

# Asymmetric Claisen-Cope rearrangements

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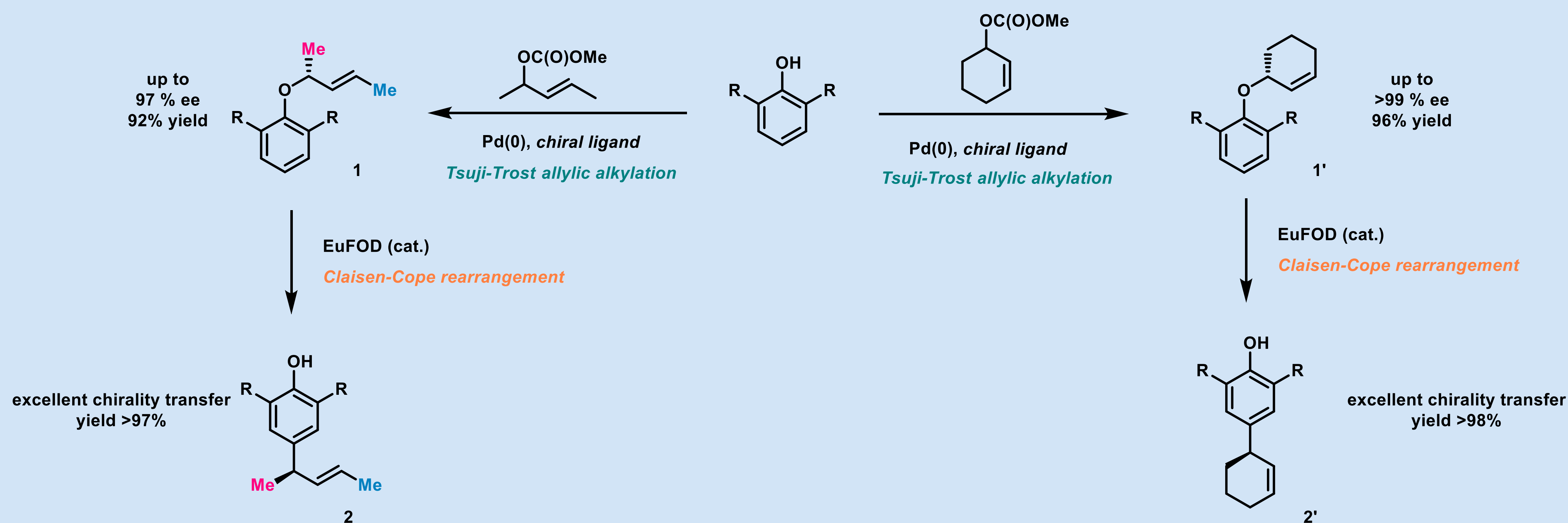
## Introduction

The Claisen rearrangement of allylic aryl ethers typically results in the formation of *ortho*-allylated phenols. However, if the *ortho* positions are substituted, rearrangement occurs to the *para* position, concluding the Claisen-Cope reaction. These [3,3]-sigmatropic rearrangements feature a transition state comprising a cyclic array of continuously bonded atoms, which enables high predictability in terms of connectivity and configuration. The aforementioned ability for stereocontrol has led to the development of a limited number of methods for the *ortho* Claisen rearrangement in recent years. In contrast, the asymmetric *para* Claisen rearrangement has been largely overlooked until now. [1,2]

## Asymmetric Aromatic Allylation

The enantioenriched starting materials **1** and **1'** were prepared via the Tsuji-Trost reaction, a highly efficient method for C-O bond formation using a chiral Palladium catalyst. To identify the optimal reaction conditions, a series of commonly used chiral ligands, palladium sources and carbonates were investigated.

Enantioenriched 2,6 disubstituted allyl-aryl ethers were prepared with up to >99% enantiomeric excess (*ee*) and high yields, which could be used for the investigation of the Claisen-Cope rearrangement.



## Claisen-Cope rearrangement

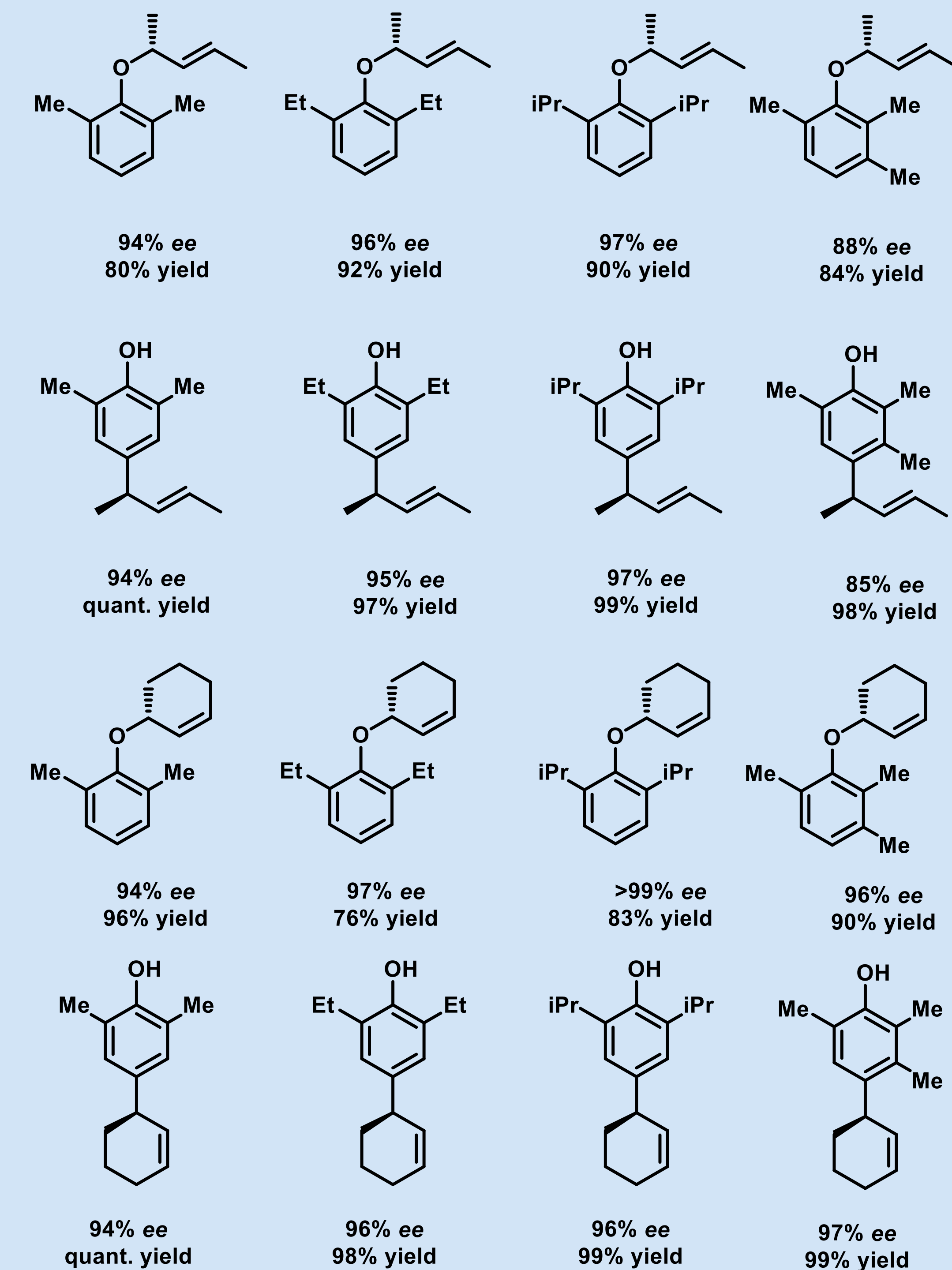
A number of different conditions were tested in order to determine the optimum reaction conditions for the *para* rearrangement. The thermally induced rearrangement was successful in transferring chirality, although it required high reaction temperatures and/or long reaction times. The use of Lewis acid catalysts resulted in a significant degree of racemization, which can be attributed to an ionic intermediate that, upon recombination, results in the loss of stereoinformation.

The optimal results were achieved by EuFOD catalysis, which facilitated the transfer of chirality under mild conditions with tolerable reaction times. The *para* allylated products **2** and **2'** were obtained with up to 97% *ee*.

entry	conditions	T	t	% <i>ee</i> <sup>1</sup>
1	N,N-Diethylaniline (0.5 M)	190	3.5 h	86
2	N,N-Diethylaniline (0.5 M)	140	23 h	86
3	o-Xylol (0.5 M)	140	23 h	86
4	Dichlorbenzol (0.5 M)	140	23 h	86
5	BF <sub>3</sub> -etherate (1.2 eq.), DCM (0.1 M)	-40	5 min	20
6	BF <sub>3</sub> -etherate (0.1 eq.), DCM (0.1 M)	-80	5 min	32
7	Et <sub>2</sub> AlCl (1.5 eq.), hexane (0.2 M)	0	5 min	2
8	Me <sub>3</sub> Al (3 eq.), hexane (0.15 M)	0	5 min	<i>decomposition</i>
9	CeCl <sub>3</sub> (0.1 eq.), PhMe (0.15 M)	r.t.	21.5 h	<i>no conversion</i>
10	ZnCl <sub>2</sub> (1.05 eq.), DCE (0.15 M)	80	2.5 h	14
11	SnCl <sub>4</sub> (1.2 eq.), DCM (0.5 M)	0	5 min	16
12	Bi(OTf) <sub>3</sub> (20 mol%), PhMe (0.1 M)	0	4 h	10
13	Eu(fod) <sub>3</sub> (10 mol%), PhMe (1 M)	40	4 h	86

<sup>1</sup>starting material: 86% *ee*

## Scope & results



## References:

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