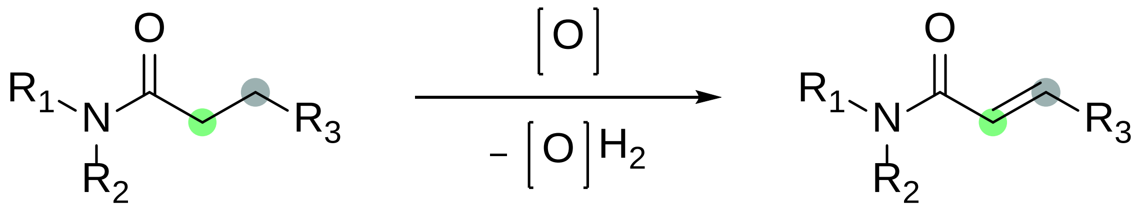
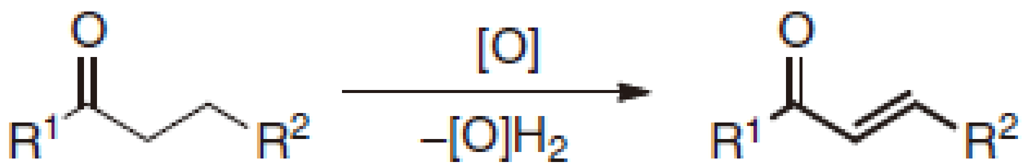
Dehydrogenation to Afford α,β Unsaturated Amides



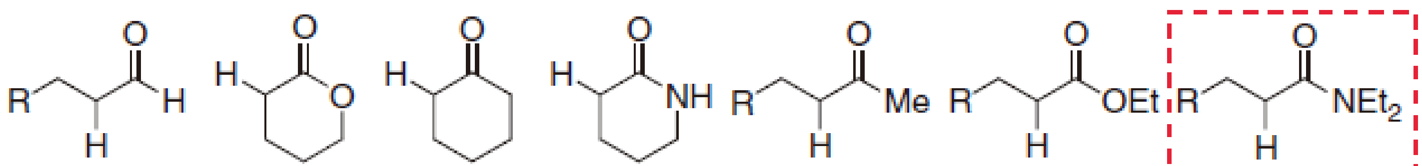
Reporter: Jinglei Yang
Supervisor: *Prof*. Yong Huang
2019-08-22

CONTENTS

1. Introduction



Substrate

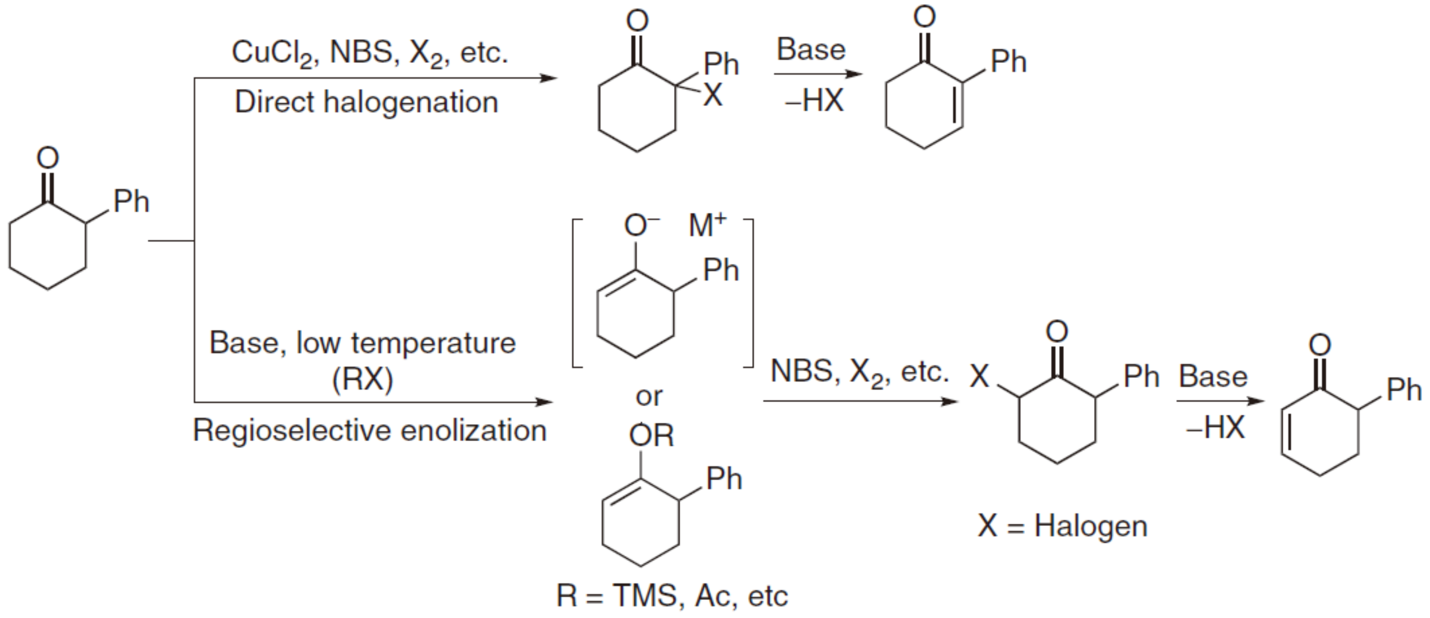


α-pK_a in DMSO		25.2	26.4	26.6	27.1	29.5	34
α-pK_a in H_2O	16.7				19.3		

2. Methods of α, β Dehydrogenation of Carbonyls

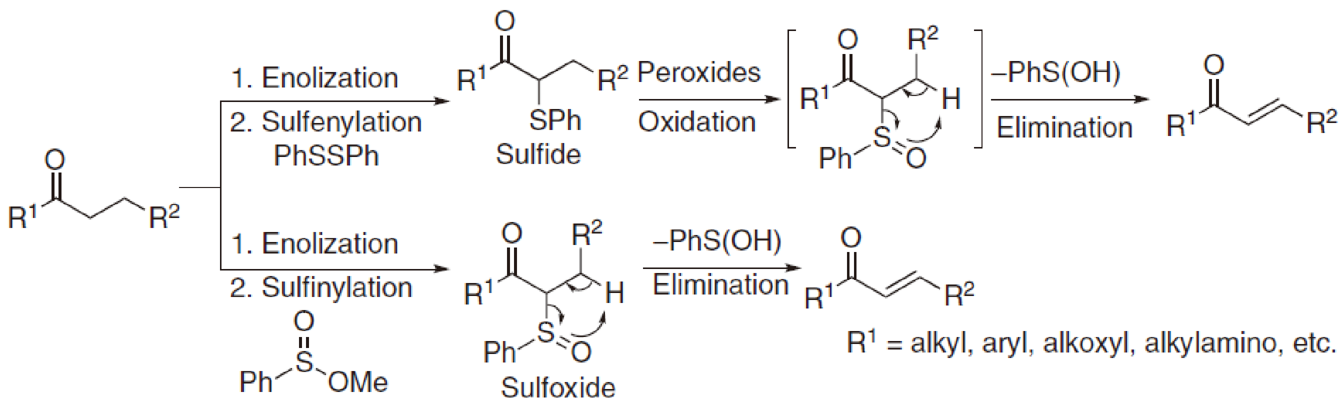
2.1 Halogenation-Dehydrohalogenation Reactions

- Various Halogenation Reagents
- Abundance of Conditions for Regioselective Enolate Formation and Halogenation of Enolates
- Basic Condition
- Difficult to Halogenate Amides

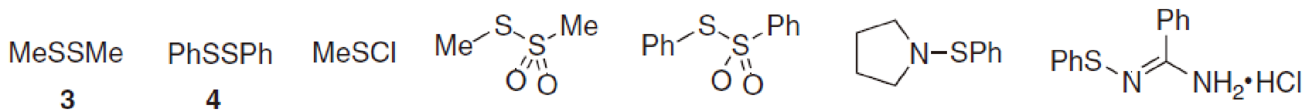


2. Methods of α, β Dehydrogenation of Carbonyls

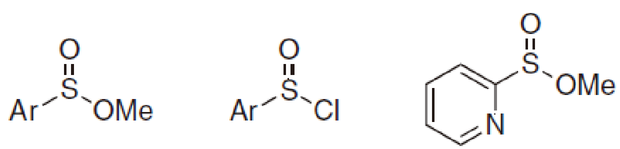
2.2 Organosulfur Reagents



Sulfenylation reagents



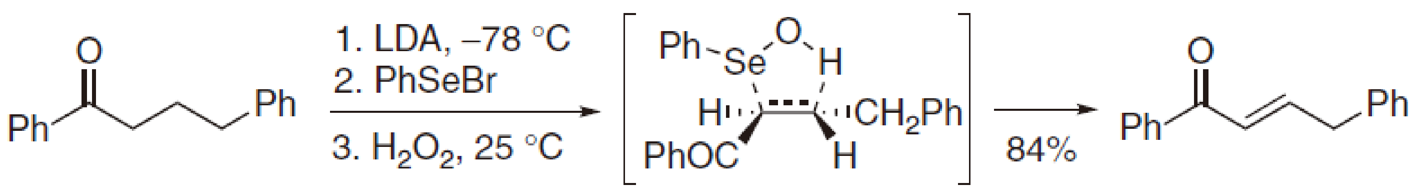
Sulfinylation reagents

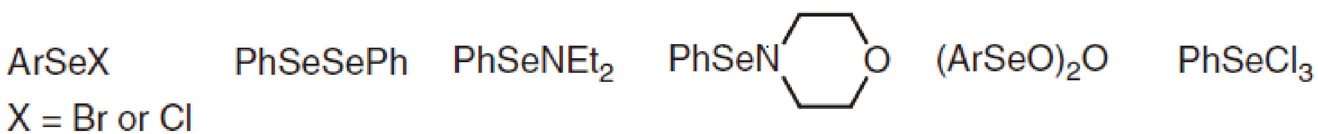


2. Methods of α, β Dehydrogenation of Carbonyls

2.3 Organoselenium Reagents

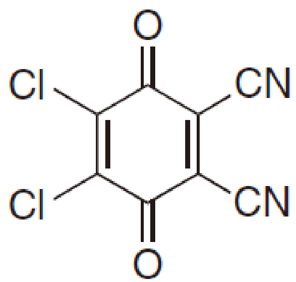
- Enhanced Basicity/More Facile Elimination
- Higher Functional Group Tolerance

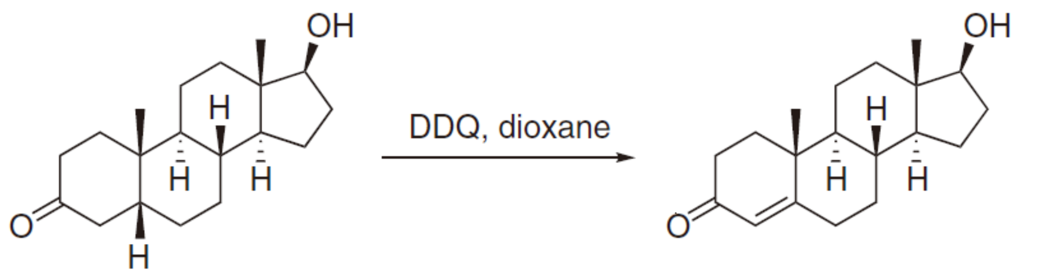




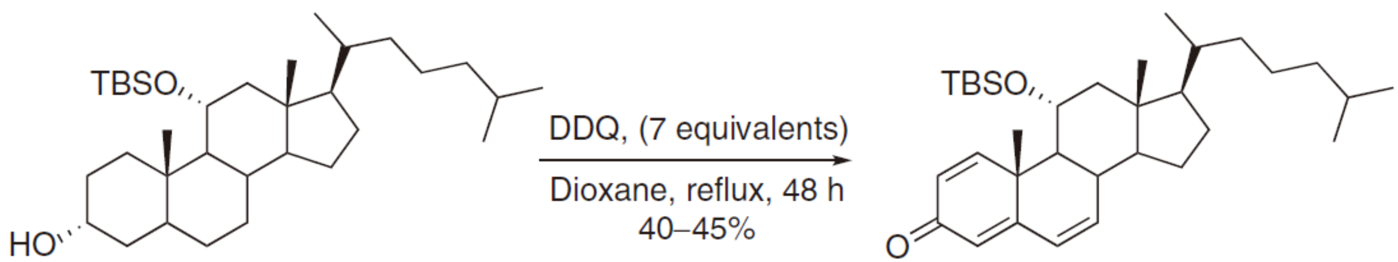
2. Methods of α, β Dehydrogenation of Carbonyls

2.4 Dichlorodicyanoquinone (DDQ)

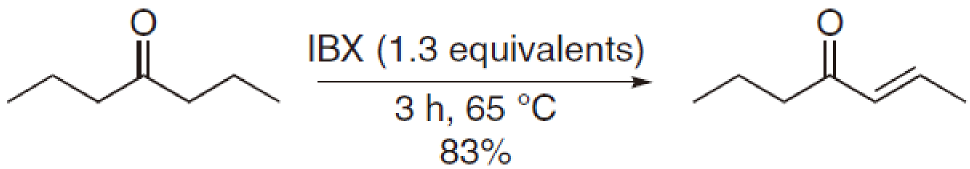


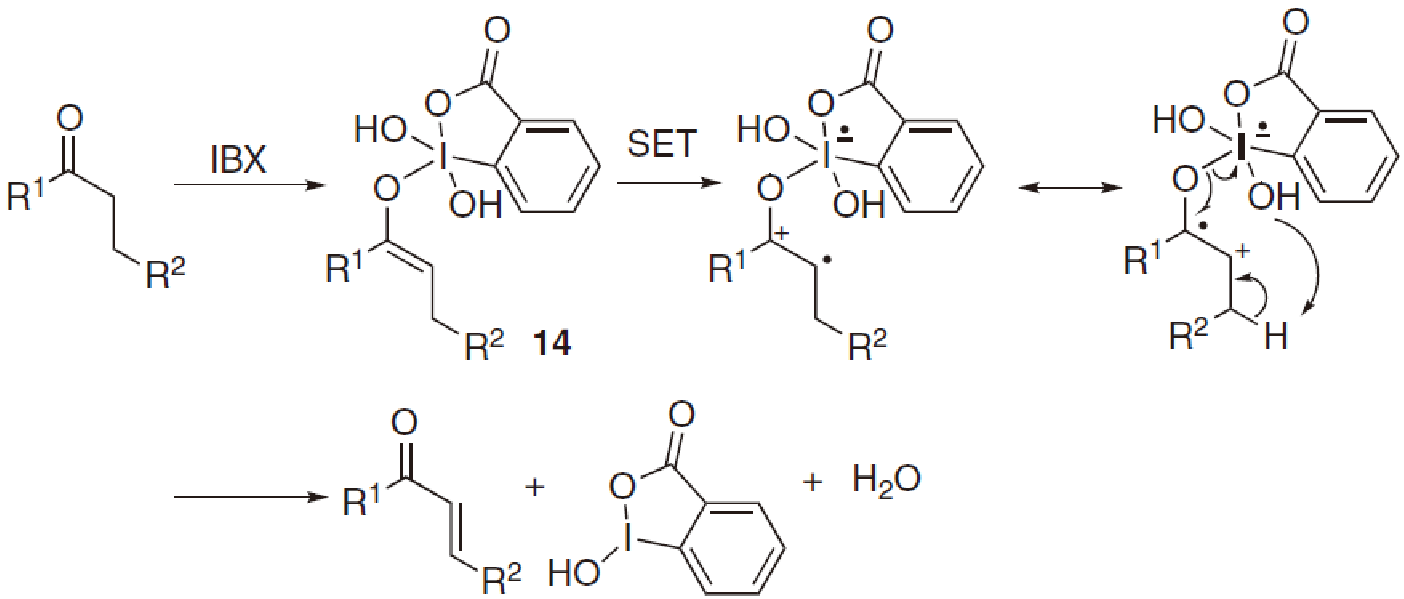


5β-Androstan-17β-ol-3-one   Androst-4-ene-17β-ol-3-one



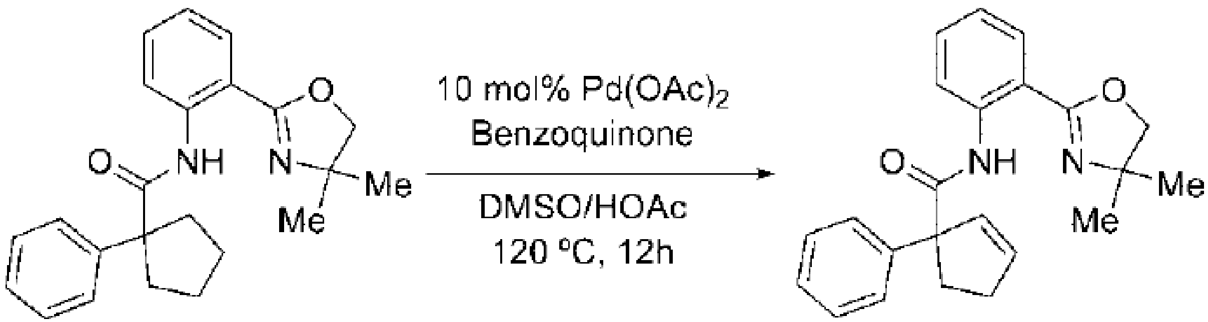
2.5 2-Iodoxybenzoic Acid (IBX)



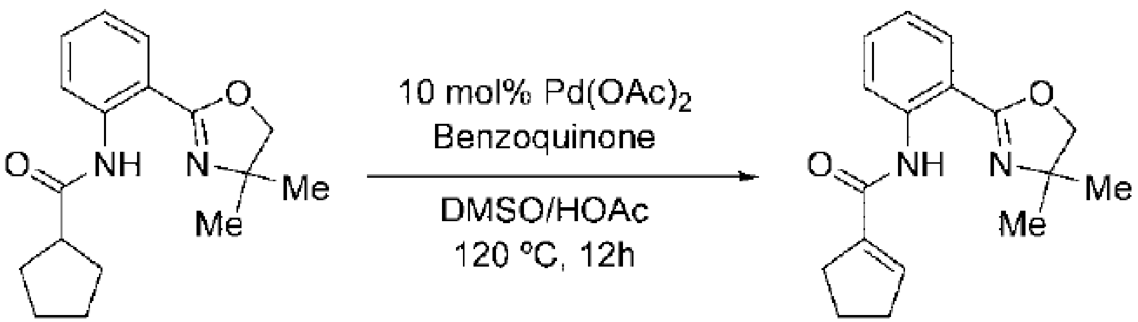


3. Dehydrogenation of Amides

2008 Yu' Group



1h **1i**, 30% yield

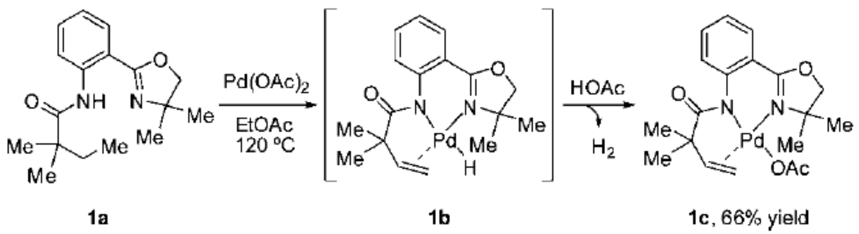


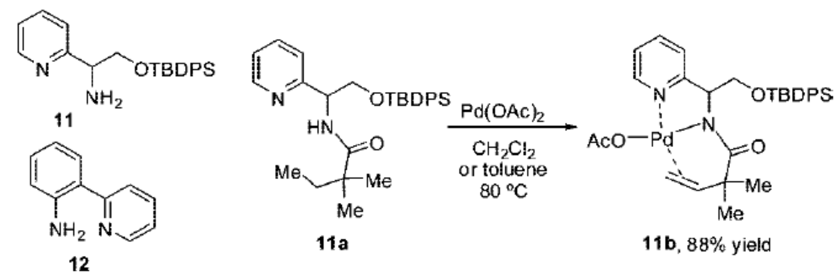
1j **1k**, 75% yield

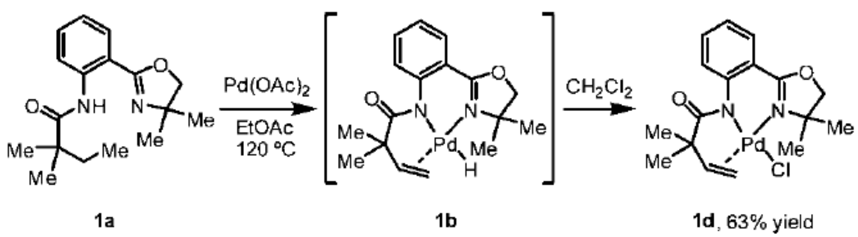
Giri,R.;Maugel,N.;Foxman,B.M.;Yu,J.-Q. *Organometallics* **2008**, 27, 1667–1670.

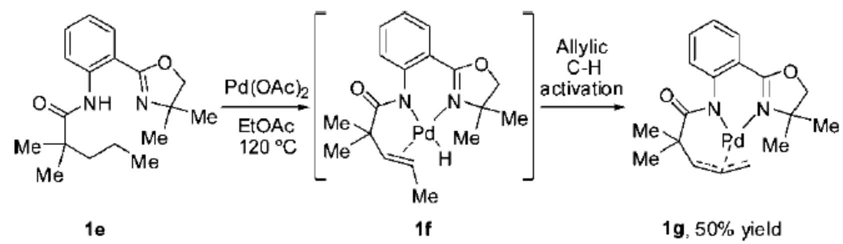
3. Dehydrogenation of Amides

2008 Yu' Group









Giri,R.;Maugel,N.;Foxman,B.M.;Yu,J.-Q. *Organometallics* **2008**, 27, 1667–1670.

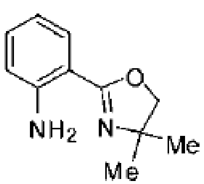
3. Dehydrogenation of Amides

2008 Yu' Group

Table 1. Pd(OAc)$_2$-Mediated Dehydrogenation of 2,2-Dimethylbutyric Acid using Various Auxiliaries[a]

entry	auxiliary	yield (%)[b]	entry	auxiliary	yield (%)[b]
1	**1**	66	4	**4**	62
2	**2**	35	5	**5**	40
3	**3**	90[c]	6	**6**	10[d]

[a] Conditions: substrate (0.1 mmol), Pd(OAc)$_2$ (1 equiv), ethyl acetate (1 mL), 120 °C, 30 min. [b] Isolated yields. [c] 100 °C. [d] Determined by ^{1}H NMR.



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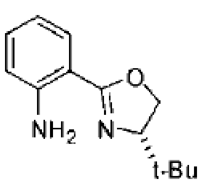

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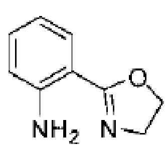

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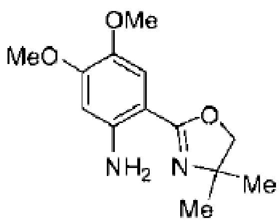

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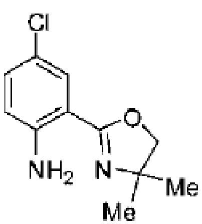

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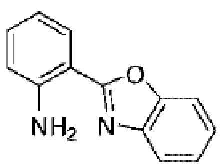

6

Giri,R.;Maugel,N.;Foxman,B.M.;Yu,J.-Q. *Organometallics* **2008**, 27, 1667–1670.

3. Dehydrogenation of Amides

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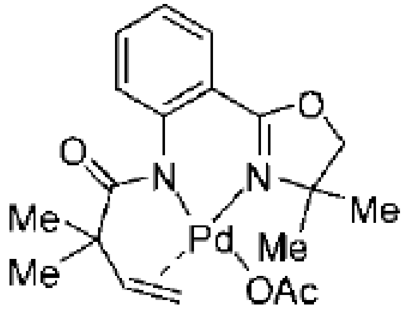

1c,

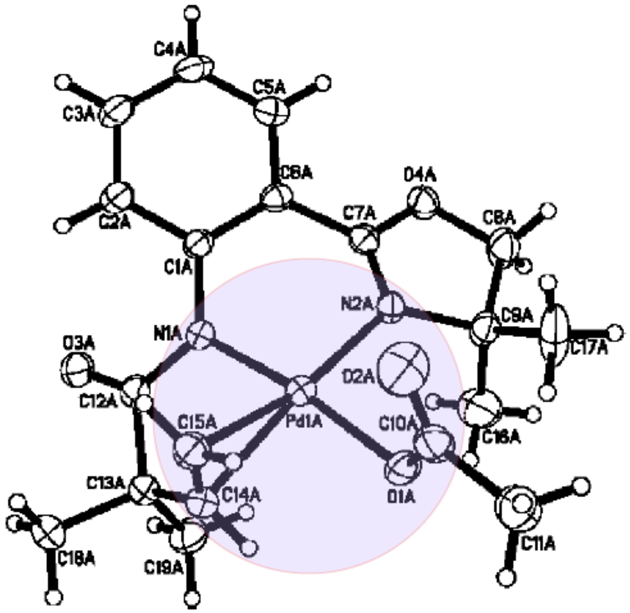

Figure 1. Molecular structure of **1c**. Pertinent bond lengths (Å) and angles (deg): Pd1A−N1A, 1.980(3); Pd1A−N2A, 2.049(3); Pd1A−C15A, 2.155(4); Pd1A−C14A, 2.137(4); Pd1A−O1A, 2.019(3); N1A−Pd1A−N2A, 89.83(13); N1A−Pd1A−C14A, 82.07(16); N1A−Pd1A−C15A, 86.91(17); C14A−Pd1A−O1A, 91.30(16); C15A−Pd1A−O1A, 90.03(17); N2A−Pd1A−O1A, 94.88(13).

Giri,R.;Maugel,N.;Foxman,B.M.;Yu,J.-Q. *Organometallics* **2008**, 27, 1667–1670.

3. Dehydrogenation of Amides

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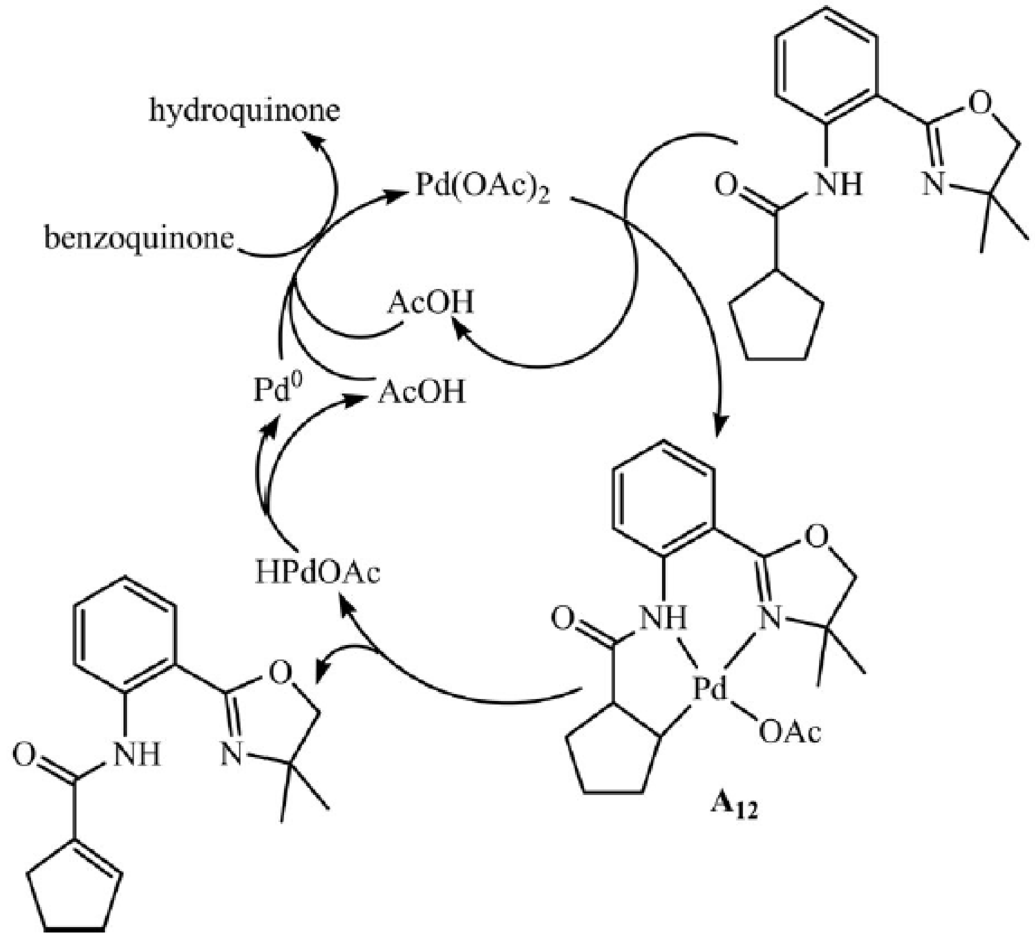
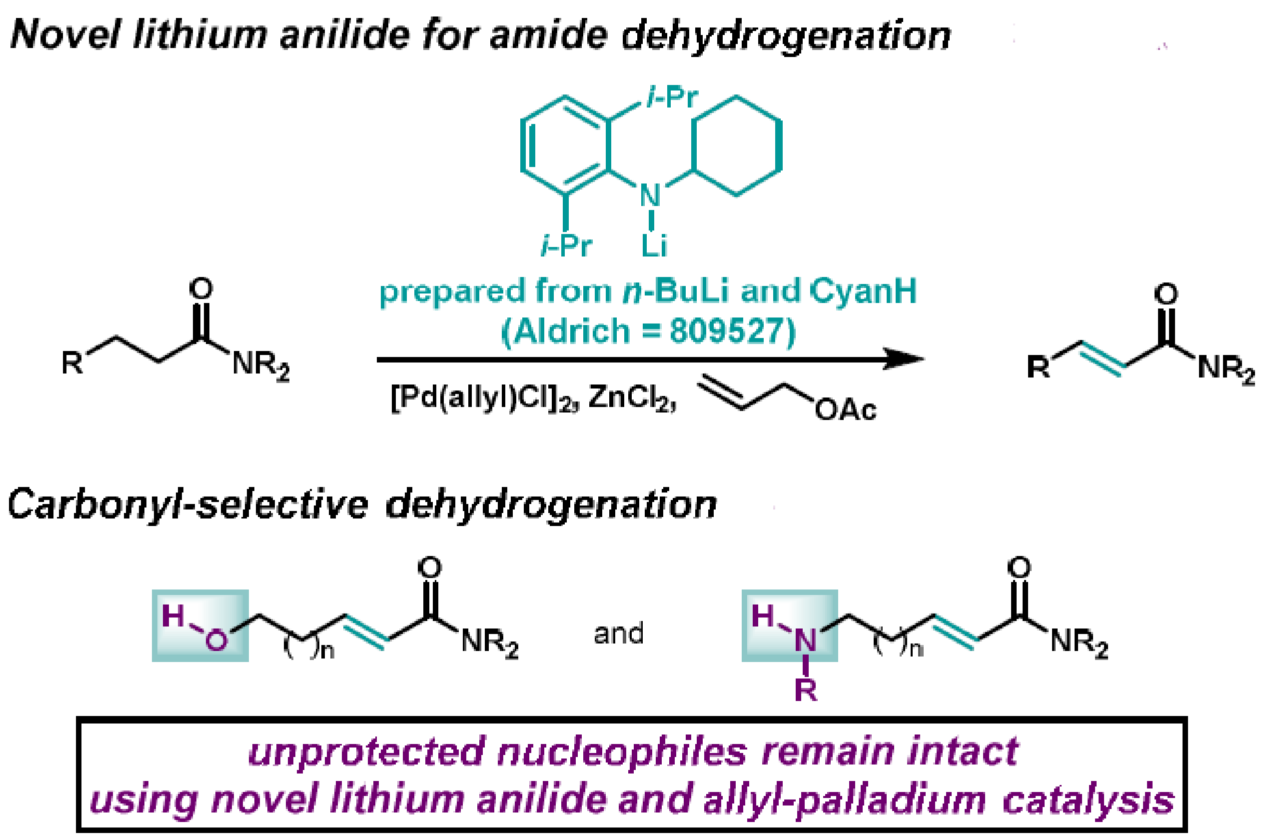


Giri,R.;Maugel,N.;Foxman,B.M.;Yu,J.-Q. *Organometallics* **2008**, 27, 1667–1670.

3. Dehydrogenation of Amides

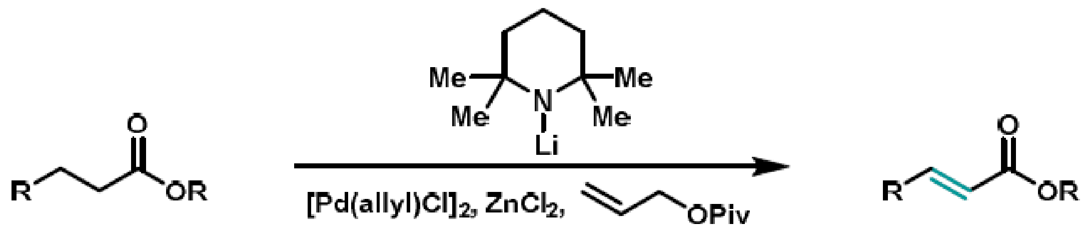
2016 Newhouse

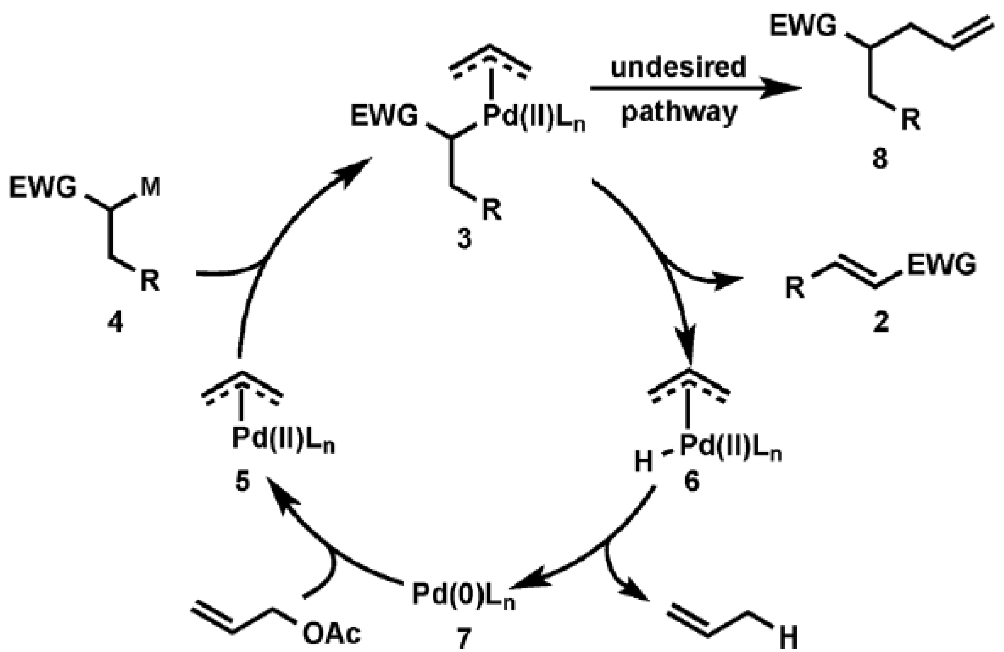


Chen, Y.; Turlik, A.; Newhouse, T. R. *J. Am. Chem. Soc.* **2016**, 138, 1166.

3. Dehydrogenation of Amides

2016 Newhouse

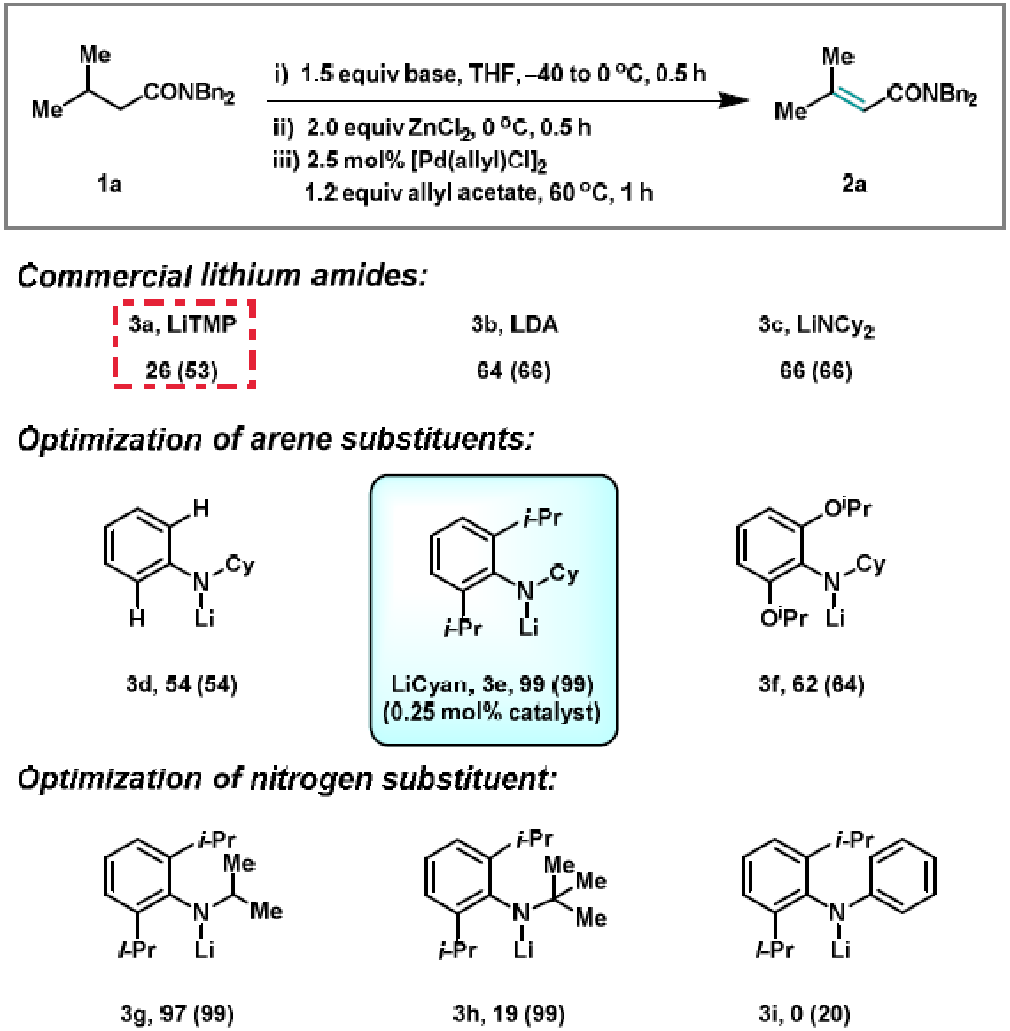




Chen, Y.; Turlik, A.; Newhouse, T. R. *J. Am. Chem. Soc.* **2016**, 138, 1166.

3. Dehydrogenation of Amides

2016 Newhouse

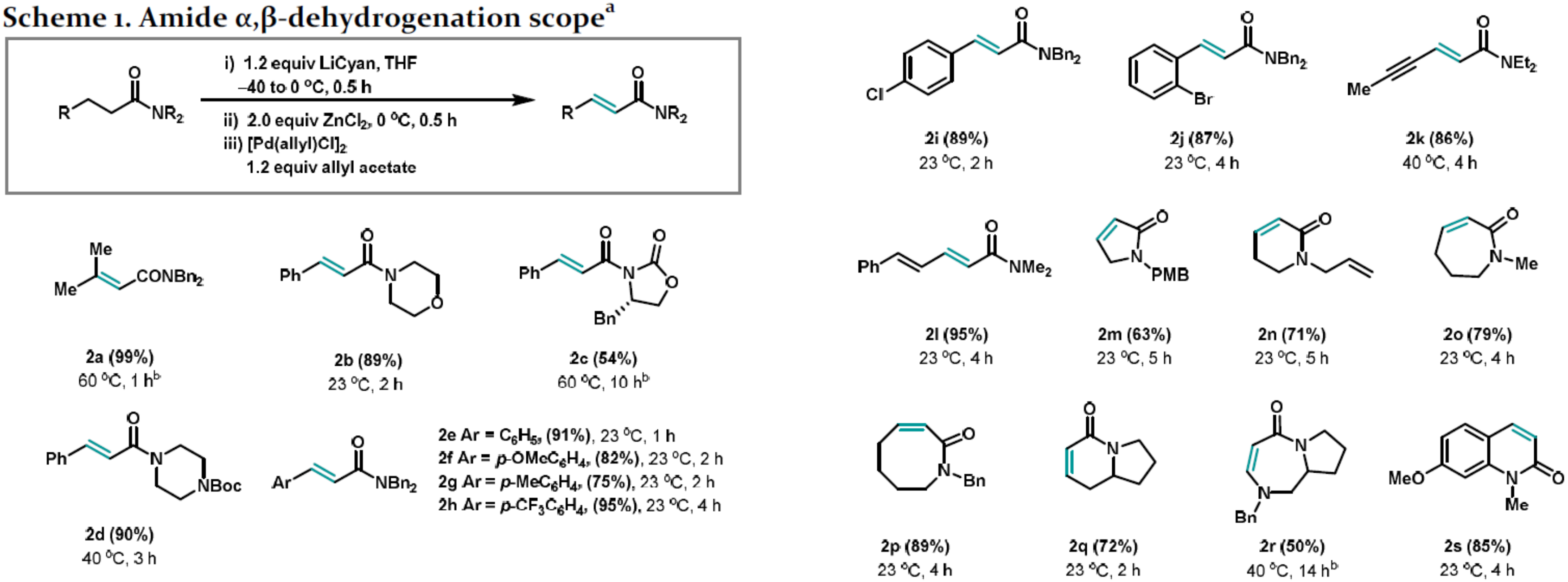


Chen, Y.; Turlik, A.; Newhouse, T. R. *J. Am. Chem. Soc.* **2016**, 138, 1166.

3. Dehydrogenation of Amides

2016 Newhouse

Scheme 1. Amide α,β-dehydrogenation scope[a]



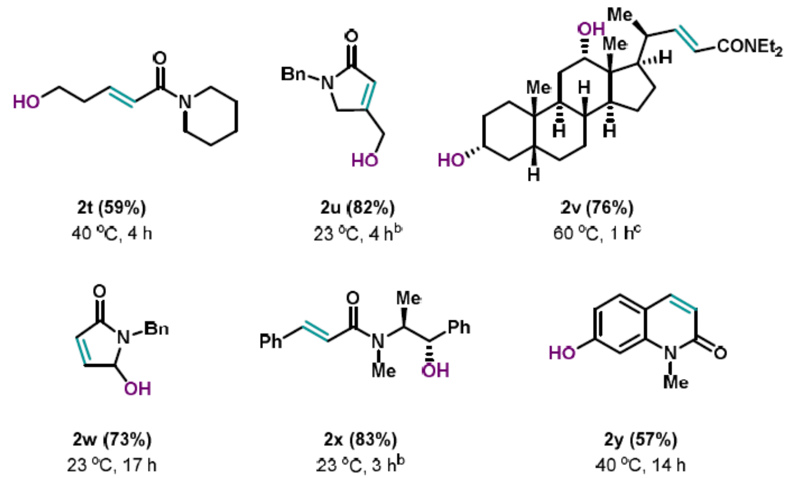
[a] Isolated yield, temperature, and time for the oxidation stage are indicated.
[b] 1.5 equivalents of LiCyan were used.

Chen, Y.; Turlik, A.; Newhouse, T. R. *J. Am. Chem. Soc.* **2016**, 138, 1166.

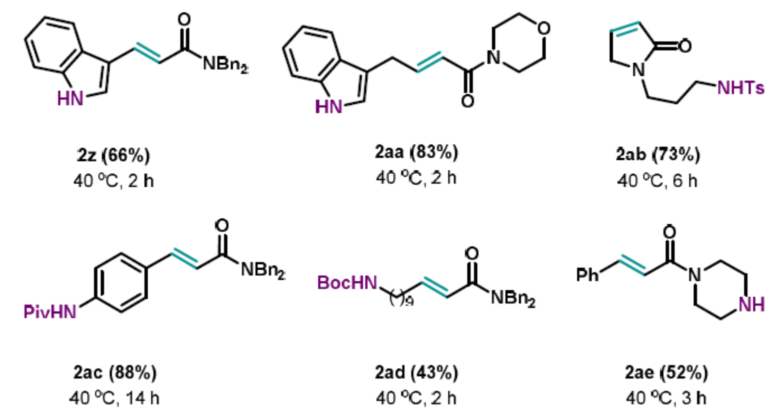
3. Dehydrogenation of Amides

2016 Newhouse

(a) Dehydrogenation in the presence of O-H functionality:



(b) Dehydrogenation in the presence of N-H functionality:

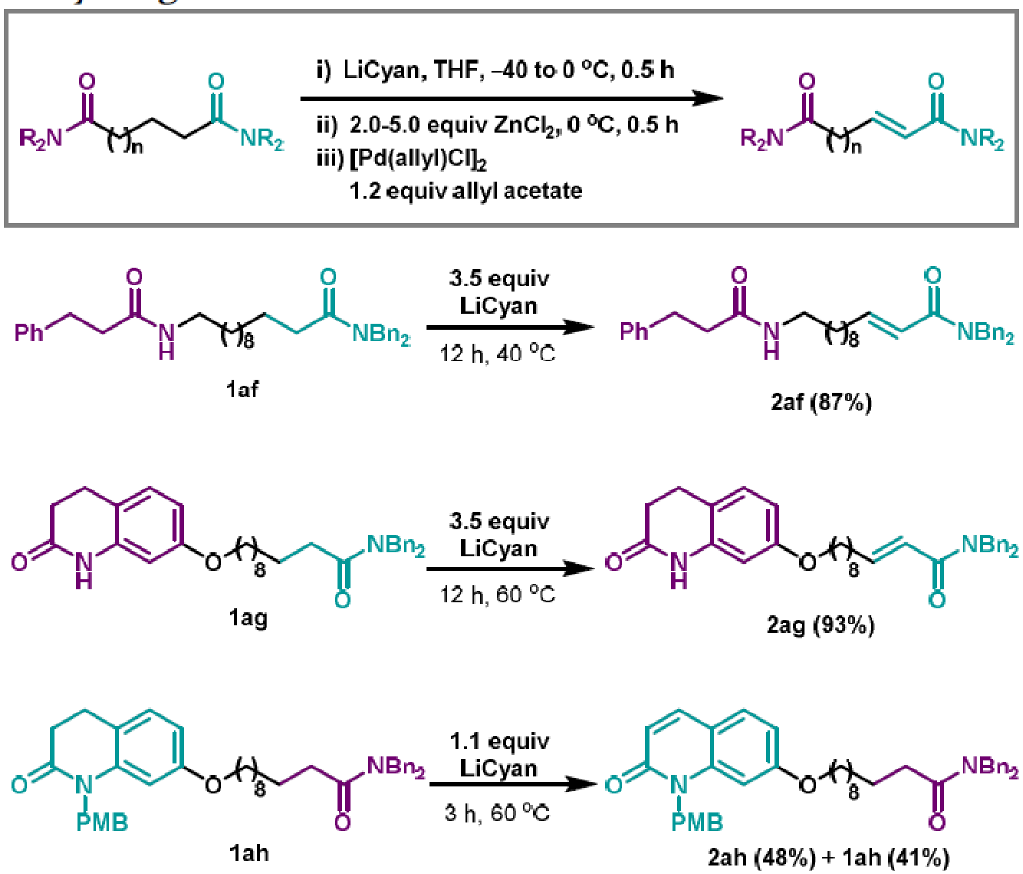


Chen, Y.; Turlik, A.; Newhouse, T. R. *J. Am. Chem. Soc.* **2016**, 138, 1166.

3. Dehydrogenation of Amides

2016 Newhouse

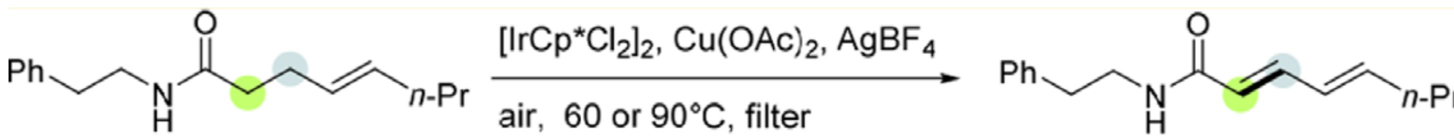
Scheme 3. Protecting-group controlled α,β-dehydrogenation

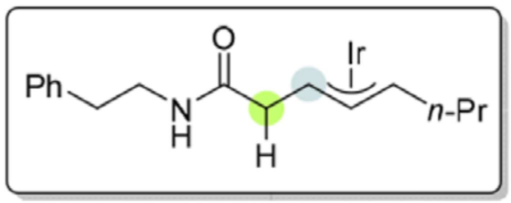


Chen, Y.; Turlik, A.; Newhouse, T. R. *J. Am. Chem. Soc.* **2016**, 138, 1166.

3. Dehydrogenation of Amides

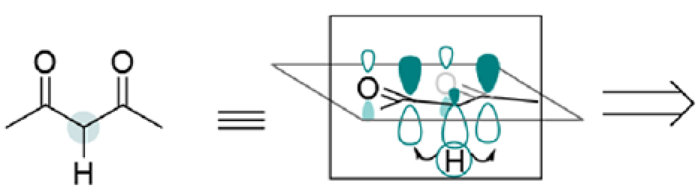
2019 Huang's Group



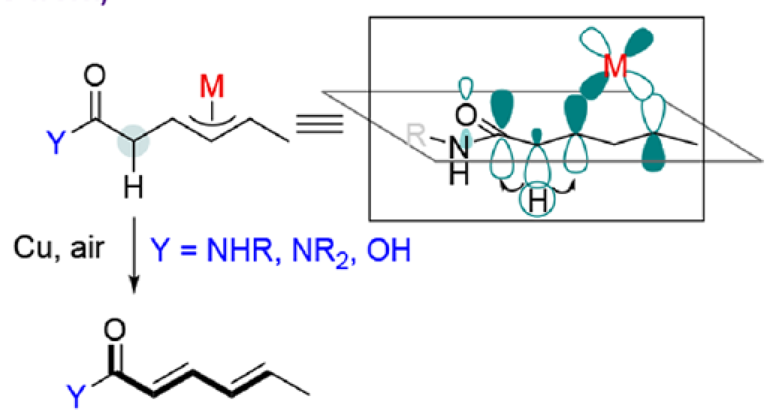


Aerobic dehydrogenation of amides and acids
Amide: 31 examples, acids: 8 example
Exclusive chemoselectivity among carbonyls
Ir-allyl enhanced α-acidity

Activation of both α– and β–C-H using Ir (this work)



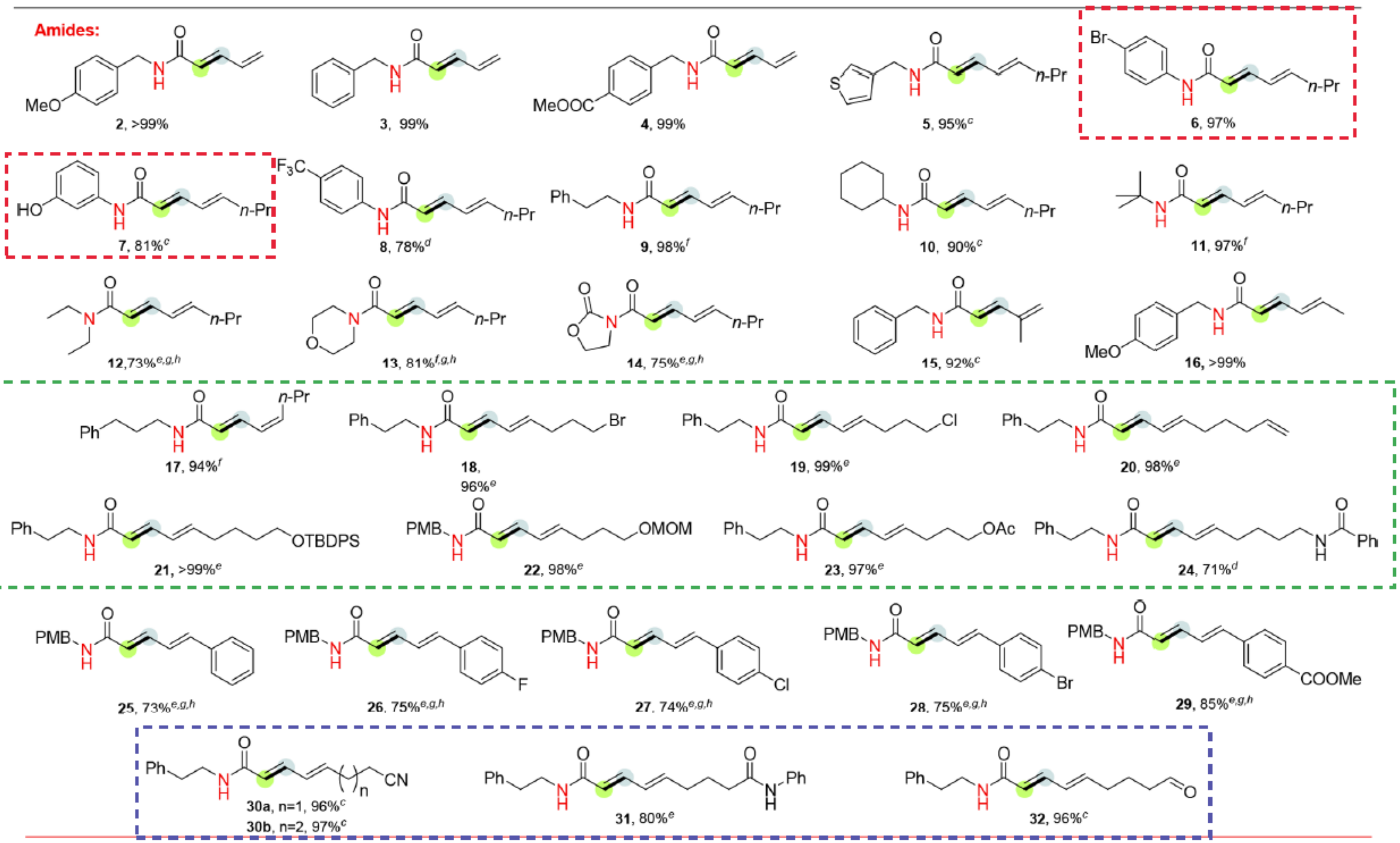
Directed β C-H activation followed by accelerated α-deprotonation



Z. Wang, Z. He, L. Zhang, Y. Huang, *J. Am. Chem. Soc.* **2018**, 140, 735–740.

3. Dehydrogenation of Amides

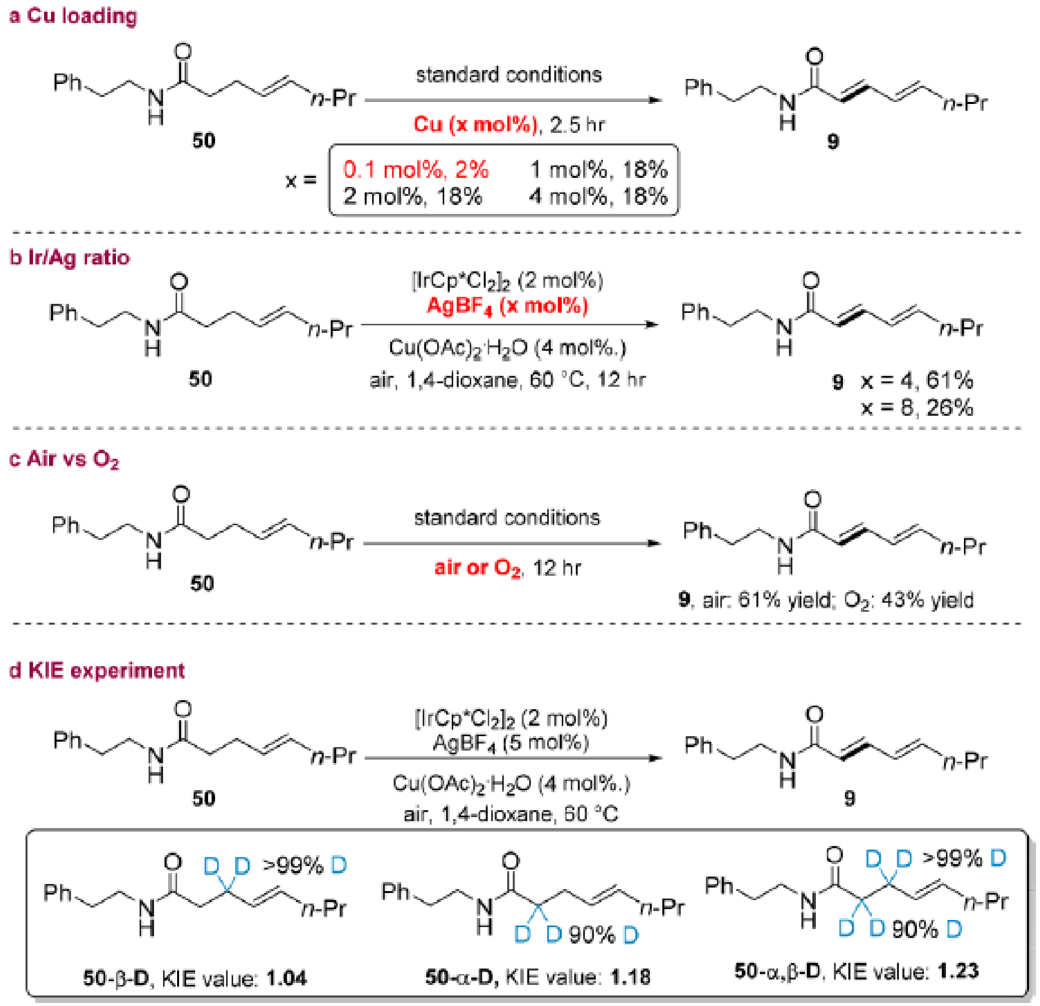
2019 Huang's Group



Z. Wang, Z. He, L. Zhang, Y. Huang, *J. Am. Chem. Soc.* **2018**, 140, 735–740.

3. Dehydrogenation of Amides

2019 Huang's Group



Z. Wang, Z. He, L. Zhang, Y. Huang, *J. Am. Chem. Soc.* **2018**, 140, 735–740.

3. Dehydrogenation of Amides

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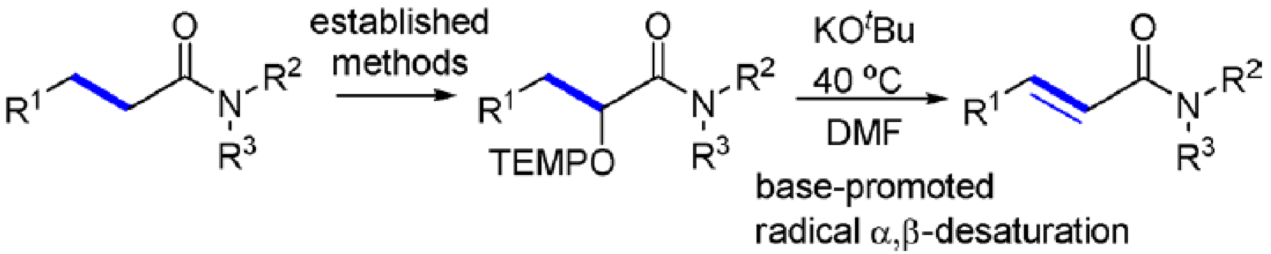

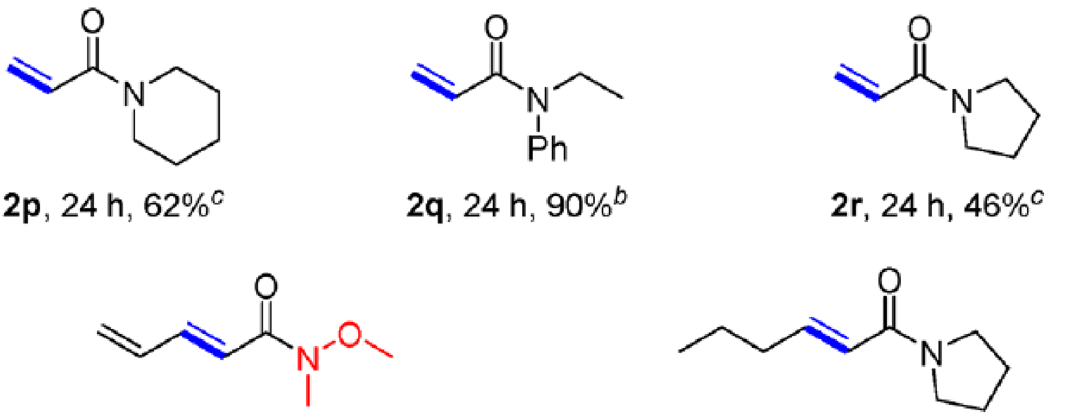

2p, 24 h, 62%[c] **2q**, 24 h, 90%[b] **2r**, 24 h, 46%[c]

2s, 24 h, 72%[b] **2t**, 48 h, 24%[b]

Wang, M. M.; Sui, G. H.; Cui, X. C.; Wang, H.; Qu, J. P.; Kang, Y. B. *J. Org. Chem.* **2019**, 84, 8267−8274

3. Dehydrogenation of Amides

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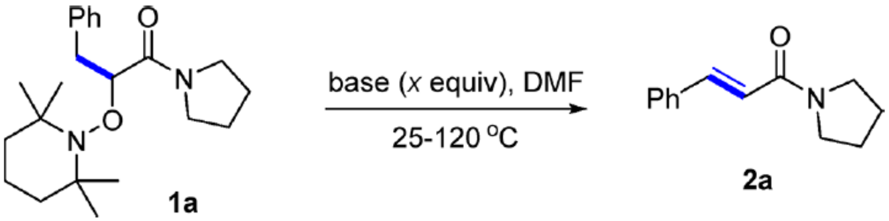
Table 1. Reaction Conditions[a]



entry	base	x	T (°C)	t (h)	**2a** (%)
1			120	24	92
2			90	24	20
3			40	24	0
4	KO^tBu	1.0	90	5	70
5	KO^tBu	1.0	60	5	72
6	KO^tBu	1.2	40	1.5	90
7	NaO^tBu	1.2	40	5	19
8	KHMDS	1.2	40	24	5
9	KO^tBu	1.2	25	5	56
10	KO^tBu	1.5	25	5	46

[a]Reaction conditions: **1a** (0.25 mmol), base (1.2 equiv), DMF (1 mL), argon, 25−120 °C.

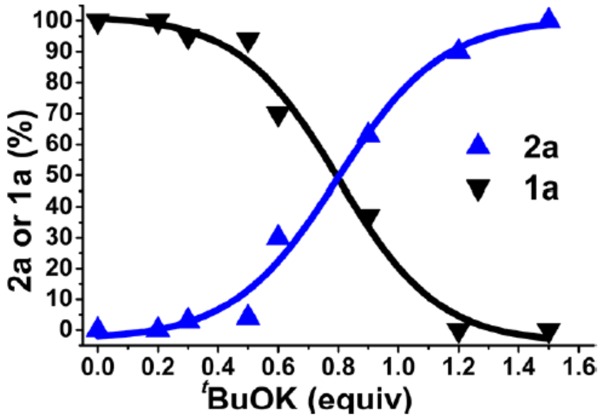


Figure 1. Base effect of the α,β-dehydrogenation of **1a** to **2a**.

Wang, M. M.; Sui, G. H.; Cui, X. C.; Wang, H.; Qu, J. P.; Kang, Y. B. *J. Org. Chem.* **2019**, 84, 8267−8274

3. Dehydrogenation of Amides

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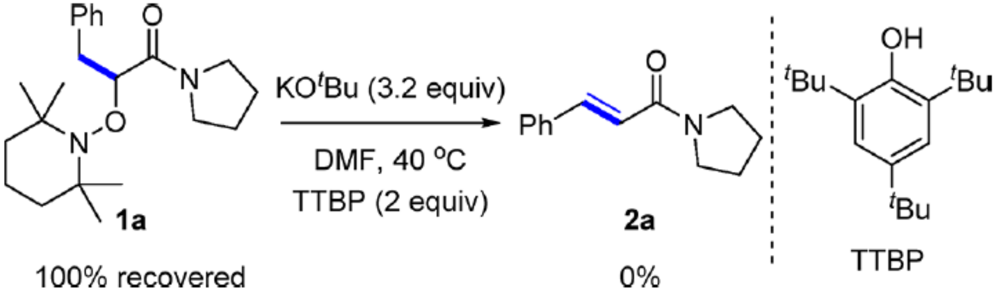
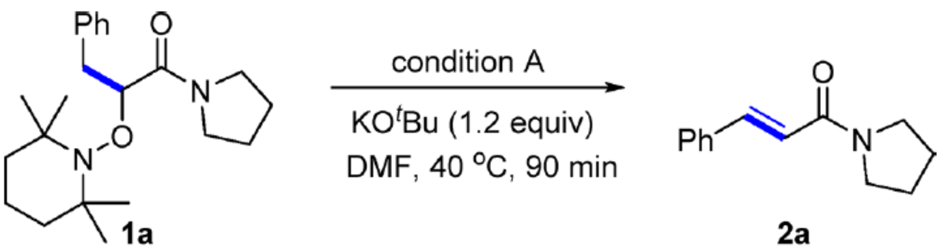
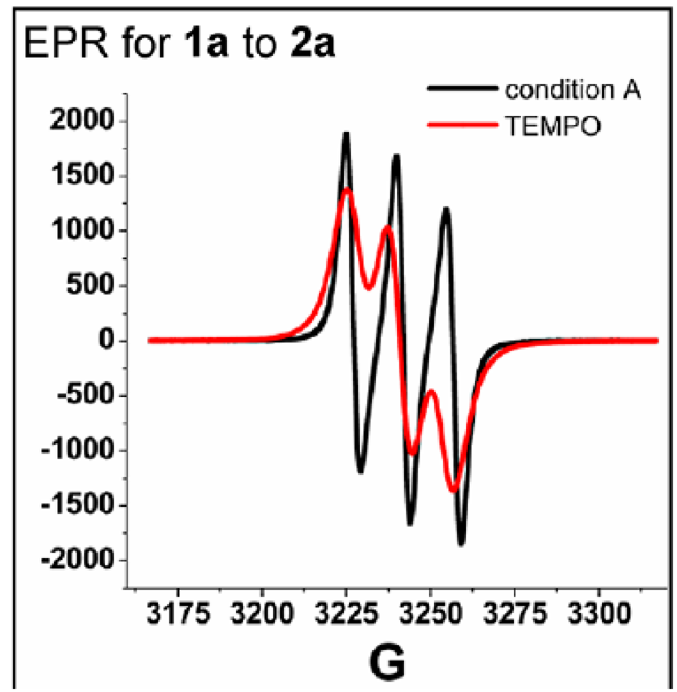
Scheme 3. Radical Trapping Experiments



Scheme 4. EPR Experiments



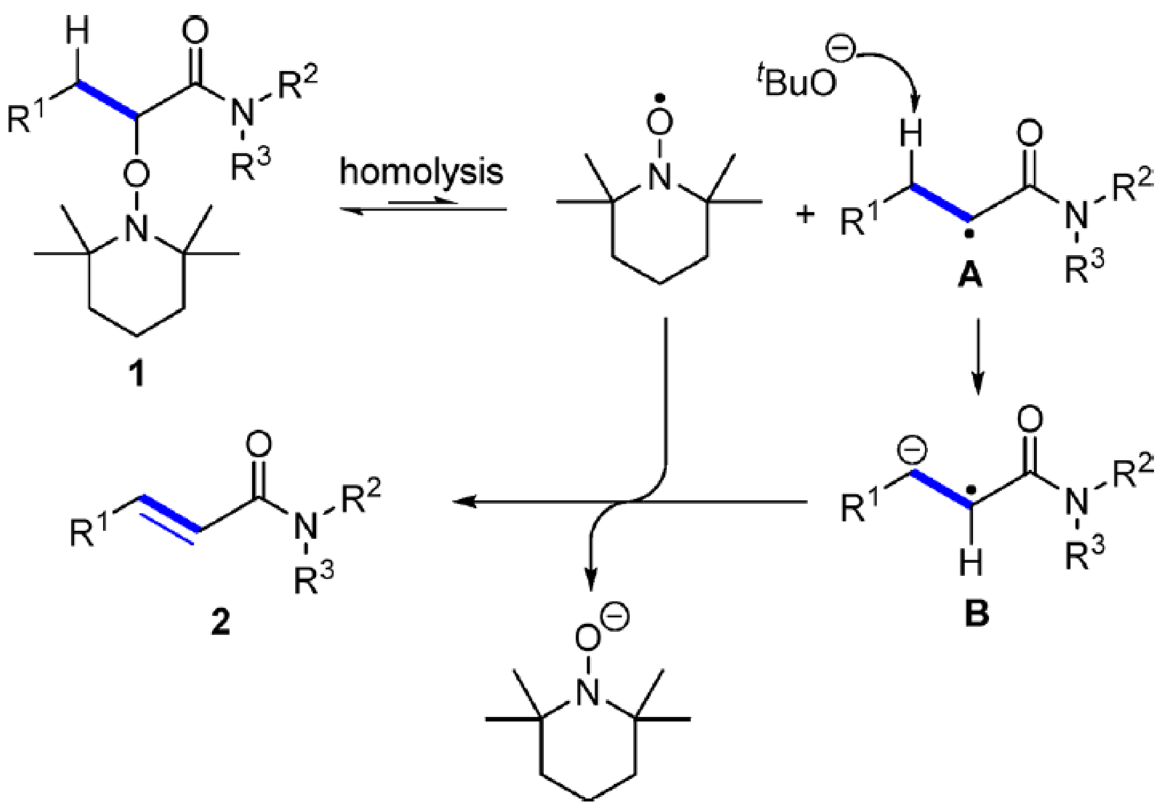


Wang, M. M.; Sui, G. H.; Cui, X. C.; Wang, H.; Qu, J. P.; Kang, Y. B. *J. Org. Chem.* **2019**, 84, 8267−8274

3. Dehydrogenation of Amides

2019 Kang's Group

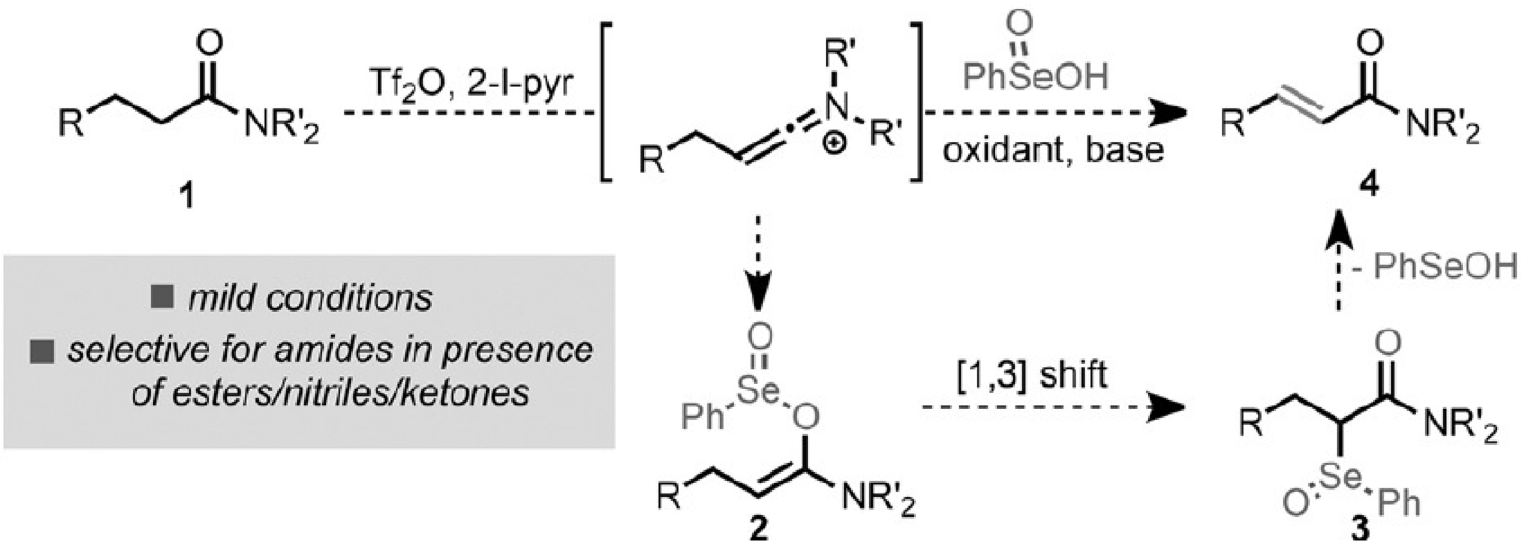
Scheme 5. Reaction Mechanism



Wang, M. M.; Sui, G. H.; Cui, X. C.; Wang, H.; Qu, J. P.; Kang, Y. B. *J. Org. Chem.* **2019**, 84, 8267−8274

3. Dehydrogenation of Amides

2019 Maulide’s Group

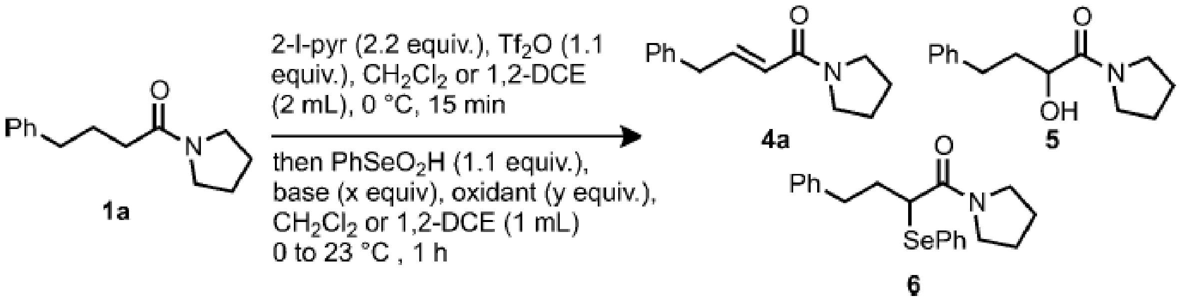


Teskey, C. J.; Adler, P.; Gonçalves, C. R.; Maulide, N. *Angew. Chem., Int. Ed.* **2019**, 58, 447.

3. Dehydrogenation of Amides

2019 Maulide's Group

Table 1: Optimization of the reaction.



Entry	[Se] (equiv)	Base (equiv)	Oxidant (equiv)	Yield [%][a] 4a	5	6	1a
1	$PhSeO_2H$ (1)	Ag_2CO_3 (1.1)	–	48	20	–	41
2	$PhSeO_2H$ (1)	Et_3N (1.1)	–	–	24	50	14
3	$PhSeO_2H$ (1)	Et_3N (2.2)	PIDA (2.2)	22	12	–	25
4	$PhSeO_2H$ (1)	Et_3N (2.2)	IBX (2.2)	29	45	–	21
5	**$PhSeO_2H$ (1)**	**Et_3N (2.2)**	**DMP (2.2)**	**73**	–	–	**10**
6	–	Et_3N (2.2)	DMP (2.2)	8	2	–	50

[a] Yields determined by ^{1}H NMR analysis with bromoform as an internal standard. 1,2-DCE = 1,2-dichloroethane, PIDA = iodobenzene diacetate.

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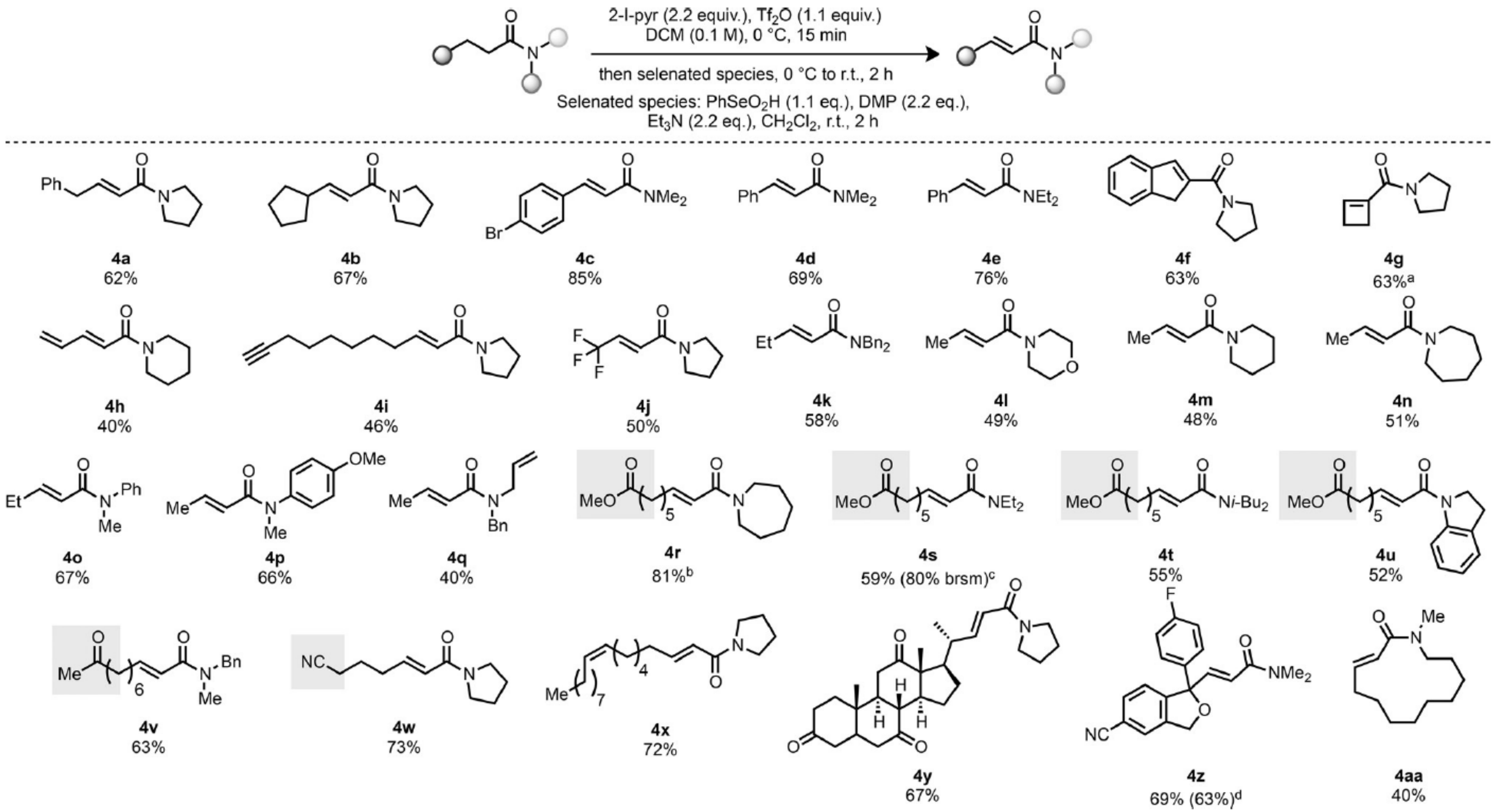
3. Dehydrogenation of Amides

2019 Maulide's Group



Scheme 2. Scope of amide dehydrogenation. [a] On 1 mmol scale. [b] Reaction carried out at −20 °C. [c] Reaction carried out at −10 °C. [d] On 4.2 mmol scale. DCM = dichloromethane.

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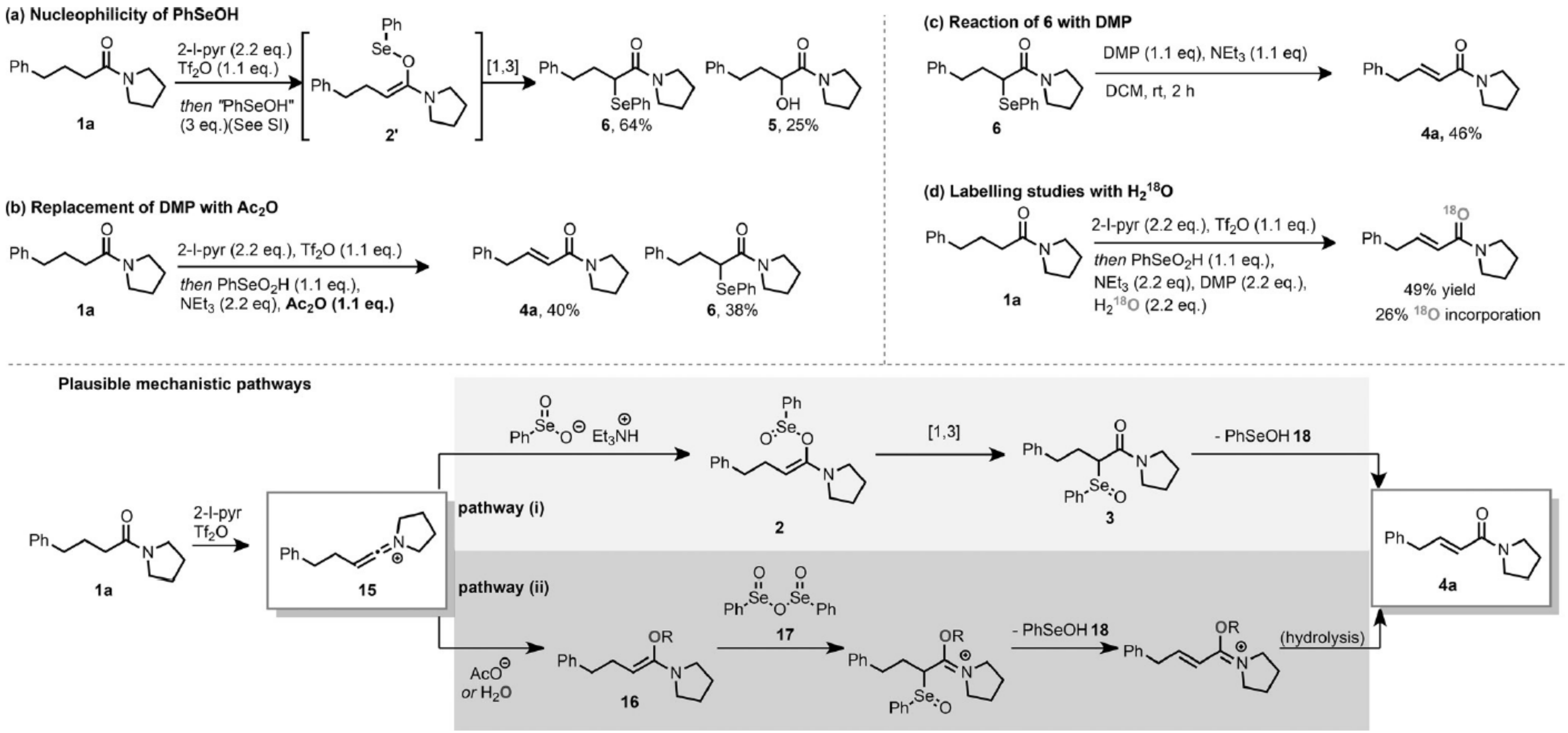

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4. Summary

- Limited Substrate Scope (Often with Aryl or Unsaturated β Substituents)
- Usage of Toxic Reagents
- Not Catalytic
- Catalytic, Aerobic, Mild Methodologies Be Established

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Thanks for Your Attention!