
Expanding the Scope of α -Hydroxy-spiro-Carbonates and Optimizing the Synthesis with a “Design of Experiments” Approach

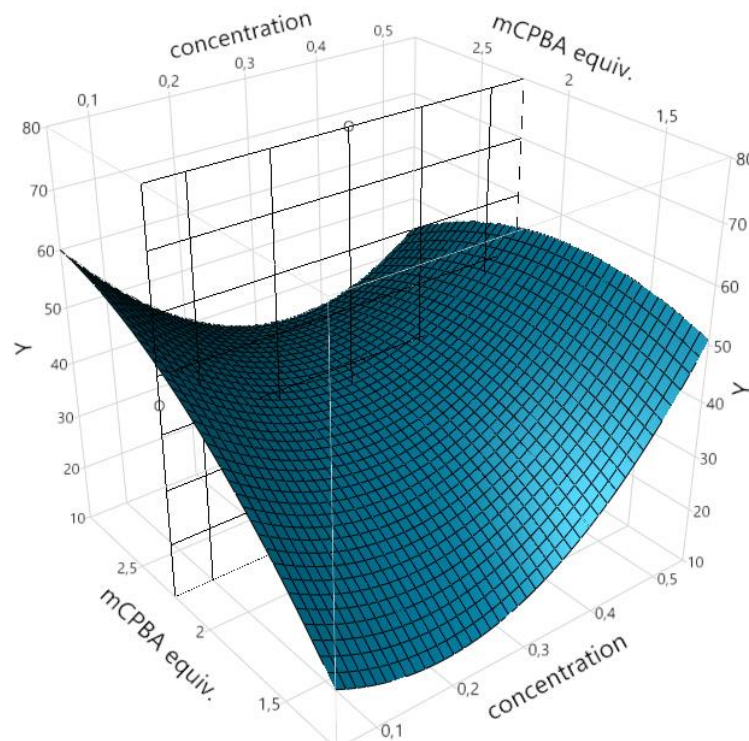
24.09.2021

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Justus-Liebig-University

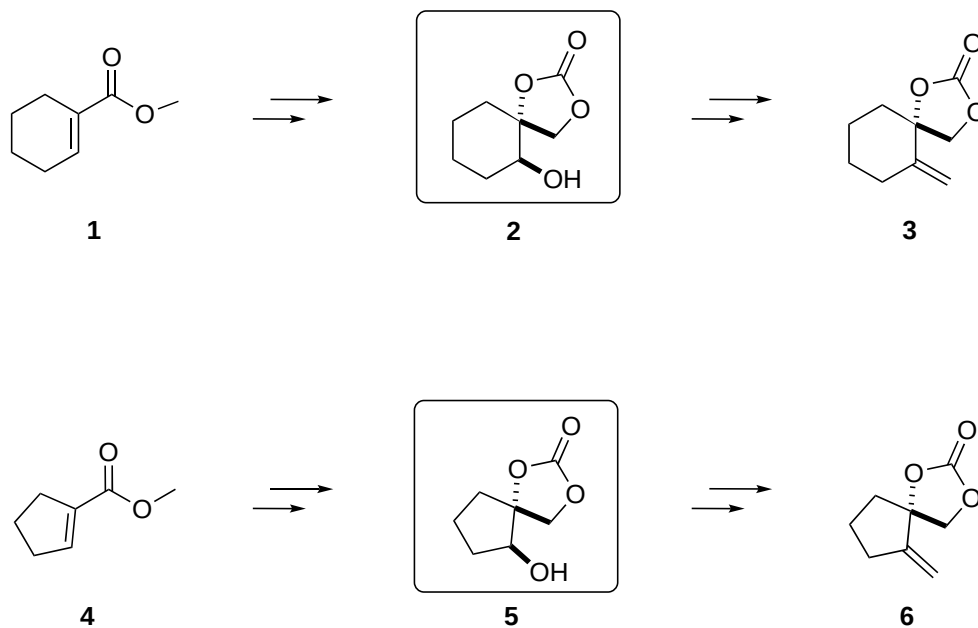
35392 Giessen, Germany

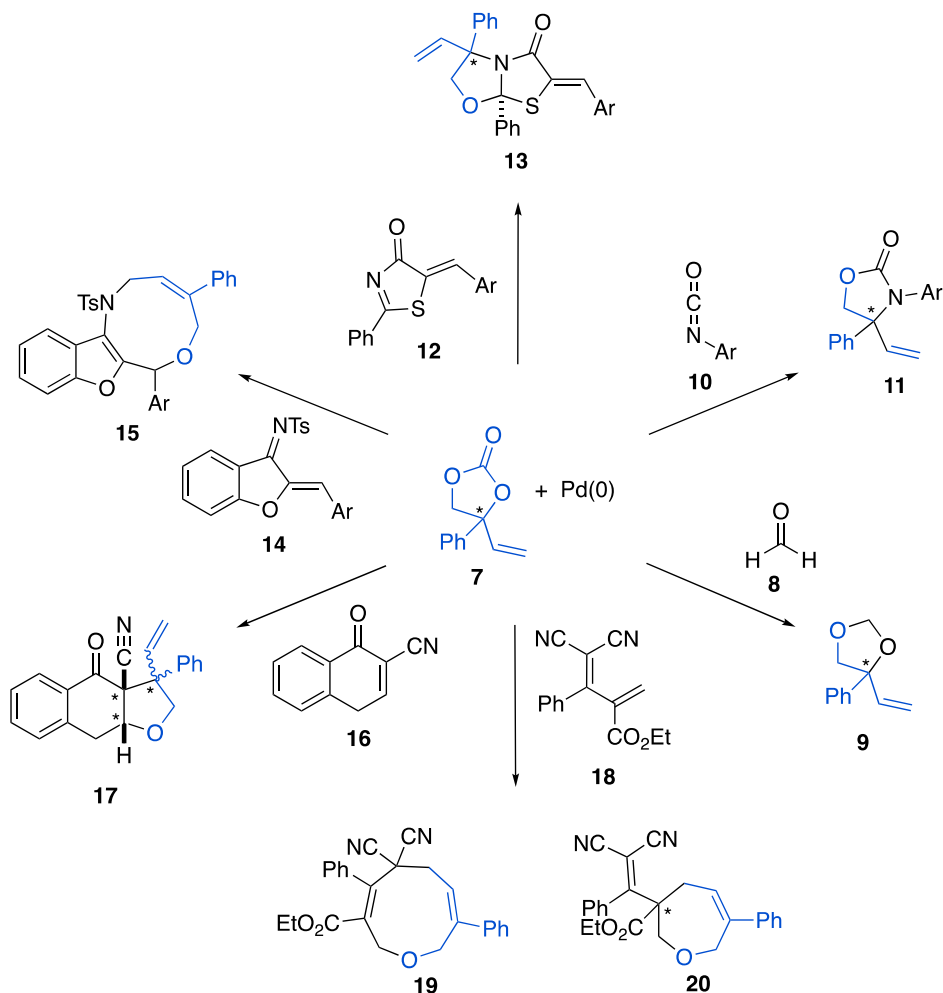


Why synthesizing α -Hydroxy-spiro-carbonates?



- Starting material for VECs





A. Khan, R. Zheng, Y. Kan, J. Ye, J. Xing, Y. J. Zhang, *Angew. Chem.* **2014**, *126*, 6557–6560.

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

Y. Liu, Q. W. Huang, Q. Z. Li, H. J. Leng, Q. S. Dai, R. Zeng, Y. Q. Liu, X. Zhang, B. Han, J. L. Li, *Org. Lett.* **2019**, *21*, 7478–7483.

L. C. Yang, Z. Q. Rong, Y. N. Wang, Z. Y. Tan, M. Wang, Y. Zhao, *Angew. Chem. Int. Ed.* **2017**, *56*, 2927–2931.

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.

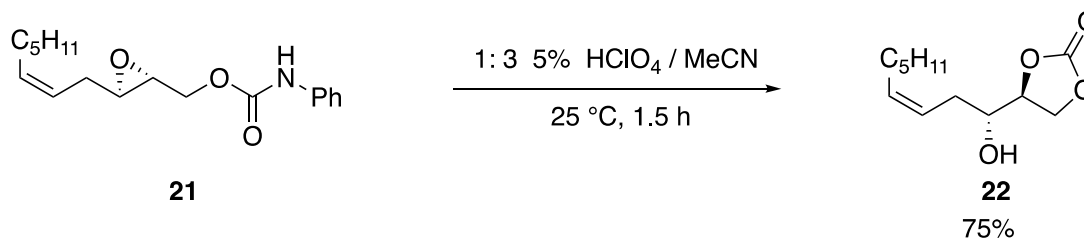
I. Khan, C. Zhao, Y. J. Zhang, *Chem. Comm.* **2018**, *54*, 4708 – 4711.

Previous Research into the Synthesis

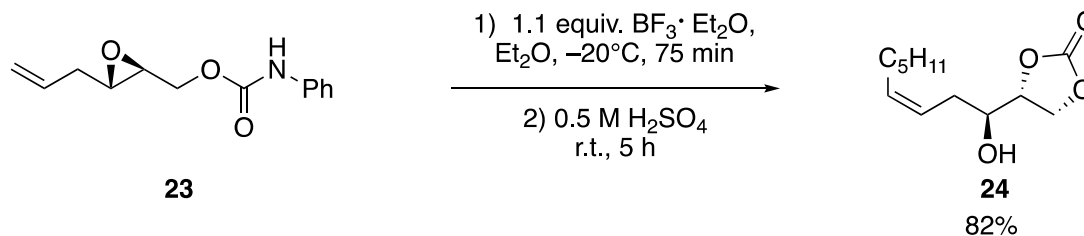


- Carbonate formation earlier observed by Corey *et al.* and Roush *et al.*

Corey *et al.* 1980



Roush *et al.* 1983

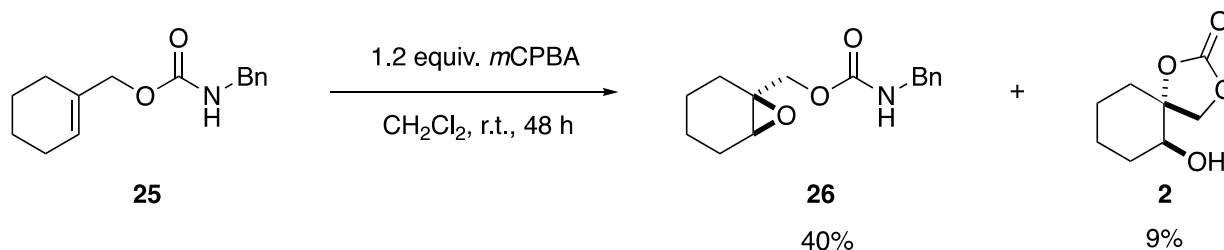


E. J. Corey, P. B. Hopkins, J. E. Munroe, A. Marfat, S. Hashimoto, *J. Am. Chem. Soc.* **1980**, 102, 7986–7987.

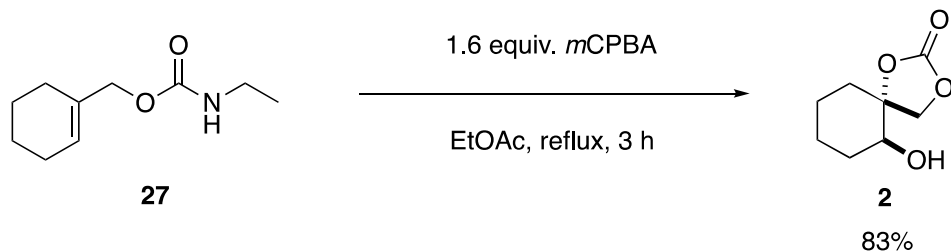
W. Roush, R. Brown, M. DiMare, *J. Org Chem.* **1983**, 48, 5083–5093.



- Schuler reported formation of spiro-carbonate



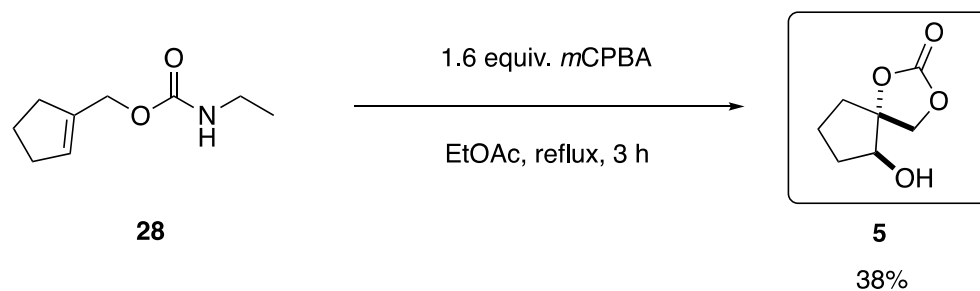
- Metzler performed DoE approach to optimize the formation



Previous Research into the Synthesis of α -Hydroxy-spiro-carbonates



- Expansion to other Substrates



→ Optimization of the synthesis as main objective of this Thesis

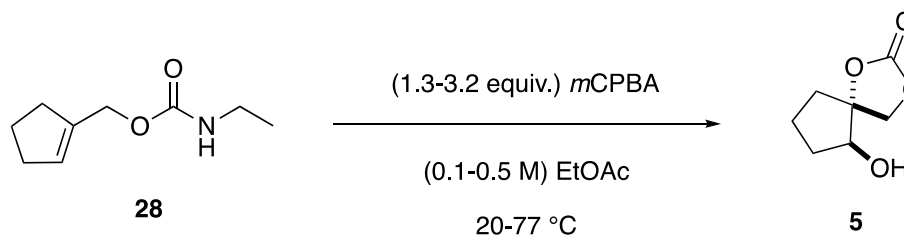
The DoE approach



- Pre screening to determine a suitable solvent:

	DCE	ACN	EtOAc	DMF	DMF
T / °C	84	82	77	153	80
Yield / %	33	39	55	16	19

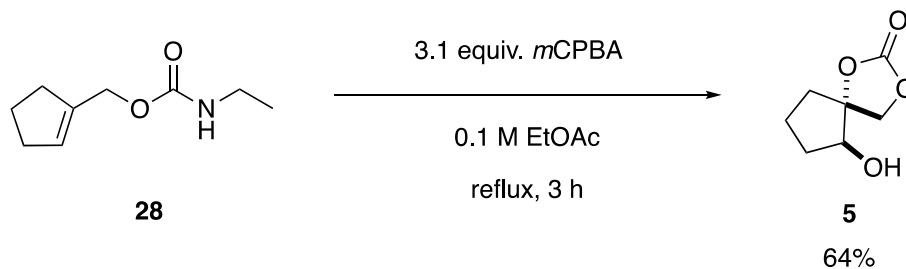
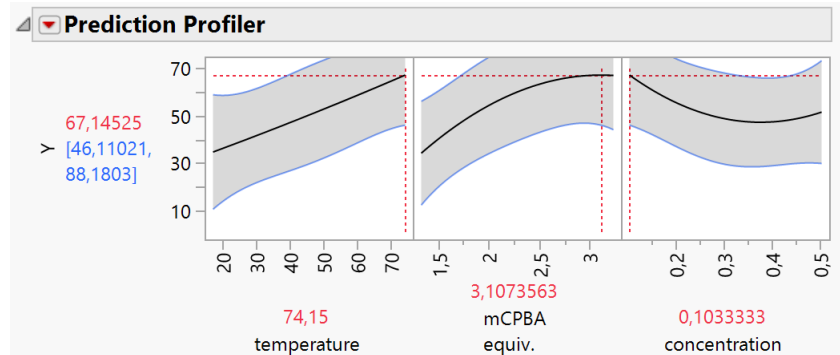
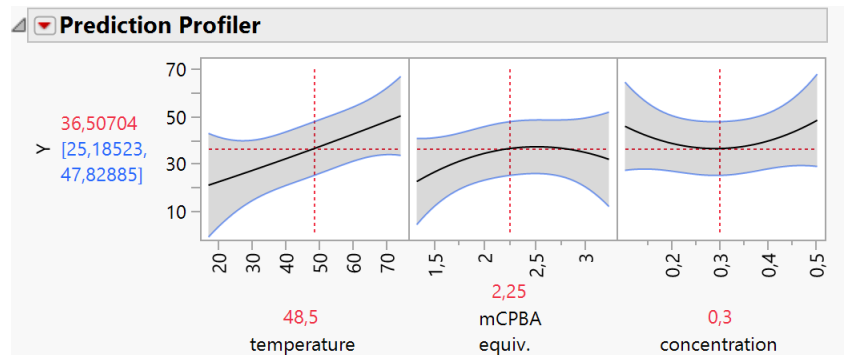
- The DoE approach:
 - Three Factors selected with three levels.
 - Central composite design with 17 individual runs.





Results of the DoE Analysis

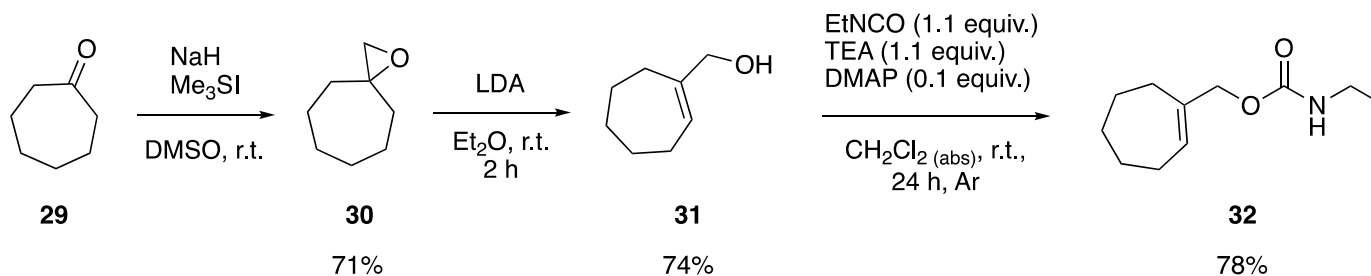
- Temperature is significant
- Correlation between *m*CPBA equiv. and concentration
- Prediction of optimal conditions



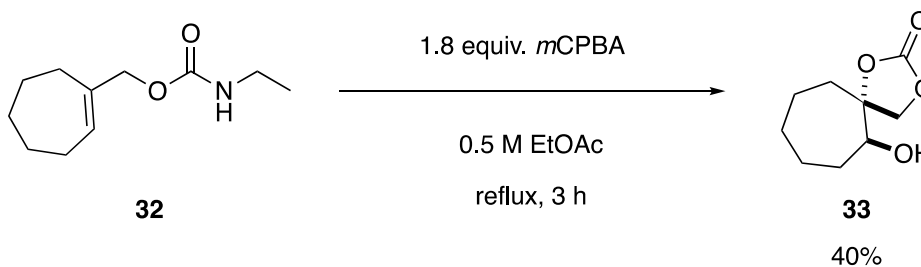
How to save some money?



- Corey-Chaykovski Route:



- Testing the protocol of Metzler on spiro-carbonate **31**

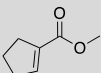
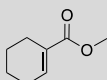
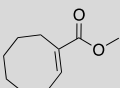


C. A. Falcicola, K. Tissot-Croset, H. Reyneri, A. Alexakis, *Adv. Synth. Catal.* **2008**, 350, 1090–1100.

G. Peris, C. E. Jakobsche, S. J. Miller, *J. Am. Chem. Soc.* **2007**, 129, 8710–8711.

How to save some money?



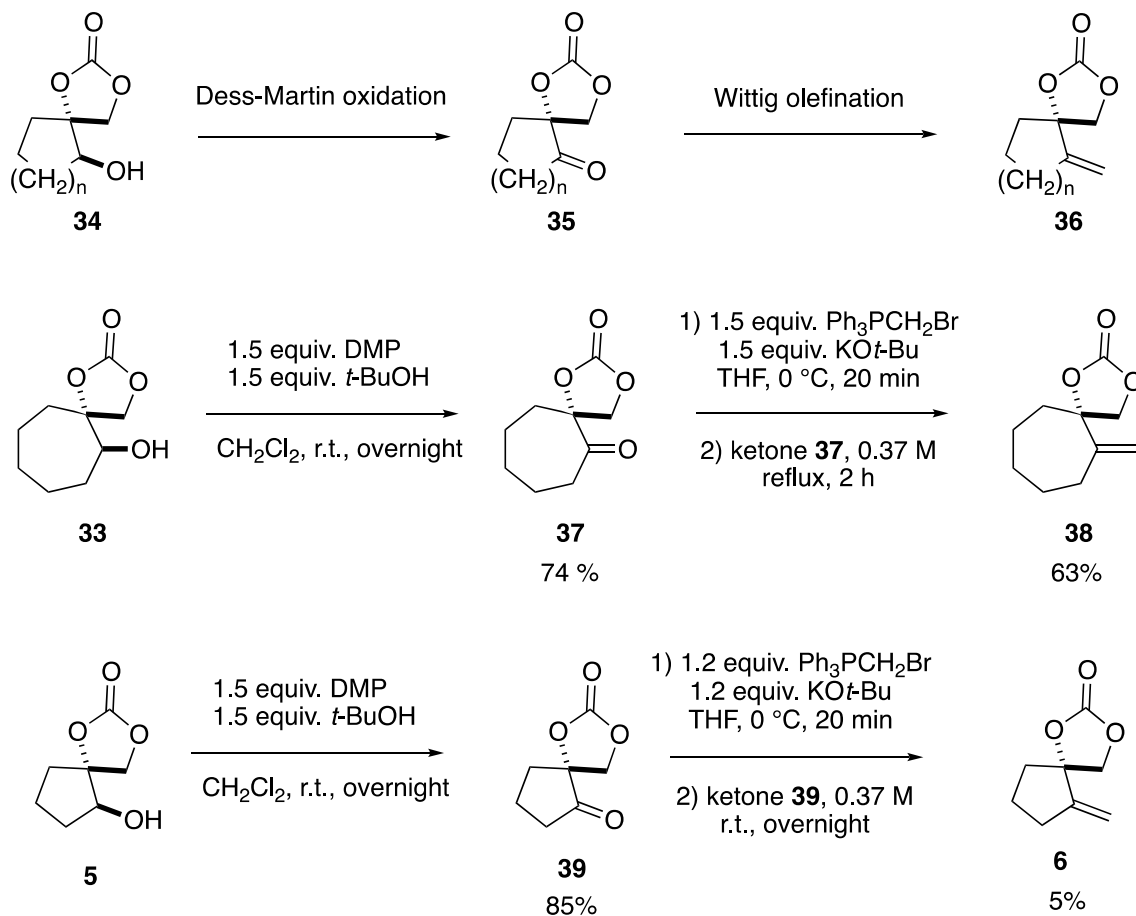
Compound	supplier	amount	Cost
	TCI	1 g	38.00 €
	BLDpharm	1 g	518.00 €
	Merck	10 g	2.30 €
	BLDpharm	10 g	66 €
	Merck	10 g	6.80 €
	BLDpharm	10 g	94.00 €
	Merck	1 g	1.06 €
	BLDpharm	1 g	776.00 €

[status 23.09.21]



From α -Hydroxy-Spiro-Carbonates to VECs

- To create various ring-sized VECs:

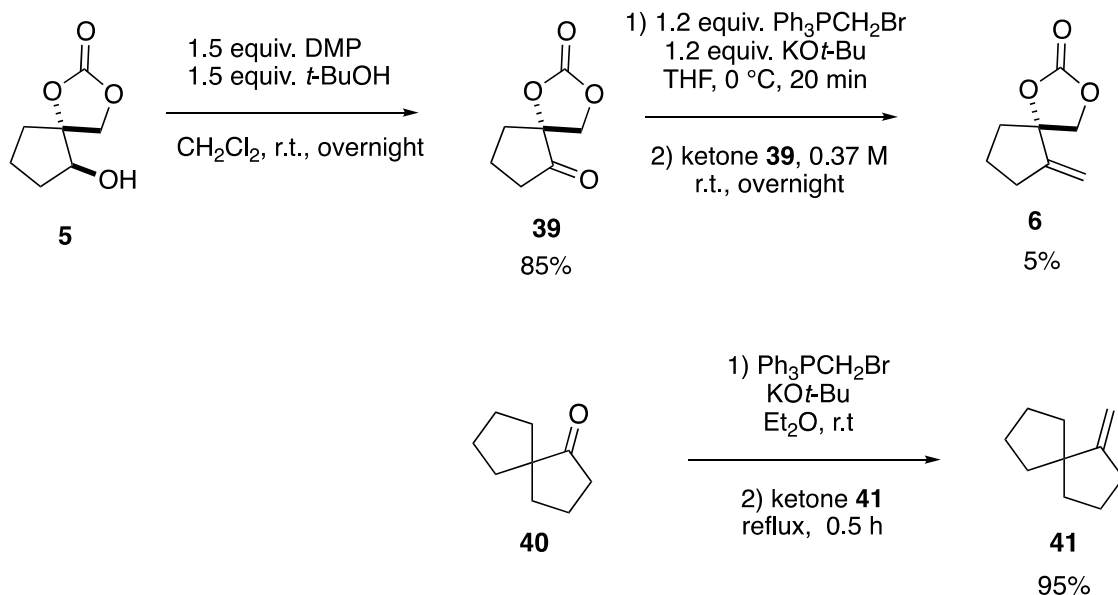


K. M. Werner, J. M. De Los Santos, S. M. Weinreb, M. Shang, *J. Org. Chem.* **1999**, *64*, 686–687.

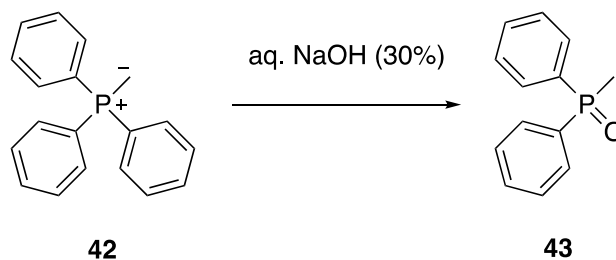
M. L. Conner, M. K. Brown, *J. Org. Chem.* **2016**, *81*, 8050–8060.



Challenges in the synthesis of VEC



- ^1H -NMR showed formation of Methyl-diphenylphosphinoxide



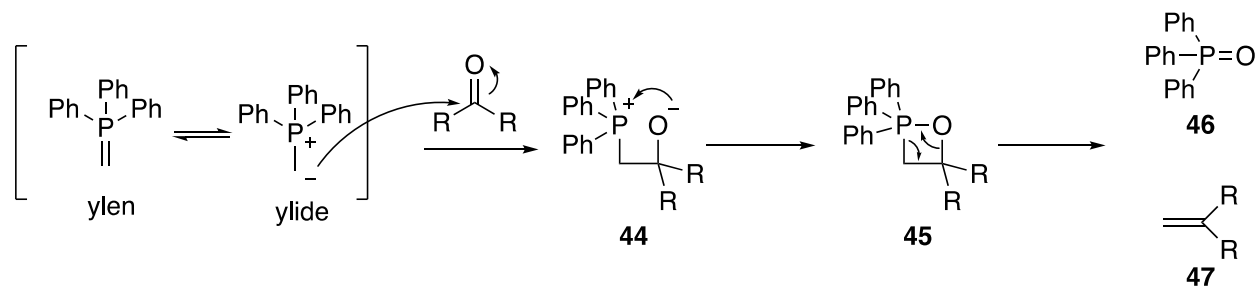
T. Widjaja, L. Fitjer, A. Pal, H. Schmidt, M. Noltemeyer, C. Dietrich, S. Grimme, *J. Org. Chem.* **2007**, 72, 9264–9277.

Y. Zhao, T. Feng, G. Li, F. Liu, X. Dai, Z. Dong, X. Qiu, *RCS Adv.* **2016**, 6, 42482–42494.

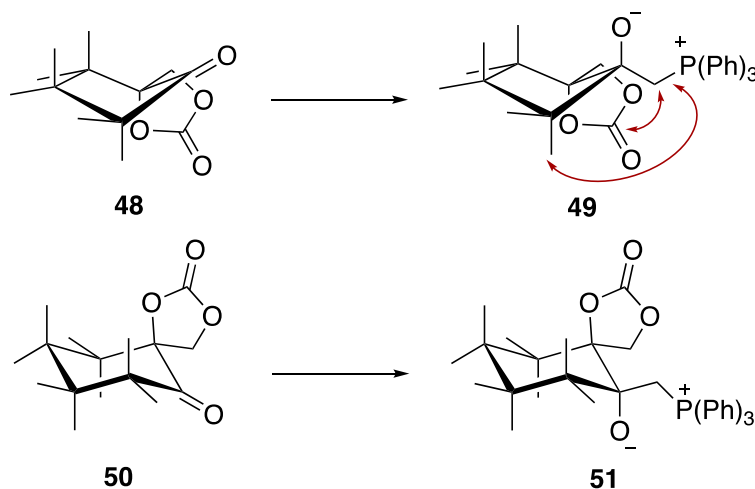


Possible reasons for the challenging Wittig reaction

- Mechanism of the Wittig reaction:

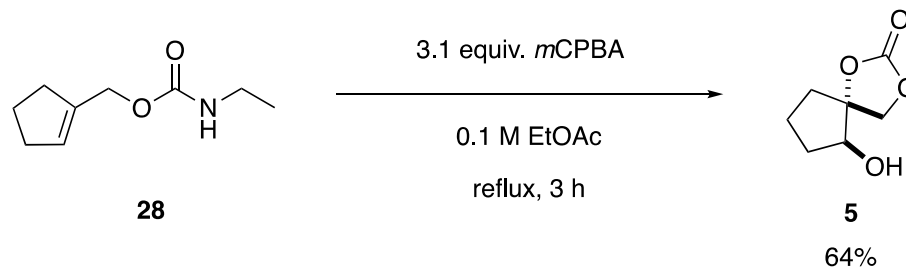


- Configurational changes: sp^2 (carbonyl) $\rightarrow$ sp^3 (betaine) **21** $\rightarrow$ sp^2 (olefin) **23**

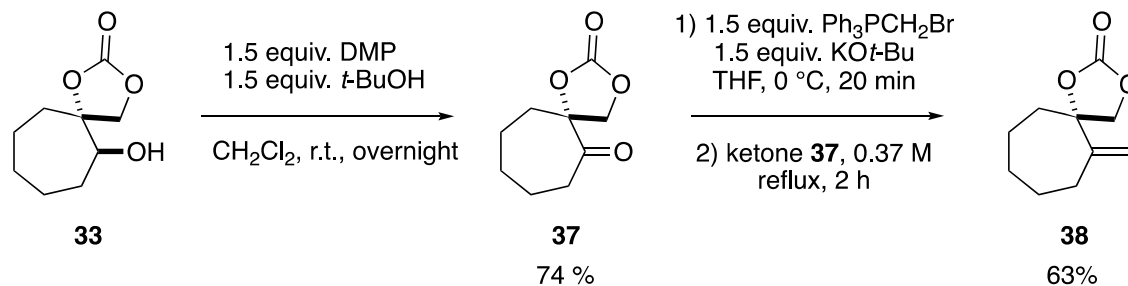




- Optimization of the Synthesis of spiro-carbonate **5**



- Synthesis of additional VEC and establishing the Corey-Chaykovsky route

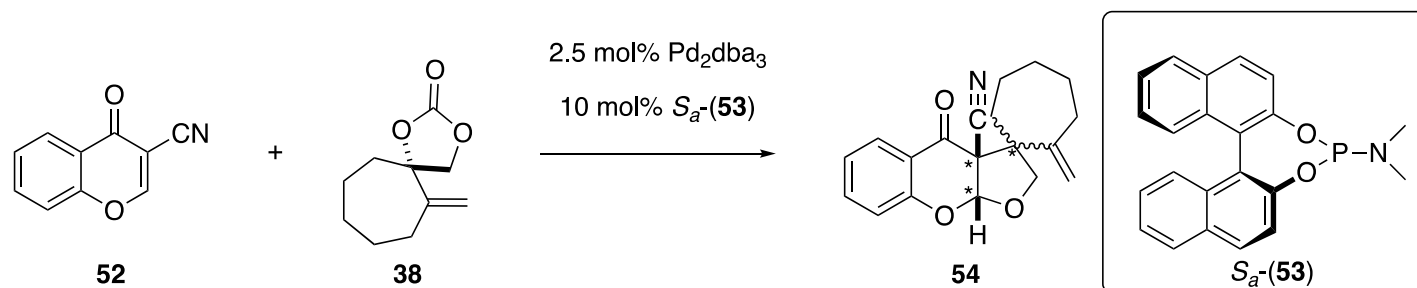


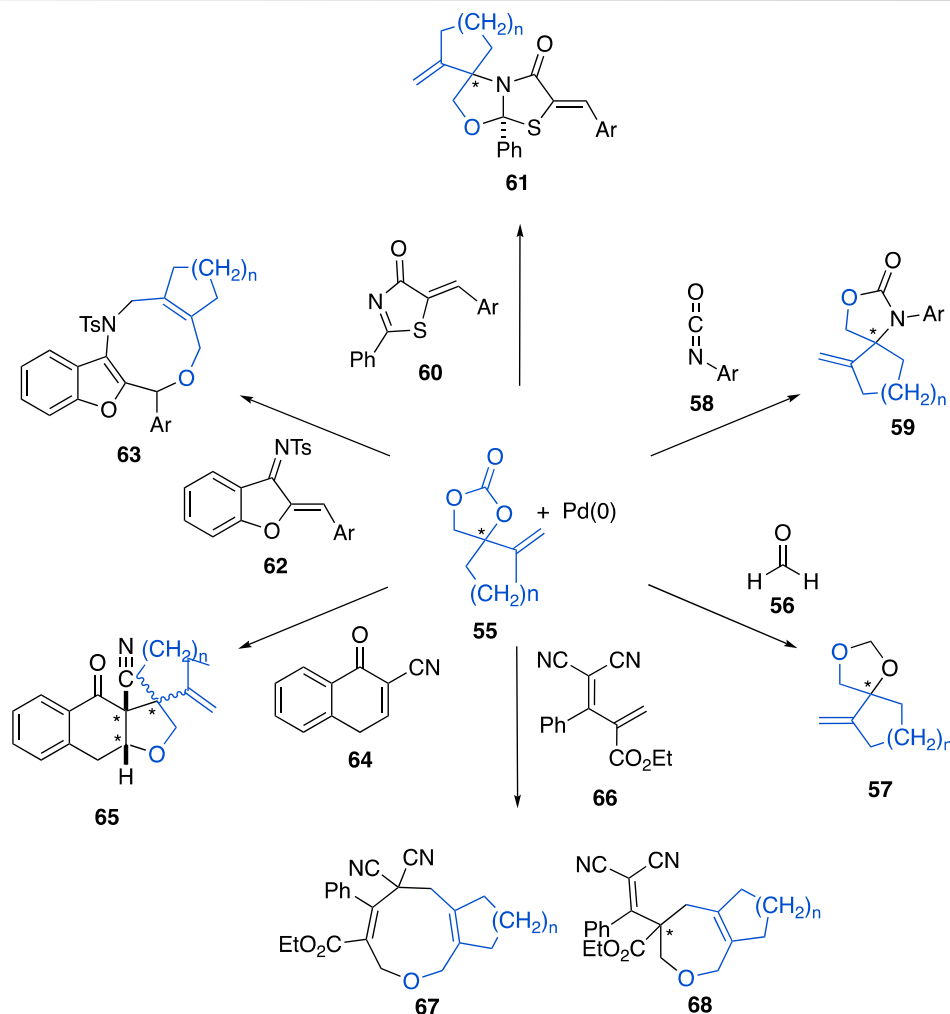


DoE approach



- Reaction with cyanochromone





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



I would like to thank...

Prof. Dr. Peter R. Schreiner

M. Sc. Christopher Topp

M. Sc. Friedemann Dreßler

B. Sc. Jan Metzler

The Schreiner Group

