Catalytic Kinetic Resolution of Biaryl Compounds

Group Seminar

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Dec. 14th, 2017

*Laboratory of Synthesis and Natural Products (**LSPN**)*

*Ecole Polytechnique Fédérale de Lausanne (**EPFL**)*

Outline

1. Introduction

2. Kinetic Resolution of BINOL-Derivative

3. Kinetic Resolution of BINAM/NOBIN-Derivative

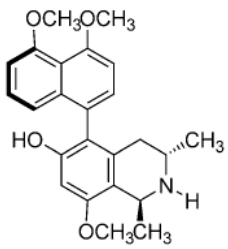
4. Kinetic Resolution of Quinolines-Derivative

5. Summary and Outlook

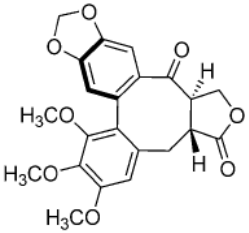
Introduction

Selected examples of axially chiral molecules

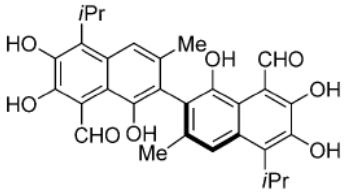
Natrual products



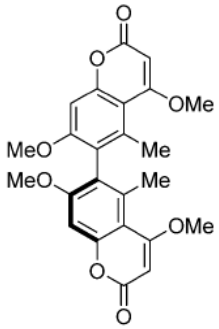
ancistrocladine



steganone

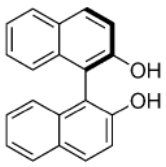


gossypol

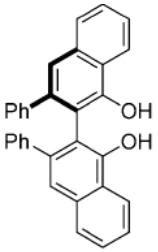


isokotanin A

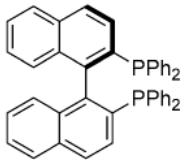
Ligands



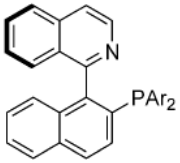
BINOL



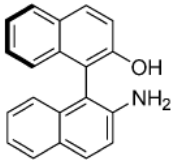
VANOL



BINAP

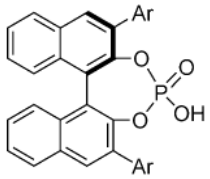


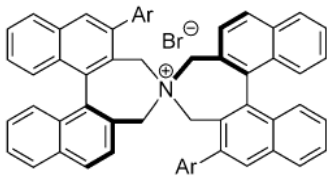
QUINAP



NOBIN

Catalyst

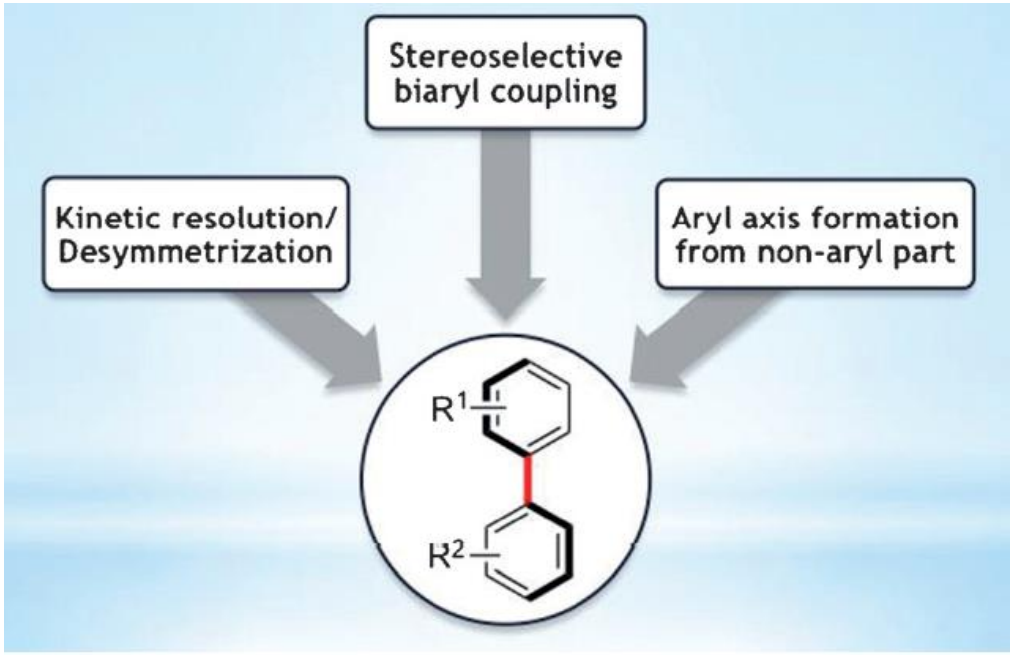




Ma, G.; Sibi, M. P. *Chem. Eur. J.* **2015**, *21*, 11644.

Introduction

Major synthetic approaches towards biaryl compounds

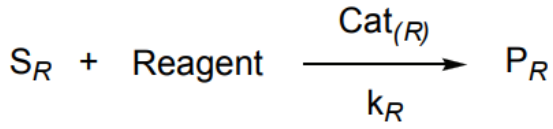


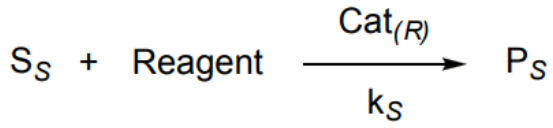
1) Stereoselective biaryl coupling of two aryl counterparts.
2) Aryl axis formation from non-aryl substituents attached to an aromatic ring.
3) Kinetic resolution/desymmetrization of prostereogenic biaryls

Ma, G.; Sibi, M. P. *Chem. Eur. J.* **2015**, *21*, 11644.

Introduction

The Basic of KR (1)





Efficiency (relative rate or selectivity factor)

$s = k_{rel} = k_{fast}/k_{slow}$

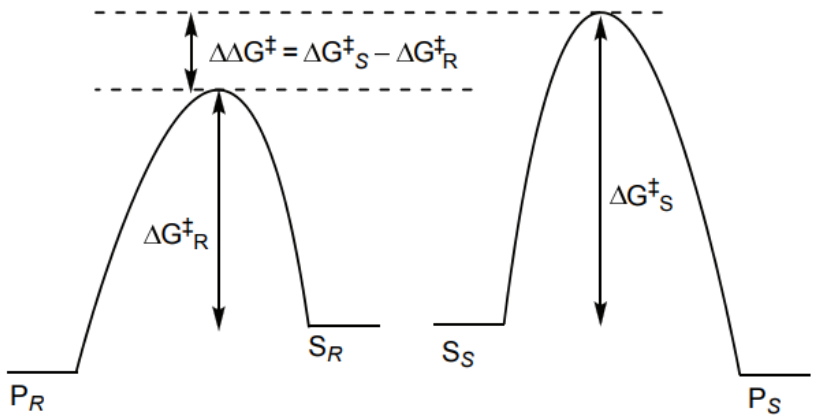
$= k_R / k_S$

$= \exp(\Delta\Delta G^{\ddagger}/RT)$

Why perform KR:

1. Racemate is cheap
2. No reasonable enantioselective approach
3. Classical resolution (stoichiometric) does not provide high ee

For $k_R > k_S$



"selectivity-determining diastereomeric transition states"

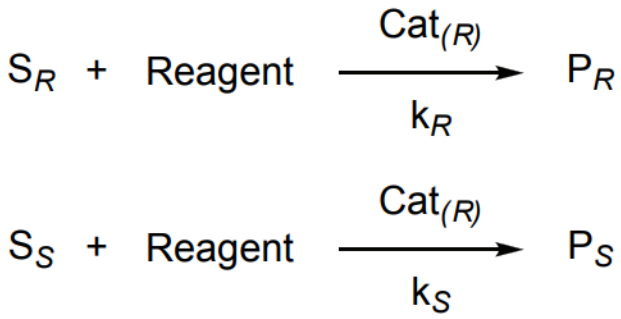
KR Consideration:

1. S and P are easily separated
2. High yield (~50%), high ee
3. Short reaction time
4. Scalibility
5. Low cat. loading
6. Inexpensive cat.
7. Minimal waste
8. Reproducibility
9. Broad scope
10. Functional group compatibility

Walsh P. J.; Kozlowski, M. C. *Fundamentals of Asymmetric Catalysis* Chapter 7.

Introduction

The Basic of KR (2)



$s = k_{rel} = \ln[(1 - C)(1- ee) / \ln[(1 - C)(1 + ee)]$ (1)

C = conversion

ee = ee of S

s can be measured experimentally by knowing C and ee

$s = k_{rel} = \ln[1 - C(1 + ee')] / \ln[1 - C(1 - ee')]$ (2)

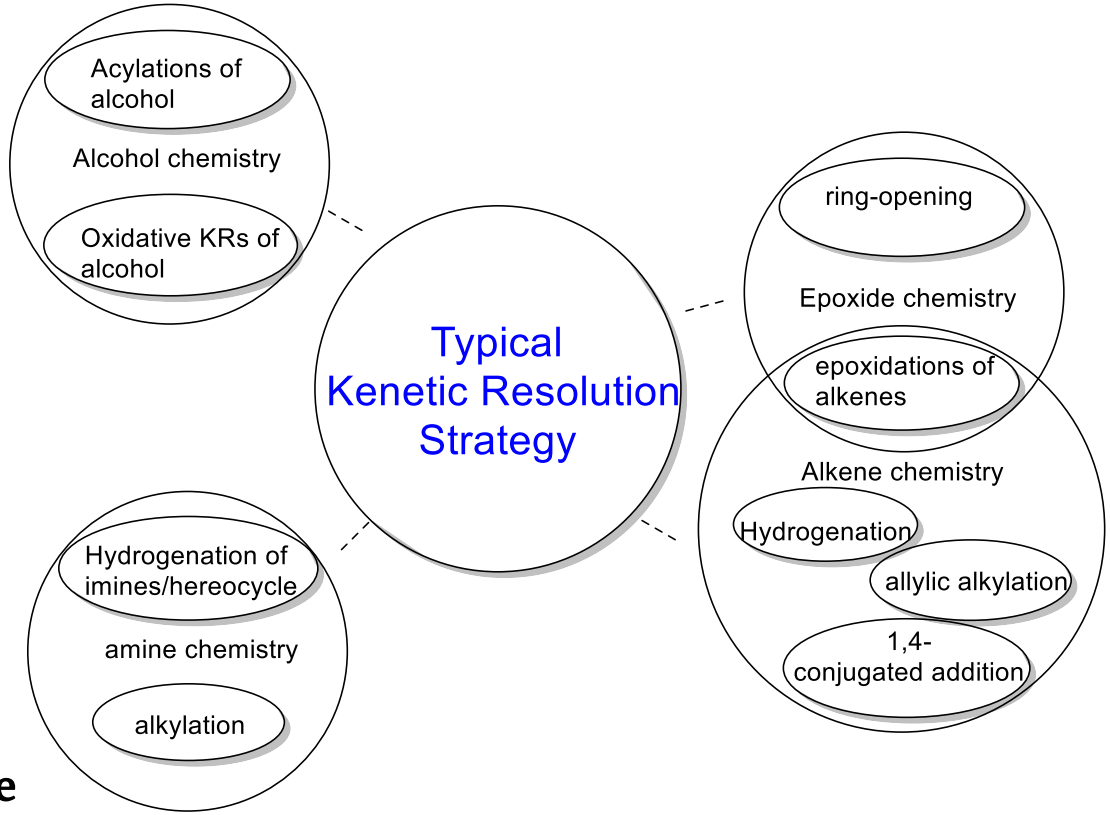
ee' = ee of P

Combine (1) and (2): $ee / ee' = C / (1-C)$

It is impossible to obtain both good yield and high ee at the same time with moderate s.

Introduction

Strategy for Kinetic resolution



BINOL-Derivative

BINAM/NOBIN-Derivative

Quinolines-Derivative

Pellissier H. *Seperation of Enantiomers: Synthetic Method* Chapter 3.

Outline

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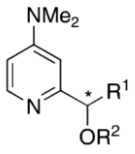
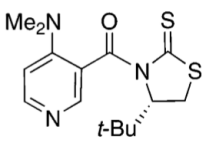
5. Summary and Outlook

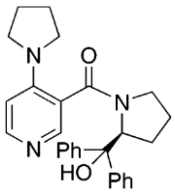
Kinetic Resolution of BINOL-Derivatives

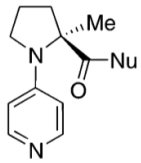
Well-developed Acylation by DMAP Catalyst

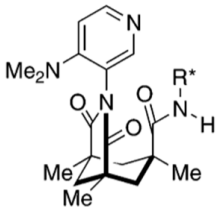
Catalysts with a Stereogenic Center

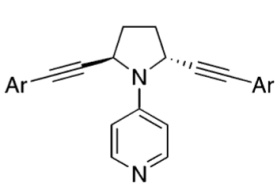


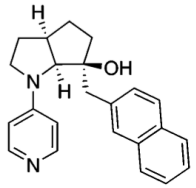


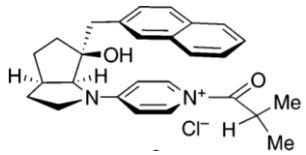




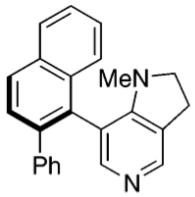


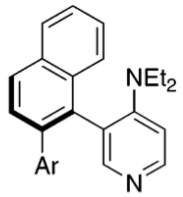


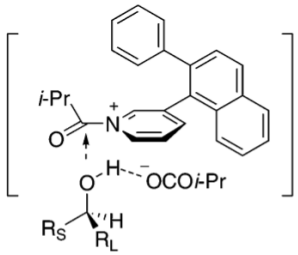




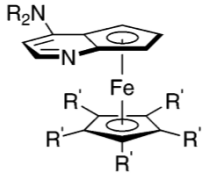
Catalysts with a Chiral Axis.

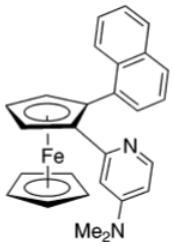


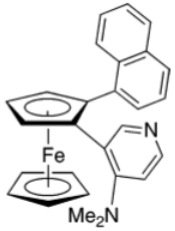




Planar-Chiral Catalysts



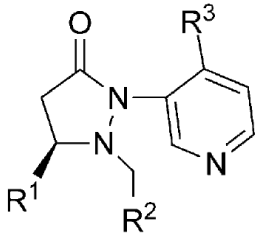




Wurz, R. P. *Chem. Rev.* **2007**, *107*, 5570.

Kinetic Resolution of BINOL-Derivative

DMAP Catalysts



fluxionality

Cat 1a R^1 = *i*Pr, R^2 = phenyl, R^3 = dimethylamino

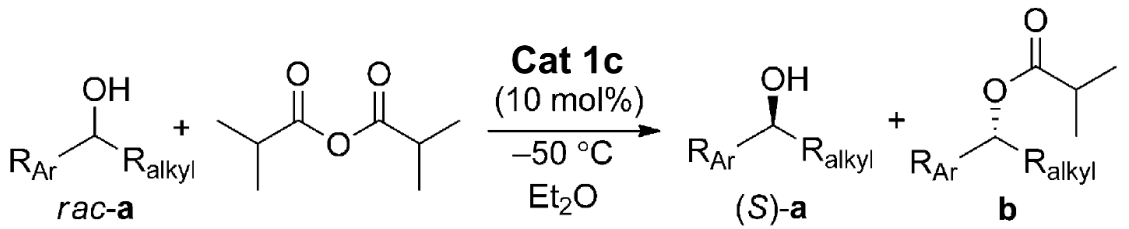
Cat 1b R^1 = *t*Bu, R^2 = phenyl, R^3 = dimethylamino

Cat 1c R^1 = *t*Bu, R^2 = 1-naphthyl, R^3 = dimethylamino

Cat 1d R^1 = *t*Bu, R^2 = 9-anthracenyl, R^3 = dimethylamino

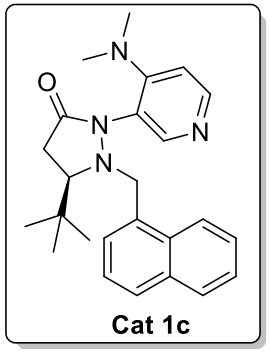
Cat 1e R^1 = *t*Bu, R^2 = 1-naphthyl, R^3 = pyrrolidine

Cat 1f R^1 = *t*Bu, R^2 = 1-naphthyl, R^3 = di-*n*-butylamino



upto 77% ee upto 88% ee

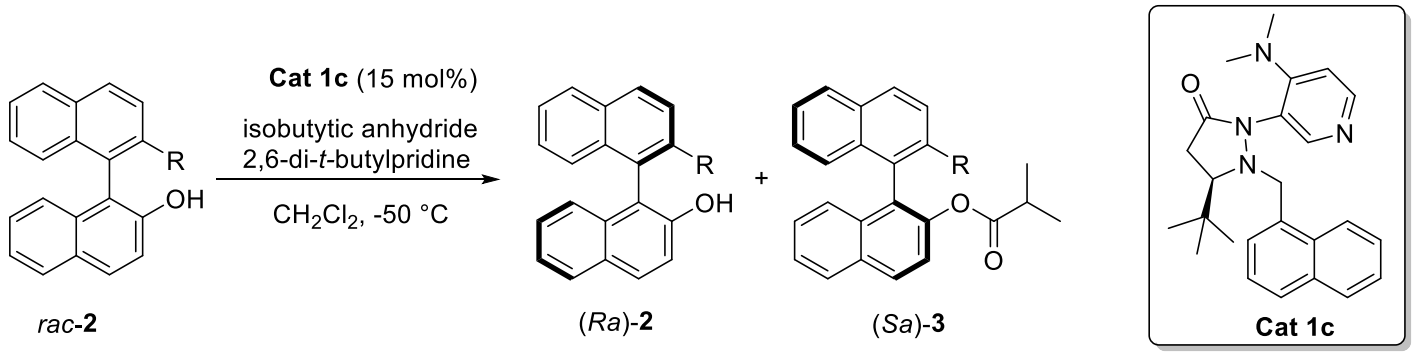
s upto 37

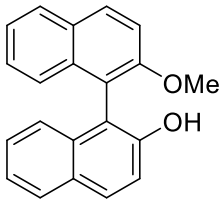


Ma, G.; Deng, J.; Sibi, M. P. *Angew. Chem. Int. Ed.* **2014**, *53*, 11818.

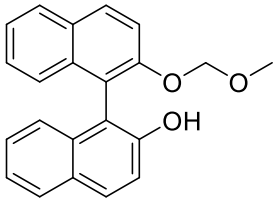
Kinetic Resolution of BINOL-Derivative

By acylation using DMAP cat

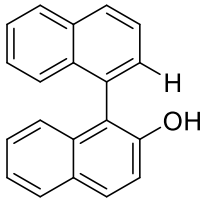




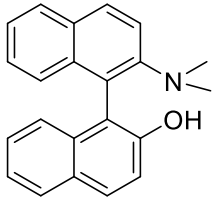
(*Ra*)-**2** 63% ee
(*Sa*)-**3** 90% ee
41% conv., s = 36



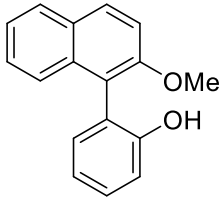
(*Ra*)-**2** 62% ee
(*Sa*)-**3** 85% ee
42% conv., s = 23



(*Ra*)-**2** 73% ee
(*Sa*)-**3** 63% ee
41% conv., s = 10



(*Ra*)-**2** 46% ee
(*Sa*)-**3** 86% ee
41% conv., s = 21

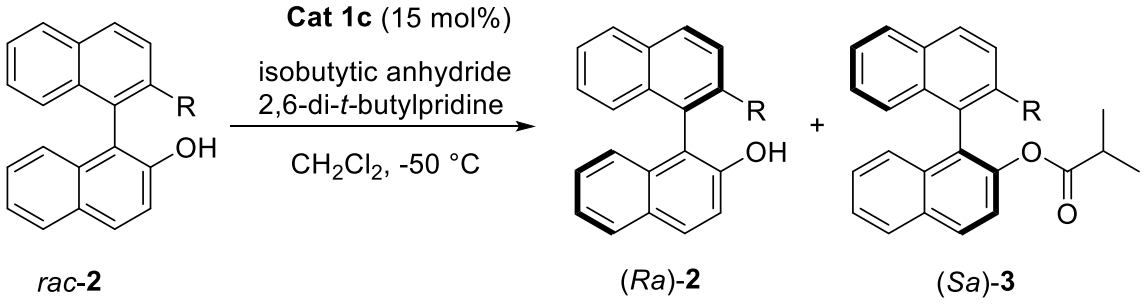


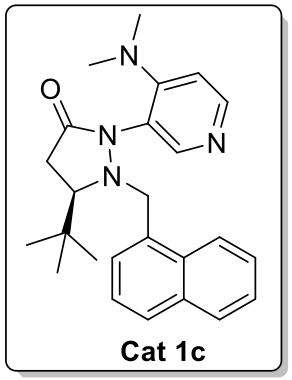
(*Ra*)-**2** 90% ee
(*Sa*)-**3** 89% ee
41% conv., s = 51

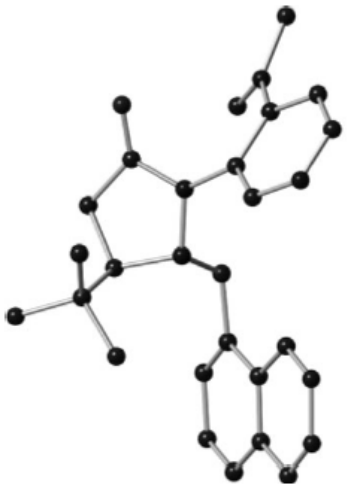
Ma, G.; Deng, J.; Sibi, M. P. *Angew. Chem. Int. Ed.* **2014**, *53*, 11818.

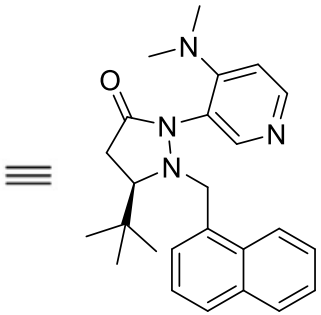
Kinetic Resolution of BINOL-Derivatives

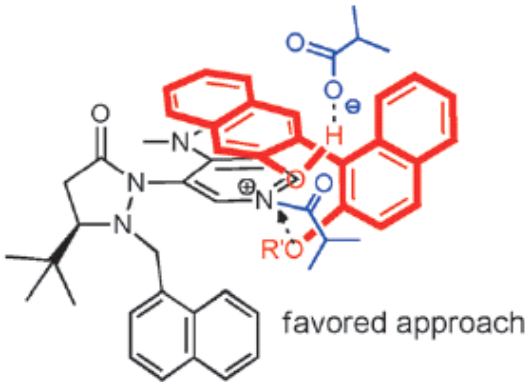
Origin of the catalytic activity and stereoselctivity









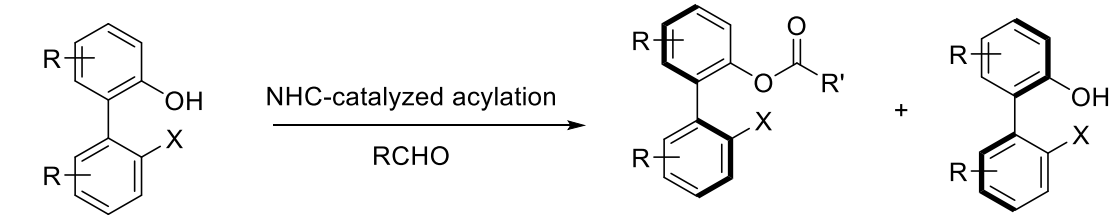


Proposed stereochemical model

Ma, G.; Deng, J.; Sibi, M. P. *Angew. Chem. Int. Ed.* **2014**, *53*, 11818.

Kinetic Resolution of BINOL-Derivative

By acylation using NHC

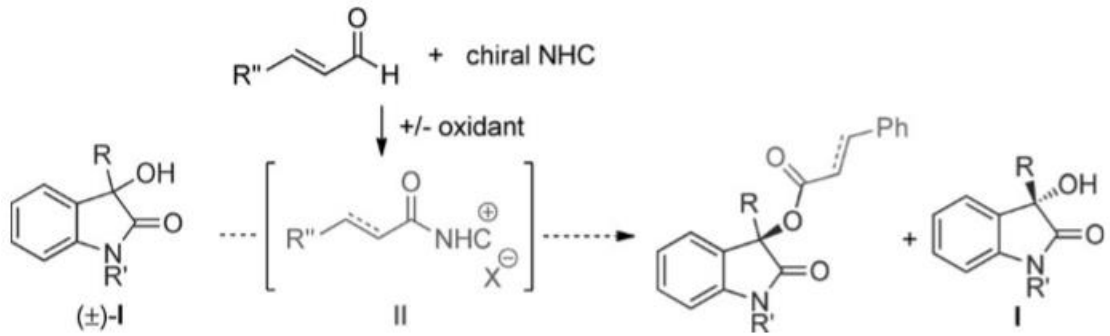


X = OH or NHBoc

s upto >100

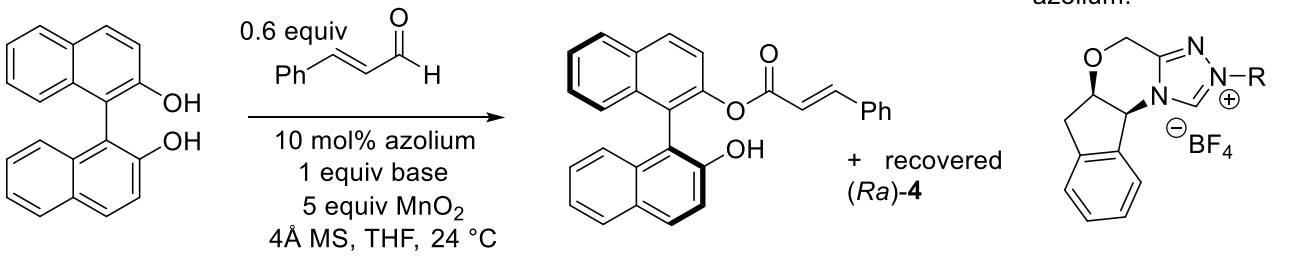
≥99% ee for alll recovered starting materials

Lu, S.; Poh, S. B.; Zhao, Y. *Angew. Chem. Int. Ed.* **2014**, *53*, 11041.



Lu, S.; Poh, S. B.; Siau, W.-Y.; Zhao, Y. *Angew. Chem. Int. Ed.* **2013**, *53*, 1731.

Kinetic Resolution of BINOL-Derivatives



rac-**4a**

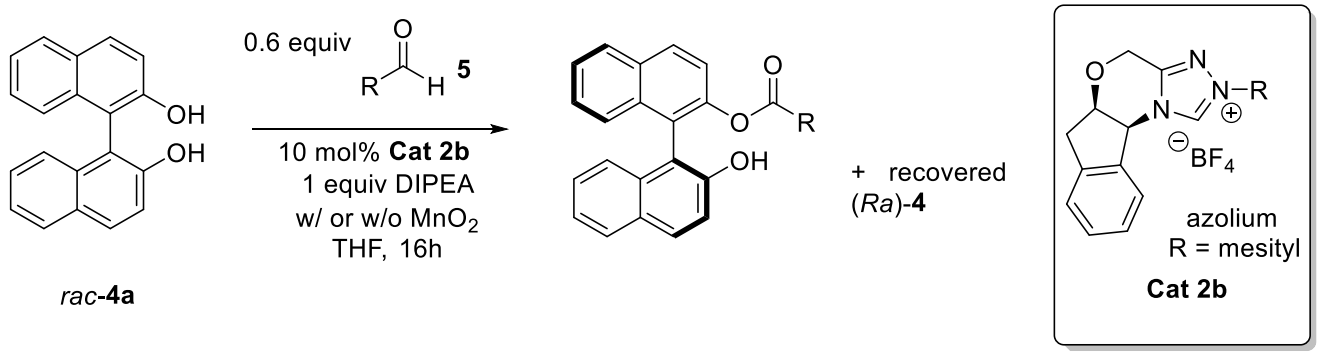
Cat 2a R = C_6F_5

Cat 2b R = mesityl

with azolium **Cat 2a** and DBU as base, 43% conv., s = 1.2
with azolium **Cat 2b** and DIPEA as base, 46% conv., s = 3.5

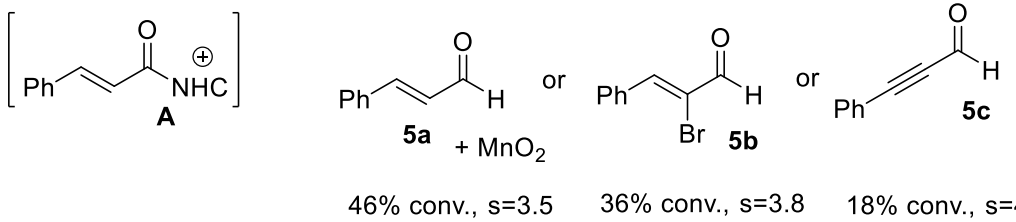
Lu, S.; Poh, S. B.; Zhao, Y. *Angew. Chem. Int. Ed.* **2014**, *53*, 11041.

Kinetic Resolution of BINOL-Derivative

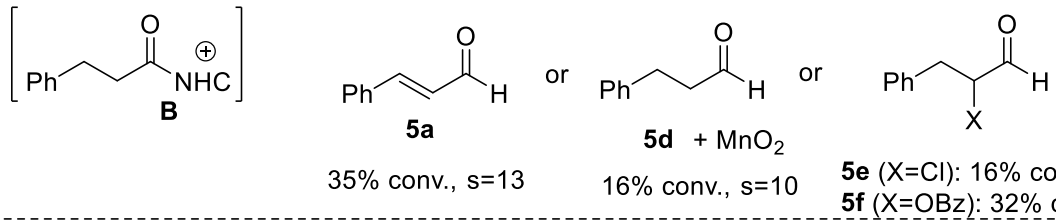


rac-**4a**

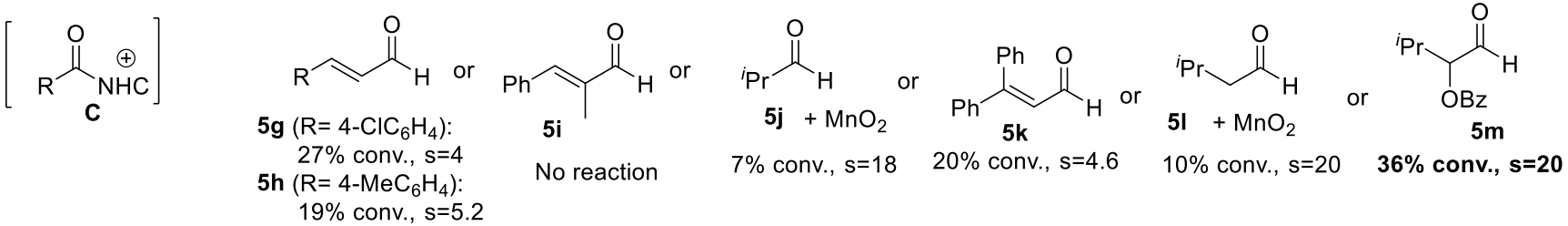
a)



b)

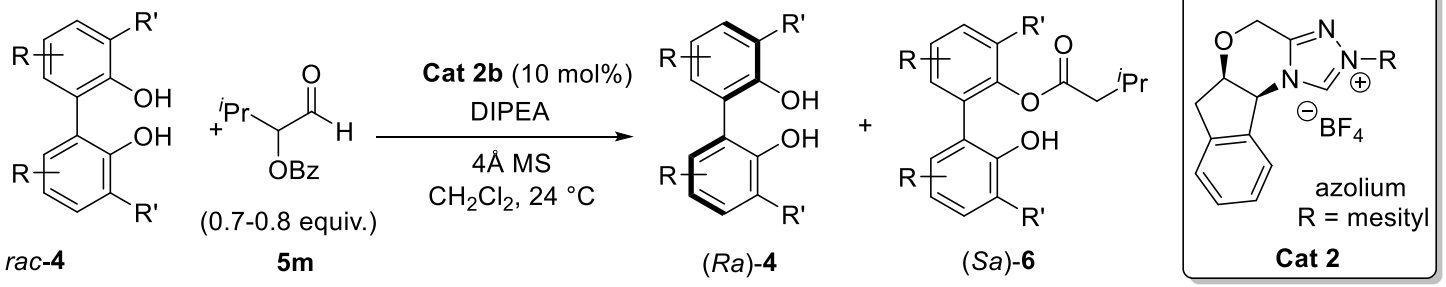


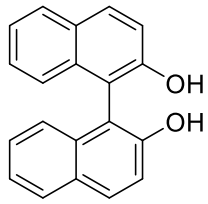
c)



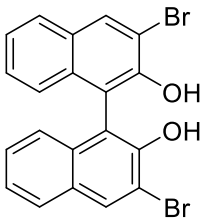
Lu, S.; Poh, S. B.; Zhao, Y. *Angew. Chem. Int. Ed.* **2014**, *53*, 11041.

Kinetic Resolution of BINOL-Derivatives

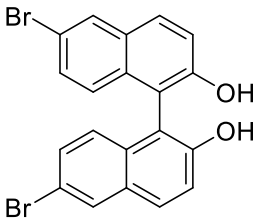




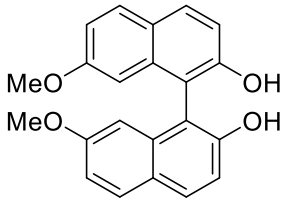
(*Ra*)-**4a** 99% ee
(*Sa*)-**6a** 82% ee
55% conv., *s* = 52



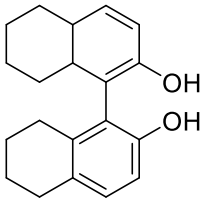
(*Ra*)-**4b** 99% ee
(*Sa*)-**6b** 77% ee
56% conv., *s* = 38



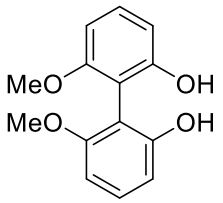
(*Ra*)-**4c** 99% ee
(*Sa*)-**6c** 81% ee
55% conv., *s* = 49



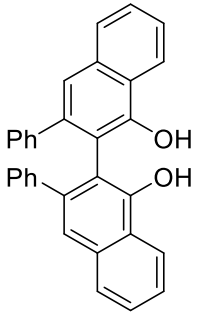
(*Ra*)-**4d** 99% ee
(*Sa*)-**6d** 77% ee
56% conv., *s* = 40



(*Ra*)-**4e** 99% ee
(*Sa*)-**6e** 72% ee
58% conv., *s* = 31



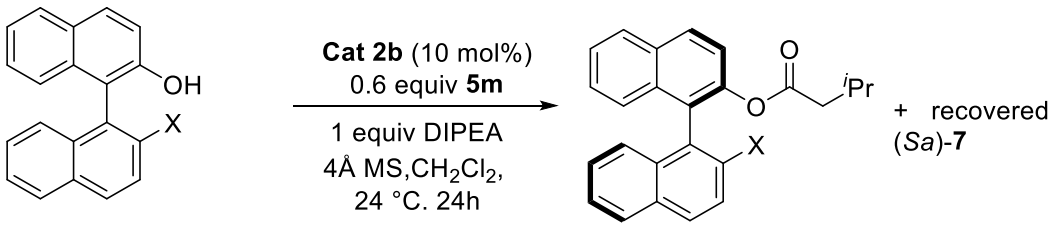
(*Ra*)-**4f** 99.5% ee
(*Sa*)-**6f** 60% ee
62% conv., *s* = 22



(*Ra*)-**4g** 99% ee
(*Sa*)-**6g**92% ee
52% conv., *s* = 116

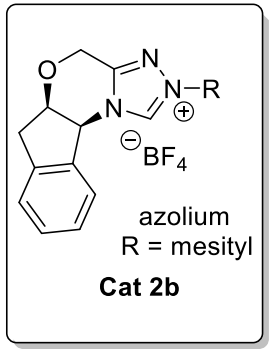
Lu, S.; Poh, S. B.; Zhao, Y. *Angew. Chem. Int. Ed.* **2014**, *53*, 11041.

Kinetic Resolution of BINOL-Derivative



rac-**7**

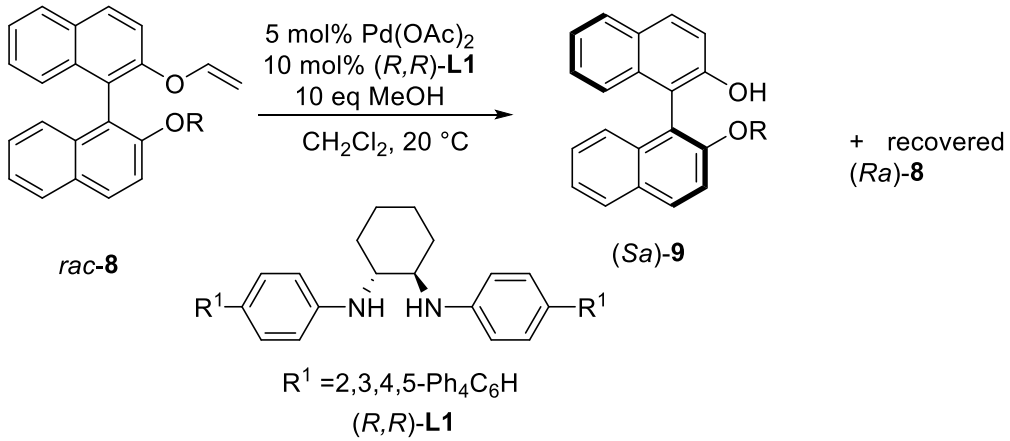
7a (X= OMe): 31% conv., s=1.5
7b (X= NMe_2): 14% conv., s=2



Lu, S.; Poh, S. B.; Zhao, Y. *Angew. Chem. Int. Ed.* **2014**, *53*, 11041.

Kinetic Resolution of BINOL-Derivatives

By alcoholysis catalyzed by palladium

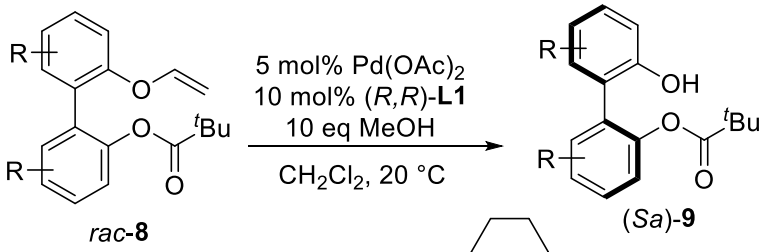


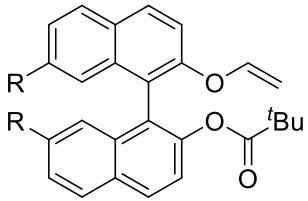
BINOL	R	Conv. [%]	*ee* [%] (*Ra*)-**8**	*ee* [%] (*Sa*)-**9**	*s* factor
8b	H	43	4	6	1.1
8c	$COCH_3$	49	54	57	6.1
8d	$CO(nC_6H_{13})$	44	61	77	14.3
8a	CO(*t*Bu)	58	96	69	20.3
8e	CO(1-adamantyl)	56	96	77	28.7

Aoyama, H.; Tokunaga, M.; Kiyosu, J.; Iwasawa, T.; Obora, Y.; Tsuji, Y. *J. Am. Chem. Soc.* **2005**, *127*, 10474.

Kinetic Resolution of BINOL-Derivatives

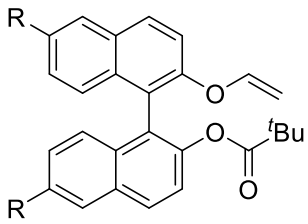
By alcoholysis catalyzed by palladium





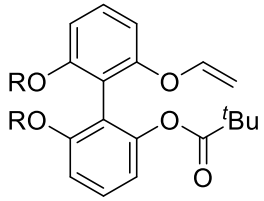
R=H (*Ra*)-**8a** 96% ee, (*Sa*)-**9a** 69% ee
58% conv., *s* = 20.3

R=OMe (*Ra*)-**8f** 97% ee, (*Sa*)-**9f** 65% ee
58% conv., *s* = 18.5



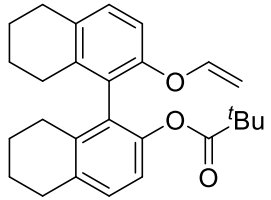
R=Ph (*Ra*)-**8g** 63% ee, (*Sa*)-**9g** 77% ee
45% conv., *s* =14.9

R=Br (*Ra*)-**8h** 45% ee, (*Sa*)-**9h** 79% ee
37% conv., *s* = 13.1



R=Me (*Ra*)-**8i** 95% ee, (*Sa*)-**9i** 79% ee
55% conv., *s* =31.4

R=^{i}Pr (*Ra*)-**8j** 84% ee, (*Sa*)-**9j** 81% ee
51% conv., *s* = 24.3

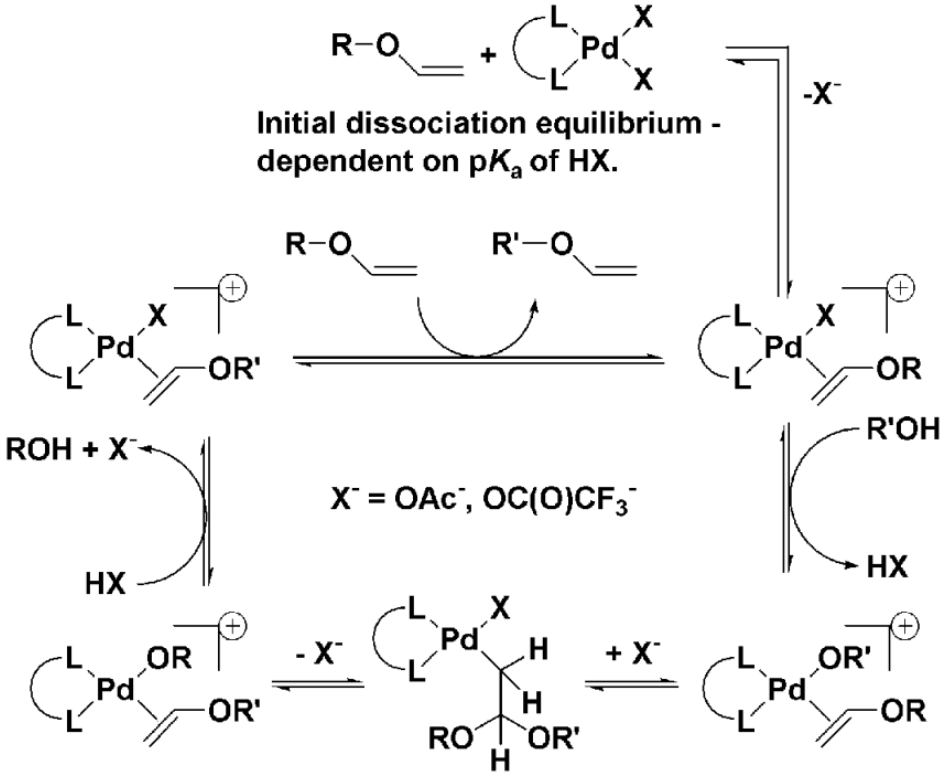


(*Ra*)-**8k** 95% ee,
(*Sa*)-**9k** 75% ee
56% conv., *s* = 27.0

Aoyama, H.; Tokunaga, M.; Kiyosu, J.; Iwasawa, T.; Obora, Y.; Tsuji, Y. *J. Am. Chem. Soc.* **2005**, *127*, 10474.

Kinetic Resolution of BINOL-Derivative

Alcoholysis mechanism

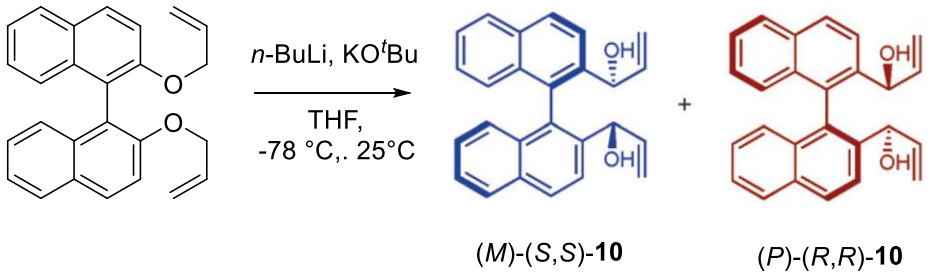


Bosch, M.; Schlaf, M. *J. Org. Chem.* **2003**, *68*, 5225-5227.

Aoyama, H.; Tokunaga, M.; Kiyosu, J.; Iwasawa, T.; Obora, Y.; Tsuji, Y. *J. Am. Chem. Soc.* **2005**, *127*, 10474.

Kinetic Resolution of BINOL-Derivatives

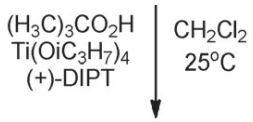
By alcoholysis catalyzed by palladium



(*M*)-(*S*,*S*)-**10** (*P*)-(*R*,*R*)-**10**

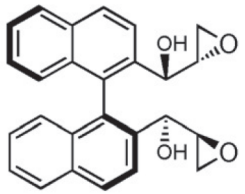
Consumed

Sharpless, K. B.; Katsuki, T. *J. Am. Chem. Soc.* **1980**, *102*, 5974.



(*M*)-(*S*,*S*)-**10** +

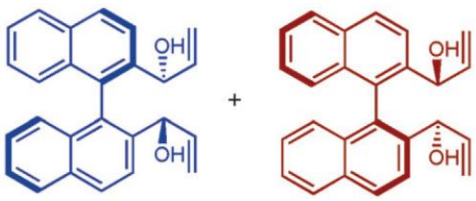
48% Recov'd (ee≥ 99%)



(*P*)-(*R*,*R*)-**27**

Schlosser, M.; Bailly, F. *J. Am. Chem. Soc.* **2006**, *128*, 16042.

Kinetic Resolution of BINOL-Derivatives

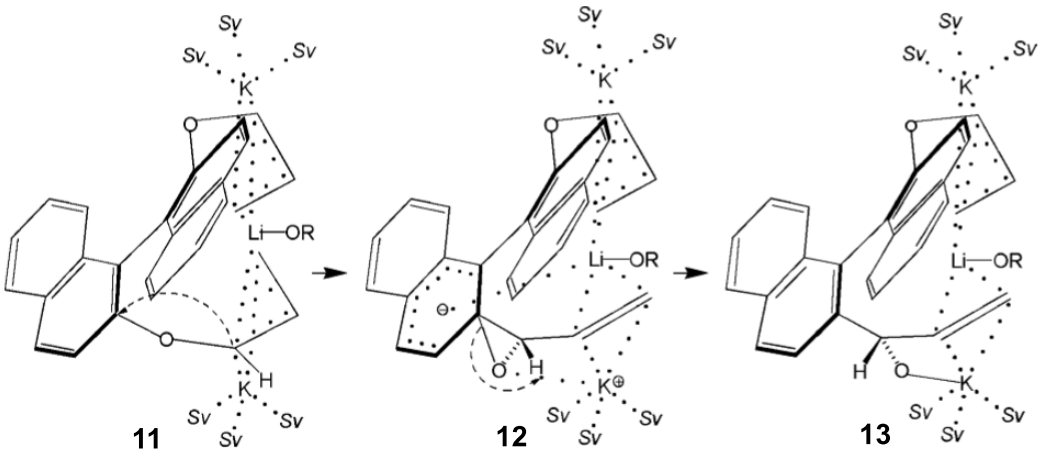


(*M*)-(*S*,*S*)-**10** (*P*)-(*R*,*R*)-**10**

allyl-allyl distance 4.5 Å

average C-Li distance 2.3 Å

average C-K distance 3.2 Å



[OR = $OC(CH_3)_3$; *Sv* = solvent (*i.e.* THF)]

Thank Balazs for the helpful discussion.

Schlosser, M.; Bailly, F. *J. Am. Chem. Soc.* **2006**, *128*, 16042.

Outline

1. Introduction

2. Kinetic Resolution of BINOL-Derivatives

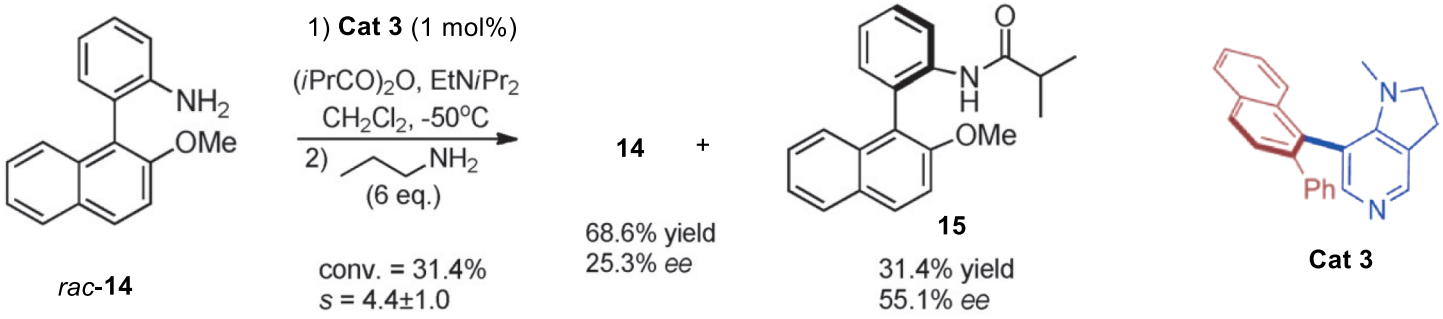
3. Kinetic Resolution of BINAM/NOBIN-Derivatives

4. Kinetic Resolution of Quinolines-Derivatives

5. Summary and Outlook

Kinetic Resolution of NOBIN/BINAM-Derivatives

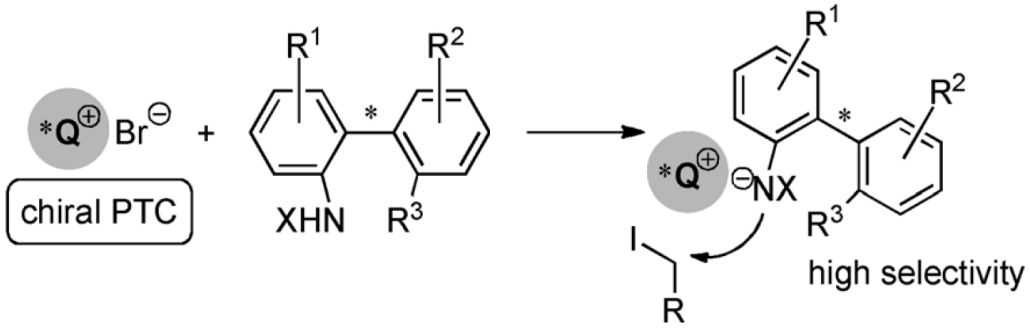
By acylation using DMAP cat

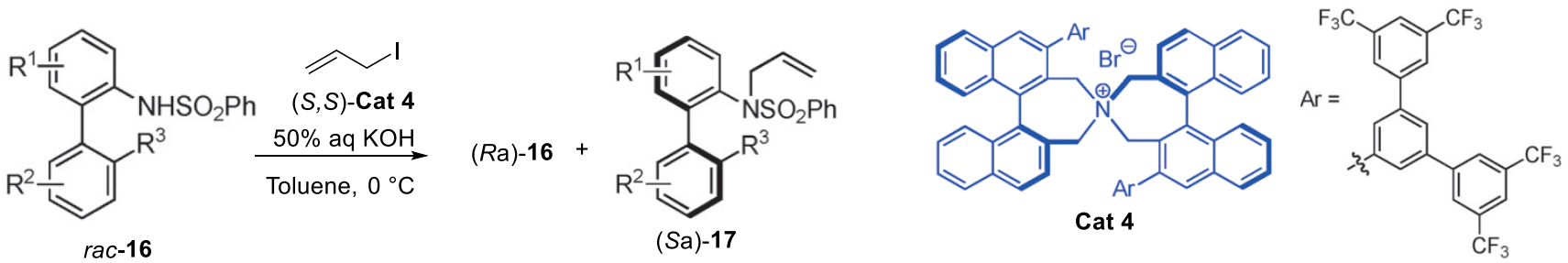


Arseniyadis, S.; Mahesh, M.; McDaid, P.; Hampel, T.; Davey, S. G.; Spivey, A. C. *Collect. Czech. Chem. Commun.* **2011**, *76*, 1239.

Kinetic Resolution of BINAM/NOBIN-Derivatives

Via asymmetric N-alkylation catalyzed by PTC



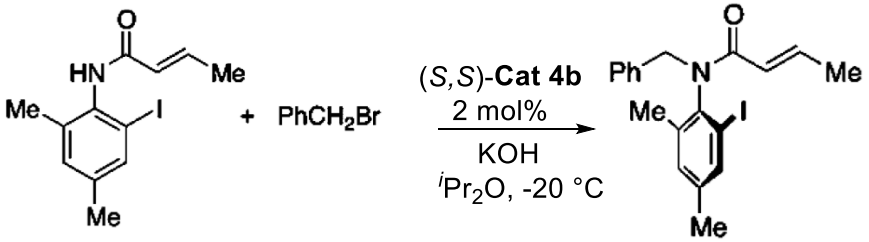


rac-**16** (*Sa*)-**17**

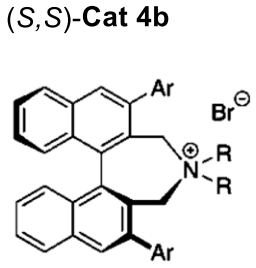
Shirakawa, S.; Wu, X.; Maruoka. K. *Angew. Chem. Int. Ed.* **2013**, *52*, 14200.

Kinetic Resolution of BINAM/NOBIN-Derivatives

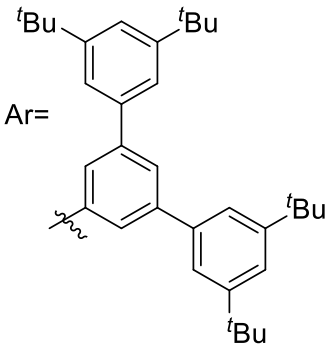
Via asymmetric N-alkylation catalyzed by PTC



83% yield, 90% ee



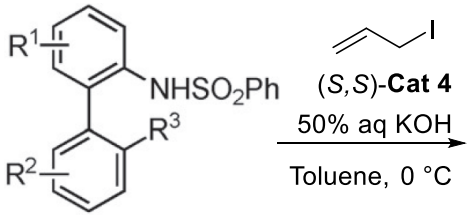
R = ^{n}Bu



Shirakawa, S.; Liu, K.; Maruoka. K. *J. Am. Chem. Soc.* **2012**, *134*, 916.

Shirakawa, S.; Wu, X.; Maruoka. K. *Angew. Chem. Int. Ed.* **2013**, *52*, 14200.

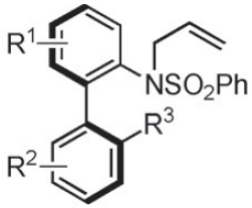
Kinetic Resolution of BINAM/NOBIN-Derivatives



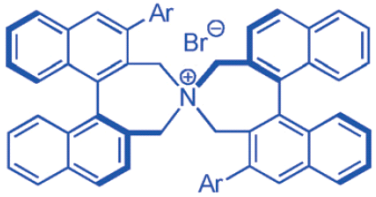
rac-**16**

(*S*,*S*)-**Cat 4**
50% aq KOH
Toluene, 0 °C

(*Ra*)-**16** +

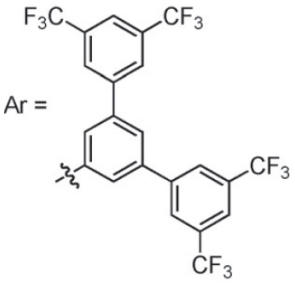


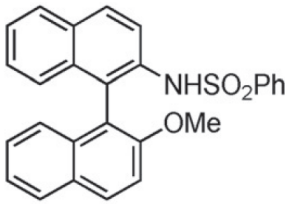
(*Sa*)-**17**



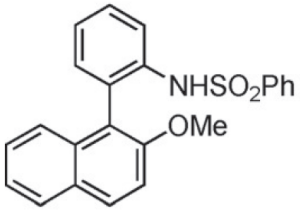
Cat 4

Ar =

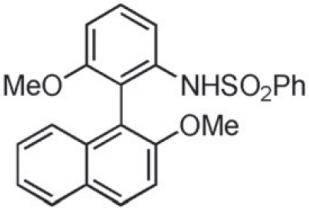




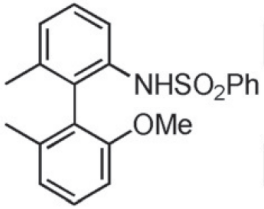
(*Ra*)-**16a** 93% ee
(*Sa*)-**17a** 81% ee
s = 32



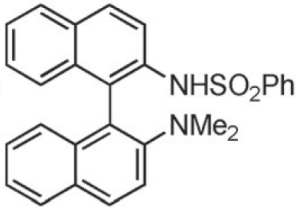
(*Ra*)-**16b** 74% ee
(*Sa*)-**17b** 62% ee
s = 9.2



(*Ra*)-**16c** 94% ee
(*Sa*)-**17c** 85% ee
s = 43



(*Ra*)-**16d** 37% ee
(*Sa*)-**17d** 60% ee
s = 5.7

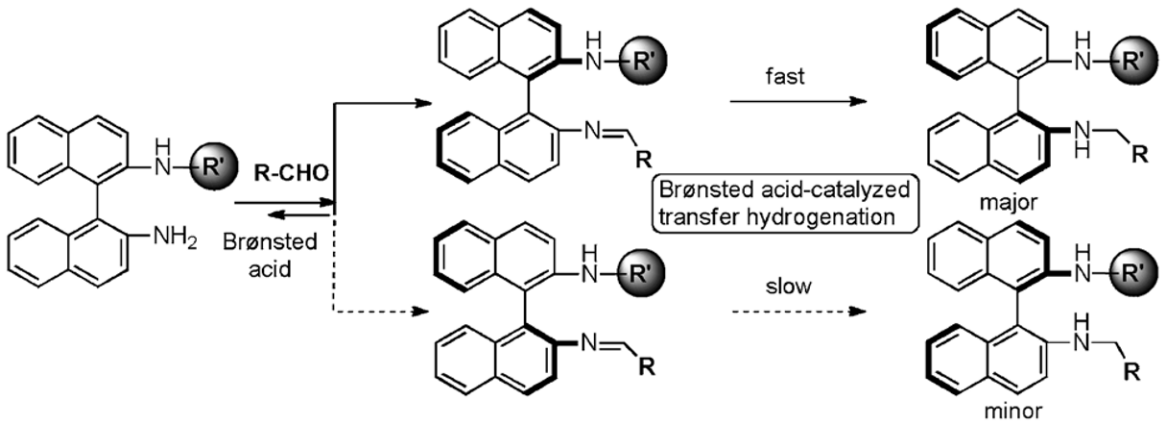


(*Ra*)-**16d** 67% ee
(*Sa*)-**17d** 86% ee
s = 32

Shirakawa, S.; Wu, X.; Maruoka. K. *Angew. Chem. Int. Ed.* **2013**, *52*, 14200.

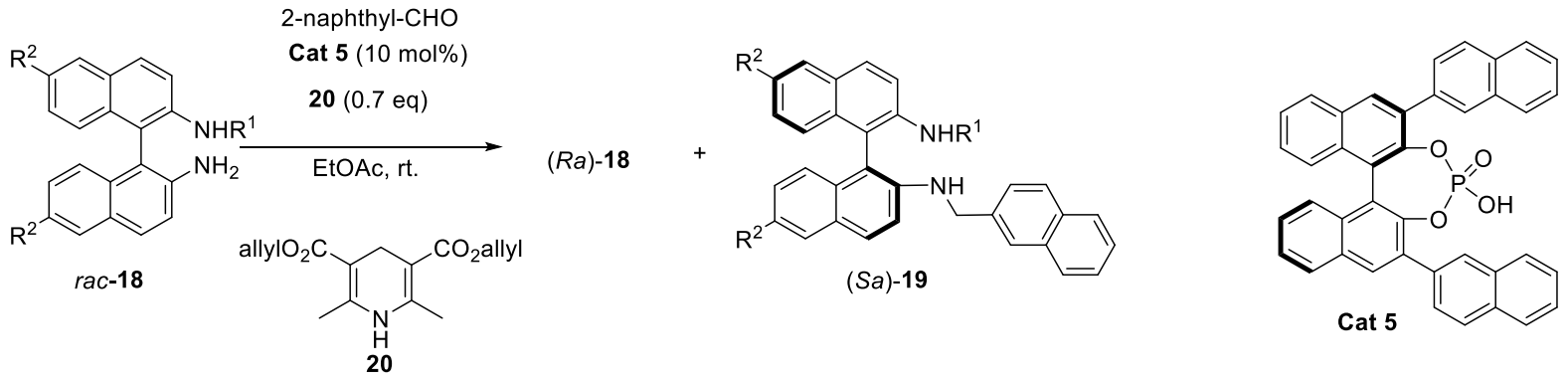
Kinetic Resolution of BINAM/NOBIN-Derivatives

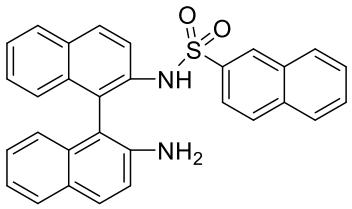
Via hydrogenation of imine catalyzed by CPA



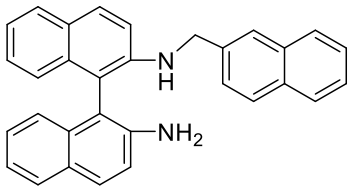
Cheng, D.-J.; Tan, B.; et al. *Angew. Chem. Int. Ed.* **2014**, *53*, 3684.

Kinetic Resolution of BINAM/NOBIN-Derivatives

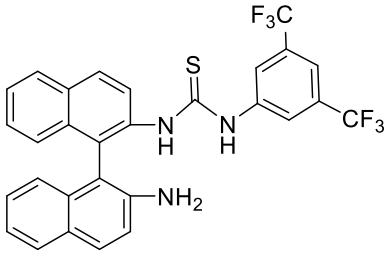




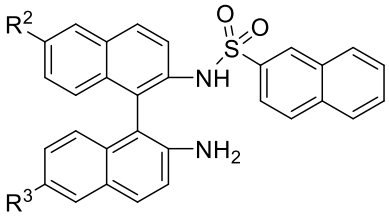
(*Ra*)-**18a** 98% ee
(*Sa*)-**19a** 97% ee
s = 303



(*Ra*)-**18b** 96% ee
(*Sa*)-**19b** 92% ee
s = 94



(*Ra*)-**18c** 92% ee
(*Sa*)-**19c** 44% ee
s = 8



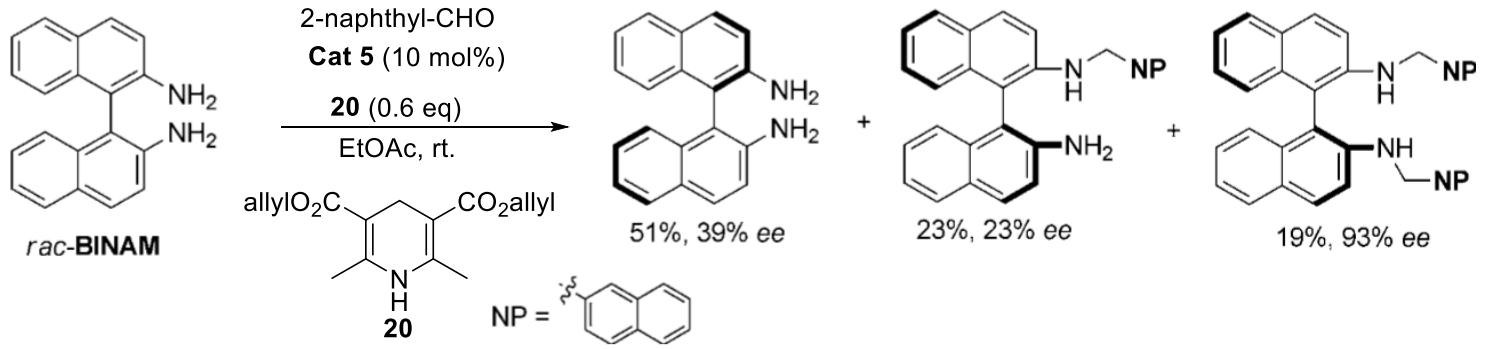
$R^2 = R^3 = Br$
(*Ra*)-**18d** 90% ee
(*Sa*)-**19d** 85% ee
s = 38

$R^2 = H$; $R^3 = Br$
(*Ra*)-**18e** 90% ee
(*Sa*)-**19e** 98% ee
s = 307

$R^2 = H$; $R^3 = TMS$
(*Ra*)-**18f** 96% ee
(*Sa*)-**19f** 93% ee
s = 108

Cheng, D.-J.; Tan, B.; et al. *Angew. Chem. Int. Ed.* **2014**, *53*, 3684.

Kinetic Resolution of BINAM/NOBIN-Derivatives



Cheng, D.-J.; Tan, B.; et al. *Angew. Chem. Int. Ed.* **2014**, *53*, 3684.

Outline

1. Introduction

2. Kinetic Resolution of BINOL-Derivatives

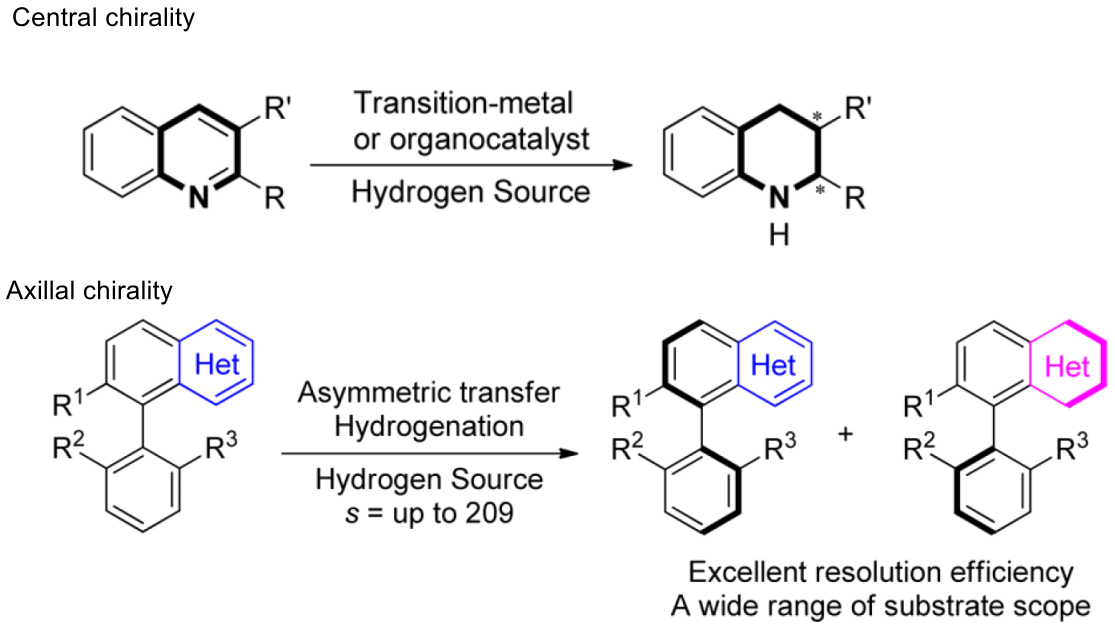
3. Kinetic Resolution of BINAM/NOBIN-Derivatives

4. Kinetic Resolution of Quinolines-Derivatives

5. Summary and Outlook

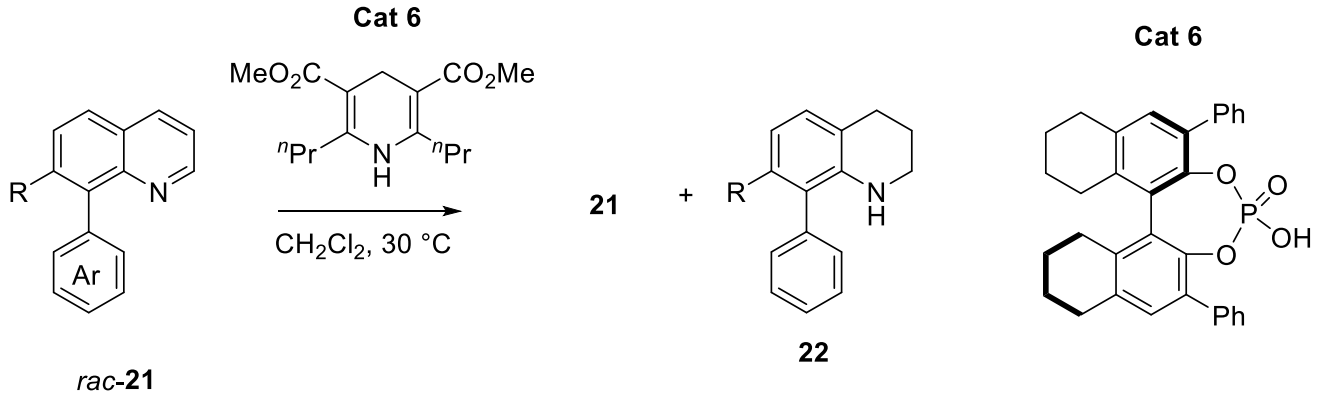
Kinetic Resolution of Quinolines-Derivatives

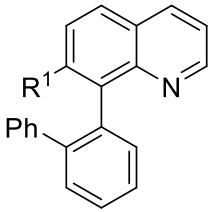
Via hydrogenation of heteroaromatics



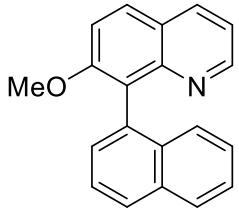
Wang, J.; Zhou, Y. -G. *et al. J. Am. Chem. Soc.* **2016**, *138*, 10413.

Kinetic Resolution of Quinolines-Derivatives

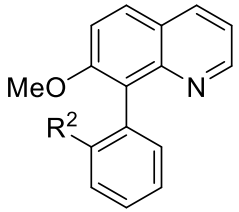




R^1=OMe: **21a** 96% ee, **22a** 94% ee s = 125
R^1 =OEt: **21b** 97% ee, **22b** 95% ee s = 169
R^1 =O^{i}Pr: **21c** 86% ee, **22c** 97% ee s = 187
R^1 =Me: **21d** 96% ee, **22d** 94% ee s = 131



21i 62% ee, **22i** 90% ee s = 36

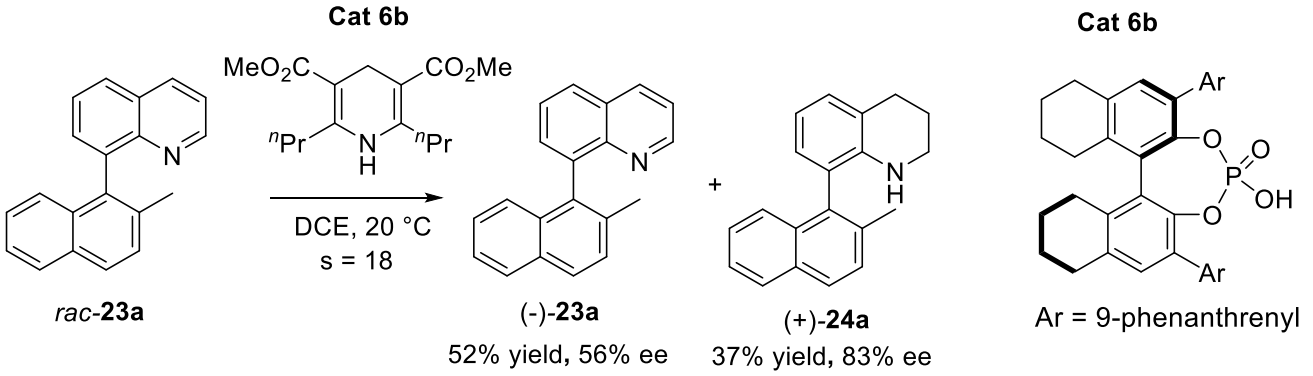


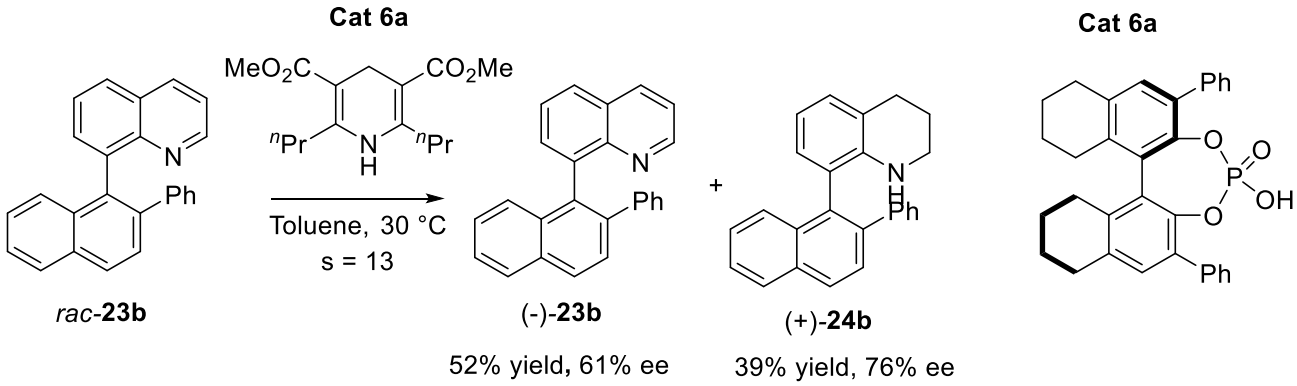
R^2=*p*-Tolyl: **21e** 86% ee, **22e** 97% ee s = 209
R^2 =*p*-Anisyl: **21f** 99% ee, **22f** 81% ee s = 50
R^2 = Me: **21g** 89% ee, **22g** 78% ee s = 23
R^2 =OBn: **21h** 97% ee, **22h** 72% ee s = 25

Wang, J.; Zhou, Y. -G. *et al. J. Am. Chem. Soc.* **2016**, *138*, 10413.

Kinetic Resolution of Quinolines-Derivatives

2′,6′-Substituted Quinoline-Based Biaryls

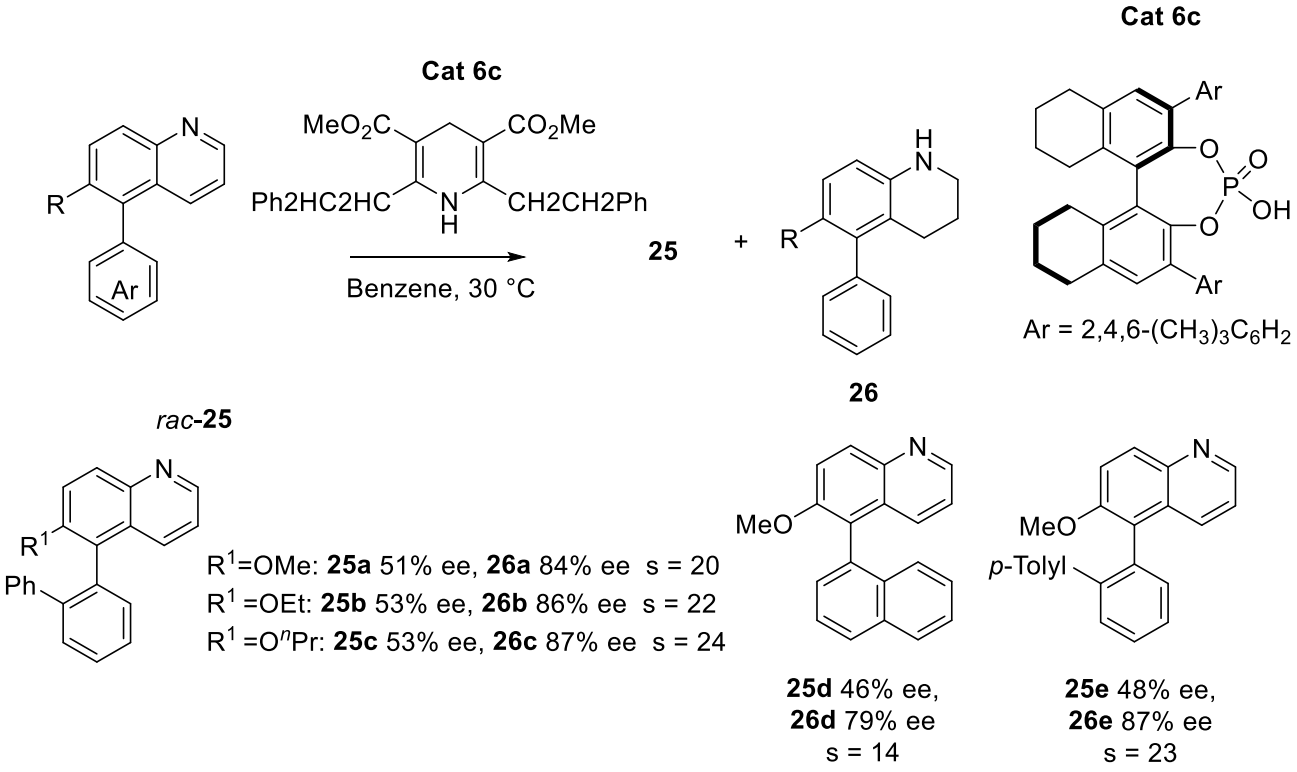




Wang, J.; Zhou, Y. -G. *et al. J. Am. Chem. Soc.* **2016**, *138*, 10413.

Kinetic Resolution of Quinolines-Derivatives

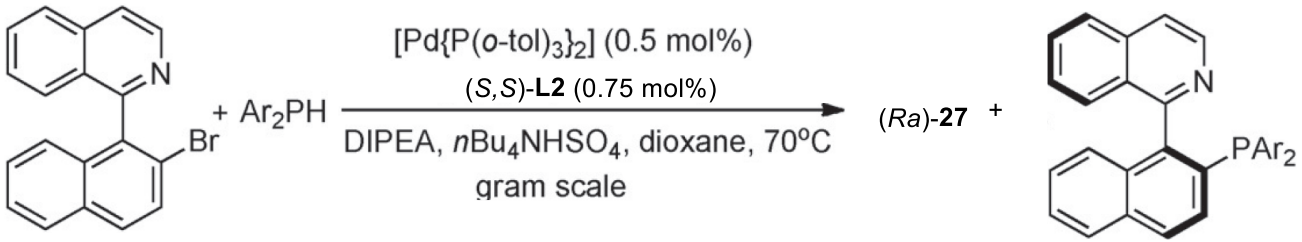
Kinetic Resolution of 5-Substituted Quinoline-Derived Biaryls

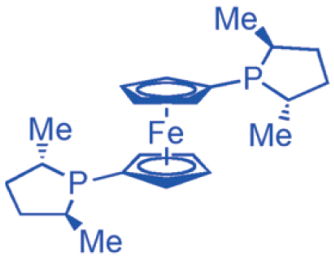


Wang, J.; Zhou, Y. -G. *et al. J. Am. Chem. Soc.* **2016**, *138*, 10413.

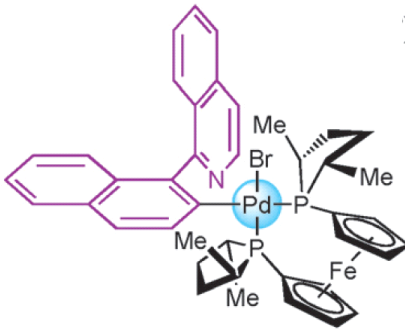
Kinetic Resolution of Quinolines-Derivatives

Via coupling of Aryl halides





(*S*,*S*)-**L2**

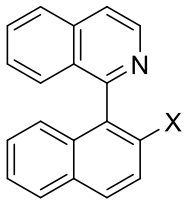


Ar	conv. [%]	(*Ra*-**27**)(% ee)	(*Sa*-**28**)(% ee)	*s*
Ph	50	96	95	154
p-Tol	50	96	92	94
p-CF_3-C_6H_4	45	75	63	52
o-tol	30	36	26	16

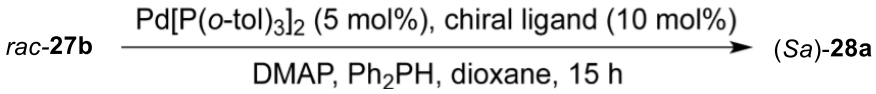
Bhat, V.; Wang, S.; Stoltz, B. M.; Virgil, S. C. *J. Am. Chem. Soc*. **2013**, *135*, 16829.

Kinetic Resolution of Quinolines-Derivatives

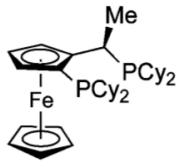
Racemization Rates of **28a** and **27a–c**



entry	substrate	X	solvent (°C)	k_{epi} (s^{-1})	$t_{1/2}^{rac}$ (h)
1	**27a**	Br	mesitylene (150)	1.2 x 10^{-6}	78
2	**28a**	PPh_2	mesitylene (150)	1.8 x 10^{-4}	0.5
3	**28a**	PPh_2	toluene (90)	3.9 x 10^{-7}	246
4	**27b**	OTf	toluene (90)	1.6 x 10^{-6}	62
5	**27c**	OSs	toluene (90)	5.7 x 10^{-6}	17
6	**27b**	OTf	toluene (80)	5.2 x 10^{-7}	187
7	**27b**	OTf	dioxane (80)	4.2 x 10^{-6}	230



entry	temp. (°C)	chiral ligand	% conv.	ee of **28a**
1	70	(*S*,*S*)-Et-FerroTane	68	–4
2	90	(*S*,*S*,*R*,*R*)-TangPhos	75	58
3	80	(*R*,*R*,*S*,*S*)-DuanPhos	75	–4
4	80	(*S*,*S*)-Me-DuPhos [(*S*,*S*)-**L3**]	NR	--
5	80	(*S*,*S*)-Me-Ferrocelane [(*S*,*S*)-**L2**]	100	0
6	60	(*S*,*S*)-^{i}Pr-Ferrocelane	76	–30
7	80	(R,S_{Fc})-Josiphos SL-J001-1	100	24
8	80	(R,S_{Fc})-Josiphos SL-J004-1	100	14
9	80	(R,S_{Fc})-Josiphos SL-J009-1	100	8
10	80	(R,S_{Fc})-Josiphos SL-J003-1 [(R,S_{Fc})-**L4**]	100	60
11	80	(R,S_{Fc})-Josiphos SL-J003-1 [(R,S_{Fc})-**L4**]	100	8

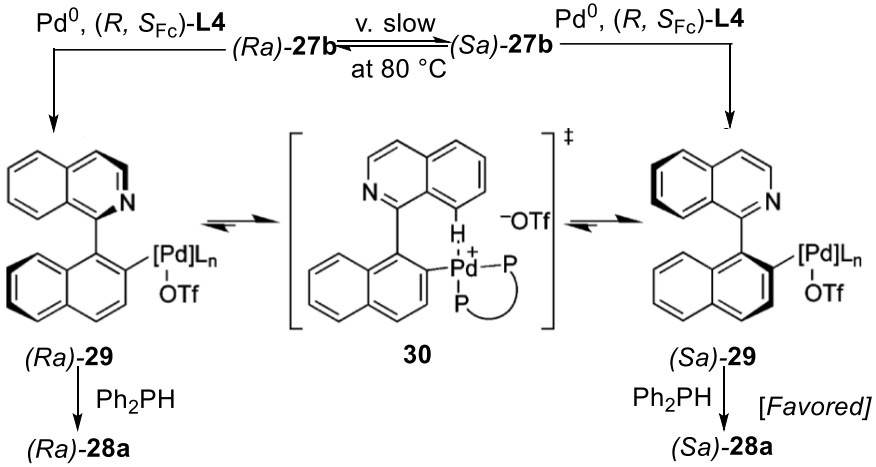


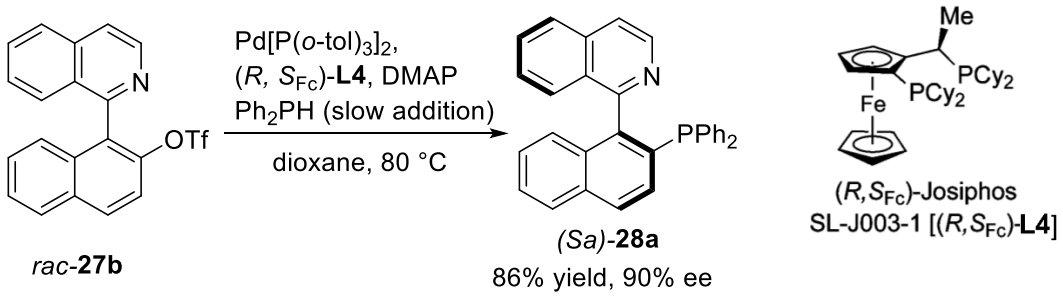
(R,S_{Fc})-Josiphos
SL-J003-1 [(R,S_{Fc})-**L4**]

Bhat, V.; Wang, S.; Stoltz, B. M.; Virgil, S. C. *J. Am. Chem. Soc*. **2013**, *135*, 16829.

Kinetic Resolution of Quinolines-Derivatives

Isomerization of Arylpalladium Intermediate

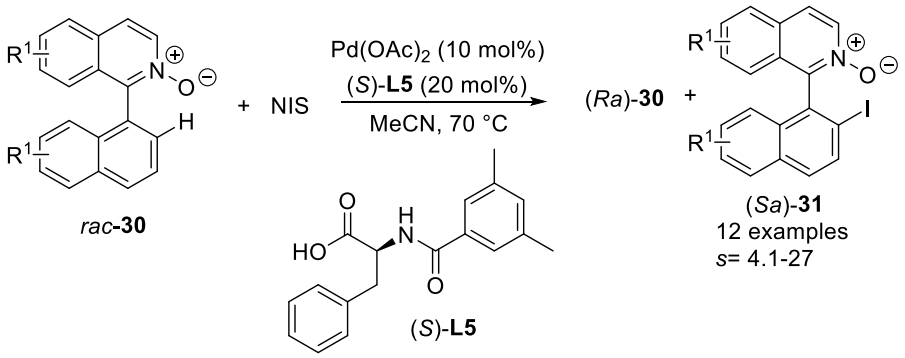


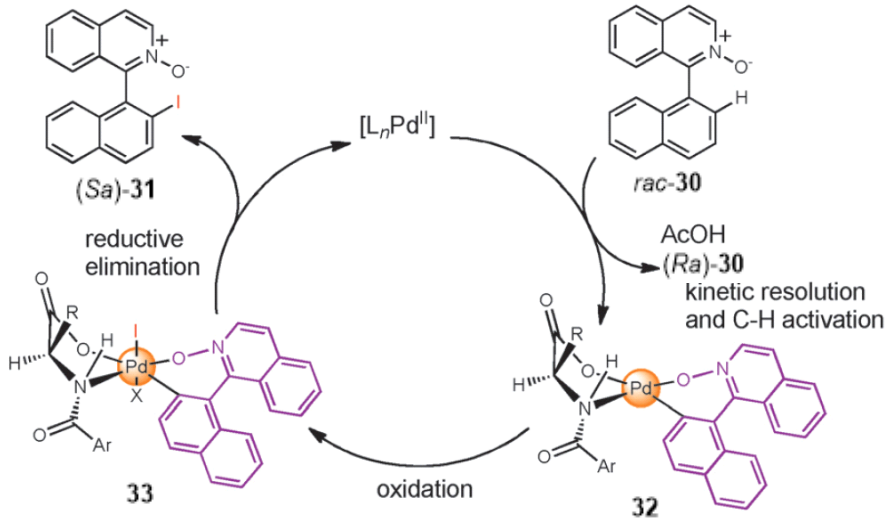


Bhat, V.; Wang, S.; Stoltz, B. M.; Virgil, S. C. *J. Am. Chem. Soc*. **2013**, *135*, 16829.

Kinetic Resolution of Quinolines-Derivatives

Via C-H functionalization





Gao, D.-W.; Gu, Q.; You, S.-L. ACS Catal. **2014**, *4*, 2741.

Summary

BINOL-Derivative

BINAM/NOBIN-Derivative

Quinolines-Derivative

By acylation
- hydrogenation
- Alkylation
- C-H functionalization
- Coupling

…….

Thanks for your attention !