Pd-Catalyzed Intramolecular C-N Bond Cleavage, 1,4-Migration, sp^3 C-H Activation, and Heck Reaction: Four Controllable Diverse Pathways Depending on the Judicious Choice of the Base and Ligand

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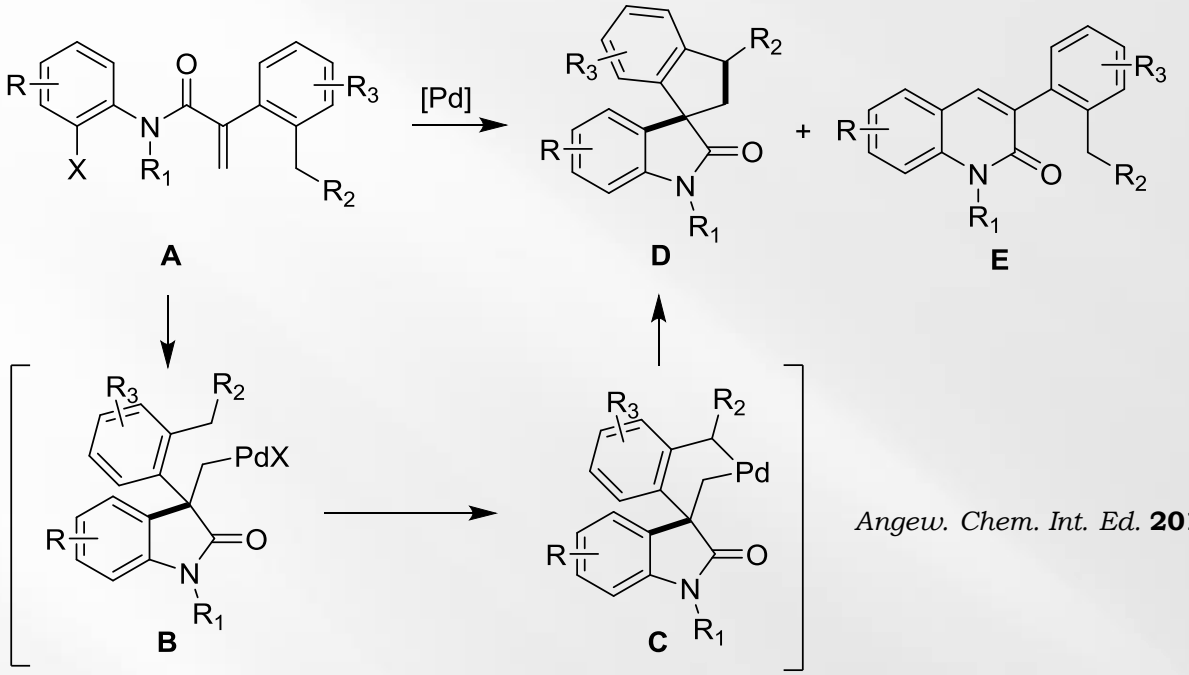
DOI: 10.1021/ja512212x

Joseph Salamoun
Current Literature 1/31/15
Wipf Group

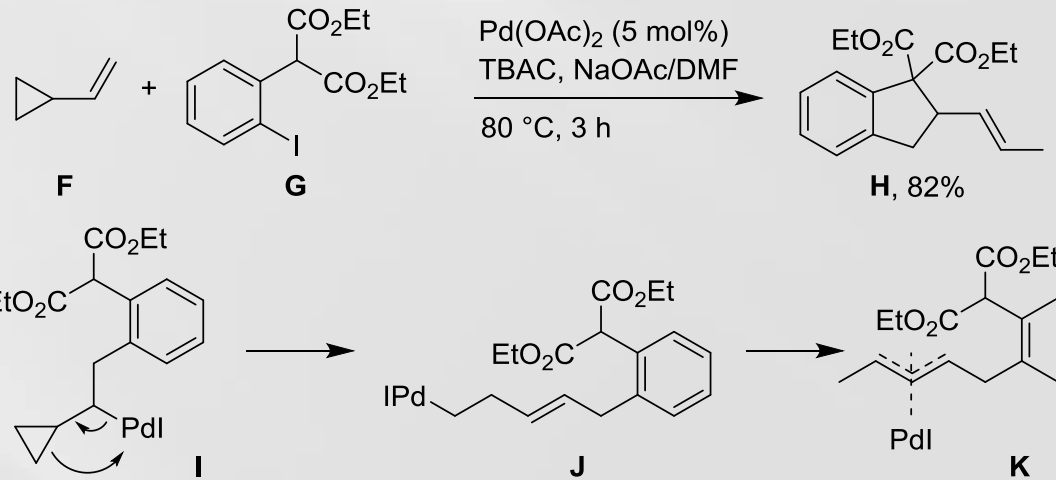
Versatility of Pd in Synthesis

- Cross-couplings
- Hydrogenations
- Oxidations
- Allylation
- Synthesis of Heterocycles
- Carbonylation
- Rearrangements

Examples of Pd-Catalyzed Domino Transformations

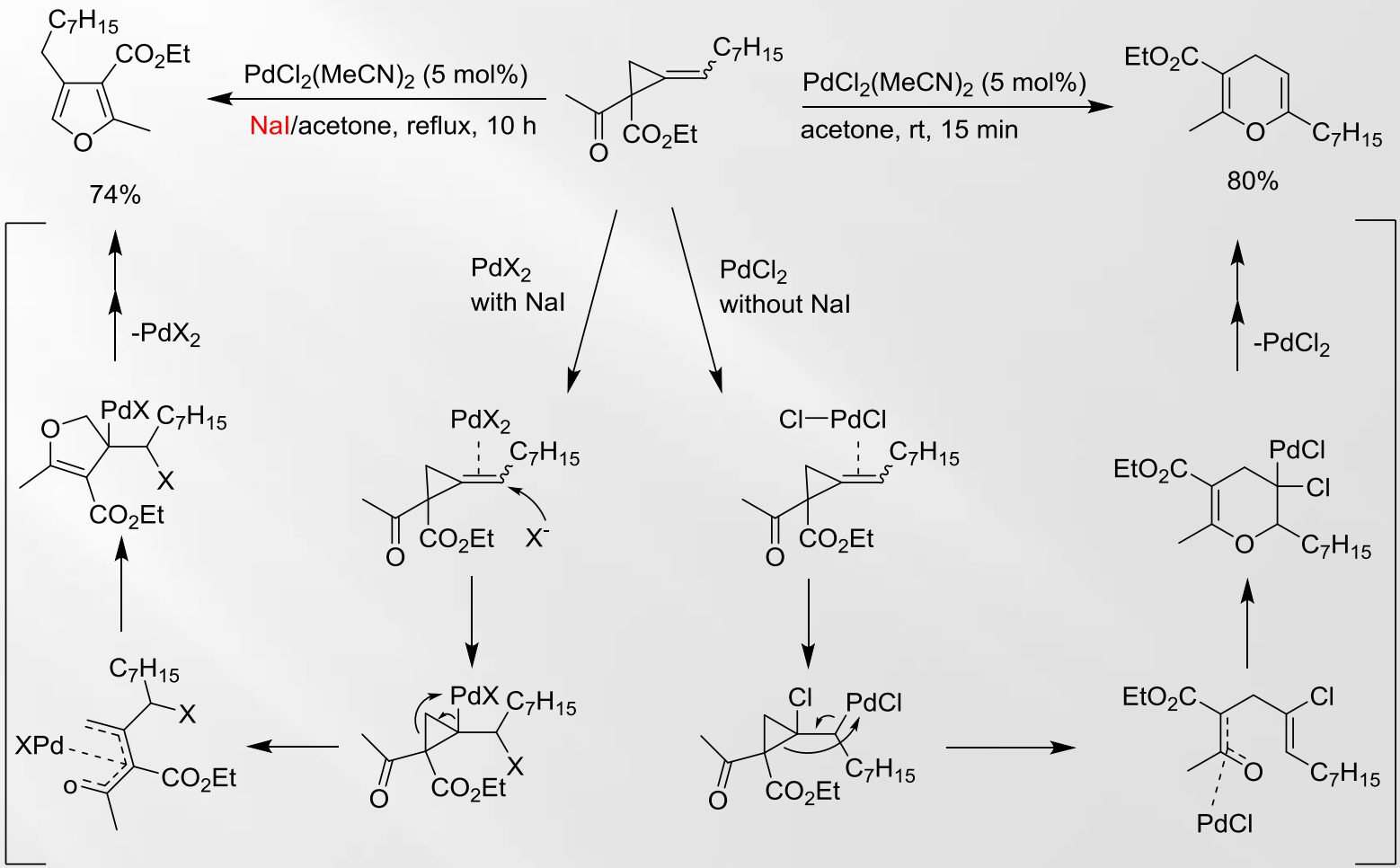


Angew. Chem. Int. Ed. **2012**, *51*, 11561.



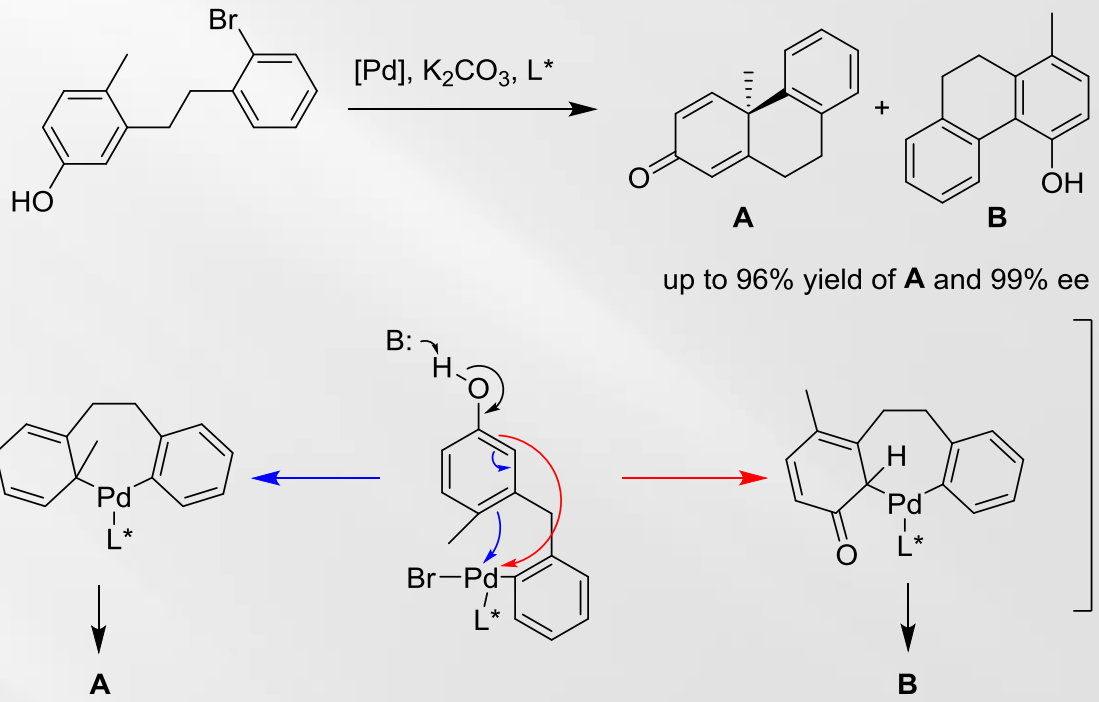
Tetrahedron **1996**, *52*, 2743.

Examples of Pd-Catalyzed Domino Transformations, contd.



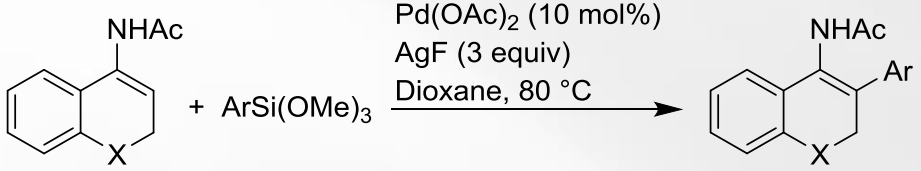
Angew. Chem. Int. Ed. **2003**, *42*, 183.

Examples of Pd-Catalyzed Domino Transformations, contd.

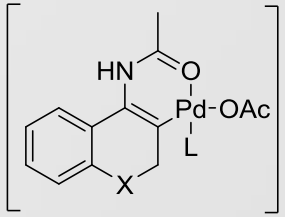


Angew. Chem. Int. Ed. **2015**, *54*, ASAP.
DOI: 10.1002/anie.201411817

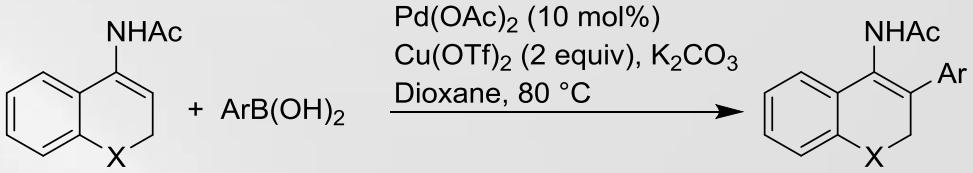
Previous Work from the Loh Group with Vinylacetamides



19-95%

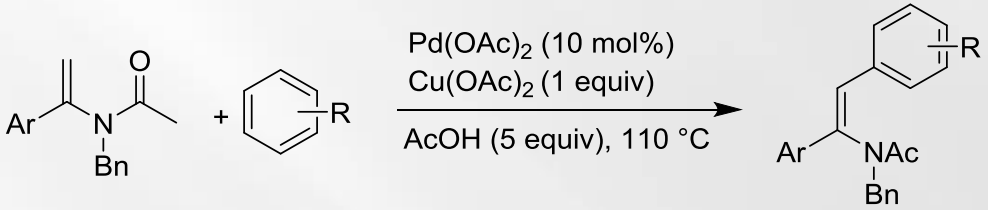


Angew. Chem. Int. Ed. **2009**, *48*, 5355.



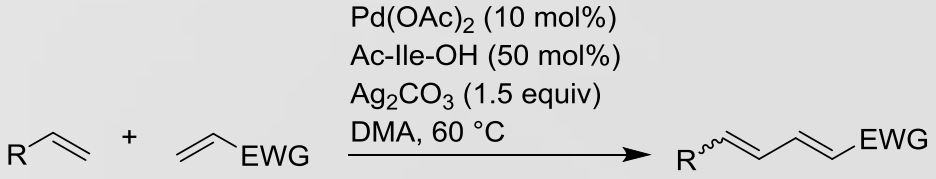
57-90%

Chem. Commun. **2009**, *45*, 3472.



43-86%

Angew. Chem. Int. Ed. **2012**, *51*, 5701.



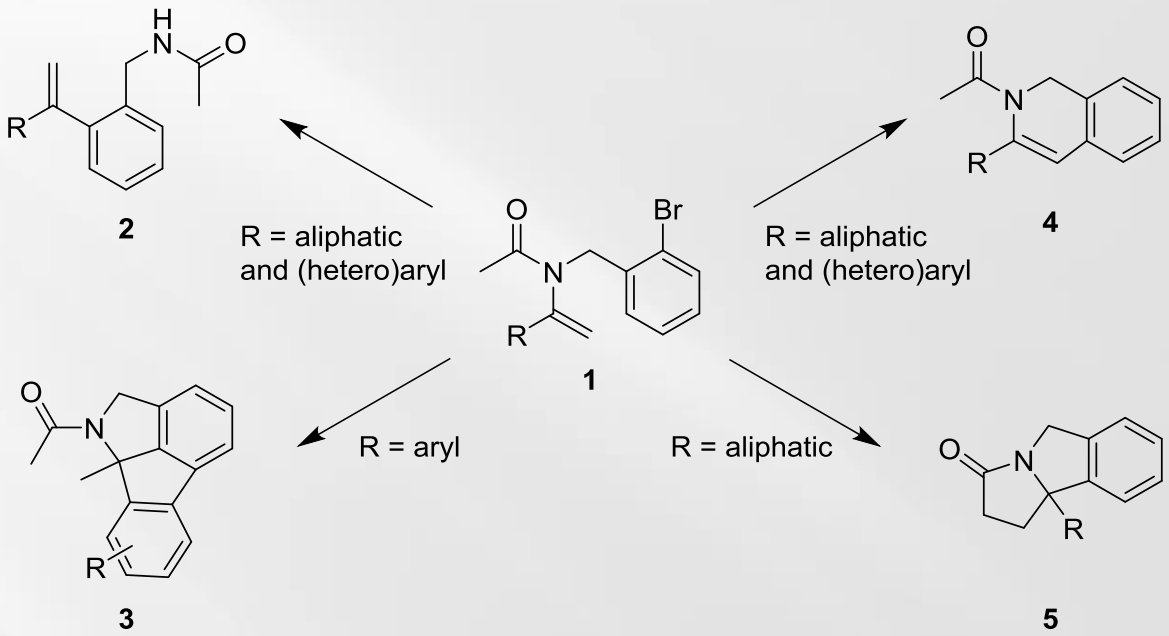
R = alkyl, aryl; EWG: $-CO_2R$, $-CONR_2$, $-PO_3R_2$

35-86%

E/*Z* = 80:20 to >99:1

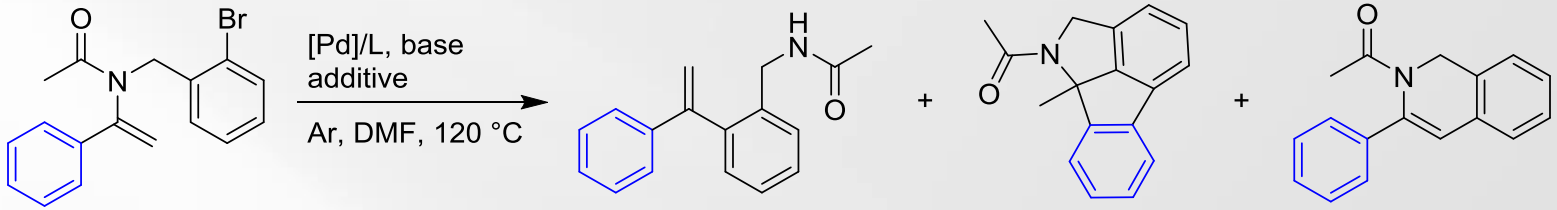
Chem. Sci. **2013**, *4*, 4320.

Current Work



DOI: 10.1021/ja512212x

Reaction Optimization

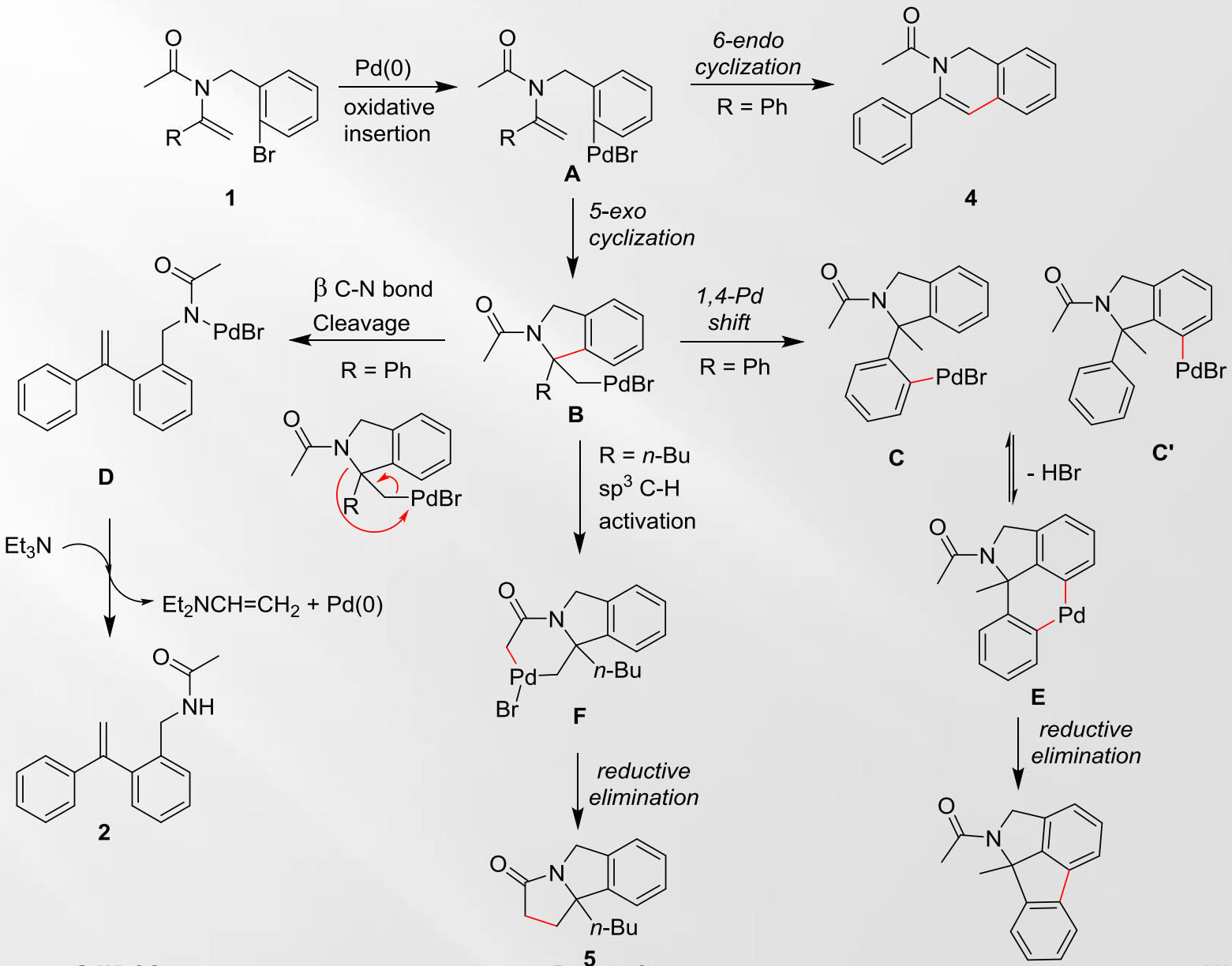


2 3 4

entry	**catalyst** (10 mol%)	**ligand** (mol%)	**base** (equiv)	**additive** (equiv)	**2** (%)	**3** (%)	**4** (%)
1	none	PPh_3 (20)	K_2CO_3 (1.2)	none	0	0	0
2	$Pd(OAc)_2$	PPh_3 (20)	none	none	0	0	0
3	$Pd(OAc)_2$	PPh_3 (20)	K_2CO_3 (1.2)	none	4	40	56
4	$Pd(PPh_3)_4$	none	K_2CO_3 (1.2)	none	0	0	0
5	$Pd(PhCN)_2Cl_2$	PPh_3 (20)	K_2CO_3 (1.2)	none	trace	trace	10
6	$Pd(OAc)_2$	PPh_3 (20)	Et_2NH (2.0)	none	20	0	0
7	**$Pd(OAc)_2$**	**PPh_3** (20)	**Et_3N (2.0)**	**none**	**90 (80)**	**0**	**0**
8	$Pd(OAc)_2$	PPh_3 (20)	DBU (2.0)	none	16	0	0
9	$Pd(OAc)_2$	PCy_3 (20)	Et_3N (2.0)	none	11	0	0
10	$Pd(OAc)_2$	dppb (10)	Et_3N (2.0)	none	23	0	0
11	$Pd(OAc)_2$	dppb (10)	K_2CO_3 (1.2)	none	4	38	54
12	$Pd(OAc)_2$	XantPhos (10)	K_2CO_3 (1.2)	none	3	43	52
13	$Pd(OAc)_2$	Johnphos (20)	K_2CO_3 (1.2)	none	5	45	50
14	$Pd(OAc)_2$	Johnphos (30)	K_2CO_3 (1.2)	none	4	47	47
15	$Pd(OAc)_2$	Johnphos (10)	K_2CO_3 (1.2)	none	3	54	43
16	$Pd(OAc)_2$	Johnphos (10)	K_3PO_4 (1.2)	none	18	48	33
17	$Pd(OAc)_2$	Johnphos (10)	Ag_2CO_3 (1.2)	none	0	0	0
18	$Pd(OAc)_2$	Johnphos (10)	Na_2CO_3 (1.2)	none	19	55	9
19	$Pd(OAc)_2$	Johnphos (10)	Na_2CO_3 (1.2)	PivOH (0.3)	16	62	18
20	**$Pd(OAc)_2$**	**Johnphos (10)**	**Na_2CO_3 (1.2)**	**TBAC (1.0)**	**10**	**76 (75)**	**trace**
21	$Pd(OAc)_2$	Johnphos (10)	Na_2CO_3 (1.2)	TBAB (1.0)	16	62	18
22	**$Pd(OAc)_2$**	**PPh_3** (20)	**Cs_2CO_3 (1.2)**	**none**	**10**	**trace**	**71 (68)**

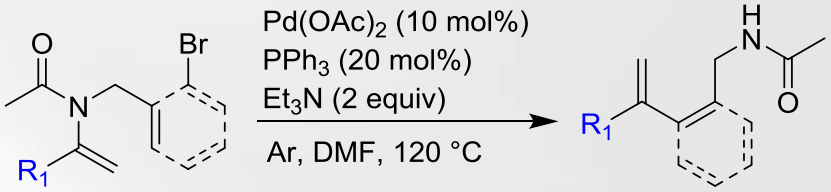
DOI: 10.1021/ja512212x

Proposed Mechanisms

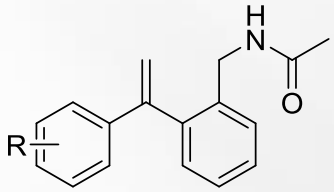


2/14/2015
DOI: 10.1021/ja512212x

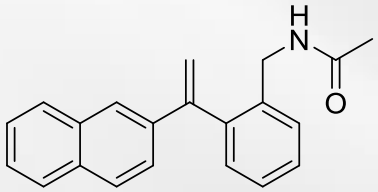
β-C-N Elimination for Synthesis of 1,1-Disubstituted Ethylene Derivatives



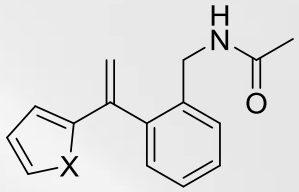
1 **2**



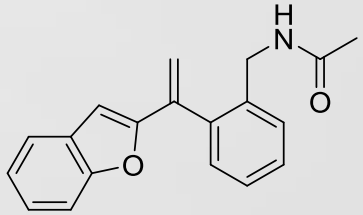
2a, R = H, 80%
2b, R = 2-Me, 40%
2c, R = 3-Me, 87%
2d, R = 4-Me, 77%
2e, R = 4-OMe, 76%
2f, R = 4-F, 61%
2g, R = 4-Cl, 66%
2h, R = 4-Br, 61%
2i, R = 4-NO_2, 64%



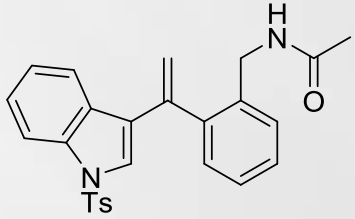
2j, 74%



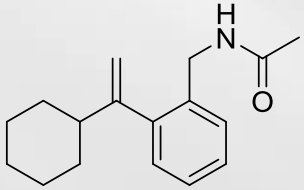
2k, X = O, 61%
2l, X = S, 67%



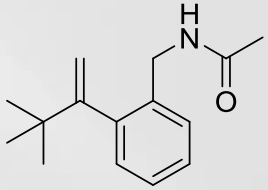
2m, 49%



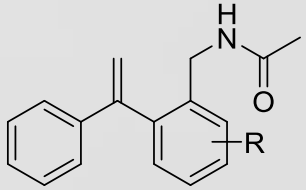
2n, 31%



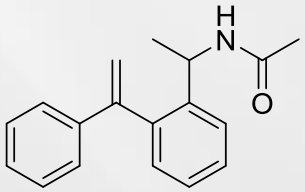
2o, 48%



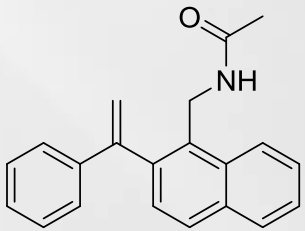
2p, 32%



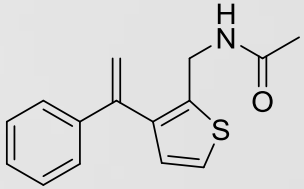
2q, R = 4-Me, 73%
2r, R = 6-Cl, 48%
2s, R = 4-Cl, 53%



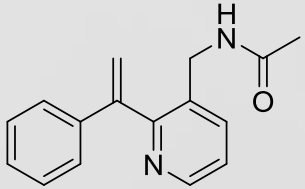
2t, 39%



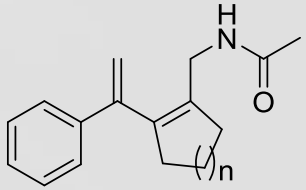
2u, 80%



2v, 50%



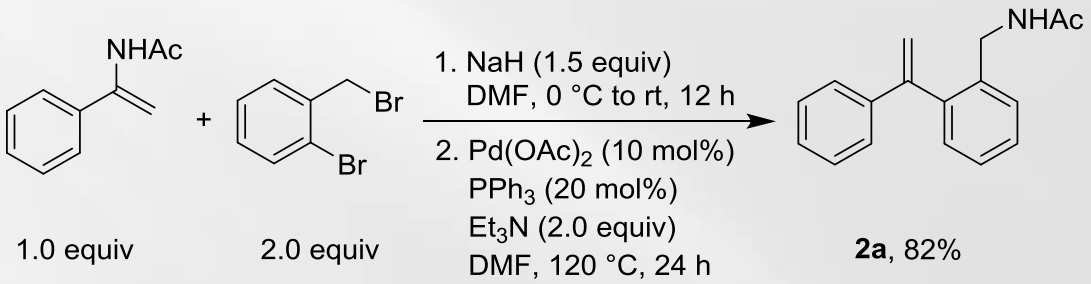
2w, 54%



2x, n =1, 37%
2y, n = 2, 35%

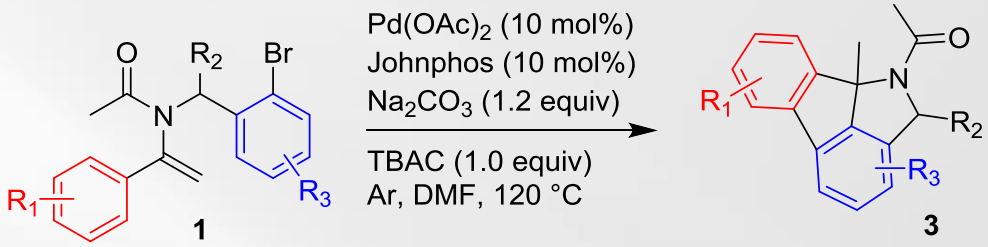
DOI: 10.1021/ja512212x

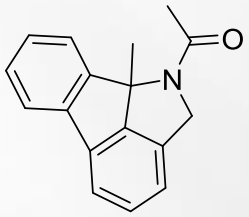
β-C-N Elimination for Synthesis of 1,1-Disubstituted Ethylene Derivatives



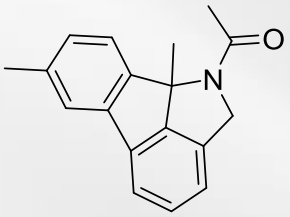
DOI: 10.1021/ja512212x

Pd-Catalyzed 5-*exo*-Heck, 1,4-Pd Migration, and Aryl-Aryl Coupling

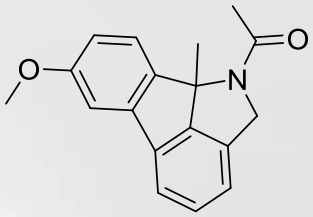




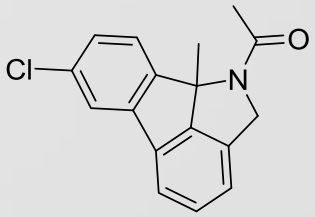
3a, 75%



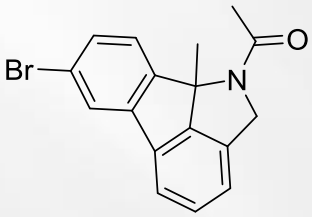
3b, 70%



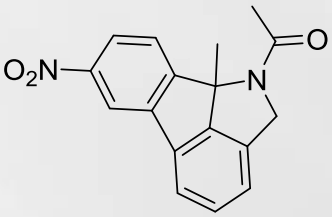
3c, 61%



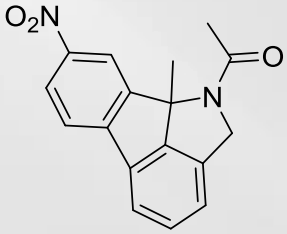
3d, 83%



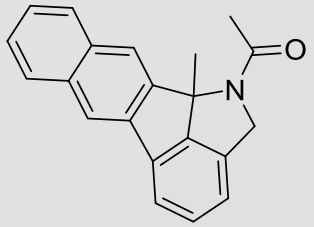
3e, 36%



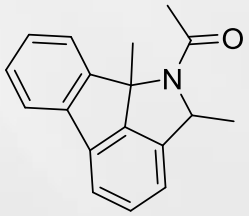
3f, 67%



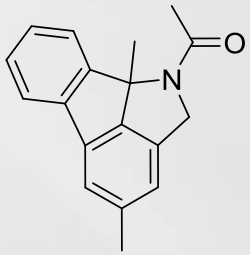
3g, 68%



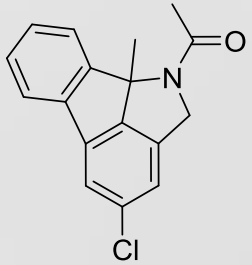
3h, 80%



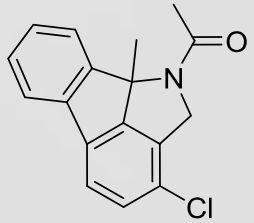
3i, 74%
dr = 90:10



3j, 59%



3k, 61%



3l, 50%

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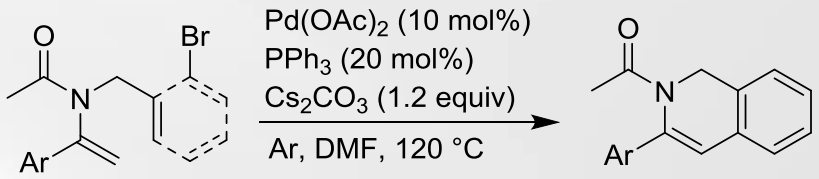
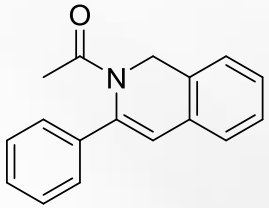
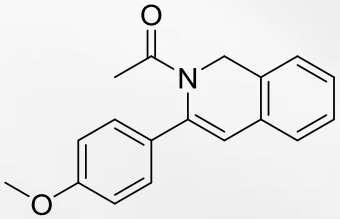
Pd-Catalyzed 6-*endo* Heck



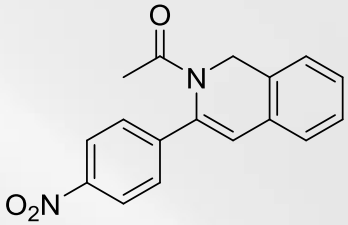
1 **4**



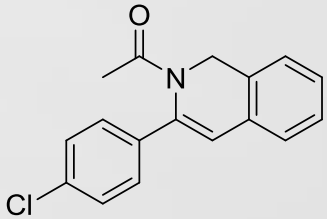
4a, 68%



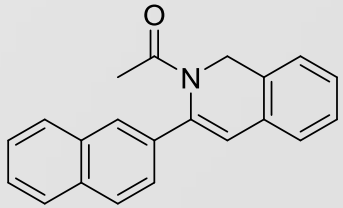
4b, 82%



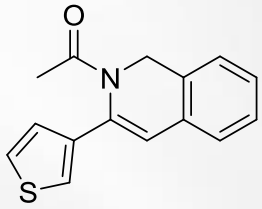
4c, 35%



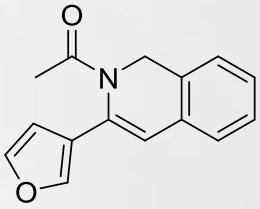
4d, 53%



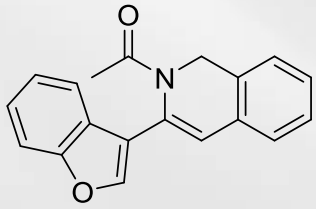
4e, 65%



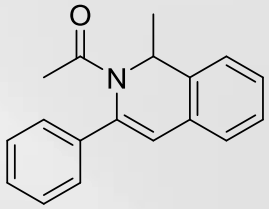
4f, 52%



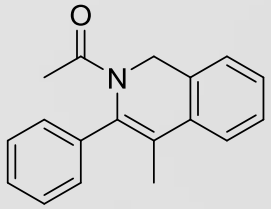
4g, 48%



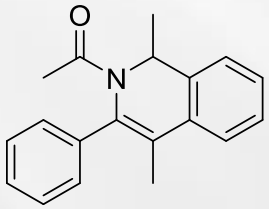
4h, 40%



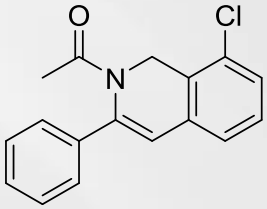
4i, 53%



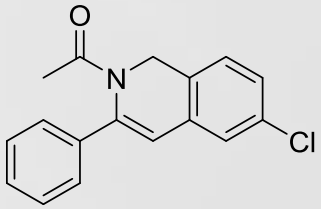
4j, 84%



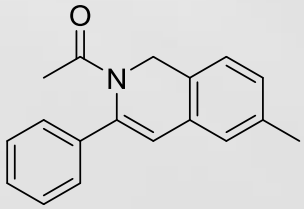
4k, 74%



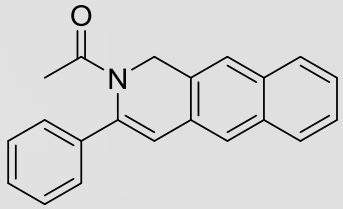
4l, 73%



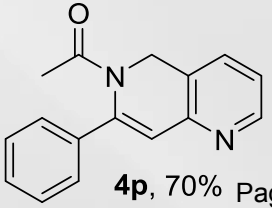
4m, 62%



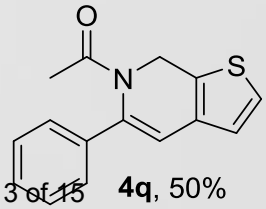
4n, 73%



4o, 56%



4p, 70%



4q, 50%

2/14/2015
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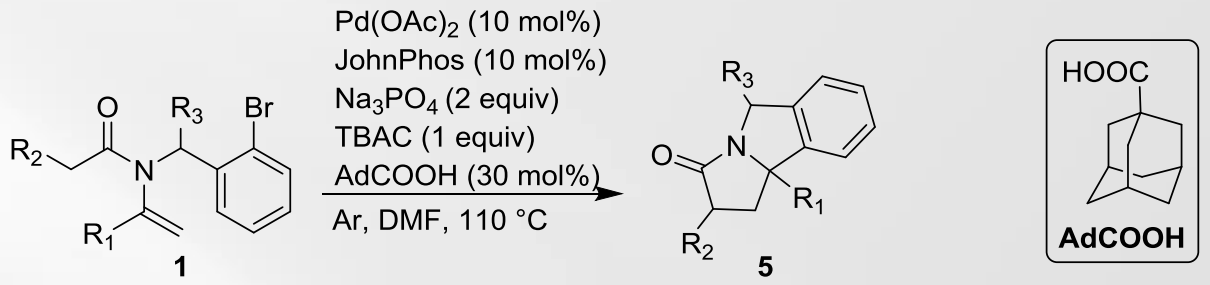
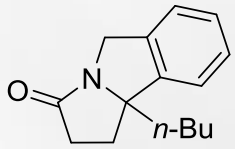
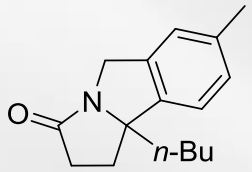
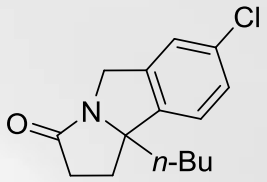
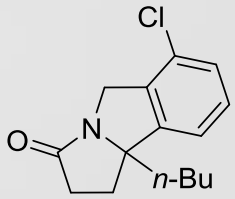
Pd-Catalyzed α-C-H Bond Direct Functionalization

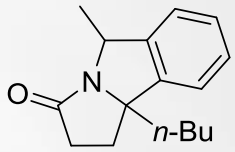


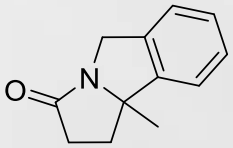

5a, 64%

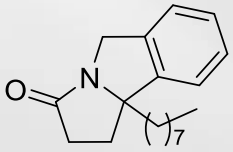

5b, 70%

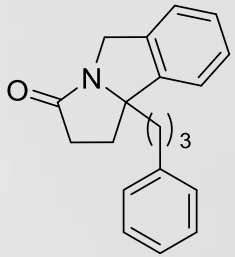

5c, 57%

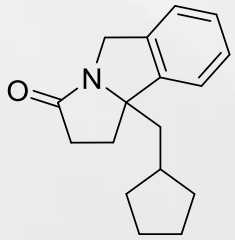

5d, 68%

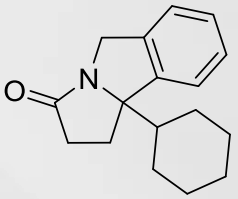

5e, 66% (dr = 5:1)

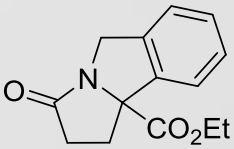

5f, 71%

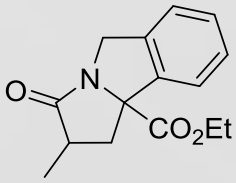

5g, 72%


5h, 73%


5i, 62%


5j, 55%


5k, 65%


5l, 20% (dr > 95:5)

DOI: 10.1021/ja512212x

Conclusions

- Choice of ligand and base impacts reaction pathway allowing for selective product formation.
- Good yields for multiple bond breaking/forming reactions that may be useful for a variety of scaffolds.
- Need a better mechanistic understanding of the impact of ligand and base selections. Future studies?
- Low yields are not adequately explained. Are any undesired products seen (i.e. selectivity problems)?