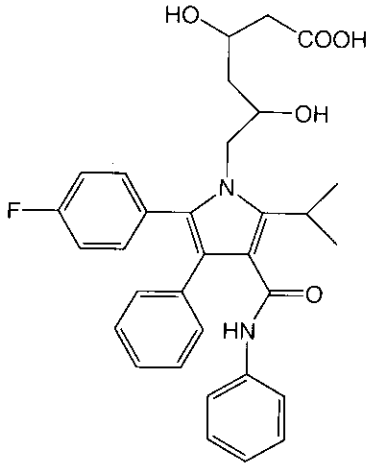
Erick Iezzi
Current Lit - Group B
1/10/04

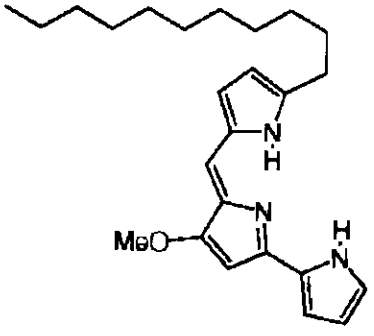
Palladium-Catalyzed Multicomponent Coupling of Alkynes, Imines, and Acid Chlorides: A Direct And Modular Approach to Pyrrole Synthesis

R. Dhawan and B. A. Arndtsen, JACS, 2003, ASAP

Pyrrole derivatives found in:
- natural products
- bioactive molecules
- conjugated polymers



Atorvastatin (Lipitor)



undecylprodigiosin

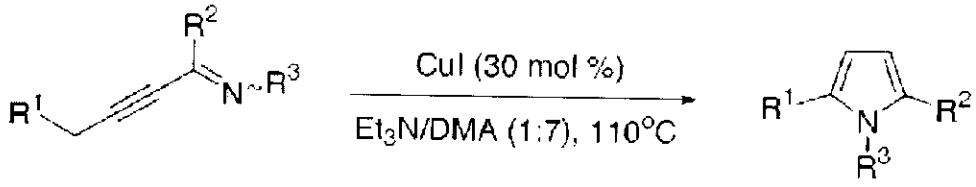
Synthetic routes to pyrroles

Traditional route

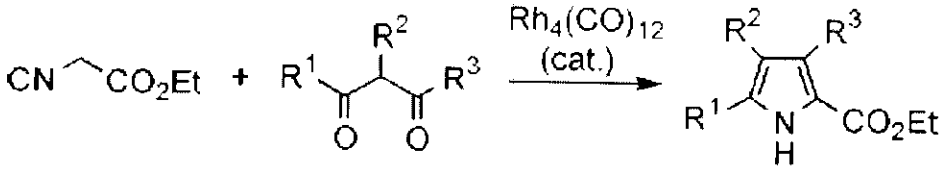
- Cyclization of amines with 1,4-diketones (Paal-Knorr, 1885)

Metal-based routes

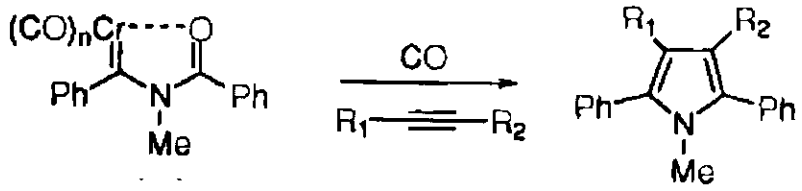
- Isomerization of alkynyl imines (Gevorgyan, et al. JACS 2001)



- Isonitrile/ketone couplings (Murahashi, et al. Org. Lett. 2001)

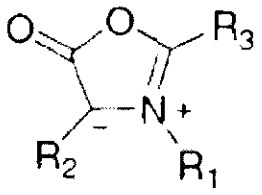


- Alkyne additions to chrominum carbenes (Merlic, et al. JACS 2000)



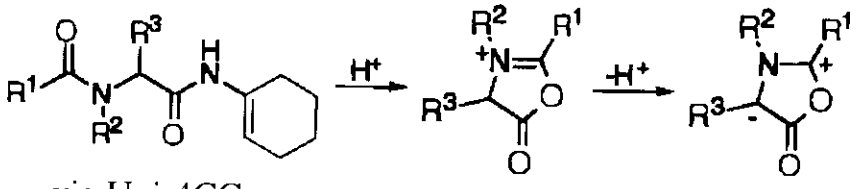
* formation ot a Münchnone intermediate

Münchnones as 1,3-dipolar substrates

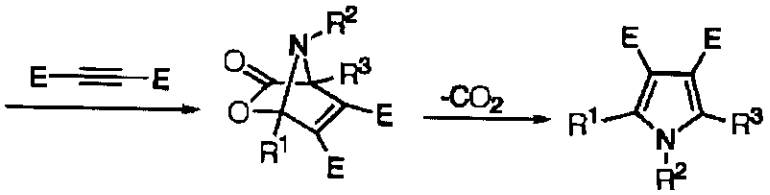


1,3-oxazolium-5-oxide

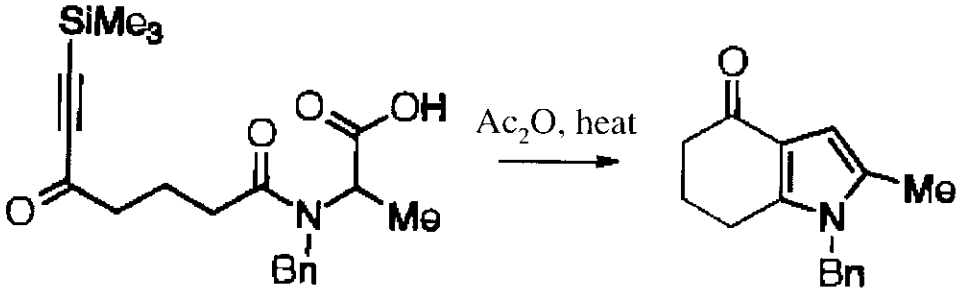
-Typically formed from in-situ amino acid derivs.
-Used to synthesize:
- **pyrroles**
- imidazoles
- pyrrolidines
- indole derivatives



via Ugi-4CC



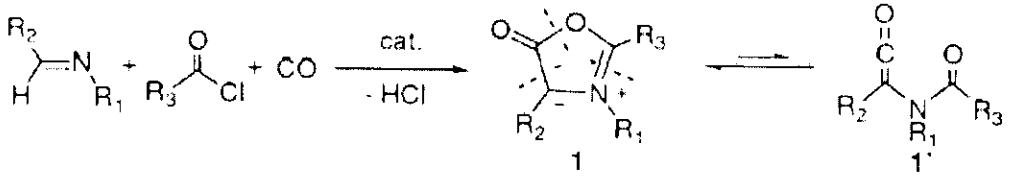
Keating, T. A.; Armstrong, R. W. JACS 1996, 118, 2574.



Martinelli, et al. J. Org. Chem. 1997, 62, 982.

One-pot catalytic synthesis of Münchnones

Arndtsen, et al. JACS 2003, 125, 1474.
*foundation for current lit. article



Scheme 1. Mechanistic Rationale for Münchnone Formation

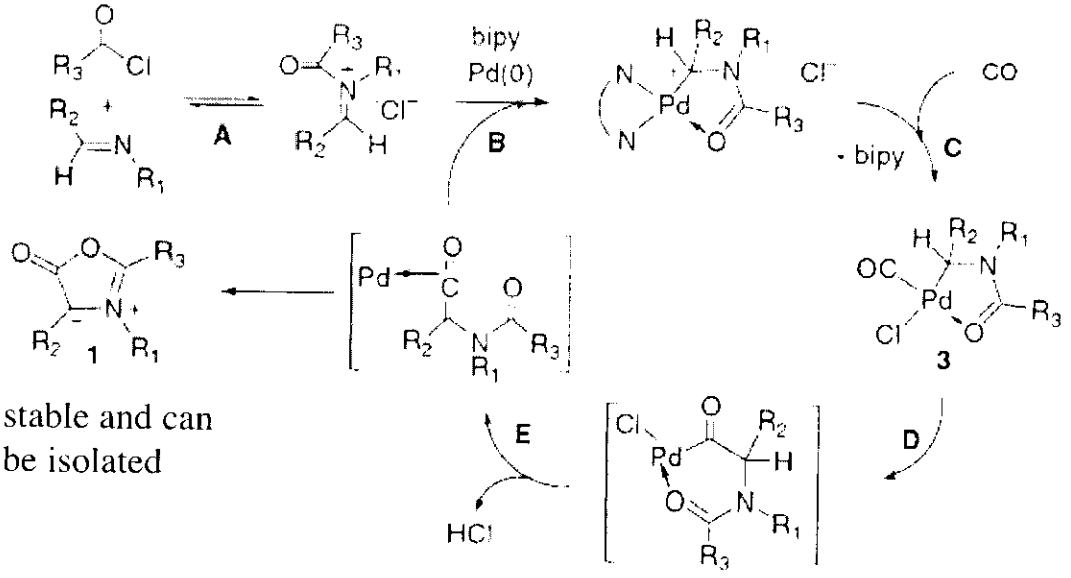
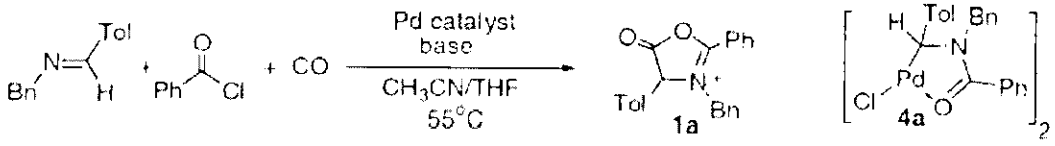


Table 1. Catalytic Synthesis of **1a**[a]



#	[CO]	Pd catalyst	base	additive	%**1a** (%**2**)[b]
1	1 atm	$Pd_2(dba)_3 \cdot CHCl_3$	$NEt(^iPr)_2$	bipy, 5%	5% (—)[c]
2	1 atm	$Pd_2(dba)_3 \cdot CHCl_3$		bipy, 5%	— (82%)[c]
3	1 atm	$Pd_2(dba)_3 \cdot CHCl_3$	$NEt(^iPr)_2$		10%
4	4 atm	$Pd_2(dba)_3 \cdot CHCl_3$	$NEt(^iPr)_2$		13%
5	4 atm	$Pd_2(dba)_3 \cdot CHCl_3$	$NEt(^iPr)_2$	LiCl	30%
6	4 atm	$Pd_2(dba)_3 \cdot CHCl_3$	$NEt(^iPr)_2$	LiBr	50%
7	4 atm	$Pd_2(dba)_3 \cdot CHCl_3$	$NEt(^iPr)_2$	Bu_4NBr	69%
8	4 atm	**4a**	$NEt(^iPr)_2$	Bu_4NBr	83%

[a] 0.48 mmol of imine and additive, 0.67 mmol of acid chloride, 0.74 mmol of base, and 5 mol % catalyst for 24—30 h at 55 °C. [b] NMR yield. [c] 4 days.

Lessons learned:

- Bipy inhibits Münchnone formation
- stabilize Pd to keep from precipitating

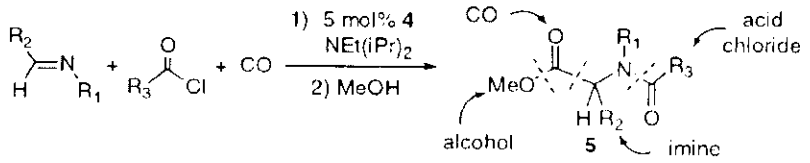
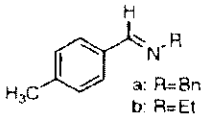
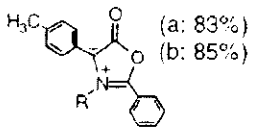
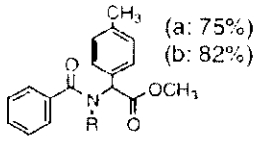
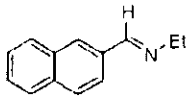
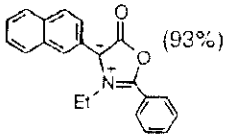
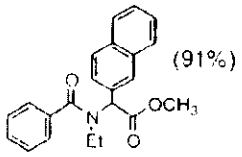
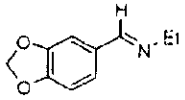
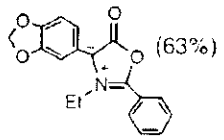
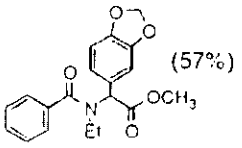
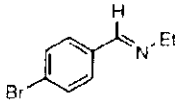
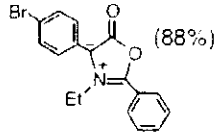
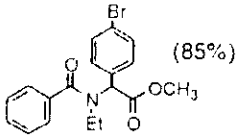
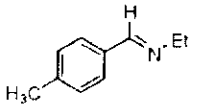
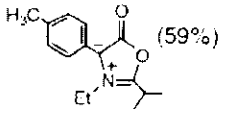
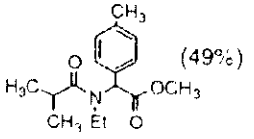
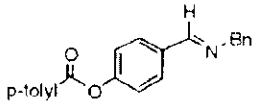
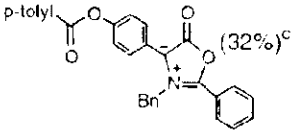
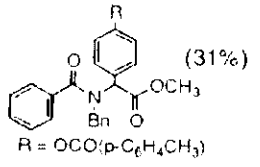
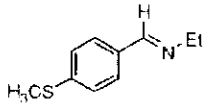
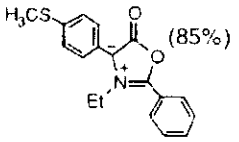
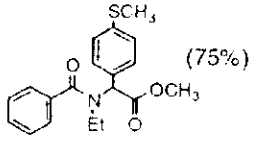
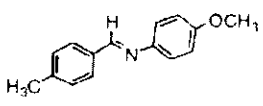
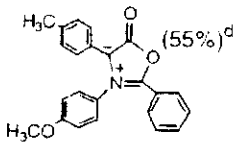
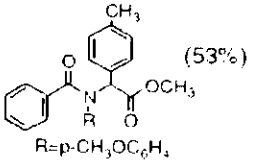


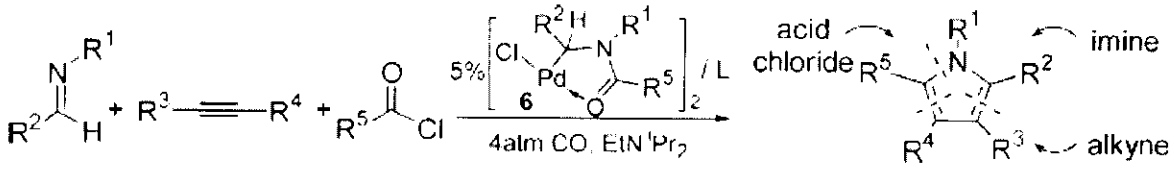
Table 2. Scope of Palladium-Catalyzed Münchnone Synthesis[a]

Cpd	Imine	Acid Chloride	Munchnone 1 (% yield)[b]	Amido Ester 5 (% yield)
a,b	 a: R=Bn b: R=Et	PhCOCl	 (a: 83%) (b: 85%)	 (a: 75%) (b: 82%)
c		PhCOCl	 (93%)	 (91%)
d		PhCOCl	 (63%)	 (57%)
e		PhCOCl	 (88%)	 (85%)
f			 (59%)	 (49%)
g		PhCOCl	 (32%)[c]	 (31%) R = OCO(p-$C_6H_4CH_3$)
h		PhCOCl	 (85%)	 (75%)
i		PhCOCl	 (55%)[d]	 (53%) R=p-$CH_3OC_6H_4$

[a] Analogous to Table 1, # 8.[13] [b] NMR. [c] $Pd_2(dba)_3$·$CHCl_3$ cat. [d] 96 h.

One-pot catalytic synthesis of pyrroles

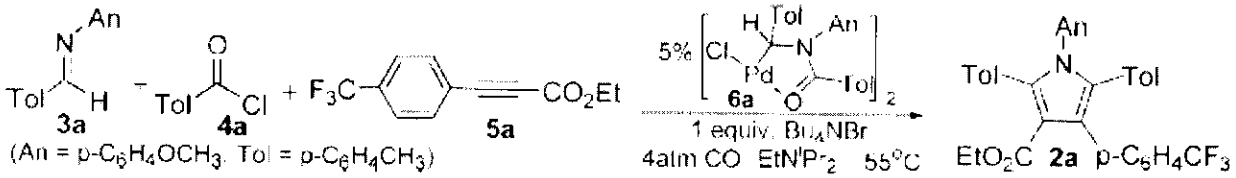
* current lit. article



Why is this work novel?

- one step
- simple, readily available and easily varied substrates

An initial attempt to synthesize a pyrrole deriv.
(via the in-situ generated Münchnones)



Trace of product

Scheme 1. Potential Mechanism for a Catalytic Pyrrole Synthesis

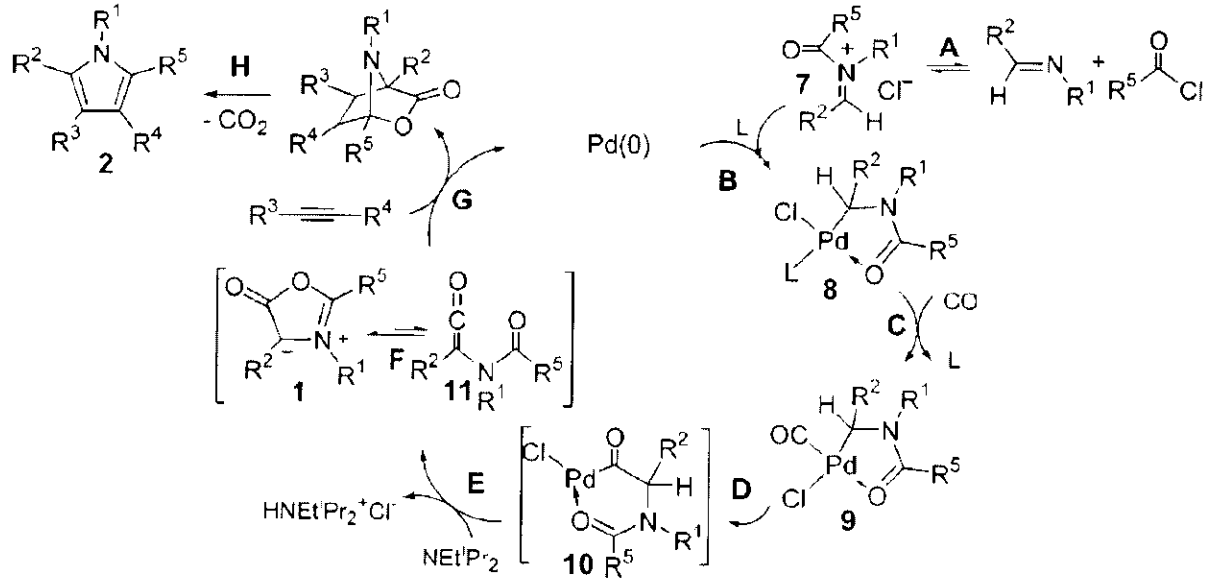
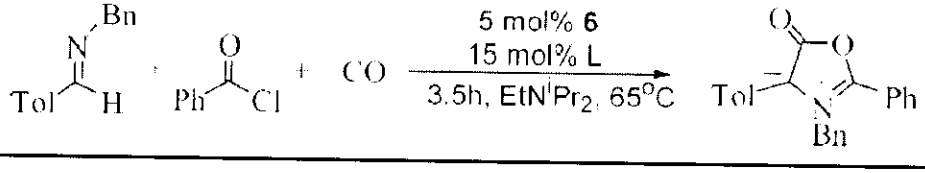


Table 1. Ligand Influence on Münchnone Formation[a]

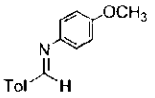
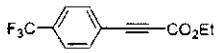
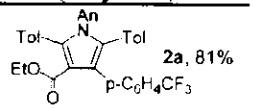
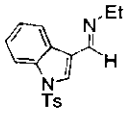
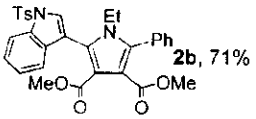
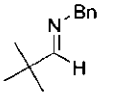
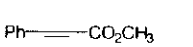
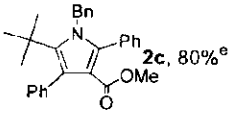
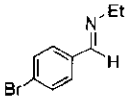
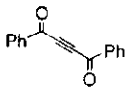
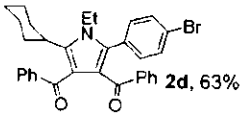
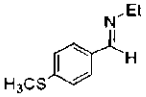
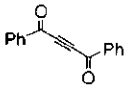
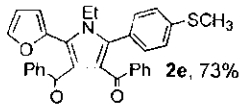
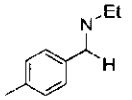
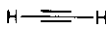
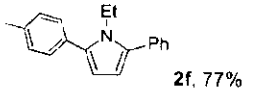
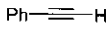
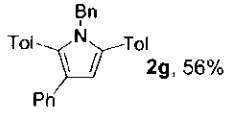
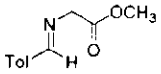
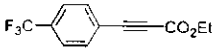
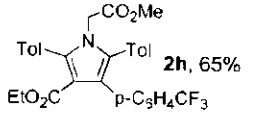
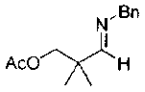
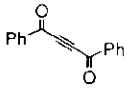
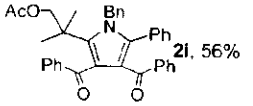
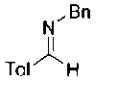
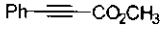
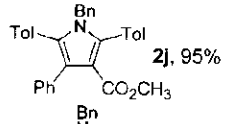
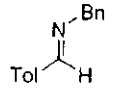
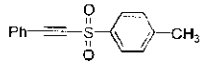
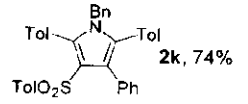
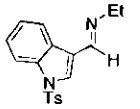
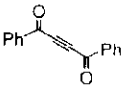
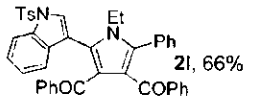
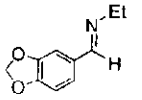
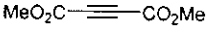


entry	ligand	yield (%)[b]	entry	ligand	yield (%)[b]
1	[c]	33	5	P^tBu_3	29
2	PCy_3	0	6	P^tBu_2(2-biphenyl)	31
3	PPh_3	0	7	P(1-naphthyl)$_3$	51
4	dppe	0	8	P(o-tolyl)$_3$	78

[a] See Supporting Information for details. [b] NMR yield. [c] One equivalent of Bu_4NBr.

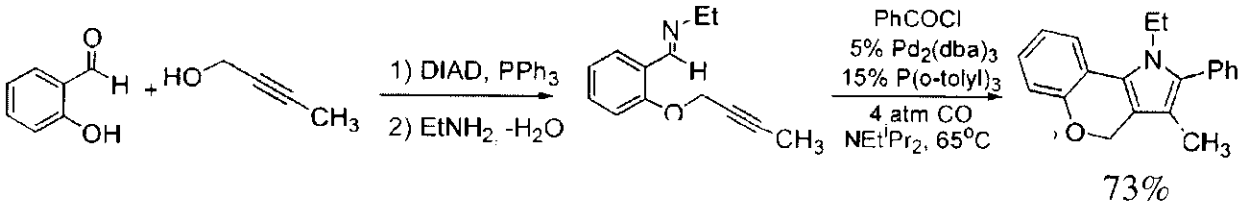
P(*o*-tolyl)$_3$ - a sterically encumbered phosphine

Table 2. Palladium-Catalyzed Pyrrole Synthesis (Eq 1)[a,b]

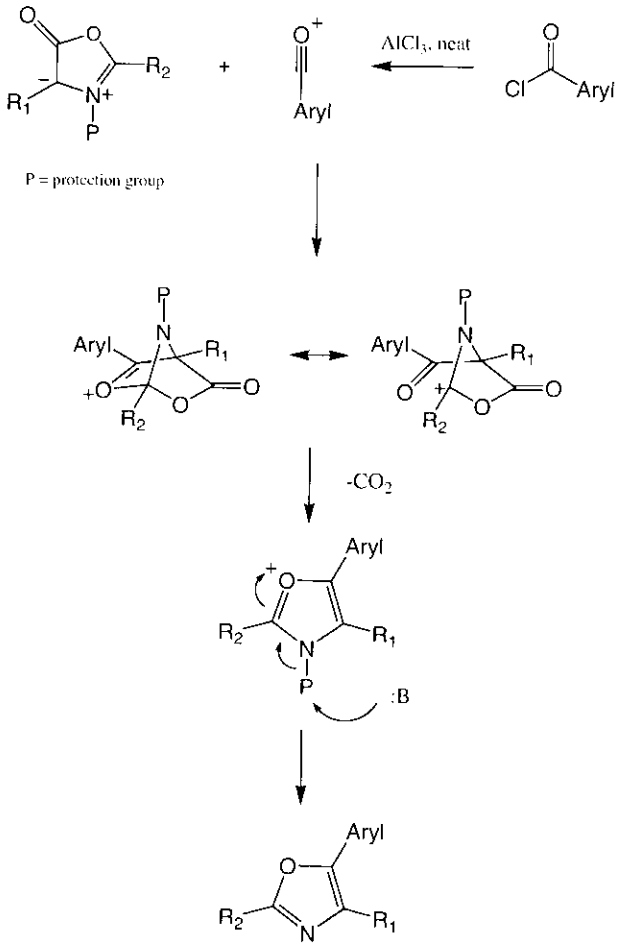
	cpd	imine	acid chloride	alkyne	2 (% yield)
	a		TolCOCl		 **2a**, 81%
	b[c]		PhCOCl		 **2b**, 71%
*	c[d]		PhCOCl		 **2c**, 80%[e]
	d				 **2d**, 63%
	e				 **2e**, 73%
	f[c]		PhCOCl		 **2f**, 77%
	g		TolCOCl		 **2g**, 56%
	h		TolCOCl		 **2h**, 65%
*	i[d]		PhCOCl		 **2i**, 56%
	j		TolCOCl		 **2j**, 95%
	k		TolCOCl		 **2k**, 74%
	l		PhCOCl		 **2l**, 66%
	m[c]		PhCOCl		**2m**, 81%
	n[c]		PhCOCl		**2n**, 88%

[a] Imine (0.7 equiv), acid chloride, alkyne (1.4 equiv), EtN^iPr_2, CO (4 atm), 5% **6**, and 15% P(*o*-tolyl)$_3$ in CH_3CN/THF, 16 h, 65 °C. [b] Pd_2dba_3·$CHCl_3$ or $[Pd(allyl)Cl]_2$ are viable catalysts at ca. 10% lower yield. [c] Alkyne added to preformed **1**. [d] 75 °C, 1 equiv of LiOTf in CH_3CN, **6f** catalyst. [e] Major isomer (5:1 ratio).

Use of catalytic method to generation a complex product with minimal steps



Future extension of work?



2,3,5-trisubstituted oxazole