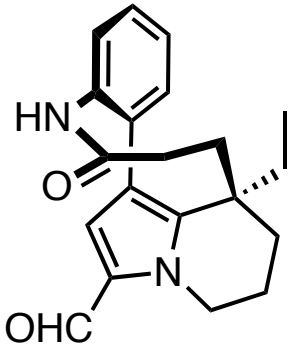
Pd-Catalyzed Chemoselective Catellani *Ortho*-Arylation of Iodopyrroles: Rapid Total Synthesis of Rhazinal

Sui, X.; Zhu, R.; Li, G.; Ma, X.; Gu, Z.
J. Am. Chem. Soc. **2013**, 135, 9318

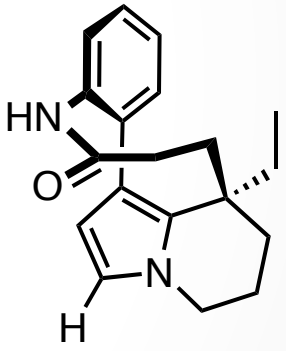
Joshua Sacher
13 July 2013

Rhazinal

- Isolated from Kopsia teoi in Malaysia (semi-synthesized before isolation)
- Rhazinal and rhazinalam have similar MoA as vinblastine and Taxol; 0.5 μM IC_{50} in KB cells for rhazinalam)
- Structurally interesting



(–)-rhazinal

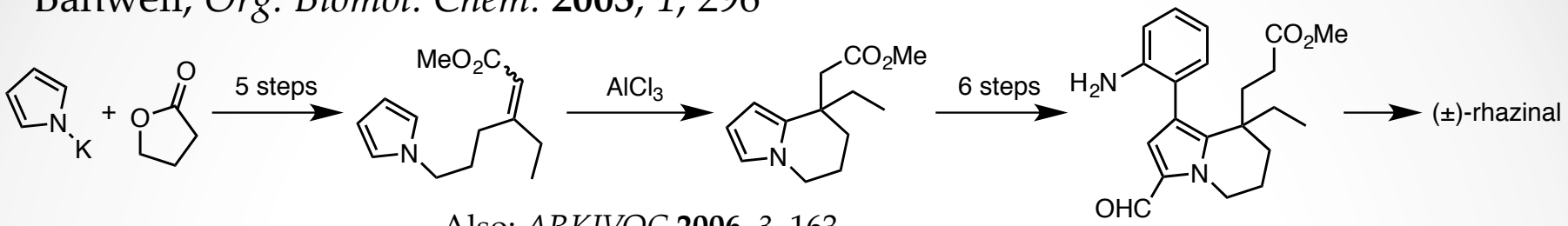


(–)-rhazinalam

Kam, T. S.; Tee, Y. M.; Subramaniam, G. *Nat. Prod. Lett.* **1998**, *12*, 307
David, B.; Sévenet, T.; Thoison, O.; Awang, K.; Païs, M.; Wright, M.; Guénard, D. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2155

Total Syntheses of (±)-Rhazinal

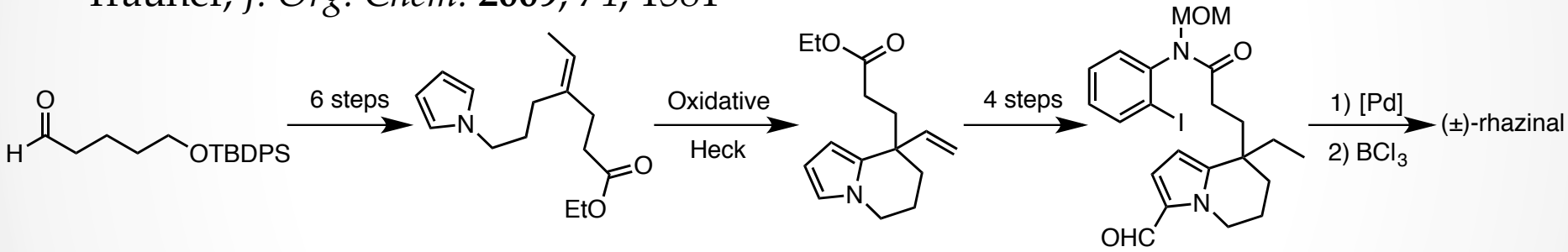
Banwell, *Org. Biomol. Chem.* **2003**, *1*, 296



Also: *ARKIVOC* **2006**, *3*, 163

13 steps, 4.4–6.6% overall yield

Trauner, *J. Org. Chem.* **2009**, *74*, 1581



15 steps from known, 0.8% overall yield

(±)-Rhazinilam:

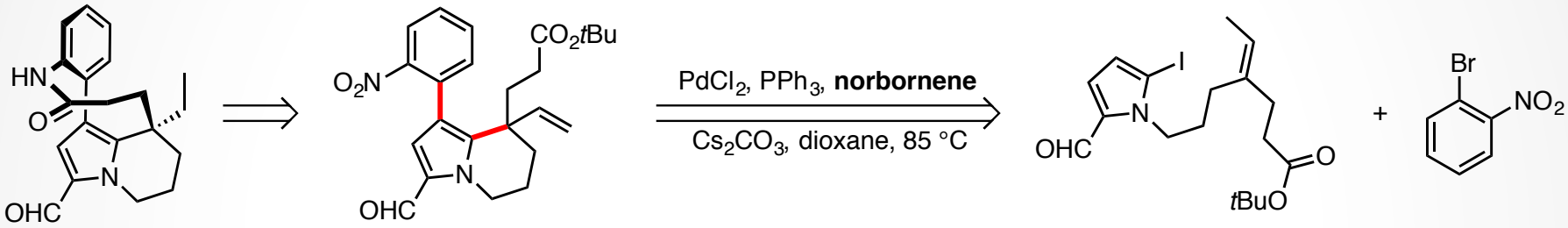
- Smith, *Tetrahedron Lett.* **1973**, *14*, 5179
- Magnus, *Tetrahedron*, **2001**, *57*, 8647

(–)-Rhazinilam:

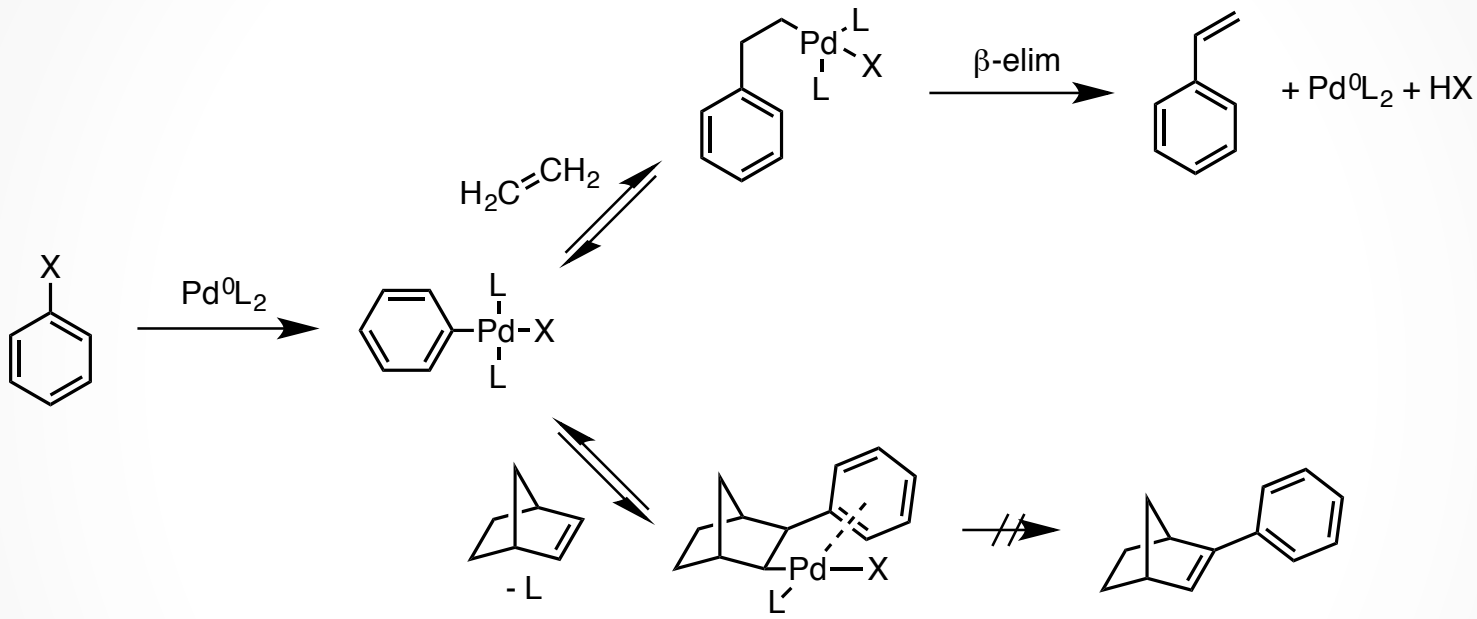
- Sames, *J. Am. Chem. Soc.* **2002**, *124*, 6900
- Banwell, *ARKIVOC*, **2006**, *3*, 163
- Nelson, *J. Am. Chem. Soc.* **2006**, *128*, 10352
- Zakarian, *Org. Lett.*, **2010**, *12*, 4224 (also (+))

Title Paper

Catellani Reaction



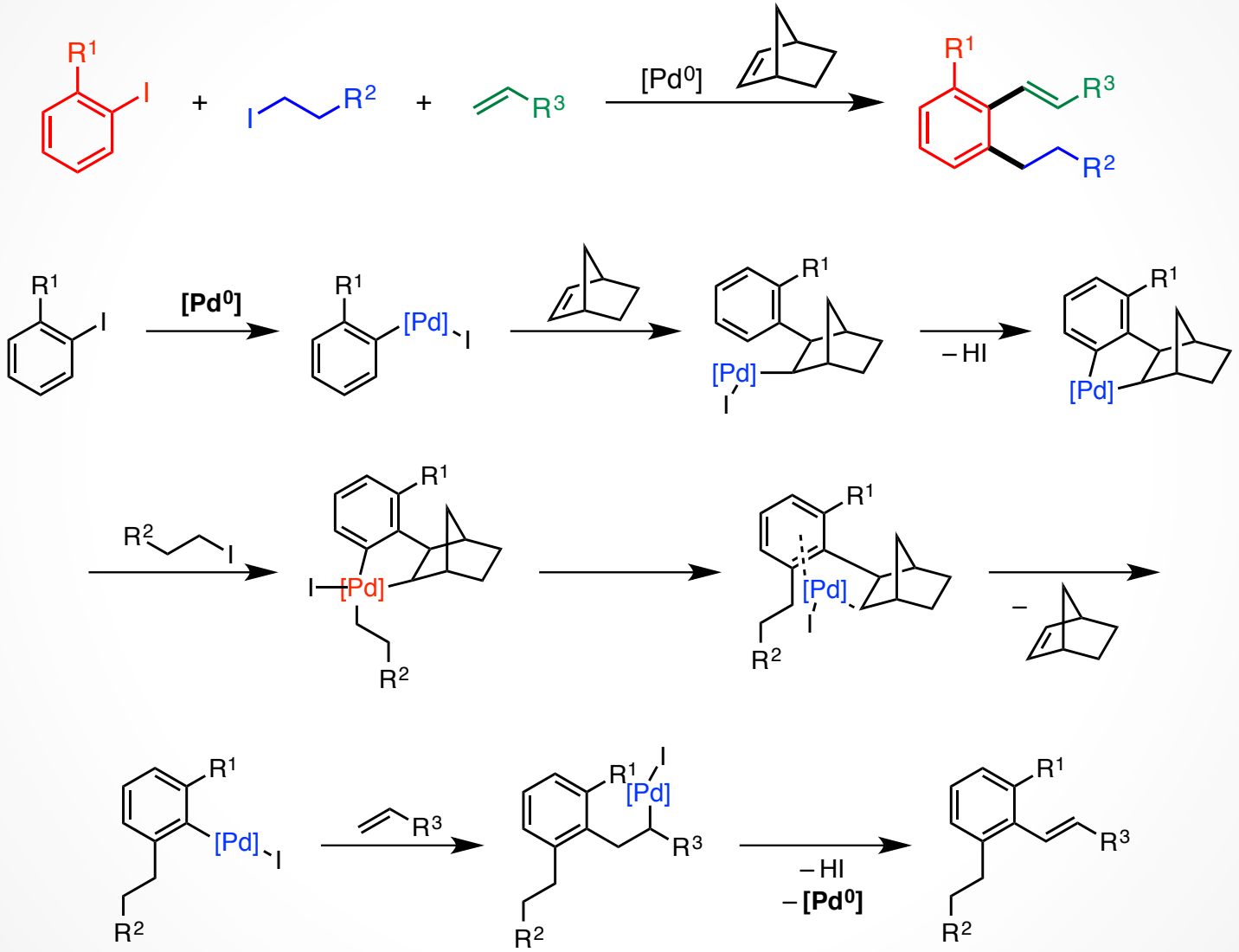
Why Norbornene?



β-Hydride is *anti*

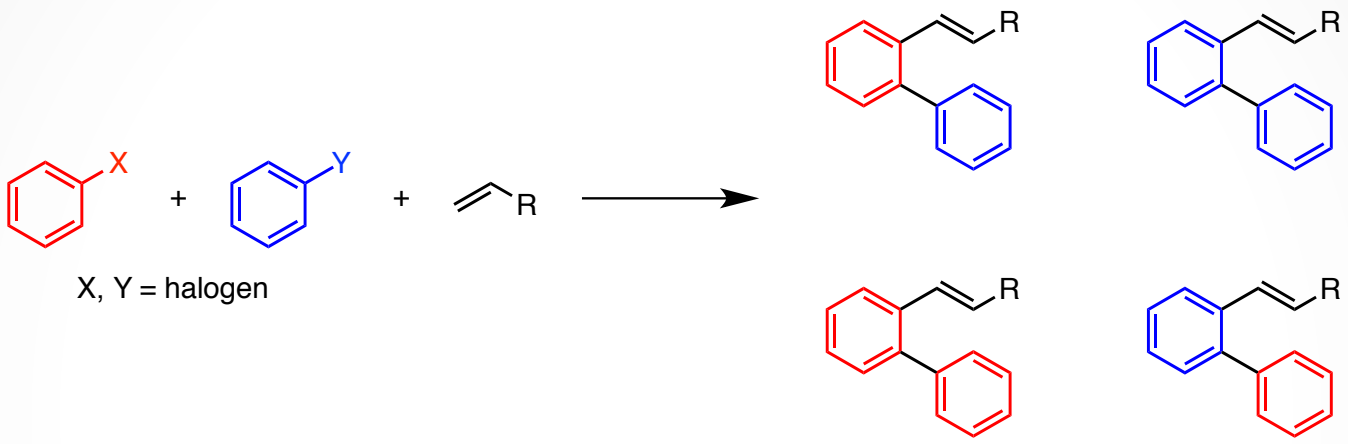
Catellani, M. *Synlett* **2003**, 298

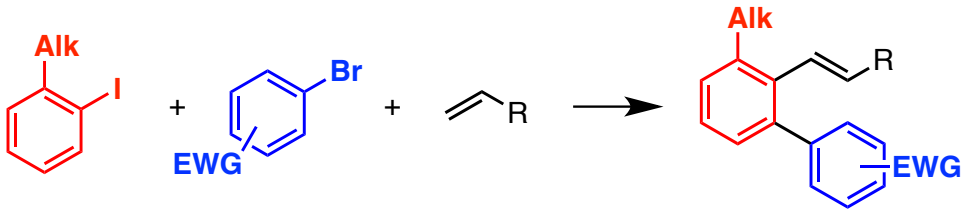
The Catellani Reaction



Catellani, M. *Synlett* **2003**, 298

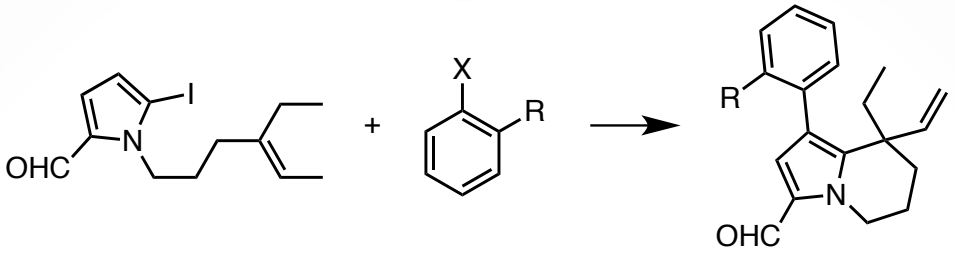
Tandem Biaryl Coupling/Heck



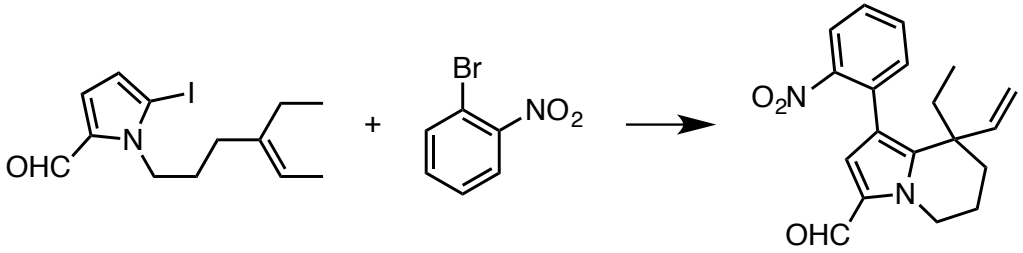


Faccini, F.; Motti, E.; Catellani, M. *J. Am. Chem. Soc.* **2004**, *126*, 78

Preliminary Screening

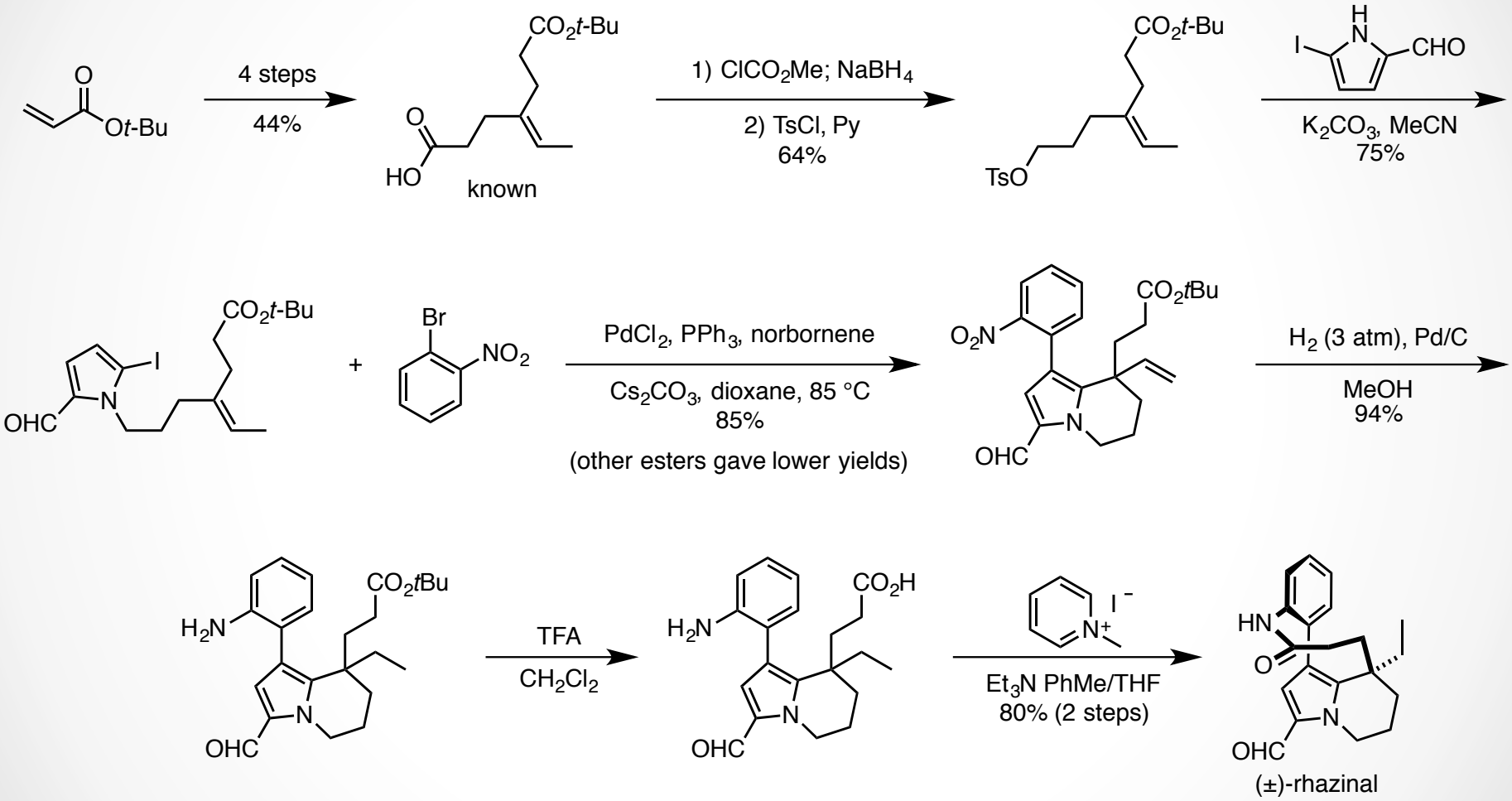


X = **Br**, I
R = **NO_2**, NH_2, NHBoc, NHAc, NHTs, CO_2Me



entry	ligand	base	solvent	yield
1	PPh_3	Cs_2CO_3	MeCN	11
2	PPh_3	Cs_2CO_3	DMF	< 2
3	PPh_3	Cs_2CO_3	PhMe	67
4	PPh_3	Cs_2CO_3	dioxane	77
5	$P(2\text{-furyl})_3$	Cs_2CO_3	dioxane	72
6	*rac*-BINAP	Cs_2CO_3	dioxane	< 2
7	dppe	Cs_2CO_3	dioxane	35
8	PPh_3	K_2CO_3	dioxane	51
9	PPh_3	KO*t*-Bu	dioxane	< 2
10	PPh_3	2,6-lut	dioxane	< 2

Synthesis of (±)-Rhazinal



Acid: Gu, Z.; Zakarian, A. *Org. Lett.* **2010**, *12*, 4224

Conclusion

- Total synthesis of (±)-rhazinal
  - 7 steps from known (11 total)
  - 31% overall yield (13% total)
- Catellani tandem *o*-arylation/intramolecular Heck reaction
- Unusual, selective coupling of two different aryl halides