Applications of Cinchona OrganoCatalysts in Asymmetric Catalysis

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requimte
LABORATÓRIO ASSOCIADO PARA A QUÍMICA VERDE

coimbra chemistry centre

ChiraTecnics
Chiral Solutions for a Better Life

1 2 9 0
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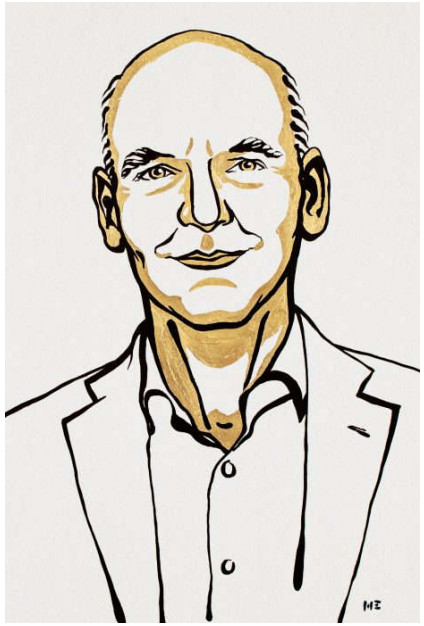
Content

- Imine Hydrosilylation
- Cinchona-Picolinamides
- API Targets
- Mechanism
- Continous Flow
- Cinchona-Squaramides (Michael addition)
- Catalytic Chiral Solvents (Deep Eutectic solventes)

The Nobel Prize 2021

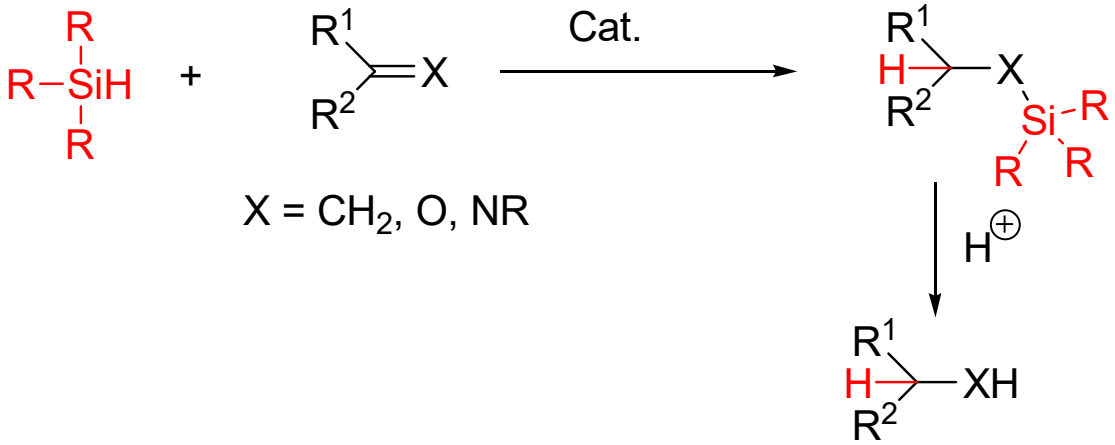
David MacMillan



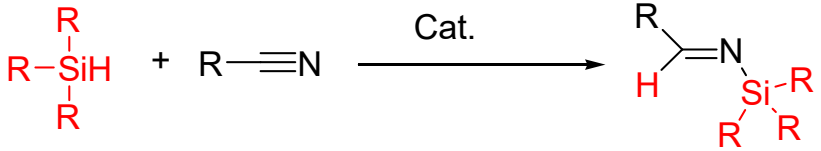
Ben List

“for the development of asymmetric organocatalysis."

Hydrosilylation of Double Bonds



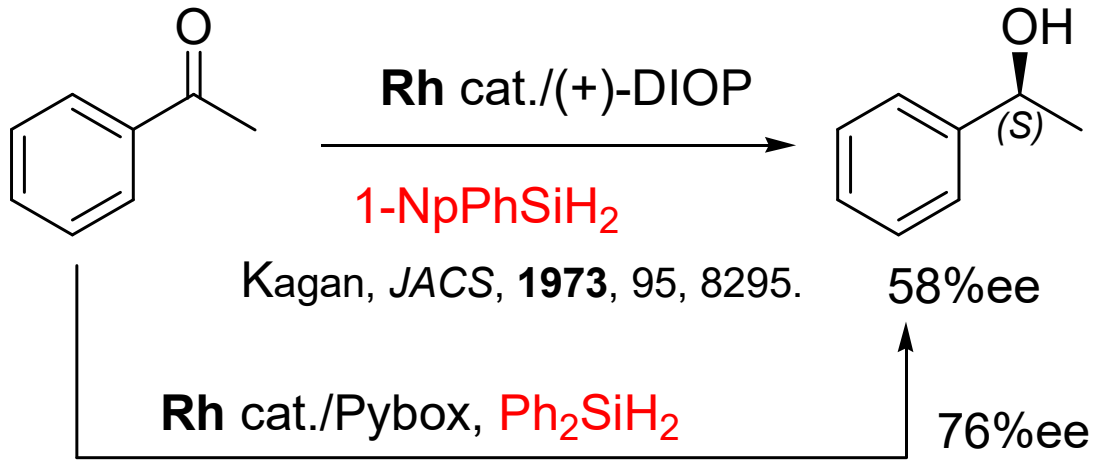
And Nitriles



And Enamines!

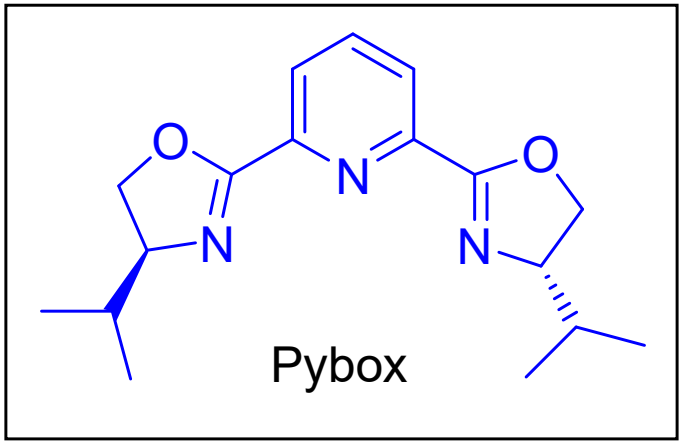
Hashimoto *et al. JACS*, **2003**, 22, 2199.

Pioneering work with Ketones



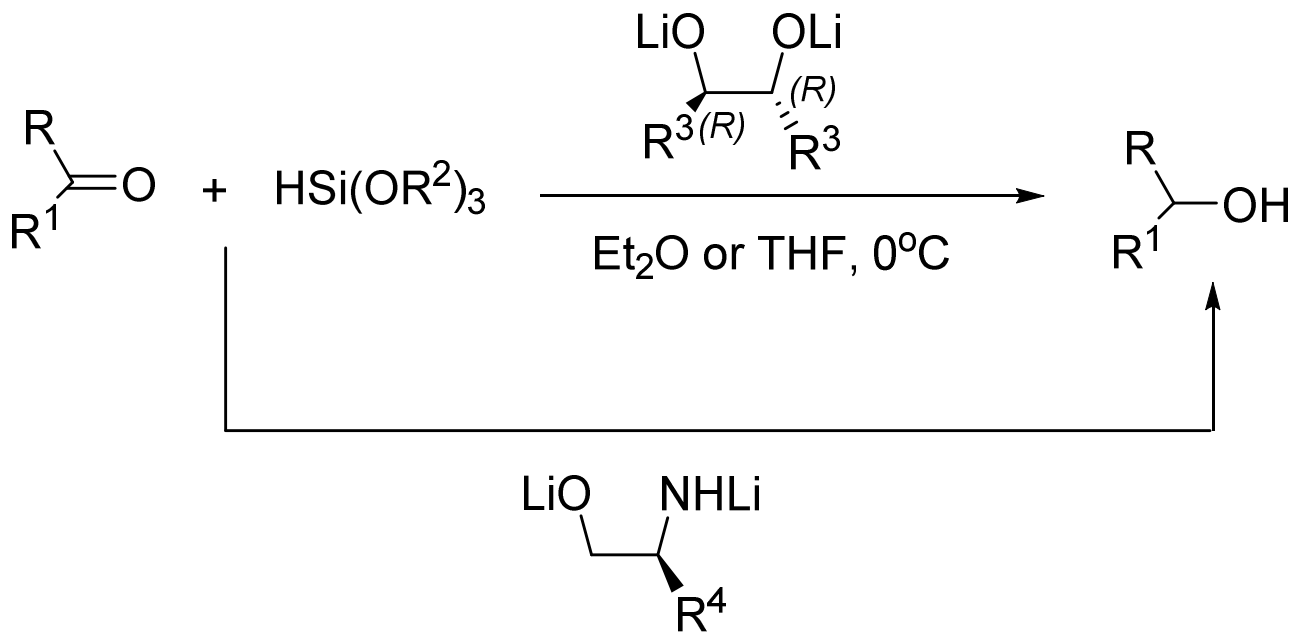
Kagan, *JACS*, **1973**, 95, 8295.

Nishiyama, *Organometallics*, **1989**, 8, 846.



Using organocatalysts

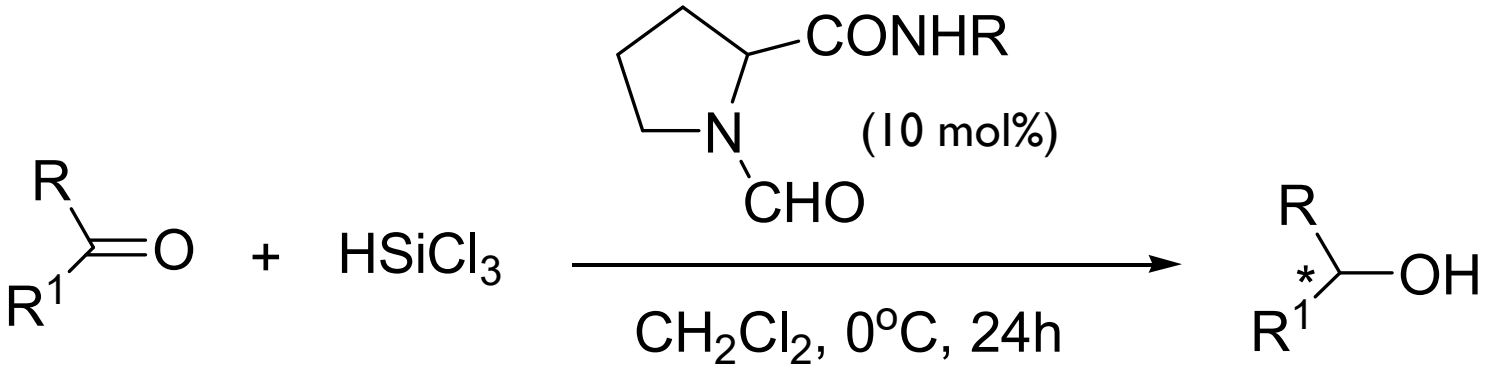
Lithium Diolates and aminoalcoholates

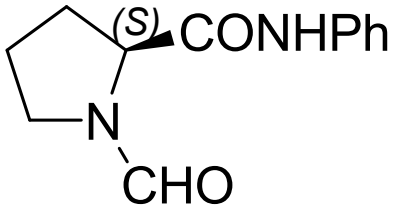


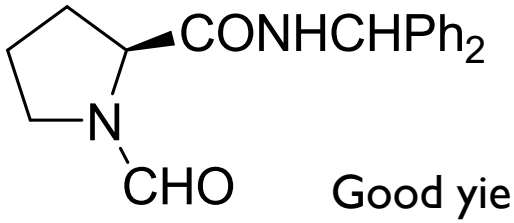
Hosomi, *Tet. Lett.* 1988, 29, 89.

Milestone: *N*-Formylpyrrolidine activation

(DMF-$HSiCl_3$), Kobayashi, *Chem. Lett.* 1996, 25, 407.



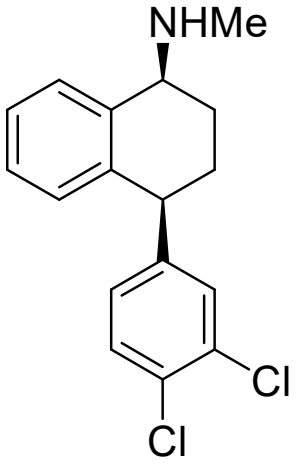




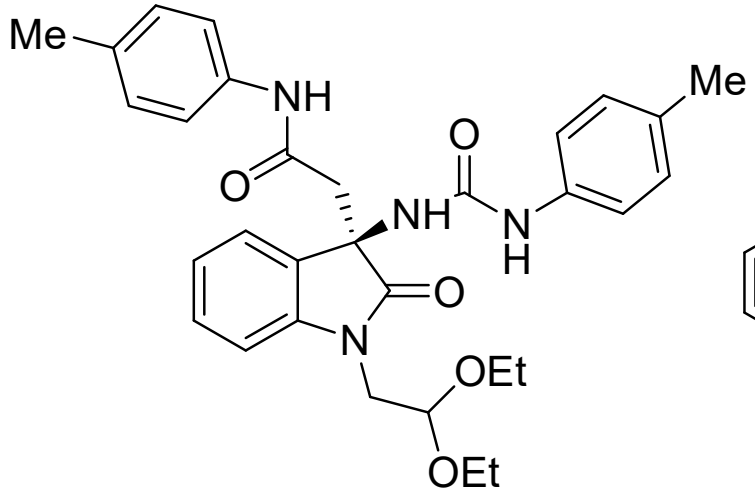
Good yields but low ees!

Matsumura, *Tet. Lett.* 1999, 40, 7507.

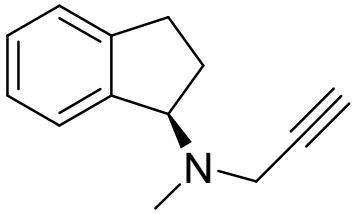
Bioactive Chiral Amines



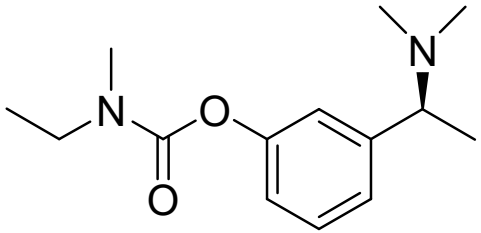
Sertraline (anti-depressant)



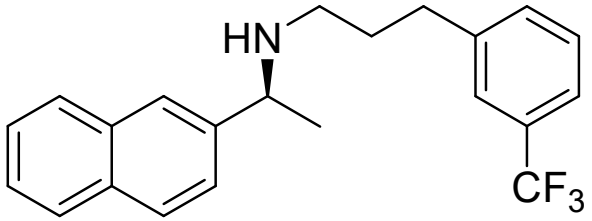
AG-041R (Gastrin/CCK-B receptor agonist



Rasagline

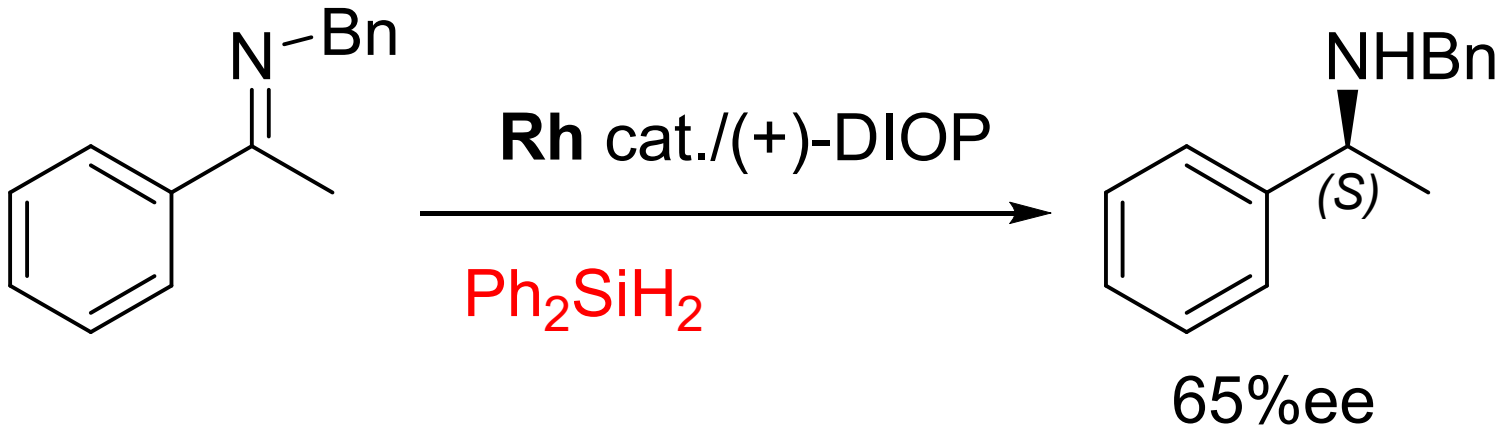


Rivastigmine



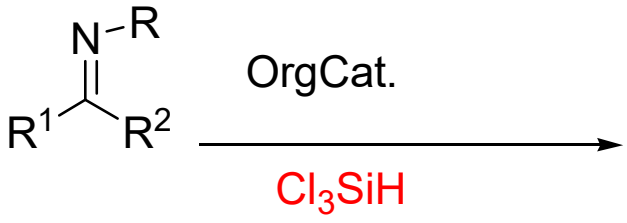
Cinacalcet

Early developments with Ketimines

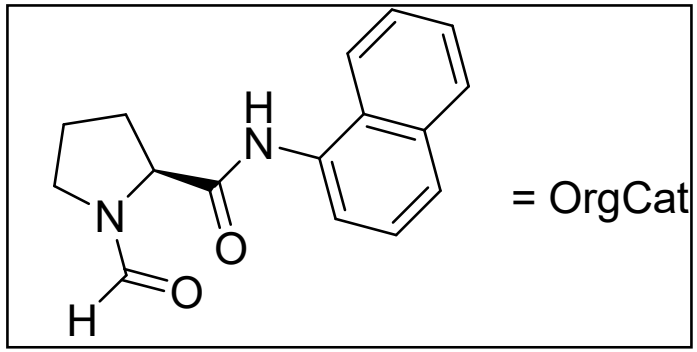


Kagan, *J. Organomet. Chem.* **1975**, 90, 353.

With Organocatalysts



52%, 66%ee



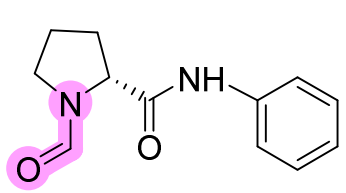
= OrgCat

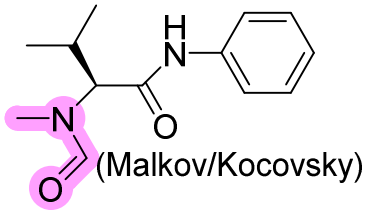
Ketones and Enamines

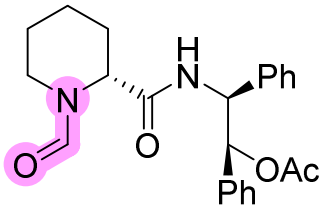
Matsumura, *Tet. Lett.* 2001, 42, 2525.

Organocatalytic Imine Hydrosilylation: Types

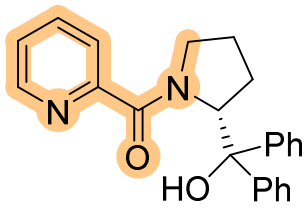
Chiral Lewis Bases (with Cl_3SiH)

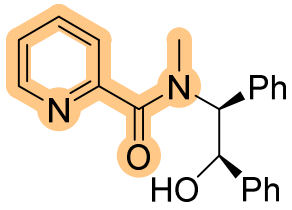




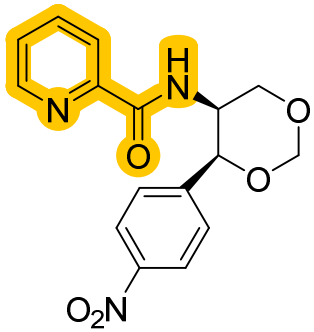


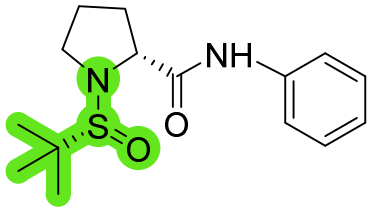
Formamides

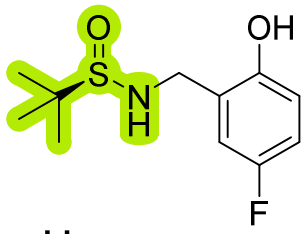




Picolinamides



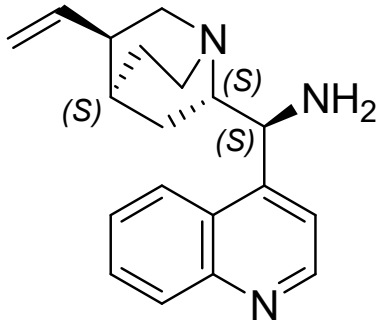




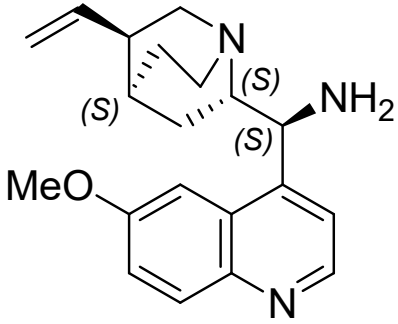
Sulfinilamides

Cinchona Organocatalysts: Bifunctional catalysts

Bernardino Gomes (1811)

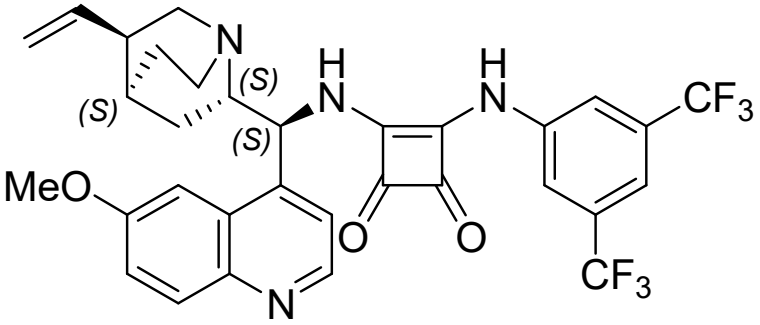


9-Amino-*epi*-Cinchonidine

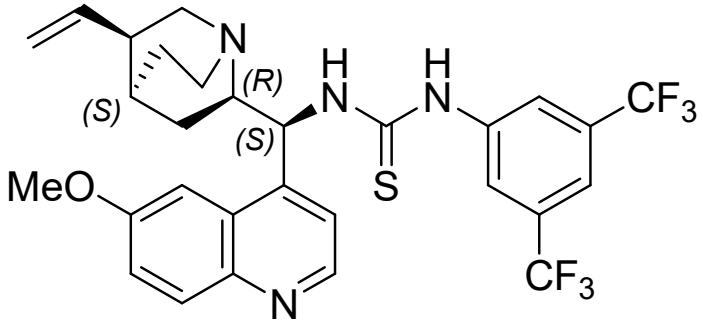


9-Amino-*epi*-Cinchonine (Brunner)

Enamine



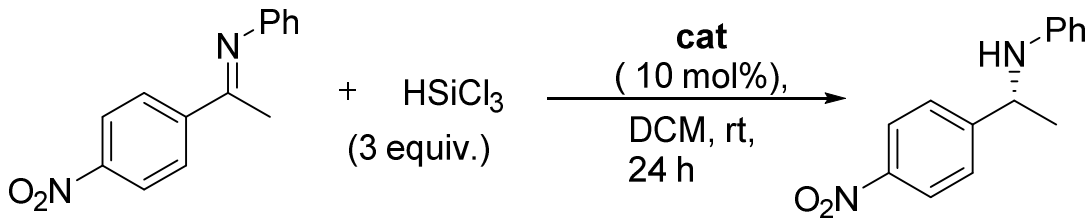
Cinchona Squaramide (Rawal, 2008)

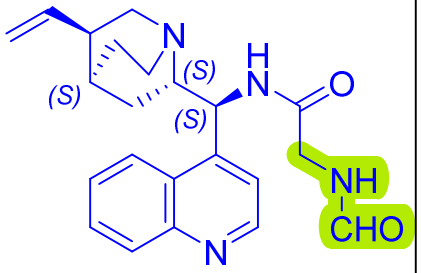


Cinchona thiourea (Dixon, 2005)

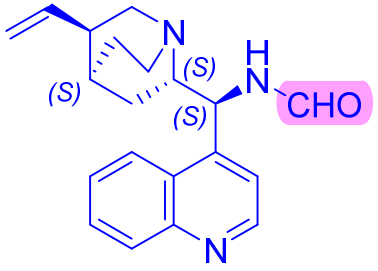
H-Bonding networks

Cinchona-Formamides

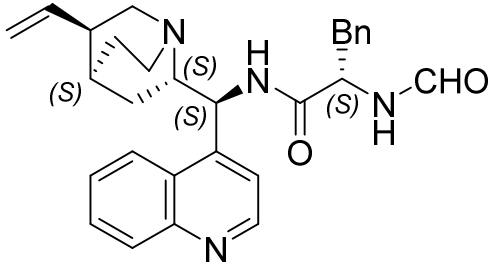




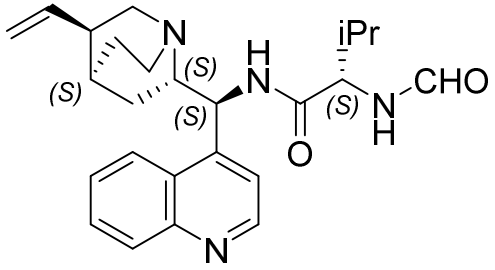
66% (13% ee)



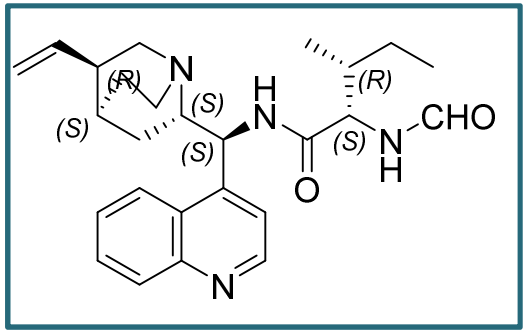
64% (7% ee)



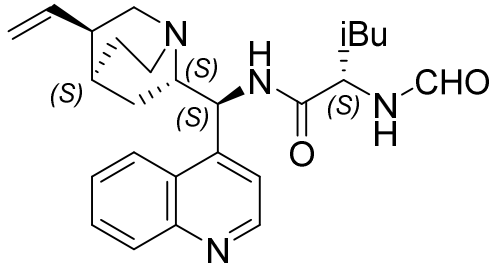
62% (33% ee)



56% (35% ee)



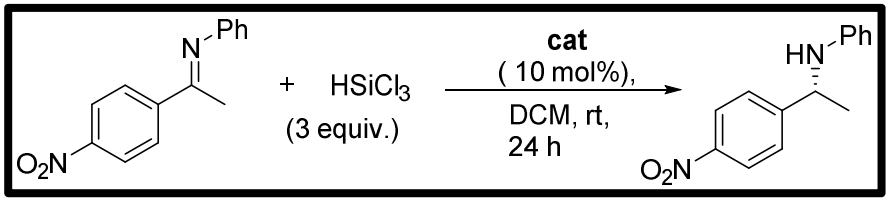
76% (27% ee)

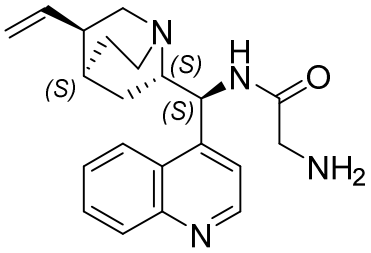


74% (29% ee)

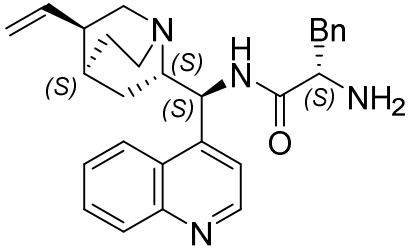
Barrulas, *Tetrahedron: Asymmetry*, **2014**, *25*, 923-35

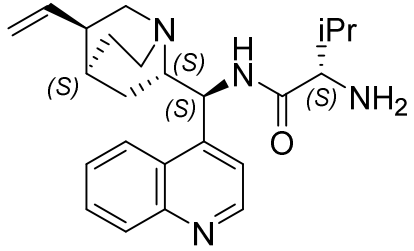
Cinchona-amine-aminoacids

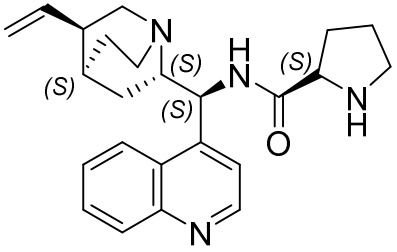




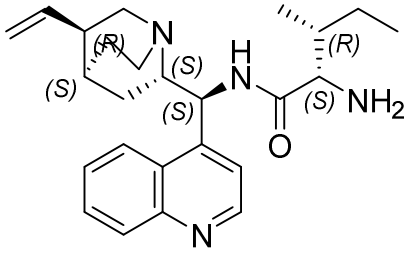
72%, 31% ee

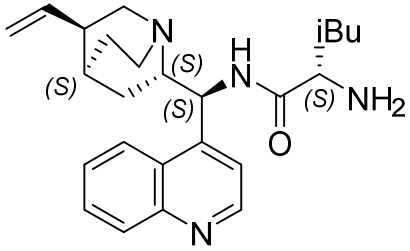


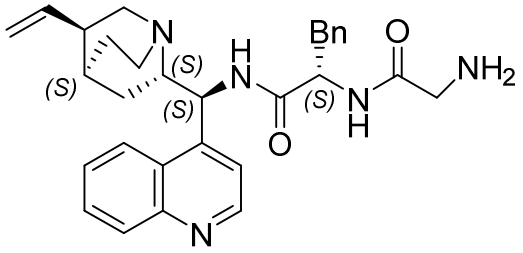




74%, 37% ee







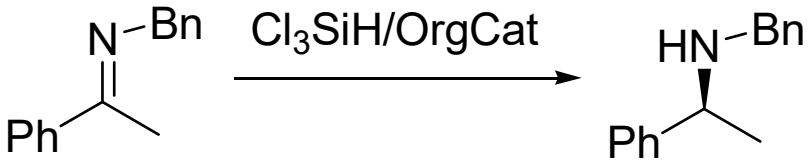
84%, 45% ee

Synthesis of novel cinchona-amino acid hybrid organocatalysts for asymmetric catalysis

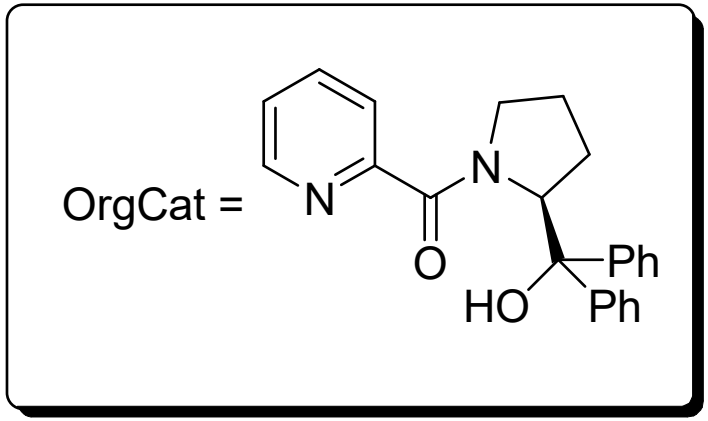
Pedro Barrulas [a], Maurizio Benaglia [b,†], Anthony J. Burke [a,*]

Tetrahedron: *Asymmetry* 25 (2014) 923–935

Chiral Picolinamides

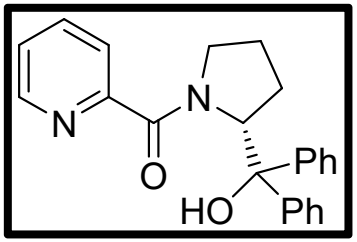


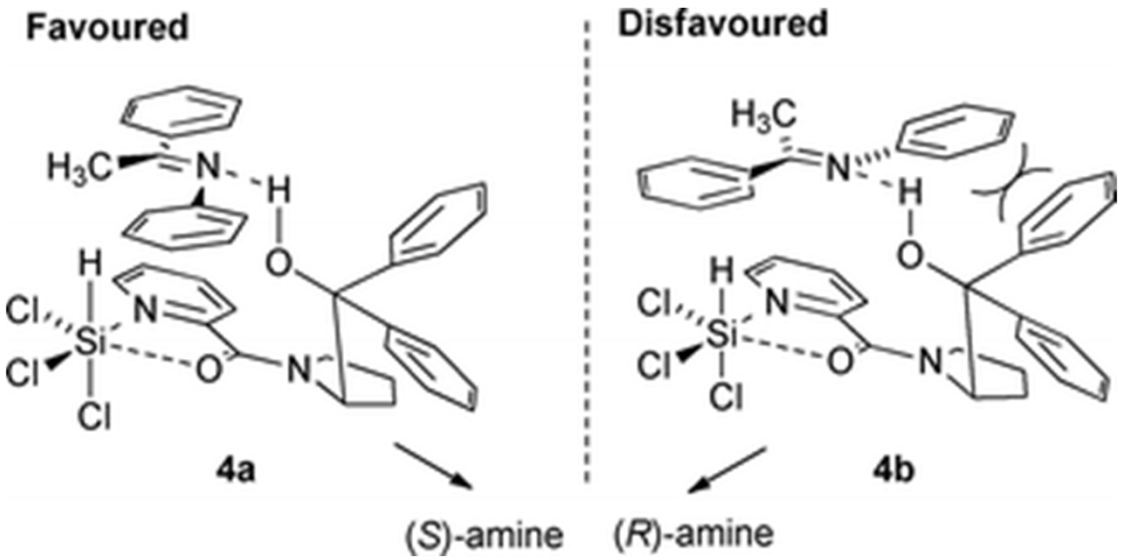
67%, 80% ee



Matsumura, *JP 2005029503*, *Tet. Lett.* 2006, 47, 3751.

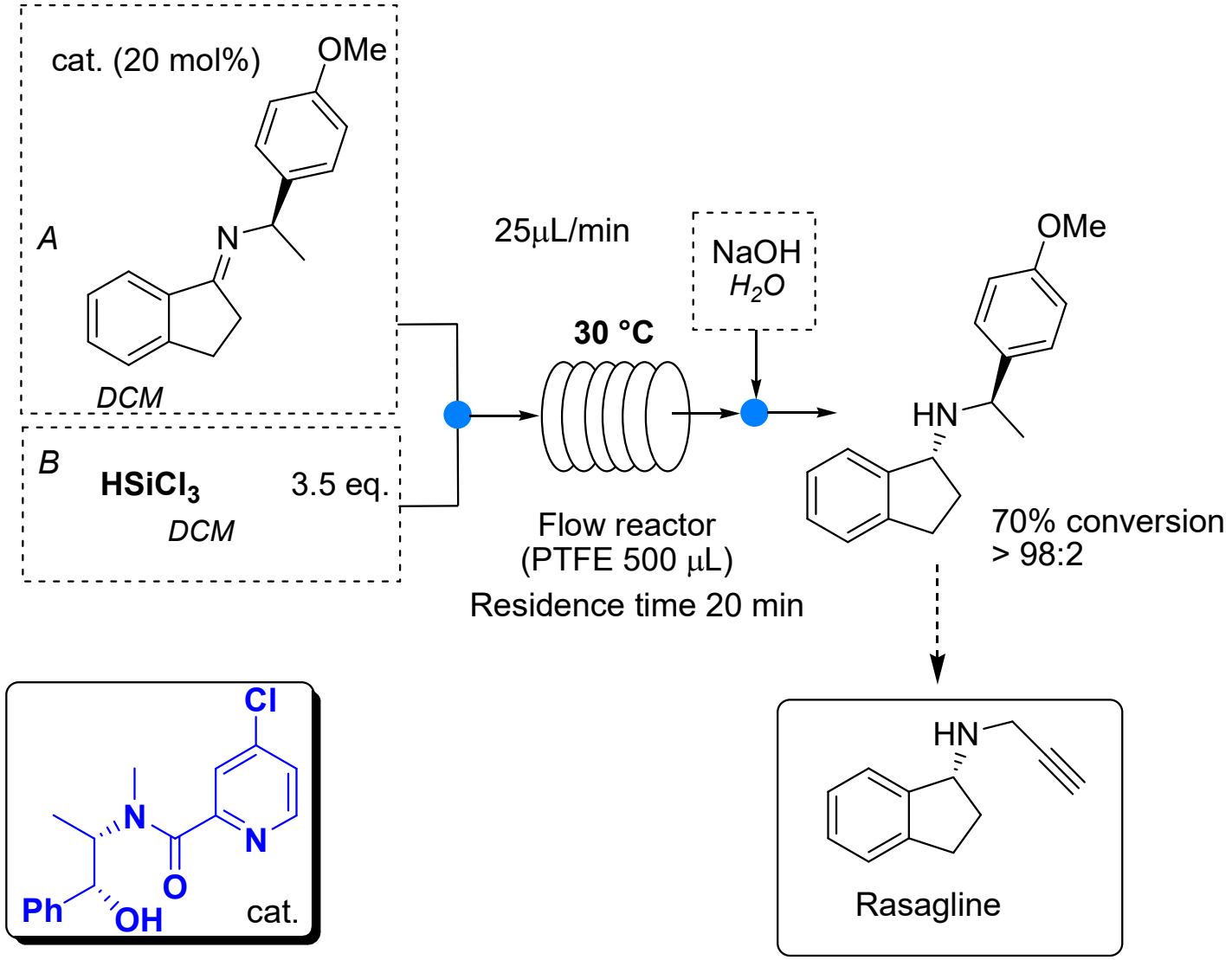
Picolinamide Organocatalysts



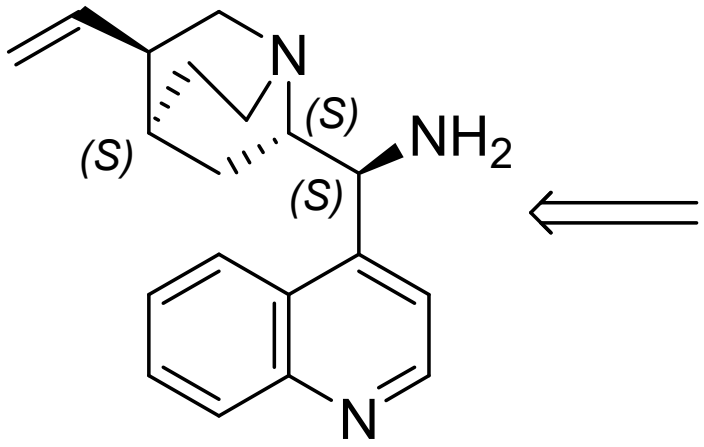


Matsumura's working model (Reproduced from Jones, *Org. Biomol. Chem*. **2012**, 10, 2189)

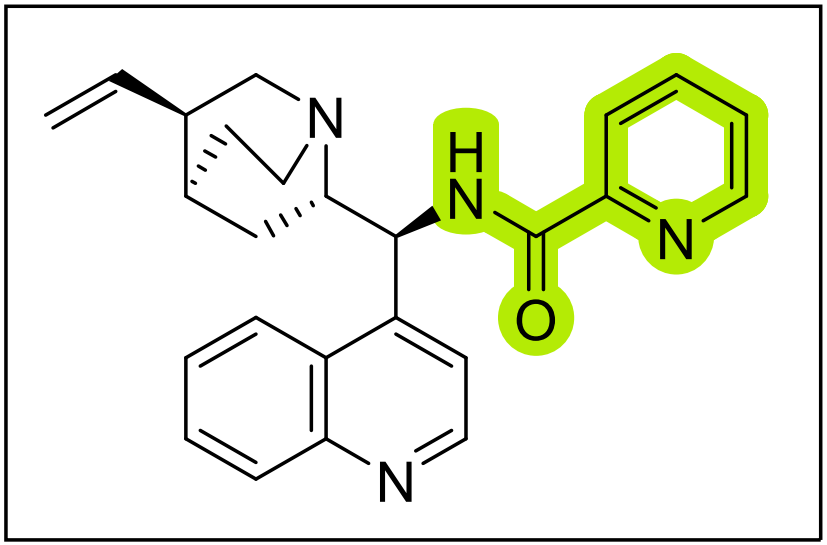
Brenna, *Eur, J. Org. Chem.* **2017**, 39-44



Picolinamides



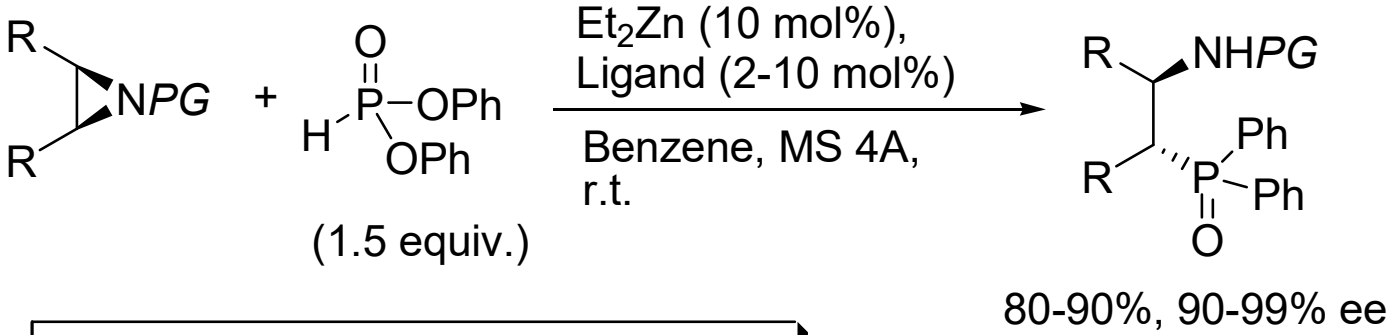
9-Amino-*epi*-Cinchonidine

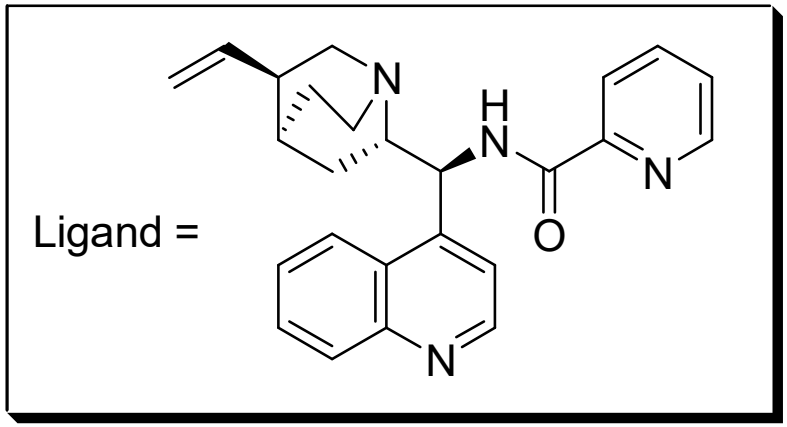


Prototype catalyst

Barrulas, *EJOC*, **2014**, 7339.

Enantioselective Desymmetrization

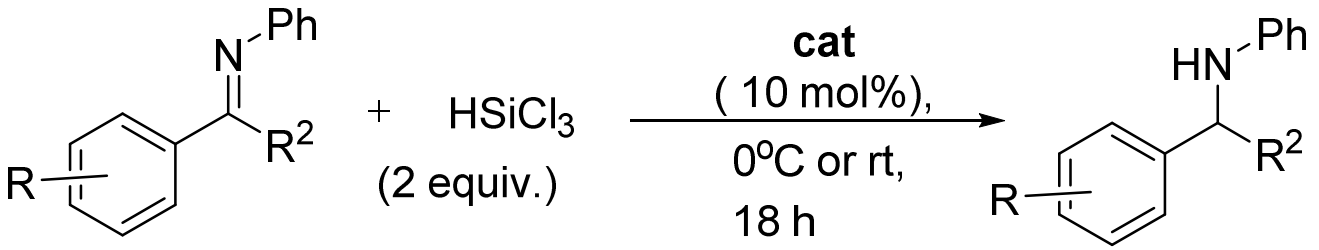


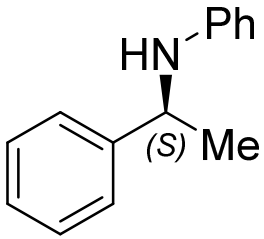


Nakamura, *JACS*. **2012**, 134, 19366.

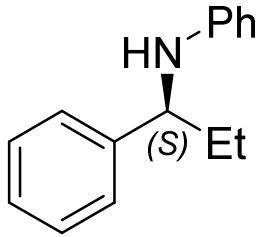
Initial Results

Prototype Catalyst





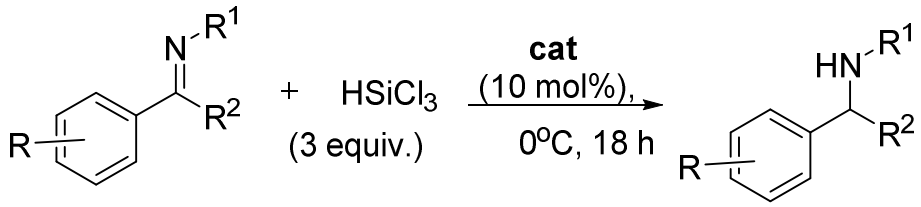
97%, 80% ee
(rt and 0ºC)

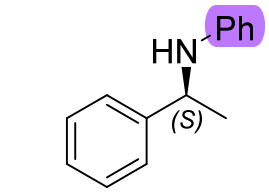


77%, 81% ee

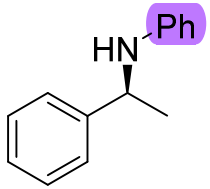
P. Barrulas, PhD Dissertation, University of Evora, **2014.**

Catalyst Screening

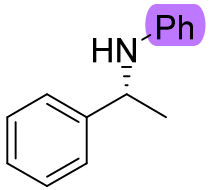




A (91%, 77% ee)



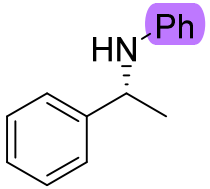
B (83%, 81% ee)



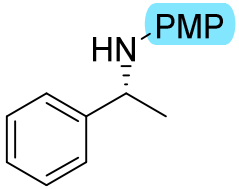
C (98%, 81% ee)

C (51%, 83% ee, -20°C)

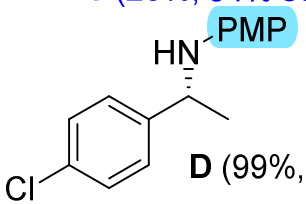
C (23%, 84% ee), -40°C



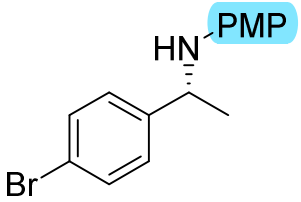
D (99%, 90% ee)



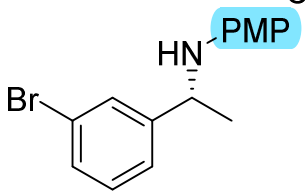
D (97%, 90% ee)



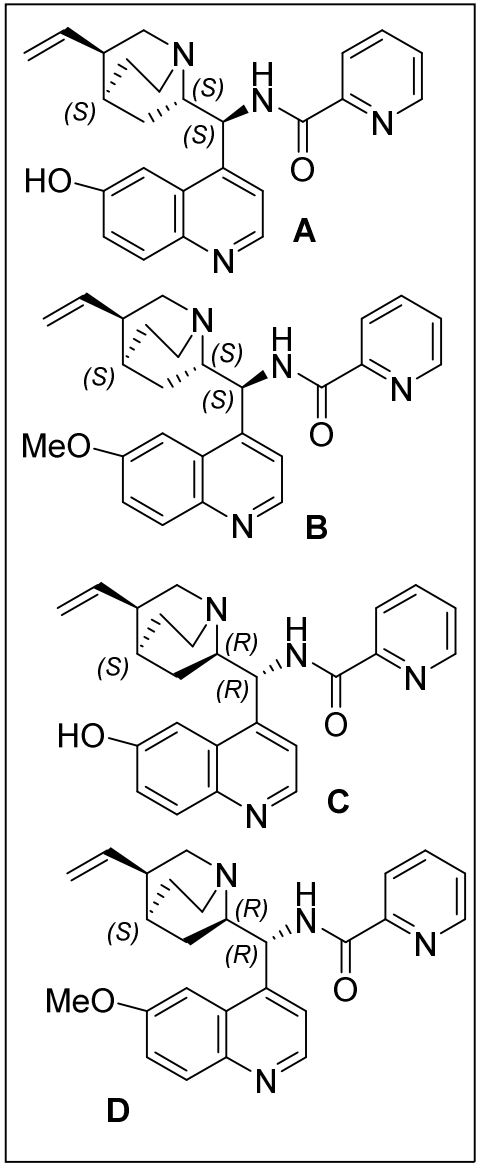
D (99%, 91% ee)



D (98%, 88% ee)

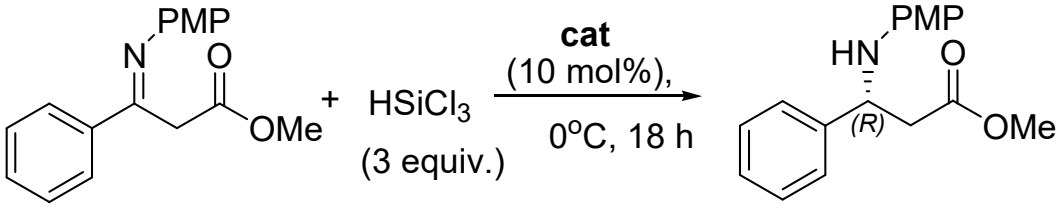


D (77%, 89% ee)

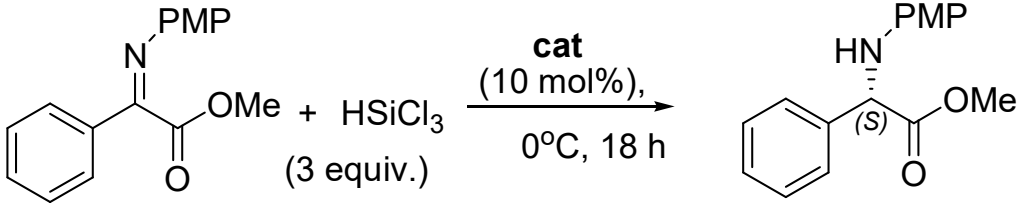


Barrulas, *EJOC*, 2014, 7339.

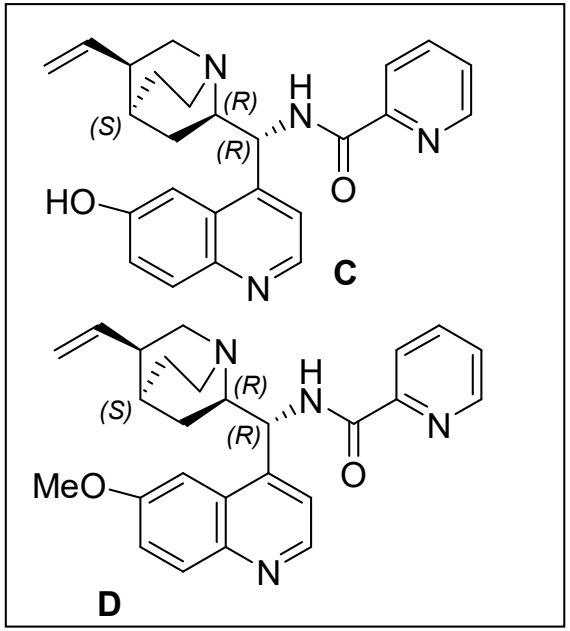
Further Screening



C (87%, 83% ee)
D (99%, 90% ee)

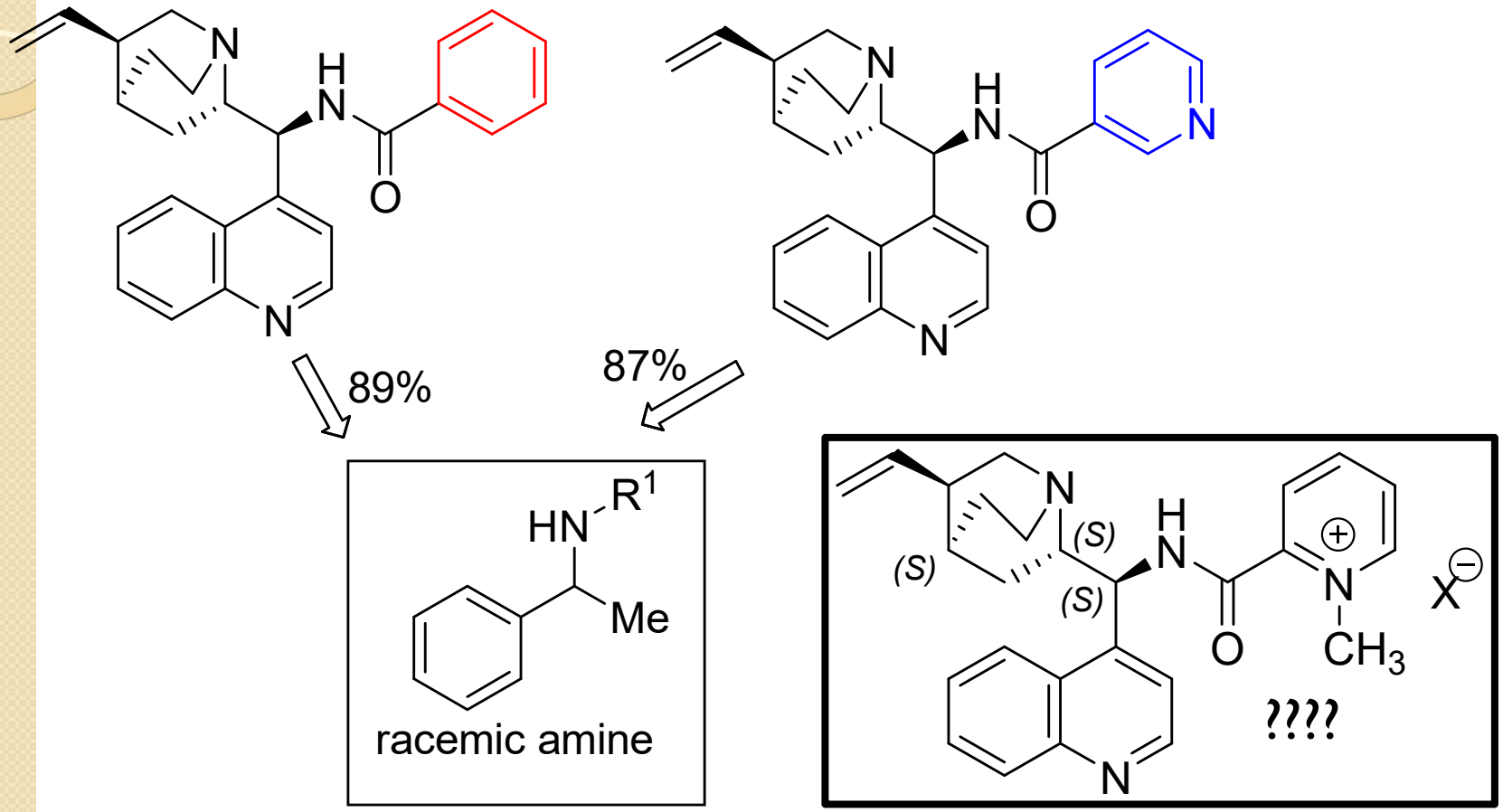


D (93%, 80% ee)



Barrulas, *EJOC*, 2014, 7339.

Probing the Mechanism



P. Barrulas, PhD Dissertation, University of Evora, **2014**.

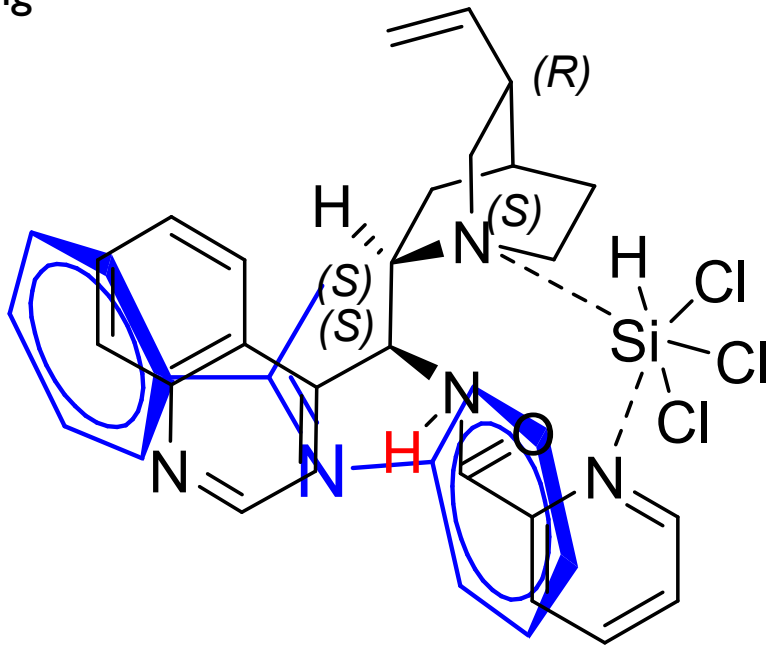
Initial Working Model

π–π stacking

Transition state Stabilization

Catalyst preorganization

Tight/compact transition state

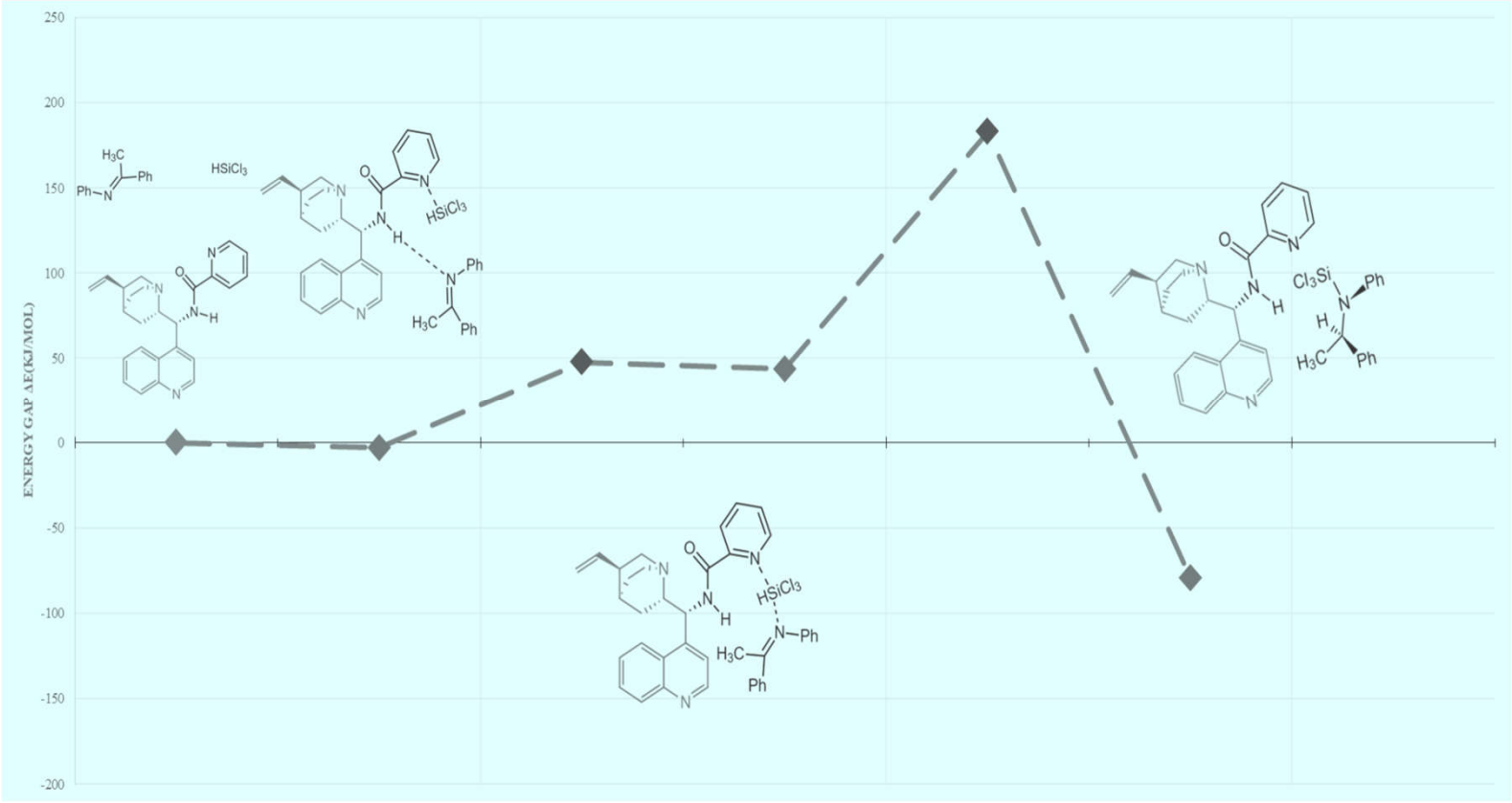


***Si*-face attack of the hydride**

DFT calculations

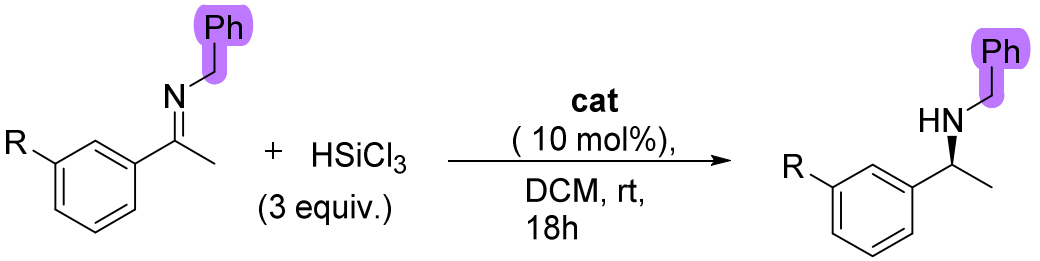
Tools = B97 functional with a D3 dispersion correction and triple-zeta basis set.

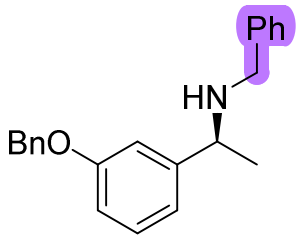
- **Transition state profile**



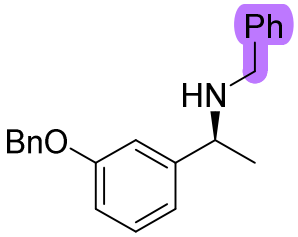
Further studies

Supports our mechanistic model.

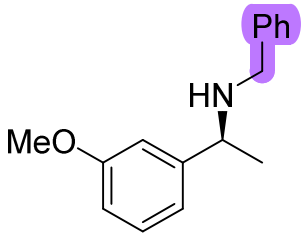




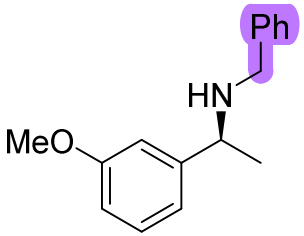
(57%, 29% ee, **Prototype**)



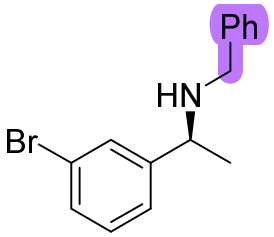
(71%, 28% ee, **B**)



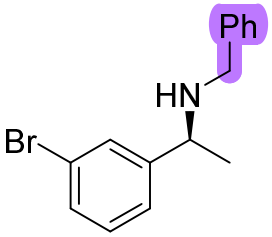
(52%, 31% ee, **Prototype**)



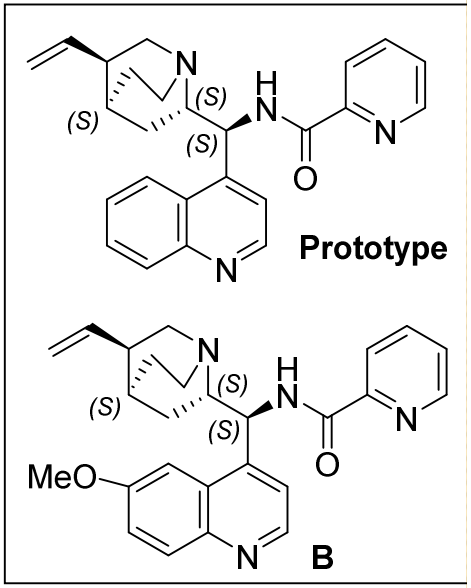
(60%, 32% ee, **B**)



(56%, 14% ee, **Prototype**)



(56%, 14% ee, **B**)



You need the Phenyl!

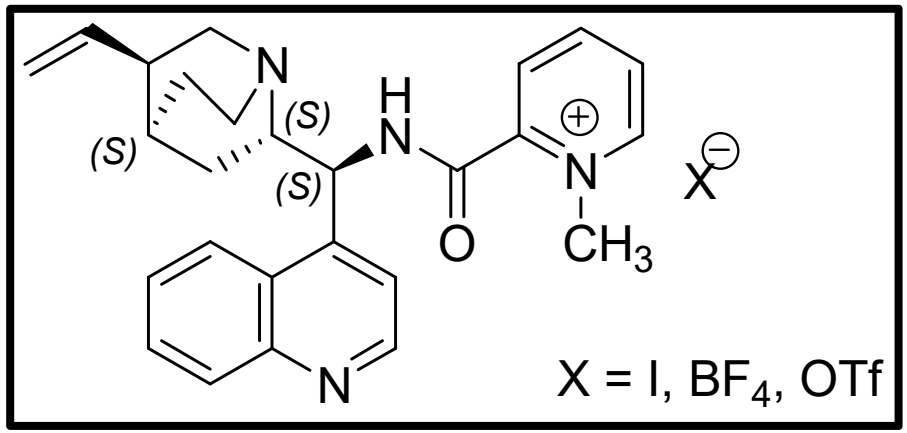
Sílvia Fernandes

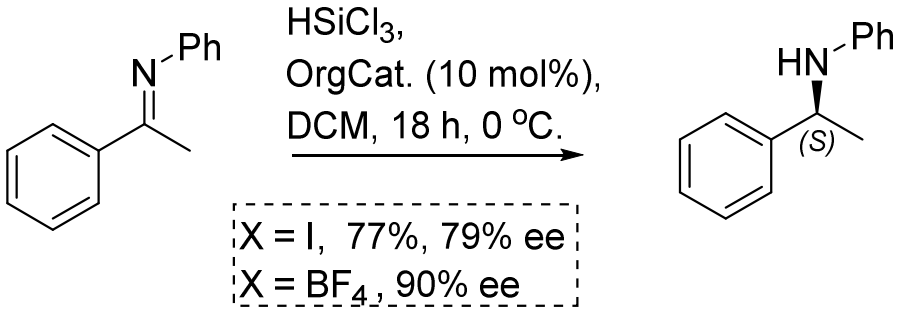
S. Fernandes, *MSc Thesis*, University of Evora, **2016.**

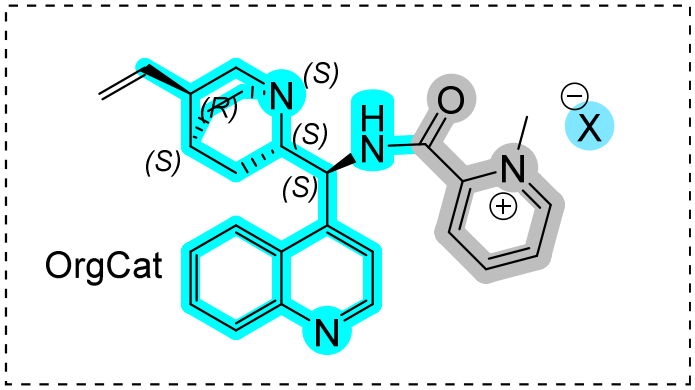
N-Methyl Cinchona-Picolinamide

Cation-π interactions
Counter ion effects

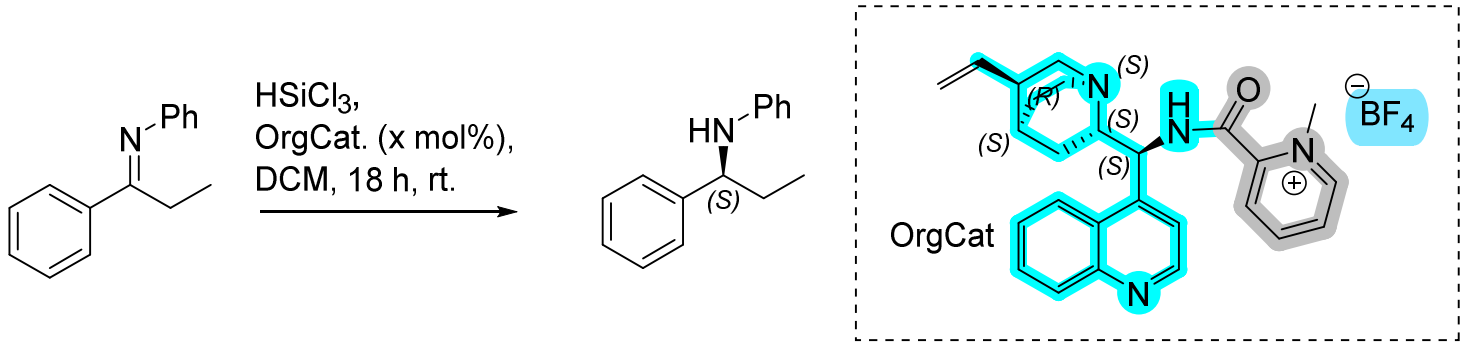
Jacobsen, *ACIE*, **2016**, 55, 12596.





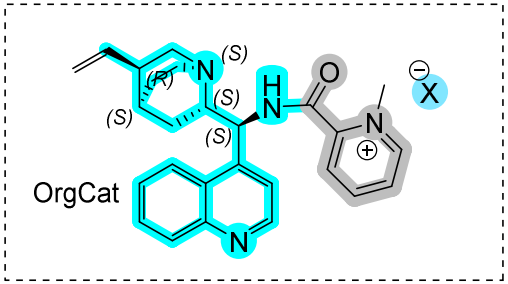


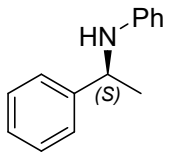
Barrulas, Burke, WO2015052656, US9844773.
Barrulas, *EJOC*, **2014**, 7339



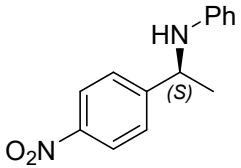
Entry	x mol %	Yield %	e.e. %	TOF ($mol.mol^{-1}.h^{-1}$)
1	20	85	85	0.28
2	10	86	84	0.56
3	5	88	82	1.11
4	1	86	80	5.56
5	0.5	78	72	11.1
6	0.1	53	18	55.6

P. Barrulas, PhD Dissertation, University of Evora, **2014**.

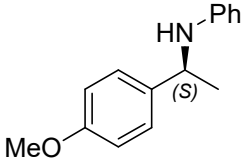




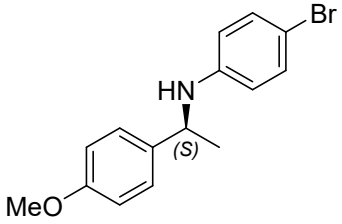
79%, 80% ee (-20 °C)
80%, 80% ee (0°C)
86, 84% ee (rt)



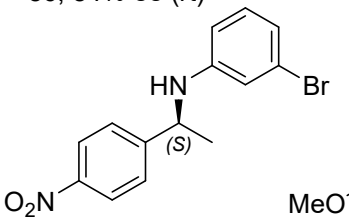
68%, 83% ee (rt)



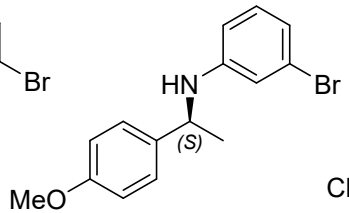
58%, 84% ee (rt)



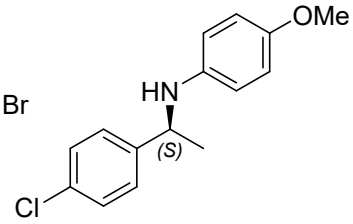
10%, 69% ee (rt)



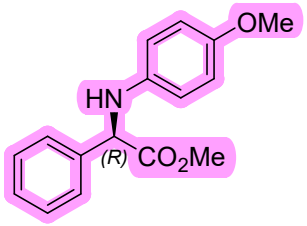
75%, 76% ee (rt)



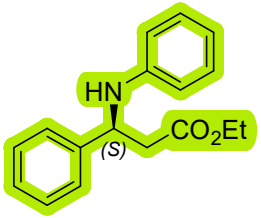
20%, 69% ee (rt)



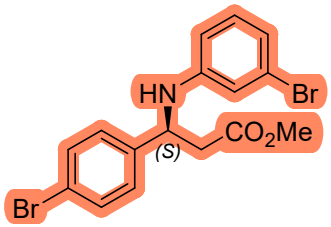
85%, 83% ee (0 °C)



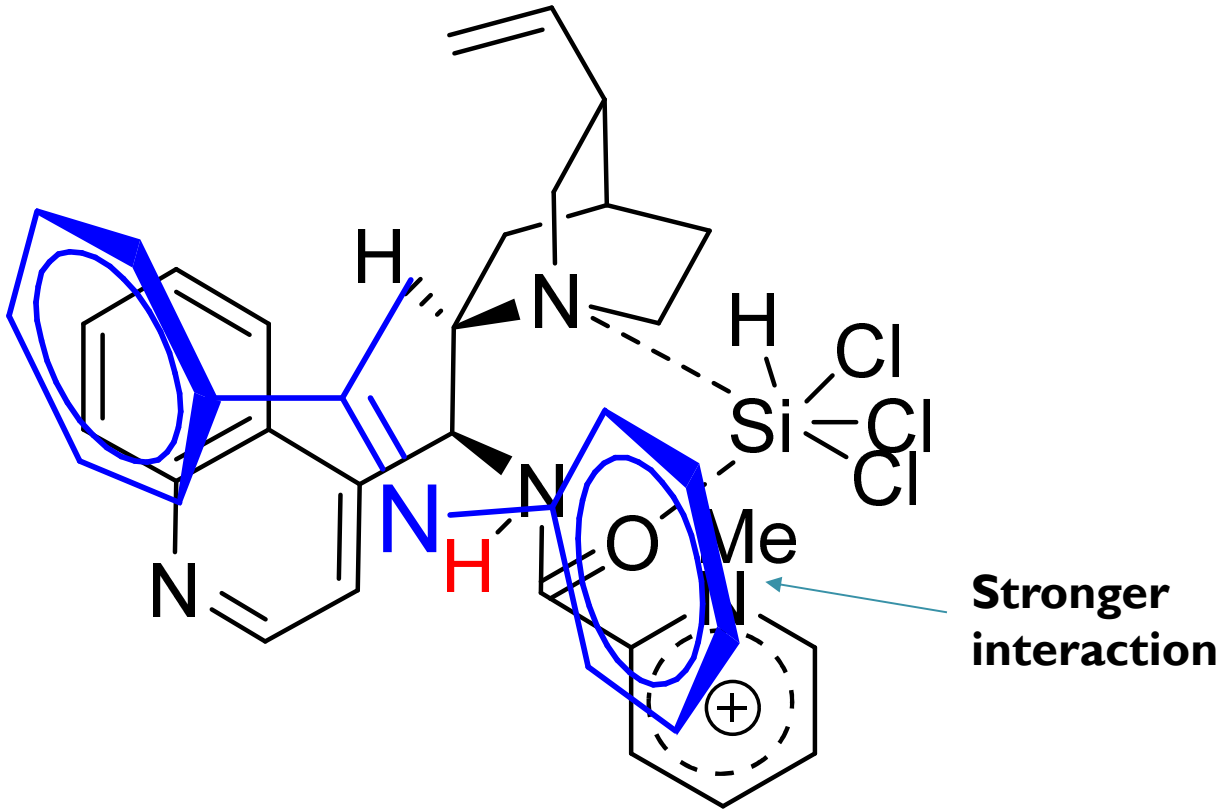
93%, 81% ee (0 °C)



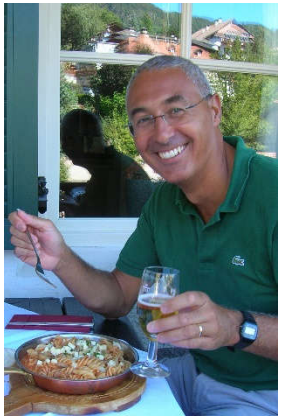
72%, 70% ee (rt)



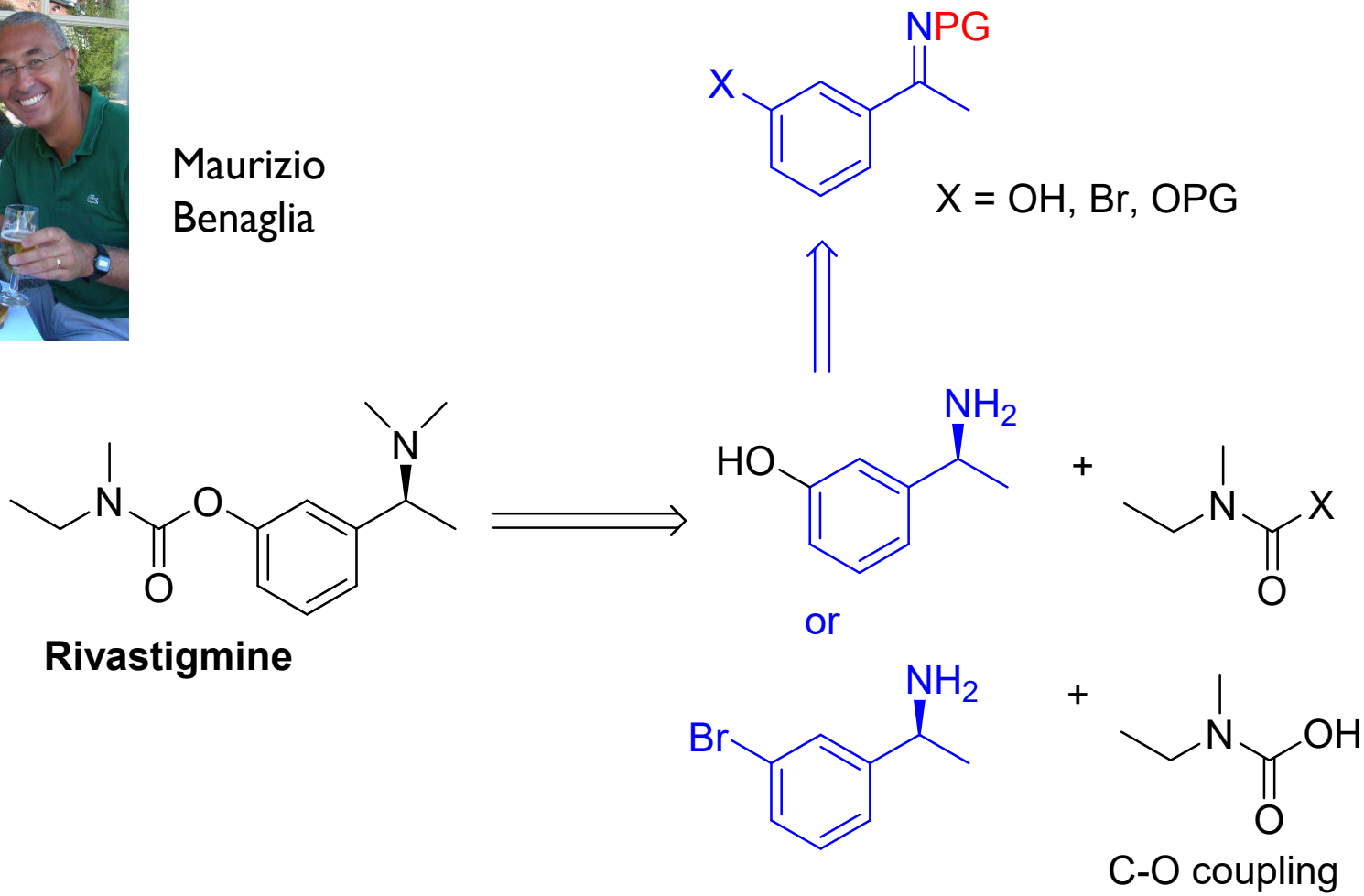
>99%, 85% ee (0 °C)


H
N
H
Cl
Si
Cl
Cl
N
N
H
O
Me
N
Stronger interaction

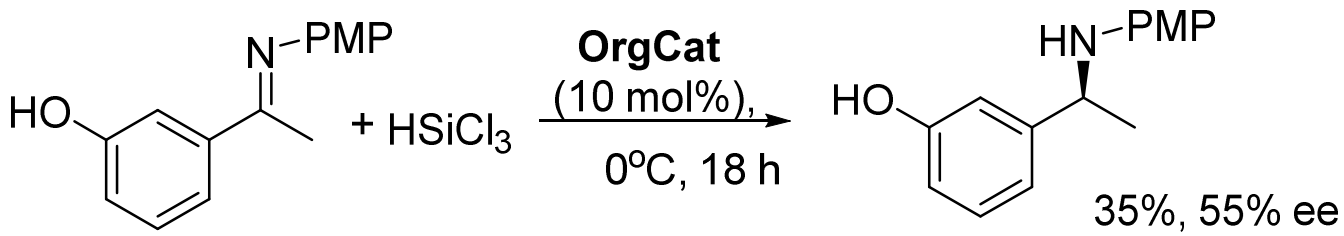
Formal Route to Rivastigmine

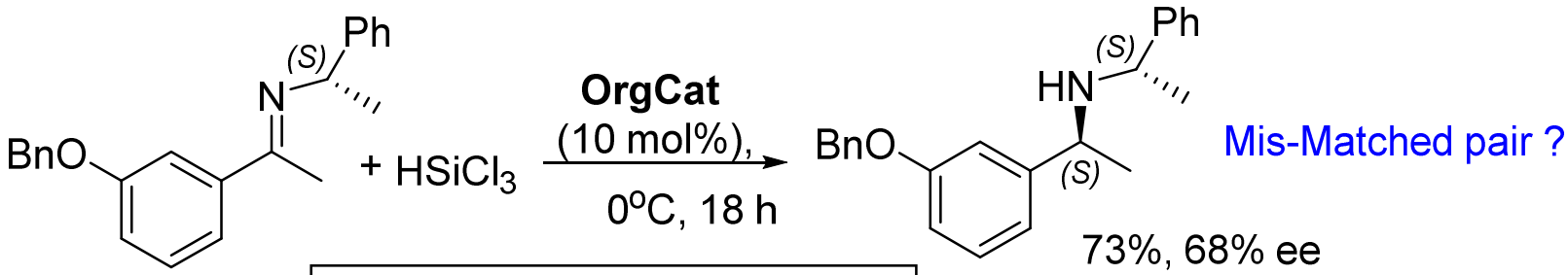


Maurizio Benaglia

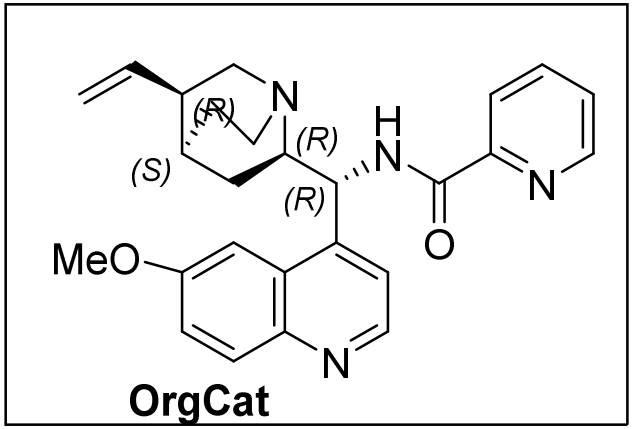


Key reactions



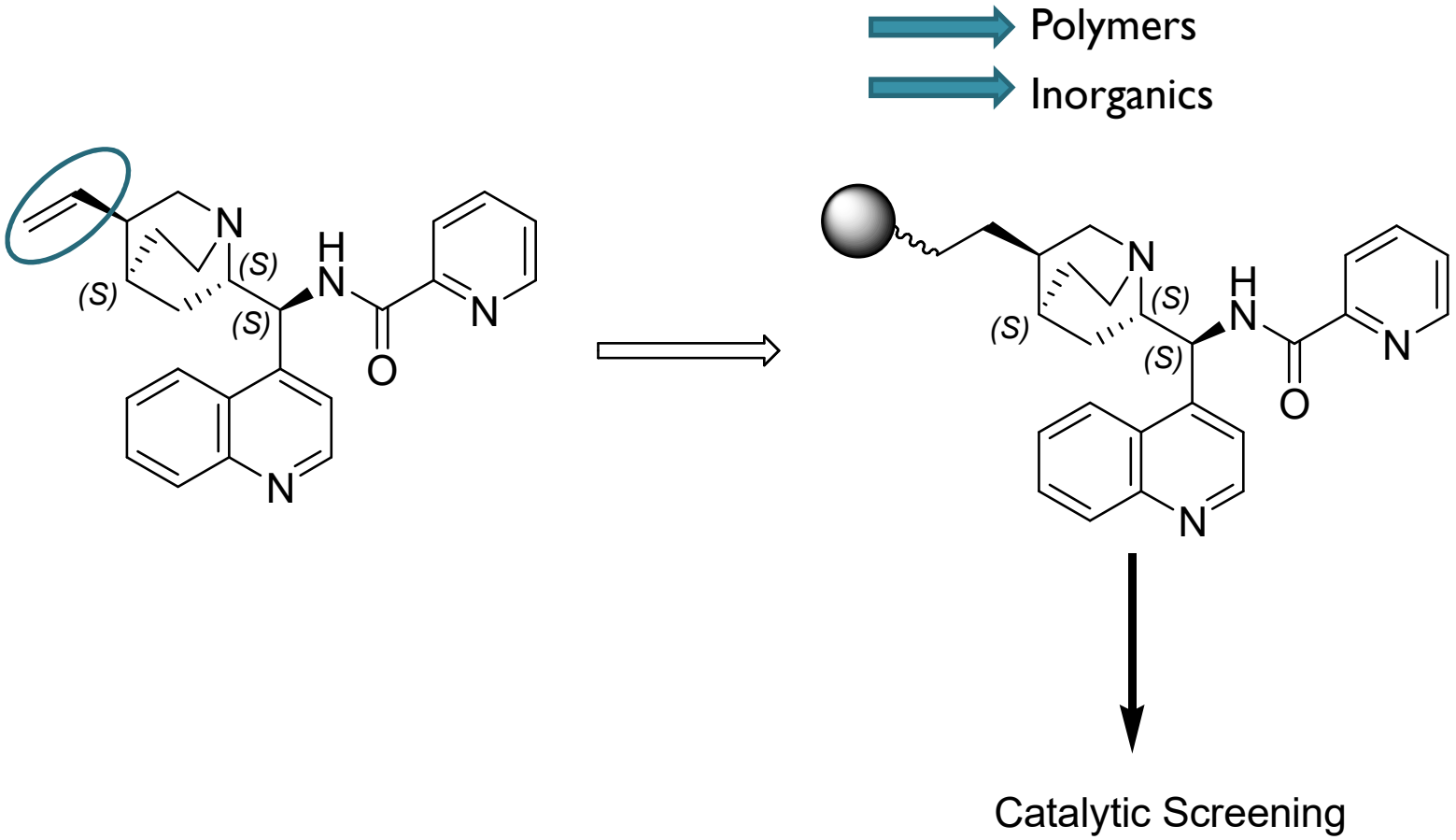


Mis-Matched pair ?



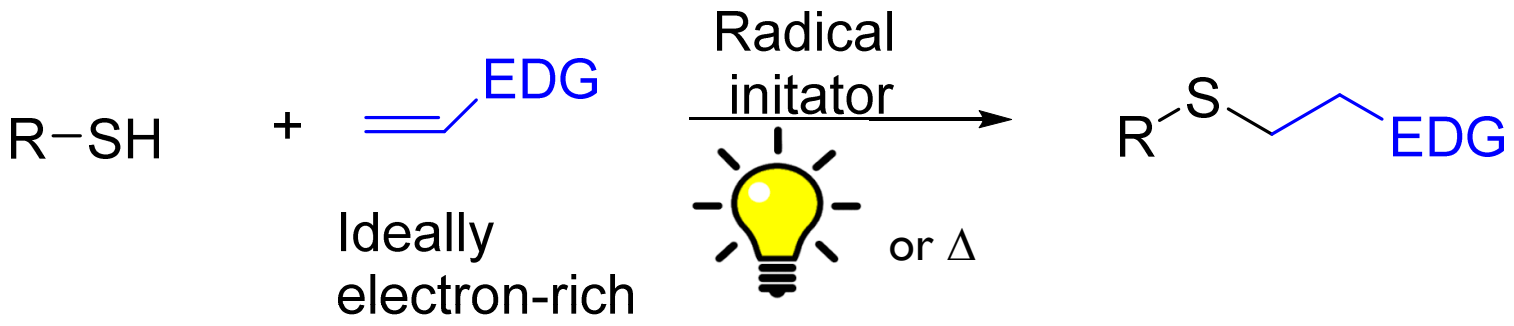
Genoni *et al. Tet. Lett.* 2015, 56, 5752.

Immobilized Picolinamide catalysts



Thiol-Ene Click (TEC) Chemistry

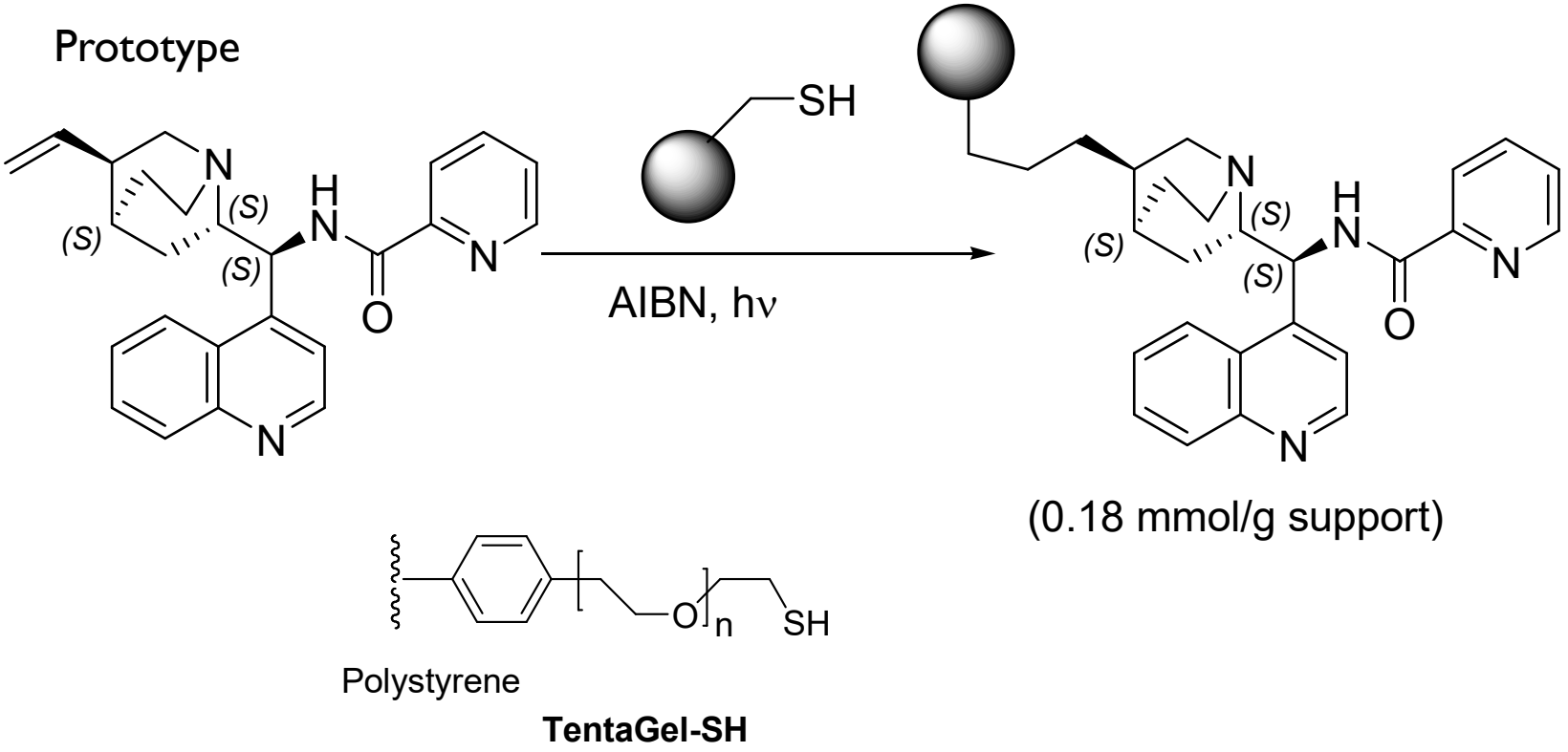
(Morgan, Ketley, Grace, 70s)



Polymer immobilized Catalyst I

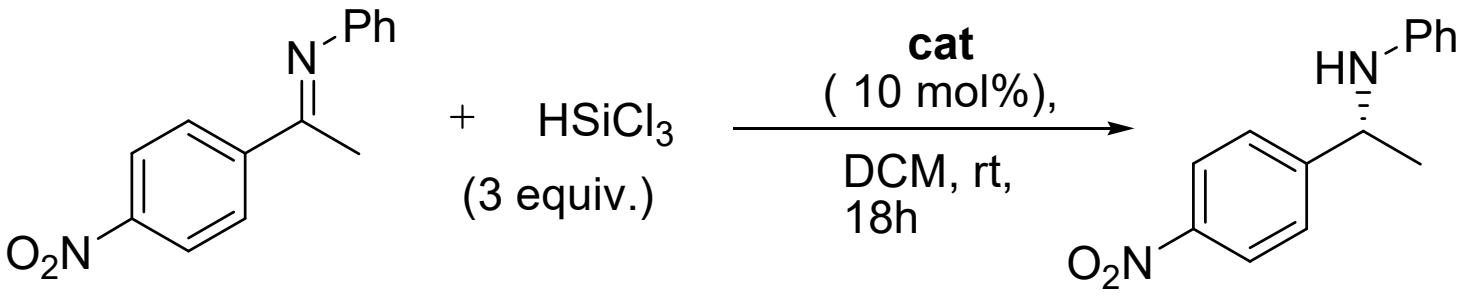
Thiol-ene chemistry (Garrell, *JACS*, **2011**, 133, 11026)

Marina Costa



Marina Costa, *MSc Thesis*, University of Evora, **2017.**

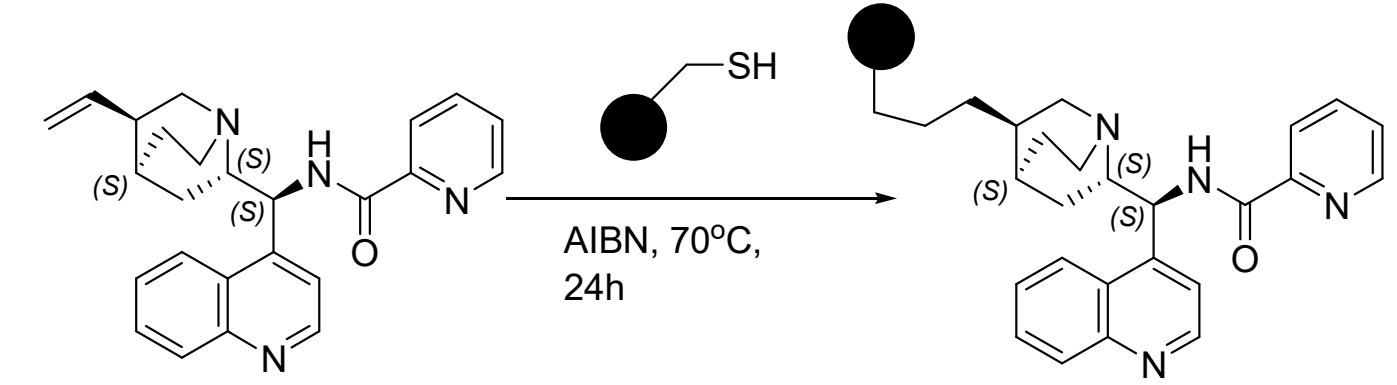
Catalytic Cycles: Proof of Concept Studies



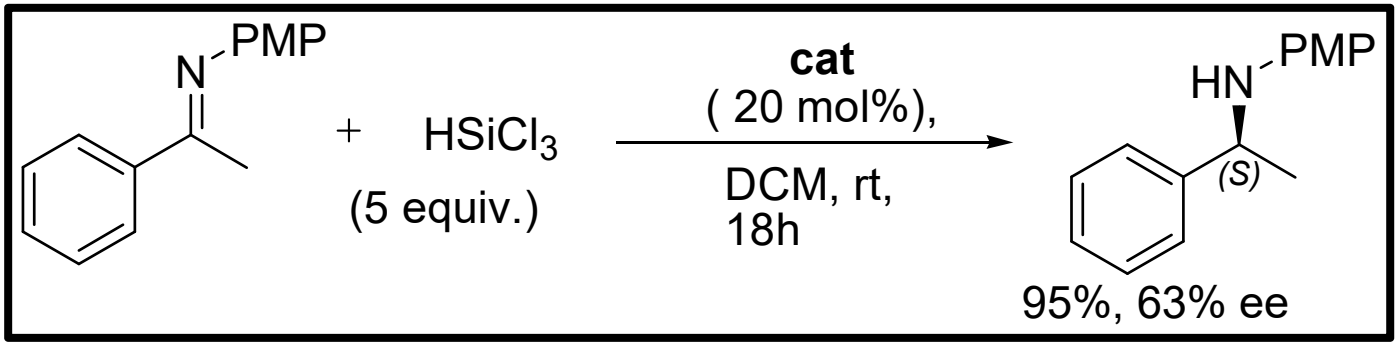
Cycle	Yield (%)	Ee (%)
1	80	69
2	21	12
3	22	19
4	46	1

Marina Costa, *MSc Thesis*, University of Evora, **2017**.

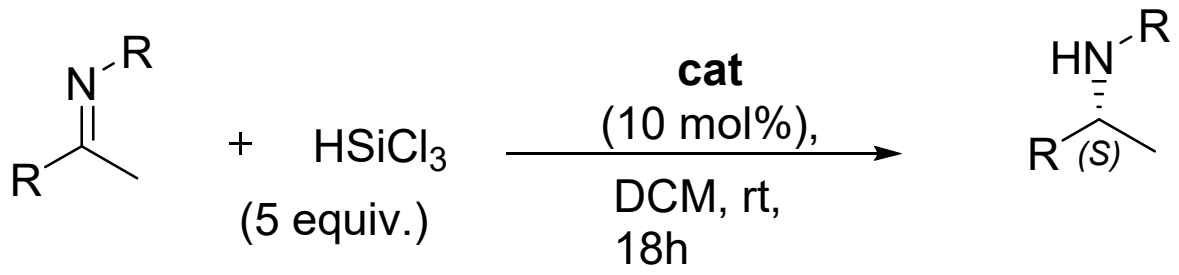
Polymer immobilized Catalyst II

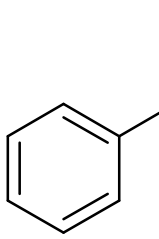


Braslau, *React. Funct. Polym.* **2013**, 73, 624.

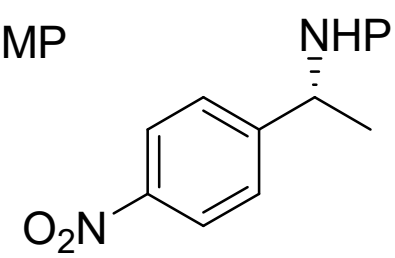


Fernandes *et al. Molecules,* **2016**, 21, 1182.

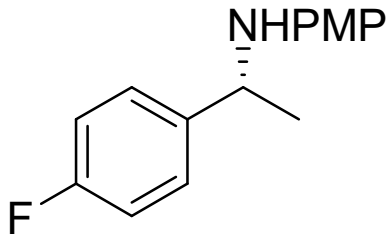




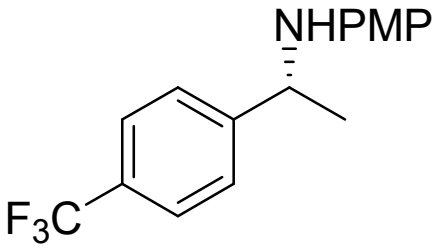
95%, 91%ee



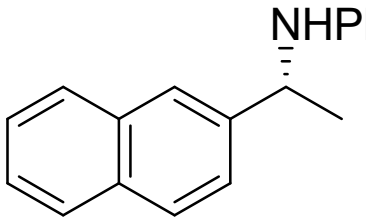
93%, 85%ee



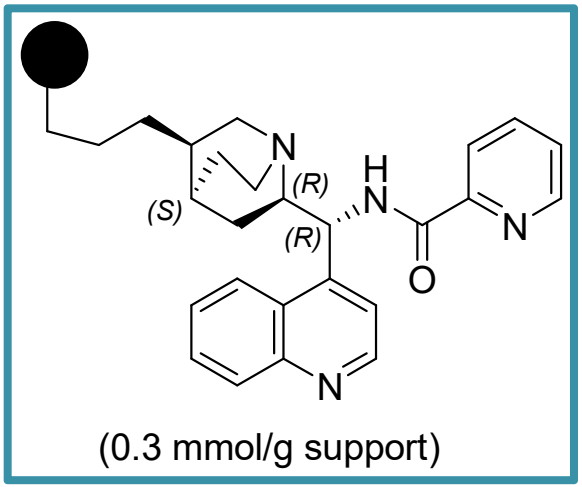
98%, 87%ee



97%, 84%ee



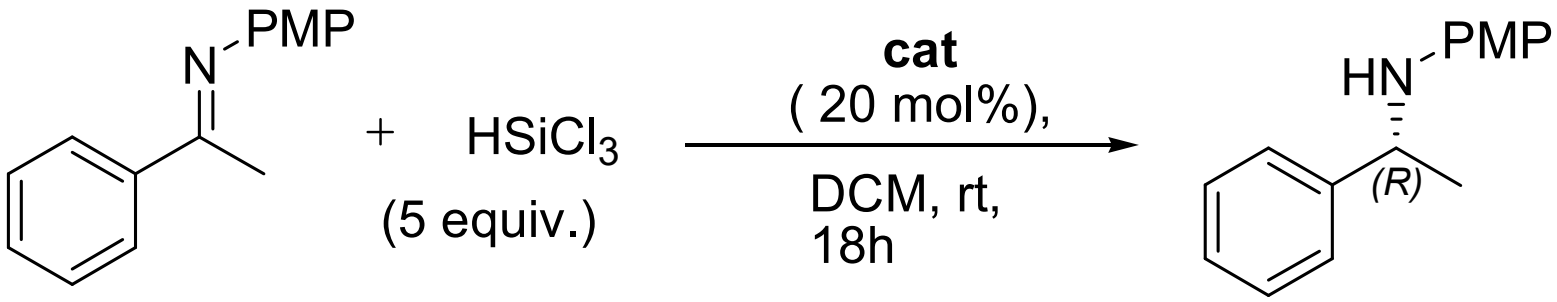
96%, 85%ee



(0.3 mmol/g support)

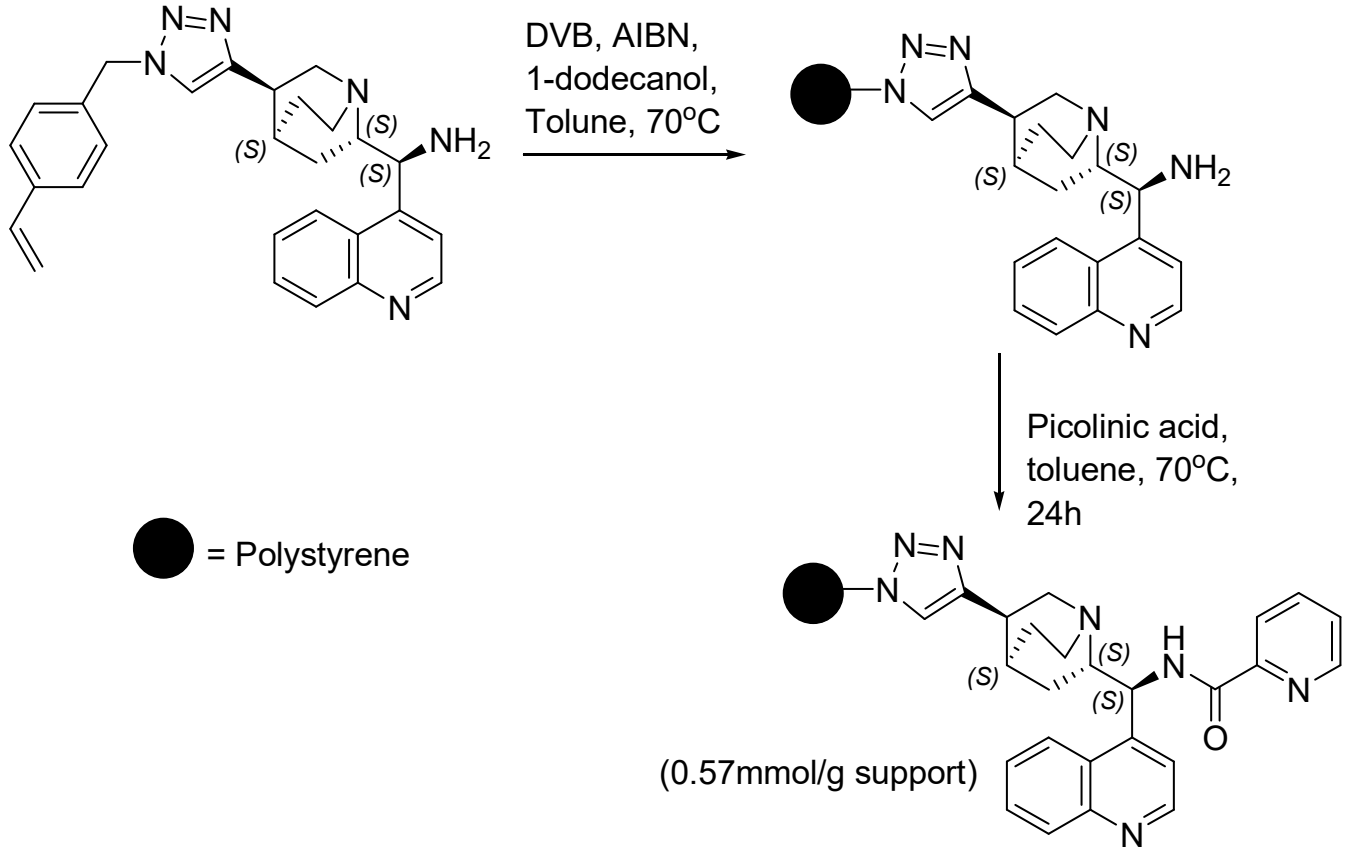
Fernandes *et al. Molecules,* **2016**, 21, 1182.

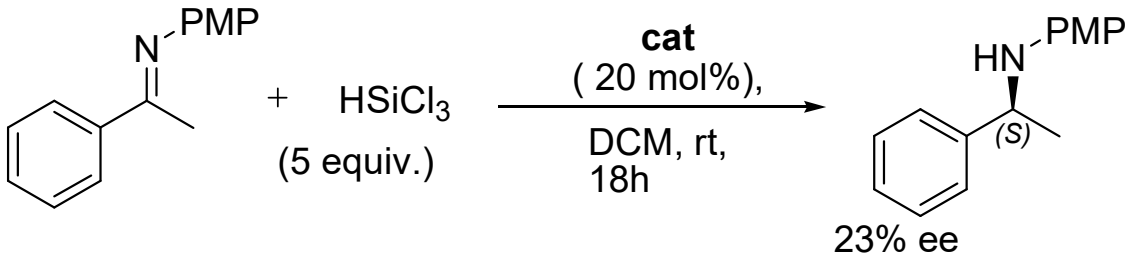
Catalyst Recycling



Run	Yield (%)	Ee (%)
1	95	91
2	90	88
3	80	67
4	77	37

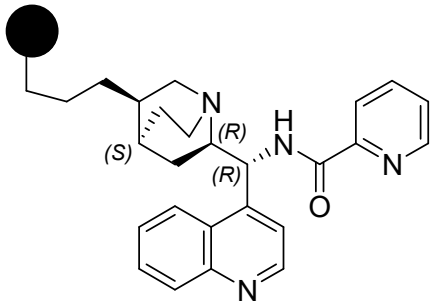
Catalyst Immobilization III





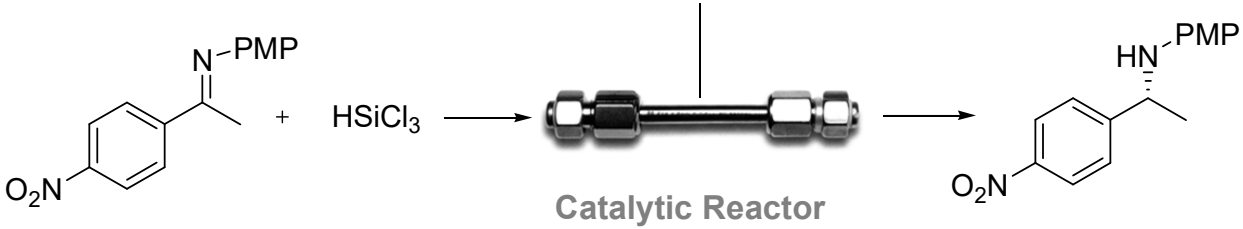
S. Fernandes, *MSc Thesis*, University of Evora, **2016.**

Continuous Flow



(0.3 mmol/g support)

0.02 mL/min res. time 25 mins



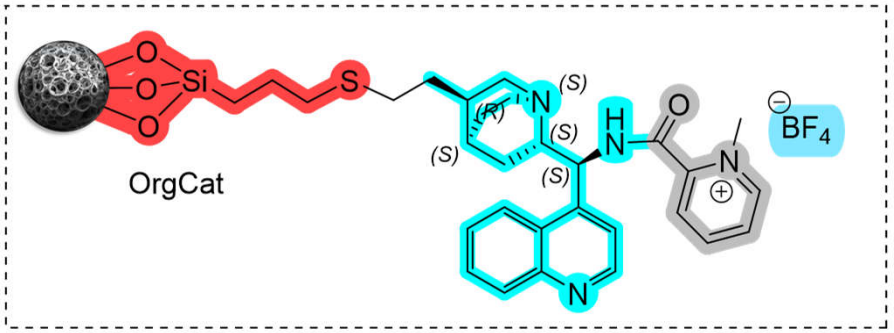
Catalytic Reactor

Run	Time (mins)	Yield (%)	Ee (%)
1	0-50	98	47
2	50-75	98	44
3	75-100	93	30
4	100-125	93	25
5	125-150	87	22
6	150-175	86	20

Fernandes *et al. Molecules,* **2016**, 21, 1182.

Immobilizations

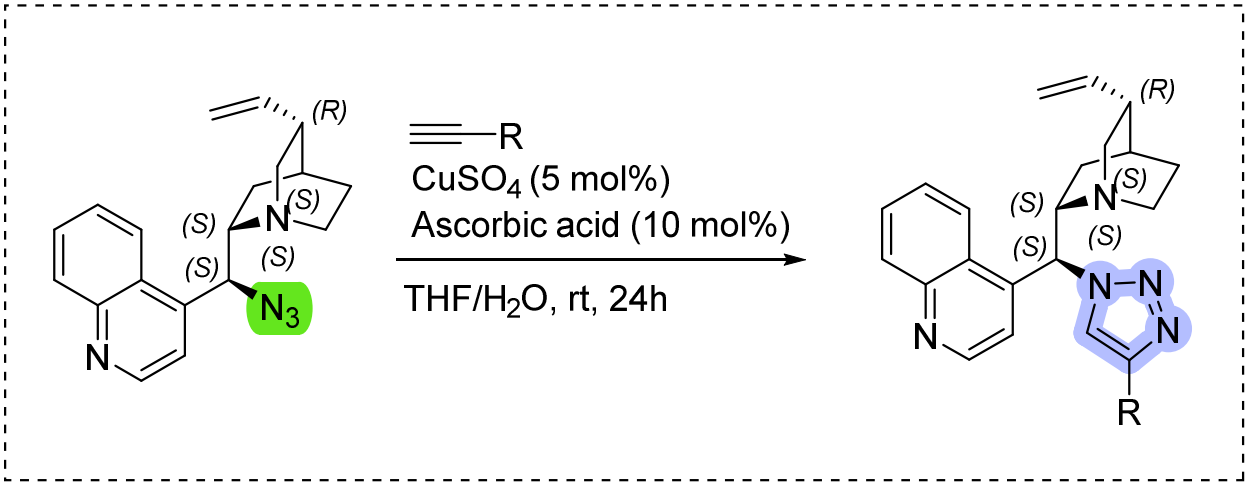
TOF = 0.54



Entry	Support	Cycle	Yield	Ee (%)
1	NanoSilica	1	47	34
2	NanoSilica	2	50	38
3	NanoSilica	3	17	27
4	MCM-41	1	71	37
5	MCM-41	2	36	24
6	MCM-41	3	47	8
7	Magnetic NPs*	1	97	64
8	Magnetic NPs	2	30	50
9	Magnetic NPs	3	30	25

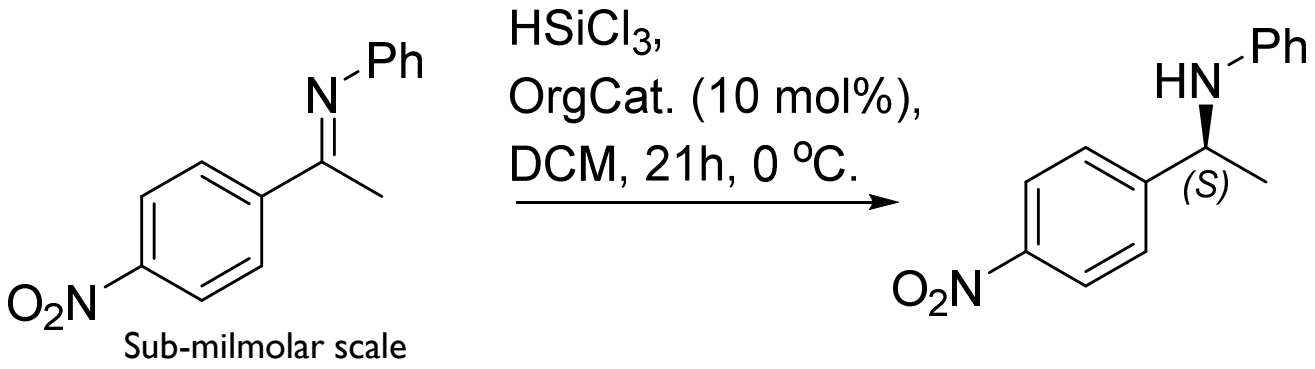
*Magnetite derived (Fe_3O_4)

CINCHONA-TRIAZOLES



Entry	R	Yield[b] (%)	Global yield[c] (%)	Product
1	-C_6H_5	85	76	**1a**
3	-CH_2OH	55[d]	49	**1b**
4	-$(CH_2)_2CH_3$	76	68	**1c**
5	-$C(CH_3)_2NH_2$	98[e]	87	**1d**
6	-$C(CH_3)_2OH$	97[d]	87	**1e**
7	-cyclopropyl	69[e]	62	**1f**
8	-6-methoxynaphthalene	67[e]	60	**1g**

Barrulas, *Synth. Communications,* **2021**, 51, 2954.



Sub-milmolar scale

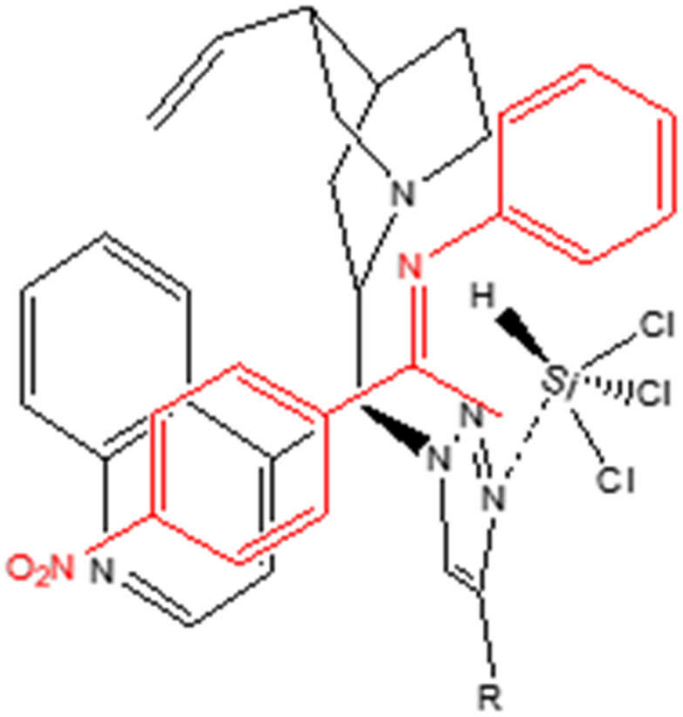
Entry	Organocatalyst	Yield[b] (%)	ee[c] (%)
1	1a	61	3
2	1b	60	Rac
3	1c	58	Rac
4	1d	74	Rac
5	1e	80	Rac
6	1f	27	10
7	1g	23	10

Enantioselectivity Optimization: Solvent screening

Entry	Solvent	If		Ig	
		Yield (%)	ee (%)	Yield (%)	ee (%)
1	DCM	27	10	23	10
2	THF	54	11	52	10
3	DMF	52	10	41	12
4	Toluene	4	12	23	9
5	Dioxane	74	10	53	9

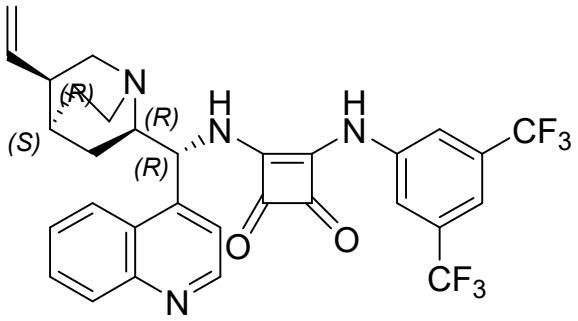
Barrulas, *Synth. Communications,* **2021**, 51, 2954.

Working Model

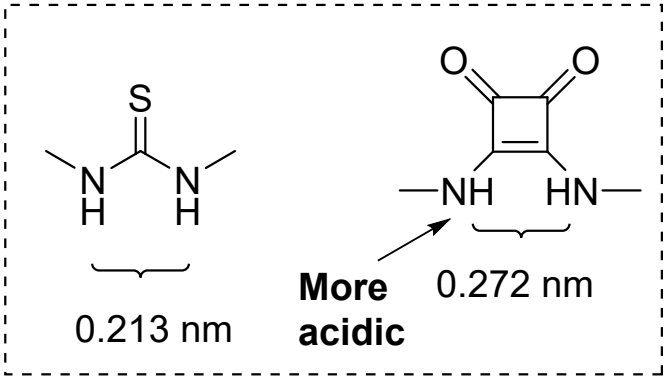


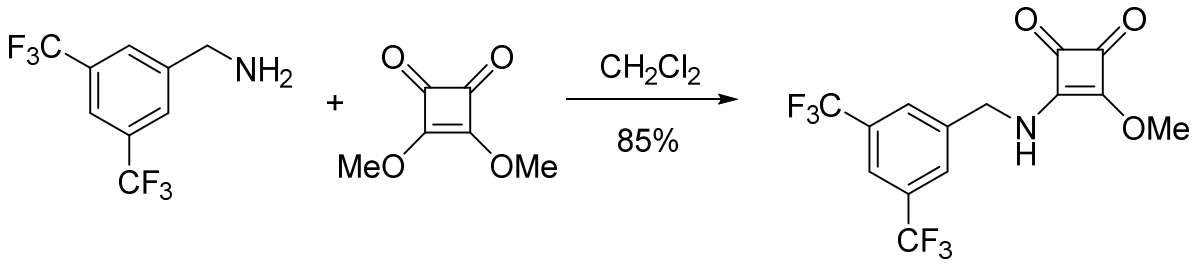
Barrulas, *Synth. Communications,* **2021**, 51, 2954.

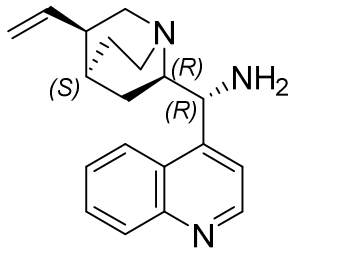
CINCHONA-SQUARAMIDES



Rawal Cinchona-Squaramide organocatalyst

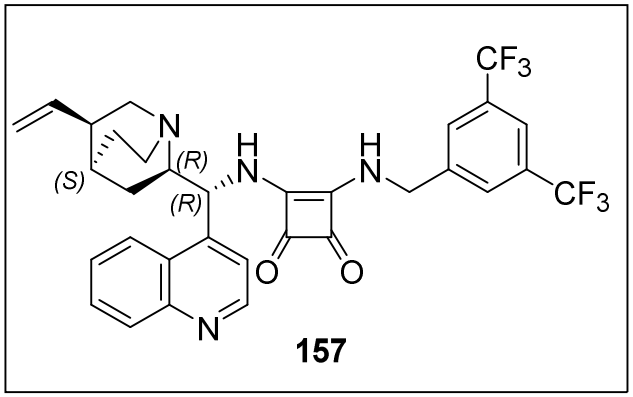






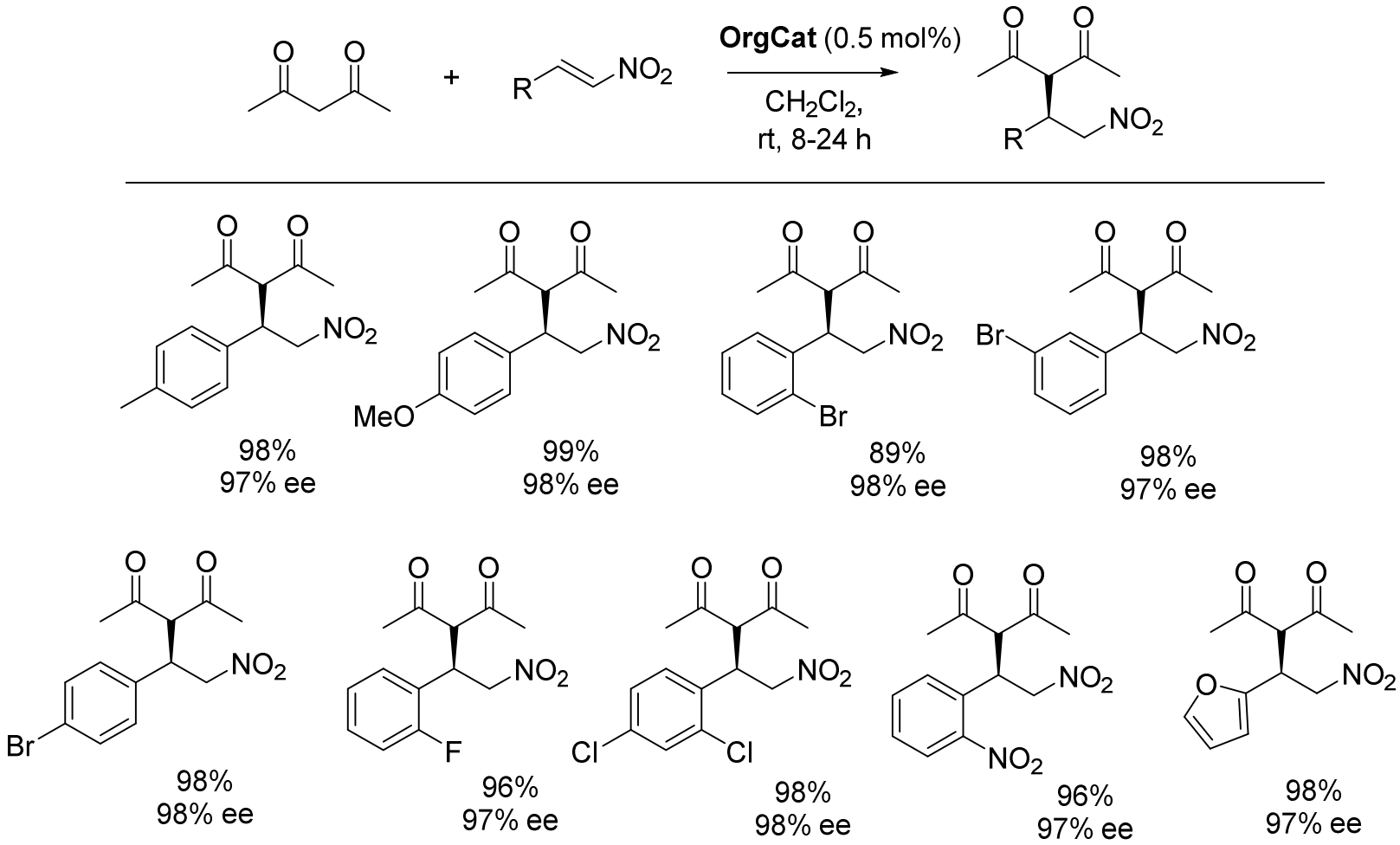
9-Amino-*epi*-Cinchonine

72%

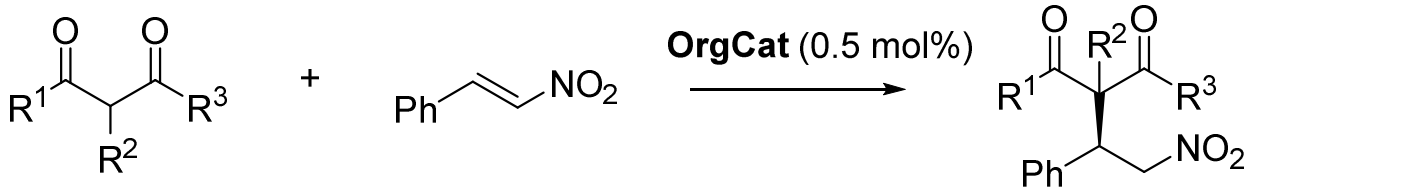


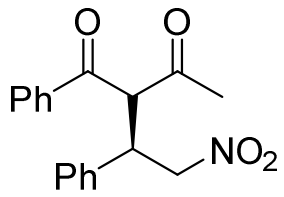
157

J. Am. Chem. Soc. **2008**, 130, 14416.

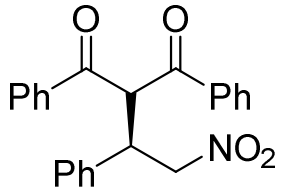


J. Am. Chem. Soc. **2008**, 130, 14416.

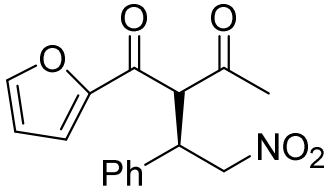




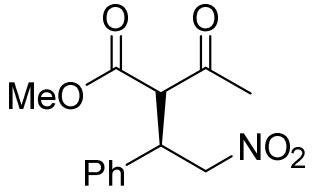
91% (dr = 2:1)
95% ee (major)
94% ee (minor)



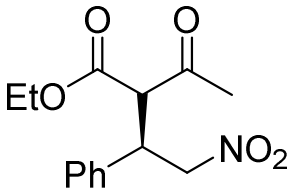
93%
88% ee



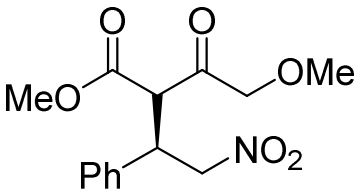
97% (dr = 1.4:1)
92% (major)
81% (minor)



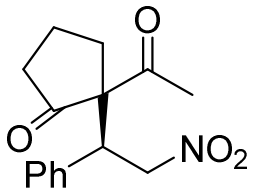
75% (dr = 1:1)
96% (major)
98% (minor)



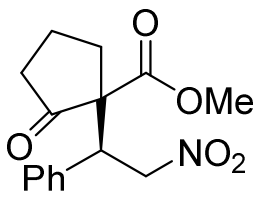
89% (dr = 1.6:1)
97% ee (major)
96% ee (minor)



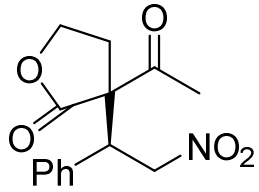
83% (dr = 1.3:1)
94% ee (major)
86% ee (minor)



96% (dr = 18:1)
98% (major)
96% (minor)



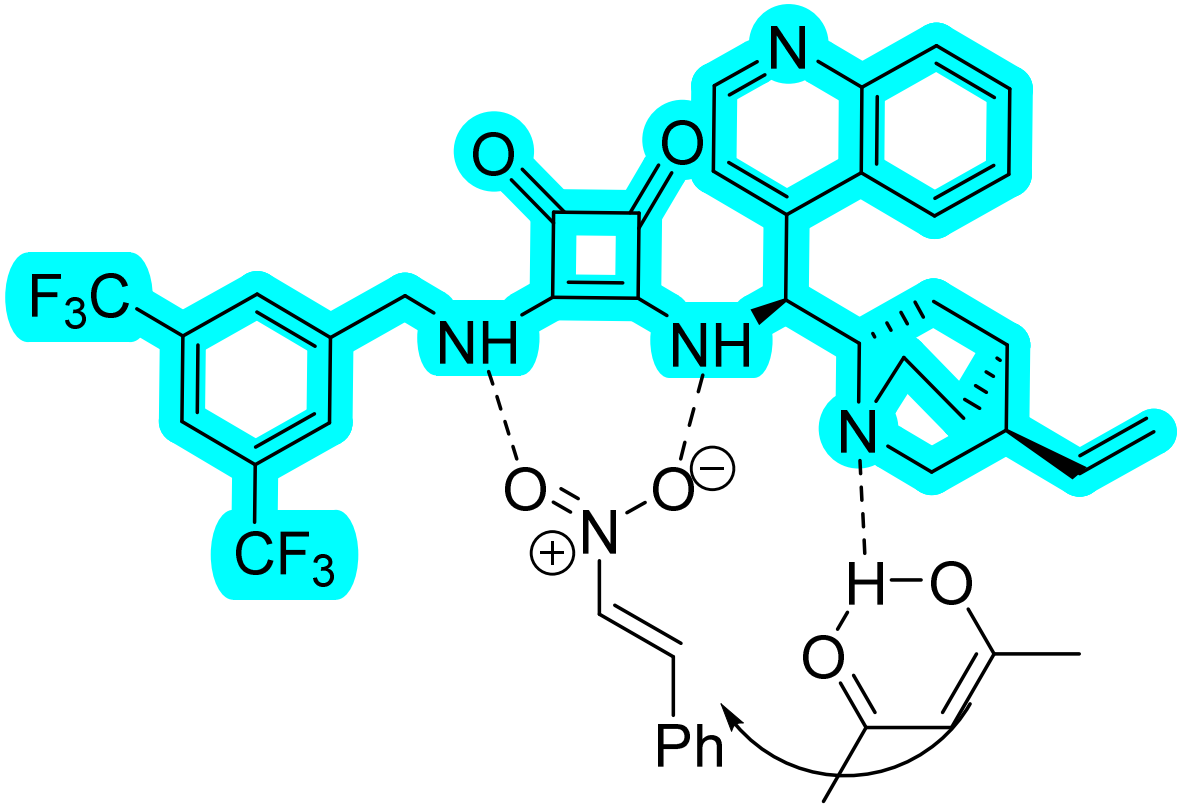
75% (dr = 50:1)
93% (major)
77% (minor)



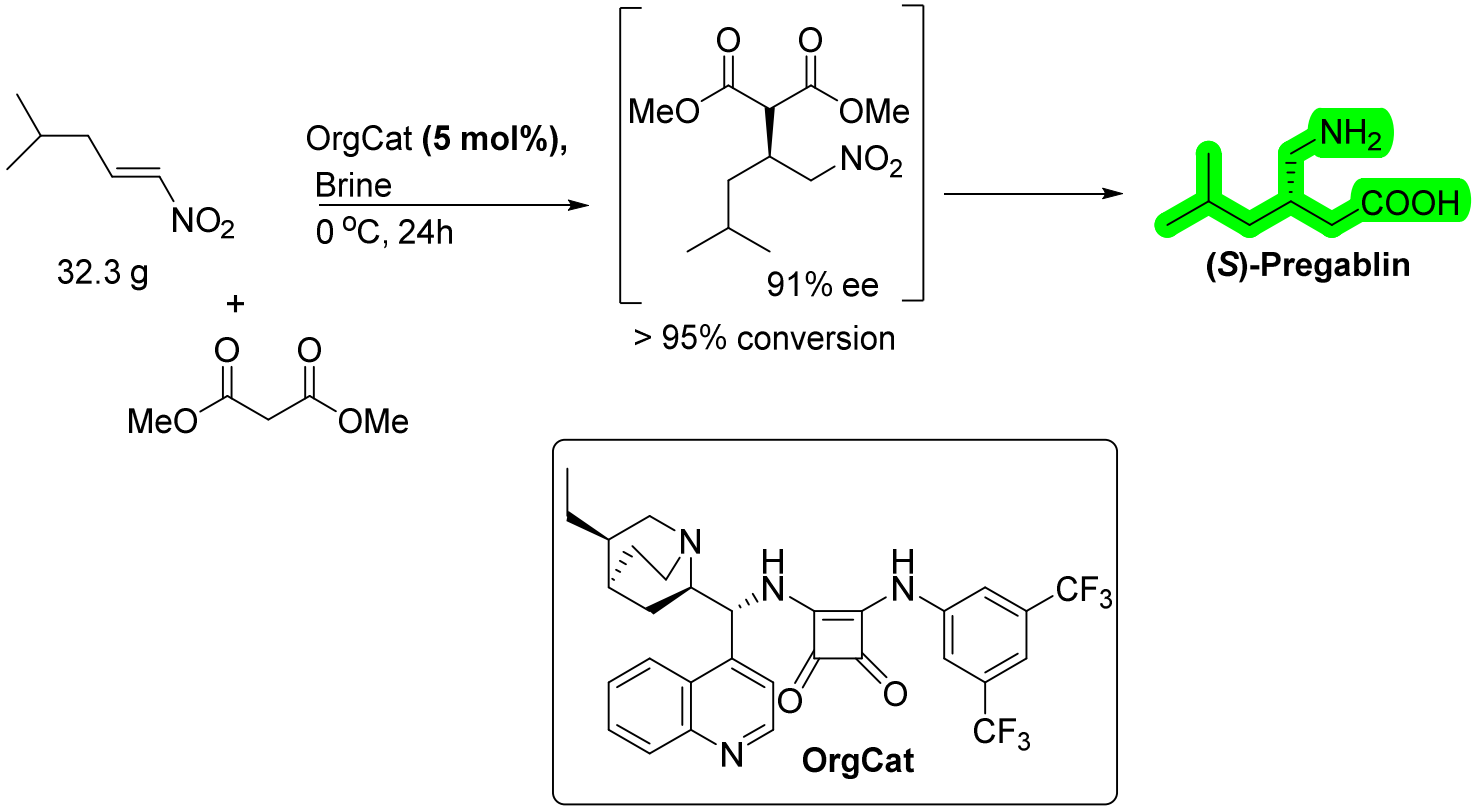
65% (dr = 4:1)
94% (major)
91% (minor)

J. Am. Chem. Soc. **2008**, 130, 14416.

Rawal Bifunctional Catalyst: Lewis base/Brønsted acid

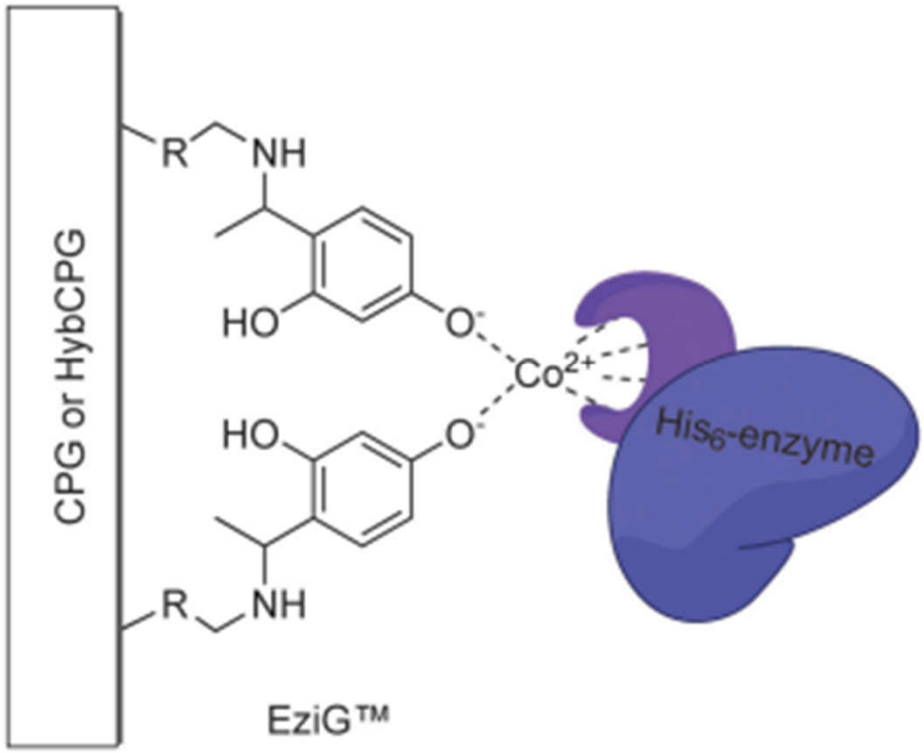


(S)-Pregablin (Lyrica®)



Bae and Song, *ACS Cat.* **2015**, 5, 3613.

Controlled Porosity Glass (CPG) Beads



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A general protein purification and immobilization method on controlled porosity glass: biocatalytic applications†

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K. Engelmark Cassimjee,*[a] M. Kadow,[a] Y. Wikmark,[a] M. Svedendahl Humble,[a] M. L. Rothstein,[b] D. M. Rothstein[b] and J.-E. Bäckvall*[a]

EnginZyme

Opal

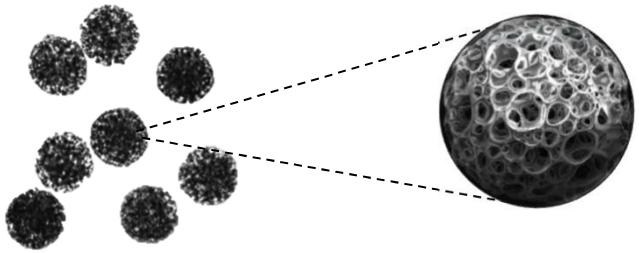
Hydrophilic derivatized silica surface

Amber

Semi-hydrophobic polystyrene derivative surface

Coral

Hydrophobic surface with poly(vinylbenzyl chloride) coating



Continuous Flow

Batch mode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Accounts and Rapid Communications in Chemical Synthesis
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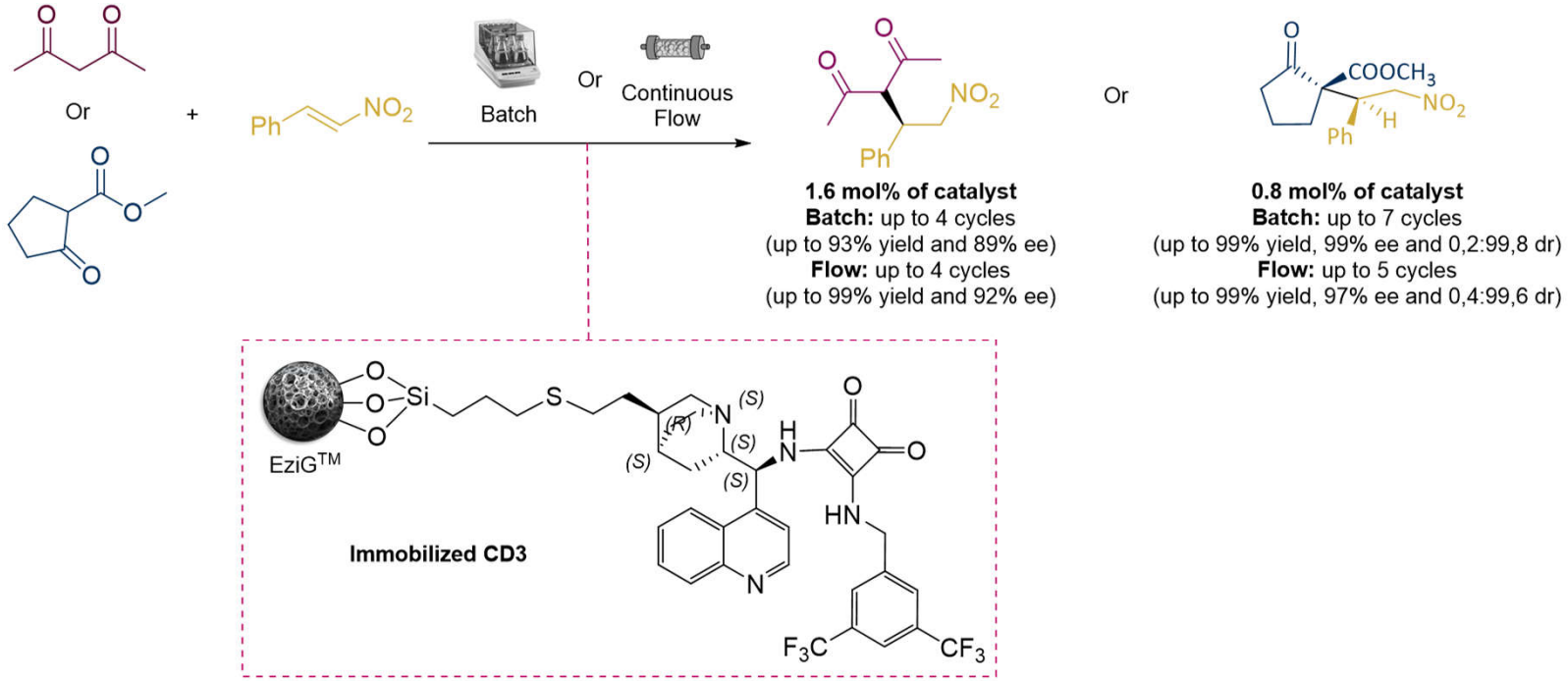
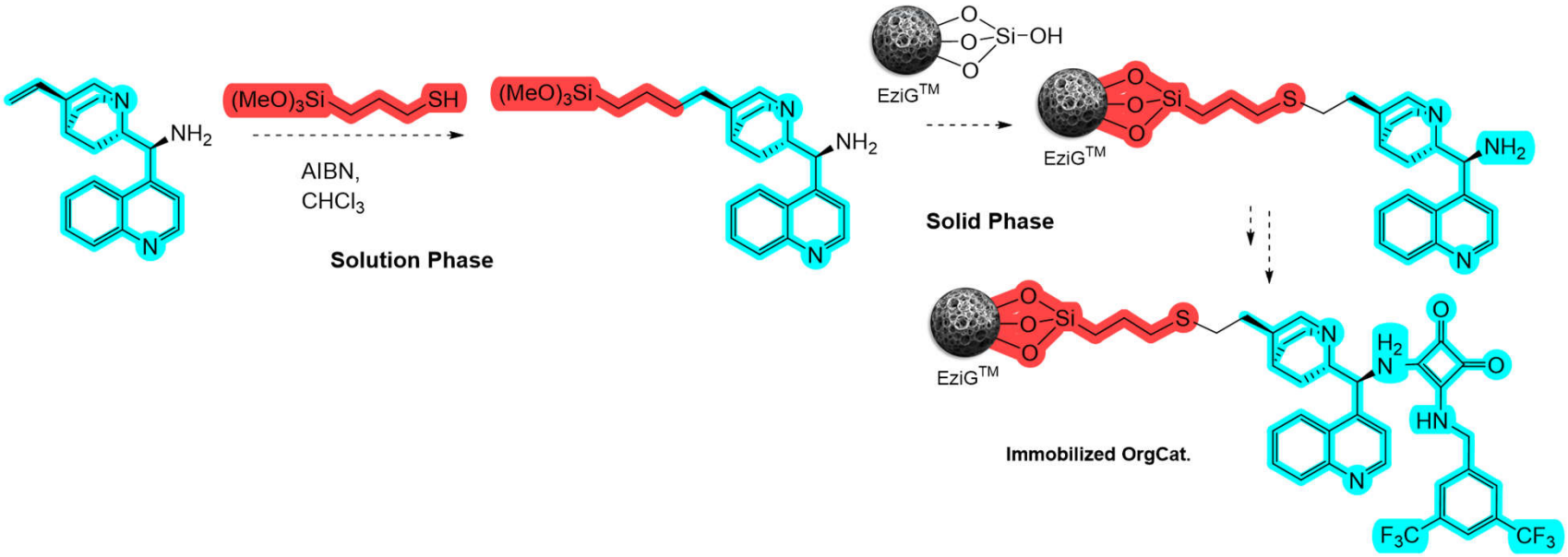
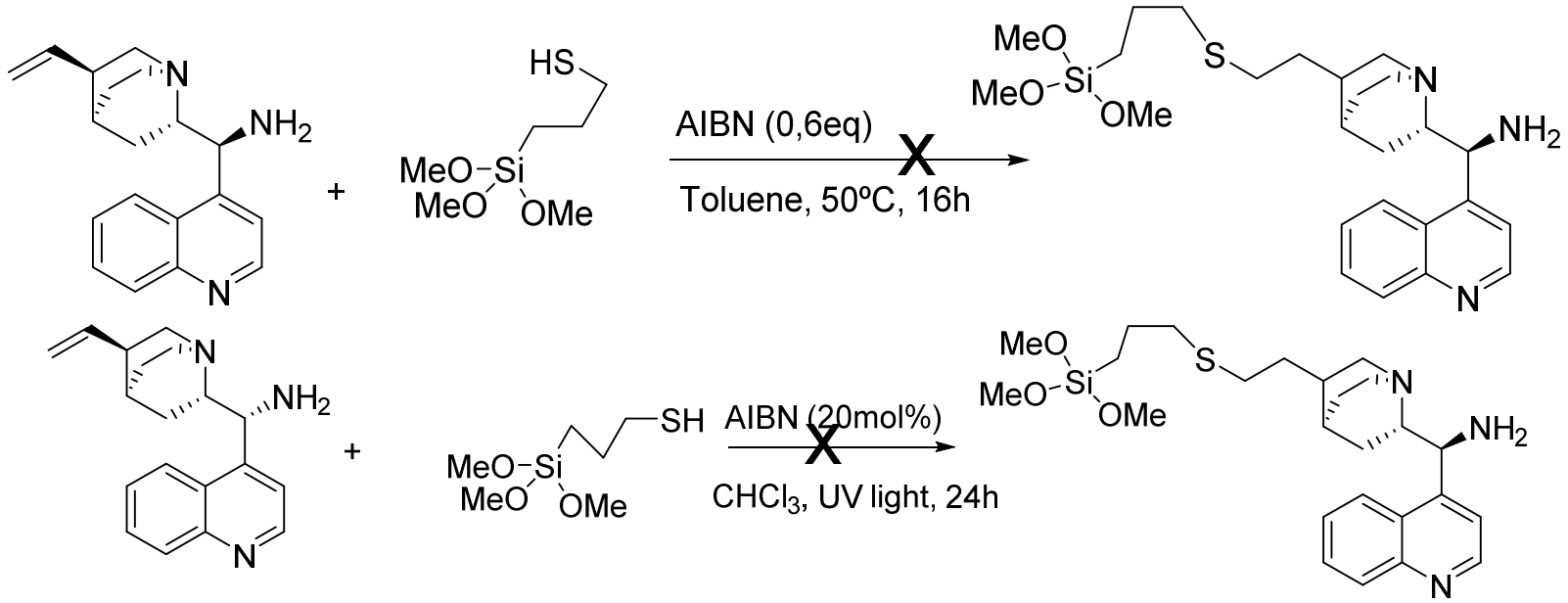
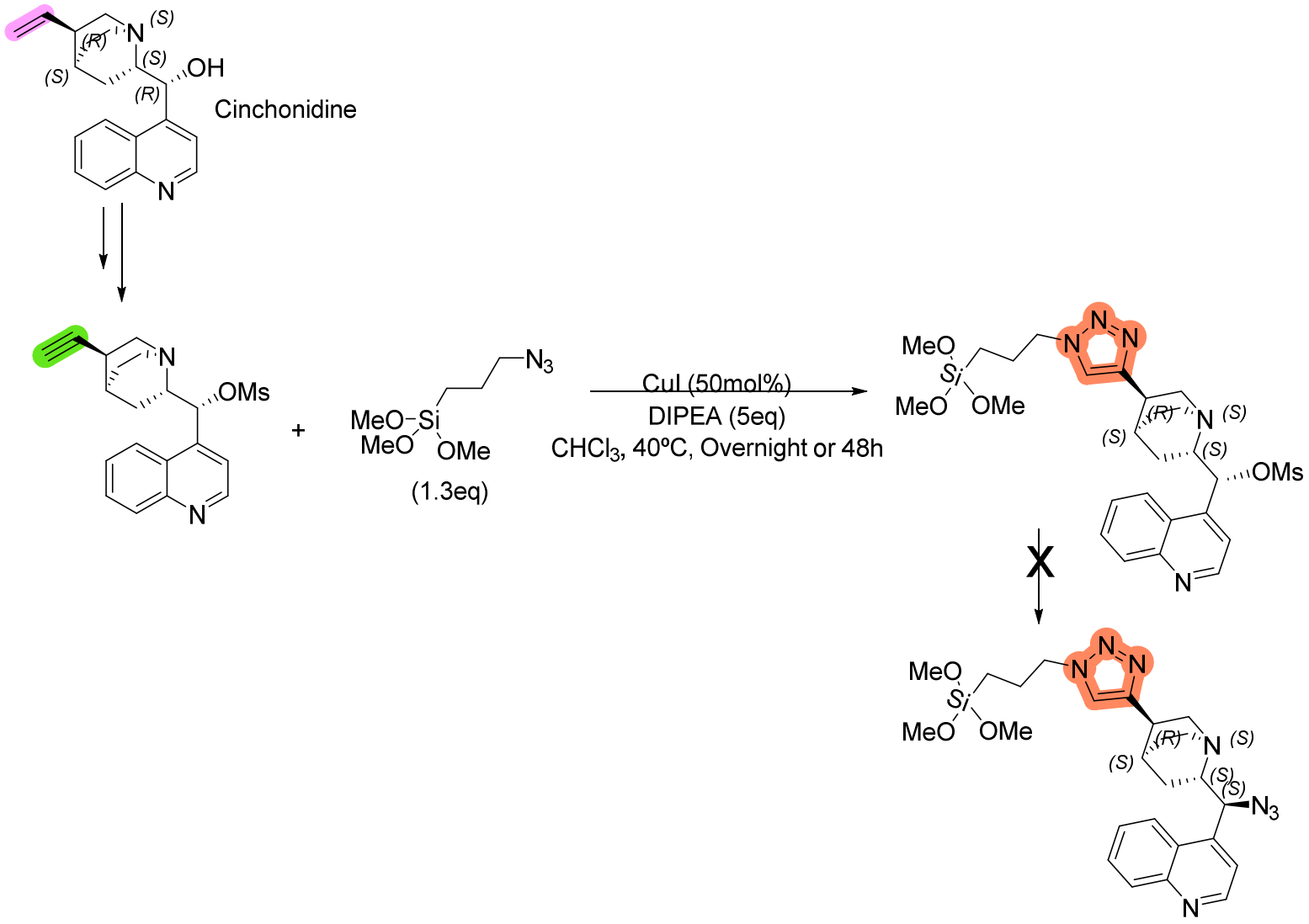
Thieme


Or
+
Ph
NO2
Batch
Or
Continuous Flow
Ph
NO2
Or
COOCH3
NO2
Ph
H
1.6 mol% of catalyst
Batch: up to 4 cycles
(up to 93% yield and 89% ee)
Flow: up to 4 cycles
(up to 99% yield and 92% ee)
0.8 mol% of catalyst
Batch: up to 7 cycles
(up to 99% yield, 99% ee and 0,2:99,8 dr)
Flow: up to 5 cycles
(up to 99% yield, 97% ee and 0,4:99,6 dr)
EziG™
Si
S
(S)
(R)
(S)
(S)
(S)
N
H
N
O
HN
N
F3C
CF3
Immobilized CD3


(MeO)3Si
SH
AIBN,
CHCl3
Solution Phase
EziG™
Si–OH
Solid Phase
Immobilized OrgCat.
NH2
HN
F3C
CF3


HS
MeO
Si
OMe
AIBN (0,6eq)
Toluene, 50ºC, 16h
AIBN (20mol%)
CHCl3, UV light, 24h
NH2
S
N


Cinchonidine
OMs
MeO–Si
MeO
OMe
(1.3eq)
N3
CuI (50mol%)
DIPEA (5eq)
CHCl3, 40ºC, Overnight or 48h
MeO
Si
MeO
OMe
OMs
N3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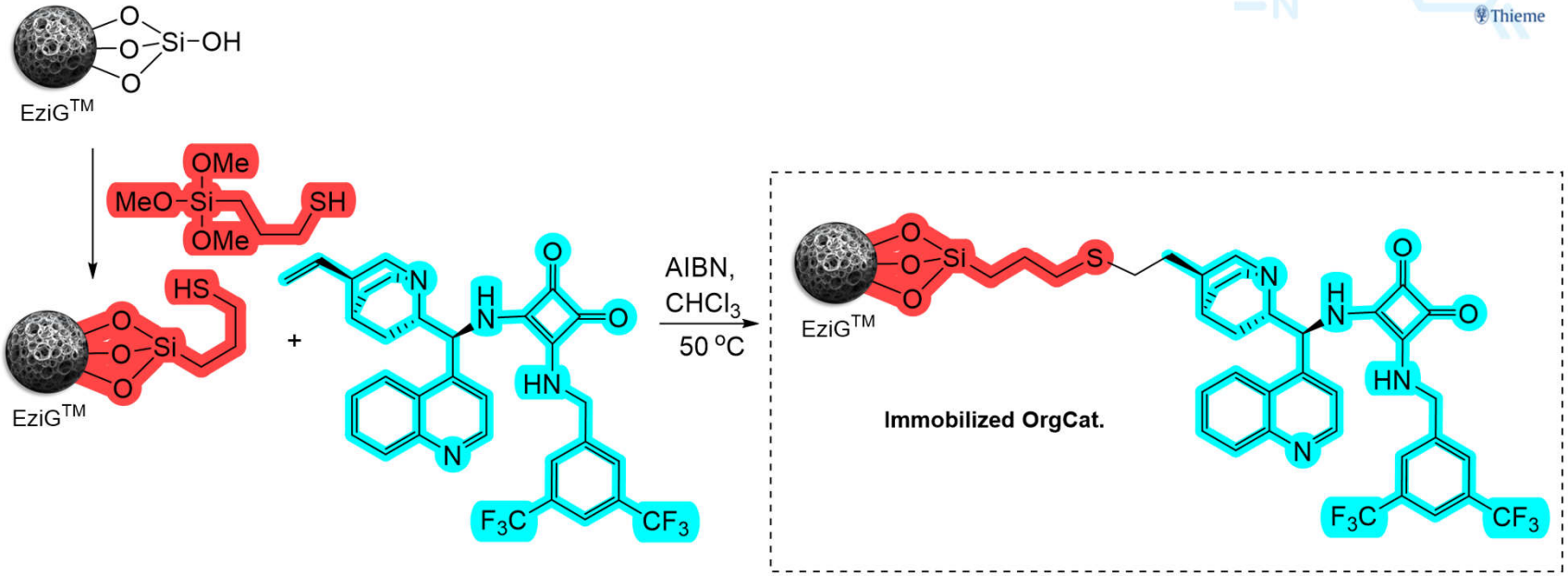
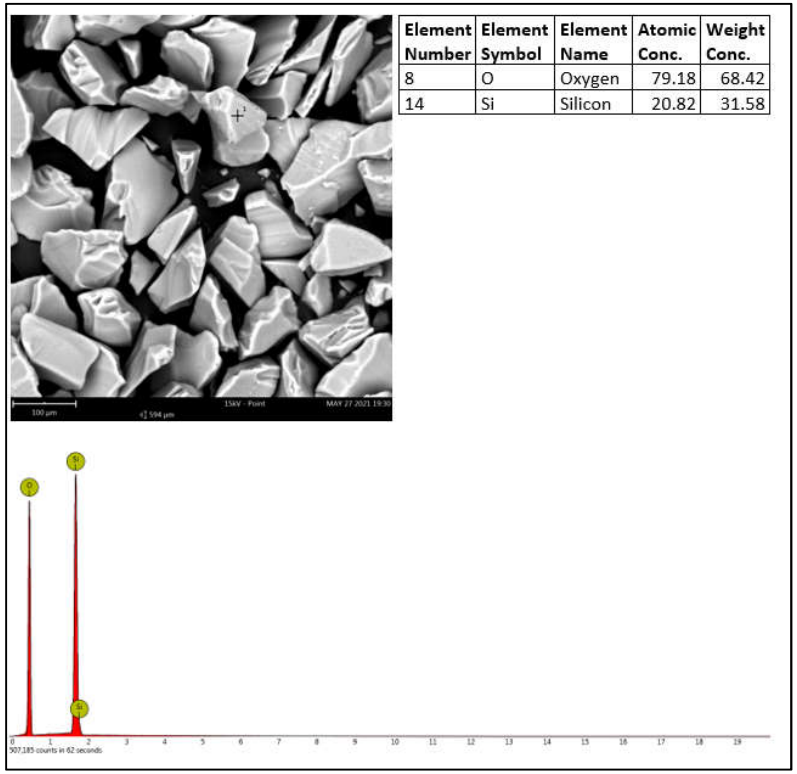
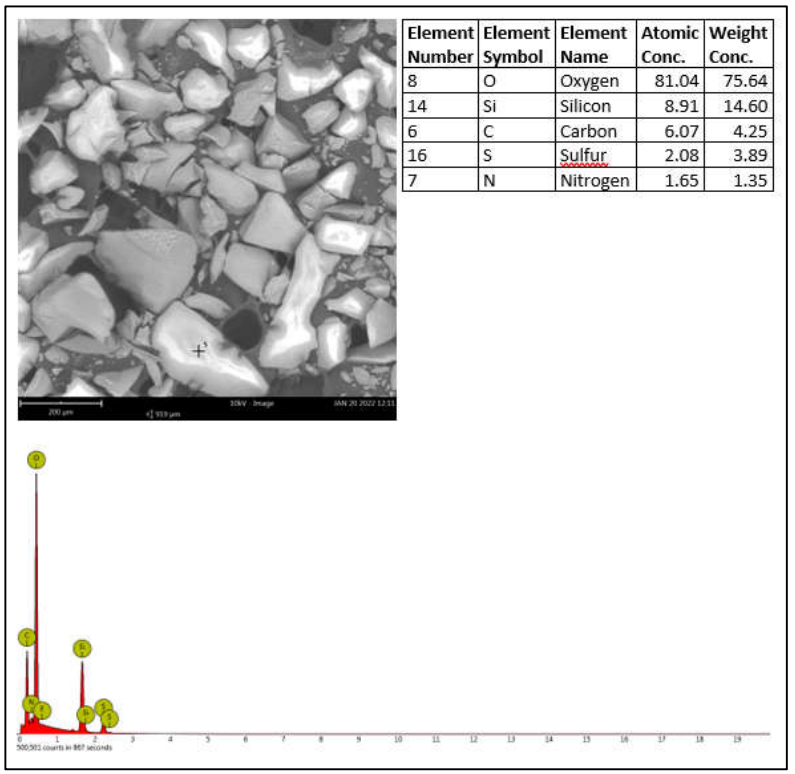
17
Thieme


EziG™
Si–OH
OMe
MeO–Si
OMe
SH
HS
EziG™
+
AIBN,
CHCl3
50 °C
EziG™
Immobilized OrgCat.



Element Number	Element Symbol	Element Name	Atomic Conc.	Weight Conc.
8	O	Oxygen	79.18	68.42
14	Si	Silicon	20.82	31.58

Without catalyst on amber (SEM)



Element Number	Element Symbol	Element Name	Atomic Conc.	Weight Conc.
8	O	Oxygen	81.04	75.64
14	Si	Silicon	8.91	14.60
6	C	Carbon	6.07	4.25
16	S	Sulfur	2.08	3.89
7	N	Nitrogen	1.65	1.35

With catalyst on amber (SEM)

Synlett **2022**, 33(17) 1756

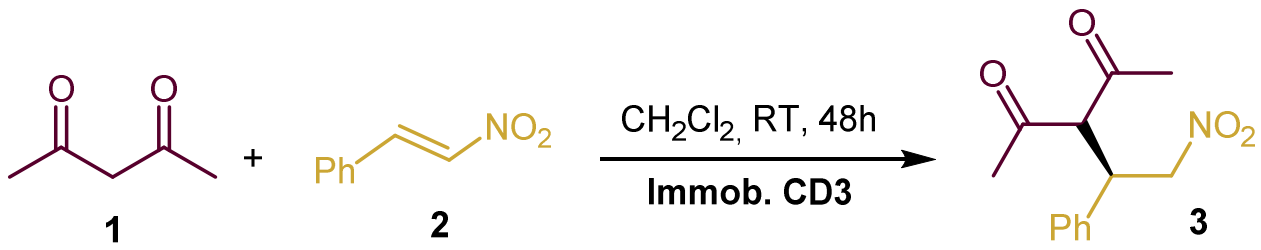


TABLE 1

Entry	Immobilized OrgCat	f (mmol g^{-1})	Amount of beads used (g)	Cycles	Yield (%)	ee (%)
1	OCD3 (OPAL)	0.05176	0.055	1	86	89
2				2	93	84
3				3	56	31
4				4	22	77
5	ACD3 (AMBER)	0.13386	0.030	1	54	87
6				2	1	65
7	CCD3 (CORAL)	0.14457	0.028	1	53	78
8				2	6	55

$$f\ (\text{mmol g}^{-1}) = \%N \times 1000 \times (\text{number of N atoms})^{-1} \times MW(N)^{-1} \times 100^{-1}$$

(*Chem. Sci.* **2019**, *10*, 11141)

Synlett **2022**, 33(17) 1756.

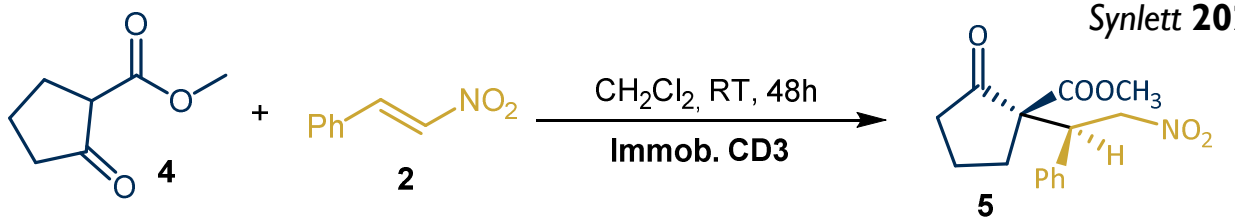


TABLE 2

Entry	Immobilized catalyst	f (mmol g^{-1})	Cycles	Yield (%)	ee (%)	dr
1	**OCD3**	0.05176	1	88	99	0.3:99.7
2			2	98	95	0.4:99.6
3			3	99	63	0.8:99.2
4			4	99	86	0.2:99.8
5			5	97	96	0.3:99.7
6			6	47	>99	1.2:98.8
7			7	62	97	1.6:98.4
8	**ACD3**	0.12493	1	84	92	0.1:99.9
9			2	66	88	0.3:99.7
10			3	53	77	1.4:98.6
11	**CCD3**	0.07853	1	83	93	0.2:99.8
12			2	60	81	0.2:99.8
13			3	21	79	1.5:98.5

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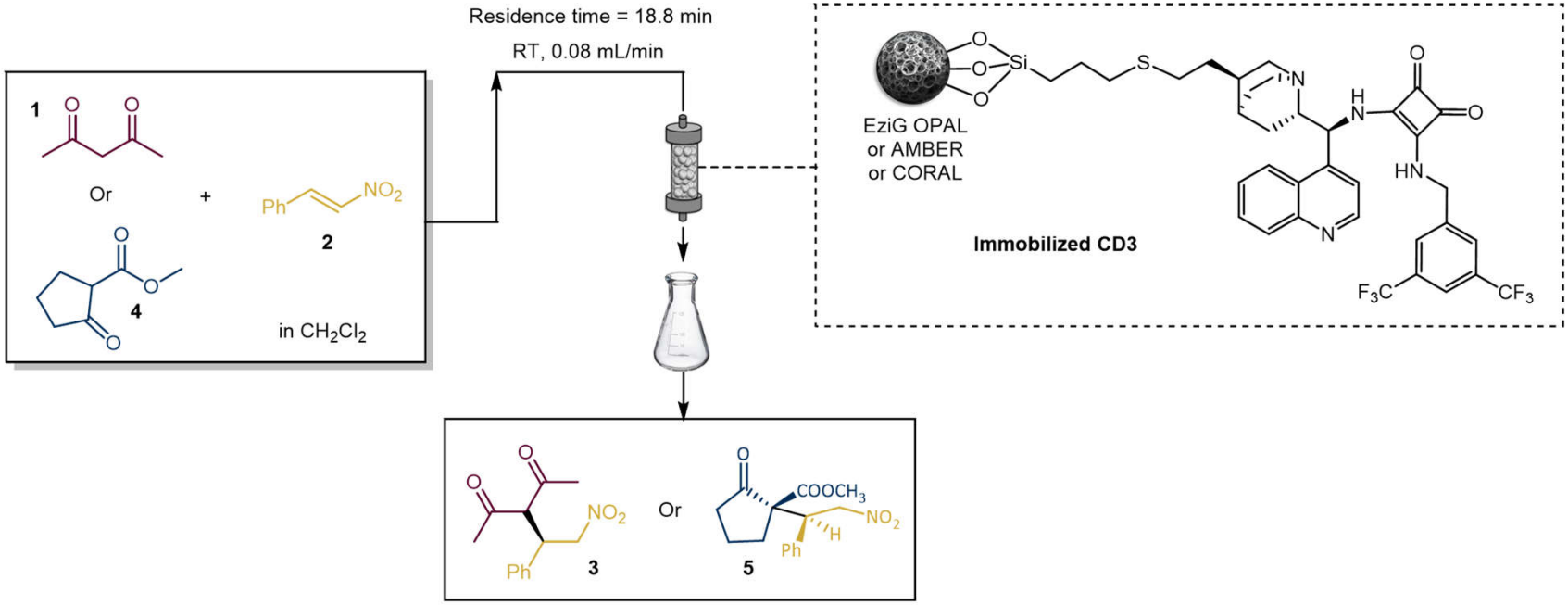


Synlett **2022**, 33(17) 1756.

Table 3

Entry	Immob. Org Cat.	f (mmol g^{-1})	Amount of Beads used (g)	Cycles	Yield (%	ee (%)
1	OCD3	0.08567	0.277	1	10	69
2				2	68	86
3				3	-[g]	-[g]
4	ACD3	0.12493	0.173	1	66	95
5				2	29	95
6				3	13	47
7	CCD3	0.07853	0.179	1	99	92
8				2	87	91
9				3	23	88
10[c]				4	16	61

[g] Contained impurities

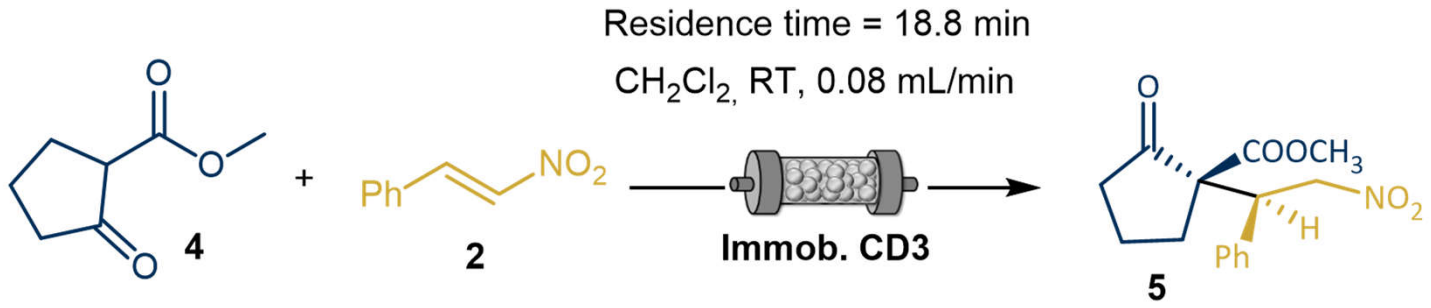
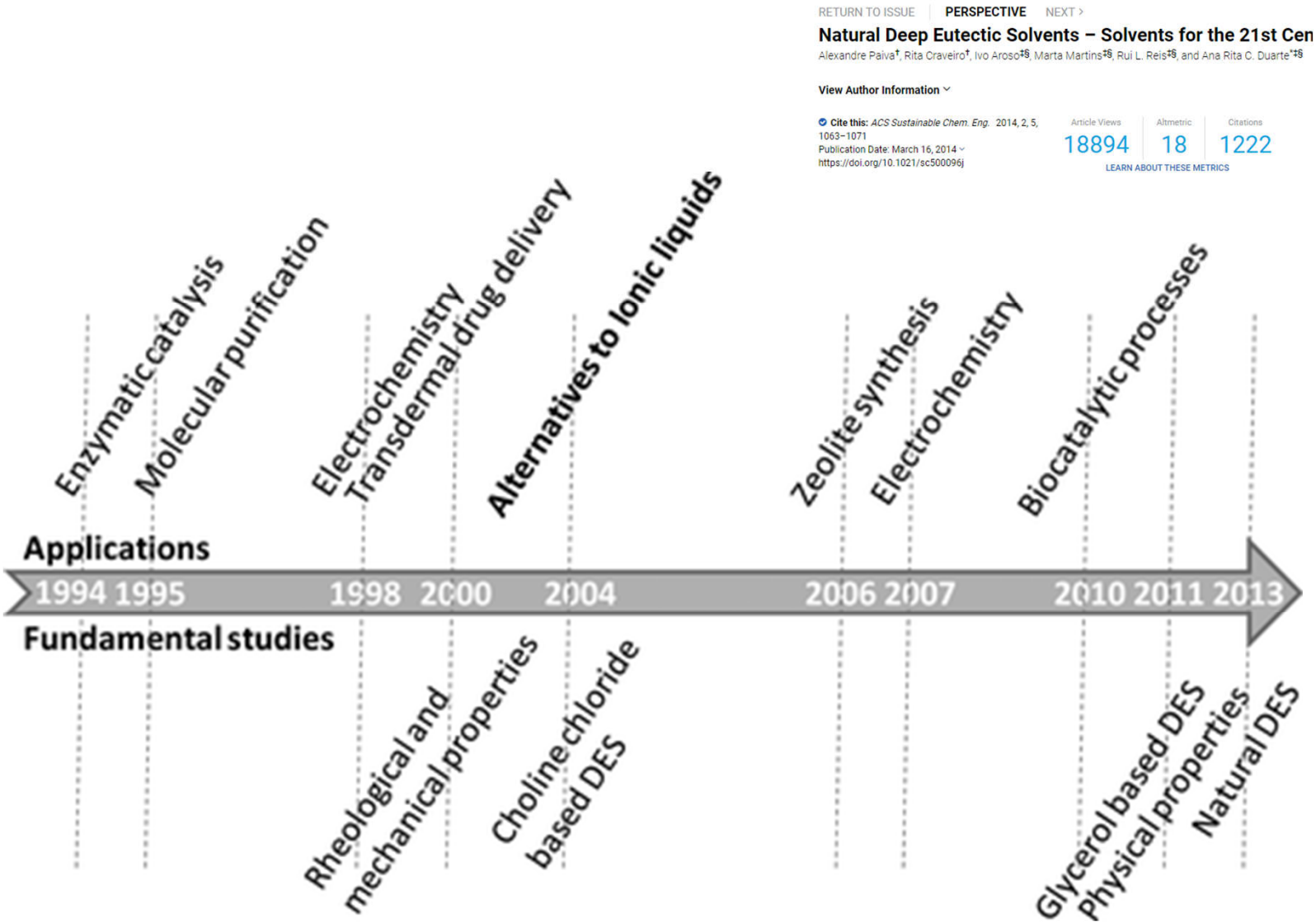


Table 4							
Entry	**Immob. OrgCat**	**f (mmol g^{-1})**	**Amount of Beads used (g)**	**Cycles**	**Yield (%)**	**ee (%)**	**dr**
1	**OCD3**	0.08567	0.442	1	24	-[g]	-[g]
2	**ACD3**	0.15706	0.286	1	99	-[g]	-[g]
3				2	30	-[g]	-[g]
4				3	10	-[g]	-[g]
5	**CCD3**	0.07853	0.183	1	99	95	0.6:99.4
6				2	38	94	0.8:99.2
7				3	47	92	1.3:98.7
8				4	43	86	4.9:95.1
9				5	28	97	0.4:99.6

[g] Contained impurities

DEEP EUTECTIC SOLVENTS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PERSPECTIVE
NEXT >
Natural Deep Eutectic Solvents – Solvents for the 21st Cen
Alexandre Paiva†, Rita Craveiro†, Ivo Aroso‡§, Marta Martins‡§, Rui L. Reis‡§, and Ana Rita C. Duarte*‡§
View Author Information
Cite this: ACS Sustainable Chem. Eng. 2014, 2, 5, 1063−1071
Publication Date: March 16, 2014
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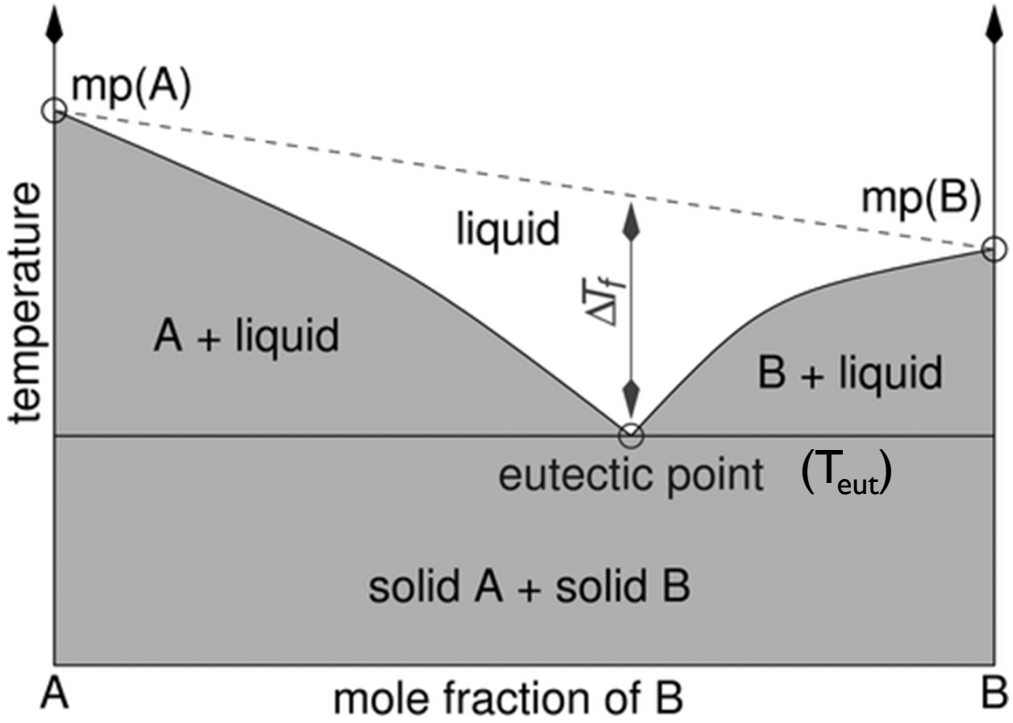
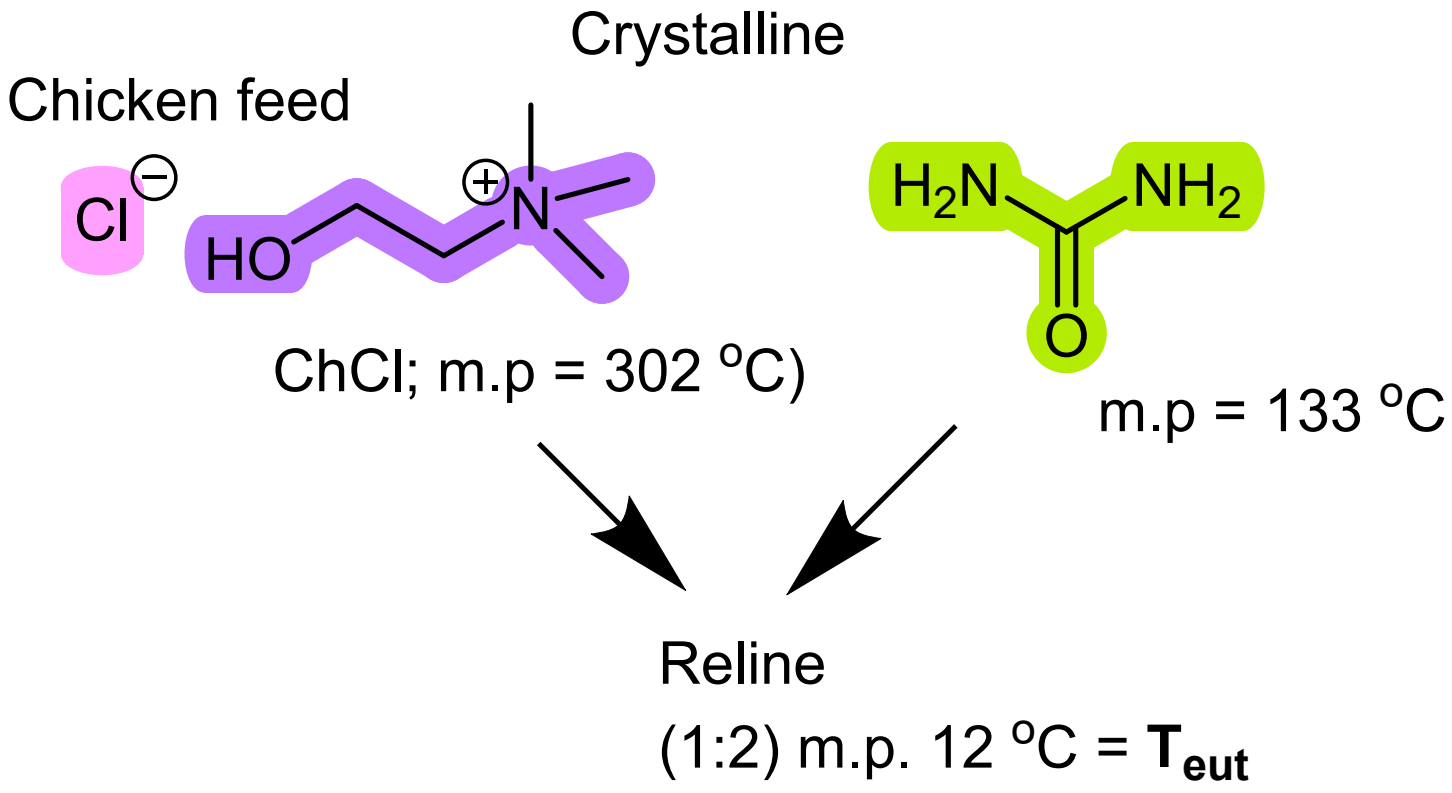
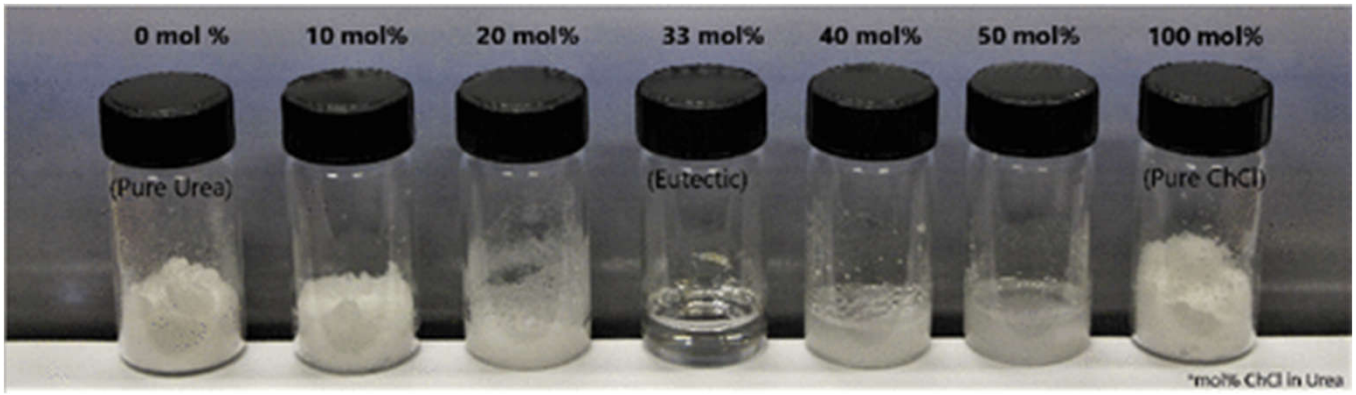

mp(A)
mp(B)
liquid
ΔT_f
A + liquid
B + liquid
temperature
eutectic point (T_{eut})
solid A + solid B
A
mole fraction of B
B


Crystalline
Chicken feed
Cl
HO
N
ChCl; m.p = 302 °C)
H2N
NH2
O
m.p = 133 °C
Reline
(1:2) m.p. 12 °C = Teut

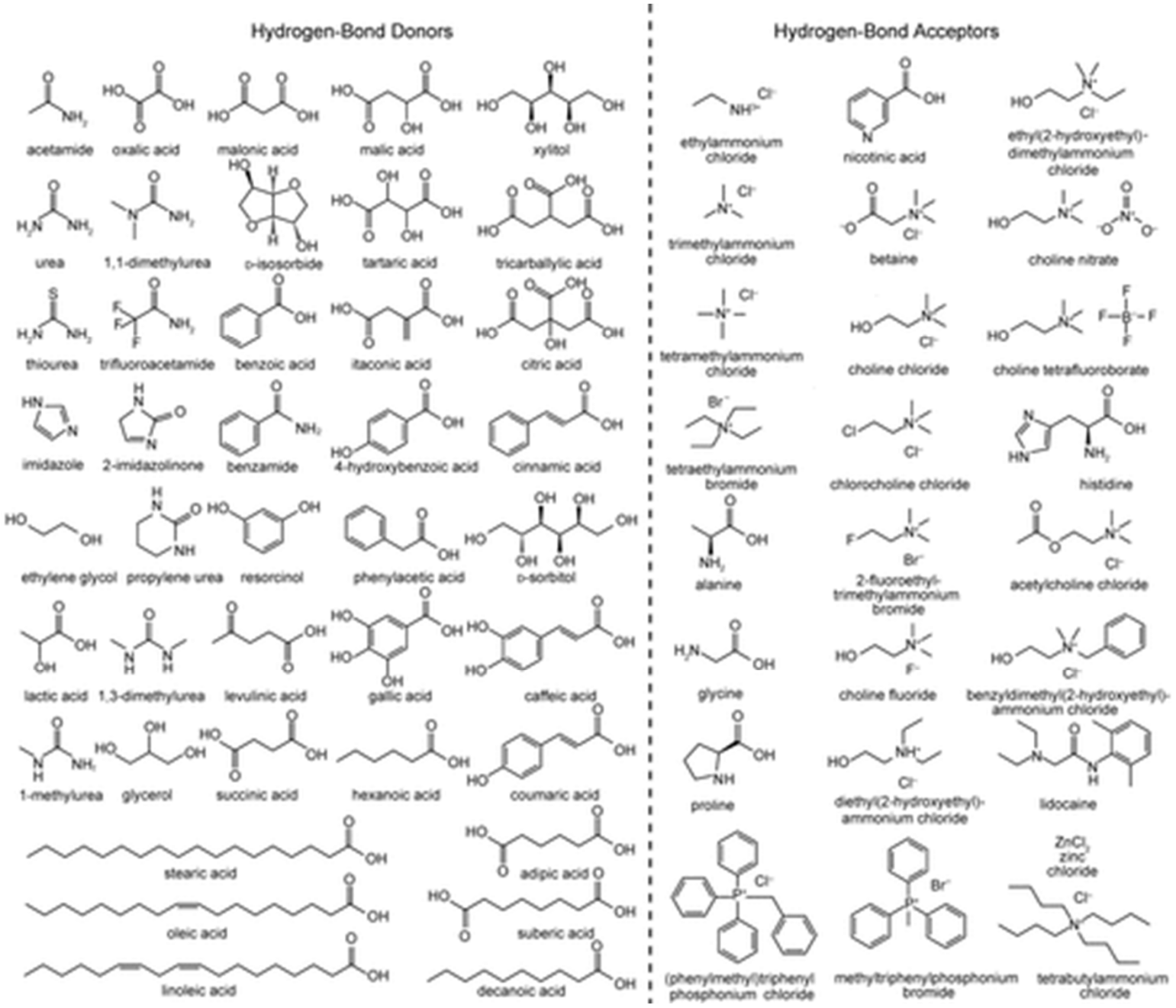
Deep Eutectic Solvents: A Review of Fundamentals and Applications

Benworth B. Hansen, Stephanie Spittle, Brian Chen, Derrick Poe, Yong Zhang, Jeffrey M. Klein, Alexandre Horton, Laxmi Adhikari, Tamar Zelovich, Brian W. Doherty, Burcu Gurkan, Edward J. Maginn, Arthur Ragauskas, Mark Dadmun, Thomas A. Zawodzinski, Gary A. Baker, Mark E. Tuckerman, Robert F. Savinell, and Joshua R. Sangoro*

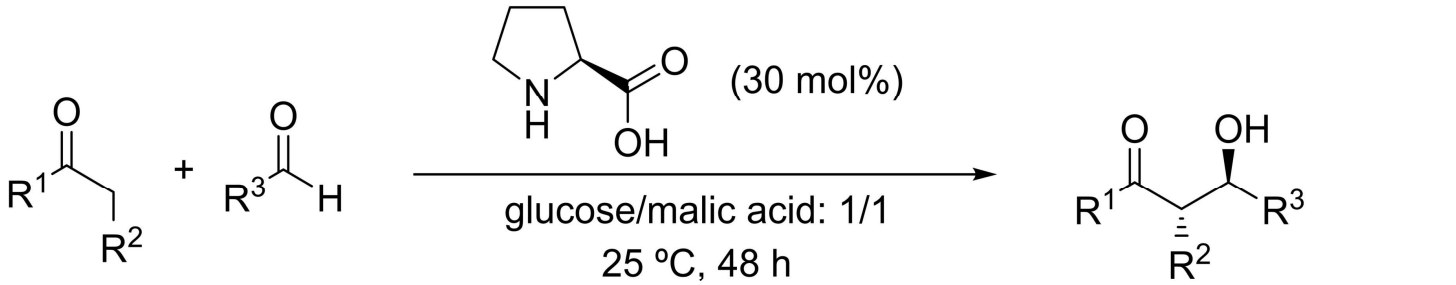
Cite this: *Chem. Rev.* 2021, 121, 3, 1232−1285
Publication Date: December 14, 2020
https://doi.org/10.1021/acs.chemrev.0c00385



Choline chloride + urea mixtures at 303 K (mol % ChCl, left to right −0, 10, 20, 33 (χ_{eut}), 40, 50, 100). The lowest observed melting point for this binary mixture occurs at a 1:2 ratio and has a melting point of 12 °C, *eutectic composition* (χ_{eut}).


Hydrogen-Bond Donors
acetamide
oxalic acid
malonic acid
malic acid
xylitol
urea
1,1-dimethylurea
d-isosorbide
tartaric acid
tricarballylic acid
thiourea
trifluoroacetamide
benzoic acid
itaconic acid
citric acid
imidazole
2-imidazolinone
benzamide
4-hydroxybenzoic acid
cinnamic acid
ethylene glycol
propylene urea
resorcinol
phenylacetic acid
d-sorbitol
lactic acid
1,3-dimethylurea
levulinic acid
gallic acid
caffeic acid
1-methylurea
glycerol
succinic acid
hexanoic acid
coumaric acid
stearic acid
adipic acid
oleic acid
suberic acid
linoleic acid
decanoic acid
Hydrogen-Bond Acceptors
ethylammonium chloride
nicotinic acid
ethyl(2-hydroxyethyl)-dimethylammonium chloride
trimethylammonium chloride
betaine
choline nitrate
tetramethylammonium chloride
choline chloride
choline tetrafluoroborate
tetraethylammonium bromide
chlorocholine chloride
histidine
alanine
2-fluoroethyl-trimethylammonium bromide
acetylcholine chloride
glycine
choline fluoride
benzyldimethyl(2-hydroxyethyl)-ammonium chloride
proline
diethyl(2-hydroxyethyl)-ammonium chloride
lidocaine
(phenylmethyl)triphenyl phosphonium chloride
methyltriphenylphosphonium bromide
ZnCl2 zinc chloride
tetrabutylammonium chloride

Benaglia

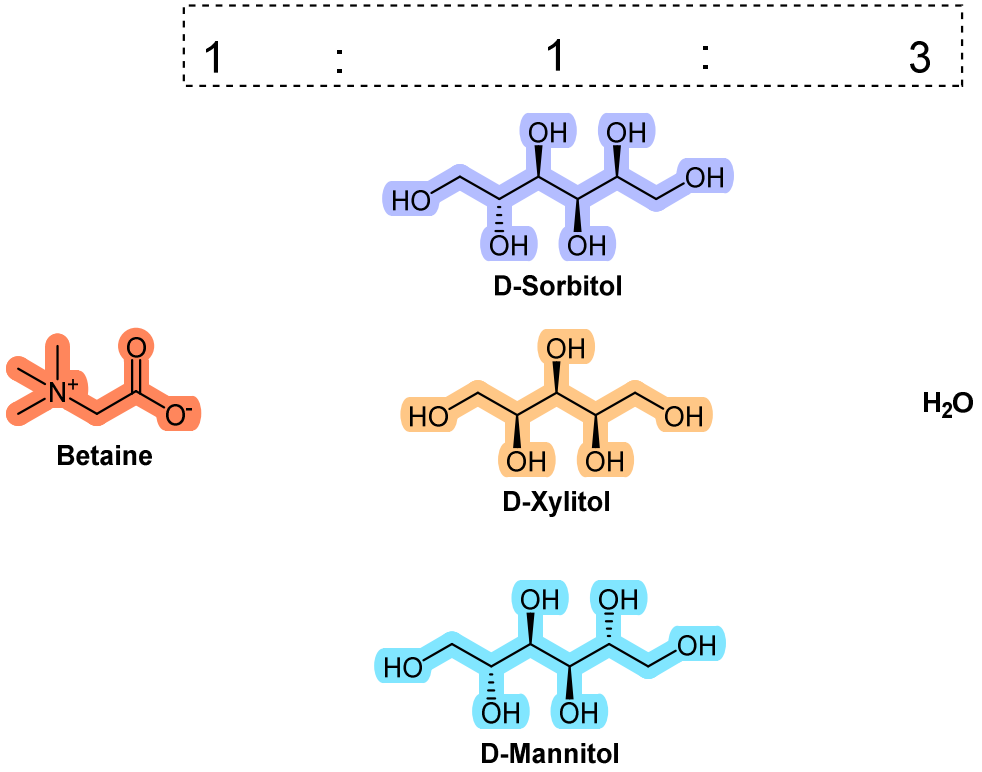


R^1-R^2 = $(CH_2)_5$, $(CH_2)_4$, $(CH_2)_2SCH_2$

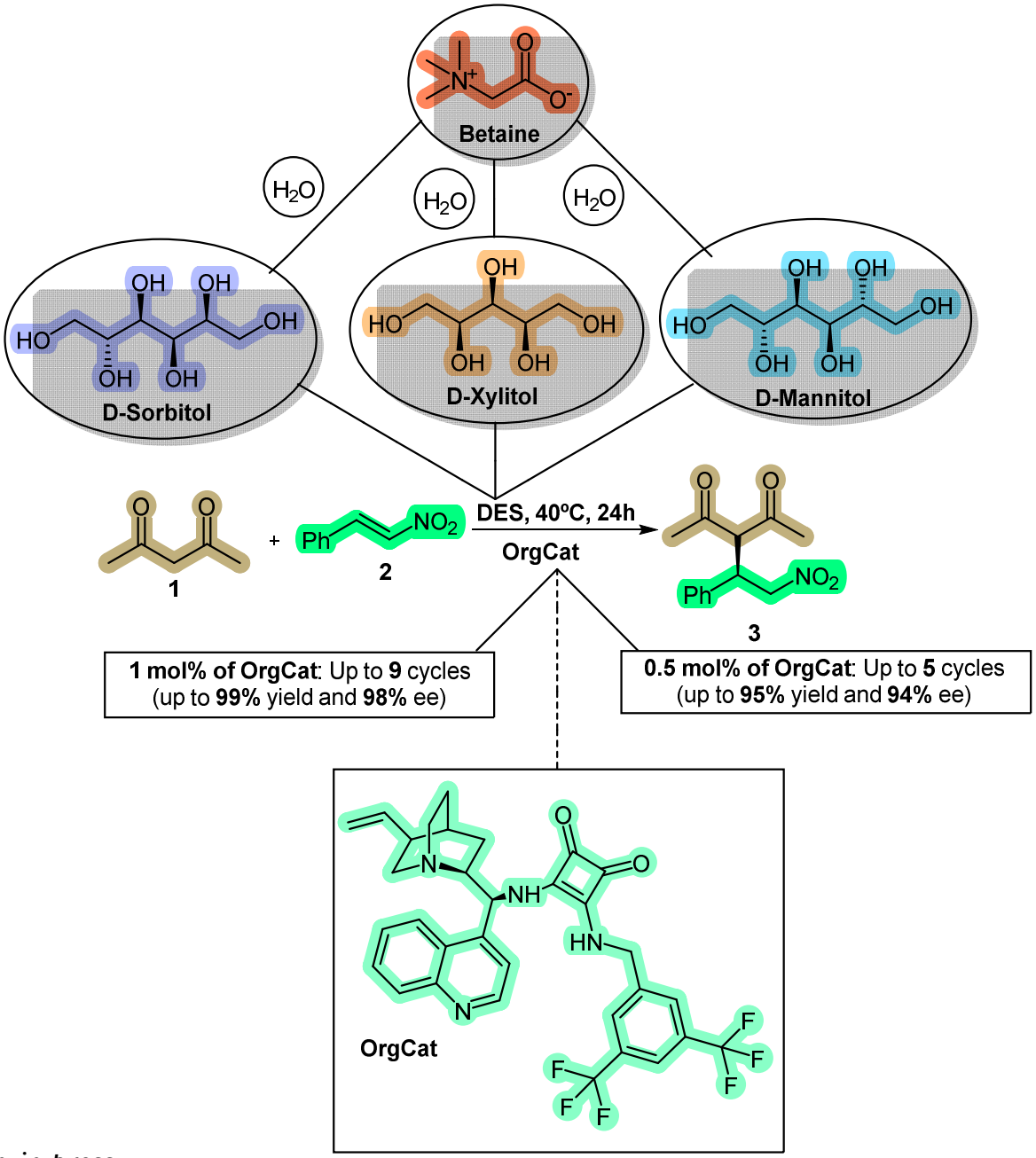
R^1 = Me ; R^2 = OH

R^3 = 4-$O_2NC_6H_4$, 4-$CF_3C_6H_4$, 2-ClC_6H_4, 4-FC_6H_4, $Me(CH_2)_9$

Beilstein J. Org. Chem. **2016**, 12, 2620. Benaglia



Chiral DESs



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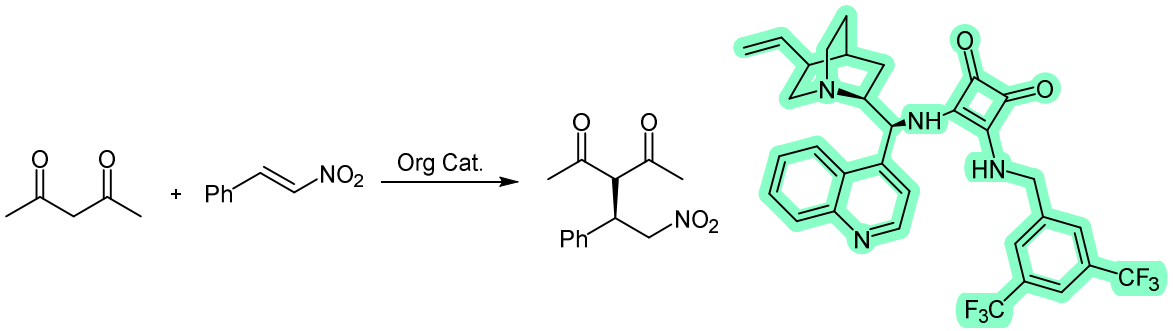


Cinchona-Squaramide

TABLE 1

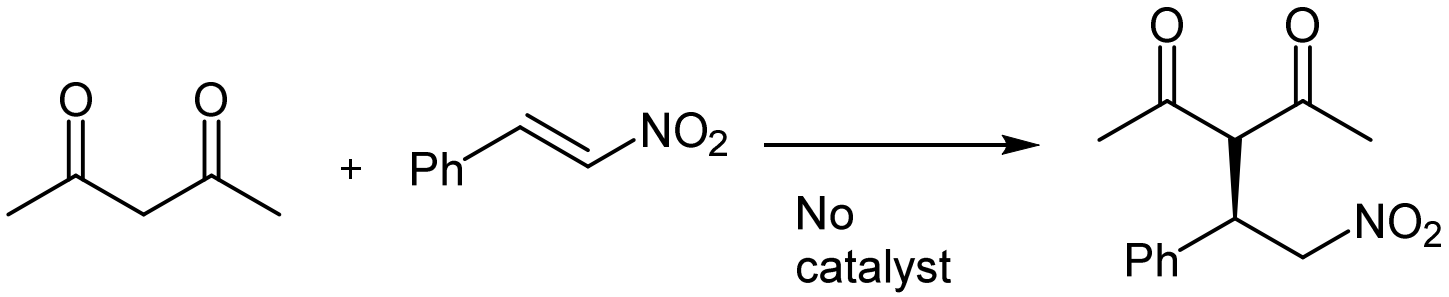
Entry	DES	Catalyst (loading)	Cycle	Yield(%)	ee (%)
1	Betaine: D-Sorbitol: Water	(5 mol%)	1	≥99	97
2			2	≥99	62
3			3	≥99	70
4			4	≥99	95
5			5	97	82
6			6	98	90
7			7	≥99	94
8			8	95	90
9			9	88	62

Fonseca, *SynOpen, in press.*

TABLE 2					
Entry	DES	Catalyst (loading)	Cycle	*Yield* (%)	ee (%)
1	Betaine: D-Sorbitol: Water	(1 mol%)	1	≥99	98
2			2	≥99	69
3			3	≥99	66
4			4	94	79
5			5	95	93
6			6	93	75
7			7	99	60
8			8	94	29
9			9	81	17

TABLE 3					
Entry	DES	Catalyst (loading)	Cycle	Yield (%)	ee (%)
1	Betaine: D-Xylitol: Water	(0.5 mol%)	1	96	87
2			2	91	93
3			3	89	63
4			4	98	10
5		(1 mol%)	1	98	92
6			2	93	67
7			3	90	93
8			4	86	84

TABLE 4					
Entry	DES	Catalyst (loading)	Cycle	*Yield* (%)	ee (%)
1	Betaine: D-Mannitol :Water	(0.5 mol%)	1	57	83
2			2	35	73
3			3	55	99
4			4	67	≥99
5		(1 mol%)	1	19	52
6			2	64	78
7			3	87	87



Back-ground asymmetric catalysis

TABLE 5				
Entry	**DES**	**RATIO**	**Yield(%)**	**ee (%)**
1	Betaine: D-Xylitol: Water	1:1:3	81	75
2			53	3
3			51	3

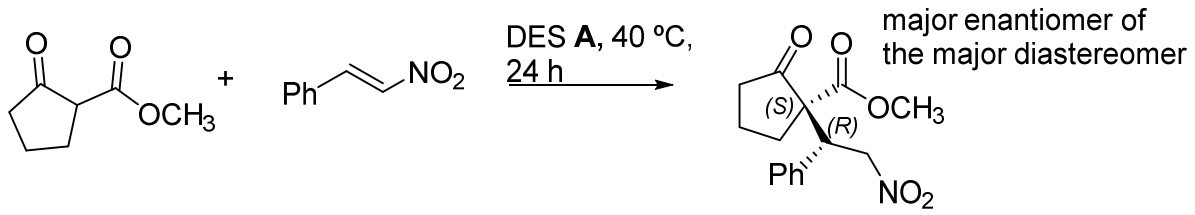
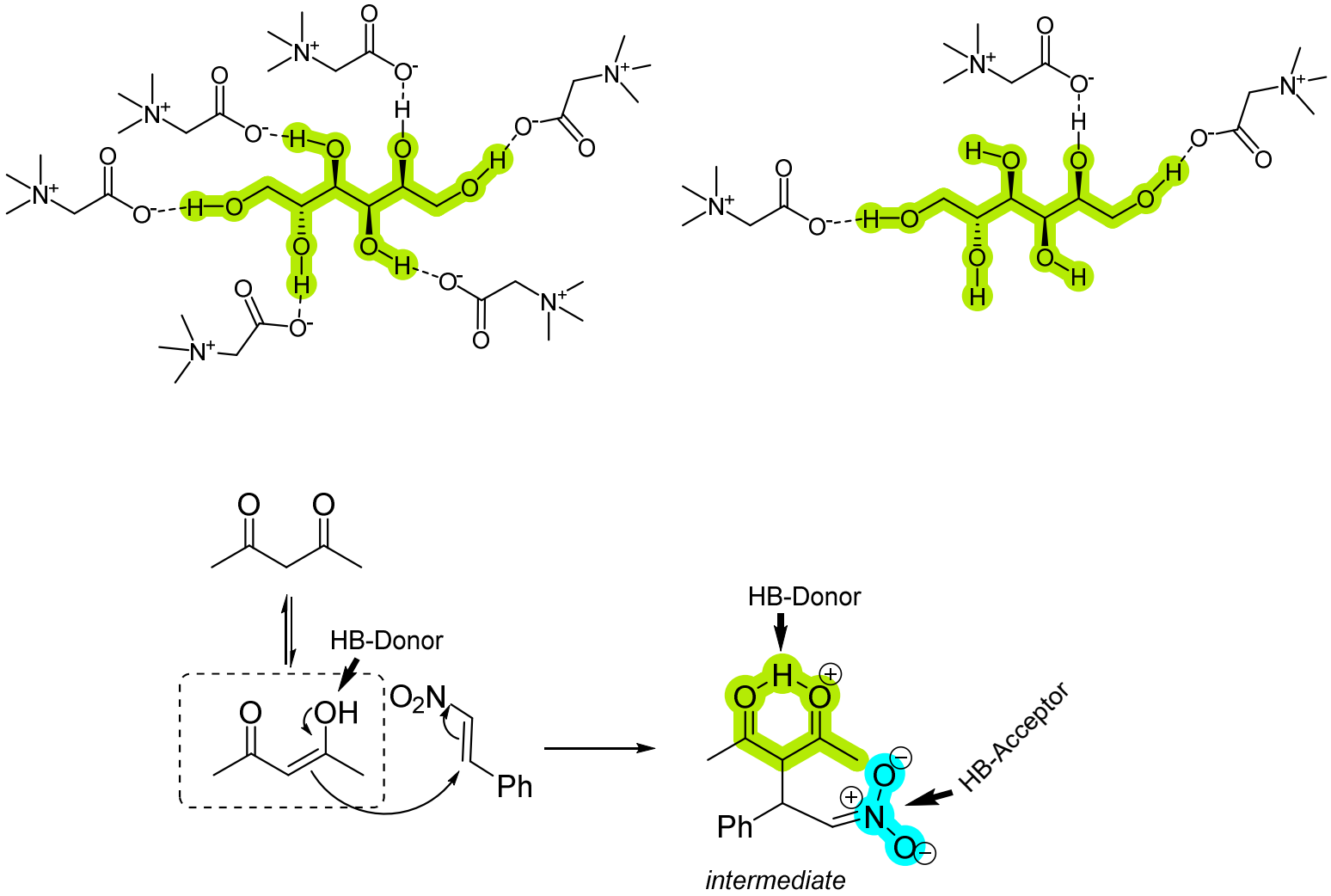
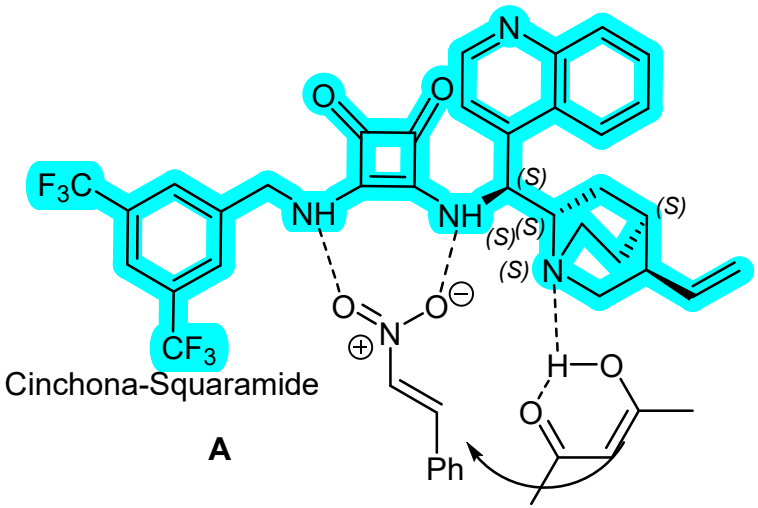
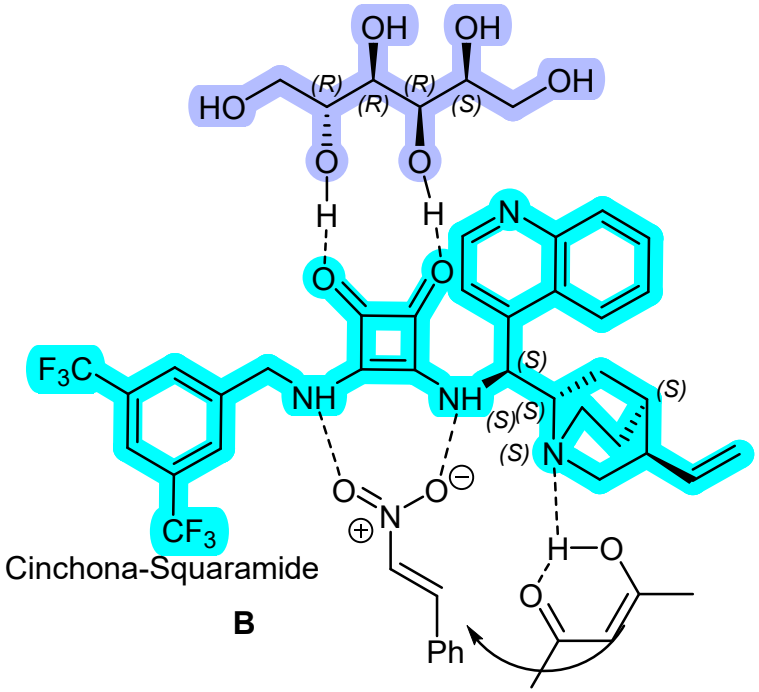


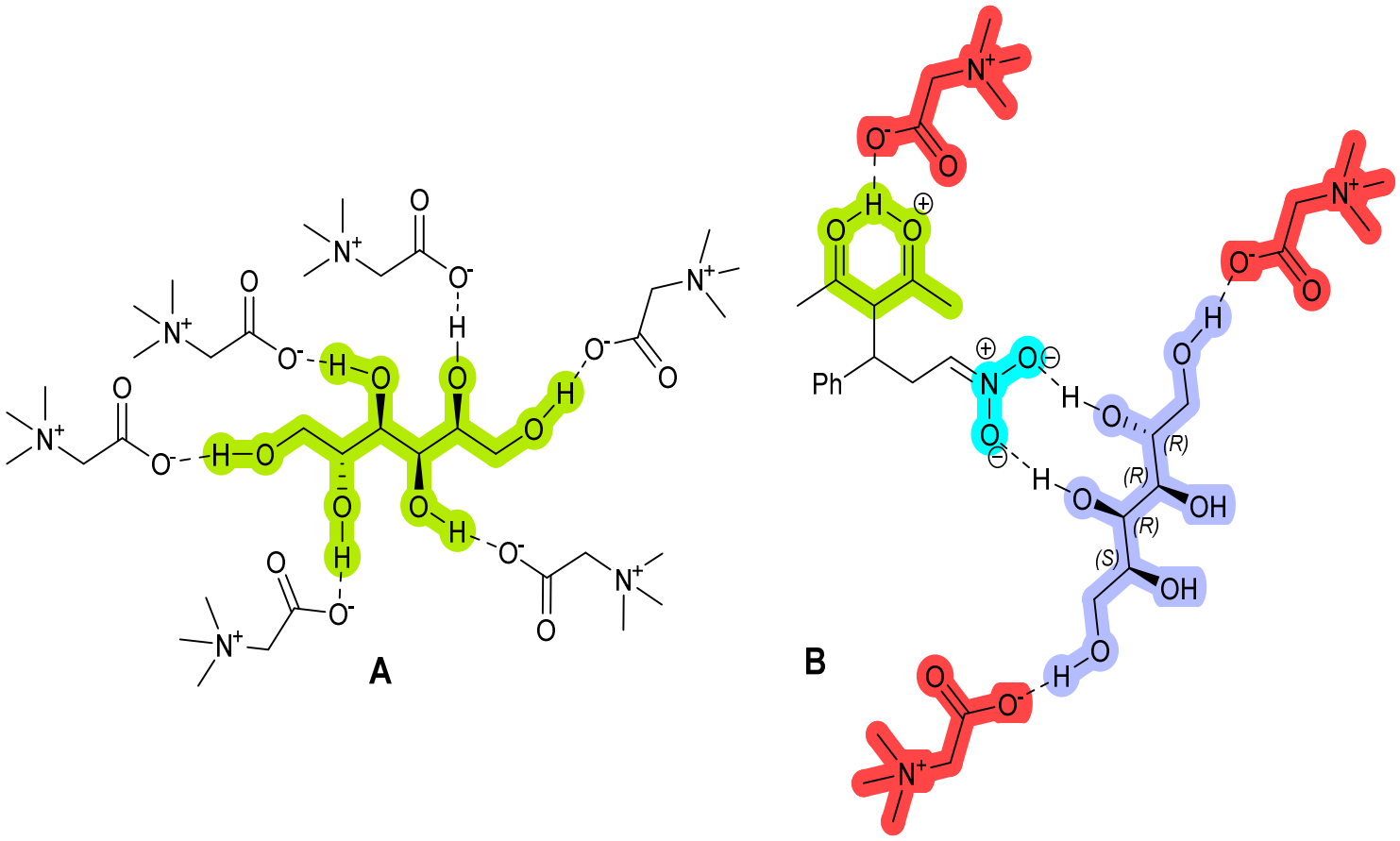
TABLE 6						
Entry	DES A	Catalyst (loading)	Cycle	**Yield** (%)[b]	de (%)[c]	ee (%)[c]
1	Betaine: D-Sorbitol: Water	none	-	99	58	rac
2		(1 mol%)	1	99	73	94
3			2	99	92	86
4			3	99	93	84
5			4	99	92	92
6			5	99	94	88
7			6	56	94	96
8			7	98	94	93
9			8	97	97	94
10			9	98	97	95
11			10	97	97	93

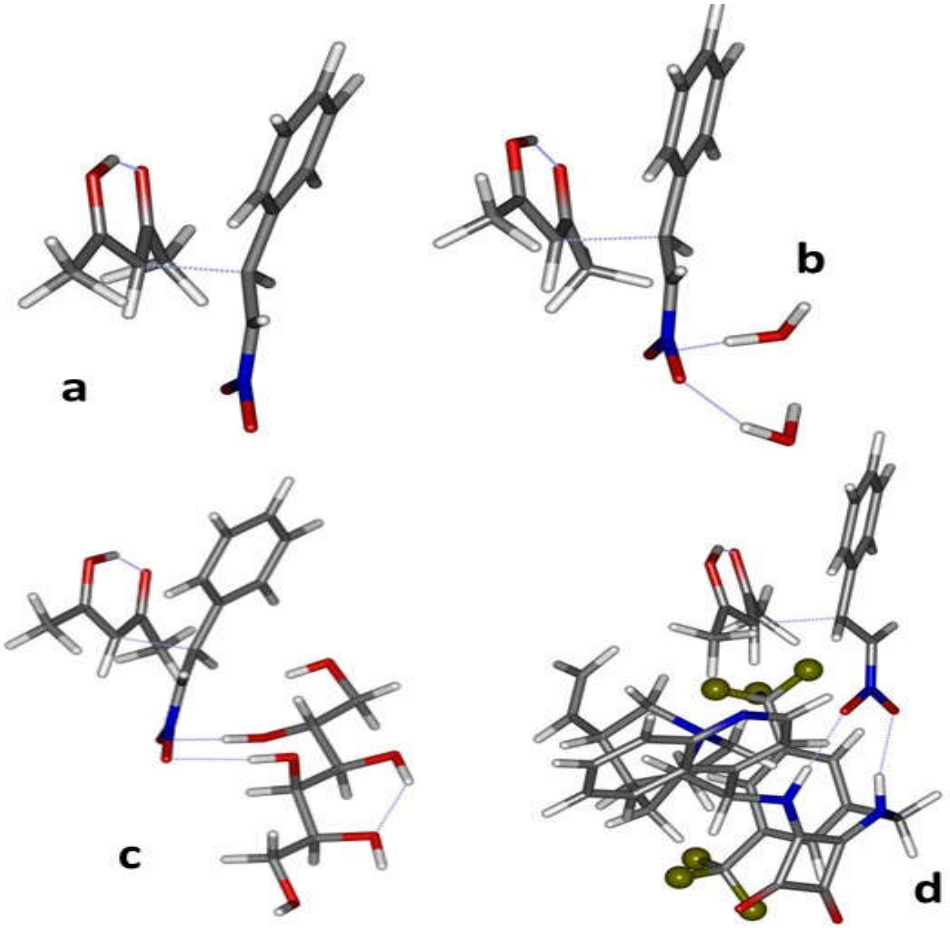


Transition state stabilization via DES

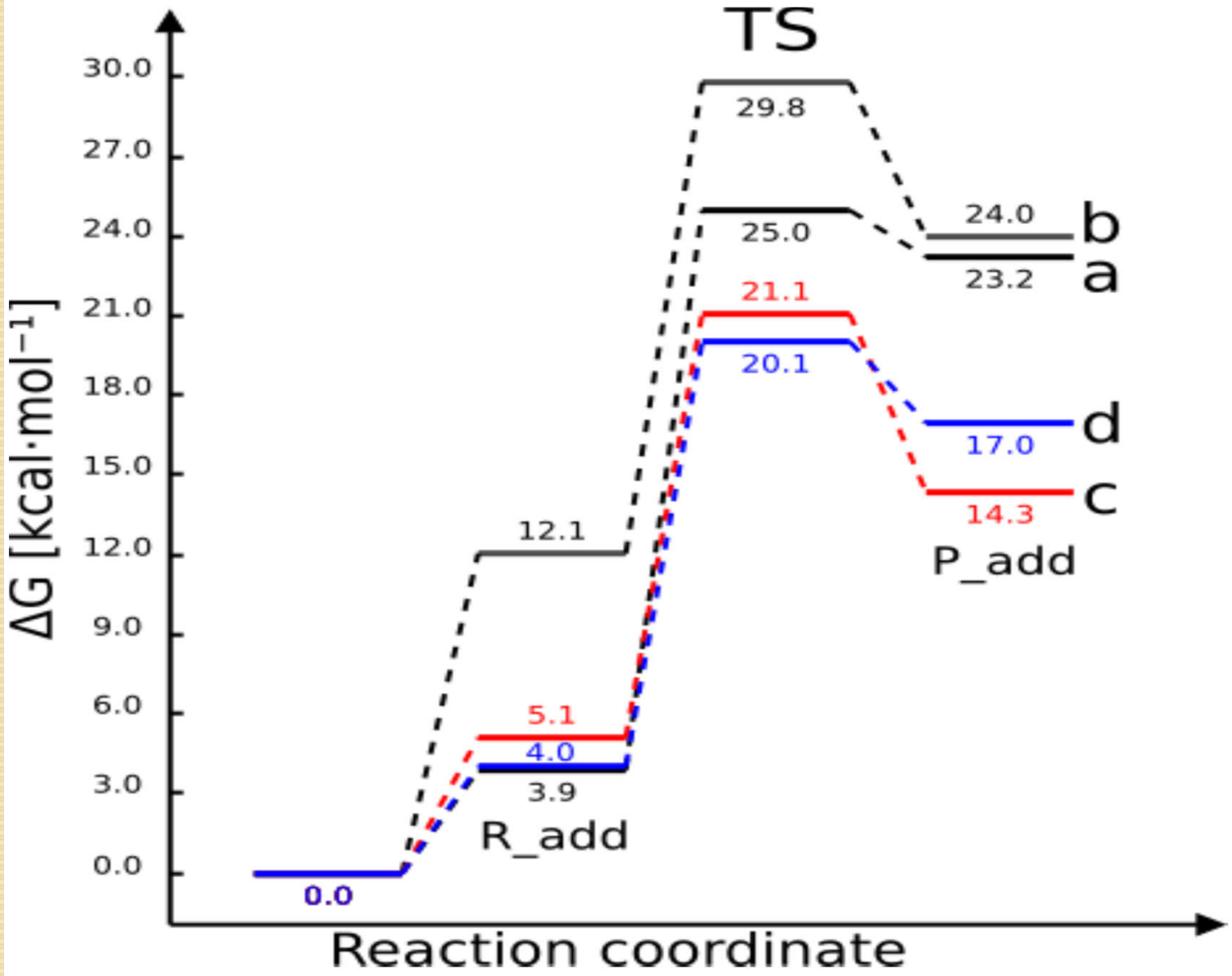

Cinchona-Squaramide
A


Cinchona-Squaramide
B


A
B
Ph
OH
OH
(R)
(R)
(R)
(S)

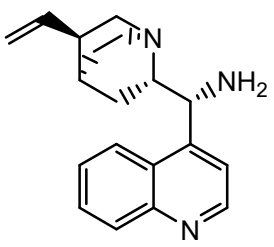
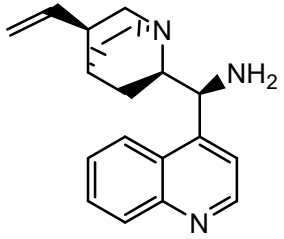
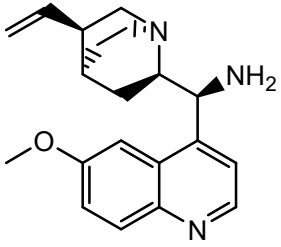
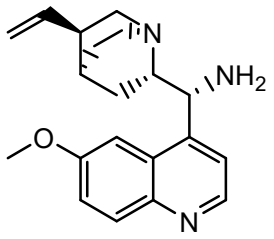
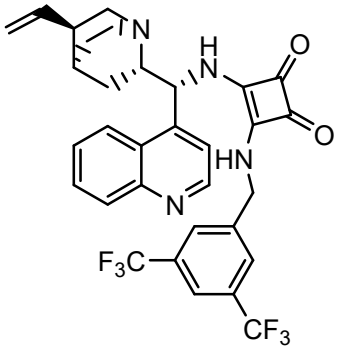
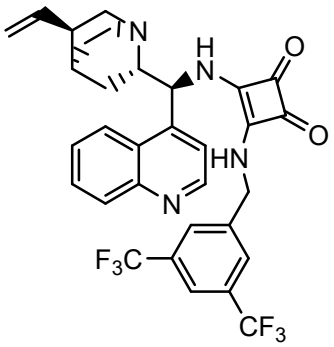
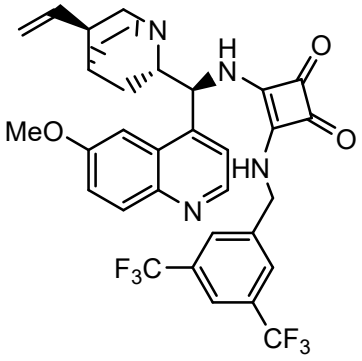
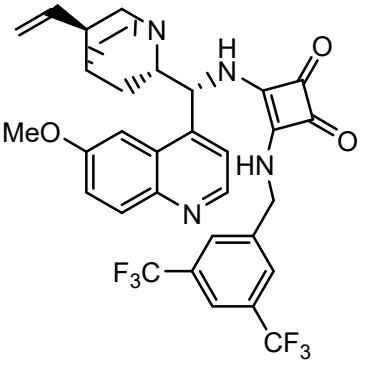
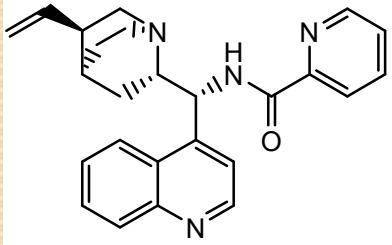
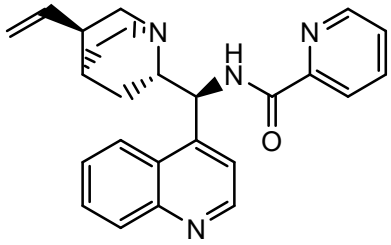
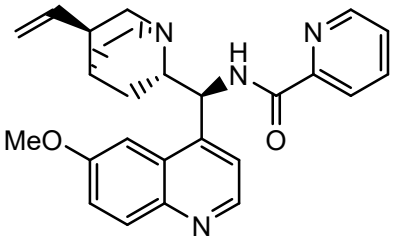
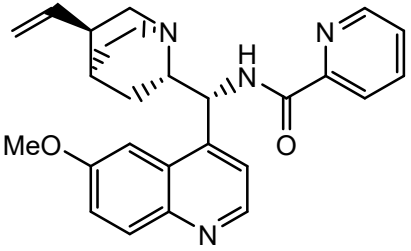


Implicit water (a), implicit water plus explicit water molecules (b), implicit water and sorbitol (c) and implicit water and cinchona-squaramide catalyst (d).


TS
30.0
27.0
24.0
21.0
18.0
15.0
12.0
9.0
6.0
3.0
0.0
ΔG [kcal·mol⁻¹]
29.8
25.0
24.0
b
23.2
a
21.1
20.1
17.0
d
14.3
c
P_add
12.1
5.1
4.0
3.9
R_add
0.0
Reaction coordinate

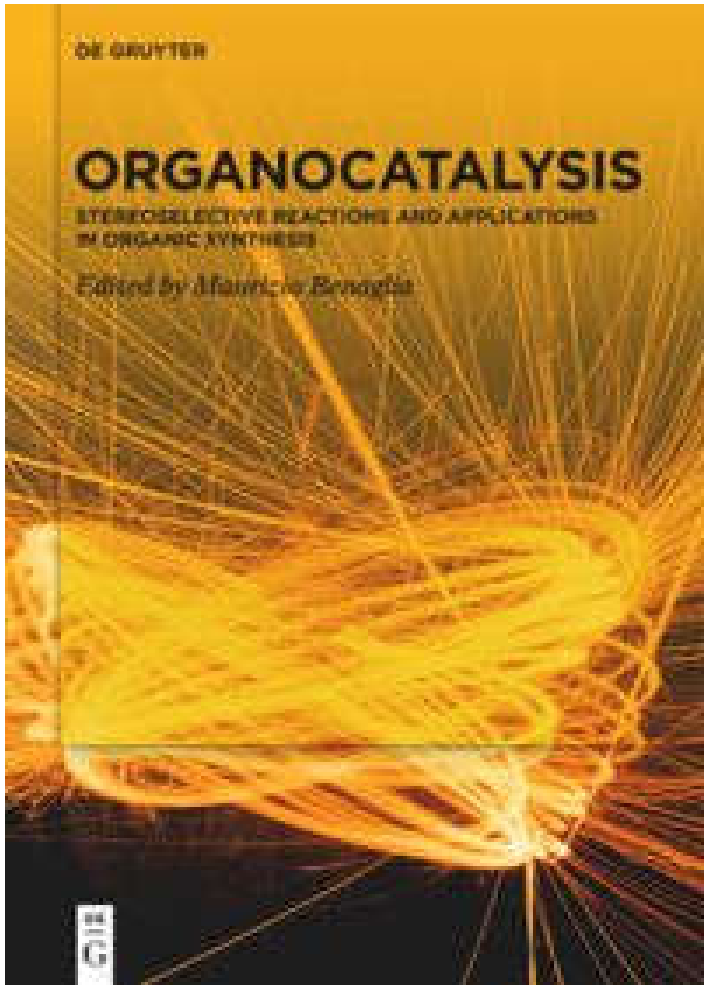
ChiraTecnics

Chiral Solutions for a Better Life

Cinchonine	Cinchonidine	Quinine	Quinidine
			
			
			

Summary

- Asymmetric catalytic hydrosilylation reactions.
- With Immobilized cinchona-pyridinamides.
- Cinchona-squaramides.
- Michael Reactions.
- Immobilized Cinchona-squaramides.
- Catalytic Solvents (Deep Eutectic Solvents)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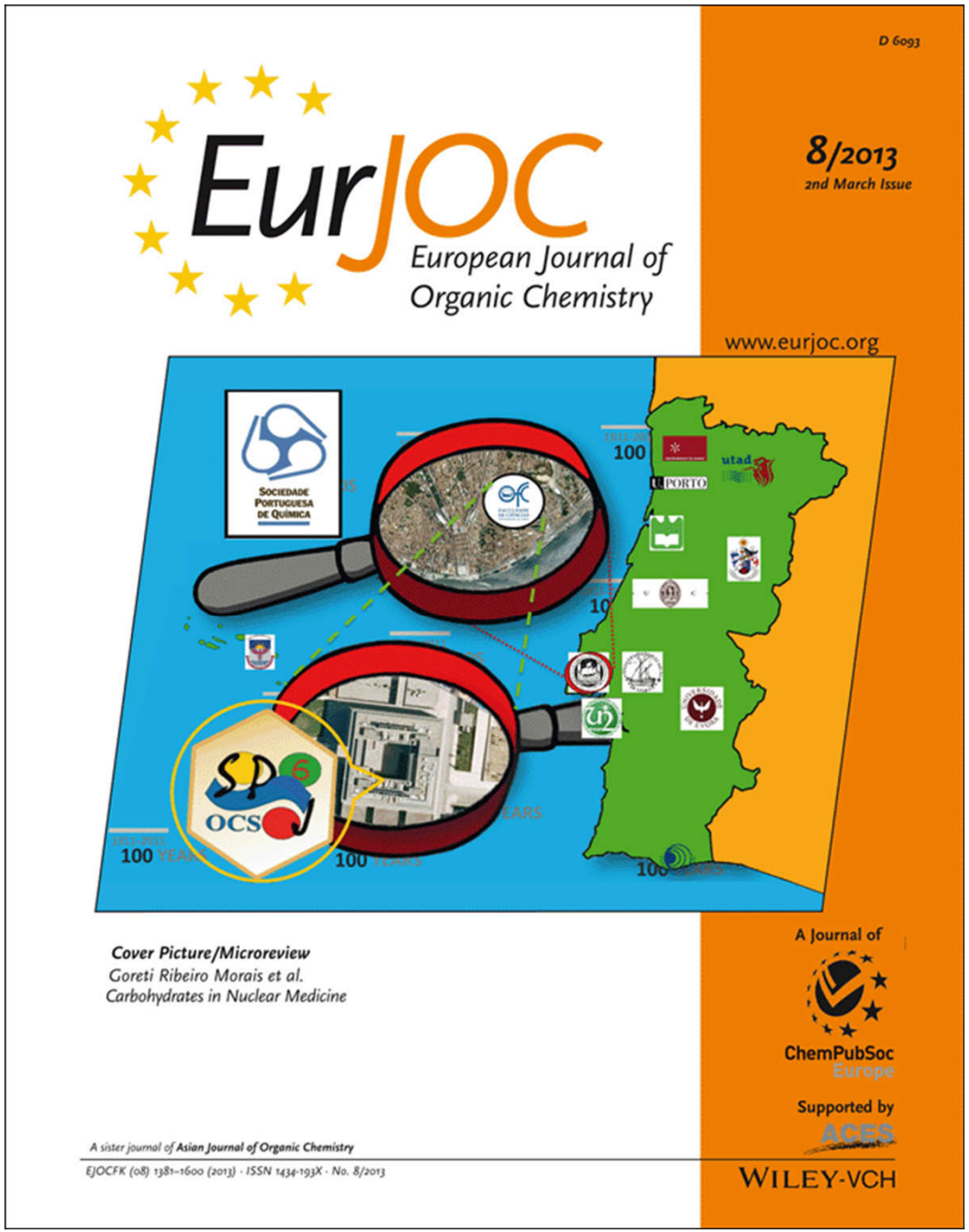
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