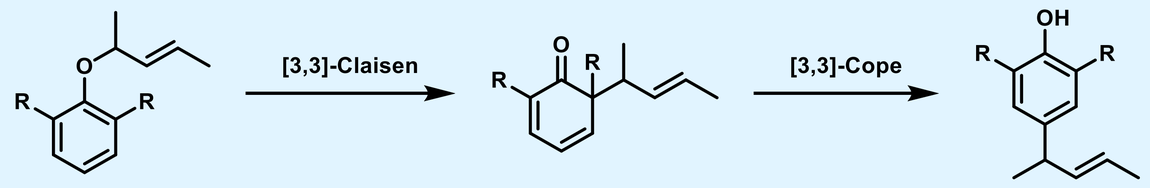
Investigating the asymmetric Claisen-Cope rearrangement

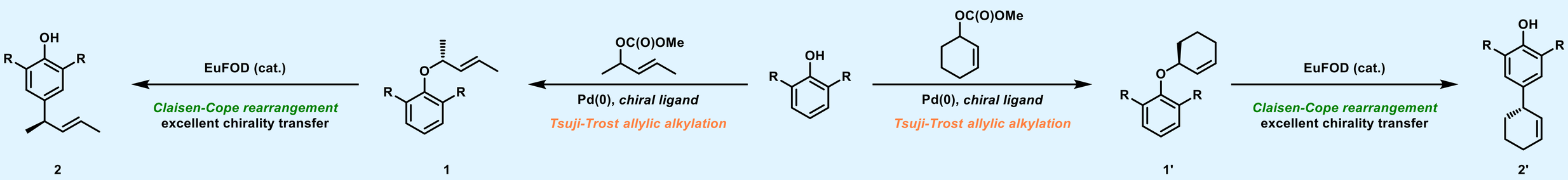
Johanna Breinsperger, Maximilian Kaiser, Peter Gärtner
Institute of Applied Synthetic Chemistry, TU WIEN, 1060 Vienna, Austria

Introduction

The Claisen rearrangement of allyl-aryl ethers **1/1'** typically results in the formation of *ortho*-allylated phenols. However, if the *ortho* positions are substituted, a Cope-rearrangement occurs to the *para* position, affording the Claisen-Cope products **2/2'**.



While a limited number of methods for the asymmetric *ortho*-Claisen rearrangement have been reported in recent years, the asymmetric *para*-Claisen-Cope rearrangement has been largely overlooked until now.[1,2]



Asymmetric Allylic Alkylation

After extensive optimization with respect to chiral ligands, palladium source, carbonates and additives, the modified literature conditions allowed the preparation of ethers **1/1'** in excellent yields and excellent enantiomeric excess *(ee)*.

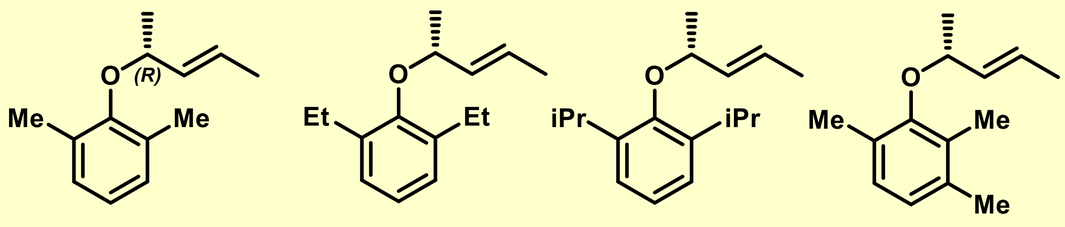
Claisen-Cope rearrangement

Initially, the thermally induced rearrangement (entry 1-2) was successful in transferring chirality, however requiring high reaction temperatures. While the use of Lewis acids (entries 3-7) resulted in a significant degree of racemization, EuFOD catalysis (entry 8) proved to be most efficient, facilitating the transfer of chirality under mild conditions. This *approach* was successfully employed to afford a variety of different *para*-allylated 2,6-disubstituted phenols **2/2'** in excellent yields and excellent enantiomeric excess.

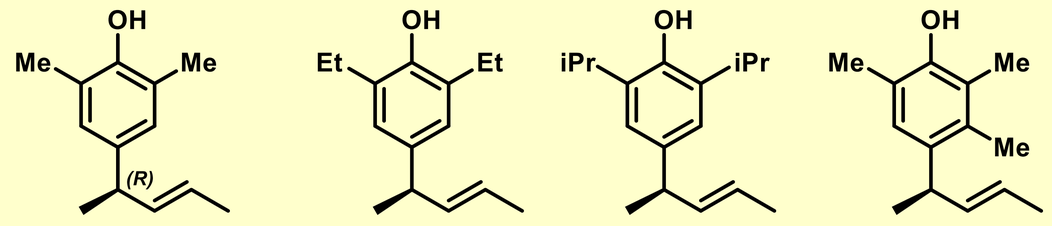
entry	conditions	T (°C)	t	% *ee*[1]
1	*N,N*-Diethylaniline (0.5 M)	190	3.5 h	86
2	*N,N*-Diethylaniline (0.5 M)	140	23 h	86
3	BF_3-etherate (0.1 eq.), DCM	-80	5 min	32
4	Et_2AlCl (1.5 eq.), hexane	0	5 min	2
5	Me_3Al (3 eq.), hexane	0	5 min	*decomposition*
6	$ZnCl_2$ (1.05 eq.), DCE	80	2.5 h	14
7	$SnCl_4$ (1.2 eq.), DCM	0	5 min	16
8	**EuFOD (cat.), PhMe**	**40**	**4 h**	**86**

[1]starting material: 86% *ee*

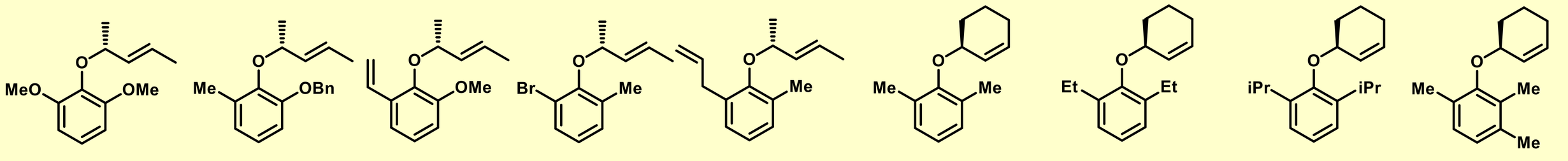
Scope & Results



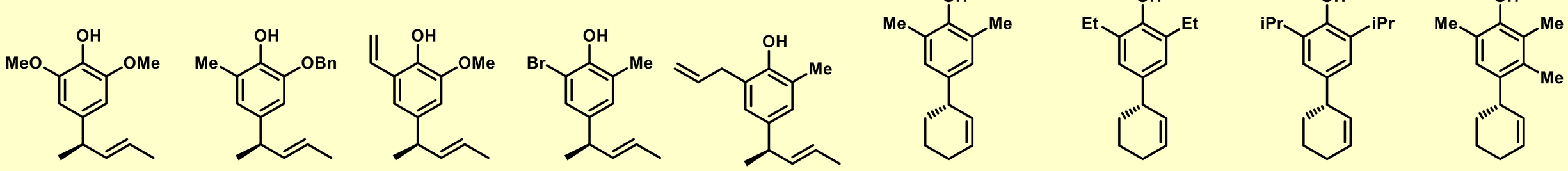
1a 95% *ee* 80% yield | **1b** 96% *ee* 92% yield | **1c** 97% *ee* 90% yield | **1d** 88% *ee* 84% yield



2a 94% *ee* quant. yield | **2b** 95% *ee* 97% yield | **2c** 97% *ee* 99% yield | **2d** 85% *ee* 98% yield



1e 91% *ee* 86% yield | **1f** 89% *ee* 42% yield | **1g** 91% *ee* 97% yield | **1h** 78% *ee* 85% yield | **1i** 94% *ee* 91% yield | **1'a** 94% *ee* 96% yield | **1'b** 97% *ee* 76% yield | **1'c** >99% *ee* 83% yield | **1'd** 96% *ee* 90% yield



2e 90% *ee* 98% yield | **2f** 84% *ee* 92% yield | **2g** 84% *ee* 27% yield | **2h** 73% *ee* 90 % yield | **2i** 96% *ee* 96% yield | **2'a** 94% *ee* quant. yield | **2'b** 96% *ee* 98% yield | **2'c** 96% *ee* 99% yield | **2'd** 97% *ee* 99% yield

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Acknowledgement
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References:
1. Rehbein, J.; Hiersemann, M.. Synthesis 2013, 45 (09), 1121–1159
2. Ito, H.; Taguchi, T. Chem. Soc. Rev. 1999, 28 (1), 43–50.