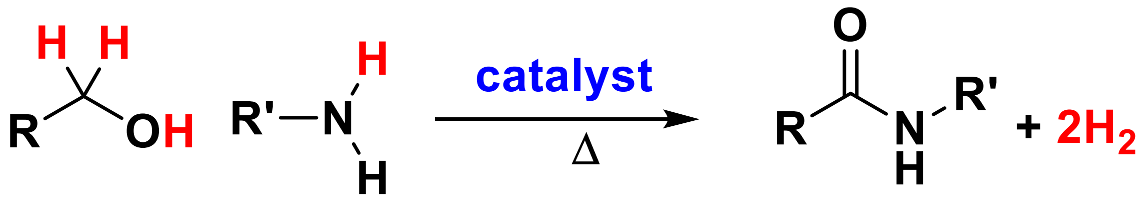
Direct Synthesis of Amides by Dehydrogenative Coupling of Amines with either Alcohols or Esters: Manganese Pincer Complex as Catalyst

Kumar, A.; Espinosa-Jalapa, N. A.; Leitus, G.; Diskin-Posner, Y.; Avram, L.; Milstein, D. Angew. Chem. Int. Ed. **2017**, *56*, 1-6

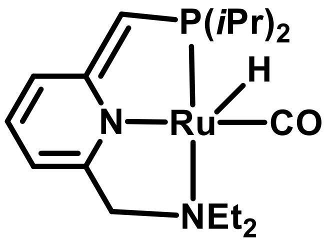
Leila Terrab
Wipf Group
Current Litterature
10/28/2017

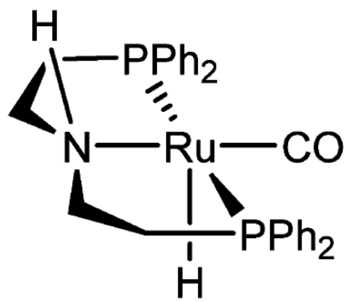
Synthesis of Amides via Dehydrogenative Coupling

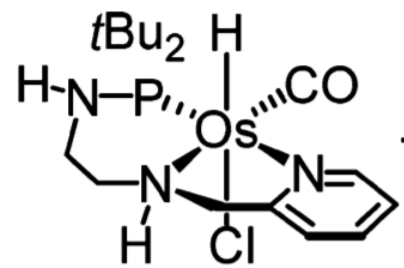
2007-Present: High Atom Economy of Amide Bond Formation



Example of Catalysts Used (2007-Present)





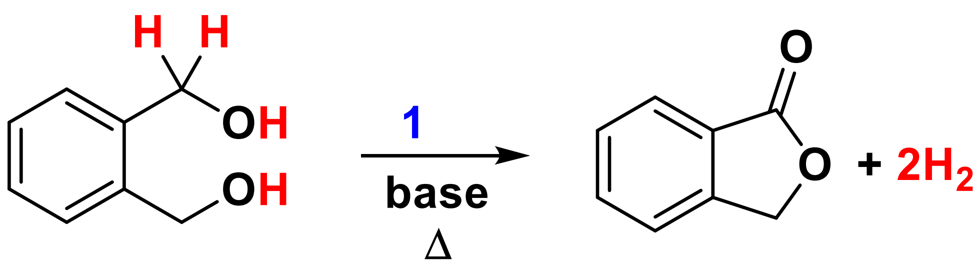


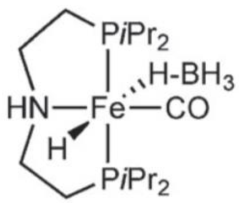
This work: Transition-metal catalysis of amide bonds using non-precious metals

Gnanaprakasam, B.; Milstein, D. *J. Am. Chem. Soc.*, **2011**, *133*, 1682-1685.
Spasyuk, D.; Vicent, D.; Gusev, D. G. *J. Am. Chem. Soc.* **2015**, *137*, 3743.
Lane, E. M.; Uttley, K. B.; Hazari, N.; Bernskoetter, W. *Organometallics*, **2017**, *36*, 2020.

Non-Precious metals used in Dehydrogenative Coupling

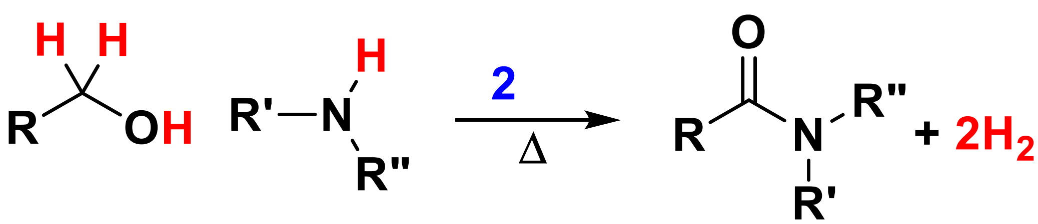
Beller Group (2015)

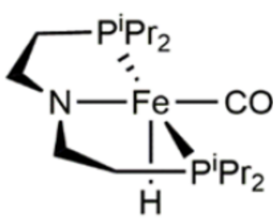




1

Bernskoetter Group (2017)





2

<u>Limitations:</u>

Only works with methanol

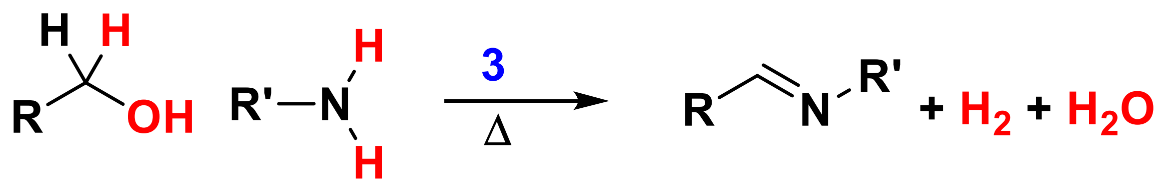
Only works with secondary amines

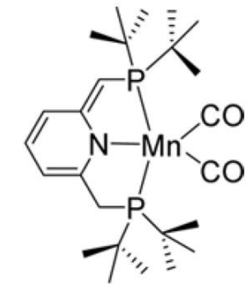
Pena-Lopez, M.; Neumann, H.; Beller, M. *ChemCatChem* **2015**, *7*, 865.

Lane, E. M.; Uttley, K. B.; Hazari, N.; Bernskoetter, W. H. *Organometallics* **2017**, *36*, 2020.

Milstein Previous Work with Mn Pincer Complex

Milstein (2016)- Imines

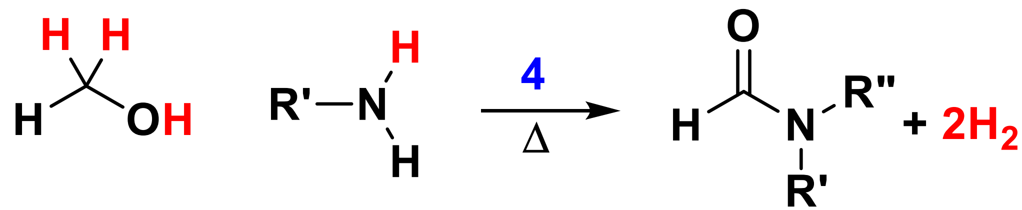


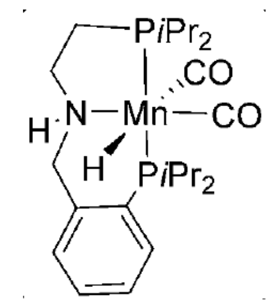


Previously reported with: Ru, Ir, Os, Co

3

Milstein (2017)- Formamides

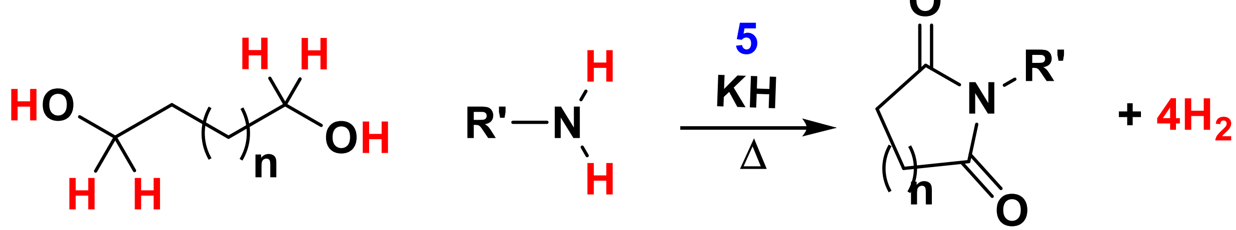


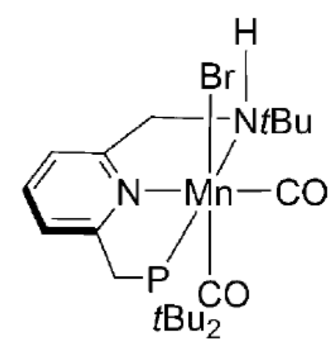


Previously reported with: Ru

4

Milstein (2017)- Amides





5

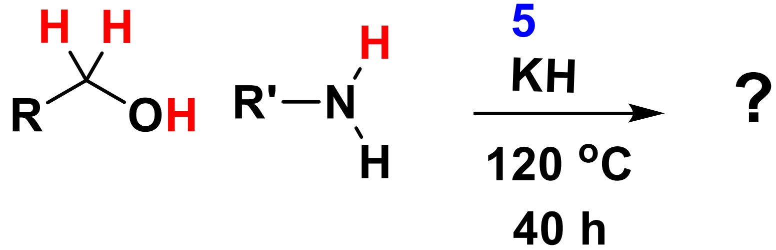
Mukherjee, A.; Nerush, A.; Leitus, L.; Shimon, J. W.; Ben-David, Y.; Espinosa-Jalapa, N. A.; Milstein, D. *J. Am. Chem. Soc.* **2016**, *138*, 4298.

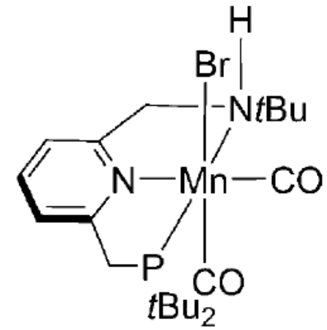
Chakraborty, S.; Gellrich, U.; Diskin-Posner, Y.; Leitus, G.; Avram, L.; Milstein, D. *Angew. Chem. Int. Ed.* **2017**, *56*, 4229.

Espinosa-Jalapa, N. A.; Kumar, A.; Leitus, G.; Diskin-Posner, Y.; Milstein, D. *J. Am. Chem. Soc.* **2017**, *139*, 11722.

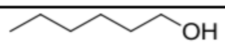
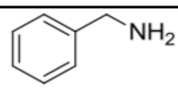
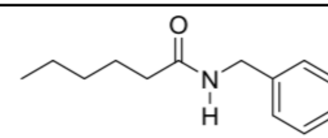
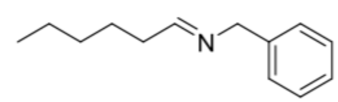
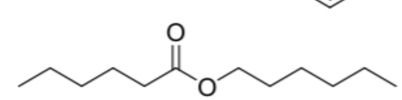
Ligand Choice 1

Milstein (2017)- This Paper: base-metal-catalysis of amides



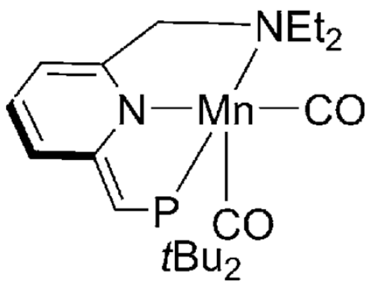


5

Entry	Alcohol	Amine	Solvent	Time (h)	Conv[a] (%)	Product(s)	Yield[b] (%)
1[c]			methyl cyclo hexane	40	70		34
							26
							18

Next Ligand Choices

Choice 2:

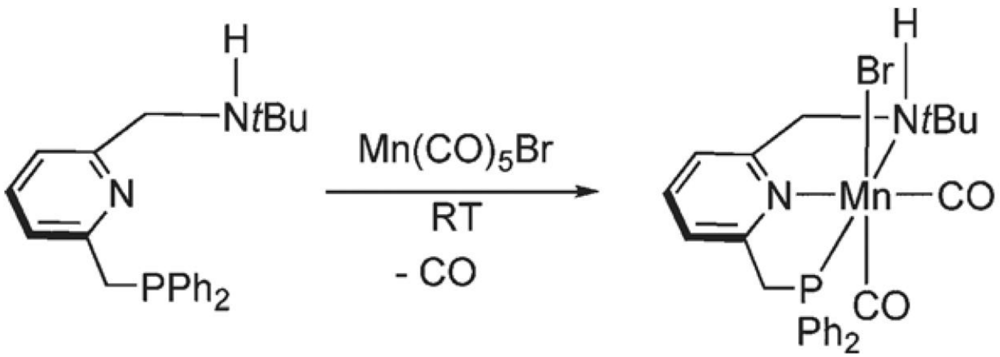


6

inactive

Analogous to Ru catalyst used for the amide coupling

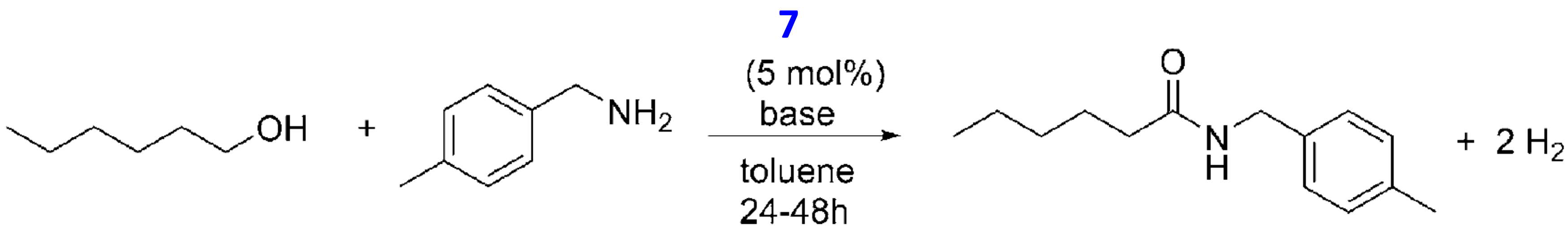
Choice 3:



7

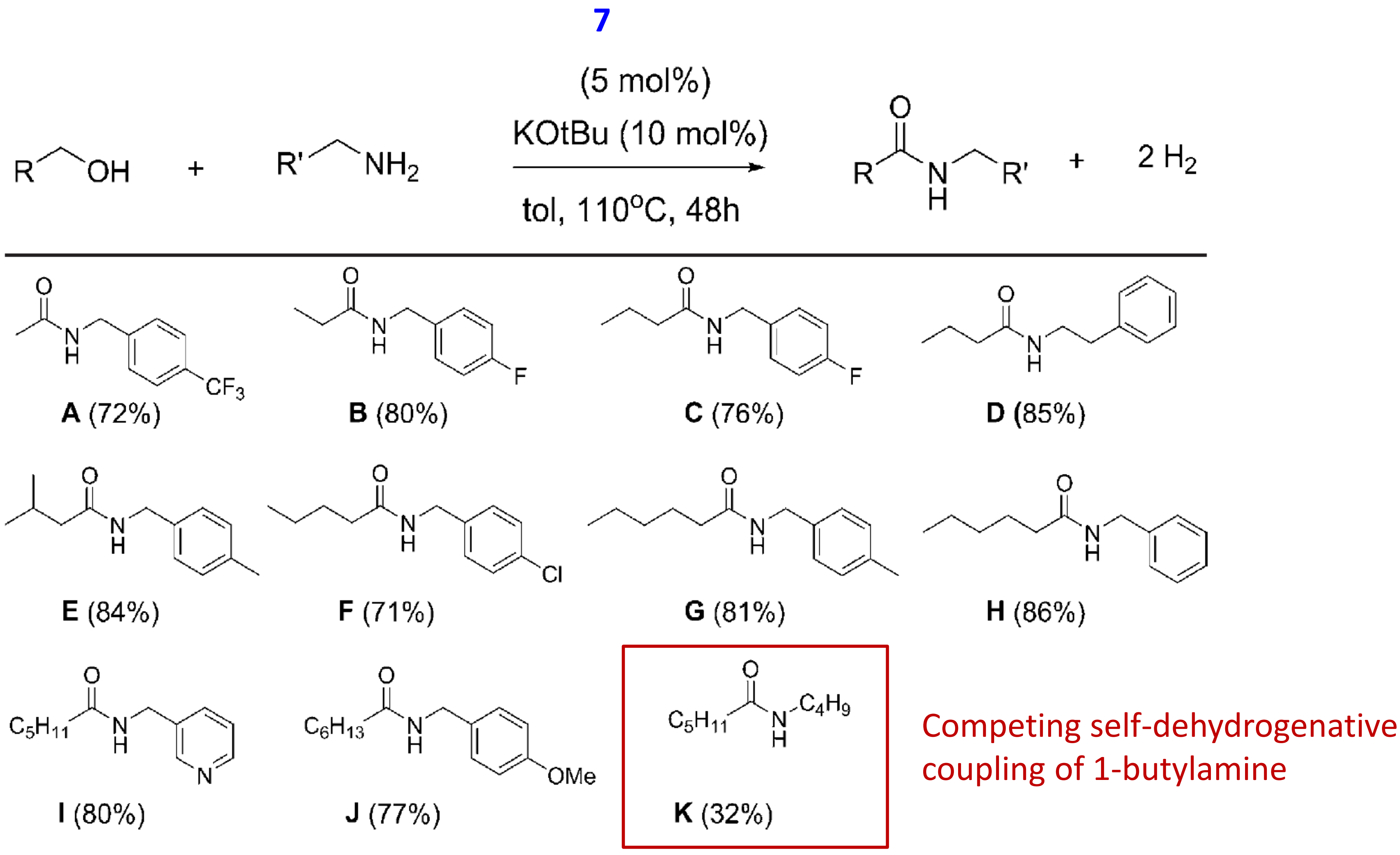
active

Reaction Optimization



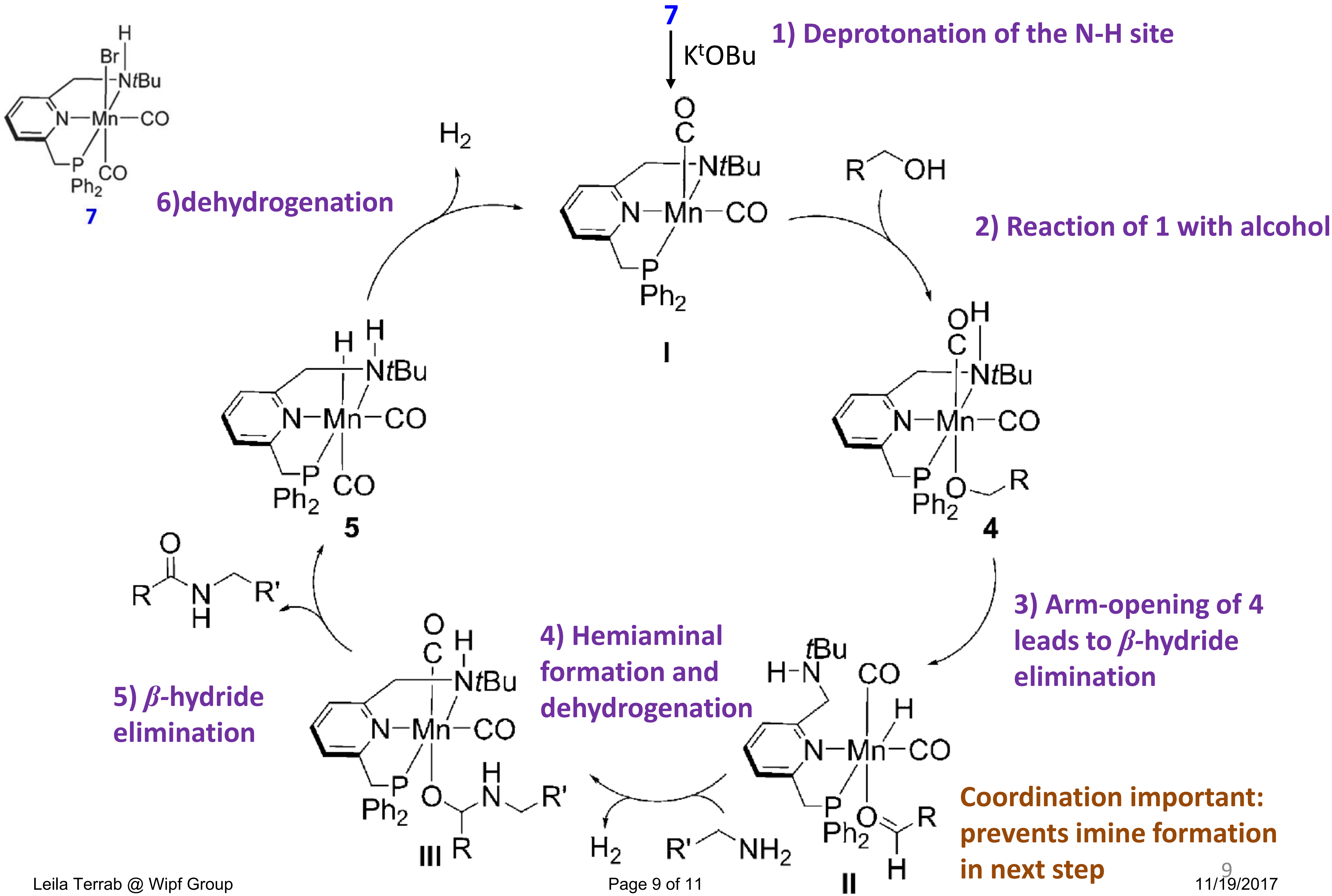
entry	time (h)	solvent	temp	base (mol%)	conversion	amide yield *
1	24	toluene	110°C	No base	0	0
2	24	toluene	110 °C	KOtBu (5%)	70%	45%
3	24	toluene	110°C	KOtBu (10%)	75%	55%
4	24	toluene	110 °C	KOtBu (20%)	27%	17%
5	24	toluene	110 °C	KOtBu (100%)	10%	10%
6	24	toluene	110 °C	KH (10%)	trace	trace
7	24	toluene	135°C	KOtBu (10%)	65%	43%
8	24	dioxane	110 °C	KOtBu (10%)	60%	40%
9	48	toluene	110°C	KOtBu (10%)	99%	89 %

Scope

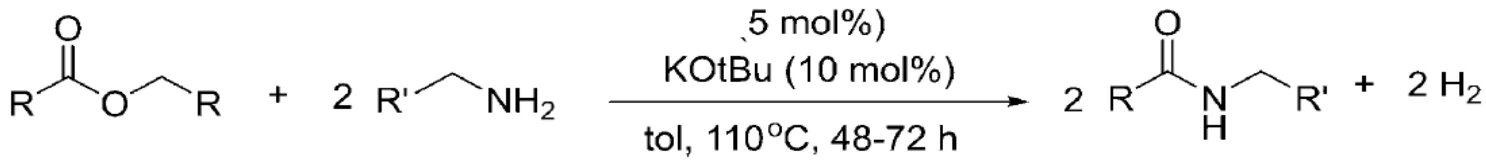


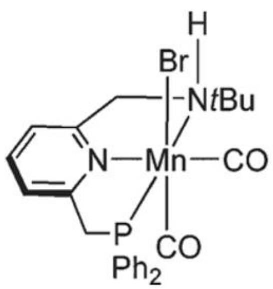
Poor yields with benzyl acohols due to imine side-products

Mechanism

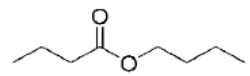
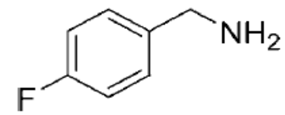
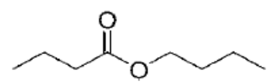
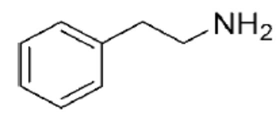
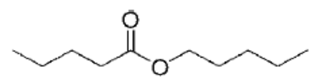
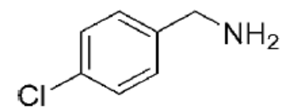
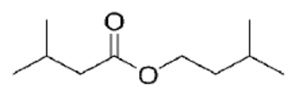
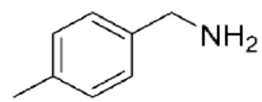
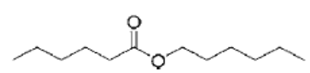
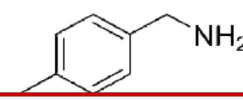
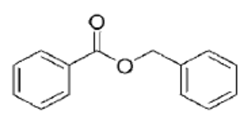
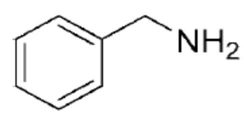
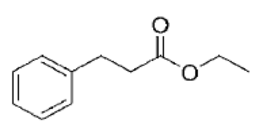
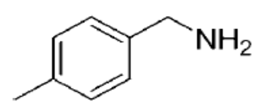
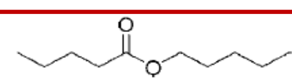
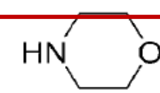
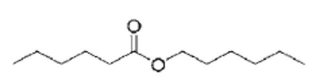
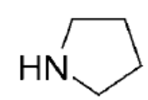
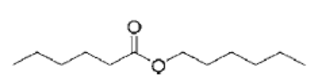
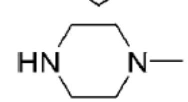

7
KtOBu
1) Deprotonation of the N-H site
2) Reaction of 1 with alcohol
3) Arm-opening of 4 leads to β-hydride elimination
4) Hemiaminal formation and dehydrogenation
5) β-hydride elimination
6)dehydrogenation
Coordination important: prevents imine formation in next step
H2
R'NH2
I
II
III
4
5
7

Amides from Esters



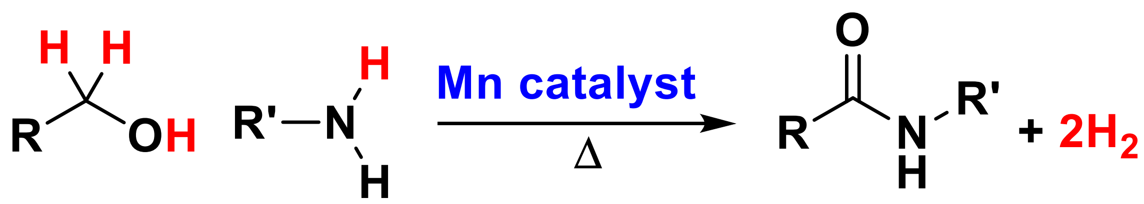


7

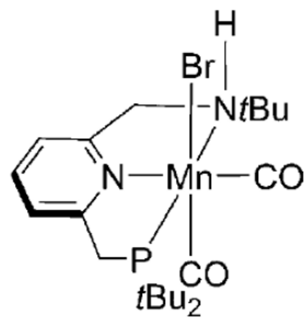
Entry	Ester	Amine	Conv. [%]	Yield [%]
1[b]			99	88
2[b]			99	85
3[b]			94	86
4[b]			91	85
5[b]			99	94
6[b]			95	55
7[c]			99	50/30
8[c]			95	95
9[c]			84	75
10[c]			75	75

Conclusion

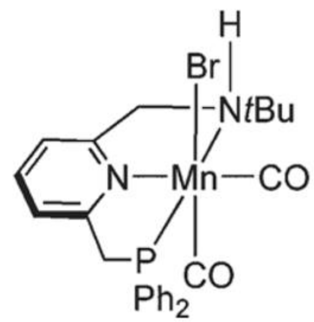
- Dehydrogenative coupling reaction between alcohols and $1^{o}/2^{o}$ amines using Mn can now be done with Mn instead of Ru.



- Optimized Ligand choice to avoid ester and imine byproducts. Lower steric bulk of **7** provides better binding than **5**. Binding crucial to selectivity: avoids imine and ester formation.



5



7

  - Used Mn ligand developed to couple esters and amides, but the selectivity is limited.