(S)–QUINAP

(R,R)

(R)-QUINAP

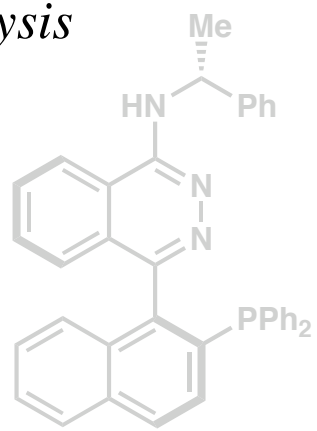
Axially chiral bidentate P,N-ligands

Syntheses and applications in asymmetric catalysis

(R)-QUINAZOLINAP

Boram Hong
Stoltz group literature presentation

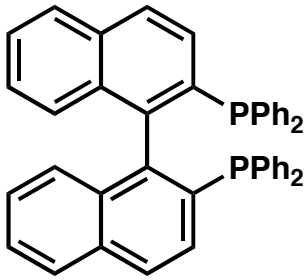
January 25, 2010
147 Noyes, 8:00 pm

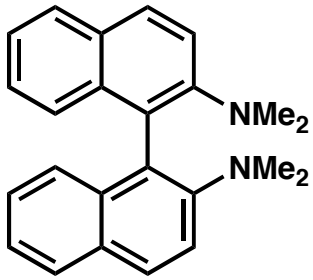


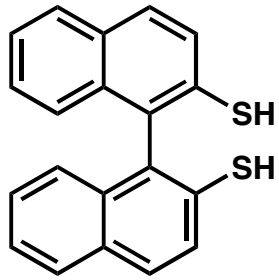
(S)-N-PINAP

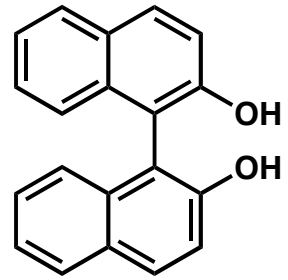
up to 98% ee

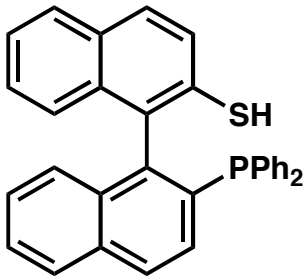
Axially chiral bidentate ligands

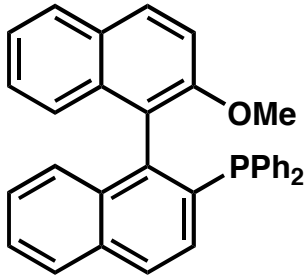


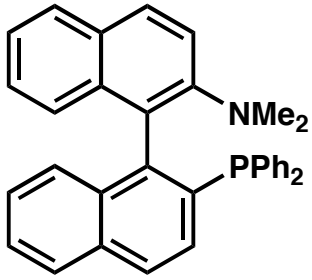


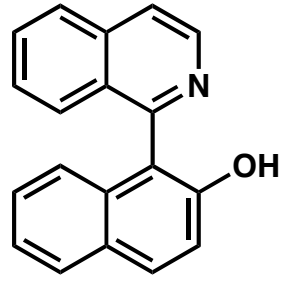


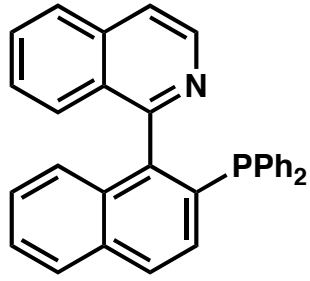


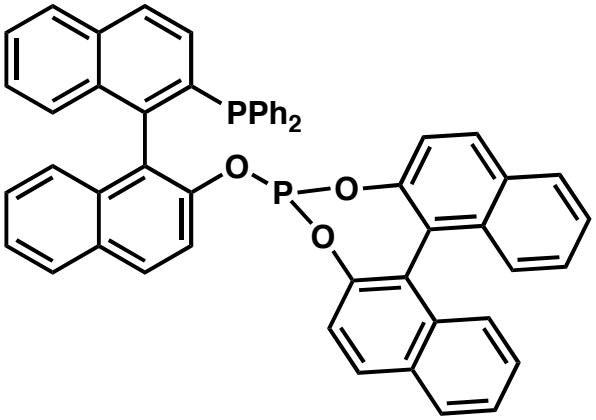


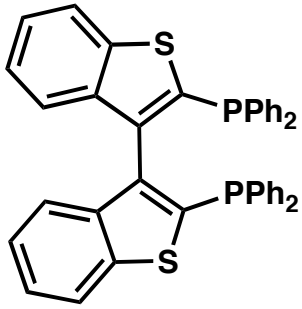


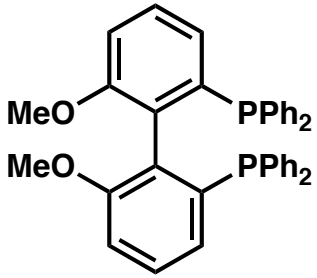


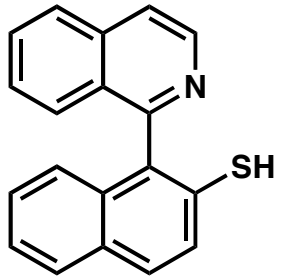






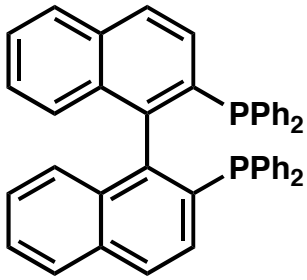


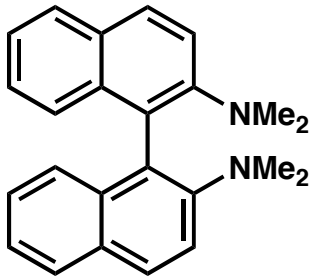


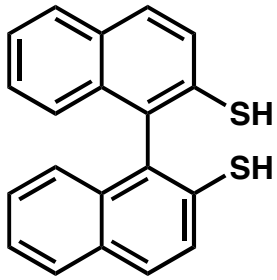


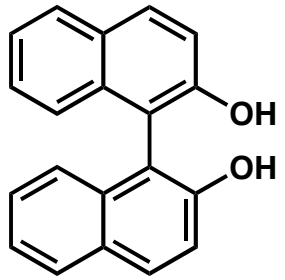
Guiry, *Tetrahedron* **2001**, *57*, 3809-3844.

Axially chiral bidentate ligands



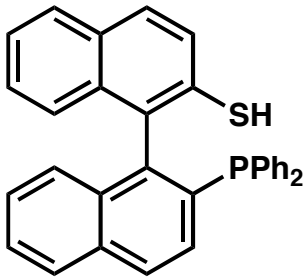


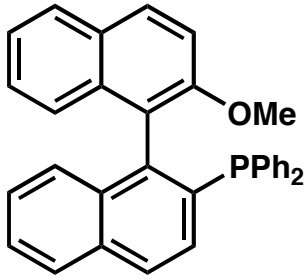


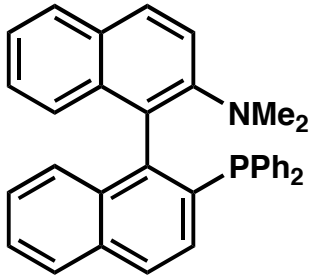


Guiry, *Tetrahedron* **2001**, *57*, 3809-3844.

Axially chiral bidentate ligands

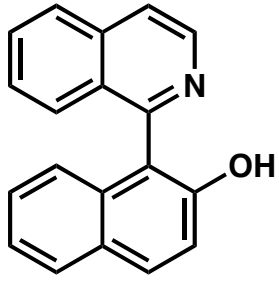


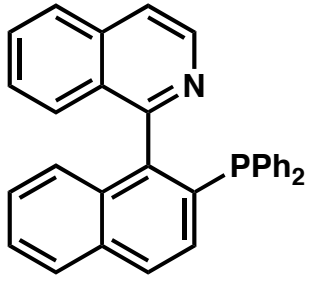


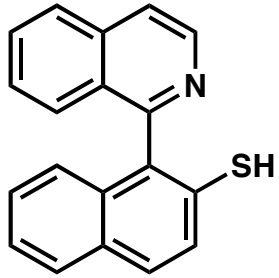


Guiry, *Tetrahedron* **2001**, *57*, 3809-3844.

Axially chiral bidentate ligands

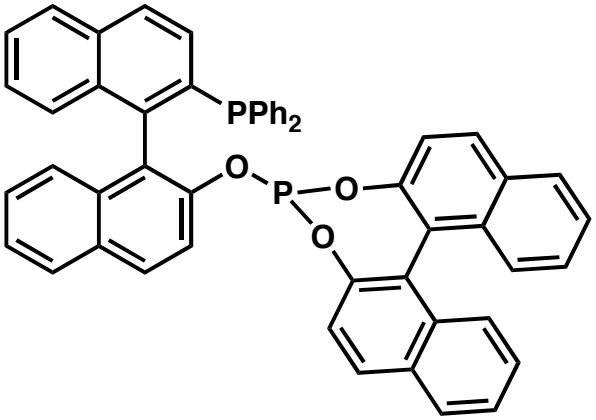


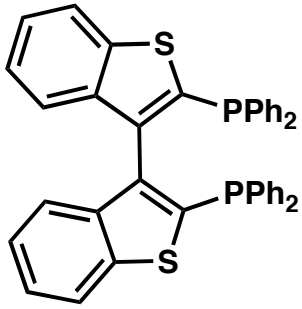


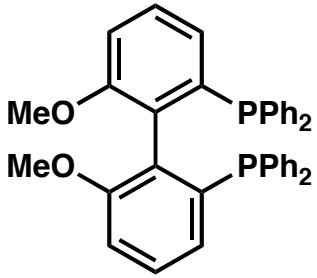


Guiry, *Tetrahedron* **2001**, *57*, 3809-3844.

Axially chiral bidentate ligands

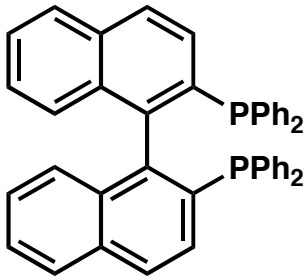




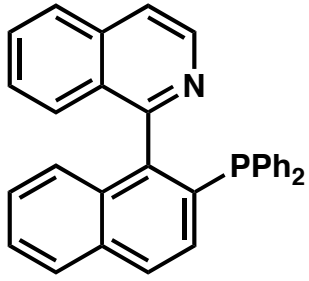


Guiry, *Tetrahedron* **2001**, *57*, 3809-3844.

Axially chiral bidentate ligands



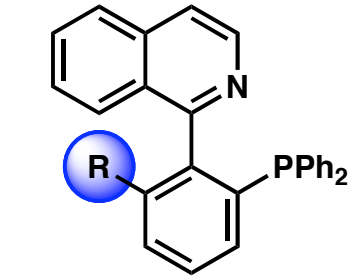
BINAP



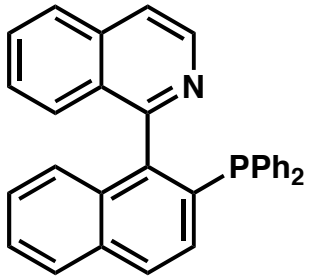
QUINAP

Guiry, *Tetrahedron* **2001**, *57*, 3809-3844.

First attempt towards a BINAP P,N analogue



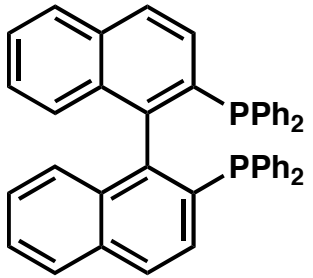
R = bulky group



1-(2-diphenylphosphino-1-naphthyl)isoquinoline

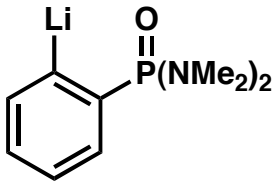
QUINAP

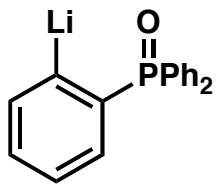
compare to



BINAP

Biaryl coupling via P(V)-directed ortho lithiation

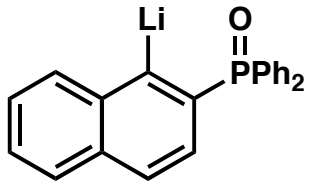




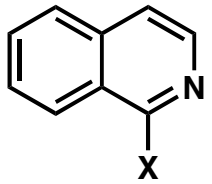
only with PhLi

apply towards

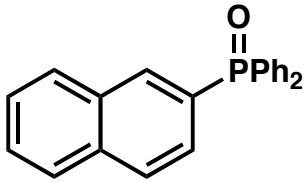
QUINAP



\+

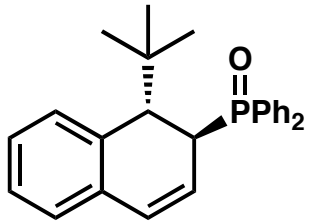


X = I, Br, Cl, OTf



t-BuLi

THF, –78 °C

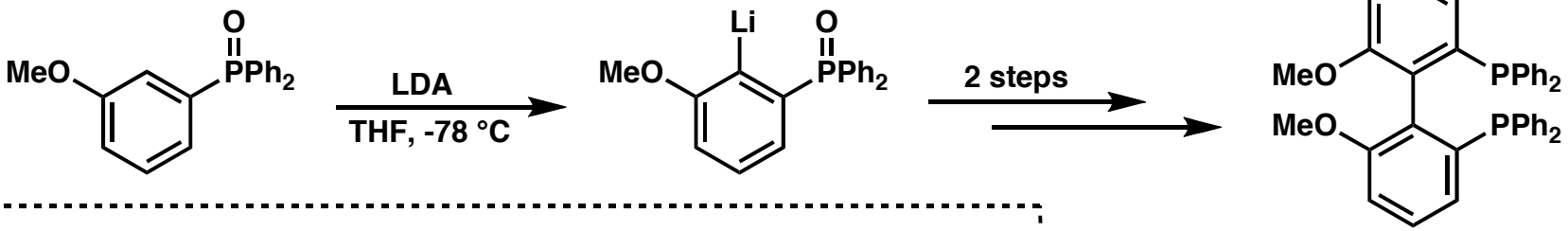


Brown, *J. Org. Chem.* **1991**, *56*, 6803-6809.

A slight change of plans

Methoxy-augmented directed metalation

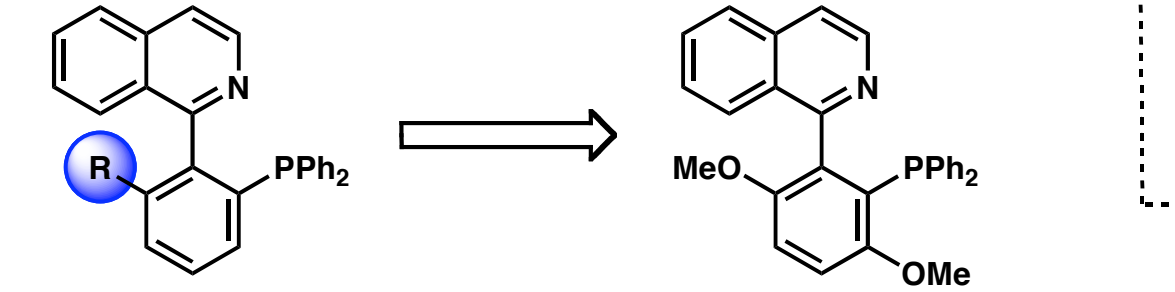
Schmid's *MeO-BIPHEP*



6,6'-dimethoxybiphenyl-2,2'-diyl)bis(diphenylphosphine)

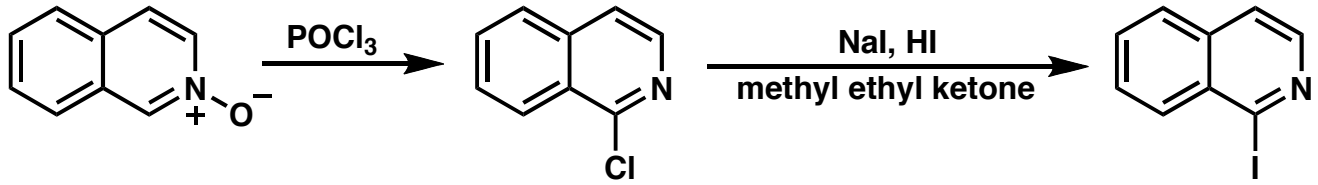
MeO-BIPHEP

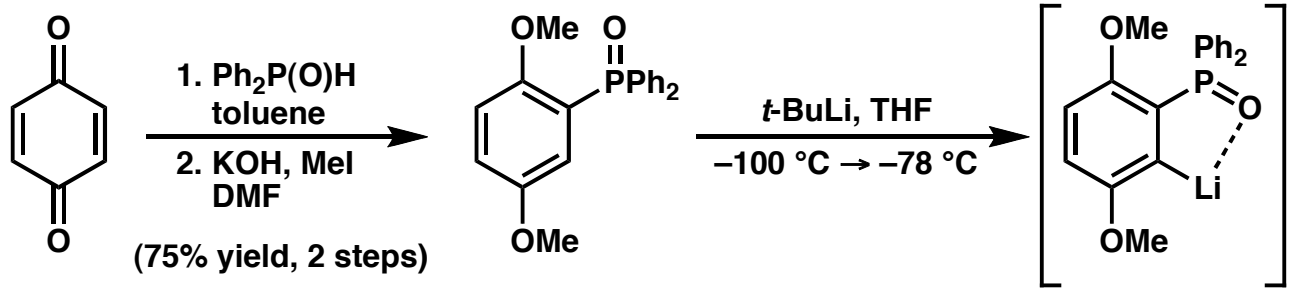
Schmid, *Helv. Chim. Acta* **1991**, *74*, 370-389.



2,5-dimethoxyphenyl(diphenyl)phosphine

R = bulky group

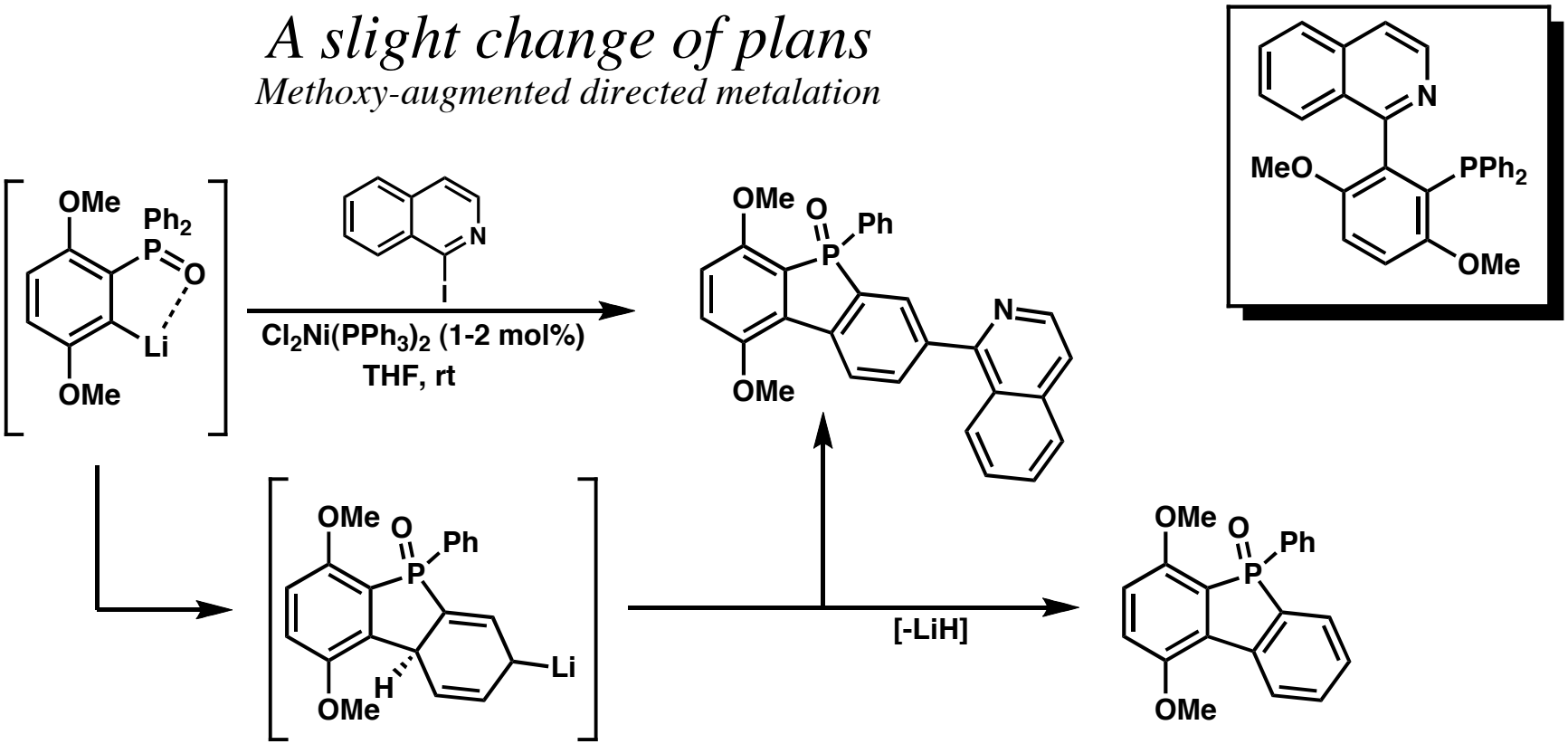


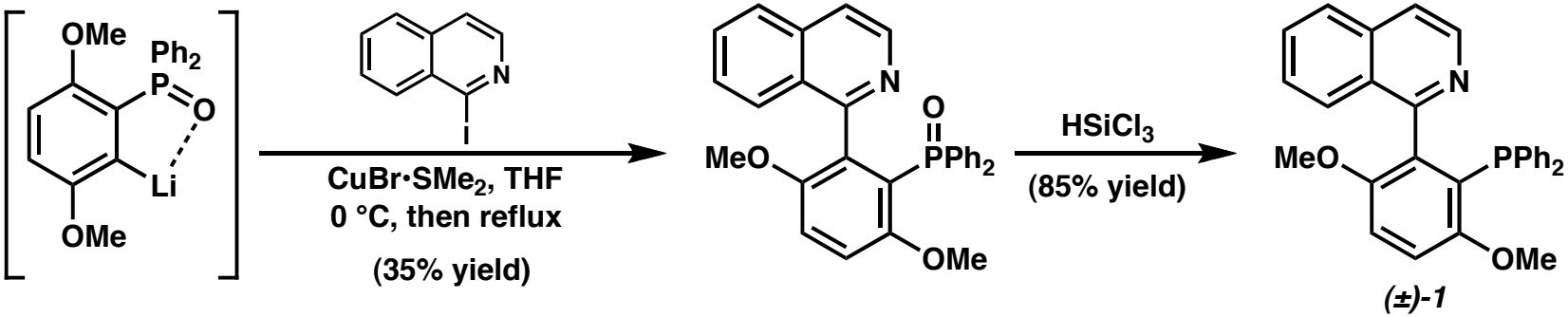


Brown, *J. Org. Chem.* **1991**, *56*, 6803-6809.
Brown, *Tetrahedron: Asymmetry* **1992**, *3*, 17-20.

A slight change of plans

Methoxy-augmented directed metalation

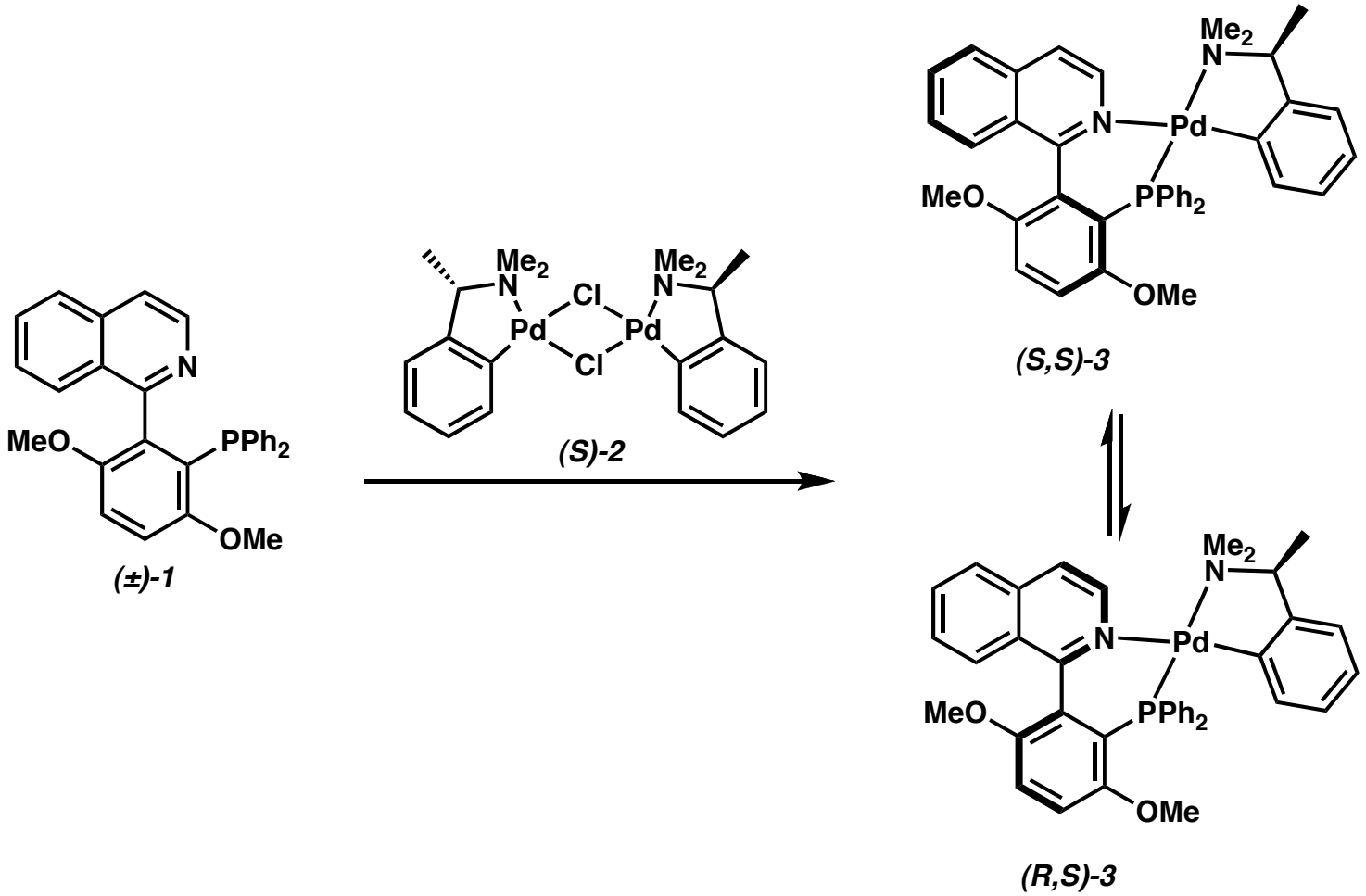




(±)-1

Brown, *Tetrahedron: Asymmetry* **1992**, *3*, 17-20.

Resolution of (±)-1



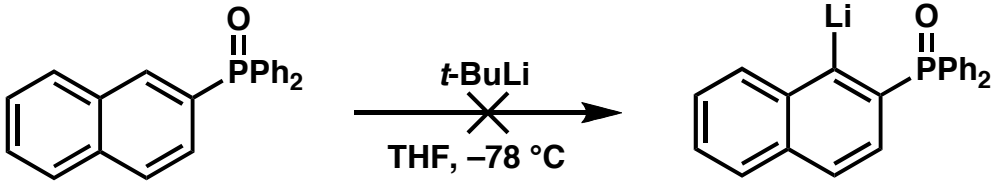
· Isolated complex 3 as a 1:1 mixture of diastereomers

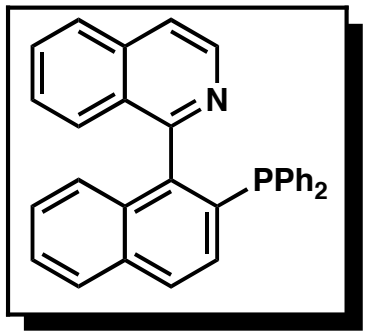
· However, on standing in acetone solution, one diastereomer becomes predominant (4:1)

· Ligand 1 must be epimerizing within complex via dissociation of isoquinoline nitrogen and subsequent rotation about the biaryl bond

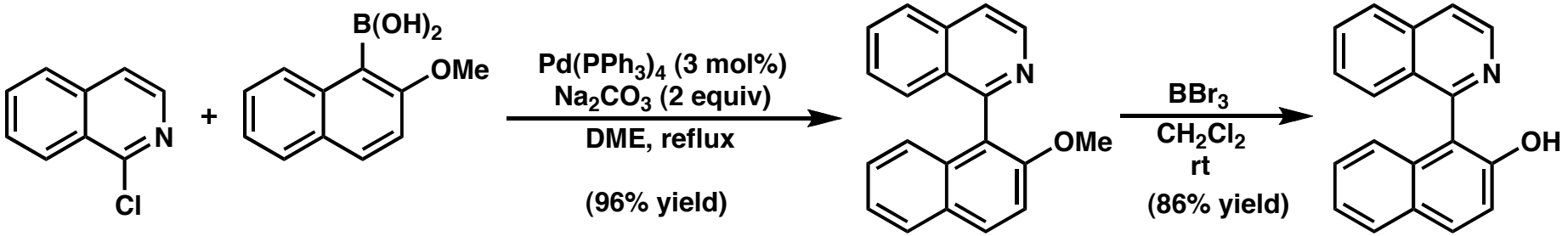
Brown, *Tetrahedron: Asymmetry* **1992**, *3*, 17-20.

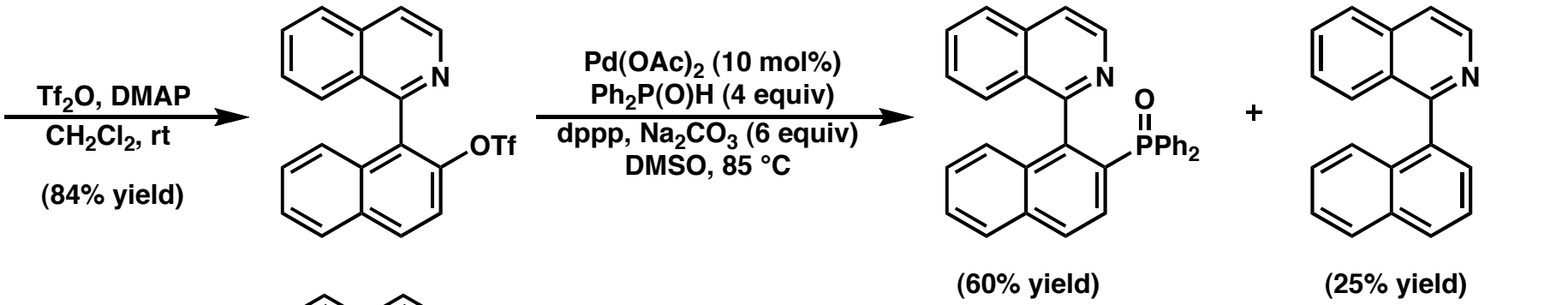
Revised synthesis of QUINAP

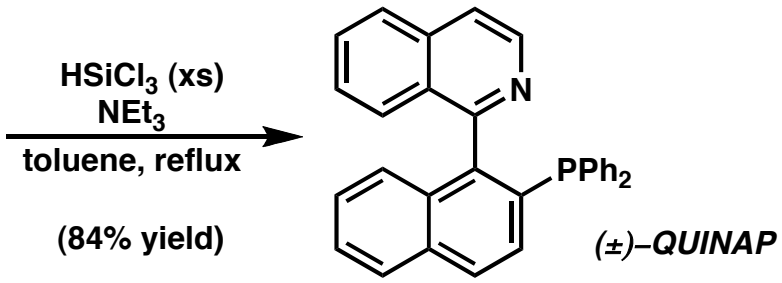




Construction of biaryl via Pd-catalyzed cross coupling

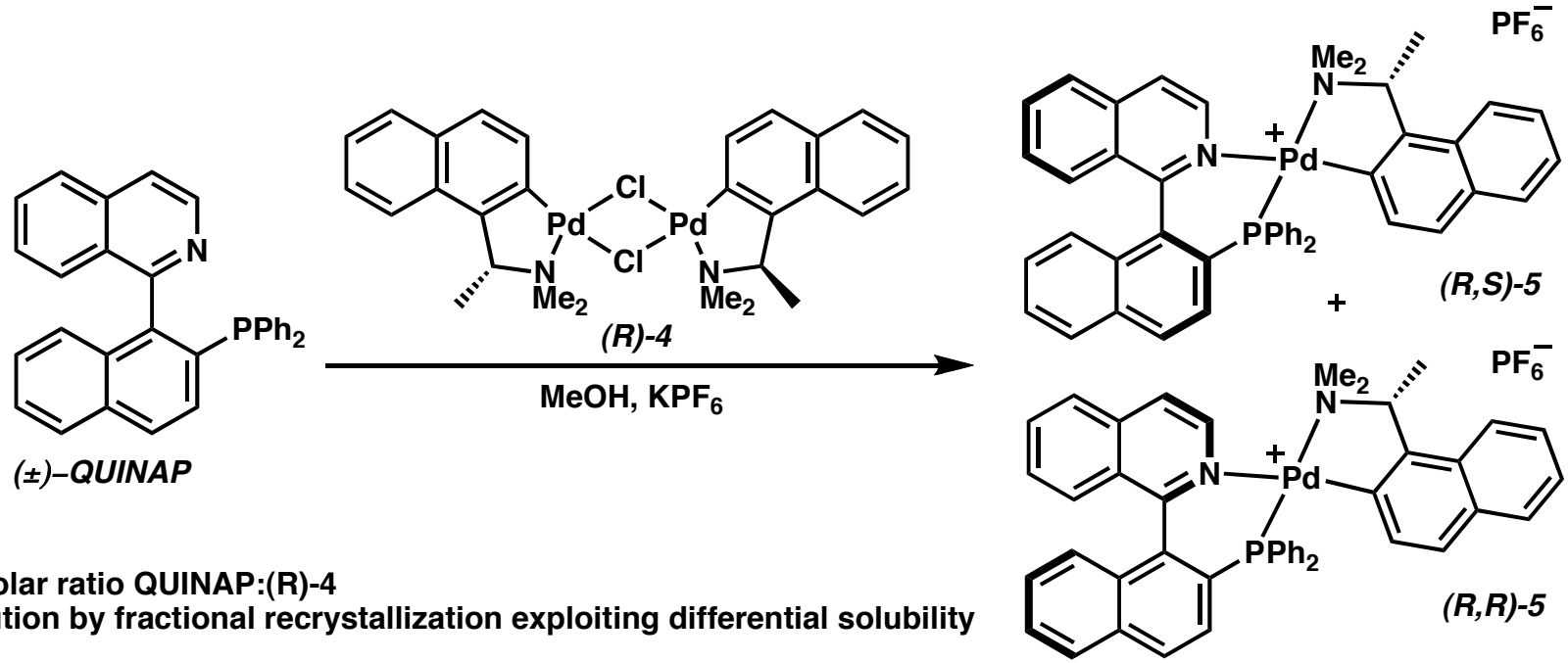




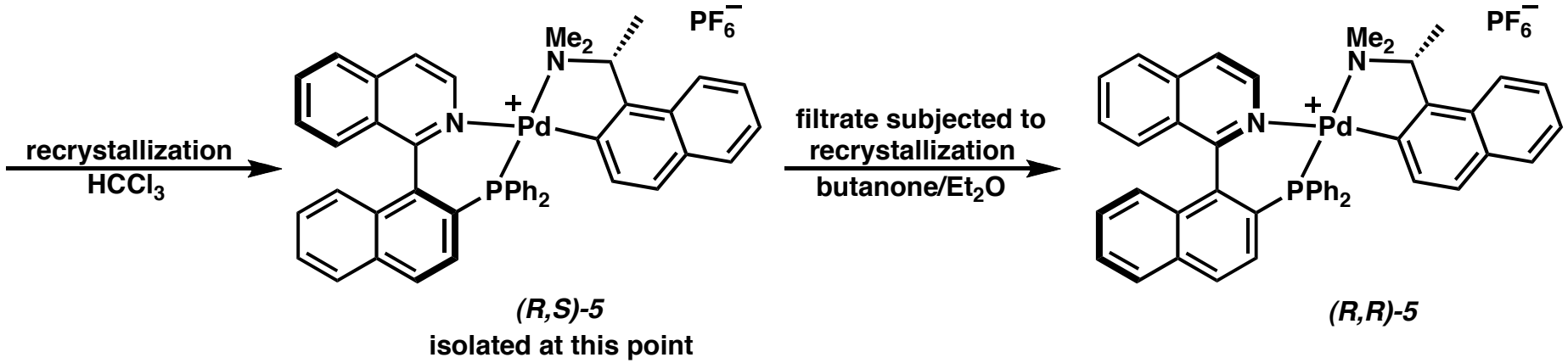


Brown, *Tetrahedron: Asymmetry* **1993**, *4*, 743-756.

Resolution of (±)-QUINAP



- **2:1 molar ratio QUINAP:(R)-4**
- **resolution by fractional recrystallization exploiting differential solubility**



Brown, *Tetrahedron: Asymmetry* **1993**, *4*, 743-756.

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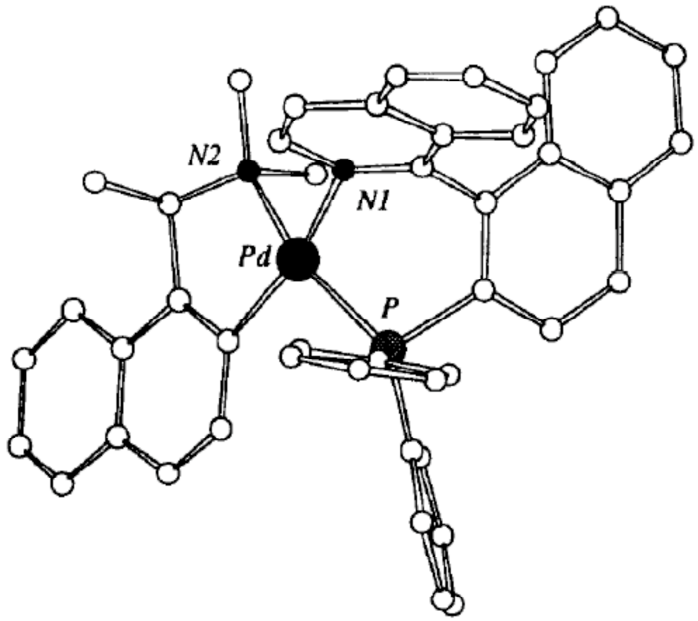

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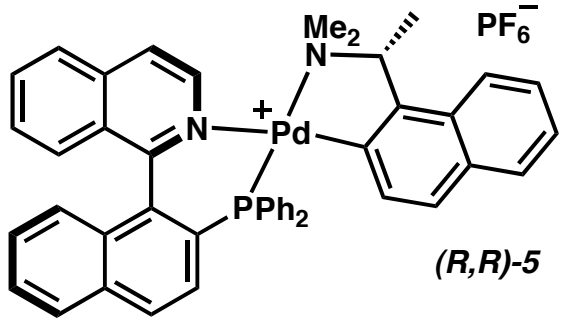
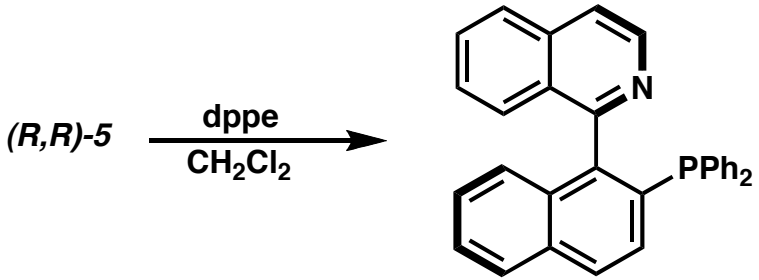
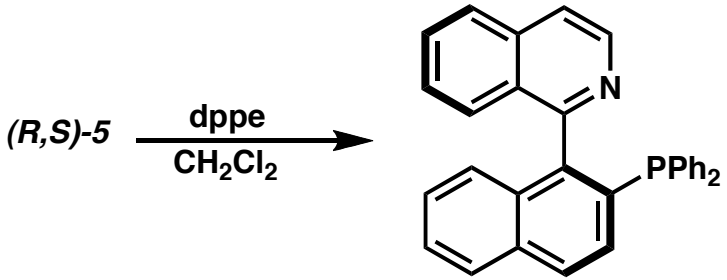


(R,R)-5

- **Formation of chelate ring requires distortion from ideal bond angles**
- **Vector of N-Pd bond out of isoquinoline ring plane (≈ 24°)**
- **Inter-aryl dihedral angle = 65°, similar to BINAP**



(R)-QUINAP



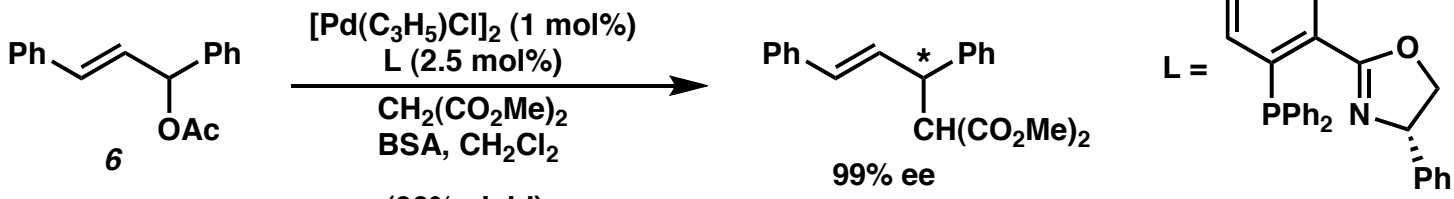
(S)-QUINAP

- **Enantiomerically pure compound does not racemize appreciably on heating to 65 °C for 24h**

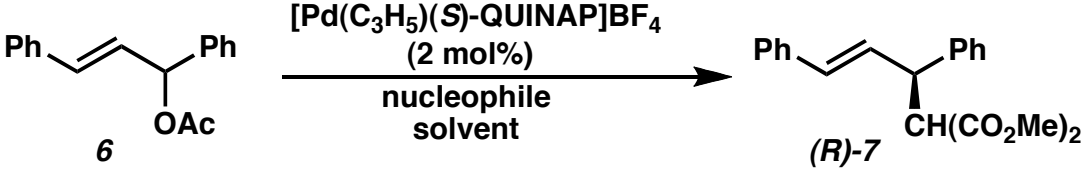
Brown, *Tetrahedron: Asymmetry* **1993**, *4*, 743-756.

Catalytic allylic alkylation

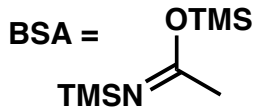
Testing QUINAP's stereoinducing ability

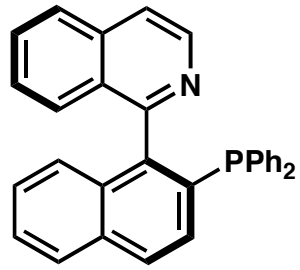


Pfaltz, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 566-568.



entry	nucleophile	solvent	T (°C)	additive	% ee
1	$CH_2(CO_2Me)_2$ BSA	THF	20	none	75
2	$CH_2(CO_2Me)_2$ BSA	CH_2Cl_2	20	none	76
3	$CH_2(CO_2Me)_2$ BSA	CH_3CN	20	none	78
4	$NaCH(CO_2Me)_2$	CH_2Cl_2	20	none	75
5	$NaCH(CO_2Me)_2$	CH_3CN	20	none	78
6	$NaCH(CO_2Me)_2$	CH_2Cl_2	20	15-crown-5	90
7	$LiCH(CO_2Me)_2$	CH_2Cl_2	20	15-crown-5	73
8	$NaCH(CO_2Me)_2$	neat 15-crown-5	20	15-crown-5	92
9	$NaCH(CO_2Me)_2$	CH_3CN	20	15-crown-5	95
10	$NaCH(CO_2Me)_2$	CH_3CN	-13	15-crown-5	98.2 (95% yield)





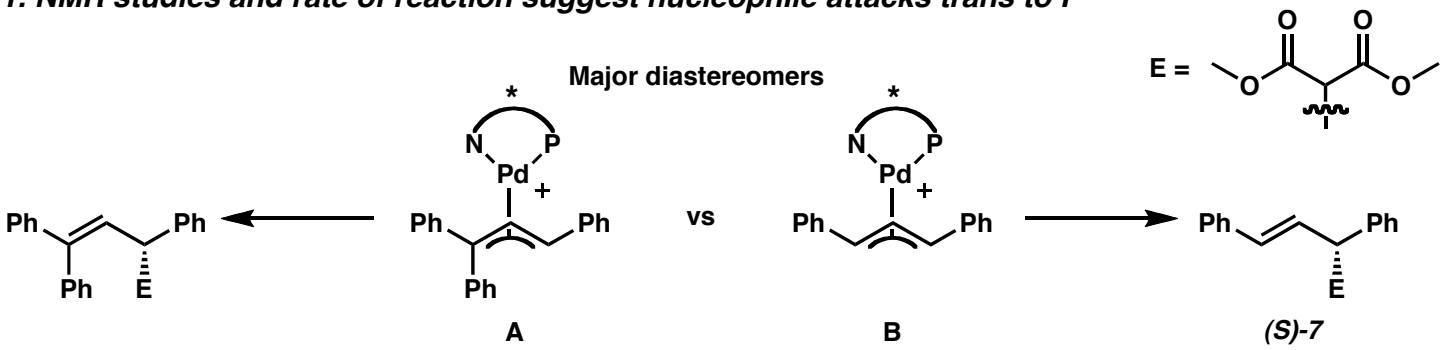
(S)–QUINAP

Brown, *Tetrahedron*, **1994**, *50*, 4493-4506.

Catalytic allylic alkylation

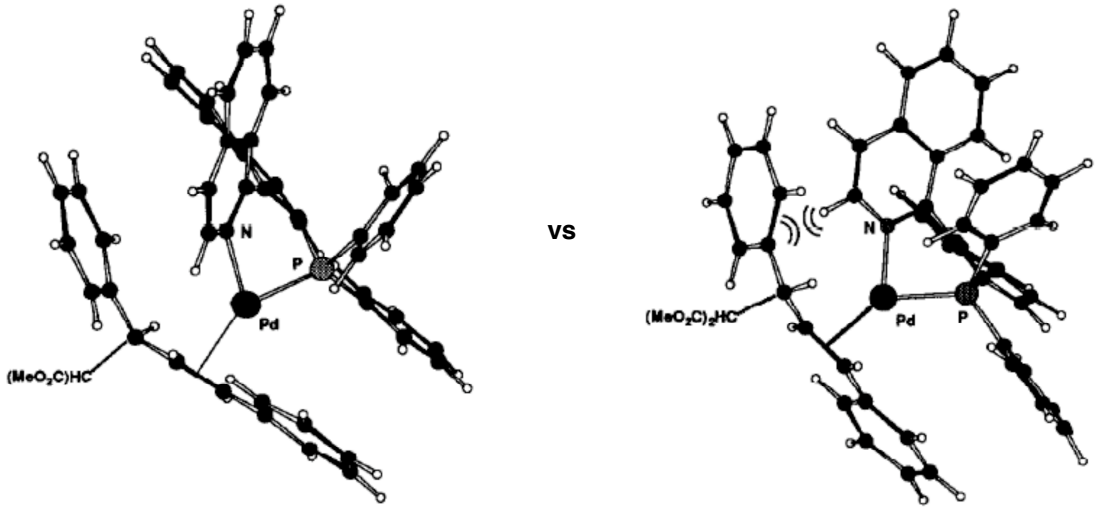
A model transition state: rationalizing stereoinduction

1. NMR studies and rate of reaction suggest nucleophile attacks trans to P



- **Major diastereomers of allylpalladium complexes of *(R)-QUINAP* determined by NMR analysis**
- **Major product has malonate bonded to less substituted terminus**
- **If reactive allyl terminus must be trans to P, then unfavorable equilibrium is necessary for A**

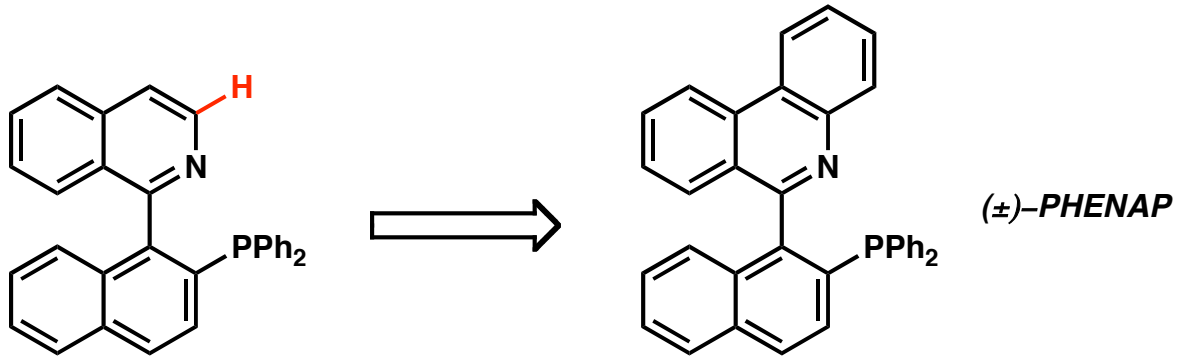
2. Assume nucleophilic attack on allyl occurs via a late transition state



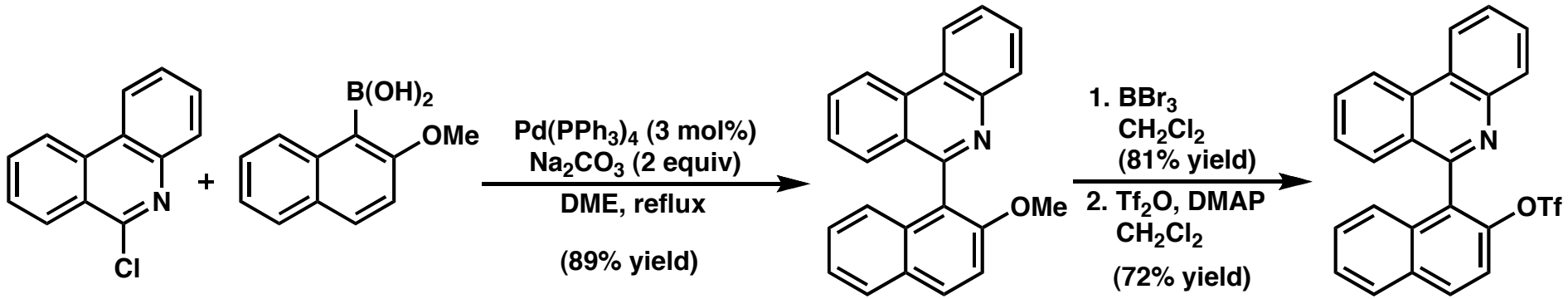
- **Attack trans to P in a product like geometry engenders steric interactions between H_3 of isoquinoline and phenyl group of allyl moiety**

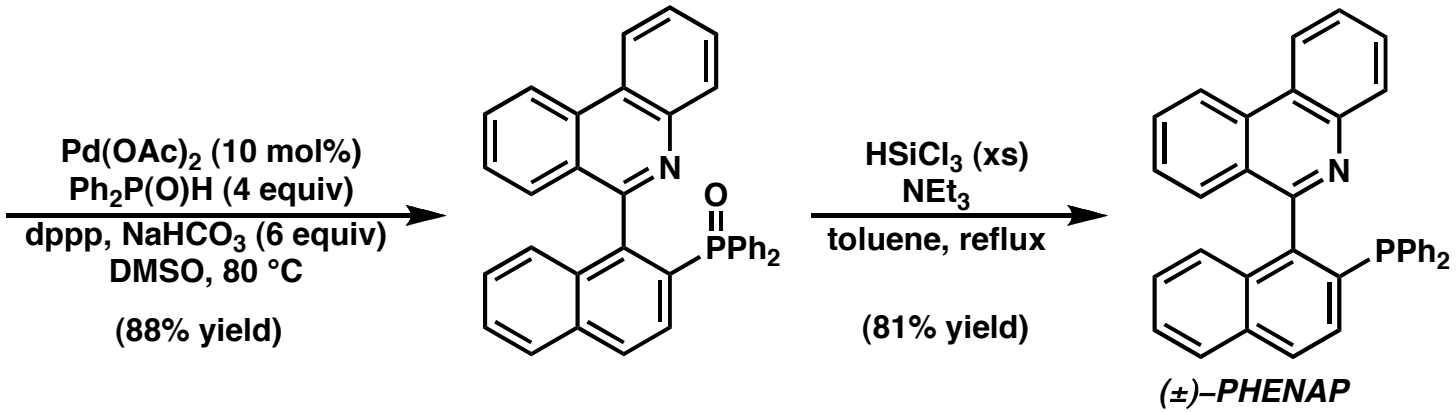
Brown, *Tetrahedron* **1994**, *50*, 4493-4506.

Increased steric demand: PHENAP



(±)–QUINAP **6-(2'-diphenylphosphino-1'-naphthyl)phenanthridine** ***(±)–PHENAP***

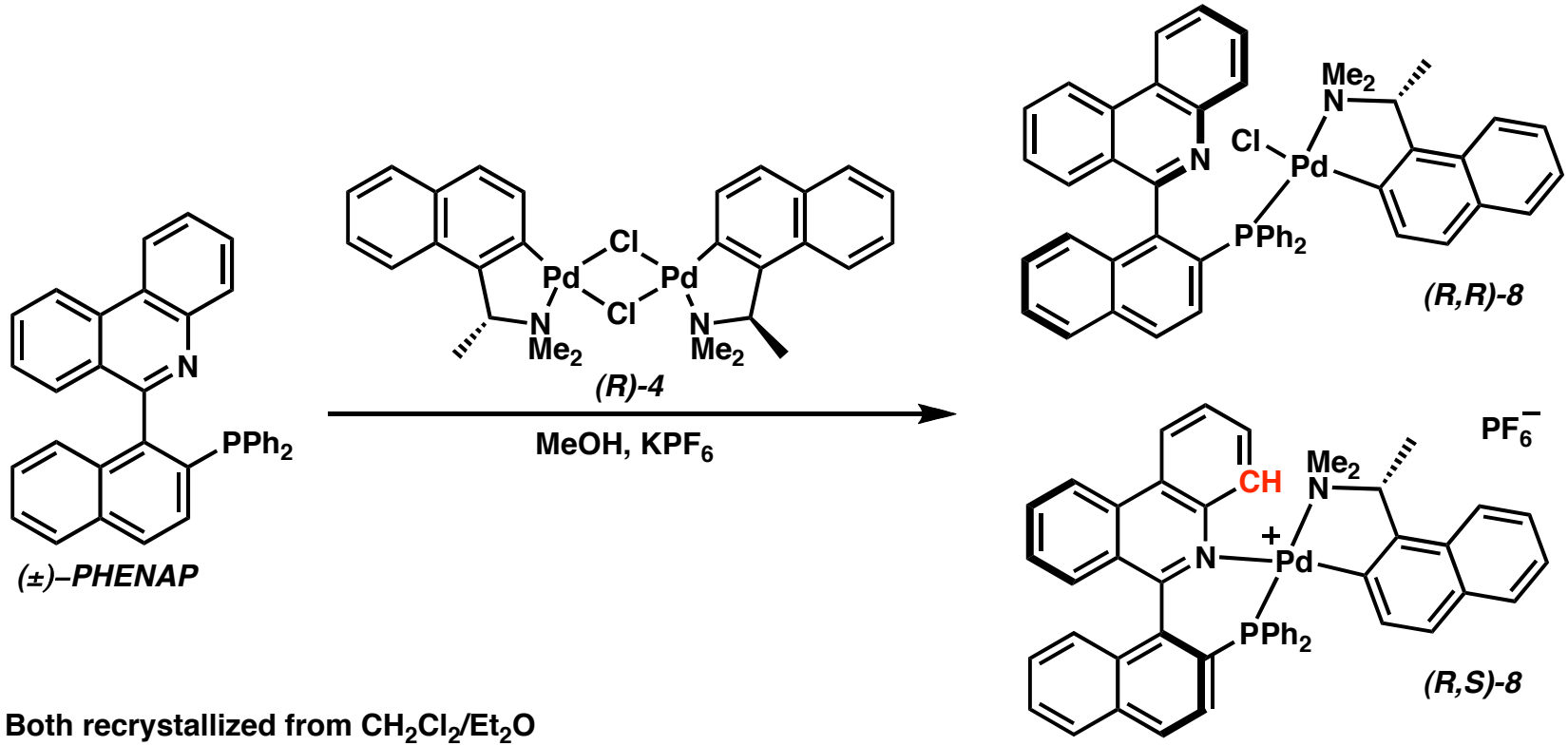




(±)–PHENAP

Brown, *Tetrahedron: Asymmetry* **1995**, *6*, 2597-2610.

Resolution of PHENAP



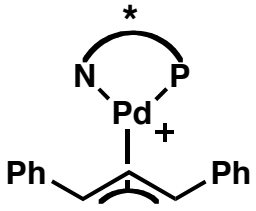
- **Both recrystallized from CH_2Cl_2/Et_2O**
- **X-ray crystal structure of (*R,S*)-8 shows once again strain in the chelate ring with N-Pd vector displaced about 18°**
- **Biaryl twist = 64°**
- **H_7 of phenanthridine in close proximity to metal; implies closer ligand-reactant contact**

Brown, *Tetrahedron: Asymmetry* **1995**, *6*, 2597-2610.

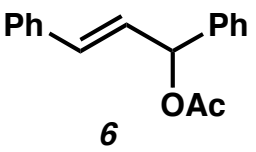
Catalytic allylic alkylation

PHENAP vs QUINAP

- **NMR studies reveal PHENAP exhibits higher diasteroselectivity on complexation**

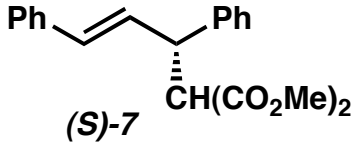


entry	ligand	solvent	major:minor
1	***QUINAP***	$CDCl_3$	2:1
2	***PHENAP***	$CDCl_3$	10:1
3	***QUINAP***	CD_2Cl_2	6:1
4	***PHENAP***	CD_2Cl_2	20:1



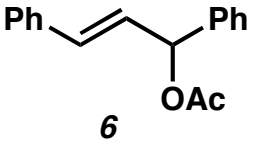
6

$[Pd(CH_3H_5)(R)\text{-PHENAP}]BF_4$
(2 mol%)
$NaCH(CO_2Me)_2$
15-crown-5
CH_3CN, 0 °C



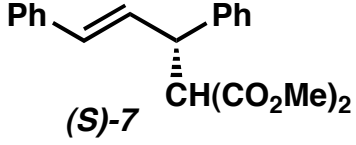
(S)-7

95% ee (cf. 98% ee w/QUINAP)



6

$[Pd(CH_3H_5)(R)\text{-PHENAP}]BF_4$
(2 mol%)
$CH_2(CO_2Me)_2$, BSA
CH_2Cl_2, 20 °C



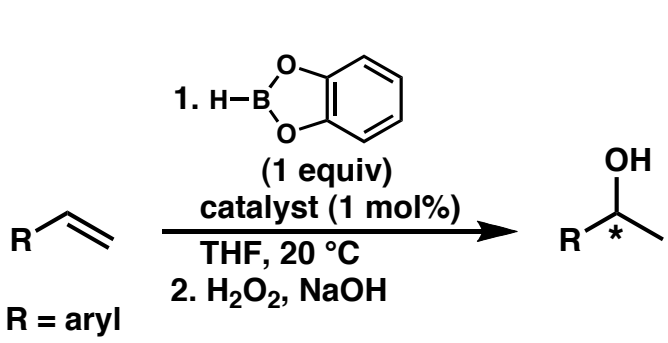
(S)-7

94% ee (cf. 76% ee w/QUINAP)

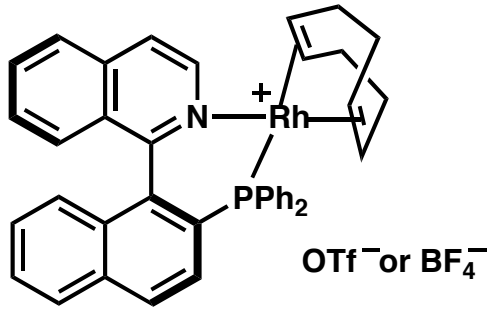
Brown, *Tetrahedron: Asymmetry* **1995**, *6*, 2597-2610.

Asymmetric hydroboration

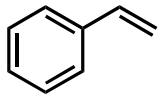
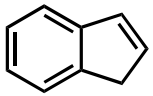
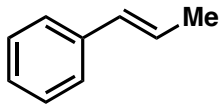
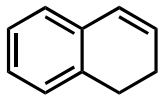
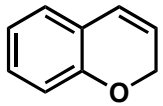
QUINAP



catalyst =



(S)-9

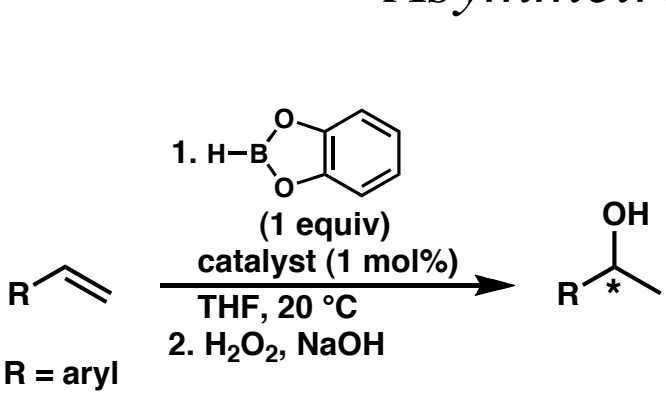
entry	reactant	catalyst	% yield	% ee	configuration
1		(*S*)-9	75	91.5	*S*
2[a]		(*S*)-9	75	86	*S*
3		(*S*)-9	80	95	*S*
4		(*S*)-9	78	96	*S*
5		(*S*)-9	82	90	*S*

[a] **In a previous publication, 99% ee is claimed, but this result could not be reproduced.**

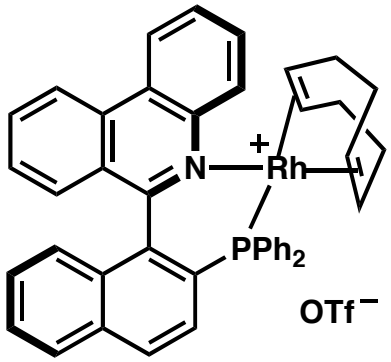
Brown, *Tetrahedron: Asymmetry* **1995**, *6*, 2593-2596; Brown, *Chem. Eur. J.* **1999**, *5*, 1320-1330.

Asymmetric hydroboration

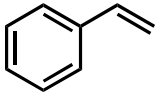
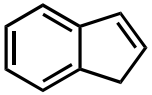
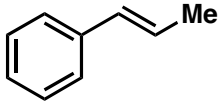
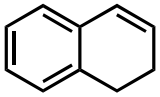
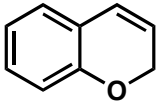
PHENAP



catalyst =



(R)-10

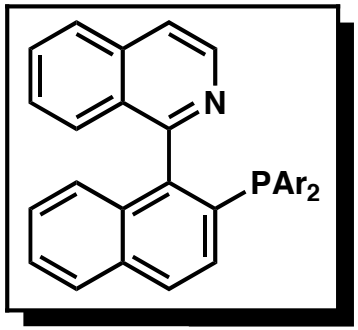
entry	reactant	catalyst	% yield	% ee	configuration
1		(*S*)-9 (*R*)-10	75 70	91.5 67	*S* *R*
2[a]		(*S*)-9 (*R*)-10	75 59	86 64	*S* *R*
3		(*S*)-9 (*R*)-10	80 60	95 91	S R
4		(*S*)-9 (*R*)-10	78 69	96 84	*S* *R*
5		(*S*)-9 (*R*)-10	82 57	90 74	*S* *R*

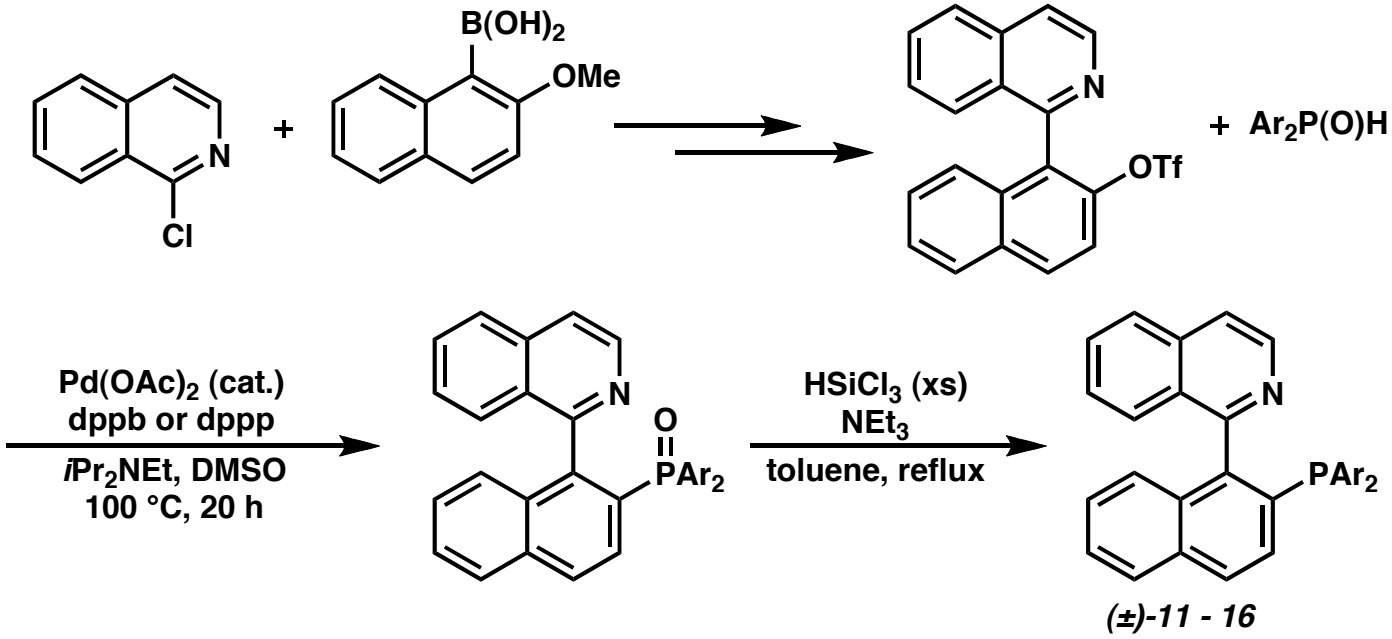
black = ***QUINAP***
blue = ***PHENAP***

[a] In a previous publication, 99% ee is claimed, but this result could not be reproduced.

Brown, *Tetrahedron: Asymmetry* **1995**, *6*, 2593-2596; Brown, *Chem. Eur. J.* **1999**, *5*, 1320-1330.

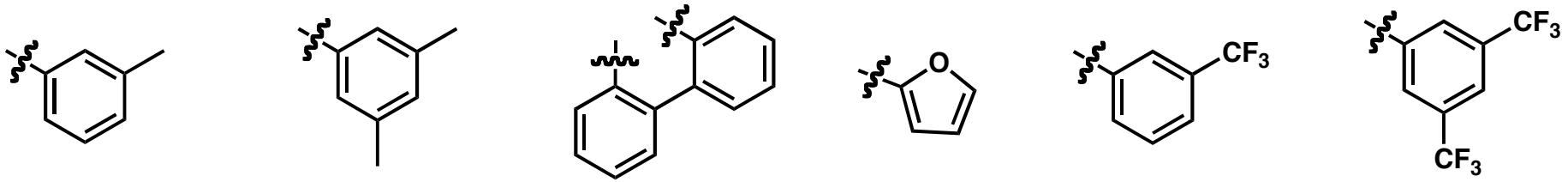
Variation of the aryl substituent





(±)-11 - 16

11 Ar = 3-MeC_6H_4 **12 Ar = 3,5-diMeC_6H_3** **13 Ar_2 = biphenylyl** **14 Ar = 2-furyl** **15 Ar = 3-$CF_3C_6H_4$** **16 Ar = 3,5-di$CF_3C_6H_3$**



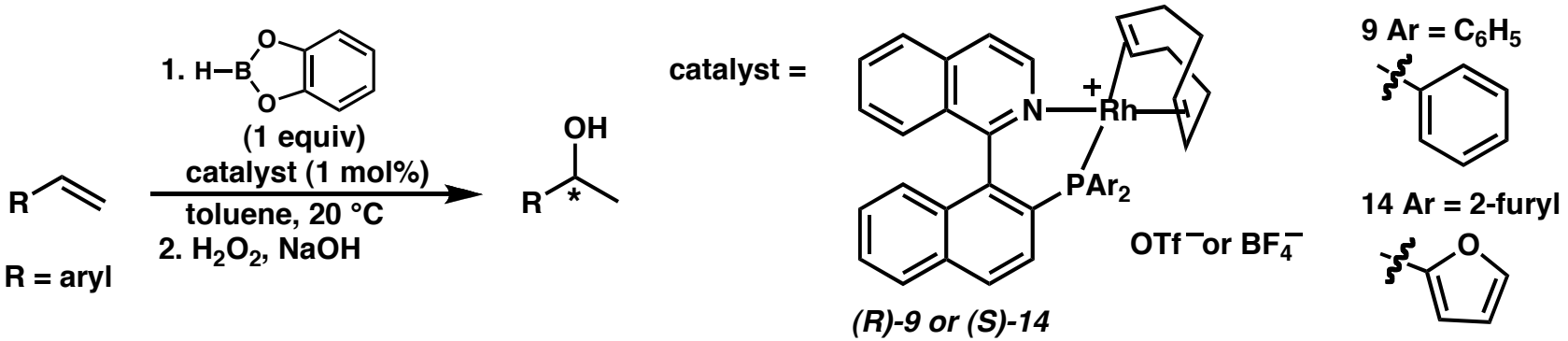
(63% yield) **(63% yield)** **(73% yield)** **(57% yield)** **(43% yield)** **(50% yield)**

- **Resolution effected via complexation with di-μ-chloro-bis[(*R*)-dimethyl(1-phenethyl)aminato-C^2, N]dipalladium**
- ***(±)-15* and *(±)-16* could not be resolved**

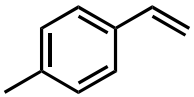
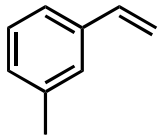
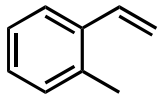
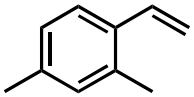
Brown, *Tetrahedron: Asymmetry* **1997**, *8*, 3775-3784.

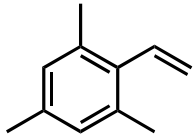
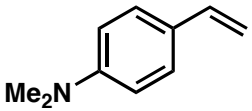
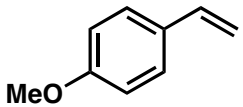
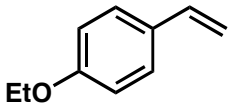
Asymmetric hydroboration

Effects of aryl substituents on enantiomer excess



Aryl groups with *electron-releasing* substituents

entry	reactant	catalyst	% yield	% *sec*-OH[a]	% ee
1		(*R*)-9 (*S*)-14	75 79	97 94	89 88
2		(*R*)-9 (*S*)-14	81 80	97 92	86 81
3		(*R*)-9 (*S*)-14	82 74	93 93	92 90
4		(*R*)-9 (*S*)-14	78 81	95 97	94 93

entry	reactant	catalyst	% yield	% *sec*-OH[a]	% ee
5[b]		(*R*)-9	21	63	77
6		(*R*)-9 (*S*)-14	55 67	97 96	62 79
7		(*R*)-9	82	96	94
8		(*R*)-9 (*S*)-14	82 72	96 91	94 78

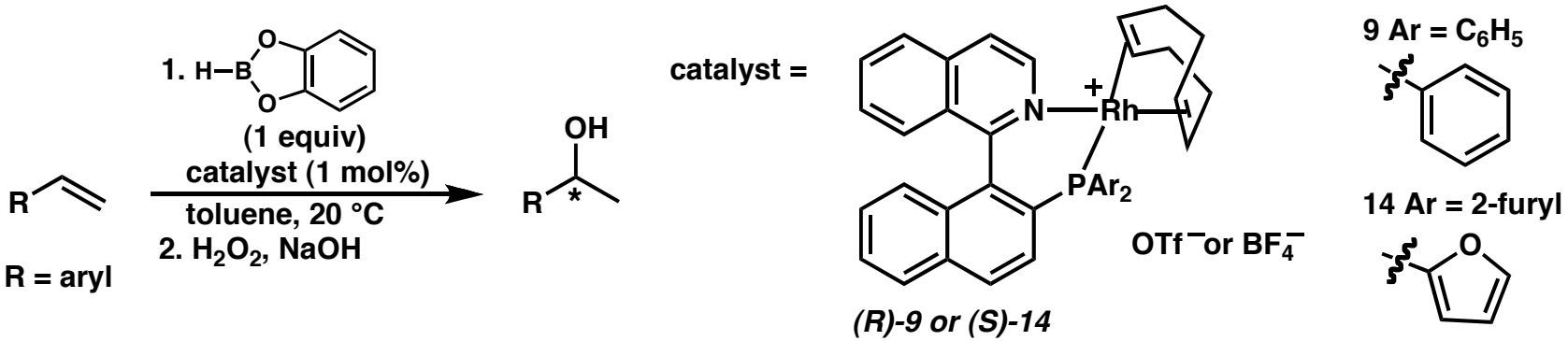
[a] Remainder primary alcohol

[b] 5% excess ligand

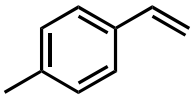
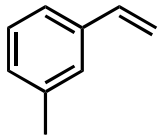
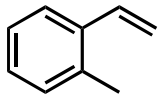
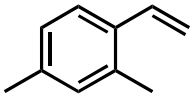
Brown, *Chem. Eur. J.* **1999**, *5*, 1320-1330.

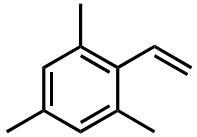
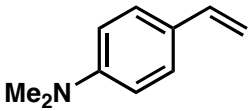
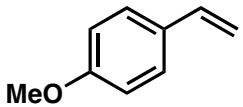
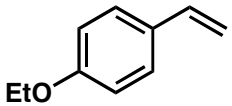
Asymmetric hydroboration

Effects of aryl substituents on enantiomer excess



Aryl groups with *electron-releasing* substituents

entry	reactant	catalyst	% yield	% *sec*-OH[a]	% ee
1		(*R*)-9 (*S*)-14	75 79	97 94	89 88
2		(*R*)-9 (*S*)-14	81 80	97 92	86 81
3		(*R*)-9 (*S*)-14	82 74	93 93	92 90
4		(*R*)-9 (*S*)-14	78 81	95 97	94 93

entry	reactant	catalyst	% yield	% *sec*-OH[a]	% ee
5[b]		(*R*)-9	21	63	77
6		(*R*)-9 (*S*)-14	55 67	97 96	62 79
7		(*R*)-9	82	96	94
8		(*R*)-9 (*S*)-14	82 72	96 91	94 78

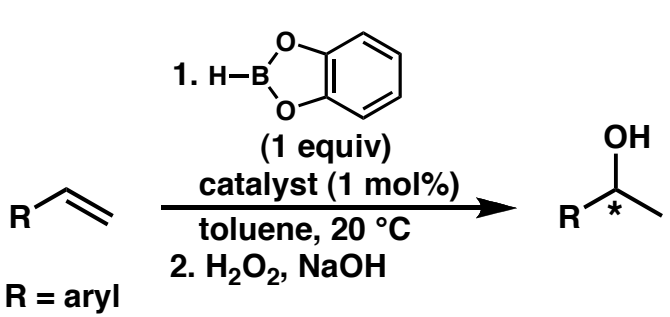
[a] Remainder primary alcohol

[b] 5% excess ligand

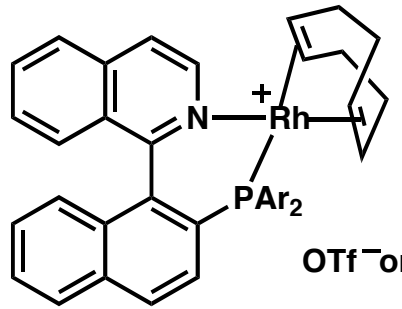
Brown, *Chem. Eur. J.* **1999**, *5*, 1320-1330.

Asymmetric hydroboration

Effects of aryl substituents on enantiomer excess



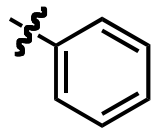
catalyst =



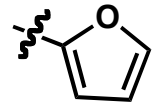
(R)-9 or (S)-14

OTf^- or BF_4^-

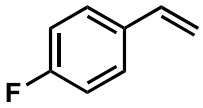
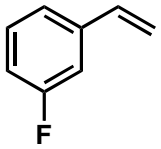
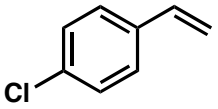
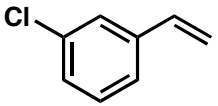
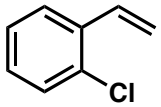
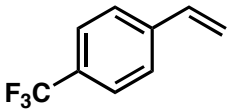
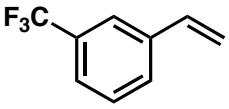
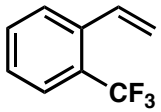
9 Ar = C_6H_5



14 Ar = 2-furyl



Aryl groups with *electron-withdrawing* substituents

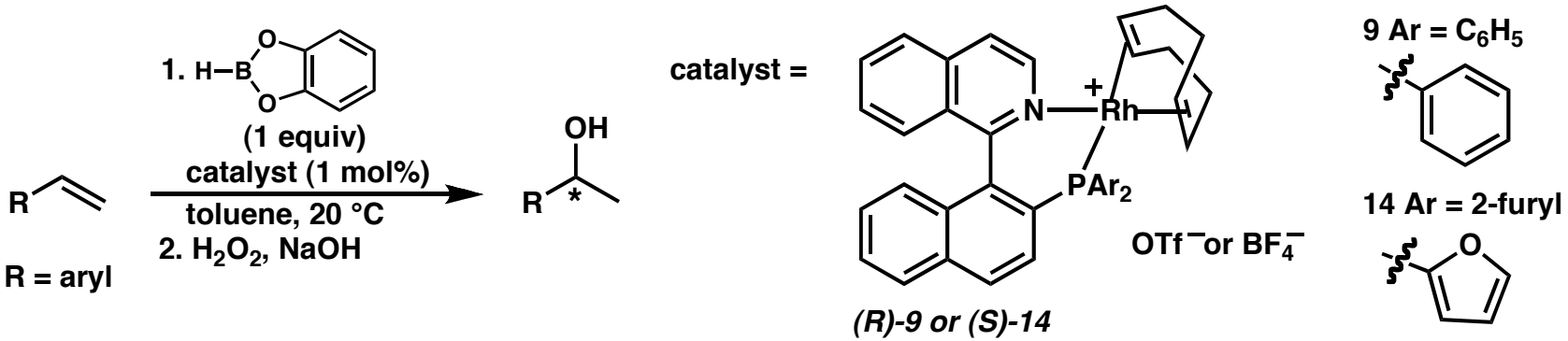
entry	reactant	catalyst	% yield	% *sec*-OH[a]	% ee
1		(*R*)-9	77	96	80
		(*S*)-14	77	92	75
2		(*R*)-9	72	97	67
		(*S*)-14	80	95	77
3		(*R*)-9	82	96	78
		(*S*)-14	78	94	82
4		(*R*)-9	82	97	63
		(*S*)-14	75	95	89
5[a]		(*R*)-9	59	96	55
		(*S*)-14	74	93	69
6		(*R*)-9	81	95	45
		(*S*)-14	82	92	74
7		(*R*)-9	81	95	37
		(*S*)-14	76	97	83
8		(*R*)-9	81	98	66
		(*S*)-14	82	97	83

[a] Remainder primary alcohol

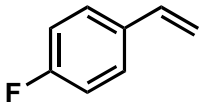
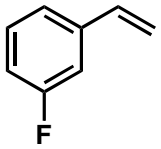
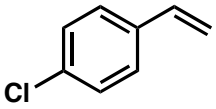
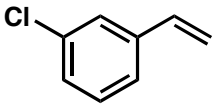
Brown, *Chem. Eur. J.* **1999**, *5*, 1320-1330.

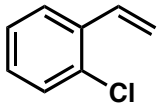
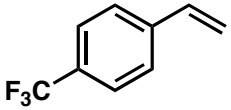
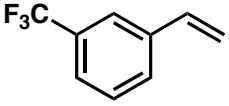
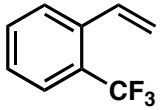
Asymmetric hydroboration

Effects of aryl substituents on enantiomer excess



Aryl groups with *electron-withdrawing* substituents

entry	reactant	catalyst	% yield	% *sec*-OH[a]	% ee
1		(*R*)-9	77	96	80
		(*S*)-14	77	92	75
2		(*R*)-9	72	97	67
		(*S*)-14	80	95	77
3		(*R*)-9	82	96	78
		(*S*)-14	78	94	82
4		(*R*)-9	82	97	63
		(*S*)-14	75	95	89

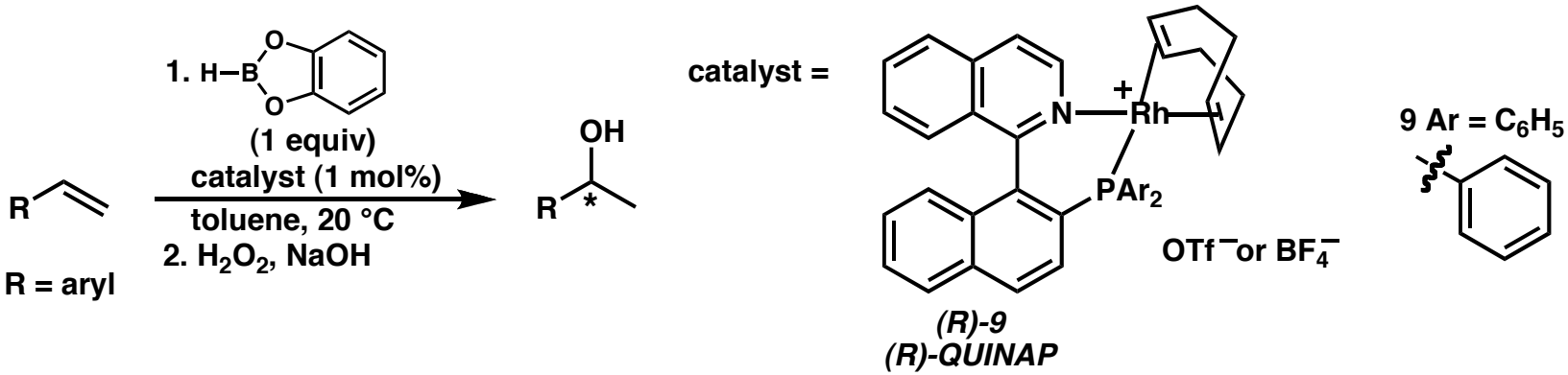
entry	reactant	catalyst	% yield	% *sec*-OH[a]	% ee
5		(*R*)-9	59	96	55
		(*S*)-14	74	93	69
6		(*R*)-9	81	95	45
		(*S*)-14	82	92	74
7		(*R*)-9	81	95	37
		(*S*)-14	76	97	83
8		(*R*)-9	81	98	66
		(*S*)-14	82	97	83

[a] Remainder primary alcohol

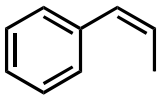
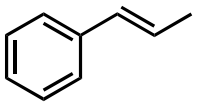
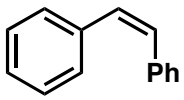
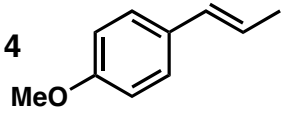
Brown, *Chem. Eur. J.* **1999**, *5*, 1320-1330.

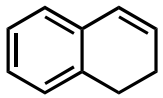
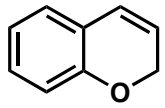
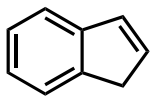
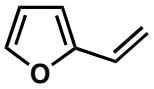
Asymmetric hydroboration

Effects of aryl substituents on enantiomer excess



β-substituted vinylarenes

entry	reactant	catalyst	% yield	% *sec*-OH[a]	% ee
1		(*R*)-9	80	99	93
2		(*R*)-9	80	99	95
3		(*R*)-9	86		91
4		(*R*)-9	84	99	97

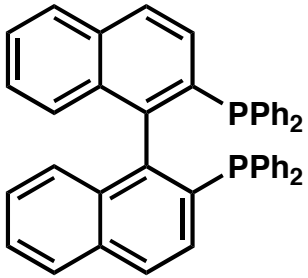
entry	reactant	catalyst	% yield	% *sec*-OH[a]	% ee
5		(*R*)-9	78	99	96
6		(*R*)-9	82	96	90
7		(*R*)-9	80	99	86
8		(*R*)-9	64	96	66

[a] Remainder primary alcohol

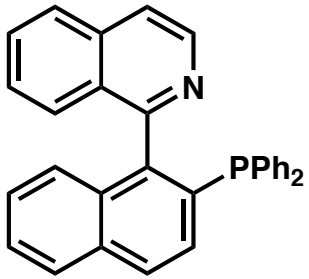
Brown, *Chem. Eur. J.* **1999**, *5*, 1320-1330.

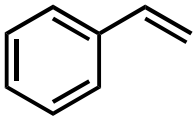
Asymmetric hydroboration

QUINAP vs BINAP



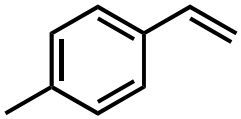
vs



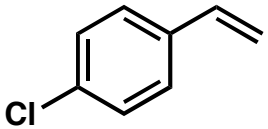


96% ee
–78 °C

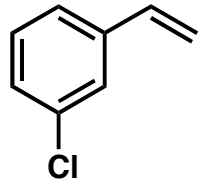
57% ee
25 °C



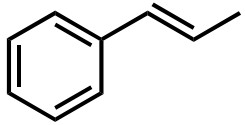
94% ee
–78 °C



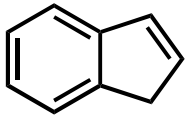
91% ee
–78 °C



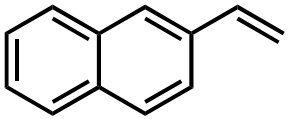
85% ee
–78°C



42% ee
–78 °C



13% ee
–78 °C

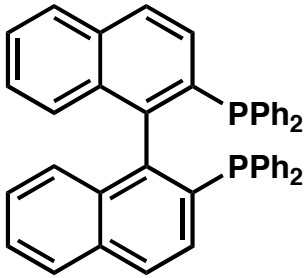


13% ee
–78 °C

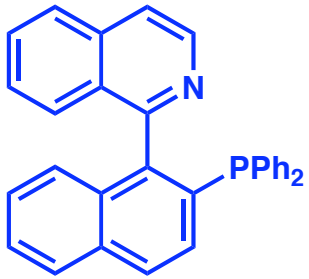
Brown, *Chem. Eur. J.* **1999**, *5*, 1320-1330.
Hayashi, *J. Am. Chem. Soc.* **1989**, *111*, 3426-3428.

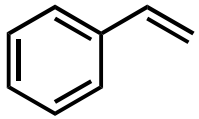
Asymmetric hydroboration

QUINAP vs BINAP



vs

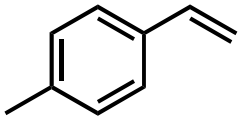




96% ee
–78 °C

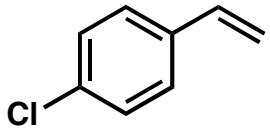
57% ee
25 °C

92% ee
20 °C



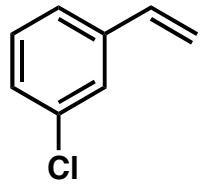
94% ee
–78 °C

89% ee
20 °C



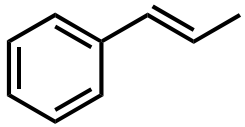
91% ee
–78 °C

82% ee
20 °C



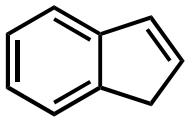
85% ee
–78°C

89% ee
20 °C



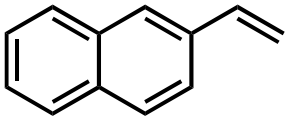
42% ee
–78 °C

95% ee
20 °C



13% ee
–78 °C

86% ee
20 °C



13% ee
–78 °C

89% ee
20 °C

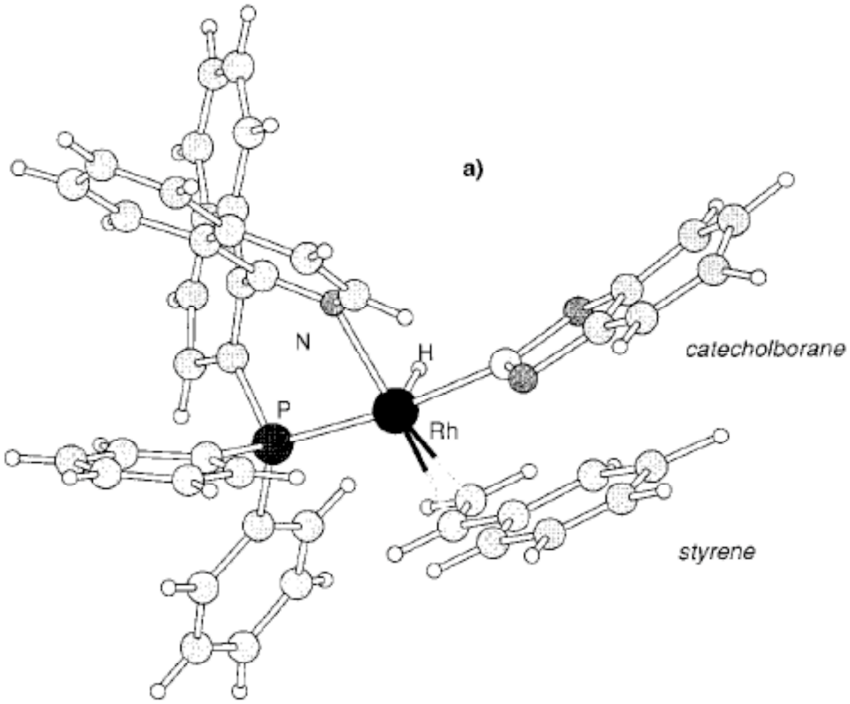
- **Metal complex needs to accomodate both borane and alkene; comparative void offered by isoquinoline of QUINAP permits greater tolerance towards reactant bulk**

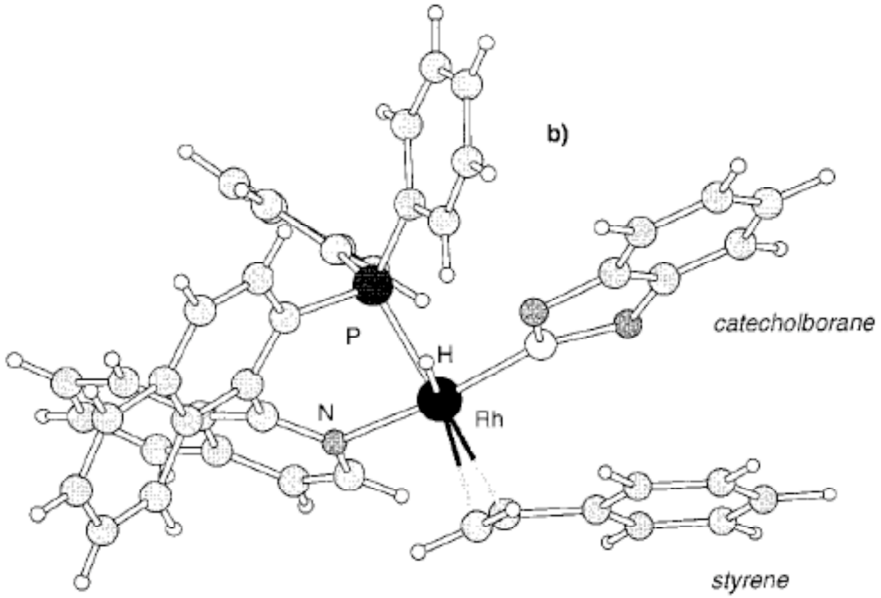
Brown, *Chem. Eur. J.* **1999**, *5*, 1320-1330.
Hayashi, *J. Am. Chem. Soc.* **1989**, *111*, 3426-3428.

Asymmetric hydroboration

Model for enantioselectivity

• Same configurational relationship between L and product holds for QUINAP and BINAP





a) Intermediate in the preferred pathway; increasingly favored as styrene is more electron-rich

b) Disfavored pathway; more probable with electron-poor styrenes

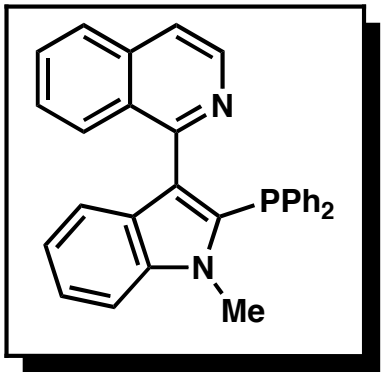
• In square-planar Pt complexes electron-rich styrenes bind more strongly *trans* to pyridine than electron-poor analogues

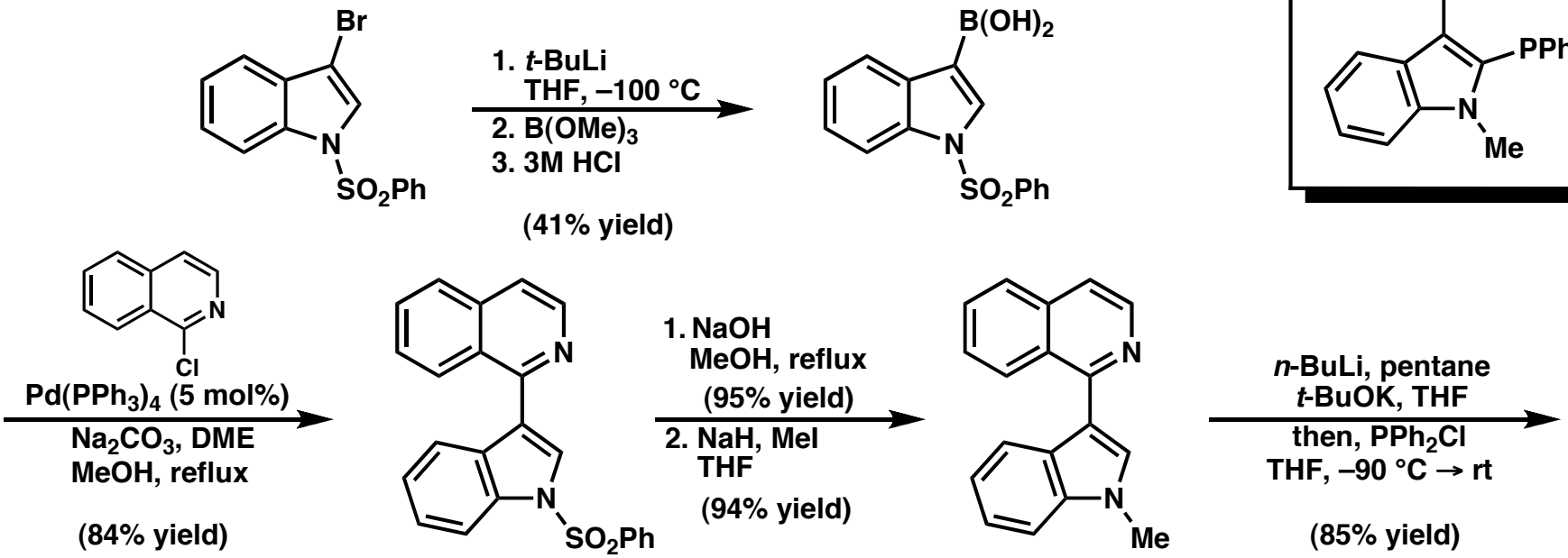
• Trend in enantioselectivity (overall higher ee's for electron-rich alkenes) can potentially be explained by a competition between the two pathways

Brown, *Chem. Eur. J.* **1999**, *5*, 1320-1330.

Varying the bite angle

From naphthalene to indole



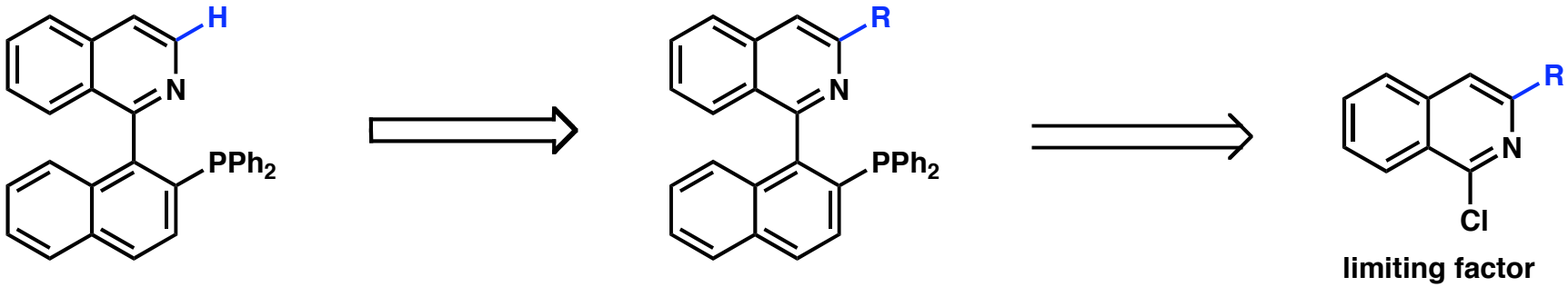


- ^{31}P NMR, singlet at 25.8 ppm
- Chelate ring less strained
- Biaryl twist = 47° (cf. 65°, QUINAP)

Brown, *Tetrahedron* **1997**, *53*, 4035-4050.

Quinazolinap

Design principle

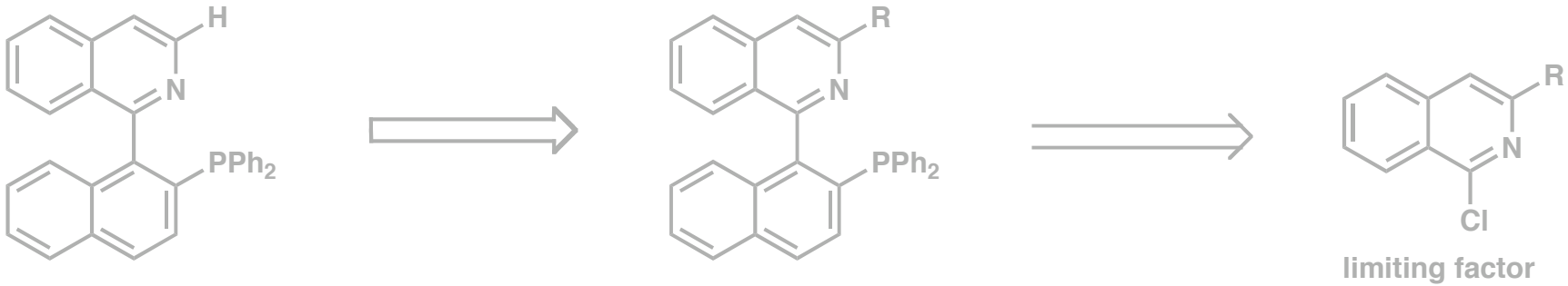


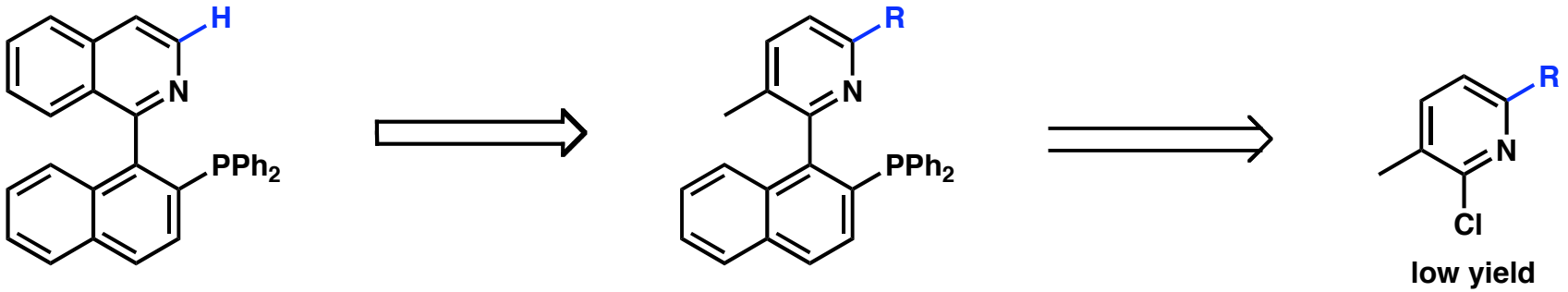
limiting factor

Guiry, *Tetrahedron* **1999**, *55*, 3061-3070.

Quinazolinap

Design principle

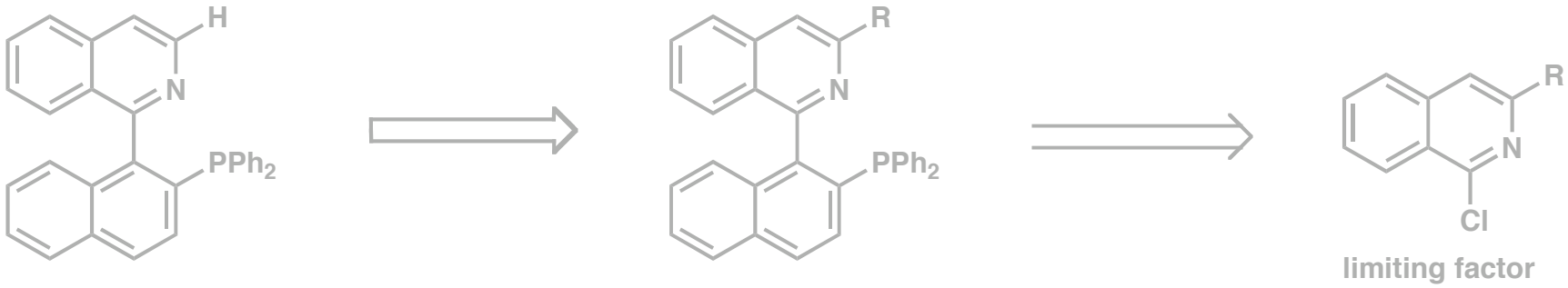


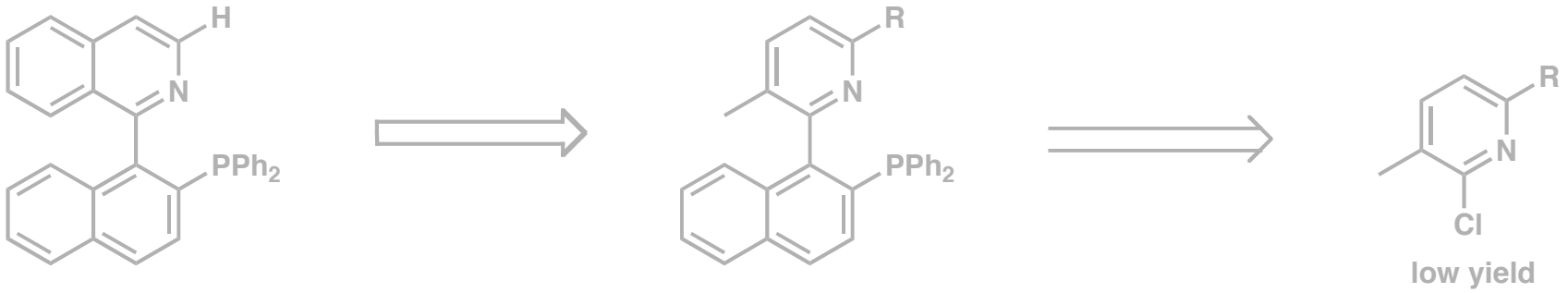


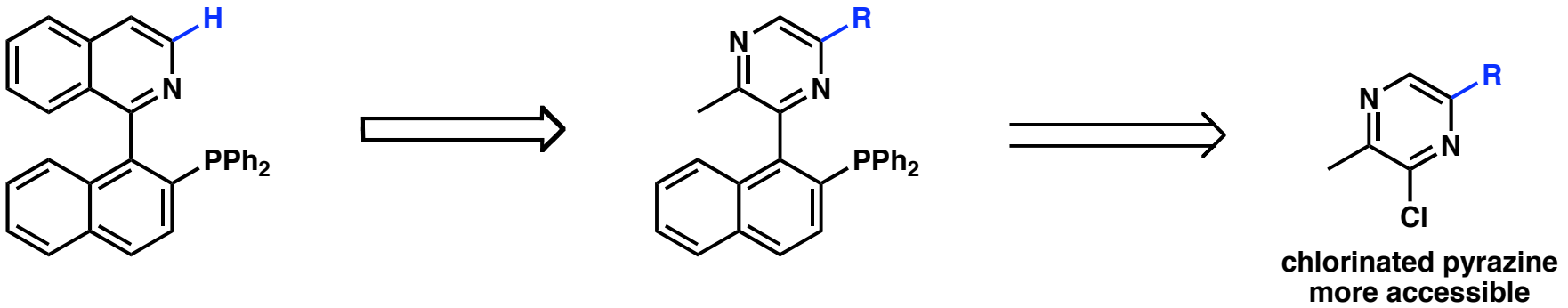
Guiry, *Tetrahedron* **1999**, *55*, 3061-3070.

Quinazolinap

Design principle





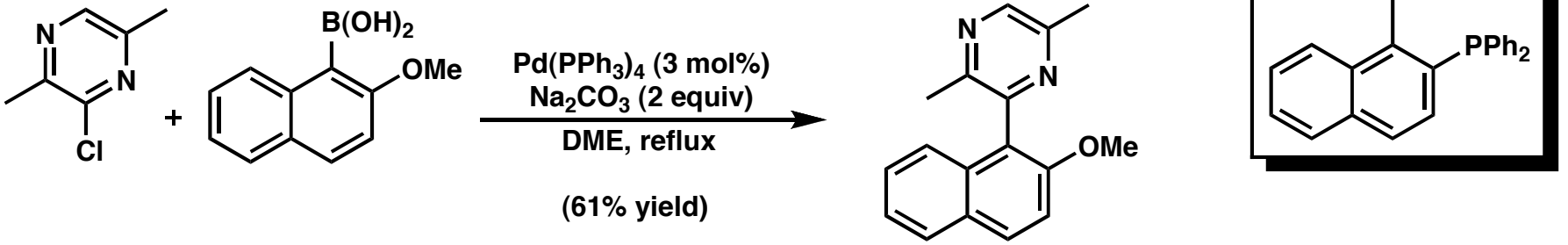


chlorinated pyrazine more accessible

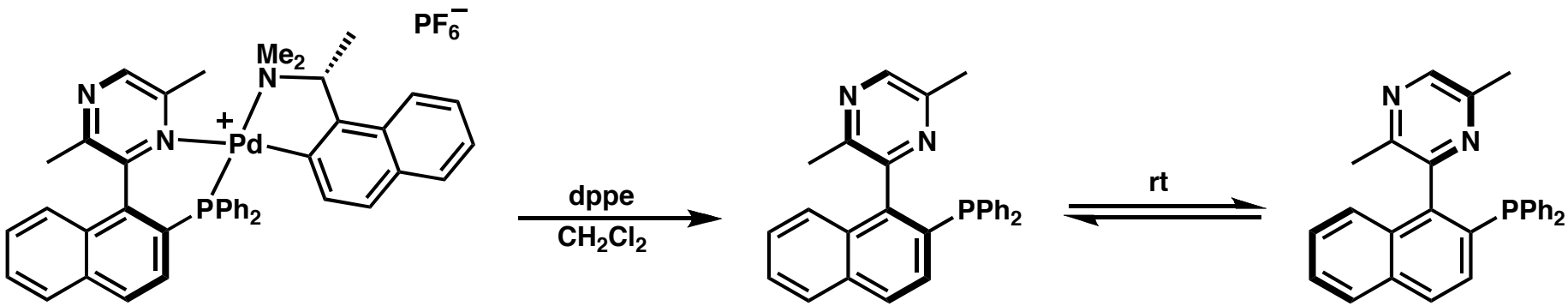
Guiry, *Tetrahedron* **1999**, *55*, 3061-3070.

Quinazolinap

Synthesis



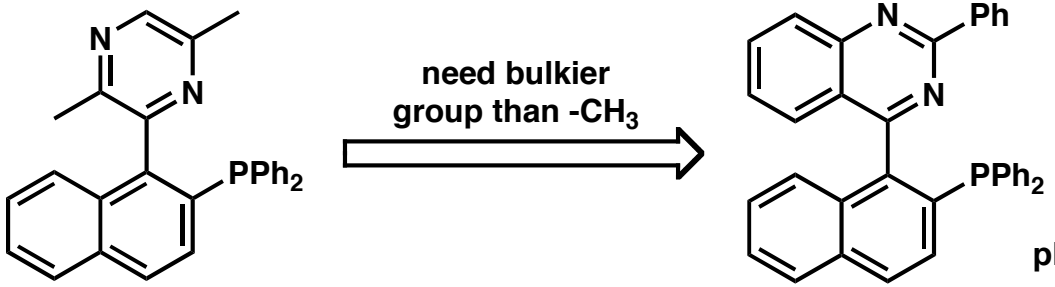
(±)-19



(S)-19 ***(R)-19***

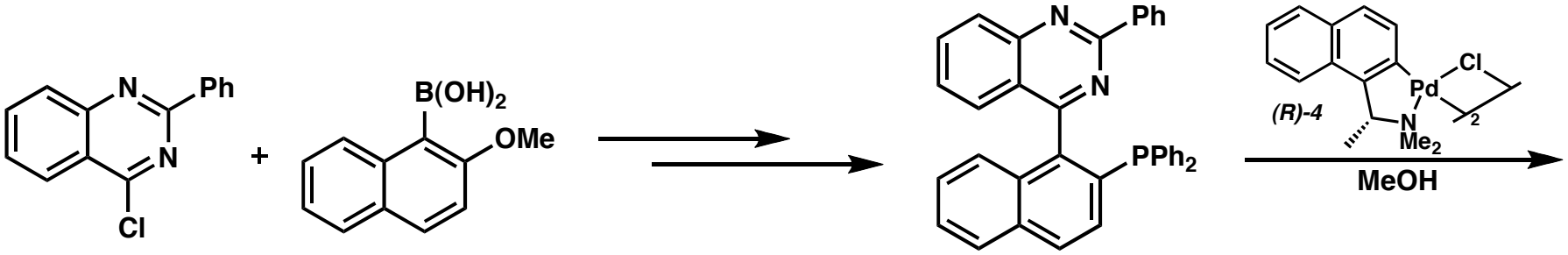
Guiry, *Tetrahedron* **1999**, *55*, 3061-3070.

2-phenyl-Quinazolinap

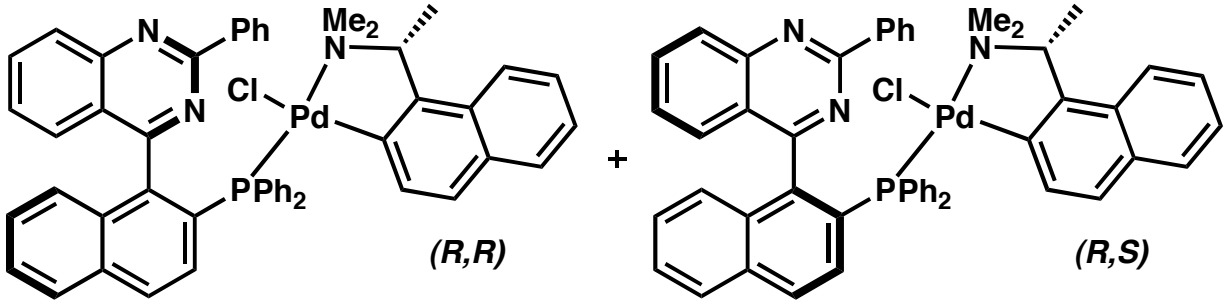


(±)-19

pKa = 3.3 (cf. 5.1, *QUINAP)*



(±)-20



(R,R) *(R,S)*

(R)-20* + *(S)-20

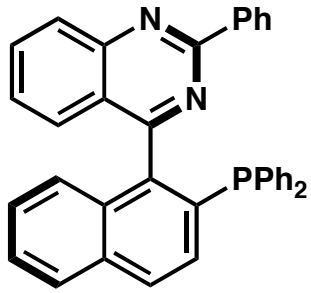
Optical stability maintained when heated to reflux in toluene for 7 days

- **Same behavior as *(R)-PHENAP***
- **Binding via P only**

Guiry, *Tetrahedron: Asymmetry* **1999**, *10*, 2797-2807.

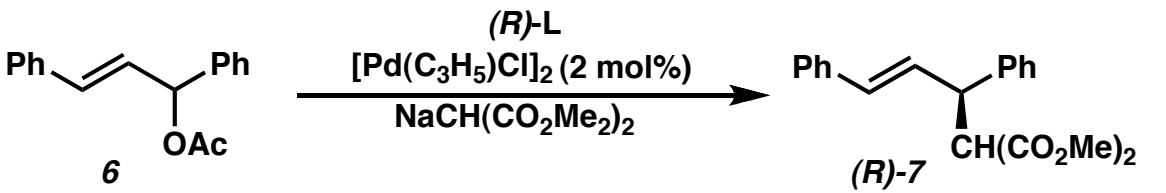
2-phenyl-Quinazolinap

Applications in catalysis

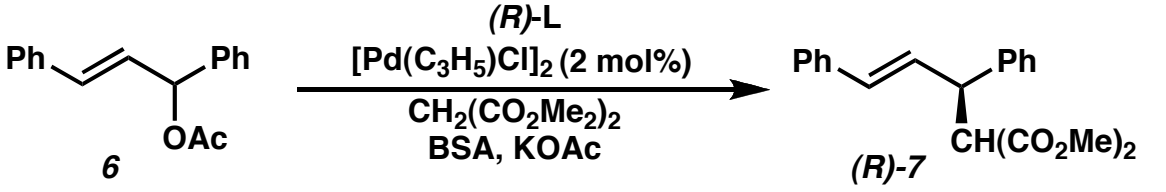
L = 

(R)-20

Asymmetric allylic alkylation

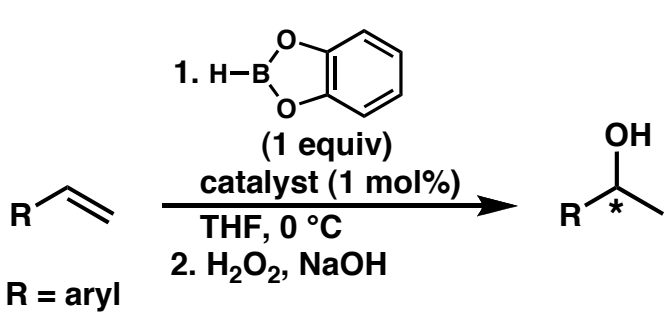


up to 99% yield
up to 66% ee

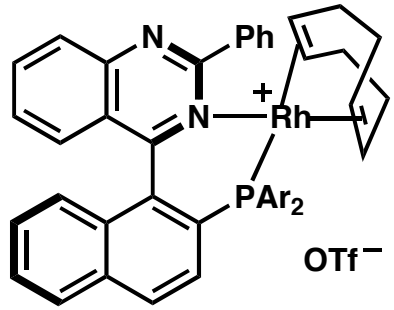


up to 99% yield
up to 38% ee

Asymmetric hydroboration



catalyst =

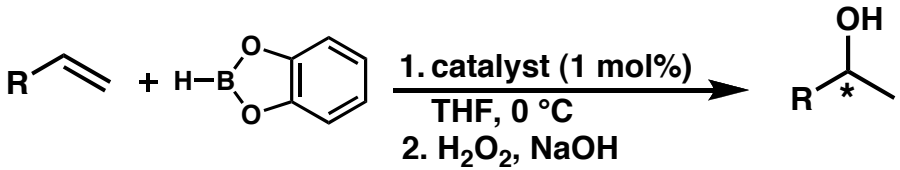


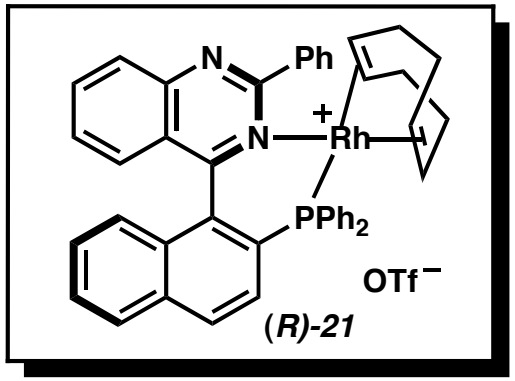
- Best results obtained when reactions run at 0 °C (cf. 20 °C, ***QUINAP***)
- catalyst prepared fresh before reaction

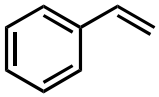
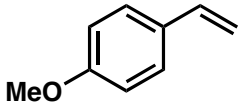
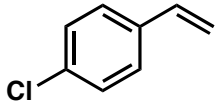
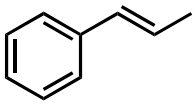
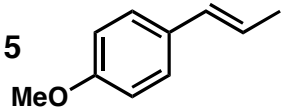
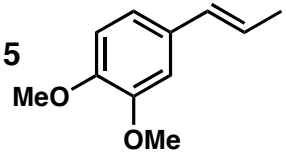
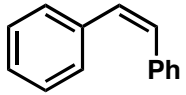
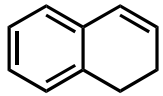
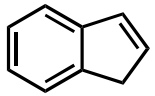
Guiry, *Polyhedron* **2000**, *19*, 541-543.

2-phenyl-Quinazolinap

Asymmetric hydroboration





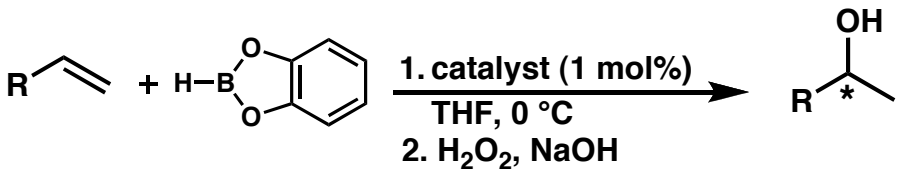
entry	reactant	catalyst	% conv	% *sec*-OH[a]	% ee
1		(*R*)-21	100	80	79
2		(*R*)-21	91	77	81
3		(*R*)-21	100	83	49
4[b]		(*R*)-21	100	91	94
5		(*R*)-21	72	89	92
5		(*R*)-21	75	93	97
6[b]		(*R*)-21	100		62
7[b]		(*R*)-21	100	99	89
8[b]		(*R*)-21	98	98	84

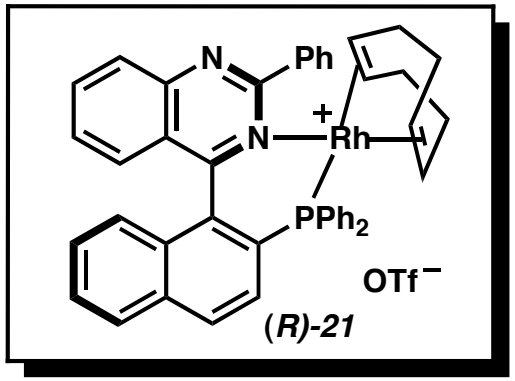
[a] Remainder primary alcohol. [b] T = 25 °C

Guiry, *Chem. Commun.* **2000**, 1333-1334.

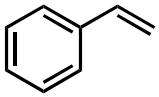
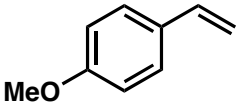
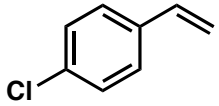
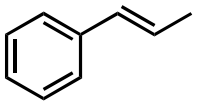
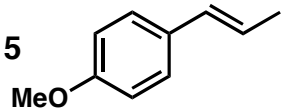
2-phenyl-Quinazolinap

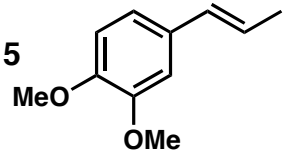
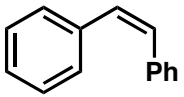
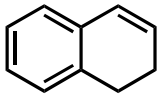
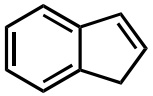
Asymmetric hydroboration





QUINAP

entry	reactant	catalyst	% conv	% *sec*-OH[a]	% ee
1		(*R*)-21	100	80	79 92
2		(*R*)-21	91	77	81 94
3		(*R*)-21	100	83	49 82
4[b]		(*R*)-21	100	91	94 95
5		(*R*)-21	72	89	92 97

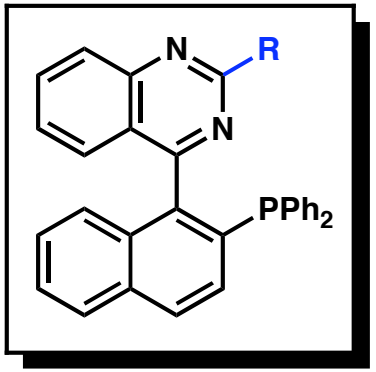
entry	reactant	catalyst	% conv	% *sec*-OH[a]	% ee
5		(*R*)-21	75	93	97
6[b]		(*R*)-21	100		62 91
7[b]		(*R*)-21	100	99	89 96
8[b]		(*R*)-21	98	98	84 86

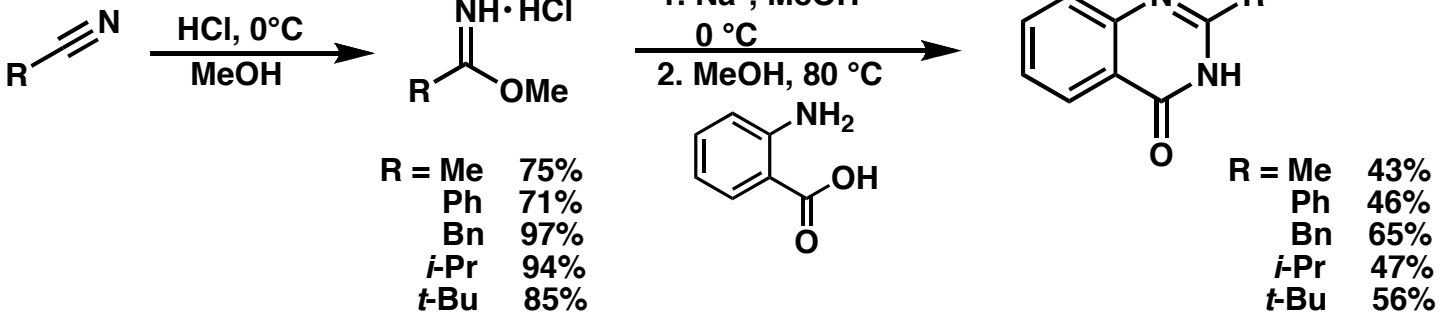
[a] Remainder primary alcohol. [b] T = 25 °C

Guiry, *Chem. Commun.* **2000**, 1333-1334.

Expanding the Quinazolinap series

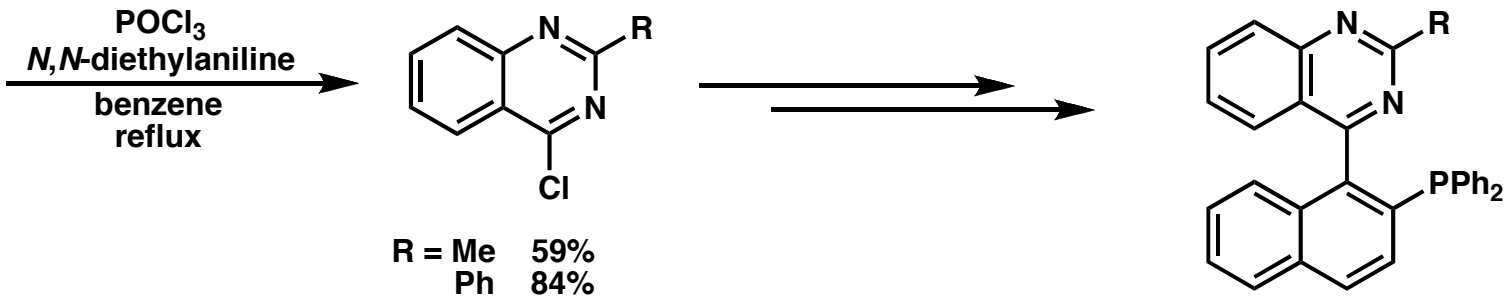
Varying the 2-position of quinazoline



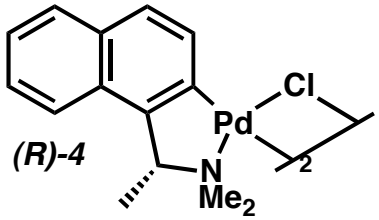


R = Me 75%
Ph 71%
Bn 97%
i-Pr 94%
t-Bu 85%

R = Me 43%
Ph 46%
Bn 65%
i-Pr 47%
t-Bu 56%



R = Me 59%
Ph 84%
Bn 88%
i-Pr 64%
t-Bu 82%



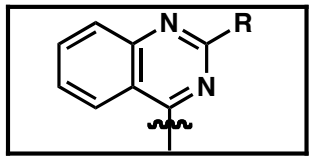
(R)-4

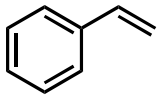
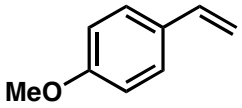
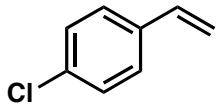
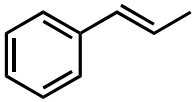
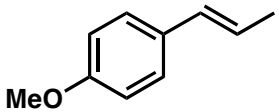
entry	R	(*R*)	(*S*)
1	H		✓
2	Me		✓
3	Ph	✓	✓
4	Bn	✓	✓
5	*i*-Pr	✓	✓
6	*t*-Bu	✓	

Guiry, *J. Org. Chem.* **2004**, *69*, 6572-6589.

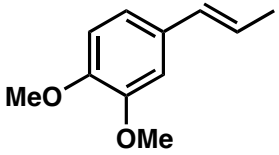
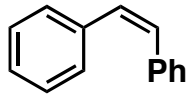
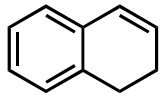
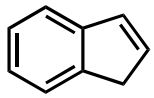
Asymmetric hydroboration

Testing the expanded series



	H	Me	Ph	Bn	*i*-Pr	*t*-Bu
	86	90	79*	87	87	84
	91	95	81*	89	92	91
	81	77	49*	71	73	70
	89	95*	94	92*	91*	91*
	88	97*	92*	90*	93	91*

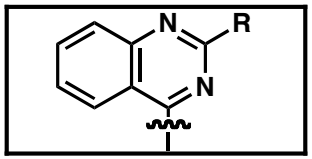
* T = 0 °C

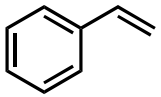
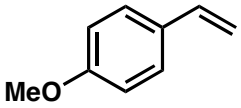
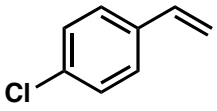
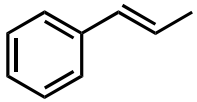
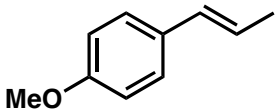
	H	Me	Ph	Bn	*i*-Pr	*t*-Bu
	93*	98*	94	90	91	86
	95*	97	62*	89	99	97*
	87	93*	89	87	86	90*
	98*	99.5	84	86*	84	80*

Guiry, *J. Org. Chem.* **2004**, *69*, 6572-6589.

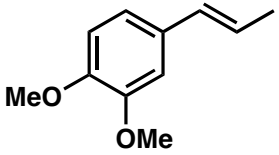
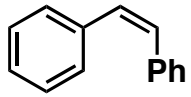
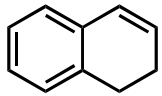
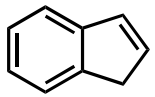
Asymmetric hydroboration

Testing the expanded series



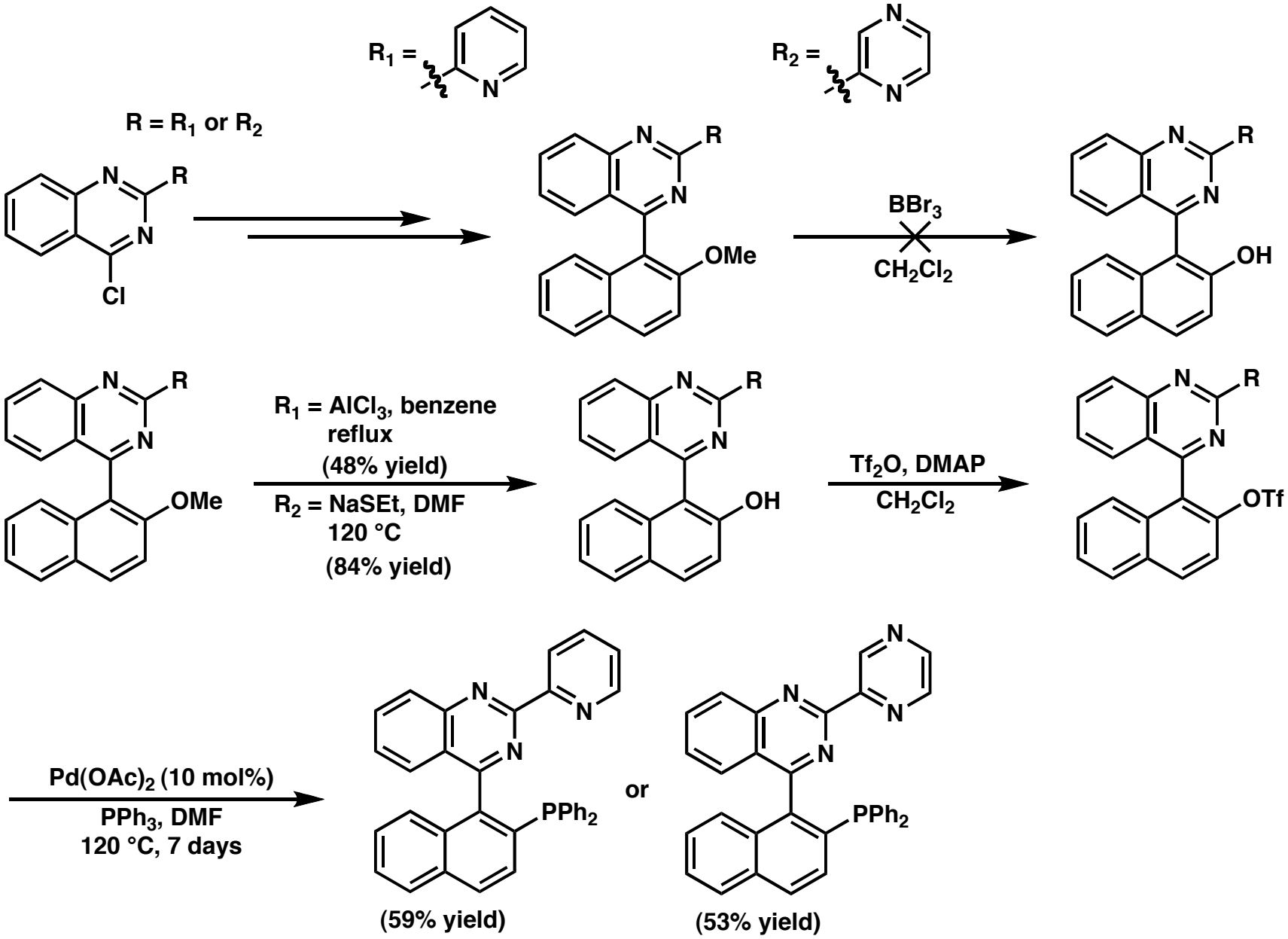
	H	Me	Ph	Bn	*i*-Pr	*t*-Bu	QUINAP
	86	90	79*	87	87	84	92
	91	95	81*	89	92	91	94
	81	77	49*	71	73	70	82
	89	95*	94	92*	91*	91*	95
	88	97*	92*	90*	93	91*	97

* T = 0 °C

	H	Me	Ph	Bn	*i*-Pr	*t*-Bu	QUINAP
	93*	98*	94	90	91	86	
	95*	97	62*	89	99	97*	91
	87	93*	89	87	86	90*	96
	98*	99.5	84	86*	84	80*	86

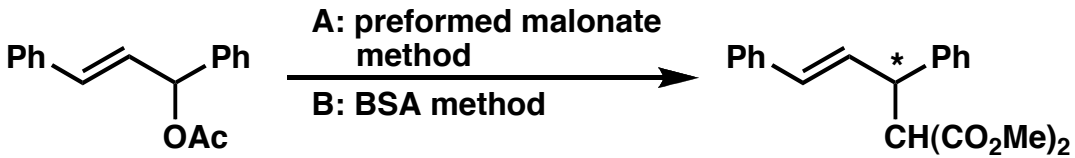
Guiry, *J. Org. Chem.* **2004**, *69*, 6572-6589.

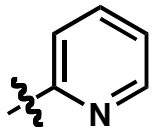
Altering the electronic nature



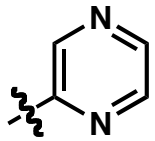
Guiry, *Tetrahedron* **2005**, *61*, 9808-9821.

Resolution and application



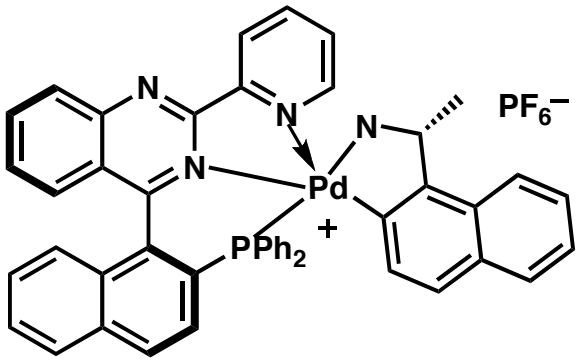
when R = 

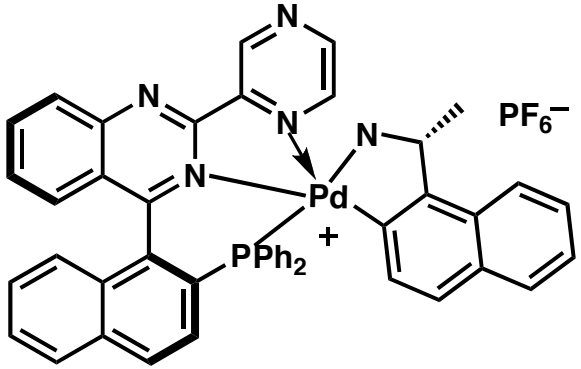
best result: 23% ee
84% conversion
rt, 3 days
method A

when R = 

best result: 81% ee
25% conversion
0 °C, 5 days
method A

- X-ray crystal structure analysis reveals tridentate binding mode
- Pd adopts a trigonal bipyramidal-like coordination geometry



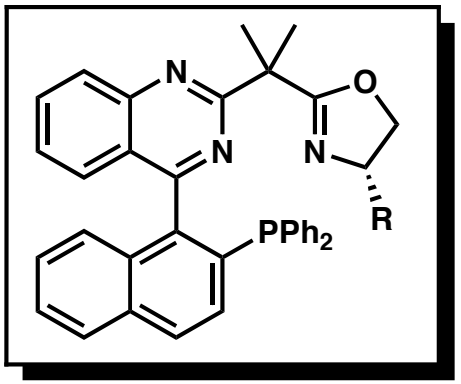


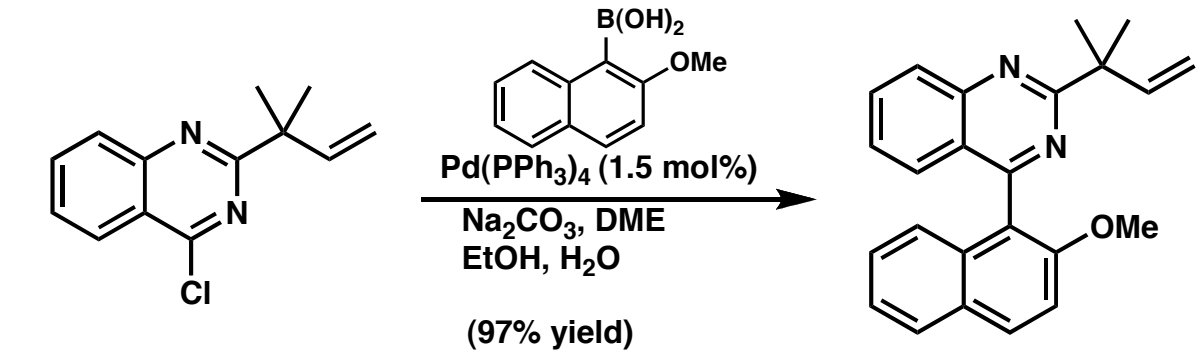
- Possible hemi-labile nature of the substituent might hinder progress and stereochemical outcome of reaction

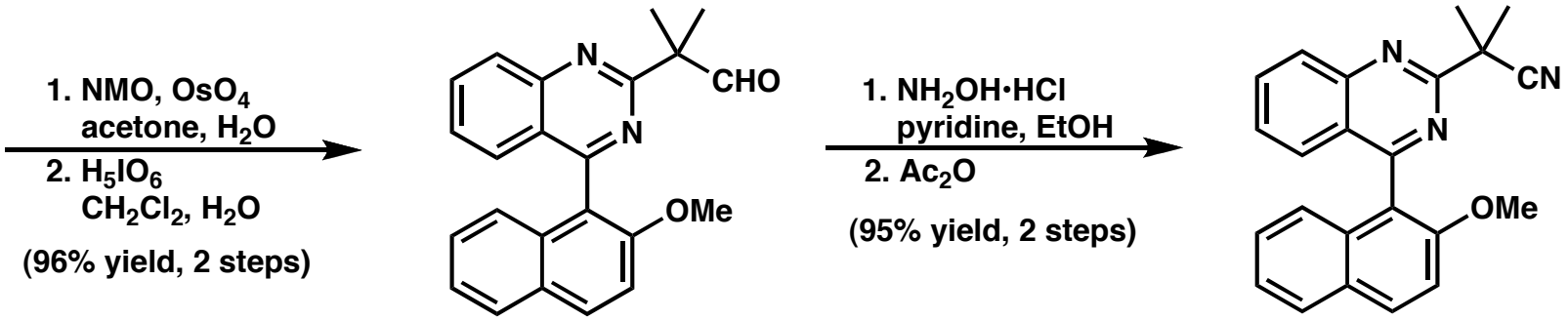
Guiry, *Tetrahedron* **2005**, *61*, 9808-9821.

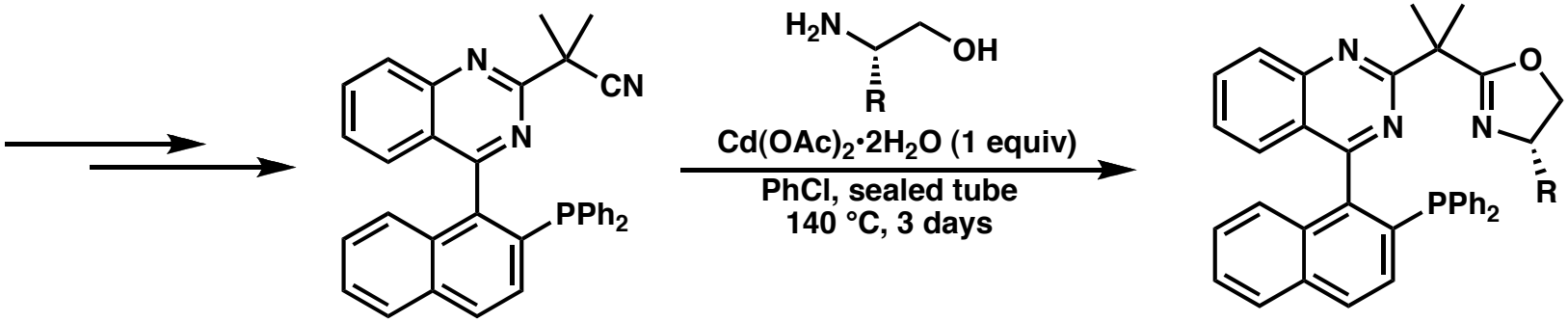
Quinazox

Incorporation of oxazoline subunits







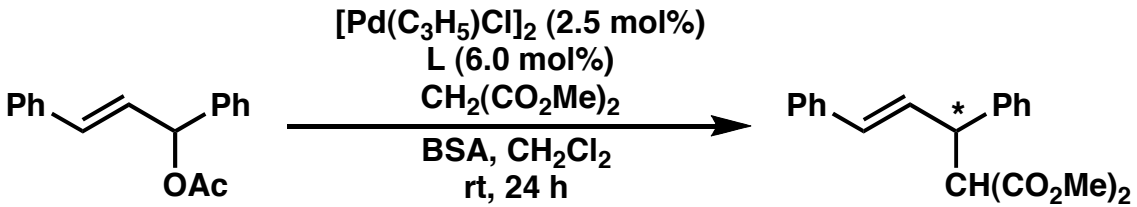


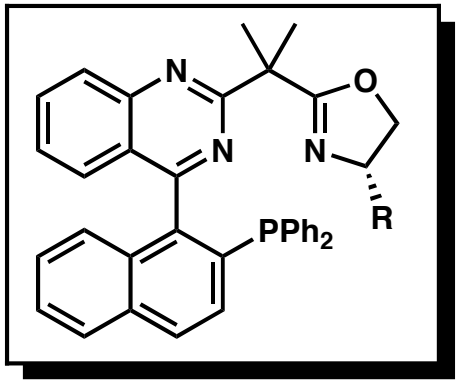
R = *i*-Pr (63% yield)
t-Bu (43% yield)

Guiry, *Org. Lett.* **2006**, *8*, 5109-5112.

Quinazox

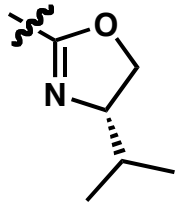
Asymmetric allylic alkylation



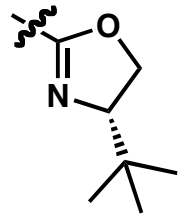


entry	ligand	base	% yield	% ee
1	(*R*)-L_1	LiOAc	> 95	81 (*R*)
2	(*R*)-L_1	KOAc	> 95	55 (*R*)
3	(*S*)-L_1	LiOAc	> 95	58 (*S*)
4	(*S*)-L_1	KOAc	> 95	15 (*S*)
5	(*R*)-L_2	LiOAc	> 95	60 (*R*)
6	(*R*)-L_2	KOAc	> 95	7 (*S*)
7	(*S*)-L_2	LiOAc	88	39 (*S*)
8	(*S*)-L_2	KOAc	> 95	55 (*R*)

L_1 =

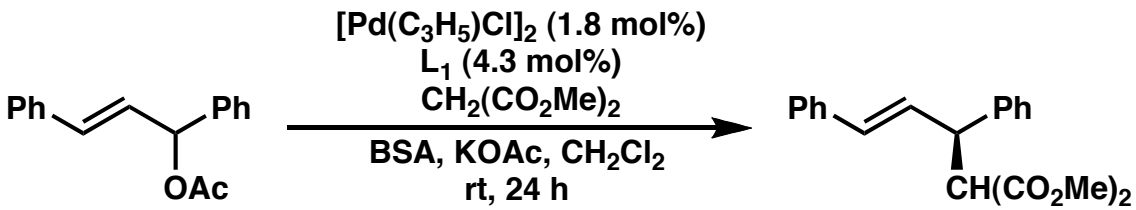


L_2 =



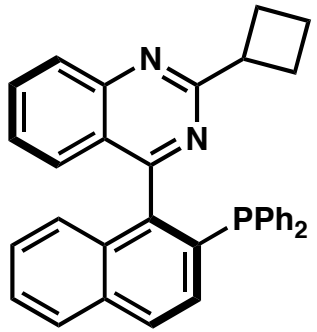
Guiry, *Org. Lett.* **2006**, *8*, 5109-5112.

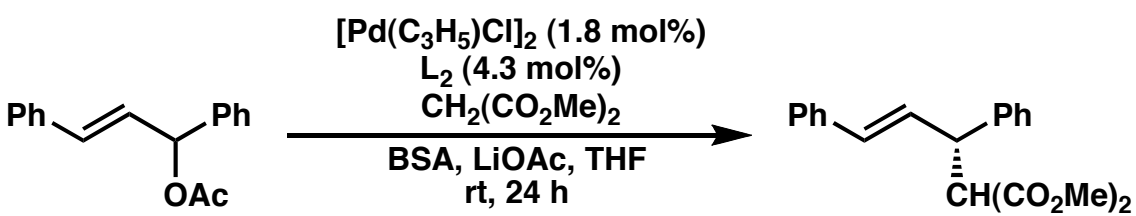
Less common 2-substituents



> 95% yield
89% ee (*R*)

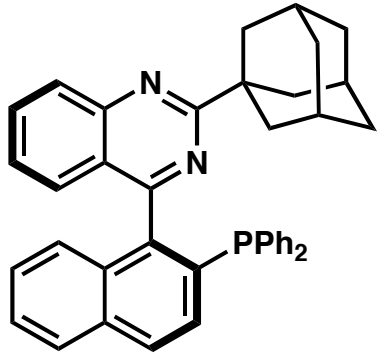
L_1 =



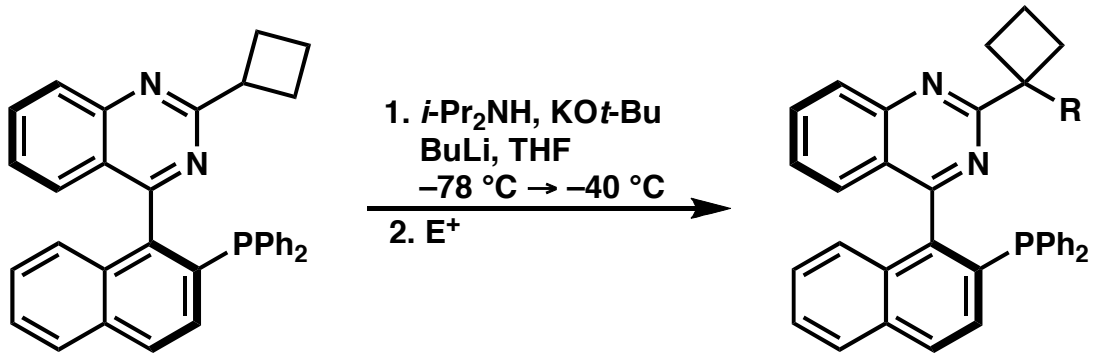


56% yield
66% ee (*S*)

L_2 =



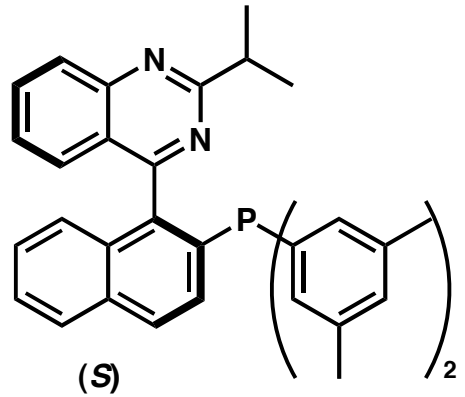
Modification of known Quinazolinap

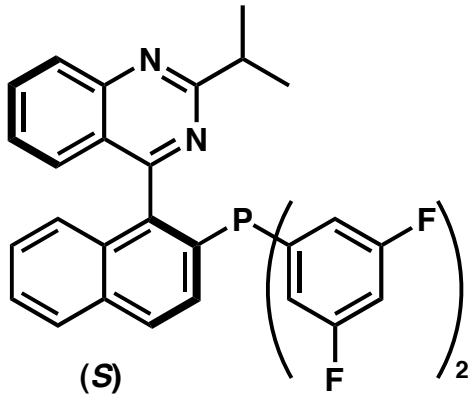


R = D	97% yield
CHO	92% yield
CO_2Me	63% yield
CH(OH)Ph	94% yield

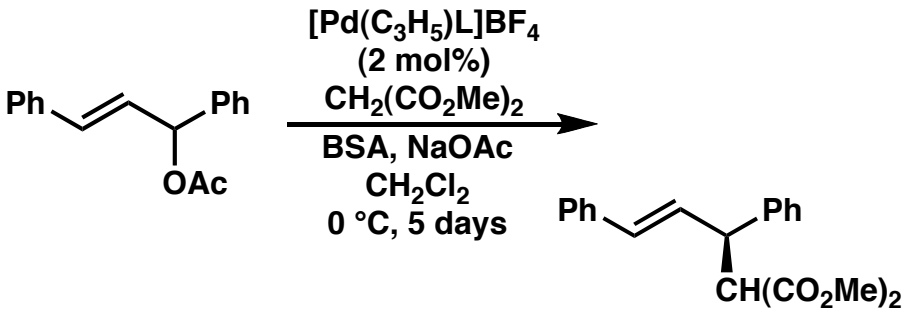
Guiry, *Eur. J. Org. Chem.* **2008**, 5055-5066.

Different aryl groups





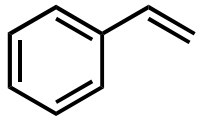
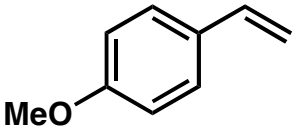
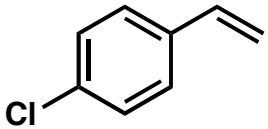
Allylic alkylation



76% yield
94% ee (*R*)

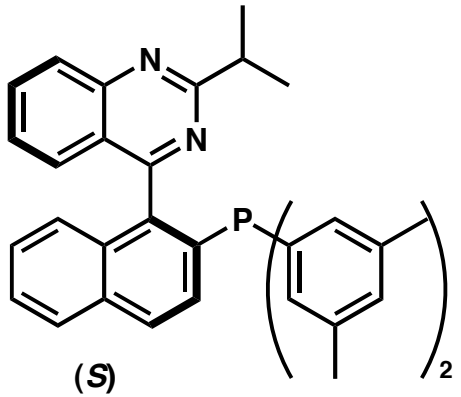
highest ee observed to date using Quinazolinap series

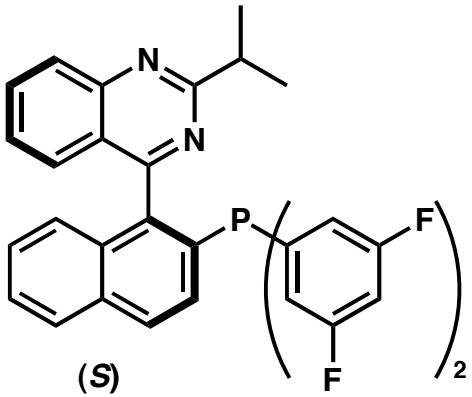
Hydroboration

	% Conversion	% *sec*-OH	% ee
	55	85	72
	76	86	92
	56	85	58

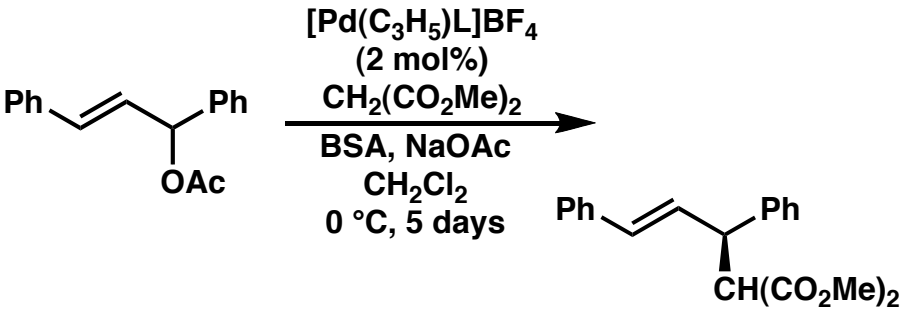
Guiry, *Org. Biomol. Chem.* **2008**, *6*, 3848-3853.

Different aryl groups





Allylic alkylation

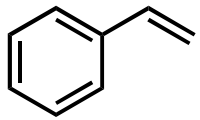
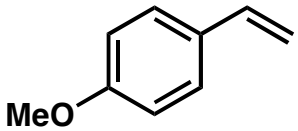
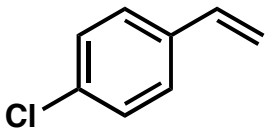


76% yield
94% ee (*R*)

highest ee observed to date using Quinazolinap series

Hydroboration

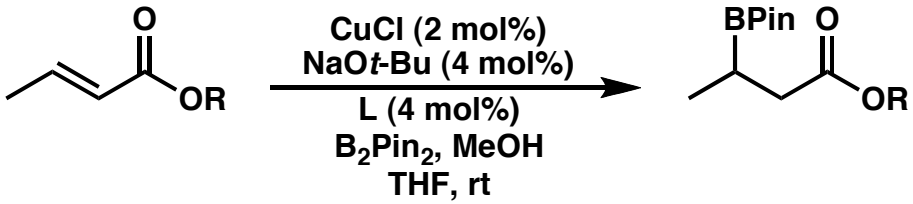
Ar_2 = phenyl

	% Conversion	% *sec*-OH	% ee
	55 100	85 77	72 87
	76 100	86 76	92 92
	56 100	85 81	58 73

Guiry, *Org. Biomol. Chem.* **2008**, *6*, 3848-3853.

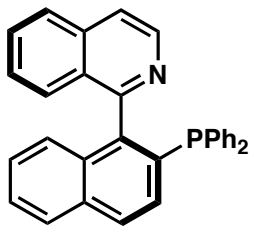
Expanding the scope of reactions

β–borylation of α,β–unsaturated esters

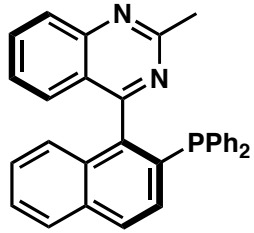


entry	R	ligand	% conversion	% ee
1	Me	1	100	50
2	Me	2	95	20
3	Me	3	65	51
4	Me	4	100	40
5	Me	5	100	25
6	Me	6	71	13
7	Et	1	100	72
8	Et	2	100	34
9	Et	3	75	40

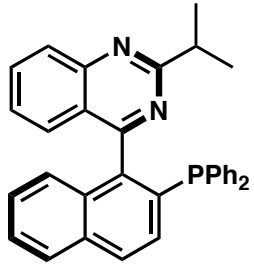
entry	R	ligand	% conversion	% ee
10	Et	4	98	38
11	Et	5	99	12
12	Et	6	82	15
13	*i*-Bu	1	100	79
14	*i*-Bu	2	100	35
15	*i*-Bu	3	100	42
16	*i*-Bu	4	23	48
17	*i*-Bu	5	100	20
18	*i*-Bu	6	26	20



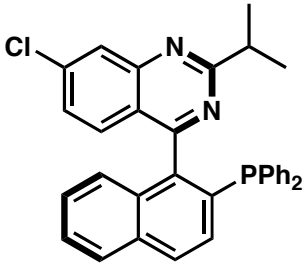
(*S*)-1



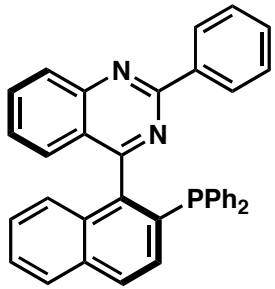
(*S*)-2



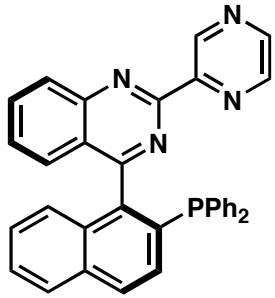
(*R*)-3



(*R*)-4



(*S*)-5

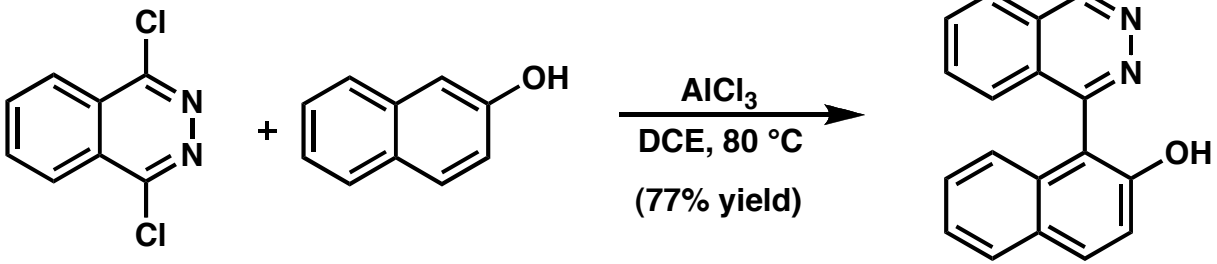


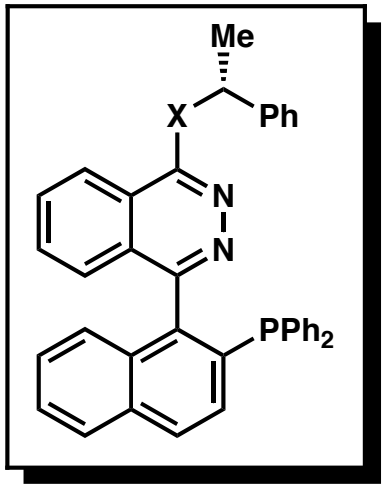
(*S*)-6

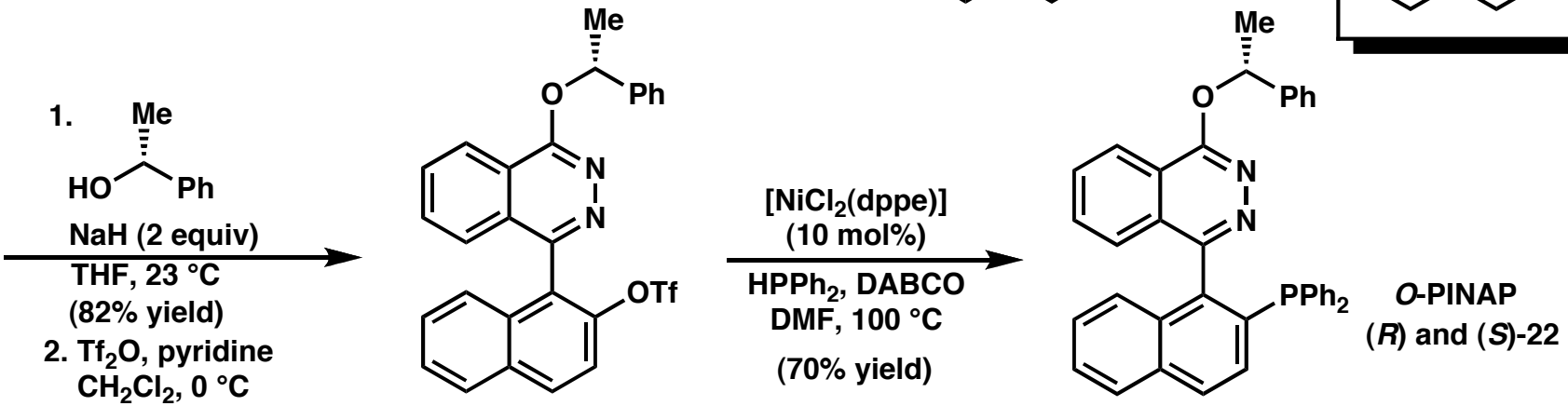
Guiry, *Org. Biomol. Chem.* **2009**, *7*, 2520-2524.

PINAP

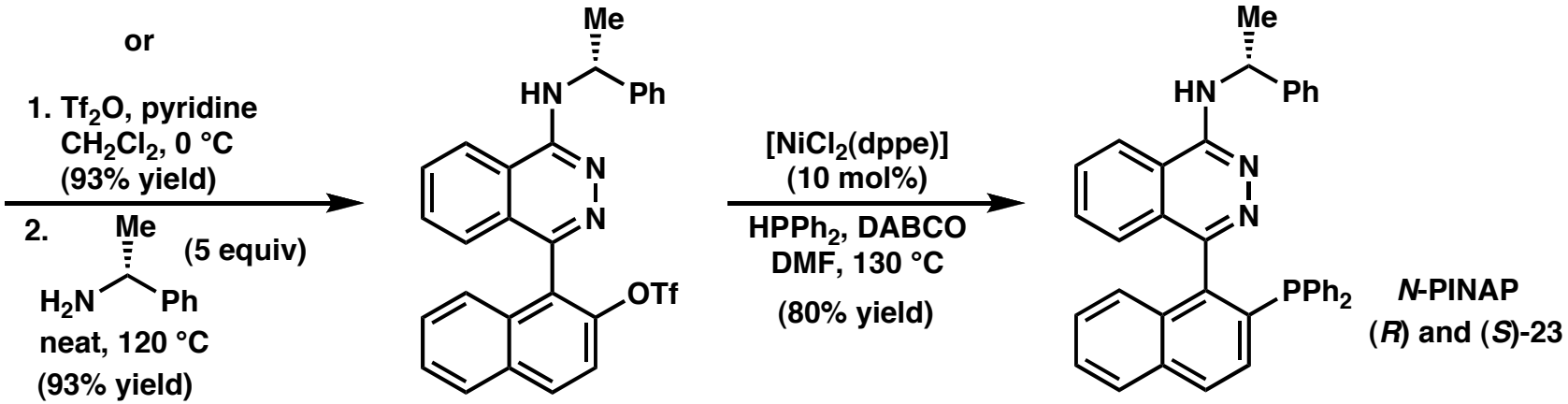
PhthalazIneNAPhthalene







***O*-PINAP**
(*R*) and (*S*)-22

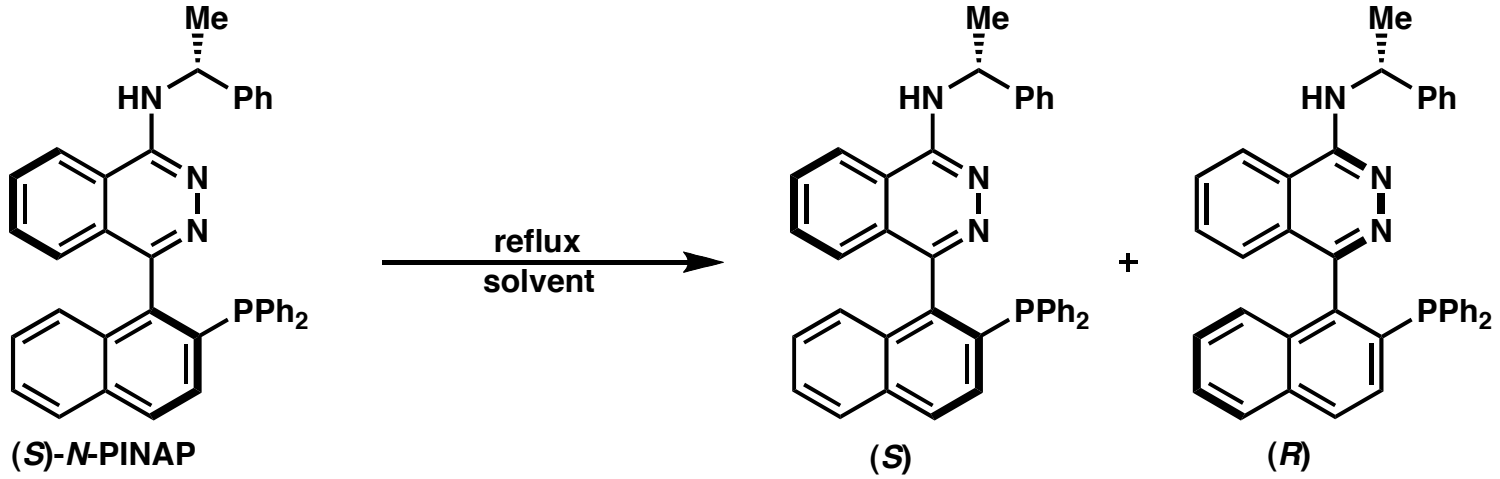


***N*-PINAP**
(*R*) and (*S*)-23

Carreira, *Angew. Chem. Int. Ed.* **2004**, *43*, 5971-5973.

PINAP

Epimerization studies



(*S*)-*N*-PINAP (*S*) (*R*)

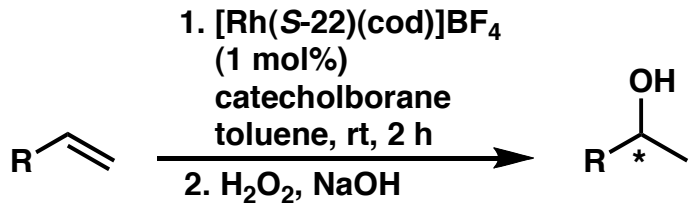
Time (h)	*p*-xylene (bp: 138 °C)	toluene (bp: 111 °C)	benzene (bp: 80 °C)
4	1:1	3:1	>98:2
8		2:1	>98:2
20		1:1	>98:2

- Ratio monitored by ^{1}H NMR spectroscopy
- Calculated half life $t_{1/2}$ at 65 °C is more than 25 days

Carreira, *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1635-1657.

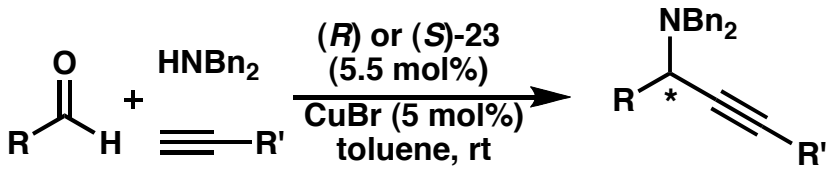
Testing PINAP

Asymmetric hydroboration



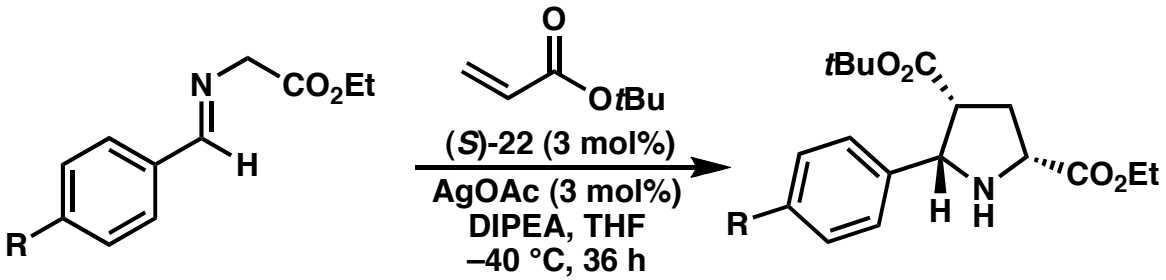
entry	R	% yield	% ee	QUINAP
1	Ph	73	92	92
2	*p*-Tol	94	92	89
3	*m*-Tol	85	84	86
4	*o*-Tol	81	91	92
5	*p*-MeOPh	80	90	94
6	*p*-ClPh	87	87	78

Addition of alkynes to imines



R	R'	L	% yield	% ee	QUINAP
i-Pr	Me_3Si	(*S*)-23	84	98	92
		(*R*)-23	82	99	
i-Pr	Ph	(*S*)-23	88	90	84
		(*R*)-23	82	95	
i-Bu	*n*-Bu	(*S*)-23	74	91	82
		(*R*)-23	72	94	

Azomethine cycloaddition



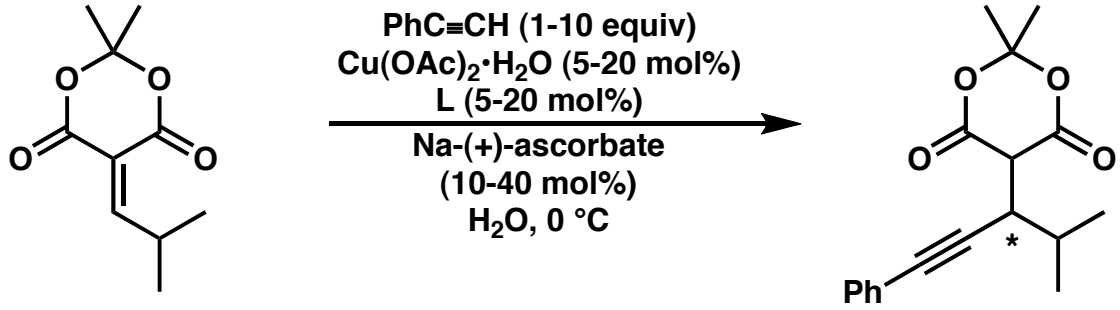
R = CN 94% yield, 95% ee
(cf. 96% ee, QUINAP)

R = OMe 88% yield, 92% ee
(cf. 95% ee, QUINAP)

Carreira, *Angew. Chem. Int. Ed.* **2004**, *43*, 5971-5973.

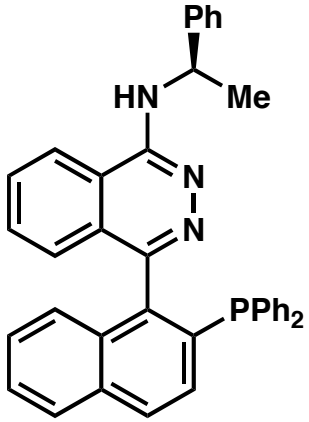
Critical role of the covalently bound chiral group

Catalytic, enantioselective, conjugate alkyne addition

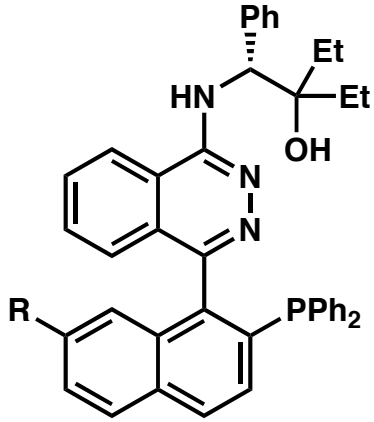


Ligand screen

entry	ligand	T (°C)	% ee	% conversion
1	QUINAP	23	42	100
2	(*S*)-1	0	80	58
3	(*R*)-1	0	37	33
4	(*R*)-2	0	94	40
5	(*S*)-2	0	48	49
6	(*R*)-3	0	95	100
7	(*S*)-3	0	8	44



1



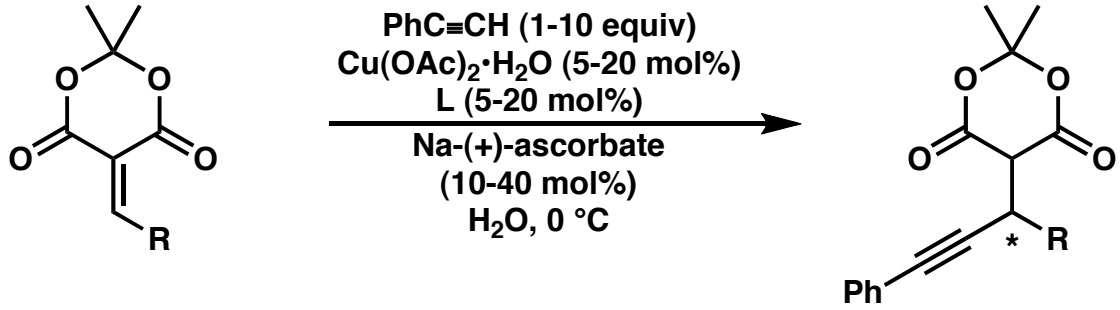
2: R = H
3: R = OMe

- Diastereomeric pairs give very different ee's
- Suggests critical role for chiral amine group (matched/mismatched)
- Underscores PINAP as a modular scaffold (amenable to steric and electronic changes)

Carreira, *J. Am. Chem. Soc.* **2005**, *127*, 9682-9683.

Critical role of the covalently bound chiral group

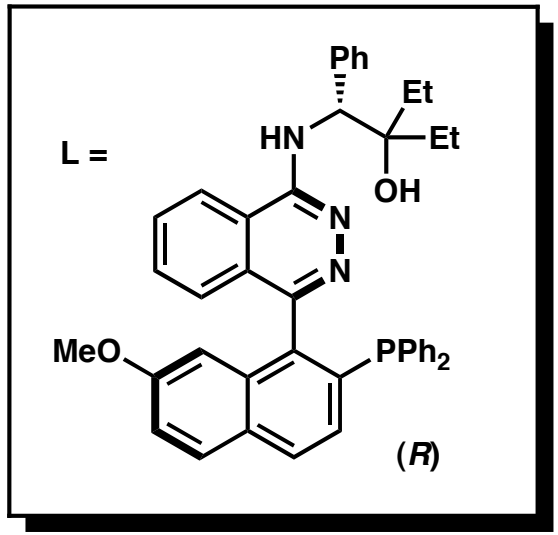
Catalytic, enantioselective, conjugate alkyne addition



Reaction scope

entry	R	L (mol%)	% yield	% ee
1	*i*-Pr	10	94	95
2	C_6H_{11}	10	81	94
3	*i*-Bu	20	85	90
4	Et	20	83	82
5	Ph	20	64	83
6	*m*-tol	20	87	90 (98)[a]

[a] After one recrystallization from EtOAc

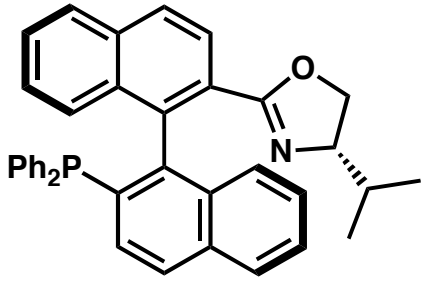


- No stereoinduction from Na-(+)-ascorbate

Carreira, *J. Am. Chem. Soc.* **2005**, *127*, 9682-9683.

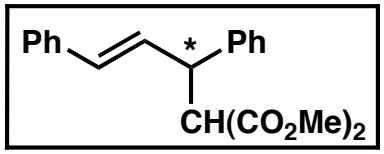
The vast world of axially chiral P,N-ligands

An active area of research

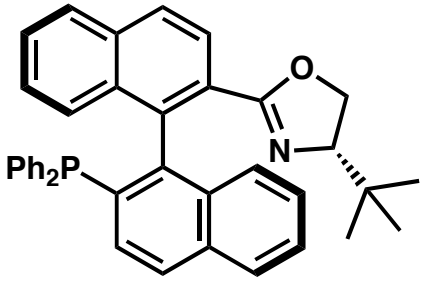


(***R***)

Allylic alkylation (malonate method)
>99% yield, 91% ee, -20 °C



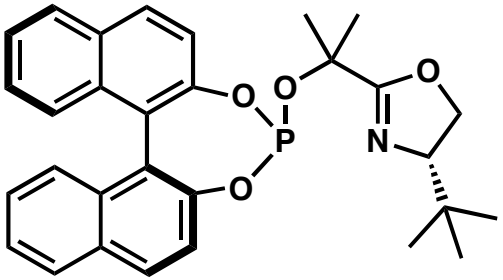
Hayashi, *Tetrahedron* **1998**, *9*, 1779-1787.



(***R***)

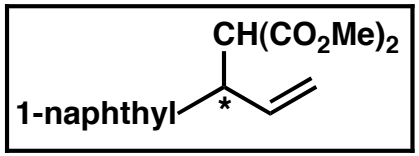
Allylic alkylation (BSA method)
90% yield, 96% ee, 0 °C

Ikeda, *Tetrahedron Lett*. **1998**, *39*, 4343-4346.

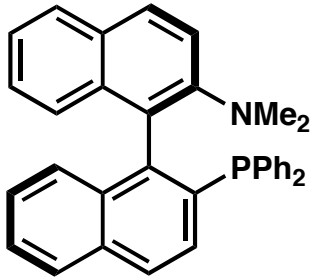


(***S***)

Allylic alkylation (BSA method)
91% yield, 96% ee, 23 °C

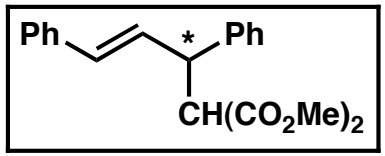


Pfaltz, *Angew. Chem. Int. Ed.* **1998**, *37*, 323-325.



(***R***)

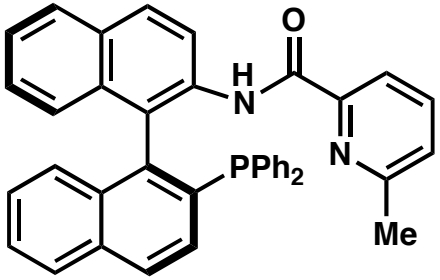
Allylic alkylation (BSA method)
85% yield, 73% ee, rt

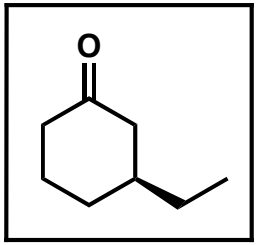


Kocovsky, *J. Org. Chem.* **1998**, *63*, 7738-7748.

The vast world of axially chiral P,N-ligands

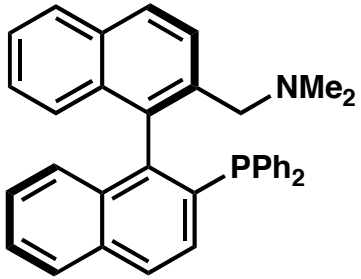
An active area of research

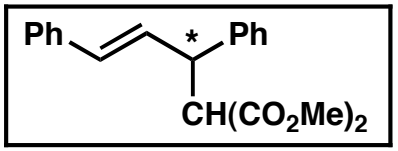




Cu-catalyzed conjugate addition
98% conversion, 92% ee

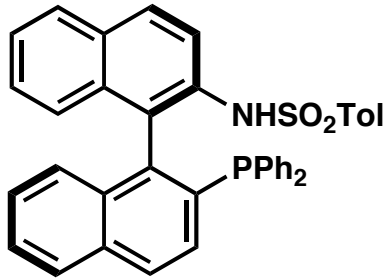
Zhang, *Angew. Chem. Int. Ed.* **1999**, *38*, 3518-3521.

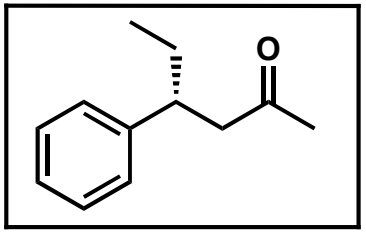




Allylic alkylation (BSA method)
82% yield, 92% ee, rt

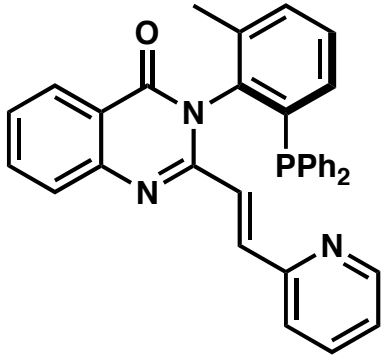
Ha, *Tetrahedron: Asymmetry* **2006**, *17*, 1688-1692.

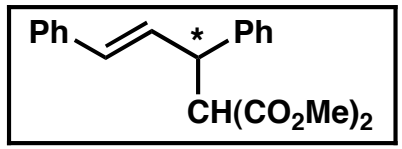




Cu-catalyzed conjugate addition
80% yield, 97% ee

Morimoto, *Tetrahedron Lett.* **2004***, 45*, 5717-5722.



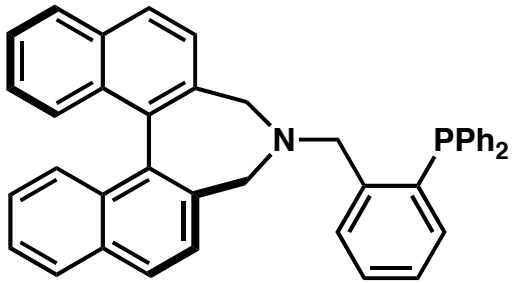


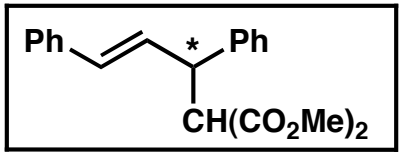
Allylic alkylation (NaH, 15-crown-5)
65% yield, 87% ee, rt

Virgil, *Tetrahedron Lett.* **1999**, *40*, 1245-1248.

The vast world of axially chiral P,N-ligands

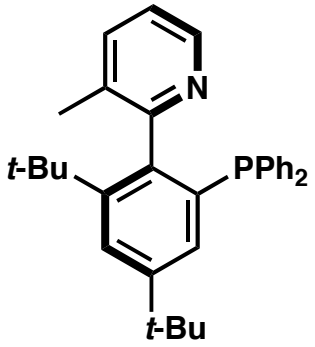
An active area of research

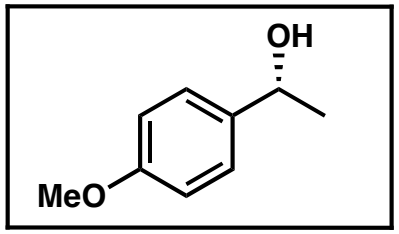




Allylic alkylation (BSA method)
95% yield, 97% ee

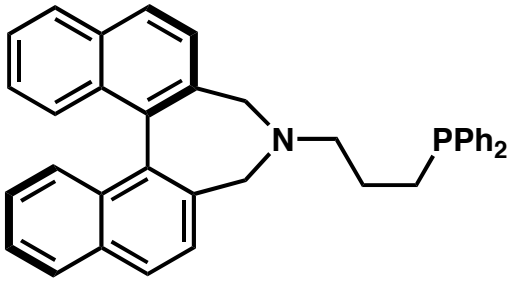
Widhalm, *Tetrahedron: Asymmetry* **1998**, *9*, 1073-1083.

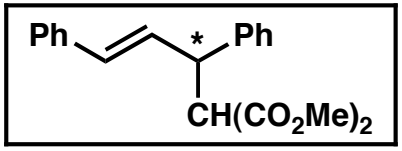




Hydroboration
94% ee

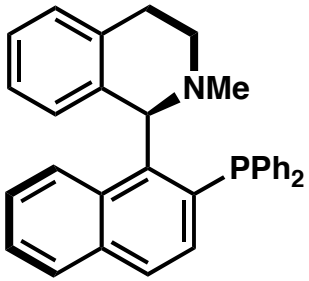
Chan, *J. Org. Chem.* **2002**, *67*, 2769-2777.

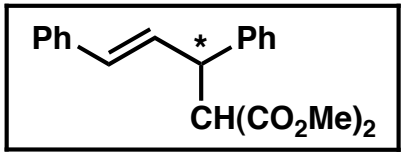




Allylic alkylation (BSA method)
96% yield, 96% ee

Koga, *Tetrahedron Lett*. **1994**, *35*, 6689-6692.



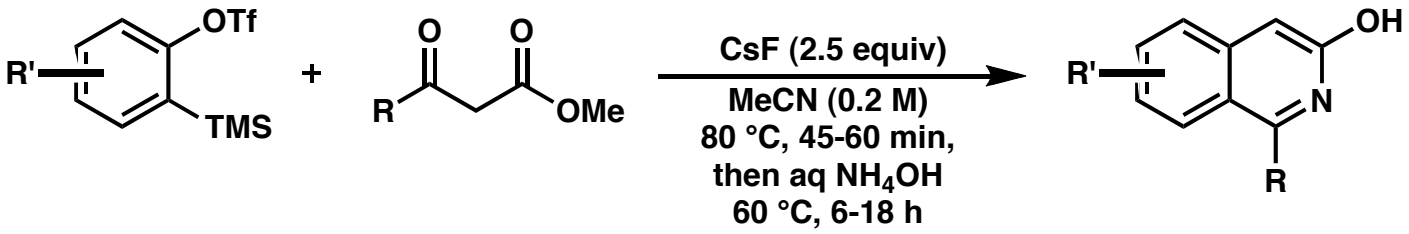


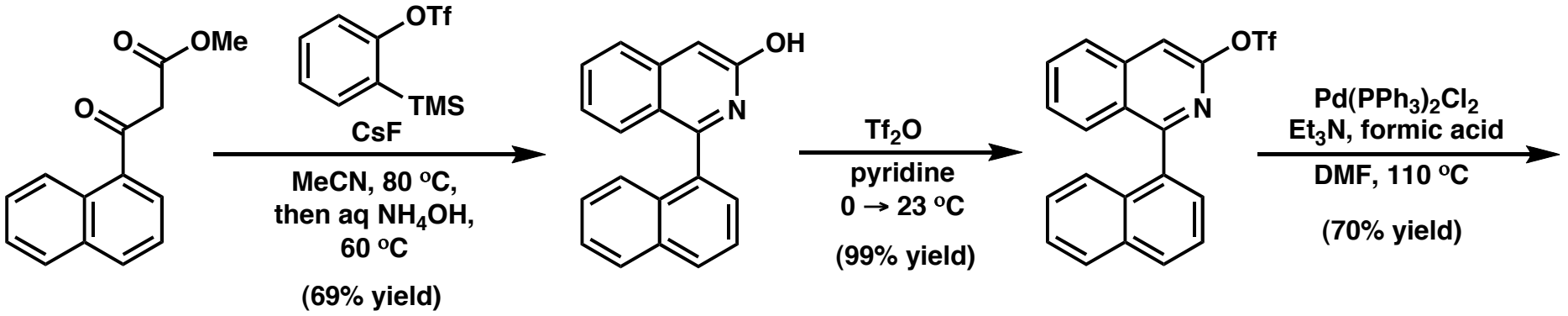
Allylic alkylation (BSA method)
74% yield, 78% ee, -25 °C

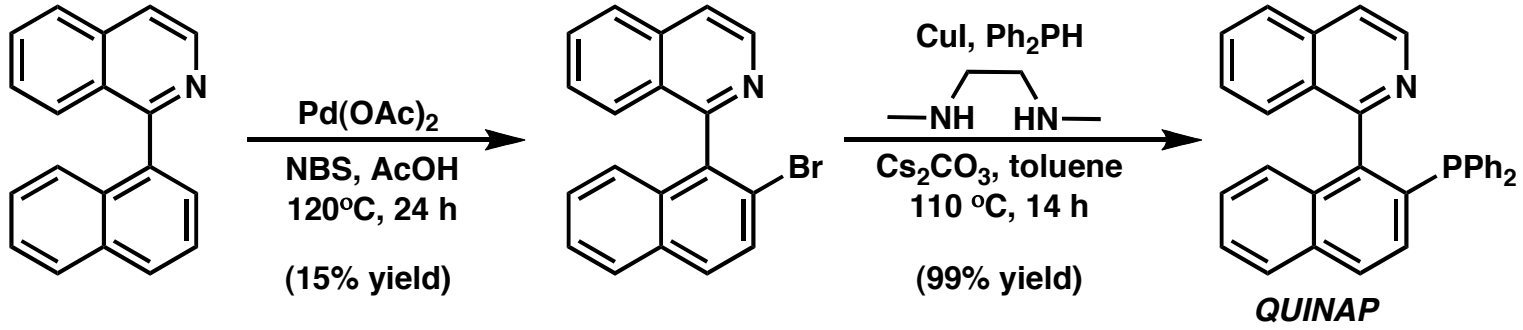
Li, *Tetrahedron: Asymmetry* **2007**, *18*, 1043-1047.

Stoltz approach towards QUINAP

Aryne acyl-alkylation/condensation



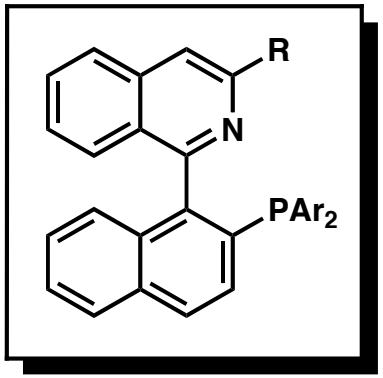


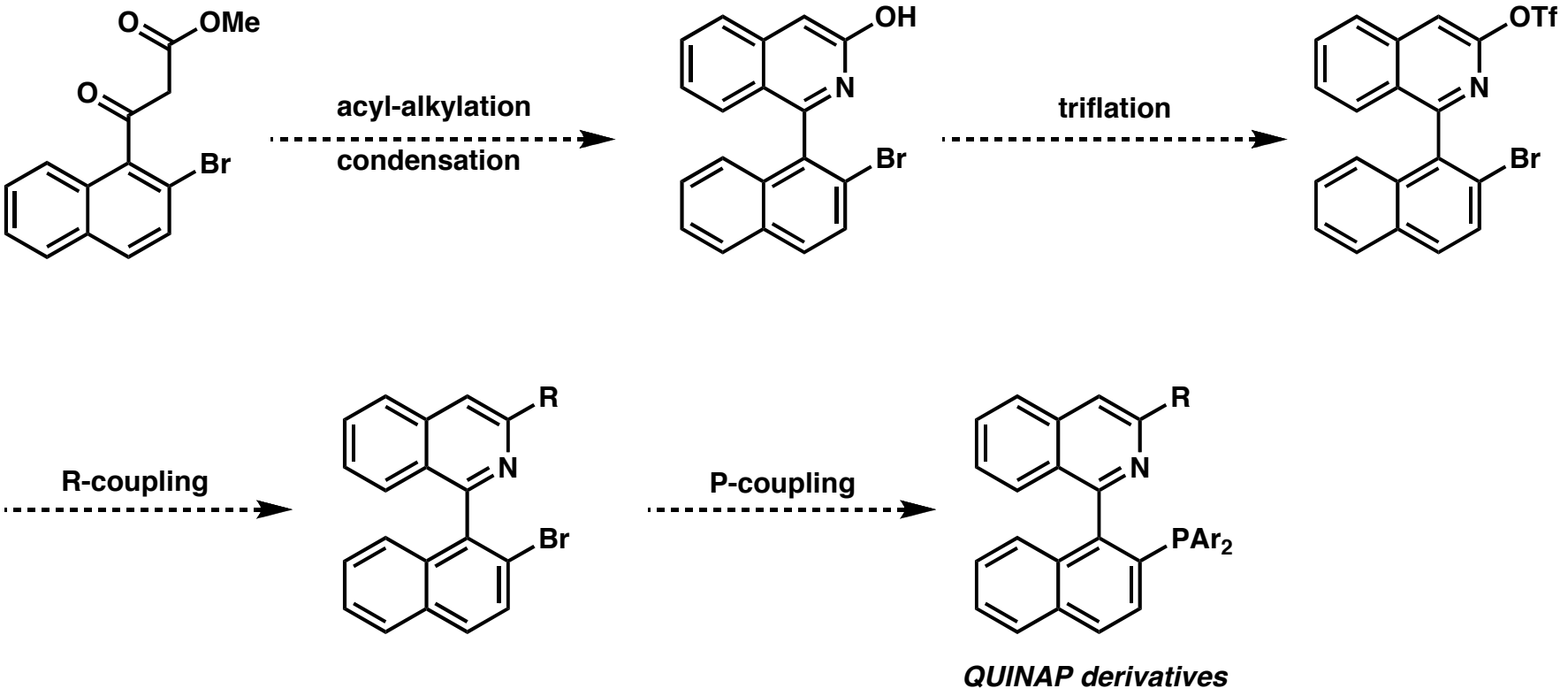


Stoltz, *Org. Biomol. Chem.* **2009**, *7*, 4960-4964.

QUINAP derivatives

Acyl-alkylation/condensation





QUINAP derivatives

Concluding remarks

• A large and diverse range of heterobidentate axially chiral P,N-ligands have been designed and prepared.

• Their application in a variety of assymetric transformations demonstrate that excellent enantioselectivities, regioselectivities and reactivities can be achieved by their metal complexes.

• However, research in this area also highlights the difficulty in finding a universal ligand.

• There is a need for the tailoring of ligands within each transformation for each substrate used.