Literature Report V

Dynamic Kinetic Asymmetric Arylation and Alkenylation of Ketones

Reporter: Kai Xue
Checker: Jian Chen
Date: 2025-3-24

Ruan, L.-X.; Sun, B.; Liu, J.-M.; Shi, S.-L.* *Science* **2023**, *379*, 662-670.

CV of Prof. Shi-Liang Shi

Background:

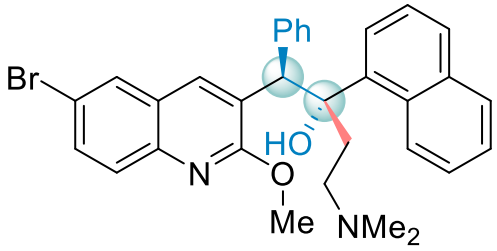
- **2008-2011** Ph.D., University of Tokyo (Prof. Masakatsu Shibasaki)
- **2011-2012** JSPS Postdoc., University of Tokyo (Prof. Motomu Kanai)
- **2012-2016** Postdoc., MIT (Prof. Stephen L. Buchwald)
- **2016-now** Professor, SIOC

Research:

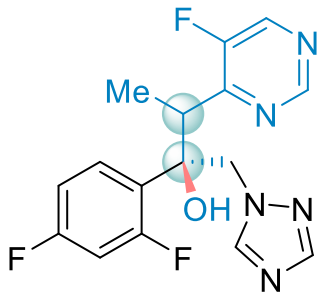
- **Development of New Privileged Chiral Ligands**
- **Development of Novel, Efficient, and Practical Enantioselective Catalytic Reactions**
- **Design and Syntheses of New Optically Active Polymers**

Contents

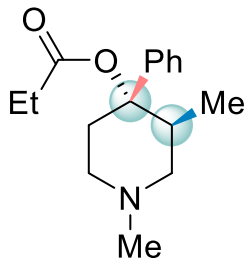
Introduction



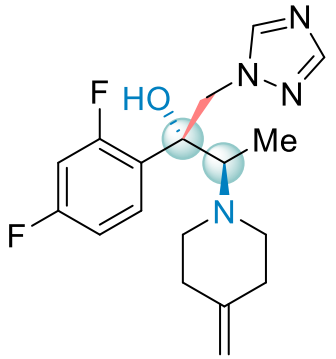
sirturo
(anti-tuberculosis drug)



voriconazole
(broad-spectrum antifungal)



prodine
(opioid analgesic)



efinaconazole
(broad-spectrum antifungal)

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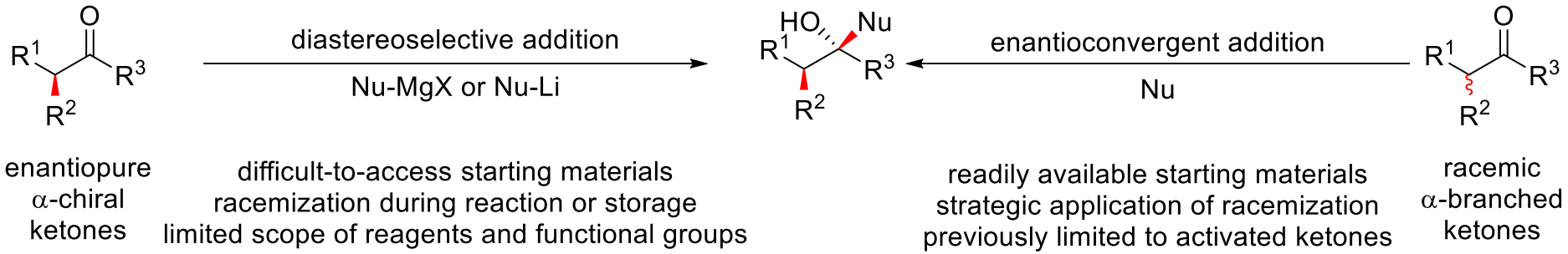
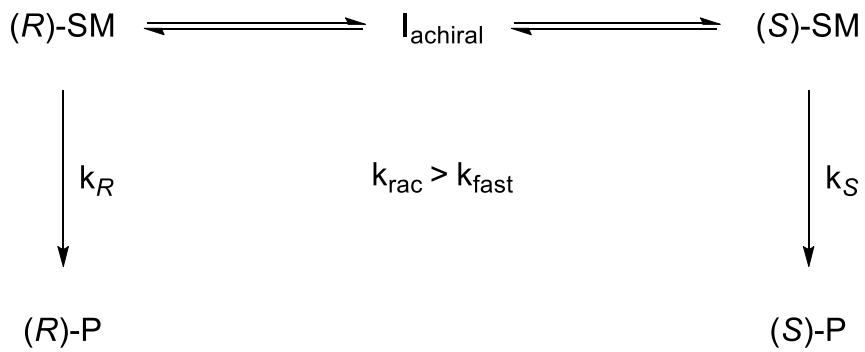
Introduction

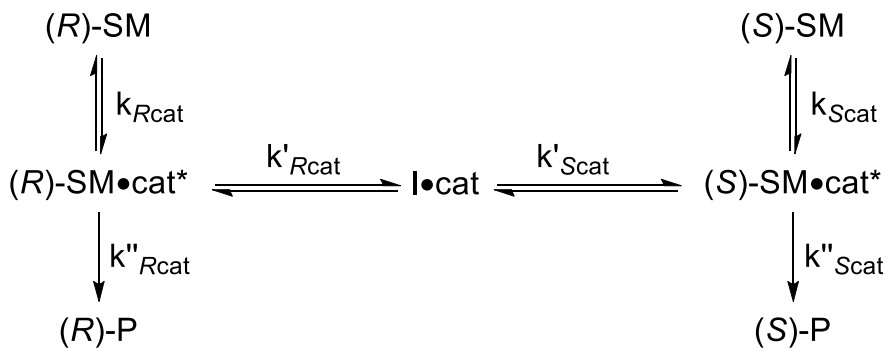
Synthesis of Enantioenriched Alcohols



Dynamic Kinetic Resolution



DyKAT



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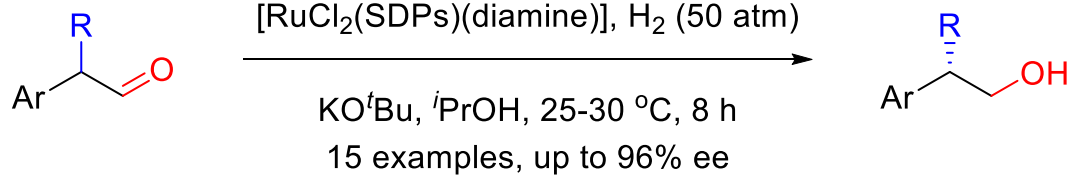
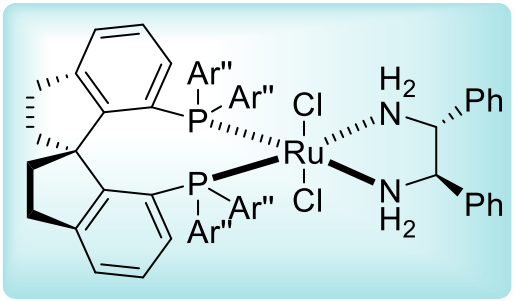
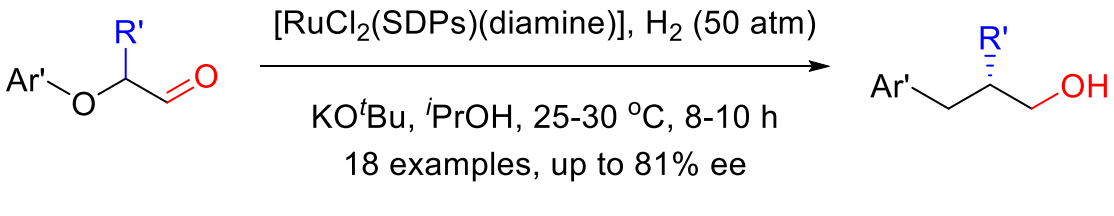
Introduction

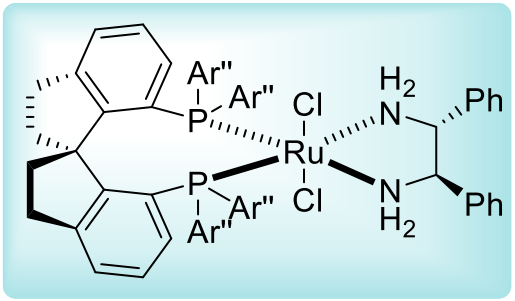
Asymmetric Hydrogenation of Racemic Aldehydes via Dynamic Kinetic Resolution





Xie, J.-H.; Zhou, Z.-T.; Kong, W.-L.; Zhou, Q.-L.* *J. Am. Chem. Soc.* **2007**, *129*, 1868.

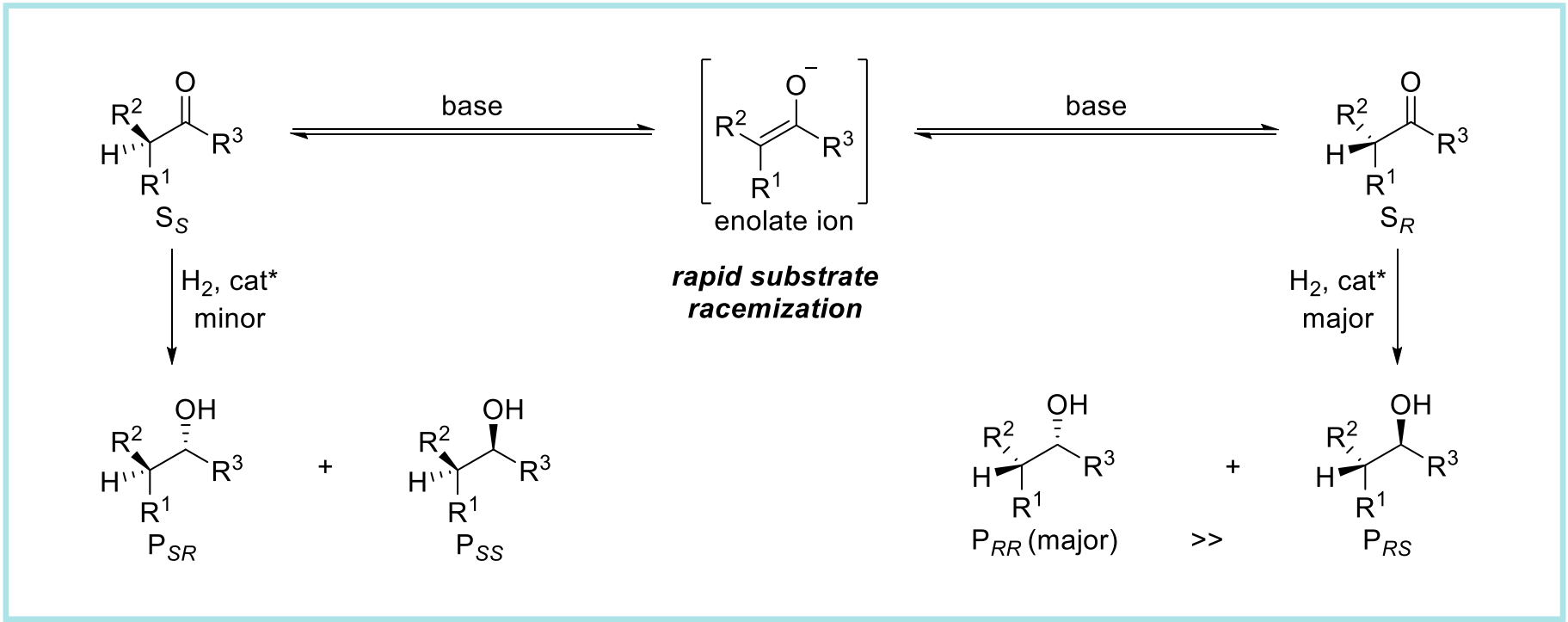




Zhou, Z.-T.; Xie, J.-H.; Zhou, Q.-L.* *Adv. Synth. Catal.* **2009**, *351*, 363.

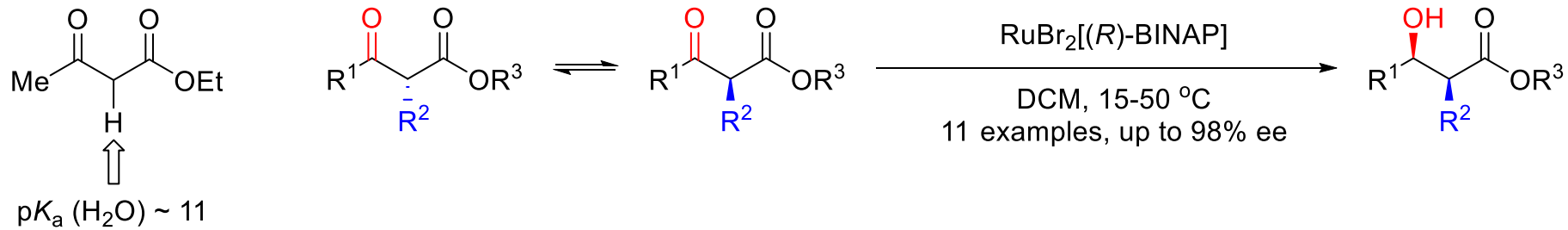
Introduction

Asymmetric Hydrogenation of Racemic Aldehydes via Dynamic Kinetic Resolution

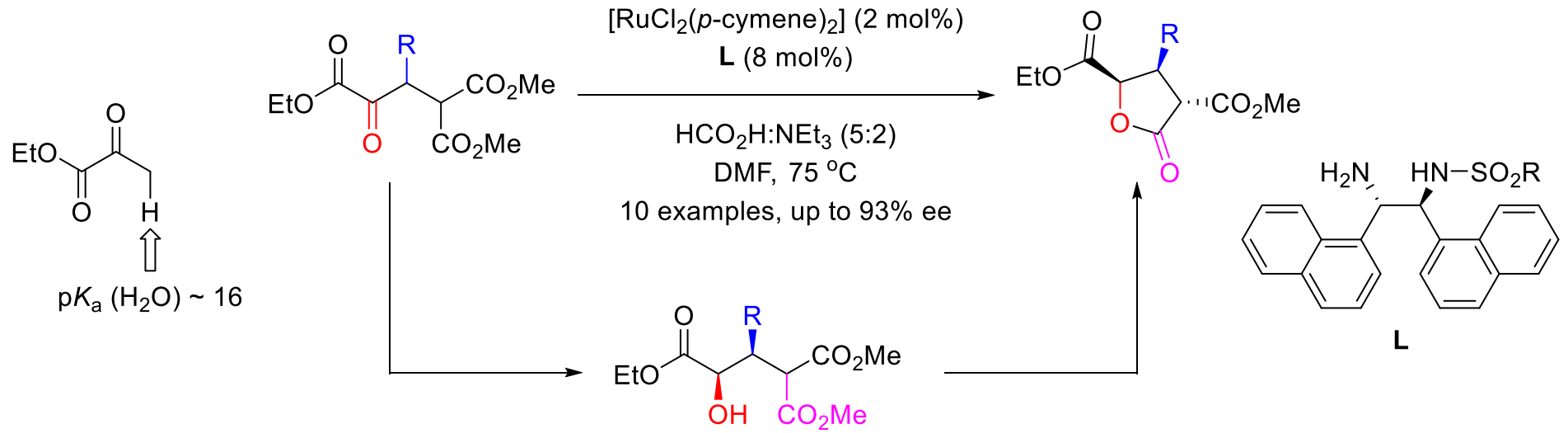


Introduction

Dynamic Kinetic Resolution of α/β-Keto Esters



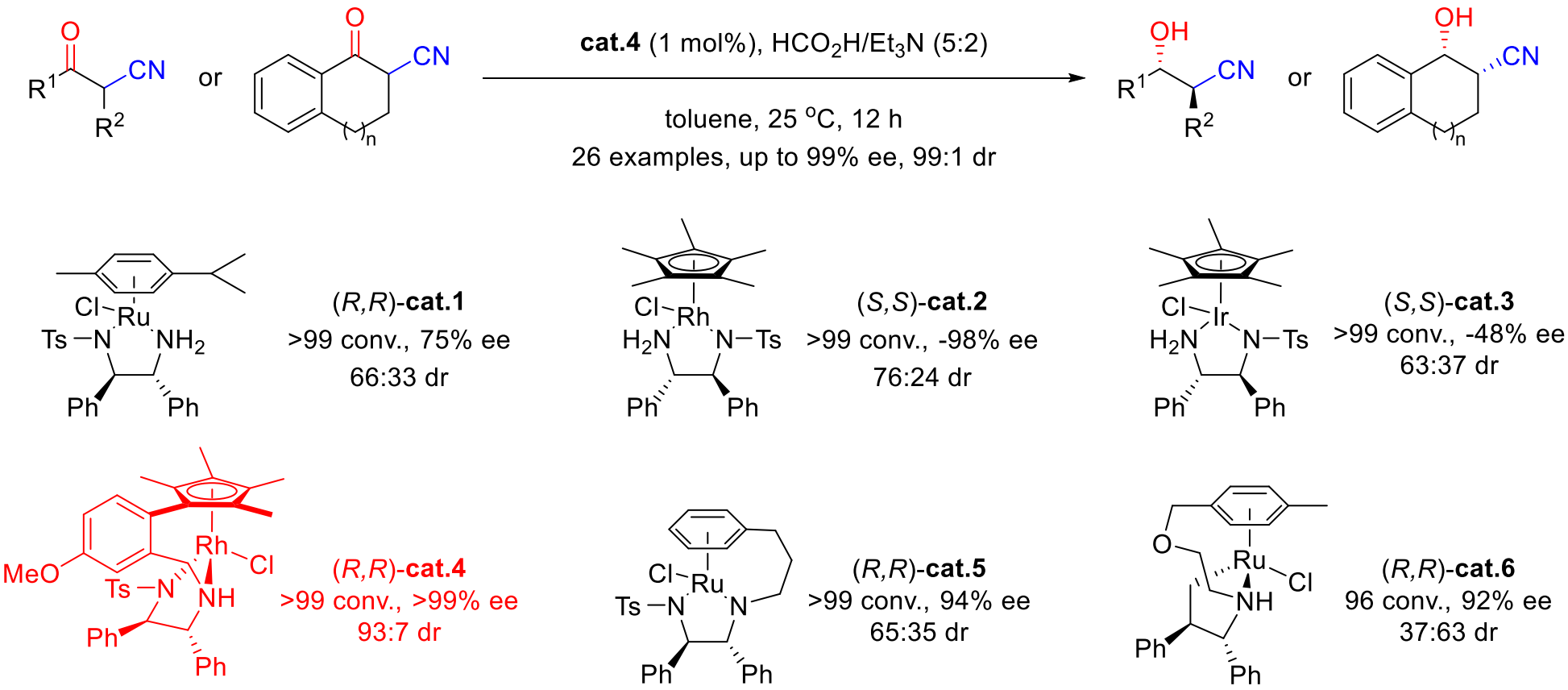
Noyori, R.*; Ikeda, T.; Ohkuma, M.; Widhalm, M.; Kitamura, H. *J. Am. Chem. Soc.* **1989**, *111*, 9134.



Steward, K. M.; Gentry, E. C.; Johnson, J. S.* *J. Am. Chem. Soc.* **2012**,*134*, 7329.

Introduction

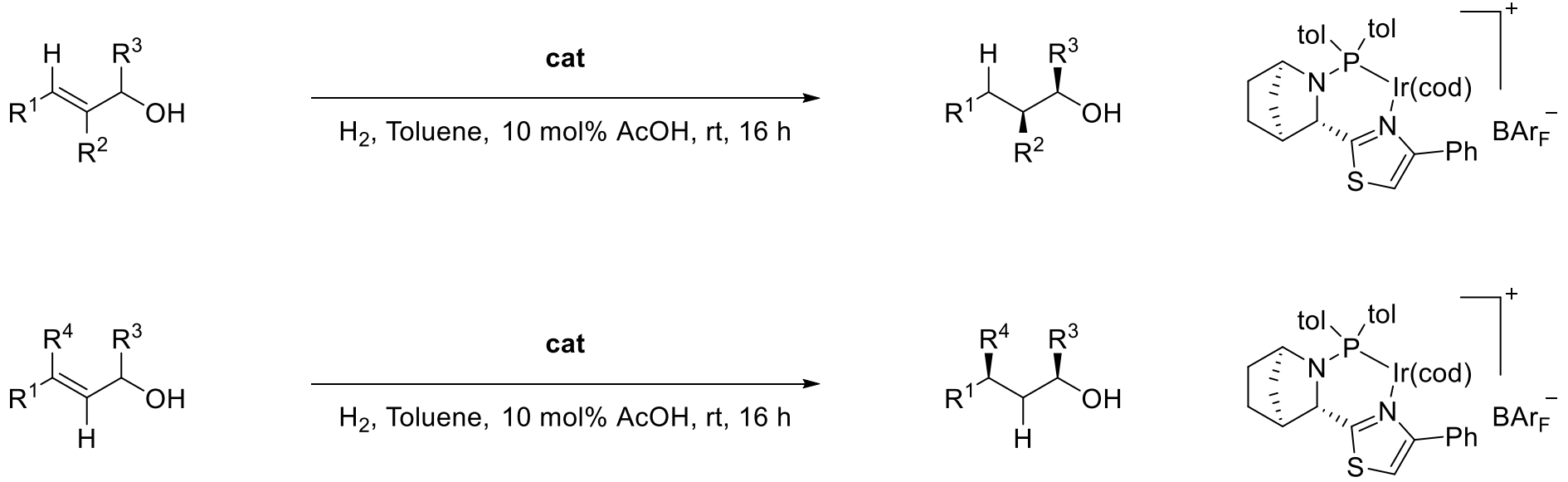
Dynamic Kinetic Resolution of α-Substituted-β-Keto Carbonitriles



Wang, F.; Yang, T.; Wu, T.; Zheng, L.-S.; Yin, C.; Shi, Y.; Ye, X.-Y.; Zhang, X.* *J. Am. Chem. Soc.* **2021**, *143*, 2477.

Introduction

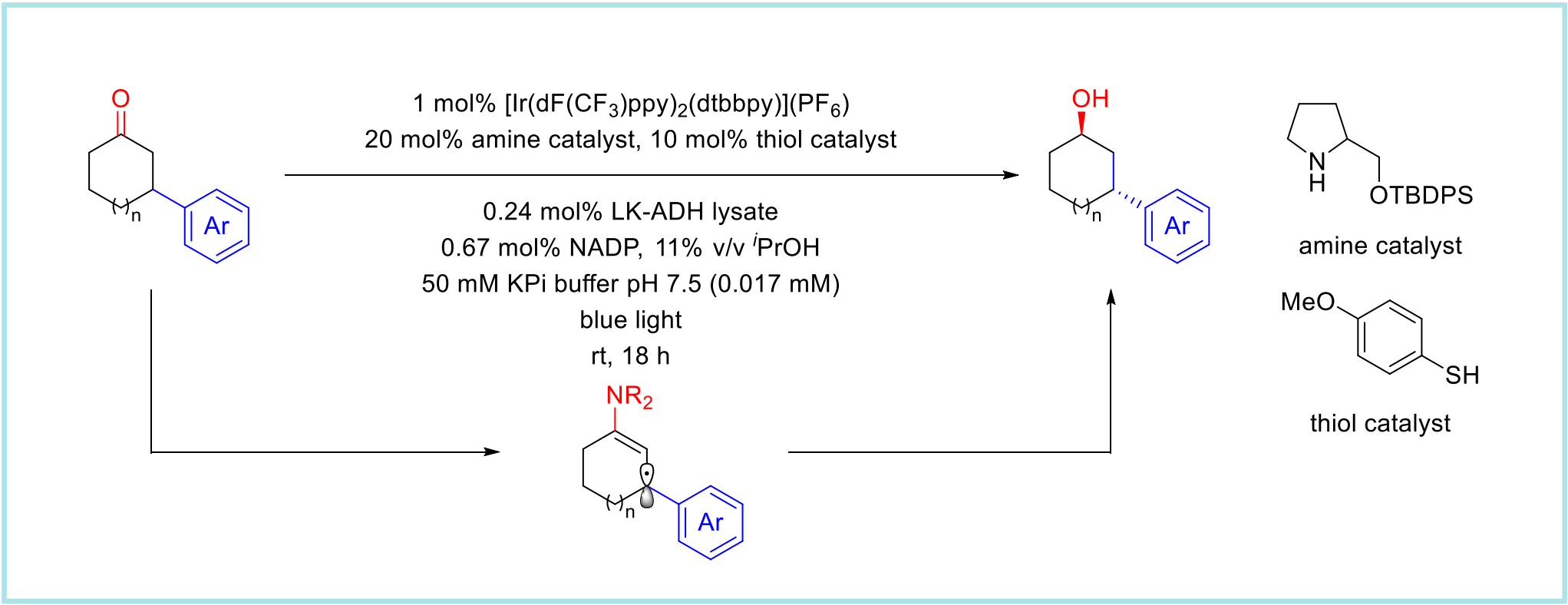
Dynamic Kinetic Resolution of Allylic Alcohols



Liu, J.; Krajangsri, S.; Yang, J.; Li, J.-Q.; Andersson, P. G.* *Nat. Catal.* **2018**, *1*, 438.

Introduction

Dynamic Kinetic Resolution of β-Substituted Ketones



DeHovitz, J. S.; Loh, Y. Y.; Kautzky, J. A.; MacMillan, D. W. C.* *Science* **2020**, *369*, 1113.

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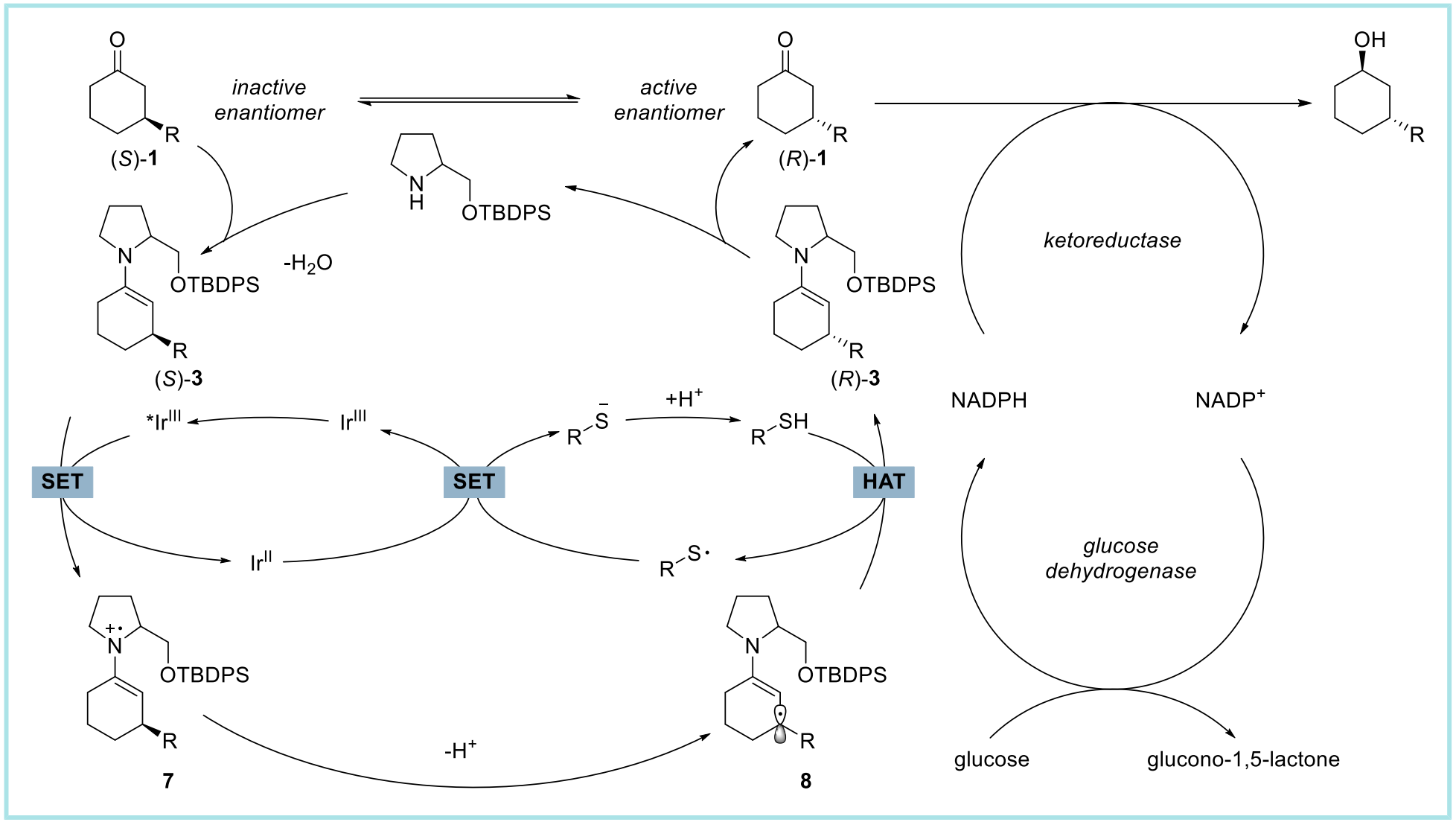
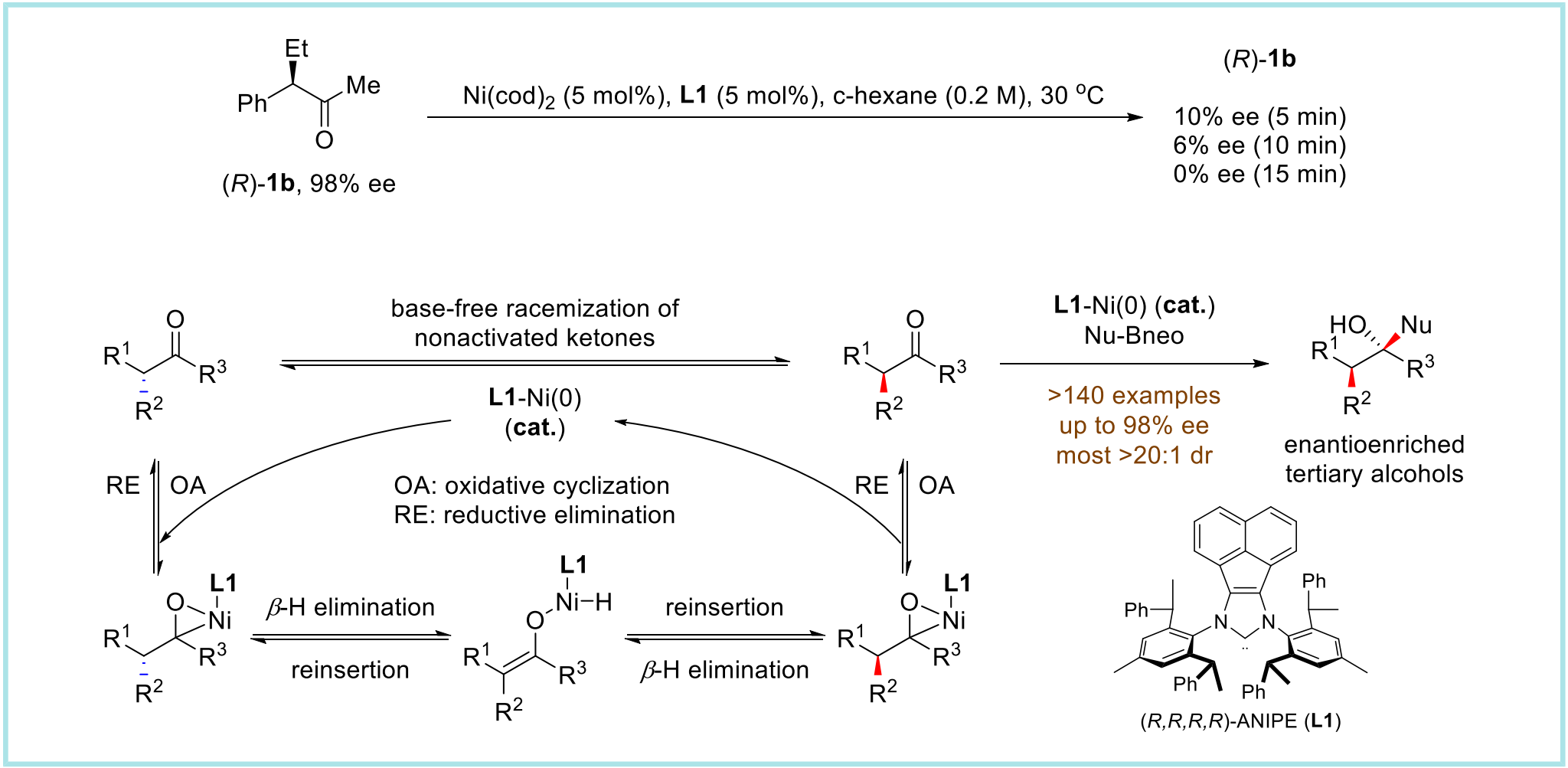
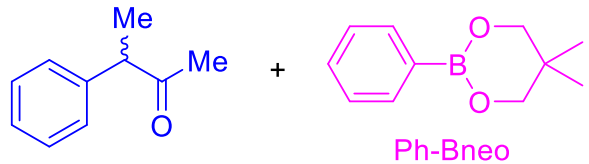


Project Synopsis



Optimization of the Reaction Conditions



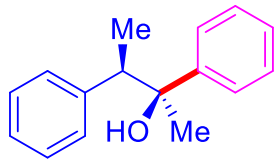
1a (0.2 mmol)
racemic

+

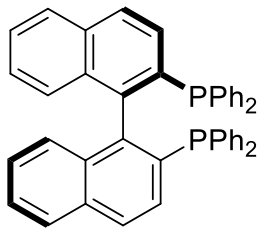
Ph-Bneo
2a (1.5 equiv.)

$Ni(cod)_2$ (5 mol%)
Phosphine or NHC/HCl (5 mol%)

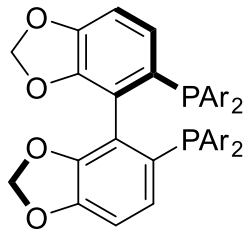
base (x mol%), solvent (0.2 M)
30 °C, 24 h



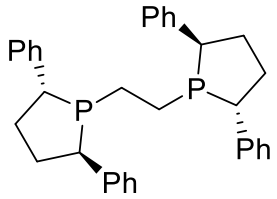
3a



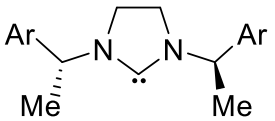
L2: (*R*)-BINAP
0% yield



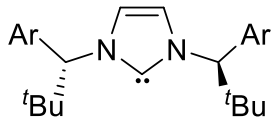
L3: (*R*)-DTBM-SegPhos
0% yield



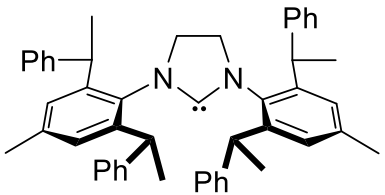
L4: (*R,R*)-Ph-BPE
0% yield



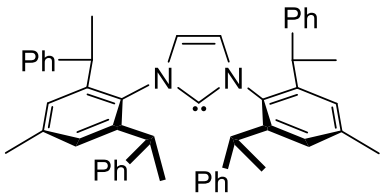
L5 (Ar = 2-naphthyl)
0% yield



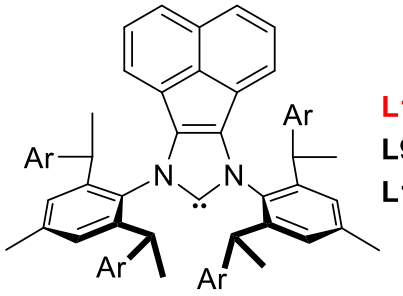
L6 (Ar = 2-naphthyl)
0% yield



L7 (*R,R,R,R*)-SIPE
79% yield, 86% ee, >20:1 dr

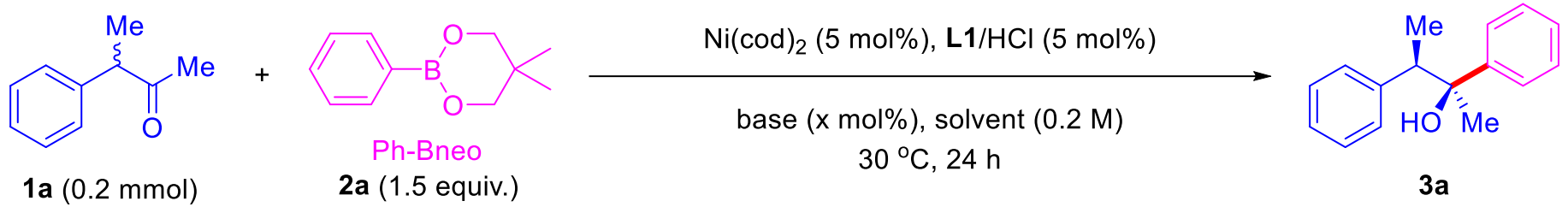


L8 (*R,R,R,R*)-IPE
88% yield, 85% ee, >20:1 dr



L1 (Ar = Ph), 99% yield, 92% ee, >20:1 dr
L9 (Ar = 3,5-Xyl), 91% yield, 91% ee, >20:1 dr
L10 (Ar = 3,5-^{t}Bu-C_6H_3), 74% yield
71% ee, >20:1 dr

Optimization of the Reaction Conditions



1a (0.2 mmol)
racemic

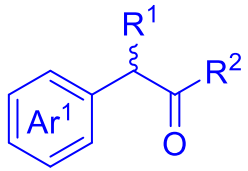
2a (1.5 equiv.)

3a

Entry	Base (mol%)	Yield (%)[a] (**3a**)	Er (%) (**3a**)[b]	Dr (%) (**3a**)[a]
1	NaO^{t}Bu (30)	99	92	>20:1
2	KO^{t}Bu (30)	93	92	>20:1
3	CsF (30)	<2		
4	KOAc (30)	<2		
5	NaO^{t}Bu (150)	45	91	>20:1
6	NaO^{t}Bu (100)	62	91	>20:1
7	NaO^{t}Bu (60)	93	92	>20:1
8	**NaO^{t}Bu (10)**	**99**	**92**	**>20:1**
9	NaO^{t}Bu (0)	<2		

[a]Measured by ^{1}H NMR analysis with 1,1,2,2-tetrachloroethane as internal standard. [b]Determined by HPLC.

Scope for Enantioconvergent Arylation of α-Aryl Ketones.



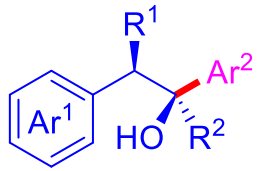
1 (0.2 mmol)
racemic

\+ Ar^2-Bneo

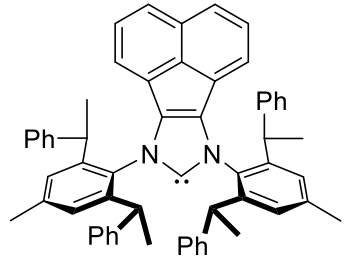
2 (1.5 equiv.)

$Ni(cod)_2$ (5 mol%), **L1**/HCl (5 mol%)
NaO^tBu (10 mol%), c-hexane (0.2 M)

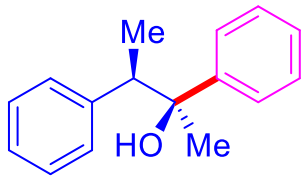
30 °C, 24 h
>20:1 dr
unless otherwise indicated



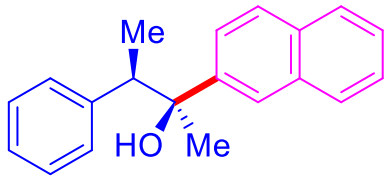
3-4



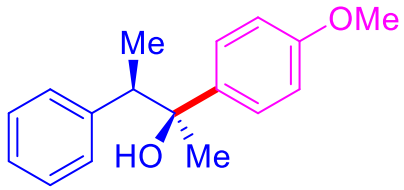
(*R*,*R*,*R*,*R*)-ANIPE (**L1**)



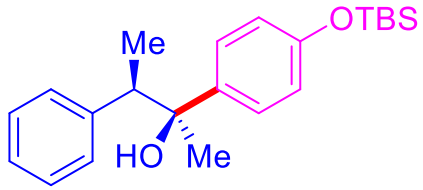
3a, 97%, 92% ee



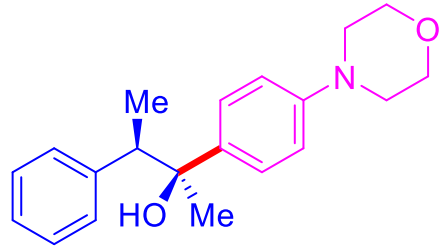
3b, 91%, 91% ee



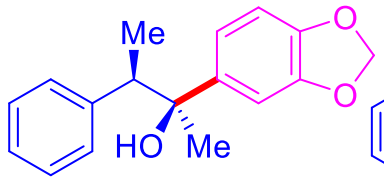
3c, 92%, 92% ee



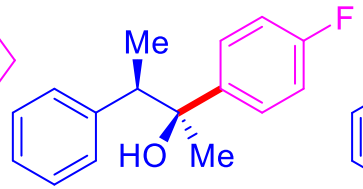
3d, 91%, 93% ee



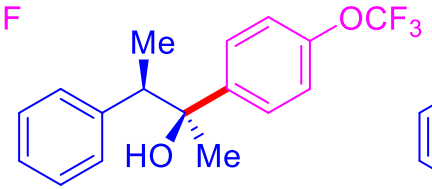
3e, 83%, 92% ee



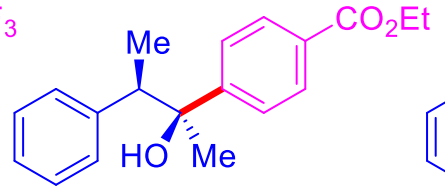
3f, 82%, 90% ee



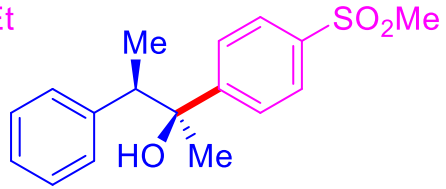
3h, 79%, 92% ee



3k, 96%, 91% ee

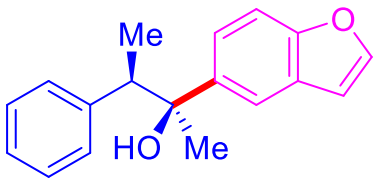


3l, 88%, 94% ee

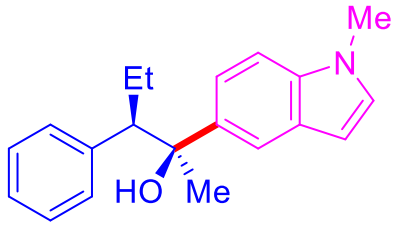


3o, 96%, 95% ee

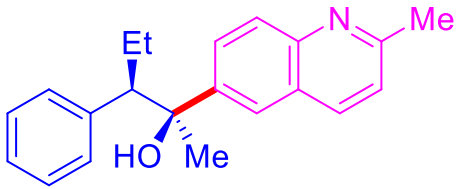
Scope for Enantioconvergent Arylation of α-Aryl Ketones.



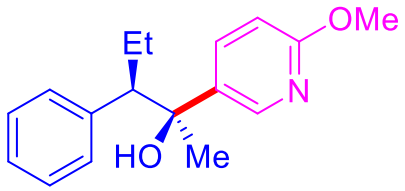
3q, 90%, 90% ee



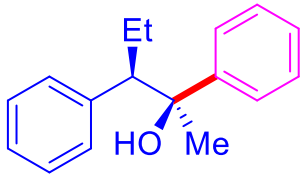
3s, 88%, 95% ee



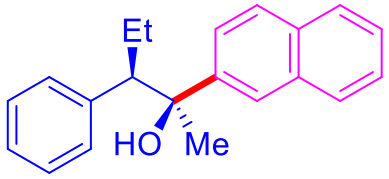
3t, 96%, 94% ee



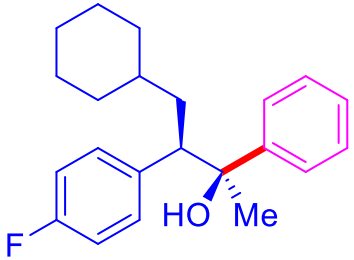
3u, 45%, 91% ee



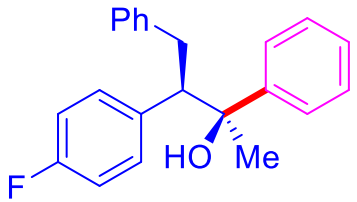
3v, 98%, 97% ee



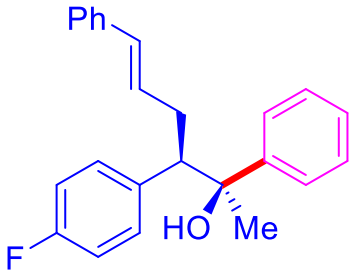
3w, 95%, 93% ee



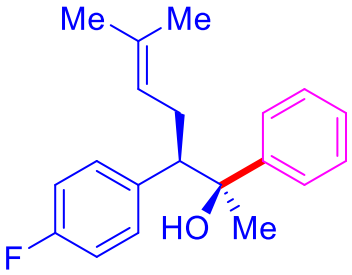
3x, 83%, 94% ee



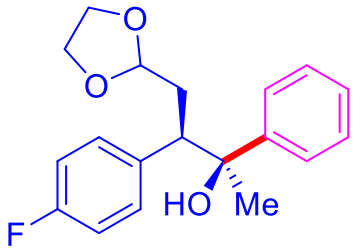
3y, 84%, 93% ee



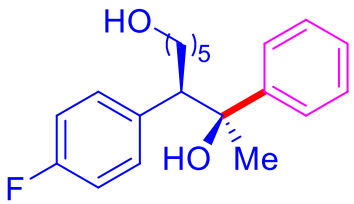
3z, 97%, 94% ee



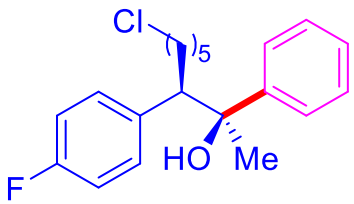
4a, 78%, 86% ee



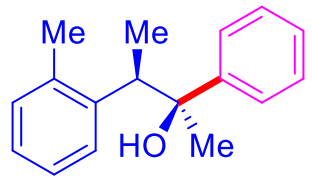
4b, 78%, 86% ee



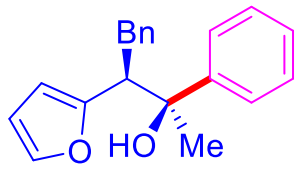
4c, 45%, 98% ee



4d, 99%, 98% ee

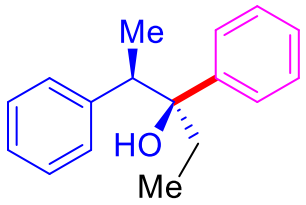


4e, 80%, 93% ee

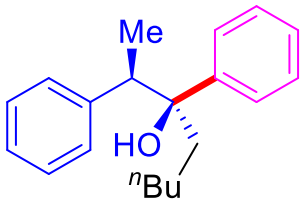


4f, 93%, 89% ee

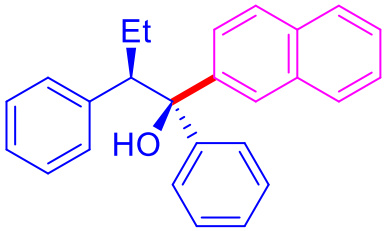
Scope for Enantioconvergent Arylation of α-Aryl Ketones.



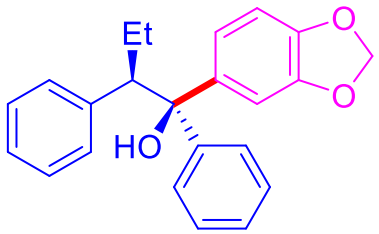
4g, 81%, 90% ee
17:1 dr



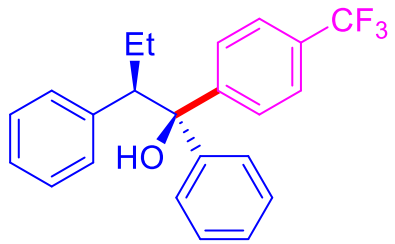
4h, 65%, 80% ee
8:1 dr



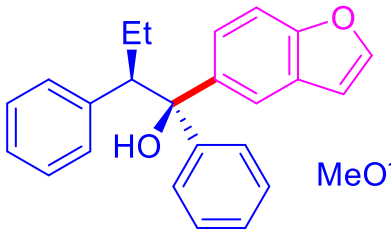
4i, 90%, 90% ee



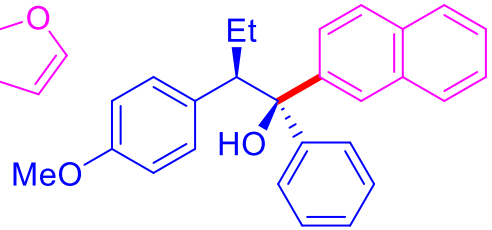
4j, 84%, 84% ee



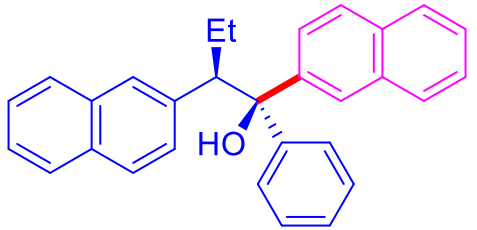
4l, 83%, 90% ee



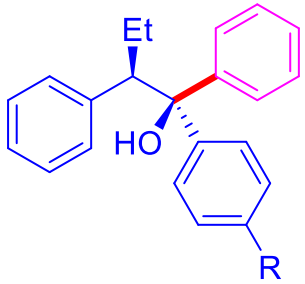
4m, 67%, 85% ee



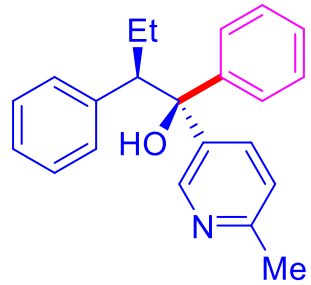
4n, 92%, 91% ee



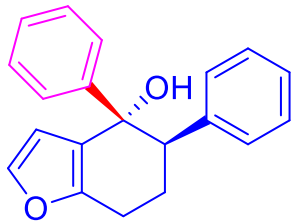
4o, 98%, 87% ee



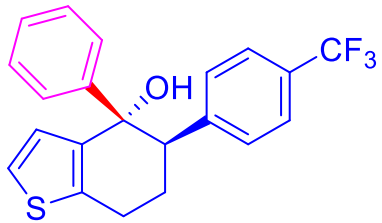
4p, R = ^{n}Bu, 65%, 88% ee
4q, R = CF_3, 82%, 86% ee



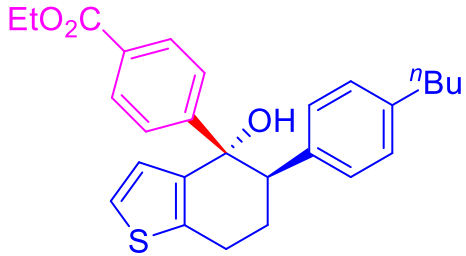
4r, 50%, 86% ee



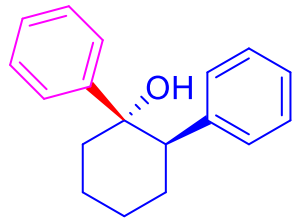
4s, 68%, 97% ee



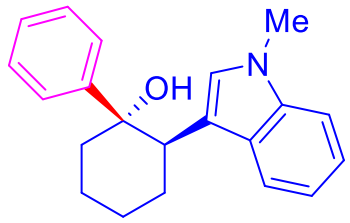
4t, 71%, 91% ee



4u, 82%, 98% ee

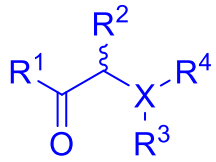


4v, 95%, 80% ee



4w, 99%, 91% ee

Scope for Arylation of α-Amino or α-Oxy Ketones



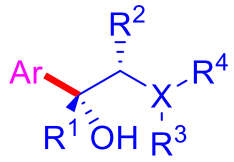
5 (X = N) or **8** (X = O)
racemic, (0.2 mmol)

\+ Ar-Bneo

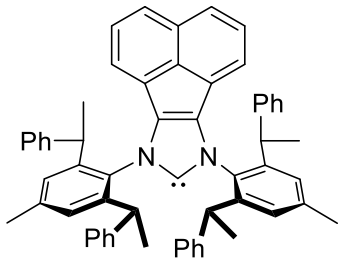
2 (1.5 equiv)

$Ni(cod)_2$ (5 mol%), **L1**/HCl (5 mol%)
NaO^tBu (10 mol%), c-hexane (0.2 M)

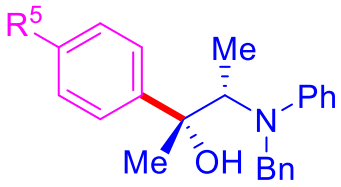
50 °C, 24 h
>20:1 dr
unless otherwise indicated



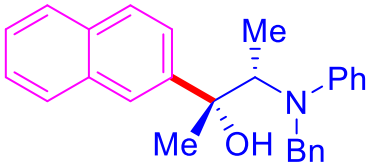
6-7, 9



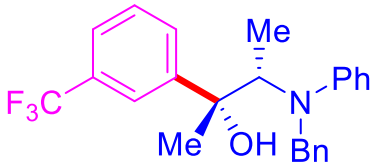
(*R,R,R,R*)-ANIPE (**L1**)



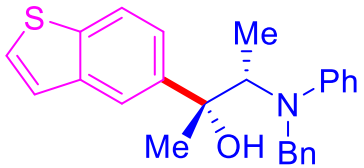
6a, R^5 = H, 99%, 94% ee
6c, R^5 = OMe, 85%, 94% ee
6d, R^5 = OTBS, 88%, 93% ee
6g, R^5 = F, 88%, 95% ee
6k, R^5 = CO_2Et, 75%, 95% ee
6m, R^5 = SO_2Me, 55%, 96% ee



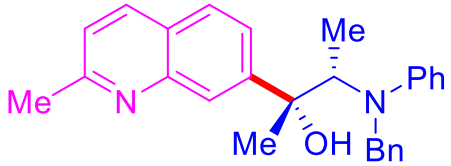
6b, 94%, 93% ee



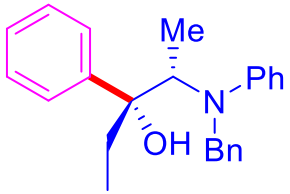
6i, 74%, 94% ee



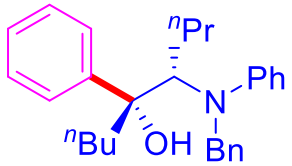
6p, 74%, 94% ee



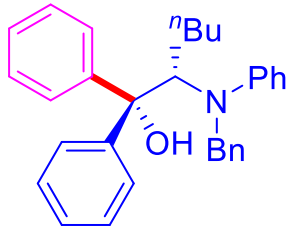
6s, 98%, 92% ee



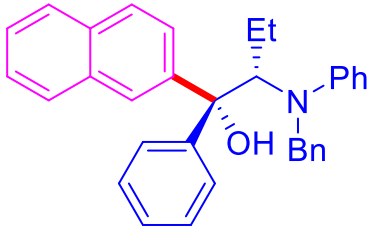
6t, 85%, 94% ee



6u, 82%, 94% ee

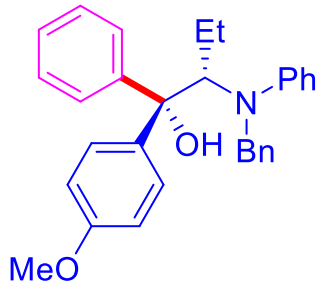


6v, 93%, 85% ee

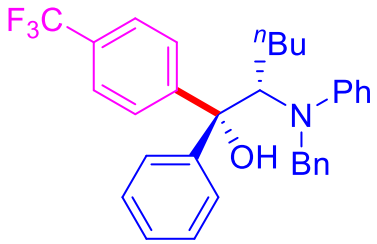


6w, 90%, 91% ee

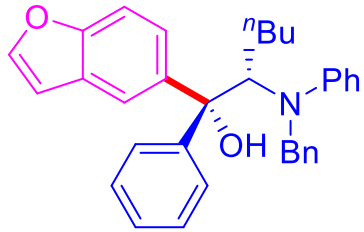
Scope for Arylation of α-Amino or α-Oxy Ketones



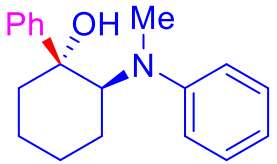
6x, 95%, 89% ee



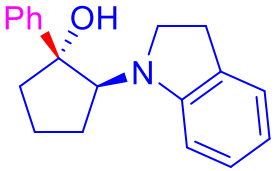
6y, 76%, 92% ee



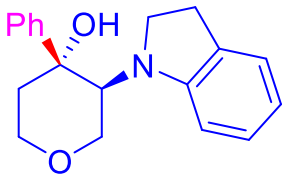
6z, 48%, 87% ee



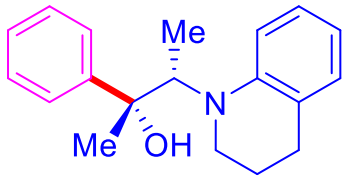
7b, 55%, 91% ee



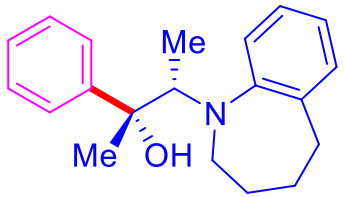
7c, 88%, 75% ee



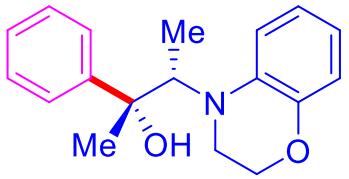
7e, 93%, 96% ee



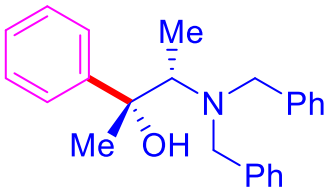
7g, 51%, 89% ee



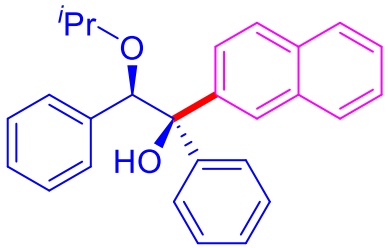
7h, 64%, 91% ee



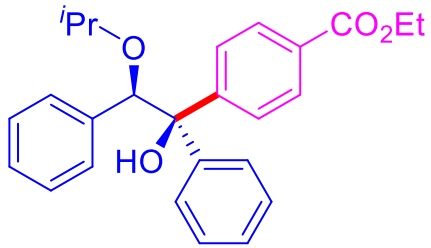
7n, 82%, 87% ee



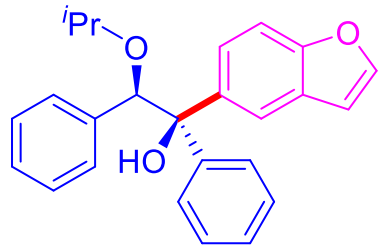
7o, 41%, 76% ee



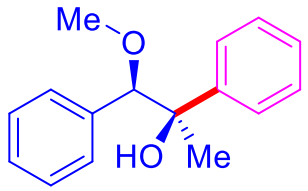
9a, 82%, 87% ee, 9:1 dr



9b, 56%, 90% ee, 7:1 dr

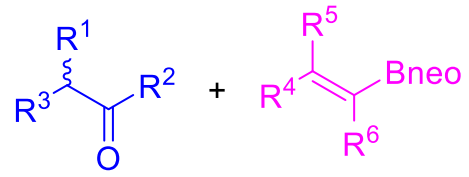


9c, 47%, 81% ee, 6:1 dr



9e, 95%, 90% ee, 6:1 dr

Scope for Alkenylation of Racemic Ketones



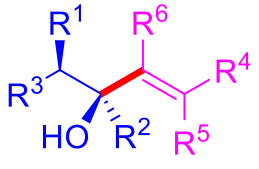
1, 5

+

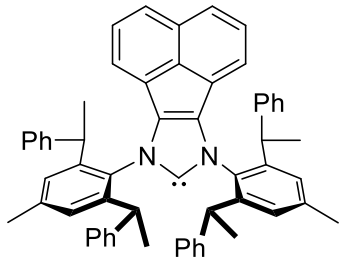
10 (1.5 equiv)

$Ni(cod)_2$ (5 mol%), **L1**/HCl (5 mol%)
NaO^tBu (10 mol%), c-hexane (0.2 M)

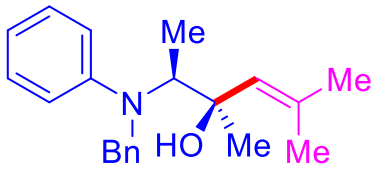
30 °C, 24 h
all >20:1 dr



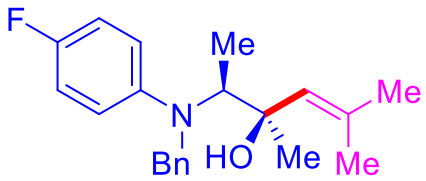
11



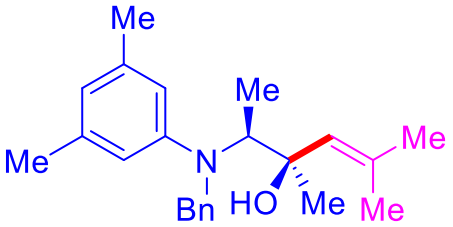
(*R,R,R,R*)-ANIPE (**L1**)



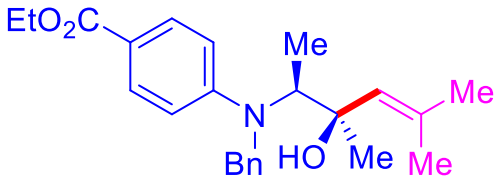
11a, 95%, 95% ee



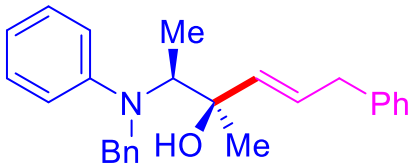
11b, 78%, 95% ee



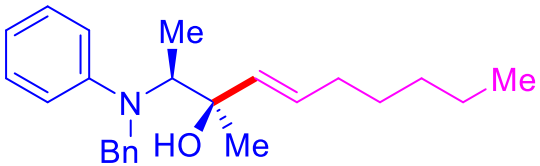
11e, 79%, 93% ee



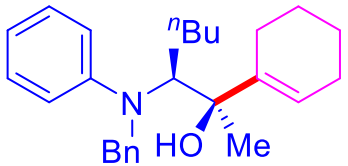
11g, 95%, 70% ee



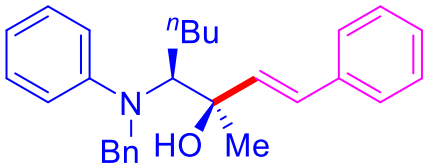
11k, 52%, 73% ee



11l, 71%, 74% ee

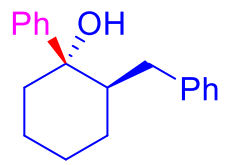


11m, 78%, 80% ee

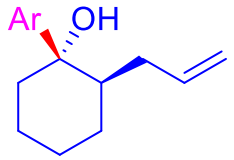


11p, 52%, 75% ee

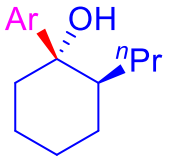
Alkyl-Substituted Ketones and Gram-Scale Reaction



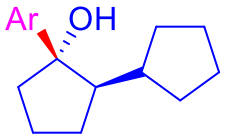
13a, 92%, 80% ee



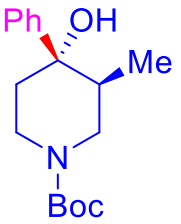
13b, Ar = 2-naphthyl
72%, 92% ee



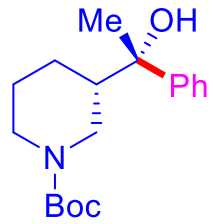
13c, Ar = 2-naphthyl
89%, 90% ee



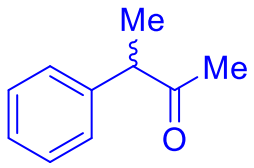
13d, Ar = 2-naphthyl
83%, 92% ee



13e, 92%, 83% ee



13f, 81%, 58% ee



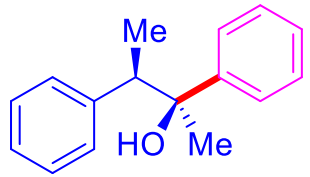
1a
(5.5 mmol)

\+ Ph-Bneo

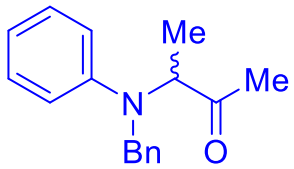
1.5 equiv.

$Ni(cod)_2$ (1 mol%), **L1**/HCl (1 mol%)

NaO^tBu (10 mol%), c-hexane (0.2 M), 30 °C, 24 h

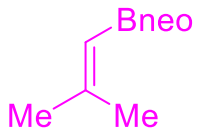


3a, 1.1 g, 88%
92% ee, >20:1 dr



5a
(4.0 mmol)

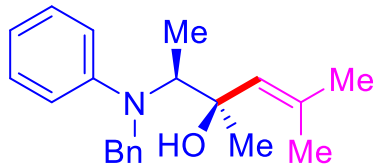
\+



1.5 equiv

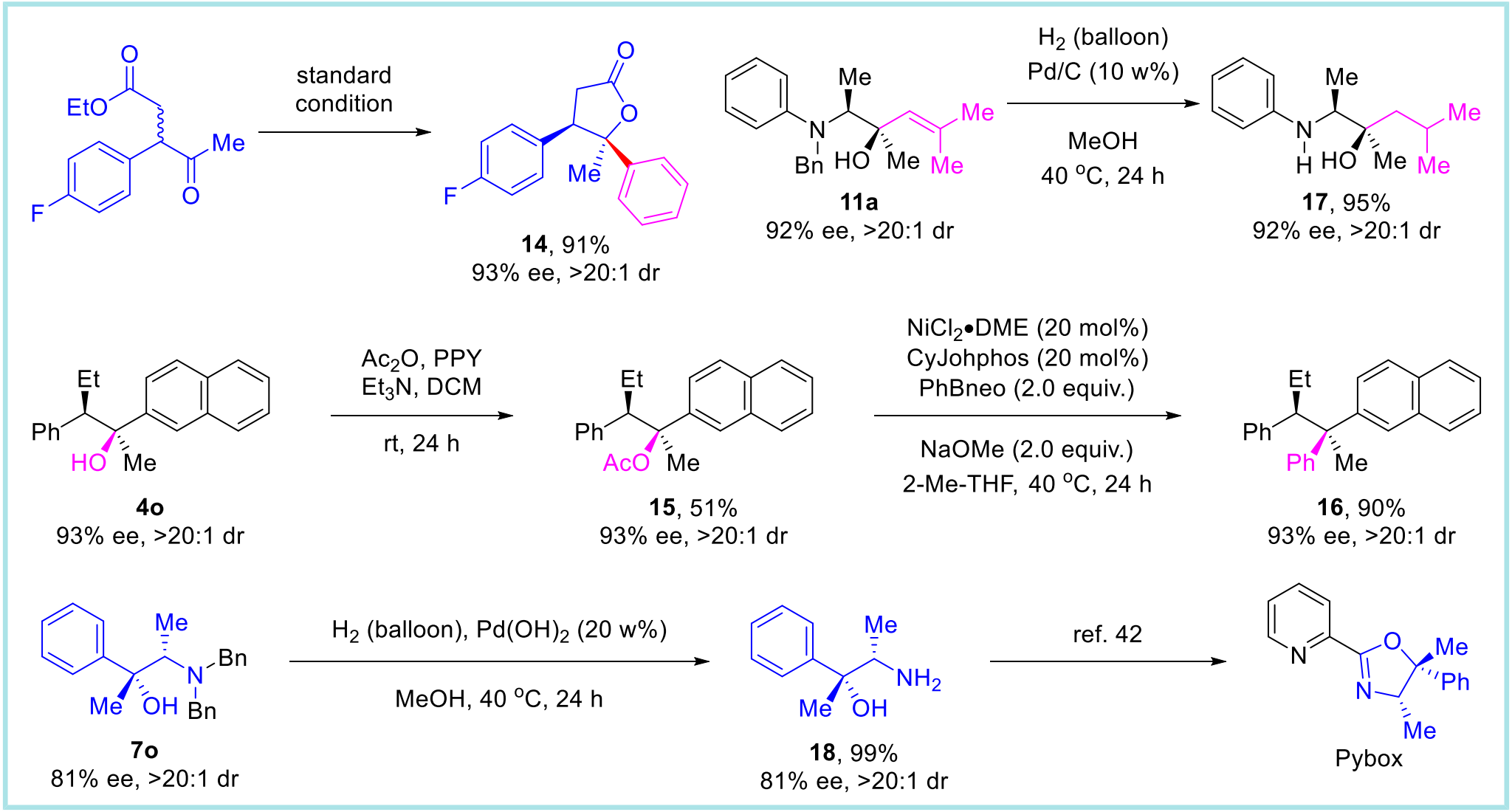
$Ni(cod)_2$ (4 mol%), **L1**/HCl (4 mol%)

NaO^tBu (10 mol%), c-hexane (0.2 M), 30 °C, 24 h

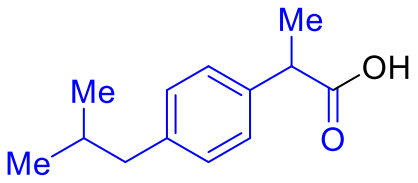


11a, 1.2 g, 97%
91% ee, >20:1 dr

Transformations

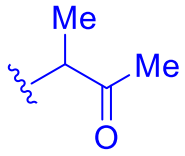


Transformations



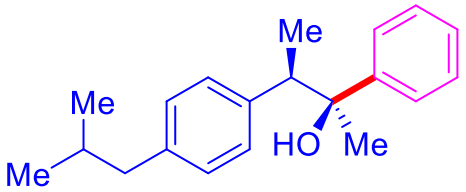
(±)-ibuprofen

a, b



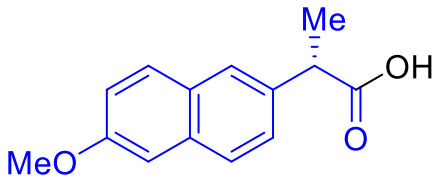
(±)

standard conditions



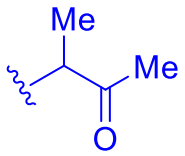
19, 94%, 90% ee, >20:1 dr

a) CDMT, NMM, THF, MeNH-OMe•HCl
b) MeMgBr, THF, 0 oC-rt



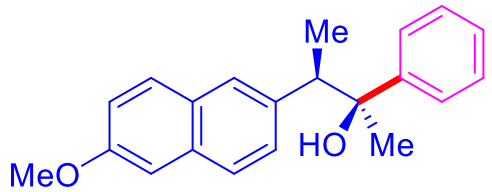
(+)-(*S*)-naproxen

a, b

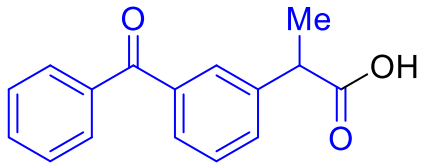


(±)

standard conditions

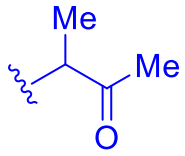


20, 93%, 92% ee, >20:1 dr



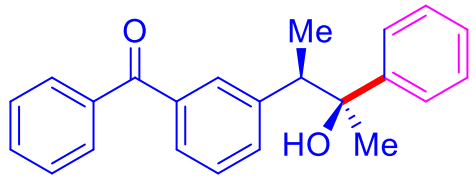
(±)-ketoprofen

a, b



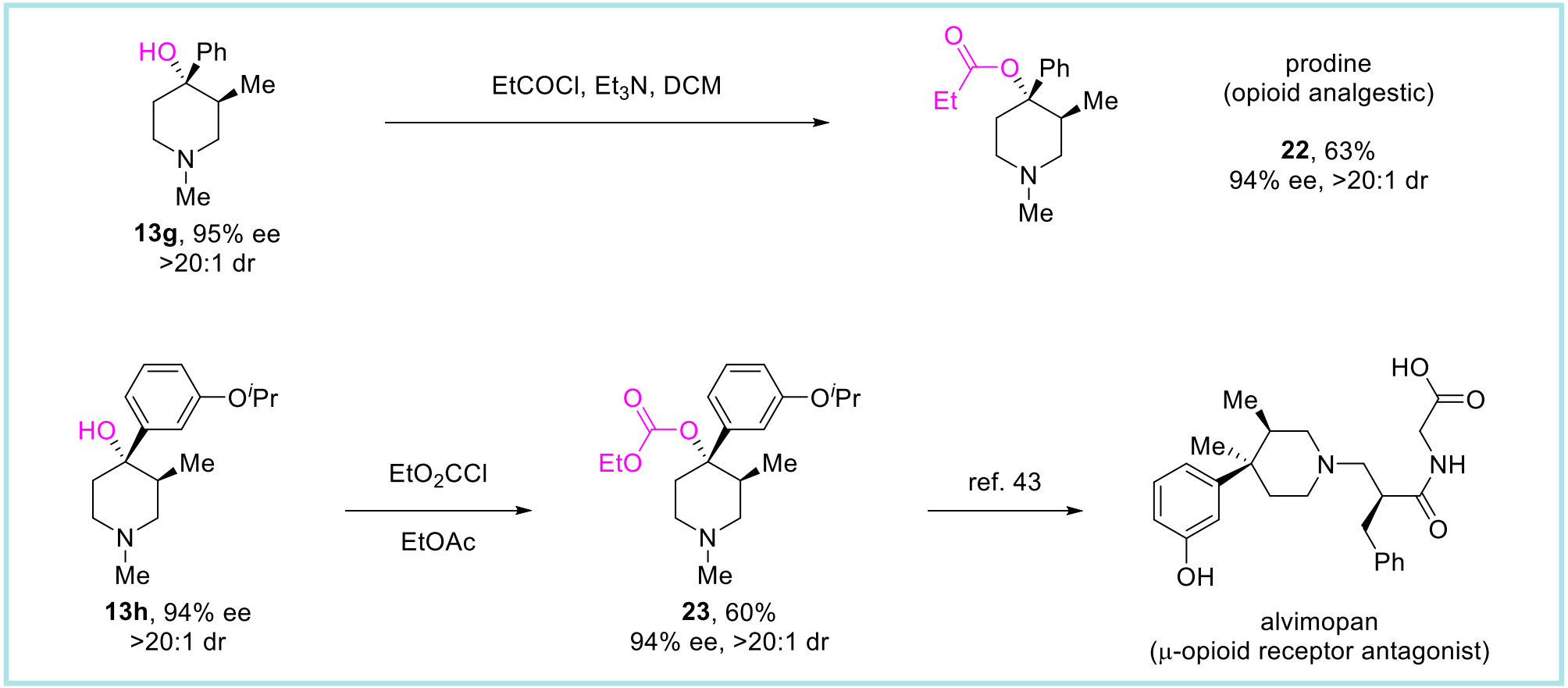
(±)

standard conditions

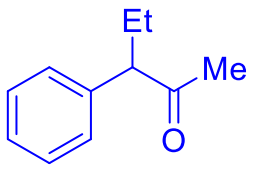


21, 34%, 95% ee, >20:1 dr

Transformations



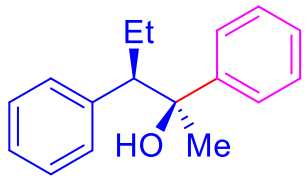
Control Experiments



1b

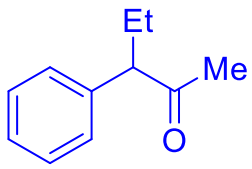
standard conditions

Ph-Bneo (1.5 equiv.)



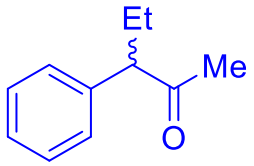
3v

\+



1b (recovered)

(*R*)-**1b**, 98% ee	1 h	59% yield, 97% ee, >20:1 dr	40% yield, 0% ee
	3.5 h	99% yield, 97% ee, >20:1 dr	<1% yield
(*S*)-**1b**, >99% ee	3.5 h	36% yield, 97% ee, >20:1 dr	65% yield, 0% ee
(±)-**1b**, 0% ee	3.5 h	75% yield, 97% ee, >20:1 dr	22% yield, 0% ee



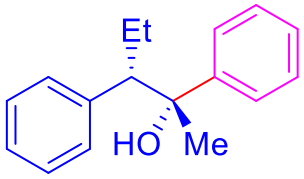
1b

\+ Ph-Bneo (1.5 equiv.)

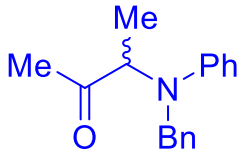
$Ni(cod)_2$ (5 mol%), ***ent*-L1**/HCl (5 mol%)

NaO^tBu (10 mol%), c-hexane (0.2 M)

30 °C, 24 h



***ent*-3v**, 87% yield
96% ee, >20:1 dr



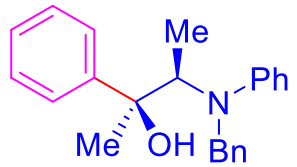
5a

\+ Ph-Bneo (1.5 equiv.)

$Ni(cod)_2$ (5 mol%), ***ent*-L1**/HCl (5 mol%)

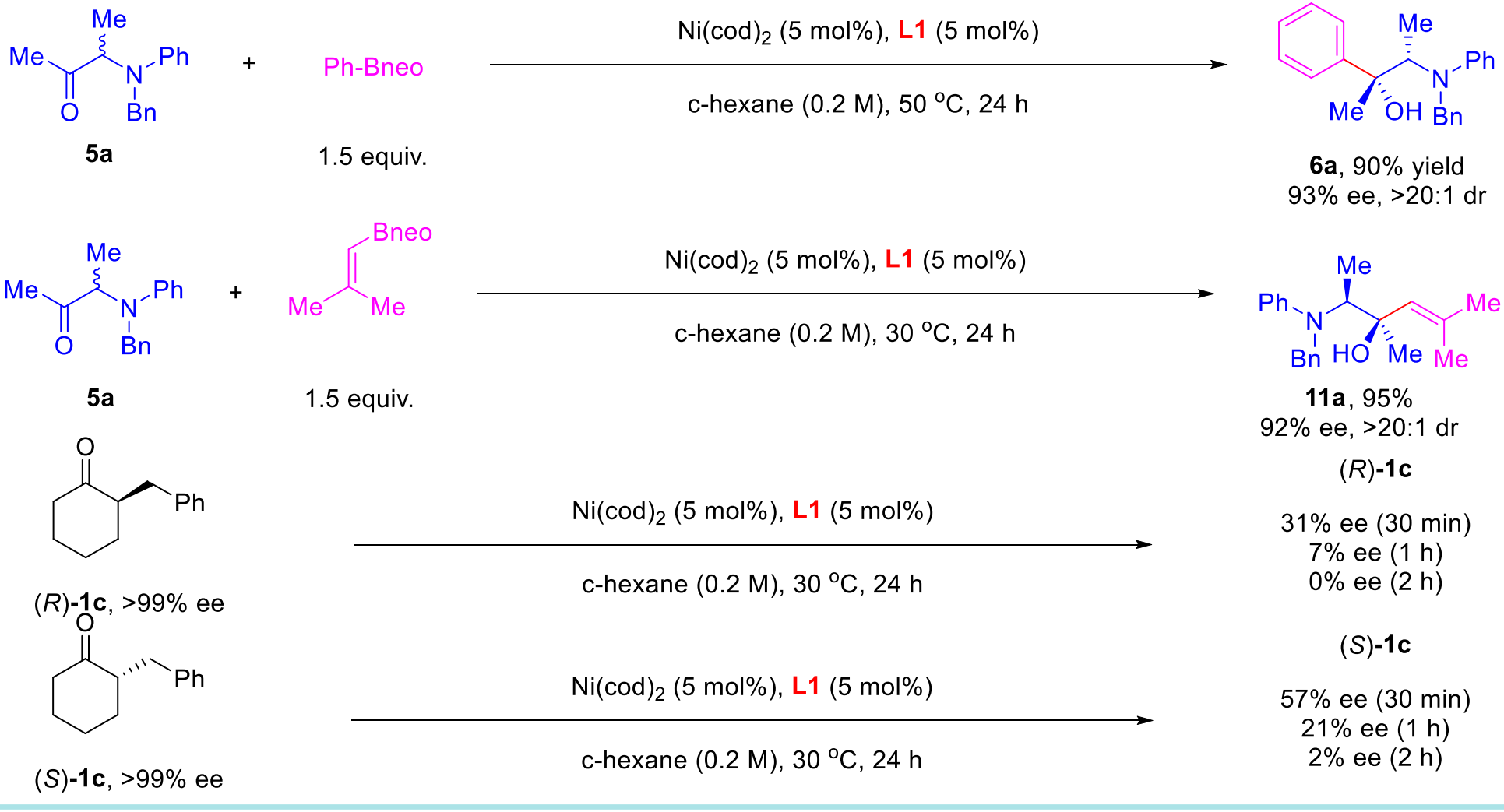
NaO^tBu (10 mol%), c-hexane (0.2 M)

50 °C, 24 h

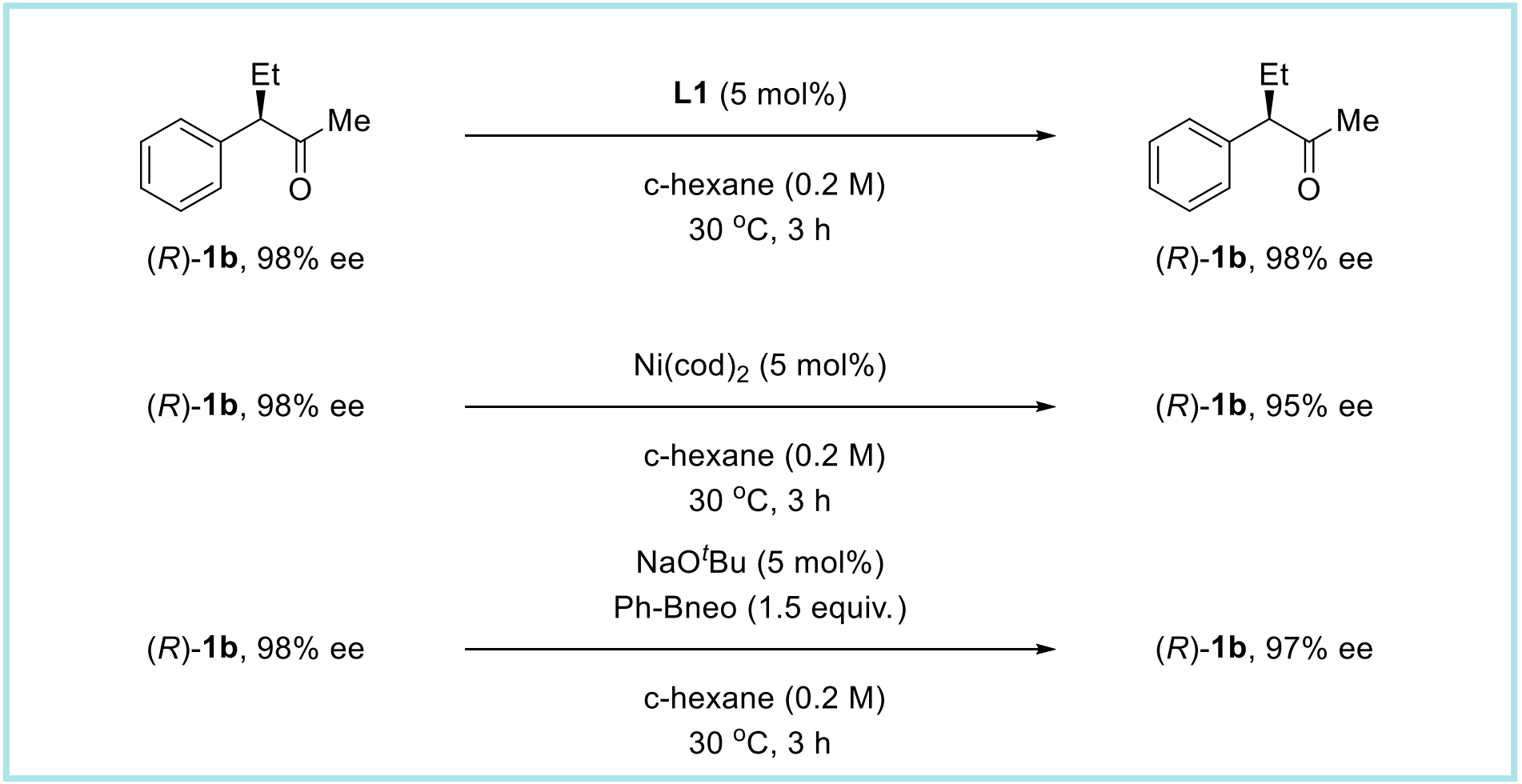


***ent*-6a**, 84% yield
92% ee, >20:1 dr

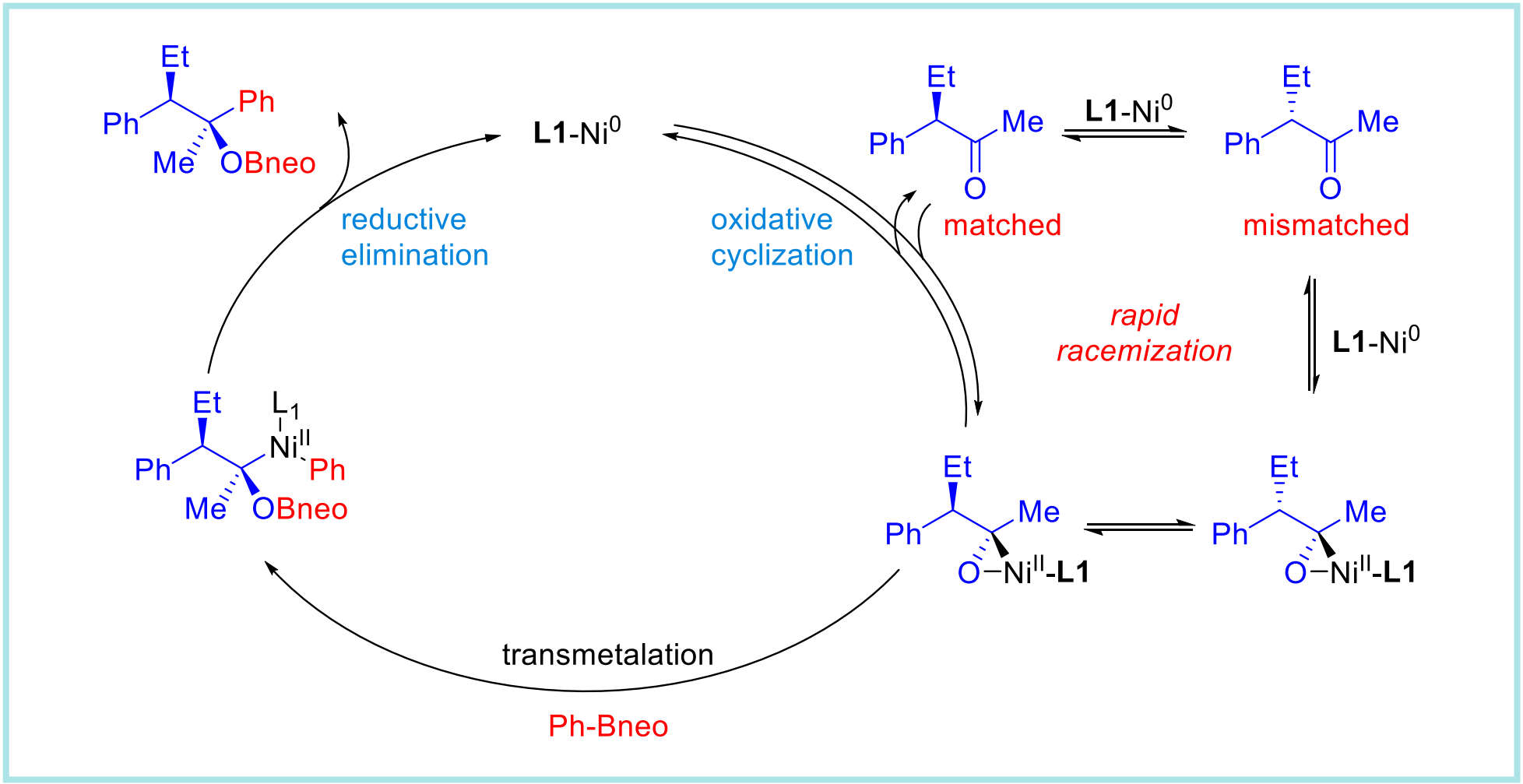
Control Experiments: Base-Free Conditions



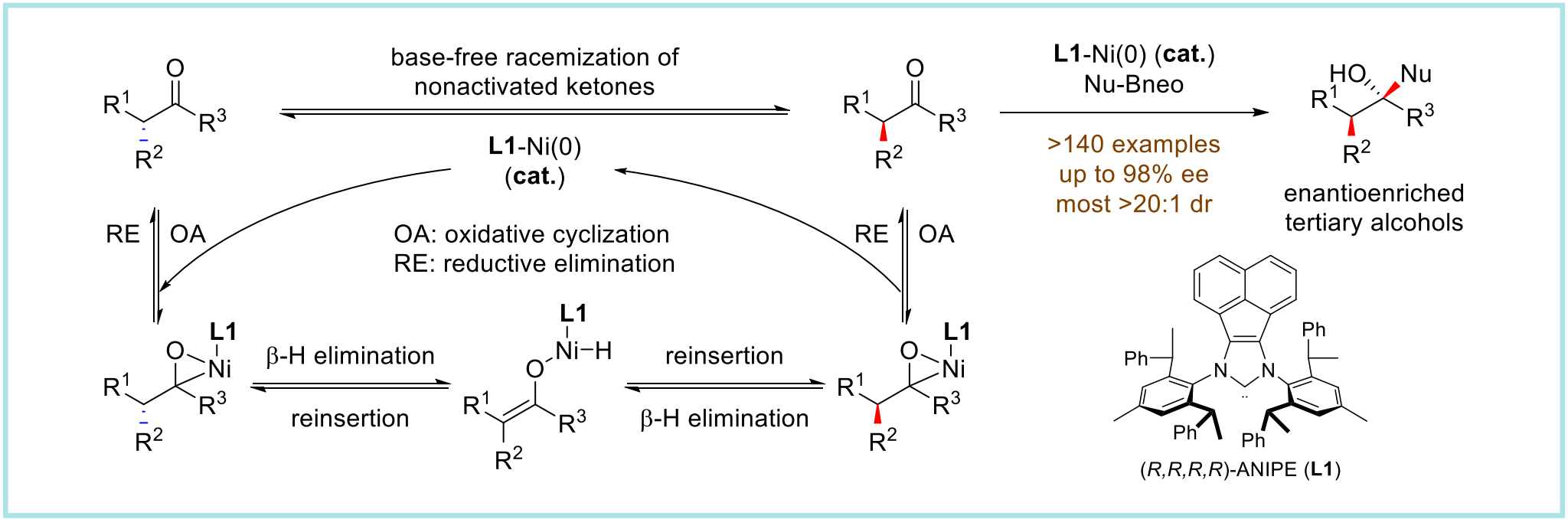
Control Experiments



Proposed Mechanism



Summary



- ***Dynamic kinetic asymmetric addition of aryl and alkenyl nucleophiles***
- ***Construction of tertiary alcohols bearing two stereocenters***
- ***Modify profen drugs and synthesize biologically relevant molecules.***

Strategy for Writing The First Paragraph

合成具有连续手性中心的醇类化合物至关重要

传统的合成方法具有诸多缺点

引出本文工作

- ✓ The development of general stereoselective methods with simultaneous control of contiguous stereocenters is critical to the efficient discovery and manufacture of new drugs.
- ✓ However, these precursors are difficult to prepare and potentially suffer from racemization during carbonyl addition reactions or during storage. Moreover, the stereocontrolled addition to the carbonyl group is generally nontrivial, and the results may be difficult to predict in many cases.
- ✓ Among general approaches for achieving an enantioconvergent synthesis of tertiary alcohols with contiguous stereocenters, the dynamic kinetic asymmetric transformation (DyKAT)…

Strategy for Writing The Last Paragraph

展望未来

✓ Beyond the immediate utility of this method, we anticipate that the Ni-NHC-enabled enantioconvergent strategy will spur the development of other DyKAT processes for the rapid synthesis of valuable complex targets.

Representative Examples

- The efficient and selective construction of enantioenriched tertiary alcohols bearing two contiguous stereocenters has remained a substantial challenge. (大量的；价值巨大的；重大的；大而坚固的)
- Enantioenriched alcohols constitute an important class of compounds that are found in a myriad of pharmaceutical agents and bioactive natural products. (无数的，大量的)
- In addition, there is a second prerequisite. (先决条件)

Acknowledgement

Thanks for your attention