Literature Report VI

Iron-catalyzed Stereoselective C-H Alkylation for Construction of C-N Axial and *C*-central Chirality

Reporter: Kai Xue
Checker: Xinyang Li
Date: 2025-7-14

Zhang, Z.-J.; Jacob, N.; Bhatia, S.; Boos, P.; Ackermann, L.* *Nat. Commun.* **2024**, *15*, 3503.

CV of Prof. Ackermann Lutz

Background:

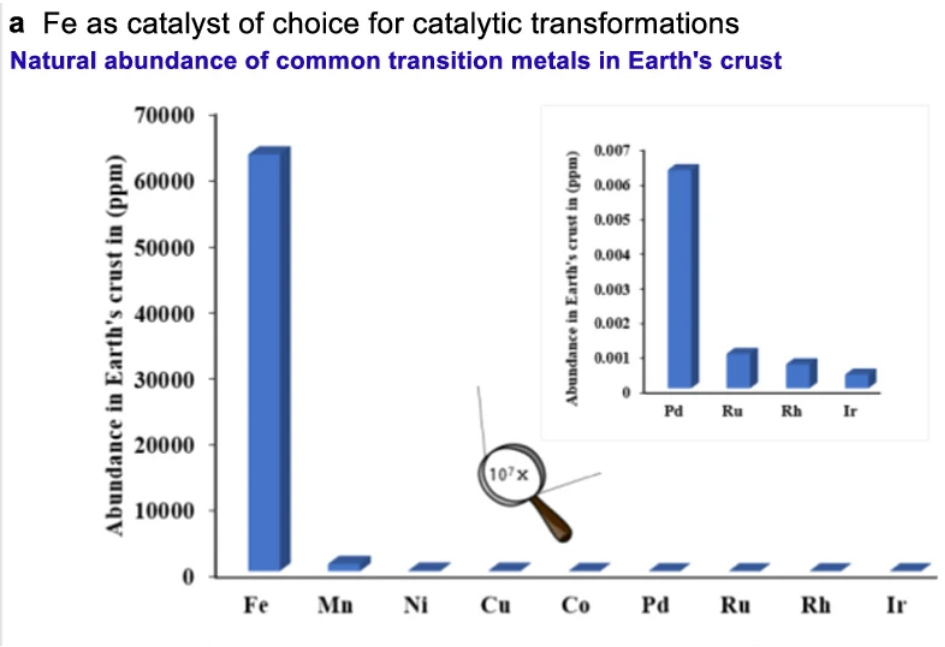
- **1998-2001** Ph.D., Max-Planck-Institut für Kohlenforschung
- **2001-2003** Postdoc., UC Berkeley (Prof. Bergman, R. G.)
- **2003-2007** Assistant Professor, LMU München
- **2007-now** Chair and Full Professor, Georg-August-University Göttingen

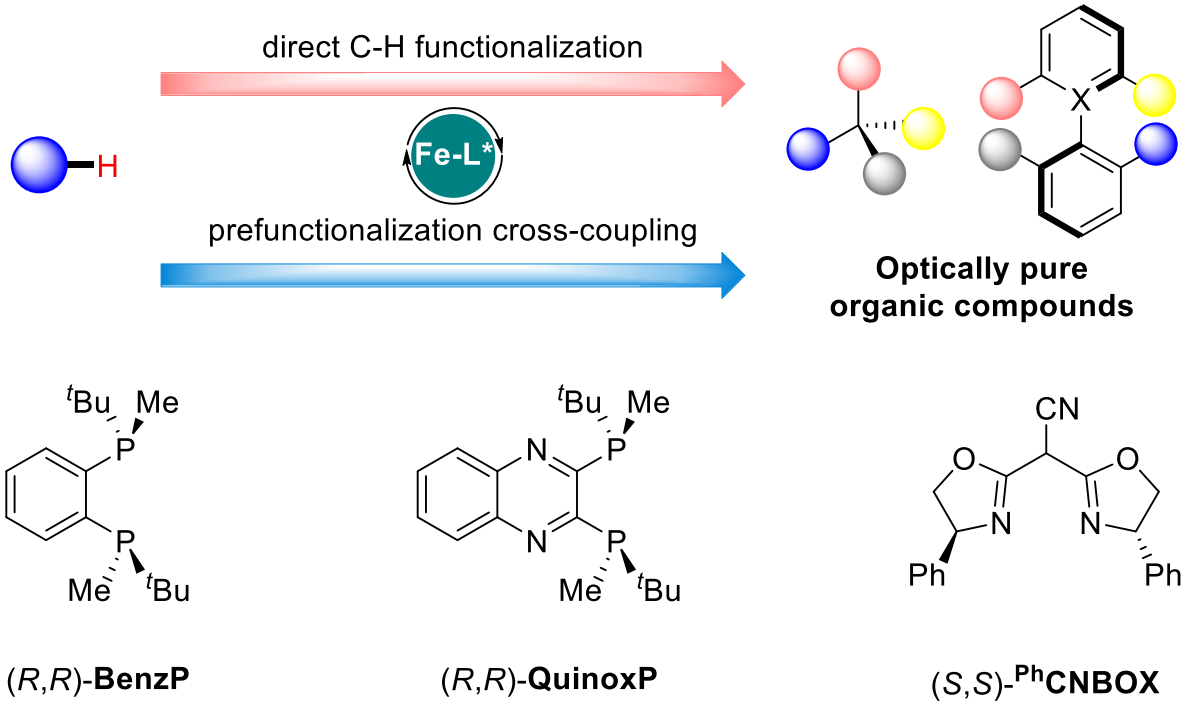
Research:

- **Catalysis through ligand design**
- **C-H activation in 3d transition metal**
- **Methodologies in photocatalysis, electrochemistry, and flow chemistry**

Contents

Introduction

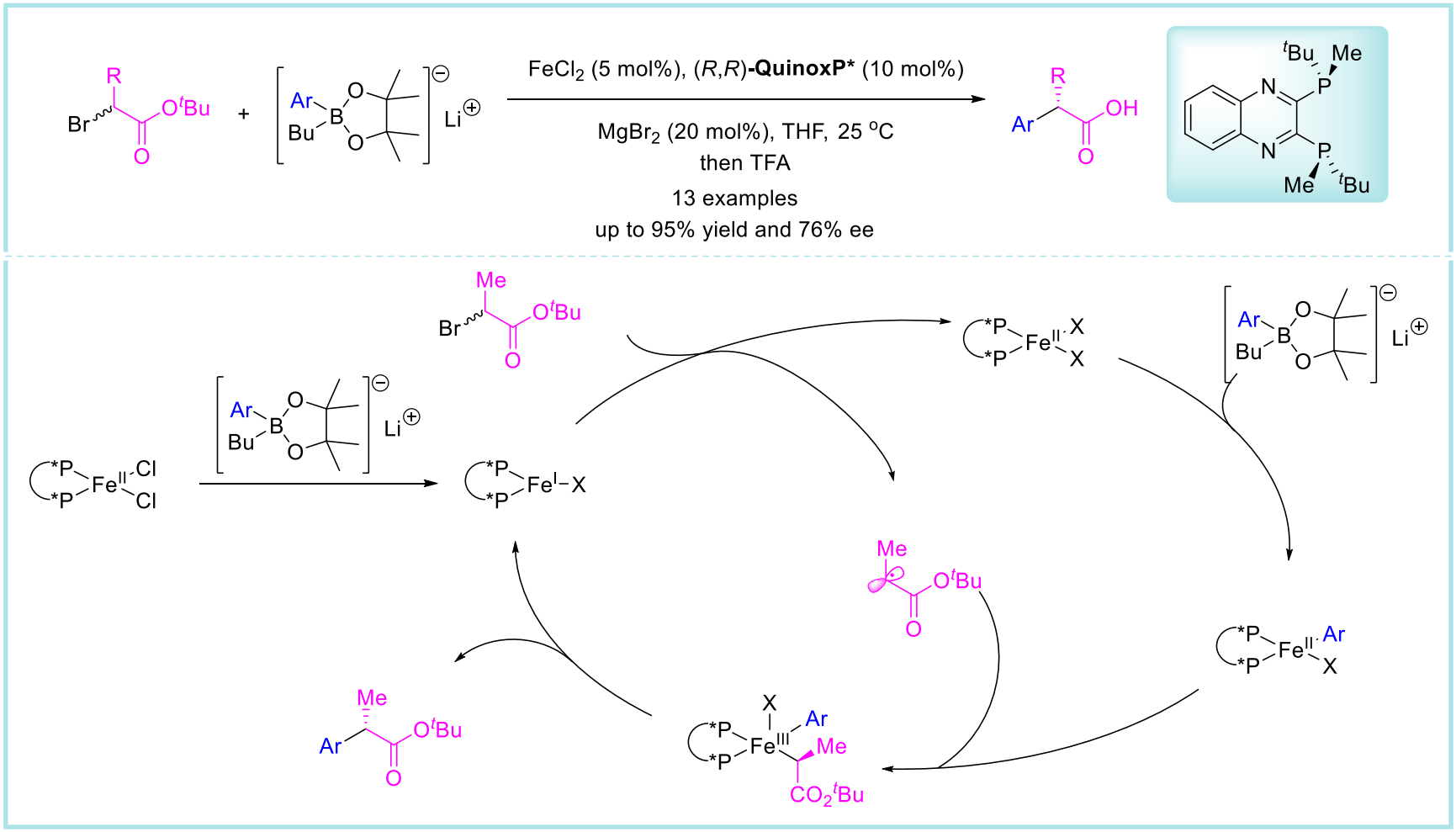




Zhang, Z.-J.; Jacob, N.; Bhatia, S.; Boos, P.; Ackermann, L.* *Nat. Commun.* **2024**, *15*, 3503.

Introduction

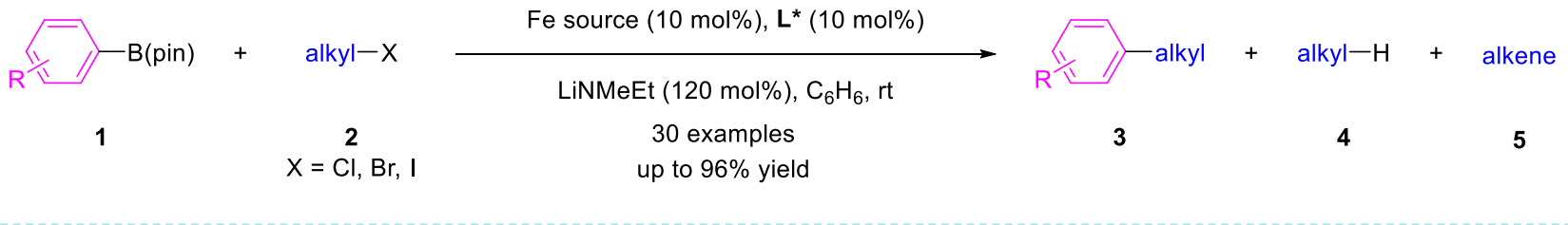
Iron-catalyzed Enantioselective Suzuki-Miyaura Coupling



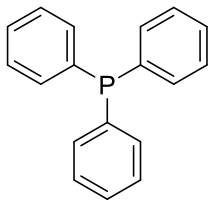
Iwamoto, T.; Okuzono, C.; Adak, L.; Jin, M.; Nakamura, M. *Chem. Commun.* **2019**, *55*, 1128.

Introduction

Iron-catalyzed Suzuki-Miyaura Coupling



1 **2** (X = Cl, Br, I) **3** **4** **5**



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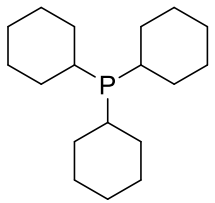

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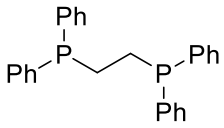

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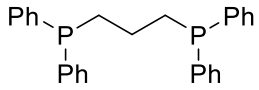

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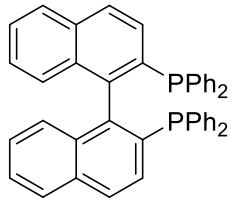

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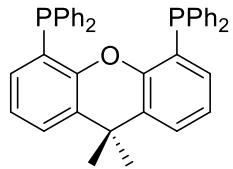

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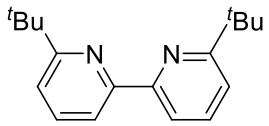

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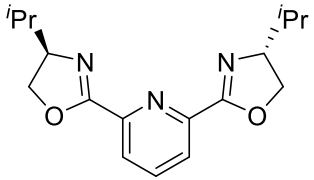

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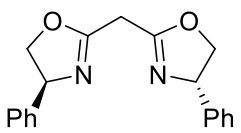

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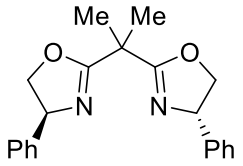

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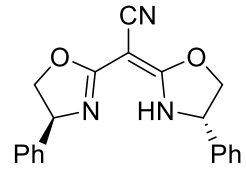
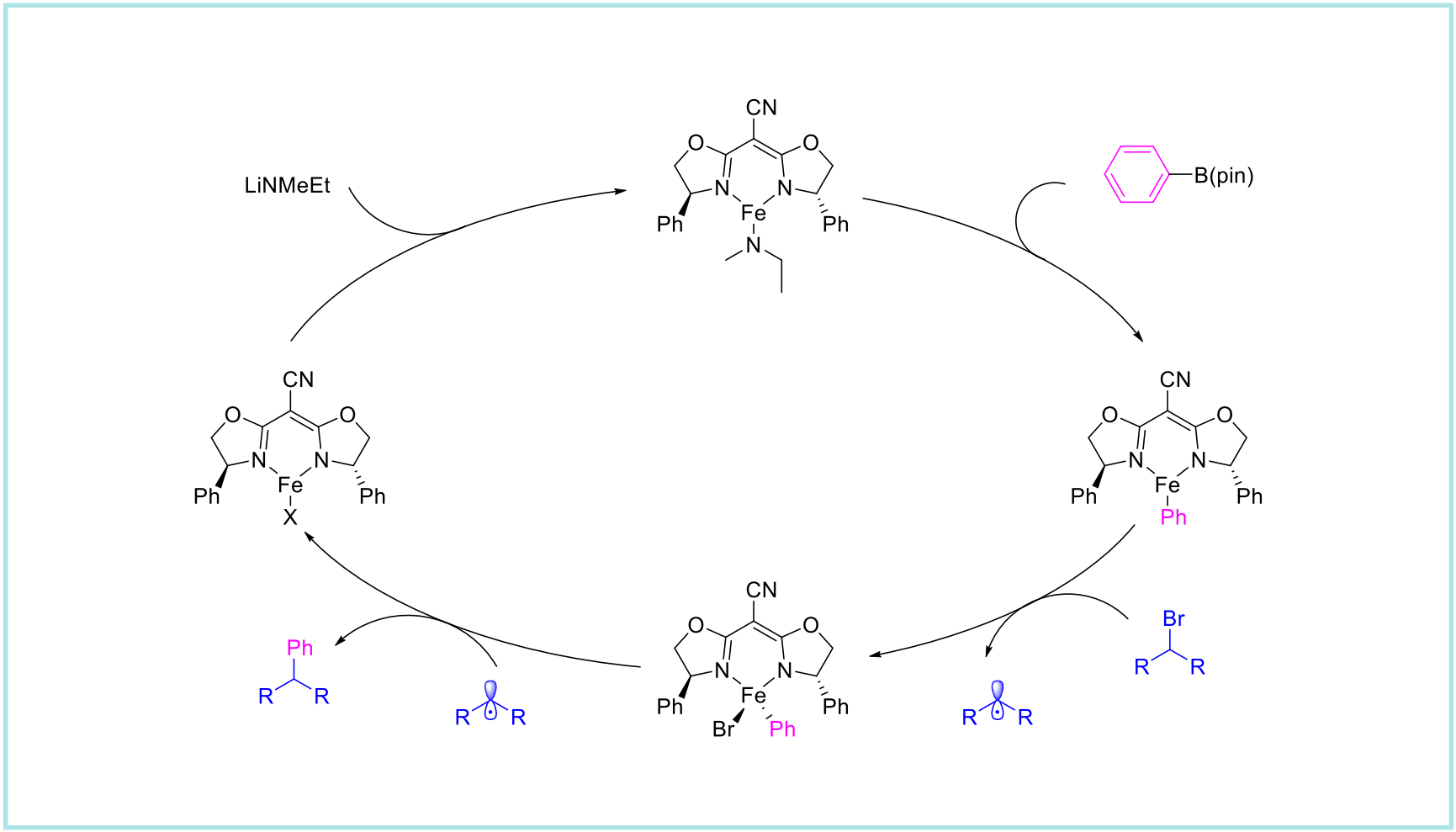


58%/14%/10%
72%/6%/6%

Crockett, M. P.; Tyrol, C. C.; Wong, A. S.; Li, B.; Byers, J. A. *Org. Lett.* **2018**, *20*, 5233.

Introduction

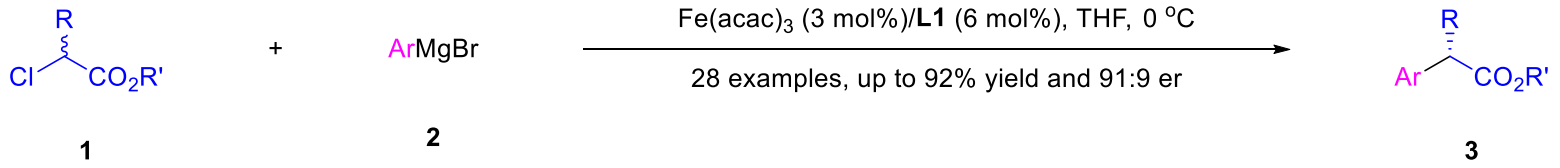
Iron-catalyzed Suzuki-Miyaura Coupling

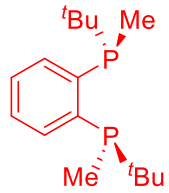


Crockett, M. P.; Tyrol, C. C.; Wong, A. S.; Li, B.; Byers, J. A. *Org. Lett.* **2018**, *20*, 5233.

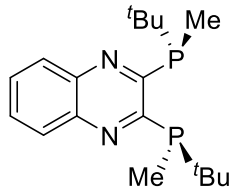
Introduction

Iron-catalyzed Enantioselective Kumada Cross-coupling

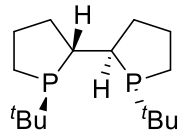




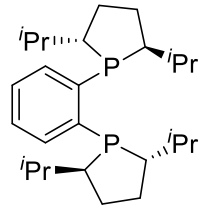
(*R*,*R*)-**BenzP**
91% yield, 85:15 er



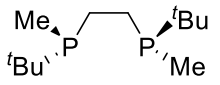
(*R*,*R*)-**QuinoxP**
66% yield, 83:17 er



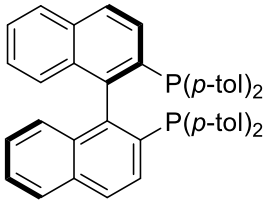
(*S*,*S*′,*R*,*R*′)-**Tangphos**
69% yield, 79:21 er



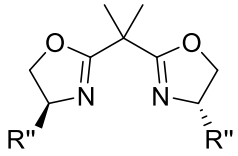
(*S*,*S*)-^{i}**Pr-DuPhos**
75% yield, 62:38 er



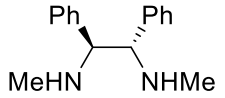
(*R*,*R*)-^{t}**Bu-BisP**
51% yield, 52:48 er



(*R*)-**T-BINAP**
39% yield, 50:50 er



BOX
R" = Ph, 80% yield, 76:24 er
R" = Bn, 78% yield, 77:23 er

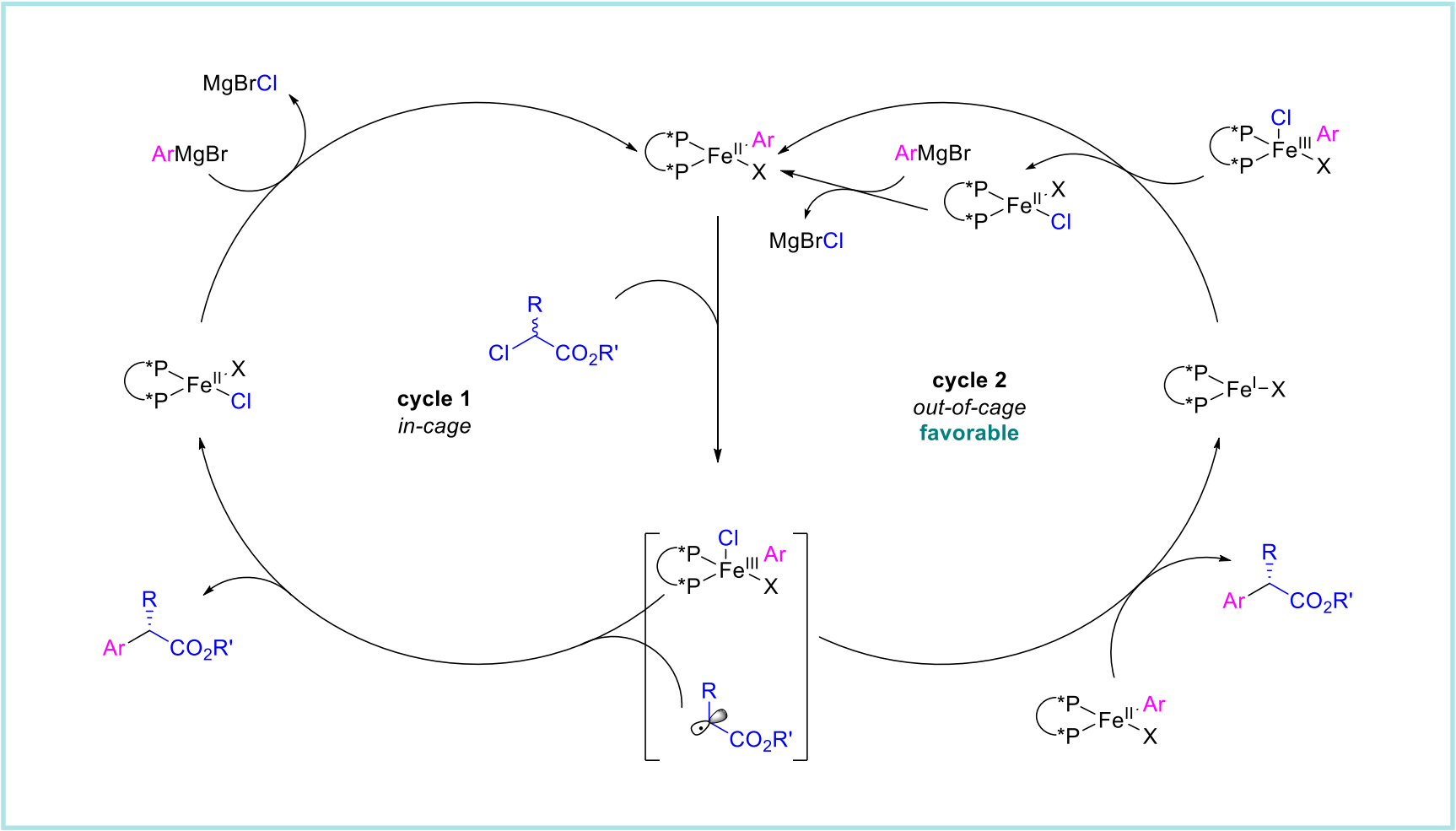


L
10% yield, 50:50 er

Jin, M.; Adak, L.; Nakamura, M. *J. Am. Chem. Soc.* **2015**, *137*, 7128.

Introduction

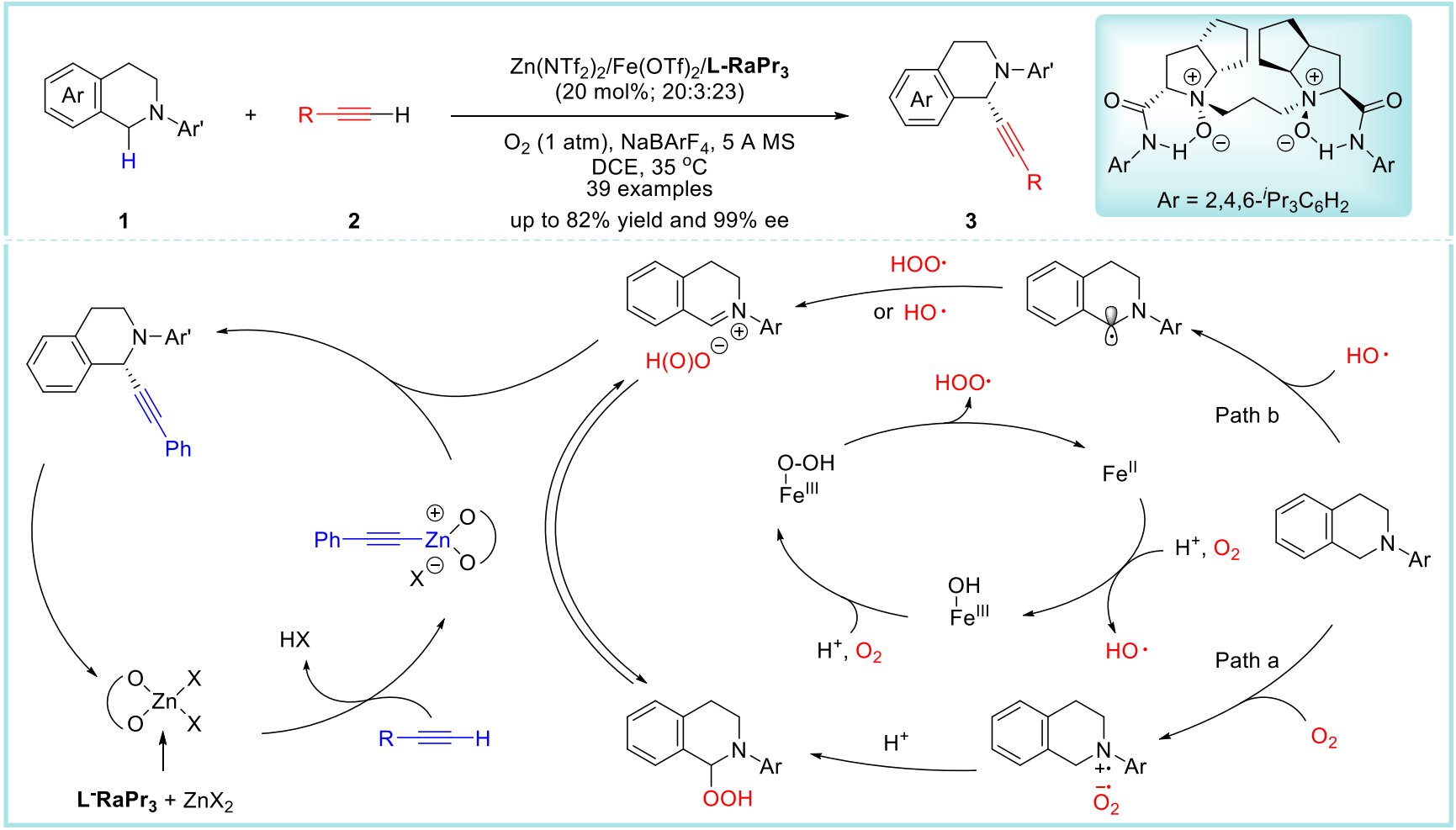
Iron-catalyzed Enantioselective Kumada Cross-coupling



Jin, M.; Adak, L.; Nakamura, M. *J. Am. Chem. Soc.* **2015**, *137*, 7128.

Introduction

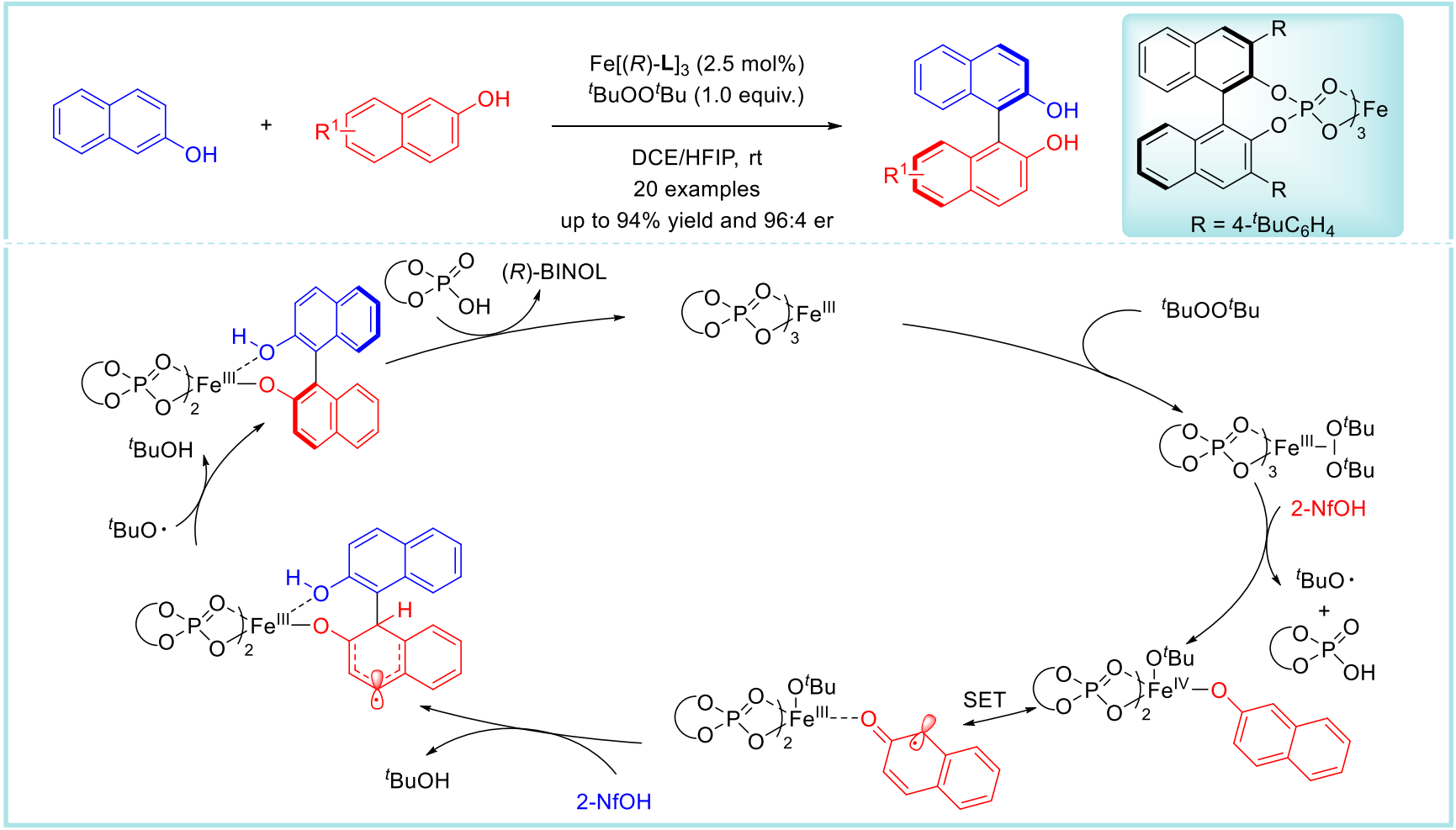
Iron-catalyzed Enantioselective Oxidative Cross-coupling



Huang, T.; Liu, X.; Lang, J.; Xu, J.; Lin, L.; Feng, X. *ACS Catal.* **2017**, *7*, 5654.

Introduction

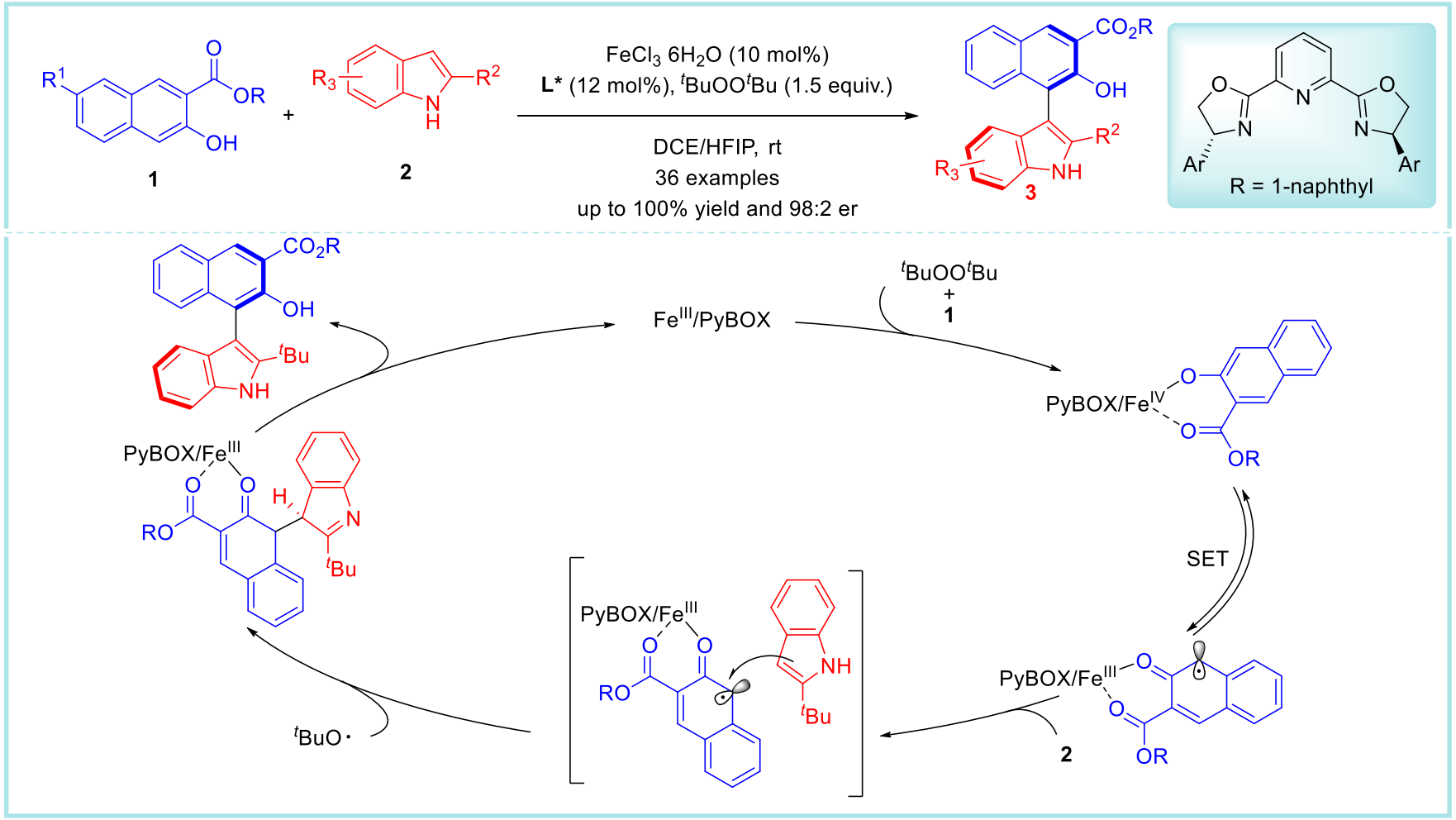
Iron-catalyzed Enantioselective Oxidative Homocoupling and Cross-coupling



Narute, S.; Parnes, R.; Toste, F. D.; Pappo, D. *J. Am. Chem. Soc.* **2016**, *138*, 16553.

Introduction

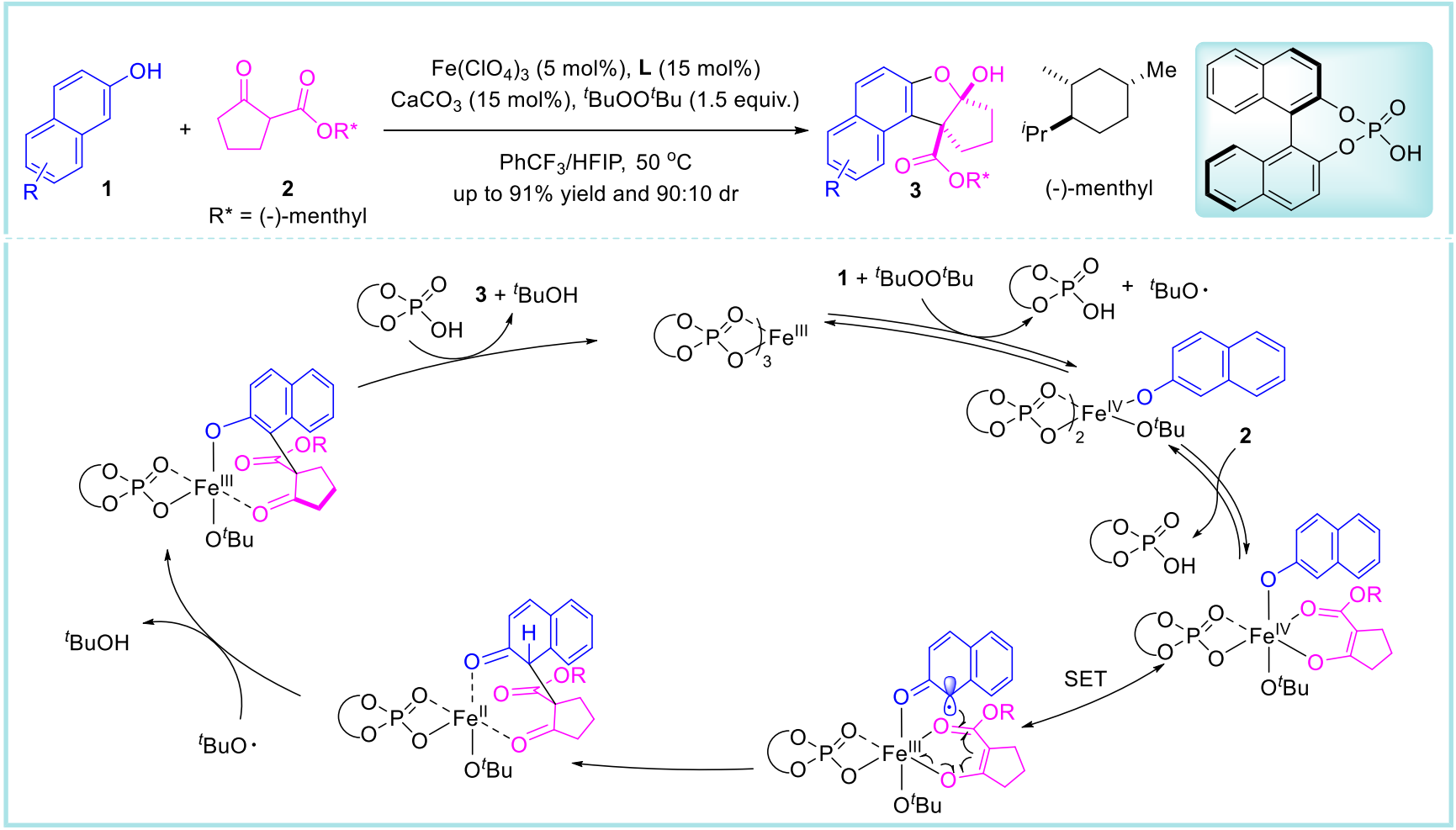
Iron-catalyzed Enantioselective Oxidative Cross-coupling



Surgenor, R. R.; Liu, X.; Keenlyside, M. J. H.; Myers, W.; Smith, M. D. *Nat. Chem.* **2023**, *15*, 357.

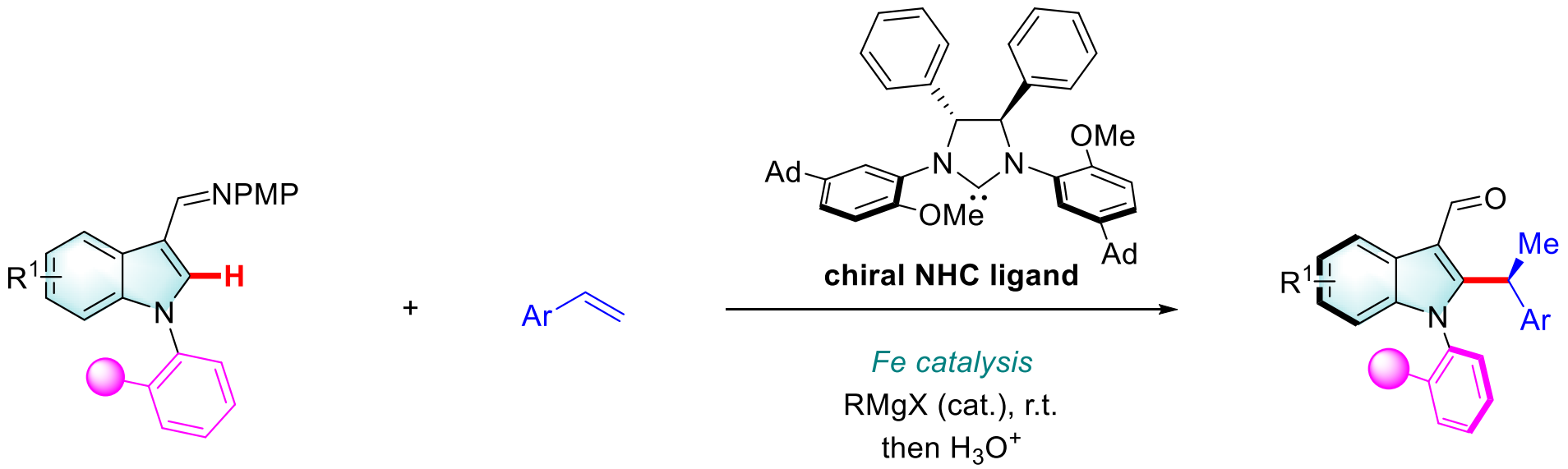
Introduction

Iron-catalyzed Enantioselective Cross-dehydrogenative Coupling



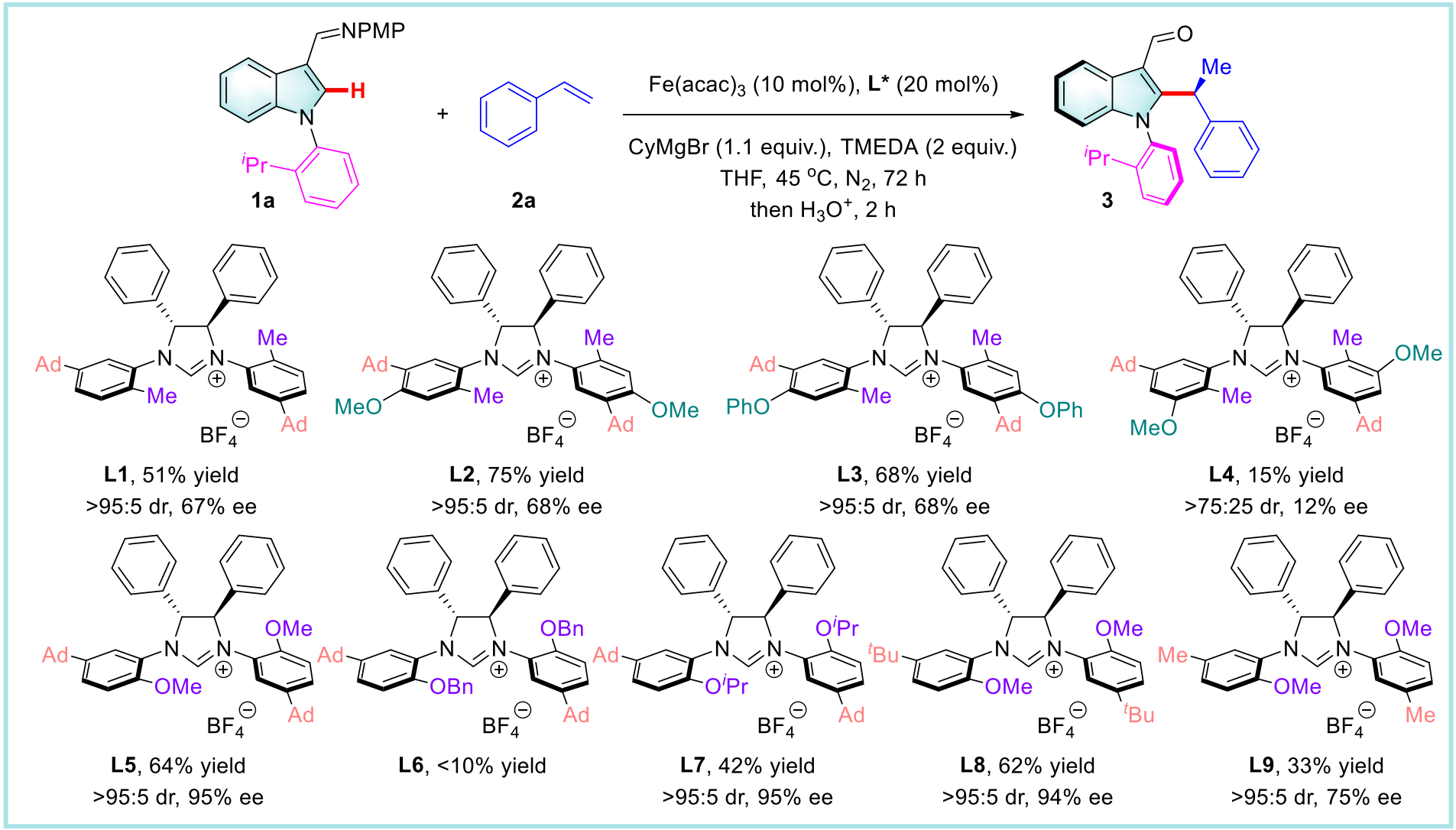
Narute, S.; Pappo, D. *Org. Lett.* **2017**, *19*, 2917.

Project Synopsis

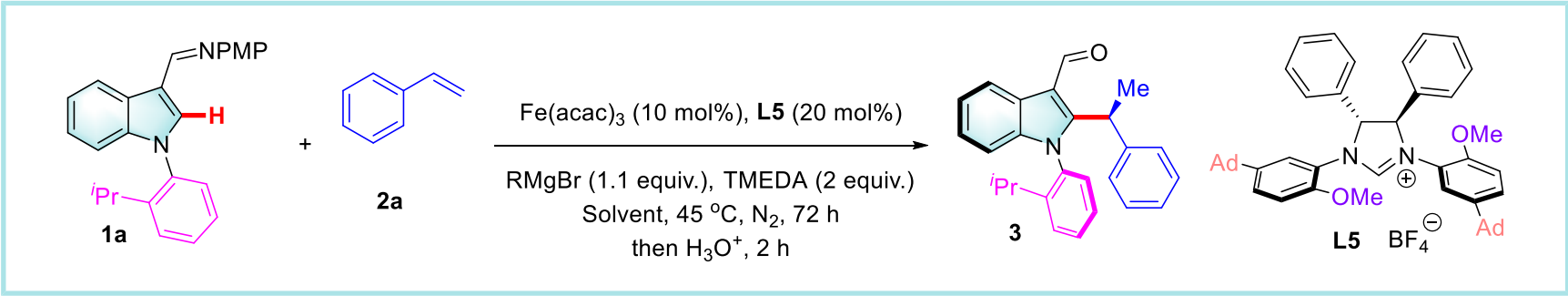


- *Fe-catalyzed stereoselective C-H alkylation*
- *Simultaneous construction of axial chirality and central chirality*
- *Generation of rare C-N axially chiral indoles*
- *Mild reaction conditions* ♦ *Detailed DFT calculations*
- *Catalytic active iron(0) species (detected by Mosssbauer spectroscopy)*

Optimization of the Reaction Conditions



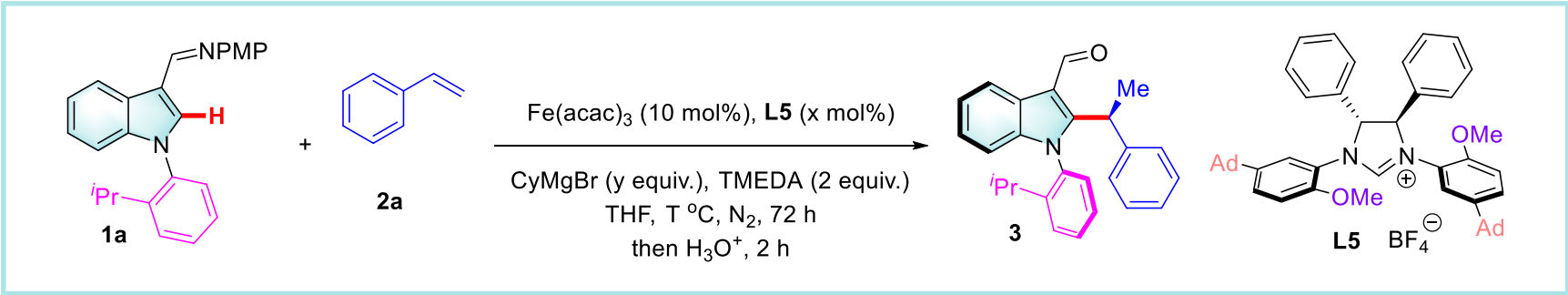
Optimization of the Reaction Conditions



Entry	RMgX	Solvent	Yield (%)[a] (**3**)	Dr (%) (**3**)[a]	Ee (%) (**3**)[b]
1	CyMgBr	THF	64	>95:5	95
2	MeMgBr	THF	n.d.		
3	EtMgBr	THF	<10		
4	^{t}BuMgBr	THF	<10		
5	PhMgBr	THF	n.d.		
6	^{i}PrCH$_2$MgBr	THF	11	>95:5	93
7	Me$_3$SiCH$_2$MgCl	THF	n.d.		
8	CyMgCl	THF	63	>95:5	95
9	CyMgBr	2-MeTHF	63	>95:5	94
10	CyMgBr	Toluene	68	>95:5	95
11	CyMgBr	Et$_2$O	74	>95:5	96

[a]Measured by ^{1}H NMR analysis with 1,3,5-trimethoxybenzene as internal standard. [b]Determined by HPLC.

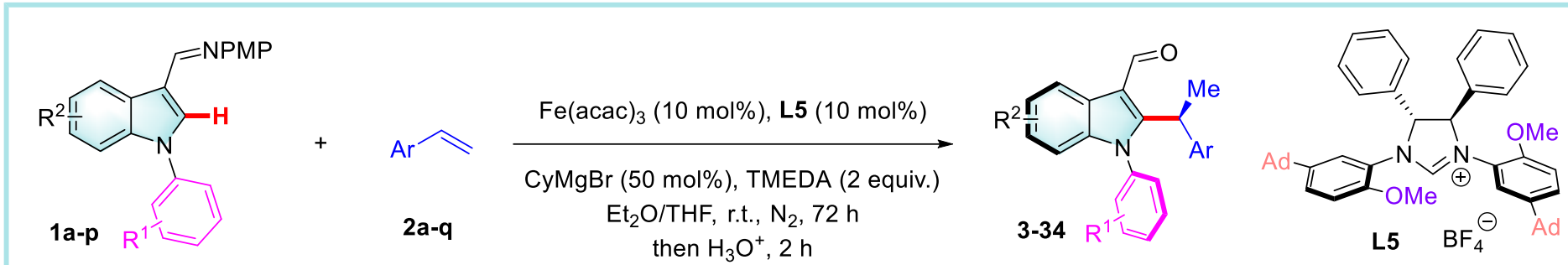
Optimization of the Reaction Conditions

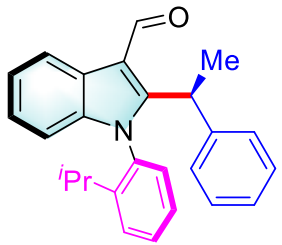


Entry	CyMgBr (y equiv.)	T (°C)	L5 (x mol%)	Yield (%)[a] (**3**)	Dr (%) (**3**)[a]	Ee (%) (**3**)[b]
12	1.1	45	20	74	>95:5	96
13	0.5	45	20	84	>95:5	96
14	2.0	45	20	21	>95:5	95
15	1.1	60	20	80	89:11	96
16	0.5	r.t.	20	92	>95:5	97
17	1.1	r.t.	0	n.d.		
18	0.5	r.t.	15	92	>95:5	97
19	**0.5**	**r.t.**	**10**	**91(90)**	**>95:5**	**97**

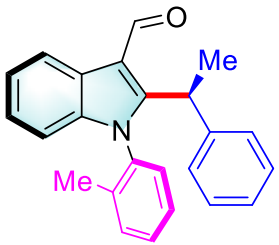
[a]Measured by ^{1}H NMR analysis with 1,3,5-trimethoxybenzene as internal standard. [b]Determined by HPLC.

Scope of *N*-substituents and Indoles

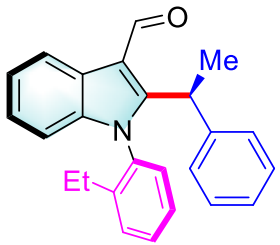




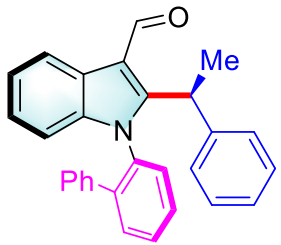
3, 90% yield
>95:5 dr, 97% ee



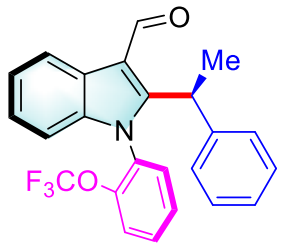
4, 91% yield
>95:5 dr, 95% ee



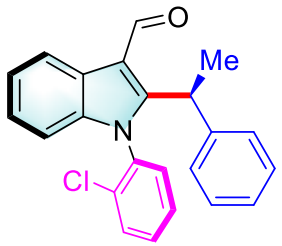
5, 91% yield
>95:5 dr, 97% ee



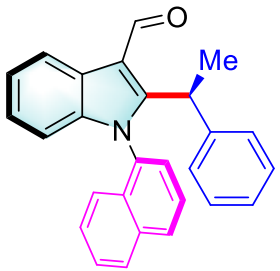
6, 73% yield
>95:5 dr, 98% ee



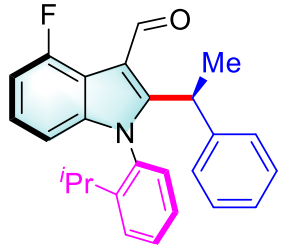
7, 68% yield
>95:5 dr, 91% ee



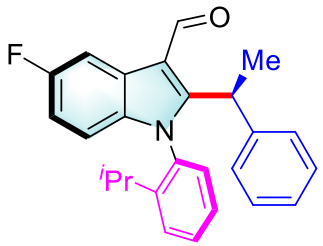
8, 56% yield
>95:5 dr, 94% ee



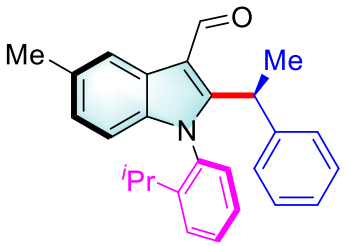
9, 86% yield
>95:5 dr, 93% ee



10, 36% yield
90:10 dr, 90% ee

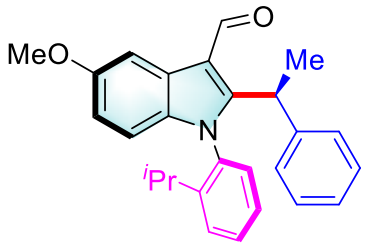


11, 63% yield
>95:5 dr, 94% ee

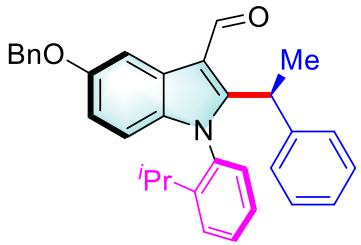


12, 82% yield
>95:5 dr, 96% ee

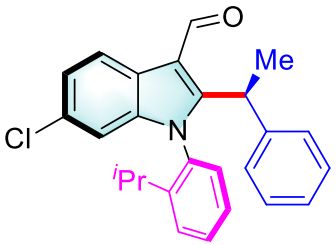
Scope of Indoles



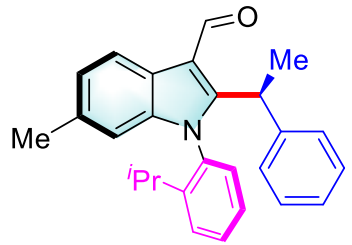
13, 70% yield
>95:5 dr, 98% ee



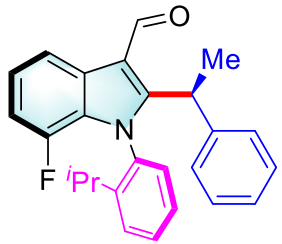
14, 54% yield
>95:5 dr, 98% ee



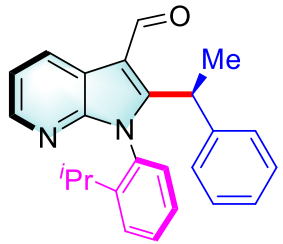
15, 50% yield
>95:5 dr, 87% ee



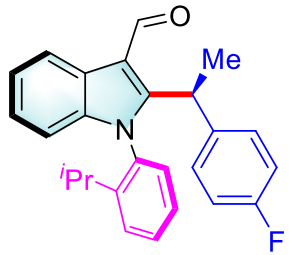
16, 52% yield
>95:5 dr, 96% ee



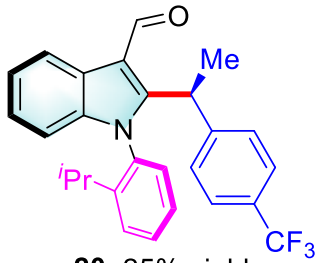
17, 57% yield
>95:5 dr, 86% ee



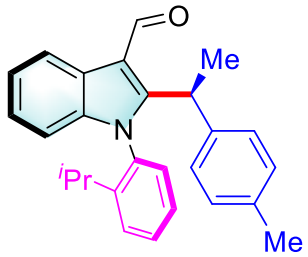
18, 84% yield
>95:5 dr, 91% ee



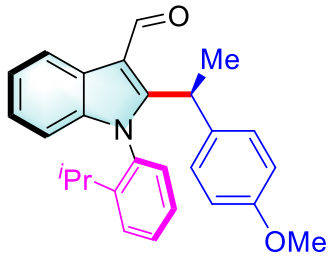
19, 93% yield
>95:5 dr, 97% ee



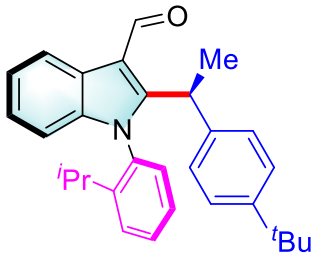
20, 25% yield
>95:5 dr, 98% ee



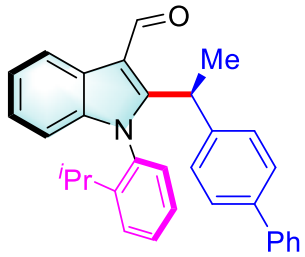
21, 67% yield
>95:5 dr, 97% ee



22, 82% yield
>95:5 dr, 98% ee

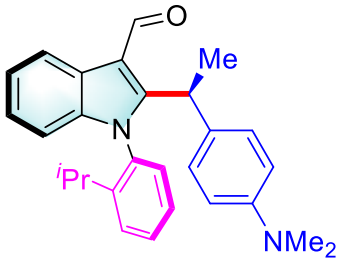


23, 95% yield
>95:5 dr, 99% ee

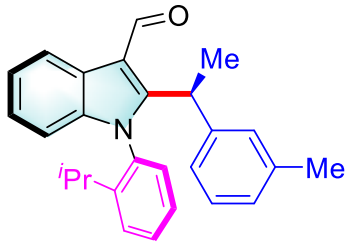


24, 93% yield
>95:5 dr, 96% ee

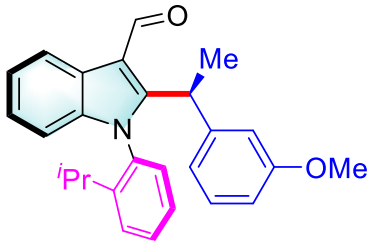
Scope of Alkenes



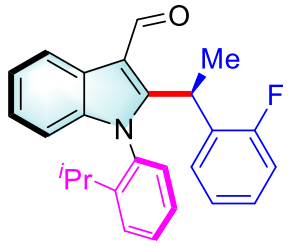
25, 64% yield
>95:5 dr, 99% ee



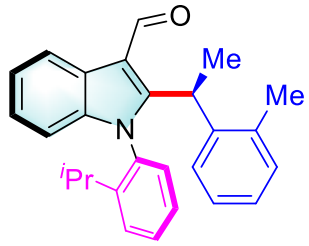
26, 89% yield
>95:5 dr, 96% ee



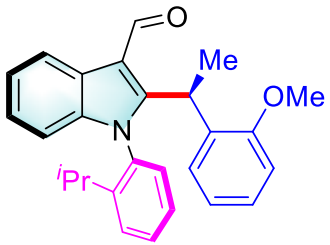
27, 89% yield
>95:5 dr, 94% ee



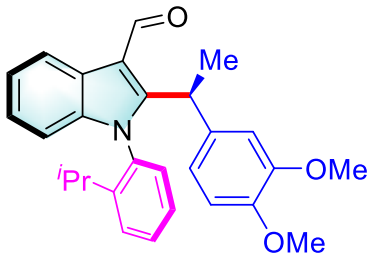
28, 36% yield
>95:5 dr, 99% ee



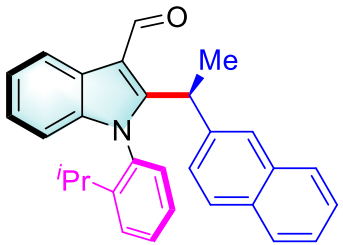
29, 85% yield
>95:5 dr, 99% ee



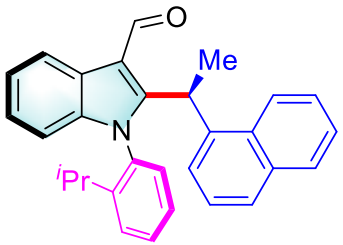
30, 55% yield
>95:5 dr, 99% ee



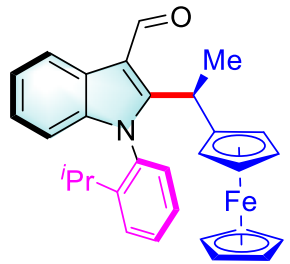
31, 94% yield
>95:5 dr, 96% ee



32, 93% yield
>95:5 dr, 90% ee

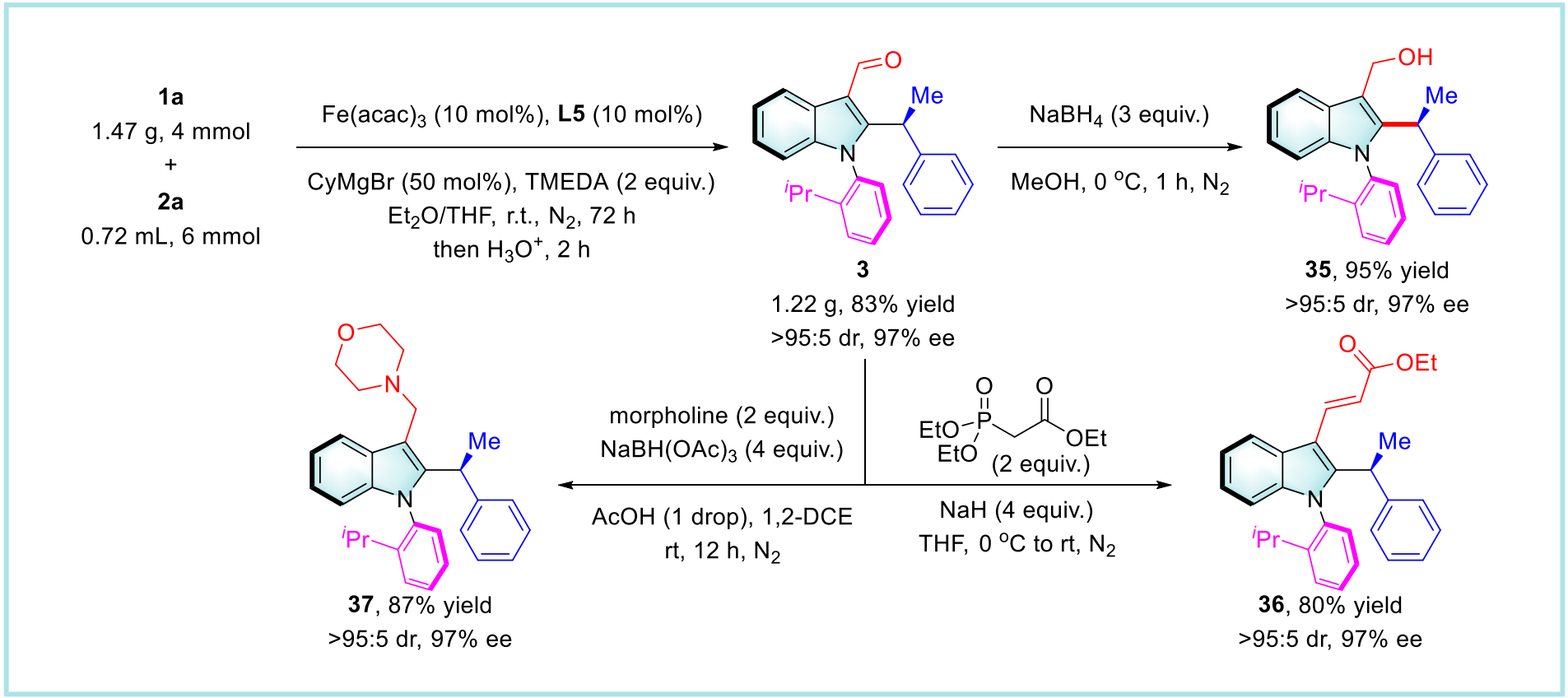


33, 61% yield
90:10 dr, 93% ee



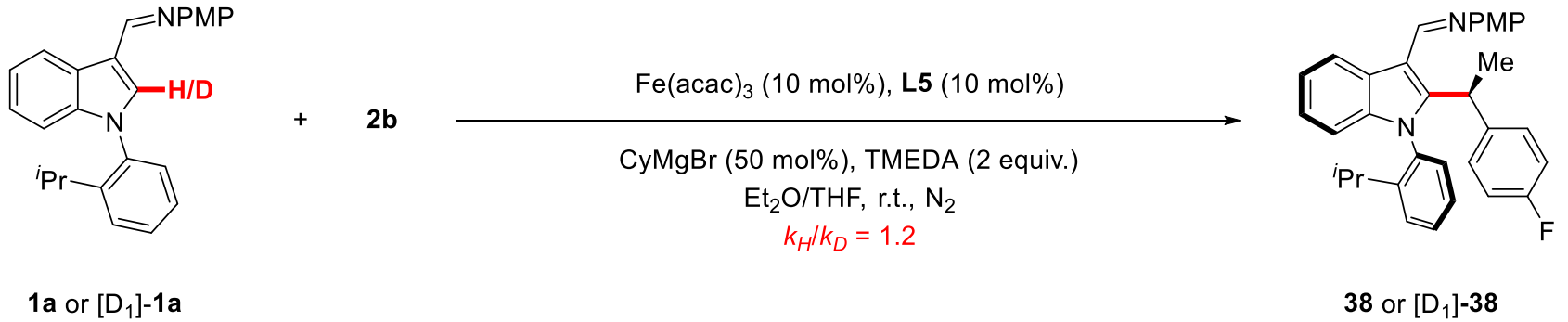
34, 61% yield
>95:5 dr, 99% ee

Scale-up and Late-stage Transformations



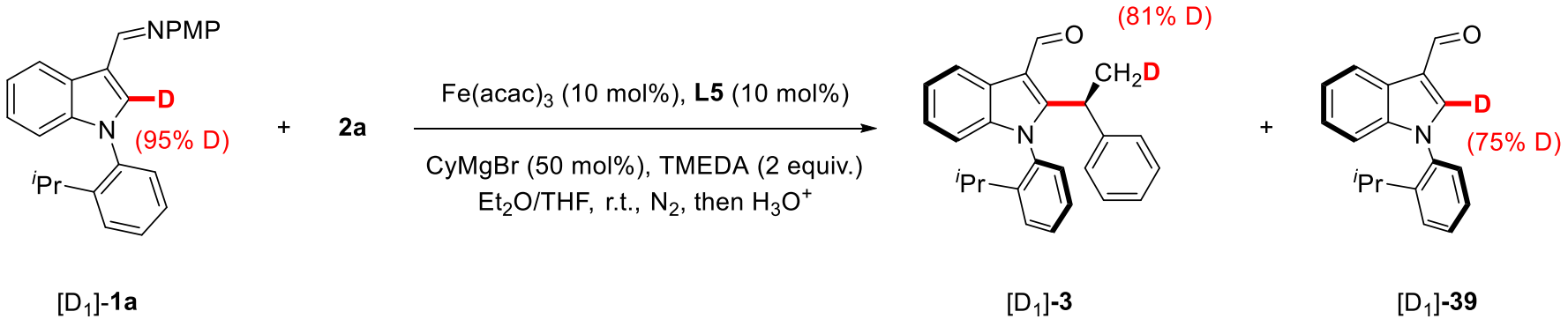
Mechanistic Studies

a Kinetic isotope effect



1a or [D_1]-**1a** — **38** or [D_1]-**38**

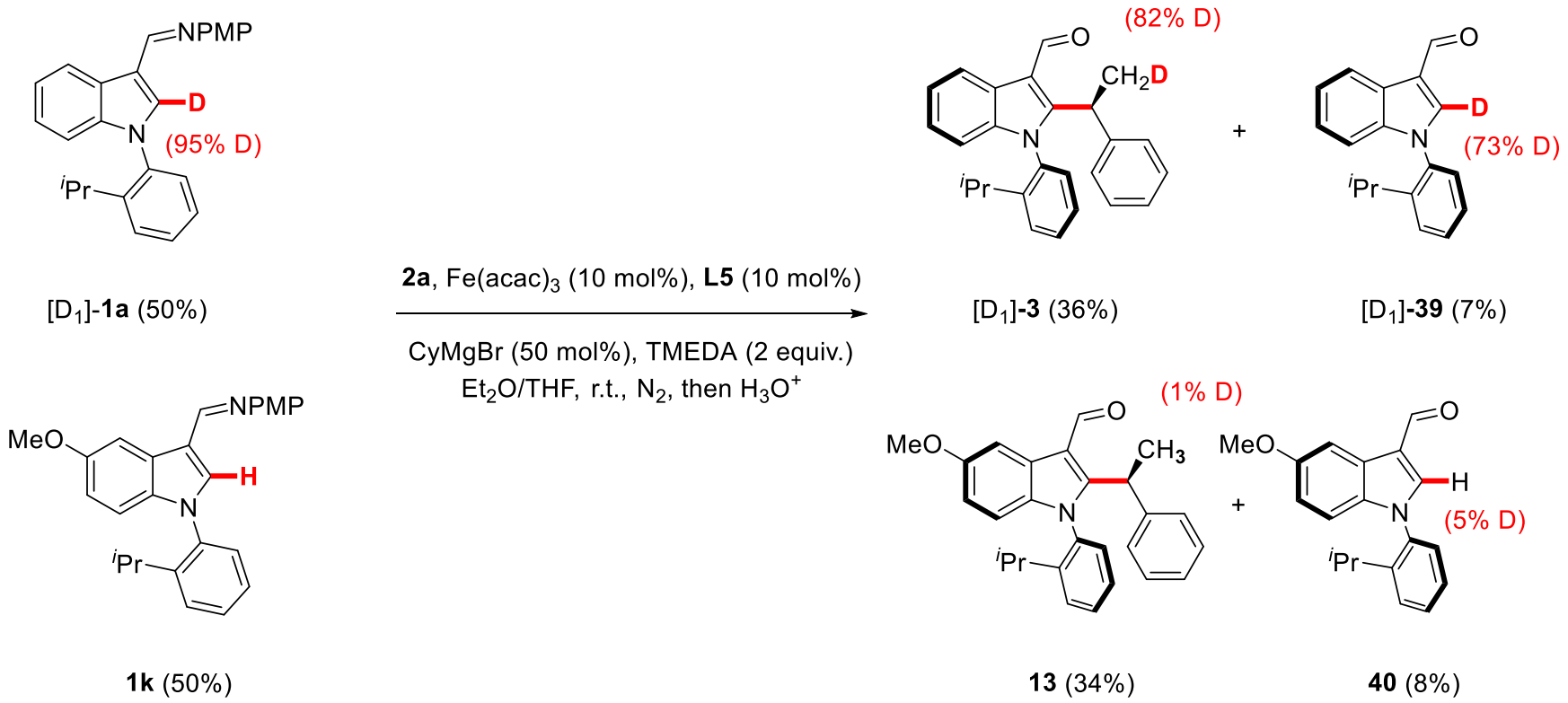
b Deuterium-labeling experiment



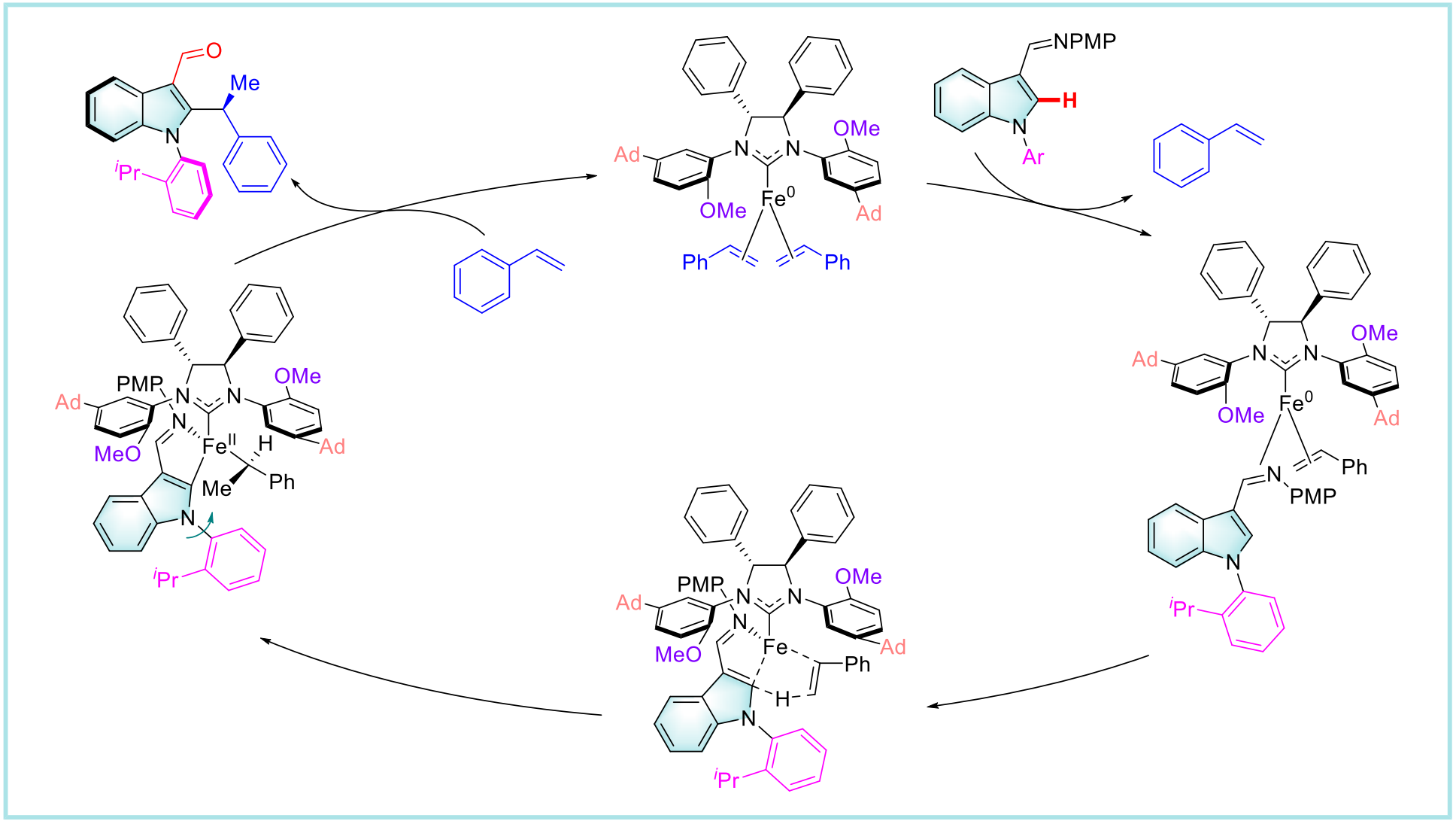
[D_1]-**1a** — [D_1]-**3** — [D_1]-**39**

Mechanistic Studies

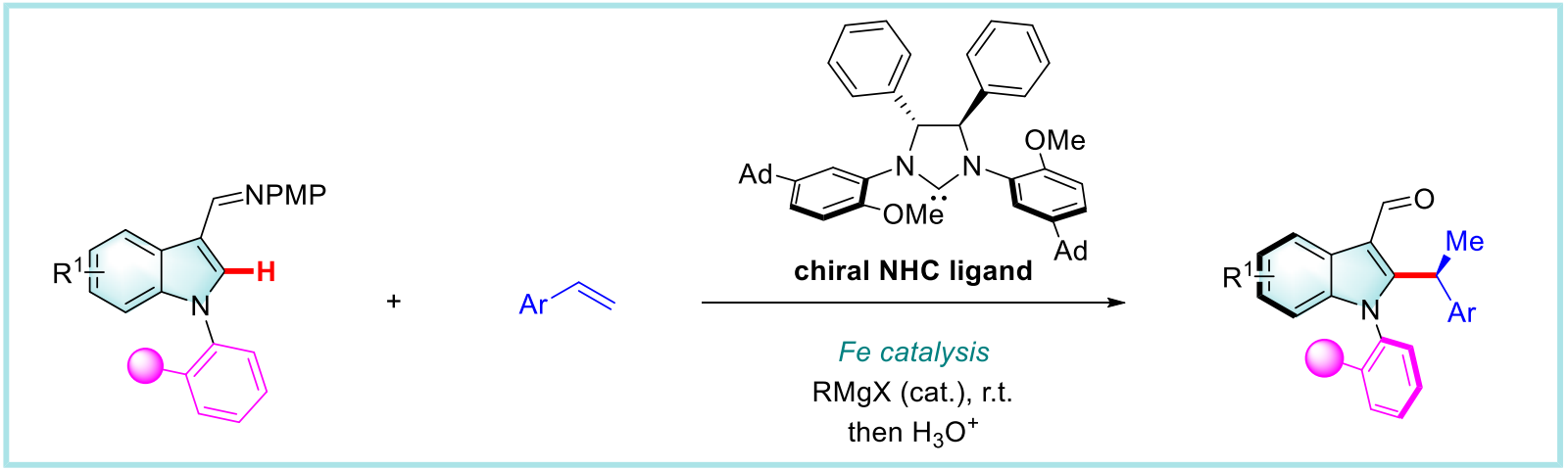
c Deuterium scrambling experiment



Proposed Mechanism



Summary



- ***Selective C−H alkylation of indoles with aryl alkenes by sustainable iron catalysis***
- ***Leading to rare atropoenriched and enantioenriched substituted indoles***

Strategy for Writing The First Paragraph

快速获得对映体纯的化合物分子是有机合成和催化的最活跃领域之一

大多数立体选择性C-H官能化强烈依赖于使用贵金属基催化剂

手性铁催化仍然处于起步阶段工作

- ✓ The development of sustainable and highly selective methodologies allowing to rapidly access enantiopure complex molecules is amongst the most vivid fields of organic synthesis and catalysis
- ✓ However, the majority of stereoselective C-H functionalization strongly rely on the use of noble metal-based catalysts, including palladium, iridium, or rhodium. In clear contrast, such transformation catalyzed by 3d-metals
- ✓ Indeed, various oxidation states of iron, combined with a diversity of reaction scenarios conceivable in a presence of such a catalyst and difficulty in isolating well-defined iron-complexes, renders the chiral iron-catalysis still in its infancy.

Strategy for Writing The Last Paragraph

总结工作

展望未来

- ✓ A highly efficient selective C−H alkylation of indoles with aryl alkenes was achieved by sustainable iron catalysis, leading to rare atropoenriched and enantioenriched substituted indoles with high structural diversity.

- ✓ We envisioned that the present approach and the mechanistic findings will promote the development in related challenging ironcatalyzed C−H functionalization constructing multiple chiral centers.

Representative Examples

- Methodologies allowing to rapidly access enantiopure complex molecules is amongst the most vivid fields of organic synthesis and catalysis (生动的；活泼的；活跃的)
- Stereoselective iron-catalyzed C-H activation holds great promise to expand the diversity of easily accessible enantiopure molecules. (拥有巨大潜力)
- This insight emphasizes the necessity for the de novo design of chiral ligands in asymmetric synthesis. (强调，着重)

Acknowledgement

Thanks for your attention