Organocatalytic Dynamic Kinetic Resolution of Carboxylic Esters

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Chi, Y. R. *et al. J. Am. Chem. Soc.* **2016**, *138*, 7212-7215.

Wang, W. *et al. J. Am. Chem. Soc.* **2016**, *138*, 6956-6959.

Contents

Introduction

- The ester moiety represents one of the most ubiquitous functional groups in organic chemistry.

- How to synthesize esters?

  - ✓ Condensation reactions of carboxylic acids (acylating reagents such as acyl halides and acid anhydrides) with alcohols.

Drawbacks:

- ☐ Some carboxylic acids are labile or sparingly soluble in organic solvents.
- ☐ Stoichiometric amounts of the condensation reagents or bases are necessary.

Introduction

◆ How to synthesize esters?

✓ Transesterification reactions of esters with alcohols.

The transesterification is an equilibrium reaction.
◆ Acid, base, amine, molecular sieves, Lewis acid and metal alkoxide, Titanium tetraalkoxide, organotin catalysts, *etc*.

✓ Other methods (from aldehydes, ketenes, *etc*).

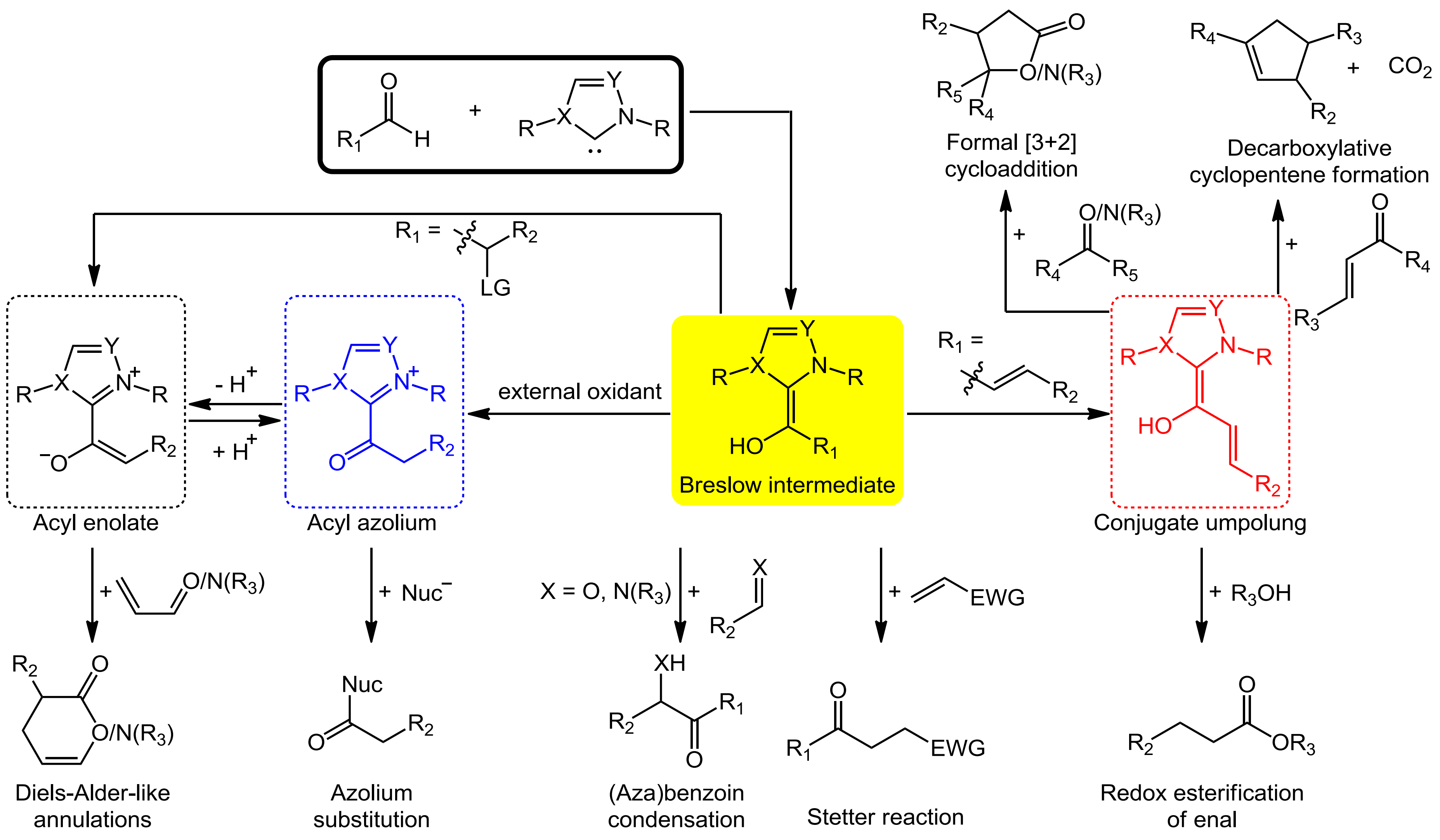
◆ How to synthesize chiral esters *via* catalytic esterification?

✓ Desymmetrization.

✓ Kinetic resolution.

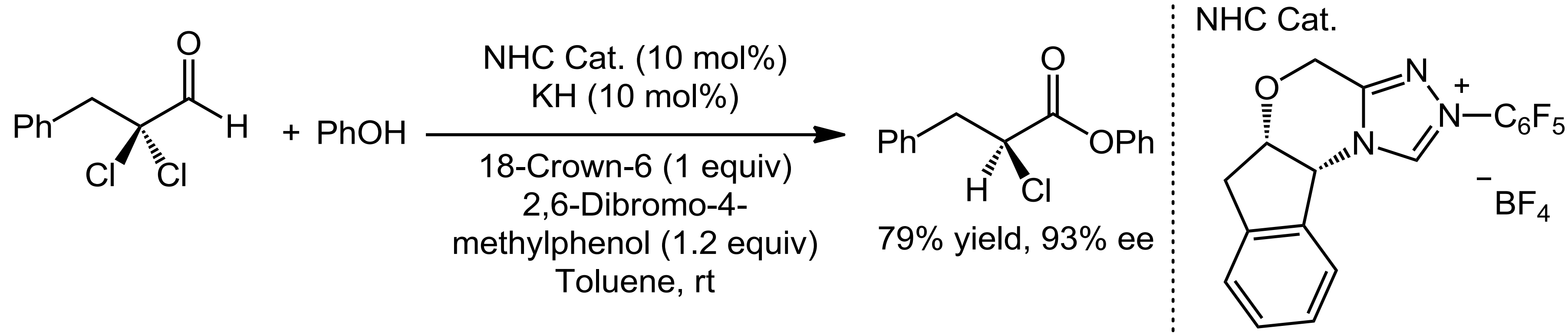
Otera, J. *et al. Chem. Rev.* **1993**, *93*, 1449.

Major NHC-Catalyzed Reactions of Aldehydes

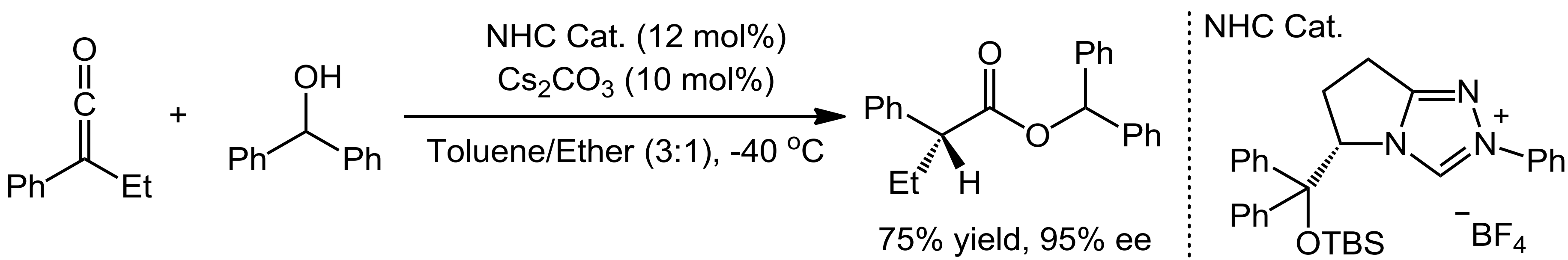


Glorius, F. *et al. Nature* **2014**, *510*, 485.

Asymmetric Protonation of Chiral Enolates *in situ*

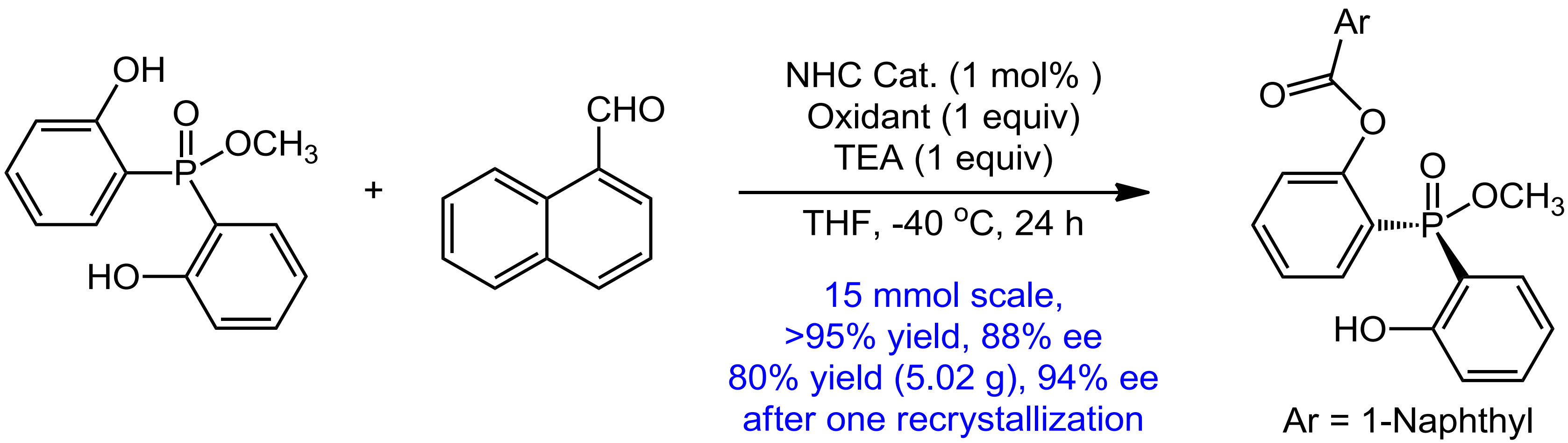


Rovis, T. *et al. J. Am. Chem. Soc.* **2005**, *127*, 16406.

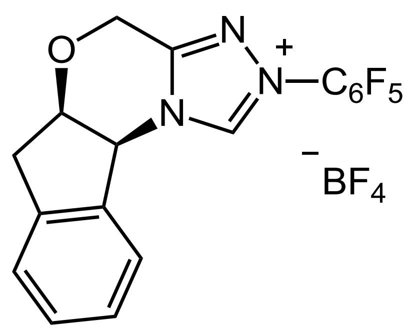


Ye, S. *et al. Org. Biomol. Chem.* **2009**, *7*, 346.

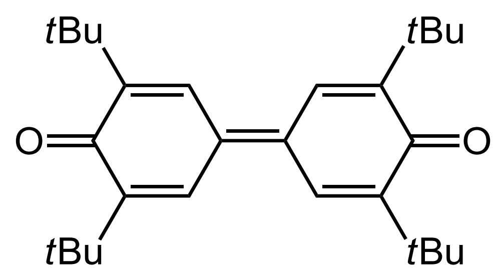
NHC-Catalyzed Desymmetrization of Bisphenols



NHC Cat.

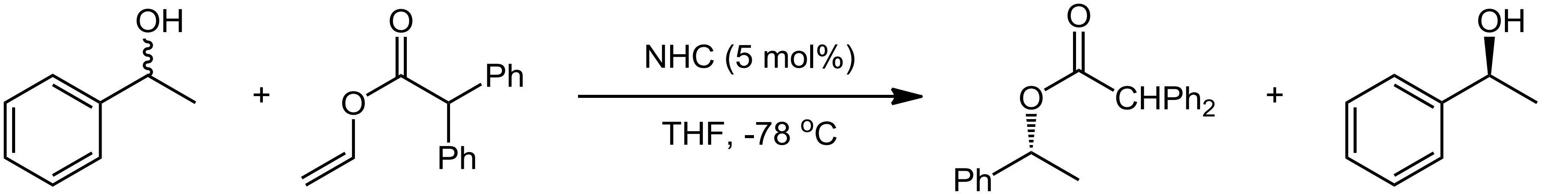


Oxidant



Chi, Y. R. *et al. J. Am. Chem. Soc.* **2016**, *138*, asap. (DOI: 10.1021/jacs.6b04624)

Kinetic Resolution of Secondary Alcohols

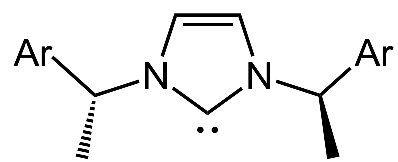


32% yield, 96% ee

62% yield, 51% ee

s = 80

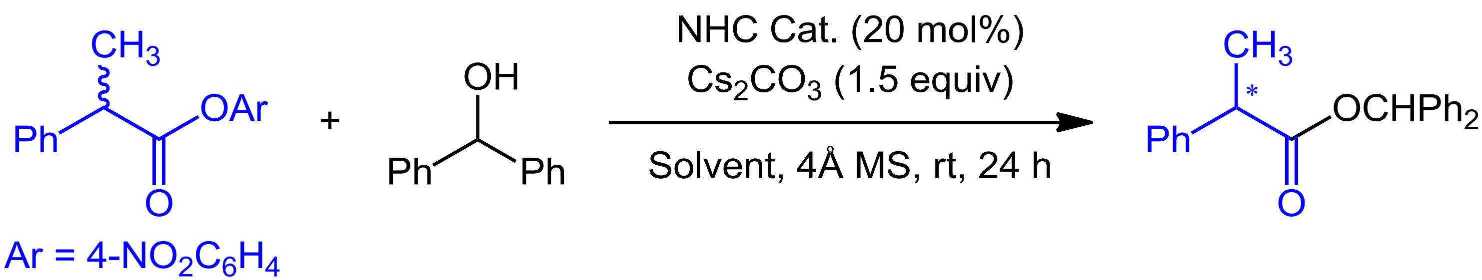
NHC



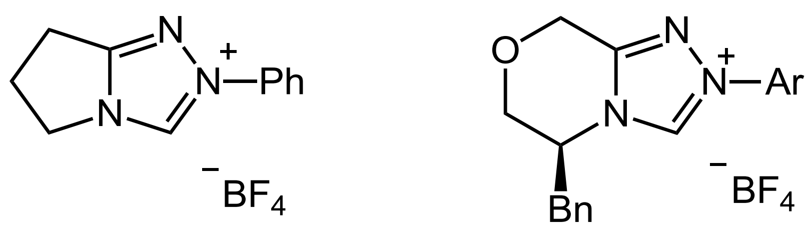
Ar = 1-naphthyl

Suzuki, Y. *et al. Chem. Commun.* **2004**, 2770; Maruoka, K. *et al. Org. Lett.* **2005**, *7*, 1347.

Dynamic Kinetic Resolution of Carboxylic Esters



Entry	NHC Cat.	Solvent	Yield[a] (%)	Ee (%)
1	--	THF	<5	--
2	A	THF	99	--
3	B	THF	99	34
4	B	$CHCl_3$	90	60
5	C	$CHCl_3$	80	76

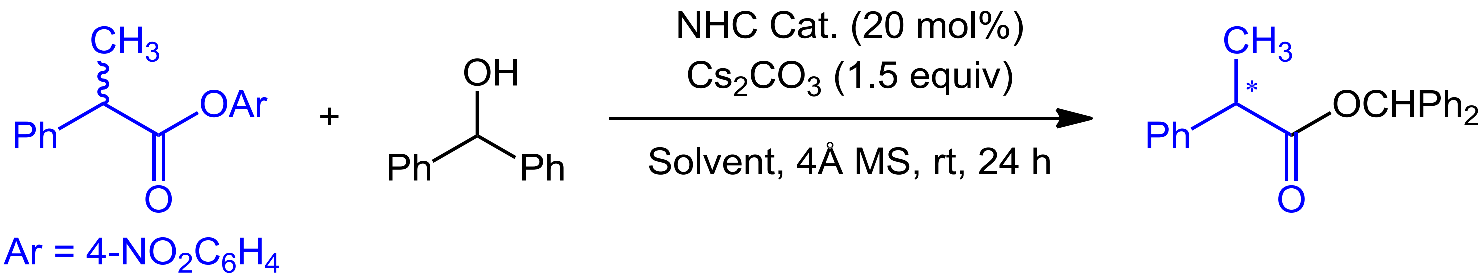


A

B: Ar = Ph
C: Ar = Mes

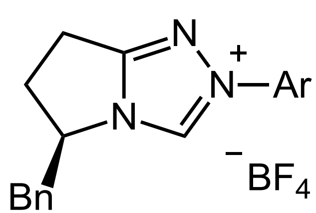
Chi, Y. R. *et al. J. Am. Chem. Soc.* **2016**, *138*, 7212.

Dynamic Kinetic Resolution of Carboxylic Esters

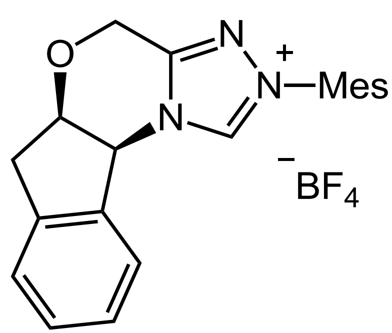


Entry	NHC Cat.	Solvent	Yield[a] (%)	Ee (%)
6	D	$CHCl_3$	99	70
7	E	$CHCl_3$	99(96)	92
8	F	$CHCl_3$	70	82
9[b]	E	$CHCl_3$	Trace	--

[a] Yield determined by NMR analysis with an internal standard. Isolated yield in parentheses. [b] 0 ºC.

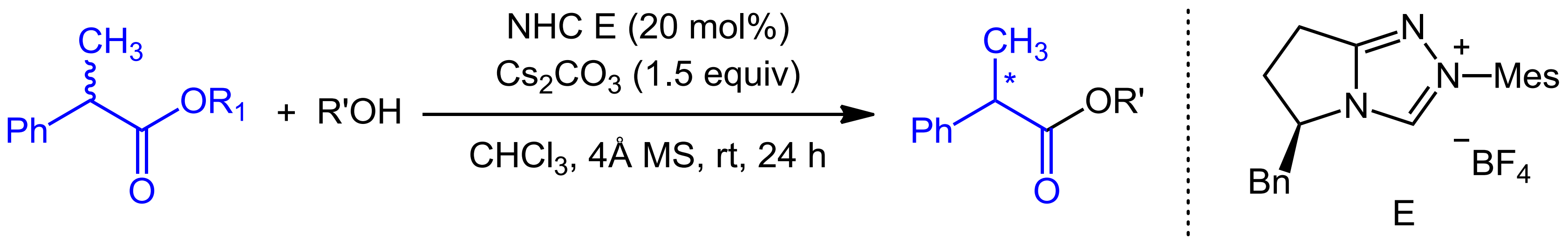


D: Ar = Ph
E: Ar = Mes



F

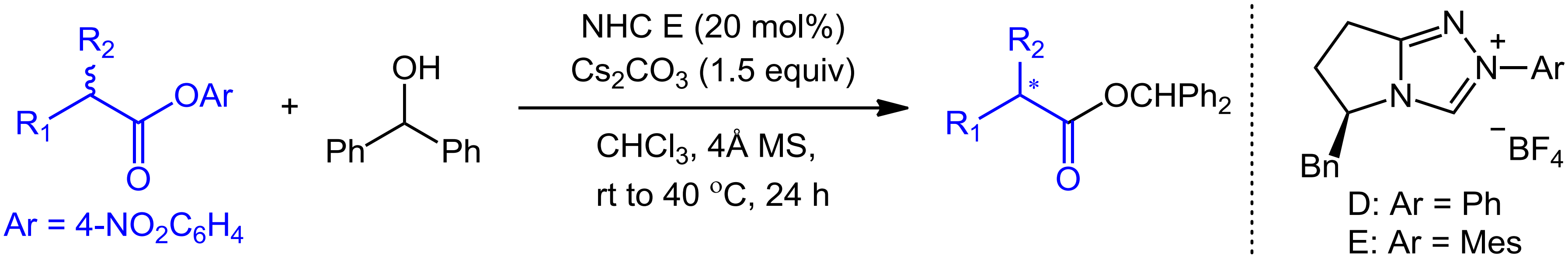
Screening of Different Esters and Alcohols

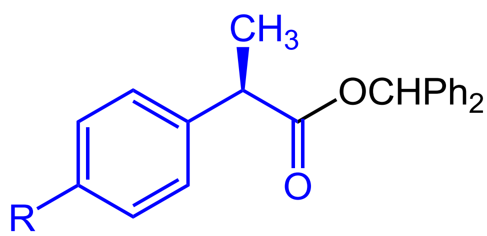


Entry	R_1	R'	Yield[a] (%)	Ee (%)
1	CH_3	Ph_2CH	N. R.	--
2	Ph	Ph_2CH	90	6
3	C_6F_5	Ph_2CH	99	88
4	4-$NO_2C_6H_4$	Ph_2CH	99	92
5	4-$NO_2C_6H_4$	CH_3	98	8
6	4-$NO_2C_6H_4$	$PhCH_2$	99	38
7	4-$NO_2C_6H_4$	Ph	92	4

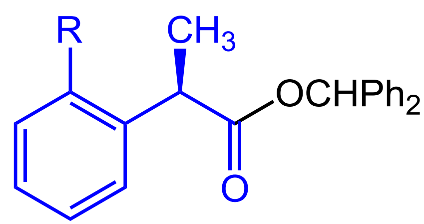
[a] Yield determined by NMR analysis with an internal standard.

Substrate Scope

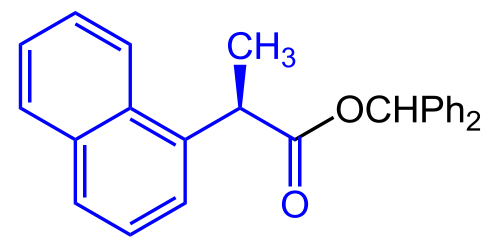




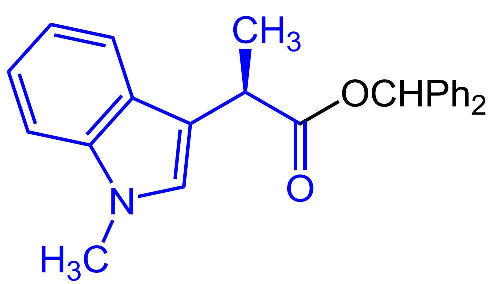
R = H, 96% yield, 92% ee
R = CH_3, 79% yield, 90% ee
R = OCH_3, 84% yield, 82% ee
R = Cl, 97% yield, 92% ee



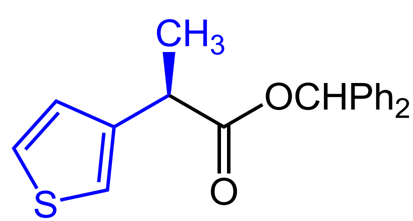
R = CH_3, 80% yield, 96% ee
R = OCH_3, 87% yield, 94% ee
R = Cl, 91% yield, 86% ee



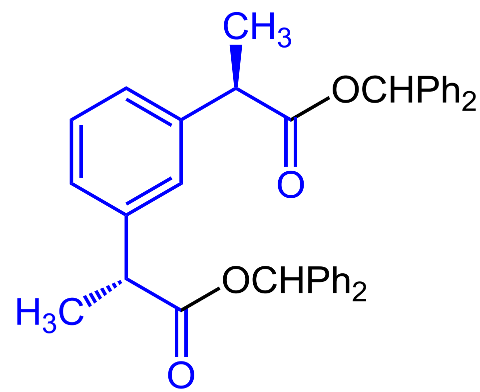
99% yield, 98% ee



83% yield, 96% ee

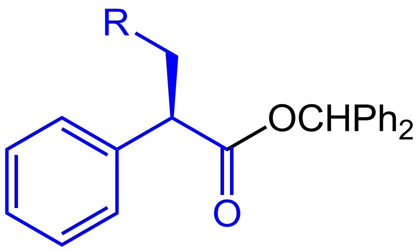


88% yield, 90% ee

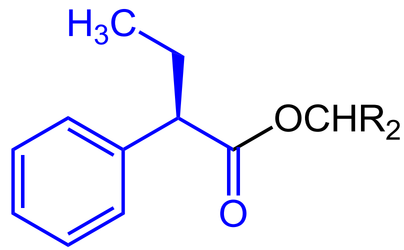


78% yield, >19:1 dr, 80% ee

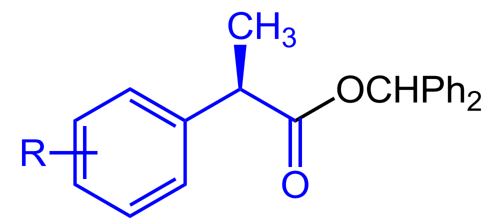
Substrate Scope



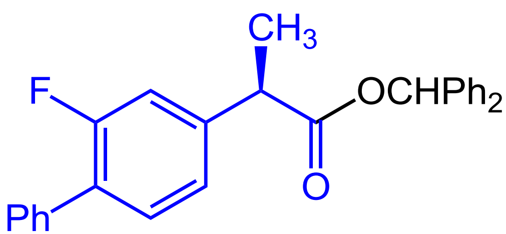
R = Ph, 87% yield, 90% ee
R = CN, 91% yield, 80% ee
R = OTBS, 84% yield, 80% ee[a]



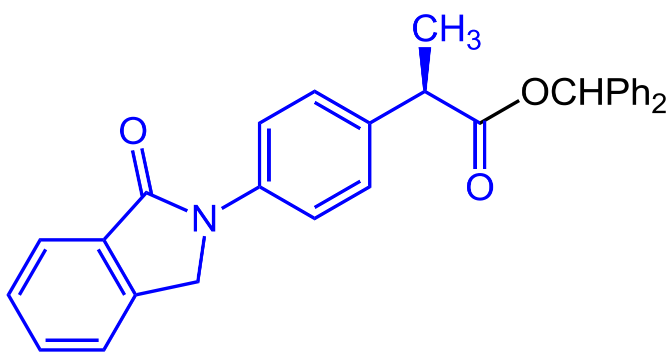
R = Ph, 87% yield, 70% ee
R = α-Np, 79% yield, 84% ee



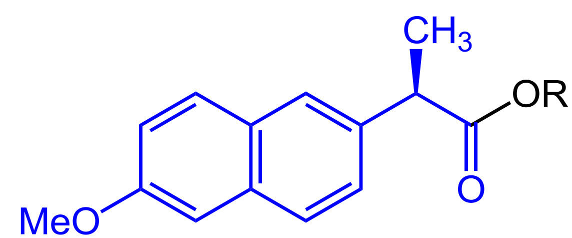
R = 4-*i*Bu, ibuprofen ester
75% yield, 96% ee
R = 3-OPh, fenaprofen ester
93% yield, 94% ee
R = 3-C(O)Ph, ketoprofen ester
95% yield, 86% ee



flurbinprofen ester
99% yield, 92% ee



indoprofen ester
85% yield, 92% ee



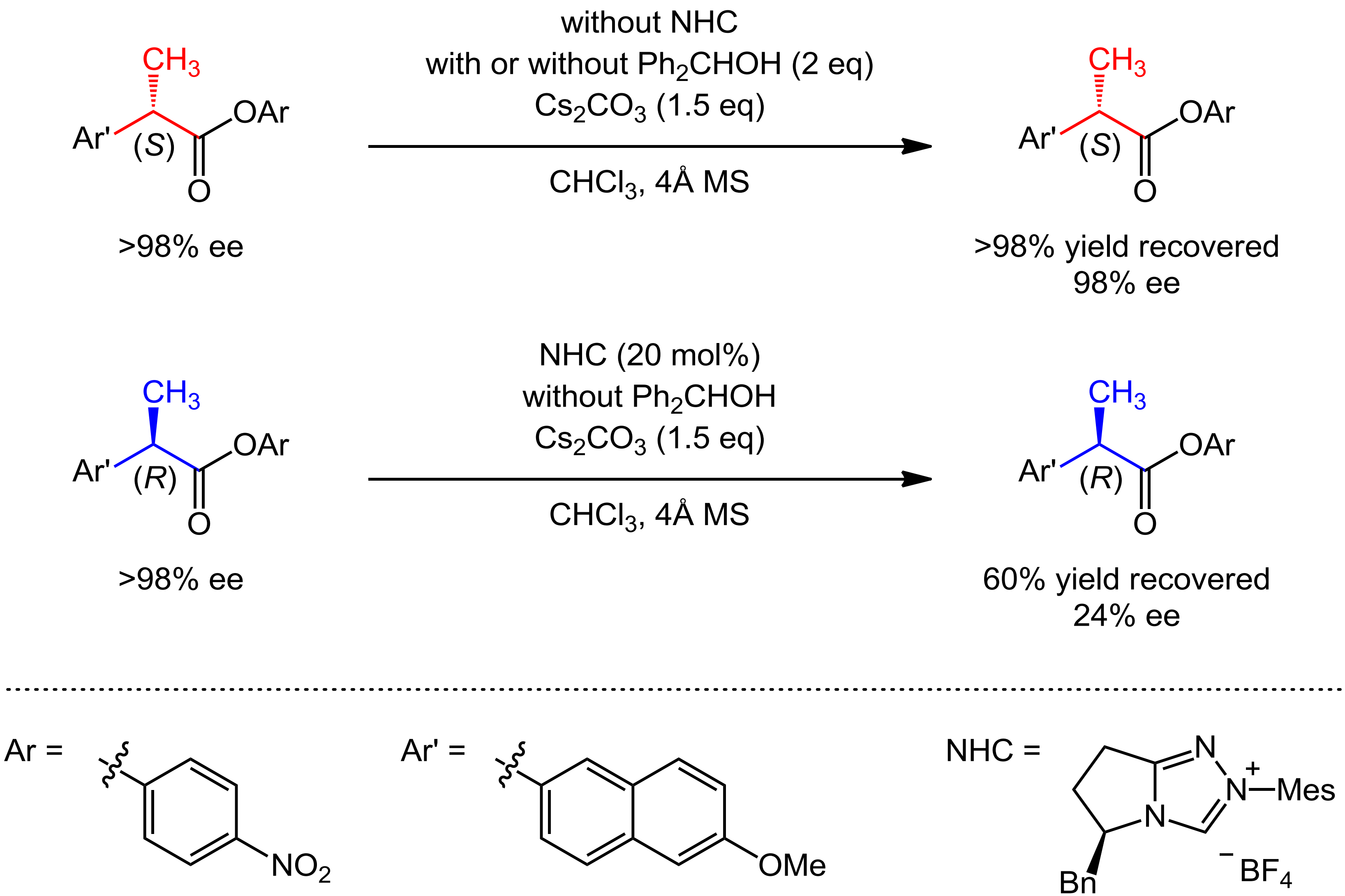
R = CHPh$_2$, naproxen ester
1.1 g, 86% yield, 94% ee

Pd/C
H_2

R = H, (*R*)-naproxen
96% yield, 92% ee

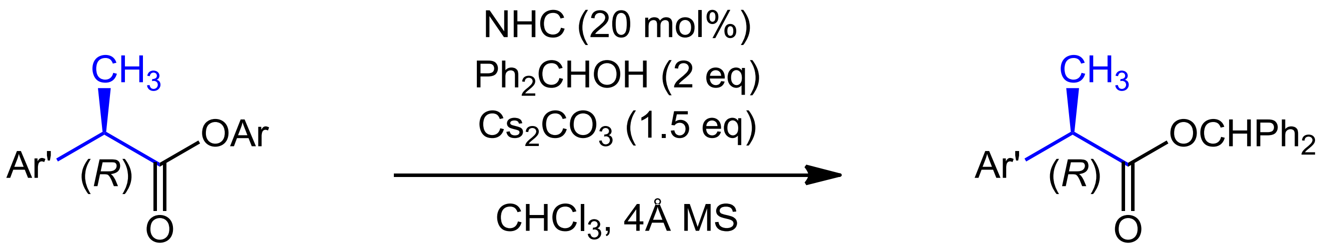
[a] 20 mol% NHC D.

Mechanistic Studies



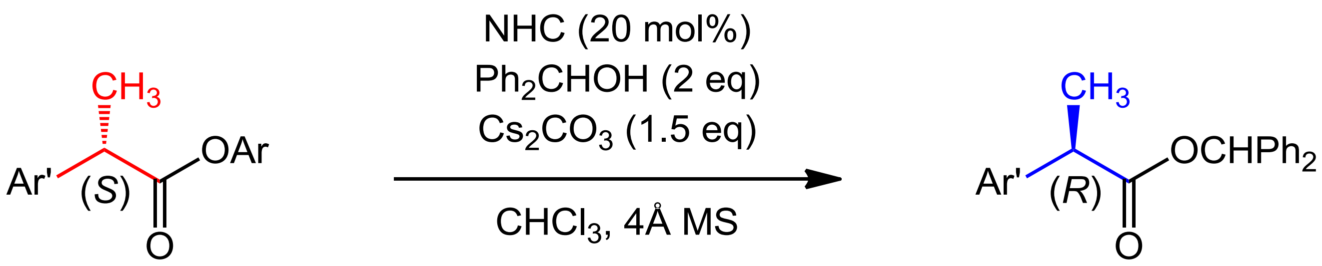
➢ The carbene catalyst is required for *the racemization of the ester substrate* and *the transesterification reaction*.

Mechanistic Studies



>98% ee

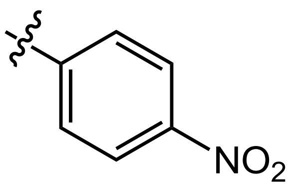
92% yield, 94% ee



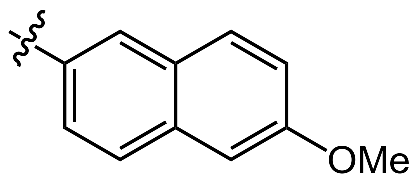
>98% ee

90% yield, 94% ee

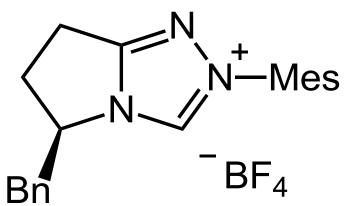
Ar =



Ar' =

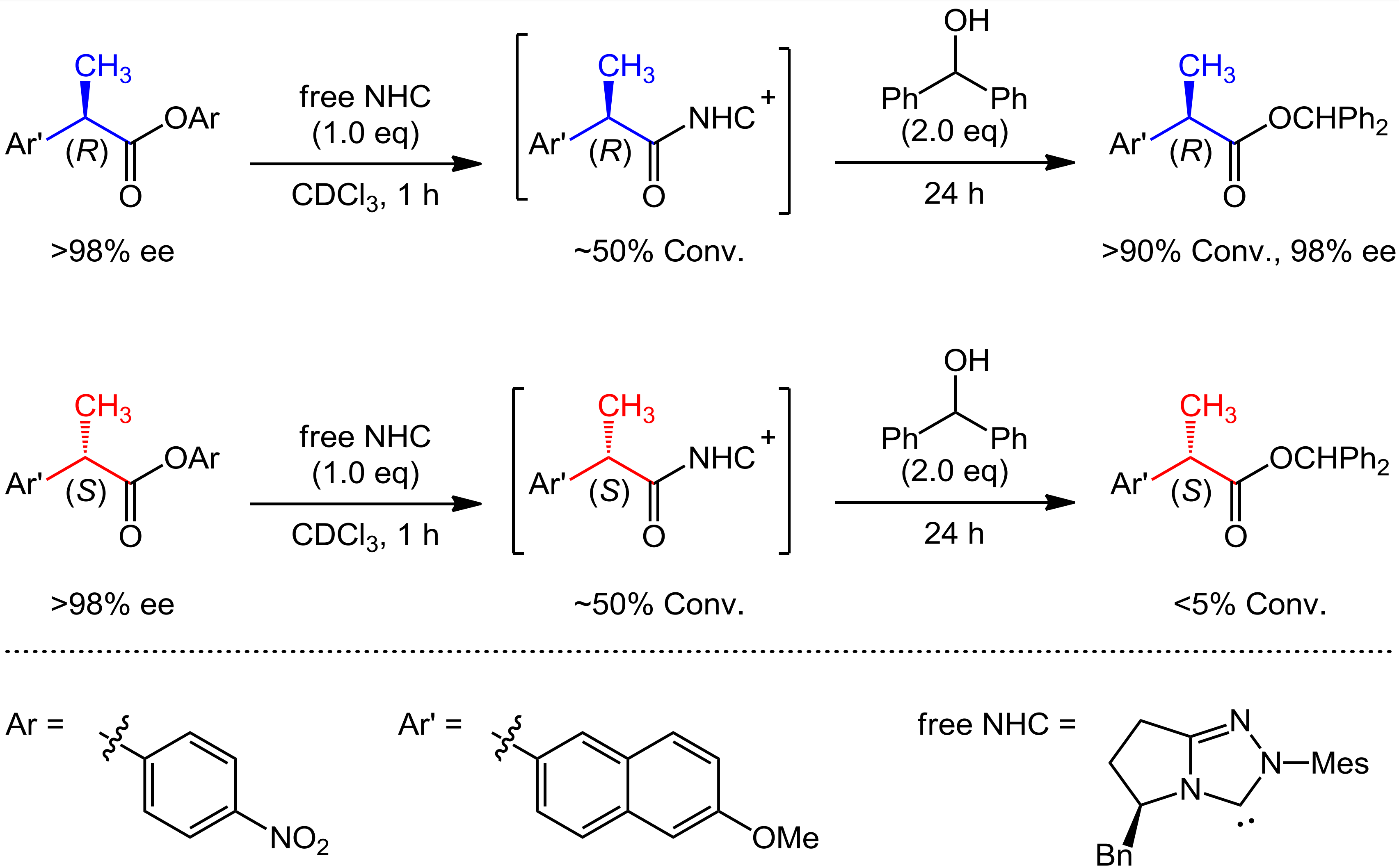


NHC =



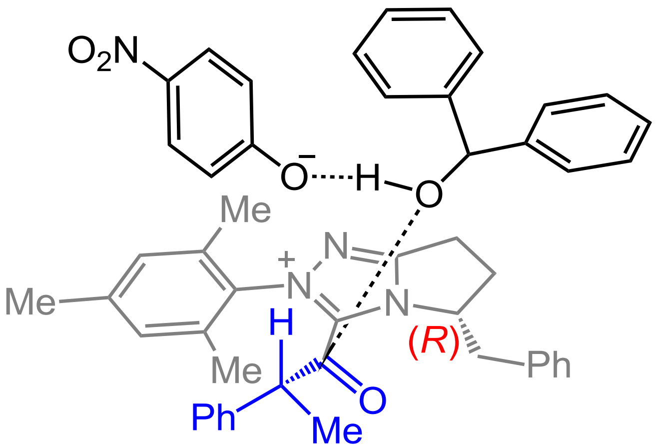
➢ Either isomer of ester substrates leads to *the same enantioselectivity*.

Mechanistic Studies

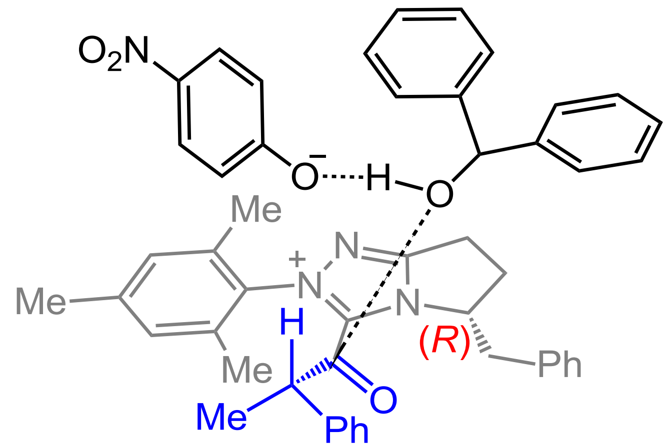


- *NHC and base* are required for *the isomerization of the ester substrate*.
- *The final step of ester formation* is the asymmetric step.
- The overall process is *a dynamic kinetic resolution*.

DFT Calculation

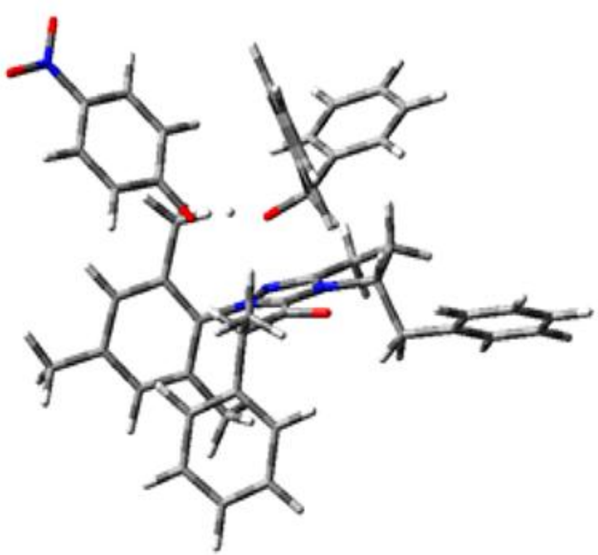


(*R*)

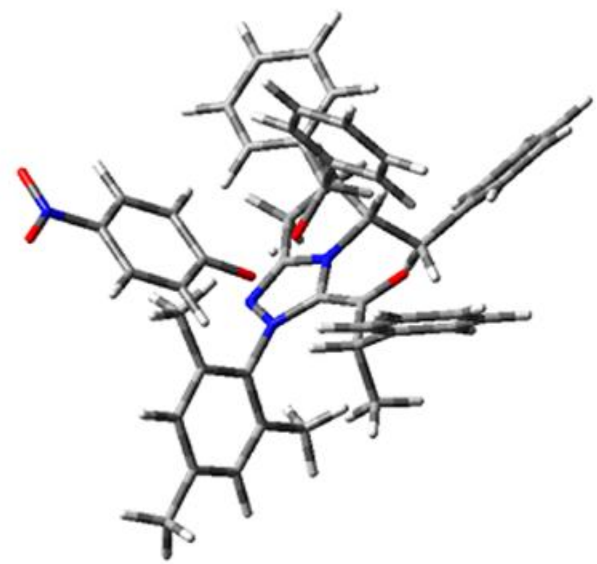


(*S*)

VS

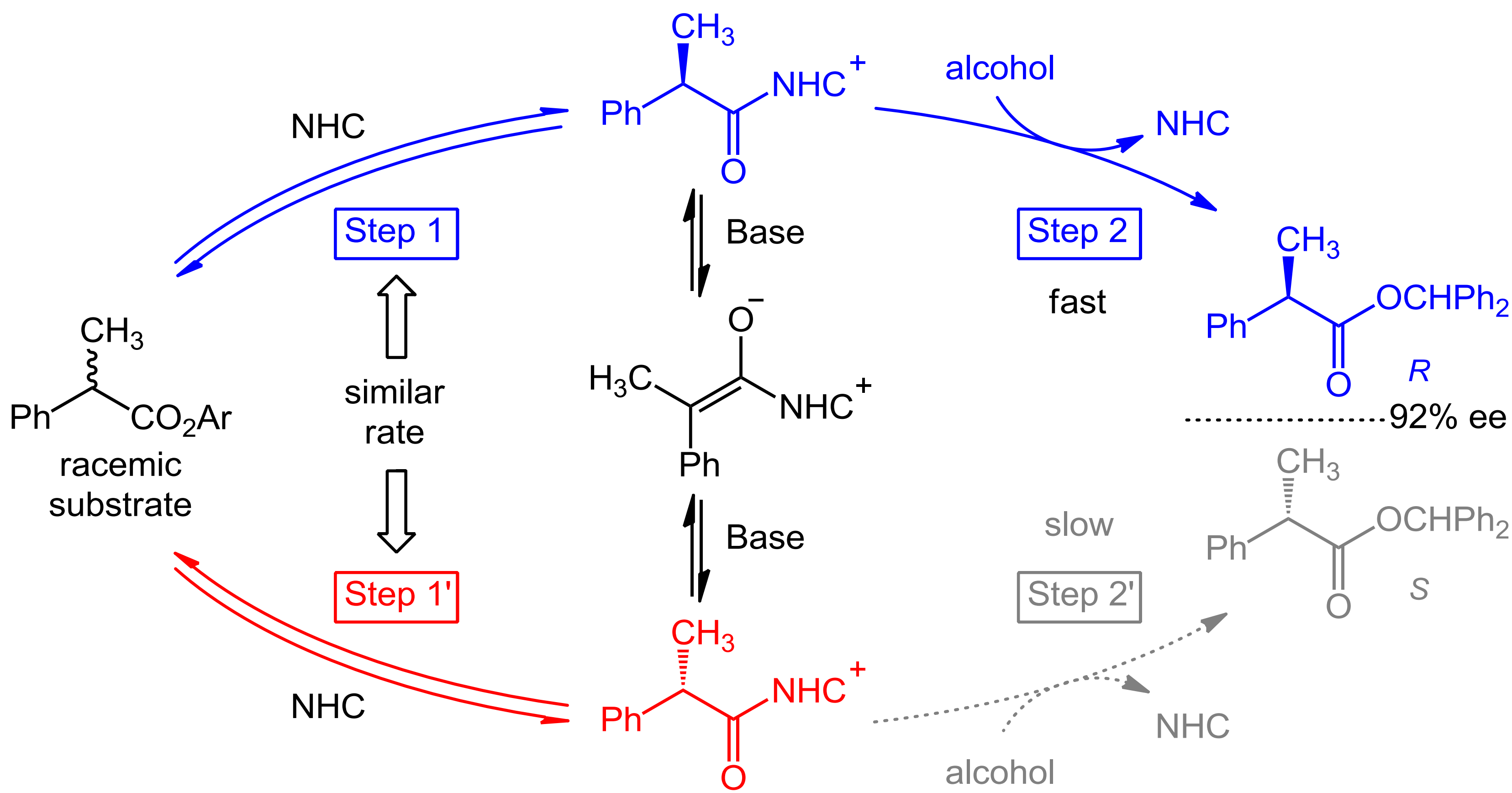


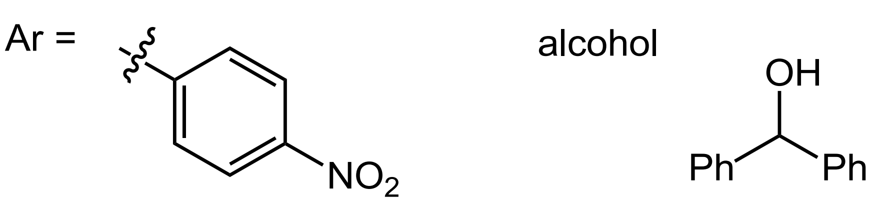
Transition state (**TS-*R***): E_{rel} = 0 kcal/mol



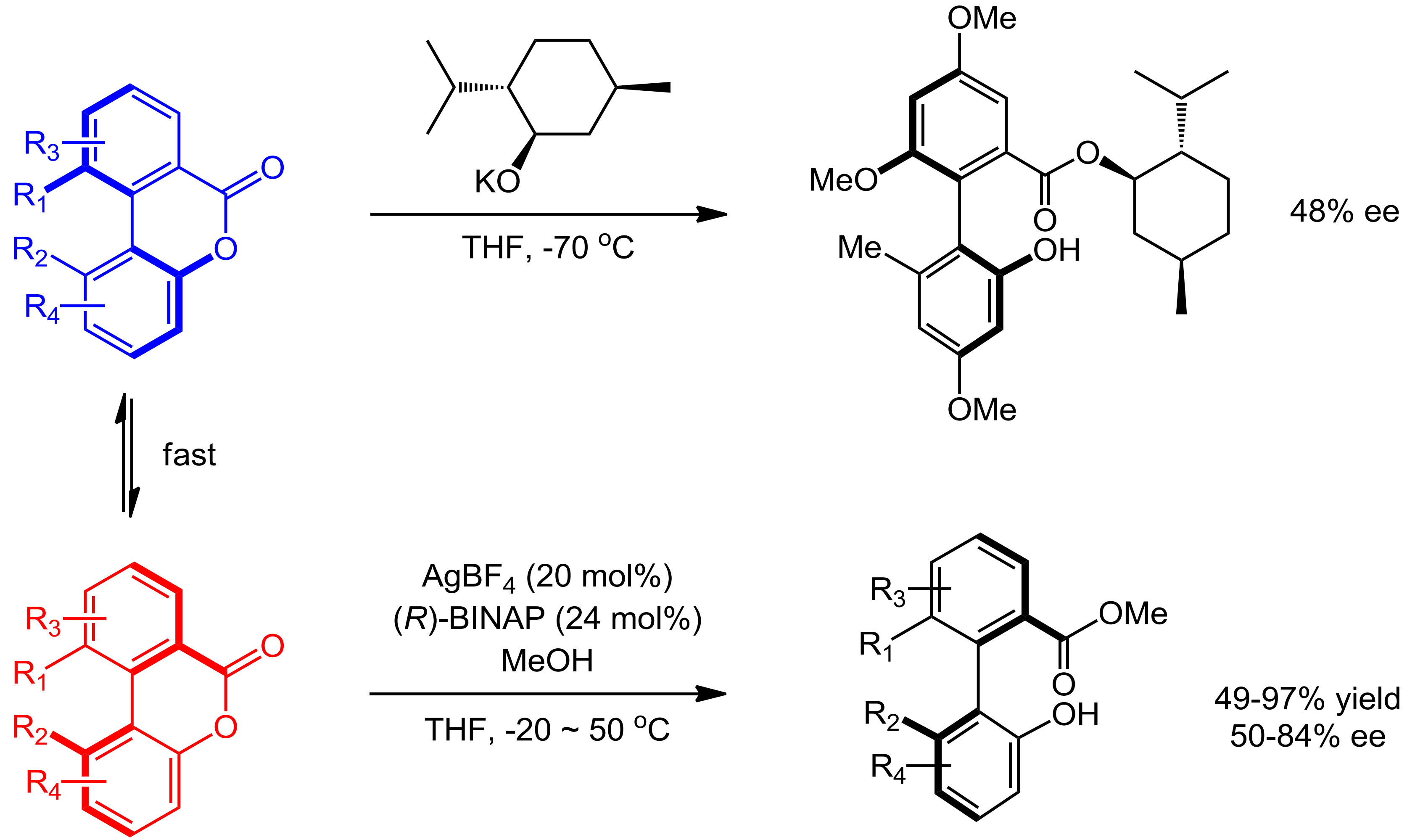
Transition state (**TS-*S***): E_{rel} = 5.02 kcal/mol

Proposed Reaction Pathway



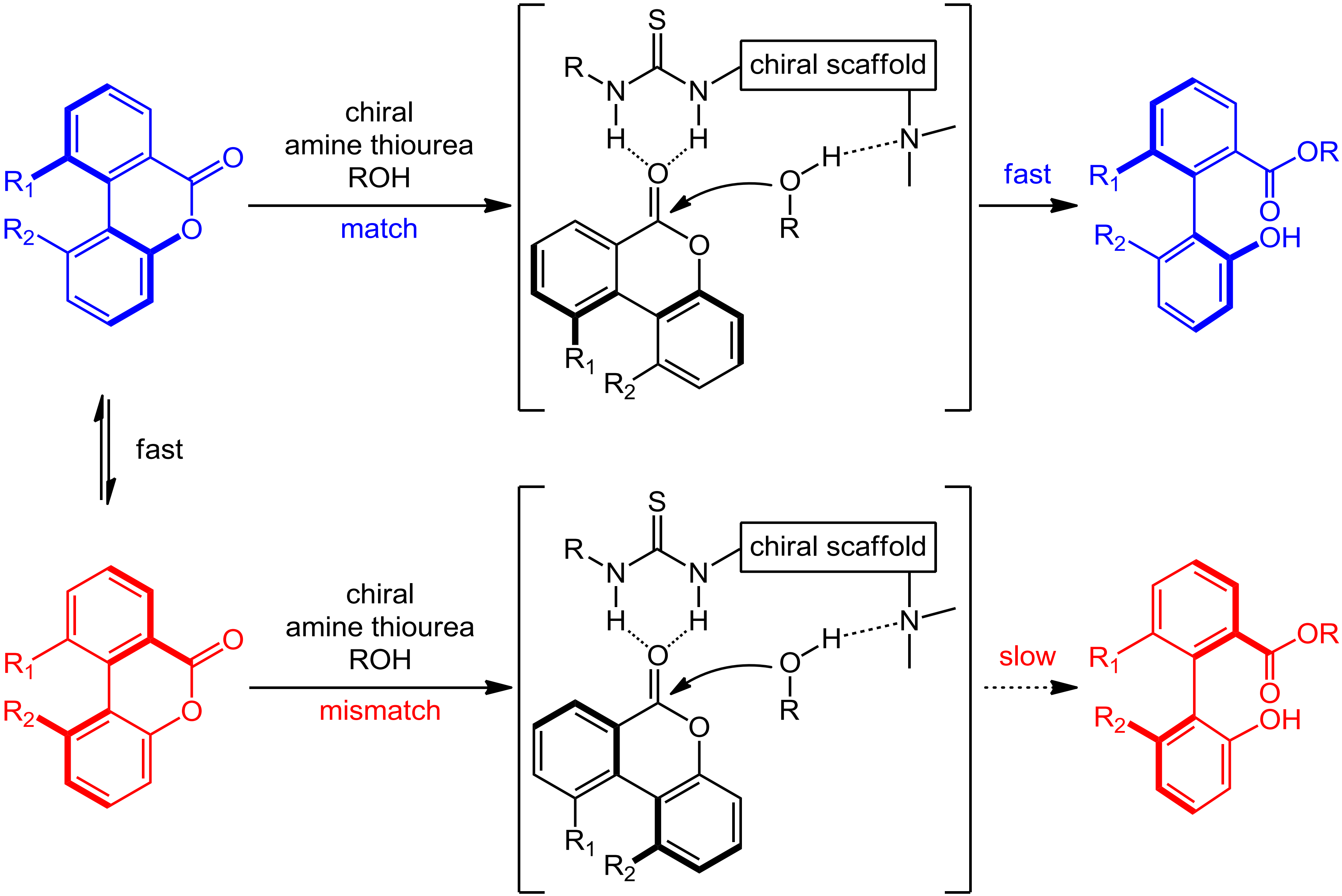


Chiral Nucleophiles and Chiral Metal Catalysis

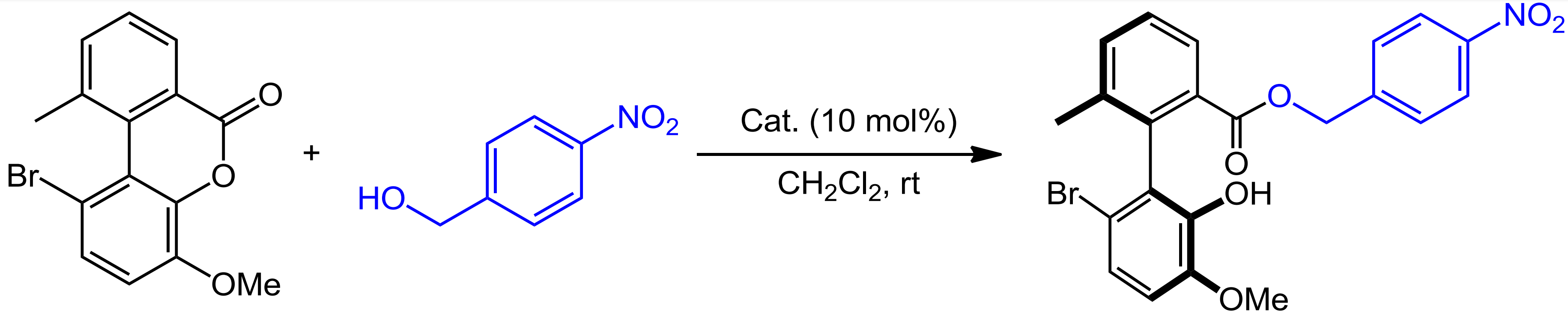


Bringmann, G. *et al. Synlett* **1991**, 581; Yamada, T. *et al. Chem. Lett.* **2009**, *38*, 246.

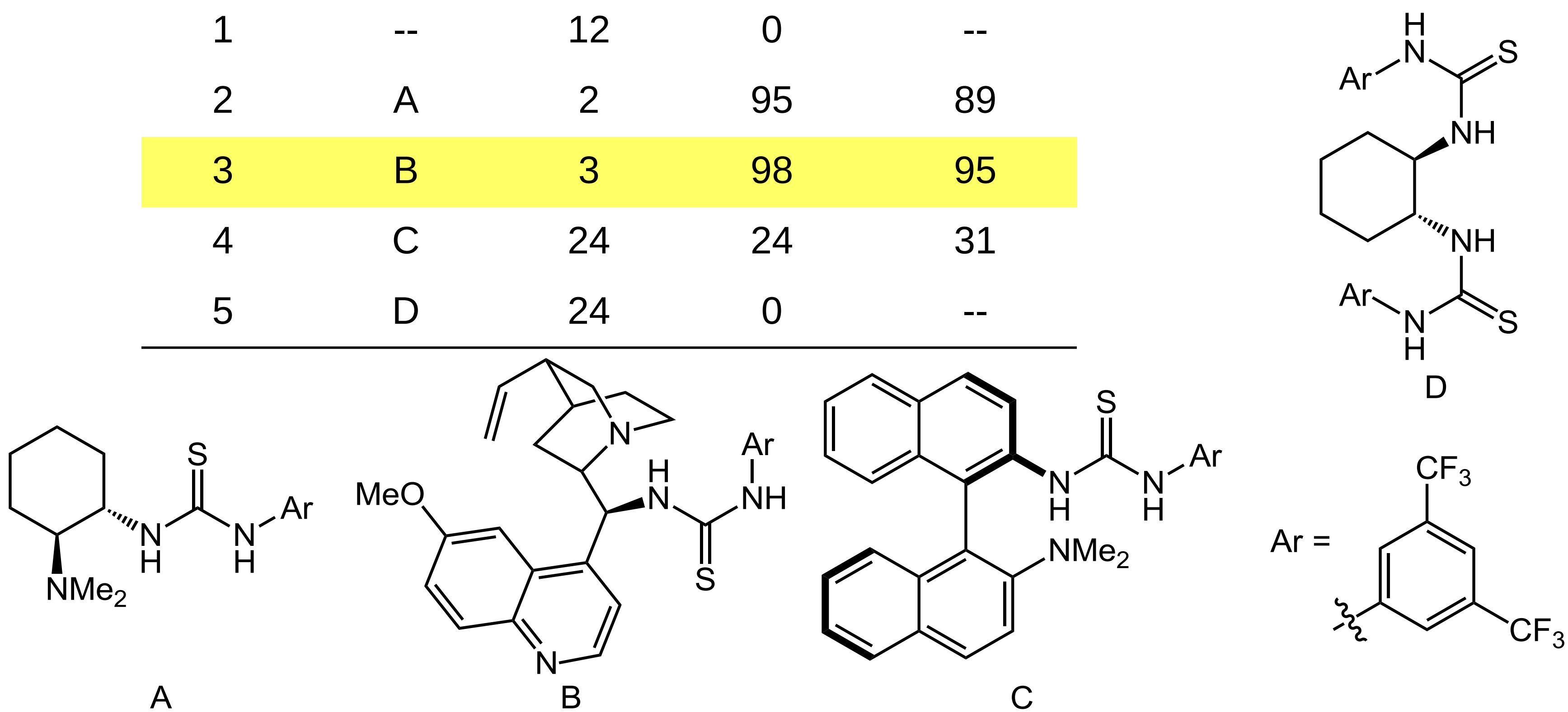
Synergistic Activation of Lactones and Alcohols



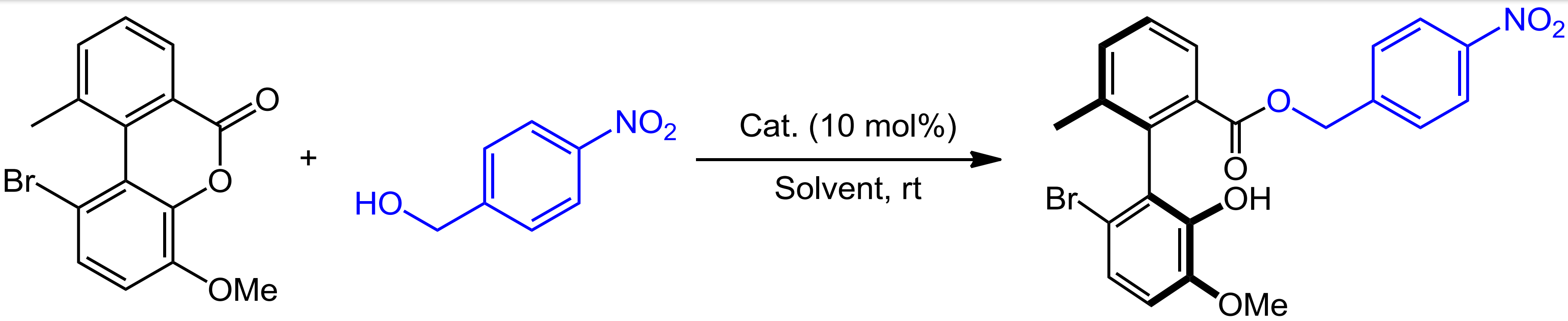
Condition Optimization



Entry	Cat.	t (h)	Yield (%)	Ee (%)
1	--	12	0	--
2	A	2	95	89
3	B	3	98	95
4	C	24	24	31
5	D	24	0	--



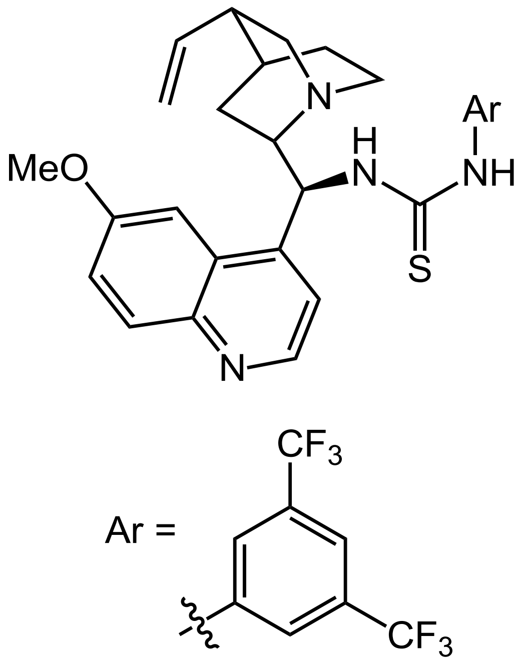
Condition Optimization



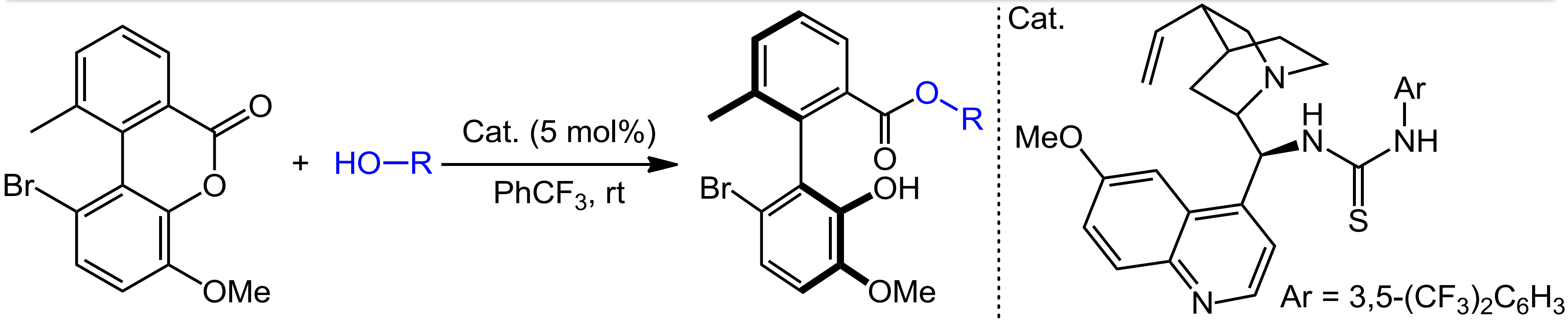
Entry	Solvent	t (h)	Yield (%)	Ee (%)
1	CH_2Cl_2	3	98	95
2	Toluene	1.5	99	93
3	Xylene	1.5	91	94
4	$PhCF_3$	0.5	98	95
5[a]	$PhCF_3$	6	99	96
6[b]	$PhCF_3$	72	61	96

[a] 5 mol% catalyst used. [b] 1 mol% catalyst used.

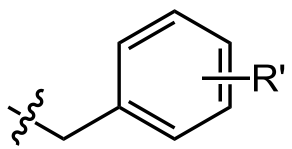
Cat.



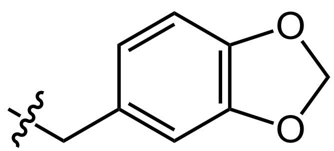
Substrate Scope



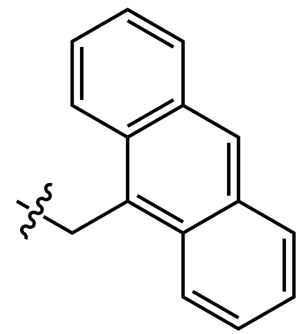
R:



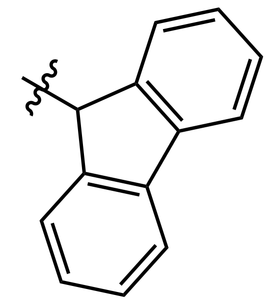
R' = 4-NO_2, 24 h, 1.167 g
99% yield, 95% ee[a]
R' = 4-OMe,
8 h, >99% yield, 93% ee
R' = 2-NO_2,
2 h, 98% yield, 96% ee



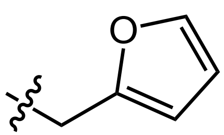
-10 ^{o}C, 48 h,
93% yield, 91% ee



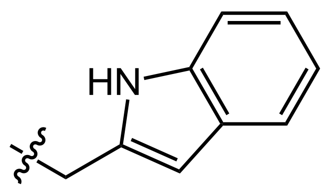
5 h, 98% yield, 90% ee



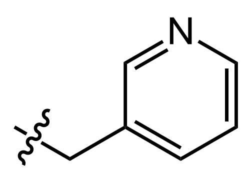
48 h, 97% yield, 92% ee



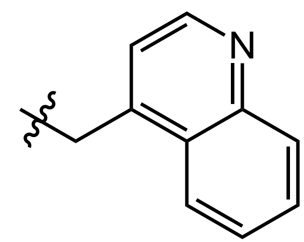
4 h, 96% yield, 90% ee



-10 ^{o}C, 24 h,
>99% yield, 91% ee



3 h, >99% yield, 90% ee

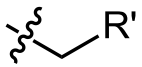


2 h, 97% yield, 93% ee

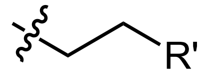
[a] 2 mol% Cat.

Substrate Scope

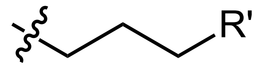
R:



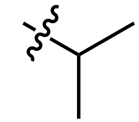
R' = Me, 36 h, 97% yield, 92% ee
R' = *n*Pr, 24 h, 90% yield, 90% ee
R' = CF_3, 0.5 h, >99% yield, 93% ee
R' = CCl_3, 0.5 h, >99% yield, 90% ee



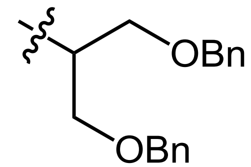
R' = OMe, 6 h, >99% yield, 95% ee
R' = OPh, 3 h, >99% yield, 90% ee



R' = OBn, 3 h, 97% yield, 96% ee
R' = NHBoc, 16 h, 95% yield, 94% ee

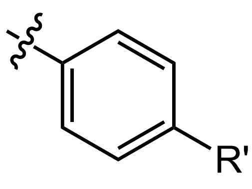


48 h, 90% yield, 91% ee[a]

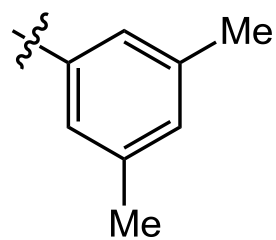


16 h, 80% yield, 99% ee

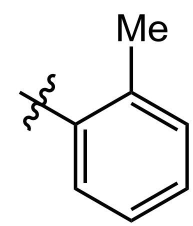
R: (-10 ^{o}C)



R' = H, 1 h, 75% yield, 96% ee
R' = SMe, 1 h, 60% yield, 94% ee
R' = Br, 16 min, 65% yield, 90% ee



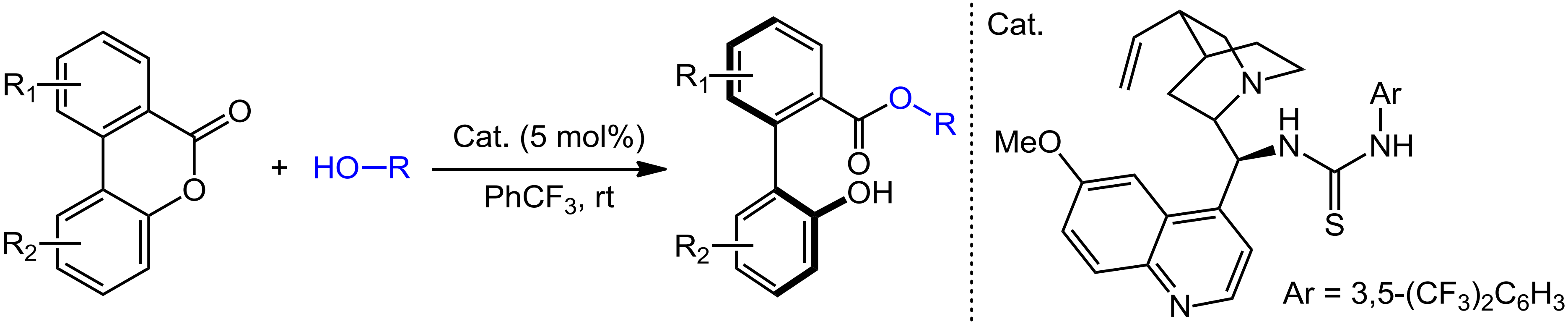
1 h, 76% yield, 98% ee



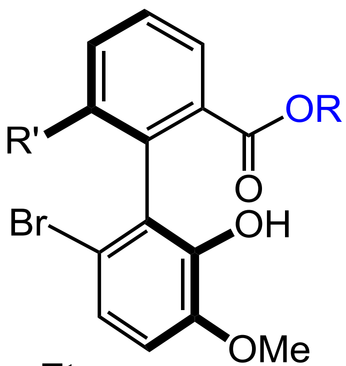
1 h, 50% yield, 97% ee

[a] 15 mol% Cat.

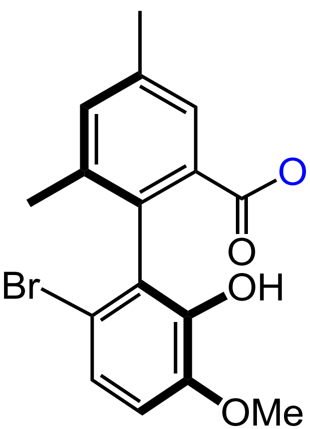
Substrate Scope



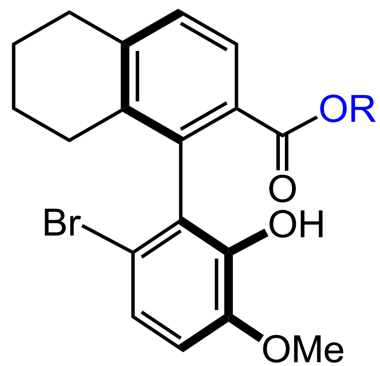
R = 4-NO_2Bn



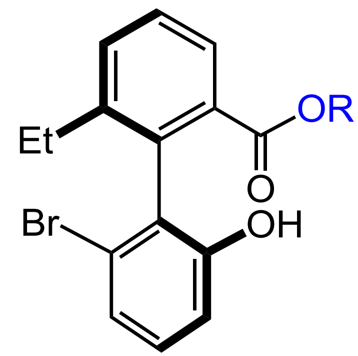
R' = Et,
0.5 h, 97% yield, 97% ee
R' = *i*Pr,
1 h, 92% yield, 94% ee
R' = Bn,
1 h, 94% yield, 96% ee



1 h, >99% yield, 94% ee



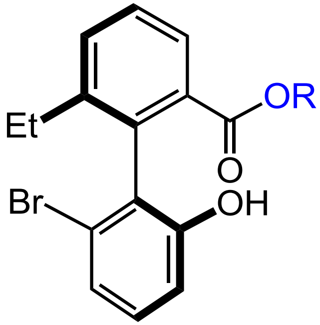
1.5 h, >99% yield, 92% ee



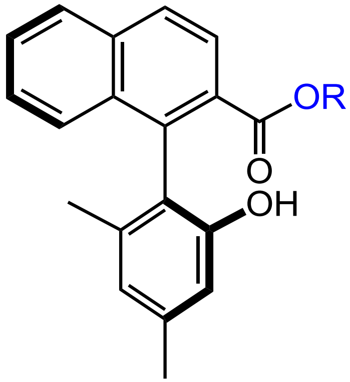
24 h, 79% yield, 62% ee

Substrate Scope and Synthetic Elaboration

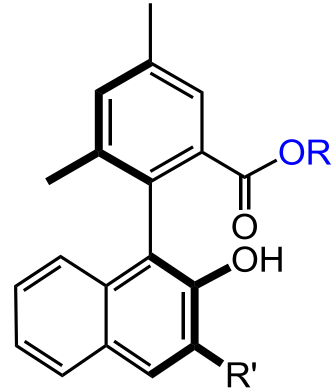
R = $-\xi-CH(CH_2OBn)_2$



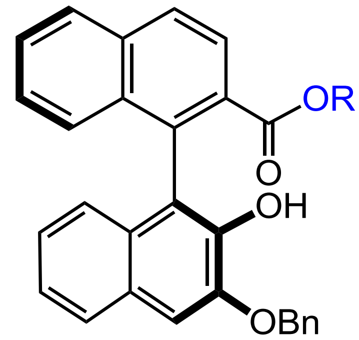
48 h, 84% yield, 96% ee



192 h, 56% yield, 90% ee[a]

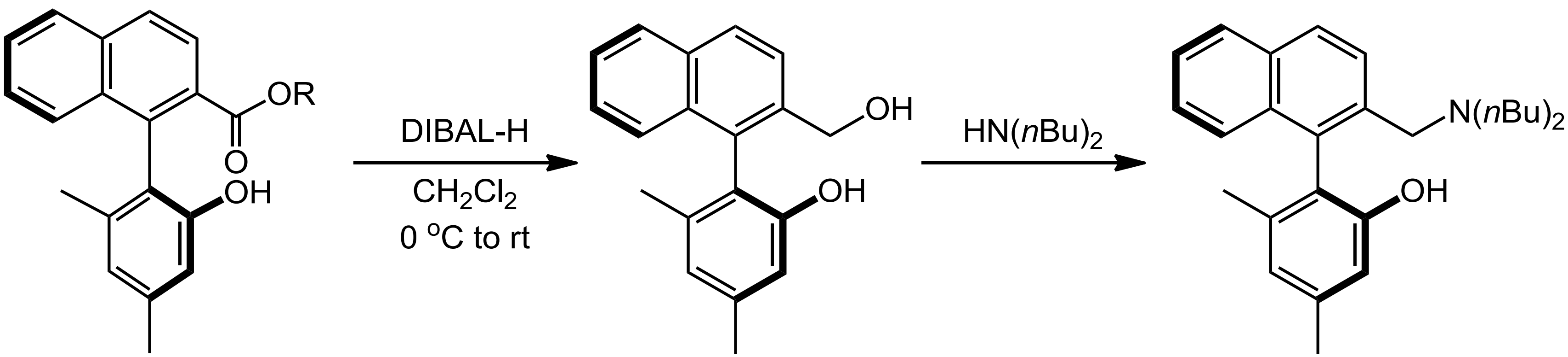


R' = Br,
96 h, 71% yield, 96% ee[a]
R' = H,
192 h, 57% yield, 96% ee[a]



96 h, 79% yield, 91% ee[a]

[a] 15 mol% Cat.



R = $-\xi-CH(CH_2OBn)_2$

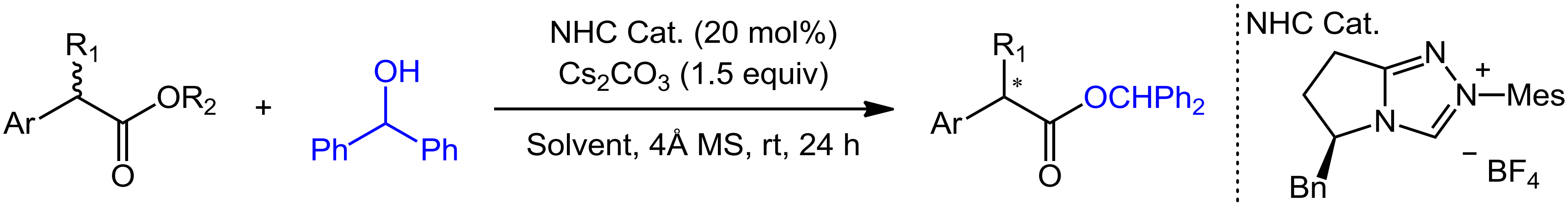
95% yield, 90% ee

tertiary aminophenol ligand

Bringmann, G. *et al. Tetrahedron: Asymmetry* **1998**, *9*, 667.

Summary

➢ Carbene-catalyzed dynamic kinetic resolution of carboxylic esters.

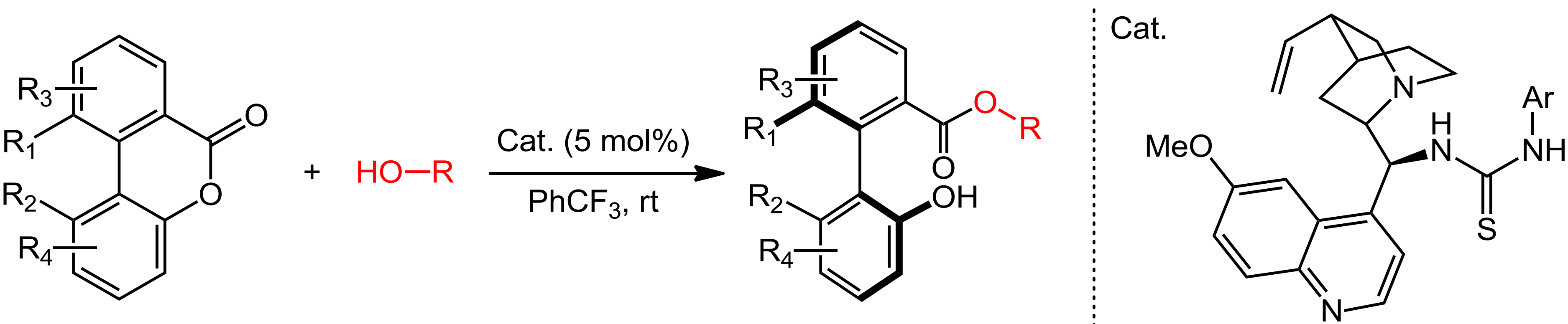


R_2 = 4-$NO_2C_6H_4$

75-99% yield
80-98% ee

Chi, Y. R. *et al. J. Am. Chem. Soc.* **2016**, *138*, 7212.

➢ Amine thiourea-catalyzed dynamic kinetic resolution of biaryl lactones.



alcohols or phenols

50-99% yield
90-99% ee

Ar = 3,5-$(CF_3)_2C_6H_3$

Wang, W. *et al. J. Am. Chem. Soc.* **2016**, *138*, 6956.

Carboxylic acids and the related carbonyl compounds bearing two or more substituents at the α-carbons are important functional molecules. For example, ibuprofen and ketoprofen, derivatives of propionic acid bearing a stereogenic α-carbon center, are widely used as nonsteroidal anti-inflammatory drugs. Thus, the synthesis and transformation of such α,α-disubstituted carbonyl compounds is of profound importance. N-Heterocyclic carbene organic catalysts have been successfully used to activate aldehydes and α,β-unsaturated aldehydes (enals) for a diverse set of asymmetric reactions. However, when an additional alkyl or aryl substituent is placed at the α-carbon of the aldehydes or enals, the reaction efficiency is dramatically reduced. This restriction on the enal/aldehyde α-carbon substitutents has limited the application of carbene catalysis to prepare some of the most important molecules such as bioactive α,α-disubstituted carboxylic acids. It remains underdeveloped at this point in using carbene-catalyzed aldehyde reactions to prepare α,α-disubstituted carboxylic acids asymmetrically.

In summary, we have developed a carbene-catalyzed reaction of esters that offers useful synthetic solutions which are not readily accessible from the conventional reactions based on aldehyde substrates. Our approach, through dynamic kinetic resolution of carboxylic esters, allows for effective access to the broadly useful α,α-disubstituted carboxylic esters with up to 99:1 er and 99% yield. The present study clearly illustrates the unique power of carbene-catalyzed activation and reaction of carboxylic esters and shall encourage further development of new activation modes.