Literature Report 6

Diastereo- and Enantioselective Formal [3+2] Cycloaddition of Cyclopropyl Ketones and Alkenes *via* Ti-Catalyzed Radical Redox Relay

Reporter: Huan-Ping Xie

Checker: Hong-Qiang Shen

Date: 2018/06/11

Hao, W.; Harenberg, J. H.; Wu, X.; MacMillan, S. N.; Lin, S. *J. Am. Chem. Soc*. **2018**, *140*, 3514.

Contents

Biography

Lin Song

Areas of interest:

- **Electrocatalysis**
- **Radical redox catalysis**
- **Organic materials**

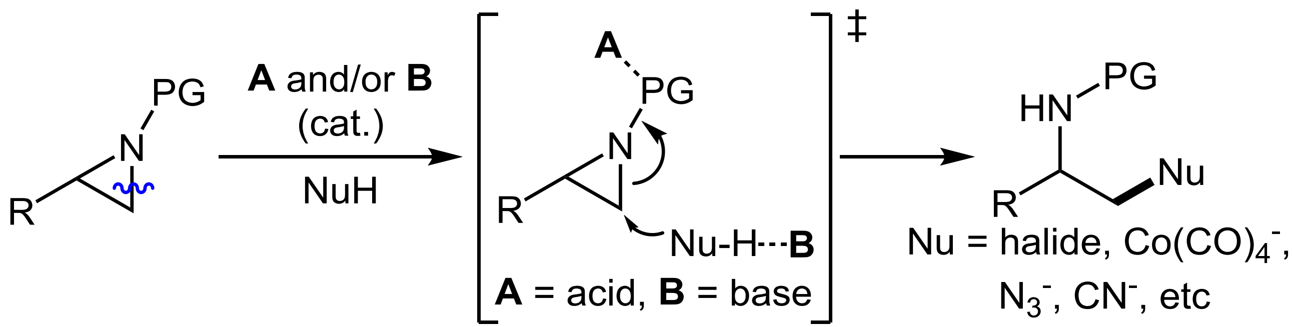
Research experience:

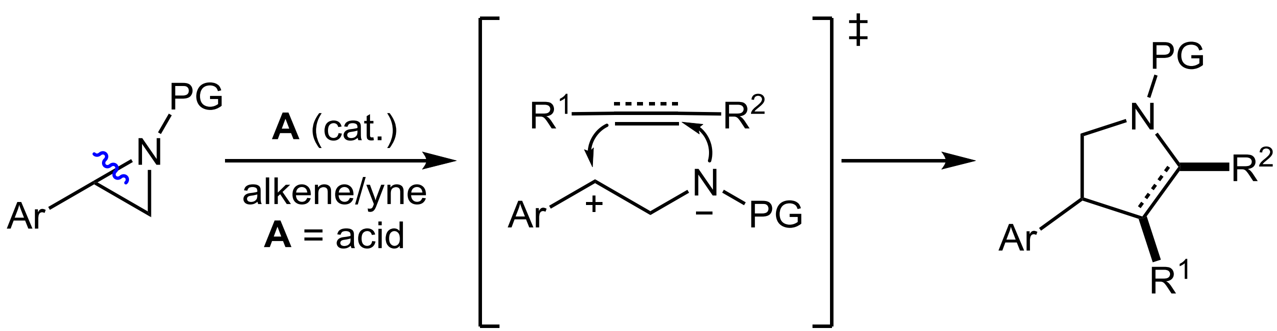
- **2016-至今** Assistant professor, Cornell University, USA
- **2013-2016** Postdoctoral, University of California, Berkly
- **2008-2013** Ph.D, Harvard University
- **2004-2008** B.S., Peking University

Introduction

Ring Opening of Aziridines:

◆ **Acid and/or base catalysis**

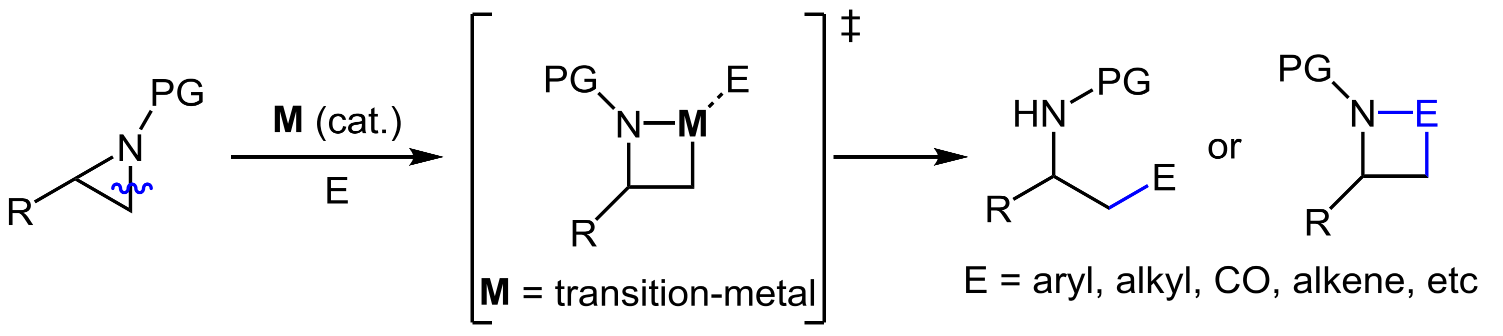




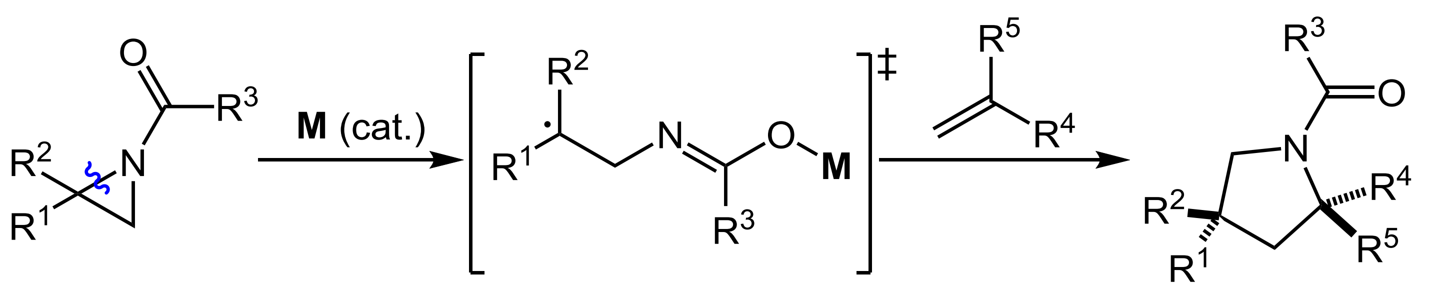
Introduction

Ring Opening of Aziridines:

◆ **Transition-metal catalysis**

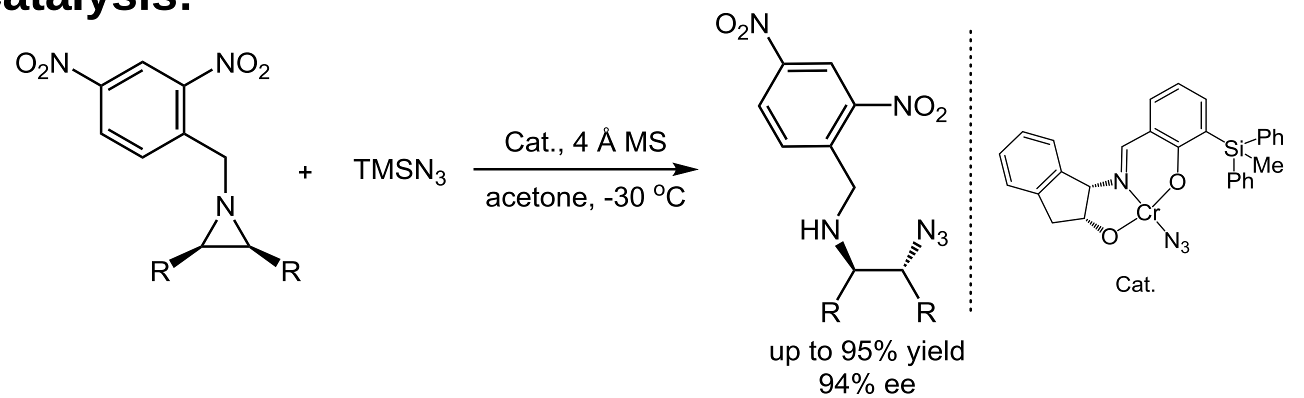


◆ **Redox-relay catalysis**

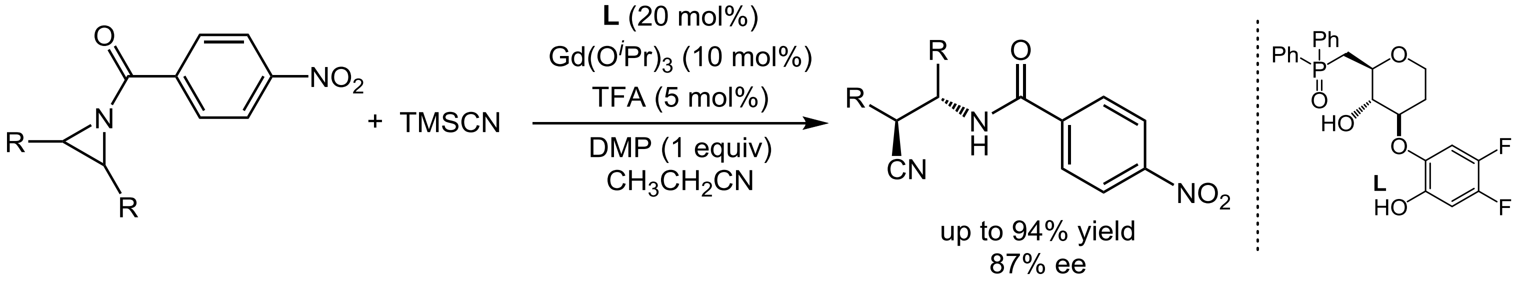


Introduction

Acid catalysis:



Jacobsen, E. N. *et al. Org. Lett.* **1999**, *1,* 1611.



Shibasaki, M. *et al. J. Am. Chem. Soc.* **2005**, *127,* 11252.

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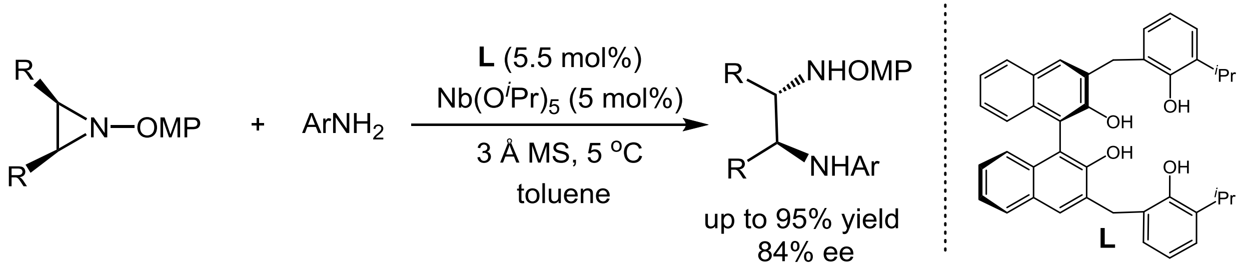
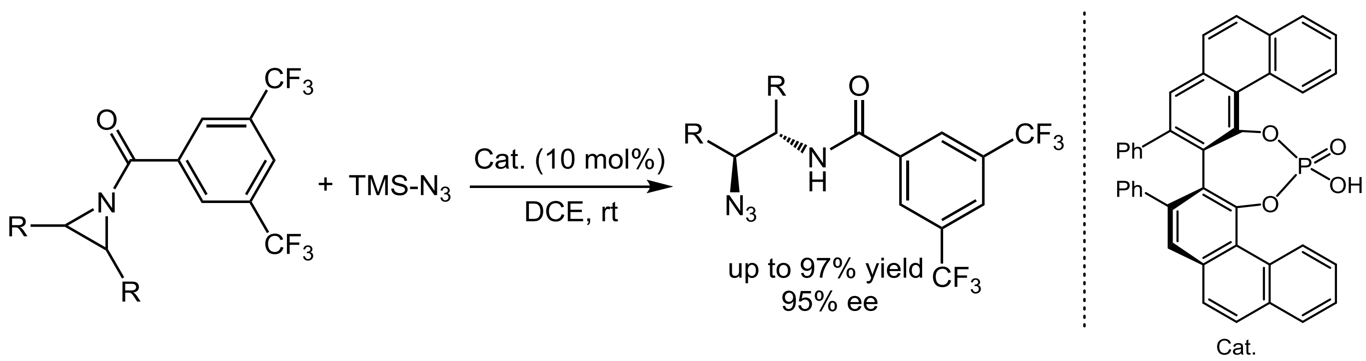


Kobayashi, S. *et al. J. Am. Chem. Soc.* **2007**, *129,* 8103.



Antilla, J. C. *et al. J. Am. Chem. Soc.* **2007**, *129*, 12084.

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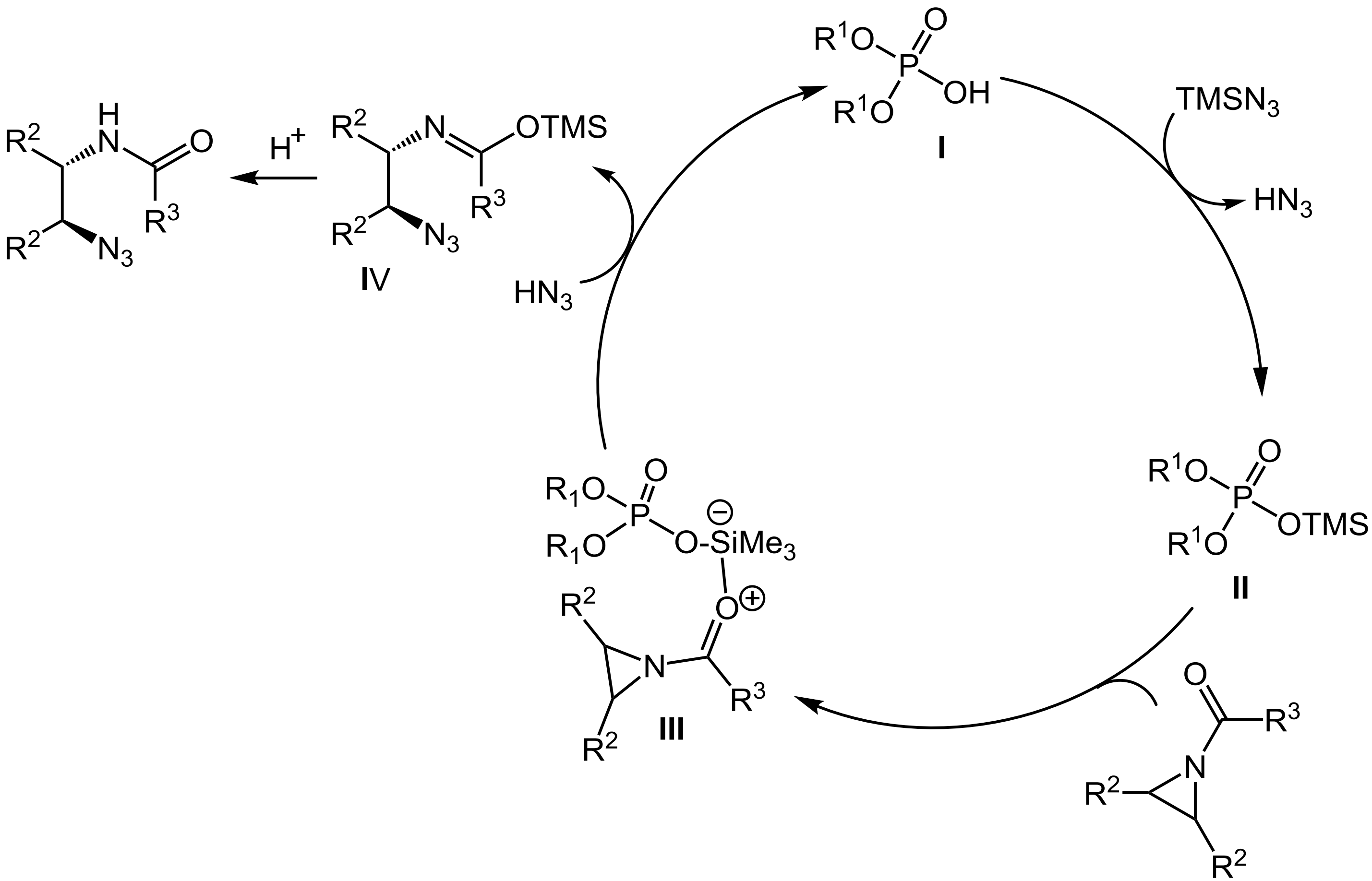

Antilla, J. C. *et al. J. Am. Chem. Soc.* **2007**, *129*, 12084.

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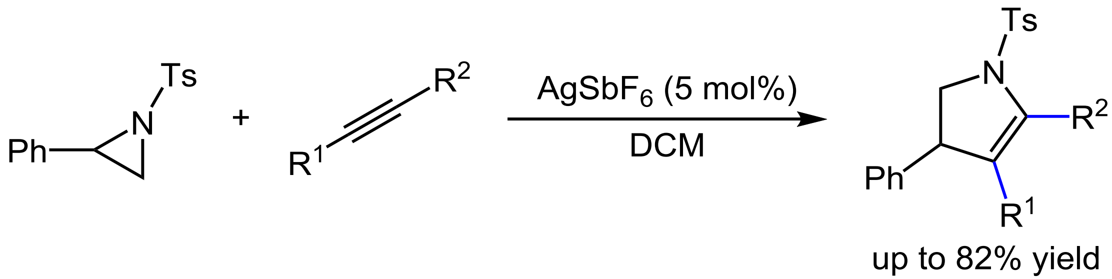
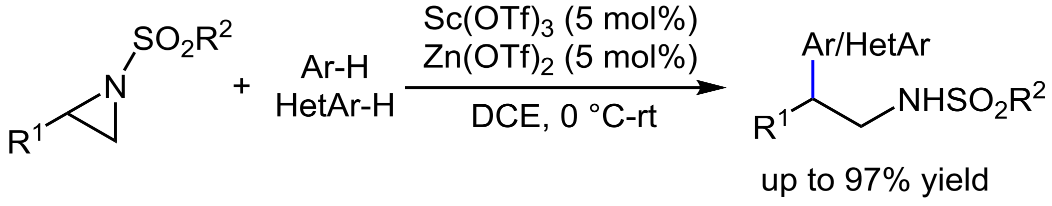


Wender, P. A. *et al. J. Am. Chem. Soc.* **2009**, *131,* 7528.



Ghorai, M. K. *et al. J. Org. Chem.* **2013**, *78,* 7121.

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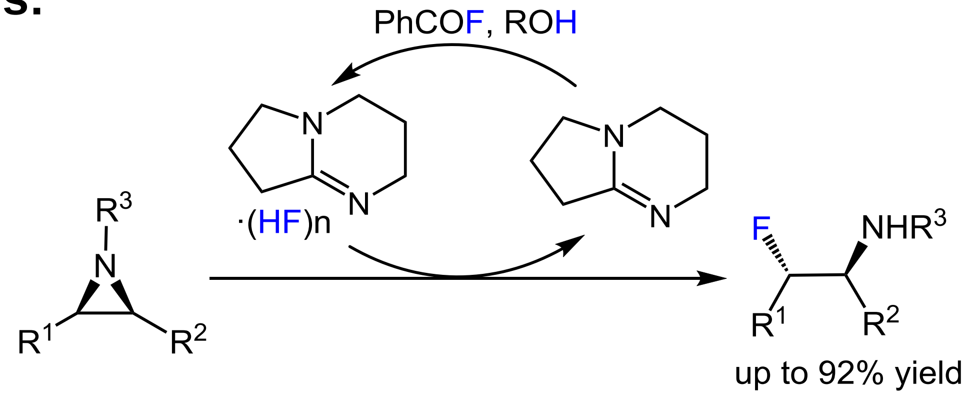
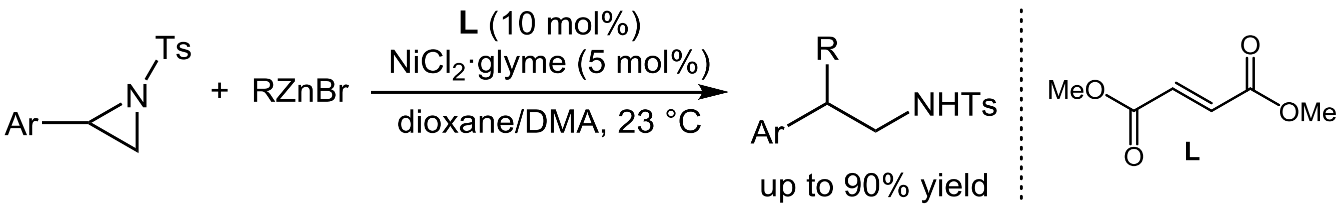
Base catalysis:



Doyle, A. G. *et al. J. Org. Chem.* **2012**, *77,* 4177.

Transition-metal catalysis:



Doyle, A. G. *et al. J. Am. Chem. Soc.* **2012**, *134,* 9541.

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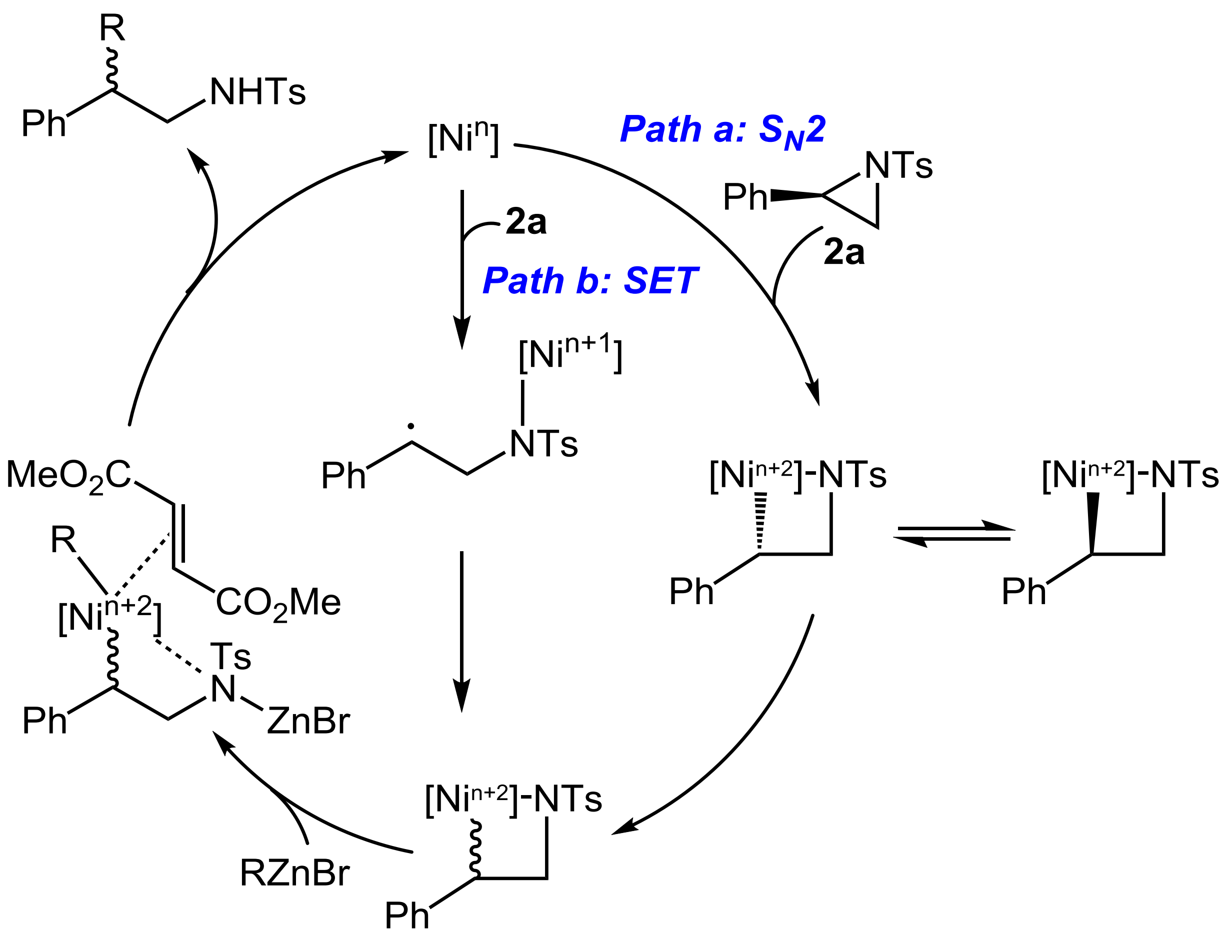

Doyle, A. G. *et al. J. Am. Chem. Soc.* **2012**, *134*, 9541.

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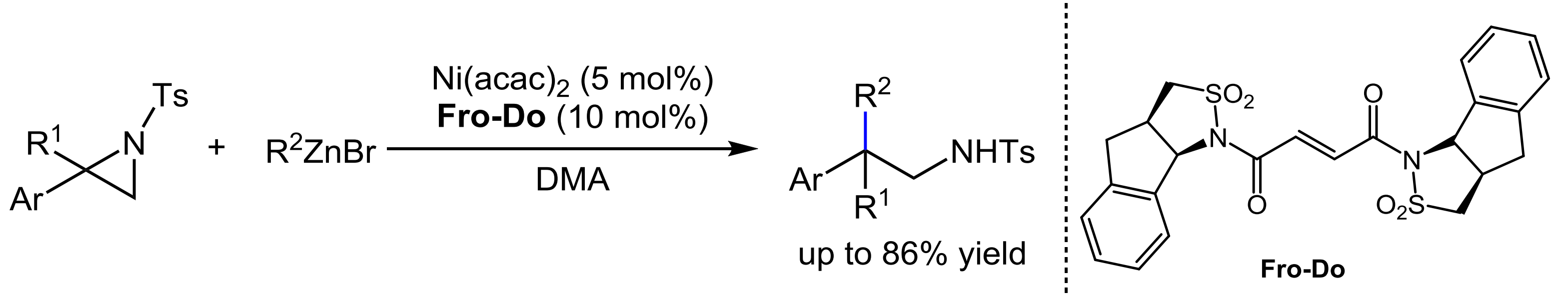
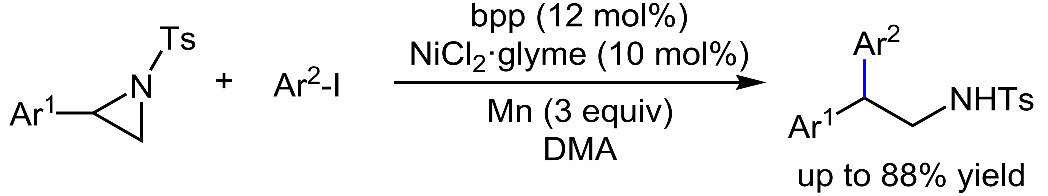


Doyle, A. G. *et al. J. Am. Chem. Soc.* **2015**, *137,* 5638.



Doyle, A. G. *et al. J. Am. Chem. Soc.* **2017**, *139,* 5688.

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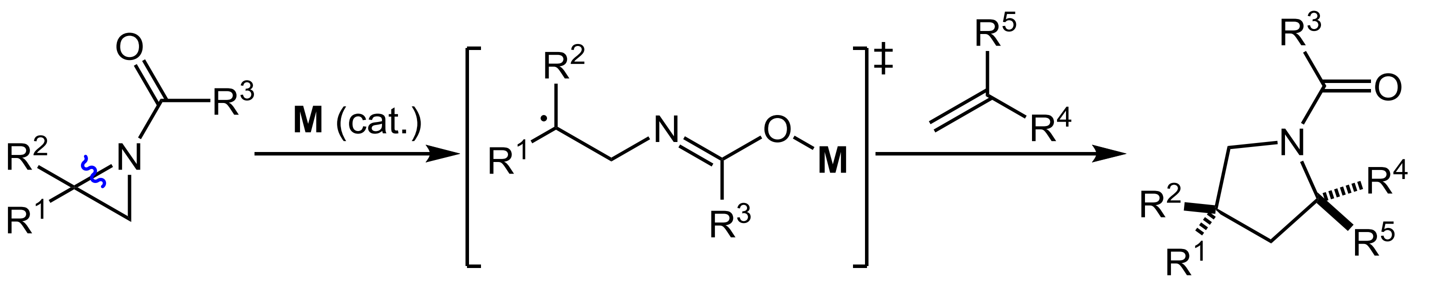
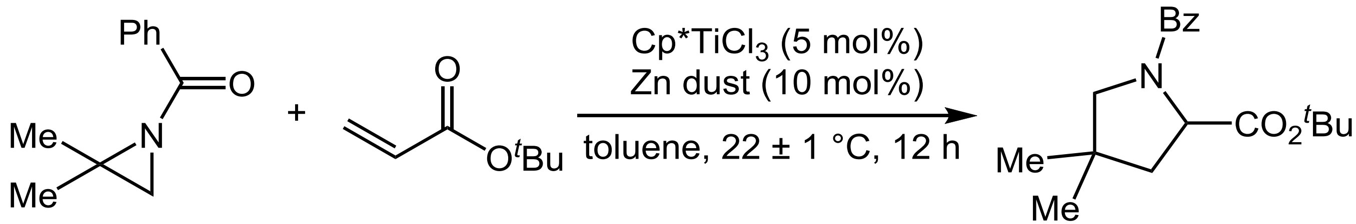
Radical Redox-Relay Catalysis



Lin, S. *et al. J. Am. Chem. Soc*. **2017**, *139*, 12141.

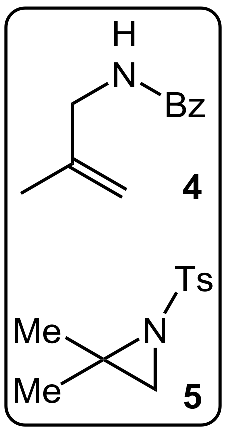
Reaction Optimization



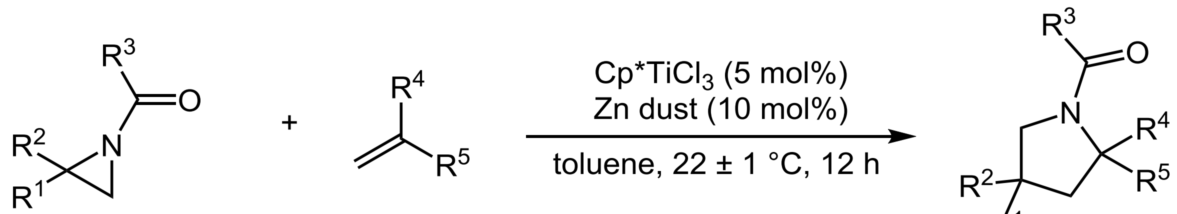
1a **2a** (1.5 equiv) **3a**

Entry	Variation from standard conditions	Yield (%)[a]
1	none	94
2	$CpTiCl_3$ instead of Cp^*TiCl_3	20 [b]
3	Cp_2TiCl_2 instead of Cp^*TiCl_3	<5 [b]
4	$TiCl_4$ instead of Cp^*TiCl_3	<5 [b] (11% **4**)
5	without Zn dust	<5 [b] (>99% **4**)
6	Mn dust instead of Zn dust	82
7	$ZnCl_2$ instead of Cp^*TiCl_3 and Zn dust	<5 [b]
8	DCM instead of toluene	82
9	THF or MeCN instead of toluene	<5 [b]
10	1.0 equiv **2a**	92
11	**4** or **5** instead of **1a**	<5 [b]

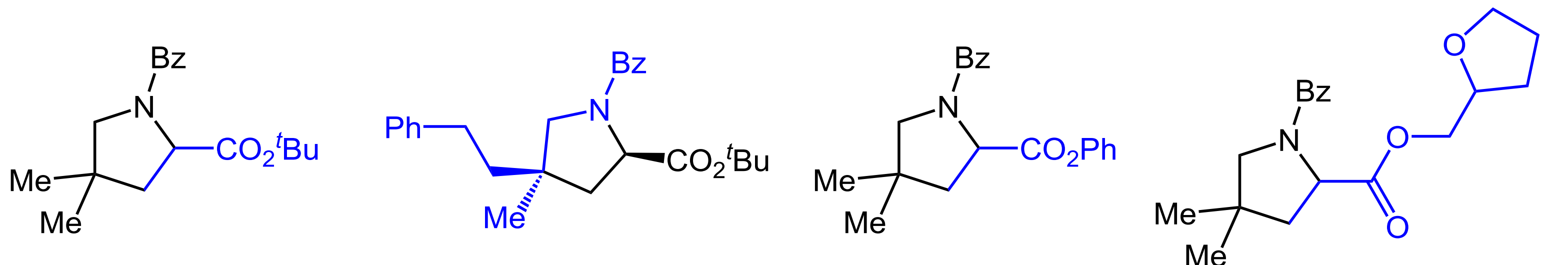
[a] Determined with ^{1}H NMR . [b] Unreacted starting material observed.



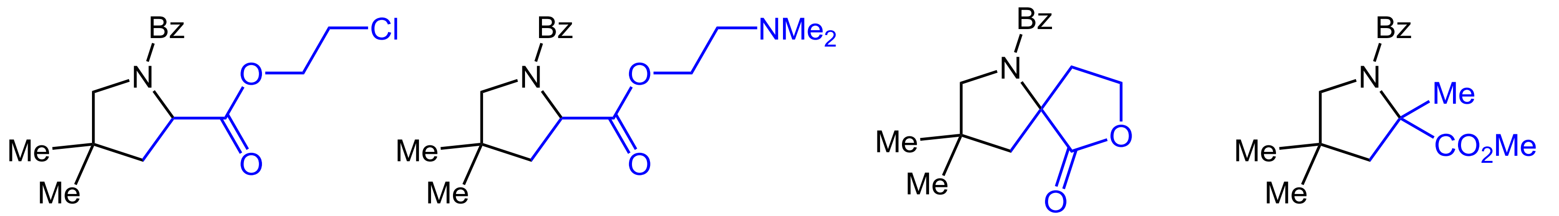
Substrate Scope



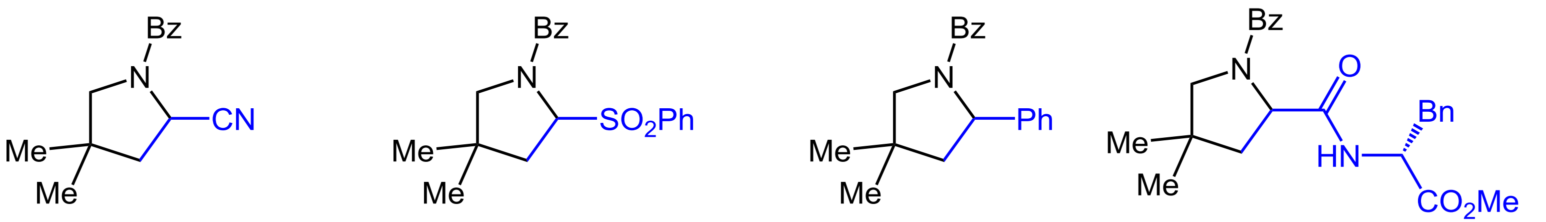
1 **2** **3**



3a 86% **3b** 82%, dr = 2.3:1 **3c** 86% **3d** 75%, dr =1:1

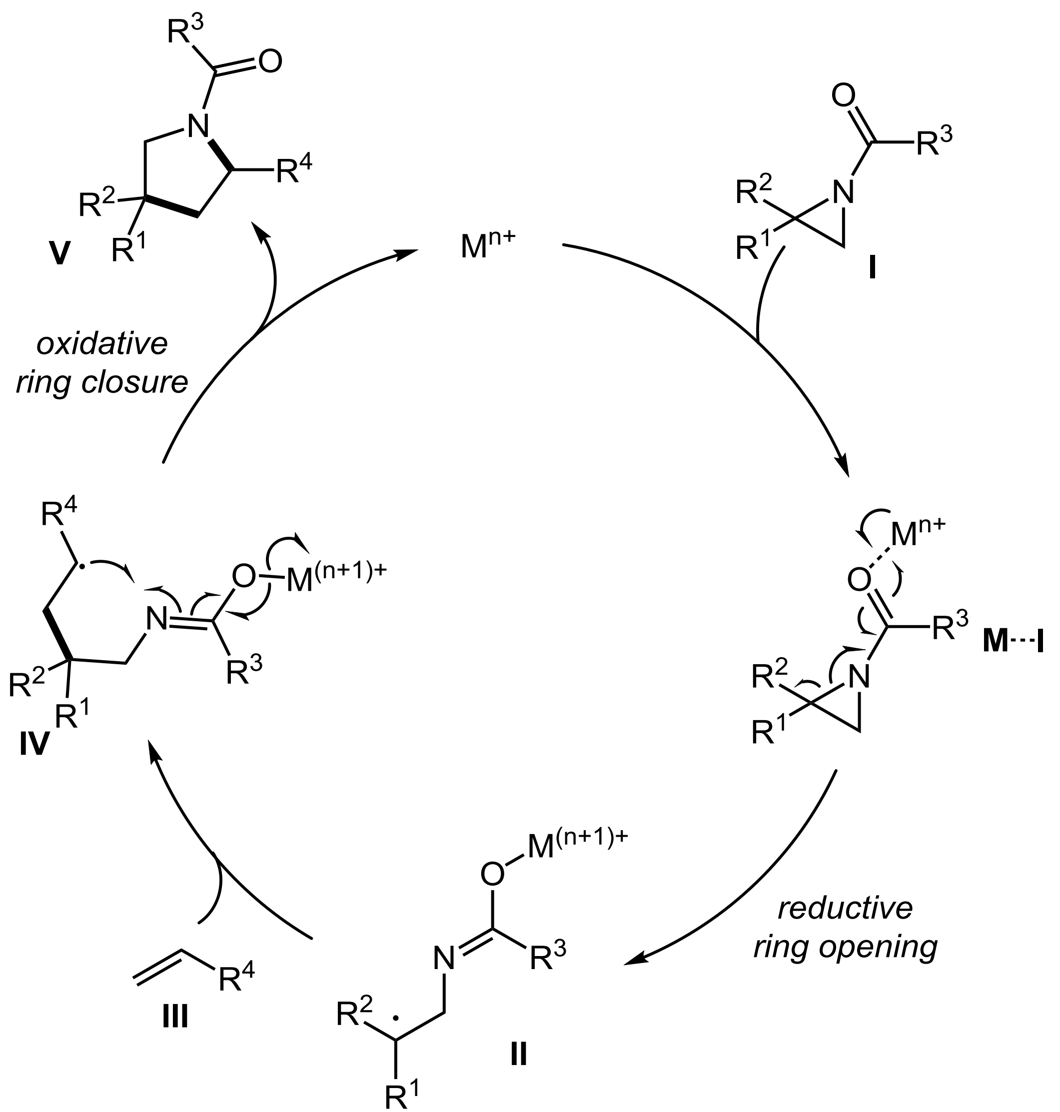


3e 93% **3f** 78% **3g** 71% **3h** 78%

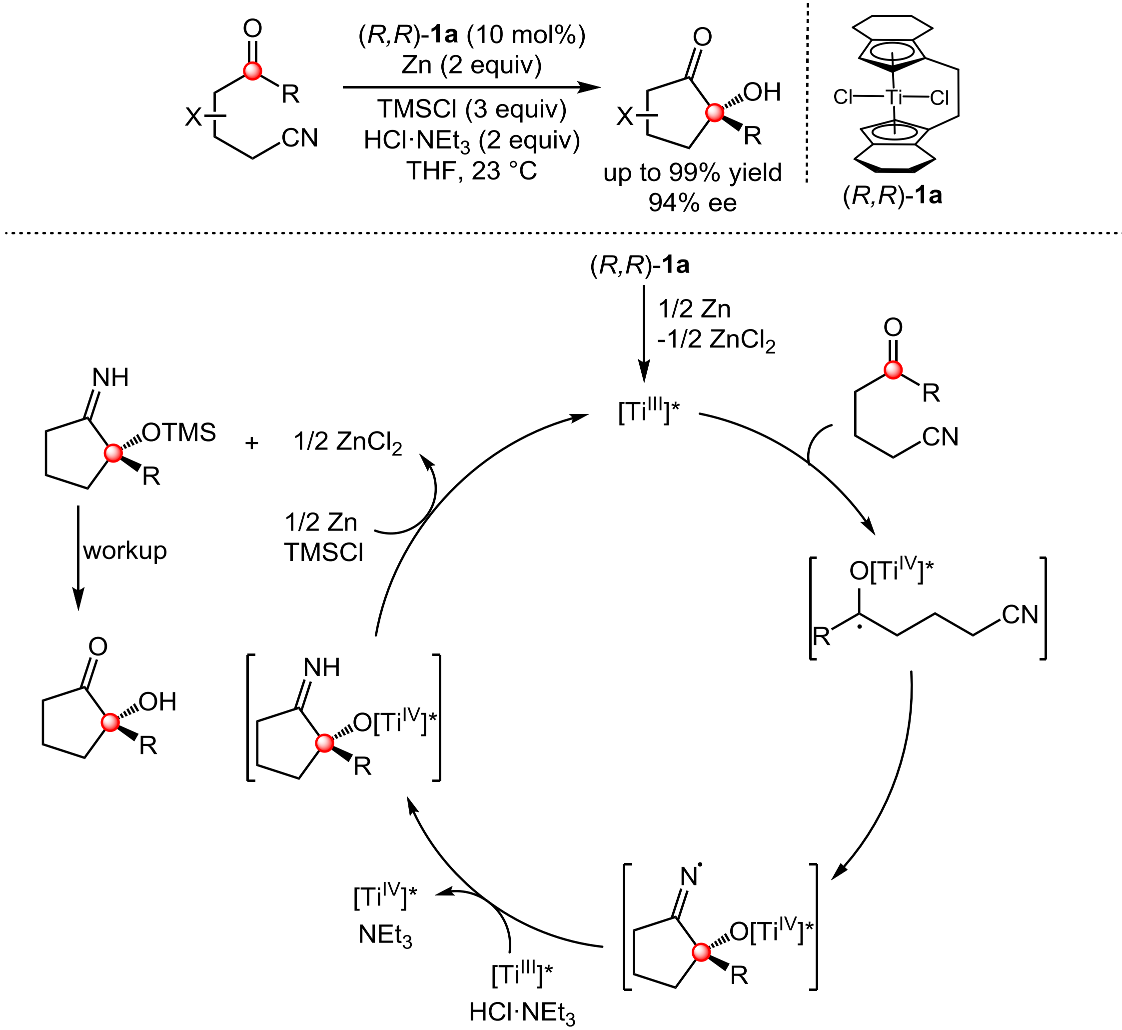


3i 69% **3j** 95% **3k** 76% **3l** 71%, dr =1:1

Plausible Reaction Mechanism

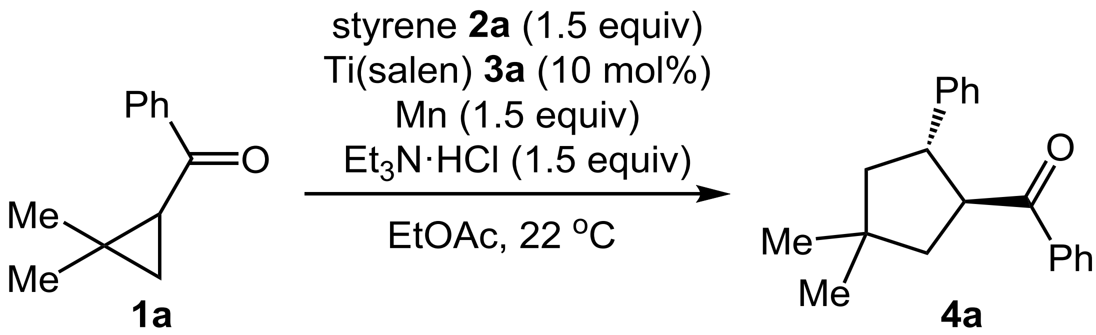


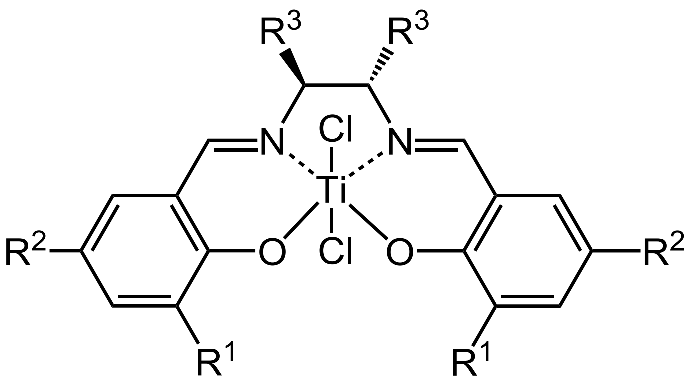
Ti(III)-Catalyzed Enantioselective Cyclization



Streuff, S. *et al. Angew. Chem. Int. Ed.* **2012**, *51*, 8661.

Ti(III)-Catalyzed Enantioselective Cyclization





3a, R^1 = 1-Ad, R^2 = Me, R^3 = Ph

98% yield, 97% ee, >19:1 dr.

3b, R^1 = R^2 = ^{t}Bu, R^3 = Ph

96% yield, 84% ee, 3:1 dr.

3c, R^1 = 1-Ad, R^2 = Me, R^3 = -$(CH_2)_4$-

94% yield, 69% ee, >14:1 dr.

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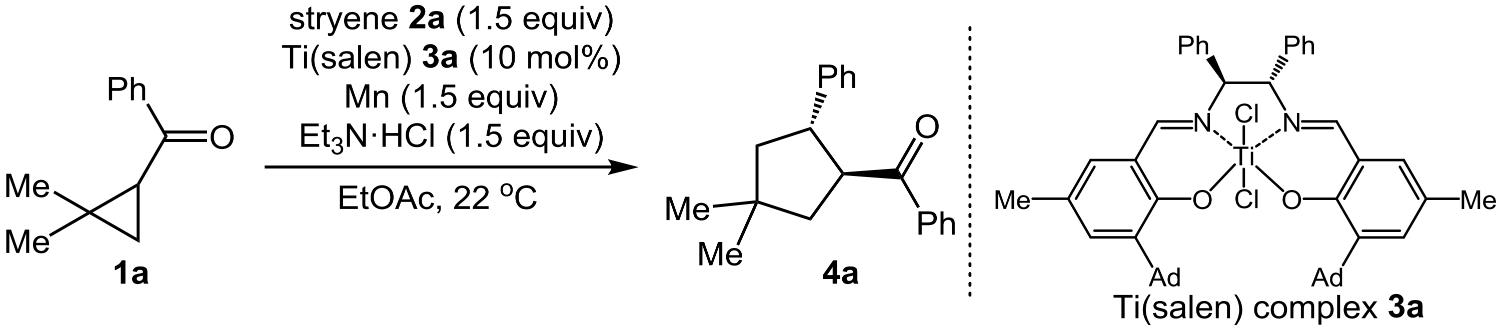
Ti(III)-Catalyzed Enantioselective Cyclization



Entry[a]	Variation from standard conditions	Yield (%)[b]	Trans/cis[b]	Ee (%)[c]
1	Zn instead of Mn	95	>19:1	90
2	50 mol% Et_3N·HCl	80	>19:1	--[d]
3	50 mol% Mn	31	>19:1	--[d]
4	THF instead of EtOAc	63	4:1	*81*
5	MeCN instead of EtOAc	34	1.4:1	73

[a] Reactions were carried out on 0.05 mmol scale. [b] Determined with ^{1}H NMR. [c] Dertermined with HPLC. [d] Not determined.

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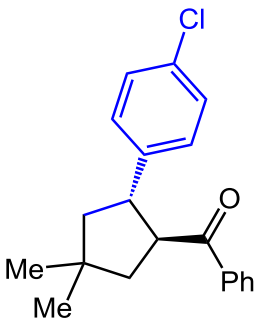
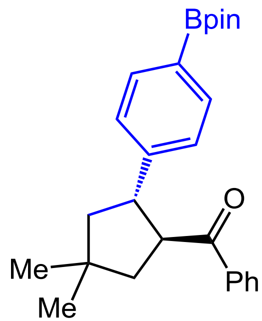
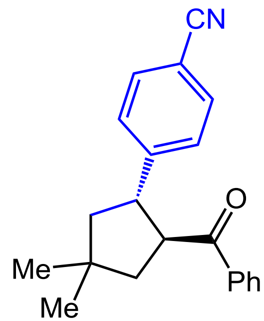
Substrate Scope



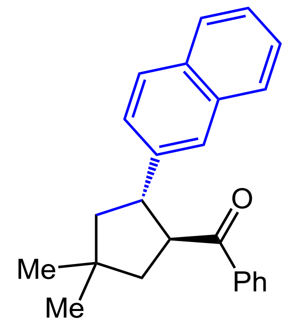
4b 12:1 dr
75%, 96% ee



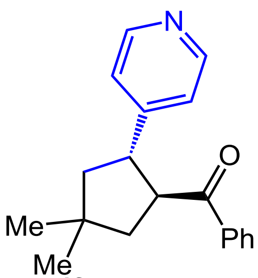
4c >19:1 dr
91%, 97% ee



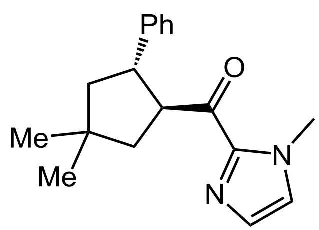
4d >19:1 dr
53%, 89% ee



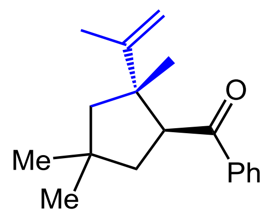
4e >19:1 dr
92%, 94% ee



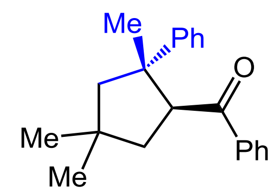
4f >19:1 dr
87%, 79% ee



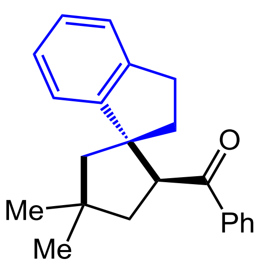
4g 6:1 dr
92%, 88% ee



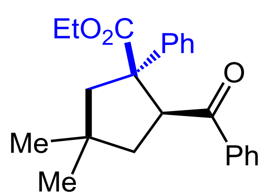
4h 4:1 dr
90%, 96% ee



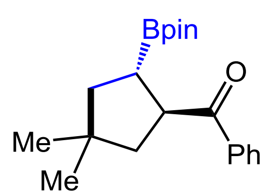
4i >19:1 dr
96%, 96% ee



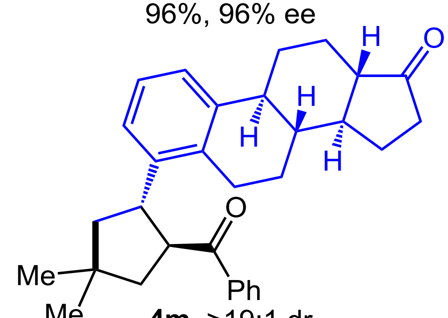
4j >19:1 dr
82%, 96% ee



4k 9:1 dr
87%, 80% ee

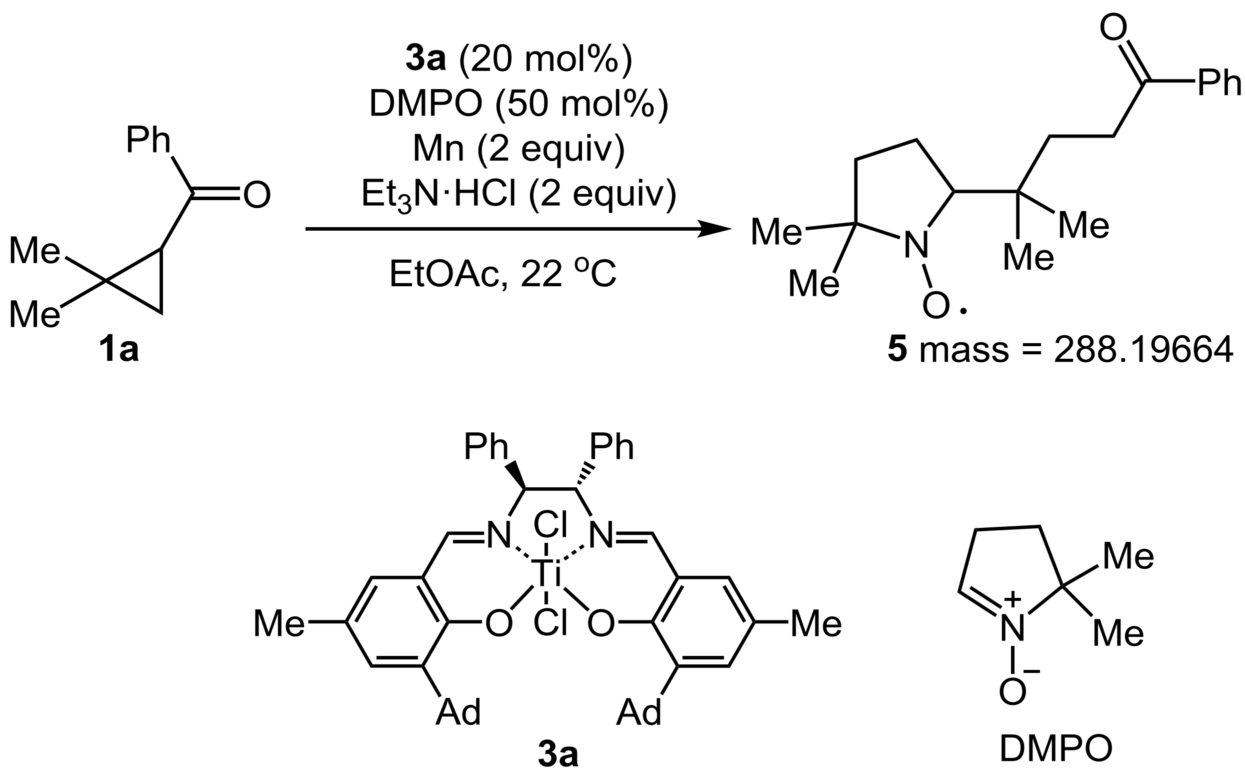


4l >19:1 dr
79%, 46% ee

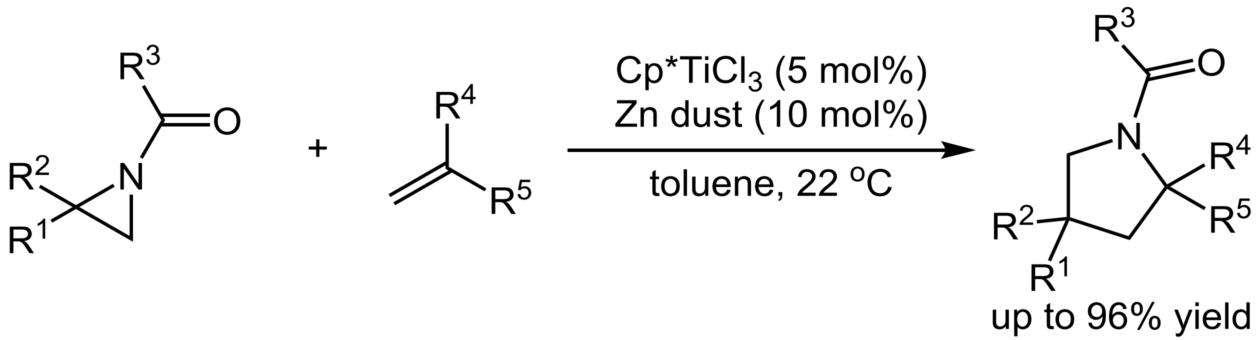


4m >19:1 dr
92%, 95% de

Spin Trapping with DMPO



Summary



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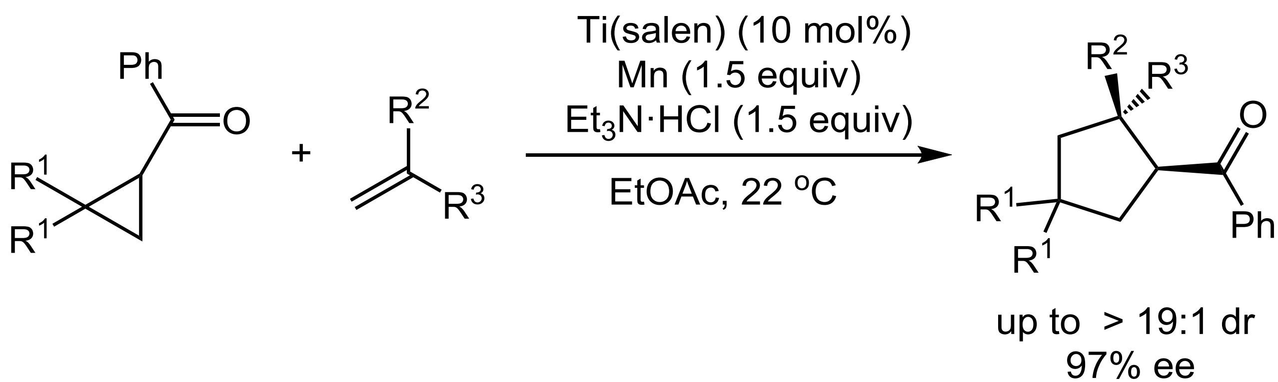

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The First Paragraph

Owing to the high reactivity and unique selectivity of organic radicals, the discovery of new reactions mediated by these open-shell intermediates continues to provide solutions to challenging synthetic problems in traditional two electron chemistry. In this context, new catalyst-controlled stereoselective reactions involving free radical intermediates remain highly desirable. Since early reports of the use of Lewis acids, transition metals, and organocatalysts, innovative catalytic strategies that regulate the absolute stereochemistry of radical addition reactions have provided powerful synthetic methods and accelerated understanding of open-shell reaction pathways.

The Last Paragraph

In summary, we developed a stereoselective formal [3+2] cycloaddition of cyclopropyl ketones and alkenes using our previous reported radical redox relay strategy. With a Ti catalyst supported by a salen ligand, the reaction yielded highly substituted cyclopentanes in generally excellent diastereo- and enantioselectivity from readily accessible starting materials. We expect this radical redox catalysis to provide solutions to other challenging synthetic problems.

Acknowledgement

Thanks for your kind attention!