Literature Report VI

Palladium-Catalyzed Enantioselective Intramolecular Arylation of Enantiotopic Secondary C-H Bonds

Reporter: Xiao-Qing Wang
Checker: Zhou-Hao Zhu
Date: 2021-4-6

Baudoin, O. *et al. Angew. Chem. Int. Ed.* **2021**, *60,* 7245.

CV of Prof. Olivier Baudoin

Education and Employment:

- **1992–1995** B.S., École Nationale Supérieure de Chimie de Paris
- **1995–1998** Ph.D., Collège de France
- **1998–1999** Postdoc., The Scripps Research Institute
- **Now** Professor, University of Basel

Research Interests:

➢Transition-metal-catalyzed C−H functionalization and cross-coupling, and their application to the synthesis of natural products and active ingredients.

Contents

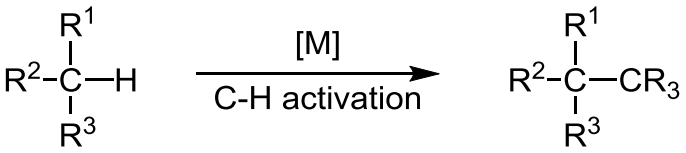
1 Introduction

2 Desymmetrization of enantiotopic alkyl groups

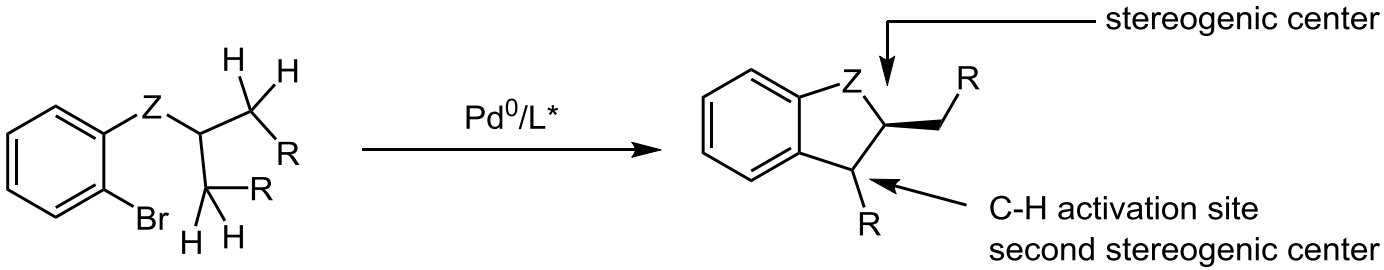
3 Desymmetrization of enantiotopic hydrogen atoms

4 Summary

Introduction

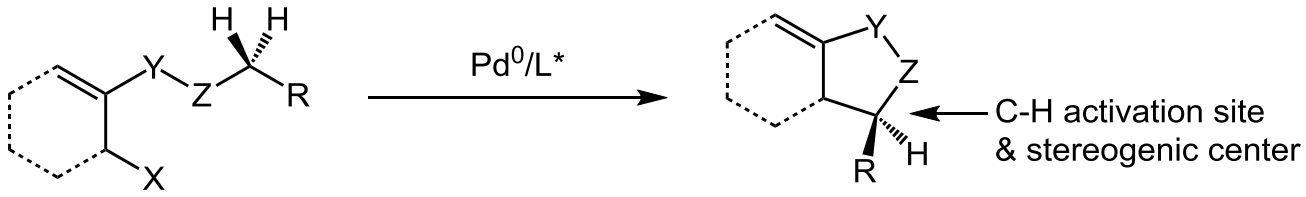


type I: desymmetrization of enantiotopic alkyl groups



enantiotopic alkyl groups
diastereotopic H atoms (if R ≠ H)

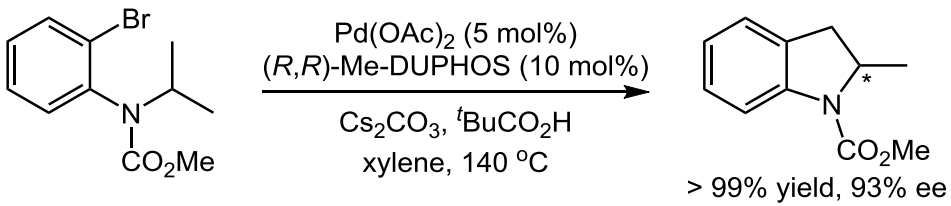
type II: desymmetrization of enantiotopic hydrogen atoms



enantiotopic H atoms

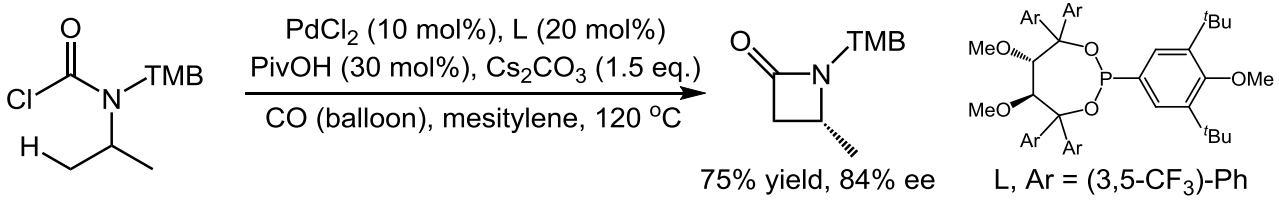
Desymmetrization of Enantiotopic Alkyl Groups

Via a chiral ligand-one stereocenter



> 99% yield, 93% ee

Kagan, H. B. *et al. Chem. Commun.* **2011**, *47,* 11483.

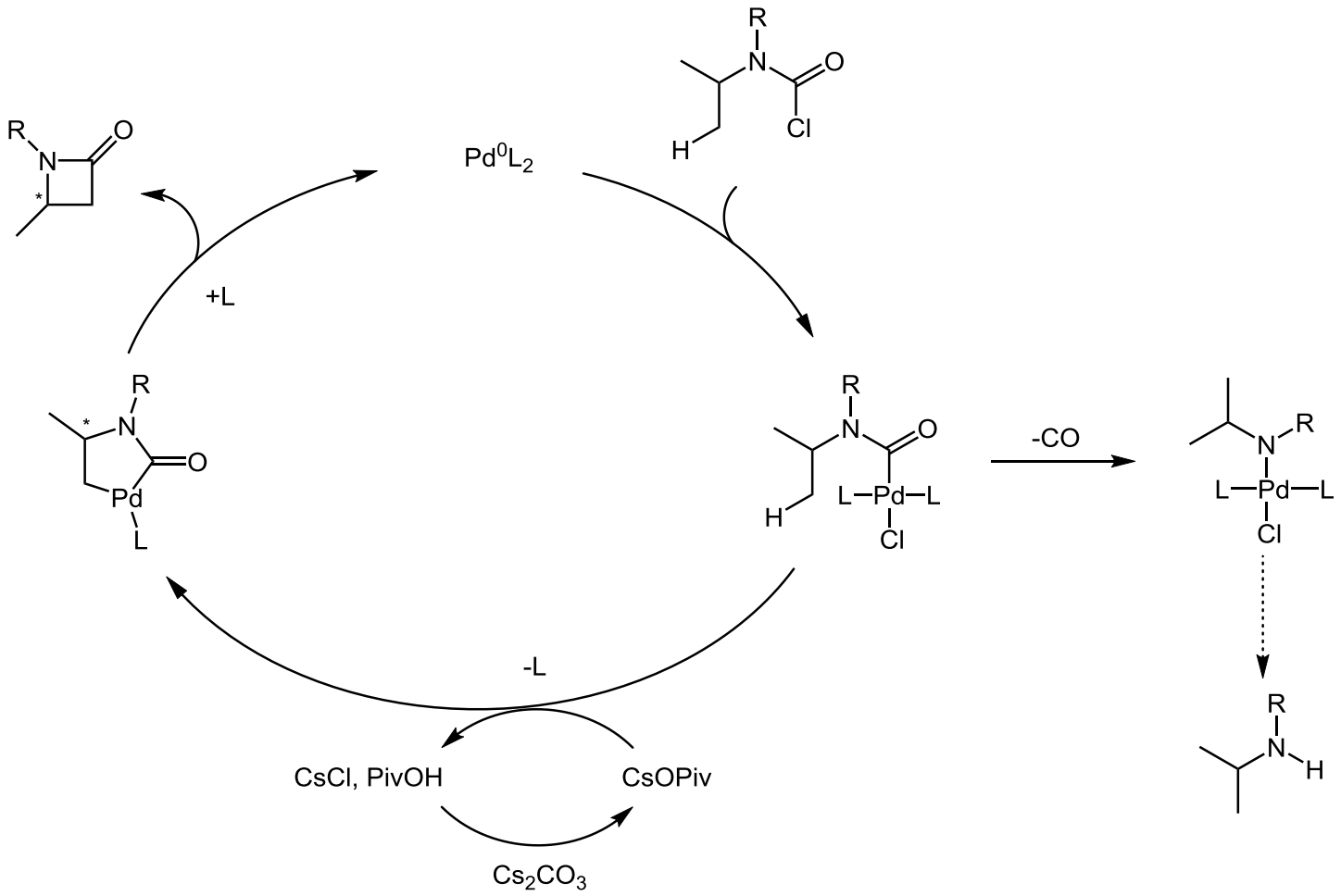


75% yield, 84% ee

L, Ar = (3,5-CF_3)-Ph

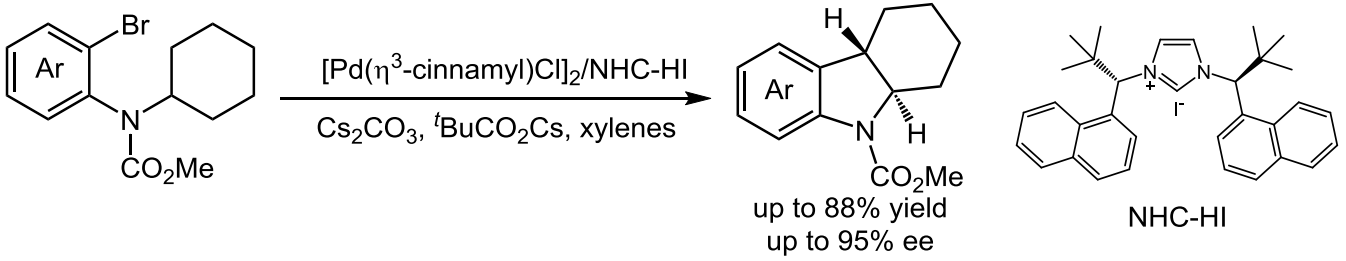
Baudoin, O. *et al. Angew. Chem. Int. Ed.* **2017**, *56,* 7218.

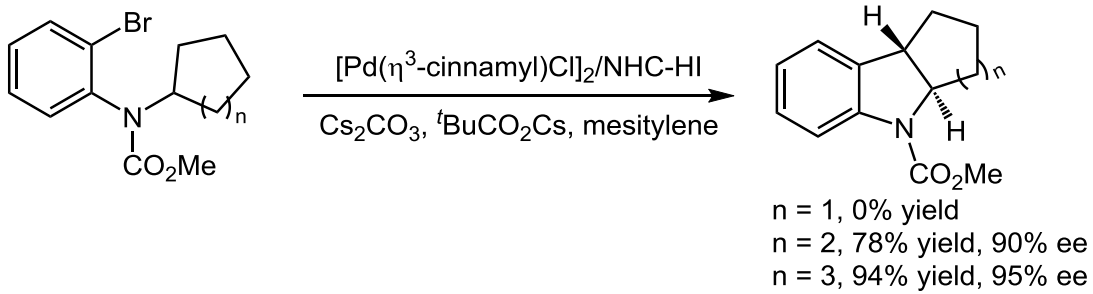
Desymmetrization of Enantiotopic Alkyl Groups



Desymmetrization of Enantiotopic Alkyl Groups

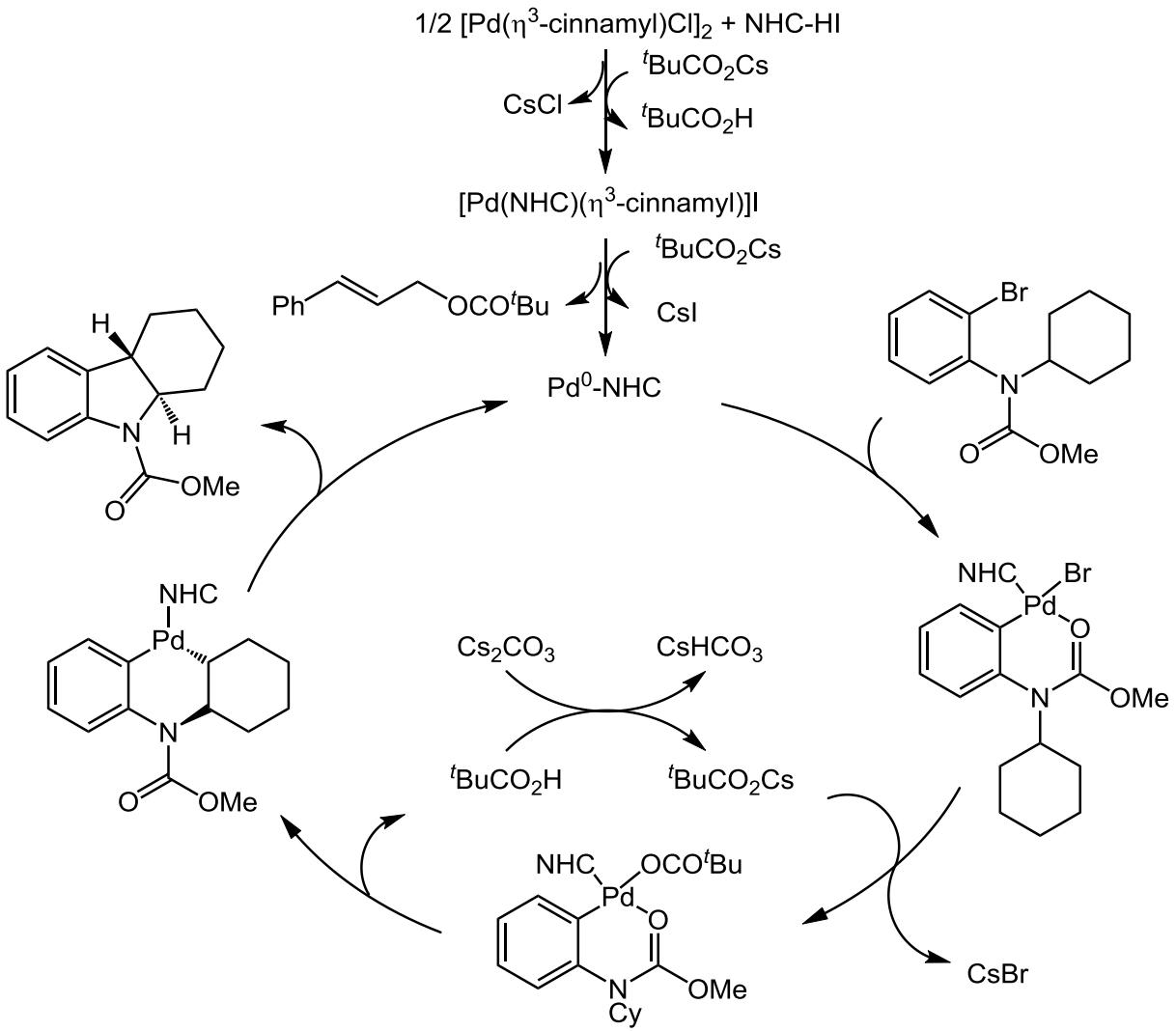
Via a chiral ligand-two stereocenters





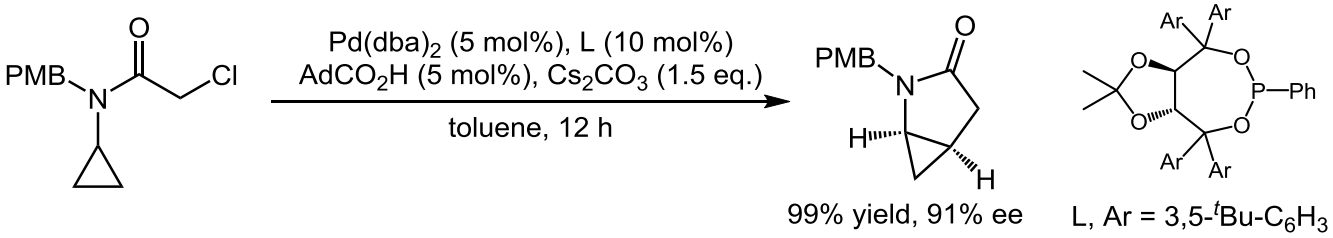
Kundig, E. P. *et al. Angew. Chem. Int. Ed.* **2011**, *50,* 7438.

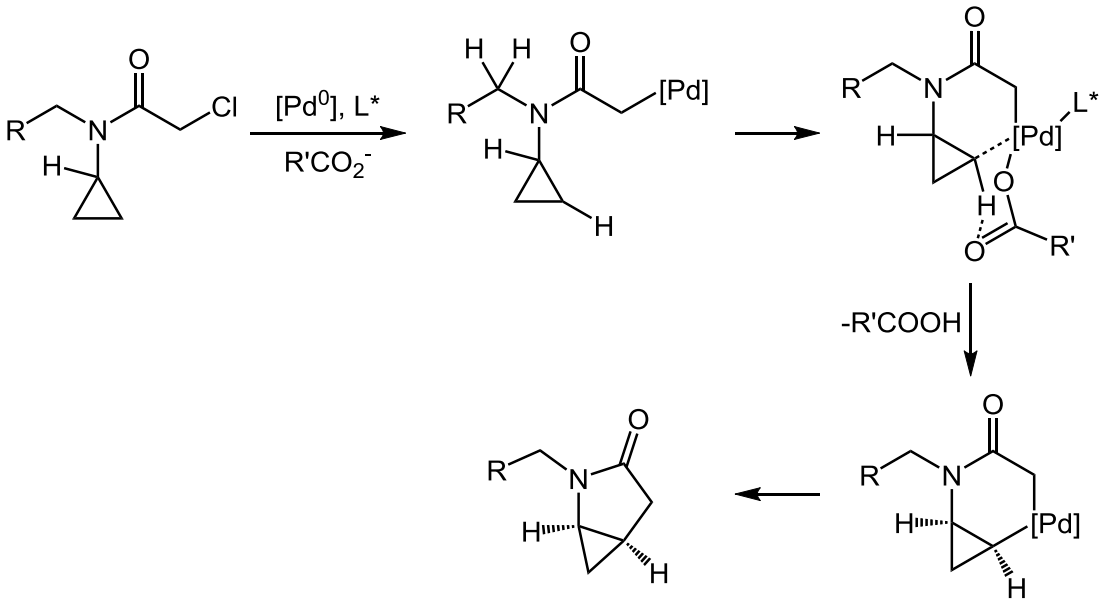
Desymmetrization of Enantiotopic Alkyl Groups



Desymmetrization of Enantiotopic Alkyl Groups

Via a chiral ligand-two stereocenters

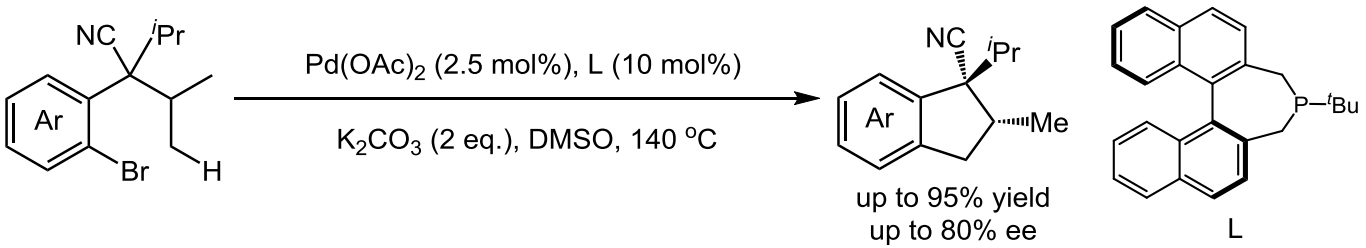




Cramer, N. *et al. Angew. Chem. Int. Ed.* **2015**, *54,* 11826.

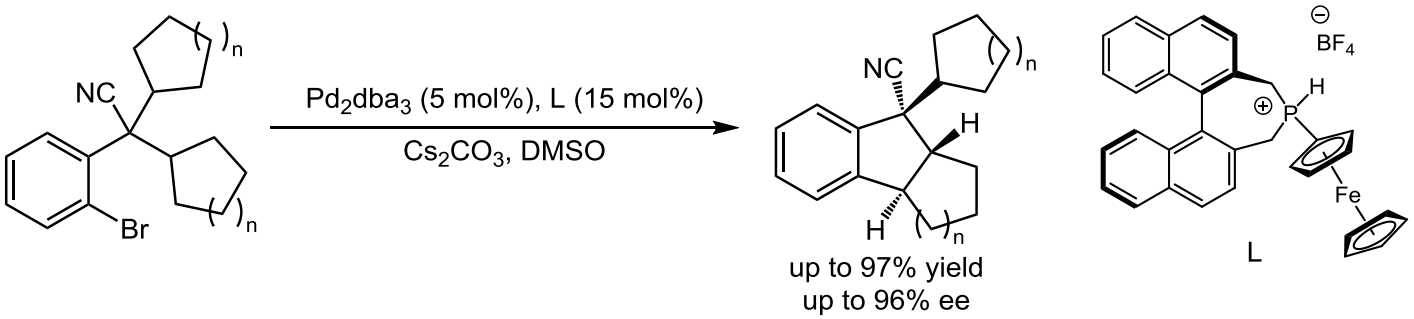
Desymmetrization of Enantiotopic Alkyl Groups

Via a chiral ligand-two stereocenters



Baudoin, O. *et al. Chem. Eur. J.* **2012**, *18,* 4480.

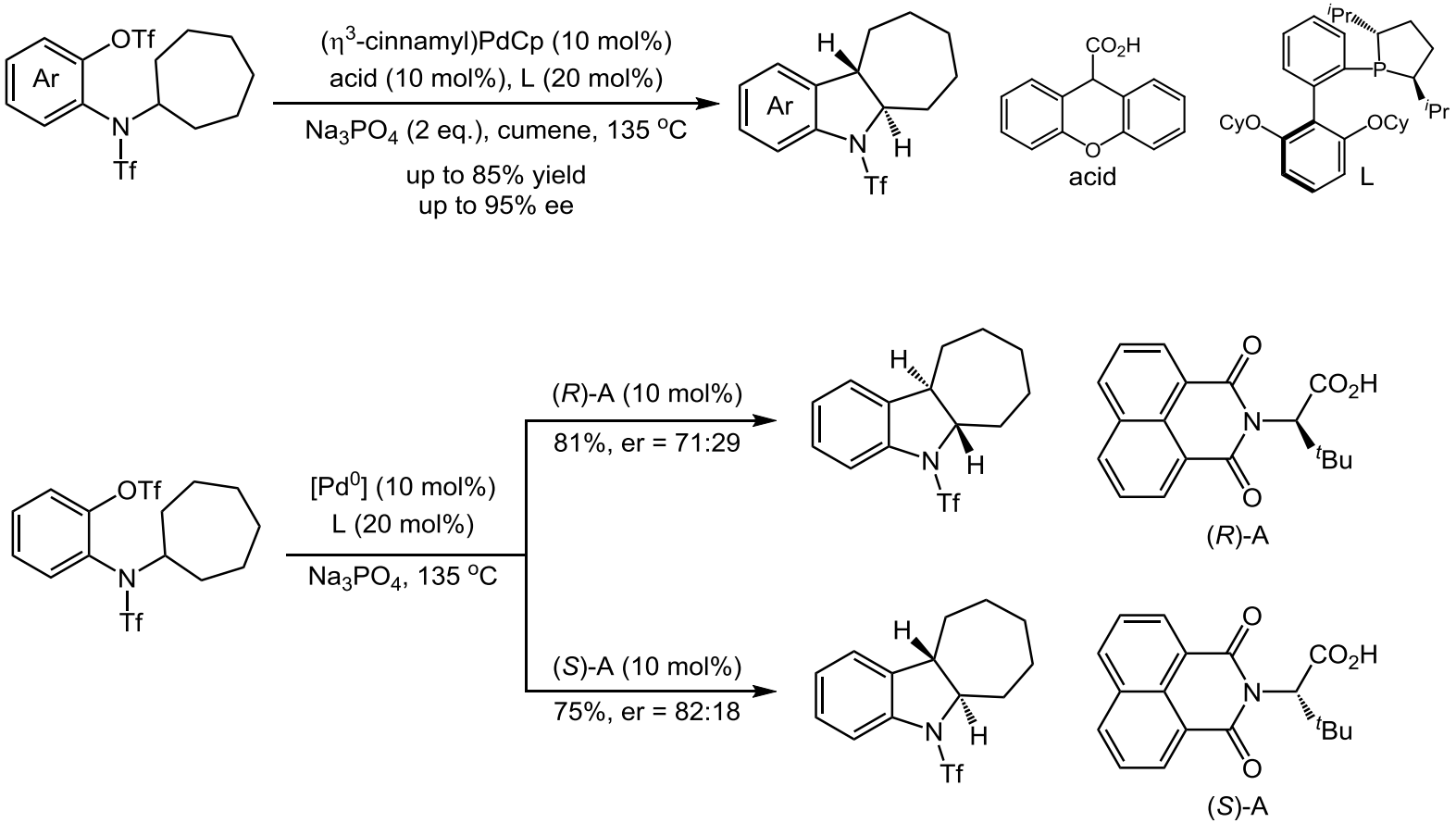
Via a chiral ligand-three stereocenters



Baudoin, O. *et al. ACS Catal.* **2015**, *5,* 4300.

Desymmetrization of Enantiotopic Alkyl Groups

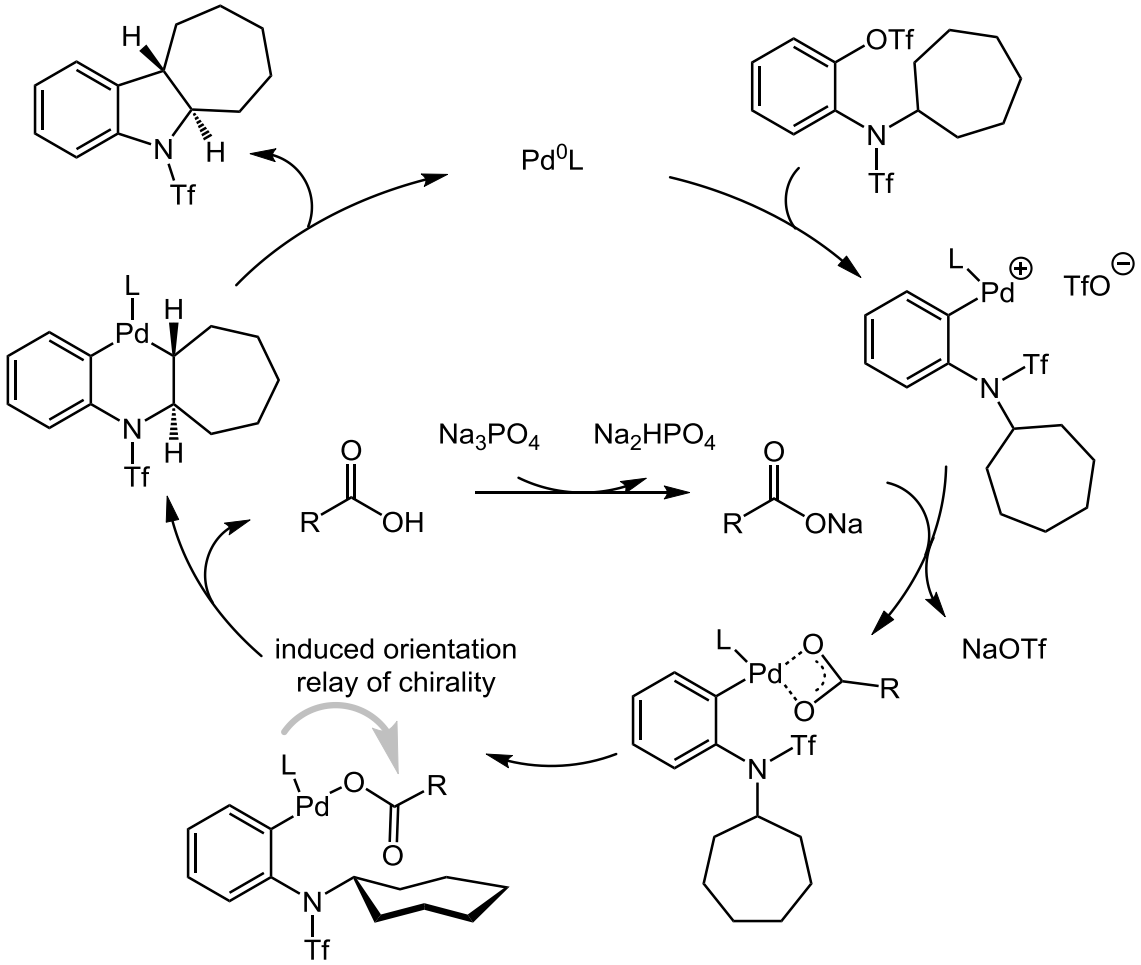
Via a chiral acid and a chiral ligand



Cramer, N. *et al. Angew. Chem. Int. Ed.* **2012**, *51,* 2238.

Desymmetrization of Enantiotopic Alkyl Groups

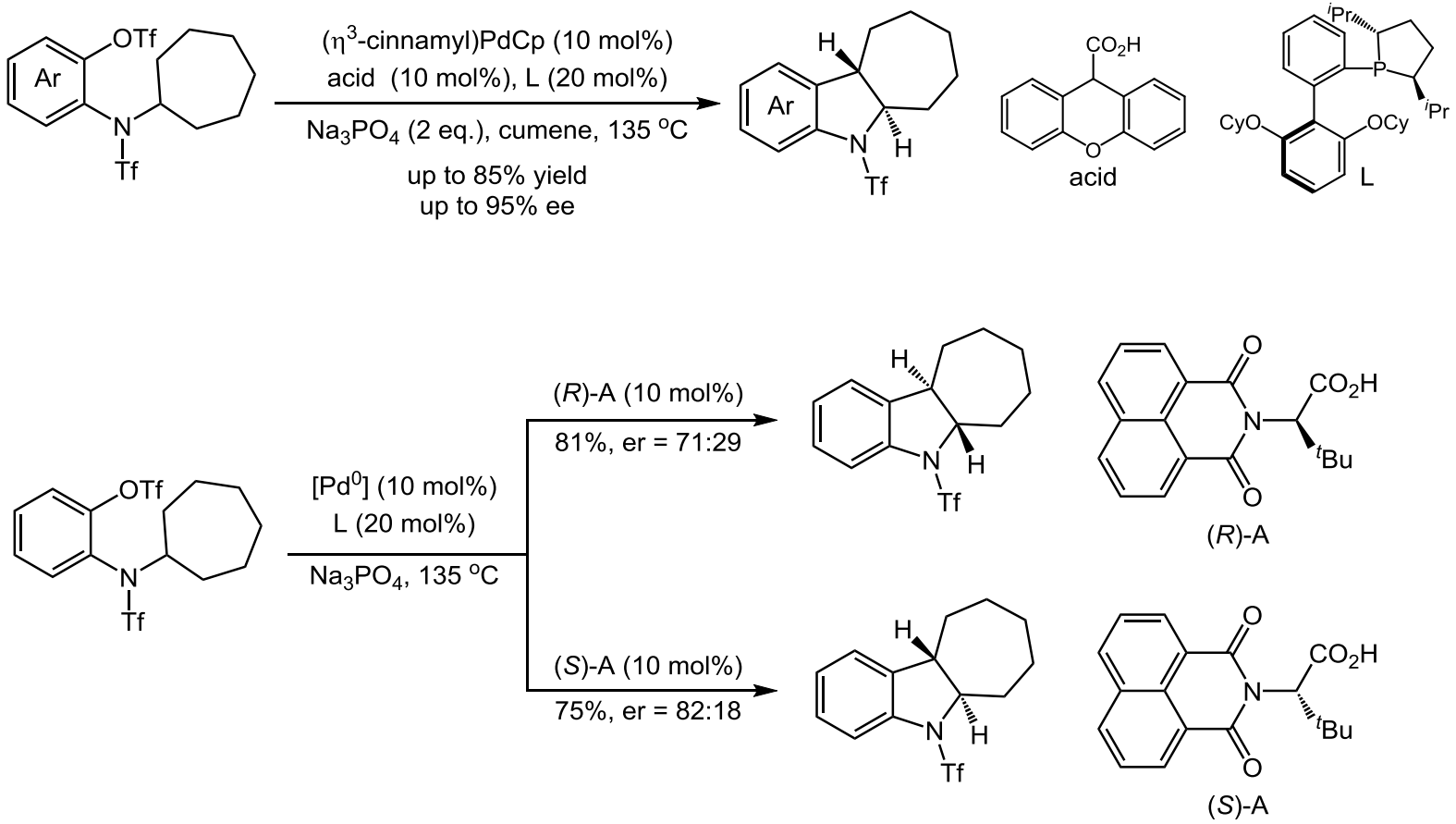
Via a chiral acid and a chiral ligand



Cramer, N. *et al. Angew. Chem. Int. Ed.* **2012**, *51,* 2238.

Desymmetrization of Enantiotopic Alkyl Groups

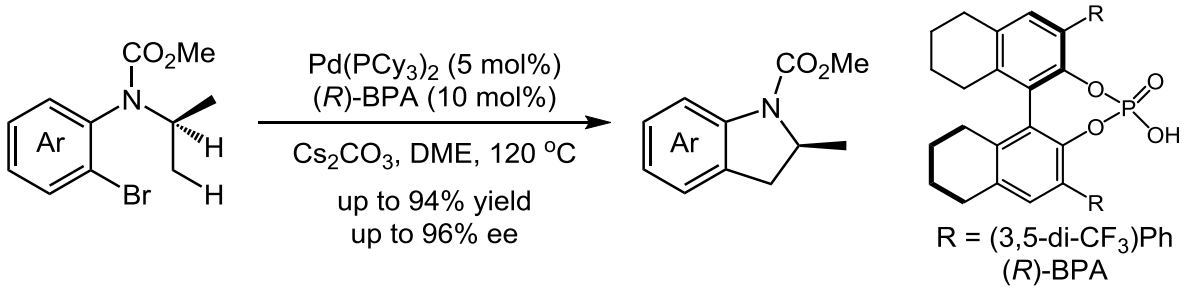
Via a chiral acid and a chiral ligand

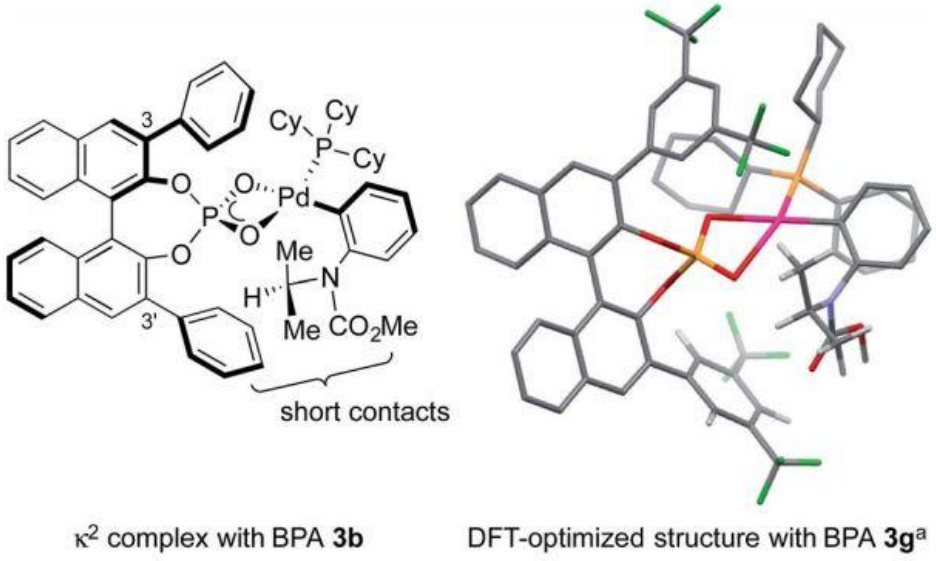


Cramer, N. *et al. Angew. Chem. Int. Ed.* **2012**, *51,* 2238.

Desymmetrization of Enantiotopic Alkyl Groups

Via a chiral phosphate and an achiral ligand





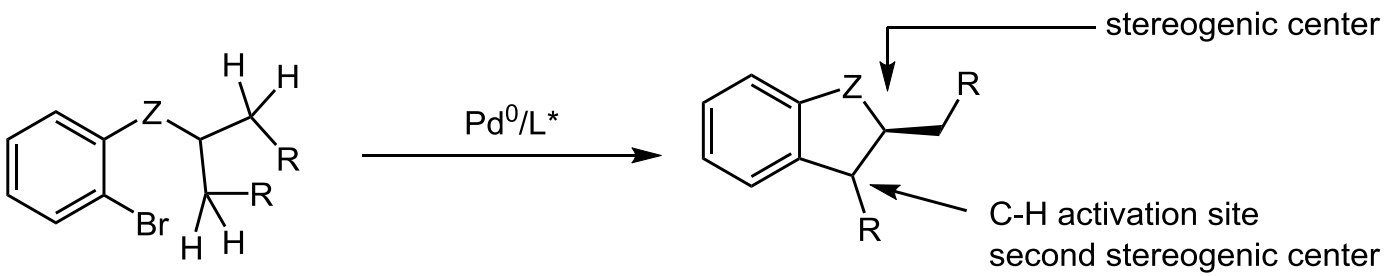
κ² complex with BPA **3b**

DFT-optimized structure with BPA **3g**[a]

Baudoin, O. *et al. Chem. Sci.* **2017**, *8,* 1344.

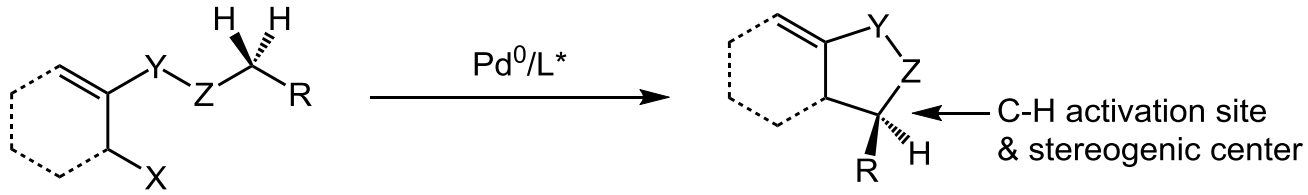
Introduction

type I: desymmetrization of enantiotopic alkyl groups



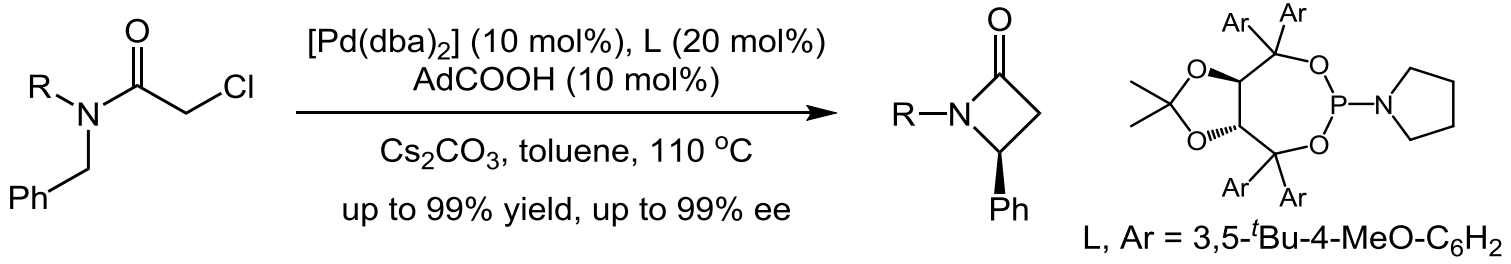
enantiotopic alkyl groups
diastereotopic H atoms (if R ≠ H)

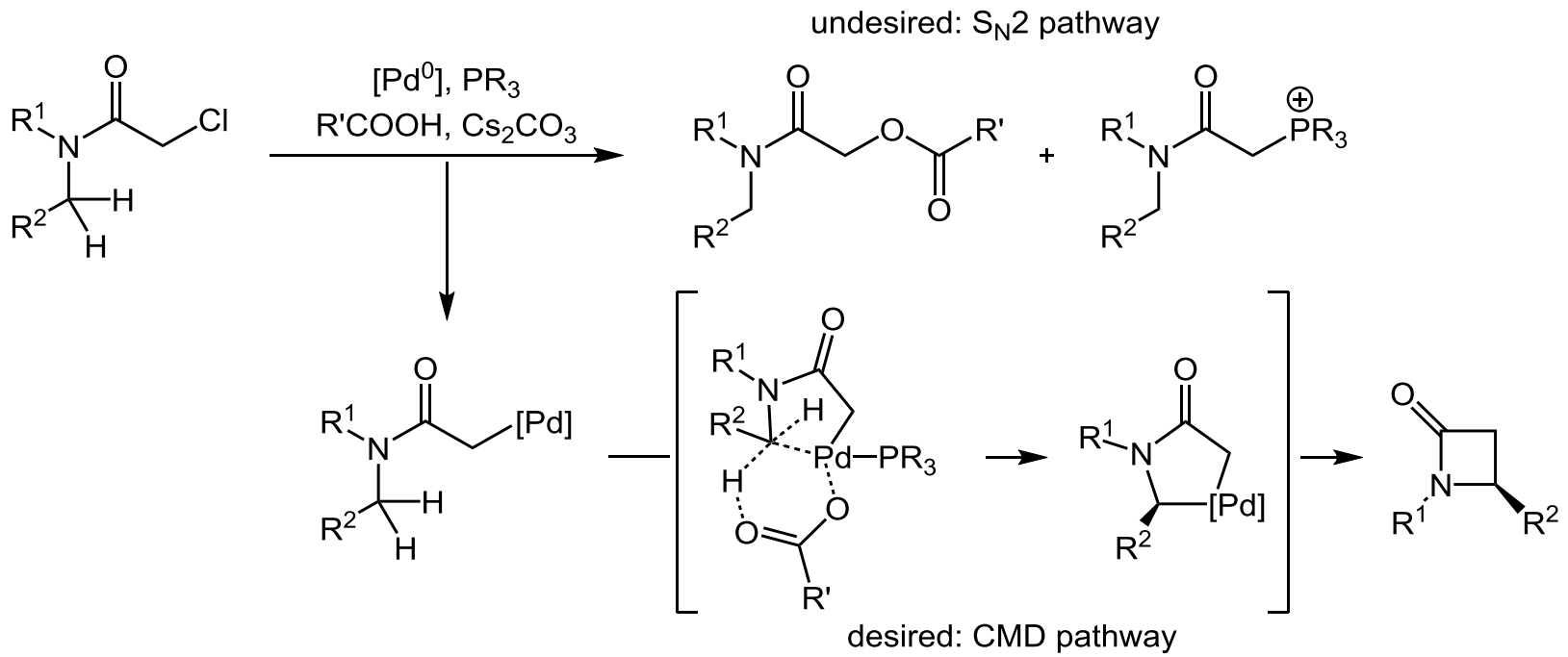
type II: desymmetrization of enantiotopic hydrogen atoms



enantiotopic H atoms

Desymmetrization of Enantiotopic Hydrogen Atoms

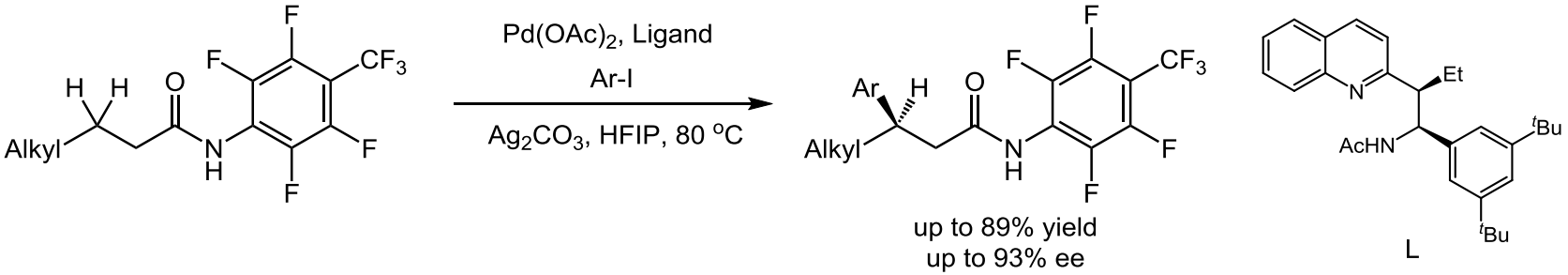




Cramer, N. *et al. Angew. Chem. Int. Ed.* **2014**, *53,* 9064.

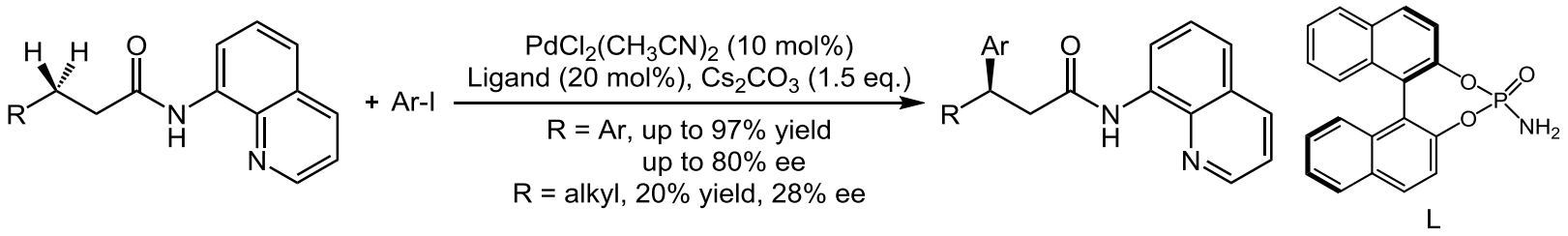
Desymmetrization of Enantiotopic Hydrogen Atoms

Weak monodentate directing group and bidentate ligand



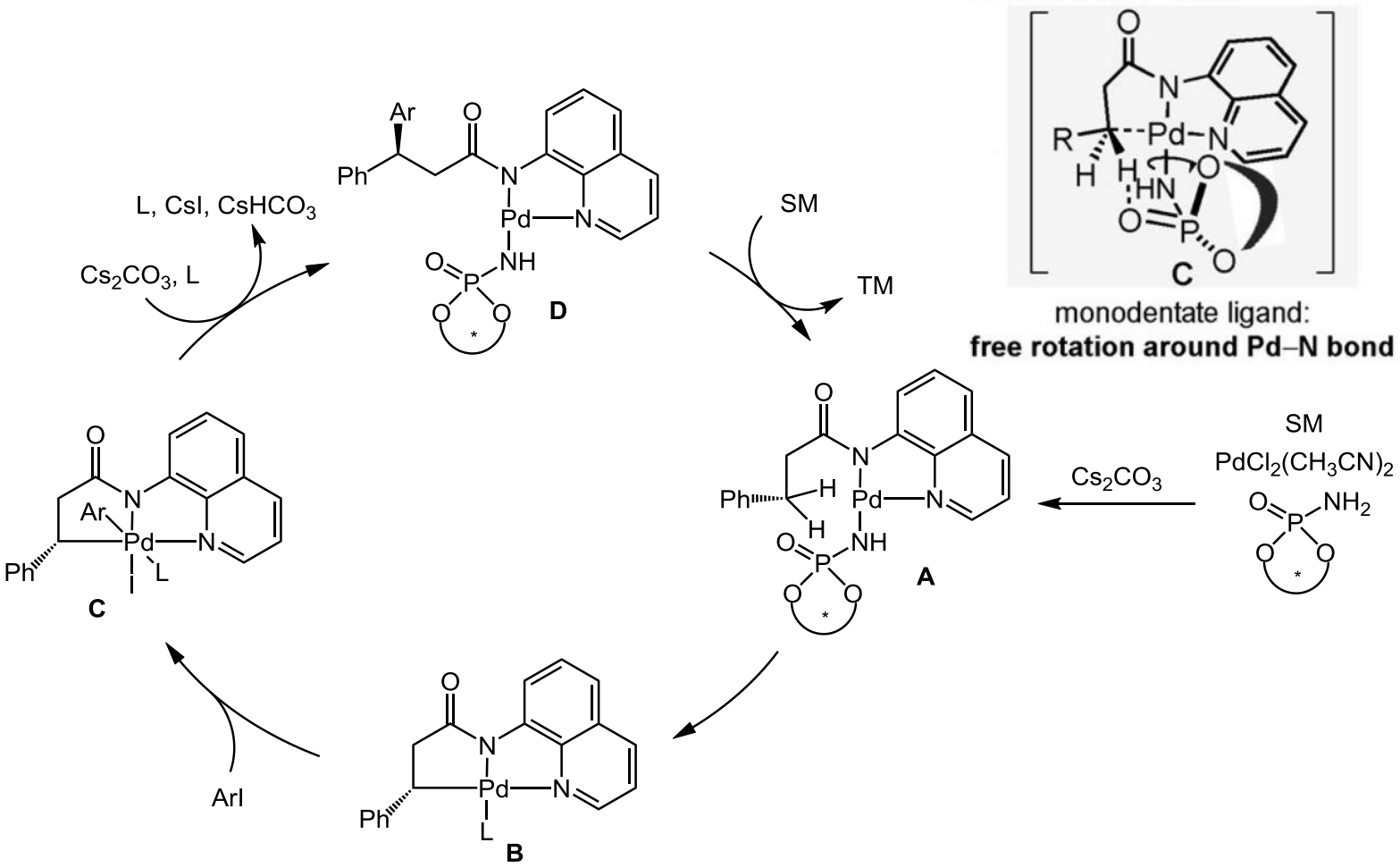
Yu, J.-Q. *et al. Science* **2016**, *353,* 1023.

Strong bidentate directing group and monodentate ligand



Duan, W.-L. *et al. Org. Lett.* **2015**, *17,* 2458.

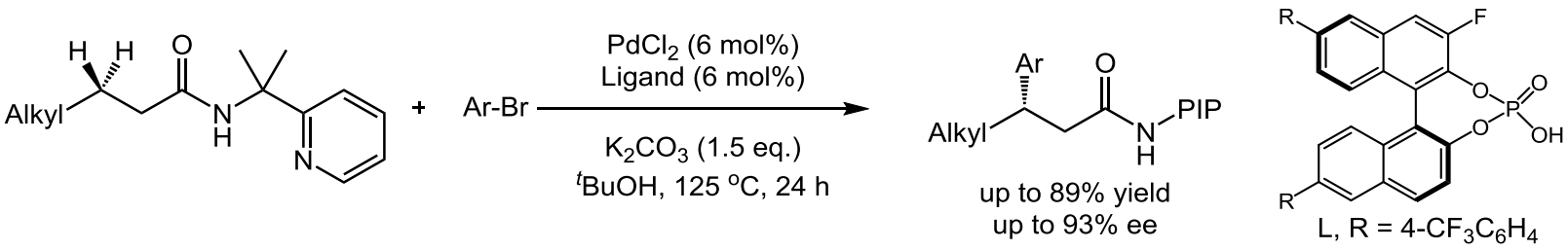
Desymmetrization of Enantiotopic Hydrogen Atoms



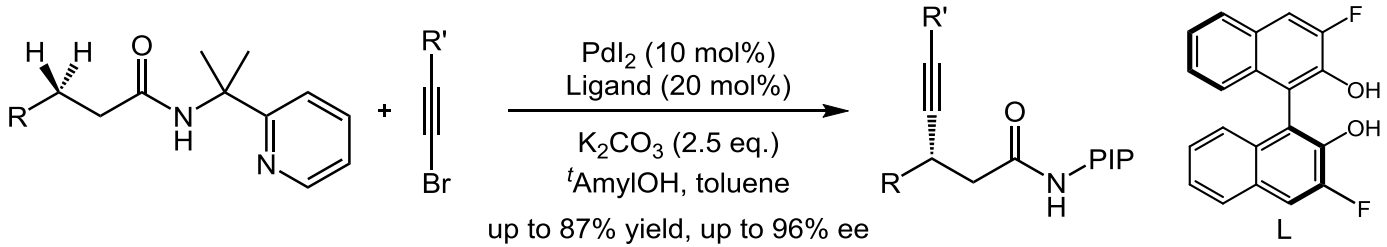
Duan, W.-L. *et al. Org. Lett.* **2015**, *17,* 2458.

Desymmetrization of Enantiotopic Hydrogen Atoms

Strong bidentate directing group and monodentate ligand



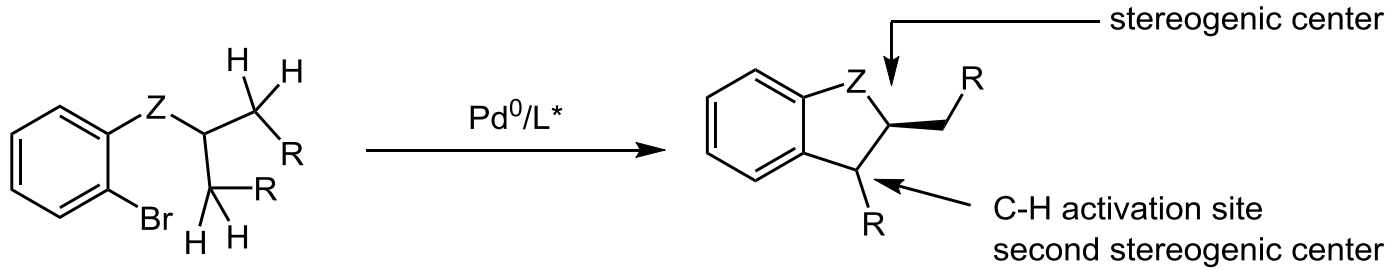
Shi, B.-F. *et al. Angew. Chem. Int. Ed.* **2018**, *57,* 9093.



Shi, B.-F. *et al. J. Am. Chem. Soc.* **2019**, *141,* 4558.

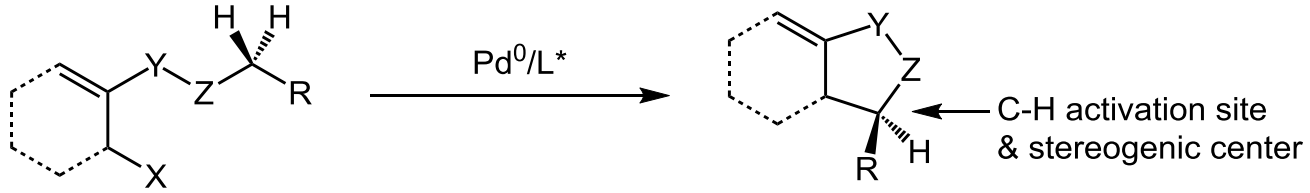
Introduction

type I: desymmetrization of enantiotopic alkyl groups

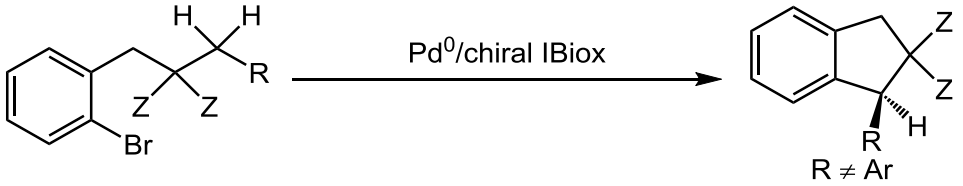


enantiotopic alkyl groups
diastereotopic H atoms (if R ≠ H)

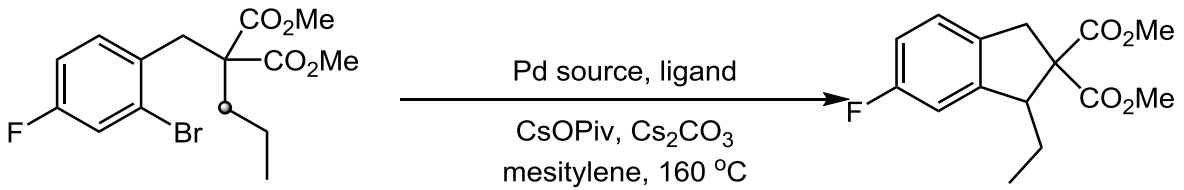
type II: desymmetrization of enantiotopic hydrogen atoms



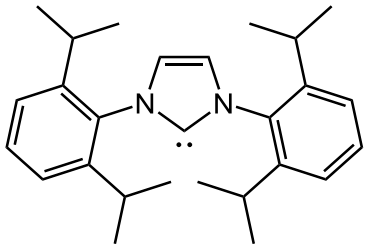
enantiotopic H atoms



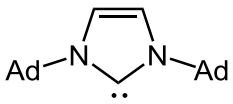
Reaction Conditions Optimization



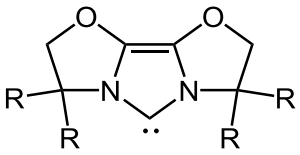
1a **2a**



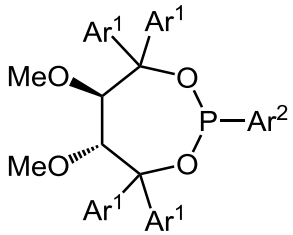
IPr



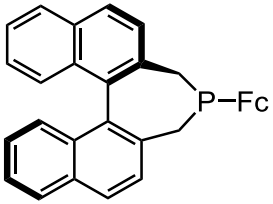
IAd



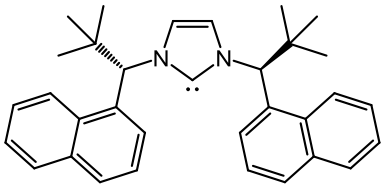
$IBioxMe_4$: R = Me
IBiox6: R,R = $(CH_2)_5$



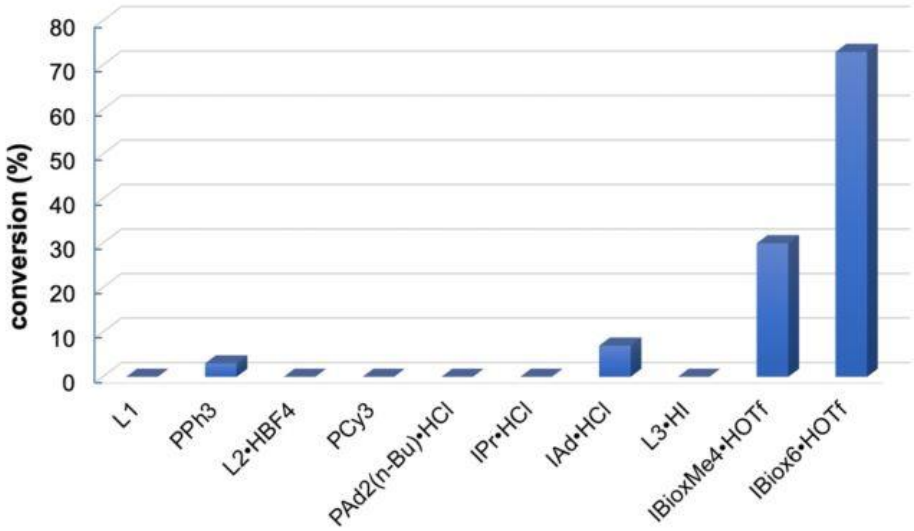
L^1, Ar^1 = 3,5-di-CF_3Ph,
Ar^2 = 3,5-di-^{t}Bu-4-OMePh



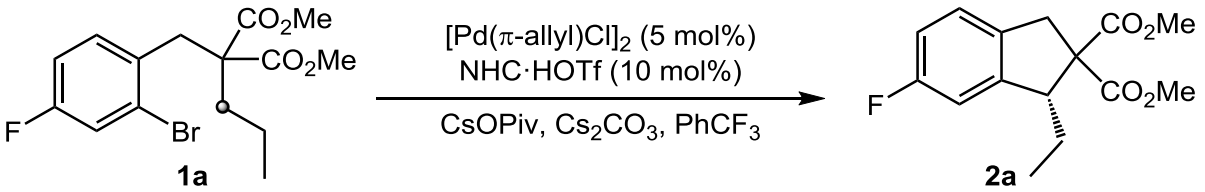
L^2

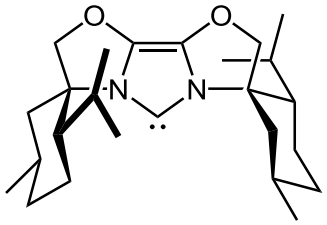


L^3

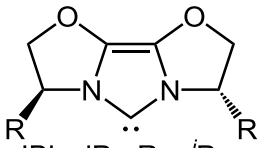


Reaction Conditions Optimization

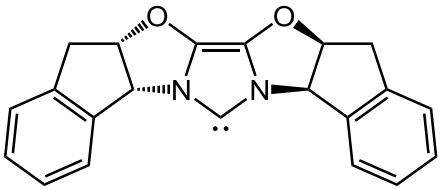




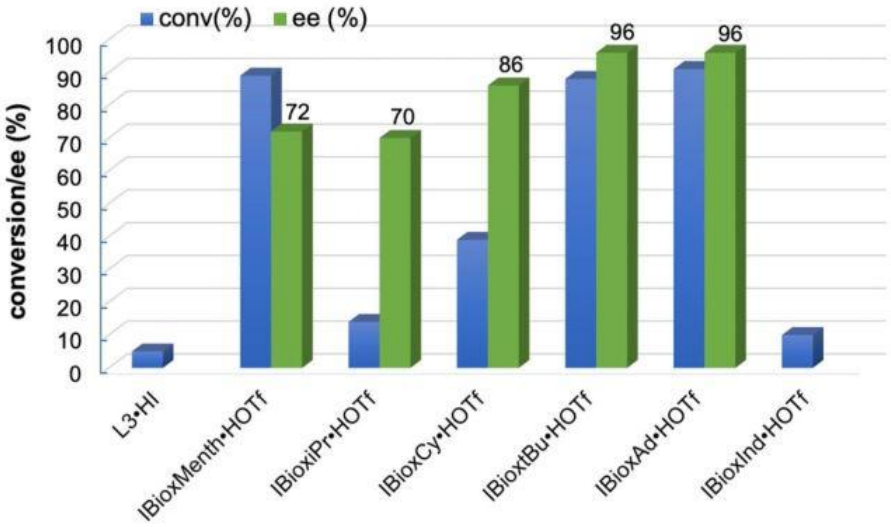
IBioxMenth



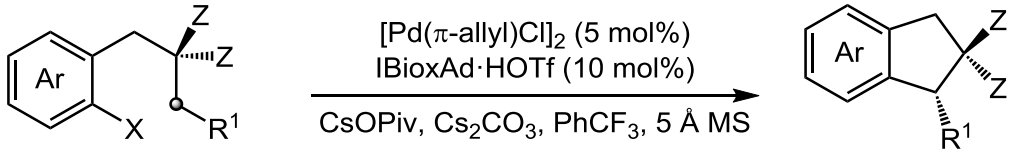
IBioxiPr: R = ^{i}Pr
IBioxCy: R = Cy
IBioxtBu: R = ^{t}Bu
IBioxAd: R = Ad



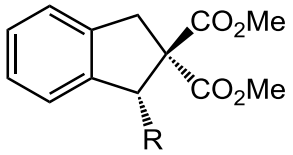
IBioxInd



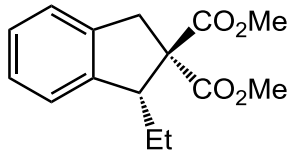
Scope of Substrates



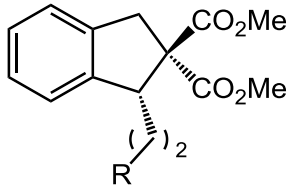
1a-q **2a-q**



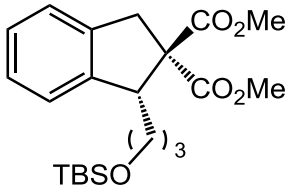
2b, R = Me: 74%, e.r. 96:4
2d, R = ^{n}Bu: 61%, e.r. 99:1
2e, R = ^{i}Bu: 61%, e.r. 98:2



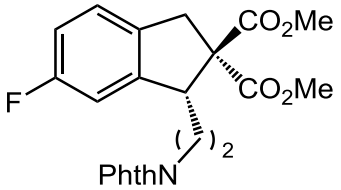
2c, X = Br: 72%, e.r. 98:2
X = Cl: 92%, e.r. 98:2



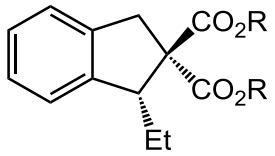
2f, R = F: 91%, e.r. 98:2
2g, R = CO_2Me: 48%, e.r. 98:2
2h, R = OPMP: 59%, e.r. >99:1[a] (99:1)[b]



2i: 77%, e.r. 98:2



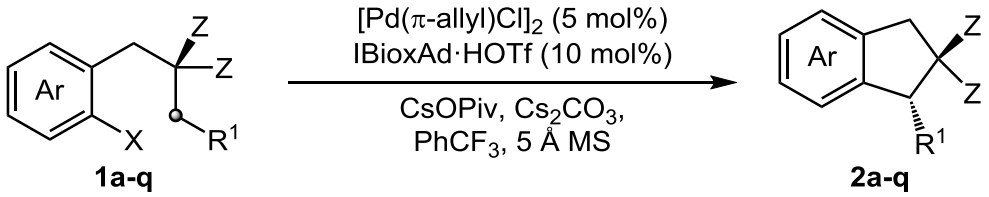
2j, 82%, e.r. 98:2[a] (97:3)[b]
63%,[c] e.r. >99:1[a] (95:5)[b]

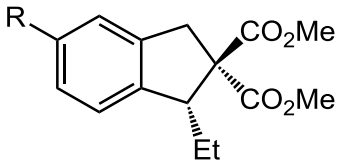


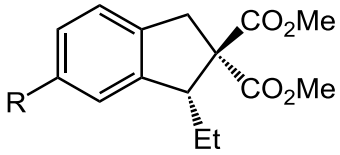
2k, R = Et: 71%, e.r. 98:2
2l, R = ^{i}Pr: 34%, e.r. 98:2

a) After recrystallization. b) E.r. of the crude mixture. c) Performed on a gram scale. d) Using the well-defined complex [Pd(IBioxAd)(π-allyl)Cl)] (10 mol%). e) Using 10 mol% $[Pd(\pi\text{-allyl})Cl)]_2$, 20 mol% IBioxAd·HOTf, 60 mol% CsOPiv and 2 equiv Cs_2CO_3.

Scope of Substrates

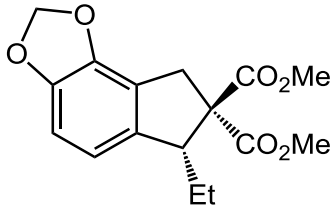




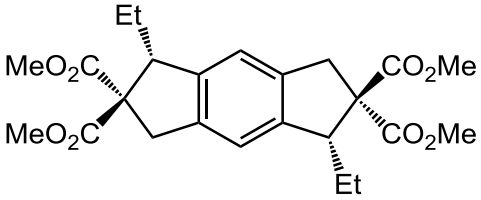


2m, R = F: 72%, e.r. 98:2
2n, R = NO_2: 61%, e.r. 94:6
2o, R = CF_3, **X = Cl**: 92%, e.r. 99:1

2a, R = F: 86%, e.r. 98:2 (84%, e.r. 98:2)[d]
2p, R = CO_2Me, **X = Cl**: 89%, e.r. 96:4
2q, R = SO_2Me, **X = Cl**: 64%, e.r. 97:3



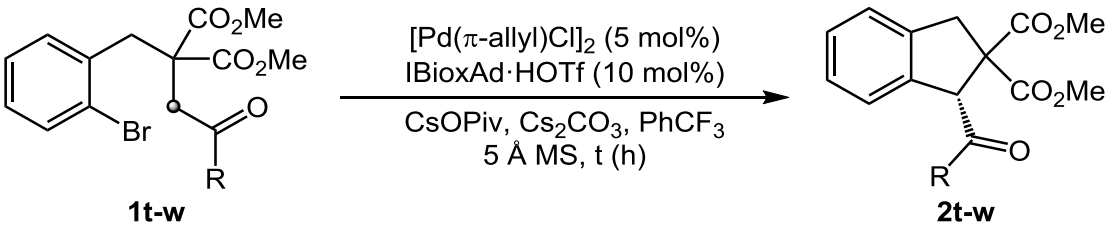
2r, 51%, e.r. 98:2



2s, 55%, e.r. >99:1[e]

a) After recrystallization. b) E.r. of the crude mixture. c) Performed on a gram scale. d) Using the well-defined complex [Pd(IBioxAd)(π-allyl)Cl)] (10 mol%). e) Using 10 mol% $[Pd(\pi\text{-allyl})Cl]_2$, 20 mol% IBioxAd·HOTf, 60 mol% CsOPiv and 2 equiv Cs_2CO_3.

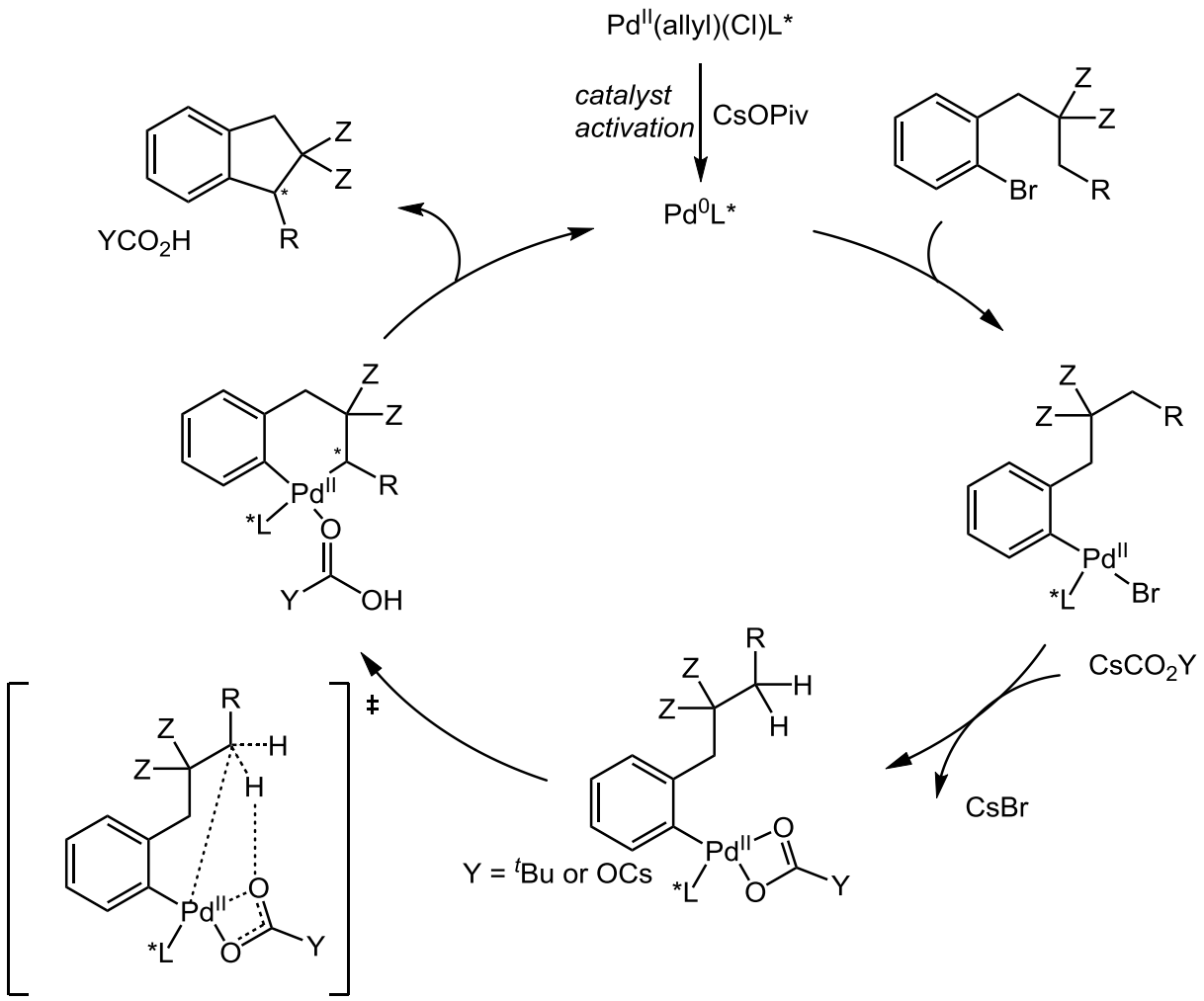
Scope of Substrates



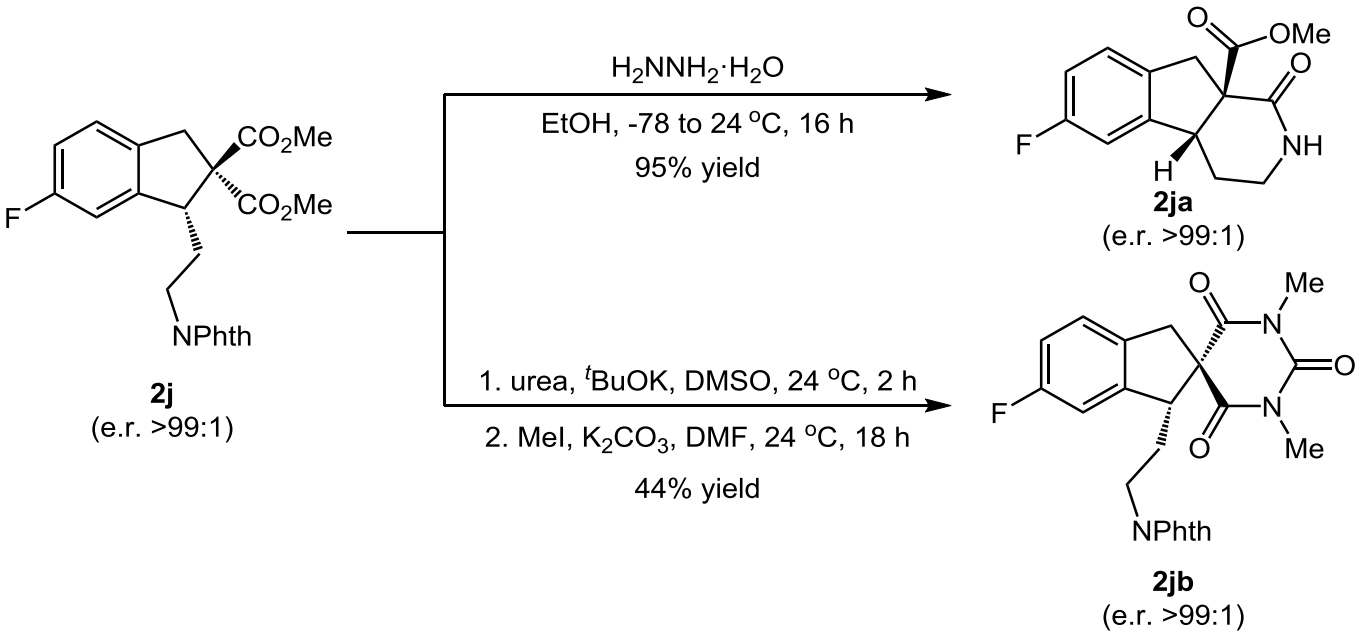
Entry	Product	R	t (h)	Yield (%)[a]	e.r.
1	**2t**	NMe_2	18	94	95:5
2	**2u**	NC_4H_8O	18	87	68:32
3	**2u**	NC_4H_8O	8	95	97:3
4	**2v**	N(Me)OMe	18	80	70:30
5	**2v**	N(Me)OMe	4	75	98:2
6	**2w**	OMe	2	n.d.	55:45

[a] Yield of isolated product.

Proposed Mechanism

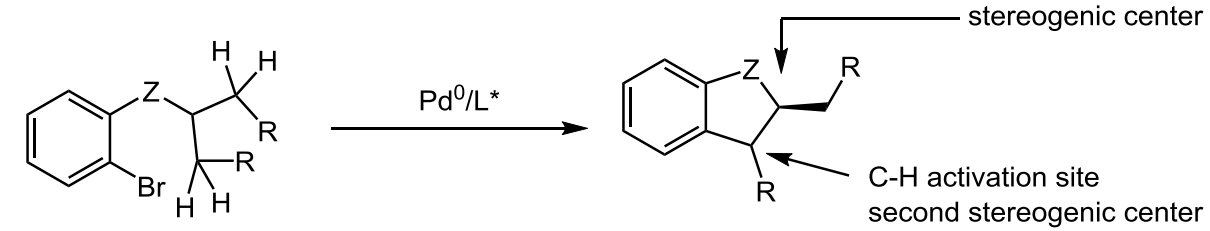


Post-functionalizations



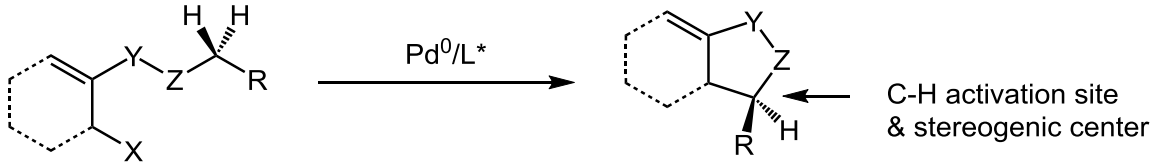
Summary

Desymmetrization of enantiotopic alkyl groups



enantiotopic alkyl groups
diastereotopic H atoms (if R ≠H)

Desymmetrization of enantiotopic hydrogen atoms



enantiotopic H atoms

The first paragraph

写作思路

介绍碳氢键活化
的重要性

↓

介绍常用的两种方法
及前人工作的受限性

↓

引出非活化二级碳氢
键的芳基化反应

The first paragraph

Enantioselective organometallic C-H activation is a current topic of great interest, providing a straightforward access to high value-added scalemic intermediates from easily accessible precursors. Indeed, the replacement of a hydrogen atom by a carbon or heteroatom on a $C(sp^3)$ center is arguably one of the simplest ways to construct stereogenic centers. Of course, this is far from trivial to achieve in practice, due to the lack of reactivity of $C(sp^3)$-H bonds towards cleavage by transition metals. To tackle this challenge, a variety of directing group and oxidative addition based strategies have been deployed to render the C-H activation step intramolecular and hence kinetically more accessible. In particular, Pd^0-catalyzed $C(sp^3)$-H activation induced by $C(sp^2)$-X oxidative addition has proven a general and effective method to construct a variety of cyclic systems.

The first paragraph

In the past decade, enantioselective versions have been developed, which can be classified in two main categories: Type I: the desymmetrization of two enantiotopic alkyl groups, leading to the generation of a stereogenic center remote to the activated C-H bond. If the activation site is secondary, then the two hydrogen atoms at this site are also diastereotopic and two adjacent stereocenters are generated. As an extension, parallel kinetic resolution may occur when the two alkyl groups are different, thereby leading to the formation of two enantioenriched regioisomeric products. Type II: the desymmetrization of enantiotopic hydrogen atoms on secondary carbons, creating a stereogenic center at the activated site. To date, type I reactions, which are enabled by a variety of chiral ancillary ligands or chiral anions, are by far the most developed. An application in natural product synthesis was recently reported by our group.

The first paragraph

The prevalence of type I reactions over type II can be explained by the high density of C-H bonds on substrates bearing two alkyl groups, that strongly favors the C-H activation step. In contrast, despite the conceptual simplicity and the potentially greater applicability of type II reactions, only one example was reported so far, i.e. the synthesis of β-lactams from α-chloroamides by Cramer and co-workers, using chiral phosphoramidite ligands. However, this transformation is so far limited to activated secondary C-H bonds on benzylic positions. Nonetheless, it should be noted that in contrast to Pd^{0} catalysis, the Pd^{II}-catalyzed enantioselective intermolecular functionalization of nonbenzylic enantiotopic secondary C-H bonds has been recently reported using a directing group strategy. However, such reactions are less suited to the construction of scalemic carbo- and heterocycles.

The last paragraph

写作思路

二级碳氢键的高对映选择性芳基化反应

↓

介绍工作亮点

The last paragraph

In conclusion, the enantioselective intramolecular arylation of enantiotopic secondary C-H bonds via Pd^0 catalysis was developed. The IBiox family of NHC ligands displayed a unique reactivity among all ligand classes tested for the arylation of nonactivated C-H bonds. The reaction showed high enantioselectivities across a broad range of indanes. Moreover, the arylation of secondary C-H bonds adjacent to amides provided indanes with a sensitive tertiary stereocenter upon careful control of the reaction time. The current method should streamline the access to complex molecules containing a chiral indane motif.

Representative examples

Analysis of the steric maps of the IBiox ligands indicated that the level of enantioselectivity correlates with the difference between the two most occupied and the two less occupied space quadrants, and provided a blueprint for the design of even more efficient ligands. (为…的设计描绘了蓝图)

Of note, indane **2c** was obtained in good yield and enantioselectivity from both the aryl bromide and aryl chloride precursors, thereby establishing the latter as competent substrates. (值得注意的是)

However, we surmised that the current basic conditions, i.e. the combination of Cs_2CO_3 and CsOPiv in an apolar solvent, could be mild enough to escape racemization. (推测)

Thanks
for your attention