Literature Report III

Ni-Catalyzed Divergent Synthesis of 2-Benzazepine Derivatives *via* Tunable Cyclization and 1,4-Acyl Transfer Triggered by Amide N-C Bond Cleavage

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Checker: Yu-Qing Bai

Ping, Y.; Li, X.; Pan, Q.; Kong, W.
Angew. *Chem*. *Int*. *Ed*. **2022**, *60*, Doi: 10.1002/anie.202201574

2022-05-09

CV of Prof. Wangqing Kong

Education:

- **2002-2006** B.S., China University of Geosciences
- **2006-2011** Ph.D., Zhejiang University, (Prof. Shengming Ma)
- **2011-2014** Postdoctor, UZH, (Prof. Cristina Nevado)
- **2014-2017** Postdoctor, EPFL, (Prof. Jieping Zhu)
- **2017-Present** Professor, Wuhan University

Research Interests:

1. Asymmetric Catalysis
2. Transition Metal-catalyzed Domino Reactions
3. Efficient Synthesis of Bioactive Natural Products and Drug Molecules

Contents

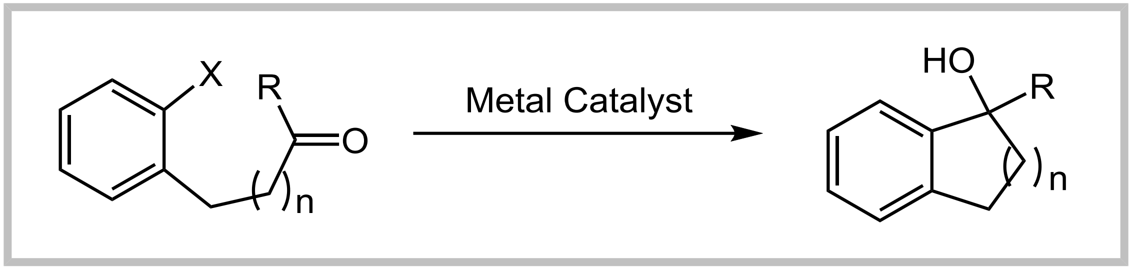
1 Introduction

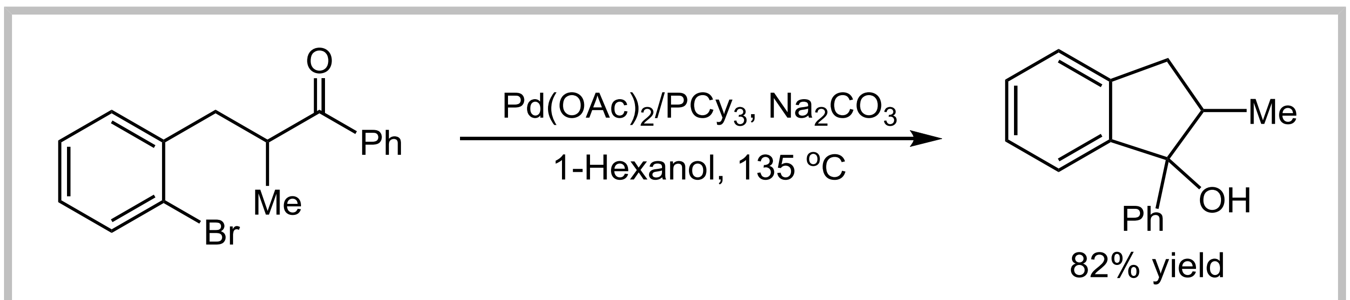
2 Ni-Catalyzed Divergent Synthesis of 2-Benzazepine Derivatives

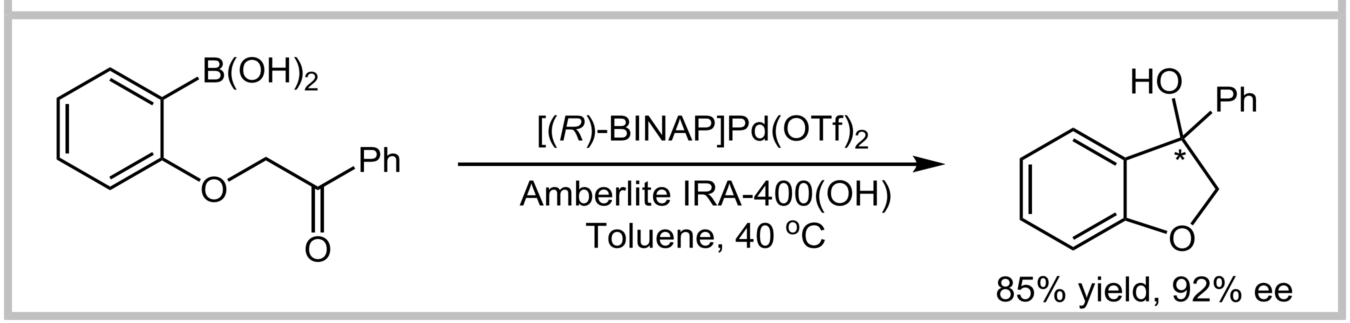
3 Summary

Introduction (Activation of Aldehydes, Ketones and Esters)

Catalytic Intramolecular Arylative Cyclization to Ketones or Aldehydes

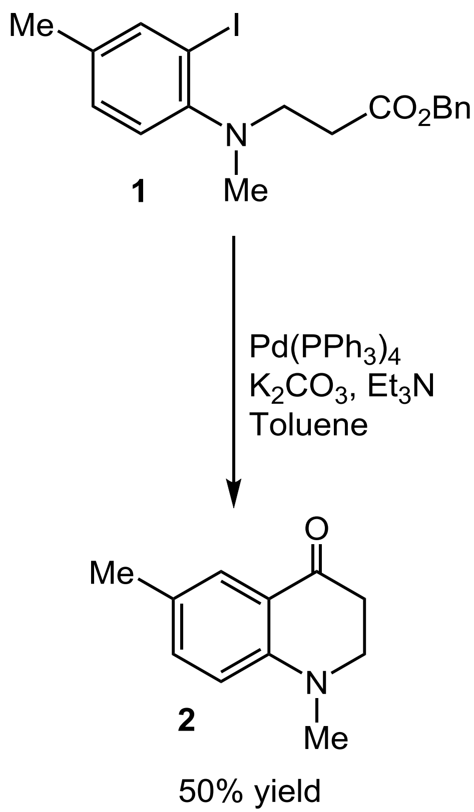


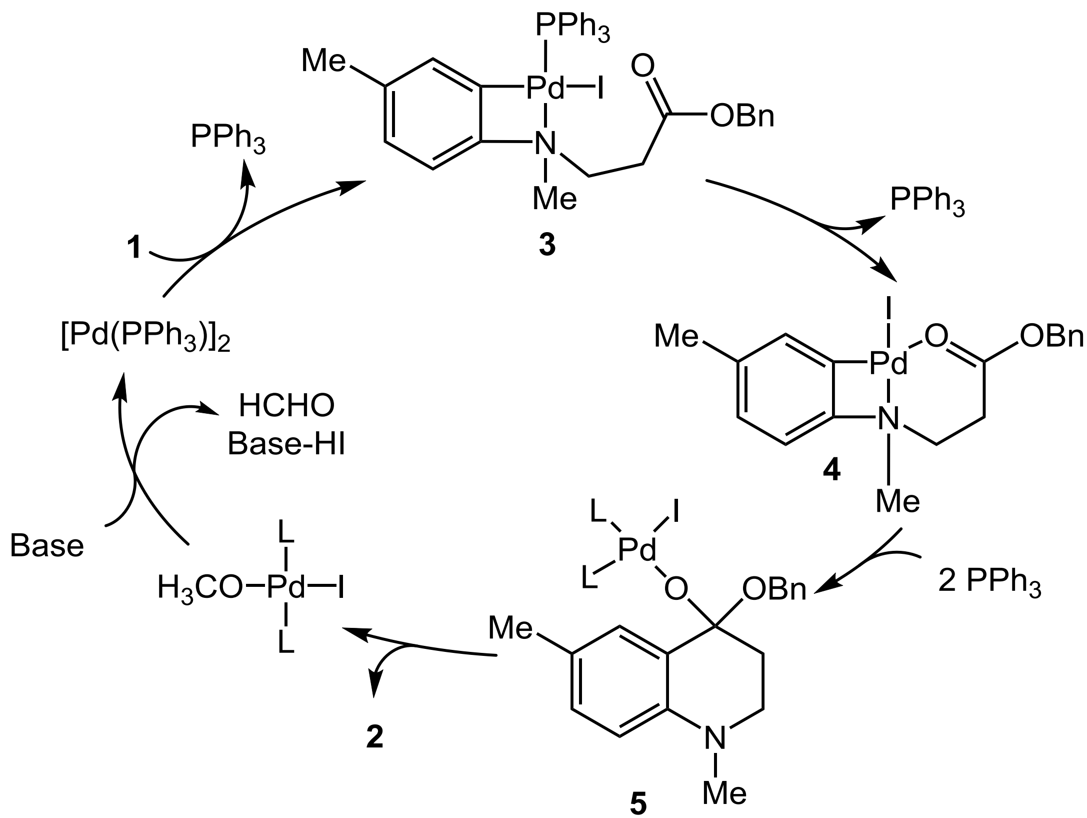




Liu, G.; Lu, X. *J. Am. Chem. Soc.* **2006**, *128*, 16504
Quan, L.-G.; Lamrani, M.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 4827

Introduction (Activation of Aldehydes, Ketones and Esters)

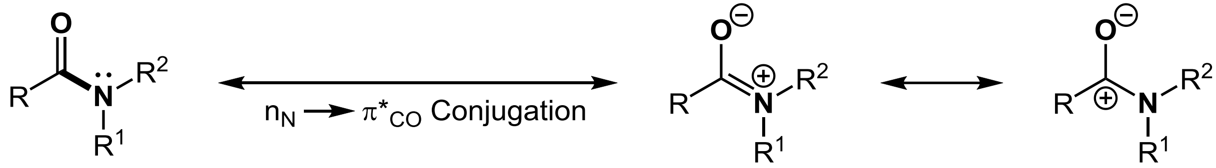




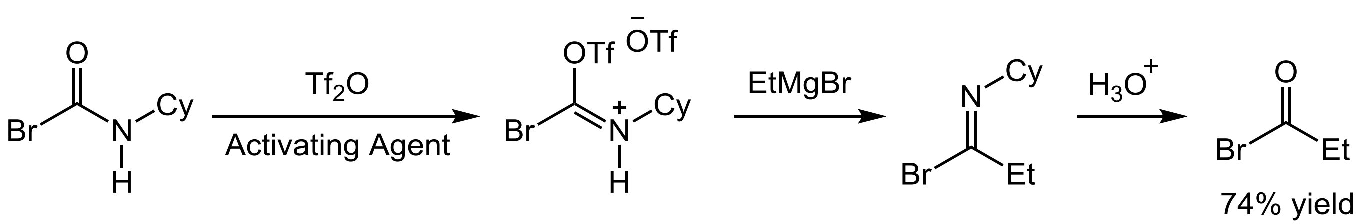
Daniel, S.; Serrano, O. *Angew*. *Chem*. *Int*. *Ed*. **2007**, *46*, 7270

Introduction (Electrophilic Preactivation of Amides)

Challenge: Amide Resonance Stabilization
(Resonance Energy of Planar Amides: 15-20 kcal/mol)



♥ Low Reactivity of Amide Carbonyl ♥ Double Bond Character of the C(O)-N Bond

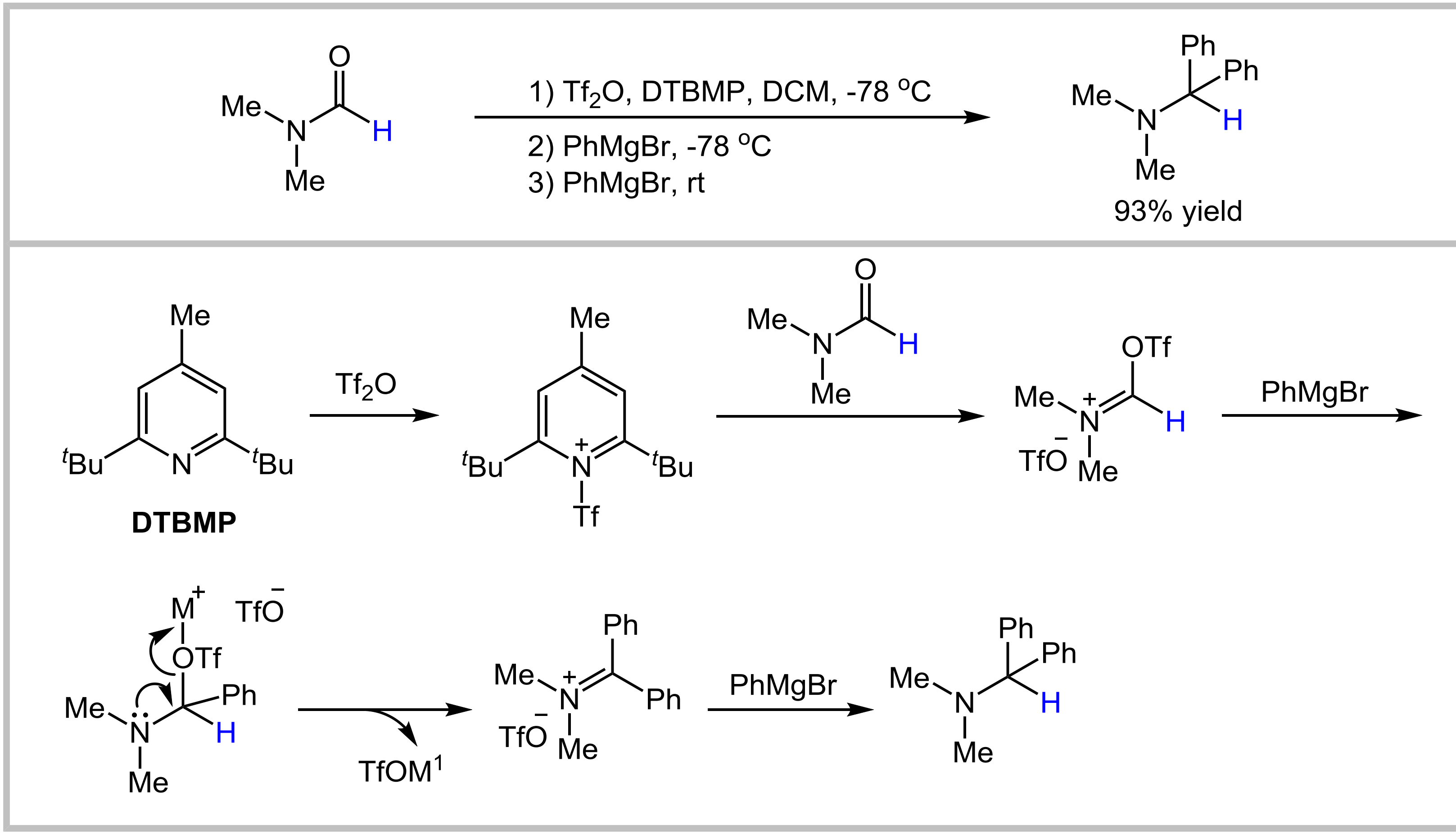


A **B** **C** **D**

Bechara, W.; Pelletier, G.; Charette, A. B. *Nat. Chem*. **2012**, *4*, 228

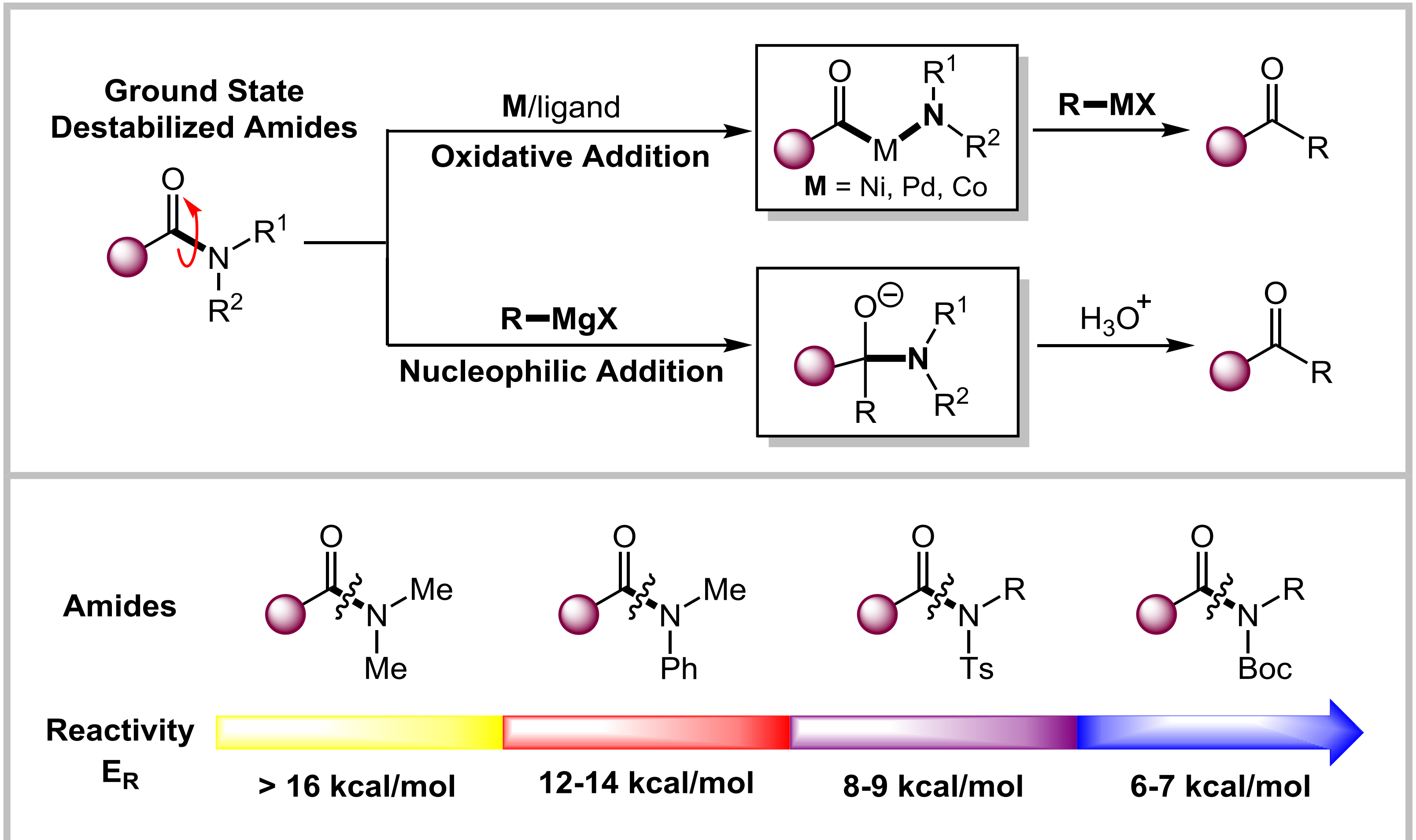
Introduction (Electrophilic Preactivation of Amides)

One-pot Transformation of Lactams/Amides into *tert*-Alkylamines with Cleavage of a C=O Bond and Formation of Two C-C Bonds



Xiao, K.; Wang, Y.; Huang, P.-Q. *Angew*. *Chem*. *Int*. *Ed*. **2010**, *49*, 3037

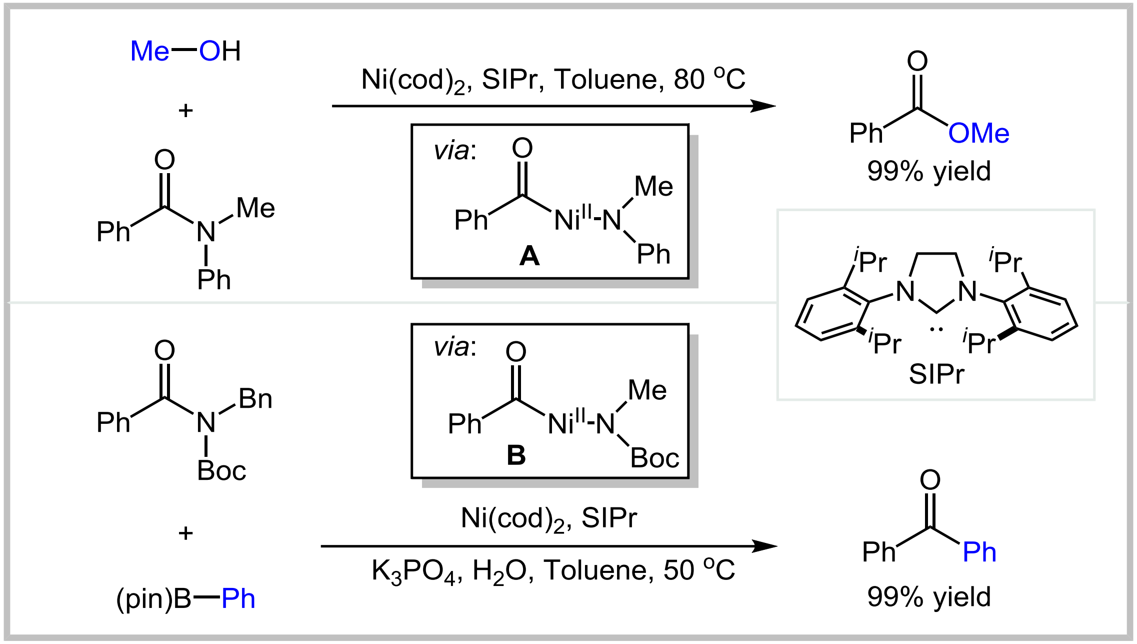
Introduction (Metal Catalyzed activation of Amides)

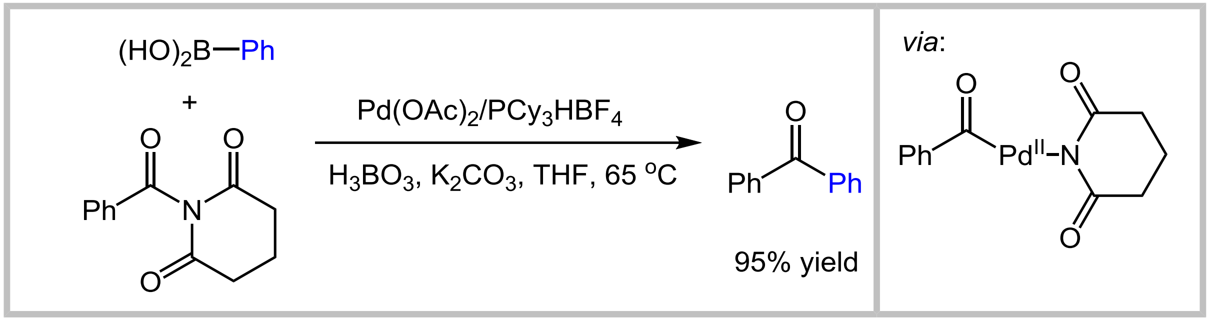


Meng, G.; Szostak, M. *Org. Lett*. **2015**, *17*, 4364

Hie, L.; Baker, E. L.; Garg, N. K. *Angew. Chem. Int. Ed*. **2016**, *55*, 15129

Introduction (Metal Catalyzed activation of Amides)



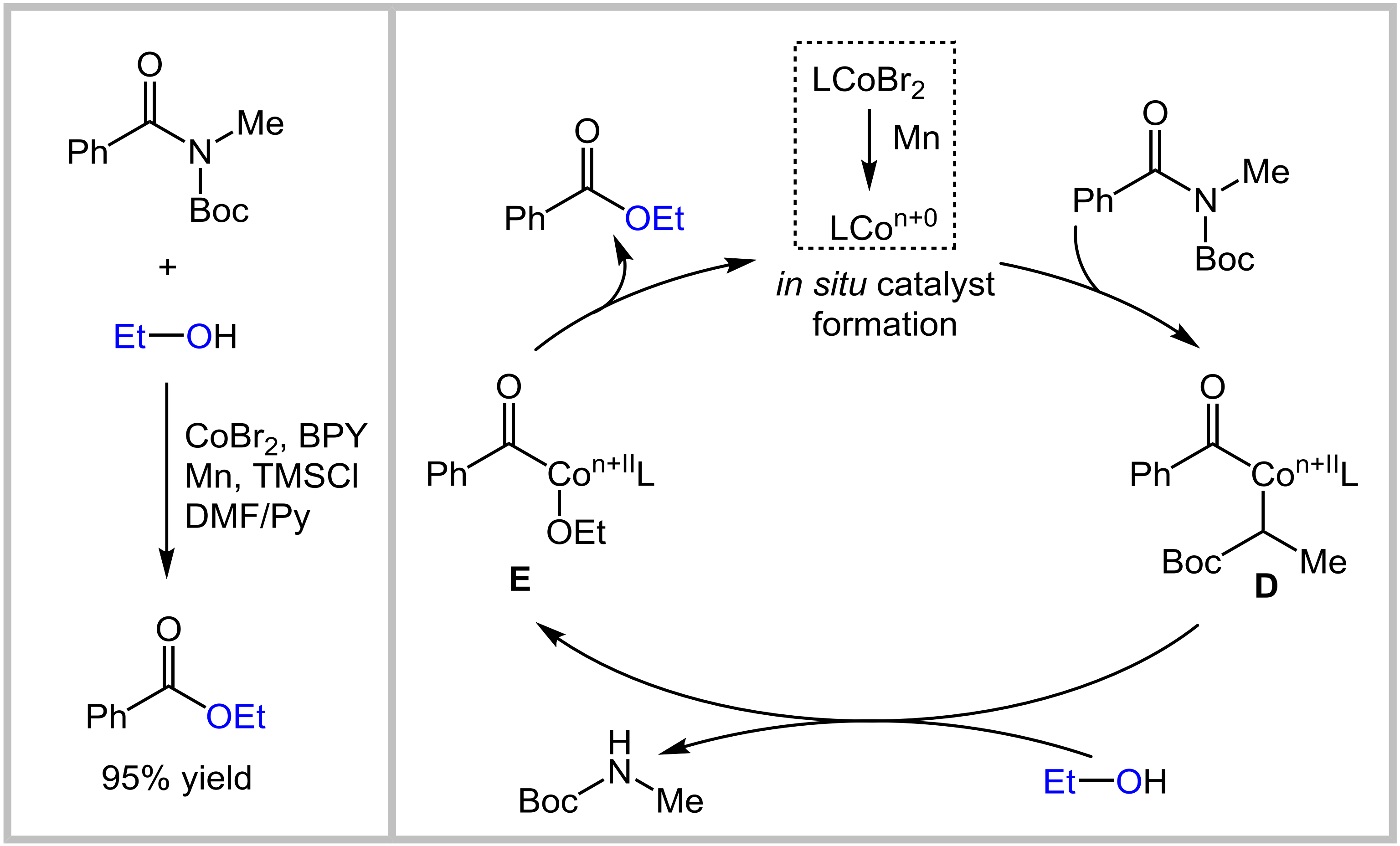


Meng, G.; Szostak, M. *Org. Lett*. **2015**, *17*, 4364

Hie, L.; Houk, K. N.; Garg, N. K. *Nature* **2015**, *524*, 79

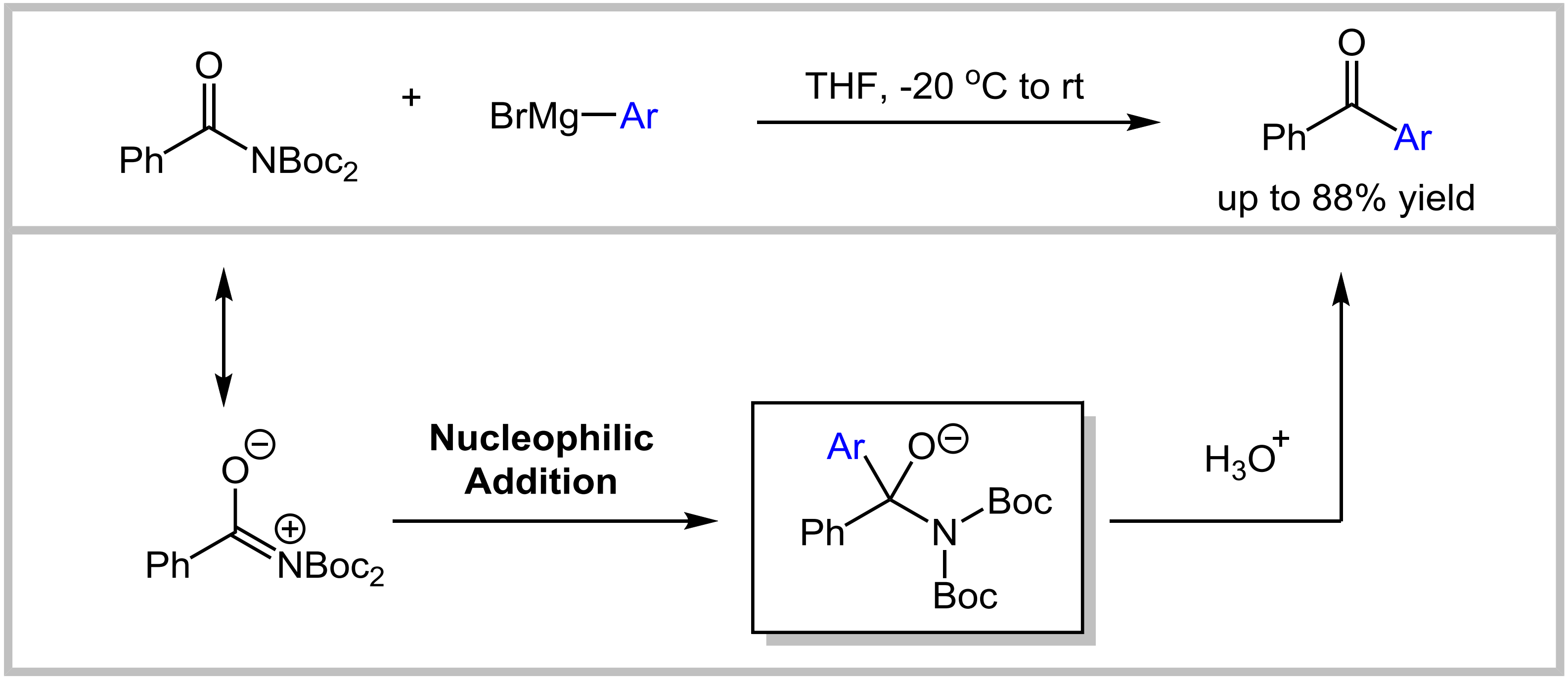
Weires, N. A.; Baker, E. L.; Garg, N. K. *Nat. Chem*. **2016**, *8*, 75

Introduction (Metal Catalyzed activation of Amides)



Yann, B.-B.; Corinne, G.; Danoun, G. *Chem*. *Eur*. *J*. **2017**, *23*, 10043

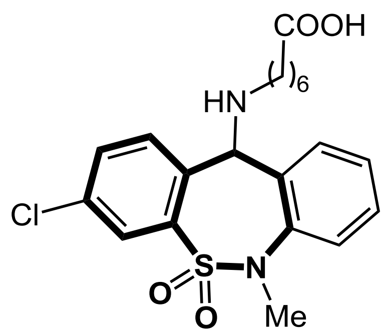
Introduction (Direct Addition of Amides)



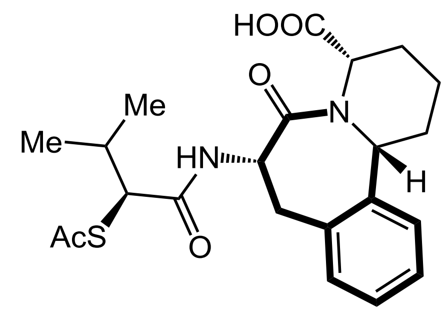
Li, G.; Szostak, M. *Chem*. *Eur*. *J*. **2020**, *26*, 611

Introduction

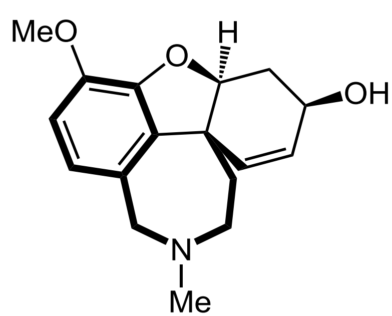
Representative Pharmaceuticals Containing 2-Benzazepine Motif



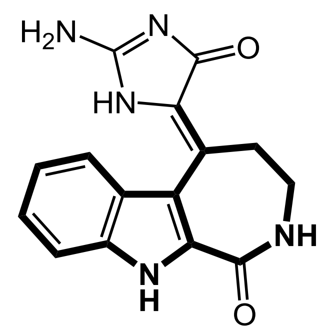
Tianeptine
Treatment of Major Depressive



Ilepatril
Treatment of Hypertension

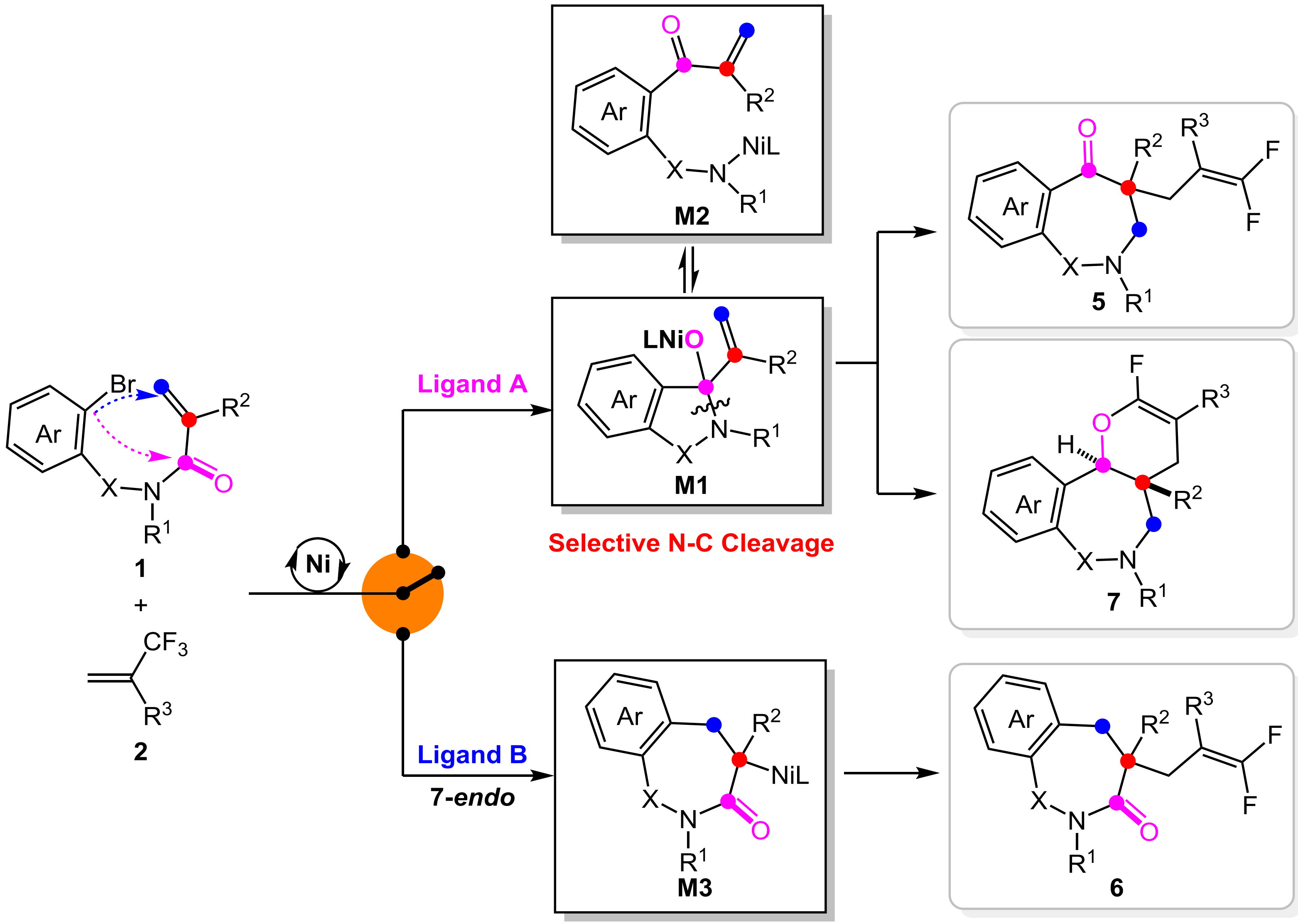


Galantamine
Treatment of Alzheimer's Disease

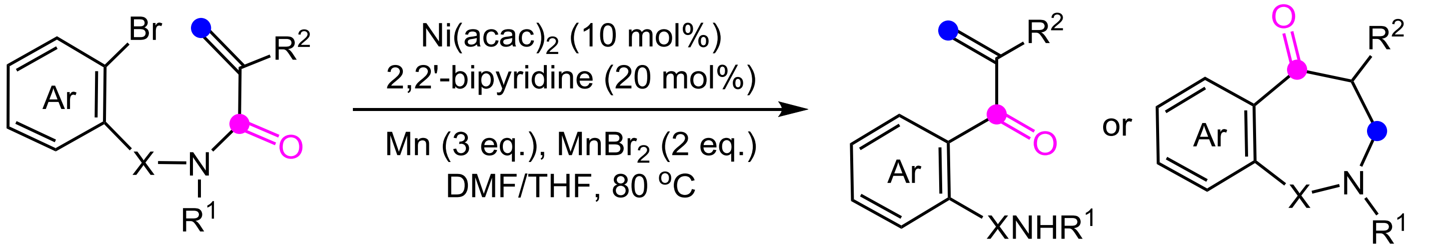


Indoloazepine
Chk2 Inhibitor (IC_{50} = 8 nM)

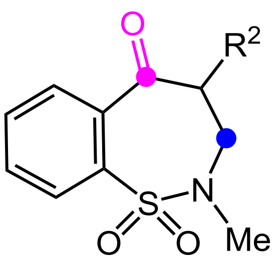
Introduction



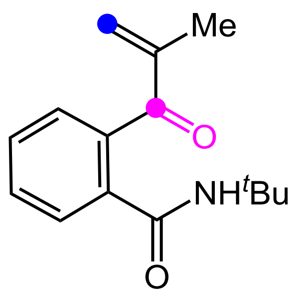
1,4-Acyl Transfer through Amide N-C Bond Cleavage



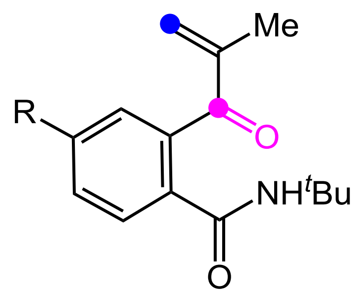
1 3 4



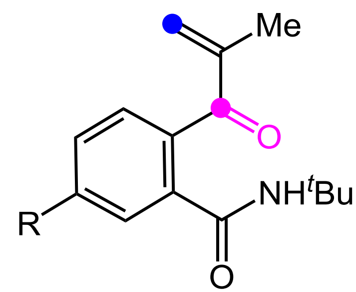
4a, 67%



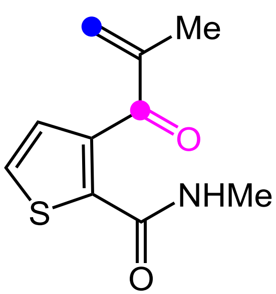
3e, 73%



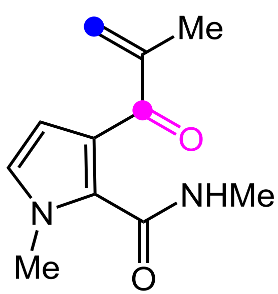
3j, R = OMe, 66%
3k, R = F, 67%



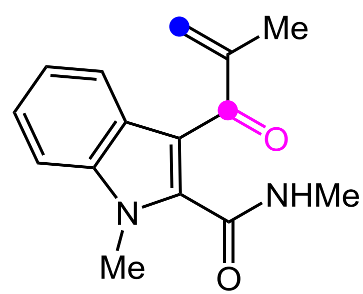
3l, R = Me, 69%
3m, R = OMe, 69%



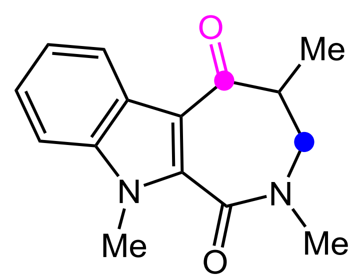
3u, 69% (40 °C)



3w, 74% (40 °C)

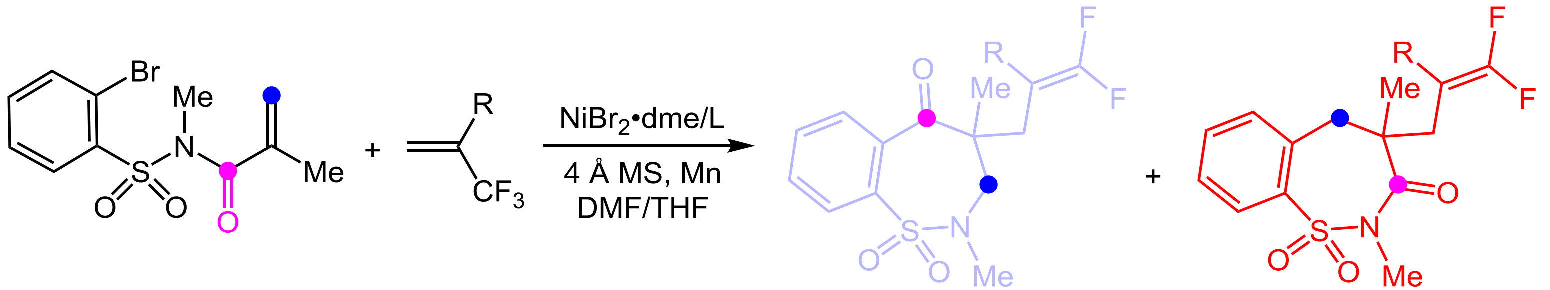


3x, 81% (25 °C)

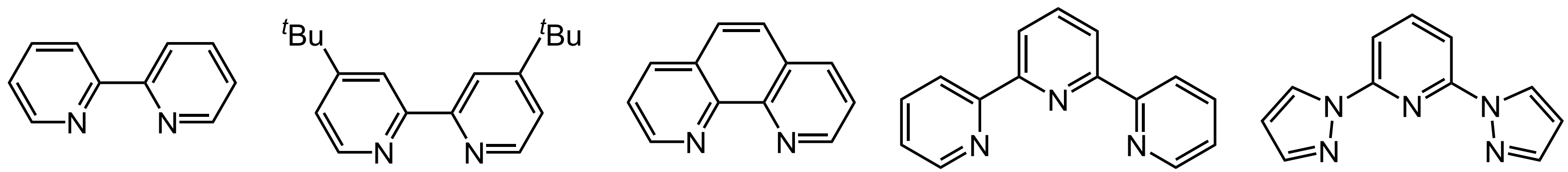


4x, 95%

Optimization of Reaction Conditions



1a 2a 5aa 6aa

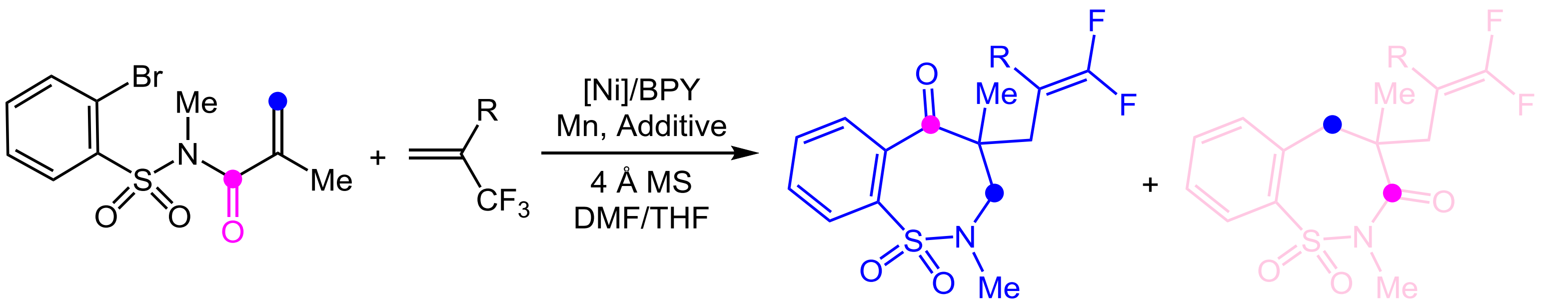


L1 L2 L3 L4 L5

Entry	L	Yield [**5aa**/%]	Yield [**6aa**/%]
1	**L1**	60	26
2	**L2**	57	24
3	**L3**	43	32
4	**L4**	**<2**	**71**
5	**L5**	8	60

1a (0.1 mmol), **2a** (0.2 mmol), $NiBr_2$·dme (0.01 mmol), **L** (0.02 mmol), Mn powder (0.3 mmol), 4 Å MS (20 mg), DMF/THF = 1/1 (0.05 M) at 60 ^oC.

Optimization of Reaction Conditions



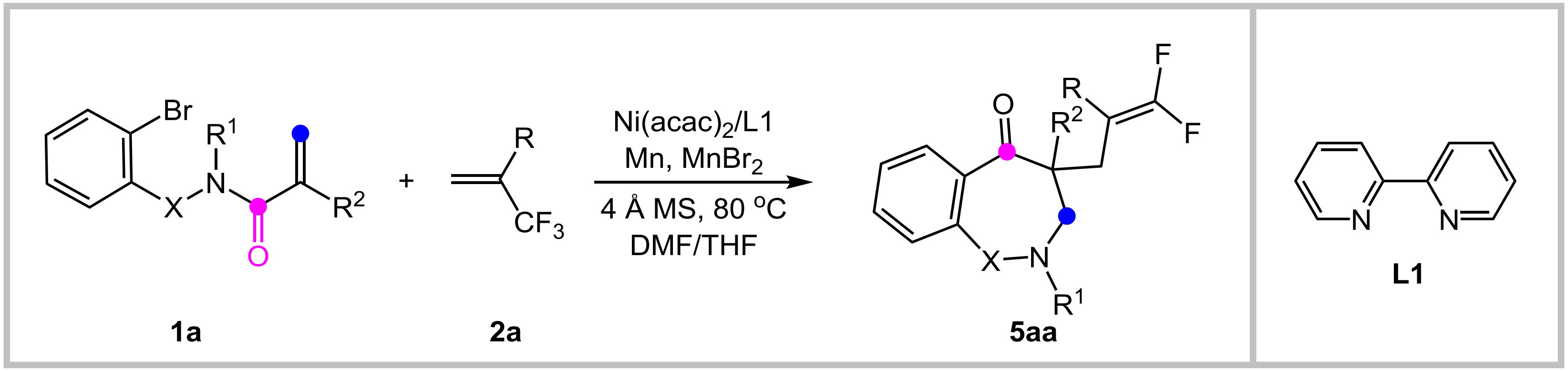
1a + **2a** → **5aa** + **6aa**

Entry	[Ni]	T [°C]	Additive	Yield [**5aa**/%]	Yield [**6aa**/%]
6	$Ni(acac)_2$	60	-	53	18
7	$Ni(OTf)_2$	60	-	43	30
8	$Ni(OAc)_2$	60	-	46	32
9[a]	$Ni(acac)_2$	60	-	68	17
10[a]	$Ni(acac)_2$	60	KI	57	12
11[a]	$Ni(acac)_2$	60	$ZnBr_2$	12	37
12[a]	**$Ni(acac)_2$**	**40**	**$MnBr_2$**	**78**	**<2**
13	-	60	$MnBr_2$	0	0
14[b]	$Ni(acac)_2$	60	$MnBr_2$	0	0

1a (0.1 mmol), **2a** (0.2 mmol), [Ni] (0.01 mmol), **L** (0.02 mmol), Mn (0.3 mmol), Additive (0.2 mmol), 4 Å MS (20 mg), DMF/THF = 1/1 (0.05 M). [a] DMF/THF = 1/1 (0.025 M). [b] Without Mn.

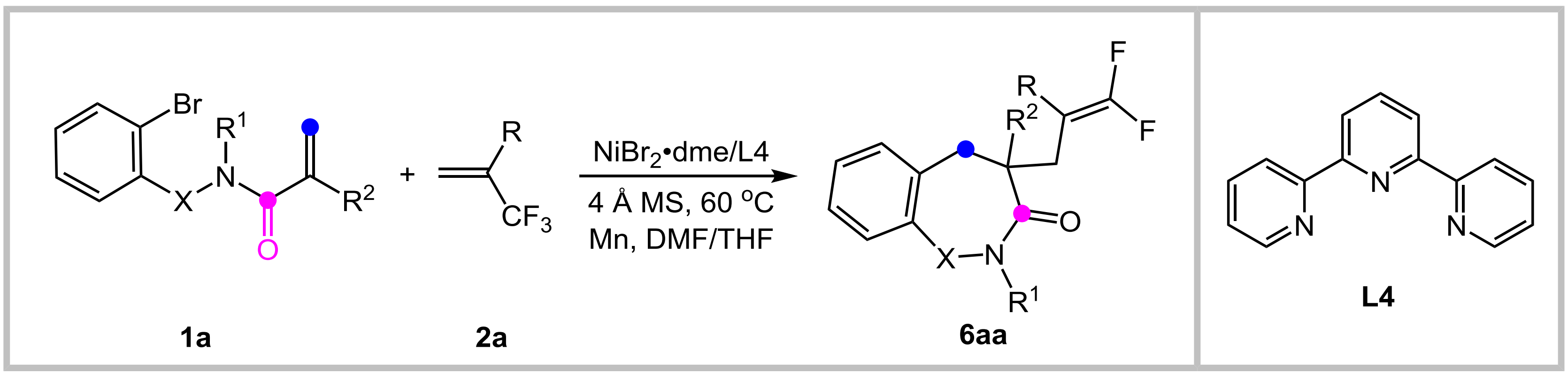
Optimal Reaction Conditions

A: The Pattern of 1,4-Acyl Transfer /Cross-coupling



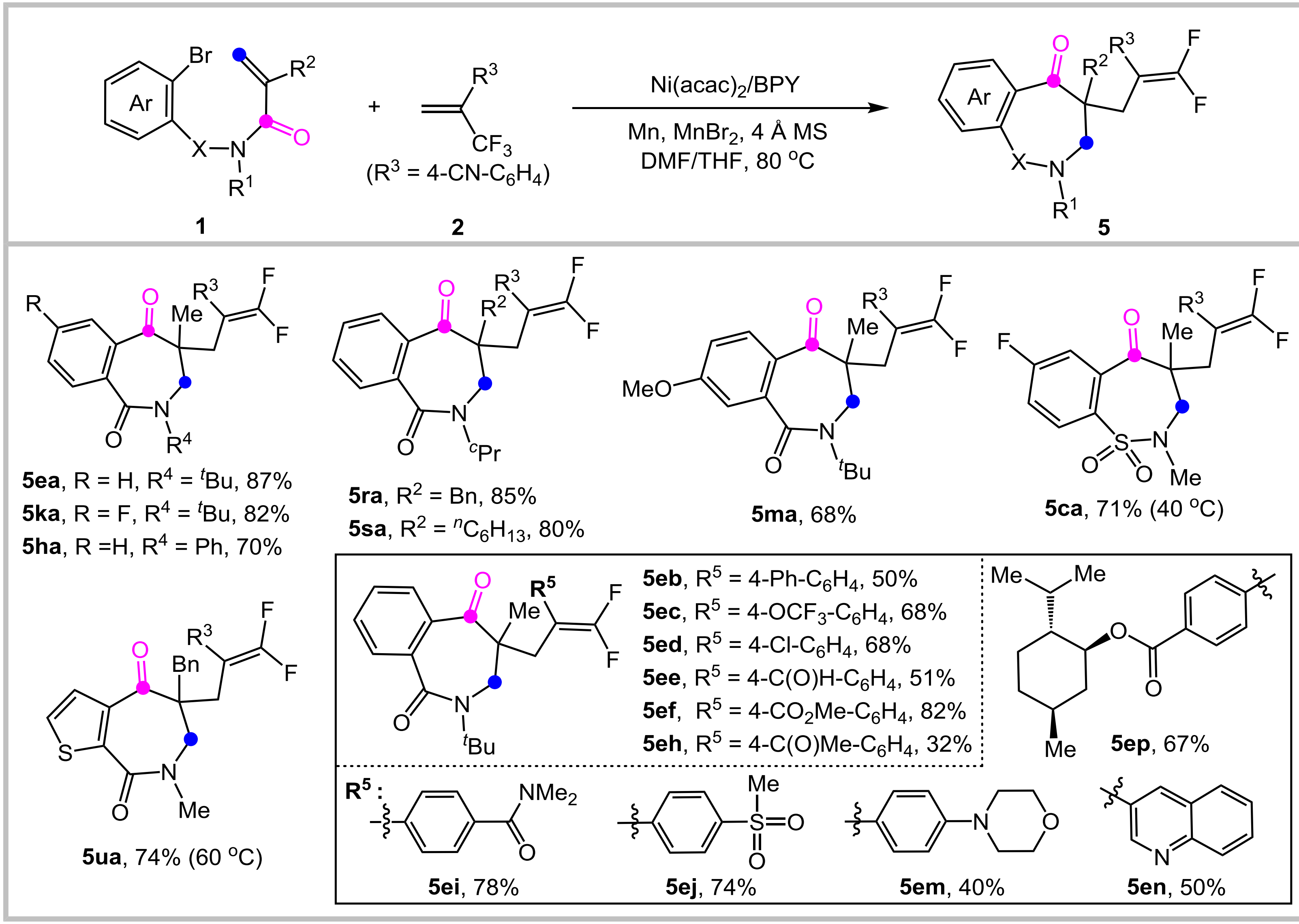
Conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), Ni(acac)$_2$ (0.01 mmol), L1 (0.02 mmol), Mn (0.3 mmol), MnBr$_2$ (0.2 mmol), 4Å MS (20 mg), DMF/THF = 1/1 at 80 ^{o}C.

B: The Pattern of 7-*endo* Cyclization/Cross-coupling

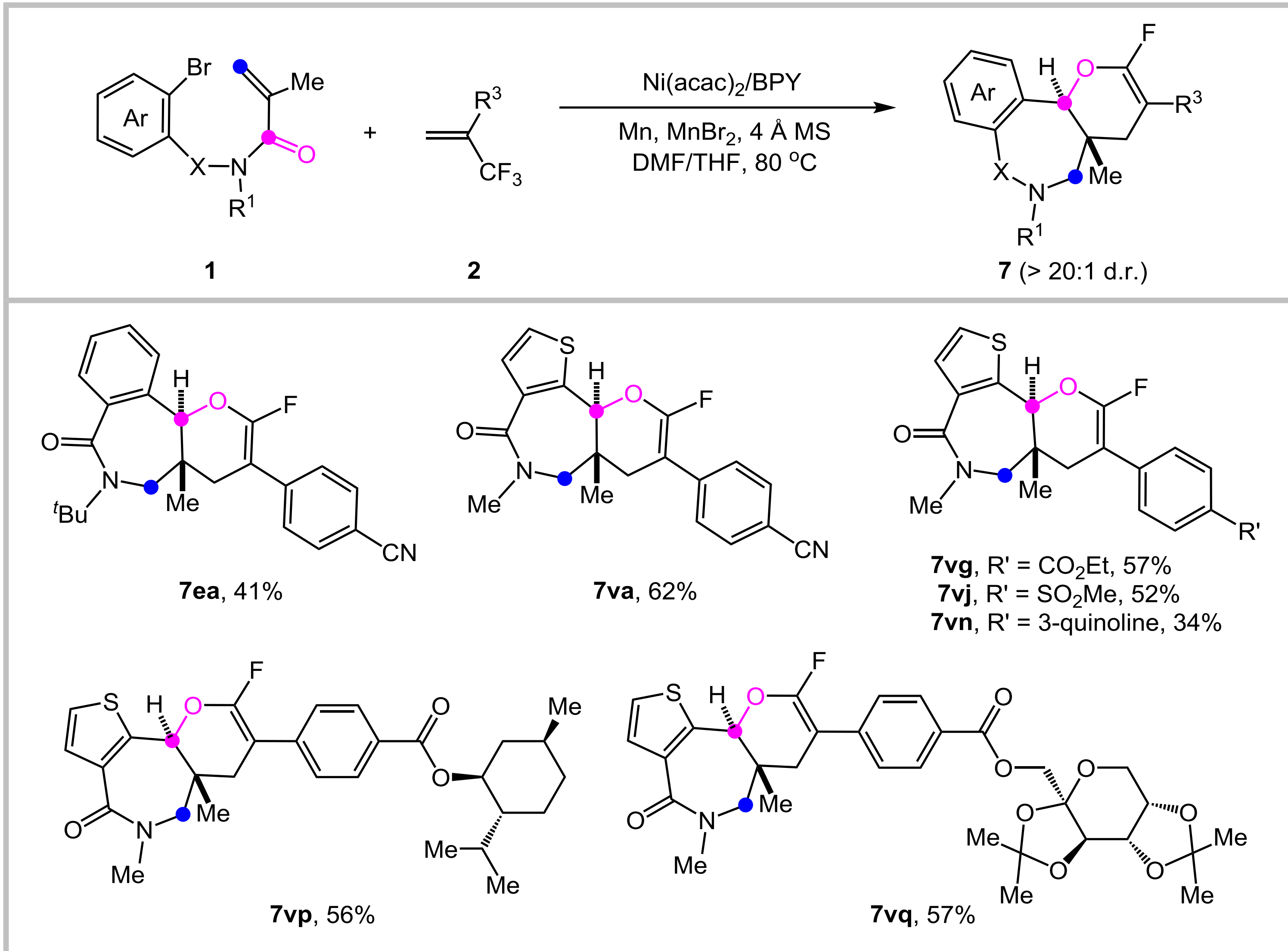


Conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), NiBr$_2$·dme (0.01 mmol), L4 (0.02 mmol), Mn (0.3 mmol), 4 Å MS (20 mg), DMF/THF = 1/1 at 60 ^{o}C.

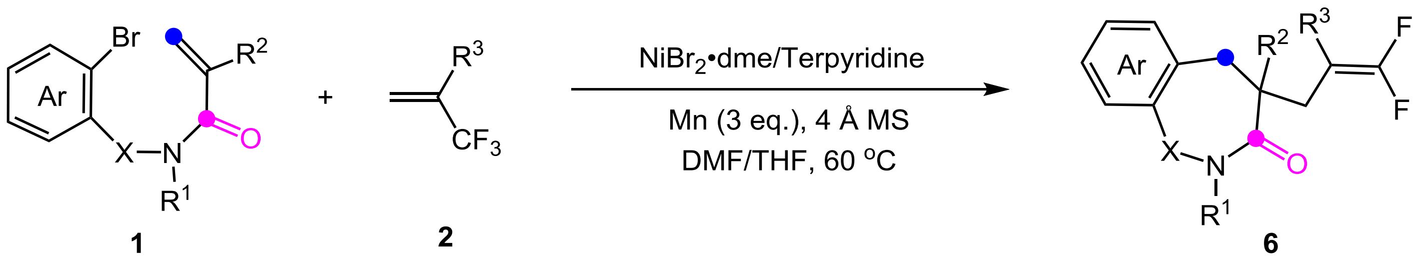
Substrate Scope (A: 1,4-Acyl Transfer Pattern)

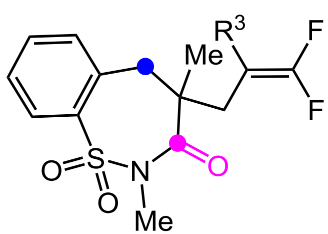


Substrate Scope (A: 1,4-Acyl Transfer Pattern)



Substrate Scope (B: 7-*endo* Cyclization Pattern)





6aa, R^3 = 4-CN-C_6H_4, 71%

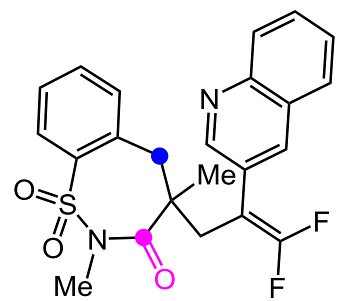
6ac, R^3 = 4-OCF_3-C_6H_4, 41%

6ad, R^3 = 4-Cl-C_6H_4, 48%

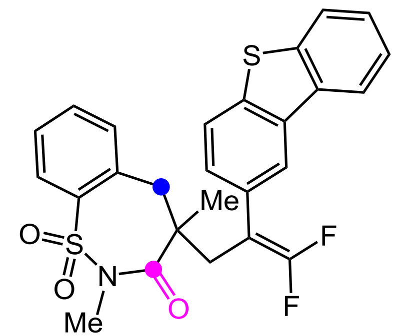
6ag, R^3 = 4-CO_2Et-C_6H_4, 66%

6ah, R^3 = 4-C(O)Me-C_6H_4, 61%

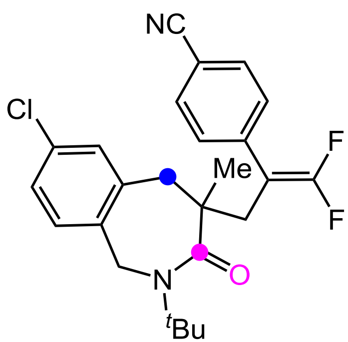
6aj, R^3 = 4-SO_2Me-C_6H_4, 73%



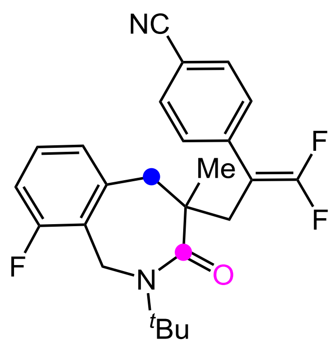
6an, 69%



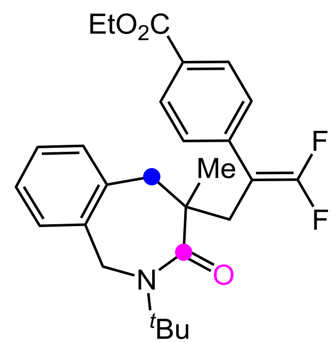
6ao, 62%



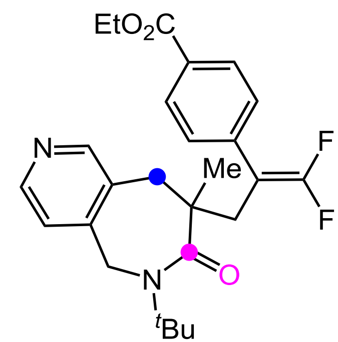
6aba, 63%



6aca, 63%

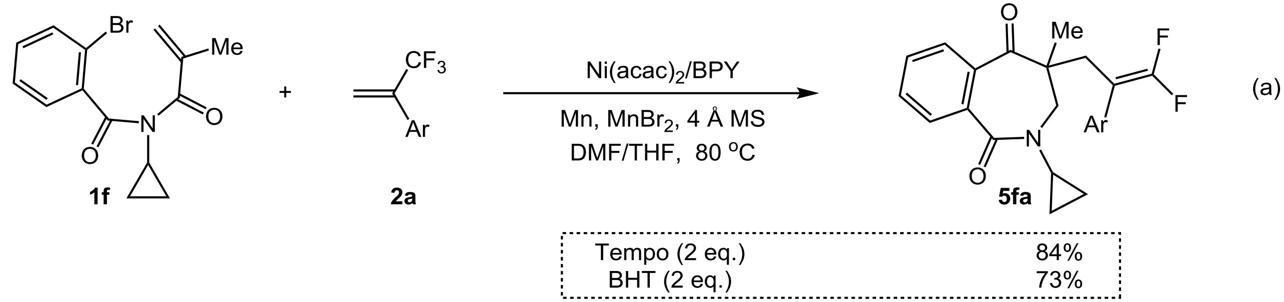


6aeg, 83%

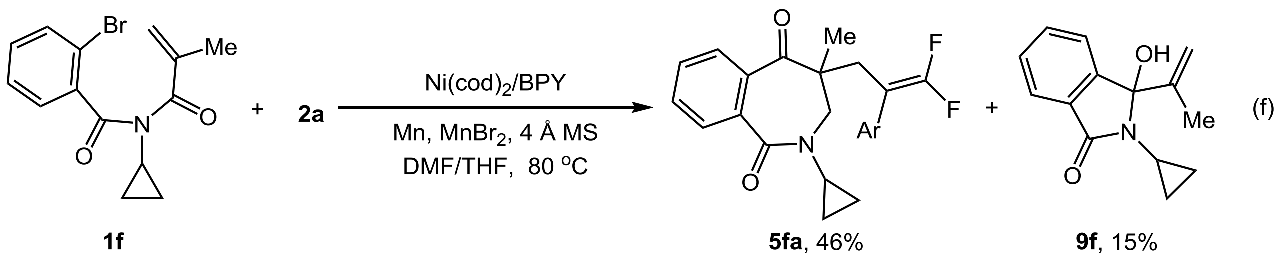


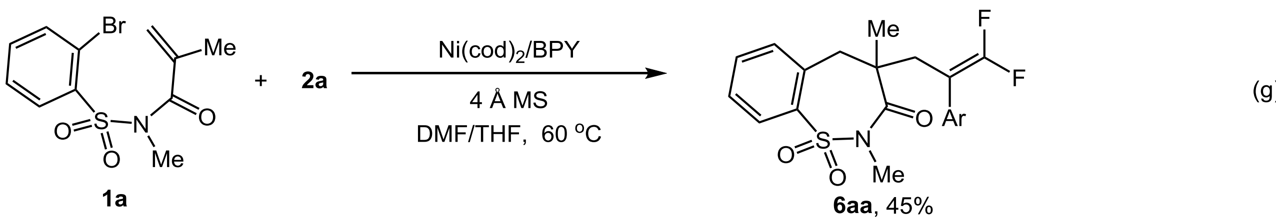
6adg, 20%

Mechanistic Experiments



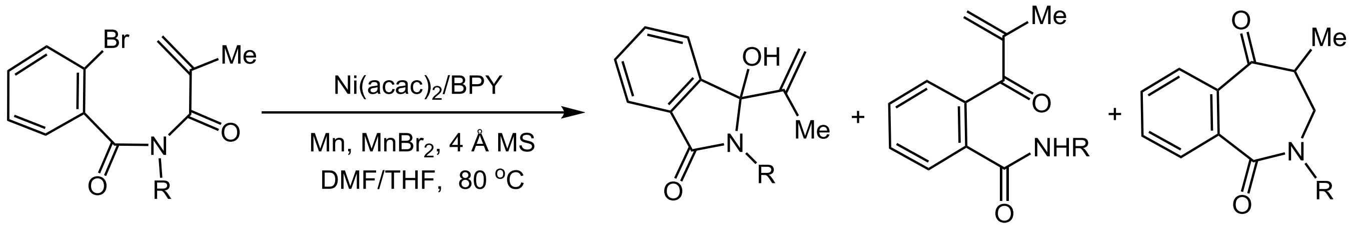
➢ No Free Radical Mechanism





➢ Possible through Ni^0/Ni^{II} Catalytic Cycle

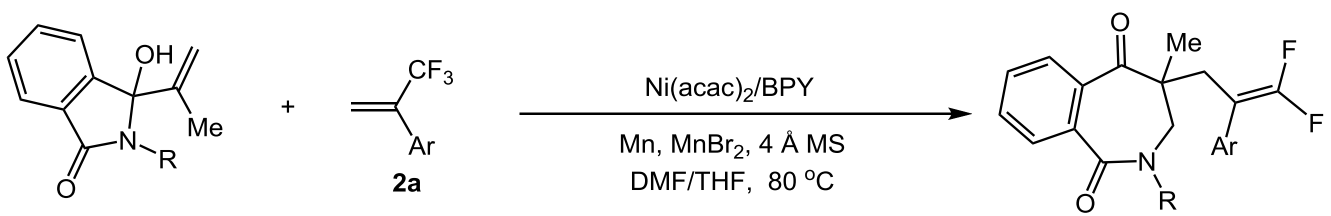
Mechanistic Experiments



(b)

1f, R = ^{c}Pr — **9f**, 29% — **3f**, 0% — **4f**, 30%

1af, R = Me — **9af**, 87% — **3af**, 0% — **4af**, 0%



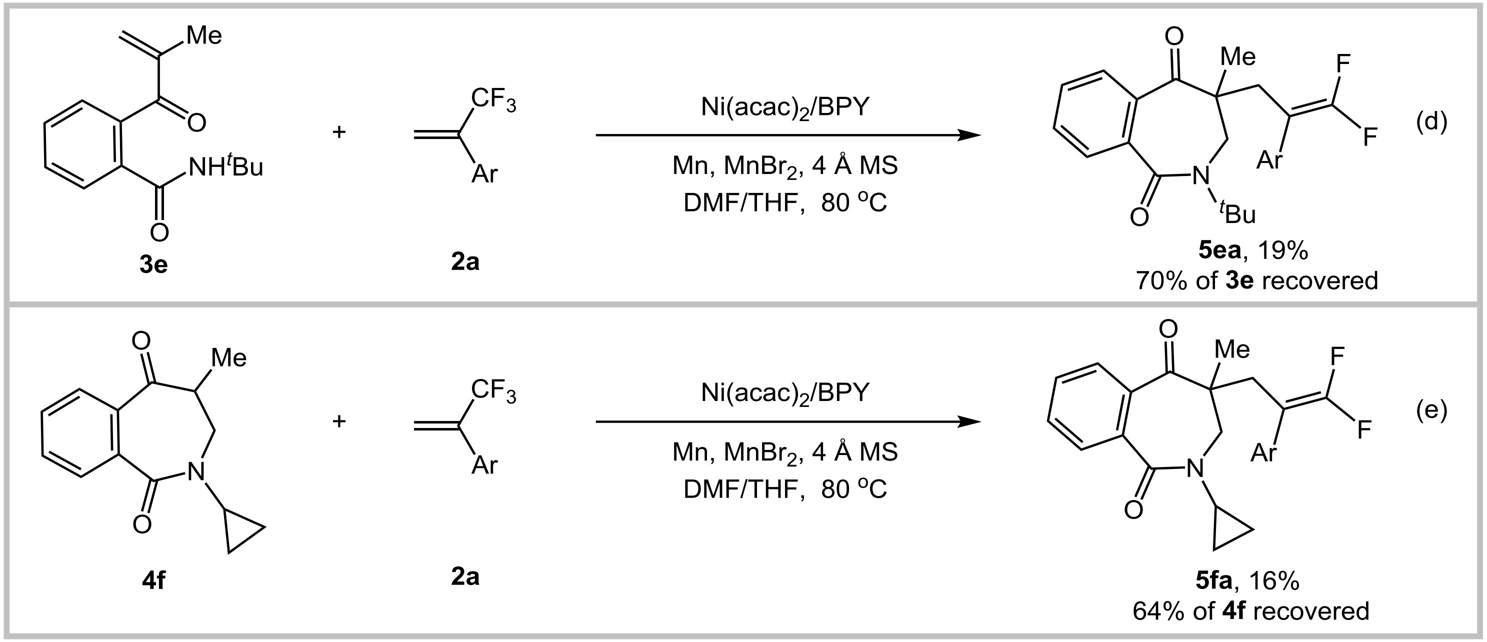
(c)

9f, R = ^{c}Pr — **5fa**, 32%

9af, R = Me — **5afa**, 0%

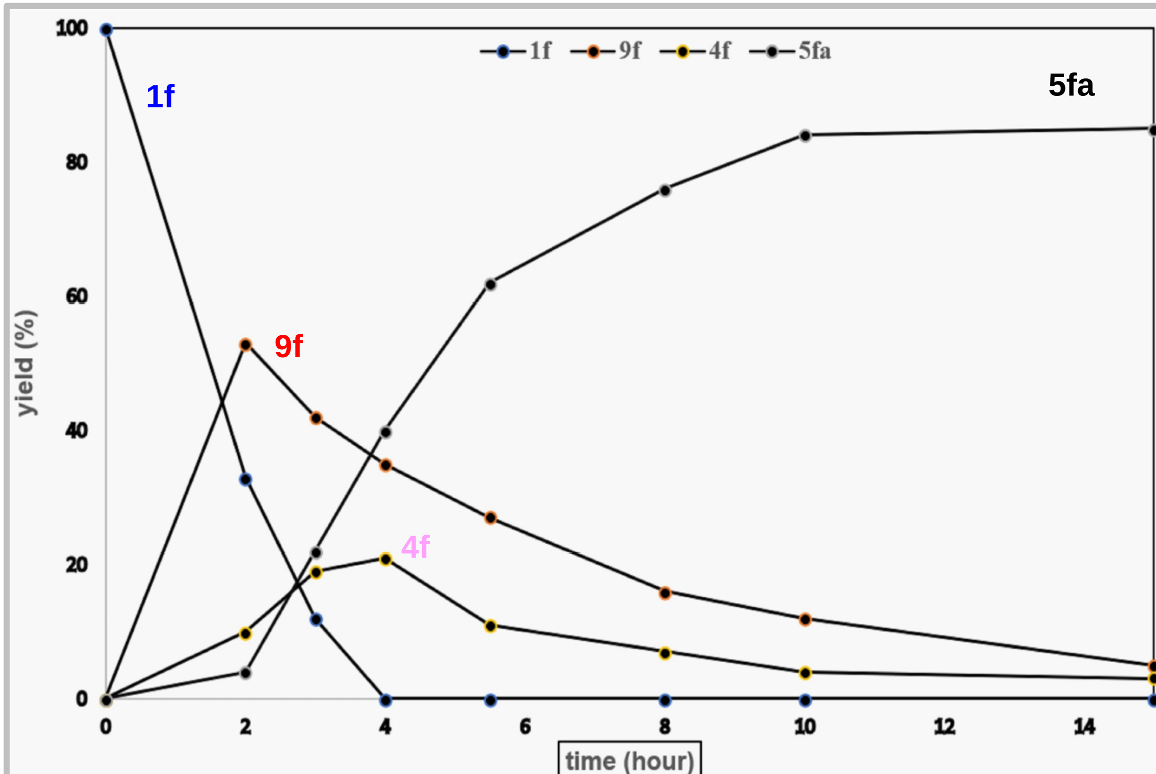
- Cyclic Allylic Alcohol **9f** is One of the Key Intermediates
- Leaving-group of Amides Have a Great Effect on the Reactivity
- Steric Hindrance of the Substituents on the Acrylamide Nitrogen Contributes to the Ring-Opening Process

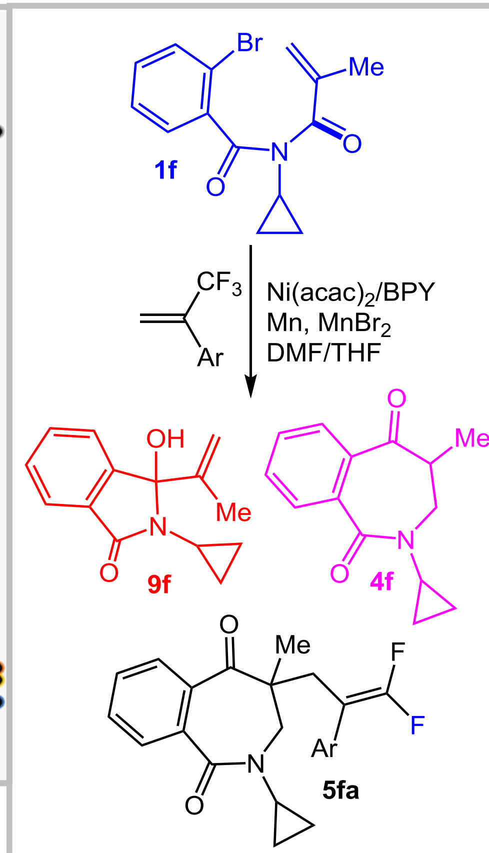
Mechanistic Experiments



- 1,4-Acyl Transfer Ketone Product **3e** is Key Intermediate
- 2-Benzazepin-5-one Product **4f** is Key Intermediate

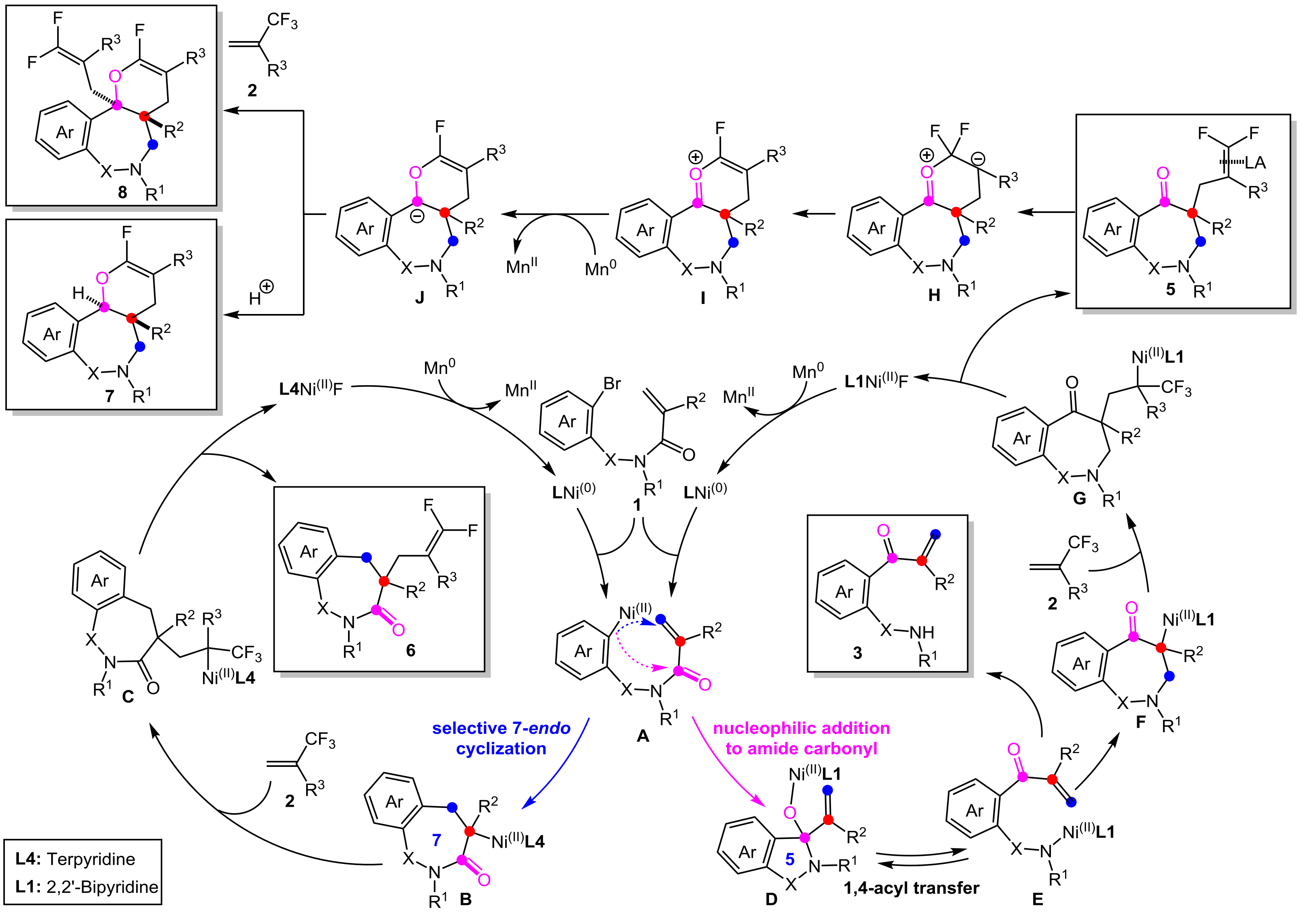
Kinetic Profile of The Reaction of 1f and 2a





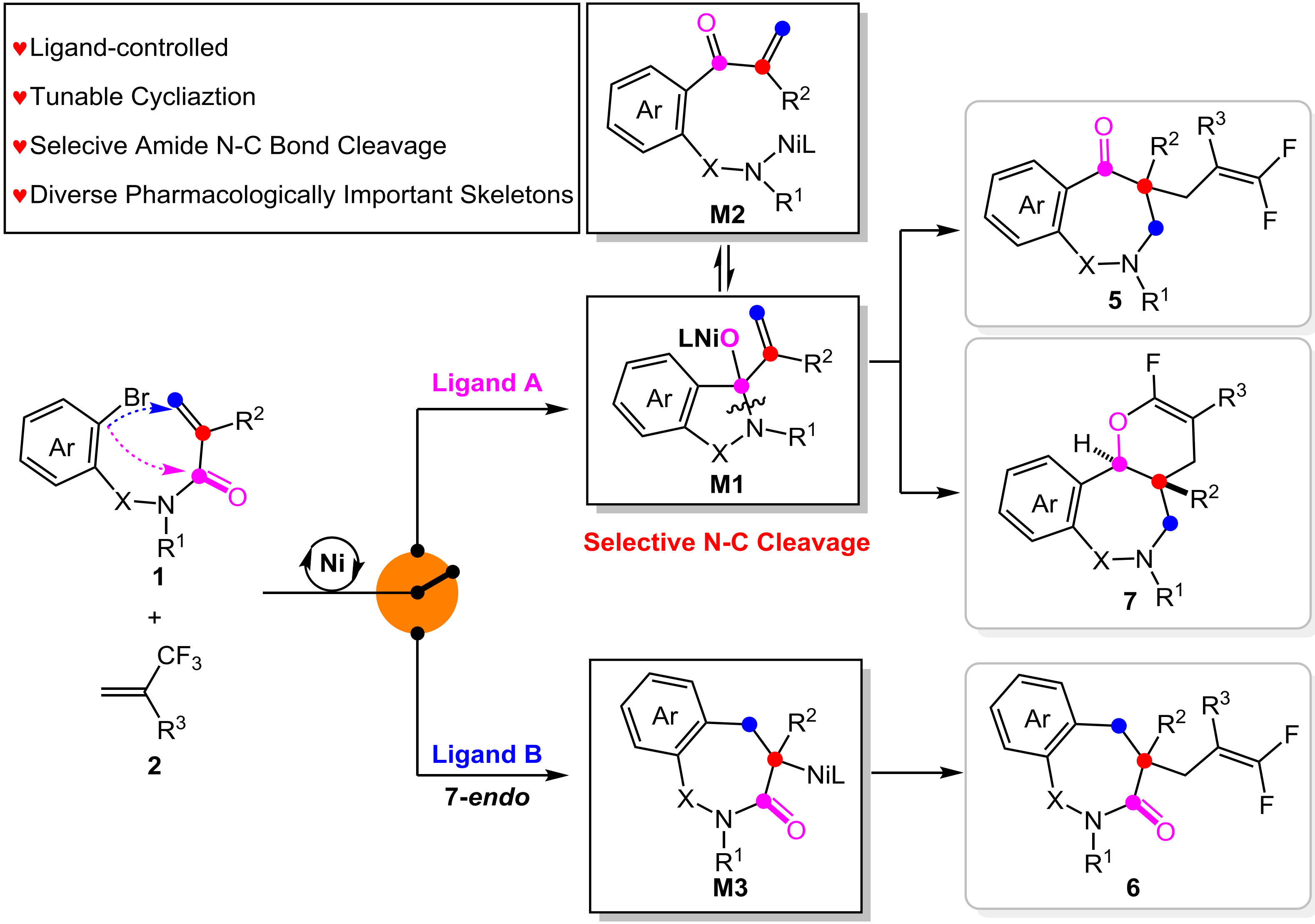
➢ Turnover-limiting Step: Ring Opening Process of **9f**

Proposed Catalytic Cycle



Summary

- ♥Ligand-controlled
- ♥Tunable Cycliaztion
- ♥Selecive Amide N-C Bond Cleavage
- ♥Diverse Pharmacologically Important Skeletons



The First Paragraph

写作思路

总结苯并稠环化合物的构建方式

↓

酰胺结构用于构建苯并稠环化合物的现状

The First Paragraph

Transition metal-catalyzed intramolecular addition of aryl halides to aldehydes, ketones and esters has been extensively investigated for the construction of benzo-fused heterocycles, but amides have been rarely described. This is perhaps unsurprising since it is textbook kno-wledge that the low reactivity of amides stems from amidic resonance stabilization. This stabilization causes the amide bond to have double-bond character, and simultaneously reduces the susceptibility of amides towards nucleophilic attack. Therefore, several strategies for amide activation have been developed. In this context, Charette and Huang developed electrophilic preactivation of amide to form highly electrophilic imidoyl intermediate, enabling chemoselective addition of organometallic reagents to synthesize ketones.

The First Paragraph

Another significant advance in this field is the discovery that twisted amides can be used for transition-metal-catalyzed cross-coupling reactions, as reported by the groups of Garg, Szostak, and others. The direct addition of organometallic reagents to twisted amides to synthesize ketones has also been developed. The key to the success of this strategy is the steric and electronic activation of the amide bonds to distort their planarity, thereby interrupting the amidic resonance, leading to the amino-ketone-like reactivity of amides.

The Last Paragraph

写作思路

总结工作

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指出工作优点以及工作展望

The Last Paragraph

In conclusion, we have developed an unconventional Ni-catalyzed ligand-controlled tunable reductive cyclization/cross-couplings for the divergent synthesis of pharmacologically important 2-benzazepine frameworks. This protocol features mild reaction conditions and exquisite chemoselectivity, and constitutes the first catalytic regiodivergent cyclization/cross-coupling and provides consistent evidence that the ligand determines the pattern of cyclization selectivity. Future investigations and extension other electrophiles as well as the development of an asymmetric version are ongoing in our laboratory.

Representative Examples

The key to the success of this strategy is the steric and electronic activation of the amide bonds to distorttheir planarity, thereby interrupting the amidic resonance, leading to the amino-ketone-like reactivity of amides. (该策略成功的关键是…)

Compared with open-chain sulfonamides, benzo[f][1,2]-thiazepine dioxide derivatives are more rigid and conformationally restricted, making these compounds relevant to drugs with a broad spectrum of biological activity. (使得…与相关…)

These results suggest that the difference in amidic resonance and leaving-group aptitude have a great effect on the reactivity, thus revealing the subtle-ties of our catalytic system. (…揭示了我们催化体系的微妙之处)

Acknowledgement

Thanks
for Your Attention