Chemoselectivity: Far to be a kid's game

Maria del Mar Sanchez

27/01/2011

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- Selectivities
- Importance of chemoselectivity
- Transformations with saturated Carbon-Heteroatom bonds
- Transformations with unsaturated Carbon-Heteroatom bonds
- Metal-promoted Carbon-Carbon bonds
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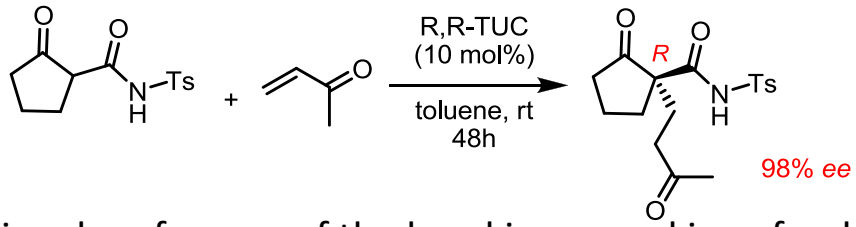
A. K. Yudin, N. A. Afagh *Angew. Chem. Int. Ed*. **2010**, *49*, 262-310.

Selectivities

Stereoselectivity: The preferential formation of one stereoisomer over another.

Enantio and diastereoselectivity

*Q. : **How** it will react?*

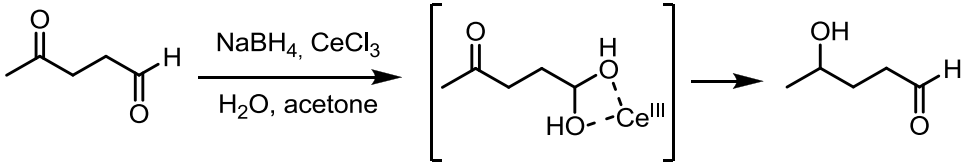


Regioselectivity: directional preference of the breaking or making of a chemical bond.

*Q. : **Where** it will react?*

Chemoselectivity: The preferential reaction of a chemical reagent with one of two or more different functional groups.

*Q. : **Which** functional group will react?*

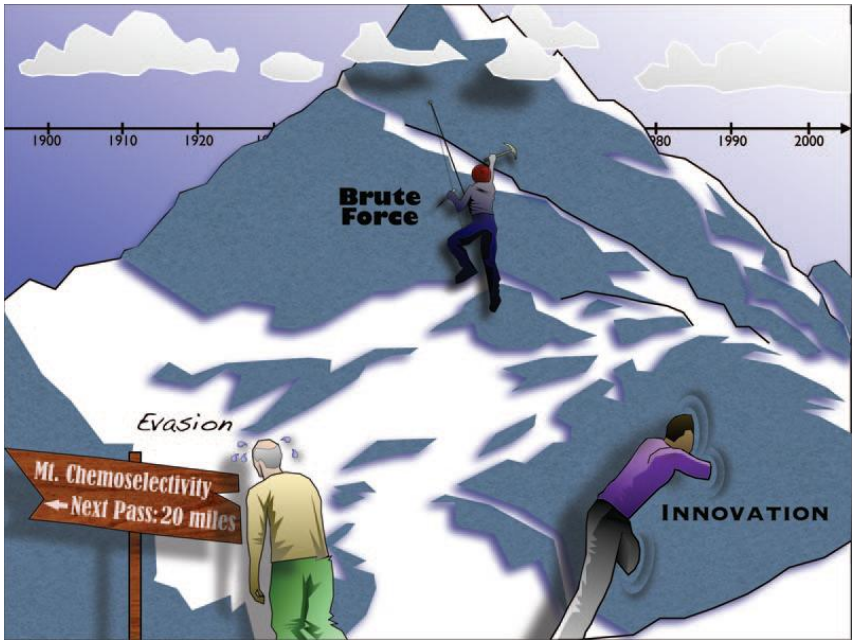


Importance of Chemoselectivity

In Total Synthesis:

➡ Obstacle to complex molecules synthesis

Nature vs Man



Tools to compare or predict reactivity:

Electronic/steric effect,
redox potential, pKa values,
hard/ soft acid/base

Advantage:

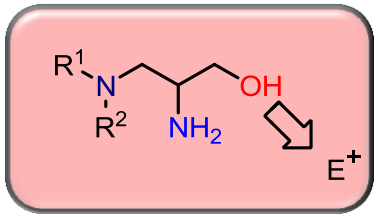
- Minimal reliance on protecting groups
- Atom and step economy

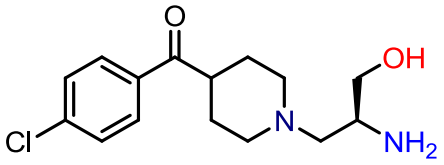
R. A. Shenvi, D. P. O'Malley, P. S. Baran, *Acc. Chem. Res.*, **2009**, *42* , 530–541.

Saturated Carbon-Heteroatom

Amine vs Hydroxy groups

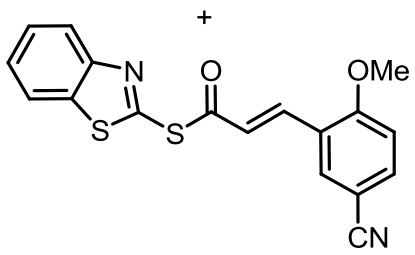
Proton-Mediated chemoselectivity





x 2 HCl

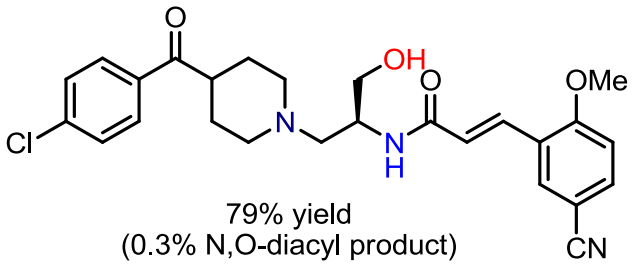
+



Mercapto benzothiazolyl thioester

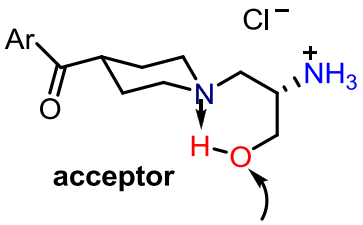
NMM (1 equiv)

EtOH, 45°C, 24h

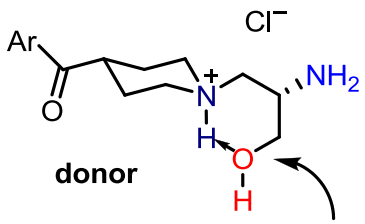


79% yield
(0.3% N,O-diacyl product)

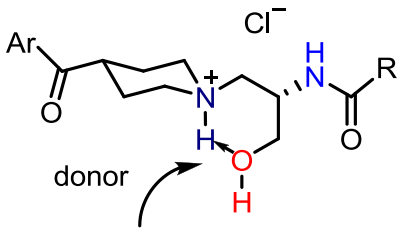
Starting material



NMM (1 equiv)



Product



enhance nucleophilicity

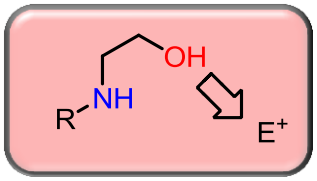
reduced nucleophilicity

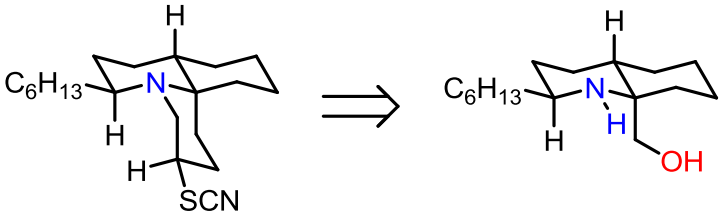
T. Storz, P. Dittmar, D. Grimler, M. Testa, H. Potgeter, D. Chappel, O. Hartmann, D. Niederer, M. Truby, *Org. Process Res. Dev*. **2006**, *10*, 1184 – 1191.

Saturated Carbon-Heteroatom

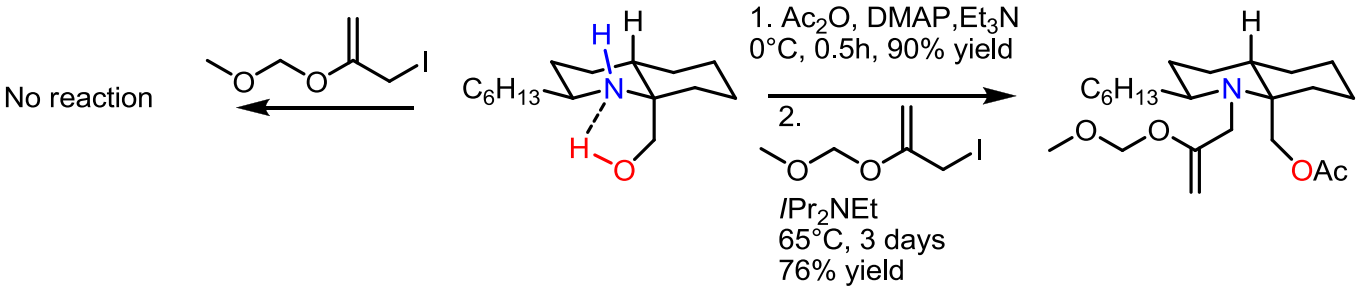
Amine vs Hydroxy groups

Proton-Mediated chemoselectivity





(±)-Fasicularin

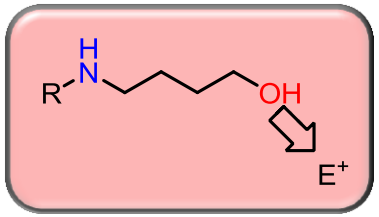


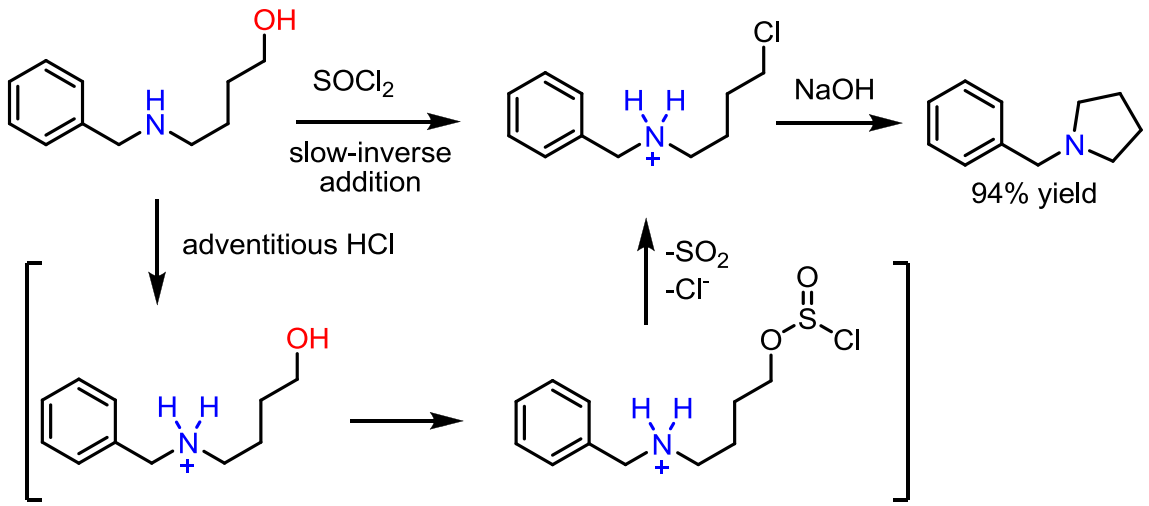
J. H. Maeng, R. L. Funk, *Org. Lett*. **2002**, *4*, 331 – 333

Saturated Carbon-Heteroatom

Amine vs Hydroxy groups

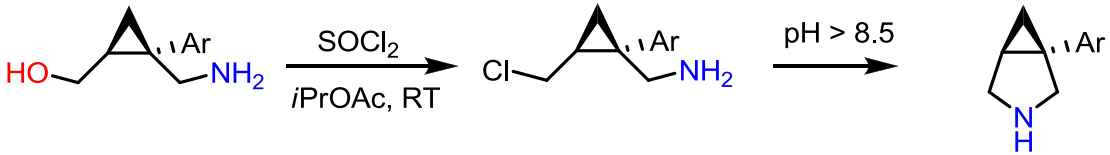
Proton-Mediated chemoselectivity





In situ protection of the amine by a proton.

Application:



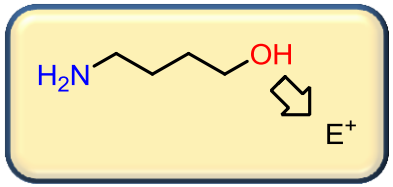
(+)-Bicifadine, 65% yield (Ar = *p*-MeC_6H_4)
DOV2194, 57% yield (Ar = 3,4-$Cl_2C_6H_3$)

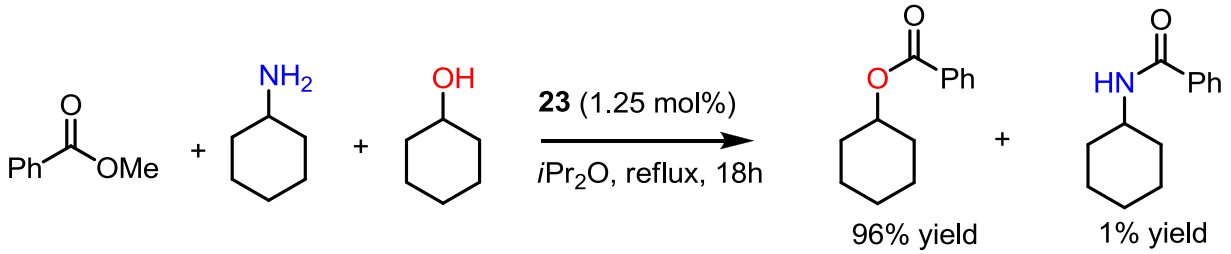
F. Xu, B. Simmons, R. A. Reamer, E. Corley, J. Murry, D.Tschaen, *J. Org. Chem*. **2008**, *73,* 312 – 315.
F. Xu, J. A. Murry, B. Simmons, E. Corley, K. Fitch, S. Karady, D. Tschaen, *Org. Lett*. **2006**, *8*, 3885 – 3888.

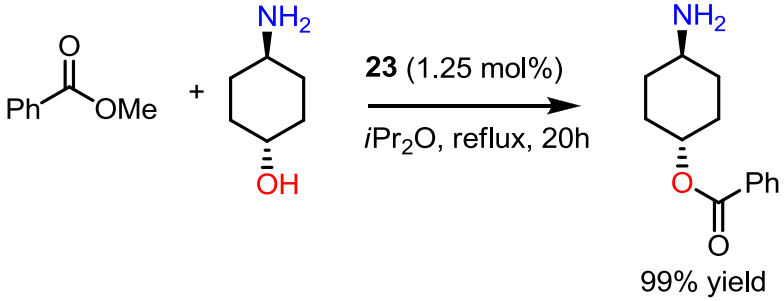
Saturated Carbon-Heteroatom

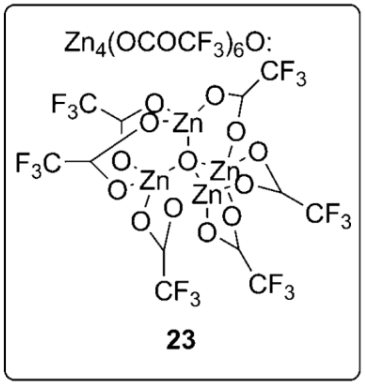
Amine vs Hydroxy groups

Metal-Mediated Chemoselectivity









Chemoselectivity controlled by the high oxophilicity of the Zn cluster.

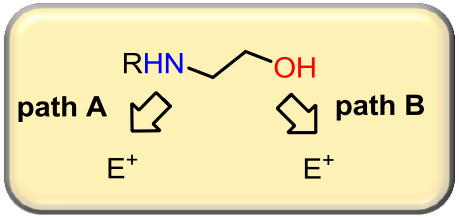
enzyme-like chemoselective reaction

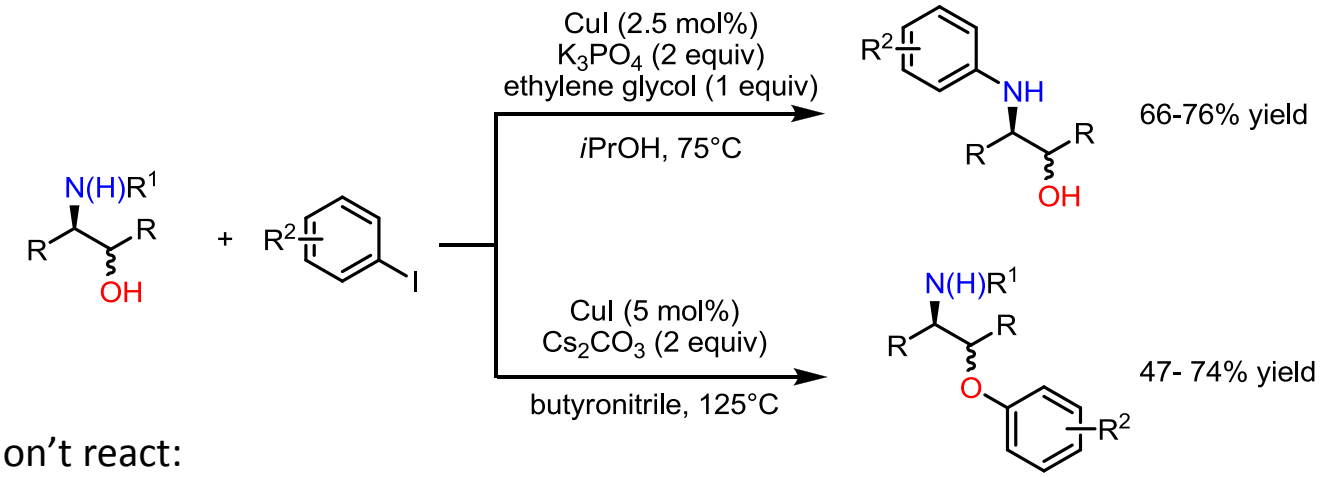
T. Ohshima, T. Iwasaki, Y. Maegawa, A. Yoshiyama, K. Mashima, *J. Am. Chem. Soc.* **2008**, *130*, 2944 – 2945.

Saturated Carbon-Heteroatom

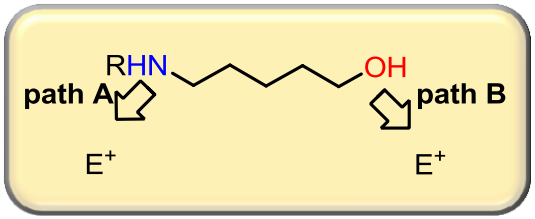
Amine vs Hydroxy groups

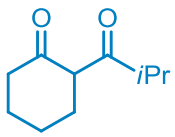
Metal-Mediated Chemoselectivity



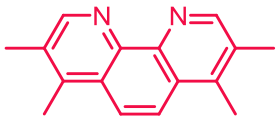


Simple alcohols or amines don't react:
chelating ability of β-amino alcohols for reactivity

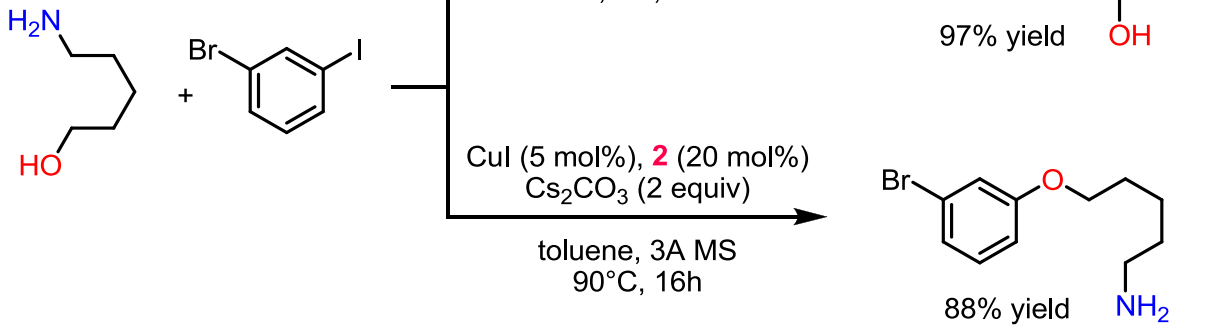




1
N-arylation



2
O-arylation



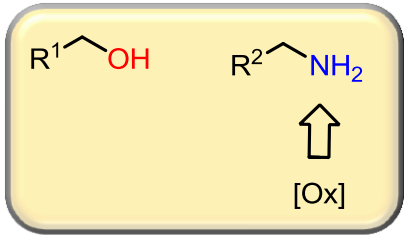
G. E. Job, S. L. Buchwald, *Org. Lett.* **2002**, *4*, 3703 – 3706.

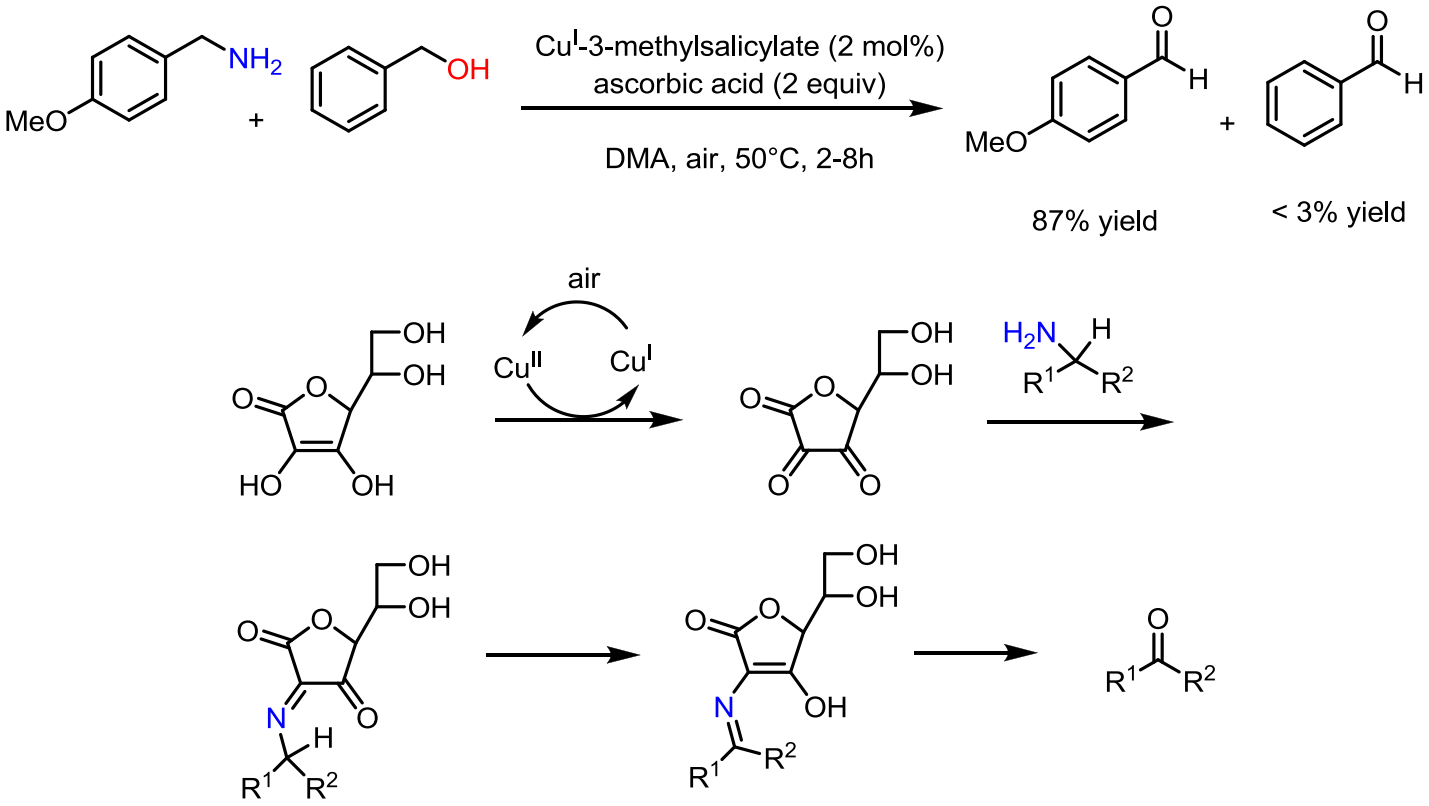
A. Shafir, P. A. Lichtor, S. L. Buchwald, *J. Am. Chem. Soc.* **2007**, *129*, 3490 – 3491.

Saturated Carbon-Heteroatom

Amine vs Hydroxy groups

Metal-Mediated Chemoselectivity



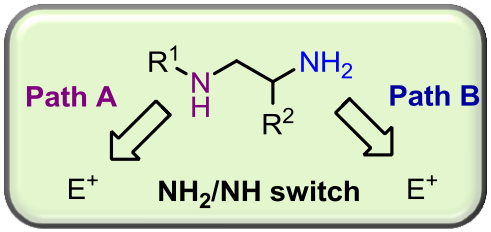


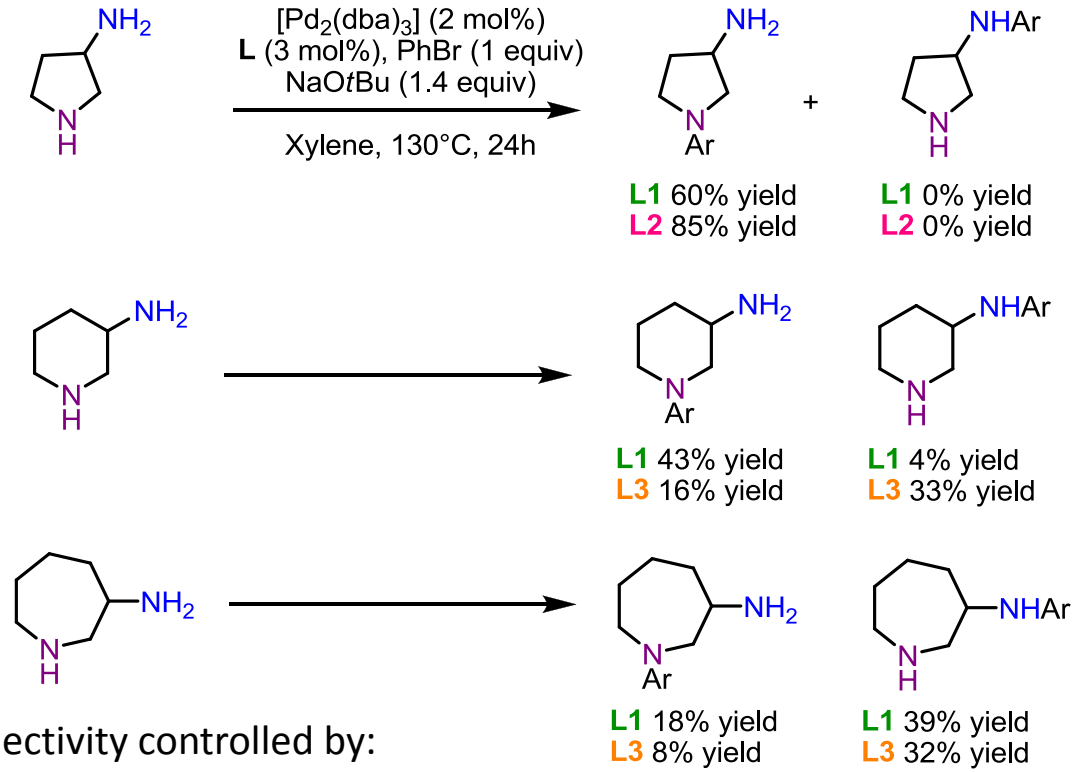
J. Srogl, S. Voltrova, *Org. Lett*. **2009**, *11*, 843 – 845.

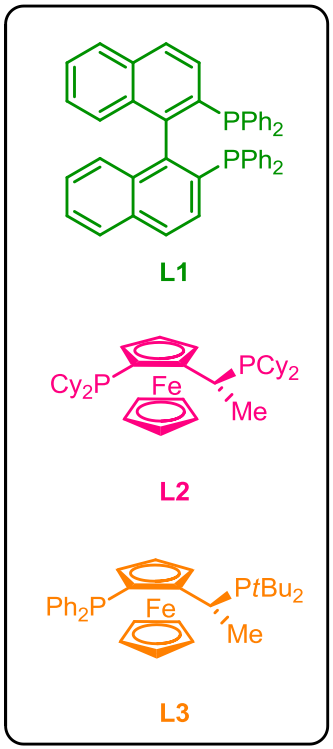
Saturated Carbon-Heteroatom

Oligoamines

Metal-Mediated Chemoselectivity







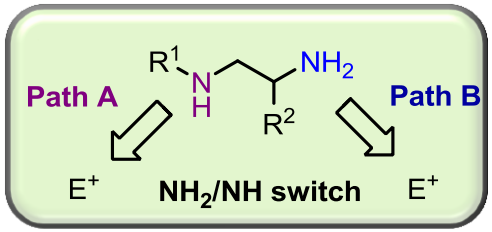
Chemoselectivity controlled by:
- Steric/electronic environment of **L**
- Ring size of diamine

N. Cabello-Sanchez, L. Jean, J. Maddaluno, M.-C. Lasne, J. Rouden, *J. Org. Chem*. **2007**, *72*, 2030 – 2039.

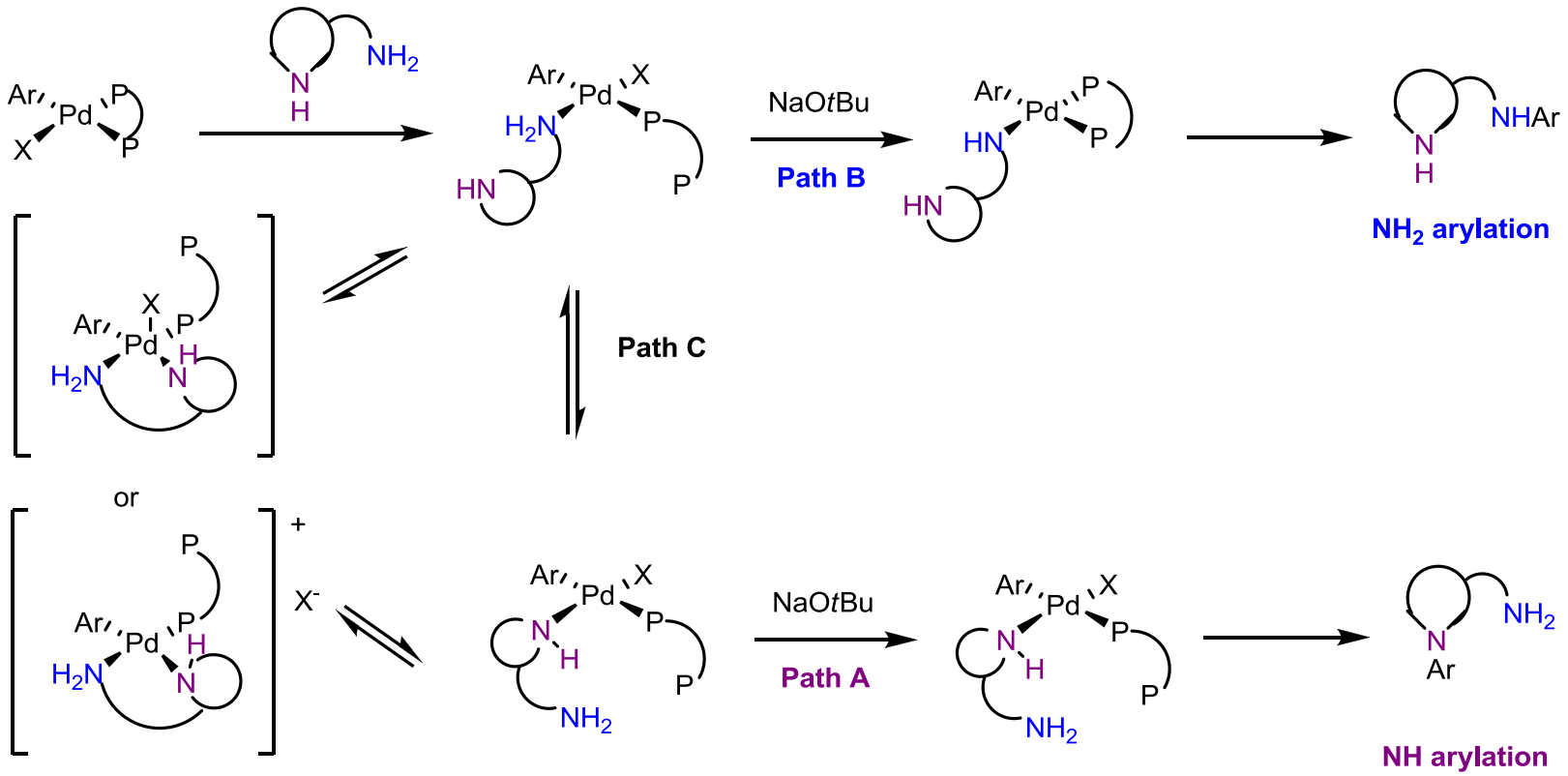
Saturated Carbon-Heteroatom

Oligoamines

Metal-Mediated Chemoselectivity



Mechanism

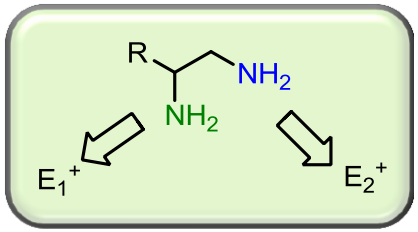


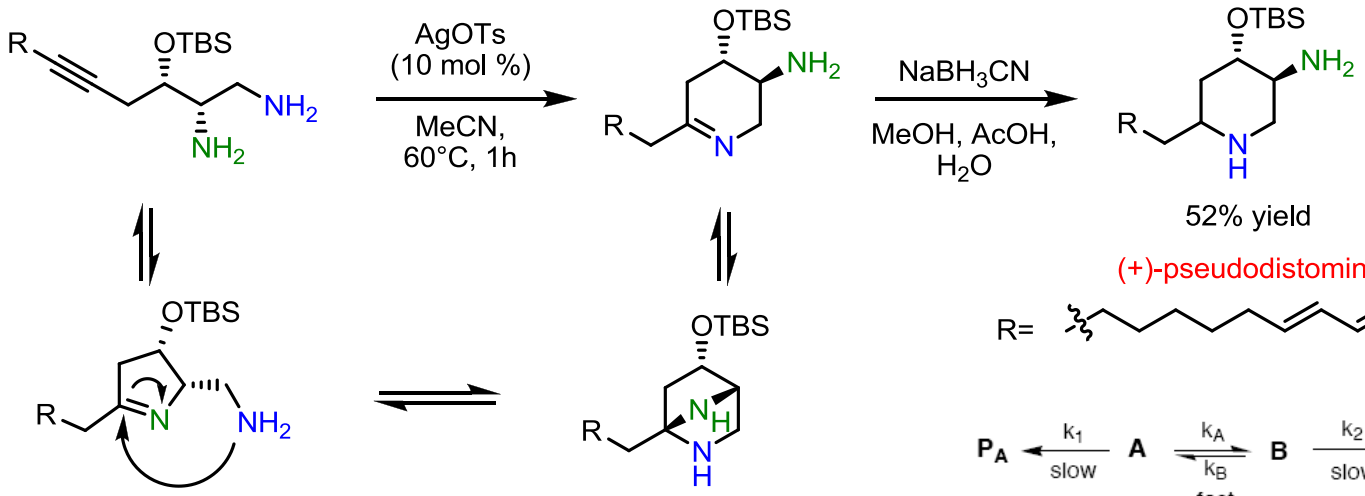
Azanorbornyl conformations

A. Corruble, D. Davoust, S. Desjardins, C. Fressign, C. Giessner-Prettre, A. Harrisson-Marchand, H. Houte, M.-C. Lasne, J. Maddaluno, H. Oulyadi, J.-Y. Valnot, *J. Am. Chem. Soc*. **2002**, *124*, 15267 – 15279.

Saturated Carbon-Heteroatom

Oligoamines

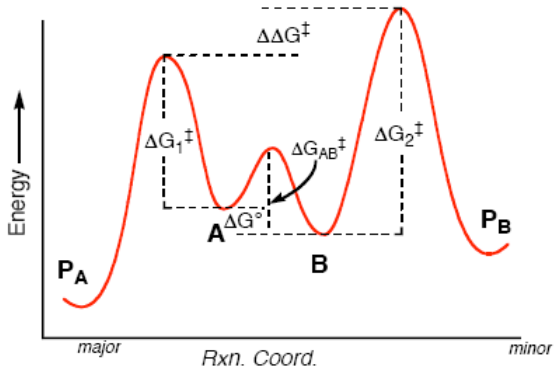




Selectivity based on Curtin-Hammett principle:

« The product composition P_A vs P_B is not solely dependent on relative proportions of the conformational isomers in the substrate;

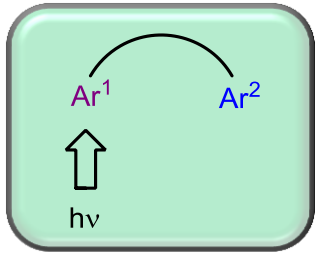
It is controlled by the difference in the free energie ($\Delta\Delta G^{\pm}$) of the respective transition states. »

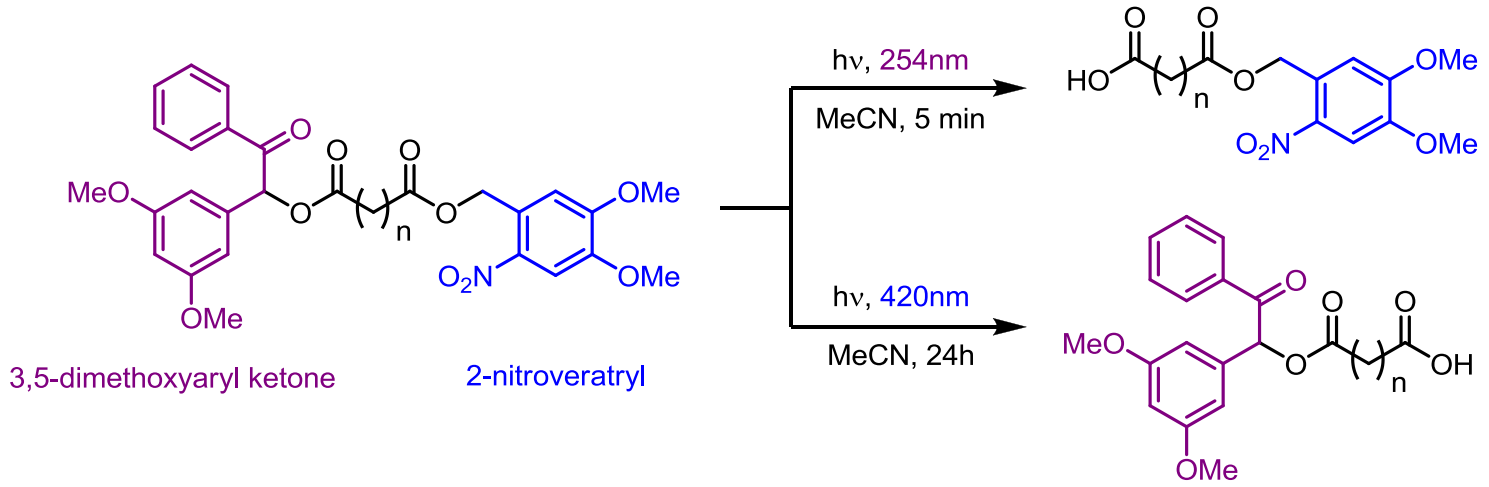


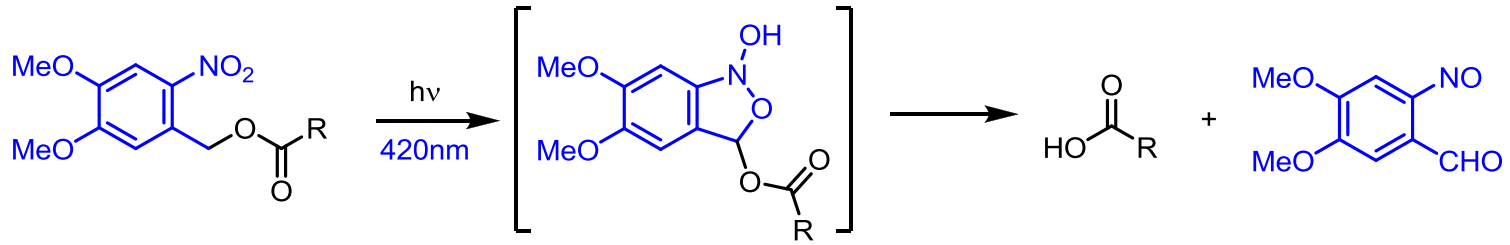
B. M. Trost, D. R. Fandrick, *Org. Lett*. **2005**, *7*, 823 – 826.

Saturated Carbon-Heteroatom

Chromatic orthogonality





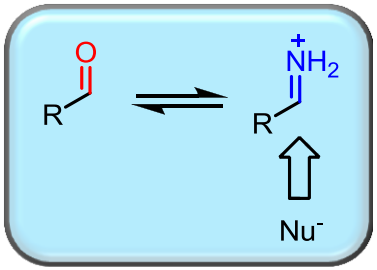


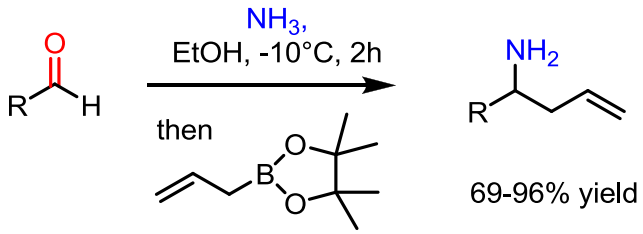
Chemoselectivity controlled by:
wavelength of irradiation

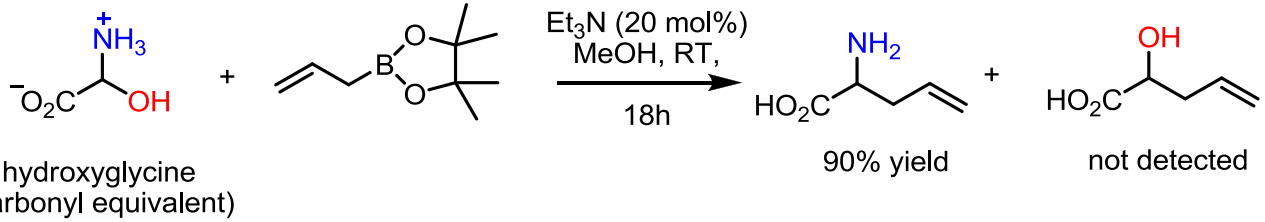
C. G. Bochet, *Angew. Chem*. **2001**, *113*, 2140 – 2142; *Angew. Chem. Int. Ed*. **2001**, *40*, 2071 – 2073.

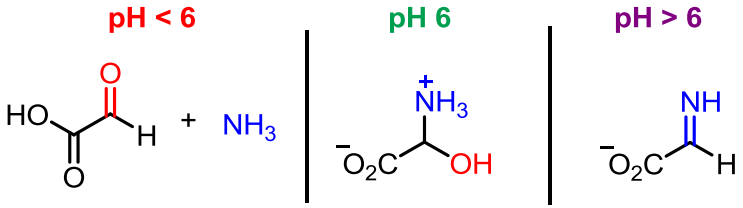
Unsaturated Carbon-Heteroatom

Iminium electrophiles







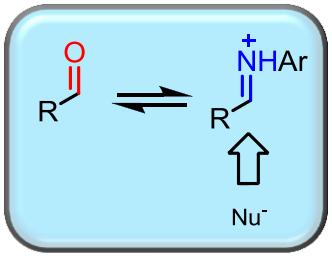


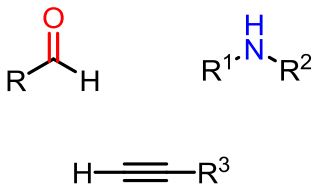
M. Sugiura, K. Hirano, S. Kobayashi, *J. Am. Chem. Soc*. **2004**, *126*, 7182 – 7183.

M. Sugiura, C. Mori, K. Hirano, S. Kobayashi, *Can. J. Chem*. **2005**, *83*, 937 – 942.

Unsaturated Carbon-Heteroatom

Iminium electrophiles

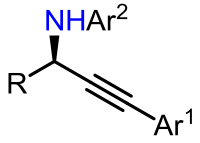




Li

Cu(OTf)/ pybox (10 mol%)

H_2O or toluene
22-35°C, 1-4 days

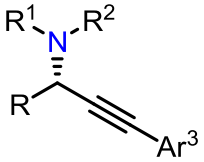


56-93% yield
78-96% *ee*

Knochel

CuBr (5 mol%)
(R)-quinap (5.5 mol%)

toluene, RT, 1-6 days

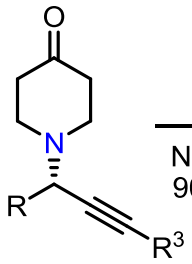


43-99% yield
32-96% *ee*

Carreira

CuBr (5 mol%)
(R)-pinap (5.5 mol%)
Et_3N (1.1 equiv)

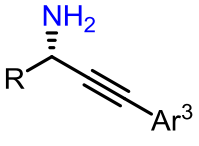
4A MS, toluene, 3-5 days



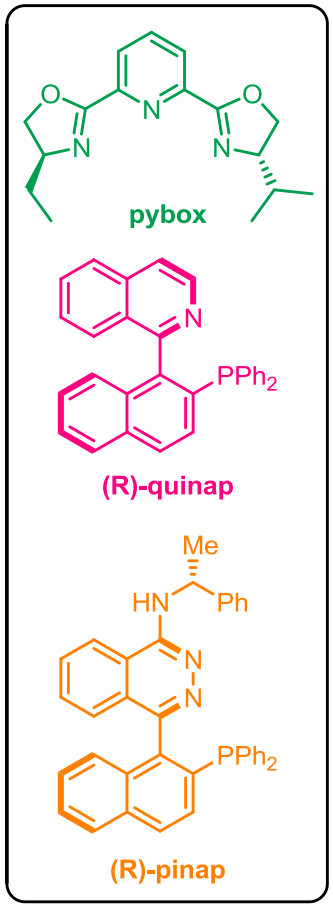
58-92% yield
70-96% *ee*

NH_4Cl

NH_3/EtOH
90°C, 14h



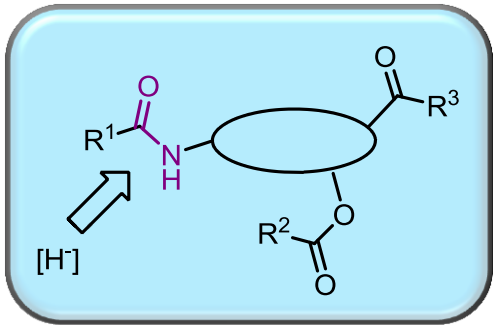
75% yield



C. Wei, C.-J. Li, *J. Am. Chem. Soc*. **2002**, *124*, 5638 – 5639.; N. Gommermann, C. Koradin, K. Polborn, P. Knochel, *Angew. Chem. Int. Ed*. **2003**, *42*, 5763 – 5766; P. Aschwanden, C. R. J. Stephenson, E. M. Carreira, *Org. Lett*. **2006**, *8*, 2437 – 2440.

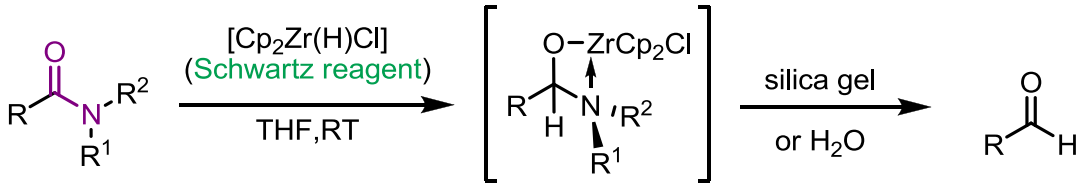
Unsaturated Carbon-Heteroatom

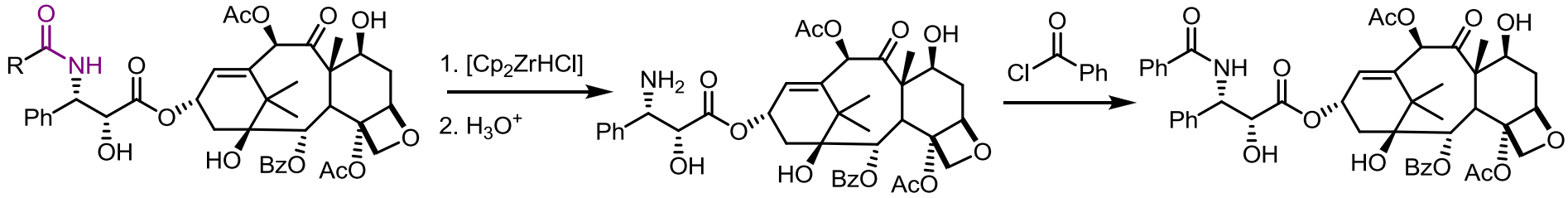
Iminium electrophiles



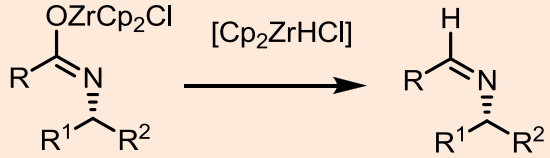
Compatible with:
esters, nitriles, nitro, carbamates, alkenes, internal alkynes

Not compatible with:
aromatic ketones, terminal alkynes





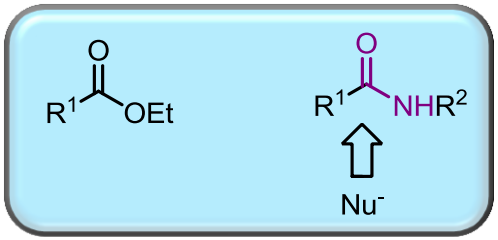
via:



J. M. White, A. R. Tumoori, G. I. Georg, *J. Am. Chem. Soc.* **2000**, *122*, 11995 – 11996.
B. Ganem, R. R. Franke, *J. Org. Chem*. **2007**, *72*, 3981 – 3987.

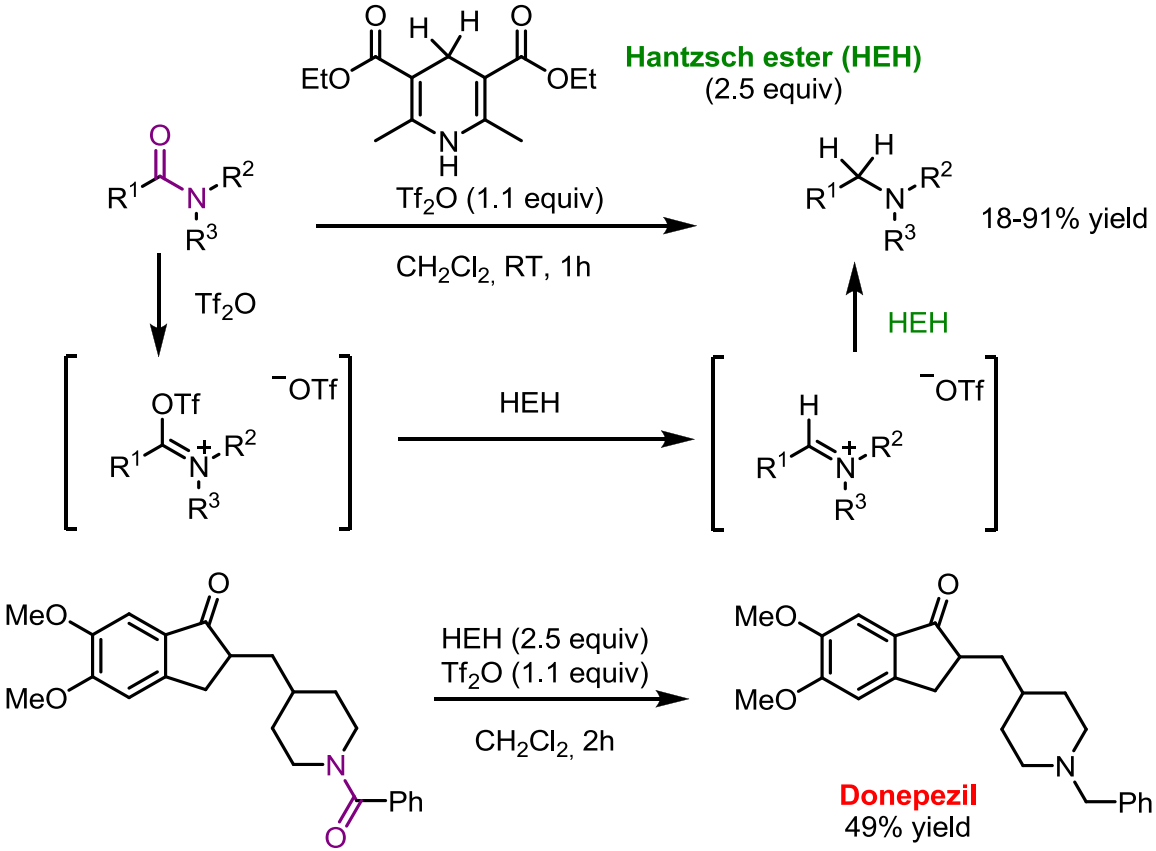
Unsaturated Carbon-Heteroatom

Iminium electrophiles



Compatible with:

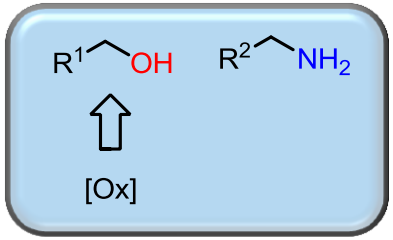
ketones, esters, α,β-unsaturated esters, nitriles, epoxides, alkynes, ethers

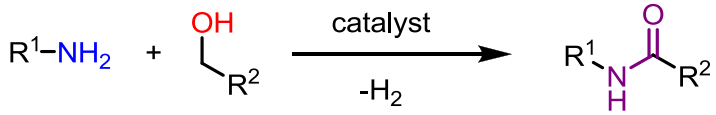


G. Barbe, A. B. Charette, *J. Am. Chem. Soc.* **2008**, *130*, 18 – 19.

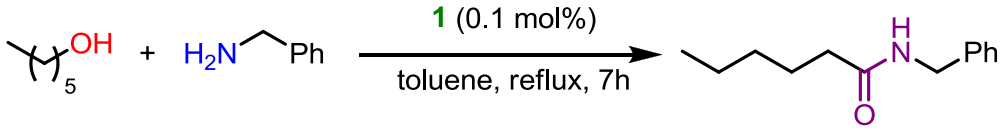
Unsaturated Carbon-Heteroatom

Redox processes



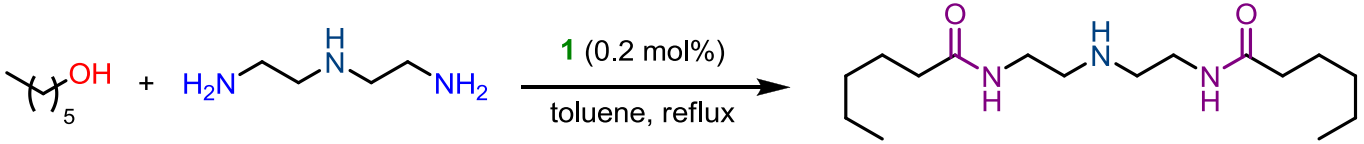


A)

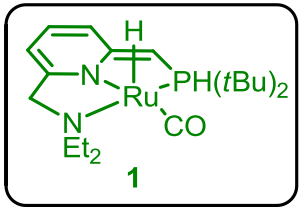


96% yield

B)



88% yield

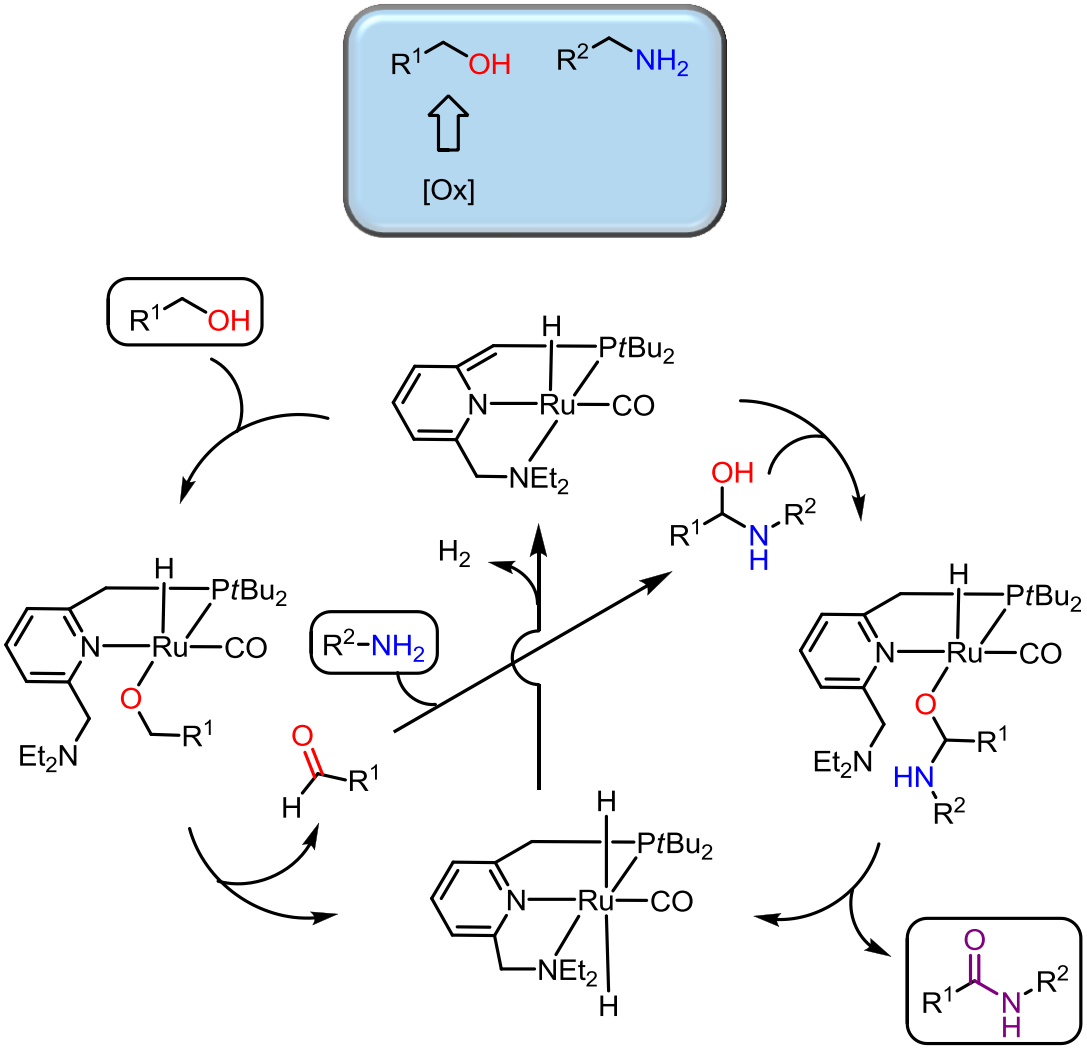


C. Gunanathan, Y. Ben-David, D. Milstein, *Science* **2007**, *317*, 790 – 792.

Unsaturated Carbon-Heteroatom

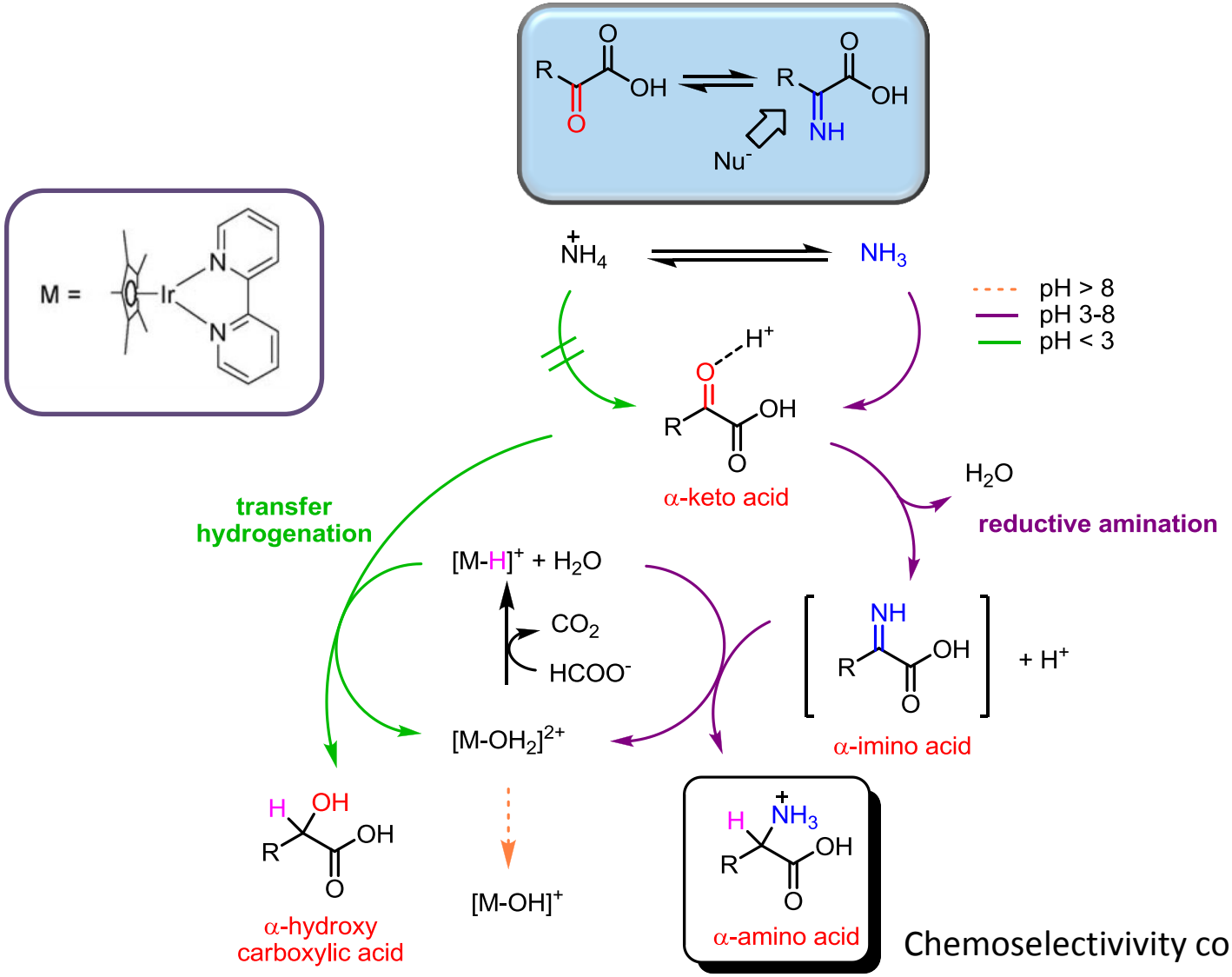
Redox processes

Mechanism:



Unsaturated Carbon-Heteroatom

Redox processes

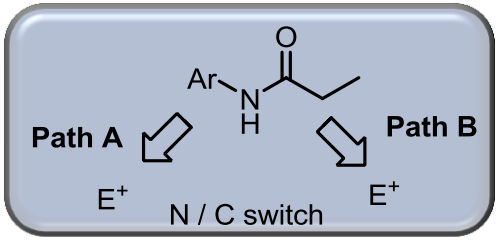


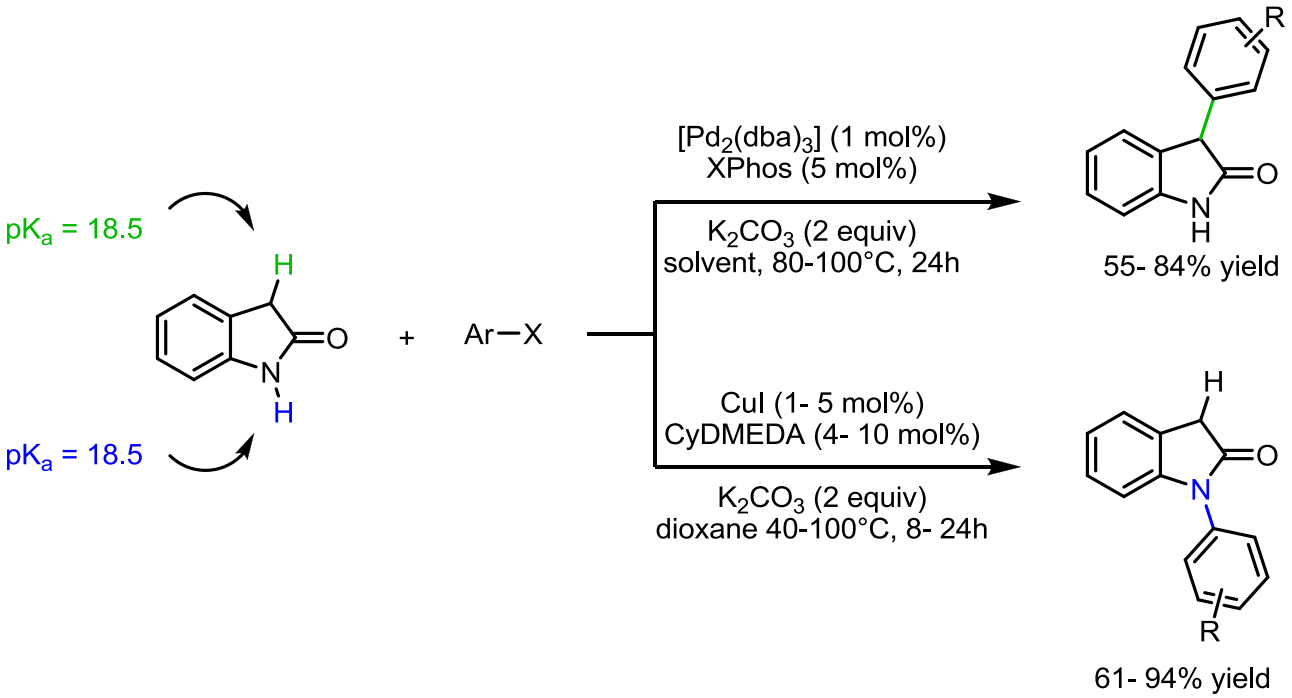
Chemoselectivivity controlled by pH

S. Ogo, K. Uehara, T. Abura, S. Fukuzumi, *J. Am. Chem. Soc*. **2004**, *126*, 3020 – 3021.

Unsaturated Carbon-Heteroatom

Cabon-Carbon vs Carbon-Heteroatom



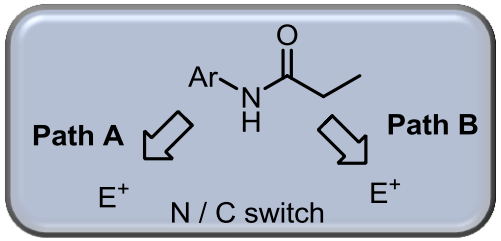


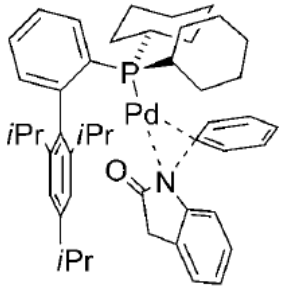
R. A. Altman, A. M. Hyde, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc*. **2008**, *130*, 9613 – 9620.

Unsaturated Carbon-Heteroatom

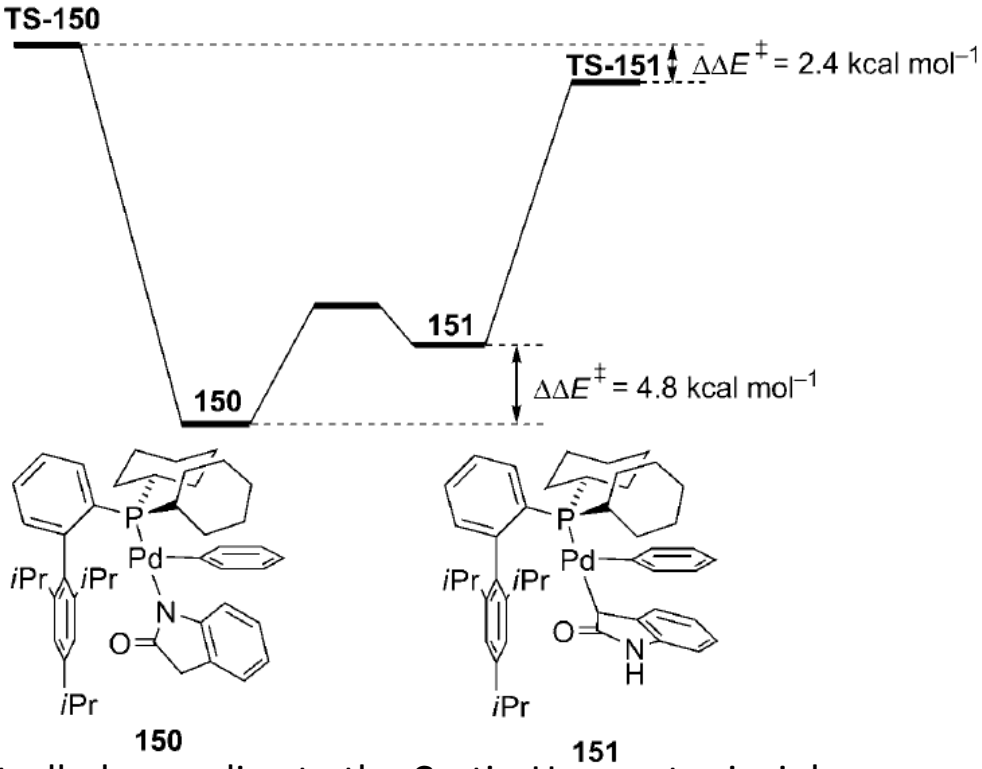
Cabon-Carbon vs Carbon-Heteroatom

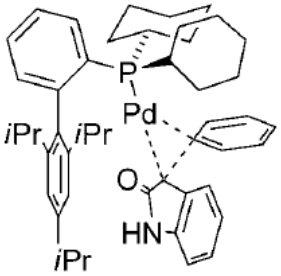
C-Arylation





TS-150





TS-151

150

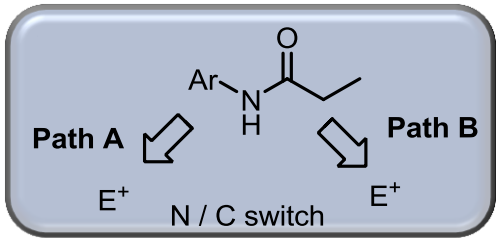
151

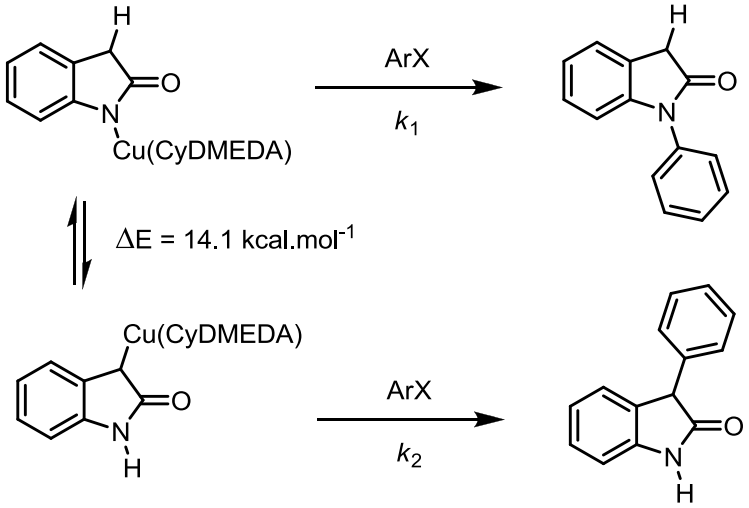
Chemoselectivity controlled according to the Curtin-Hammet principle

Unsaturated Carbon-Heteroatom

Cabon-Carbon vs Carbon-Heteroatom

N-Arylation



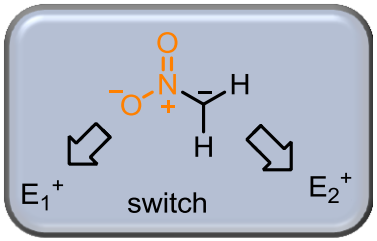


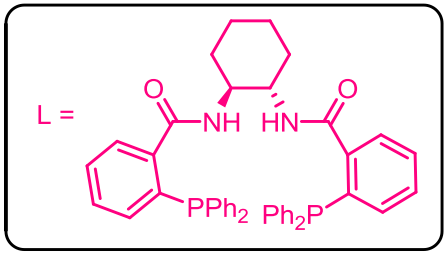
2 possible explanations of selectivity:

- Not interconversion
- $k_1 >> k_2$

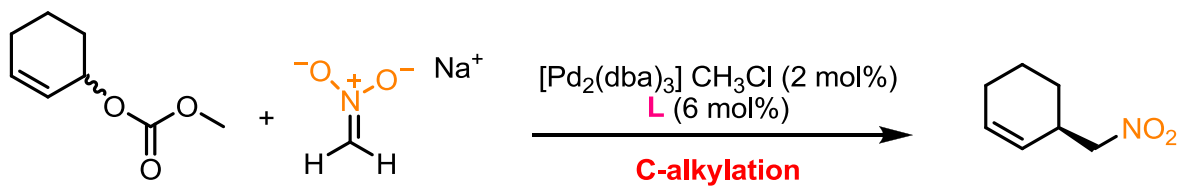
Unsaturated Carbon-Heteroatom

Cabon-Carbon vs Carbon-Heteroatom

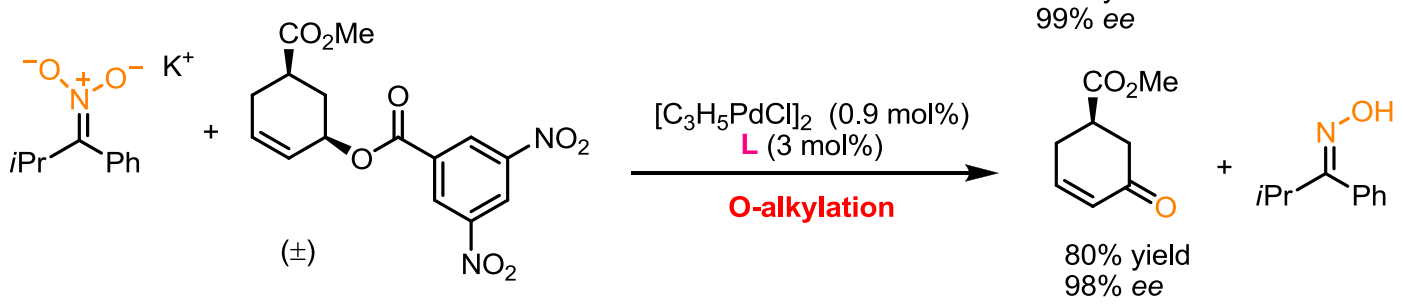


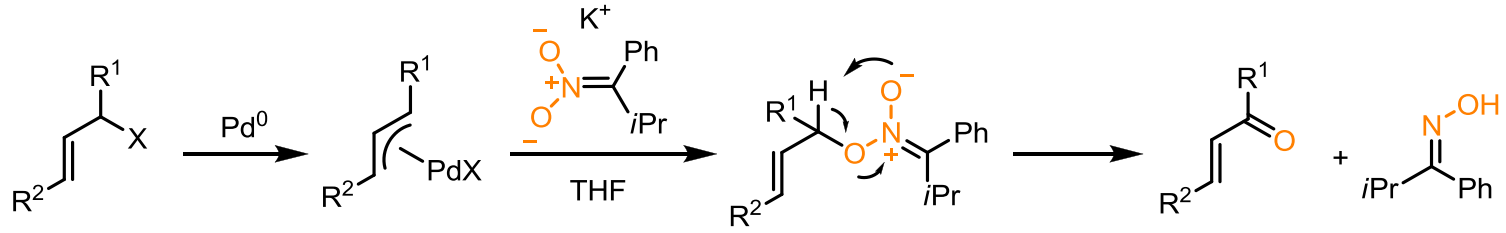


A)



B)



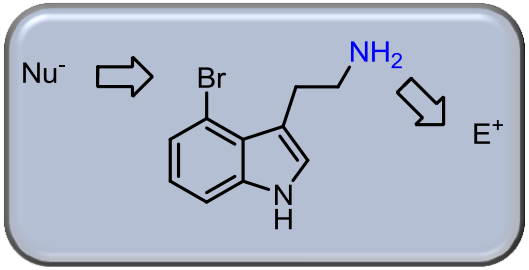


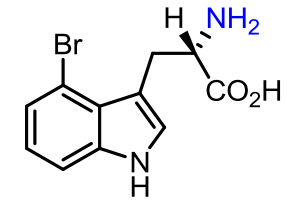
Chemoselectivity controlled by :
steric/ electronic properties of the nitronate

B. M. Trost, J.-P. Surivet, *Angew. Chem. Int. Ed*. **2000**, *39*, 3122 – 3124,
B. M. Trost, J. Richardson, K. Yong, *J. Am. Chem. Soc*. **2006**, *128*, 2540 – 2541.

Unsaturated Carbon-Heteroatom

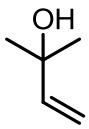
Cabon-Carbon vs Carbon-Heteroatom





4-bromotryptophan

+

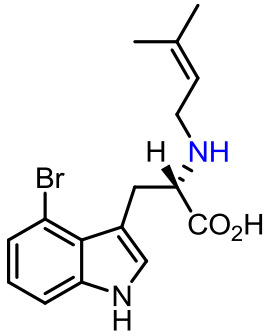


22 equiv

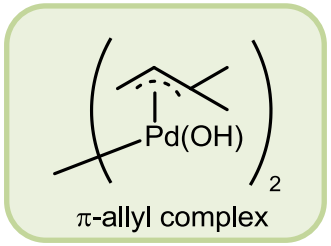
N-allylation

$Pd(OAc)_2$ (0.1 equiv)
TPPTS (0.2 equiv)
AcONa (2 equiv) in H_2O

120°C, 4.5h
sealed tube
weakly basic



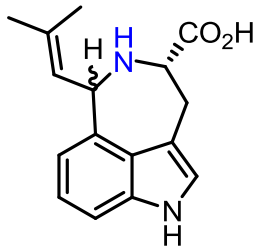
34% yield



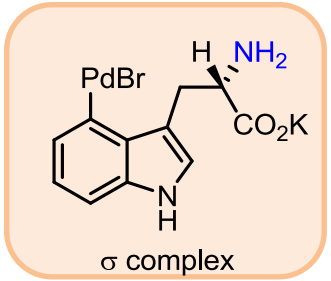
Heck

$Pd(OAc)_2$ (0.1 equiv)
TPPTS (0.2 equiv)
K_2CO_3 (3 equiv) in H_2O

130°C, 6h
sealed tube
strongly basic



91% yield

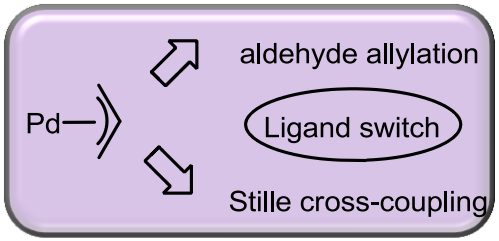


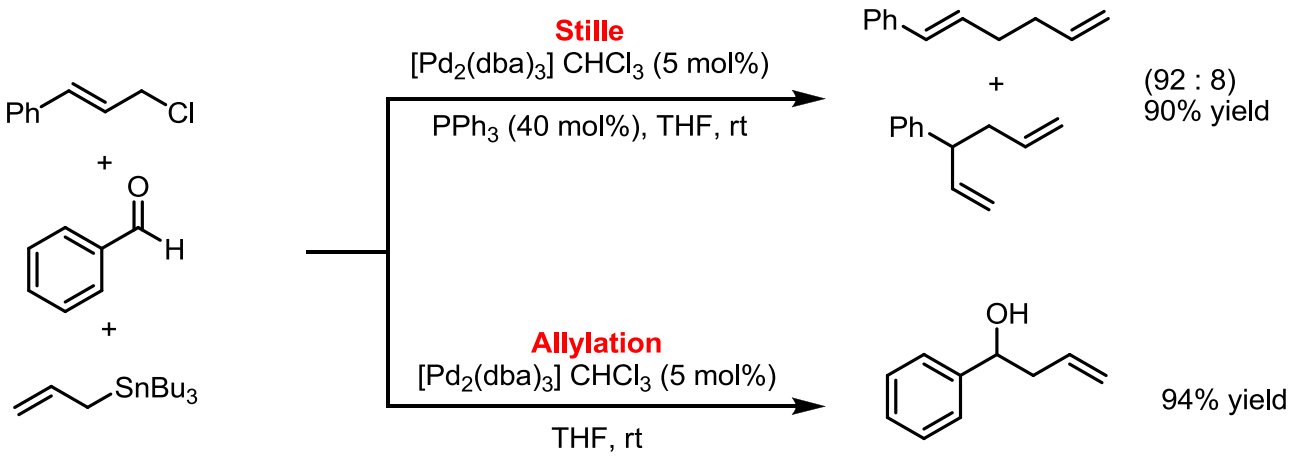
Chemoselectivivity controlled by pH

Y. Yokoyama, H. Hikawa, M. Mitsuhashi, A. Uyama, Y. Hiroki, Y. Murakami, *Eur. J. Org. Chem*. **2004**, 1244 – 1253.

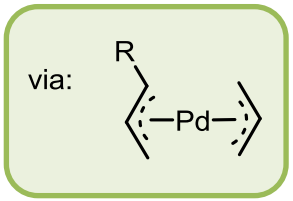
Unsaturated Carbon-Heteroatom

Cabon-Carbon couplings





Chemoselectivity controlled by:
presence/absence of PPh_3

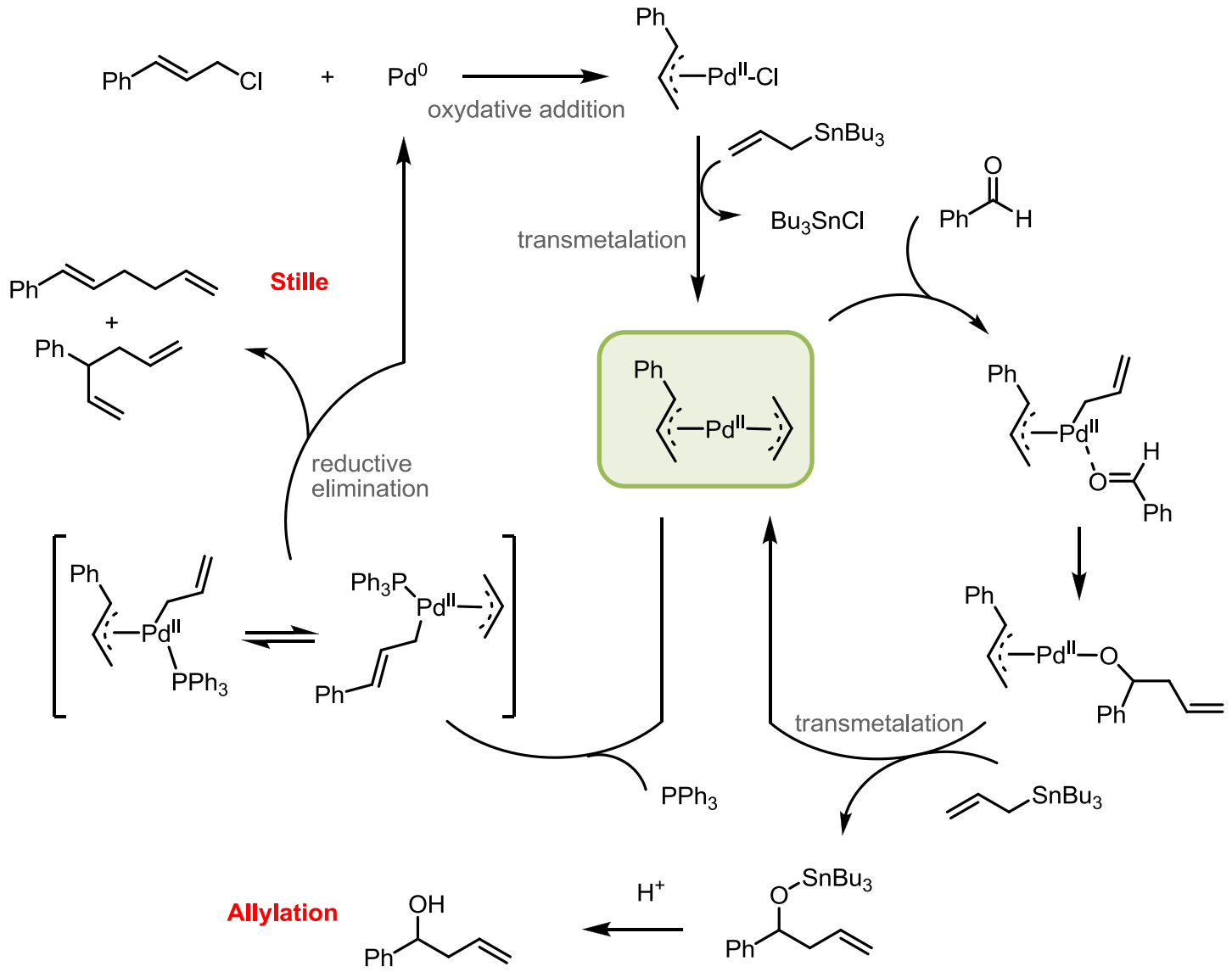


H. Nakamura, M. Bao, Y. Yamamoto, *Angew. Chem*. **2001**, *113*, 3308 – 3310; *Angew. Chem. Int. Ed*. **2001**, *40*, 3208 – 3210.

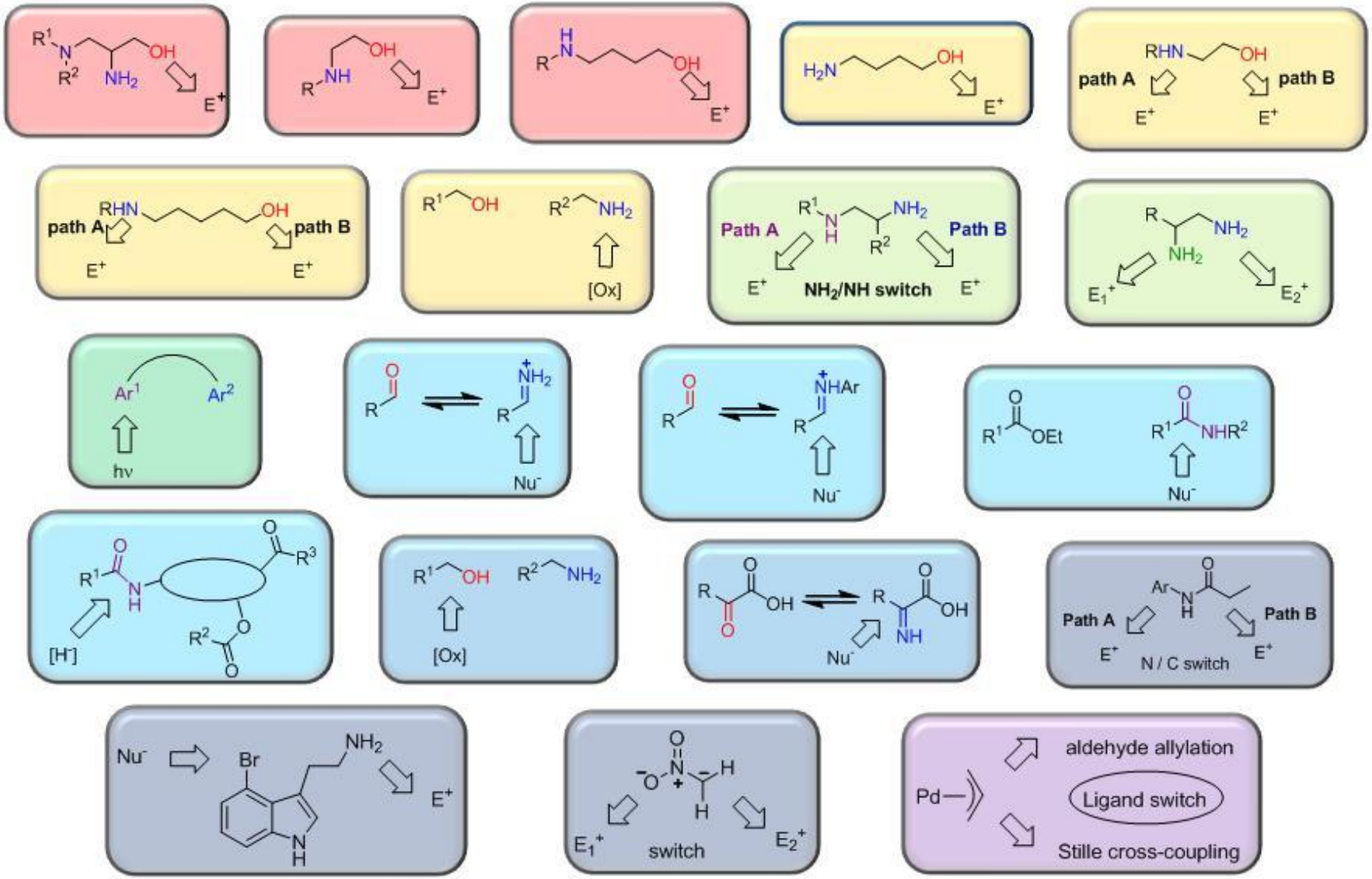
Unsaturated Carbon-Heteroatom

Cabon-Carbon couplings

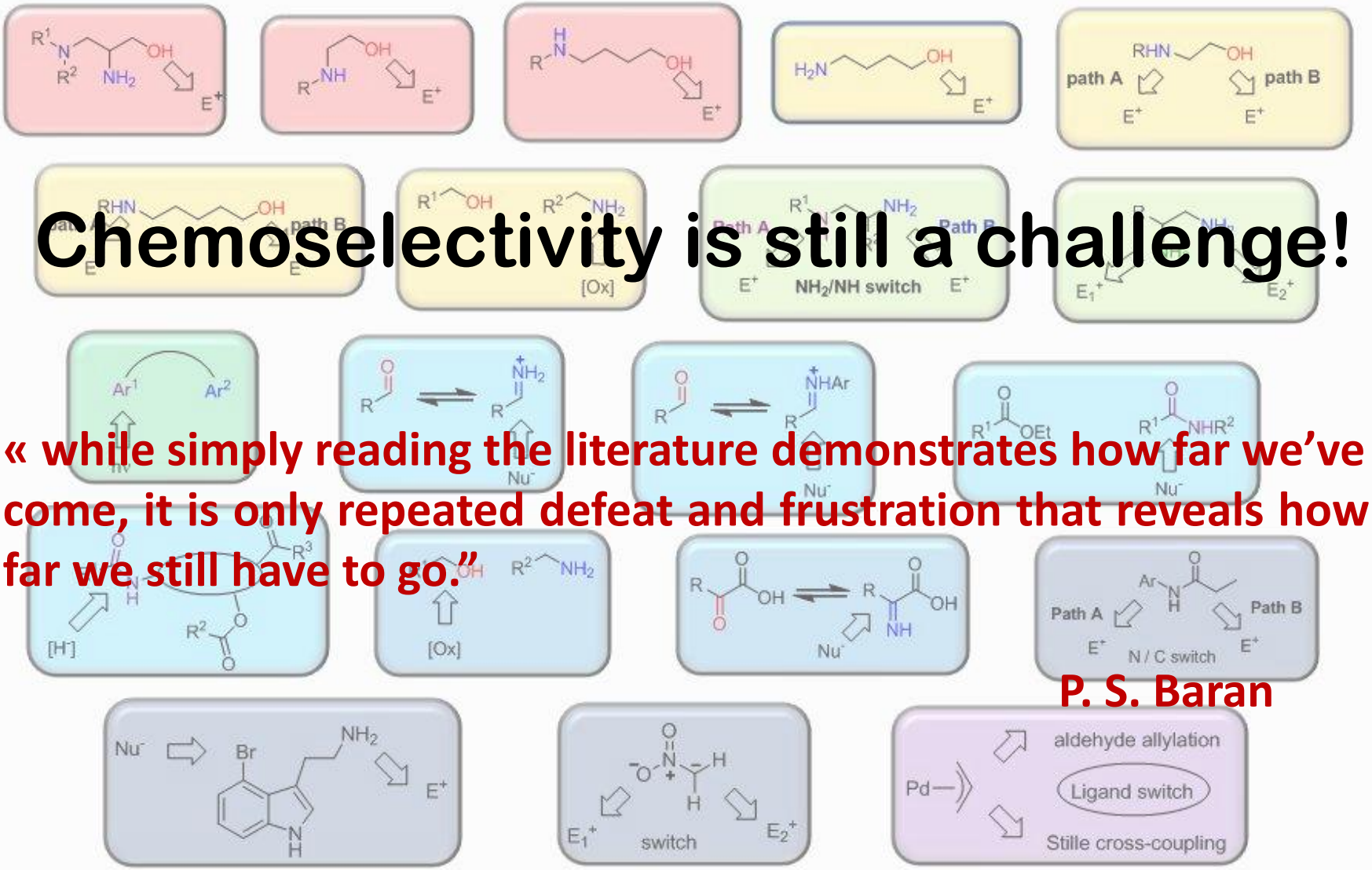
Mechanism:



Conclusion


path A
path B
E+
Path A
Path B
NH2/NH switch
[Ox]
hν
Nu-
[H-]
Ligand switch
aldehyde allylation
Stille cross-coupling
switch
N / C switch

Conclusion



Chemoselectivity is still a challenge!

« while simply reading the literature demonstrates how far we've come, it is only repeated defeat and frustration that reveals how far we still have to go."

P. S. Baran

R. A. Shenvi, D. P. O'Malley, P. S. Baran, *Acc. Chem. Res.*, **2009**, *42* , 530–541