three catalyst systems were chosen for the Mukaiyama aldol addition of **20** to aldehydes (e.g., benzaldehyde), based on the reasons as described below:

- $Ti(O^iPr)_4$/BINOL system developed by Keck and co-workers.[24]
    1. $Ti(O^iPr)_4$, (*R*)- and (*S*)-BINOL are commercially available.
    2. This catalyst system is known to work well with aromatic aldehydes (high yields and enantioselectivity) and does not need bis-coordination for high enantioselectivity.
    3. $Ti(O^iPr)_4$ is found to be compatible with the diazo functionality in vinyldiazoacetate **20** as well as diazoacetoacetates **21** (*See Chapter 1*).

- CuF_2/tol-BINAP system developed by Carreira and co-workers.[30]
    1. (*R*)- and (*S*)-tol-BINAP are commercially available.
    2. CuF_2 can be prepared in situ from commercially available $Cu(OTf)_2$ and TBAT.

3. This catalyst system is known to work well with aromatic aldehydes (high yields and high enantioselectivity) and does not need bis-coordination for high enantioselectivity.
4. Decomposition of the diazo functionality in vinyldiazoacetate **20** and diazoacetoacetate **21** by Cu(II)-salts might be very slow at the reaction condition (-78 ^{o}C).

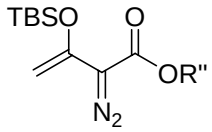
- Ag(OTf)/BINAP system developed by Yamamoto and co-workers.[33]
    1. Ag(OTf), KF, 18-Crown-6, (R)- and (S)-BINAP are commercially available.
    2. This catalyst system is known to work well with aromatic aldehydes (high yields and enantioselectivity) and does not need bis-coordination for high enantioselectivity.
    3. This catalyst system is known to work well with weakly nucleophilic silyl enol ether or equivalents.
    4. Ag(OTf) is found to be compatible with the diazo functionality in vinyldiazoacetate **20** as well as diazoacetoacetates **21** (*See Chapter 1*).

Finally, the following factors have been considered for catalyst screening for the asymmetric Mukaiyama aldol addition of **20** to aldehydes (e.g. benzaldehyde):

- Catalysts effective for common aldehydes (does not need bis-coordination for selectivity) will be preferred.
- Both the metal-salts and ligands are commercially available.

- Catalysts do not decompose the diazo functionality.

2.2.2. Results with TBS-Vinyldiazoacetate 20a:

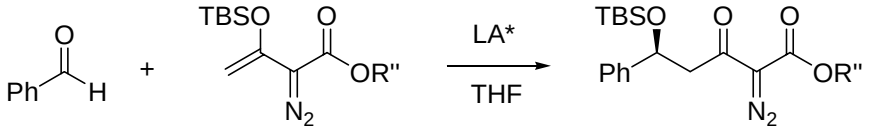


20a

TBS protected vinyldiazoacetate **20a** with high purity was synthesized using the method developed by Davies and co-workers.[85] The advantage of using **20a** is its stability towards moisture and mild acids. However, the TBDMS protected vinyldiazoacetate **20a** was found to be unreactive with 20 mol% $Ti(O^iPr)_4$/(*R*)-BINOL, 4 mol% CuF_2/(*S*)-tol-BINAP and 10 mol% Ag(OTf)/(*R*)-BINAP catalysts both at -78 ^oC and -20 ^oC (entries 1,2,4,6 in *Table 2.1*). A 40% yield of the Mukaiyama aldol adduct was obtained with benzaldehyde and **20a** using Keck's Ti(IV)-catalyst (20 mol%) at ambient temperature without any enantiocontrol (entry 3 in *Table 2.1*). Low chemical yield (30%) and low enantioselctivity (10% ee) were observed with 4 mol% CuF_2/(*S*)-tol-BINAP at 0 ^oC (entry 5 in *Table 2.1*). At ambient temperature the same reaction proceeded very sluggishly yielding ~9% yield after 5 h with Ag/BINAP catalyst (entry 7 in *Table 2.1*).

(85) Davies, H. M. L.; Ahmed, G.; Churchill, M. R. *J. Am. Chem. Soc.* **1996**, *118*, 10774-10780.

Table 2.1:



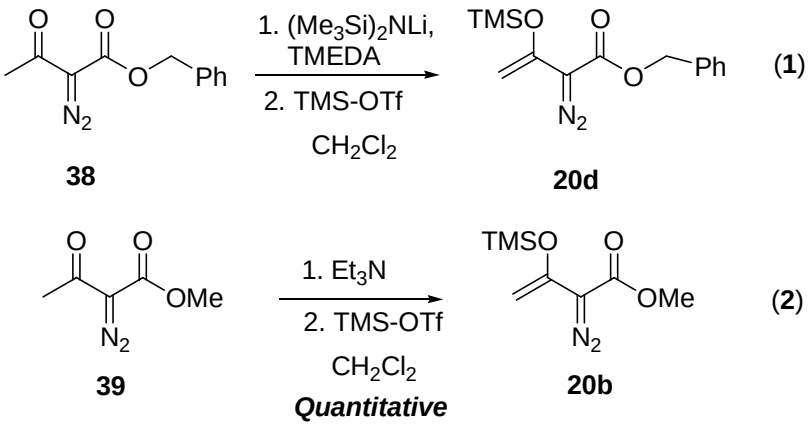
20a **21a**

entry	**LA***	T (^{o}C)	Yield of **21a** [%][a]	ee [%][b]
1	20 mol% Ti(O^{i}Pr)$_4$/40 mol% (*R*)-BINOL	-78	0	-
2	20 mol% Ti(O^{i}Pr)$_4$/40 mol% (*R*)-BINOL	-20	<10	nd
3	20 mol% Ti(O^{i}Pr)$_4$/40 mol% (*R*)-BINOL	23	40	5
4	4 mol% CuF_2/(*R*)-tol-BINAP	-78	<10	nd
5	4 mol% CuF_2/(*R*)-tol-BINAP	0	30	10
6	10% AgOTf, 6%(*R*)-tol-BINAP, 10% KF, 10% 18-Crown-6	-78	0	-
7	10% AgOTf, 6%(*R*)-tol-BINAP, 10% KF, 10% 18-Crown-6	23	~9	-

[a] Yield of isolated **21a** following column chromatography.
[b] Determined by HPLC on chiral Chirapak-AD column after deprotection of the TBS group of the product (See experimental section for details). Racemic material was used as the standard to certify enantiomeric excess.

2.2.3. Synthesis of TMS-Vinyldiazoacetate 20b:

Switching from TBS protection to TMS in the vinyldiazoacetate (**20a**), was expected to increase the rate of addition as a result of faster silyl transfer.[86] There was only one previous report of synthesis of a related TMS-protected vinyldiazoacetate **20c** in the literature. Karadi and co-workers reported the synthesis of TMS-vinyldiazoacetate **20d** from the corresponding diazoacetoacetate **38** by silylation with lithium hexamethyldisilazide, trimethylchlorosilane and tetramethylethylenediamine in THF at -78 ^{o}C, followed by warming to 0 ^{o}C (eq. 1).[87] The same reaction procedure was found to be unsuitable when attempted with methyl diazoacetoacetate (**39**), as it led to a mixture of **20b** and the diazoacetoacetate **39** in 5:1 ratio along with bis-hexamethylsilylamine and tetramethylethylenediamine.



Replacing hexamethyldisilazide/TMEDA by triethylamine and using TMSOTf instead of trimethylchlorosilane in dichloromethane was found to be beneficial. The

(86) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66-77.
(87) Karadi, S.; Amato, J.S.; Reamer, R. A.; Fi. *Tet. Lett*. **1997**, *37*, 8277 – 8280.

reaction was found to proceed with quantitative conversion of **20b,** but purification of **20b** from excess TMSOTf and triethylamine was found to be difficult. (eq. 2).

Purification of **20b** by distillation method (typical purification method for enolsilane) is not suitable, as the diazo functionality decomposes at high temperature. Efforts for purifying **20b** by chromatographic separation procedure were also unsuccessful, as **20b** was found to decompose even on silica gel. For the success of the asymmetric addition it is absolutely important to use pure **20b**, particularly when ≤ 5% catalyst is to be used. Any left-over TMSOTf would catalyze the reaction in the non-selective pathway (catalyzed by achiral TMSOTf and producing racemic mixture of the adduct). On the other hand, any left-over triethylamine will diminish the activity of Lewis acid by formation of a complex with the Lewis acid.

Careful control of the molar ratio of TMSOTf, triethylamine and **39** (in 1:1:1 ratio)**,** further improved the quality of **20b**, as evident from the ^{1}H NMR of the crude reaction mixture after removal of the solvent. Further purification of **20b** was made by solvent extraction of the product with dry hexane from a concentrated reaction mixture followed by removal of hexane.

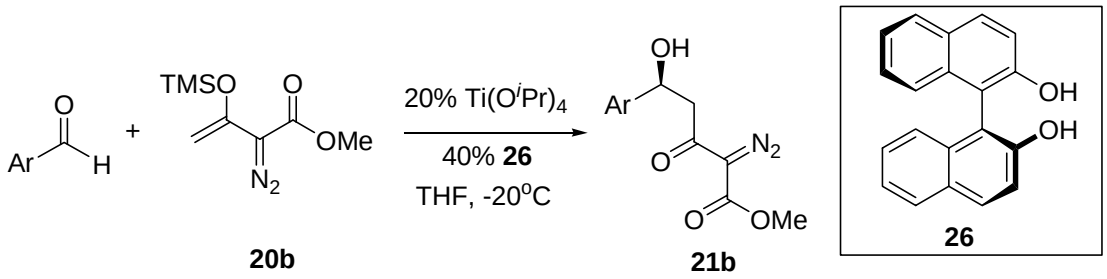
2.2.4. Asymmetric Mukaiyama Aldol Addition Reaction with TMS-Vinyldiazoacetate 20b:

2.2.4.1. Ti(IV)/BINOL Catalyst

Replacing the TBS group by trimethylsilyl group in **20a** was found to be encouraging as the reaction of benzaldehyde with **20b** was found to proceed at a faster

rate. But Ti(O*i*Pr)$_4$/(*S*)-BINOL(**26**) at -20 ^oC in 6h, both the yield (20%) and enantioselecivity (40% ee) were poor (*entry 1 in Table 2.2*). No side reaction was being observed as unreacted benzaldehyde and **38** (hydrolysis product of **20b**) were isolated along with the product. Analysis by ^1H NMR of the crude reaction mixture showed the presence of only 15% of **38**.

Table 2.2: *Asymmetric Mukaiyama aldol reaction of vinyldiazoacetate* ***20b***[a]



entry	Ar	yield of **21b** (%)[b]	ee (%)[c]
1	Ph	20	40
2	4-ClC_6H_4	22	44

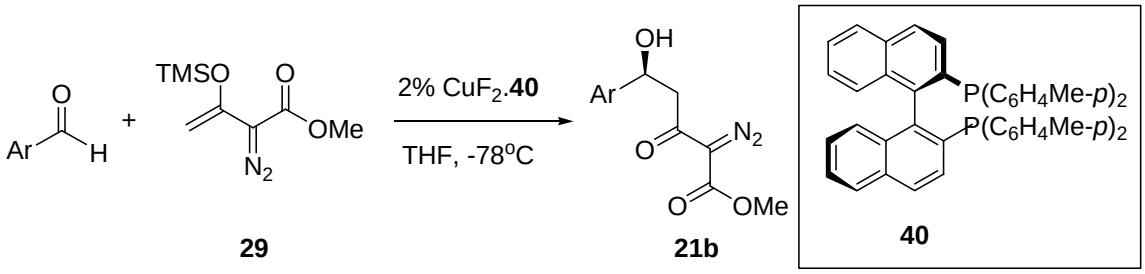
[a] Used the same procedure as that reported by Keck: 20 mol% Ti(O*i*Pr)$_4$ and 40% (*S*)-BINOL, THF, -20 ^oC, mildly acidic work-up (See ref 24).
[b] Yield of isolated **21b** following column chromatography.
[b] Determined by HPLC on chiral Chirapack-AD column (See experimental section for details). Racemic material was used as the standard to certify enantiomeric excess.

2.2.4.2. Cu(II)/tol-BINAP Catalyst

Switching to the TMS-protected **20b** was somewhat rewarding, as it offered moderate enantiocontrol (66% ee) with benzaldehyde using 2 mol% CuF_2/(*R*)-tol-BINAP(**38**)

(entry 2 in *Table 2.3*) when the reaction was carried out at -78 ^{o}C. The lower yield in this Cu(II) catalyzed addition is due, we believe, to slow diazo decomposition of **20b** and/or **21b**, as evident in the ^{1}H NMR of the crude reaction mixture. Similar yield and enantiomeric excess was observed with 4-chlorobenzaldehyde (entry 3 in *Table 2.3*). Changing catalyst loading to 1 mol% (entry 1) or 4 mol% (entry 4) did not improve enantiomeric excess or chemical yield.

Table 2.3: *Asymmetric Mukaiyama aldol reaction of vinyldiazoacetate* ***20b***[a]



29 **21b** **40**

entry	Ar	Catalyst loading (mol%)	yield of **21b** (%)[b]	ee (%)[c]
1	Ph	1	30	50
2	Ph	2	53	66
3	4-ClC_6H_4	2	60	61
4	4-ClC_6H_4	4	74	62

[a] Used the same experimental procedure as that reported by Carreira: 2 mol% (*R*)-*p*-tol-BINAP/CuF_2, THF,
-78 ^{o}C, mildly acidic work-up (See ref 30).
[b] Yield of isolated **21b** following column chromatography.
[c] Determined by HPLC on chiral Chirapack-AD column (See experimental section for details). Racemic material was used as the standard to certify enantiomeric excess.

2.2.4.3. Ag(I)/BINAP Catalyst

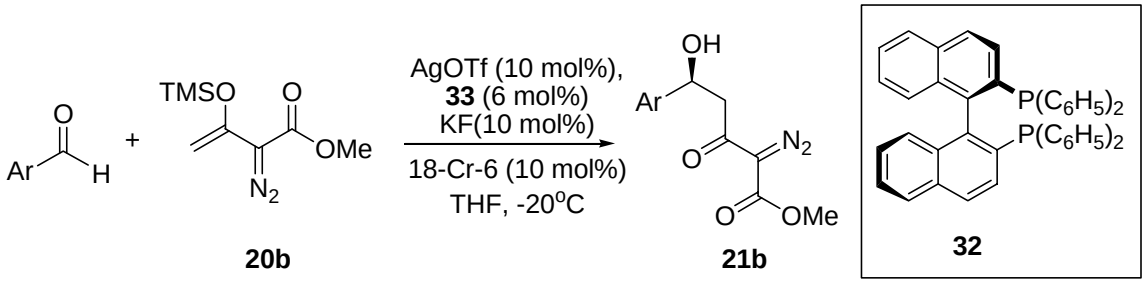
2.2.4.3.1. Results and Discussion:

Using AgOTf (10 mol %), KF (10 mol %), 18-crown-6 (10 mol %) and (*S*)-BINAP (6 mol %) as the catalyst at -20 ^{o}C, vinyldiazoacetate **20b** reacted with benzaldehyde in 6 h to give the Mukaiyama aldol adduct in 80% isolated yield and 91% enantiomeric excess (entry 1 in Table 2.4).

These reaction conditions were found to be general for electron rich aromatic aldehydes. Those with electron donating groups, *p*-anisaldehyde (entry 3) and *p*-tolualdehyde (entry 4), produced the Mukaiyama aldol adducts in good yields (>80%) and high enantiomeric excess (87-88%). Good chemical yield (78%) and high stereocontrol (92%) was also obtained with the aromatic aldehyde, *p*-chlorobenzaldehyde (entry 2), having a weakly electron withdrawing chlorine substituent. One significant limitation of this methodology might be the incompatibility with electron-withdrawing substrate, as *p*-nitrobenzaldehyde (entry 6) under the same reaction conditions did not produce any desired addition product. Unreacted starting materials were recovered after 10 h of reaction time.

The α,β-unsaturated aldehyde cinnamaldehyde (entry 5) also produced the aldol adduct in 74% yield and 88% ee. The aliphatic aldehyde octanal (entry 7) was found to be the only exception of aldehydes employed. Under the same reaction conditions octanal reacted with the vinyldiazoacetate **20b** giving only 20% conversion and 11% enantiomeric excess. Low reactivity of aliphatic aldehydes was also observed by Yamamoto[33] and by Wang in reactions with ethyl diazoacetate.[12]

Table 2.4: *Asymmetric Mukaiyama aldol reaction of vinyldiazoacetate* ***20b***[a]



20b **21b** **32**

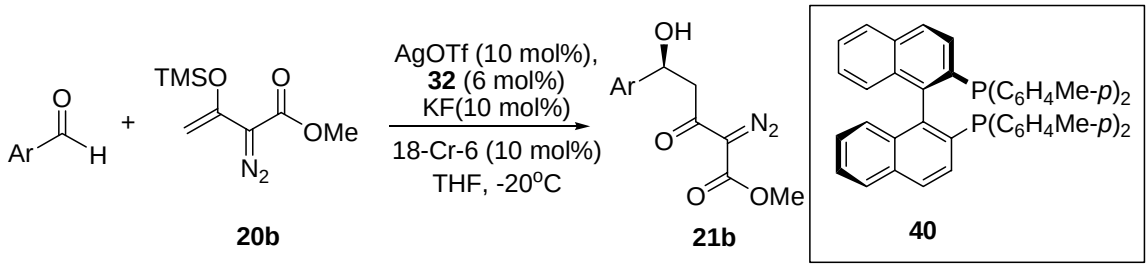
entry	Ar	yield of **21b** (%)[b]	ee (%)[c]
1	Ph	80	91
2	4-ClC_6H_4	78	92
3	4-$MeOC_6H_4$	82	87
4	4-MeC_6H_4	80	88
5	β-styryl	74	88
6	4-$NO_2C_6H_4$	0	--
7	C_7H_{15}	20	11

[a] Yield of isolated **21b** following column chromatography.
[b] Determined by HPLC on chiral Chirapack-AD column (See experimental section for details). Racemic material was used as the standard to certify enantiomeric excess.
[c] See experimental section for details. Absolute stereochemistry of the products was not determined. The major isomers formed from Cu(II)/(*R*)-tol-BINAP, Ti(IV)/(*S*)-BINOL and Ag(I)/(*S*)-BINAP catalysts are same (See section 2.2.4.1.5.).

2.2.4.4. Effects of Ligands:

Switching from BINAP (**32**) to tol-BINAP (**38**) did not improve the enantioselectivity significantly but decreased the chemical yields (*Table 2.5*).

Table 2.5: *Effect of Ligands*

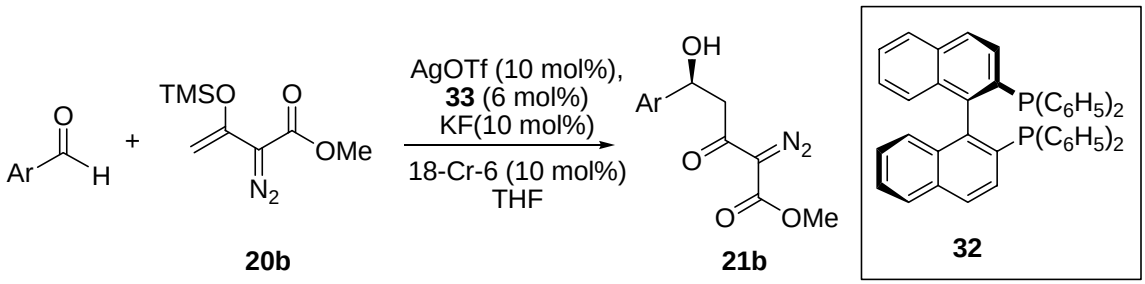


entry	Ar	yield of **21b** [%]	ee [%]
1	Ph	54	90
2	4-ClC_6H_4	58	93

1.2.4.3. Temperature Profile:

In order to understand the temperature effect of this reaction, the Mukaiyama aldol addition of TMS-vilyldiazoacetate **20b** to benzaldehyde using Ag(I)/(*R*)-BINAP, was carried out at various temperatures. When the reaction was carried out at -78 ^oC for 8 h, the yield of the reaction decreased to 20% (remaining being the unreacted starting materials) from 80% yield at -20 ^oC. Increasing the reaction temperature to rt increased the yield to 87% but the ee dropped to 55% (*Table 2.6*).

Table 2.6: *Effect of Temperature*



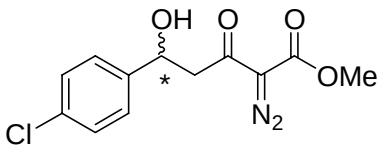
20b **21b**

entry	Ar	Temp (^{o}C)	yield of **21b** [%][a]	ee [%][b]
1	Ph	RT	87	55
2	Ph	-20	80	91
3	Ph	-78	20	nd

[a] Yield of isolated **21b** following column chromatography.
[b] Determined by HPLC on chiral Chirapack-AD column (See experimental section for details). Racemic material was used as the standard to certify enantiomeric excess.

1.2.4.4. Determination of absolute configuration (tentative):

Tentative assignment of the absolute configuration of **21b-2** as *S* comes from comparison of the sign of rotation of **21b-2** (Ar = 4-ClC_6H_4) with the following compounds on the next page.



21b-2

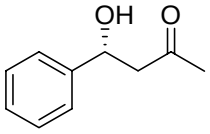
ee = 92%

$[\alpha]^{24.3}_{D}$ = -63.6 (c 0.506, CH_2Cl_2, 92%)

Source of chirality: asymmetric Mukaiyama aldol addition [AgF/(*S*)-BINAP].

Absolute configuration: (*S*) tentatively.

For determination of the absolute stereochemistry the following compounds with known specific rotation were compared.

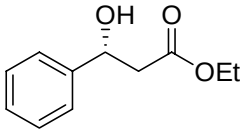


41

ee = 77%

$[\alpha]^{20}_{D}$ = +32.4(c 1.0, $CHCl_3$, for product with 77% ee)

Source of chirality: asymmetric Mukaiyama aldol addition (AgOTf/(*R*)-BINAP).[35]

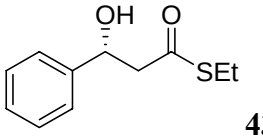


42

ee = 73%

$[\alpha]^{19}_{D}$ = +63.1(c 2.7, $CHCl_3$)

Source of chirality: asymmetric Mukaiyama aldol addition .[29]



43

ee = 92%

$[\alpha]^{27}_{D}$ = +51.6(c 0.67, C_6H_6)

Source of chirality: asymmetric Mukaiyama aldol addition.[88]

1.2.4.5. Conclusion:

In this section we have discussed the outcome of our catalyst screening for asymmetric Mukaiyama aldol addition methodology for the synthesis of chiral diazoacetoacetates using some pre-developed catalyst systems. Despite the reported success of highly enantioselective execution of Mukaiyama aldol addition of vinyldiazoacetate using Ti(IV)/BINOL and Cu(II)/tol-BINAP systems, we were unsuccessful in extending them for the addition of vinyldiazoacetates like **20a** and **20b**. But the Ag(I)/BINAP catalyst developed by Yamamoto and co-workers, has been successful in the Mukaiyama aldol addition reaction of **20b** with aromatic aldehydes. Therefore, we have developed an efficient enantioselective synthesis of chiral diazoacetoacetates *via* catalytic Mukaiyama aldol addition of 3-trimethylsilyloxy-vinyldiazoacetate **20b** without simultaneously decomposing the acid-sensitive diazo moiety. This method presents a straightforward approach for accessing chiral diazoacetoacetates from a readily accessible diazo compound using commercially available ligand and silver(I) triflate.

(88) Ishitani,H.; Yamashita, Y.; Shimizu, H.; Kobayashi, s. *J. Am. Chem. Soc.* **2000**, *122*, 5403-5404.

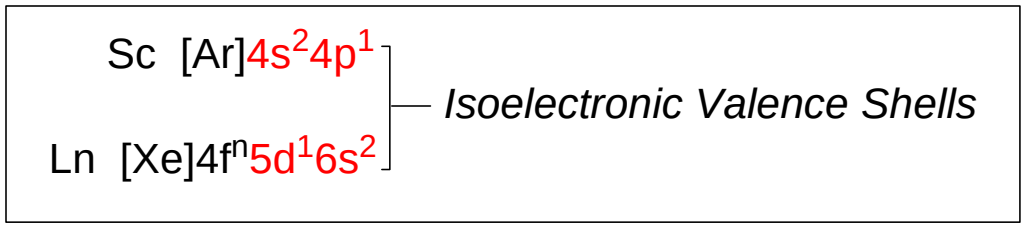
2.3. *Development of a Scandium Mixed Ligands Complex for Catalytic Asymmetric Mukaiyama Aldol Reaction.*

2.3.1. Scandium (III) Catalyzed Enantioselectve Organic Transformations:

2.3.1.1. Introduction:

Although technically not a member of the lanthanide or rare-earth families, scandium is often treated as one of them because of their electronic configurational similarities (*Scheme 2.24*).[89]

Scheme 2.24:



In the case of the lanthanides, 6s electrons are removed first and hence the first as well as the second ionization energy for all lanthanides are same. Since f-orbitals are deeply

(89) Aspinal H. C. *Chemistry of the f-Block Elements*, Gordon and Breach Science Publishers: Amsterdam. **2001**.

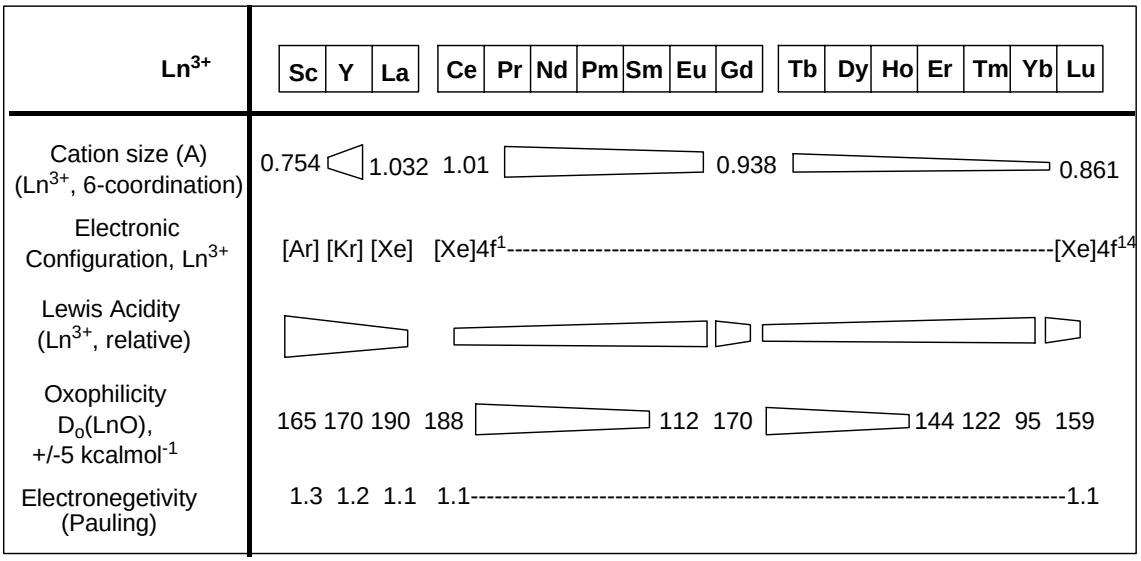
buried under filled $6s^2 5p^6$ electrons, the third ionization usually results from removal of an electron from high energy d-orbital. Therefore, for lanthanides the most stable oxidation state is (+3). Likewise, scandium has one high energy 4p electron and hence the (+3) state is also the most predominant.

A consequence of having an inert outer shell [$6s^2 5p^6$ in case of lanthanides and $3s^2 3p^6$ in case of Sc(III)] is that the ionic radii of lanthanides are larger than those of d-block elements. Because of their larger ionic radii lanthanides can accommodate larger number of ligands and therefore form complexes having co-ordination numbers greater than six. The absence of orbital rigidity accompanied with higher charges make the ligand-metal interactions ionic in nature and, therefore, coordination geometries are governed by mainly electrostatic and steric factors. The ionic nature of the ligand-metal interaction drastically reduces the σ-donation and π-backbonding interactions prevalent in d-block elements. A rapid ligand-exchange rate for scandium and other lanthanide complexes make it difficult to make complexes where the chirality resides on the metal. Therefore, in all the Sc(III)-based asymmetric catalysts chirality comes from the ligands.

Scandium is the smallest lanthanide with ionic radii of 0.754 ^{o}A. Because of the small ionic radius and high positive charge, scandium(III)-complexes act as the strongest Lewis acids among all lanthanides (*Scheme 2.25*).[90]

(90) Inanaga, J.; Furuno, H.; Hayano, T. *Chem. Rev.* **2002**, *102*, 2211-2225.

Scheme 2.25: *Trends of Intrinsic Properties of Lanthanides*[91]



A thorough search of the Cambridge Crystallographic Data Center (CCDC) revealed that all the reported scandium complexes are found to be seven co-ordinated with pentagonal bipyramid geometries.

2.3.1.2. Prior Art:

Scandium(III)-based chiral Lewis acids have gained interest in the last decade because of their ability to form high co-ordination complexes and their ability to work as catalysts in both protic and aprotic solvents without compromising their Lewis acid

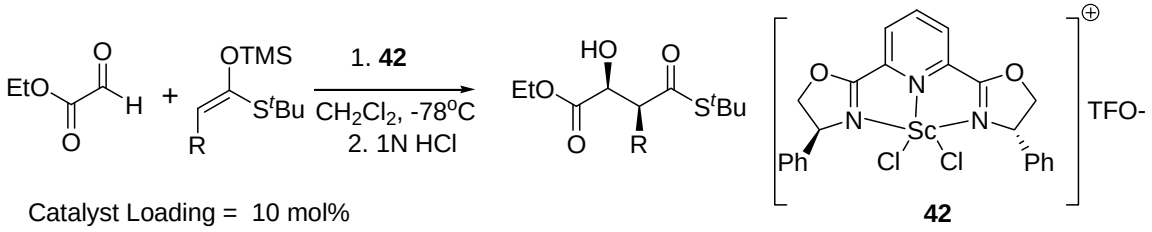
(91) Reproduced from Anwander, R. In *Lanthanides: Chemistry and Use in Organic Synthesis*, Springer-Verlag: Berlin. **1999**, Kobahashi, S. Ed. 63-118.

strength.[92] The following examples represent some of the seminal development in asymmetric catalysis using scandium(III) complexes.

Enantioselective Mukaiyama Aldol Addition:

Evans and co-workers have reported the Sc(III)-PYBOX catalyzed asymmetric Mukaiyama aldol addition with ethyl glyoxalate.[93] Although the yields as well as the % ee's of these reactions are high, the process suffers heavily on narrow substrate scope. This catalyst was found to be effective only with ethyl glyoxalate and highly nucleophilic ketene thioacetals.

Scheme 2.26:



Catalyst Loading = 10 mol%

42

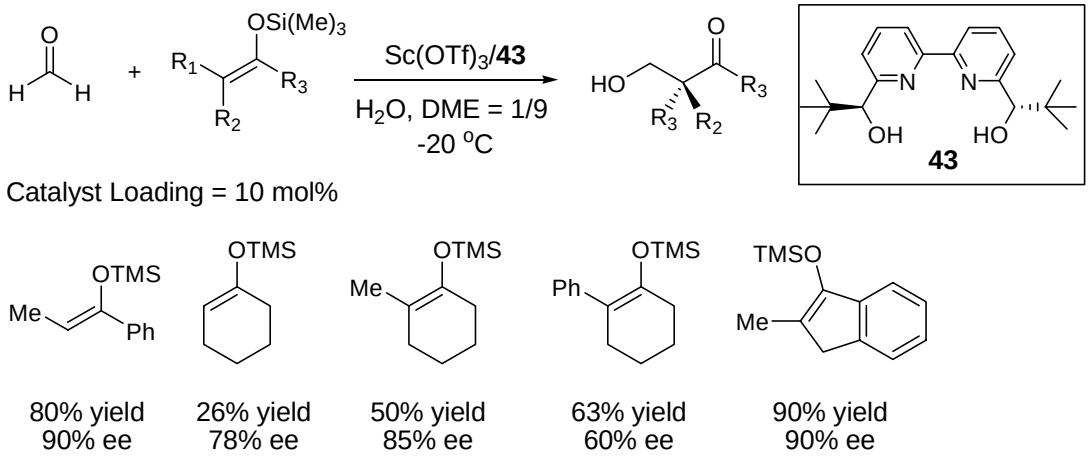
entry	R	Yield [%]	ee [%]
1	H	92	90
2	Me	93	95
3	^{i}Pr	90	93
4	^{i}Bu	94	95

(92) Kobayashi, S. In *Lanthanides: Chemistry and Use in Organic Synthesis*, Springer-Verlag: Berlin. **1999**, Kobahashi, S. Ed. 63-118.
(93) Evans, D. A.; Masse, C. E.; Wu, J. *Org. Lett.* **2002**, *4*, 3375-3378.

Enantioselective Hydroxymethylation of Silicon Enolates:

Kobayashi has reported a catalytic asymmetric hydroxymethylation of silicon enolates using an aqueous solution of formaldehyde with a chiral scandium complex (*Scheme 2.26)*. This is the first example of catalytic asymmetric reactions in aqueous media with a chiral scandium complex (*Scheme 2.27*).[94] Formaldehyde is the only aldehyde which works well in this reaction. Benzaldehyde was reported to give 76% yield and 59% ee. Free –OH groups in **43** are absolutely required for selectivity as the ee drops to 0% when –OH groups are replaced by –OMe.

Scheme 2.27:

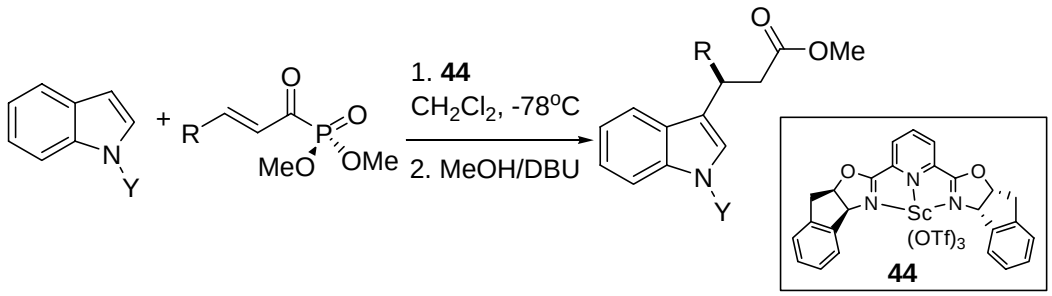


(94) Ishikawa, S.; Tomoaki, H.; Manabe, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, 12236–12237.

Enantioselective Indole Friedel-Crafts Alkylations:

A highly enantioselective Friedel-Crafts alkylation of electron-rich aromatic nucleophiles catalyzed by scandium(III) triflate-pyridyl(bis)oxazoline complexes has been accomplished by Evans and co-workers (*Scheme 2.27*). The reaction involves α,β-unsaturated acyl phosphonates as electrophiles and substituted indoles as nucleophiles. The reactive acyl phosphonate product is converted to the corresponding ester or amide in good overall yield by adding alcohol or amine directly to the reaction mixture (*Scheme 2.28*).[95]

Scheme 2.28:



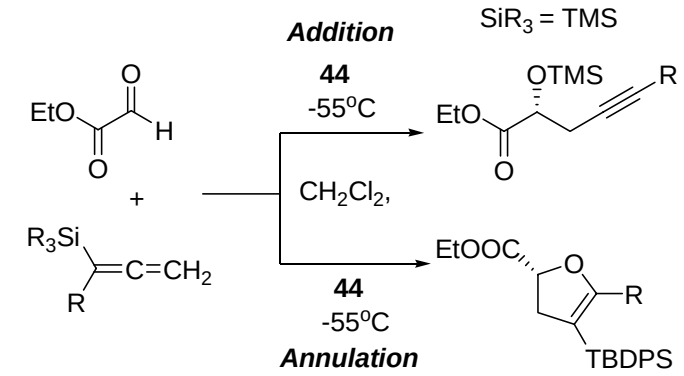
entry	Y	R	mol% **1**	Yield [%]	ee [%]
1	Me	Me	3	95	72
2	Me	Et	10	97	65
3	Me	^{i}Pr	10	99	82
4	Me	Ph	20	80	85
5	H	Me	1	83	83
6	allyl	Me	1	98	76

(95) Evans, D. A.; Scheidt, K. A.; Fandrick, K. R.; Lam, H. W.; Wu. *J. Am. Chem. Soc,* **2003**, *125*, 10780 - 10781

Enantioselective Addition of Alenylsilane to Ethyl Glyoxalate:

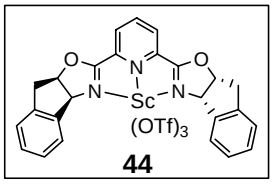
Evans and co-workers have described a highly enantioselective scandium triflate catalyzed addition and annulation reaction of allenylsilanes with ethyl glyoxylates (*Scheme 2.29*).[96]

Scheme 2.29:



R	yield [%]	ee [%]
Me	95	98
n-Bu	90	94
c-hex	95	90
Ph	63	97

R	yield [%]	ee [%]
Me	91	92
n-Bu	89	92
c-hex	63	93
Ph	32	85



44

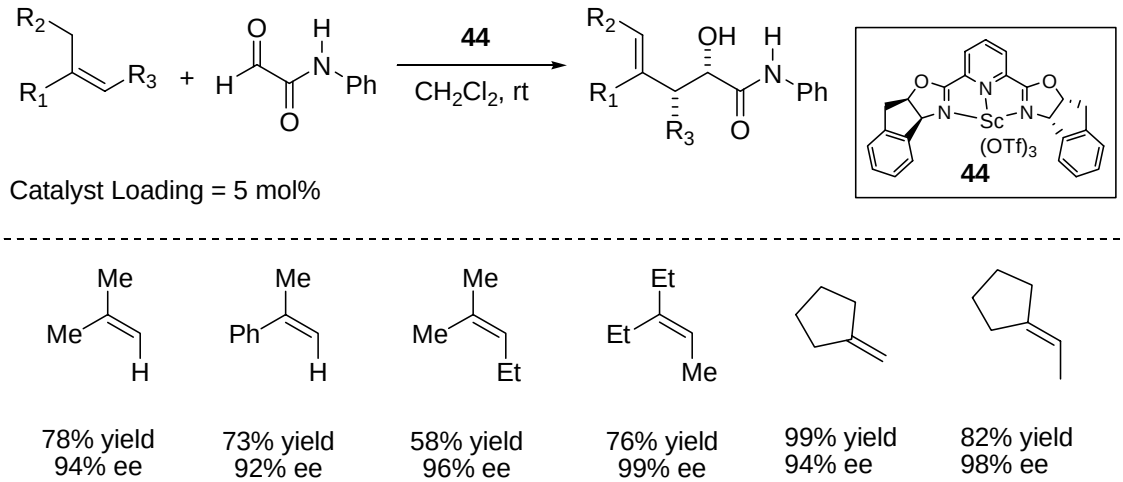
Enantioselective Ene Reactions:

An enantio- and diastereoselective carbonyl-ene reaction catalyzed by chiral scandium-PYBOX complexes has been developed recently by Evans group. Uniformly

(96) Evans, D. A.; Sweeney, Z. K.; Rovis, T.; Tedrow, J. S. *J. Am. Chem. Soc.* **2001**, *123*, 12095-12096.

high enantiomeric excesses and good yields were observed. Use of trisubstituted olefins generated the syn product in high enantio- and diastereoselectivity (*Scheme 2.30*).[97]

Scheme 2.30:

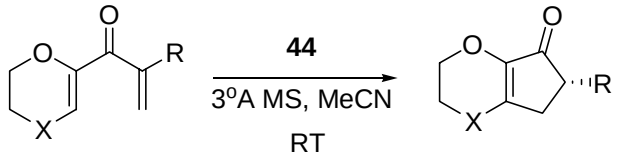


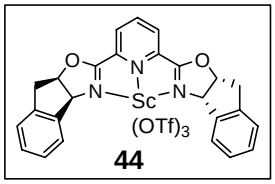
Enantioselective Nazarov Reactions:

Trauner and co-workers have described the first truly catalytic asymmetric Nazarov reaction that proceeds with high levels of enantioselectivity and in good yields (*Scheme 2.31*). The high enantioselectivity appears to arise in the proton-transfer process rather in the electrocyclizations.[98]

(97) Evans, D. A.; Wu, J. *J. Am. Chem. Soc.* **2005**, *127*, 8006-8007.
(98) Liang, G.; Trauner, D. *J. Am. Chem. Soc.* **2004**, 126, 9544-9545.

Scheme 2.31:





Catalyst Loading = 10 mol%

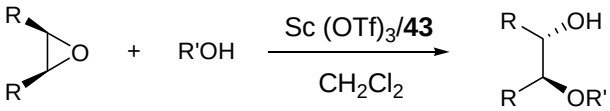
entry	X	R	Yield [%]	ee [%]
1	CH_2	Me	65	85
2	CH_2	Et	75	92
3	CH_2	^{i}Pr	88	95
4	CH_2	Ph	65	87
5	O	^{i}Pr	65	72
6	O	^{t}Bu	80	91

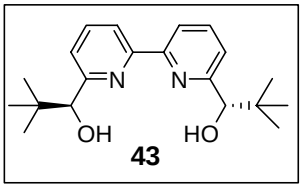
Epoxide Ring Opening By Alcohols and Amines:

Schneider group has reported a novel scandium-bipyridine complex catalyzed alcoholysis (*Scheme 2.32*) and aminolysis of *meso*-epoxides with good yields and in part excellent enantioselectivities (*Scheme 2.33*).[99a] Kobayashi and co-workers have achieved the above aminolysis in water using the same catalyst system used by Schneider.[47b]

(99) (a) Schneider, C.; Sreekanth, A. R.; Mai, E. *Angew. Chem. Int. Ed.* **2004**, *43*, 5691-5694. (b) Azoulay, S.; Manabe, K.; Kobayashi, S. *Org. Lett.***2005**,*7*, 4593-4595.

Scheme 2.32:



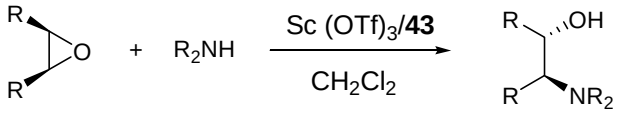


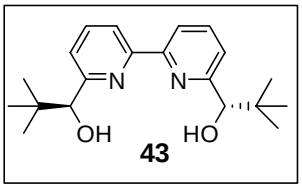
Catalyst Loading = 10 mol%

10 mol%

entry	R	R'	Yield [%]	ee [%]
1	Ph	Me	92	81
2	Ph	Et	96	75
3	Ph	Allyl	95	78
4	β-naphthyl	Me	98	83
5	2-tolyl	Me	96	75

Scheme 2.33:





Catalyst Loading = 10 mol%

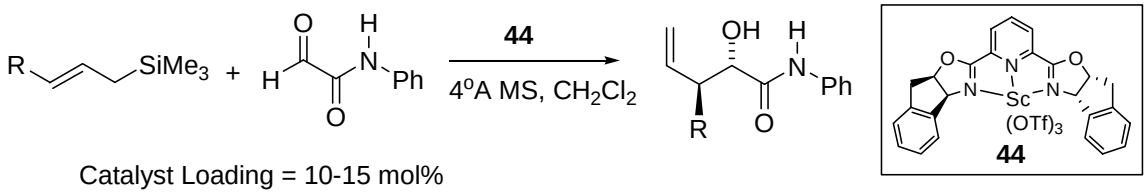
10 mol%

entry	R	amine	Yield [%]	ee [%]
1	Ph	$PhNH_2$	92	81
2	Ph	$PhNHCH_3$	96	75
3	Ph	*p*-anisidine	95	78
4	β-naphthyl	$PhNH_2$	98	83
5	2-tolyl	$PhNH_2$	96	75

Hosomi-Sakurai Addition:

Very recently Evans and co-workers have reported an enantio- and diastereoselective Sakurai-Hosomi reaction, catalyzed by chiral scandium pyridyl-bis(oxazoline) (PYBOX) complexes (*Scheme 2.34)*.[100] Both alkyl- and aryl-substituted allylsilanes are effective coupling partners with *N*-phenylglyoxamide.

Scheme 2.34:



Catalyst Loading = 10-15 mol%

entry	R	Yield [%]	ee [%]
1	Me	89	92
2	(*Z*)-Me	76	94
3	Et	76	91
4	Ph[1]	67	99

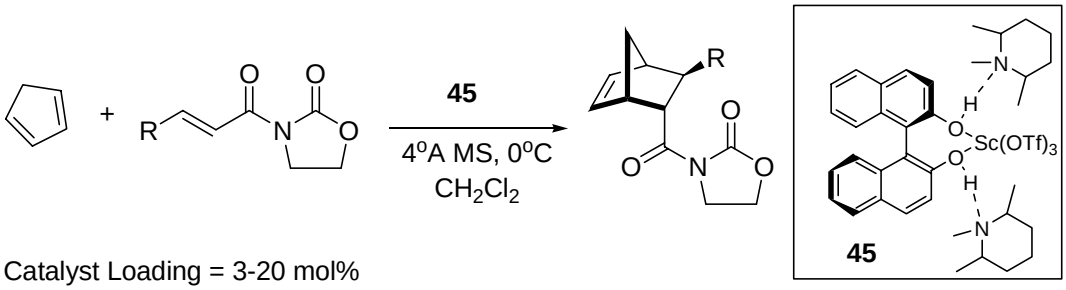
[1.] At rt and 15 mol% catalyst loading

Enantioselective Diels-Alder Addition:

Kobayashi and co-workers have reported Sc(III)-catalyzed highly enantioselective Diels-Alder reaction between cyclopentadiene and acyl-1,3-oxazolidin-2-ones. The proposed catalyst structure is shown below.[101]

(100) Evans, D. A.; Aye, Y.; Wu, J. *Org. Lett*. **2006**, *8*, 2071-2-73.
(101) Kobayashi, S.; Ishitani, H.; Araki, M.; Hachiya, I. *Tetrahedron Lett.* **1994**, *35*, 6325-6328.

Scheme 2.35:

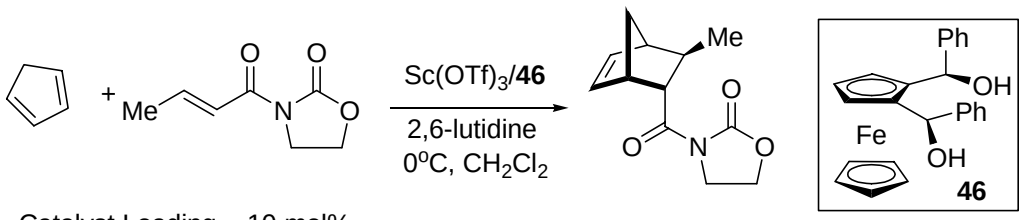


Catalyst Loading = 3-20 mol%

entry	R	mol% **1**	Yield [%]	ee [%]	endo : exo
1	Me	3	83	92	87:13
2	Ph	10	96	97	90:10
3	*n*-Pr	10	85	75	78:22

Recently Fukuzawa and co-workers have discovered enantioselective Diels-Alder addition between cyclopentadiene and substituted acryloyl-1,3-oxazolidin-2-ones catalyzed by ferrodiol-based Sc(III)-catalyst in the presence of 2,6-lutidine, yielding the cycloadduct in 91% ee and 90:10 endo/exo selectivity.[102]

Scheme 2.36:



Catalyst Loading = 10 mol%

Without lutidine: 19% ee

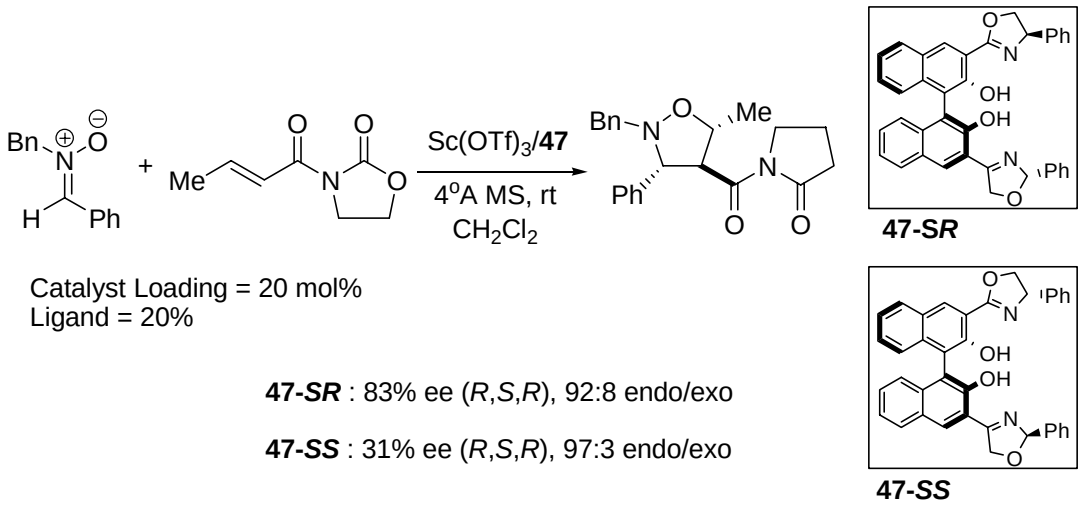
99% yield, 91% ee
90:10 endo:exo

(102) Fukuzawa, S. –I.; Fujimoto, K.; Konuro, Y.; Matsuzawa, H. *Org. Lett.* **2002**, *4*, 707-709.

Enantioselective 1,3-dipolar Cycloaddition:

Ohta and co-workers exploited intramolecular H-bonding between the nitrogen and alcohol of BINOL derivatives to achieve high enantiocontrol in Sc(III)-catalyzed asymmetric 1,3-dipolar cycloaddition of nitrones and alkenes (*Scheme 2.37*).[103]

Scheme 2.37:

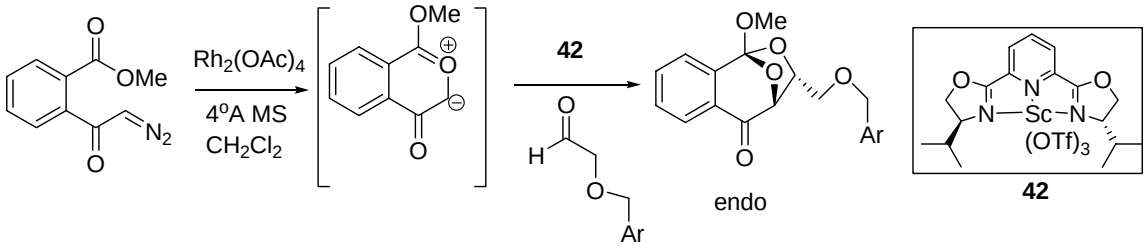


The presence of the second stereogenic center in the ligand has been found to be important in enantioselectivity as evident by the % ee obtained with the two diasteromeric ligands, presumably because of the matched/mismatched recognition.

Suga and co-workers have reported Sc(III)-PYBOX catalyzed enantioselective 1,3-dipolar cycloaddition of carbonyl ylides with aldehydes and ketones (*Scheme 2.38*).[104] The endo cycloaddition products were formed in high yield and with high enantioselectivity.

(103) Kodama, H.; Ito, J.; Hori, K.; Ohta, T.; Furukawa, I. *J. Organomet. Chem.* **2000**, *603*, 6-12.
(104) Suga, H.; Inoue, S.; Kaheki, A. *J. Am. Chem. Soc.* **2002,** *124*, 14836-14837.

Scheme 2.38:

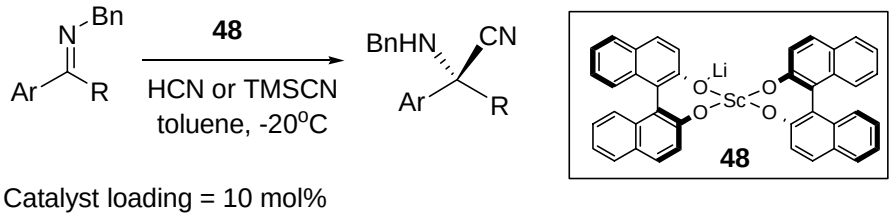


entry	-Ar	Yield [%]	ee [%]	endo : exo
1	Ph	96	91	88:12
2	2-$MeOC_6H_4$	82	82	85:15
3	4-$MeOC_6H_4$	53	89	91:9
4	4-FC_6H_4	97	93	82:18
5	4-ClC_6H_4	84	86	73:27
6	4-BrC_6H_4	77	83	67:33

Enantioselective Strecker Addition:

Vallée and co-workers have recently reported the heterobimetallic Sc-Li catalyzed asymmetric Strecker reaction with ee's of up to 91%. The proposed structure was based on the stoichiometry of the reagents used for preparation and shown in *Scheme 2.39*.[105]

Scheme 2.39:



Catalyst loading = 10 mol%

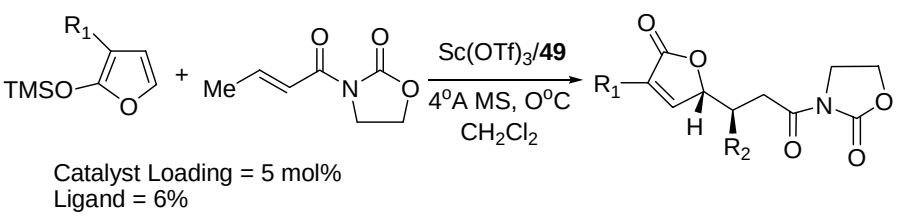
(105) Chavarot, M.; Byrne, J. J. ; Chavant, P. Y.; Vallée, Y. *Tetrahedron: Asymmetry* **2001**, *12*, 1147-1150

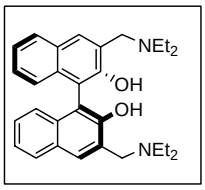
entry	Substrate	Yield [%]	XCN	ee [%]
1	Ar = Ph, R = Me	80	TMSCN	91
2	Ar = Ph, R = Me	95	HCN	81
3	Ar = β-Naphthyl, R = Me	45	TMSCN	65
4	Ar = β-Naphthyl, R = Me	80	HCN	86
5	Ar = Ph, R = H	70	TMSCN	45

Enantioselective Conjugate Addition:

Katsuki and co-workers were the first to report Sc(III)-catalyzed enantioselective conjugate addition reaction between 2-(trimethylsilyloxy)furans and acyl-1,3-oxazolidin-2-ones to afford the addition product with excellent diatereocontrol and moderate ee's but low chemical yields (*Scheme 2.40*).[106] In these reactions, the H-bonding between the binol OH groups and the tertiary-amine N-nonbonding electron pair is believed to provide more conformational rigidity and hence higher selectivity.

Scheme 2.40:





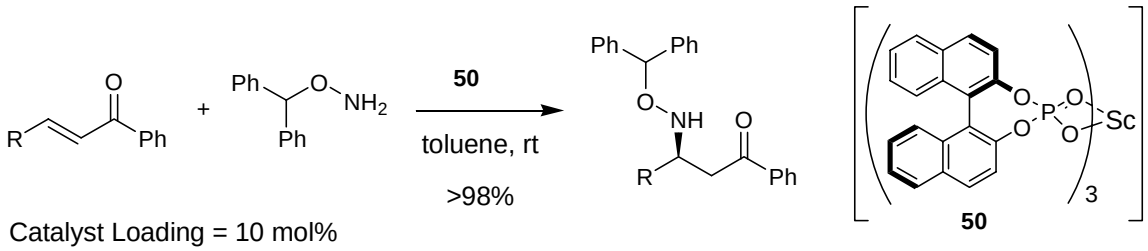
49

entry	R_1	R_2	Yield [%]	ee [%]	dr
1	H	Me	44	73	>50:1
2	Me	Me	64	60	41:1
3	H	H	59	41	-

(106) Kitajima, H.; Ito, K.; Katsuki, T. *Tetrahedron* **1997**, *53*, 17015-17028.

Probably the best results in conjugate additions were achieved by Inanaga using BINOL derived organophosphate-Sc(III) complex. Enantioselective conjugate addition of *O*-diphenylmethylhydroxylamine to various enones were achieved with excellent enantiocontrol (*Scheme 2.41)*.[107]

Scheme 2.41:



Catalyst Loading = 10 mol%

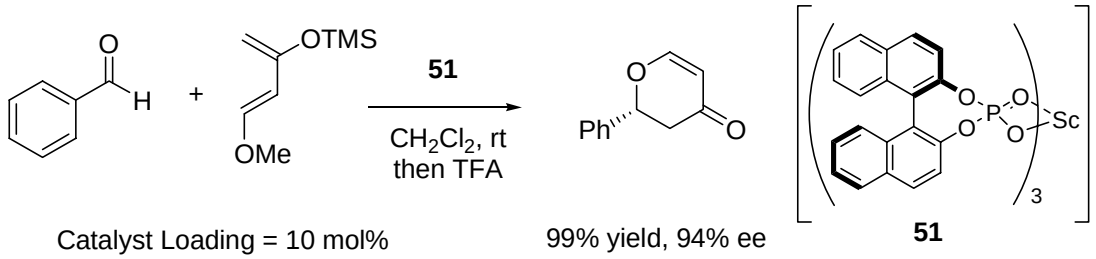
entry	R	ee [%]
1	Ph	99
2	4-MeC_6H_4	98
3	4-$MeOC_6H_4$	94
4	4-ClC_6H_4	99
5	4-FC_6H_4	98
6	4-$NO_2C_6H_4$	99

Enantioselective Hetero-Diels-Alder Addition:

Inanaga group was successful in carrying out the enantioselective hetero-Diels-Alder reaction using the same Sc(III)-organophosphate catalyst with high degree of enantiocontrol.[108]

(107) Jin, X. L.; Sugihara, H.; Daikai, H.; Tateishi, H.; Furuno, H.; Jin, Y. Z.; Inanaga, J. *Tetrahedron* **2002**, *58*, 8321-8340.
(108) Sugihara, H.; Daikai, K.; Jin, X. L.; Furuno, H.; Inanaga, J. *Tetrahedron Lett* **2002**, *43*, 2735-2739.

Scheme 2.42:



2.3.2. Novel Mixed Ligand Heterochiral Scandium(III) Catalyst:

In our initial studies, scandium(III) triflate was found to be the catalyst of choice in the condensation reaction of vinyldiazoacetates with aldehydes for product conversions and catalyst loading.[109] We considered development of a chiral scandium(III)-based catalyst to be the next challenge, as there is no Sc(III)-based chiral catalyst for general asymmetric Mukaiyama aldol addition reactions. The Sc-PYBOX catalyst developed by Evans and co-workers, suffers heavily by narrow substrate scope as only aldehydes with two point binding (e.g., benzyoxyacetaldehyde and ethyl glyoxalate) work well.[49] Kobayashi's hydroxymethylation methodology is also not very effective for aldehydes like benzaldehyde.[50]

In this effort for the development of a novel scandium based catalyst system, the following criteria were established:

- Low catalyst loading (≤ 5 mol %) considering the strong Lewis acidity of Sc(III)-complexes.
- The catalyst should be effective with aldehydes with monodentate co-ordination.
- The reaction should give high product yield and high enantioselectivity.

(109) Doyle, M. P.; Kundu, K.; Russell, A. E. *Org. Lett.* **2005**, *7*, 5171-5174.

2.3.2.1. Development of the Catalyst:

We realized the difficulty in achieving the above criteria, particularly the difficulty involved in controlling enantioselectivity. In order to achieve the goal, we concentrated on the structural features of the Sc(III)-based catalysts for asymmetric transformations. As is evident from the search in Cambridge Crystallographic Data Center (CCDC), all the scandium(III) complexes reported are seven coordinated with pentagonal bipyramid geometry, unlike tetrahedral, square planar or octahedral co-ordination geometries prevalent in transition metals. Crystal structure of [Sc((*S*,S)Ph-PYBOX)(H_2O)]($OTf)_3$ and [Sc((*S*,S)Inda-PYBOX)(H_2O)]($OTf)_3$ obtained by Evans's group show the placement of two of the three triflates (X-type ligands) in axial positions and the L-type ligand water co-ordinated in the apical position (*Fig 1*).[110]

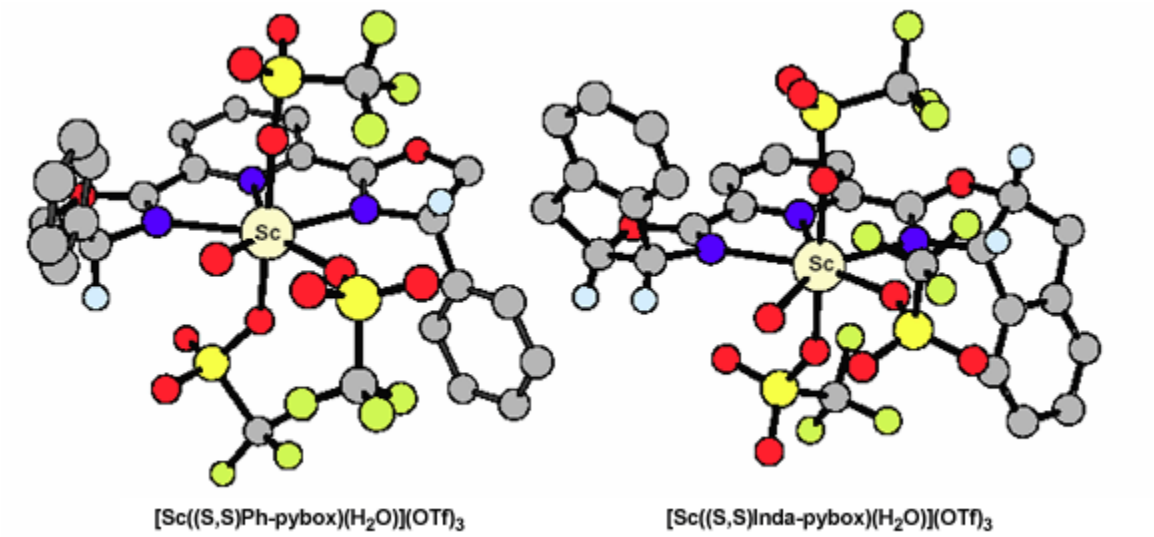
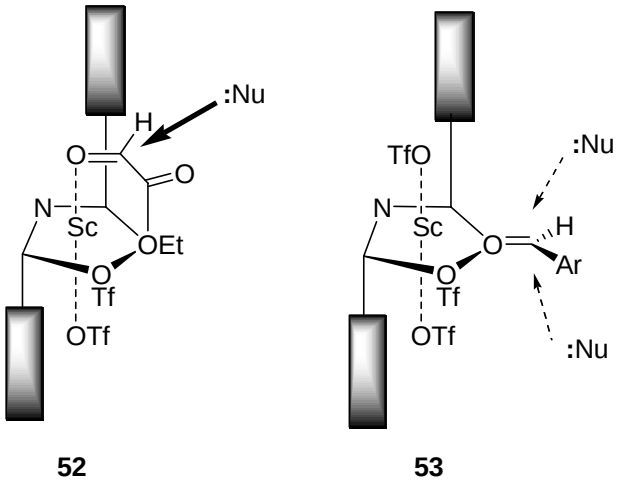


Fig 2.1: *Seven Co-ordinated Sc(III) Complexes with Pentagonal Geometry*

(110) Reproduced from ref 49.

Selectivity while using the above catalysts with aldehydes having bis-coordination (i.e., ethyl glyoxalate or benzoxyacetaldehyde) might be easier to control as they might lead to conformationally more stable aldehyde-metal complexes[49] (**52** in *Fig 2*). Therefore, it might be more difficult to control the enantioselectivity in nucleophilic addition to monodentate aldehyde by using one bidentate/tridentate chiral ligand as shown in *Fig 2.2*.

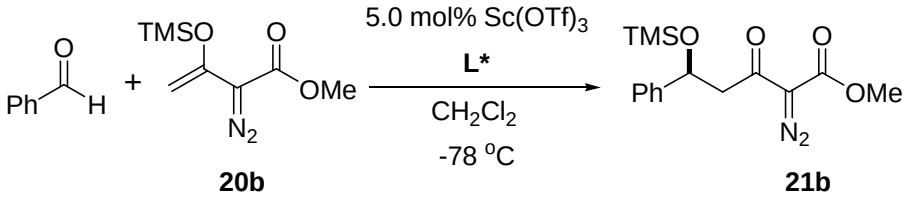


52 **53**

Fig. 2.2: *Bidentate vs Monodentate Co-ordination of Aldehyde Substrate*

As is evident from **53** in Fig 2, enantiocontrol in reactions using one tri-dentate ligand and $Sc(OTf)_3$ might be a difficult task. The addition reaction yielded the Mukaiyama aldol adduct with almost no selectivity (*Table 2.7*).

Table 2.7:



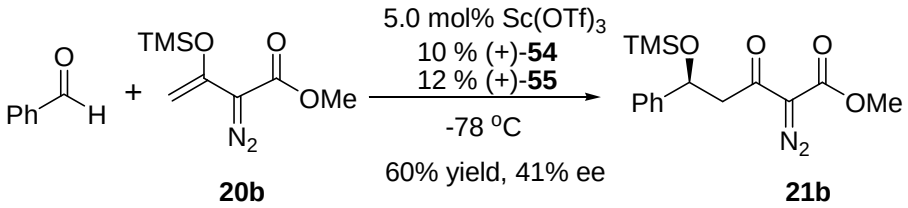
entry	L (6 mol%)	Yield[%]	ee[%]
1	(*S,S*)-*t*Bu-BOX (**59**)	90	3
2	4(*S*)-*i*Pr-PYBOX (**58**)	78	0
3	(*S,R,*S′R′)-cyclopropylindane BOX (**54**)	91	2

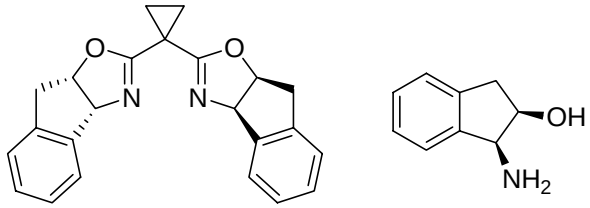
Evans and co-workers have reported their observation that the chiral product from the indole Friedel-Craft alkylation reaction (*Scheme 2.23*) leads to enhanced enantioselectivity.[51] Kobayashi and co-workers in their effort utilized the tetradentate bipyridyl ligand (**43**) to achieve enantiocontrol in hydroxymethylation.[50] We thought that using two ligands might be beneficial as this would block the co-ordination sites around Sc(III) and might result in conformational stability of the resulting aldehyde-metal complex. One added advantage of this approach would be the requirement of two easily available ligands instead of a synthetically challenging multidentate ligand. To test this hypothesis we first looked for some common ligands. Although PYBOX ligands have been used extensively by Evans' group, the Lewis basic pyridine moiety in PYBOX ligands reduce the Lewis acidity of Sc(III).[49] Instead we preferred to use cyclopropylindane-bis-oxazoline ligand, as it is the only bisoxazoline ligand which is known to form complexes with lanthanide atoms.[111] The first combination we tried was (*S,R,*S′R′)-cyclopropylindane-bis-oxazoline (**54**) and (*R,S*)-1-amino-2-indanol (**55**). The

(111) (a) Sibi, M. P.; Shay, J. J.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.***1998**, *120*, 6615-6616. (b) Aspinal, H. C. *Chem. Rev.* **2002**, *102*, 1807-1850.

reaction proceeded to give 60% chemical yield of the aldol adduct with 41% ee and provided the much needed proof of principle.

Scheme 2.43:

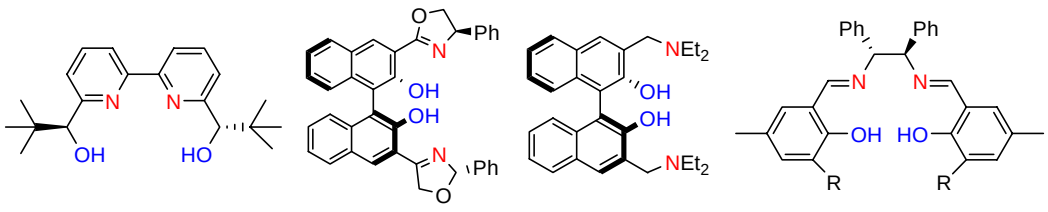




54 **55**

This encouraging result prompted us to look for more effective ligand combinations. While selecting the ligands for the Mukaiyama aldol addition of vinyldiazoacetates, we analyzed the structural features of some multidentate ligands used to make effective catalysts with lanthanide metals. A number of such ligands contain two sp^2 hybridized neutral N-atoms along with two free –OH functionalities (as shown in *Scheme 2.44*).

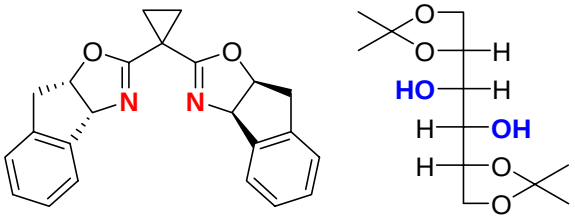
Scheme 2.44:



43 **47-*SR*** **49** **56**

These structural features of the ligands were thought to be important and formed the basis of our ligand-pair screening. Bulky (*S,R,*S′R′)-cyclopropylindane indane-bis-oxazoline (**54**) and commercially available inexpensive 1,2:5,6-di-isopropylidine *D*-mannitol (**57**) were selected on the basis of their similarity in binding motifs of the above multidentate ligands (*Scheme 2.45*). (*S,R,*S′R′)-cyclopropylindane-bis-oxazoline (**54**) was chosen because it is less basic compared to PYBOX ligands and also had two sp^2 hybridized N-atoms suitably placed for co-ordination. Di-isopropylidine *D*-mannitol (**57**) was thought to be suitable as it has two secondary free –OH groups and two bulky disiopropylidine moieties for further steric congestion.

Scheme 2.45:

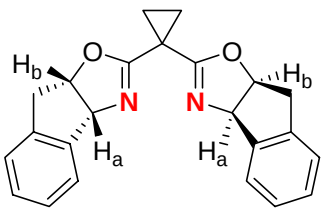


54 **57**

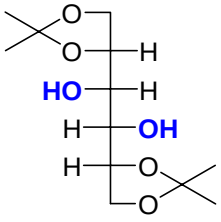
$Sc(OTf)_3$ is very sparingly soluble in dry dichloromethane, so are mixtures of $Sc(OTf)_3$ and (*S,R,*S′R′)-cyclopropylindane-bis-oxazoline (**54)** or $Sc(OTf)_3$ di-isopropylidine *D*-mannitol (**35)** in 1:1 and 1:2 ratios (entries 2, 3, 4 and 5 in *Table 2.9*). But to our surprise $Sc(OTf)_3$ in combination with (*S,R,*S′R′)-cyclopropylindanebisoxazoline (**54)** and di-isopropylidine *D*-mannitol (**35)** (Scheme 2.46) in 1.0:1.2:1.3 ratio immediately makes a clear pale greenish yellow solution in dry dichloromethane.

2.3.2. NMR Studies of The Catalyst Synthesis:

The ^{1}H NMR spectrum of the clear pale greenish solution formed by $Sc(OTf)_3$ in combination with (*S,R,*S′R′)-cyclopropylindanebisoxazoline (**54)** and di-isopropylidine *D*-mannitol **(35)** in 1.0:1.2:1.3 ratio in $CDCl_3$ were recorded. The peaks corresponding to H_a shifted downfield from 7.42 ppm to 7.71 ppm. The hydrogen atoms in the aromatic ring also changed. Two of the aromatic hydrogen atoms moved downfield from 7.21 ppm to 7.24 ppm. H_b protons on the other hand moved downfield by almost 0.4 ppm. One of the two pairs of benzylic hydrogens in **54**, moved upfield, while the others shifted downfield. The chemical shift corresponding to di-isopropylidine *D*-mannitol **(35)** also suffered changes. These data although do not provide the structural details of the chemical entity of the mixture, but they suggest the formation of a discrete complex. The spectral data have been provided in the experimental section. Mixing either $Sc(OTf)_3$ and either **54** or **55** do not change the chemical shifts for either **54** or **55**. Mixing **54** and **55** in 1.2:1.3 ratio does not bring any changes to the chemical shifts of the ligand protons.



54



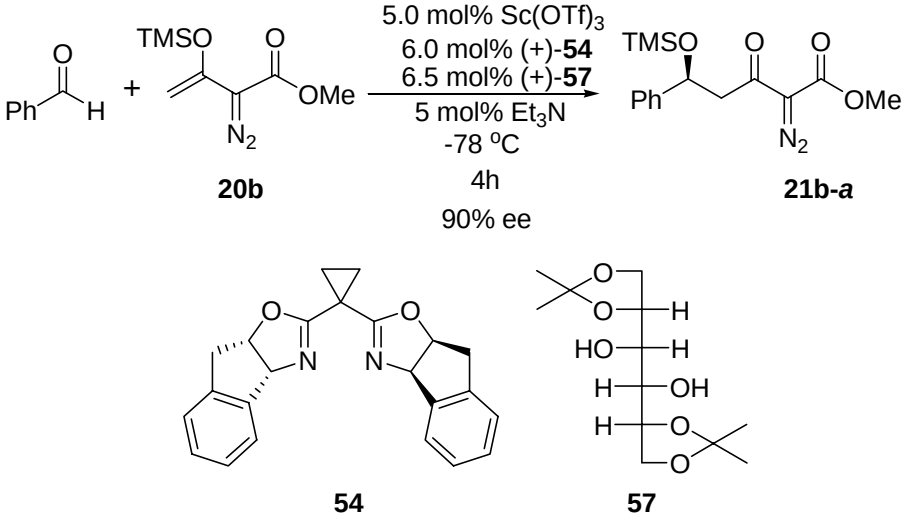
57

This ^{1}H NMR data as well as the formation of a clear solution clearly indicates the formation of a discrete complex with scandium. Efforts to crystallize this complex in various solvent systems (DCM, DCM-Hexane, DCM-THF) were unsuccessful.

2.3.2.3. Results and Discussions:

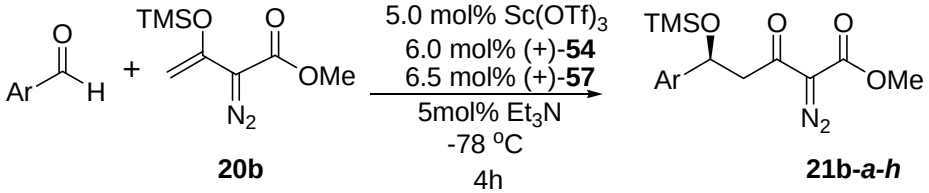
When the Mukaiyama aldol addition reaction between vinyldiazoacetate **20b** and benzaldehyde at –78 ^{o}C was carried out in a solution of 5 mol% $Sc(OTf)_3$, 6 mol% (+)-**54** and 6.5 mol% (+)-**57** in dichloromethane, the aldol adduct was obtained in 98% isolated yield and 83% enantiomeric excess. Addition of 5% triethylamine increased the ee to 90% without diminishing the product yield.

Scheme 2.46:



This chiral catalyst system was found to be very effective overall for aromatic aldehydes (entries 21b-a-h in Table 2.8). However, aliphatic aldehydes (*n*-octanal) underwent the addition with lower enantiocontrol.

Table 2.8: Asymmetric Mukaiyama aldol reaction of vinyldiazoacetate **20b**.



20b **21b-*a-h***

entry	Ar	Yield (%)[a] of 21b	ee (%)[b] of 21b
21b-a	Ph	97	90
21b-b	4-$MeOC_6H_4$	98	88
21b-c	4-MeC_6H_4	96	94
21b-d	4-ClC_6H_4	97	95
21b-e	β-styryl	93	87
21b-f	4–$NO_2C_6H_4$	34	--
21b-g	*n*-heptyl	87	33
21b-h	2-Fural	--	--

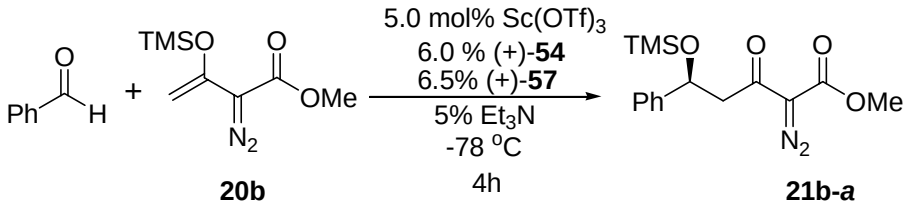
[a] Yield of isolated **21b** following column chromatography (see Supporting Information). [b] Determined by chiral HPLC (See the supporting information for details).

2.3.4. Control Experiments:

The effects of various reaction parameters on the chemical yields and enantioselectivity are summarized in Table 2.8. Control experiments using only (*S,R,*S′R′)-cyclopropylindanebisoxazoline 5**4** (entry 2 and 3 in Table 2.9) or di-isopropylidine *D*-mannitol **57** in different ratios (entry 4 and 5) with $Sc(OTf)_3$ do not form a clear solution and do not provide very high product conversion, and product is

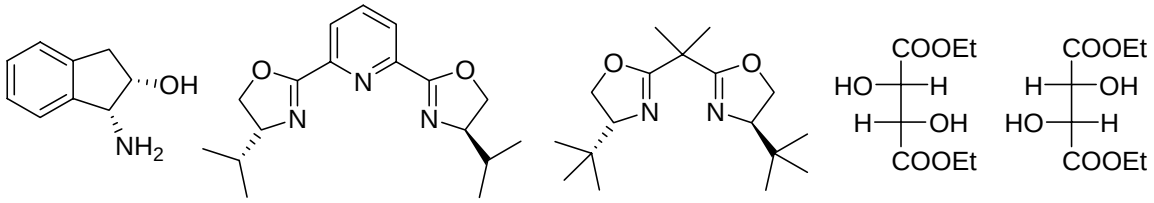
formed with no enantiocontrol. But when (4*S*)-iPr-PYBOX (**58**) was used in place of **54** the yields were high but the enantioselectivity was found to be moderate (57%). Addition of 10 mol% Et_3N surprisingly stops the reaction and crude ^1H NMR spectra of the reaction mixture was matched with un-reactive starting materials.

Table 2.9: Control Experiments



Entry	Change from Standard Condition	yield [%][a]	ee [%][b]
1	None	98	90
2	6.0% (+)-**54**; no (+)-**57**	70	7
3	12% (+)-**54**; no (+)-**57**	78	11
4	6.5% (+)-**57**; no (+)-**54**	88	3
5	13% (+)-**57**; no (+)-**54**	88	3
6	6.0% (+)-**54** and 13% cyclohexanol	78	7
7	6.0% (+)-**54** and 6.5% (+)-**56**	60	40
8	6.0% (+)-**58** and 6.5% (+)-**57**	89	57
9	6.0% (+)-**59** and 6.5% (+)-**57**	90	3
10	6.0% (-)-**54** and 6.5% (+)-**57**	90	45
11	6.0% (+)-**54** and 6.5% (+)-**60-*D***	92	34
12	10% Et_3N	0	-

[a]Isolated Yield, [b]Determined by Chiral HPLC using Chirapack AD column using the TMS-deprotected aldol adduct

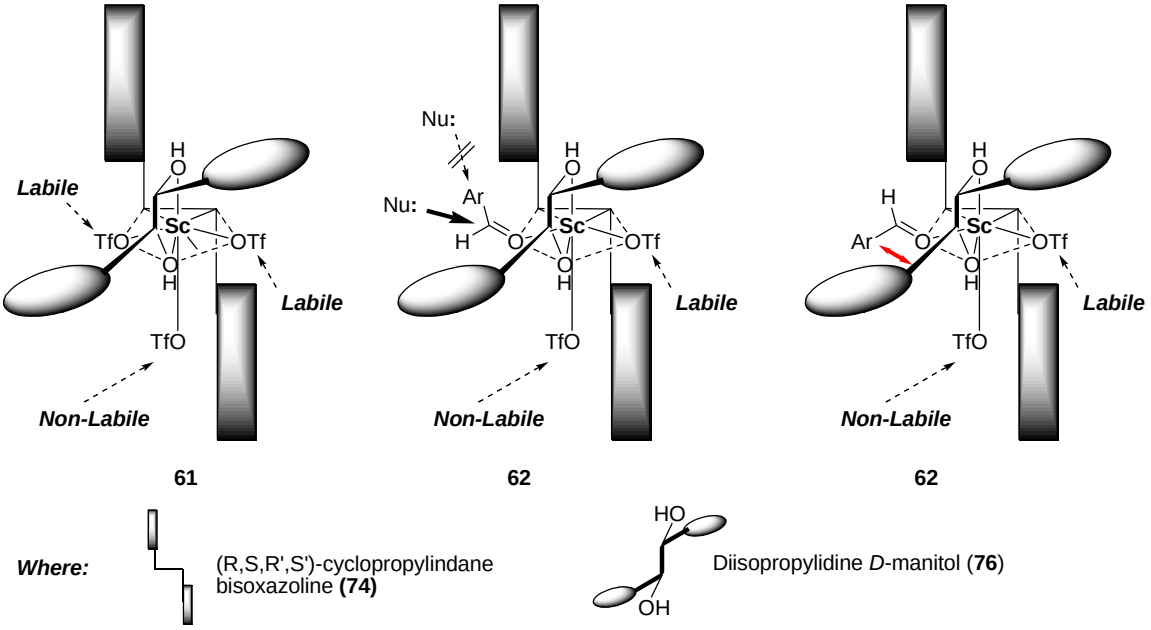


56-SR **58** **59** **60-D** **60-L**

2.3.2.5. Plausible Model for Enantioselection:

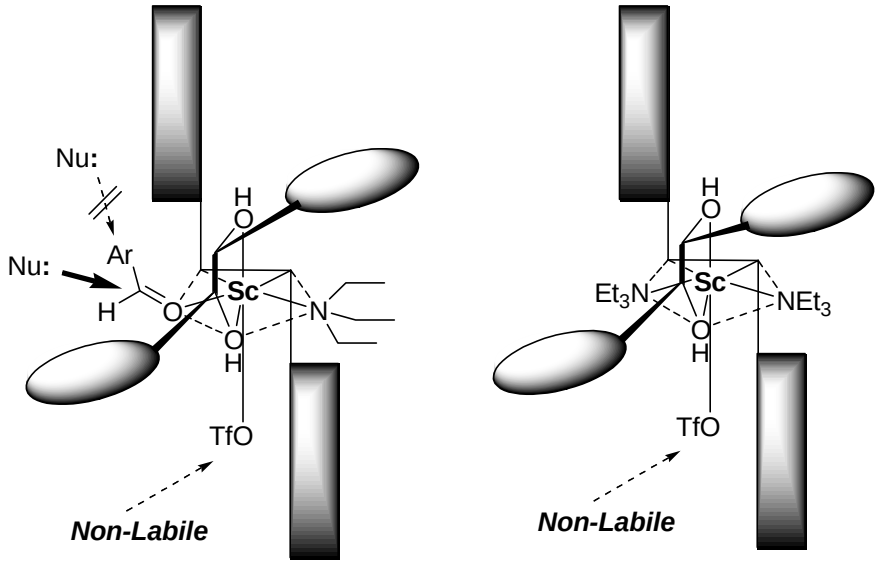
Without a crystal structure to describe the structure of the mixed ligands (heterochiral) Sc(III)-catalyst obviously includes several assumptions. Considering the bulky nature of both the ligands and also considering the proposal put forward by Evans and co-workers[49], we presume that a complex like **61** is formed; the bulky groups are placed as far apart as possible. Furthermore, among three triflates, it can be assumed that the axial triflate is least labile considering the more ionic nature of the axial ligand-Sc(III) bonds.[45] Therefore, according to this model, carbonyl oxygen of aldehyde will replace one of the two apical triflates (two triflates are in two pseudo-C_2-symmetric co-ordination sites for aldehyde binding) to form an outer sphere complex. Once aldehyde binds to Sc(III), steric crowding might lead to conformational rigidity of the aldehyde-metal complex and allow the nucleophile to come from the same face (as shown in **62** and **63**) and hence control the enantioselectivity.

Scheme 2.47:



The increase in enantioselectivity by adding 1-equivalent of triethylamine can be explained by the fact that it blocks one of the two apical co-ordination sites available for aldehyde binding (**64**) and in that process by virtue of its own bulkiness, makes the remaining co-ordination site more compact (Scheme 2.49). Adding two equivalents of triethylamine according to this hypothesis should shut down the reaction, and that is exactly what has been observed (Scheme 2.48).

Scheme 2.48:



64 **65 (*Catalytically Inactive*)**

Finally, it is really difficult to propose a concrete model for enantioselectivity observed with the heterochiral complex, particularly when the details of the structural features of this complex are not known.

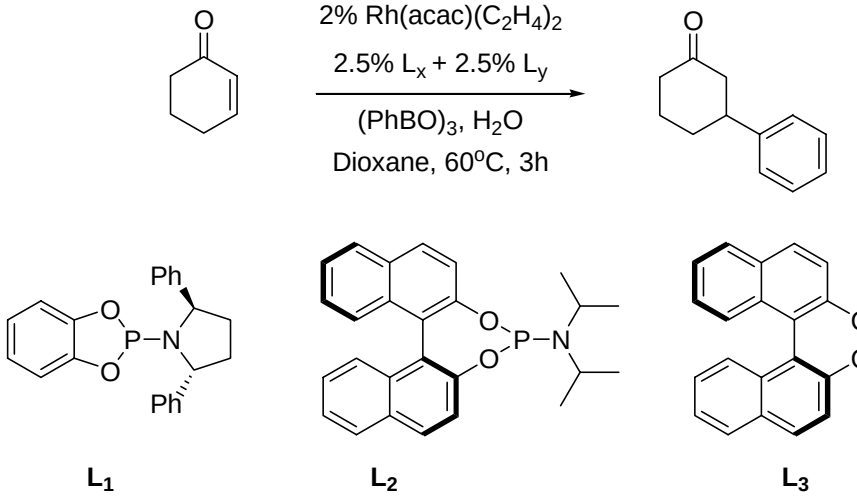
2.3.4. Critical Analysis and Comparison with Reported Heterochiral Catalysts:

2.3.4.1. Heterochiral Systems with Transitional Metals:

The efficacy of heterochiral complexes in asymmetric catalysis has been demonstrated by various groups. Recently Feringa and co-workers have reported the first example of improved catalytic asymmetric C—C bond formation using two monodentate

ligands.[112] In this communication they have shown the effectiveness of using hetero combination of two monodetate ligands over their homo combinations. While mixing L_1 and L_2, a huge change in the chemical yield was observed as well as a significant increase in enantioselectivity. The most surprising result was the formation of different enantiomers with the combinations L_1/L_3 and L_2/L_3.

Table 2.10:



L_X/ L_Y	Conv[%]	ee[%]	L_X/ L_Y	Conv[%]	ee[%]
L_1/ L_1	26	33	**L_1/ L_2**	93	75
L_2/ L_2	22	-27	**L_1/ L_3**	40	77
L_3/ L_3	18	-16	**L_2/ L_3**	16	-60

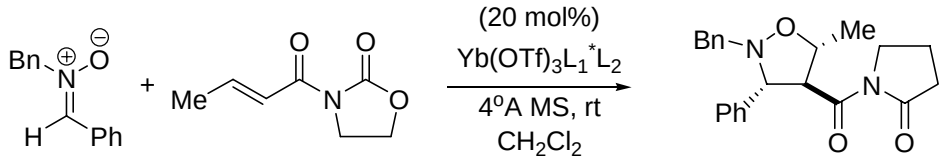
(112) Duursma, A.; Hoen, R.; Schuppan, J.; Hulst, R.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2003**, *5*, 3111-3113.

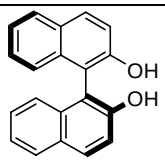
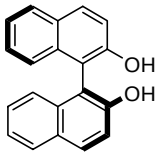
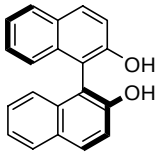
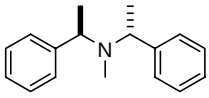
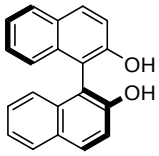
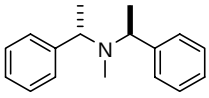
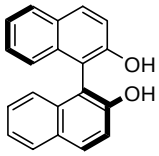
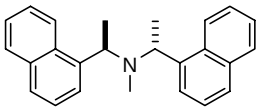
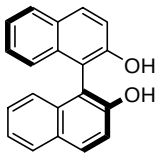
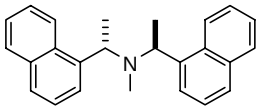
2.3.4.2. Heterochiral Systems with Lanthanide Metals:

Kobayashi and co-workers were the first group to report a mixed ligand lanthanide complex (heterochiral catalyst) catalyzed enantioselective transformation, where they executed asymmetric 1,3-dipolar cycloadditions between nitrones and alkenes.[113] 1,3-dipolar cycloadditions between nitrones and 3-(2-alkenoyl)-1,3-oxazolidine-2-ones using their heterochiral catalyst produced the adduct with high yields, diastereo- and enantioselectivity. They also obtained high enentiocontrol from alkenes with monodentate co-ordination (N-phenylmaleimide). This result is particularly interesting because it has shown the efficacy of heterochiral Yb(III) catalyst to produce good selectivity even with monodentate co-ordination of the substrate.

(113) Kobayashi, S.; Kawamura, M. *J. Am. Chem. Soc.* **1998**, *120*, 5840-5841.

Table 2.11:



Entry	L_1^*	L_2	yield [%][a]	ee [%][b]
1		Et_3N	65	63
2		*i*-Pr_2Net	73	62
3			92	71
4			80	35
5			92	96
6			87	62

2.3.4.3. Implications of the Study:

The combination of scandium triflate, (*S,R,*S′R′)-cyclopropylindanebisoxazoline 5**4** and di-isopropylidine *D*-mannitol (**57**) is to best of our knowledge, the first example of a truly heterochiral lanthanide catalyst development based on design principle for a rather complex reaction and its successful execution in a highly enantioselective Mukaiyama aldol addition reaction. The design of the catalyst was based on the pattern of the previously developed catalysts and observations reported by various groups. This study thus demonstrates the possible applications of using two simple ligands instead of using synthetically challenging multidentate ligands to make efficient lanthanide catalyst. Furthermore, this led to the development of a straightforward synthetic methodology for chiral highly functionalized diazo compounds starting from cheap commercially available materials.

2.4. Experimental:

2.4.1. General Information:

Reactions were performed in oven-dried (140 ^{o}C) or flame-dried glassware under an atmosphere of dry nitrogen. Dichloromethane was passed through a solvent column prior to use and was not distilled. Tetrahydrofuran and diethyl ether were distilled over sodium/benzophenone ketyl. Thin layer chromatography (TLC) was carried out using EM Science silica gel 60 F_{254} plates. The developed chromatogram was analyzed by UV lamp (254 nm), ethanolate phosphomolybdic acid, potassium permanganate ($KMnO_4$) or

cerium ammonium molybdate (CAM). Liquid chromatography was performed by flash chromatography on silica gel (230-400 mesh). Silver(I) triflate was purchased from Aldrich and used as received. (*S*)-BINOL, (*S*)-BINAP, (*R*)-tol-BINAP were purchased from Strem. Methyl diazoacetoacetate was obtained from methyl acetoacetate and mesyl azide following the method reported by Boyer and co-workers.[114]

2.4.2. Synthesis of Methyl 3-Trimethylsilanyloxy-2-diazobut-3-enoate (21b)[43]

To an oven-dried 250 mL round-bottom flask were added 3.90 g (27.4 mmol) of methyl diazoacetoacetate and 3.84 ml (27.4 mmol) of triethylamine sequentially, followed by 100 mL anhydrous dichloromethane and the resultant solution was stirred at room temperature for 30 min. The reaction mixture was then cooled to 0^{o}C and 6.09 g (27.4 mmol) of trimethysilyl trifluoromethanesulfonate (TMS-OTf) was added dropwise *via* a 10-mL syringe over 10 min. The resultant orange solution was stirred at 0 ^{o}C for an additional 30 min before warming up to room temperature and the reaction mixture was concentrated to ~5 mL, and then anhydrous hexane (50 mL) was added. The mixture was stirred for 20 min at ambient temperature and was then kept undisturbed for 10 min. Two immiscible liquid layers appeared over that time. The top orange hexane layer was decanted and passed through a funnel fitted with a cotton plug. The solvent was removed under reduced pressure to give methyl 3-trimethylsilanyloxy-2-diazobut-3-enoate as a bright orange liquid (9.8 g, 92 %).

2.4.3 General Procedure for Asymmetric Mukaiyama Aldol Addition

(114) Boyer, J.H.; Mack, C. H.; Goebel, W.; Morgan, L. R. Jr. *J. Org. Chem.* **1959**, *23*, 1051-1052.

2.4.3.1. General procedure for Asymmetric Mukaiyama Aldol Addition of Vinyldiazoacetate by Ag(I)/BINAP Catalyst:

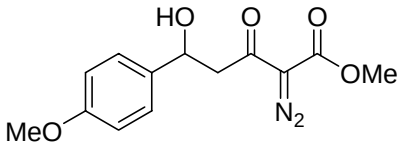
To an oven-dried 5-mL round-bottomed flask containing a stir bar and fitted with a septum, were added (*S*)-BINAP (21 mg, 0.033 mmol), KF (3.2 mg, 0.055 mmol), 18-crown-6 (14 mg, 0.055 mmol) and anhydrous AgOTf (14 mg, 0.055 mmol) followed by 1 mL dry THF *via* syringe. The reaction mixture was stirred for 10 min at room temperature before cooling to –20 ^{o}C. Methyl 3-trimethylsilanyloxy-2-diazobut-3-enoate (120 mg, 0.550 mmol) was then added drop wise using a 1-mL syringe, followed by benzalaldehyde (58 mg, 0.55 mmol). The flask was kept at –20 ^{o}C for 6 h under nitrogen with stirring. Then the reaction mixture was treated with brine (5 mL) and solid KF (ca. 1 g) at ambient temperature for 30 min. The resulting solution was then extracted with CH_2Cl_2 (3x1mL) and dried over anhydrous Na_2SO_4. Enantiomeric excesses of the products from the asymmetric Mukaiyama aldol addition were determined by chiral stationary phase HPLC analysis using a Daicel Chirapack AD-H chiral column (0.5 cm x 25 cm).

2.4.3.1. General procedure for Asymmetric Mukaiyama Aldol Addition of Vinyldiazoacetate by Sc(III)/Heterochiral Catalyst:

To an oven-dried 5-mL round-bottomed flask containing a stir bar and fitted with a septum, were added (*R,S,R′,S′*)-cyclopropylindanebisoxazoline (12 mg, 0.033 mmol),

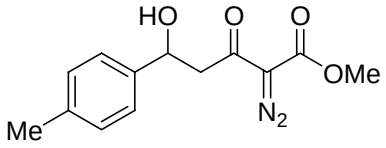
1,2:5,6-di-isopropylidine-*D*-mannitol (10 mg, 0.036 mmol) and anhydrous scandium triflate (13 mg, 0.028 mmol) followed by 1 mL dry dichloromethane *via* syringe. To the reaction mixture was added distilled triethylamine (0.3 mg, 0.028 mmol) *via* a 10-μL microsyringe. The clear pale yellow solution was stirred at room temperature for 30 min, before transferring the clear solution to an oven-dried 5-mL round-bottomed flask containing a stir bar and 20 mg 4 Å molecular sieve and fitted with a septum. The reaction mixture was stirred for 10 min at room temperature before cooling to –78 ^{o}C. Methyl 3-trimethylsilanyloxy-2-diazobut-3-enoate (120 mg, 0.550 mmol) was then added drop wise using a 1-mL syringe, followed by benzalaldehyde (58 mg, 0.55 mmol). The flask was kept at –78 ^{o}C for 4 h under nitrogen with stirring. The reaction was quenched with 0.5 mL saturated sodium bicarbonate solution. The reaction mixture was treated with brine (5 mL) and solid KF (ca. 1 g) at ambient temperature for 30 min. The resulting biphasic mixture was stirred vigorously for 1 h, and the organic phase was then extracted with CH_2Cl_2 (3x1mL) and dried over anhydrous Na_2SO_4. **21b-a**[115] and **21b-e**[116] have been prepared previously and their full spectroscopic data was reported. Enantiomeric excesses of the products from the asymmetric Mukaiyama aldol addition were determined by chiral stationary phase HPLC analysis using a Daicel Chirapack AD-H chiral column (0.5 cm x 25 cm).

(115) Calter, M. A.; Sugathapala, P. M.; Zhu, C. *Tet. Lett.* **1997**, *38*, 3837-3840.
(116) Deng, G.; Tian, X.; Qu, Z.; Wang, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2773-2776.



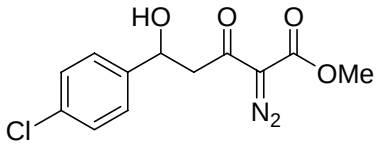
21b-b

Methyl 2-Diazo-5-hydroxy-5-(*p*-methoxyphenyl)-3-oxopentanoate (21b-b). IR (neat): 3509, 2912, 2138, 1720, 1641, 1508; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (d, J = 8.8 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 5.10 (dd, J = 7.8, 4.2 Hz 1H), 3.81 (s, 3 H), 3.78 (s, 3 H), 3.24-3.23 (comp, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 192.2, 161.5, 159.1, 135.0, 127.0, 114.3, 69.8, 55.2, 52.3, 48.5 (not seen, C=N_2); HRMS (FAB) for $C_{13}H_{14}N_2O_5$ $[M+H]^+$ calcd: 303.0940; found 303.0946; HPLC (Chirapack-AD): hexanes: *i*PrOH 85:15, 1.5 mL/min; minor 15.2 min, major 17.8 min (R_f = 0.37 in 4:1 hexane and ethyl acetate).



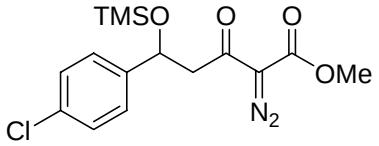
21b-c

Methyl 2-Diazo-5-hydroxy-5-(p-tolyl)-3-oxopentanoate (21b-c). IR (neat): 3507, 2908, 2135, 1727, 1651, 1441; ^{1}H NMR (400 MHz, $CDCl_3$):δ 7.26 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 5.15 (dd, *J* = 8.4, 3.6 Hz, 1H), 3.80 (s, 3 H), 3.31-3.20 (comp, 3H), 2.32 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): 192.1, 161.6, 139.8, 137.3, 129.1, 125.7, 70.1, 52.3, 48.6, 21.1 (not seen, C=N_2); HRMS (ESI) for $C_{13}H_{14}O_4N_2$ $[M+H]^+$ calcd: 263.1928; found 263.1932. HPLC (Chirapack-AD): hexanes: iPrOH 85:15, 1.0 mL/min; major 15.1 min, minor 16.8 min. (R_f = 0.37 in 4:1 hexane : ethyl acetate).



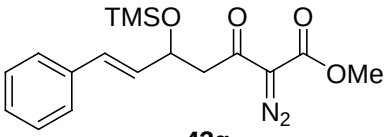
21b-d

Methyl 5-(*p*-Chlorophenyl)-2-diazo-5-hydroxy-3-oxopentanoate (21b-d). IR (neat): 3503, 2956, 2141, 1719, 1653, 1437, 1313; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.31 (comp, 4H), 5.16 (m, 1H), 3.81 (s, 3 H), 3.48 (bs, 1H), 3.23-3.20 (comp, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 192.1, 161.5, 142.7, 128.5, 127.7, 125.7, 70.3, 52.3, 48.6 (not seen, C=N_2); HRMS (FAB) for $C_{12}H_{11}ClN_2O_4$ $[M+Na]^+$ calcd: 305.0305; found 305.0322; HPLC (Chirapack-AD): hexanes: *i*PrOH 85:15, 1.0 mL/min; minor 16.1 min, major 18.9 min. (R_f = 0.4 in 4:1 hexane and ethyl acetate).



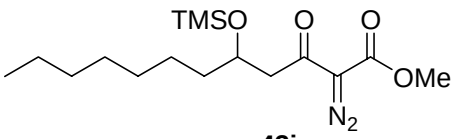
43c-b

2-Diazo-3-oxo-5-(4-chlorophenyl)-5-trimethylsilanyloxy-methylpentanoate (43c-b): IR (neat):3504, 2952, 2143, 1723, 1655; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.18 (comp, 5H), 7.24 (d, *J* = 8.8 Hz, 2H), 5.19 (dd, *J* = 8.8, 4.0 Hz 1H), 3.79 (s, 3 H), 3.32 (dd, *J* = 15.2, 8.8 Hz, 1H), 2.98 (dd, *J* = 15.2, 4.4 Hz, 1H), -0.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 190.2, 162.2, 143.2, 133.4, 128.8, 127.7, 70.9, 52.7, 50.9, 0.1 (not seen, C=N_2); HRMS for $C_{15}H_{19}O_4ClN_2Si$ [M+1] calcd: 354.8641; found 354.8646.



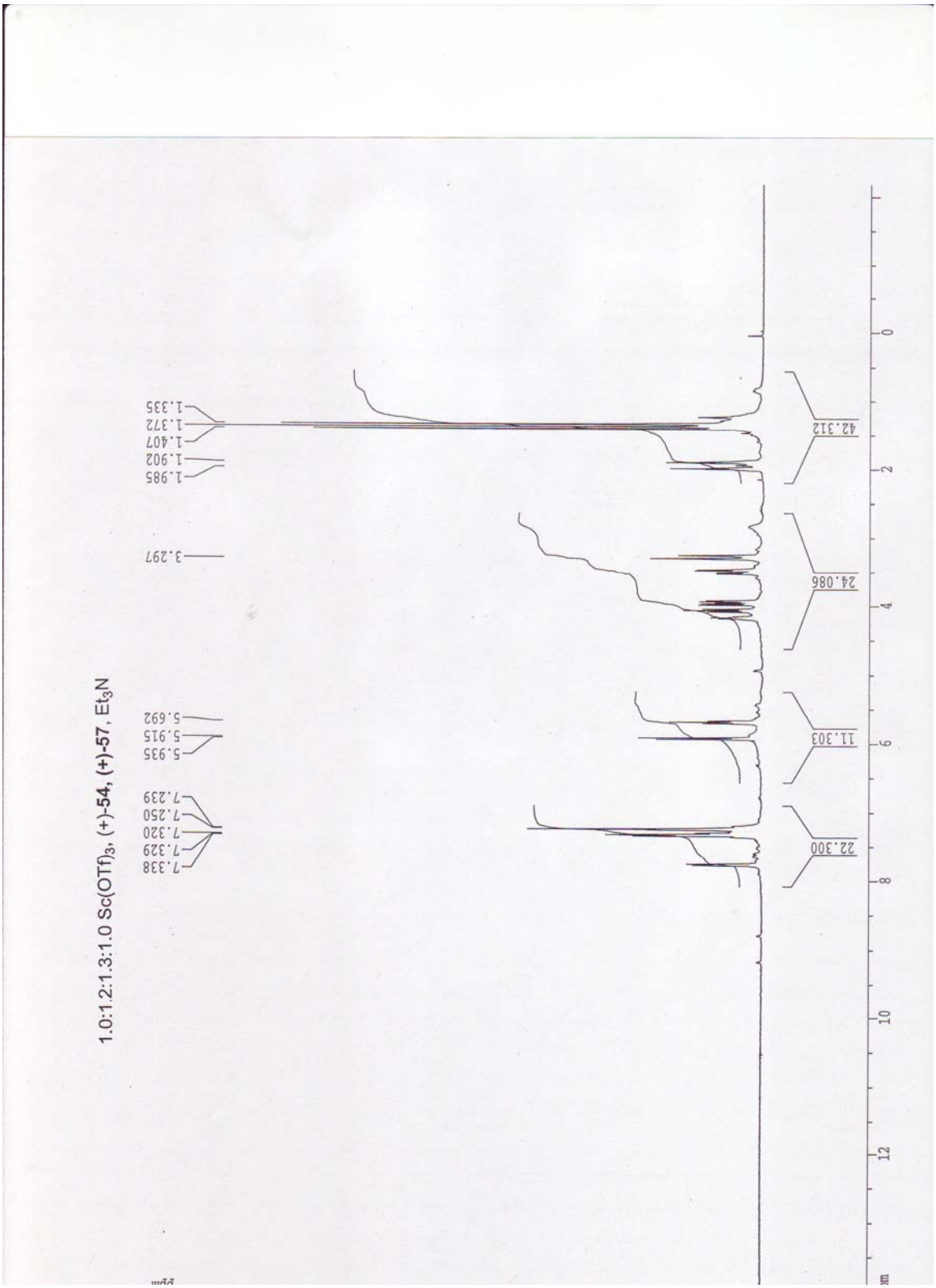
43g

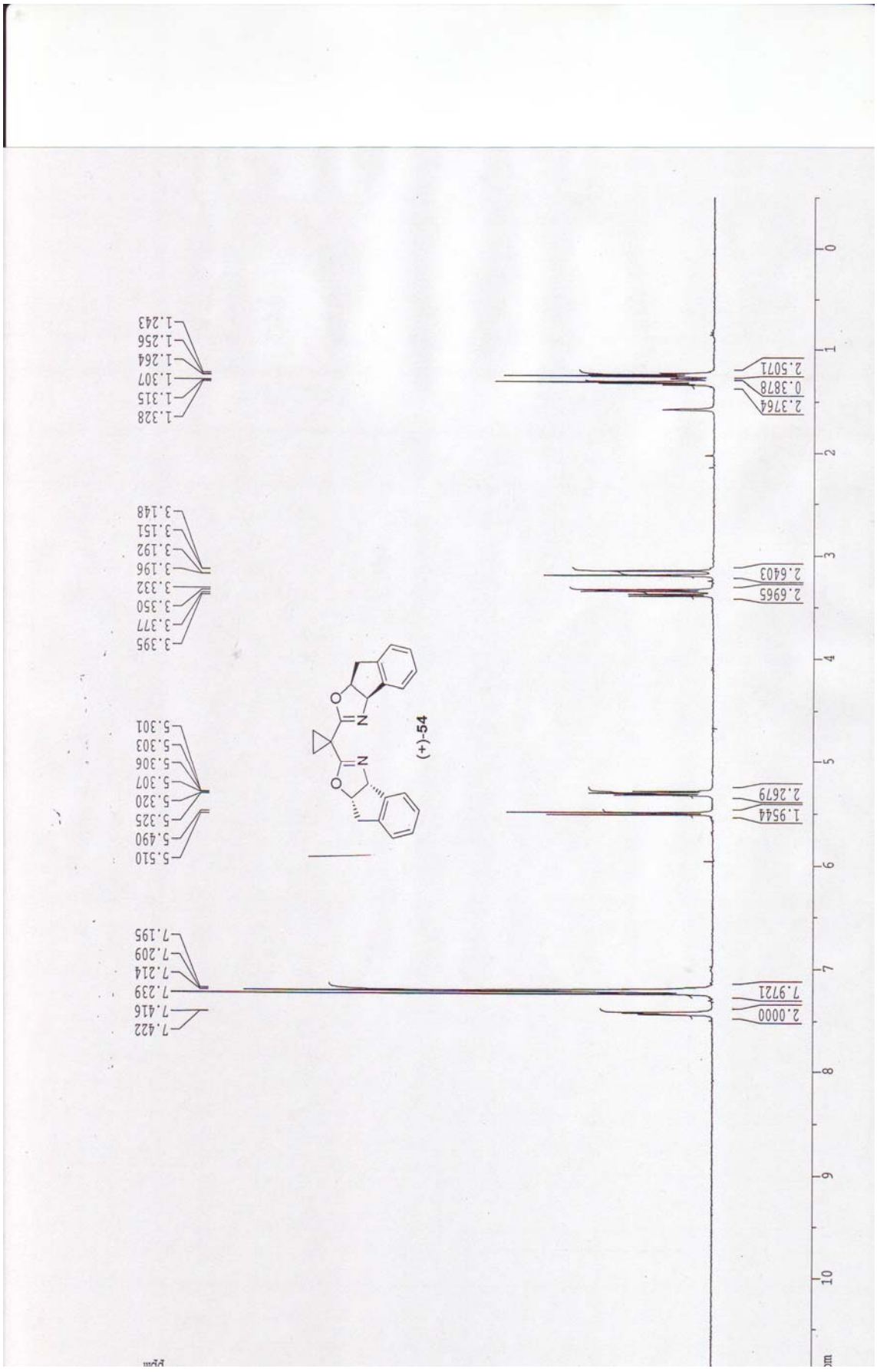
Methyl (*E*)-5-(trimethylsilanoxy)-2-diazo-3-oxo-7-phenylhept-6-enoate (43g). IR (neat): 2955, 2134, 1725, 1654 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.20 (comp, 5H), 6.54 (d, *J* = 15.6 Hz, 1H), 6.21 (ddd, *J* = 15.6, 6.0 Hz, 1H), 4.84 (ddd, *J* = 6.4, 5.6, 0.8 Hz, 1H), 3.81 (s, 3H), 3.32 (dd, *J* = 15.2, 6.4 Hz, 1H), 2.98 (dd, *J* = 15.2, 5.6 Hz, 1H), 0.10 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.0, 161.6, 136.7, 131.7, 129.7, 128.5, 127.5, 126.5, 69.9, 52.1, 46.2, 25.7, 1.9 (not seen, C=N_2); HRMS (ESI) for $C_{17}H_{22}N_2O_4Si$ $[M+Na]^+$ calcd: 346.4546; found 346.4529.

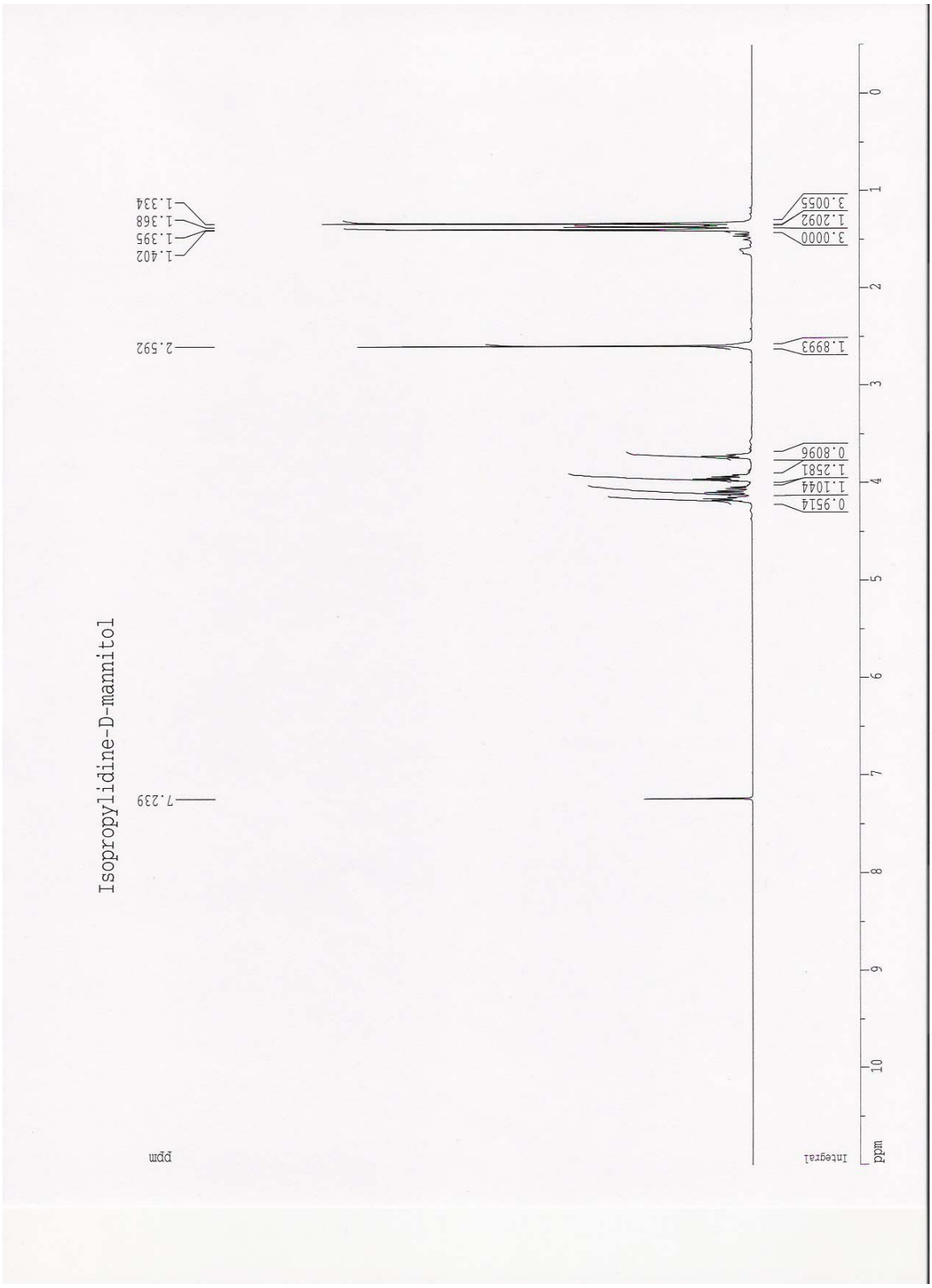


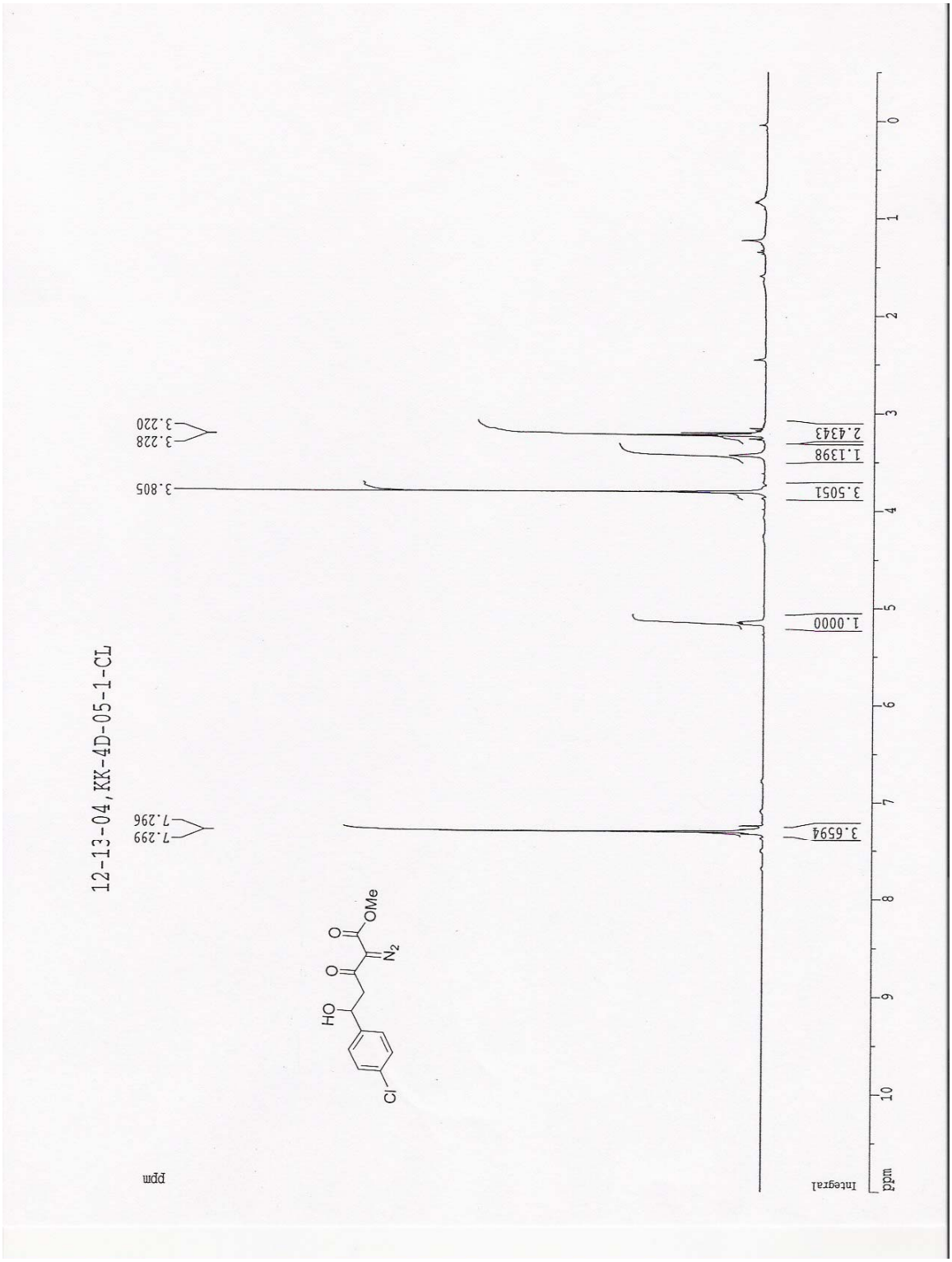
43j

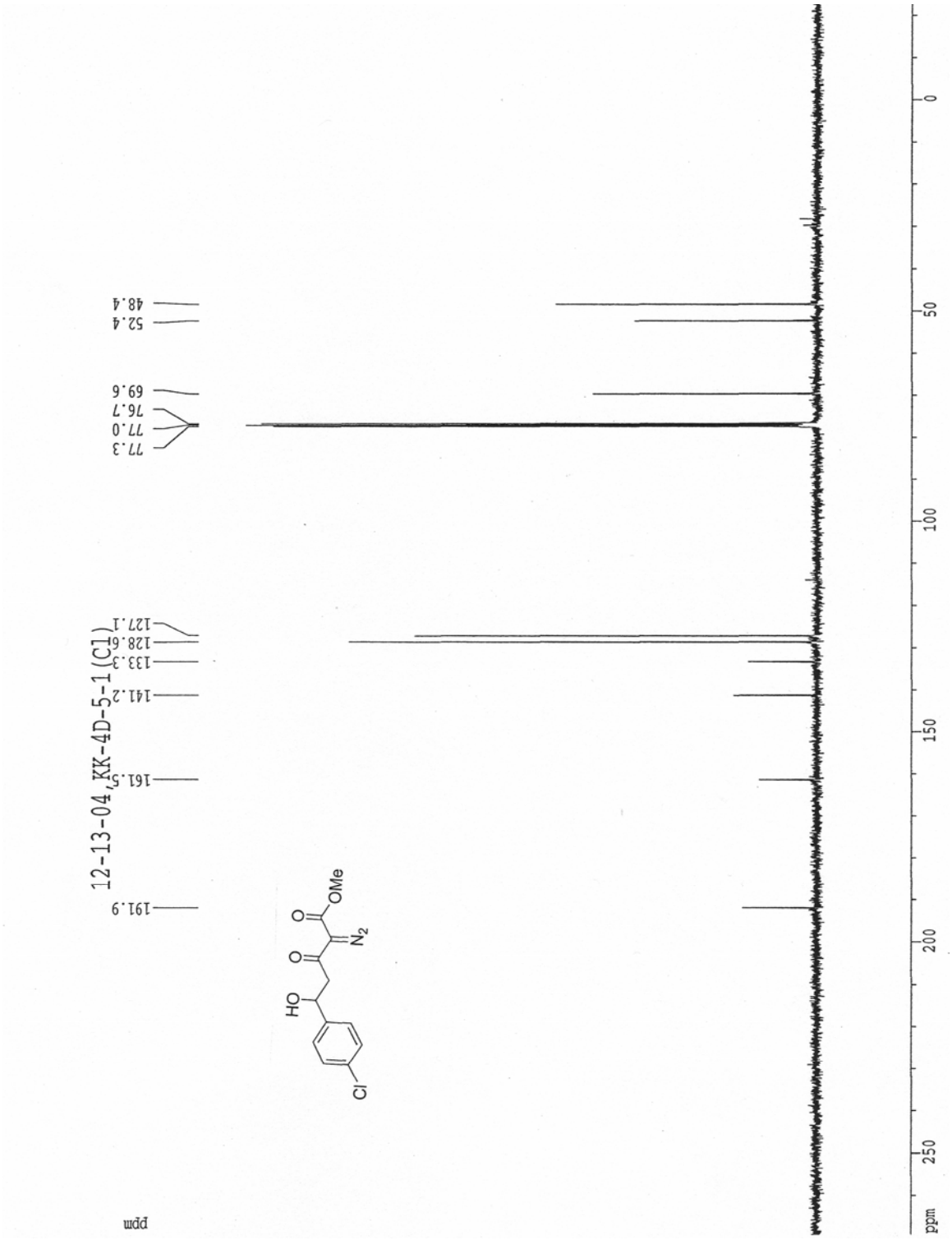
Methyl 5-(trimethylsilanoxy)-2-diazo-3-oxododecanoate (43j). IR (neat): 2929, 2856, 2134, 1731, 1653 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.14-4.08 (comp, 1H), 3.75 (s, 3H), 3.02 (dd, *J* = 15.2, 7.6 Hz, 1H), 2.78 (dd, *J* = 15.2, 4.8 Hz, 1H), 1.38 (comp, 2H), 1.20-1.16 (comp, 10H), 0.78 (t, *J* = 8.0 Hz, 3H), -0.01 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.6, 161.4, 69.0, 51.9, 47.5, 37.9, 31.7, 29.4, 29.1, 25.3, 22.5, 13.9, 0.02 (not seen, $C=N_2$); HRMS (FAB) for $C_{17}H_{22}N_2O_4Si$ $[M+H]^+$ calcd: 346.4523; found: 346.4541.

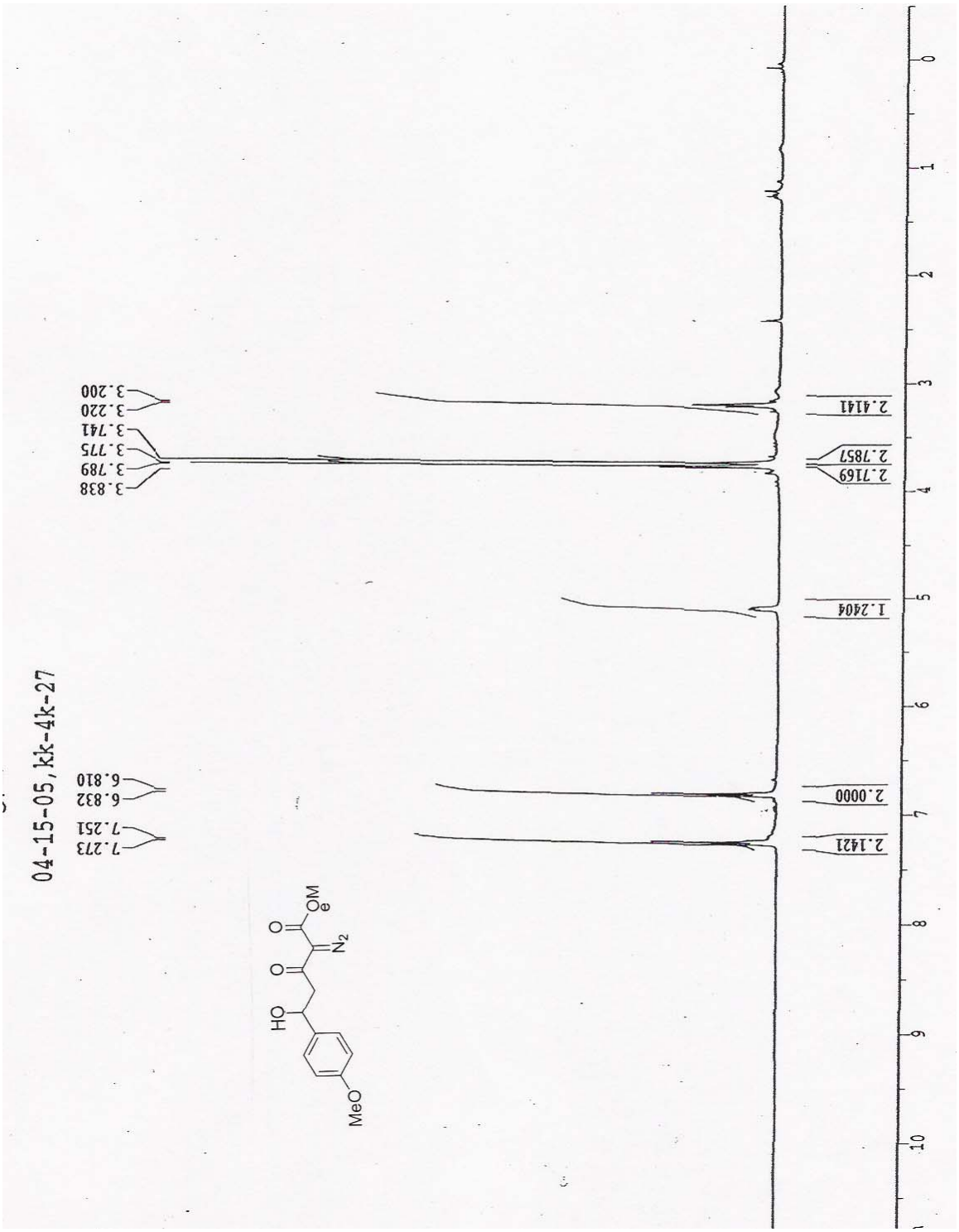

1.0:1.2:1.3:1.0 Sc(OTf)3, (+)-54, (+)-57, Et3N
1.335
1.372
1.407
1.902
1.985
3.297
5.692
5.915
5.935
7.239
7.250
7.320
7.329
7.338
42.312
24.086
11.303
22.300
0
2
4
6
8
10
12

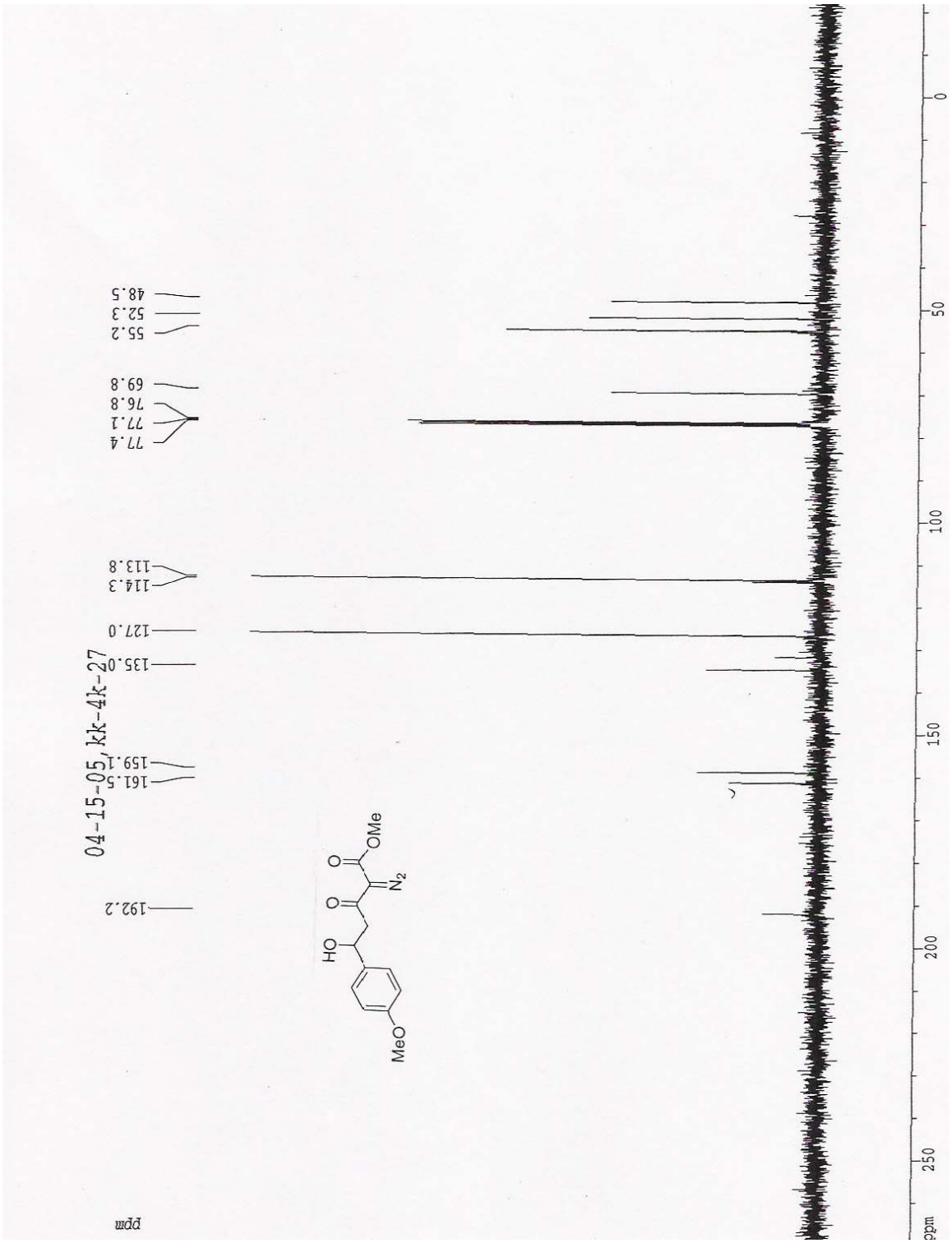

(+)-54
7.422
7.416
7.239
7.214
7.209
7.195
5.510
5.490
5.325
5.320
5.307
5.306
5.303
5.301
3.395
3.377
3.350
3.332
3.196
3.192
3.151
3.148
1.328
1.315
1.307
1.264
1.256
1.243
2.0000
7.9721
1.9544
2.2679
2.6965
2.6403
2.3764
0.3878
2.5071
ppm

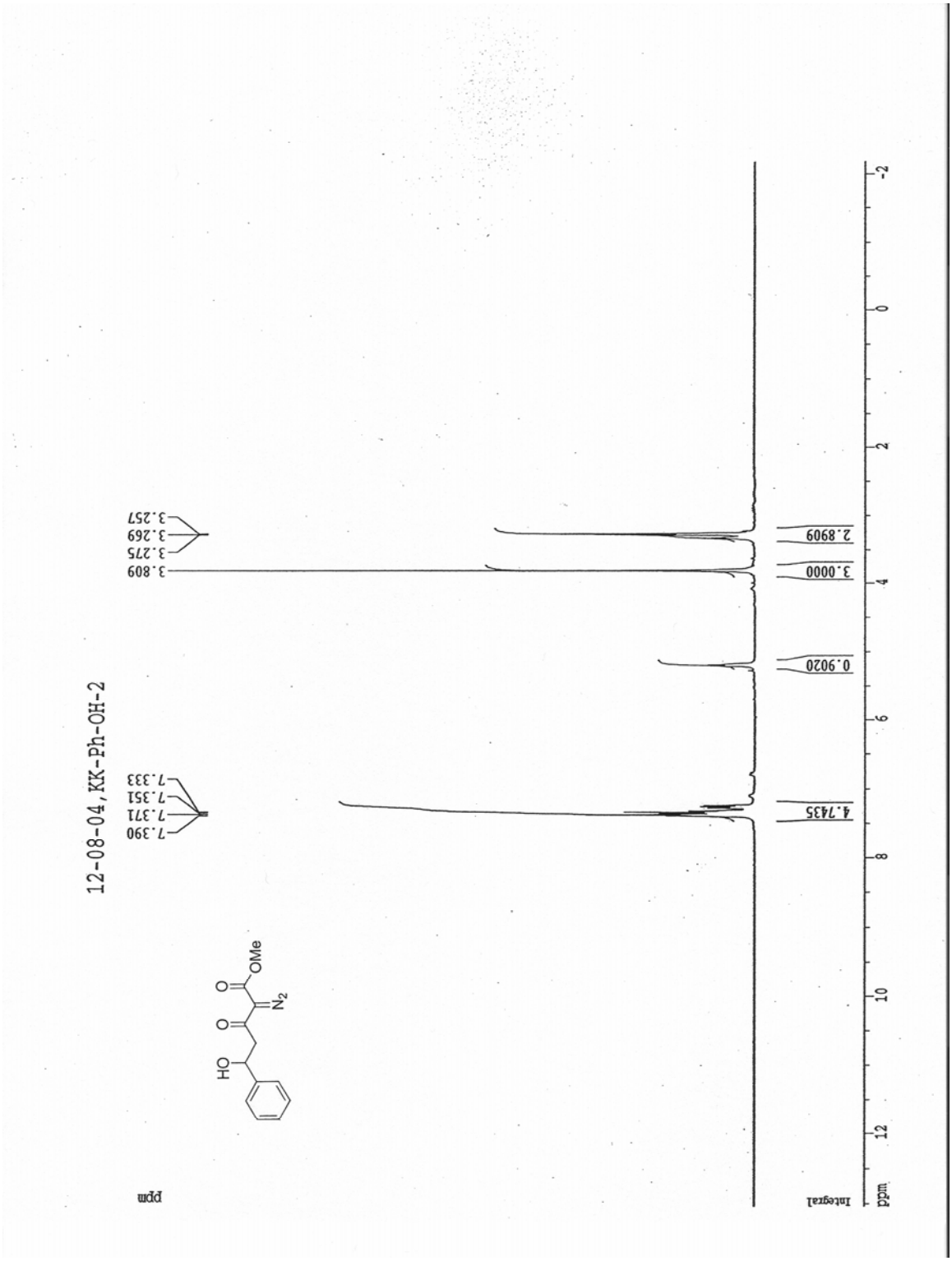

Isopropylidine-D-mannitol
ppm
7.239
2.592
1.402
1.395
1.368
1.334
Integral
0.9514
1.1044
1.2581
0.8096
1.8993
3.0000
1.2092
3.0055
ppm

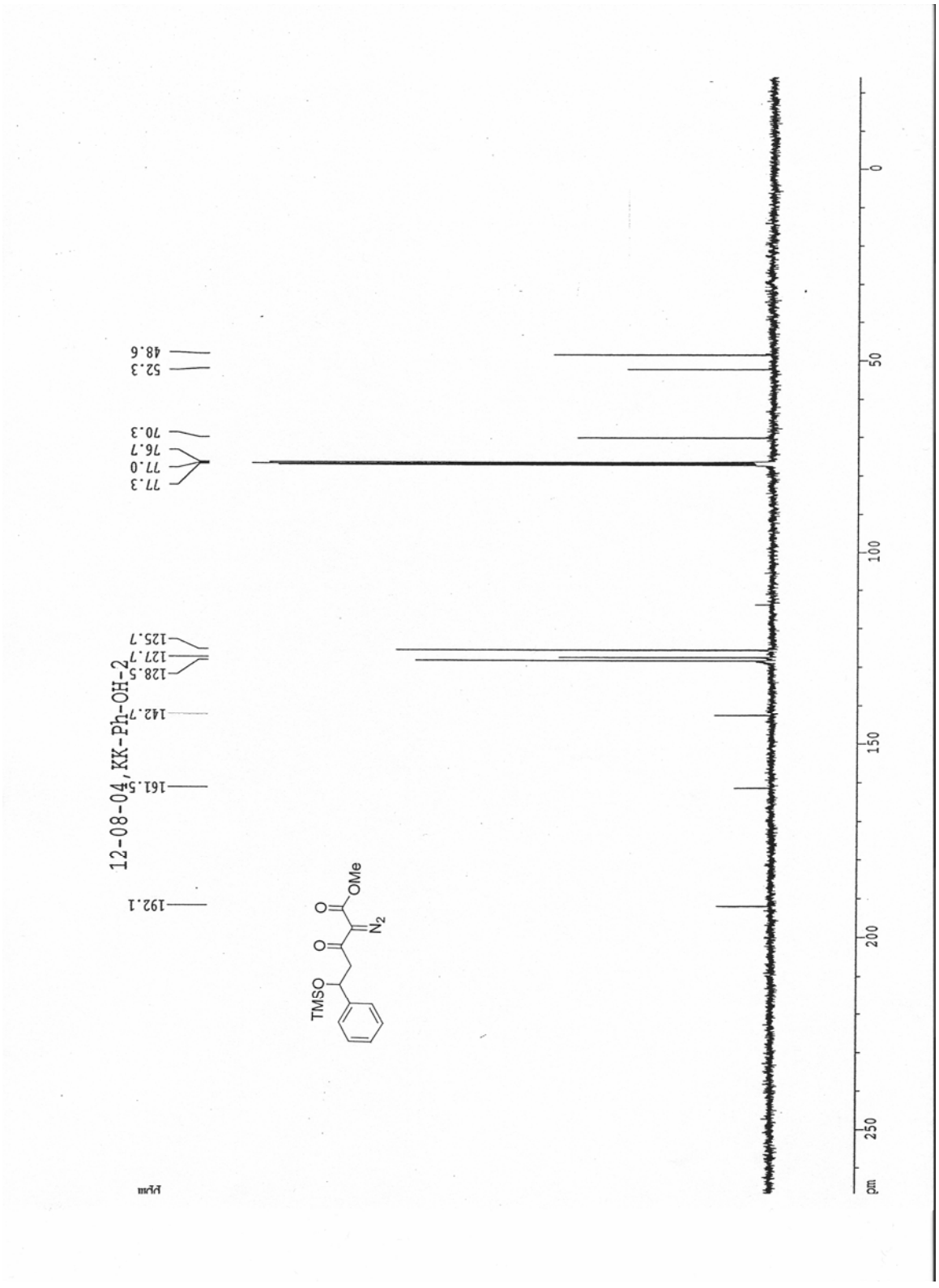

12-13-04,KK-4D-05-1-CL
7.299
7.296
3.805
3.228
3.220
3.6594
1.0000
3.5051
1.1398
2.4343
HO
O
O
OMe
N2
Cl
ppm
Integral


12-13-04,KK-4D-5-1(Cl)
191.9
161.5
141.2
133.3
128.6
127.1
77.3
77.0
76.7
69.6
52.4
48.4
OMe
O
O
N2
HO
Cl
ppm
0
50
100
150
200
250
ppm


04-15-05, kk-41k-27
7.273
7.251
6.832
6.810
3.838
3.789
3.775
3.741
3.220
3.200
2.1421
2.0000
1.2404
2.7169
2.7857
2.4141
HO
O
O
N2
OMe
MeO


04-15-05,kk-4k-27
192.2
161.5
159.1
135.0
127.0
114.3
113.8
77.4
77.1
76.8
69.8
55.2
52.3
48.5
HO
O
O
N2
OMe
MeO
ppm
0
50
100
150
200
250


12-08-04,KK-Ph-OH-2
7.390
7.371
7.351
7.333
3.809
3.275
3.269
3.257
4.7435
0.9020
3.0000
2.8909
OMe
N2
O
O
HO
PPM
Integral


12-08-04, KK-Ph-OH-2
192.1
161.5
142.7
128.5
127.7
125.7
77.3
77.0
76.7
70.3
52.3
48.6
TMSO
O
O
N2
OMe
ppm
250
200
150
100
50
0

Chapter 3:

Synthetic Applications of the Functionalized Diazoacetoacetates Prepared by Catalytic Mukaiyama Aldol Addition

3.1. *Introduction*

3.1.1. Rh(II)-Catalyzed Carbene Transformations:

Catalysts:

Dirhodium(II) complexes are the most effective and versatile catalysts for diazo decomposition.[117] Dirhodium(II) tetraacetate was first prepared and characterized in 1960s[118] and introduced as a catalyst for diazo decomposition by Teyssie and co-workers in 1973.[119] Since then $Rh_2(OAc)_4$ became the most widely used catalyst for metal carbene transformations.[120] Previously copper bronze, copper salts, particularly copper(II) sulfate and copper(II) bisacetylacetonate were known to be effective catalysts for diazo decomposition.[121]

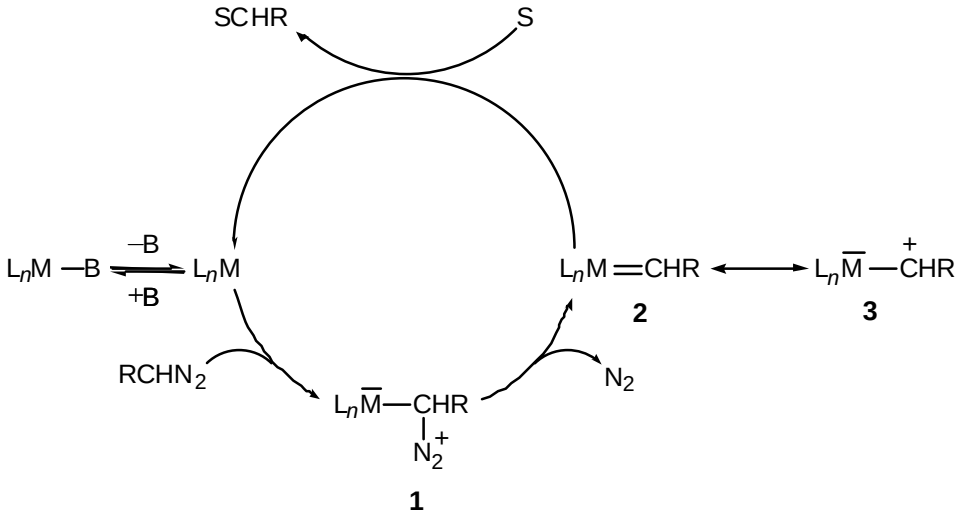
(117) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds,* John Wiley & Sons, Inc., New York, **1998**.
(118) (a) Nazarova, L. A.; Chernyaev, I. I.; Morozova, A. S. *Zh. Neorgn. Khim.* **1965**, *10*, 539-541. (b) Cotton, F. A.; Curtis, N. F.; Harris, C. B.; Johnson, B. F. G.; Lipperd, S. J.; Mague, J. T.; Robinson, W. R.; Wood, J. S. *Science*, **1964,** *145*, 1305-1307.
(119) Paulissenen, R.; Reimlinger, H.; Hayez, E.; Hubert, A. J.; Teyssie, P. H. *Tetrahedron Lett.* **1973**, *14*, 2233-2236.
(120) (a) Doyle, M. P. In *Modern Rhodium-Catalyzed Organic Reactions*, Evans, P. A. Ed.; Wiley-VCH, Weinheim, 2005, Chapter 15. (b) Davies, H. M. L.; Walji, A. M. In *Modern Rhodium-Catalyzed Organic Reactions*, Evans, P. A. Ed.; Wiley-VCH, Weinheim, 2005, Chapter 14. (c) Taber, D. F.; Joshi, P. V. In *Modern Rhodium-Catalyzed Organic Reactions*, Evans, P. A. Ed.; Wiley-VCH, Weinheim, 2005, Chapter 16. (d) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003***, 103*, 2861.
(121) Silberrad, O.; Roy, C. S. *J. Chem. Soc.* **1906**, *89*, 179-182.

Mechanism:

Through extensive research on rhodium(II) and copper(I)-catalyzed diazo decomposition reactions over the last 25 years, the mechanism for diazo decomposition is now widely understood.[122] The ligated metal (ML_n), having an open co-ordination site and acting as a Lewis acid, undergoes electrophilic addition to the carbon atom adjacent to the diazo group. Loss of dinitrogen from the diazonium ion intermediate **1**, then forms the metal carbene **2**. This intermediate can be depicted with two resonance-contributing structures; one is the metal carbene (**2**) and the other being the metal-stabilized carbocation (**3**).[123] The metal carbene thus formed, is able to transfer the carbene from the metal to a substrate and thereby regenerate the catalytically active ligated metal (*Scheme 3.1*). The rate-limiting step is either electrophilic addition or loss of dinitrogen.[9] Confirmation of this pathway was originally established by the correlation of reactivity and selectivity between reactions of pentacarbonyltungsten(phenylcarbene) with alkenes and reactions of phenyldiazomethane and alkenes catalyzed by dirhodium(II) tetraacetate.[124]

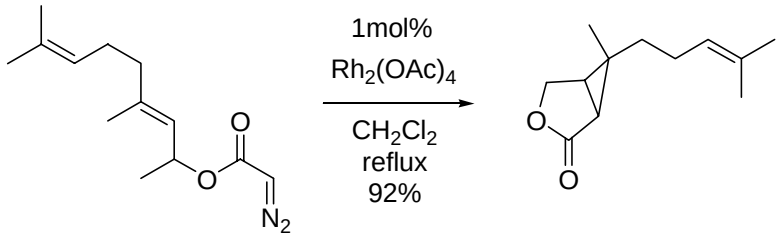
(122) (a) Doyle, M. P.; Devora, G. A.; Nefedov, A. O.; High, K. G. *Organometallics* **1992**, *11*, 549. (b) Doyle, M. P.; High, K. G.; Nesloney, C. L.; Clayton, T. *Organometallics* **1991**, *10*, 1225.
(123) Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919-939.
(124) Doyle, M. P.; Griffin, J. H.; Bagheri, V.; Dorow, R. L. *Organometallics* **1984**, *3*, 53.

Scheme 3.1:



The metal carbene thus formed, is itself electrophilic and primed for reaction with electron-rich substrates.[1] Cyclopropanation is perhaps the best known catalytic transformation (*eq. 1*),[125] but carbon-hydrogen insertion (*eq. 2*),[126] ylide transformation (*eq. 3*),[127] and addition to multiple bonds other than C=C (eq. 4)[128] are also well established.

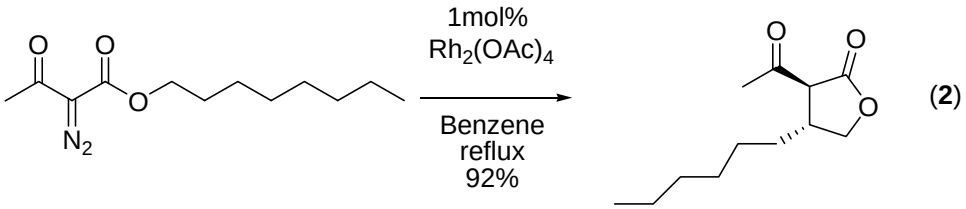
Cyclopropanation:



(**1**)

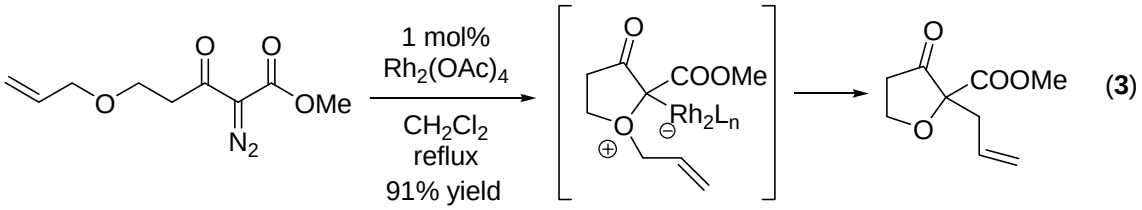
(125) Doyle, M. P.; Austin, R. E.; Bailey, A. S.; Dwyer, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Kwan, M. M. Y.; Liras, S.; Oalmann, C. J.; Pieters, R. J.; Protopopova, M. N.; Raab, C. E.; Roos, G. H. P.; Zhou, Q.-L.; Martin, S. F. *J. Am. Chem. Soc.* **1995**, *117*, 5763-5775.
(126) Doyle, M. P.; Bagheri, V.; Pearson, M. M.; Edwards, J. D. *Tetrahedron Lett.* **1989**, *30*, 7001-7004.
(127) Pirrung, M. C.; Werner, J. A. *J. Am. Chem. Soc.* **1986**, *108*, 6060-6062.
(128) Doyle, M. P.; Hu, W.; Timmons, D. J. *Org. Lett.* **2001**, *3*, 933-935.

C—H Insertion:



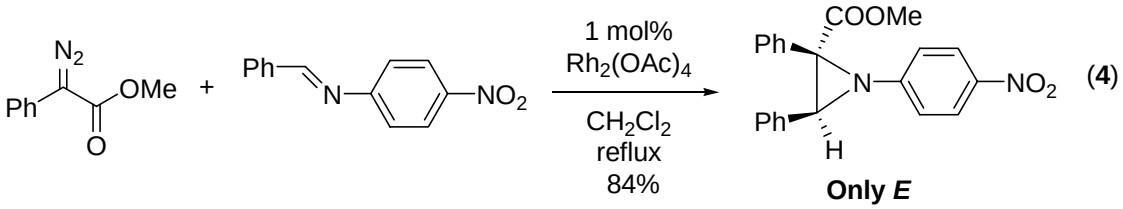
(**2**)

Ylide transformation:



(**3**)

Addition:



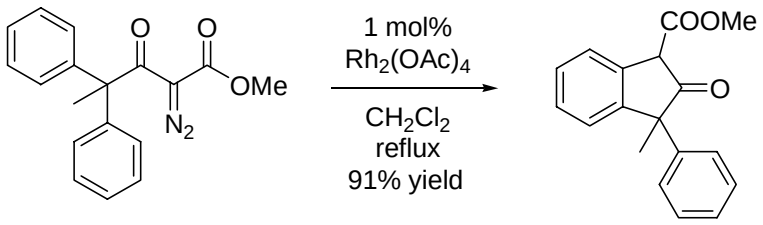
(**4**)

Dirhodium(II)-catalysts also promote reactions of diazocarbonyl compounds that are significantly different from standard addition, insertion, and ylide transformations. These reactions demonstrate the enormous versatility of diazo compounds as metal carbene precursors in organic synthesis. Dirhodium(II)-catalyzed aromatic substitution (*eq. 5*),[129] aromatic cycloaddition (*eq. 6*),[130] N—H insertion (*eq. 7*),[131] O—H insertion

(129) Watanabe, N.; Ohtake, Y.; Hashimoto, S.; Shiro, M.; Ikegami, S. *Tetrahedron Lett.* **1995**, *36*, 1491-1494.
(130) Taylor, E. C.; Davies, H. M. L. *Tetrahedron Lett.* **1983**, *24*, 5453-5456.
(131) Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G.; Bouffard, F. A. *J. Am. Chem. Soc.* **1980**, *102*, 6161-6163.

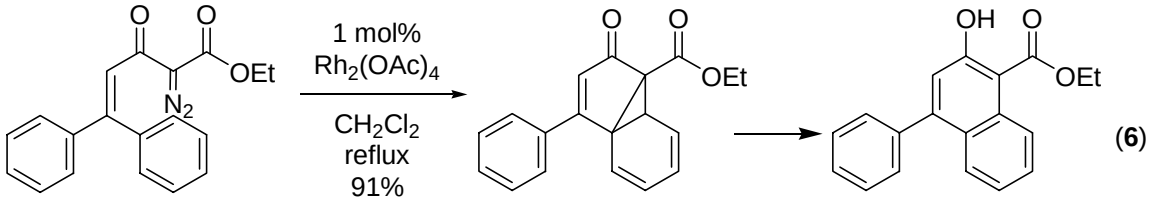
(*eq. 8*)[132] and cycloaddition (*eq. 9*) [133] reactions are equally important as synthetic methods for the construction of complex structures.

Aromatic Substitution:



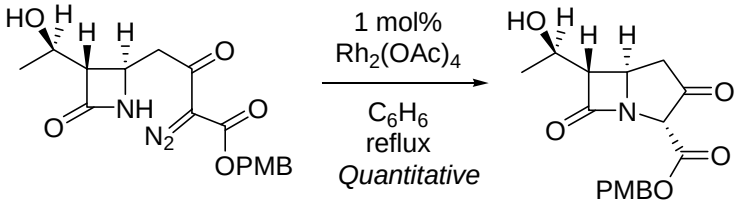
(**5**)

Aromatic Cycloaddition:



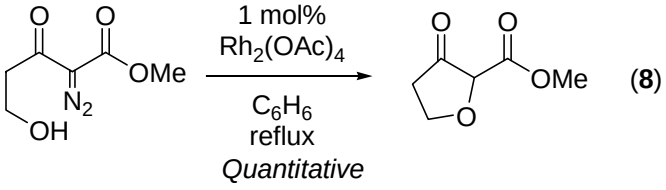
(**6**)

N—H Insertion:



(**7**)

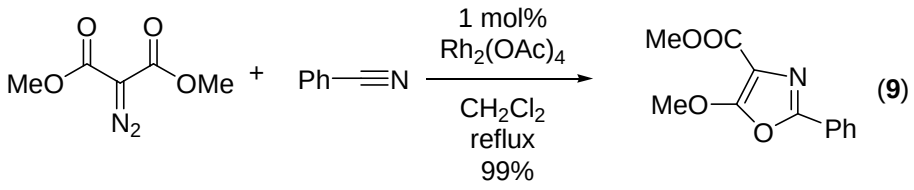
O—H Insertion:



(**8**)

Cycloaddition:

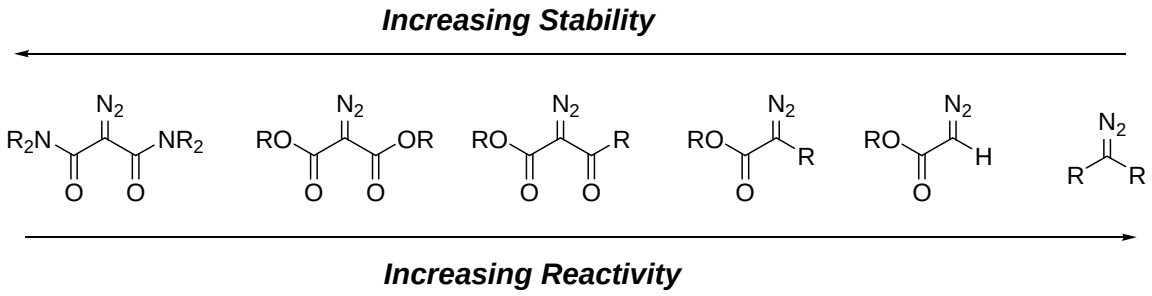
(132) Moyer, M. P.; Feldman, P. L.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 5223-5230.
(133) Connell, R.; Scavo, F.; Helquist, P.; Akermark, B. *Tetrahedron Lett.* **1986**, *27*, 5559.



(**9**)

The effectiveness of catalytically active transition metal complexes towards diazo decomposition depends on their electrophilicity as well as on the stability of the diazo compounds. Diazocarbonyl compounds are more stable than diazoalkanes. Among diazocarbonyl compounds, diazoesters are more stable than diazoketones, and diazoamides are more stable than diazoesters (*Scheme 3.2*).

Scheme 3.2:



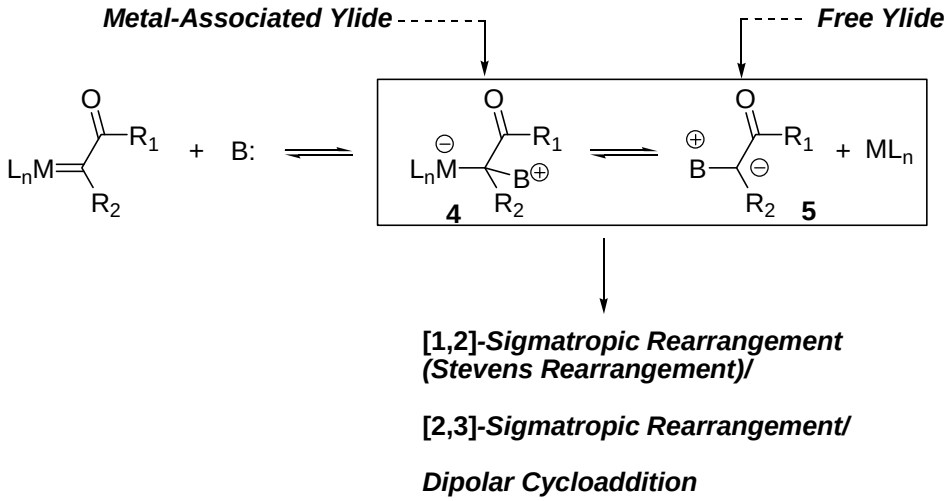
3.1.2. Rh(II)-Catalyzed Ylide Transformation:

Metal carbenes derived from α-diazocarbonyl compounds are highly electrophilic in nature and hence react readily with any available Lewis base (B:) to form ylides[134] (*Scheme 3.3*)**.** Organic compounds with heteroatoms (O, N, S, etc.) having lone pair(s) of

(134) (a) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911-935. (b) Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919-939.

electrons, generally act as Lewis bases and react with catalytically generated electrophilic carbenes to form ylides. Ylides thus formed can still keep the metal attached to form metal associated ylides (**4**) or they can dissociate from the metal to form free ylides (**5**). Ylides derived from copper or rhodium carbenes generally form free ylides because the C—M bonds are weaker compared to C—B bonds.[135] The ylide **4** (or **5)** can then undergo various rearrangement processes. The most common reactions of these catalytically generated ylides are [1,2]-rearrangement or Stevens rearrangement, [2,3]-sigmatropic rearrangement and dipolar cycloaddition.[1] These processes have been shown to have tremendous synthetic utility and have been successfully utilized in the synthesis of various biologically active natural products.[136]

Scheme 3.3:



(135) (a) Adams, J.; Spero, D. M. *Tetrahedron* **1991**, *47*, 1765. (b) Padwa, A.; Krumpe, K. E. *Tetrahedron* **1992**, *48*, 5385. (c) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091.
(136) (a) West, F. G.; Naidu, B. N. *J. Am. Chem. Soc.* **1993**, *115*, 8420. (b) Vanecko, J. A.; West, F. G. *Org. Lett.* **2002,** *4*, 2831. (c) Marmsäter, F. P.; Vanecko, J. A.; West, F. G. *Tetrahedron*, **2002**, *58*, 2027-2040. (d) Padwa, A.; Beall, L. S.; Eidell, C. K.; Worsencroft, K. J. *J. Org. Chem.* **2001**, *66*, 2414.

Relative instability of the oxonium ylides is due to their equilibrium position favoring the metal carbene.[137] Oxonium ylides are therefore, characterized by their instability and high reactivity. Unlike ammonium and sulfonium ylides, they are not isolable and difficult to characterize. Evidence for the existence of oxonium ylides has been provided by the isolation of products expected from the rearrangement of these reactive intermediates.[138]

3.1.3. Rearrangement Processes Involving Oxonium Ylides:

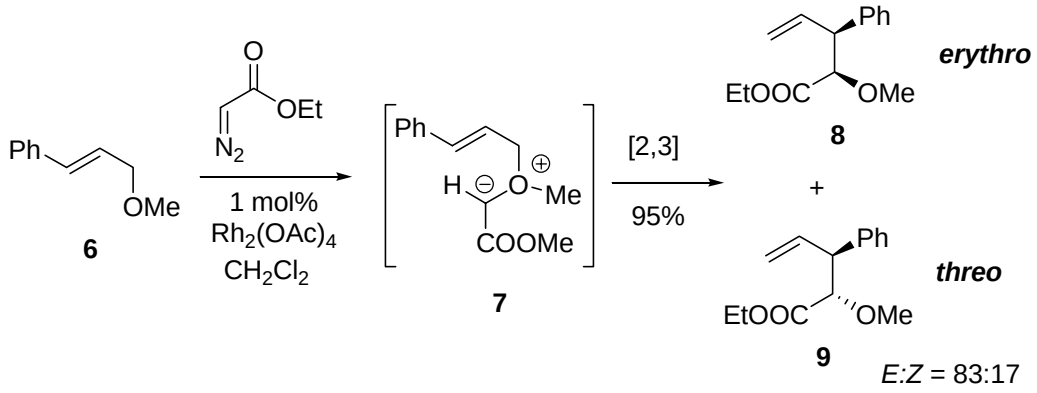
Over the last two decades extensive research efforts have been made to use oxonium ylide to undergo various rearrangement processes as well as cycloaddition methods to form important synthetic building blocks. Elegant work by the Doyle, Padwa, Hodgson and West research groups have built up the present day understanding of the oxonium ylide chemistry.

Intermolecular [2,3]-Sigmatropic Rearrangement:

Allylic acetals and substituted allylic methyl ethers (**6**) proved to be quite efficient in the formation of oxonium ylide (**7**) as well as the subsequent [2,3]-rearrangements exhibiting high degree of diastereocontrol favoring the *erythro* isomer **8** (*Scheme 3.4*).[139]

Scheme 3.4:

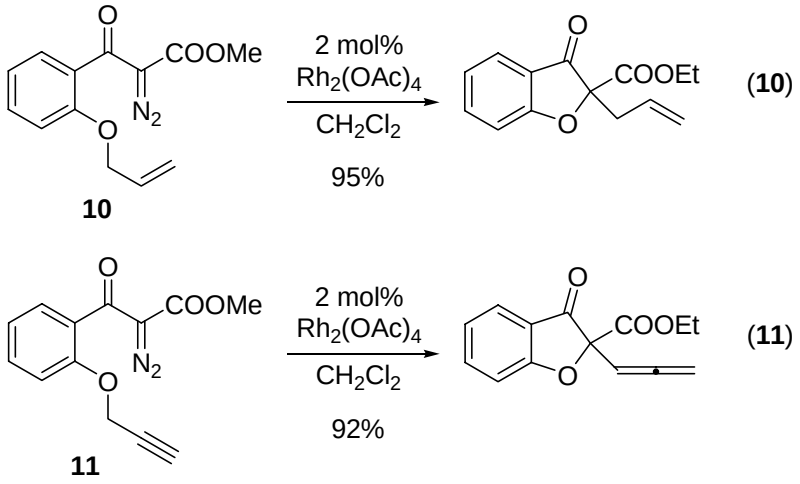
(137) Doyle, M. P.; Griffin, J. H.; Chinn, M. S.; Leusen, D. *J. Org. Chem.* **1984**, *49*, 1917-1925.
(138) Clark, J. S. In *Nitrogen, Oxygen and Sulfur Ylide Chemistry*, Clark, J. S. Ed. Oxford University Press, Oxford, **2002**, Chapter 1.
(139) Doyle, M. P.; Bagheri, V.; Harn, N. K. *Tetrahedron. Lett.* **1988**, *29*, 5119-5122.



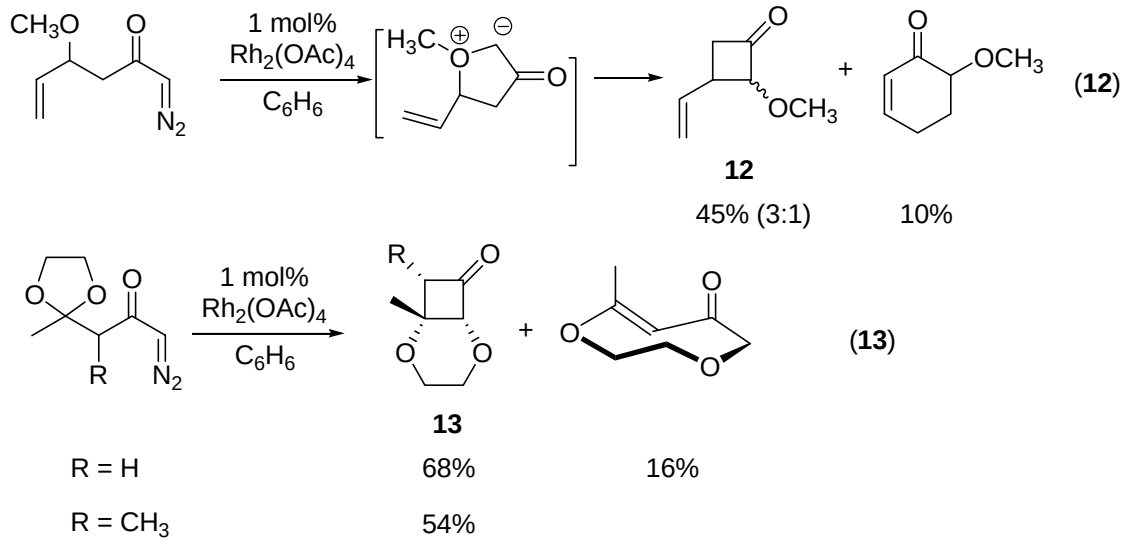
Intramolecular [2,3] Rearrangements:

Two back-to-back articles published by Pirrung[140] and Johnson[141] in 1986 described $Rh_2(OAc)_4$ catalyzed generation of cyclic oxonium ylides by intramolecular addition of electrophilic rhodium carbenes to pendant ethers. Pirrung reported the efficient use of $Rh_2(OAc)_4$ (2 mol%) for the generation of cyclic oxonium ylides by decomposition of α-diazocarbonyl compounds. Allylic (**10**) and propargylic (**11**) ethers derived cyclic oxonium ylides led to substituted furans (*eq. 10 and 11*) *via* an efficient [2,3]-rearrangement.[30]

(140) Pirrung, M. C.; Werner, J. A. *J. Am. Chem. Soc.* **1986**, *108*, 6060-6062.
(141) Johnson, C. R.; Roscamp, E. J. *J. Am. Chem. Soc.* **1986**, *108*, 6062-6063.

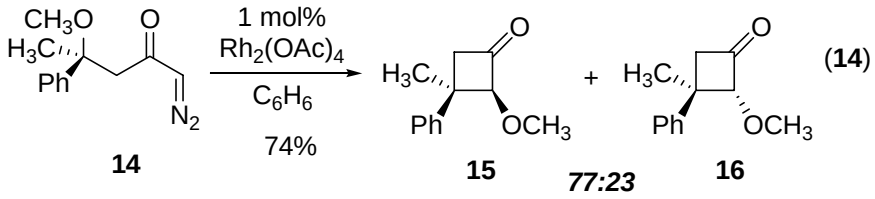


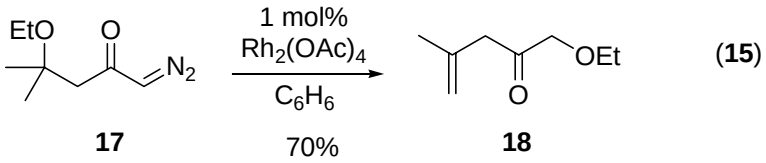
Johnson and co-workers reported two examples where cyclic oxonium ylides resulted in the dominant cyclobutanone products (**12** and **13**) *via* a [1,2]-insertion reaction (*eq. 12 and eq. 13*).[31]



Rhodium acetate catalyzed diazo decomposition of α-diazoketone with benzyl ether **14** exclusively yielded cyclobutanones (**15** and **16**) *via* a [1,2]-insertion in 3:1

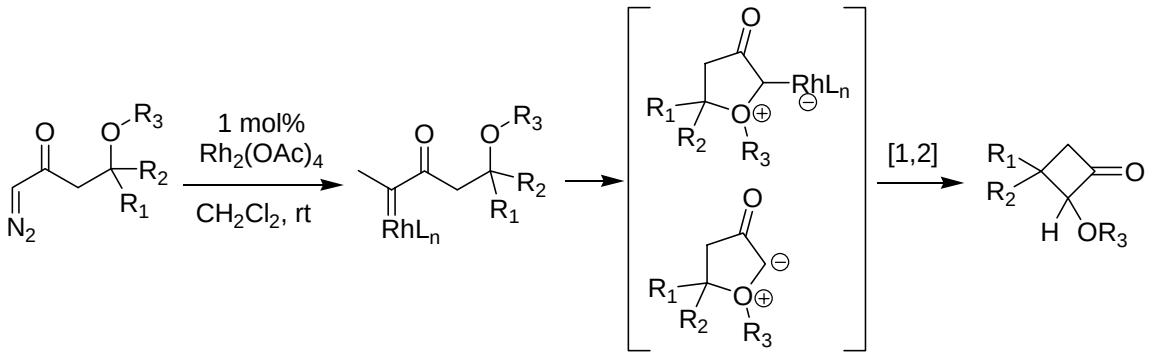
diastereomeric ratio (*eq. 14*).[31] Surprisingly, alkyl ether **17** exclusively produced the elimination product **18** (*eq. 15*).

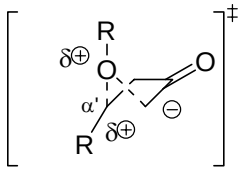




The proposed mechanism of the [1,2]-shift is depicted in *Scheme 3.5*. The key to cyclobutanone formation appears to be stabilization of the positive charge at the α′-carbon by oxygen, vinyl or aryl substitution (**19** *in Scheme 3.5*).[31] The [1,2]-shift can proceed *via* the intermediacy of either metal associated or metal free oxonium ylide.

Scheme 3.5:





19

R = Ph, $CH{=}CH_2$, OCH_3

3.2. Synthesis of Highly Substituted Cyclobutanes By Rh(II)-Catalyzed by Oxonium Ylide Pathway:

3.2.1. Prior Art:

3.2.1.1. Importance of Functionalized Cyclobutanes:

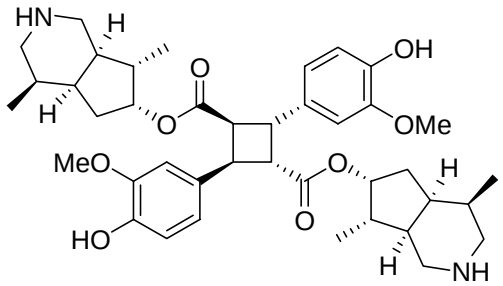
Functionalized cyclobutanes have two major uses in synthesis. The first one is its ubiquity in biologically active natural products. The second one is its transformation to various carbocycles and heterocycles *via* ring-expansions or ring-contractions.[142]

Natural Products with Biological Activities:

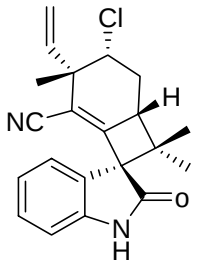
There are a number of biologically active natural products containing highly substituted cyclobutane ring e.g. antinociceptive agent incarvillateine (**20**), multiple drug resistance reversing agent welwitindolinone A isonitrile (**21**), anticancer agent providencin (**22**) (*Scheme 3.6*).

(142) Namyslo, J. C.; Kaufmann, D. E. *Chem. Rev.* **2003**, *103*, 1485-1537.

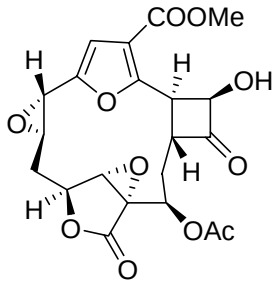
Scheme 3.6:



incarvillateine (20)



welwitindolinone A isonitrile (21)



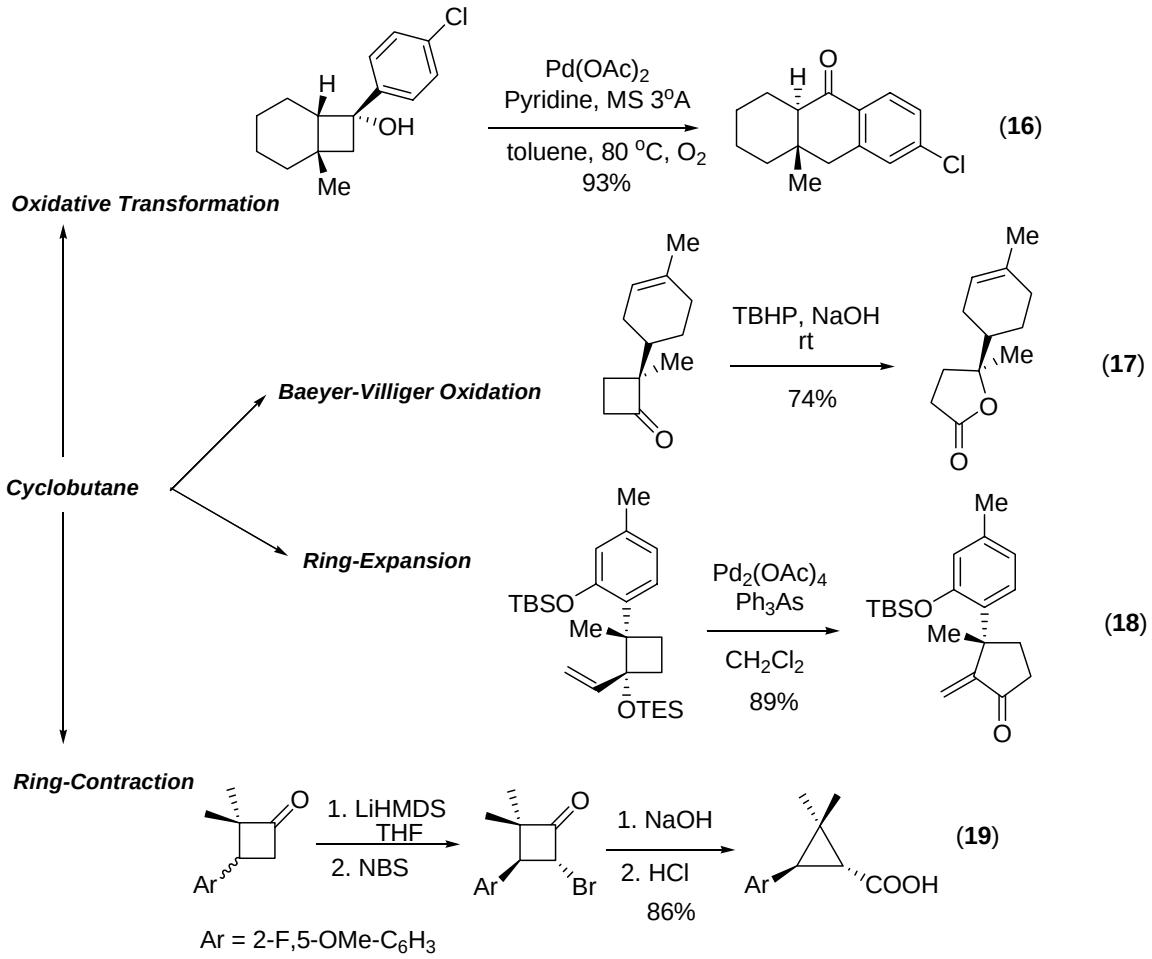
providencin (22)

Applications of Cyclobutanes in Transformations to Various Cyclic Systems:

Primarily because of intrinsic torsional and angle strain in the cyclobutane ring, cleavage of cyclobutane is a very facile process and has been extensively used in natural product synthesis.[26] Metal-catalyzed oxidative transformation (*eq. 16*),[143] Baeyer-Villiger oxidation (*eq. 17*),[144] ring-expansion (*eq. 18*),[145] ring-contraction (*eq. 19*)[146] are some of the most useful transformations of cyclobutane ring (*Scheme 3.7*). These examples have been chosen from a plethora of reports on applications of the cyclobutane skeleton in synthesis, based on their relevance to the cyclobutane structure obtained by diazo decomposition of a Mukaiyama aldol adducts.

(143) Nishimura, T.; Uemura, S. *J. Am. Chem. Soc.* **1999**, *121*, 11010.
(144) Nemoto, H.; Shiraki, M.; Nagamochi, M.; Fukumoto, K. *Tetrahedron Lett.* **1993**, *34*, 4939.
(145) Nemoto, H.; Nagamochi, M.; Ishibashi, H.; Fukumoto, K. *J. Org. Chem.* **1994**, *59*, 74.
(146) Chen, B. –C.; Ngu, K.; Guo, P.; Liu, W. Sundeen, J. E.; Weinstein, D. S.; Atwal, K. S.; Ahmad, S. *Tetrahedron Lett.* **2001**, *42*, 6227.

Scheme 3.7:

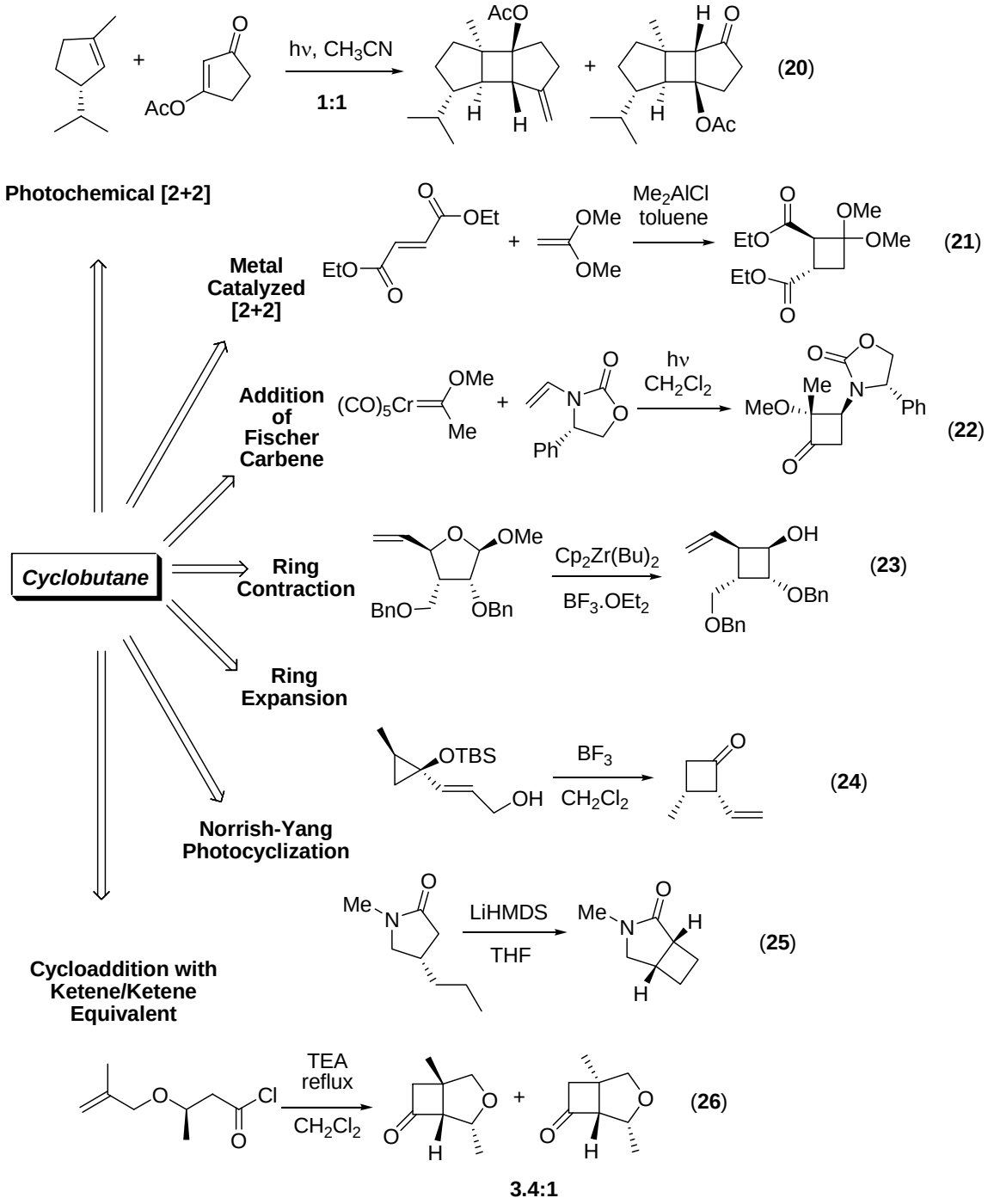

Cl
H
OH
Me
Pd(OAc)2
Pyridine, MS 3oA
toluene, 80 oC, O2
93%
O
H
Me
Cl
(16)
Oxidative Transformation
Baeyer-Villiger Oxidation
Me
Me
O
TBHP, NaOH
rt
74%
Me
Me
O
O
(17)
Cyclobutane
Ring-Expansion
Me
TBSO
Me
OTES
Pd2(OAc)4
Ph3As
CH2Cl2
89%
Me
TBSO
Me
O
(18)
Ring-Contraction
O
Ar
1. LiHMDS
THF
2. NBS
O
Ar
Br
1. NaOH
2. HCl
86%
Ar
COOH
(19)
Ar = 2-F,5-OMe-C6H3

Synthetic Methods for Cyclobutanones:

The common synthetic methods for accessing cyclobutane derivatives include photochemical [2+2] cycloaddition reactions (*eq. 20* in *Scheme 3.8*)[147], metal catalyzed [2+2] cycloaddition reactions (*eq. 21* in *Scheme 3.8*),[148] addition of Fischer carbene to alkenes (*eq. 22* in *Scheme 3.8*),[149] ring contractions (*eq. 23* in *Scheme 3.8*),[150] ring expansion of cyclopropylcarbinyl precursors (*eq. 24* in *Scheme 3.8*),[151] Norris-Yang photocyclizations (*eq. 25* in *Scheme 3.8*)[152] and cycloaddition with ketenes or ketene equivalents (*eq. 26* in *Scheme 3.8*)[153],

(147) Hansson, T.; Wickberg, B. *J. Org. Chem.* **1992**, *57*, 5370-5376
(148) Ahmad, S. *Tetrahedron Lett.* **1991**, *32*, 6997.
(149) Hegedus, L. S.; Bates, R. W.; Soderberg, B. C. *J. Am. Chem. Soc.* **1991**, *113*, 923-927.
(150) Ito, H.; Motoki, Y.; Taguchi, T.; Hanzawa, Y. *J. Am. Chem. Soc.* **1993**, *115*, 8835
(151) Salaun, J.; Karkour, B.; Ollivier, J. *Tetrahedron* **1989**, *45*, 3151-3162.
(152) Galeazzi, R.; Mobbili, G.; Orena, M. *Tetrahedron* **1999**, *55*, 261-270.
(153) Mori, K.; Miyake, M. *Tetrahedron* **1987**, *43*, 2229-2239.

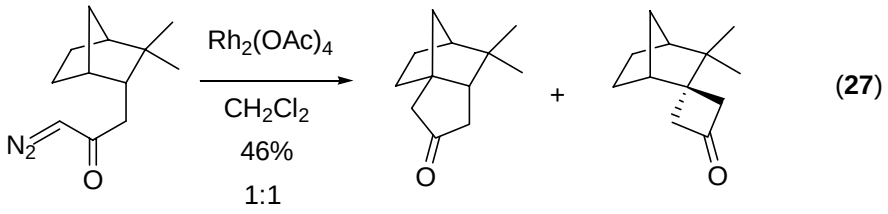
Scheme 3.8:


hν, CH3CN
1:1
(20)
Photochemical [2+2]
Me2AlCl
toluene
(21)
Metal Catalyzed [2+2]
Addition of Fischer Carbene
hν
CH2Cl2
(22)
Cyclobutane
Ring Contraction
Cp2Zr(Bu)2
BF3.OEt2
(23)
Ring Expansion
BF3
CH2Cl2
(24)
Norrish-Yang Photocyclization
LiHMDS
THF
(25)
Cycloaddition with Ketene/Ketene Equivalent
TEA
reflux
CH2Cl2
(26)
3.4:1

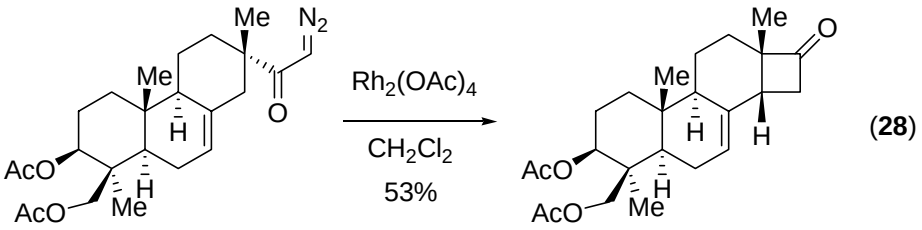
3.2.1.3. Synthesis of Cyclobutanones via Carbene Transformations:

By C—H Insertion:

The preference for the formation of cyclopentanone rings by C—H insertion reaction of diazoketones is well documented.[4] But in structurally rigid systems, competing cyclobutanone formation has also been observed (*eq. 27*[154]*and eq. 28*[155]). Although in both of the following examples the reactions suffer from low product conversions.



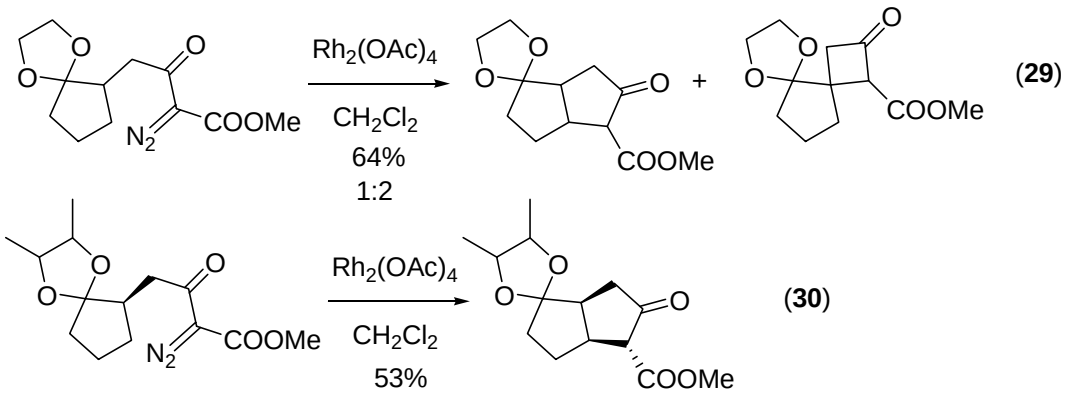
(**27**)



(**28**)

Subtle changes in the structure of the diazo compounds play an important role in determining the regioselectivity (*eq. 29*[156] *and 30*[157]).

(154) Sonawane, H. R.; Bellur, N. S.; Ahuja, J. R.; Kulkarni, D. G. *J. Org. Chem.* **1991**, *56*, 1434-1439.
(155) Ceccherelli, P.; Curini, M.; Marcotullio, M. C.; Rosati, O. *Tetrahedron,* **1991**, *47*, 7403-7408.
(156) Hashimoto, S.; Watanabe, N.; Ikegami, S. *Tetrahedron Lett.* **1992**, *33*, 2709-2712.
(157) Hashimoto, S.; Shinda, T.; Ikegami, S. *J. Chem. Soc., Chem. Commun.* **1988**, 1137-1139.

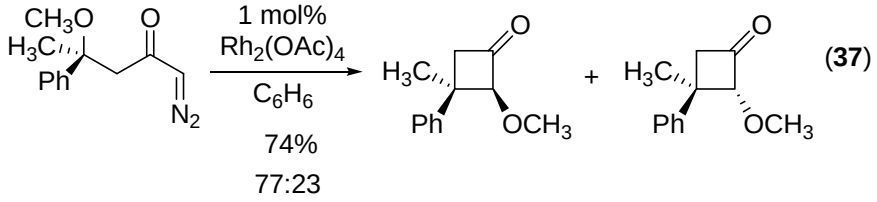


(**29**)

(**30**)

By Ylide Transformations:

Another method for formation of cyclobutanones by diazo decomposition is *via* oxonium ylide reported by Johnson (*eq. 31*). Although the reaction proceeds with good yield but suffers from low diastereocontrol and the substrate scope of the reaction has not been determined.[31]

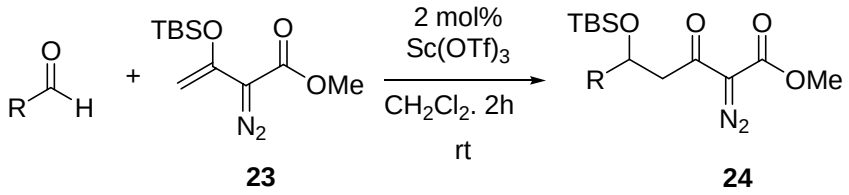


(**37**)

3.2.2. Results and Discussion:

The Lewis acid catalyzed Mukaiyama aldol addition reaction of vinyldiazoacetate **23** with various aldehydes provided an efficient and straightforward method for accessing functionalized diazoacetates **24** (*Scheme 3.9*).[158]

Scheme 3.9:



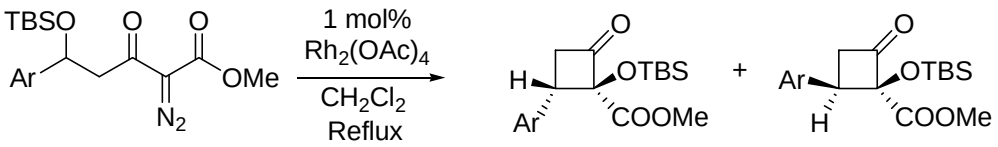
R = Ph, 4-$OMeC_6H_4$, 4-MeC_6H_4, 4-ClC_6H_4, 4-$CF_3C_6H_4$, COOEt, $BnOCH_2$, C_7H_{15}

90-98% yield

The potential of the condensation process for synthetic transformations achieved through diazo decomposition was explored by reactions performed with rhodium acetate. The TBDMS-protected Mukaiyama aldol adducts (**24a-c**) of aromatic aldehydes in the presence of 1 mol% rhodium(II) acetate led to the formation of highly substituted cyclobutanones in high yields and high diastereoselectivity favoring diastereomer **25** (*Table 3.1*).

(158) Doyle, M. P.; Kundu, K.; Russell, A. E. *Org. Lett.* **2005**, *7*, 5171-5174.

Table 3.1: *Cyclobutanone Formation by Rhodium Acetate Catalyzed Diazo Decomposition of* ***24***[a]



24a-c **25a-c** **26a-c**

Adduct	Ar	yield, %[b] **25+26**	**25:26**[c]
24a	4-Me-C_6H_4	84	12:1
25b	C_6H_5	80	10:1
26c	4-Cl-C_6H_4	84	10:1

[a] The Mukaiyama aldol adduct (1.0 mmol) in CH_2Cl_2 (2 mL) was added via a syringe pump over 5 h to a refluxing solution of $Rh_2(OAc)_4$ (1.0 mol%) in 2 mL of CH_2Cl_2 [b] Isolated yield of **25+26**. [c] Determined by integration of the characteristic ^{1}H NMR signals of **25** (δ = 3.37 ppm) and **26** (δ = 3.39 ppm).

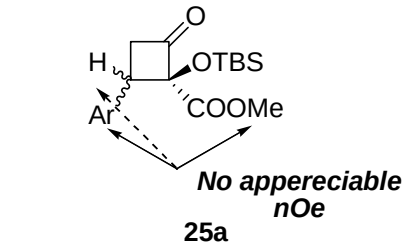
The synthesis of highly substituted cyclobutanes with multiple stereogenic centers is considered to be a challenging task,[159] and to our knowledge there has only been one prior report of cyclobutanone formation through oxonium ylides.[31] The chemical yield and higher diastereoselectivity makes this Mukaiyama aldol/diazo decomposition sequence an attractive synthetic methodology for accessing highly substituted cyclobutanones.

(159) Lee-Ruff, E.; Mladenova, G. *Chem. Rev.*, **2003**, *103*, 1449-1483.

3.2.3. Determination of the Major Diastereoisomer:

The next challenge was to determine the relative stereochemistry of the substituents in the major isomer **25**. Straightforward methods for determination of the relative stereochemistry of substituents in **25a**, like nOe or NOESY, were inconclusive as the H's in the substituents are far apart from each other (*Scheme 3.10*). No signal enhancement was observed for the benzylic proton nor for the aromatic protons upon irradiation of the singlet at 3.35 ppm corresponding to the carbemethoxy group. Similarly, upon irradiation of the aromatic protons no signal enhancement was observed for the carbemethoxy CH_3 signal.

Scheme 3.10:



25a

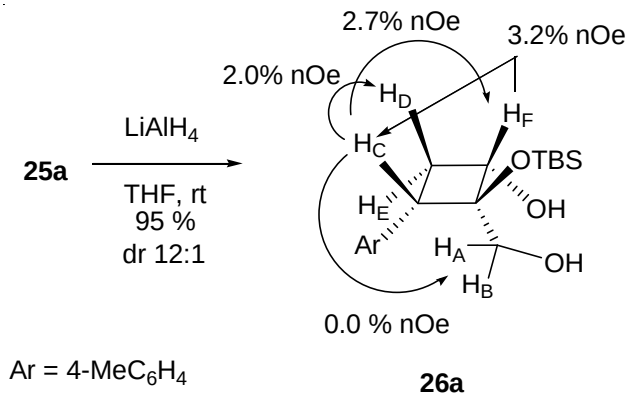
Ar = 4-MeC_6H_4

However, reduction of **25a** by lithium aluminium hydride[160] produced a diol (**26a**) from which nOe experiments provided evidence for the relative stereochemistry reported in Table 3.1 (*Scheme 3.11*). The relative stereochemistry of substituents in **26a** was determined by nOe experiments with Gauss1.1000 shape pulse and gradient selection. Upon irradiation of the multiplet at δ 4.27 ppm (H_F) 3.2% and 2.3% enhancements were

(160) Ramnauth, J.; Lee-Ruff, E. *Can. J. Chem*. **2001**, *79*, 114-120.

observed for the multiplets at δ 3.15 ppm (H_C) and at δ 2.43 ppm (H_D), respectively, and no enhancement was observed for the doublets at δ 3.76 ppm (H_A) and δ 3.33 ppm (H_B). Similarly upon irradiation of either of the doublets at δ 3.76 ppm (H_A) or δ 3.33 ppm (H_B) no enhancement was observed for the multiplets at δ 3.15 ppm (H_C) and at δ 2.43 ppm (H_D). But 2.7% and 2.0% signal enhancements were seen for multiplets at δ 4.27 ppm (H_F) and δ 2.43 ppm (H_D) upon irradiation of the multiplet at δ 3.15 ppm (H_C). These observations could only be reconciled with the *cis* orientation of the aryl and hydroxymethyl group in the major diol product **26a**. Therefore, the aryl and carbemethoxy groups in **25a** are also in *cis* orientations.

Scheme 3.11:

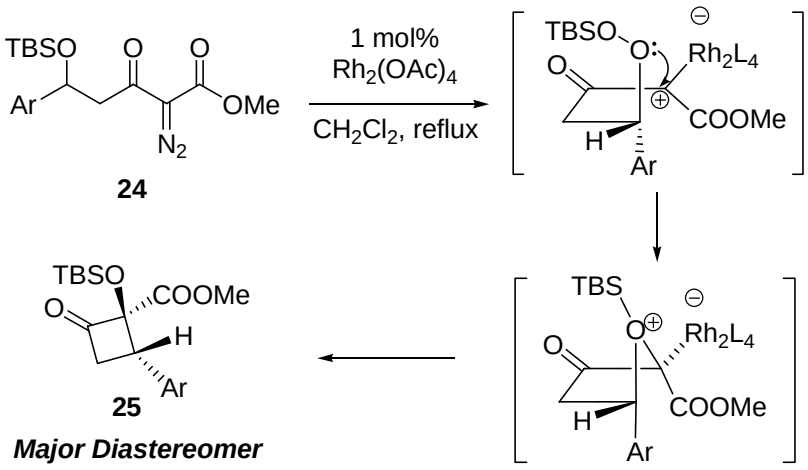


3.2.4. Mechanism:

The formation of cyclobutanones can only be explained by invoking the oxonium ylide pahway. The oxonium ylide thus formed undergoes a [1,2]-shift to form the

cyclobutane as described in *Scheme 3.12*. This is the same mechanism proposed by Johnson and co-workers.[31]

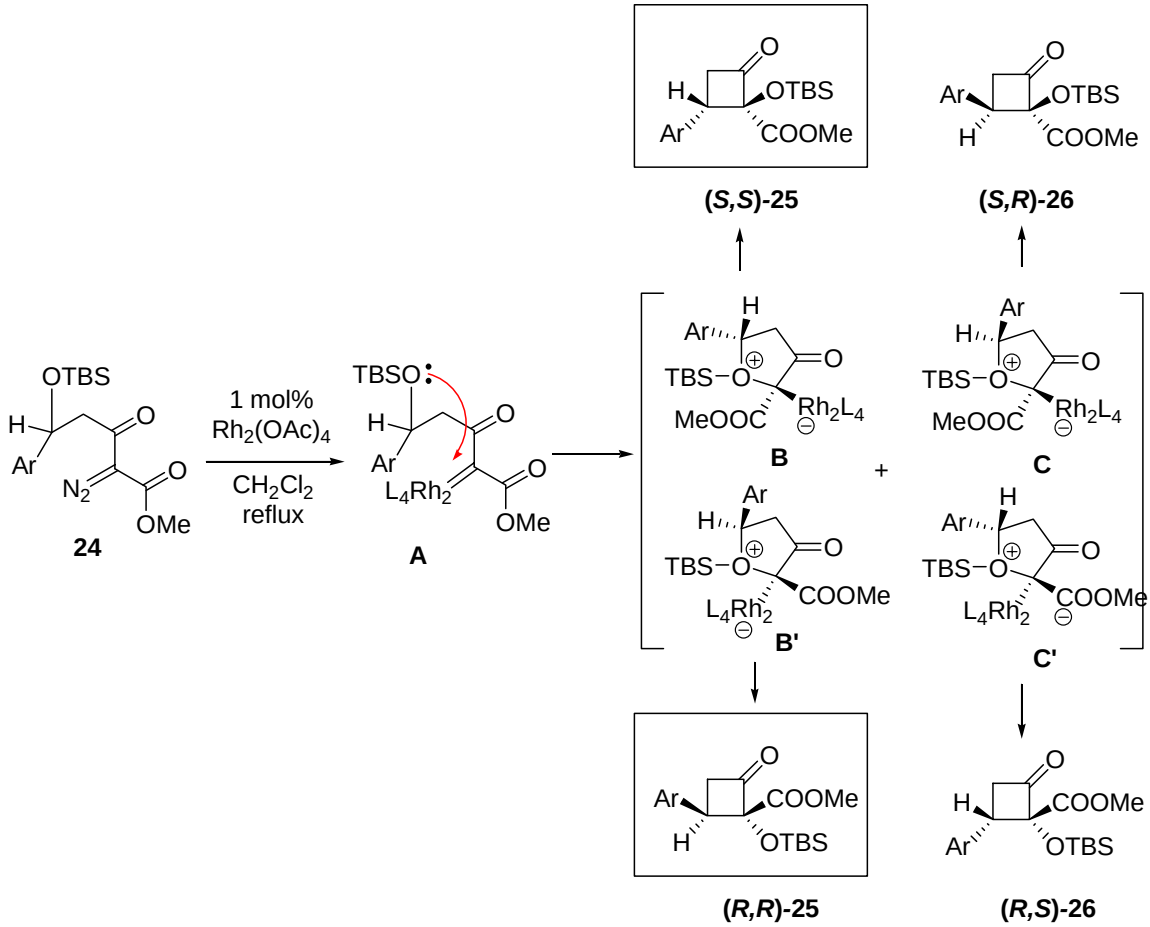
Scheme 3.12:



3.2.5. Model for Diastereoselectivity:

The proposed ylide mechanism for the formation of cyclobutanone product should also offer a plausible explanation for observed diastereoselectivity. The rhodium(II) carbene (**A**) upon attack by oxygen lone pair (of OTBS group) can form either of the oxonium ylide intermediates **B** (and **B′**) and **C** (and **C′**). The steric interaction between the aryl substituent and the dirhodium complex in **C** and **C′** probably hinders the formation of **26** and therefore favoring **B** and **B′** which leads to **25** (*Scheme 3.13*).

Scheme 3.13:

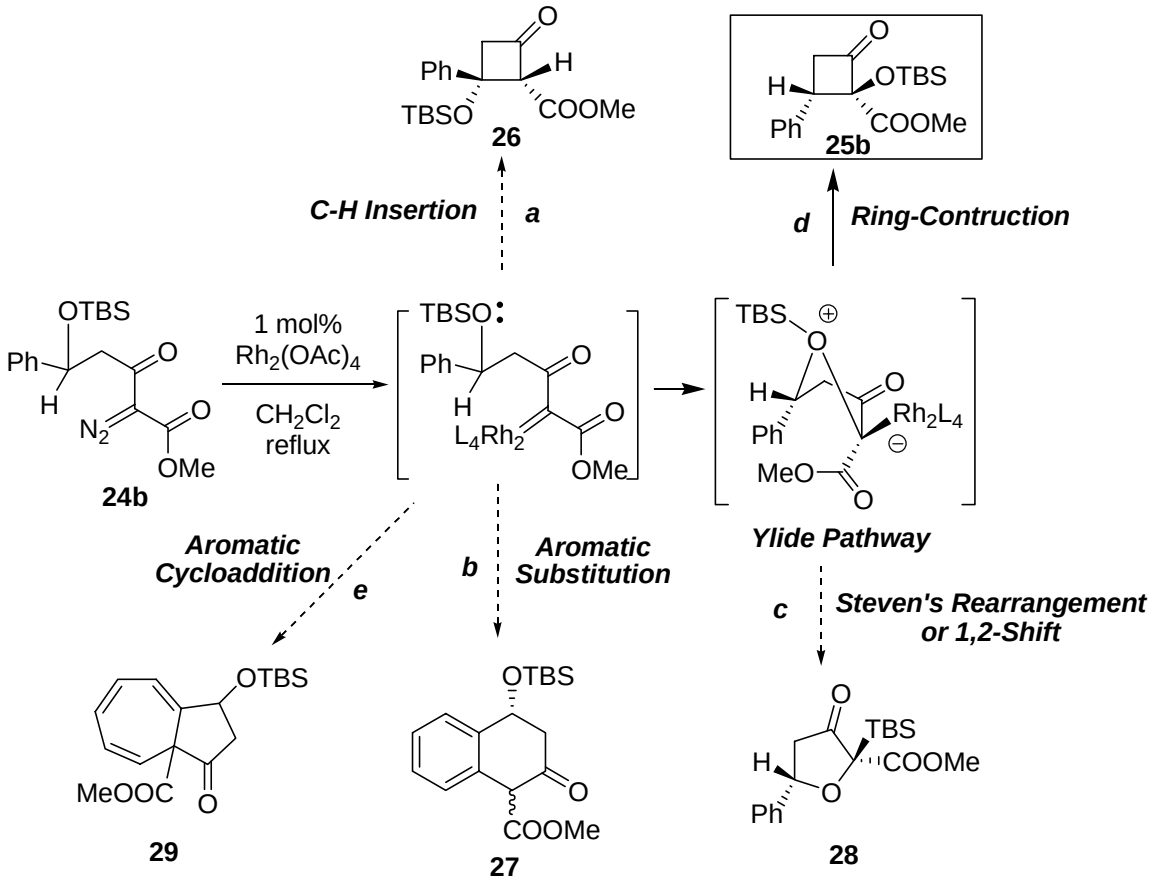


3.2.6. Chemoselectivity:

Another striking feature of the cyclobutanone formation is the apparently surprising chemoselectivity. There are various possible diazo decomposition reaction pathways for diazoacetoacetates like **24** as depicted in *Scheme 3.14*. C—H insertion into the activated benzylic C—H bond (*path* a) is a possibility but, presumably, involvement of a highly constrained 4-membered transition state inhibits this reaction pathway. Aromatic substitution (*path b*) can also occur. But this pathway involves intermediates

with disrupted aromaticity. In comparison, the oxonium ylide pathway can be a facile process under the reaction conditions. Once the 5-membered oxonium ylide is formed, it can undergo either [1,2]-shift (Stevens rearrangement) (*path c*) or ring contraction (*Path d*). Stevens rearrangement involves formation of a less stable C—Si bond from more stable O—Si bond. Another possibility includes an aromatic cycloaddition reaction leading to a trienone formation (*path e*), which again disrupts the aromaticity of the starting material. Therefore, despite the possibility of various reaction pathways, high chemoselectivity might not be as surprising as it looked to begin with.

Scheme 3.14:



3.3. Synthesis of Functionalized Dihydrofuran via Oxonium Ylide:

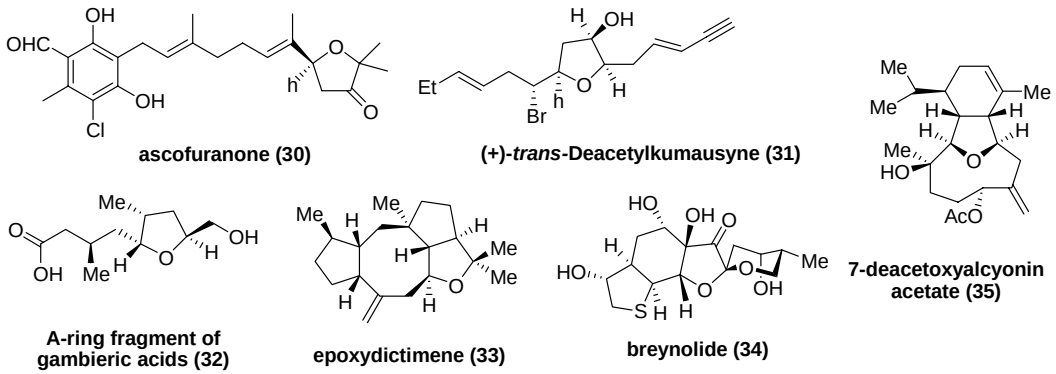
3.3.1. Prior Art:

3.3.1.1. Importance of Functionalized Dihydrofurans and Tetrahydrofurans:

Natural Products with Biological Activities:

Functionalized tetrahydrofurans constitute a class of compounds with potential biological activity and tremendous synthetic applications (*Scheme 3.15*). Ascofuranone (**30**),[161] (+)-trans-deacetylkumausyne (**31**),[62] gambieric acids (**32**),[162] epoxydictimene (**33**),[163] breynolide (**34**),[164] 7-deacetoxyalcyonin acetate (**35**)[165] have therapeutic applications and contain a highly functionalized tetrahydrofuran core.

Scheme 3.15:



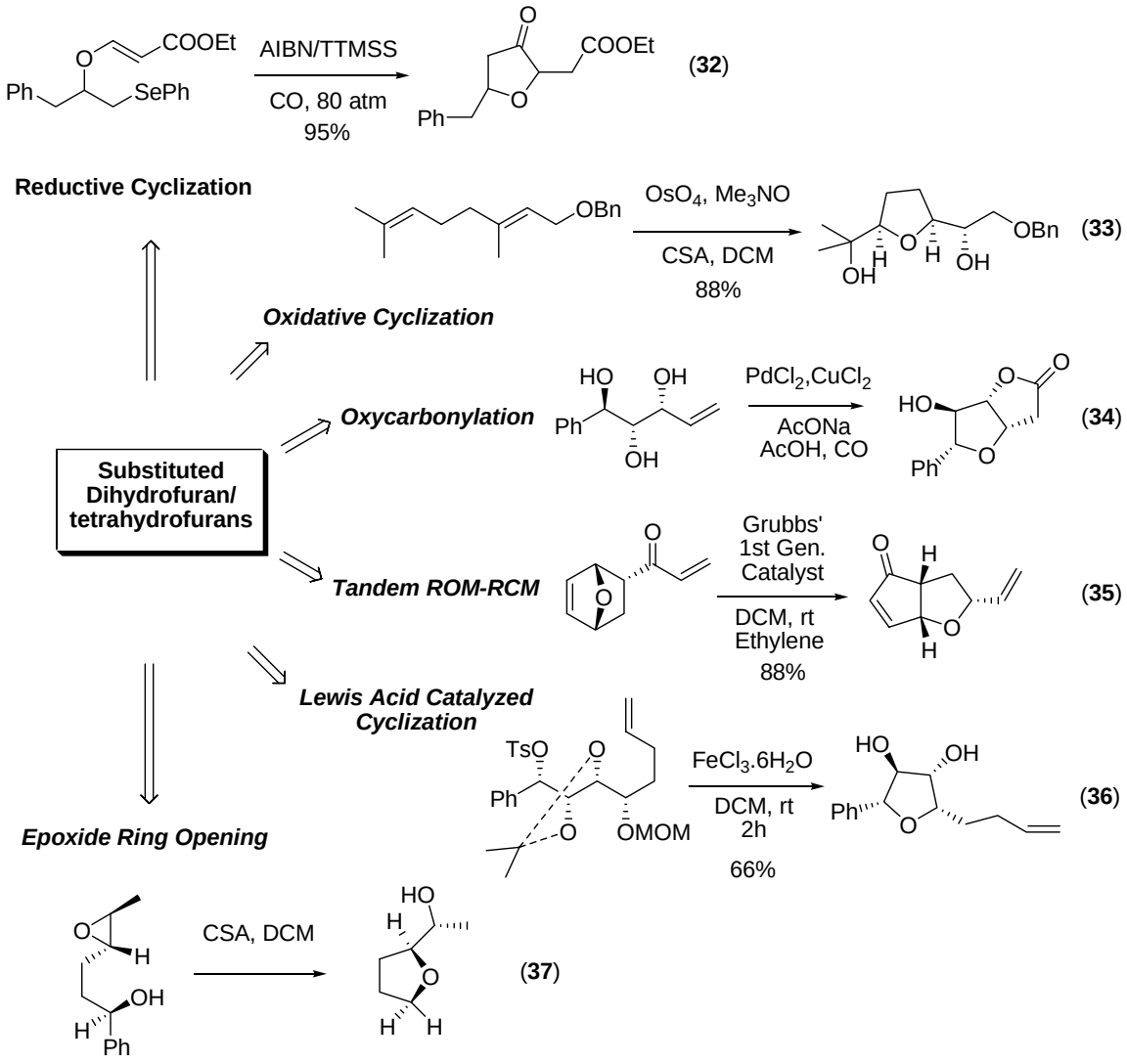
(161) Magae, J.; Hyasaki, J.; Matsuda, Y.; Hotta, M.; Hosokawa, T.; Suzuki, S.; Nagai, K.; Ando, K.; Tamura, G. *J. Antibiot.* **1988**, *41*, 959-965.
(162) Nagai, H.; Mikami, Y.; Yazawa, K.; Gonoi, T.; Yasumoto, T. *J. Antibiot.* **1993**, *46*, 520.
(163) Jamison, T. M.; Shambayati, S.; Crowe, W. E.; Schrieber, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 4353-4363.
(164) Smith (III), A. B.; Emfield, J. R.; Rivero, R. A.; Vaccaro, H. A. *J. Am. Chem. Soc.* **1991**, *113,* 4037-4038.
(165) MacMillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc.* **1995**, *117*, 10391-10392.

3.3.1.2. Synthetic Methods for Functionalized Dihydrofurans:

Accessing functionalized dihydro- and tetrahydrofurans for the total synthesis of natural products with biological and pharmaceutical activities by synthetic methods are always challenging.[166] Over the years several synthetic methods have been developed for accessing this class of molecules. The common methods include reductive cyclization (*eq. 32*),[167] oxidative cyclization (*eq. 33*),[168] oxycarbonylation (*eq. 34*),[169] tandem-ROM-RCM (*eq. 35*),[170] Lewis acid catalyzed cyclization (*eq. 36*),[171] epoxide opening (*eq. 37*)[172] etc. A brief overview on various synthetic methodologies has been depicted in *Scheme 3.16*.

Scheme 3.16:

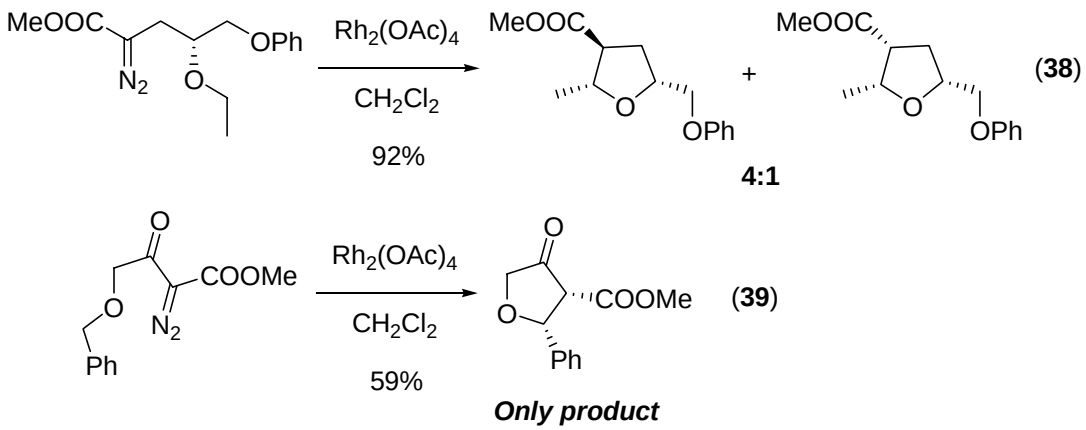
(166) Chavre, S. N.; Choo, H.; Cha, J. H.; Pae, A. N.; Choi, K. I.; Cho, Y. S. *Org. Lett*. **2006**, *8*, 3617-3619.
(167) Berlin, S.; Ericsson, C.; Engman, L. *Org. Lett.* **2002**, *4*, 3-6
(168) Donohoe, T. J.; Butterworth, S. *Angew. Chem. Int. Ed.* **2005**, *44*, 4766-4768.
(169) Babjak, M.; Papitan, P.; Gracza, T. *Tetrahedron* **2005**, *61*, 2471-2479.
(170) Chundler, C. L.; Phillips, A. J. *Org. Lett.* **2005**, *7*, 3493-3495.
(171) Prasad, K. R.; Gholap, S. L. *J. Org. Chem.* **2006**, *71*, 3643-3645.
(172) Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 9328.



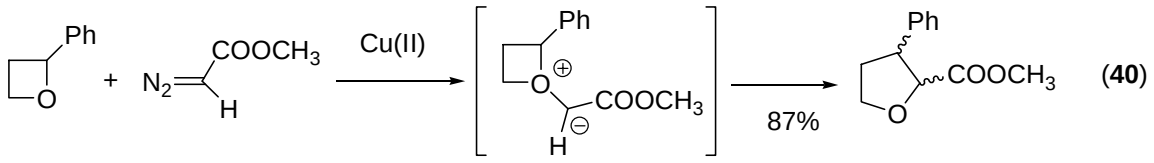
3.3.1.3. Synthesis of Functionalized Dihydofurans via Carbene Transformations:

C——H Insertion: Functionalized tetrahydrofurans have been synthesized by Rh(II)-catalyzed C——H insertion in good to high yields and moderate diastereocontrol (*eq. 38*[173] *and 39*[174]).

(173) Taber, D. F.; Song, Y. *Tetrahedron Lett.* **1995**, *36*, 2587-2590.
(174) Ye, T.; McKervey, M. A.; Brandes, B. D.; Doyle, M. P. *Tetrahedron Lett.* **1994**, *35*, 7269-7272.

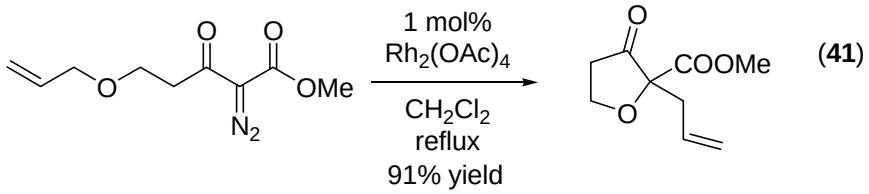


Intermolecular Oxonium Ylide Transformations: One of the earliest examples of the formation of oxonium ylide was the formation of tetrahydrofuran derivatives *via* the [1,2]-Stevens rearrangement of the oxonium ylide (*eq 40*).[175]

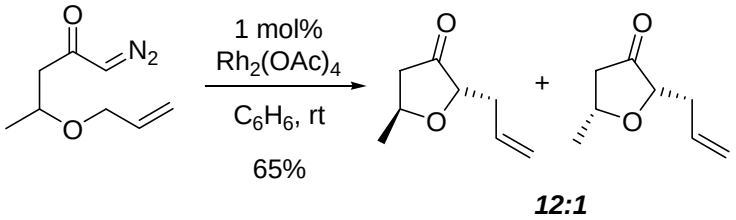


Intramolecular Oxonium Ylide Transformations: Pirrung[30] and Johnson[31] have reported the oxonium ylide based rearrangements to functionalized tetrahydrofuran synthesis catalyzed by Rh(II)-acetate (*eq. 41 and 42*).

(175) (a) Nozaki, H.; Takaya, H.; Noyori, R. *Tetrahedron* **1966**, *22*, 3393-3401. (b) Nozaki, H.; Takaya, H.; Moriuti, S.; Noyori, R. *Tetrahedron* **1968**, *24*, 3655-3669.



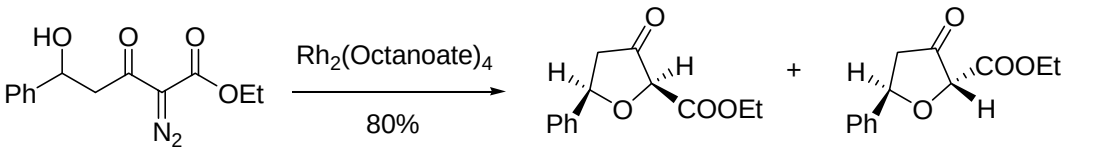
(**41**)



12:1

(**42**)

O—H Insertion: The applications of the intramolecular O—H insertion for the construction of substituted furans has been developed simultaneously by Moody[176] and Rapaport.[177] Calter used the same protocol to access tetrahydrofurans from the aldol adducts (*eq. 43*).[178]



1:1

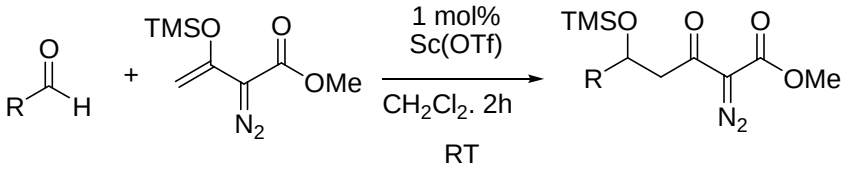
(**43**)

(176) Moyer, M. P.; Feldman, P. L.; Rapaport, H. *J. Org. Chem.* **1985**, *50*, 5223-5230.
(177) Haslin, J.; Moody, C. J.; Slawin, A. M. Z.; Williams, D. J. *Tetrahedron Lett.* **1986**, *27*, 1403-1406.
(178) Calter, M. A.; Sugathapala, P. M.; Zhu, C. *Tet. Lett.* **1997**, *38*, 3837-3840.

3.3.2. Results and Discussions:

TMS-protected vinyl diazoacetate (**36**) undergoes Sc(III)-catalyzed Mukaiyama aldol addition to both aromatic and aliphatic aldehydes producing diazoacetoacetates (**37**) with very high chemical yields (*Scheme 3.17*).

Scheme 3.17:



36 **37**

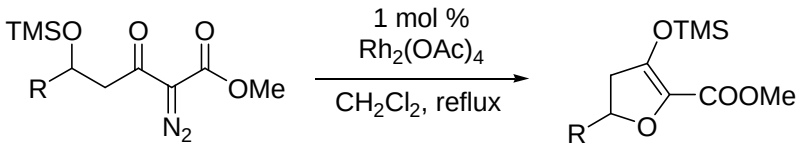
R = Ph, 4-$OMeC_6H_4$, 4-MeC_6H_4, 4-ClC_6H_4, 4-$CF_3C_6H_4$, COOEt, $BnOCH_2$, C_7H_{15}

95-98% yield

Like the TBS-protected Mukaiyama aldol adduct (**24**), the TMS-protected adduct (**36**) was subjected to diazo decomposition with rhodium(II) acetate and to our surprise the reaction proceeded to form dihydrofurans (**37**) with quantitative conversion (*Table 3.2*). Aromatic aldehyde adducts (***36a-36c***) have undergone diazo decomposition to form dihydrofurans in excellent yields. The adduct from aliphatic aldehyde ***36d*** did not form a cyclopentanone *via* C—H insertion; rather it formed the corresponding dihydrofuran exclusively. The α,β-Unsaturated aldehyde *trans*-cinnamaldehyde derived Mukaiyama aldol adduct (***36e***) is a suitable substrate for cycloproponation, but oxonium ylide formation is found to be more favorable, producing the corresponding dihydrofuran in 96% isolated yield. In all cases, the reactions were found to be clean, and the pure

products were obtained by filtering the reaction mixture through a celite plug with the washings of dichloromethane.

Table 3.2:



36 **37**

Adduct	Ar	Yield of **37** %[a]
36a	4-Me-C_6H_4	98
36b	C_6H_5	97
36c	4-Cl-C_6H_4	97
36d	C_7H_{15}	94
36e	β-styryl	89

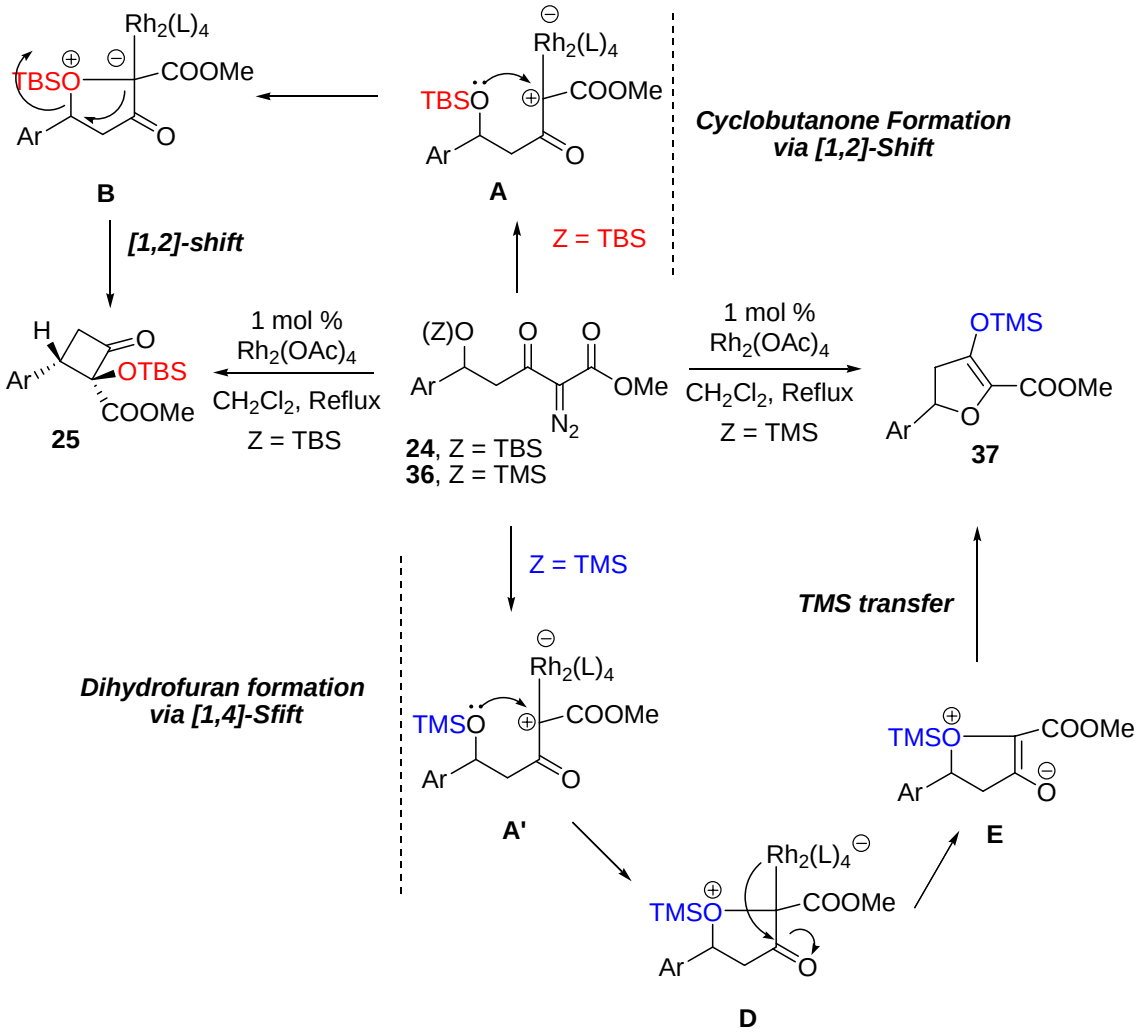
[a] The Mukaiyama aldol adduct (1.0 mmol) in CH_2Cl_2 (2 mL) was added *via* a syringe pump over 5 h to a refluxing solution of $Rh_2(OAc)_4$ (1.0 mol%) in 2 mL of CH_2Cl_2 [b] Isolated yield of **37**.

3.3.3. Rational for Mechanistic Dichotomy:

The divergent product formation under the same diazo decomposition conditions using TBS- or TMS- protected adducts is mechanistically very intriguing. Generation of the dihydrofuran can be explained by proposing the same oxonium ylide intermediate invoked for cyclobutanone formation (*Scheme 3.18*). The rhodium carbene **A′** formed by diazo decomposition upon attack by the oxygen of TMSO- group in **36**, leads to the formation of oxonium ylides **D**. Oxonium ylide **D** is structurally similar to **B** differing

only in the silyl group. Oxonium ylide **B** undergoes a ring contraction (a formal [1,2]-shift) leading the cyclobutanone formation. In contrast, the kinetically labile TMS-group provides the possibility of a so called [1,4]-shift to the enolate oxygen as shown in **E**, thus bypassing the high torsional and angular strain involved in cyclobutanone formation. The TMS-shift in **E** can be intermolecular in nature and in that case the effect of concentration in the diazo decomposition will be crucial in product selectivity.

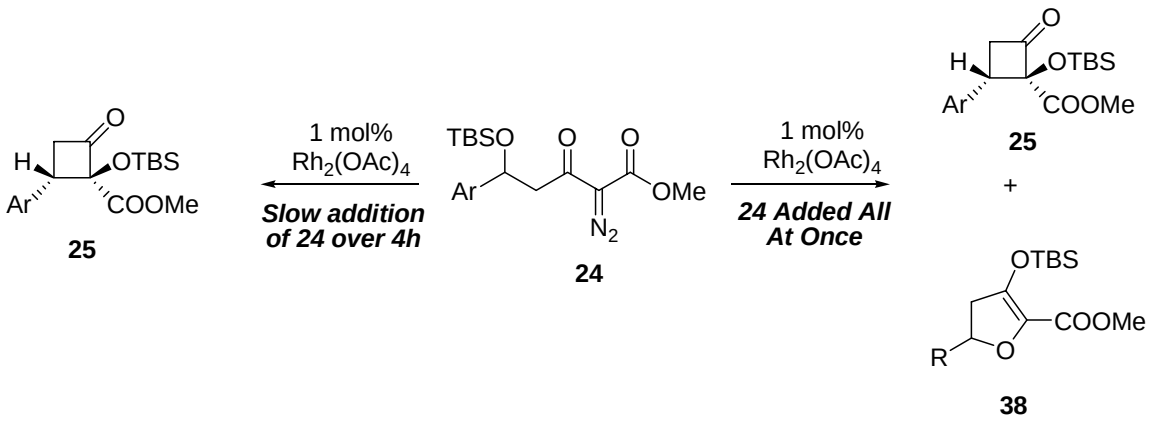
Scheme 3.18:



3.3.4. Effect of Concentration on Chemoselectivity:

TMS-transfer in the intermediate **E** can occur either *via* intermolecular or intramolecular process. In the case of intermolecular transfer of the silyl group it might be possible to control the chemoselectivity of the reaction by controlling the concentration of the reactants. Even for a bulky TBS-group as in the intermediate **B**, if the concentration is too high it might be possible to transfer the TBS-group to the enolate oxygen of a second molecule. So it was thought that instead of running the diazo decomposition reaction of **24** by adding 2**4** all at once to the catalyst system might lead to [1,4]-product. To our pleasure the reaction proceeded as we thought and both [1,2]- and [1,4]-products were formed in 1:1 ratio (*Scheme 3.19*).

Scheme 3.19:

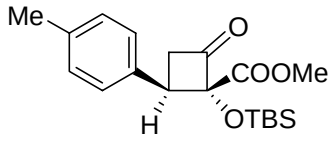


3.4. Conclusions:

The significance of this study is the control of chemoselectivity in the oxonium ylide pathway, leading to two different classes of products starting from structurally similar diazo compounds. The resulting oxonium ylide led to the synthesis of highly substituted cyclobutanones *via* a [1,2]-shift, with high chemical yields and excellent diastereoselectivity. Moving to the more labile TMS as the silyl group, the oxonium ylide preferred [1,4]-shift to make dihydrofurans in excellent yields.

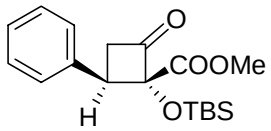
3.5. Experimental:

General Procedure for the Synthesis of Cyclobutanones: A solution of the Mukaiyama aldol adduct **24a** (1.0 mmol) in anhydrous CH_2Cl_2 (2 mL) was added *via* syringe pump over 5 h to a refluxing solution of $Rh_2(OAc)_4$ (4 mg, 0.01 mmol) in anhydrous CH_2Cl_2 (2 mL). The reaction mixture was then allowed to cool to room temperature, and then passed through a short silica gel plug to remove the catalyst with washings of dichloromethane (3x5 mL). The solvent was removed under reduced pressure. The dominant product was isolated by flash column chromatography on silica gel using 20:1 hexane/ethyl acetate solution.



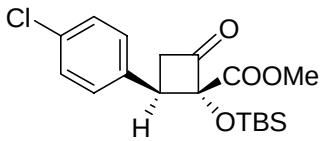
25a

Methyl 1-(*tert*-Butyldimethylsilanoxy)-2-oxo-4-(*p*-tolyl)cyclobutanecarboxylate (25a). IR (neat): 2956, 2856, 1798, 1756, 1473 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.13-7.12 (comp, 4H), 3.74-3.60 (comp, 2H), 3.35 (s, 3H), 3.16 (dd, J = 16.4, 9.6 Hz, 1H), 2.33 (s, 3H), 0.93 (s, 9H), 0.17 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.7, 169.0, 136.8, 133.5, 129.0, 126.7, 51.6, 45.6, 44.3, 29.7, 25.8, 21.1, 18.4, -3.6, -4.1; HRMS (EI) for $C_{19}H_{28}O_4Si$ $[M+H]^+$ calcd: 348.1757; found: 348.1758; TLC R_f = 0.34 (19:1 hexanes: ethyl acetate).



25b

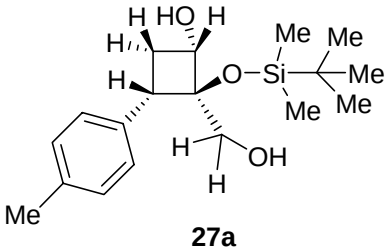
Methyl 1-(*tert*-Butyldimethylsilanoxy)-2-oxo-4-phenylcyclobutanecarboxylate (25b). IR (neat): 2954, 2855, 1797, 1754, 1462 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.32-7.20 (comp, 5H), 3.76-3.60 (comp, 2H), 3.30 (s, 3H), 3.18 (dd, *J* = 16.4, 9.6 Hz, 1H), 0.94 (s, 9H), 0.16 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.5, 168.9, 136.7, 128.2, 127.2, 126.8, 51.6, 45.8, 44.2, 29.6, 25.8, 18.3, -4.1, -5.4; HRMS (FAB) for $C_{18}H_{26}O_4Si$ $[M+H]^+$ calcd: 334.1600; found: 334.1596; TLC R_f = 0.34 (19:1 hexanes: ethyl acetate).



25c

Methyl 1-(*tert*-Butlydimethylsilanoxy)-2-oxo-4-(*p*-chlorophenyl)cyclobutanecarboxylate (25c). IR (neat): 2954, 2857, 1798, 1756, 1493 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 8.4 Hz, 2H), 3.71-3.56 (m, 1H), 3.35 (s, 3H), 3.17 (dd, *J* = 16.4, 9.6 Hz, 1H), 0.91 (s, 9H), 0.16 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.9, 168.8, 135.2, 133.1, 128.5, 128.2, 51.7, 45.4, 44.2, 29.7, 25.8, 18.3, -3.7, -4.1; HRMS (FAB) for $C_{18}H_{25}ClO_4Si$ $[M+H]^+$ calcd: 368.1211; found: 368.1209; TLC R_f = 0.34 (19:1 hexanes: ethyl acetate).

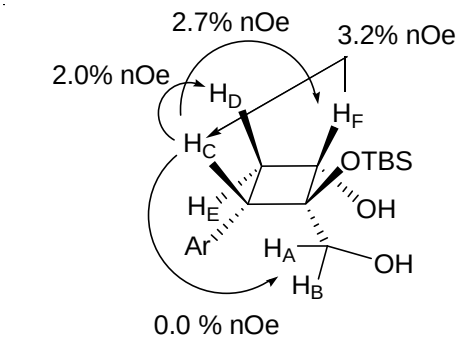
Synthesis of 2-(*tert*-Butyldimethysilanoxy)-2-hydroxymethyl-3-(*p*-tolyl)cyclobutanol (27a). To an oven dried 10-mL round-bottomed flask containing magnetic stir bar and septum under nitrogen was added 1 mL anhydrous THF, followed by lithium aluminium hydride (1.5 mg, 1.0 mmol). The flask was then placed in an ice-water bath. **25a** (201 mg, 0.570 mmol) was dissolved in 1 mL dry THF and was slowly added over 20 min. The reaction mixture was then stirred at room temperature for 4 h. After cooling the flask in an ice bath, 1 mL of water was added, and the product was extracted with THF (3 x 1 mL) and then dried over anhydrous sodium sulphate. Solvent was removed under reduced pressure. Product diol was isolated by flash column chromatography eluting with 3:1 hexanes: ethyl acetate to yield pure **27a** (162 mg, 88%, 95% overall yield) in 12:1 diastereomeric ratio.



27a

Major Isomer of 2-(*tert*-Butlydimethysilanoxy)-2-hydroxymethyl-3-(p-tolyl)cyclobutanol (27a). IR (neat): 3421, 2926, 2855, 1798, 1559 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10 (d, J = 8.0 Hz, 2H), 7.06 (d, J = 8.0 Hz, 2H), 4.29-4.25 (m, 1H), 3.76 (d, J = 10.4 Hz, 1H), 3.33 (d, J = 10.4 Hz, 1H), 3.17-3.12 (m, 1H), 2.43 (ddd, J = 10.8, 8.4, 2.4 Hz, 1H), 2.32 (s, 1H), 1.95-1.87 (m, 1H), 0.82 (s, 9H), -0.08 (s, 3H), -0.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.3, 135.0, 129.3, 127.7, 80.9, 74.1, 63.6, 41.8, 26.2, 23.1,

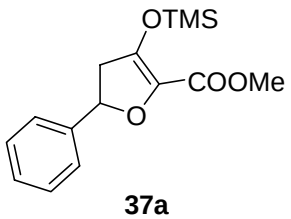
18.3, -5.4, -5.5; HRMS (FAB) for $C_{18}H_{30}O_3Si$ $[M+Na]^+$ calcd: 345.1862; found: 345.1870.



Ar = 4-MeC_6H_4 **27a**

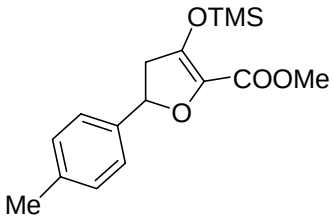
Determination of Relative Stereochemistry in 27a: The relative stereochemistry of substituents in **27a** was determined by nOe experiments with Gauss1.1000 shape pulse and gradient selection. Upon irradiation of the multiplet at δ 4.27 ppm (H_F) 3.2% and 2.3% enhancements were observed for the multiplets at δ 3.15 ppm (H_C) and at δ 2.43 ppm (H_D), respectively, and no enhancement was observed for the doublets at δ 3.76 ppm (H_A) and δ 3.33 ppm (H_B). Similarly upon irradiation of either of the doublets at δ 3.76 ppm (H_A) or δ 3.33 ppm (H_B) no enhancement was observed for the multiplets at δ 3.15 ppm (H_C) and at δ 2.43 ppm (H_D). But 2.7% and 2.0% signal enhancements were seen for multiplets at δ 4.27 ppm (H_F) and δ 2.43 ppm (H_D) upon irradiation of the multiplet at δ 3.15 ppm (H_C). These observations could only be reconciled with the *cis* orientation of the aryl and hydroxymethyl group in the major diol product **27a**. These observations clearly indicate **25a** to be the major cyclobutanone product.

General Procedure for the Synthesis of Dihydrofuranones: A solution of the Mukaiyama aldol adduct **36a** (1.0 mmol) in anhydrous CH_2Cl_2 (2 mL) was added *via* syringe pump over 2 h to a refluxing solution of $Rh_2(OAc)_4$ (4 mg, 0.01 mmol) in anhydrous CH_2Cl_2 (2 mL). The reaction mixture was then allowed to cool to room temperature and passed through a short celite plug (1.5") to remove the catalyst which was rinsed with 3x5 mL of dichloromethane. The solvent was removed under reduced pressure, and the pure product was obtained.



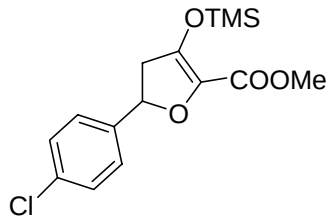
37a

5-phenyl-3-trimethylsilanyloxy-4,5-dihydrofuran-2-carboxylic acid methyl ester (37a): IR (neat): 3155, 2254, 1716, 1659, 1512; ^{1}H NMR (400 MHz, $CDCl_3$):δ 7.38-7.26 (comp, 5H), 5.45 (t, *J* = 9.2 Hz, 1H), 3.78 (s, 3H), 3.17 (dd, *J* = 16.4, 9.2 Hz, 1 H), 2.81 (dd, *J* = 16.4, 9.2 Hz, 1 H), 0.23 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$):160.4, 144.8, 141.5, 128.7, 128.6, 128.0, 126.2, 78.8, 51.3, 42.3, 0.3; HRMS (EI) for $C_{15}H_{20}O_4Si$ [M^+] calcd: 292.1131; found 292.1127, (colorless oil; R_f = 0.44 in 19:1 hexane and ethyl acetate).



37b

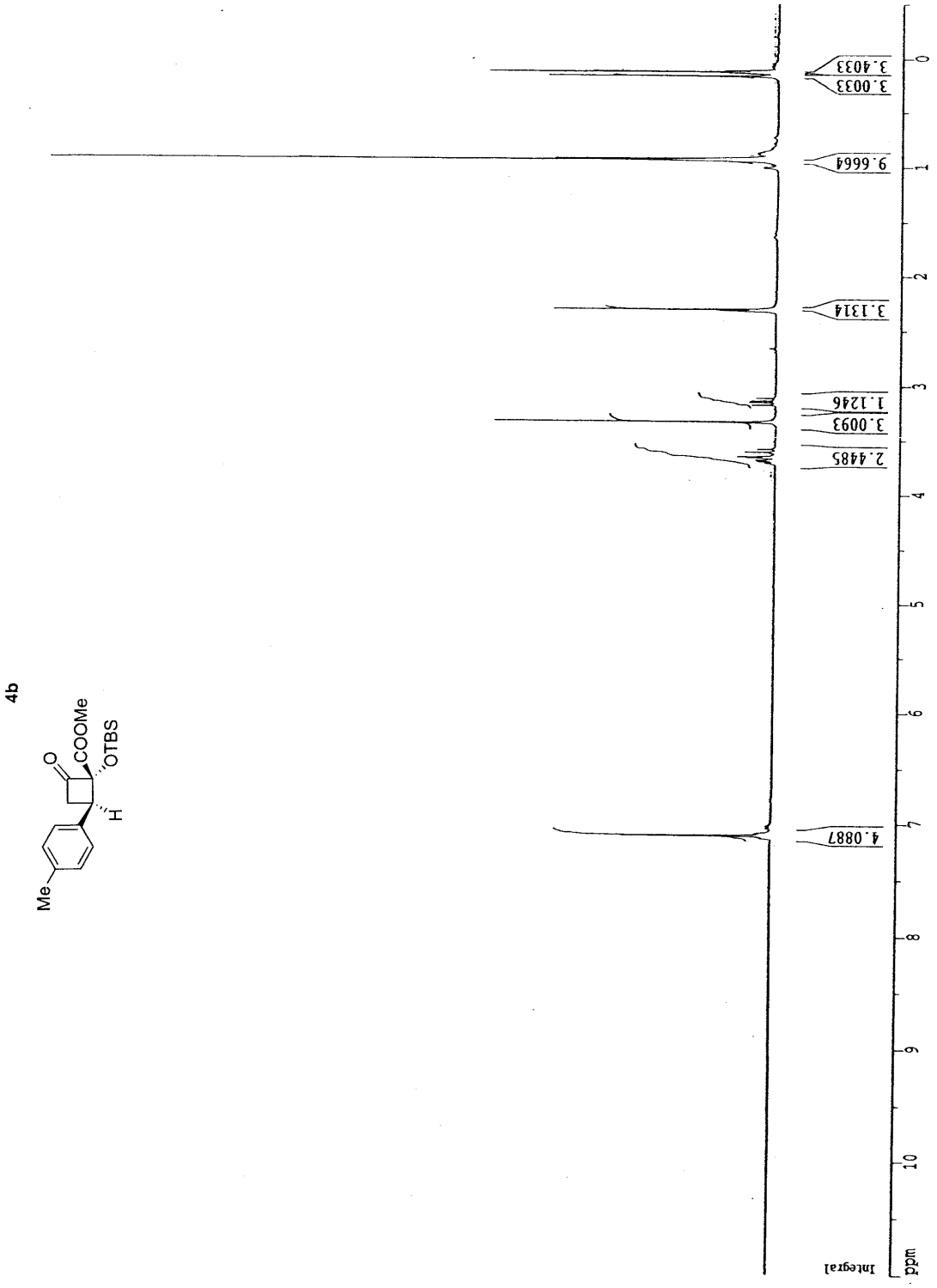
5-(4-tolyl)-3-trimethylsilanyloxy-4,5-dihydrofuran-2-carboxylic acid methyl ester (37b): IR (neat): 3154, 2256, 1719, 1659, 1511; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 8.4 Hz, 2H), 5.45 (t, J = 9.2 Hz, 1H), 3.79 (s, 3 H), 3.18 (dd, *J* = 16.4, 9.2 Hz, 1 H), 2.78 (dd, *J* = 16.4, 9.2 Hz, 1 H), 2.31 (s, 1H), 0.23 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$):160.5, 144.9, 141.8, 128.4, 128.3, 128.0, 126.2, 78.8, 51.3, 42.3, 21.8, 0.3; HRMS (EI) for $C_{16}H_{22}O_4Si$ [M^+] calcd: 316.1211; found 316.1207, (colorless oil; R_f= 0.43 in 19:1 hexane and ethyl acetate).

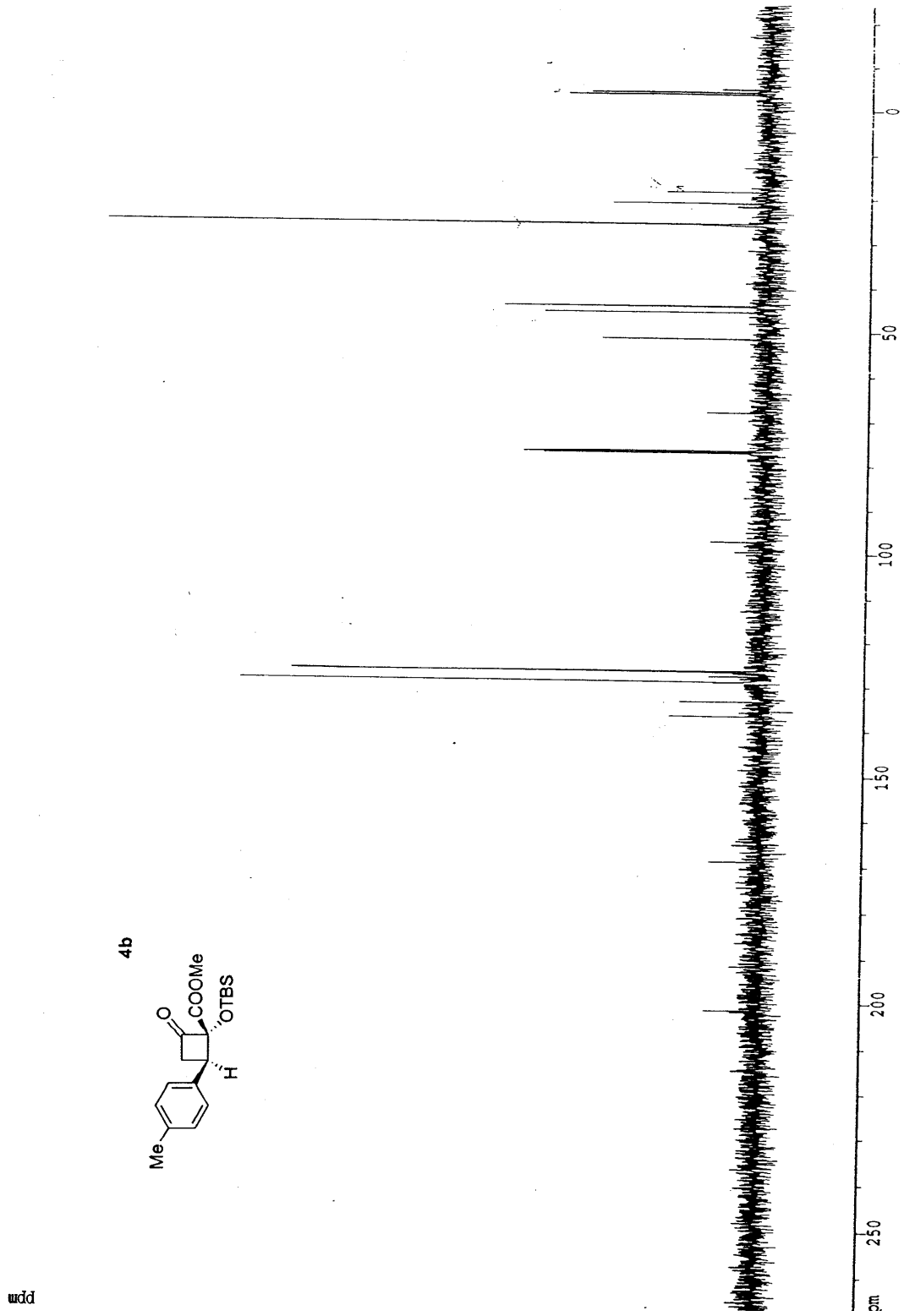


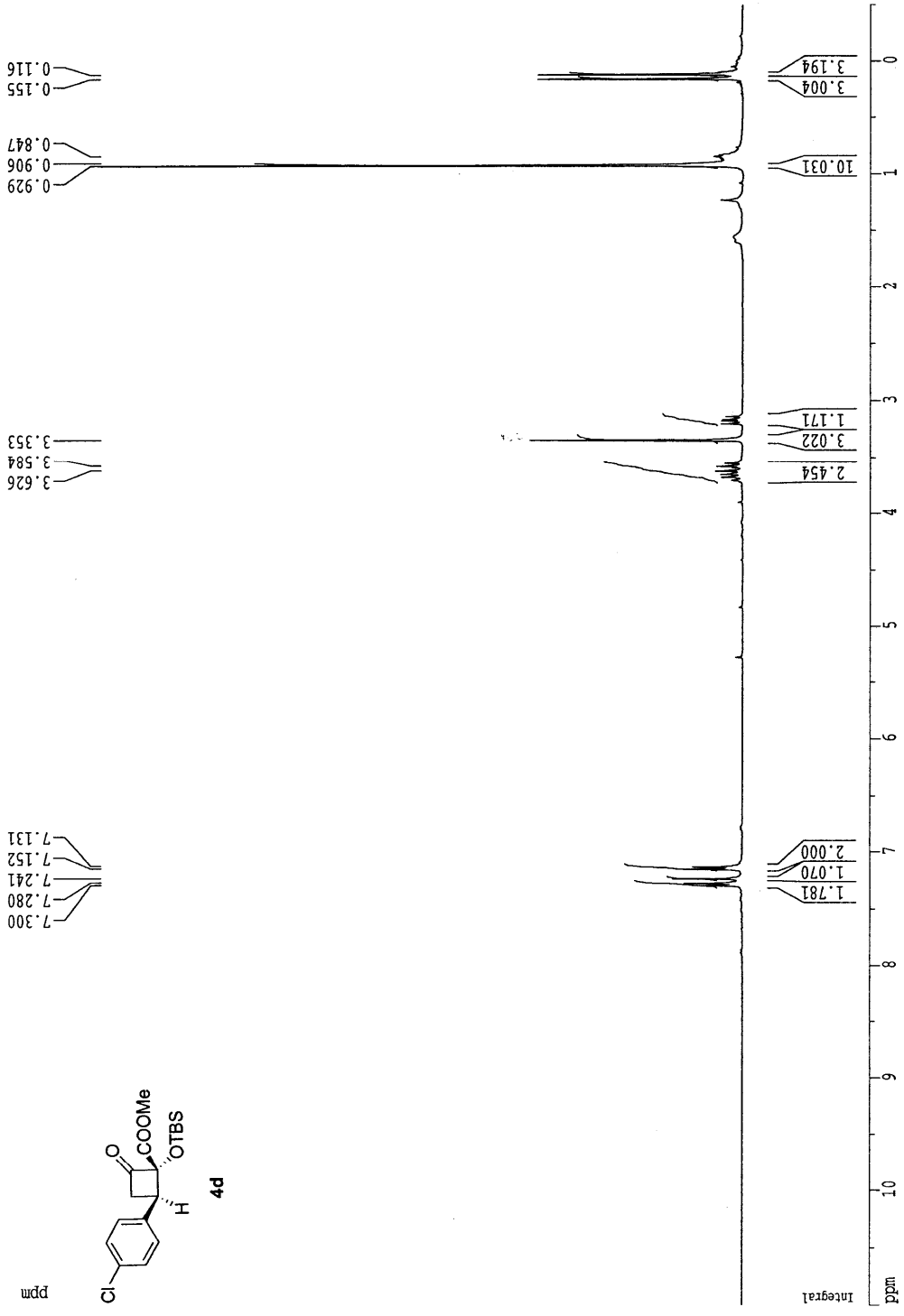
37c

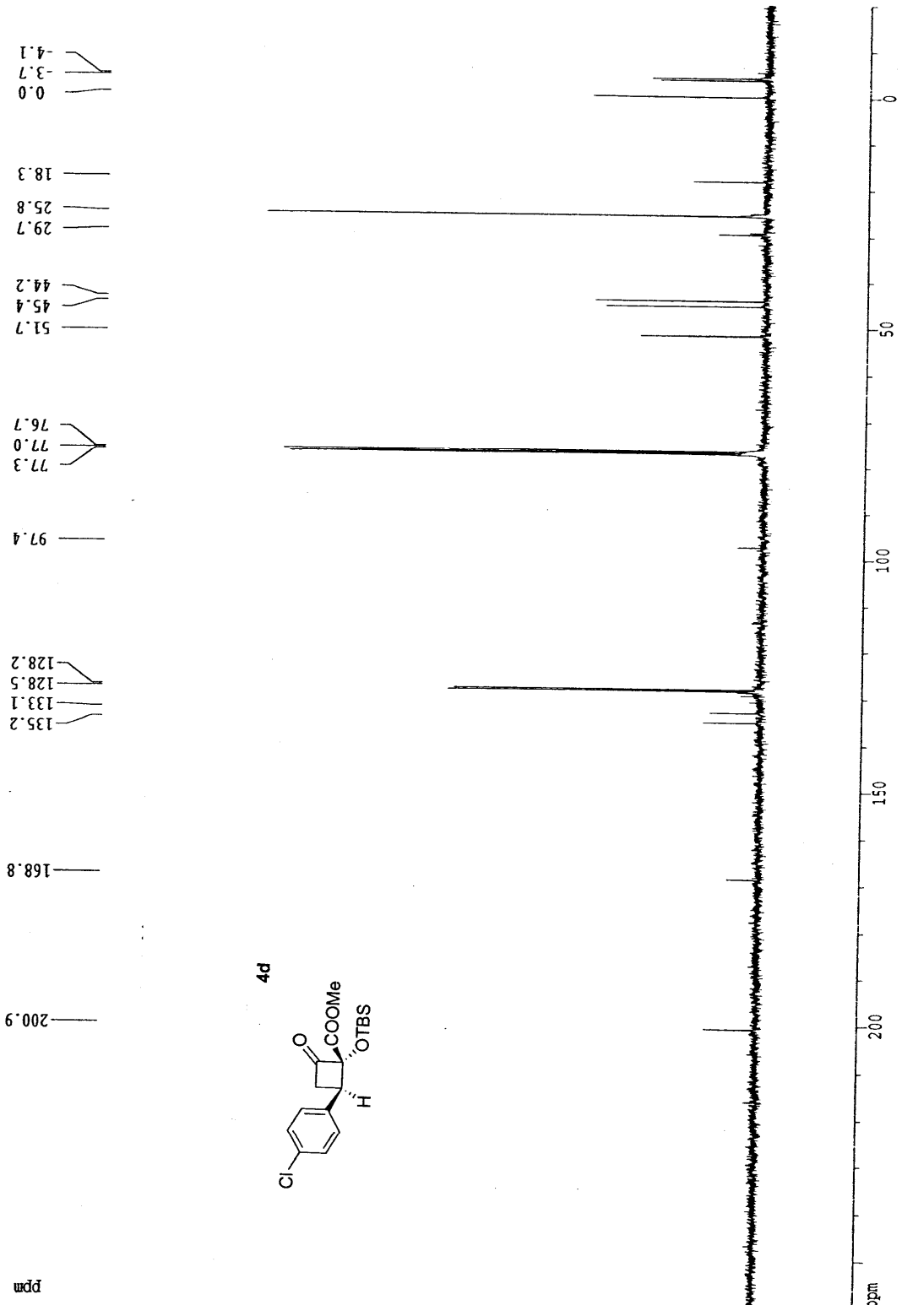
5-(4-chloro-phenyl)-3-trimethylsilanyloxy-4,5-dihydrofuran-2-carboxylic acid methyl ester (37c): IR (neat): 3152, 2254, 1719, 1657; ^{1}H NMR (400 MHz, $CDCl_3$):δ 7.25-7.23 (comp, 4H), 5.44 (t, J = 9.2 Hz, 1H), 3.77 (s, 3H), 3.16 (dd, J = 16.4, 9.2 Hz, 1 H), 2.82 (dd, J = 16.4, 9.2 Hz, 1 H), 0.23 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$):160.4,

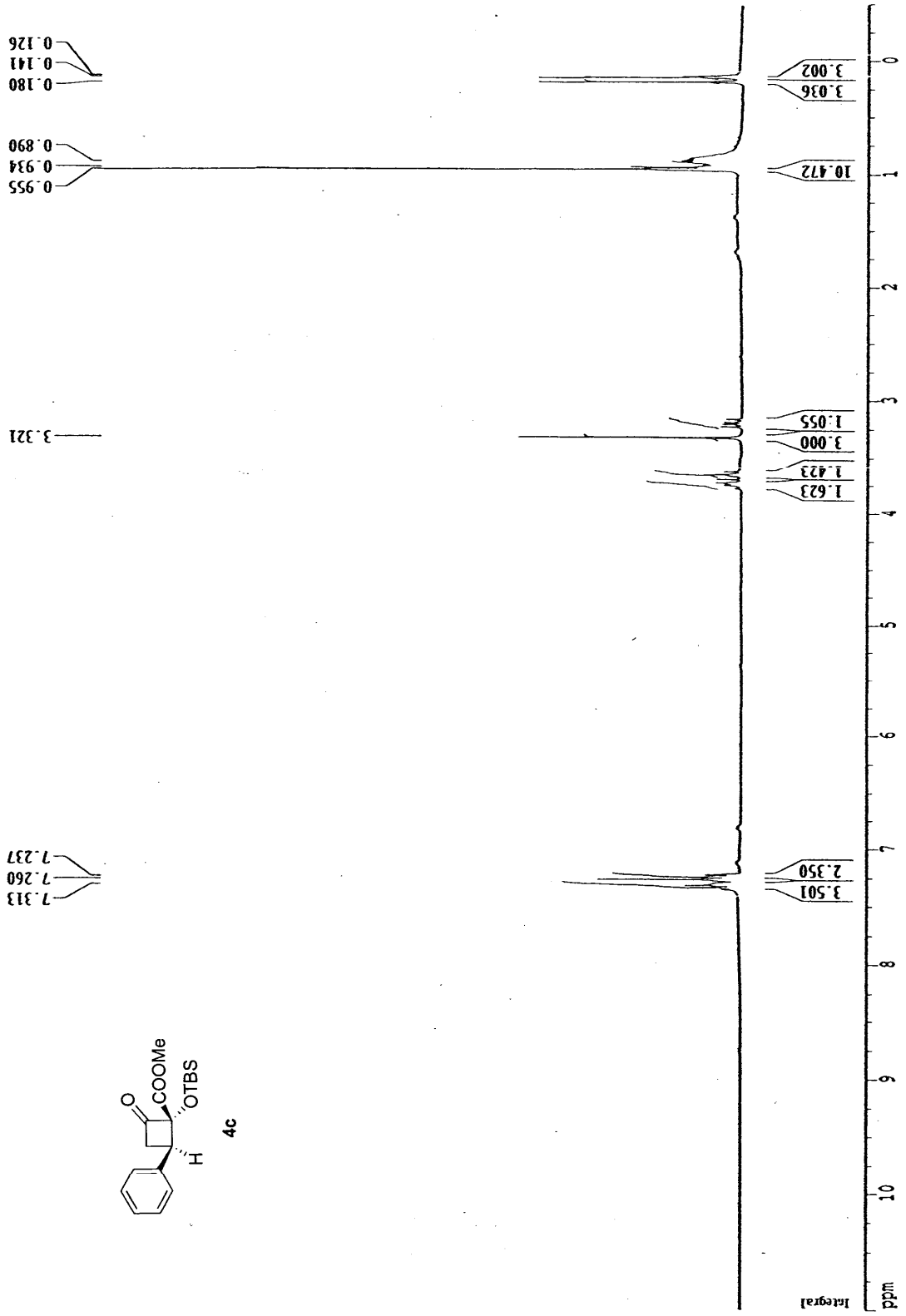
145.1, 141.3, 128.6, 128.4, 128.3, 126.4, 78.8, 51.1, 42.4, 0.31; HRMS (FAB) for $C_{15}H_{19}O_4ClSi$ [M+1] calcd: 326.6332; found 326.6332.

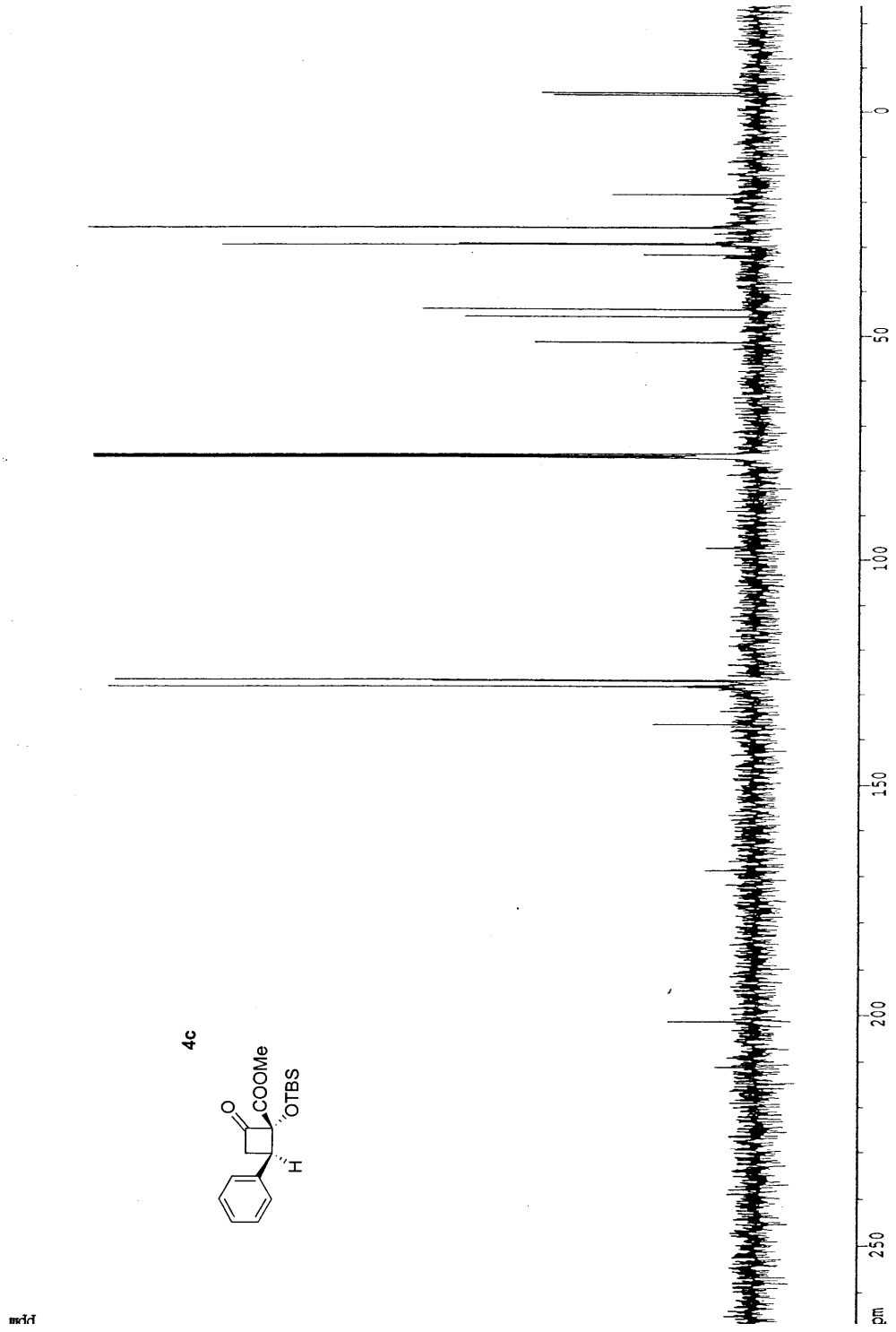

4b
O
COOMe
OTBS
H
Me
Integral
4.0887
2.4485
3.0093
1.1246
3.1314
9.6664
3.0033
3.4033
ppm

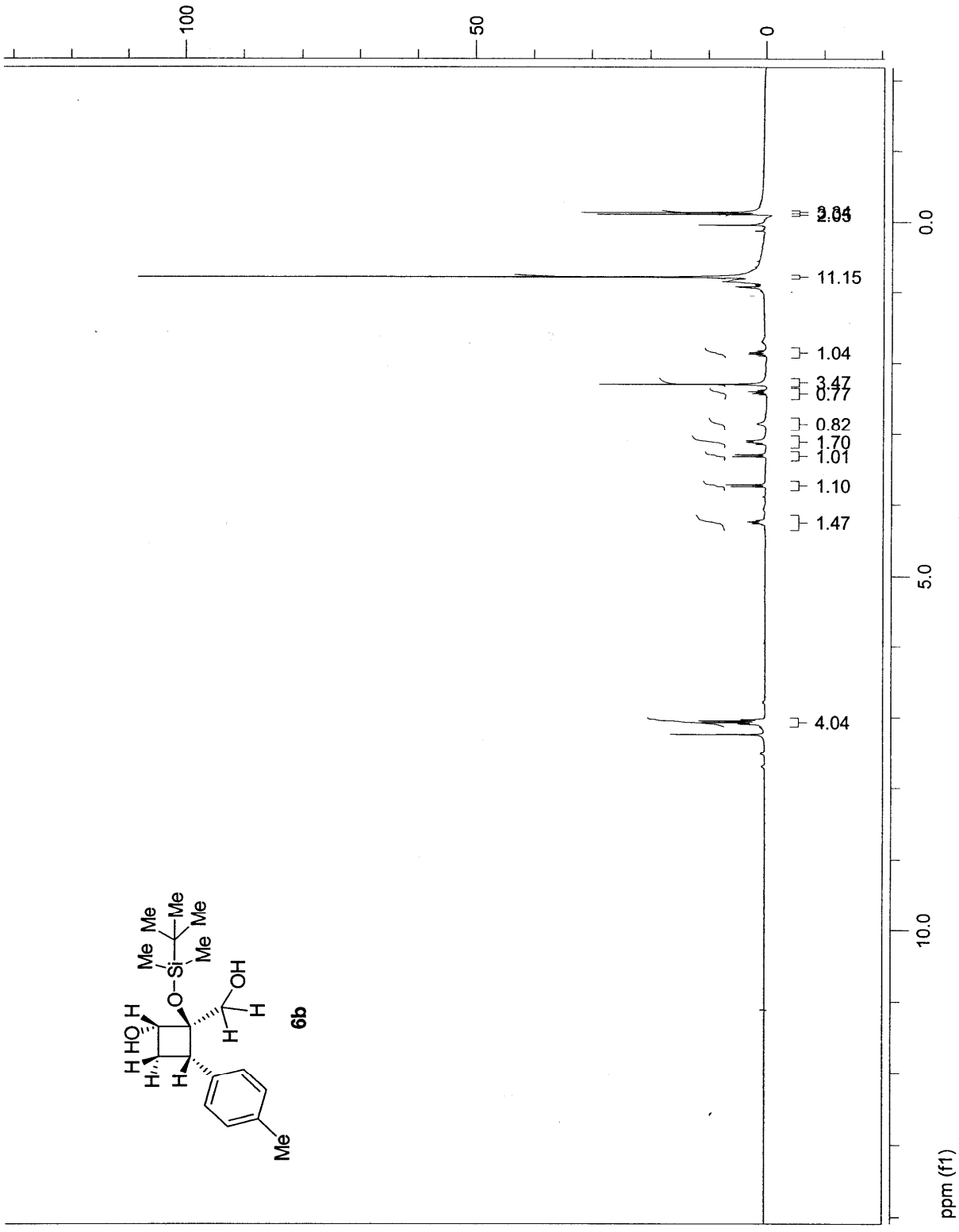

4b
O
COOMe
OTBS
H
Me
ppm
0
50
100
150
200
250

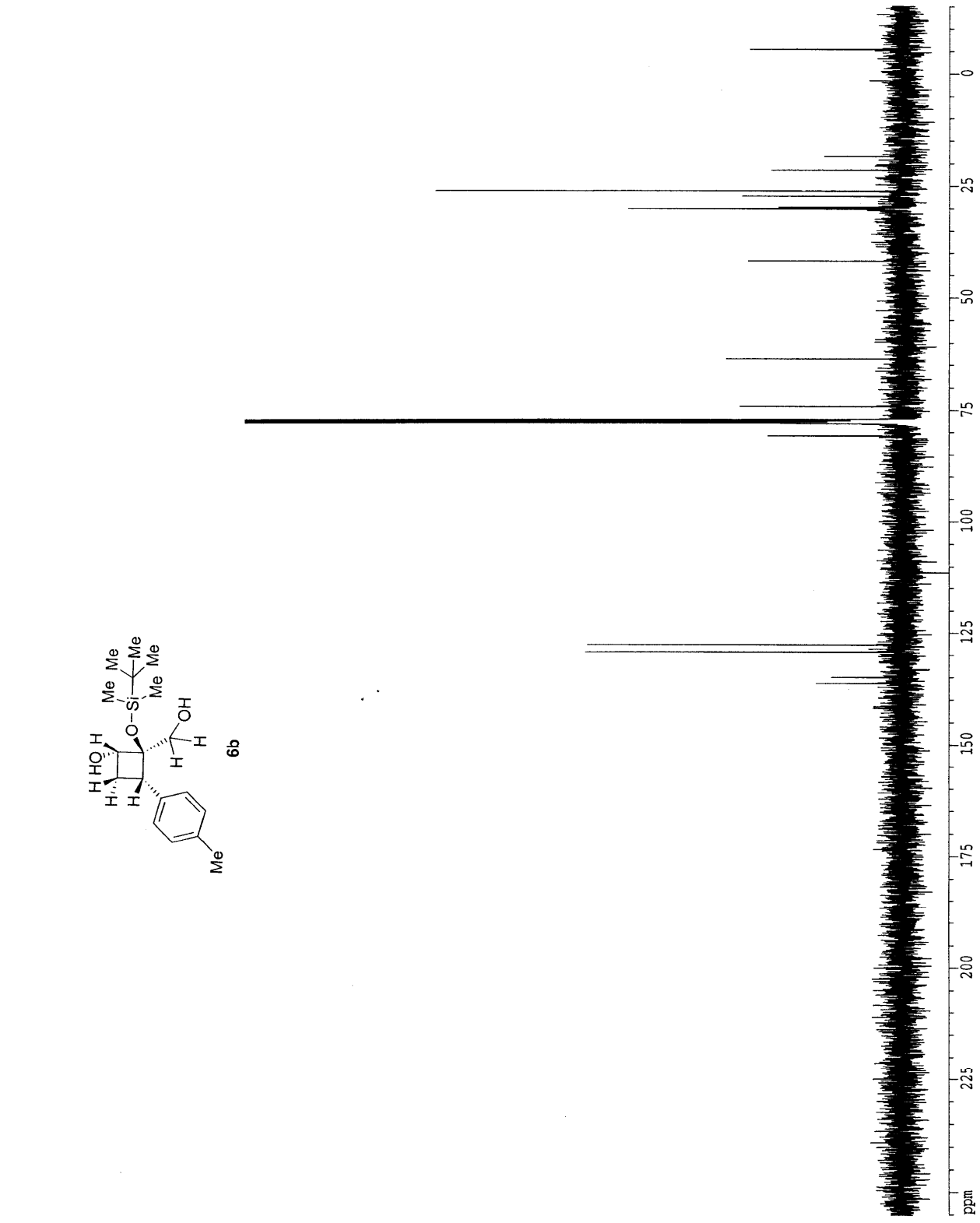

7.300
7.280
7.241
7.152
7.131
3.626
3.584
3.353
0.929
0.906
0.847
0.155
0.116
1.781
1.070
2.000
2.454
1.171
3.022
10.031
3.004
3.194
Integral
ppm
Cl
H
OTBS
COOMe
O
4d

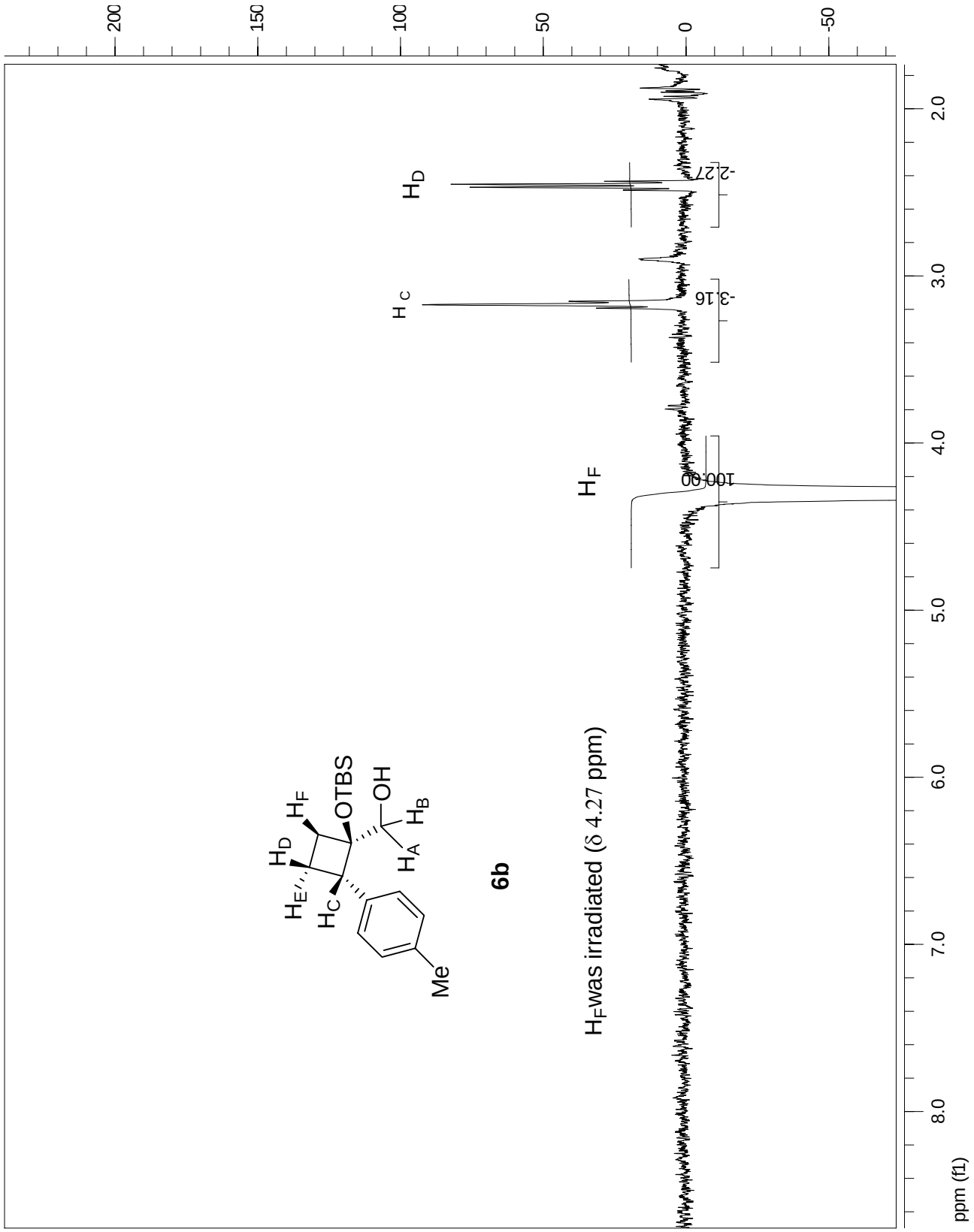

4d
COOMe
OTBS
H
Cl
-4.1
-3.7
0.0
18.3
25.8
29.7
44.2
45.4
51.7
76.7
77.0
77.3
97.4
128.2
128.5
133.1
135.2
168.8
200.9
ppm
0
50
100
150
200

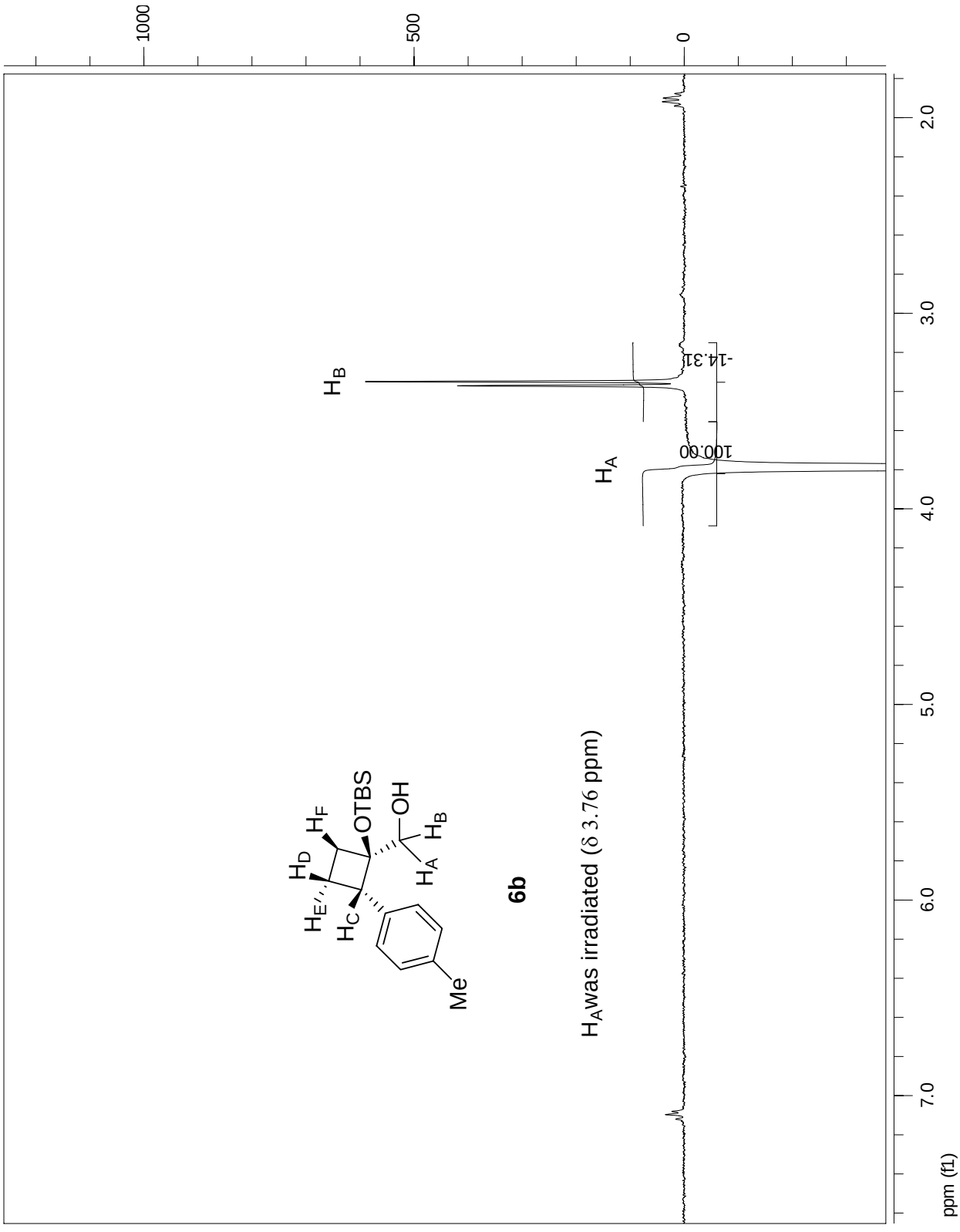

0.126
0.141
0.180
0.890
0.934
0.955
3.321
7.237
7.260
7.313
3.002
3.036
10.472
1.055
3.000
1.423
1.623
3.501
2.350
Integral
ppm
COOMe
OTBS
H
4c

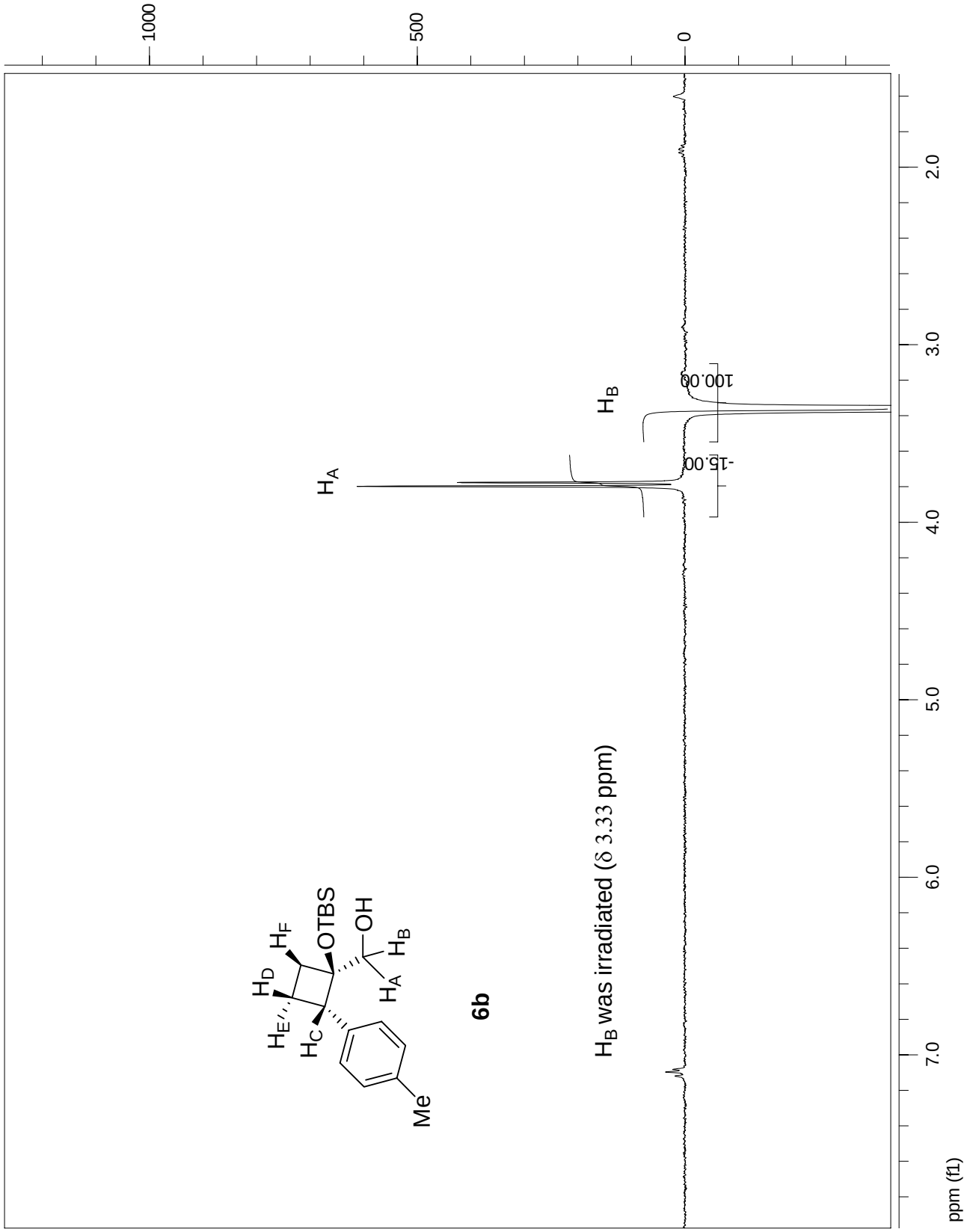

4c
COOMe
OTBS
H
0
50
100
150
200
250
ppm

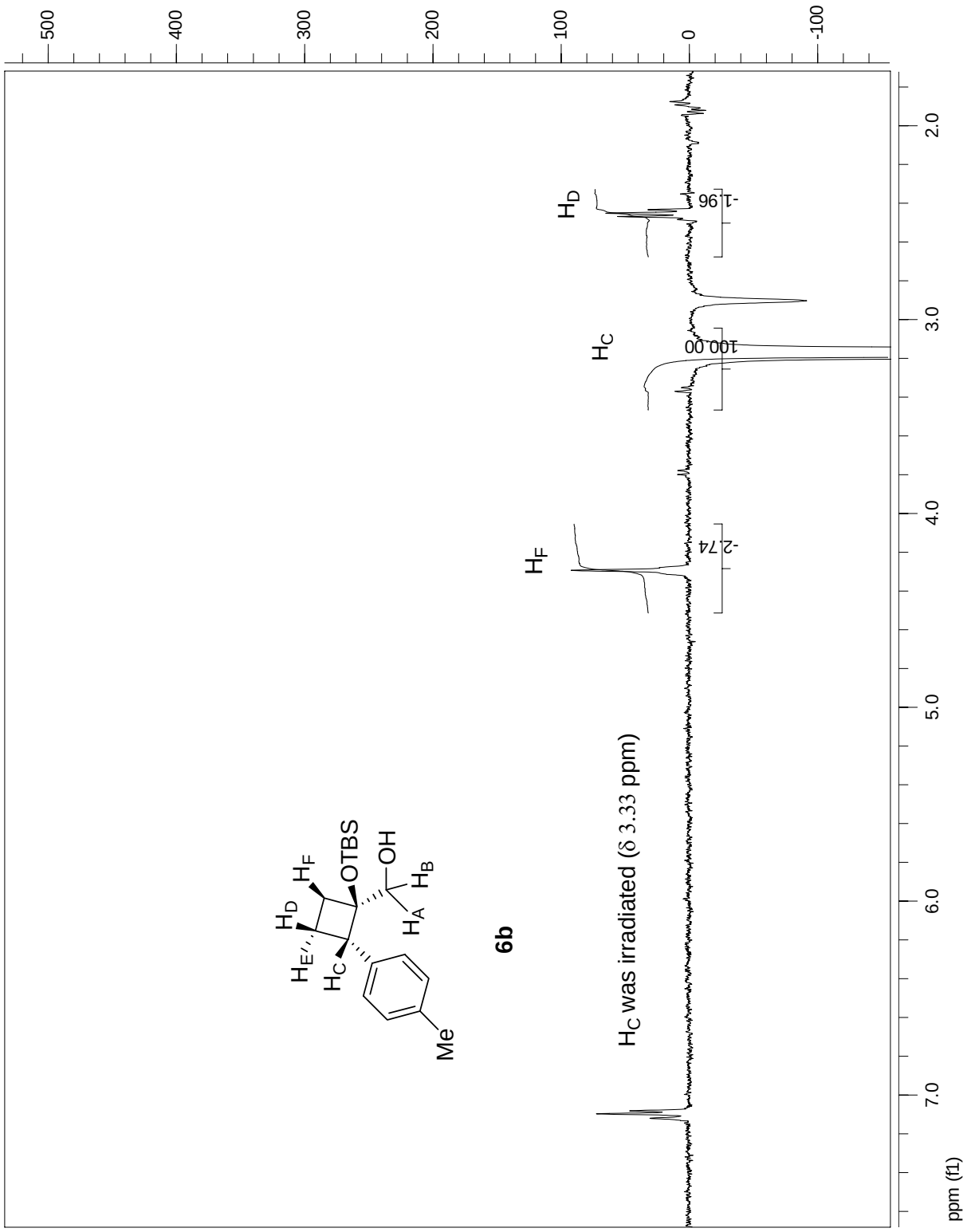

100
50
0
2.04
2.03
11.15
1.04
3.47
0.77
0.82
1.70
1.01
1.10
1.47
4.04
0.0
5.0
10.0
ppm (f1)
Me
Me
Me
Me
Me
Si
O
OH
H
HO
H
H
H
H
Me
6b

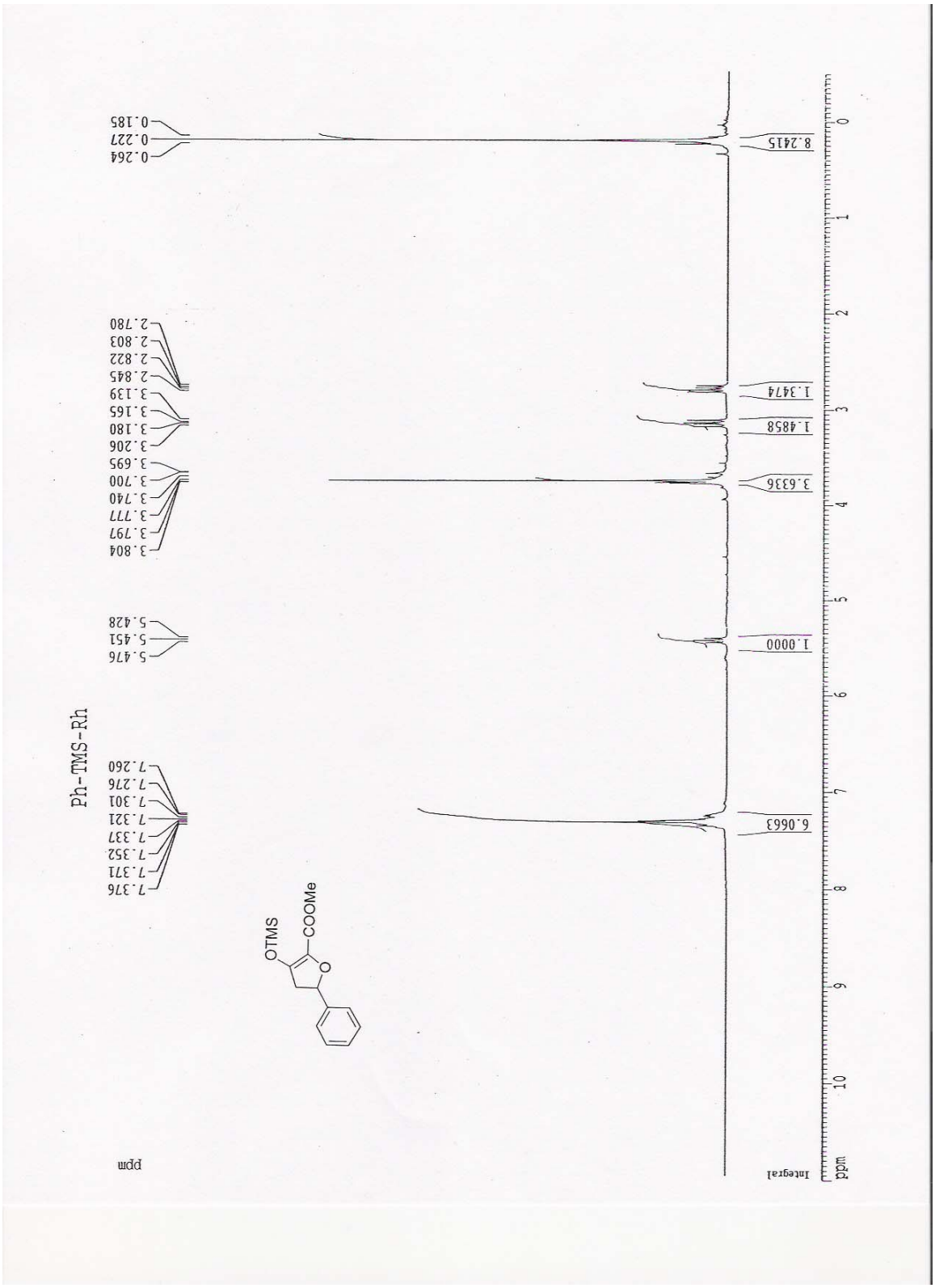

Me Me
Me Me
Me Me
O–Si
OH
H
H
HO H
H
H
Me
6b
0
25
50
75
100
125
150
175
200
225
ppm

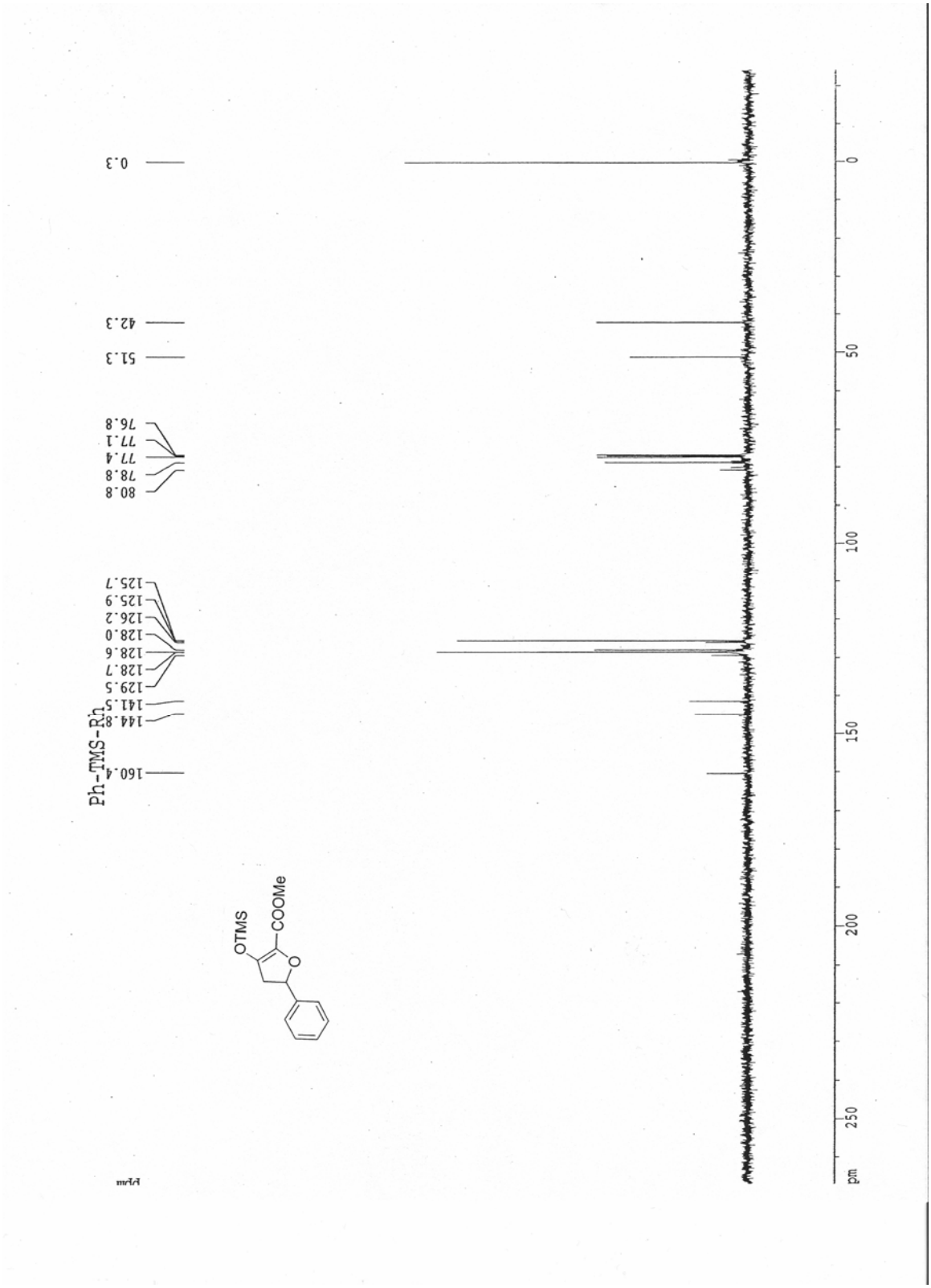

200
150
100
50
0
-50
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (f1)
H_D
H_C
H_F
-2.27
-3.16
100.00
H_F was irradiated (δ 4.27 ppm)
6b
OTBS
OH
Me
H_D
H_F
H_E
H_C
H_A
H_B


1000
500
0
2.0
3.0
4.0
5.0
6.0
7.0
ppm (f1)
H_B
H_A
-14.31
100.00
H_A was irradiated (δ 3.76 ppm)
6b
H_D
H_F
OTBS
OH
H_B
H_A
H_E'
H_C
Me


1000
500
0
2.0
3.0
4.0
5.0
6.0
7.0
ppm (f1)
100.00
-15.00
H_A
H_B
H_B was irradiated (δ 3.33 ppm)
H_D
H_F
OTBS
OH
H_B
H_A
$H_{E'}$
H_C
Me
6b


500
400
300
200
100
0
-100
2.0
3.0
4.0
5.0
6.0
7.0
ppm (f1)
H_D
-1.96
H_C
100.00
H_F
-2.74
H_C was irradiated (δ 3.33 ppm)
6b
H_D
H_F
OTBS
OH
H_B
H_A
H_E'
H_C
Me


Ph-TMS-Rh
OTMS
COOMe
Integral
ppm
8.2415
1.3474
1.4858
3.6336
1.0000
6.0663
0.264
0.227
0.185
2.780
2.803
2.822
2.845
3.139
3.165
3.180
3.206
3.695
3.700
3.740
3.777
3.797
3.804
5.428
5.451
5.476
7.260
7.276
7.301
7.321
7.337
7.352
7.371
7.376


Ph-TMS-Rh
160.4
144.8
141.5
129.5
128.7
128.6
128.0
126.2
125.9
125.7
80.8
78.8
77.4
77.1
76.8
51.3
42.3
0.3
OTMS
COOMe
0
50
100
150
200
250
ppm

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