Optimization of the Synthesis of α-Hydroxy-spiro-Carbonates and Further Functionalization of the spiro-Carbonate Moiety

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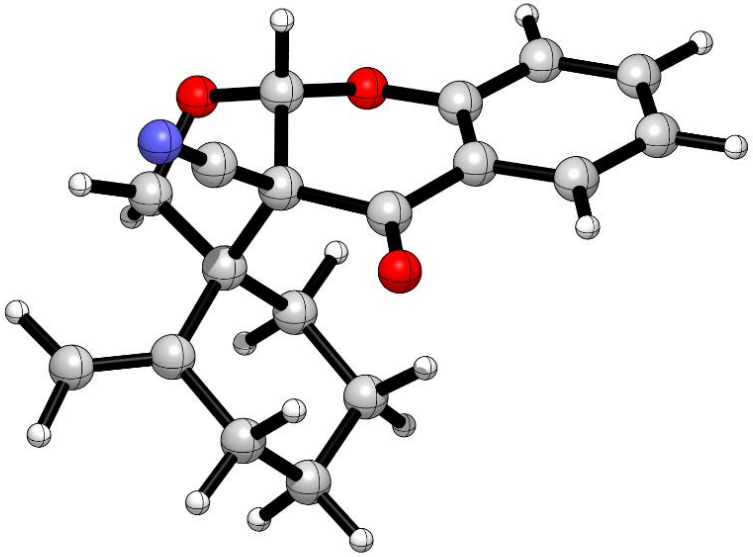
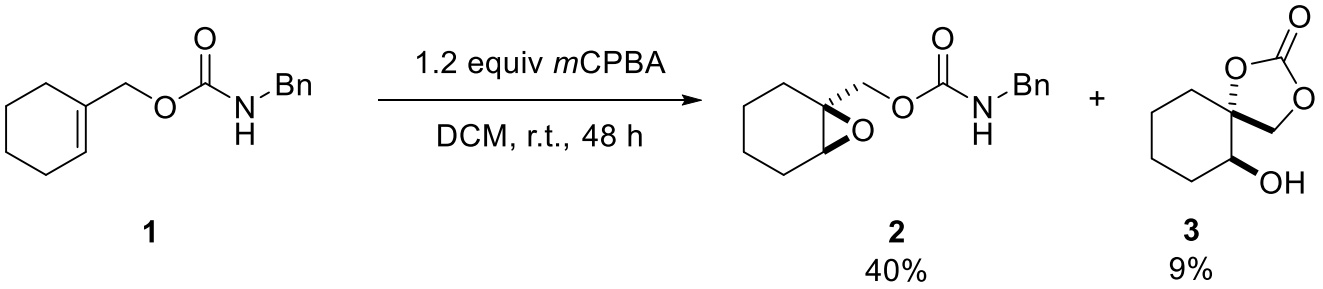


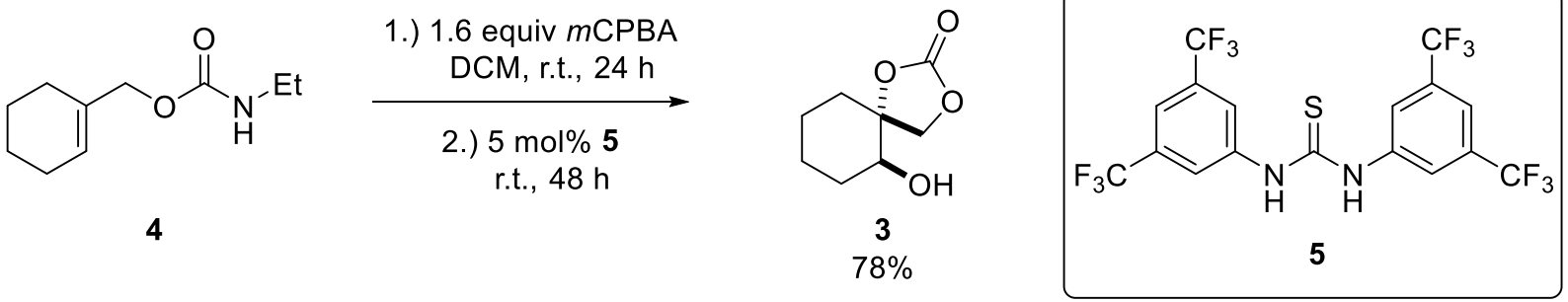
Initial Research into the Formation of α-Hydroxy-spiro-Carbonates

- Schuler observed that the Prilezhaev epoxidation of **1** yielded spiro-carbonate **3** as a side-product



1 | **2** 40% | **3** 9%

- Yield of **3** was increased to 78% by an OFAT (one-factor-at-a-time-design)



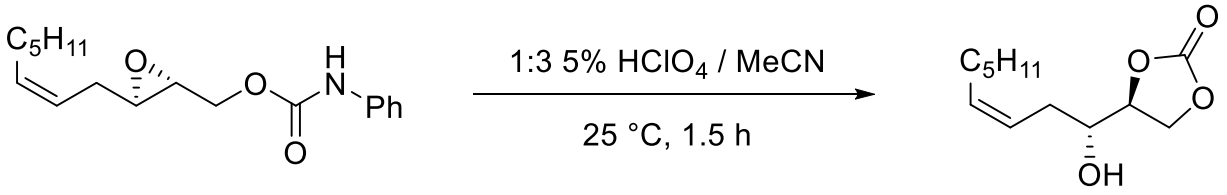
4 | **3** 78% | **5**

S. M. M. Schuler, **2016**, *(Un)expected Extenions of the Multicatalysis Concept*, Justus-Liebig-Universität Gießen, Germany, hds.hebis.de/ubgi/Record/HEB39880575X, 46 – 52.

Earlier Reported Carbonate Formations from Epoxides

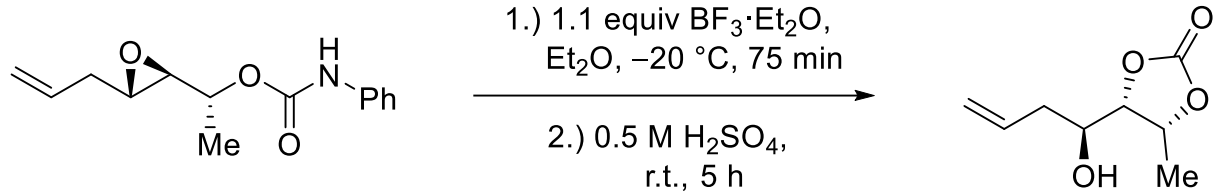
- Comparable carbonate formations have been observed by Corey *et al.* and Roush *et al.*

Corey *et al.* 1980:



6 **7**
75%

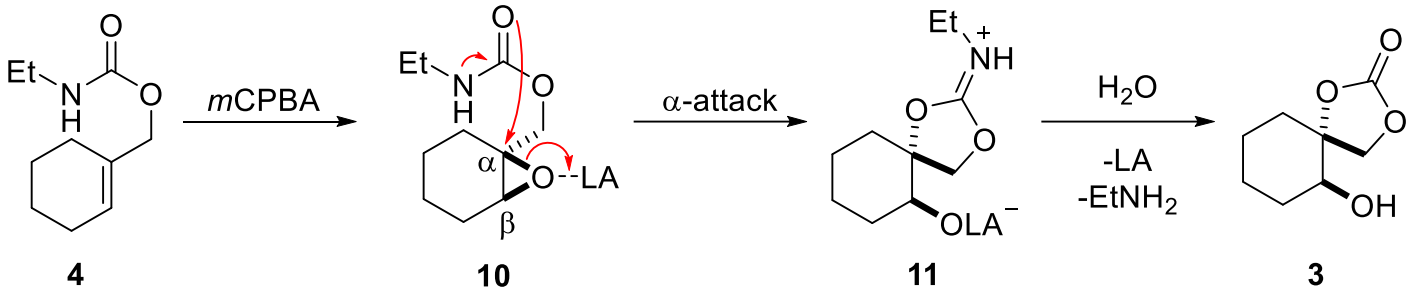
Roush *et al.* 1983:



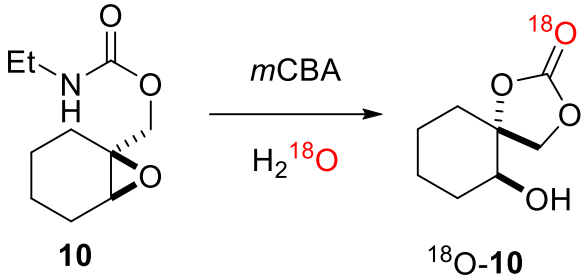
8 **9**
82%

E. Corey, P. Hopkins, J. Munroe, A. Marfat, S.-C. Hashimoto, J. Am. Chem. Soc. 1980, 102, 7986 − 7987.
W. Roush, R. Brown, M. DiMare, *J. Org Chem.* **1983**, *48*, 5038 − 5093.

- Epoxide **10** is opened by an α-attack of the carbonyl oxygen

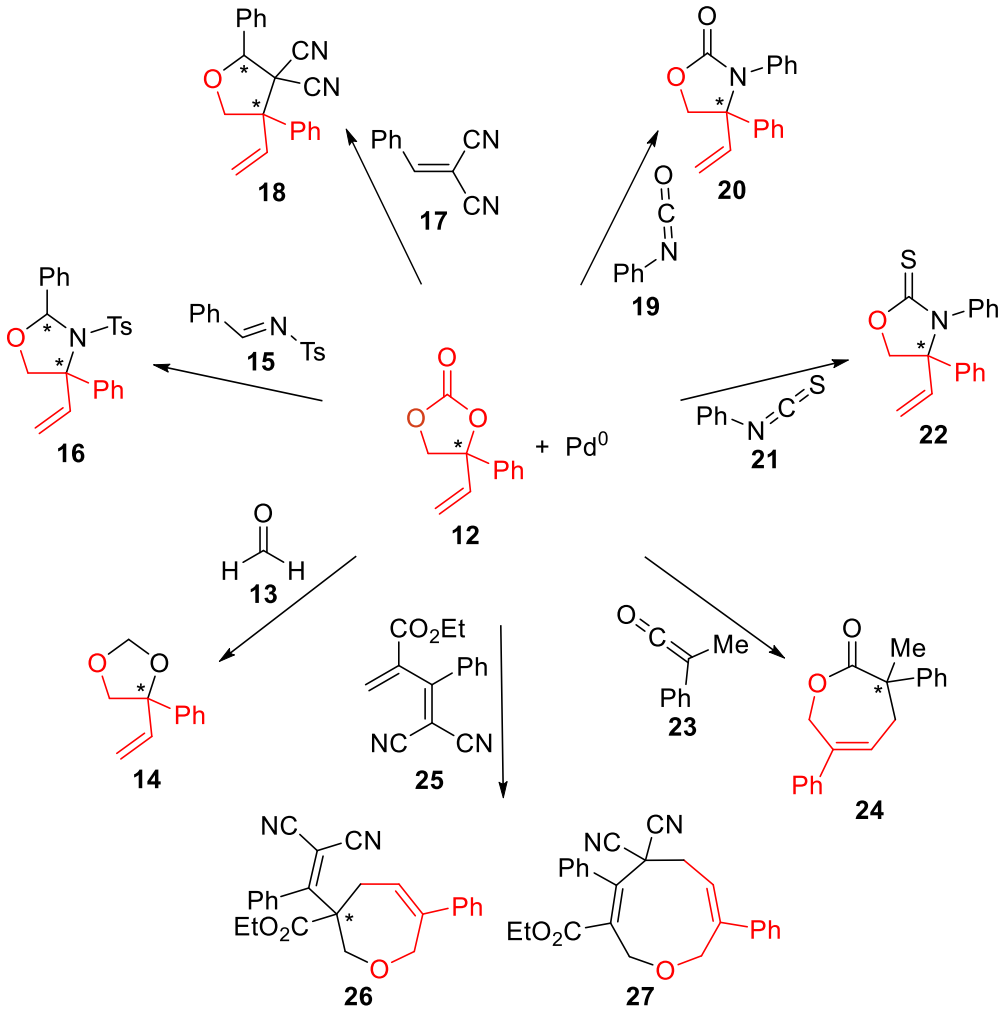


- Further evidence for this mechanism obtained by isotopic labeling



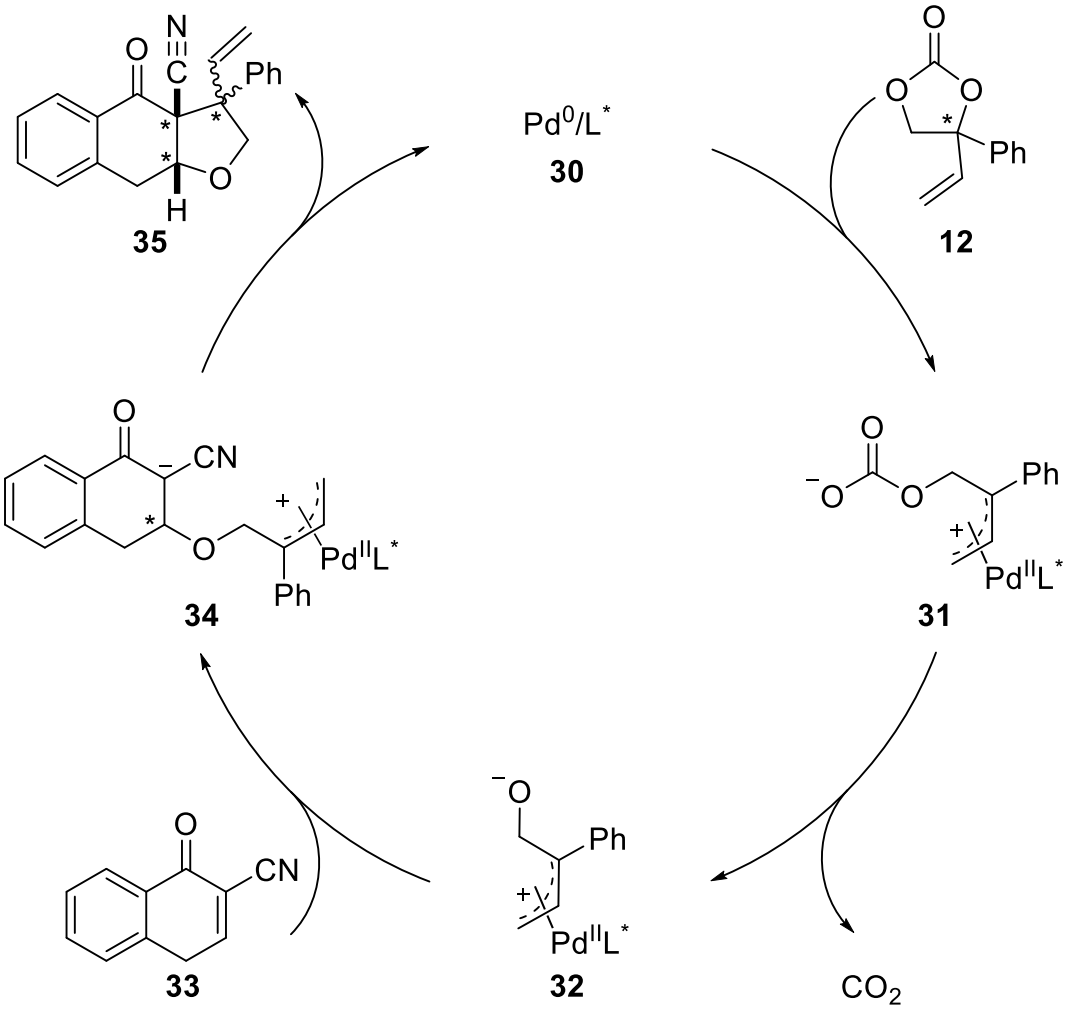
W. Roush, R. Brown, M. DiMare, *J. Org Chem.* **1983**, *48*, 5038 − 5093.
S. M. M. Schuler, **2016**, *(Un)expected Extenions of the Multicatalysis Concept*, Justus-Liebig-Universität Gießen, Germany, hds.hebis.de/ubgi/Record/HEB39880575X, 51.

VEC Reactions



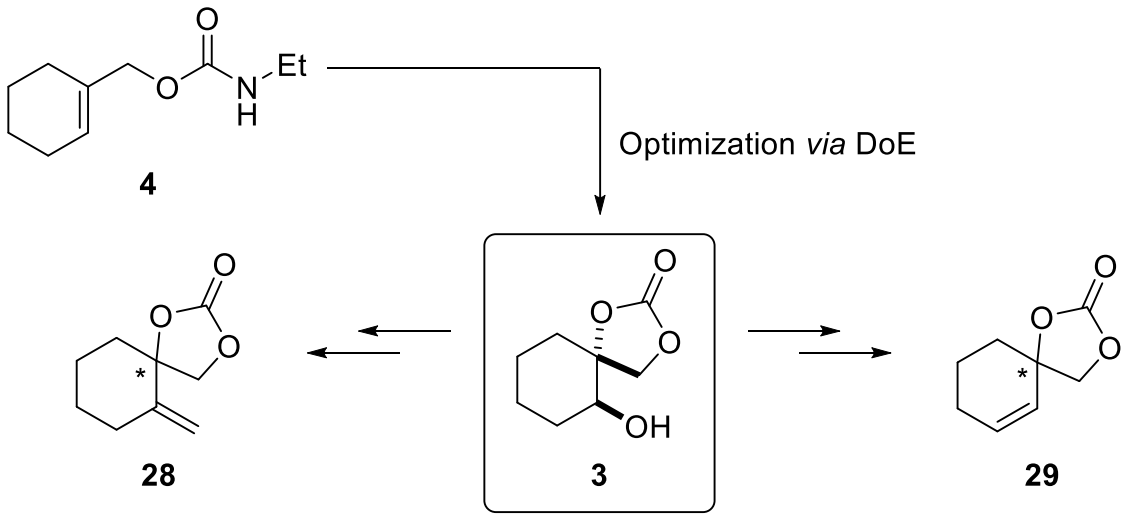
A. Khan, R. Zheng, Y. Khan, J. Ye, J. Xing, Y. J. Zhang, *Angw. Chem. Int Ed.* **2014**, *53*, 6439–6442.
L. Yang, A. Khan, R. Zheng, L. Y. Jin, Y. J. Zhang, *Org. Lett.* **2015**, *17*, 6230 – 6233.
A. Khan, L. Yang, J. Xu, L. Y. Jin, Y. J. Zhang, *Angew. Chem. Int. Ed.* **2014**, *53*, 42, 11257 – 11260.
A. Khan, J. Xing, J. Zhao, Y. Kan, W. Zhang, Y. J. Zhang, *Chem. Eur. J.* **2015**, *21*, 120 – 124.
W. Xiong, S. Zhang, H. Li, Z. Zhang, T. Xu, *J. Org. Chem.* **2020**, *85*, 8773 – 8779.
Y. Wei, S. Liu, M.-M. Li, Y. Li, Y. Lan, L.-Q. Lu, W.J. Xiao, *J. Am. Chem. Soc.* **2019**, *141*, 133 – 137.
X. Zhang, X. Li, J.-L. Li, Q.-W. Wang, W.-L. Zou, Y.-Q. Liu, Z.-Q. Jia, F. Peng, B. Han, *Chem. Sci.* **2020**, *11*, 2888 – 2894.

Catalytic Cycle of the Formal [3+2] Cycloaddition

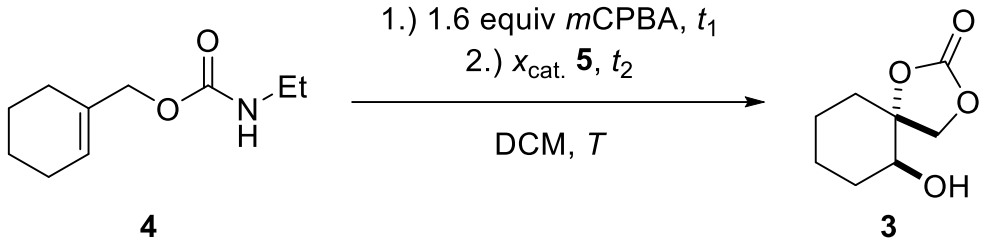


I. Khan, C. Zhao, Y. J. Zhang, *Chem. Comm.* **2018**, *54*, 4708 − 4711.
P. J. Clemens, R. Hayes, T. W. Wallace, *Tetrahedron* **1991**, *47*, 9431 − 9438.

- Optimization of the synthesis of spiro-carbonate **3**
- Functionalization of **3** with the goal of obtaining VECs (vinylethylene carbonates) **28** and **29**



- Five factors, each with three levels
- Central composite design with 28 individual experiments

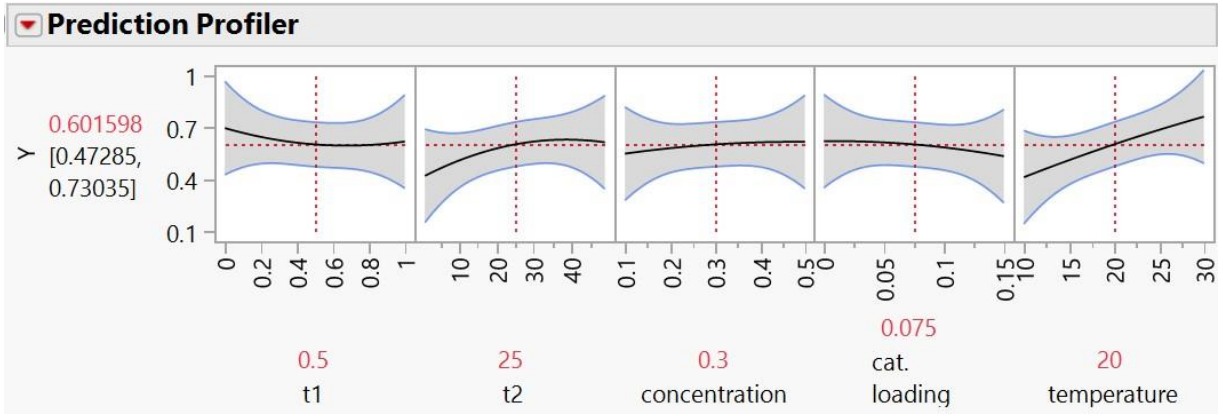


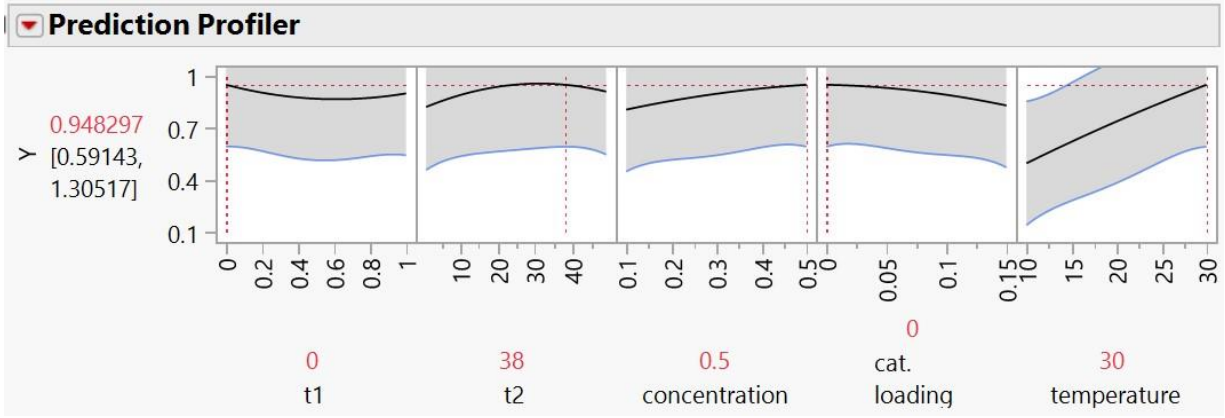
Factor	Description	Range
t_1	time before adding **5**	0 – 1 h
t_2	reaction time after addition of **5**	1 – 49 h
c	concentration of carbamate **4**	0.1 – 0.5 M
$x_{cat.}$	catalyst loading	0 – 0.15 eq.
T	temperature	10 – 30 °C

JMP®, Version 14.0.0 (32 bit), SAS Institute Inc., Cary, NC, 1989-2019.

Results of the DoE Analysis

- Concentration and catalyst loading show no significant influence
- Temperature and reaction time affect the yield
- Highest yield in single run 91% (determined by ^{1}H-NMR)

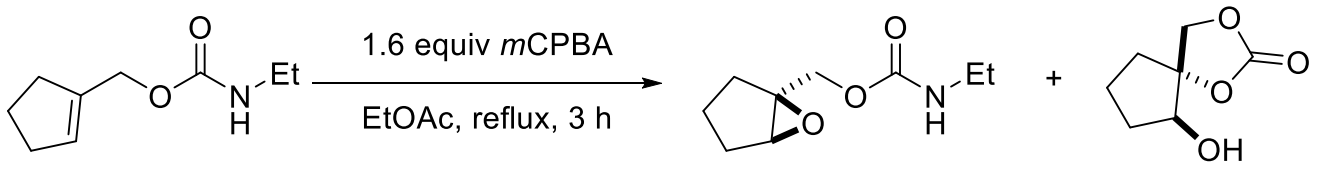




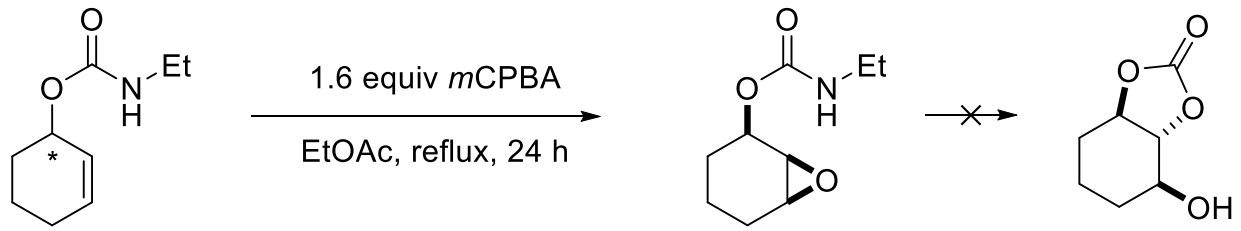
JMP®, Version 14.0.0 SAS Institute Inc., Cary, NC, 1989-2019.

- 88% yield of isolated product under optimized conditions
- Change of solvent allows for shortened reaction times

Solvent	Temperature /° C	Reaction Time / h	Yield of isolated product / %
DCM	30	38	88
$CHCl_3$	66 (reflux)	3	81
EtOAc	77 (reflux)	3	83

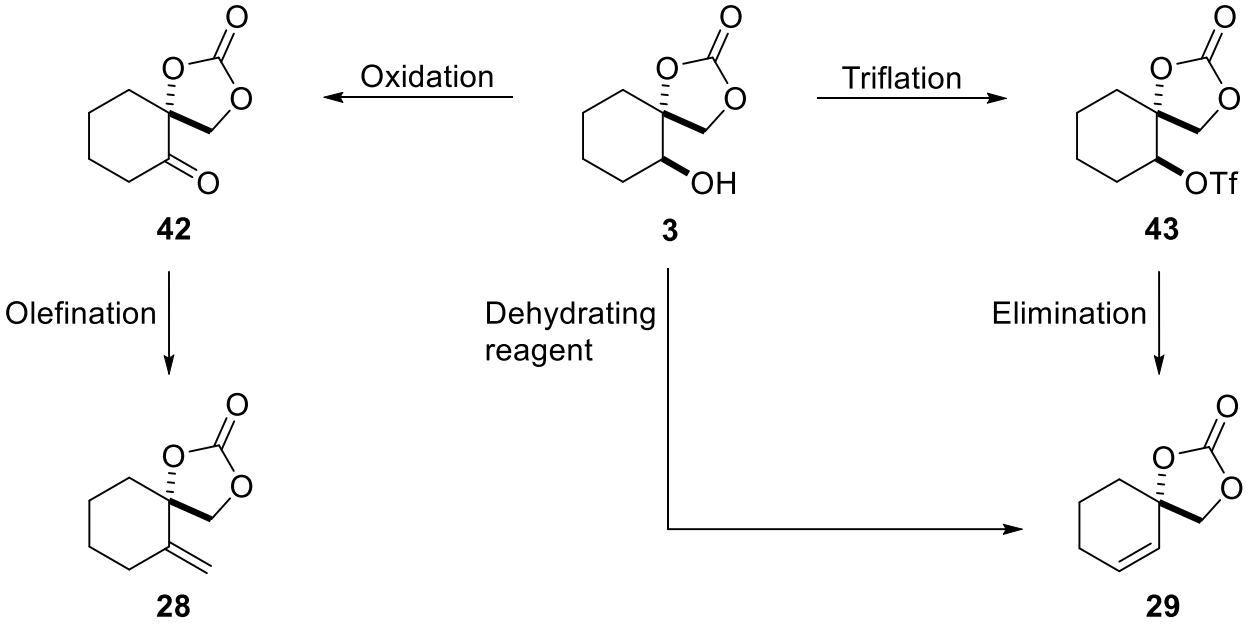


36 → **37** 30% + **38** 38%

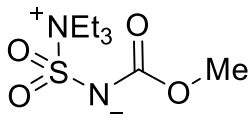


39 → **40** TLC-MS → **41**

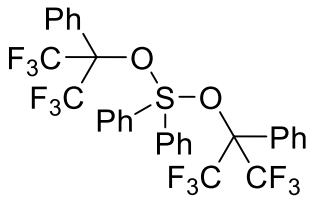
T. Laird, *Org. Process Res. Dev.* **2012**, 16, 1 − 2.



- Elimination with dehydration reagents Martin's sulfurane and Burgess reagent would offer access to **xx** in one step



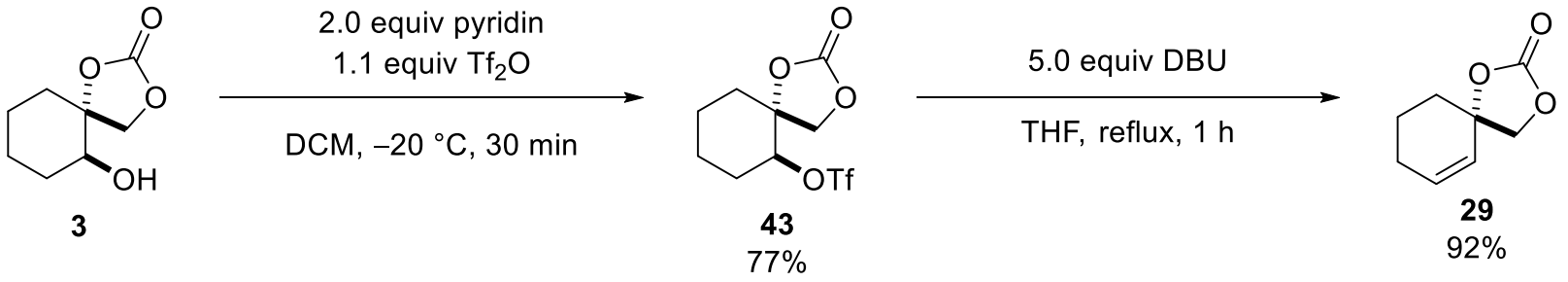
44



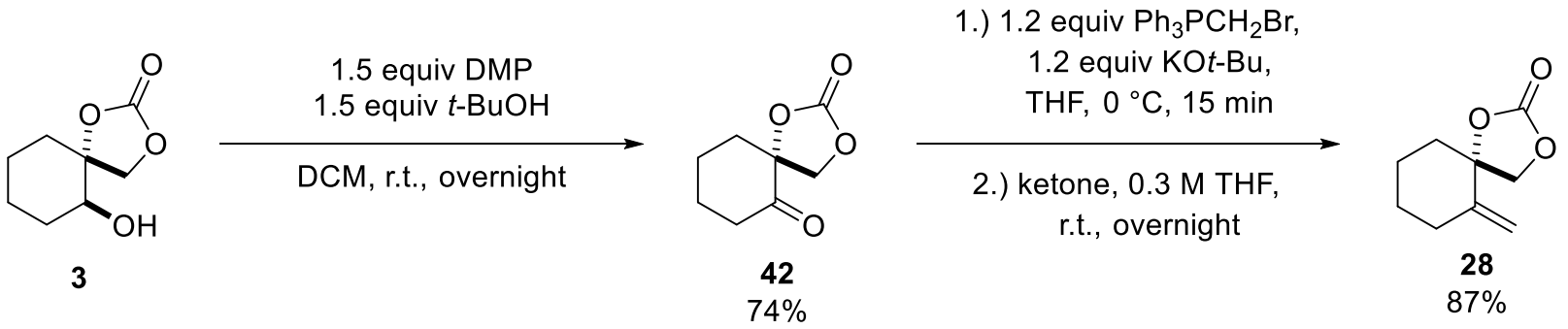
45

E. Burgess, H. Penton Jr., E. Taylor, *J. Org. Chem.* **1973**, *38*, 26 − 31.
J. Martin, R. Arhart, *J. Am. Chem. Soc.* **1971**, *93*, 4327 − 4329.

- Synthesis of **29** by triflation followed by elimination

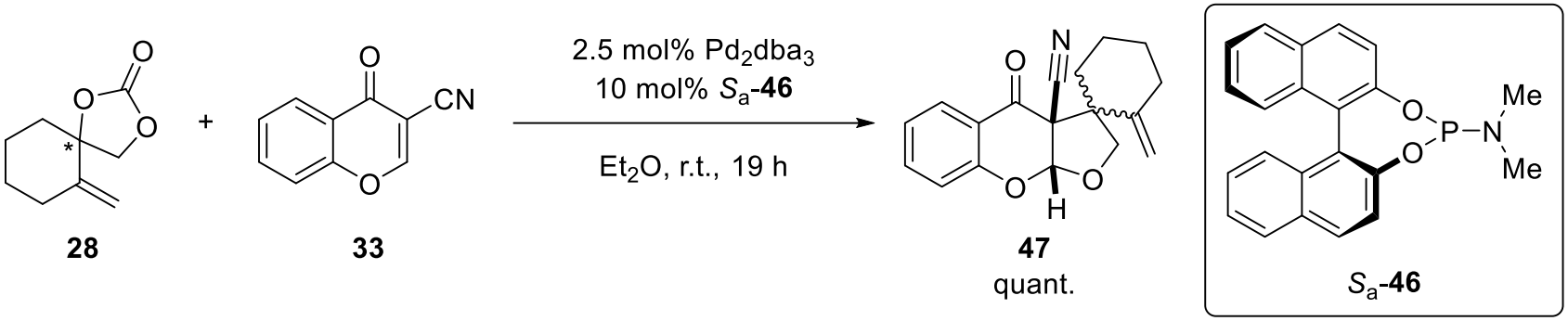


- Synthesis of **28** by oxidation with Dess-Martin periodinane followed by Wittig olefination

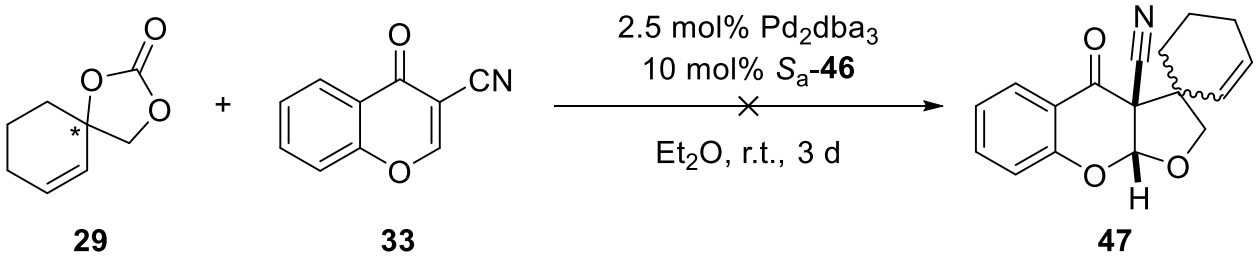


D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4156 − 4158.

- Reaction of *exo*-VEC **28** and 3-cyanochromone yields four stereoisomers of **46**

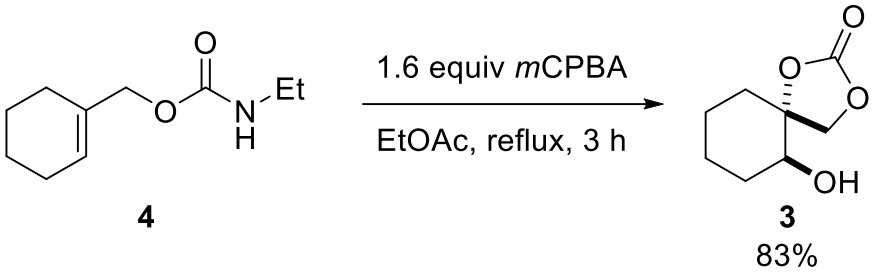


- No conversion for the reaction of *endo*-VEC **29**



I. Khan, C. Zhao, Y. J. Zhang, *Chem. Comm.* **2018**, *54*, 4708 – 4711.

- Yield of spiro-carbonate **3** increased
- Shortened reaction times
- No need for catalysis



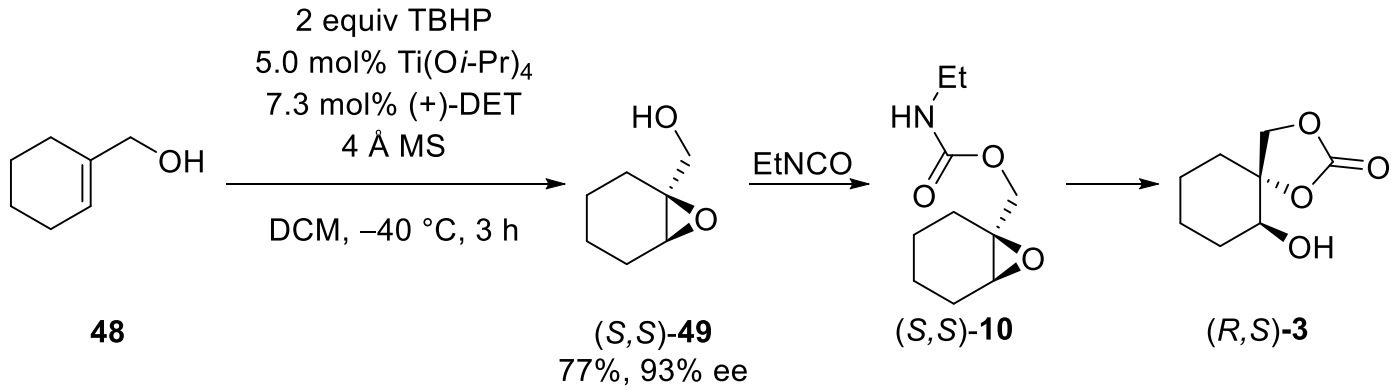
4 **3** 83%

- Successful synthesis of two new VECs
- **28** reacts with 3-cyanochromone in a palladium-catalyzed formal [3+2] cycloaddition
- **29** shows no reactivity under palladium catalyses

28 **29**

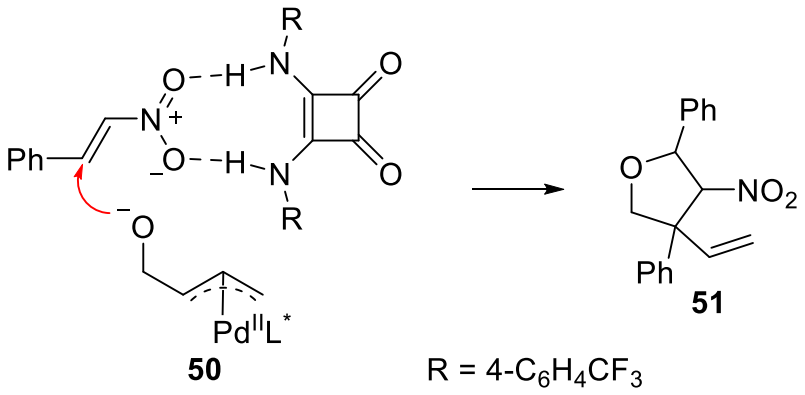
Outlook

- Enantioselective Sharpless epoxidation of allyl alcohol **48** gives access to one enantiomer of **3**



- Further broadening of the substrate scope for the carbonate formation

- Cooperative catalysis by squaramides and palladium

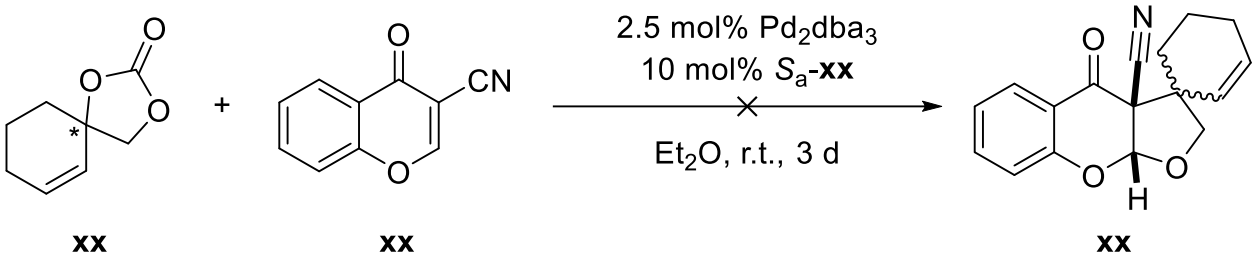


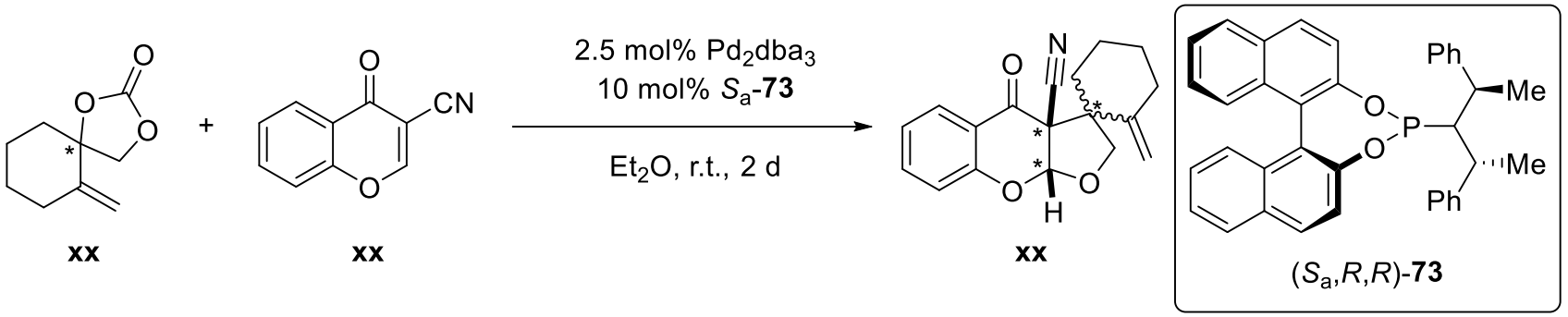
Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, K. B. Sharpless, *J. Am Chem. Soc.* **1987**, 109, 5765 − 5780.
K. Liu, I. Khan, J. Cheng, Y. J. Hsueh, Y. J. Zhang, *ACS Catalysis* **2018**, *8*, 11600 − 11604.

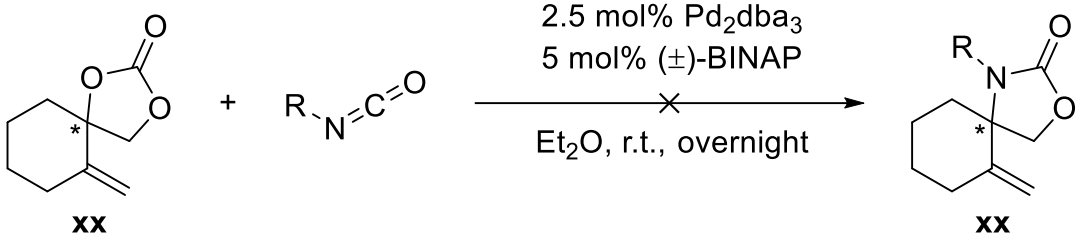
Acknowledgements

Finally, I would like to thank…

- … Prof. Dr. Peter R. Schreiner, Ph. D.
- … M. Sc. Christopher Topp
- … all coworkers in the Schreiner group
- … Benito, Charlotte, Chris, and Gina


2.5 mol% Pd2dba3
10 mol% Sa-xx
Et2O, r.t., 3 d
CN
N
H
xx
xx
xx

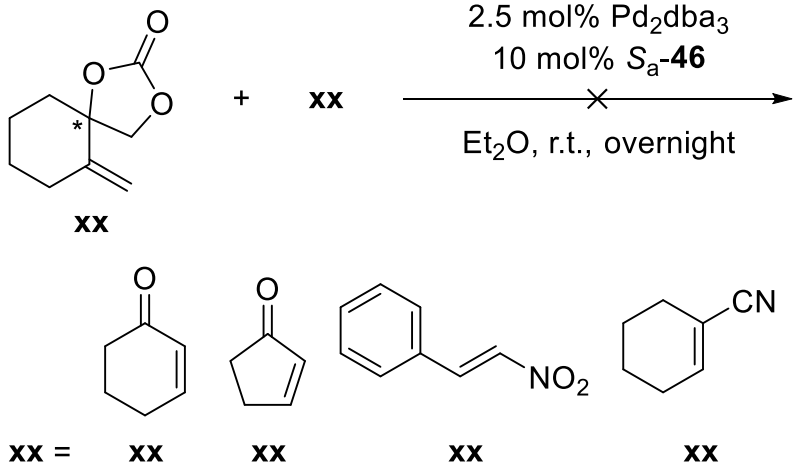

2.5 mol% Pd2dba3
10 mol% Sa-73
Et2O, r.t., 2 d
CN
N
H
Ph
Me
Me
Ph
xx
xx
xx
(Sa,R,R)-73



xx **xx**

	xxa	**xxb**	**xxc**[a]
R =	Ph	Bn	Ts

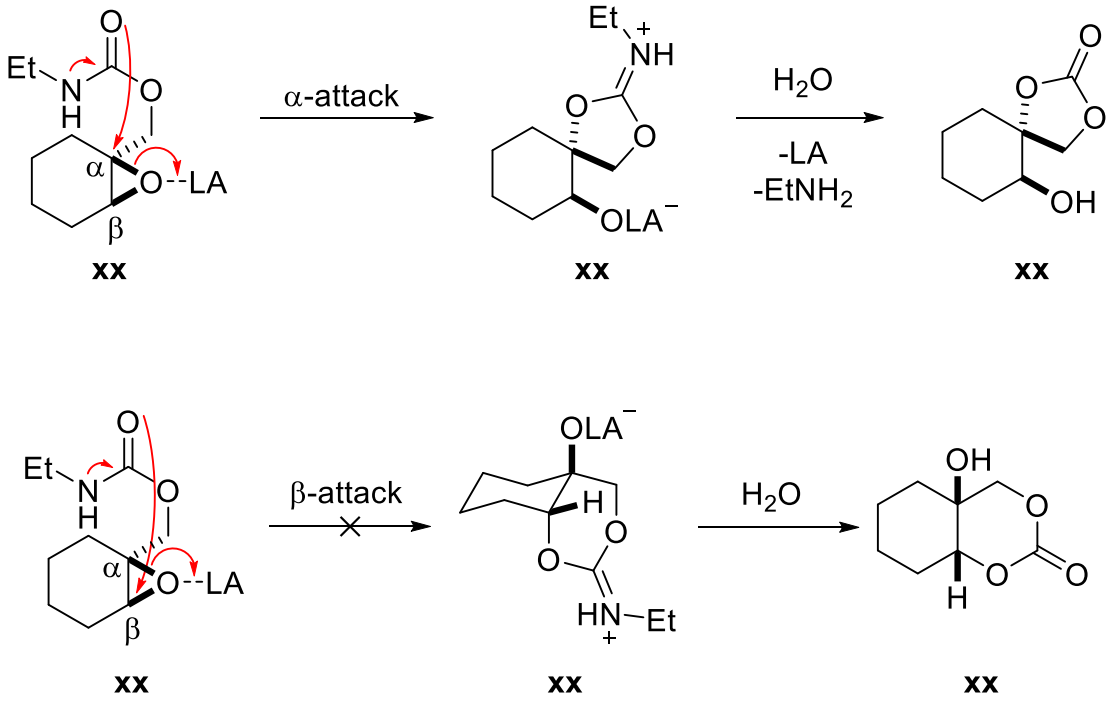
[a] 10 mol% (S_a)-**46** were used in place of (±)-BINAP



xx **xx** = **xx** **xx** **xx** **xx**

A. Khan, J. Xing, J. Zhao, Y. Kan, W. Zhang, Y. J. Zhang, *Chem. Eur. J.* **2015**, *21*, 120 – 124.

β-Attack on Epoxide

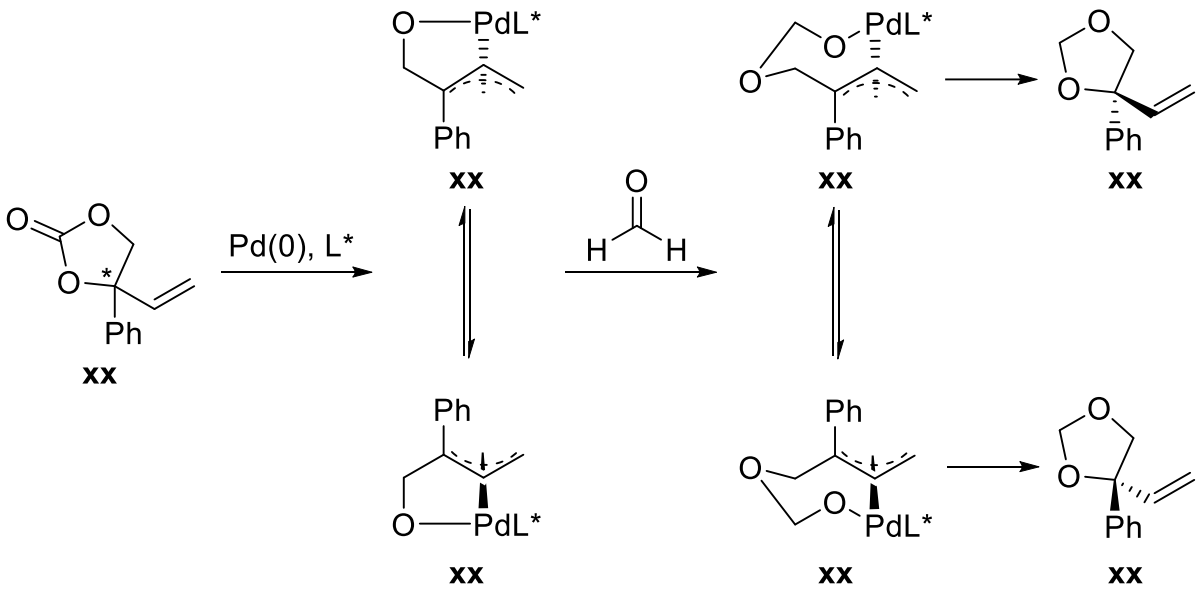


xx **xx** **xx**

xx **xx** **xx**

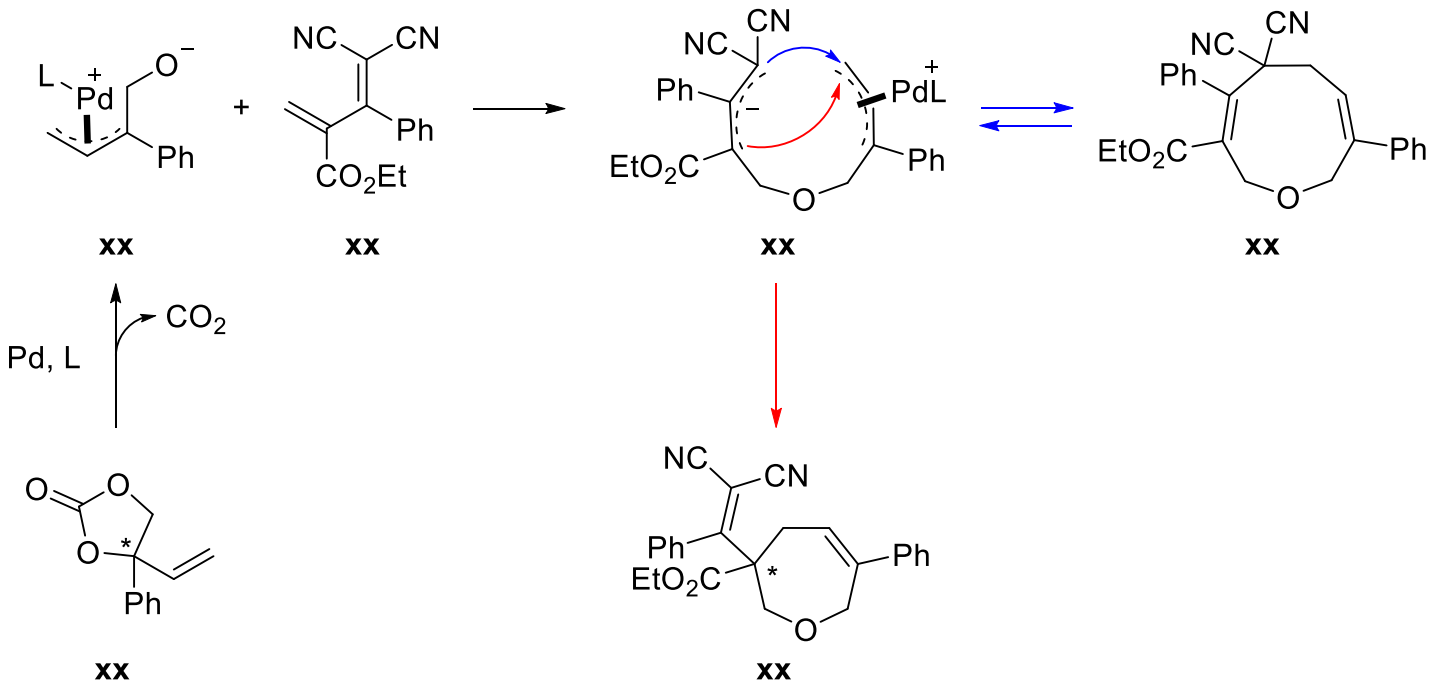
W. Roush, R. Brown, M. DiMare, *J. Org Chem.* **1983**, *48*, 5038 – 5093.

Dynamic Kinetic Asymmetric Transformation (DYKAT)



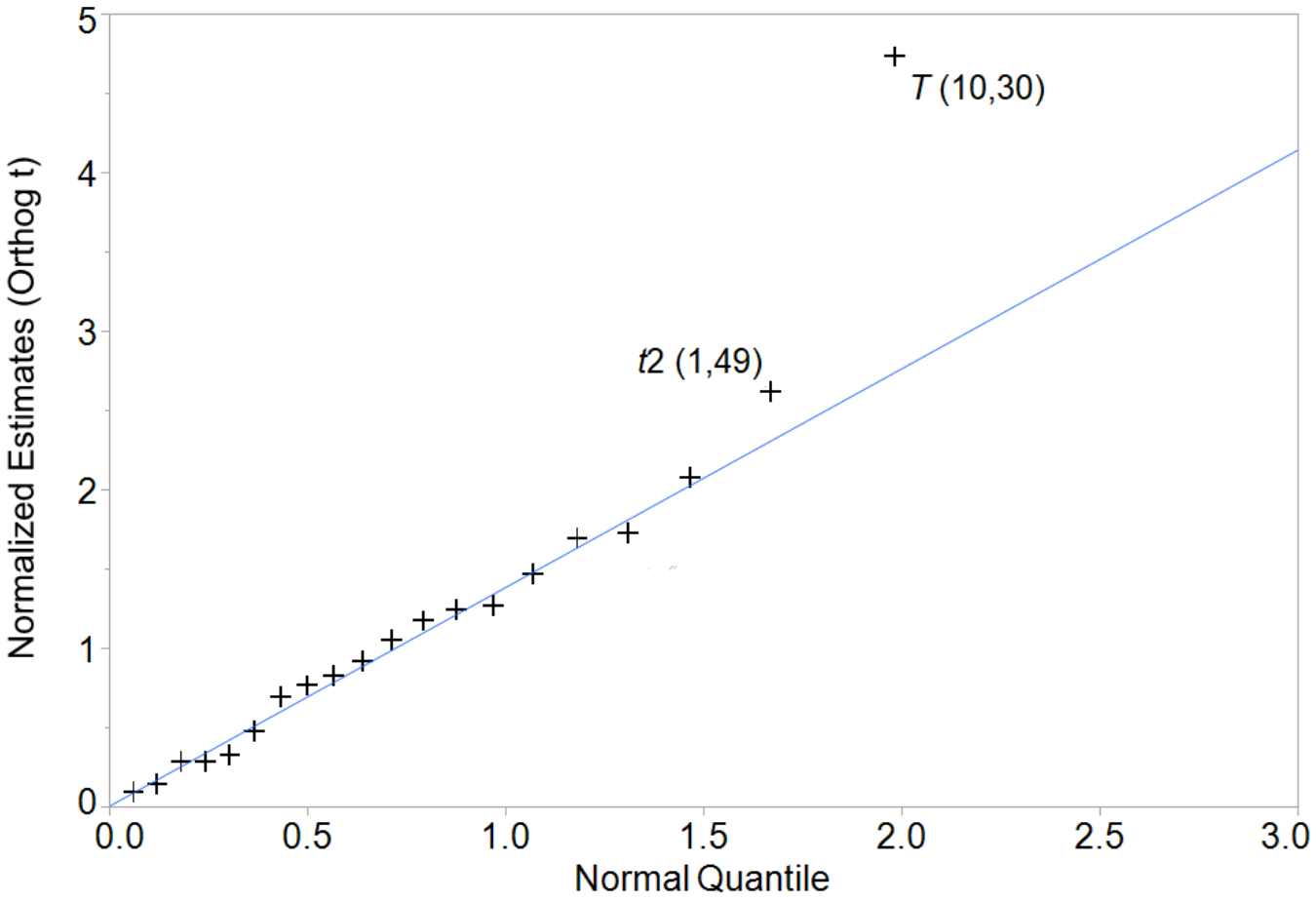
A. Khan, R. Zheng, Y. Khan, J. Ye, J. Xing, Y. J. Zhang, *Angw. Chem. Int Ed.* **2014**, *53*, 6439–6442.
B. Trost, R. Bunt, R. Lemoine, T. L. Chalkins, *J. Am. Chem. Soc.* **2000**, *122*, 5968 – 5976.

[5+2] or [5+4] formal Cycloaddition

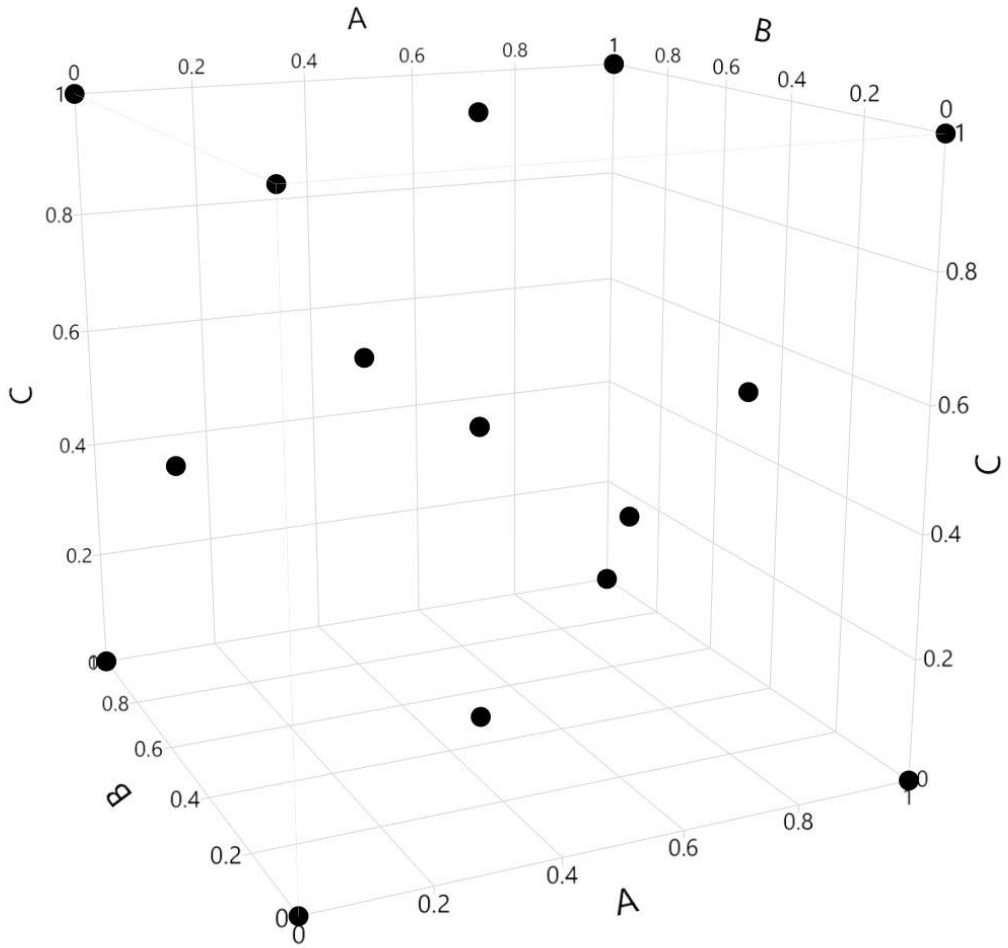


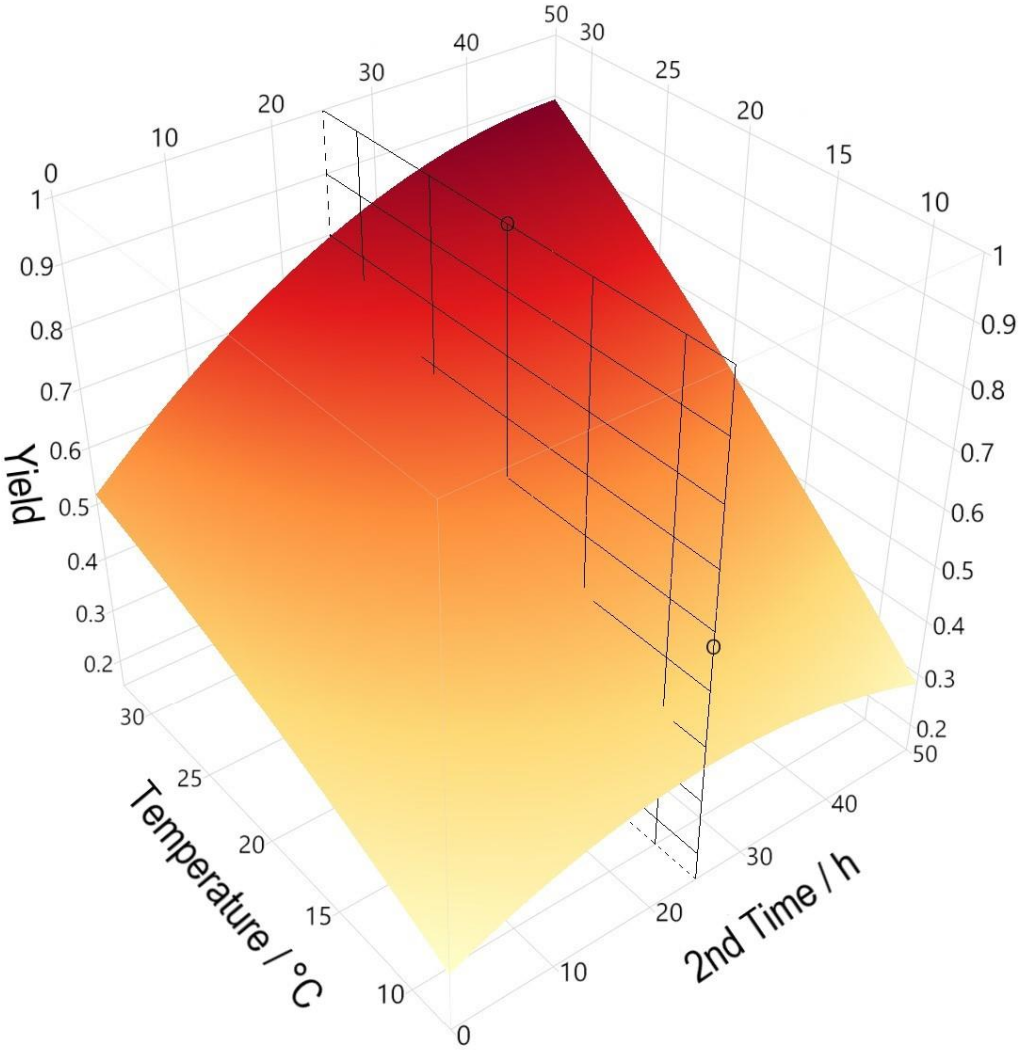
X. Zhang, X. Li, J.-L. Li, Q.-W. Wang, W.-L. Zou, Y.-Q. Liu, Z.-Q. Jia, F. Peng, B. Han, *Chem. Sci.* **2020**, *11*, 2888 – 2894.

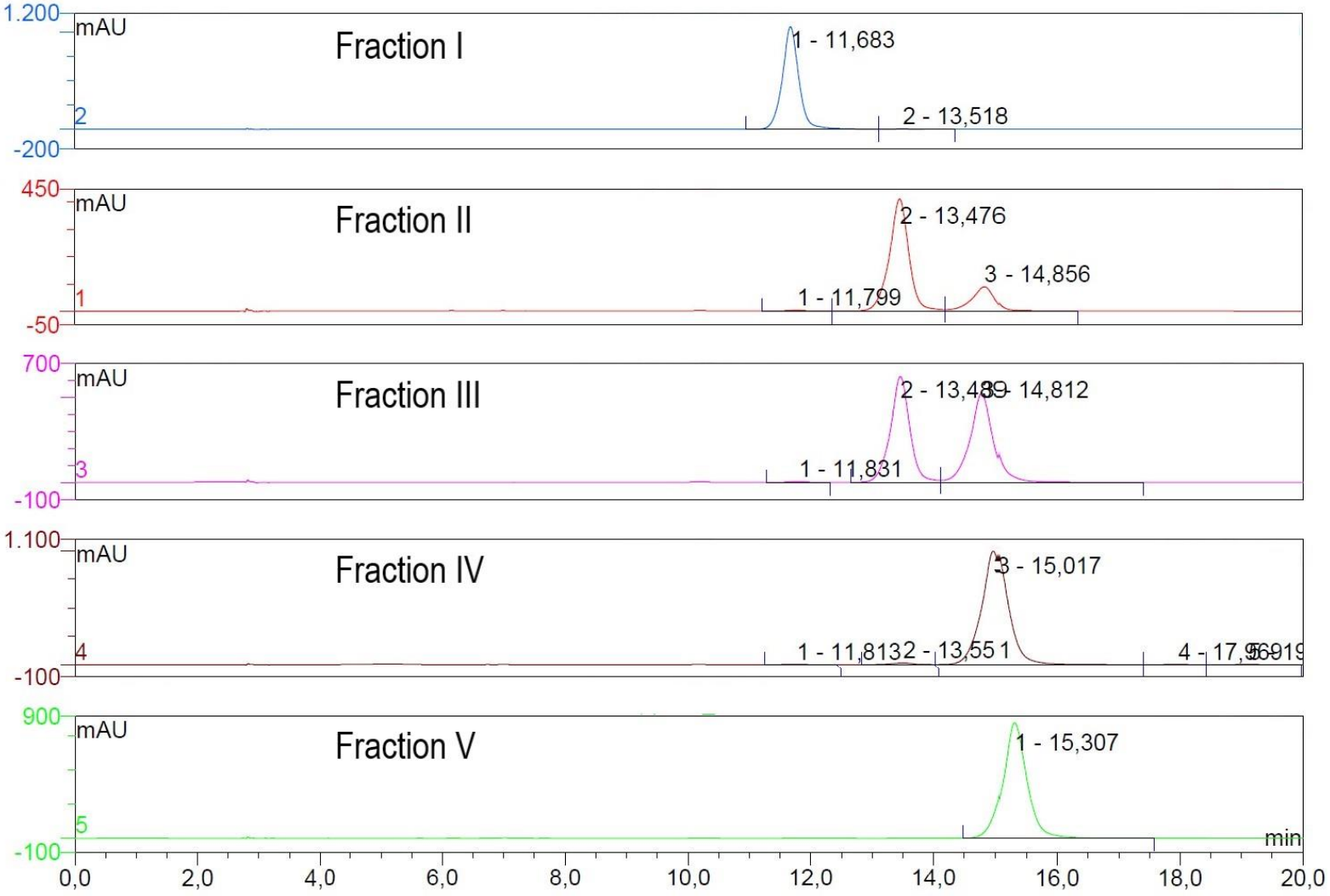
Nr.	Pattern	t_1 / h	t_2 / h	c / mol·L^{-1}	$x_{cat.}$ / mol%	T / ° C	Yield / %
1	−−−−−	0	1.0	0.1	0	10.0	73
2	++−−−	1.0	49.0	0.1	0	10.0	30
3	+−+−−	1.0	1.0	0.5	0	10.0	29
4	−++−−	0	49.0	0.5	0	10.0	41
5	0000−	0.5	25.0	0.3	7.5	10.0	29
6	+−−+−	1.0	1.0	0.1	15.0	10.0	15
7	−+−+−	0	49.0	0.1	15.0	10.0	29
8	−−++−	0	1.0	0.5	15.0	10.0	20
9	++++−	1.0	49.0	0.5	15.0	10.0	47
10	000a0	0.5	25.0	0.3	0	20.0	54
11	00a00	0.5	25.0	0.1	7.5	20.0	52
12	0a000	0.5	1.0	0.3	7.5	20.0	24
13	a0000	0	25.0	0.3	7.5	20.0	57
14	00000	0.5	25.0	0.3	7.5	20.0	73
15	00000	0.5	25.0	0.3	7.5	20.0	85
16	A0000	1.0	25.0	0.3	7.5	20.0	65
17	0A000	0.5	49.0	0.3	7.5	20.0	70
18	00A00	0.5	25.0	0.5	7.5	20.0	55
19	000A0	0.5	25.0	0.3	15.0	20.0	52
20	+−−−+	1.0	1.0	0.1	0	30.0	31
21	−+−−+	0	49.0	0.1	0	30.0	74
22	−−+−+	0	1.0	0.5	0	30.0	85
23	+++−+	1.0	49.0	0.5	0	30.0	91
24	0000A	0.5	25.0	0.3	7.5	30.0	79
25	−−−++	0	1.0	0.1	15.0	30.0	50
26	++−++	1.0	49.0	0.1	15.0	30.0	85
27	+−+++	1.0	1.0	0.5	15.0	30.0	49
28	−++++	0	49.0	0.5	15.0	30.0	83


T (10,30)
t2 (1,49)
Normalized Estimates (Orthog t)
Normal Quantile
0
1
2
3
4
5
0.0
0.5
1.0
1.5
2.0
2.5
3.0

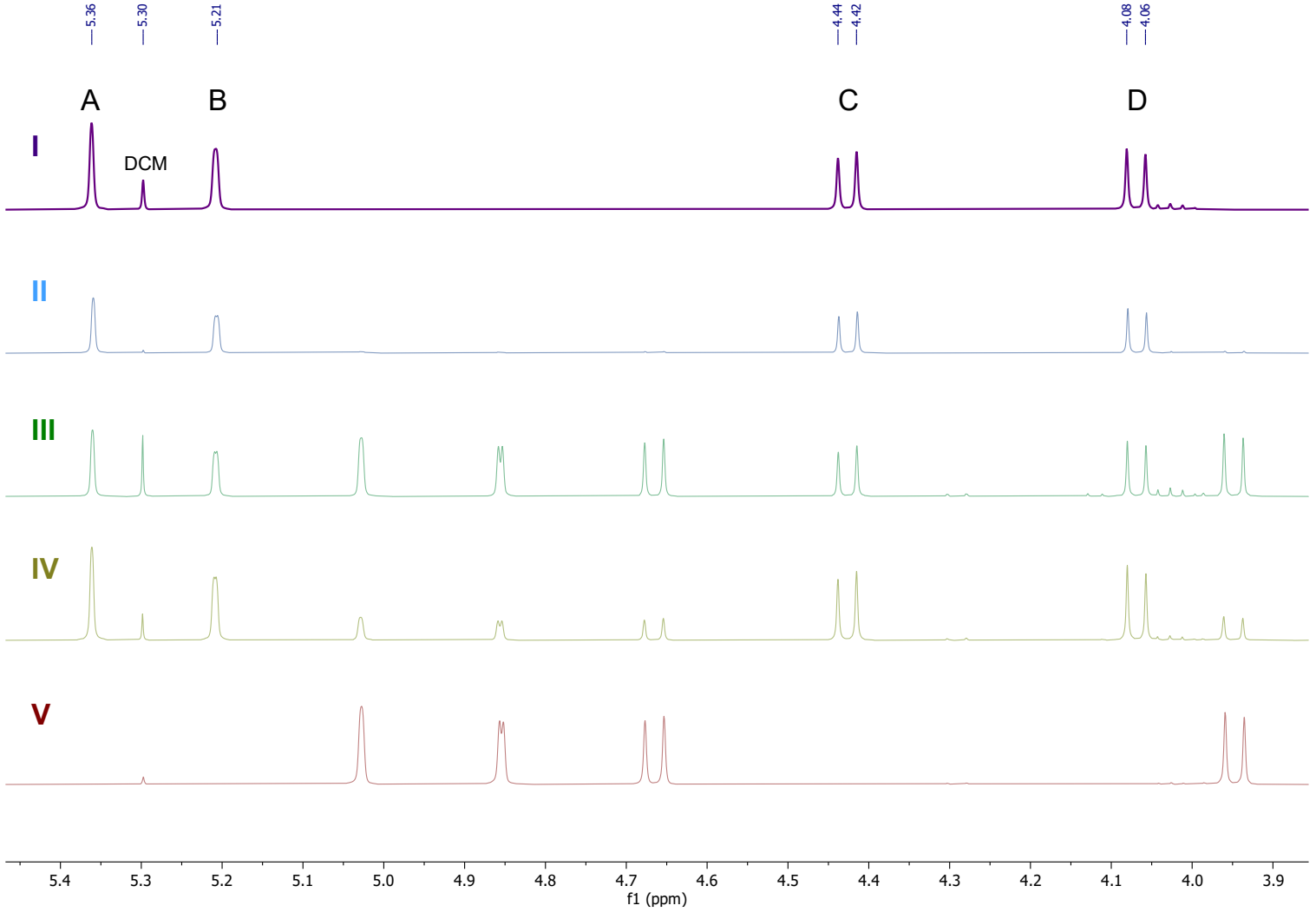
Central Composite Design



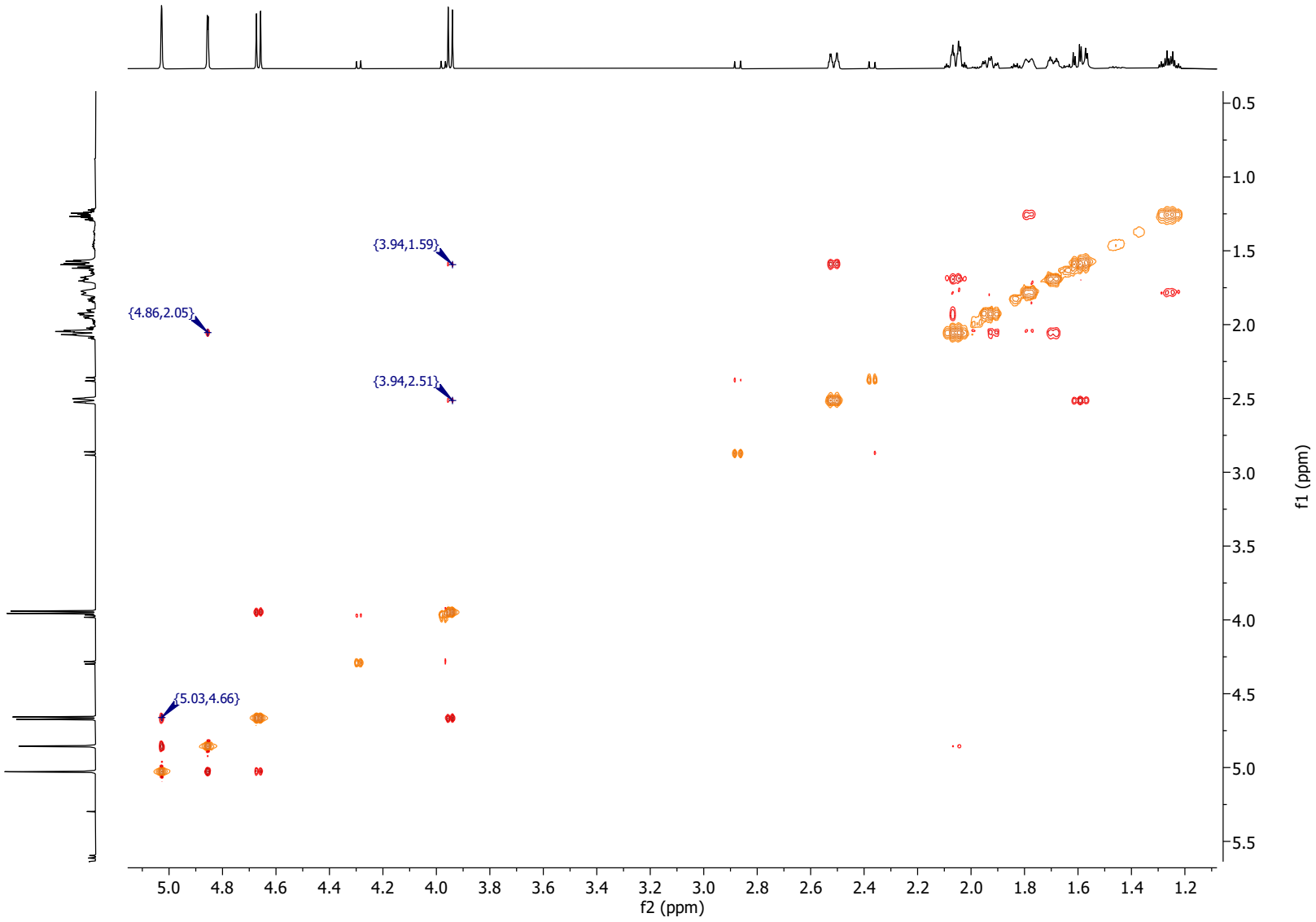

Yield
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
Temperature / °C
30
25
20
15
10
2nd Time / h
50
40
30
20
10
0


1.200
mAU
Fraction I
1 - 11,683
2
2 - 13,518
-200
450
mAU
Fraction II
2 - 13,476
3 - 14,856
1
1 - 11,799
-50
700
mAU
Fraction III
2 - 13,489
3 - 14,812
3
1 - 11,831
-100
1.100
mAU
Fraction IV
3 - 15,017
4
1 - 11,813
2 - 13,551
4 - 17,956
-100
900
mAU
Fraction V
1 - 15,307
5
min
-100
0,0
2,0
4,0
6,0
8,0
10,0
12,0
14,0
16,0
18,0
20,0

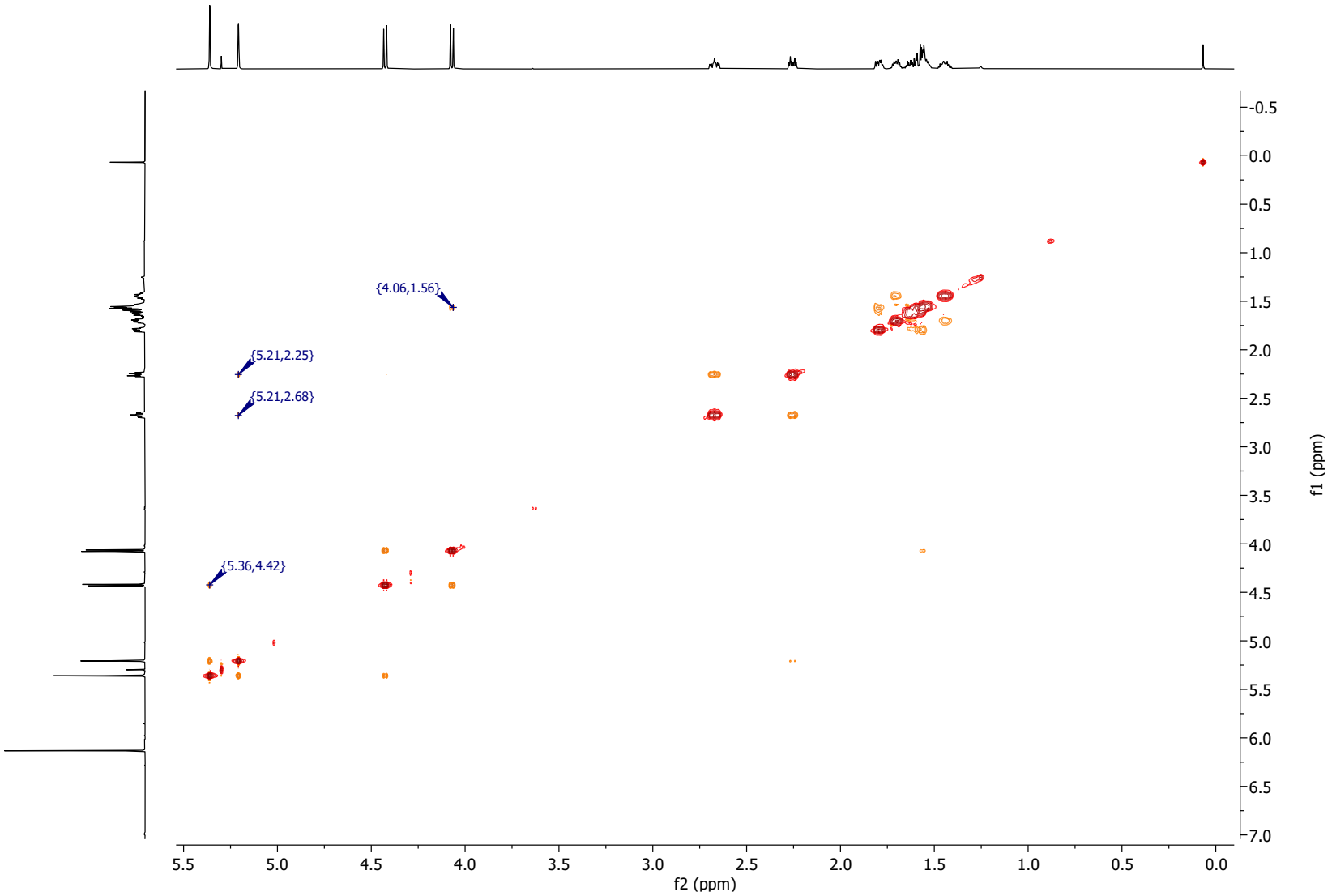
HPLC – ^{1}H-NMR of Fractions

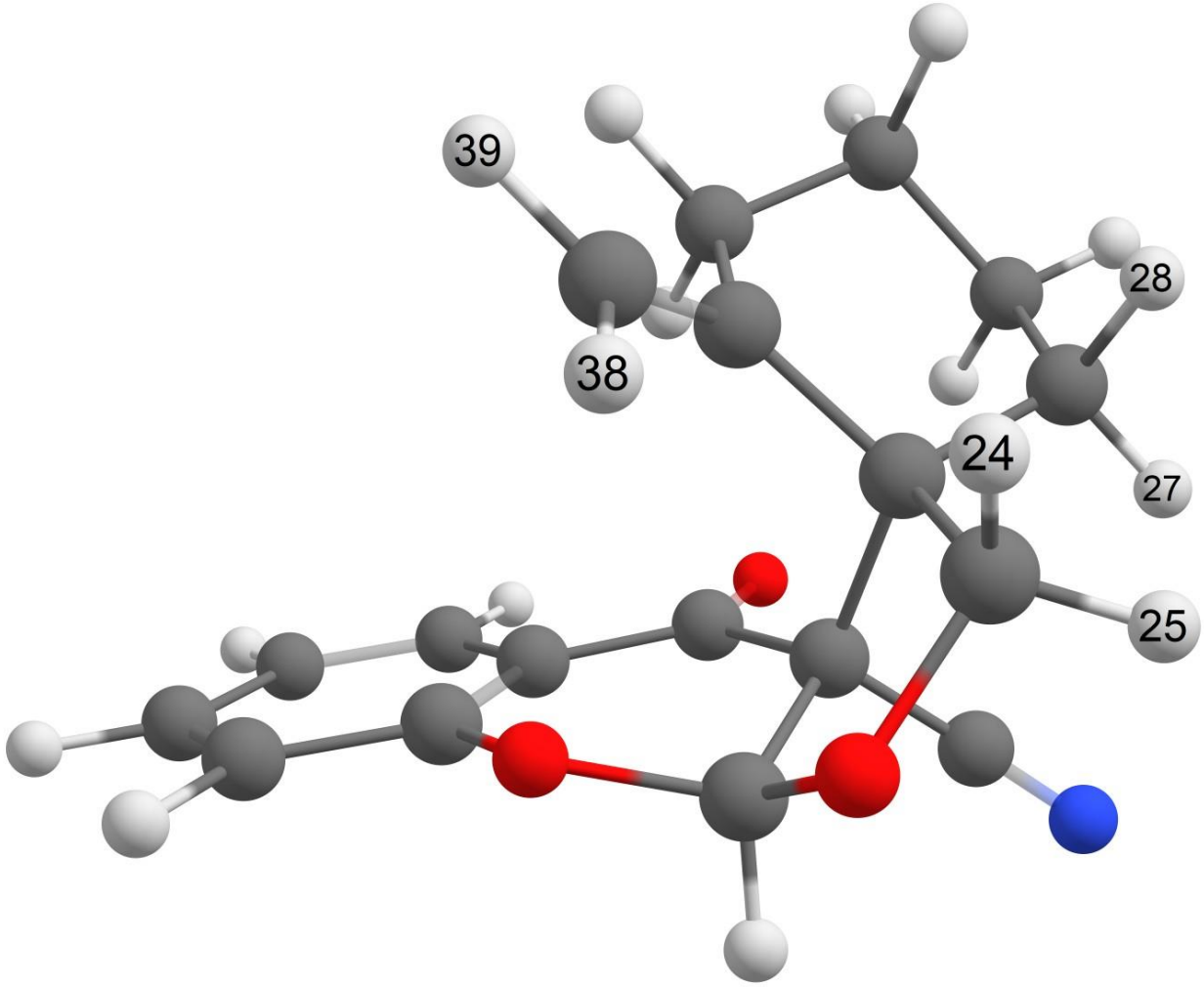


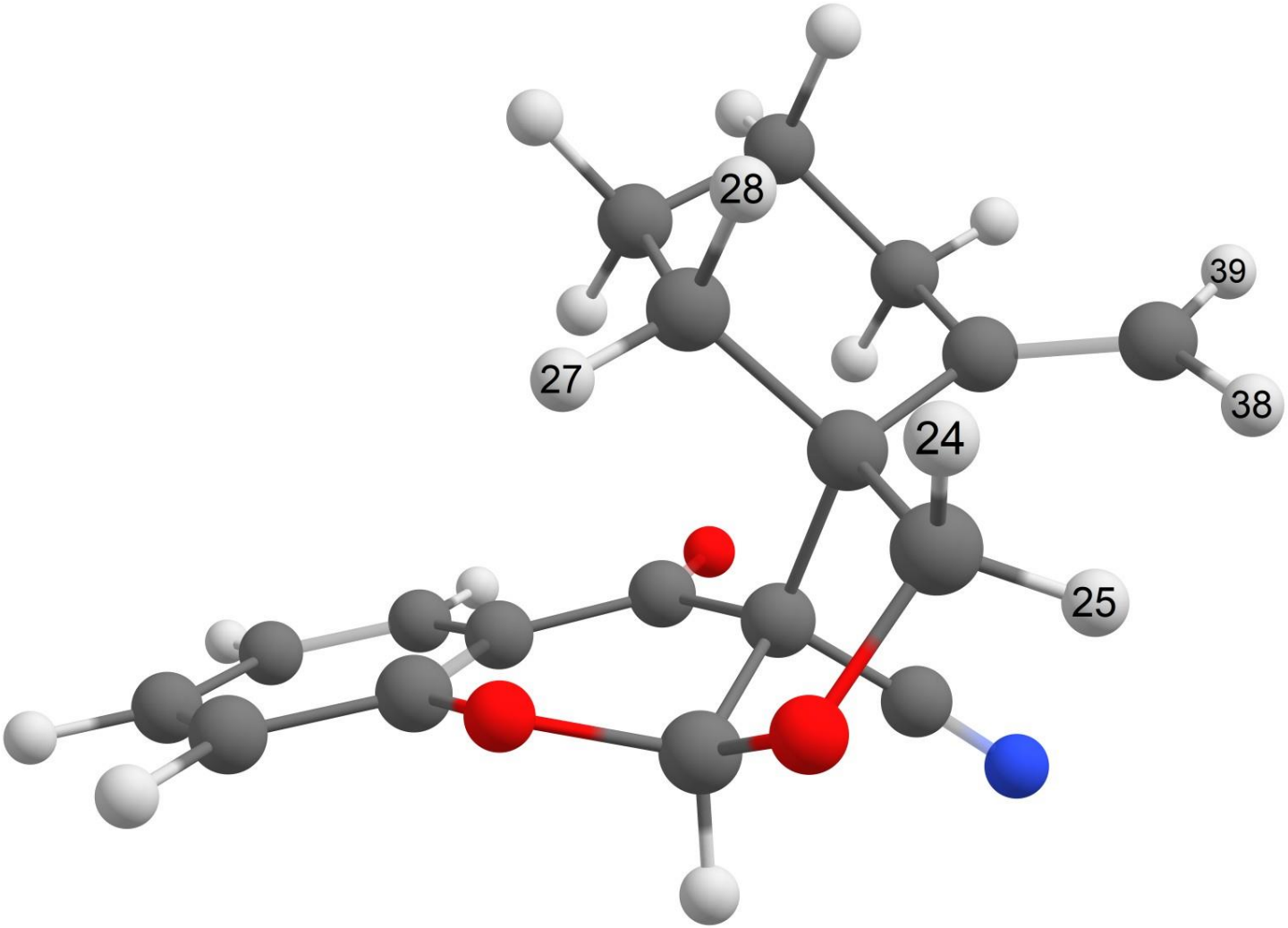
NOESY Fraction 1



NOESY Fraction 2




39
38
28
24
27
25


28
39
27
38
24
25