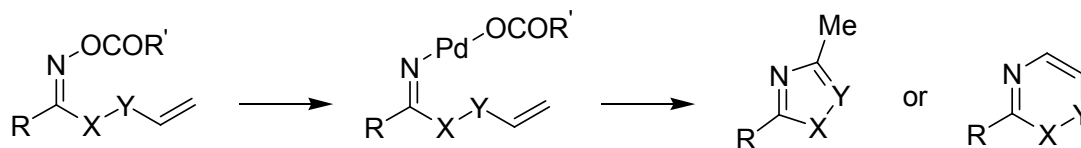


Palladium-Catalyzed Annulation of Acyloximes with Arynes (or Alkynes): Synthesis of Phenanthridines and Isoquinolines

Gerfaud, T.; Neuville, L.; Zhu, J. *Angew. Chem. Int. Ed.*
2009, *48*, 572-577.

Chad Hopkins
Wipf Group Literature Presentation
1-17-09

Methodology Concept



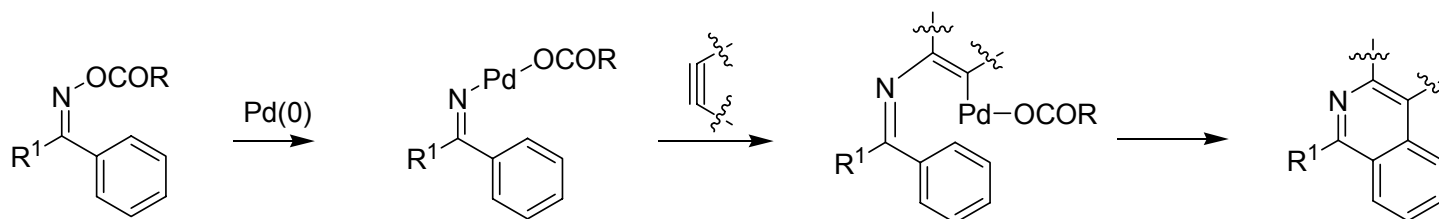
- Palladium-catalyzed intramolecular amino-Heck reaction

Kitamura, M.; Narasaka, K. *Chem. Rec.* **2002**, 2, 268-277.

Narasaka, K.; Kitamura, M. *Eur. J. Org. Chem.* **2005**, 4505-4519.

For additional reading on the use of imine nucleophiles in Pd-catalyzed coupling reactions, see:

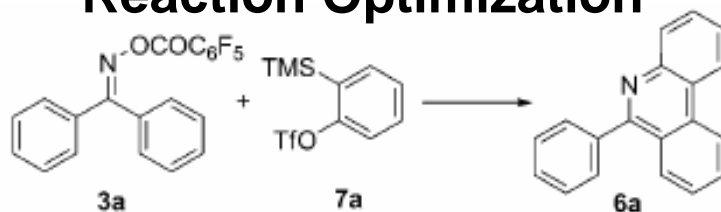
Mann, G.; Hartwig, J. F.; Driver, M. S.; Fernandez-Rivas, C. *J. Am. Chem. Soc.* **1998**, 120, 827-828; Barleunga, J.; Aznar, F.; Valdes, C. *Angew. Chem. Int. Ed.* **2004**, 43, 343-345; Wolfe, J. P.; Ahman, J.; Sadighi, J. P.; Singer, R. A.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, 38, 6367-6370; Bolm, C.; Hildebrand, J. P. *J. Org. Chem.* **2000**, 65, 169-175; Nishimura, T.; Nishiguchi, Y.; Maeda, Y.; Uemura, S. *J. Org. Chem.* **2004**, 69, 5342-5347, and refs cited therein.



- *In situ* generation of a transient imidopalladium(II) complex followed by intermolecular trapping with an alkyne and subsequent substrate directed C-H activation

For an example of a copper-catalyzed intermolecular coupling of an acyloxime with a vinyl boronic acid, see Liu, S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2008**, 130, 6918-6919.

Reaction Optimization

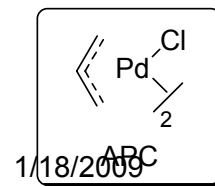


Entry	Pd	Ligand	Pd/ligand	Solvent (ratio)	T [°C]	Yield [%] ^[b]
1	[Pd(dba) ₂]	P(o-tolyl) ₃	1:1	CH ₃ CN/tol (1:9)	110	trace
2	APC	P(o-tolyl) ₃	1:2	CH ₃ CN/tol (1:9)	110	10 ^[d]
3 ^[c]	APC	P(o-tolyl) ₃	1:2	CH ₃ CN/tol (1:9)	110	trace
4	APC	P(o-tolyl) ₃	1:2	CH ₃ CN/tol (1:1)	110	27
5	APC	xphos	1:2	CH ₃ CN/tol (1:1)	110	30
6 ^[c]	APC	dppp	–	CH ₃ CN	80	trace
7 ^[d]	APC	P(o-tolyl) ₃	1:2	C ₂ H ₅ CN	100	40
8 ^[d]	APC ^[e]	P(o-tolyl) ₃	1:2	C ₃ H ₇ CN	100	40
9 ^[d]	APC	P(o-tolyl) ₃	1:2	C ₃ H ₇ CN	120	67
10 ^[d]	[Pd(PPh ₃) ₄]	–	–	C ₃ H ₇ CN	120	65
11 ^[d]	APC ^[e]	dppp	1:1	C ₃ H ₇ CN	120	53
12 ^[d]	APC ^[e]	xphos	1:2	C ₃ H ₇ CN	120	53
13 ^[d]	APC ^[e]	–	–	C ₃ H ₇ CN	120	60
14	APC ^[e]	P(o-tolyl) ₃	1:2	C ₃ H ₇ CN	120	70
15 ^[f]	APC ^[e]	P(o-tolyl) ₃	1:2	C ₃ H ₇ CN	120	74
16	–	–	–	C ₃ H ₇ CN	120	0

[a] All reactions were carried out under an argon atmosphere using Pd (5 mol %), 7a (2 equiv), CsF (3 equiv), *c* = 0.42 M for 20 hours. [b] Yield of isolated product. [c] Slow addition of 7a over 4 h. [d] 7a (3 equiv) and CsF (4 equiv). [e] 2.5 mol %. [f] *c* = 0.25 M in the presence of M.S. (4 Å). [g] Similar yields were obtained when dppe, P(2-furyl)₃, dppp, and johnphos were used as supporting ligands. dba = *trans,trans*-dibenzylideneacetone, dppe = ethane-1,2-diylbis(diphenylphosphane), dppp = propane-1,3-diylbis(diphenylphosphane), johnphos = 2-(di-*tert*-butylphosphino)biphenyl, Tf = triflate, tol = toluene, TMS = trimethylsilyl, xphos = 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl.

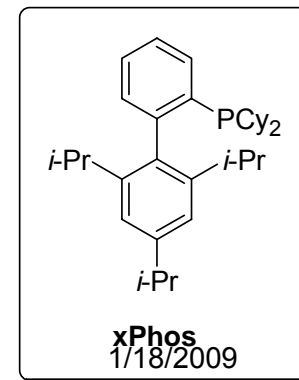
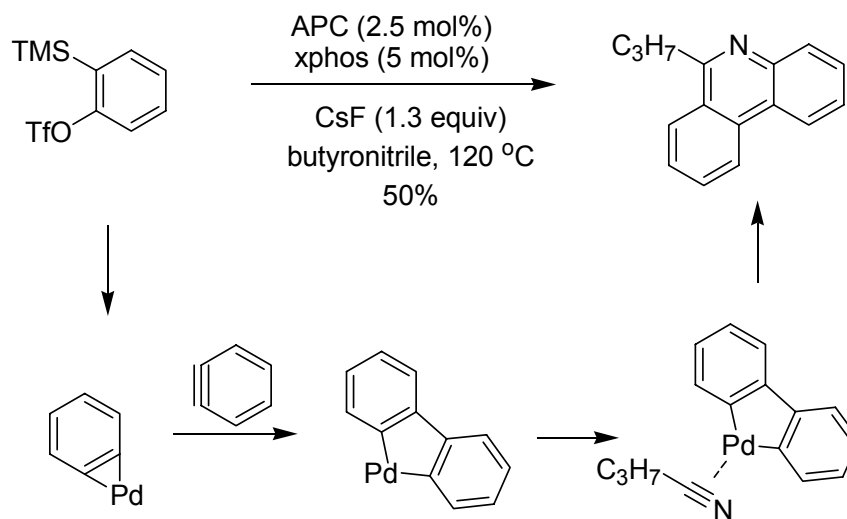
• **Optimal Conditions:** APC (2.5 mol%), P(o-Tol)₃ (5 mol%), CsF (3 equiv.), 4 Å MS,

C₃H₇CN, 120°C

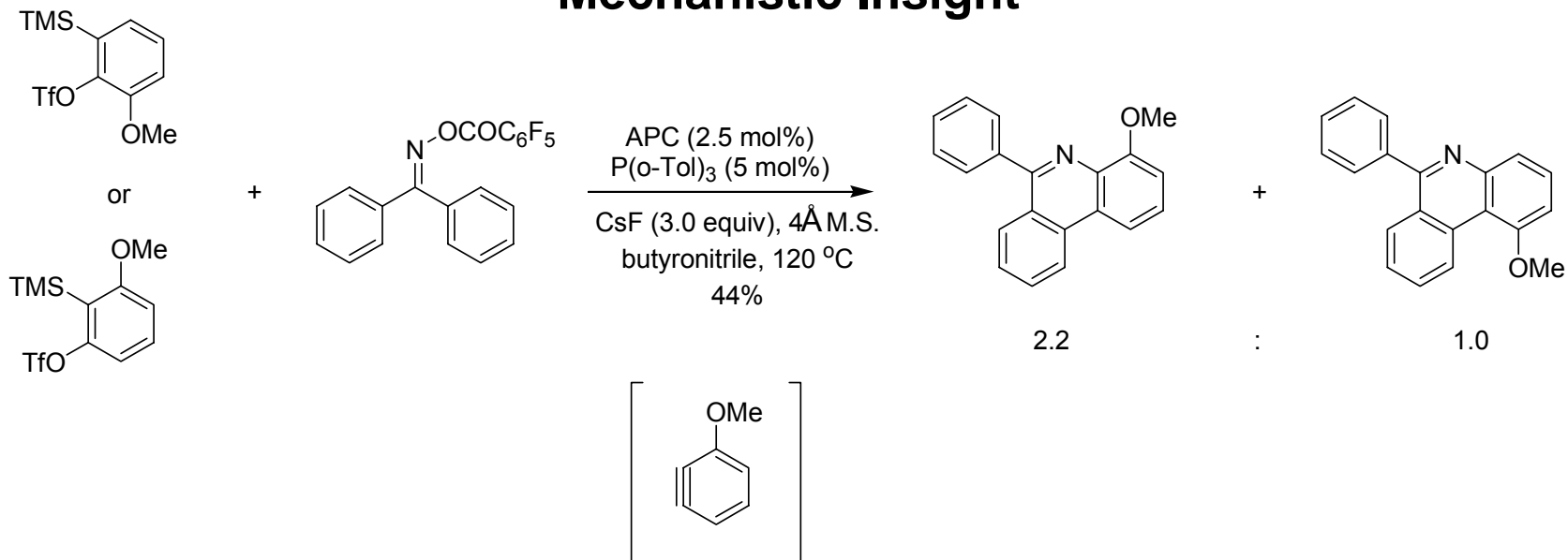


Key Observations from Optimization Studies

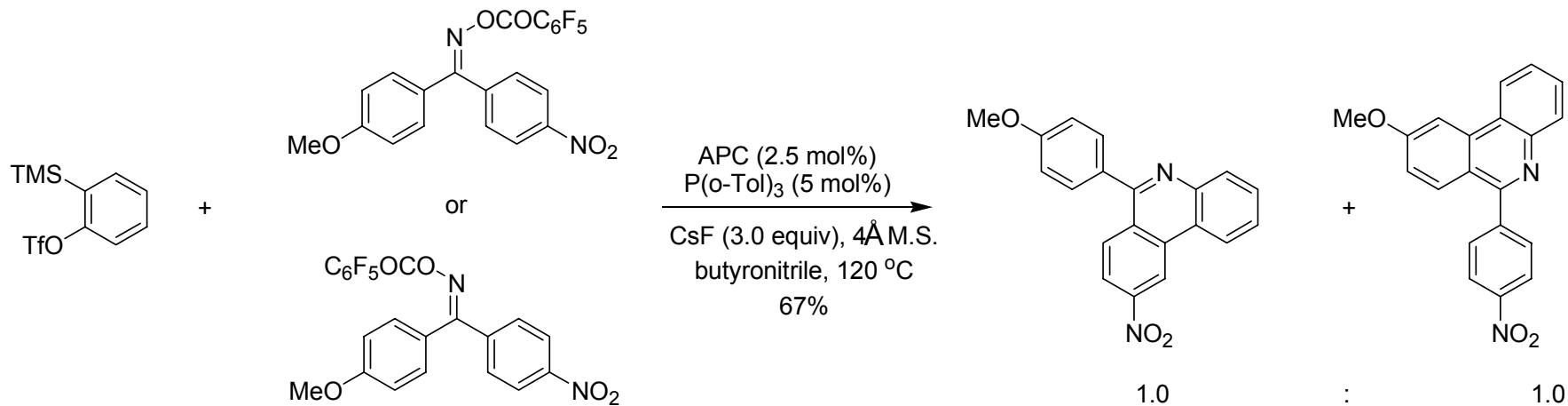
- Low solubility of CsF in butyronitrile allowed for slow generation of benzyne
- Less reactive benzophenone *O*-benzoyloxime afforded low yields of the desired product
- No products arising from a Beckmann rearrangement were isolated under the optimized conditions
- Complex mixture isolated in the absence of Pd
- 6-propylphenathridine was often observed as a side product



Mechanistic Insight

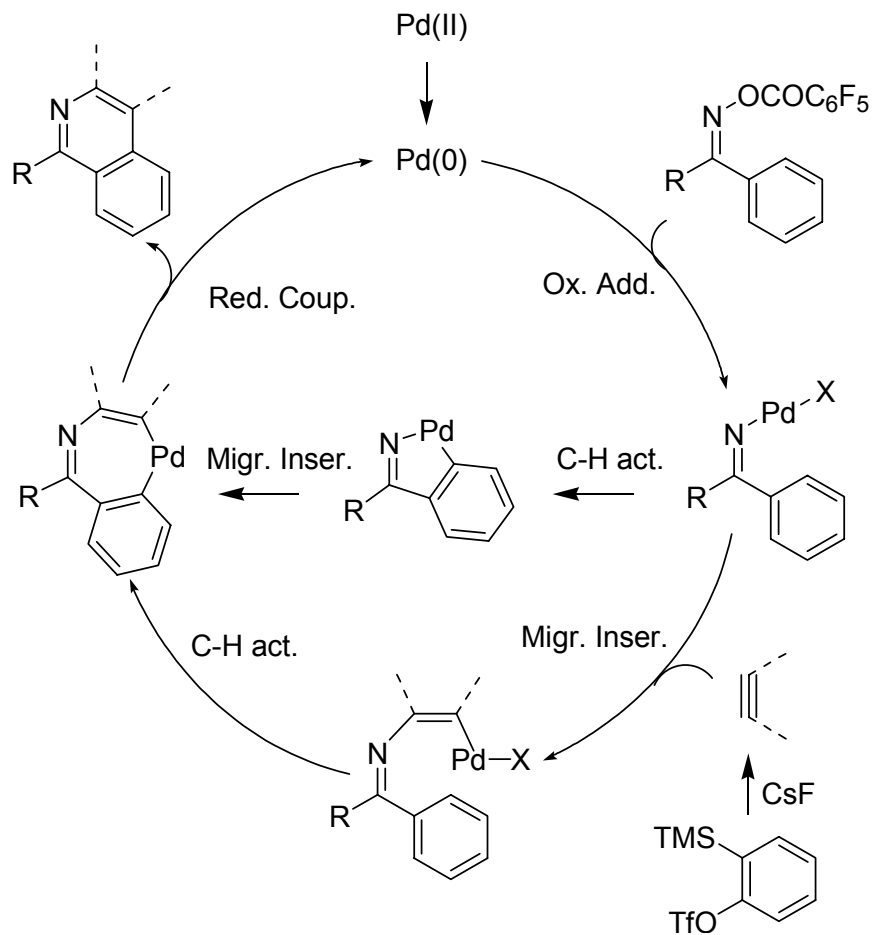


- Involvement of benzyne intermediate

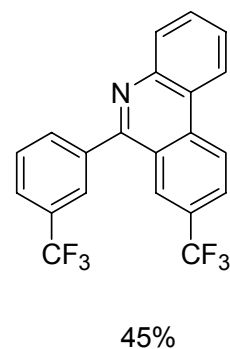
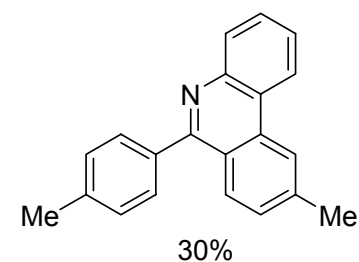
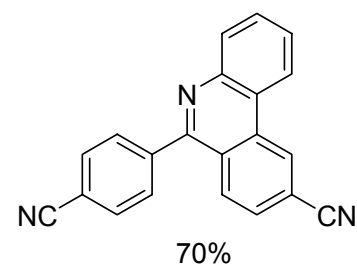
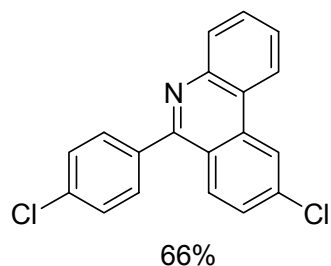
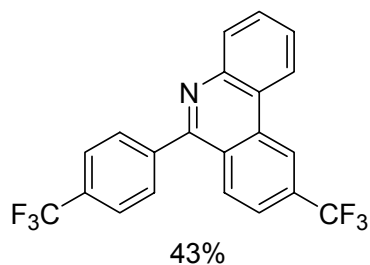
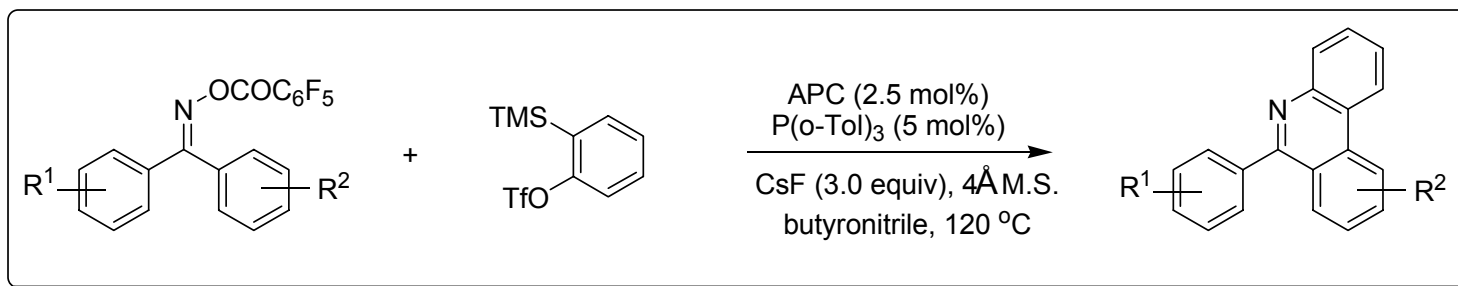


- Imine geometry (*E* or *Z*) is irrelevant due to angle of C=N-M bond

Catalytic Cycle

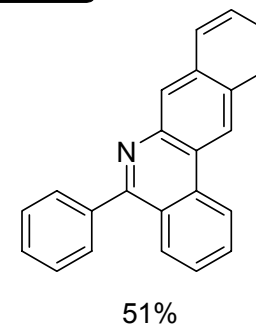
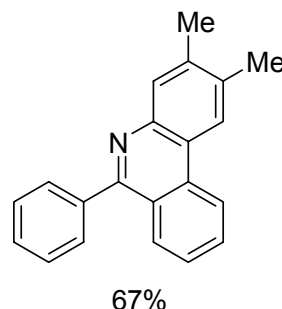
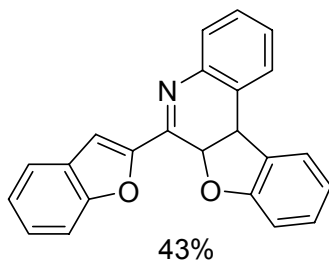
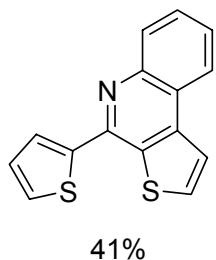
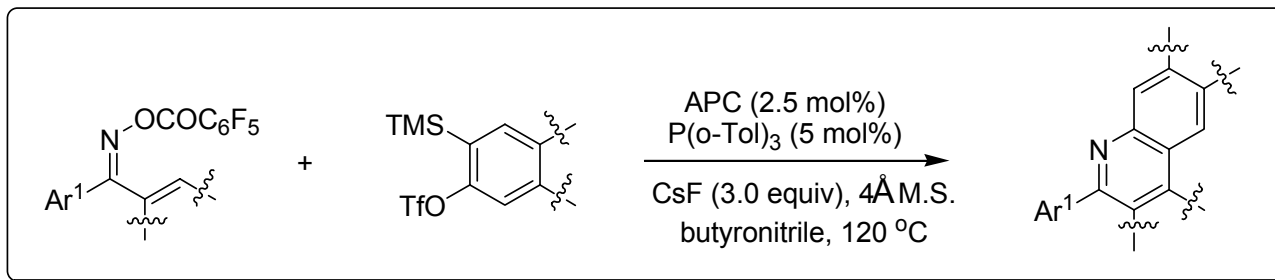


Scope and Limitations: *Substituted Aryl Oximes*

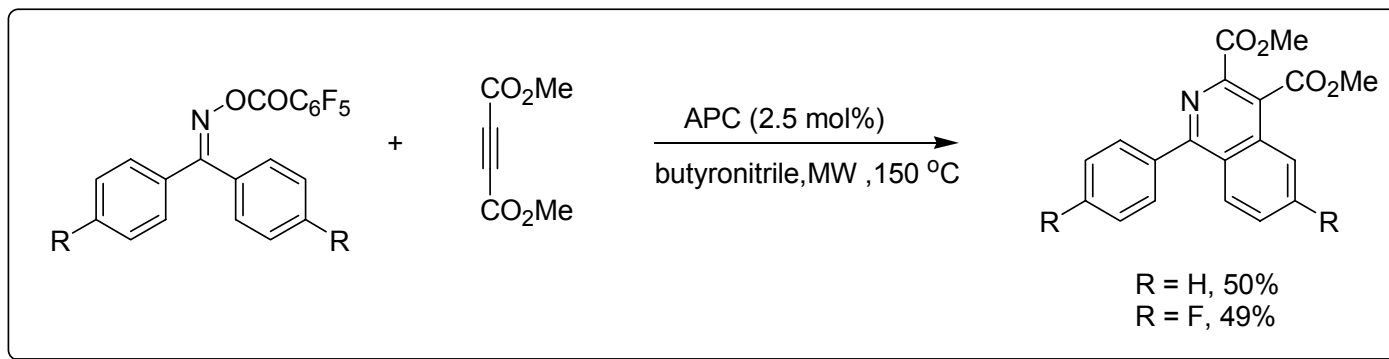


- No product was isolated when using an electron rich 4,4'-methoxy-substituted derivative

Scope and Limitations: *Heterocyclic-Substituted Oximes and Substituted Arynes*



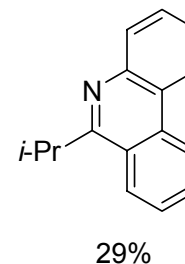
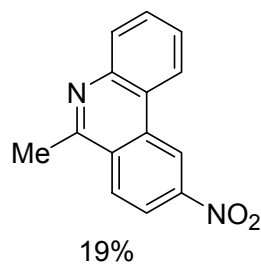
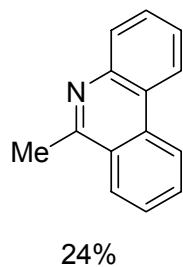
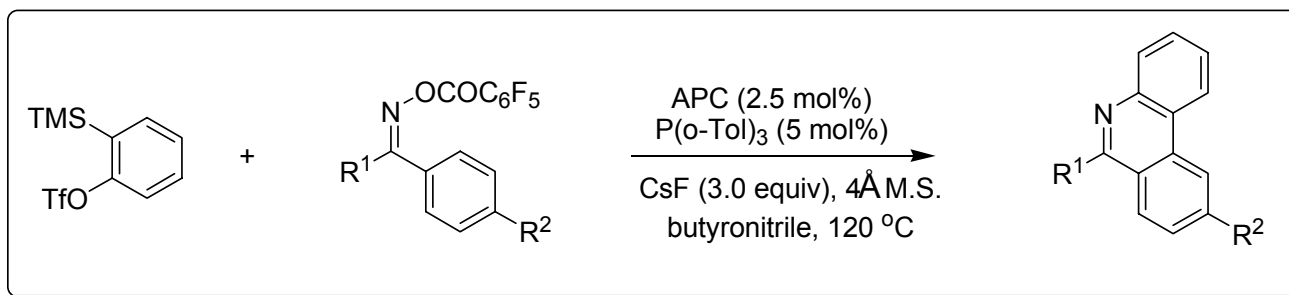
Use of dimethyl acetylenedicarboxylate (DMAD) as alkyne source



• Addition of ligand or CsF resulted in reduced yield or complete degradation, respectively

• Diphenyl acetylene was unreactive

Alkyl-Substituted Acyloximes



- Possible imine/enamine tautomerization resulting in inhibition of catalytic process

Summary

- First reported intermolecular trapping of transient C=N-Pd species using alkynes (benzyne/aminopalladation) followed by a directed C-H activation to provide phenanthridines and isoquinolines
- Incorporation of heterocyclic substrates is tolerated although scope appears somewhat limited at the time
- Alkyl-substituted oximes bearing an α -proton provided low yields
- Successful incorporation of dimethyl acetylenedicarboxylate (DMAD)