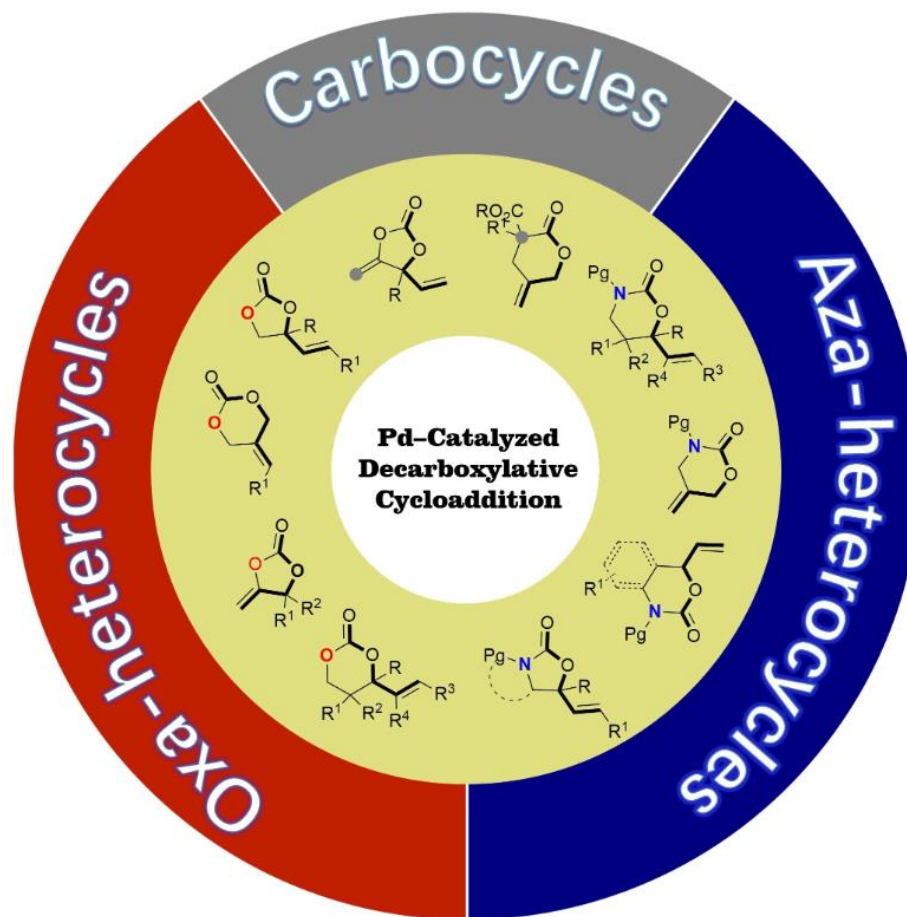


Preparation of Spirocyclic Vinylic Carbonates from Allylic Alcohols

22.07.2022

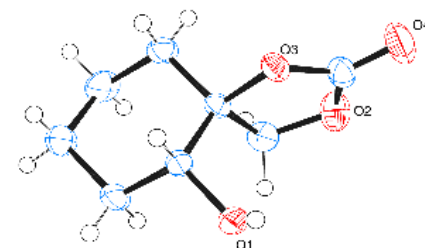
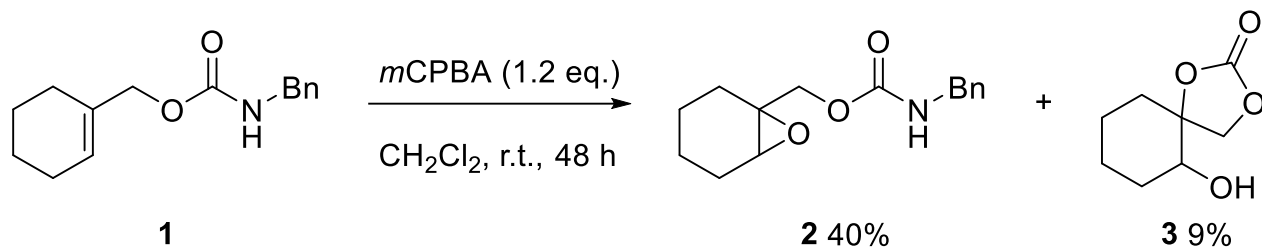
Christopher Topp, Group Seminar

*Institute of Organic Chemistry
Justus-Liebig-University
35392 Giessen, Germany*

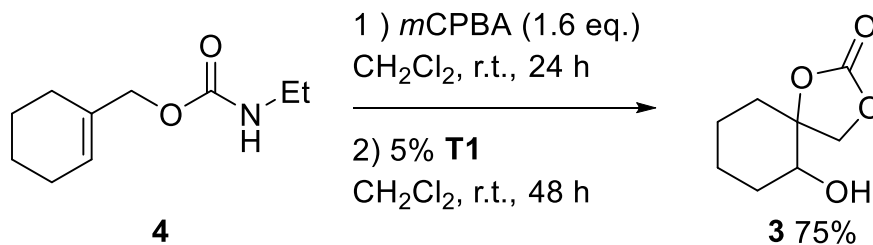




2013

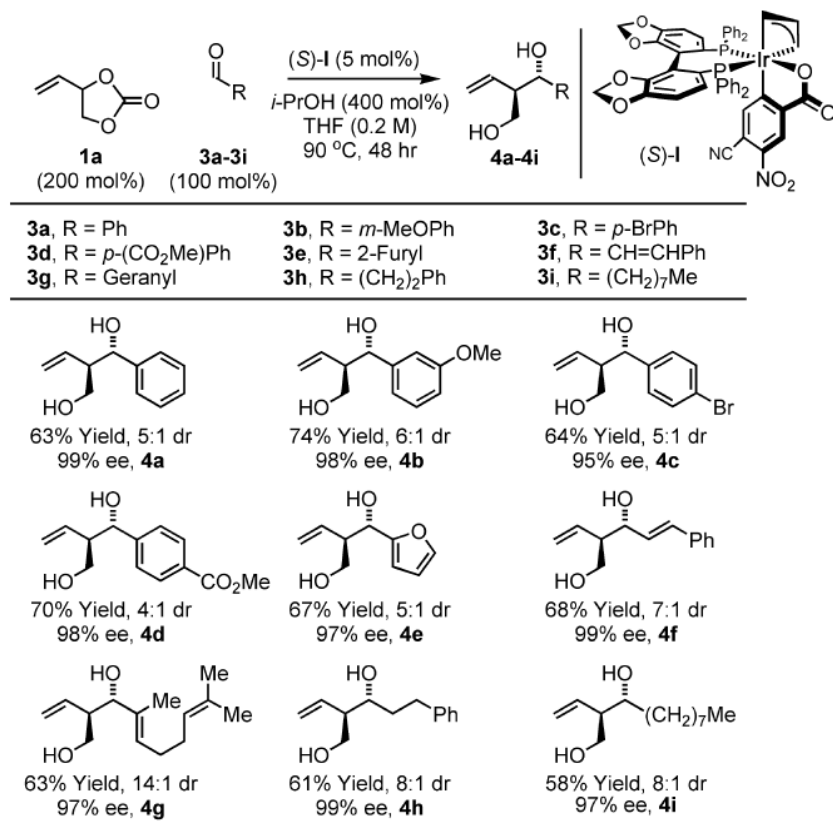


After one year of OVAT optimization

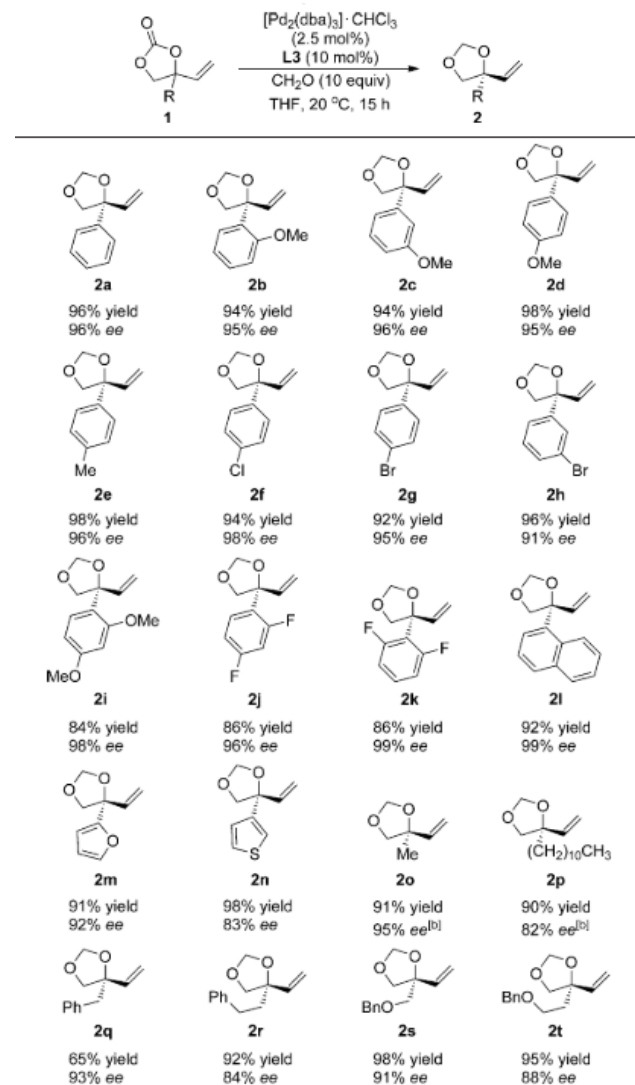




Krische et al. 2010:

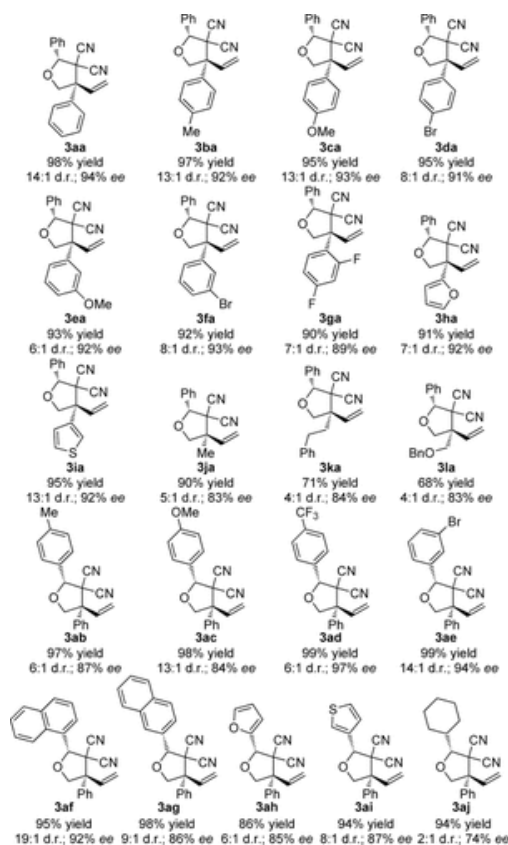
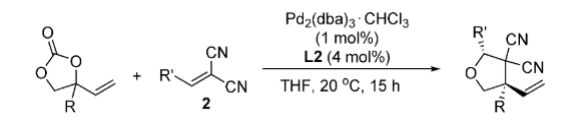


A. Khan et al. 2014:

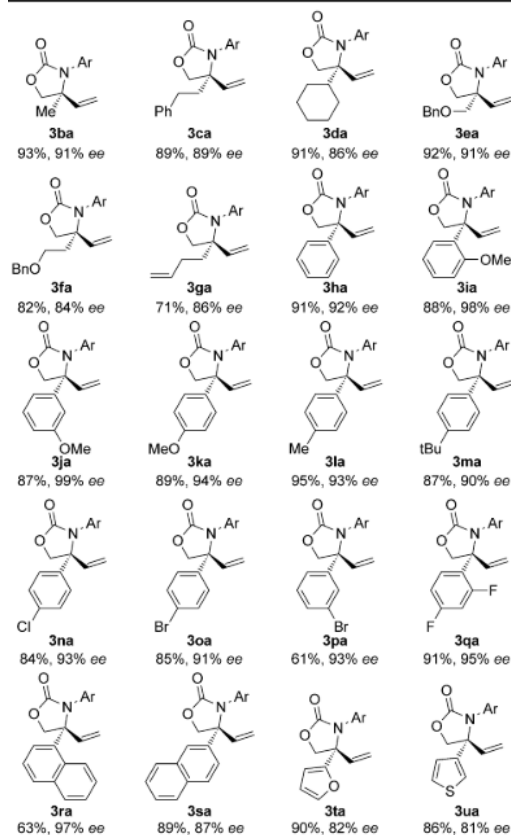
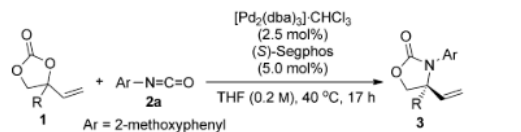
Y. J. Zhang, J. H. Yang, S. H. Kim, M. J. Krische, *J. Am. Chem. Soc.* **2010**, 132, 4562–4563A. Khan, R. Zheng, Y. Kan, J. Ye, J. Xing, Y. J. Zhang, *Angew. Chem. Int. Ed.* **2014**, 53, 6439–6442.



A. Khan et al. 2014:

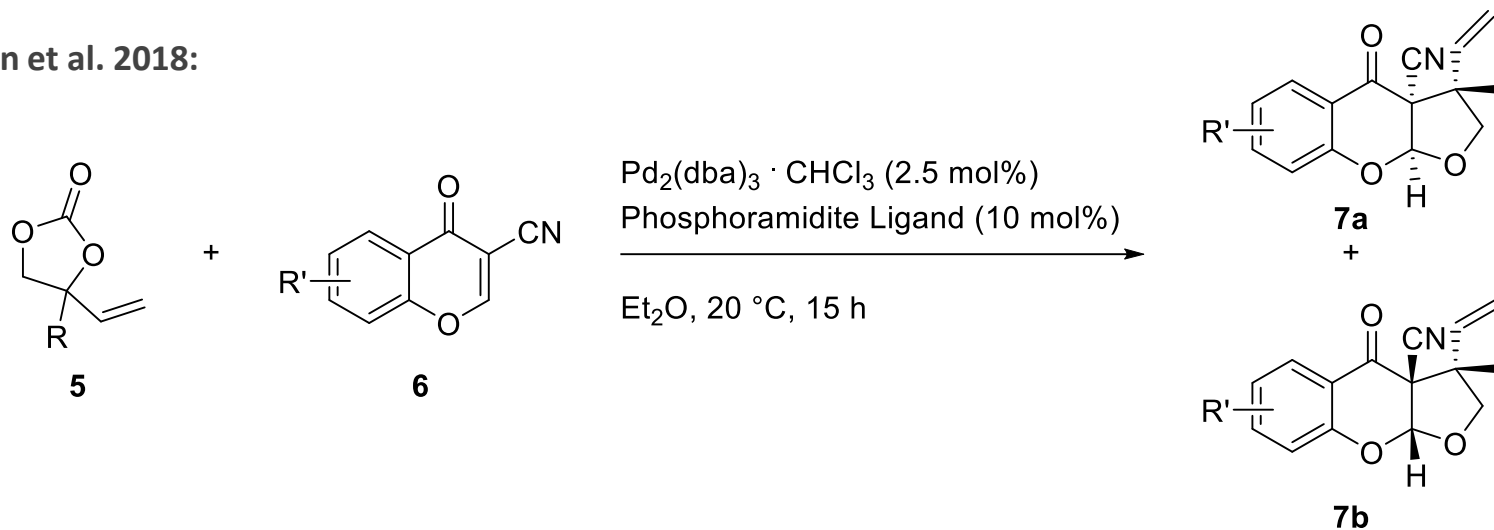


A. Khan et al. 2015:

A. Khan, L. Yang, J. Xu, L. Y. Jin, Y. J. Zhang, *Angew. Chem. Int. Ed.* **2014**, 126, 11439–11442.A. Khan, J. Xing, J. Zhao, Y. Kan, W. Zhang, Y. J. Zhang, *Chem. Eur. J.* **2015**, 21, 120–124.



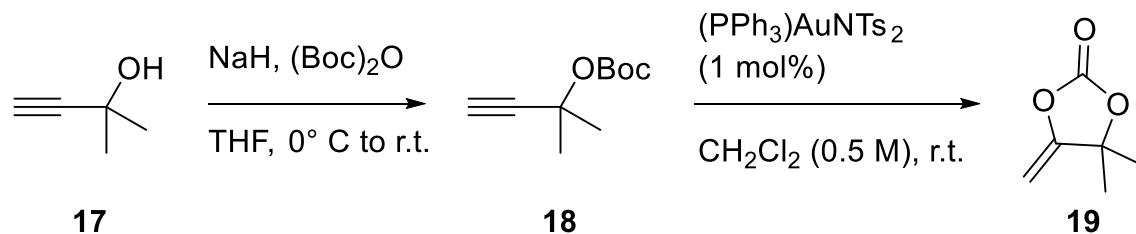
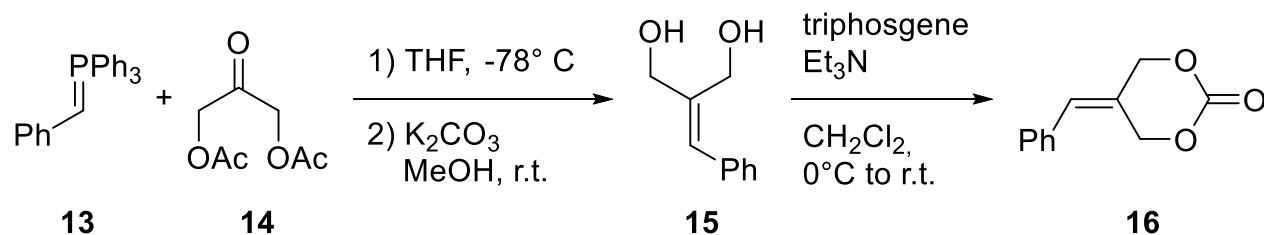
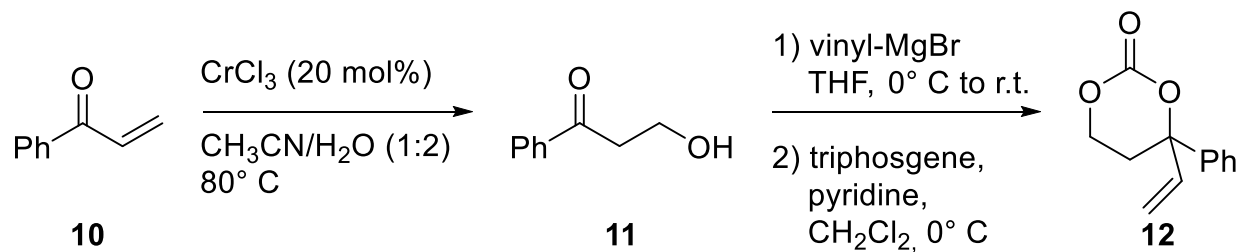
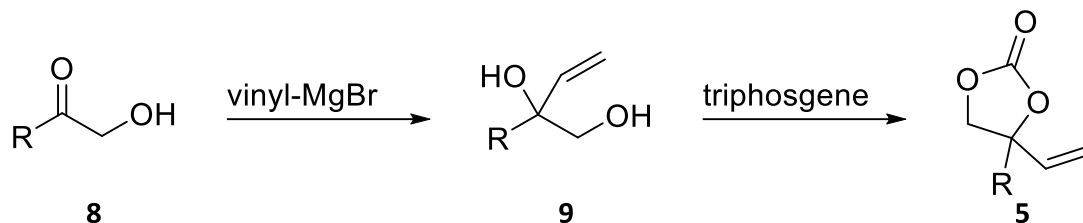
I. Khan et al. 2018:



What is the reason for this lack in VEC diversity?



What is the reason for this lack in VEC diversity?





Asymmetric Catalysis Hot Paper

How to cite: *Angew. Chem. Int. Ed.* **2021**, *60*, 5806–5810

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German Edition: doi.org/10.1002/ange.202016439

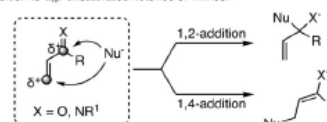
Regiodivergent Synthesis of Spirocyclic Compounds through Pd-Catalyzed Regio- and Enantioselective [3+2] Spiroannulation

Barry M. Trost* and Zhijun Zuo

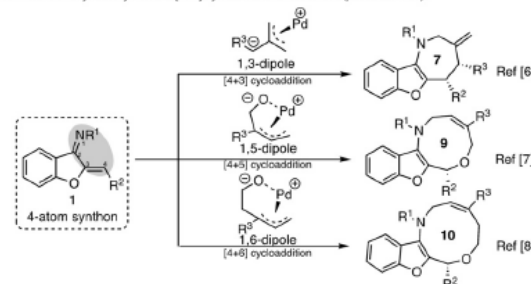
Abstract: A novel Pd⁰-catalyzed highly regio- and enantioselective [3+2] spiroannulation reaction has been developed for rapid assembly of a new class of [5,5] spirocyclic carbo- and heterocycles. Notably, the regioselectivity could be dominated by fine-tuning of the Pd- π -allyl intermediate. An array of coupling partners could be well-tolerated with excellent regio-, and enantioselectivities. Moreover, the potential application of this reaction was exemplified by several further transformations.

Nucleophilic addition to α,β -unsaturated ketones or imines represents one fundamental bond-forming reaction in organic synthesis.^[1] Because of the possibility of 1,2-addition versus 1,4-addition, a thorough understanding of the factors that govern these competing pathways is required (Scheme 1 a).

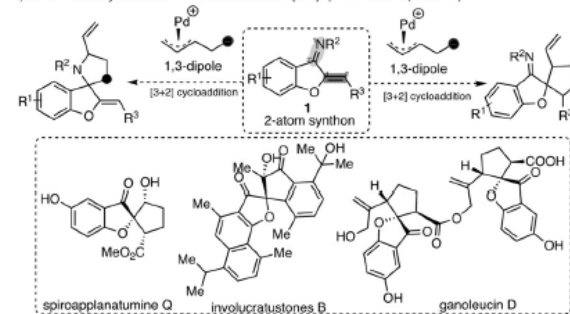
The rapidly changing landscape of both pharmaceutical and material chemistry requires the development of new synthetic methods, which can quickly and selectively construct a variety of cyclic molecular targets in an atom-economical manner.^[2] Cycloaddition reactions have been recognized as versatile synthetic tools, since these approaches provide straightforward routes for achieving an array of complex cyclic skeletons with high step economy.^[3] Among the existing variants, 1,3-dipolar cycloadditions (1,3-DCs) that consist of an active zwitterionic intermediate and an unsaturated acceptor play unique and important roles in synthesizing various valuable carbo- and heterocycles.^[4] However, the conventional 1,3-DCs are limited by the types of 1,3-dipoles

a) Nucleophilic addition to α,β -unsaturated ketones or imines:

b) Palladium-catalyzed asymmetric [4+n] cycloaddition of azadiene (previous work):



c) Palladium-catalyzed chemo- and enantioselective [3+2] spiroannulation (this work):



Scheme 1. The Pd-catalyzed asymmetric dipolar cycloaddition of azadiene.



Asymmetric [4 + 3] Annulations for Constructing Divergent Oxepane Frameworks via Cooperative Tertiary Amine/Transition Metal Catalysis

Zhi Chen, Zhi-Chao Chen,* Wei Du, and Ying-Chun Chen*

Cite This: *Org. Lett.* 2021, 23, 8559–8564

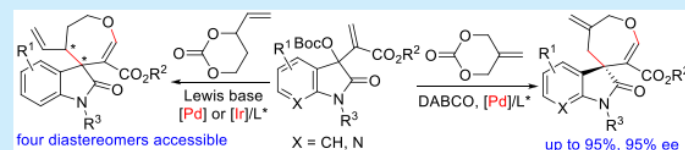
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ABSTRACT: We report asymmetric [4 + 3] annulations between isatin-derived Morita–Baylis–Hillman carbonates and two types of vinyl carbonates synergistically catalyzed by tertiary amines and transition metals, through chemoselective assemblies of in situ formed allylic ylides and metal-containing 1,4-dipoles. A range of oxepane frameworks are generally constructed in moderate to good yields with high stereocontrol. Moreover, all four diastereomers for the products bearing vicinal stereocenters are accessible by tuning tertiary amine and metal catalysts.

The seven-membered oxepane scaffold represents a unique type of oxygen-containing heterocycles, which is widely encountered in natural and bioactive products, as exemplified in Figure 1.¹ In particular, the oxepane incorporating a

Nevertheless, rapid construction of oxepane frameworks still remains a challenging task, especially in a catalytic asymmetric manner.

Over the past years, [4 + 3] and [5 + 2] annulation reactions emerged as powerful strategies for constructing oxepane derivatives.⁶ *o*-Quinone methides (*o*-QMs) and the analogues, featuring a highly reactive 4 π -system, were widely assembled with various three-atom partners,⁷ including *N*-heterocyclic carbene (NHC)-activated homoenolates,⁸ Lewis base tethered dipoles,⁹ Pd-trimethylenemethane intermediates, and 2-indolylmethanols,^{10,11} furnishing a broad range of aromatic ring fused oxepane derivatives (Scheme 1a). On the other hand, vinyl ethylene carbonates (VECs) proved to be the prevalent five-atom synthons to access oxepane derivatives via [5 + 2] annulations (Scheme 1b).¹² Nevertheless, utilizing other oxygen-containing synthons, especially aliphatic ones, to construct differently functionalized oxepane architectures, would be still desirable.

Recently, our group disclosed cooperative catalytic systems combining Lewis bases (LBs) and palladium or iridium complexes, to realize diverse assemblies between in situ

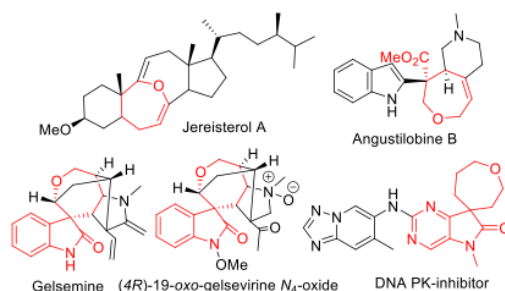
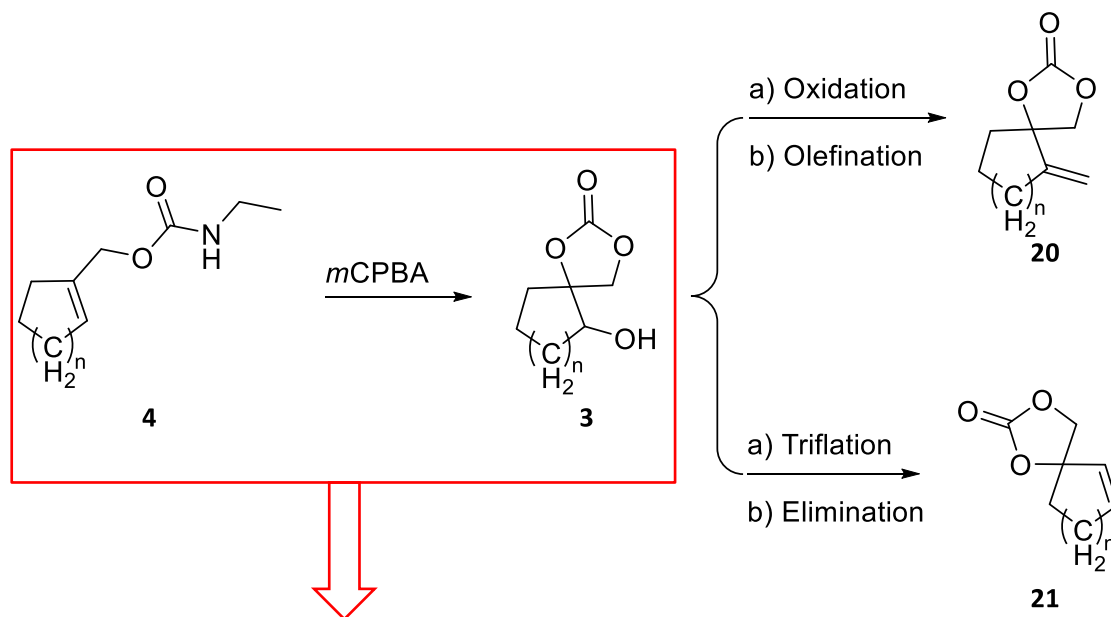
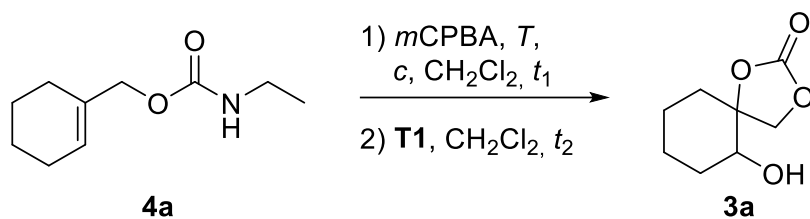


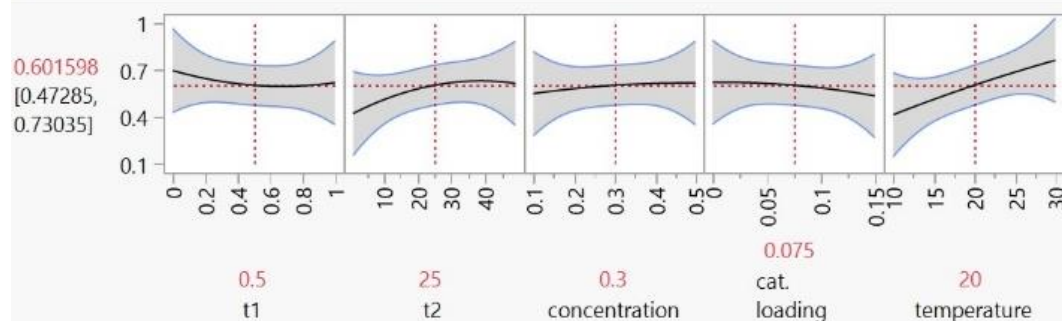
Figure 1. Selected natural products and bioactive molecules embedding an oxepane skeleton.



Access to spirocyclic carbonates with different ring sizes ($n=1,2,3$)

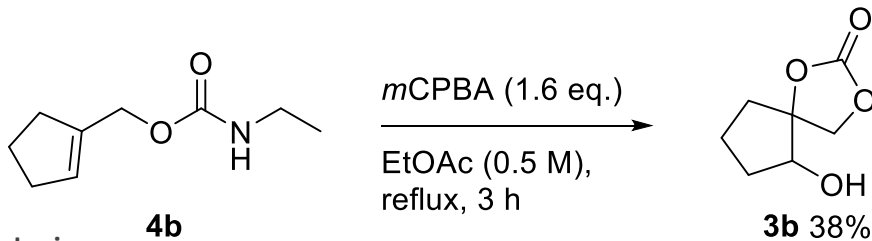
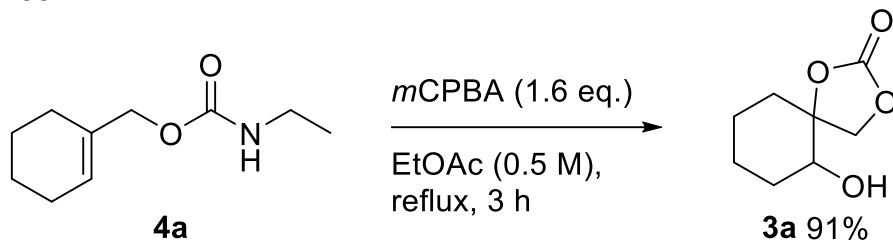


Prediction Profiler

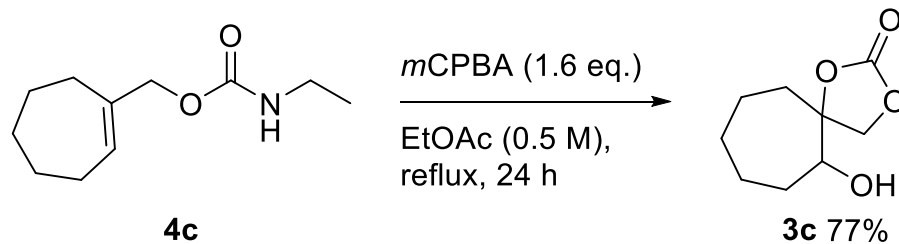
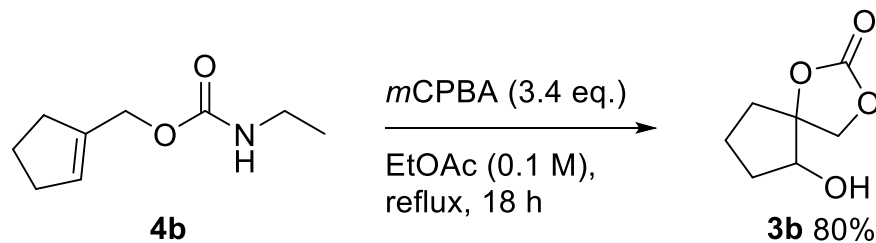


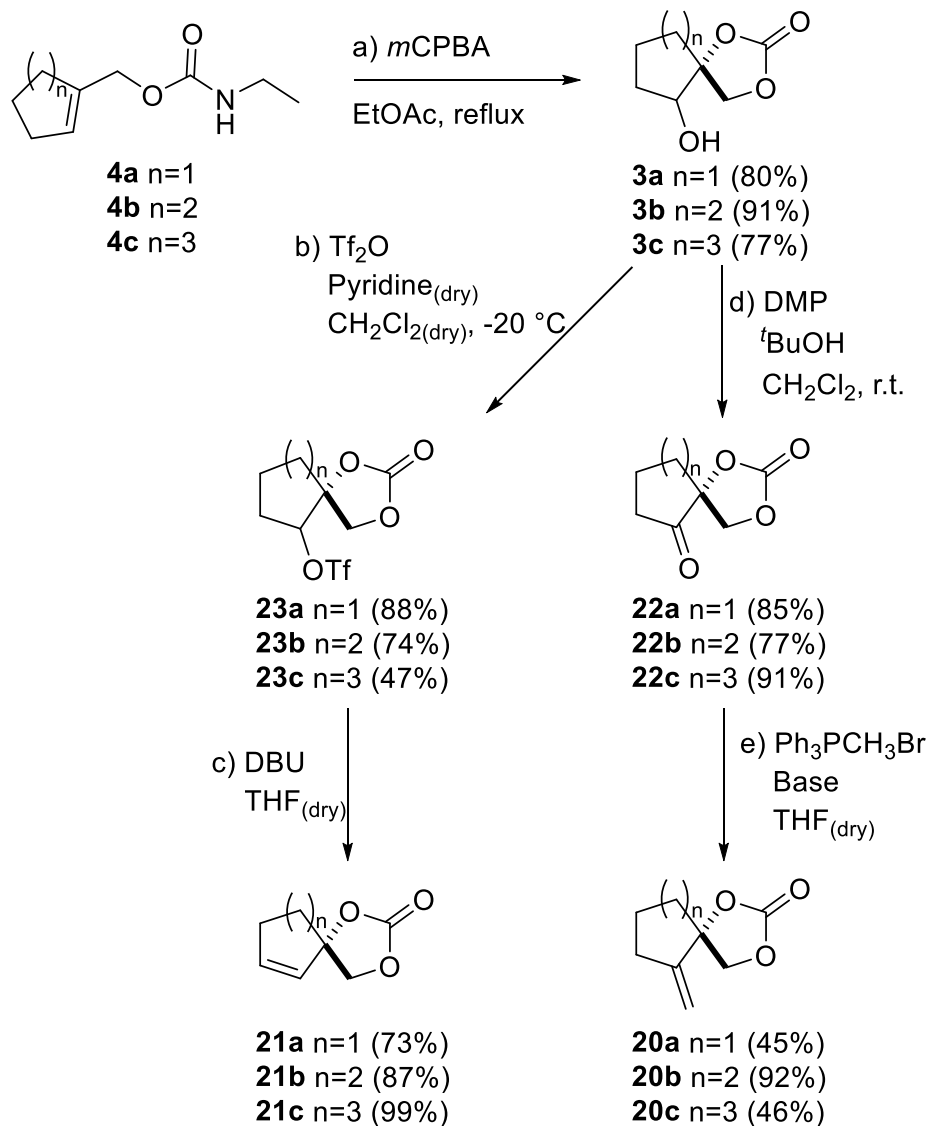


Jan

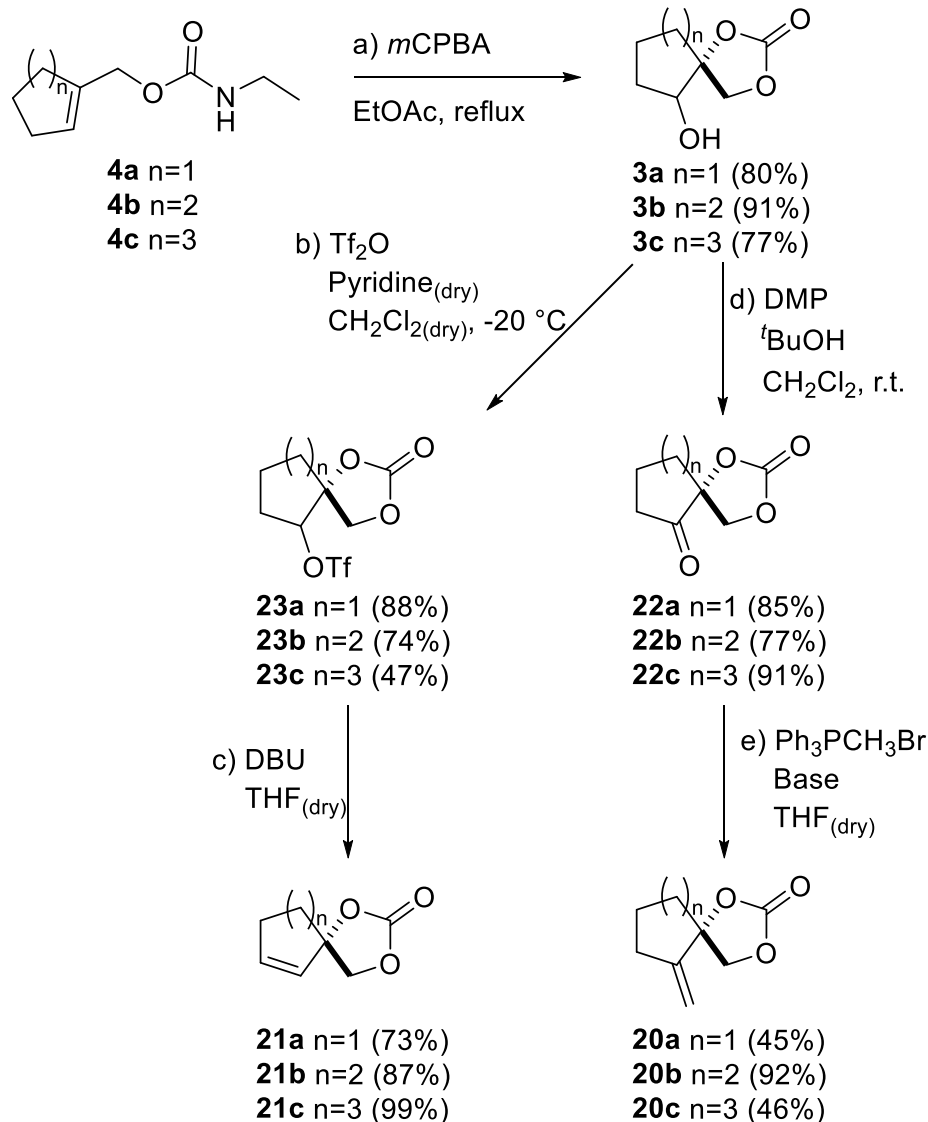


Luisa

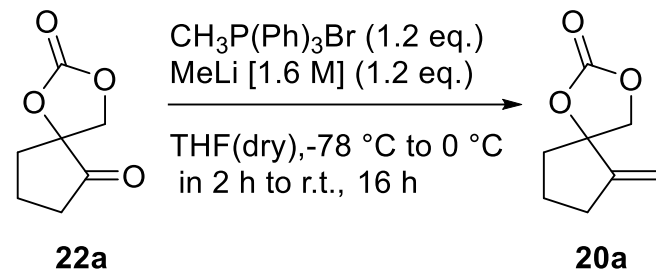




a) $n=0$: *m*CPBA (3.4 eq.), EtOAc (0.1 M), reflux, 24 h; $n=2=3$: *m*CPBA (1.6 eq.), EtOAc (0.5 M), reflux, 3 h **b)** $n=1=2=3$: TiF_2O (1.1 eq.), Pyridine (2.0 eq.), $-20\text{ }^\circ\text{C}$, 30–60 min. **c)** $n=1=2$: DBU (5.0 eq.), $\text{THF}_{(\text{dry})}$, reflux, 30 min.; $n=3$: DBU (2.0 eq.), $\text{THF}_{(\text{dry})}$, r.t., 18 h **d)** $n=1=2=3$: DMP (1.5 eq.), $t\text{BuOH}$ (1.5 eq.), r.t., 18 h **e)** $n=1$: $\text{CH}_3\text{P}(\text{Ph})_3\text{Br}$ (1.2 eq.), MeLi [1.6 M] (1.2 eq.), $\text{THF}_{(\text{dry})}$, $-78\text{ }^\circ\text{C}$ to $0\text{ }^\circ\text{C}$ in 2 h to r.t., 16 h, $n=2$: $\text{CH}_3\text{P}(\text{Ph})_3\text{Br}$ (1.2 eq.), KO^tBu (1.2 eq.), $\text{THF}_{(\text{dry})}$, $0\text{ }^\circ\text{C}$ to r.t., 18 h; $n=3$: $\text{CH}_3\text{P}(\text{Ph})_3\text{Br}$ (1.2 eq.), MeLi [1.6 M] (1.2 eq.), $\text{THF}_{(\text{dry})}$, $0\text{ }^\circ\text{C}$ to r.t., 2 h.



Most Problematic Step:

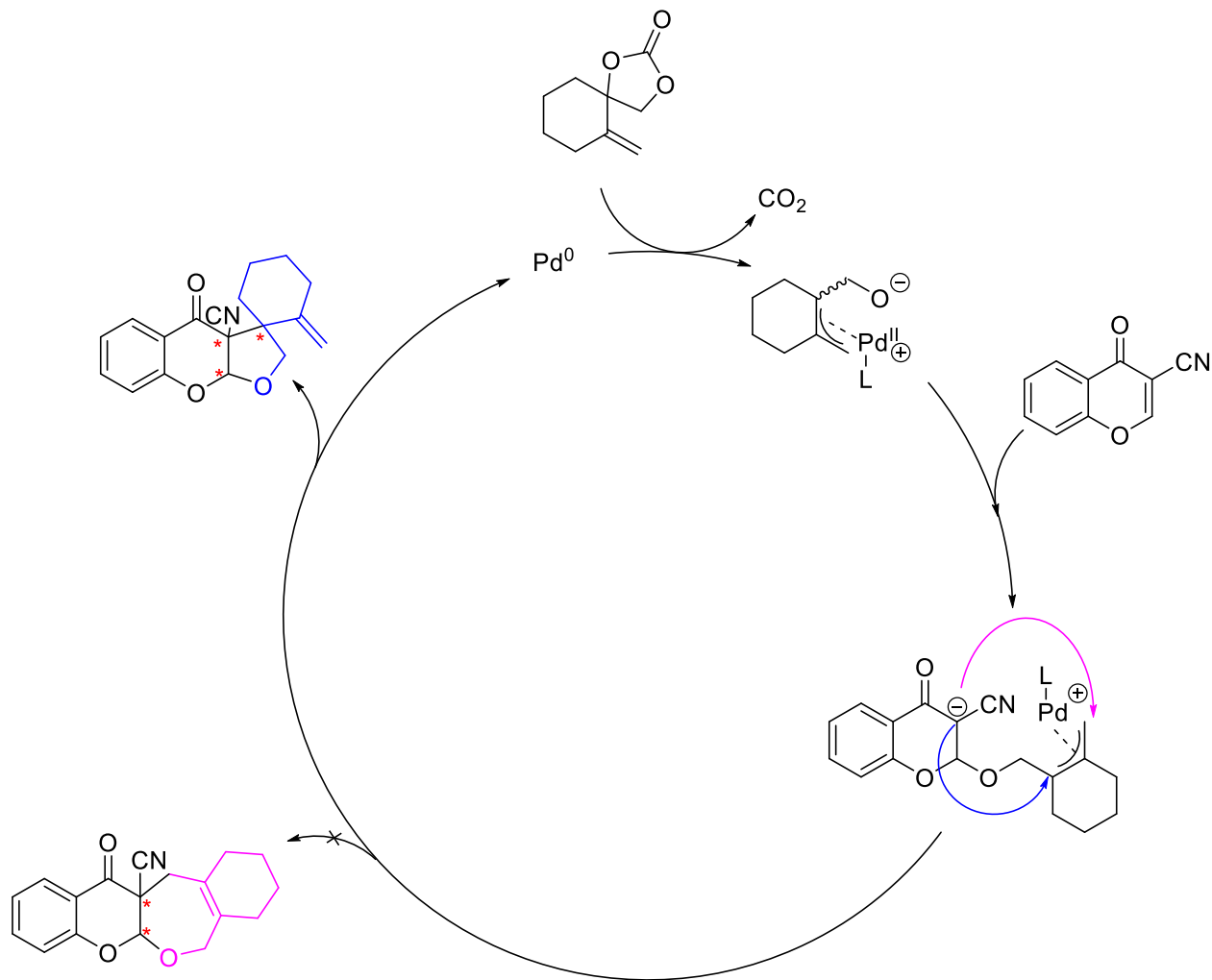


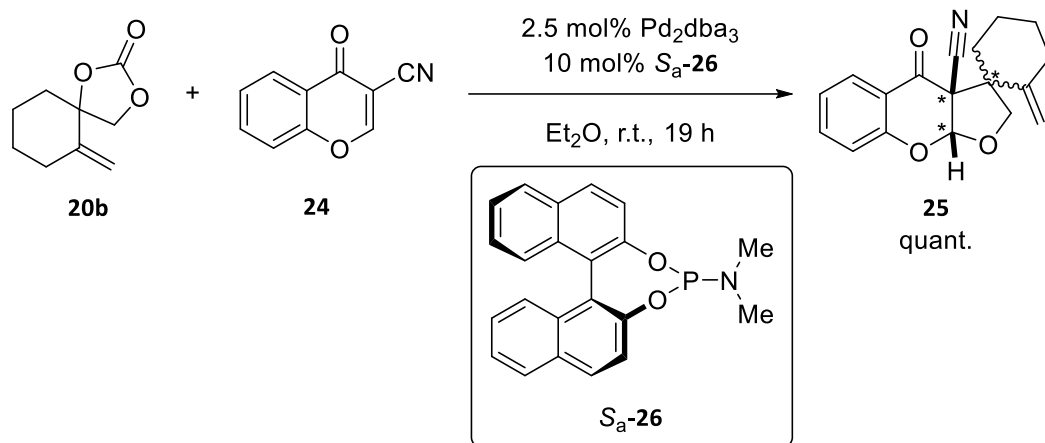
- Volatile product, distillative work-up tricky
- Sensitive with respect to the base
- Known low reactivity compared to 6-membered cyclic Ketones

a) n=0: *m*CPBA (3.4 eq.), EtOAc (0.1 M), reflux, 24 h; n=2=3: *m*CPBA (1.6 eq.), EtOAc (0.5 M), reflux, 3 h **b)** n=1=2=3: TF_2O (1.1 eq.), Pyridine (2.0 eq.), -20 °C, 30-60 min. **c)** n=1=2: DBU (5.0 eq.), THF_(dry), reflux, 30 min.; n=3: DBU (2.0 eq.), THF_(dry), r.t., 18 h **d)** n=1=2=3: DMP (1.5 eq.), $t\text{BuOH}$ (1.5 eq.), r.t., 18 h **e)** n=1: $\text{CH}_3\text{P}(\text{Ph})_3\text{Br}$ (1.2 eq.), MeLi [1.6 M] (1.2 eq.), THF_(dry), -78 °C to 0 °C in 2 h to r.t., 16 h, n=2: $\text{CH}_3\text{P}(\text{Ph})_3\text{Br}$ (1.2 eq.), KO^tBu (1.2 eq.), THF_(dry), 0 °C to r.t., 18 h; n=3: $\text{CH}_3\text{P}(\text{Ph})_3\text{Br}$ (1.2 eq.), MeLi [1.6 M] (1.2 eq.), THF_(dry), 0 °C to r.t., 2 h.

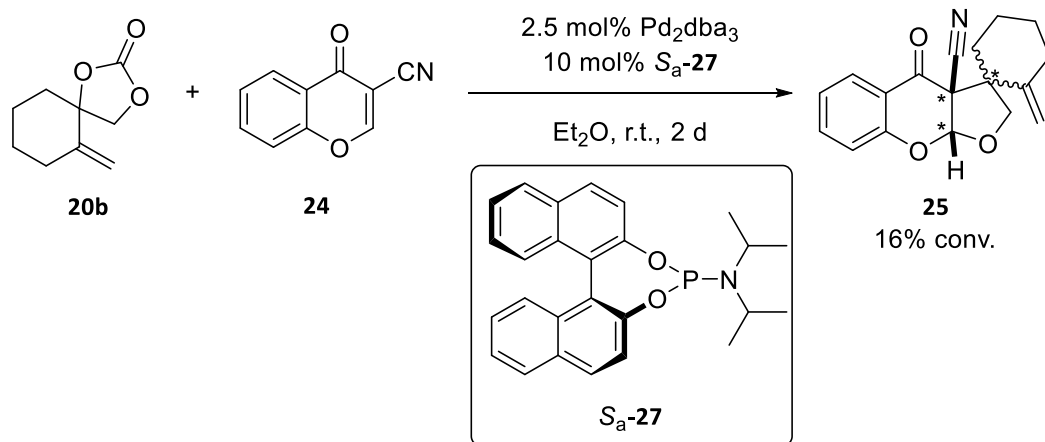


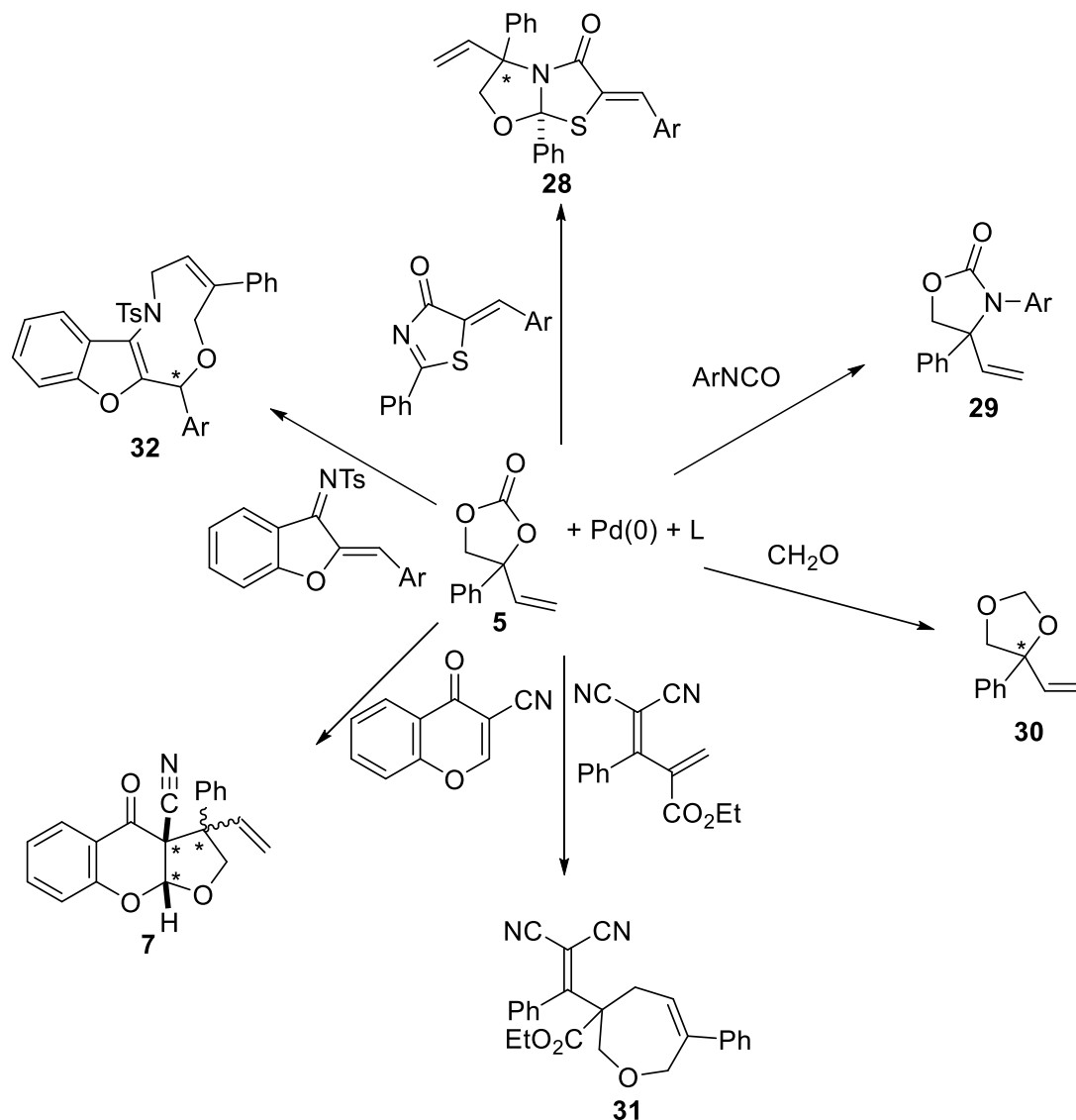
Mechanistic Proposal:

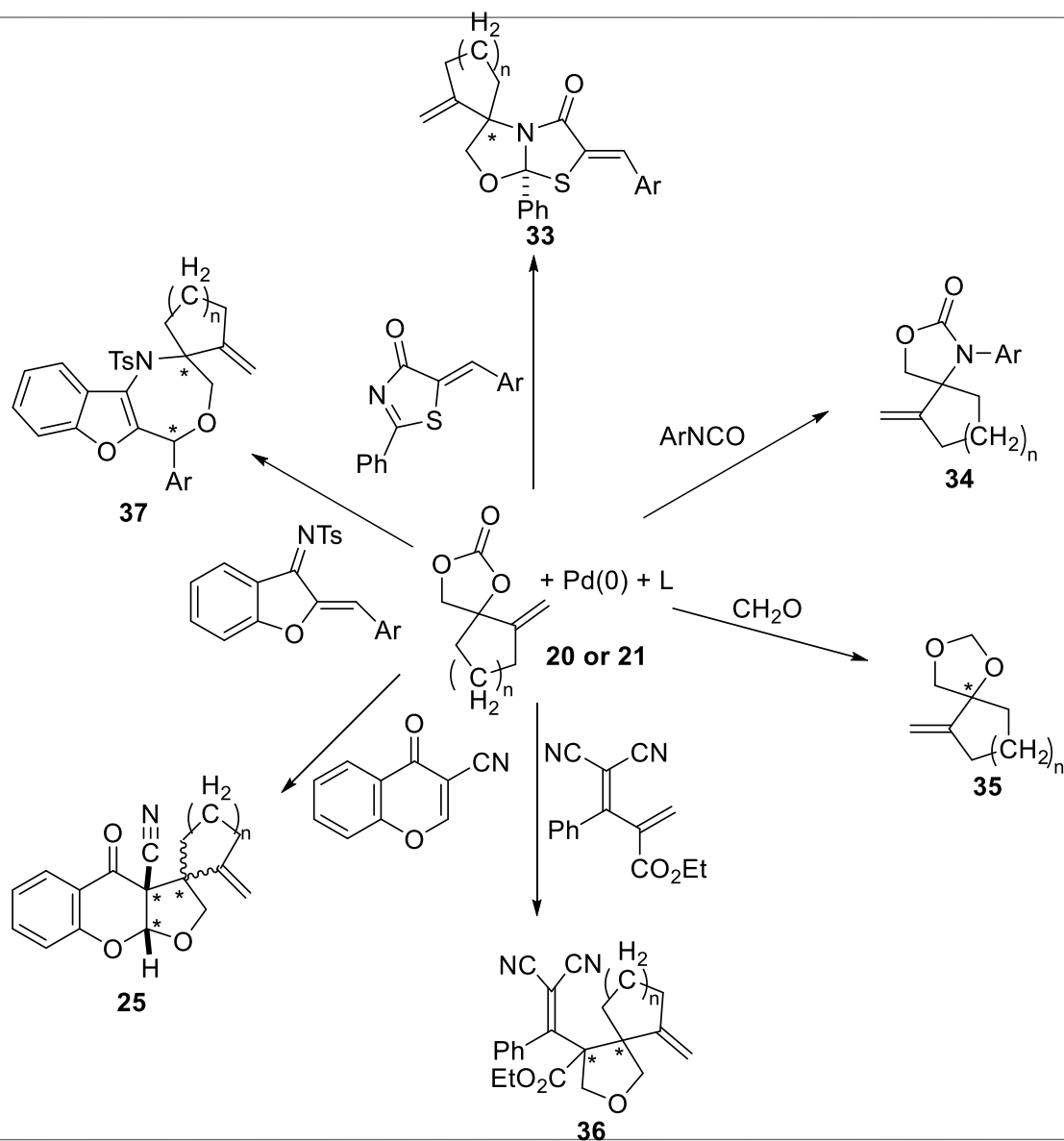




- high conversion
- low ee and de
- four of eight possible stereoisomers found *via* HPLC, but separation poorly

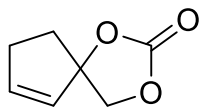




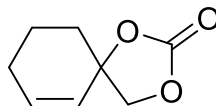




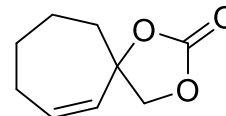
- New route to spirocyclic VECs with comparably cheap starting materials and standard transformations
- DoE optimized one pot epoxidation and cyclisation as key-step
 - Allylic alcohols are fairly abundant which offers a great platform for derivatization beyond s-VECs
- To the best of my knowledge the first synthons for “direct” transfer of a spiro center.



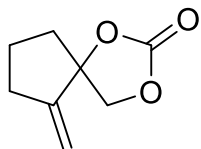
51% yield over 3 steps



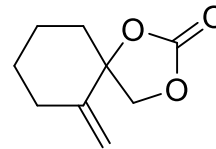
59% yield over 3 steps



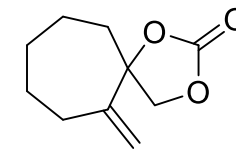
36% yield over 3 steps



31% yield over 3 steps



64% yield over 3 steps



32% yield over 3 steps



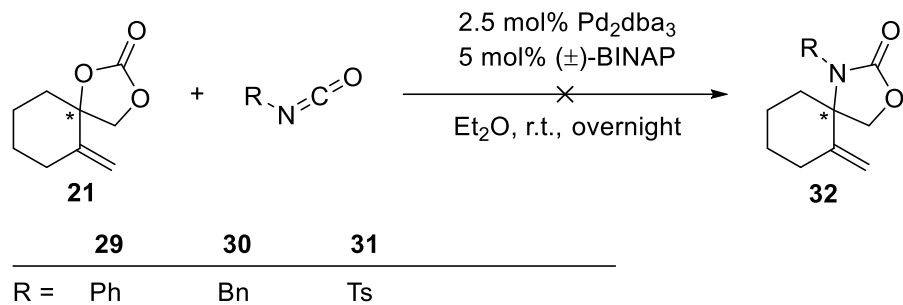
Potential Cooperation with the Denmark Group

- Goal: Find the right ligands and conditions for appropriate selectivity.
- Procedure: Subject Test-Set of ligands to each *s*-VEC and give them the data for their ML workflow...



- Prof. Dr. Peter R. Schreiner
- Dominik & Sören
- Jan & Luisa
- Friedhelm, Kai,
Lukas and Freddy
- PRS Group





^a 10 mol% (*S_a*)-**26** were used in place of (±)-BINAP

