Ynone Preparation and Applications

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DONG GROUP LITERATURE TALK

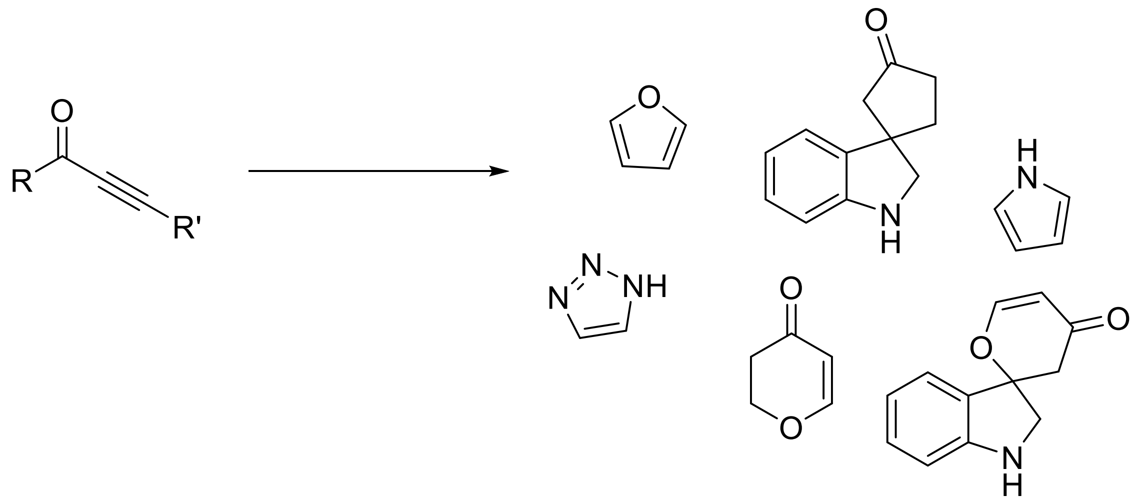
OCTOBER 1, 2014

Overview

- Background and History
- Synthesis of Ynones
  - Metal Acetylides
  - Transition Metal Catalysis
  - Others
- Applications of Ynones
  - Cyclizations
  - Use in Total Synthesis
  - Others

Why Do We Care?

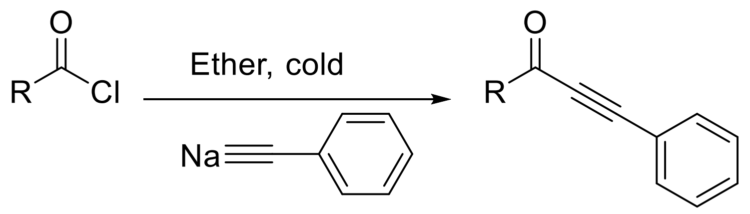
- Due to unsaturation and instability, ynones are easily cyclized in a variety of interesting ways



- These cyclized products often have interesting biological activity, either as natural products or med chem analogs
- Quick and facile construction of complicated molecules always welcome

First Example:

- Nef showed first example in 1899 using sodium acetylide

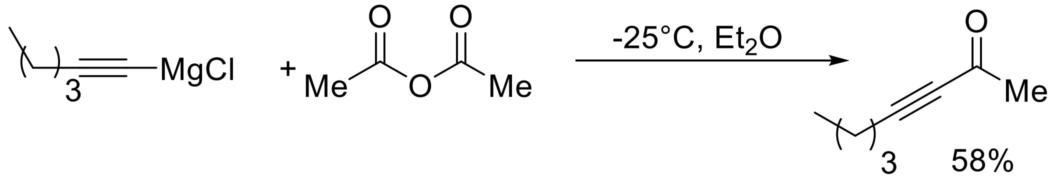


Nef, J.U.; *Liebig's Ann.* **1899**, 264.

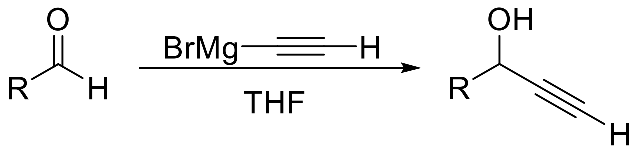
- Very violent reaction and only worked on small scales
- Nef's example set the stage for various metal acetylides to add into anhydrides, aldehydes, and other carbonyl compounds

Anhydrides/Aldehydes-Grignards

- Anhydrides (in large excess) at low temperatures showed formation of ynones directly



- Aldehydes with Grignard reagents discovered to give easily oxidizable proparglic alcohols

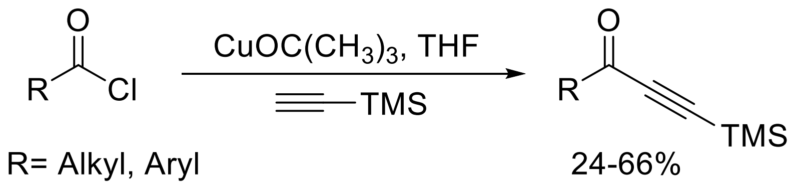


R= Bn, Alkenyl, Alkynyl 45-85%

Kroeger, J.W., Niruwland, J.A., *J. Am. Chem. Soc.*, **1936**, *58*, 1861.
Jones, E.R.H, Skattebol, L., Whiting, M.C., *J. Chem. Soc.*, **1956**, 4765.

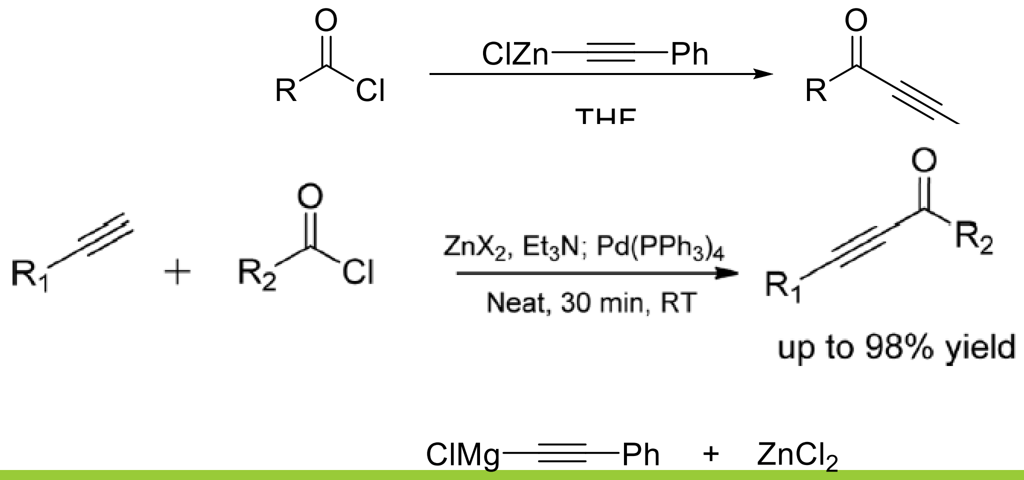
Acyl Chlorides With Copper or Zinc

- Copper acetylides with acyl chlorides allowed for more freedom than anhydrides



Logue, M.W., Moore, G.L., *J. Org. Chem.*, **1975**, *40*, 131.

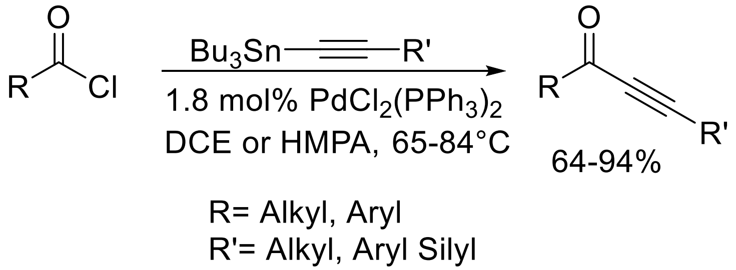
- Zinc can also be utilized



Vereshchagin, L.I., Yashina, O.G., Zarva, T.V., *Zh. Org. Khim.*, **1996**, *2*, 1895.
Yuan, H., Shen, Y., Yu, S., Shan, L., Sun, Q., Zhang, W., *Synth. Commun.*, **2013**, *43*, 2817.

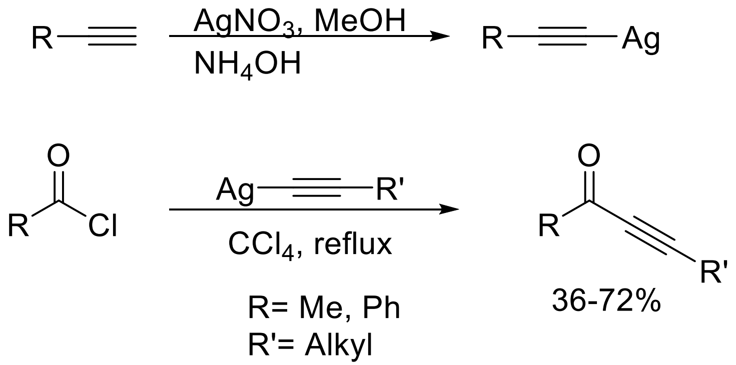
Acyl Chlorides With Tin or Silver

- Tin acetylides can be coupled with acyl chlorides in the presence of a palladium catalyst



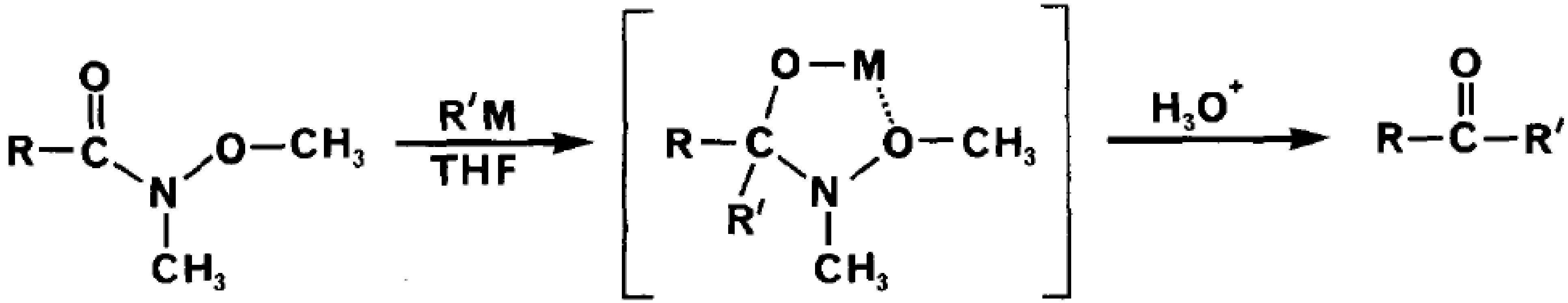
Logue, M.W., Teng, K., *J. Org. Chem.*, **1982**, *47*, 2549.

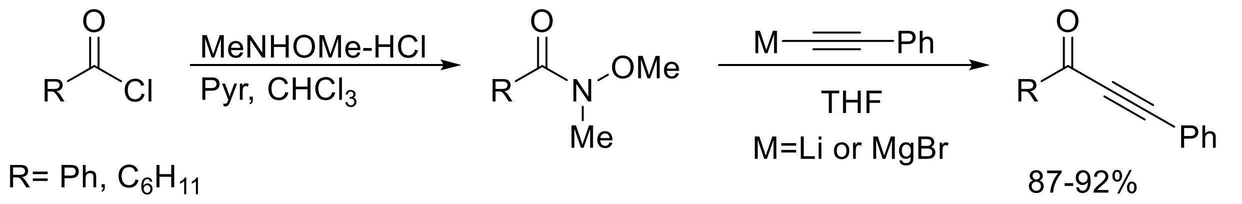
- Silver could also be utilized



Davis, R.B., Scheiber, D.H., *J. Am. Chem. Soc.*, **1956**, *78*, 1675.

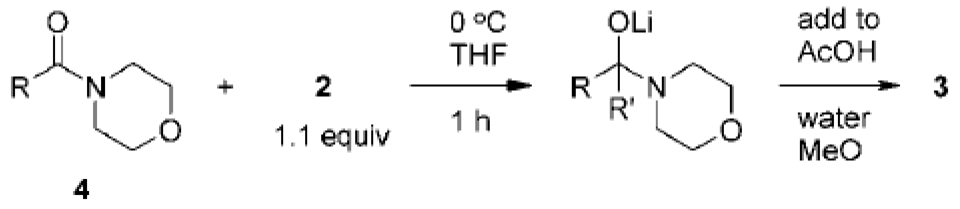
Weinreb Amides





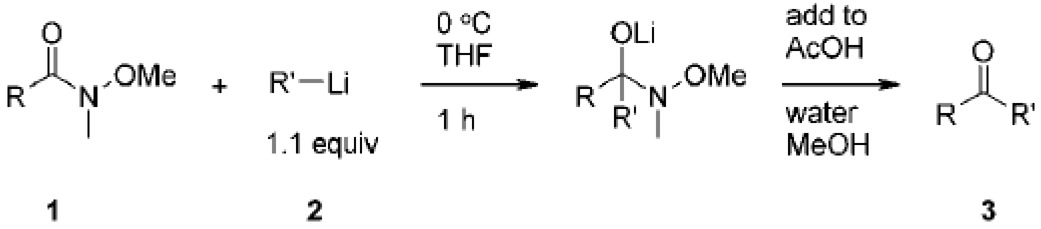
Nahm, S., Weinreb, S.M., *Tetrahedron Lett.*, **1981**, *22*, 3815.

Morpholine Amides



entry	amide: 4	amide: R	alkyllithium: 2	alkyllithium: R′-Li	3	products[a]: % AUC ketone	products[a]: % AUC byproduct	products[a]: % AUC 4
1	**4a**	$PhCH_2CH_2$	**2a**	BuC≡CLi	**3a**	75	0	25
2	**4a**	$PhCH_2CH_2$	**2b**	PhC≡CLi	**3b**	42	0	58
3	**4a**	$PhCH_2CH_2$	**2c**	BuLi	**3c**	34	22	37
4	**4b**	Ph	**2a**	BuC≡CLi	**3d**	94	0	6
5	**4b**	Ph	**2b**	PhC≡CLi	**3e**	70	0	30
6	**4b**	Ph	**2c**	BuLi	**3f**	96	4	0

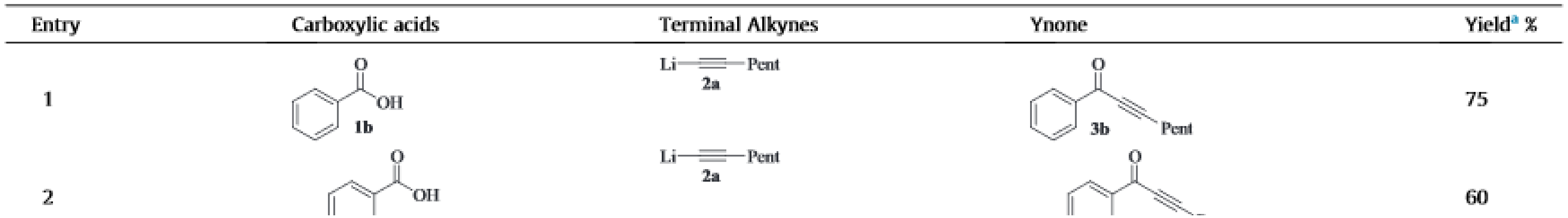
[a] As analyzed by HPLC, area under the curve (AUC) is measured at 220 nm. Structures confirmed by NMR and LC/MS.

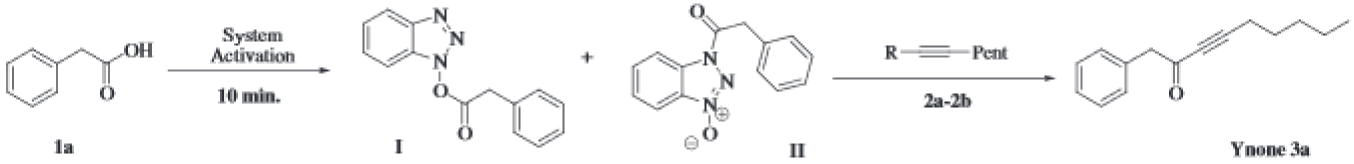


entry	amide: 1	amide: R	alkyllithium: 2	alkyllithium: R′-Li	3	products[a]: % AUC ketone	products[a]: % AUC byproduct
1	**1a**	$PhCH_2CH_2$	**2a**	BuC≡CLi	**3a**	>99	0
2	**1a**	$PhCH_2CH_2$	**2b**	PhC≡CLi	**3b**	>99	0
3	**1a**	$PhCH_2CH_2$	**2c**	BuLi	**3c**	77	7[b]
4	**1b**	Ph	**2a**	BuC≡CLi	**3d**	>99	0
5	**1b**	Ph	**2b**	PhC≡CLi	**3e**	>99	0
6	**1b**	Ph	**2c**	BuLi	**3f**	69	17[b]

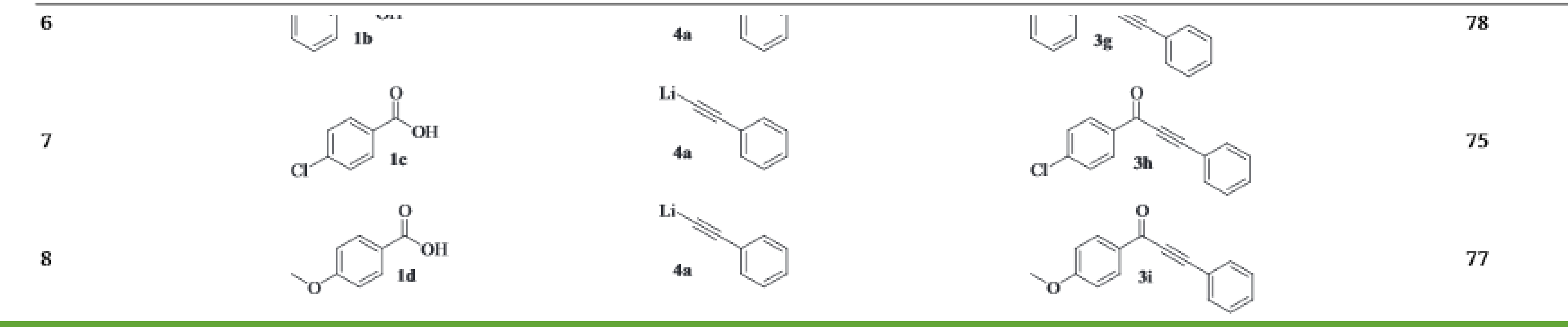
Jackson, M.M., Leverett, C., Toczko, J.F., Roberts, J.C., *J. Org. Chem.*, **2002**, *67*, 5032.

Benzotriazole Esters



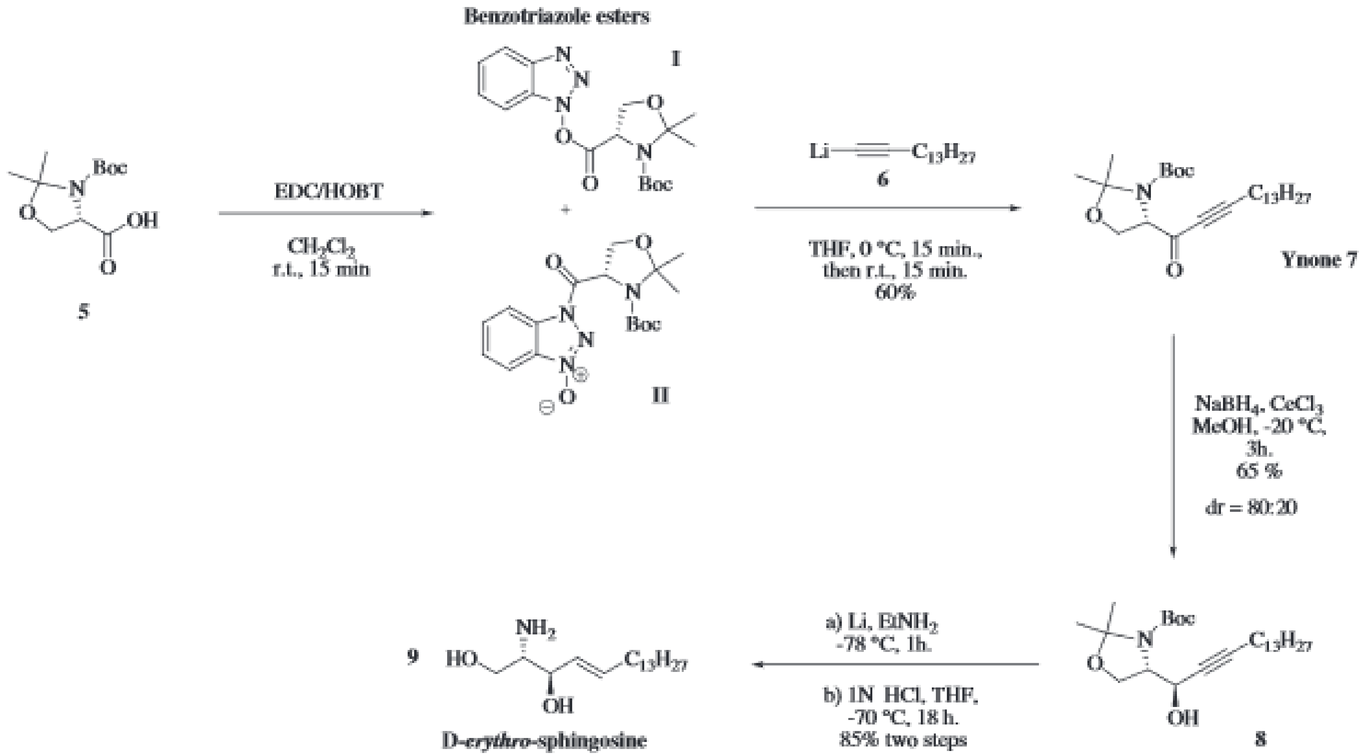


Entry	R	Activation system	Reaction conditions	Yield[c] %
1	**2a** Li[a]	EDC/HOBT[b]	THF, −70 °C, 15 min. and then rt 15 min.	92
2	**2b** H	EDC/HOBT[b]	P_2-Et, THF, −70 °C 15 min. and then rt 15 min.	–
3	**2b** H	EDC/HOBT[b]	P_2-Et, THF, rt 18 h.	–
4	**2b** H	EDC/HOBT[b]	Hydrotalcite, THF, reflux, 18 h.	–
5	**2b** H	EDC/HOBT[b]	$[PdCl_2(PPh_3)_2]$, CuI, TEA, THF or 1,4-dioxane, rt to reflux, 1 h to 18 h.	–



Morales-Serna, J.A., Sauza, A., Padron de Jesus, G., Gavino, R., Garcia de la Mora, G., Cardenas, J., *Tetrahedron Lett.*, **2013**, *54*, 7111.

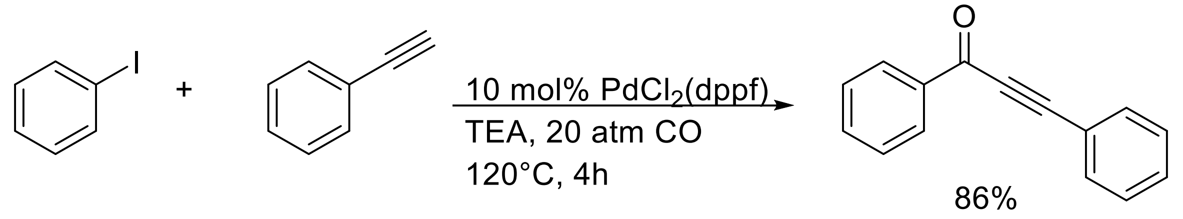
Benzotriazole Esters



Morales-Serna, J.A., Sauza, A., Padron de Jesus, G., Gavino, R., Garcia de la Mora, G., Cardenas, J., *Tetrahedron Lett.*, **2013**, *54*, 7111.

Transition Metal Catalysis…Palladium

- First example by Tanaka in 1981

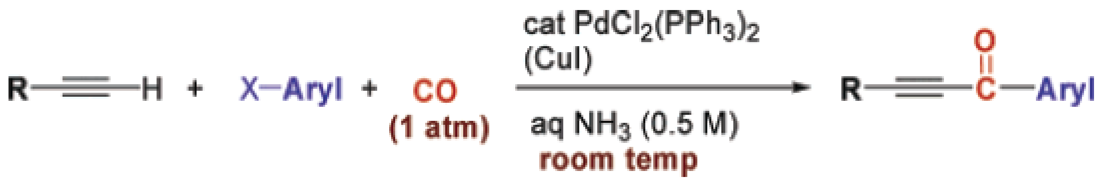


- Little byproduct observed (<1%)
- Several aryl and alkenyl halides tolerated

Kobayashi, T., Tanaka, M., *J. Chem. Soc. Chem. Comm.*, **1981**, 333.

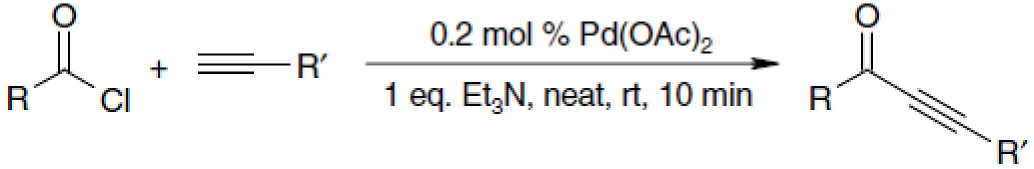
Variations on Carbonylative Songashira

- Use of dilute ammonia can reduce the need to use amines as solvents and high pressures of CO
  - Rarely saw any Songashira byproduct



Mohamed Ahmed, M.S., Mori, A., *Org. Lett.*, **2003**, *5*, 3057.

- Can also use acyl chlorides without CO

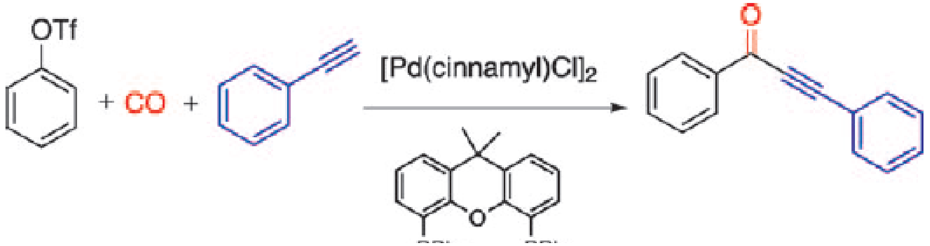


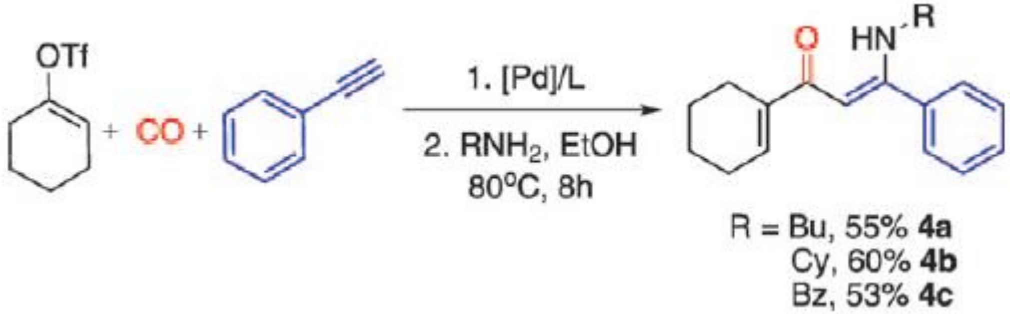
R, R’= Aryl and alkyl
Yields: 40-95%

Palimkar, S.S., Kumar, P.H., Jogdand, N.R., Daniel, T., Lahoti, R.J., Srinivasan, K.V., *Tetrahedron Lett.*, **2006**, *47*, 5527.

Variations on Carbonylative Songashira

- Recently, scope has been expanded to include aryl triflates



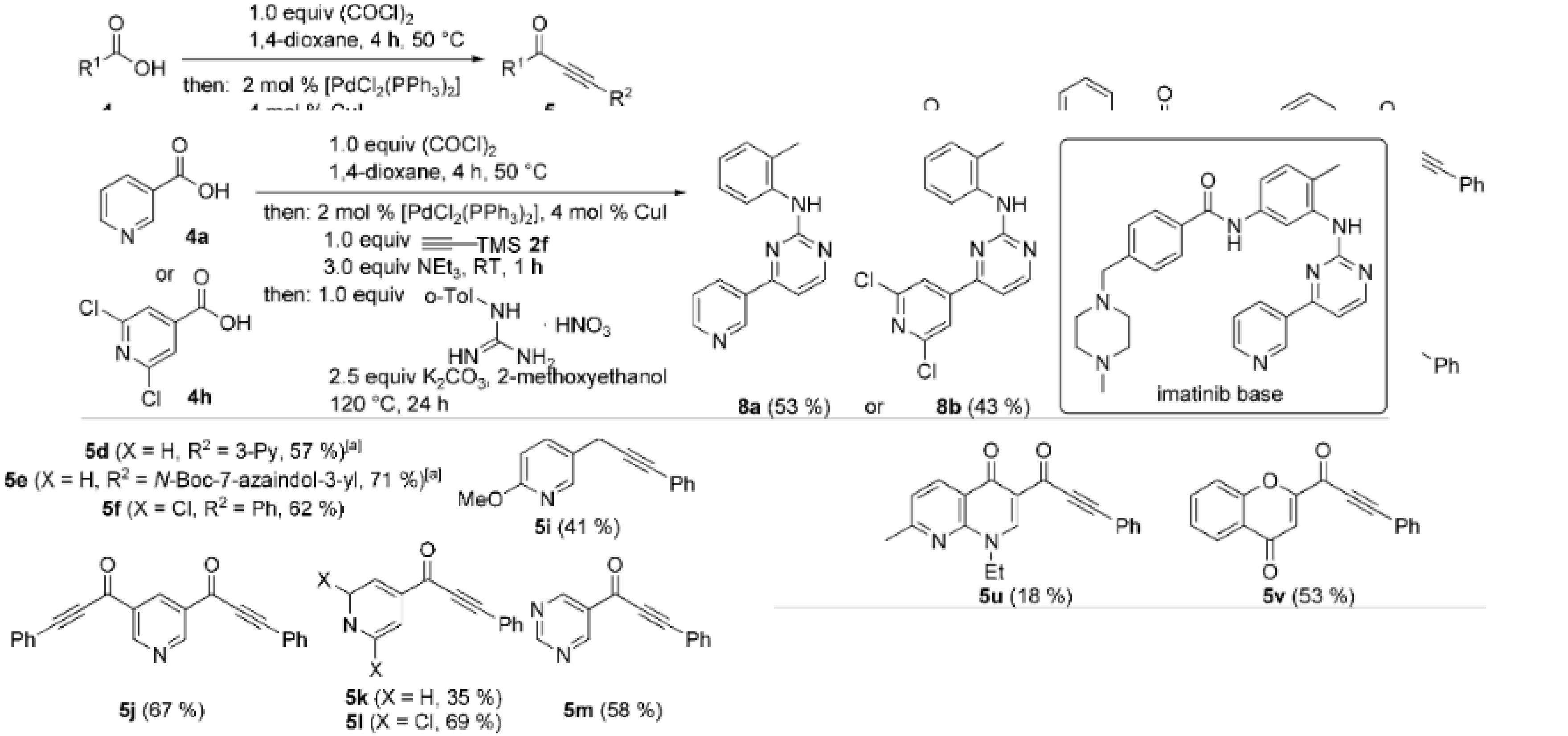


9	NMP	NEt_3	11
10	toluene	NEt_3	83[c]
11	toluene	NEt_3	0[d]
12	toluene	NEt_3	63[c,e]

[a] Phenyl triflate (1.0 mmol), phenyl acetylene (1.2 mmol), CO (10 bar), [{Pd(cinnamyl)Cl}$_2$] (1 mol %), Xantphos (2 mol %), solvent (2 mL), base (2 mmol), 100 °C, 20 h. DBACO = 1,4-diazabicyclo[2.2.2]octane;

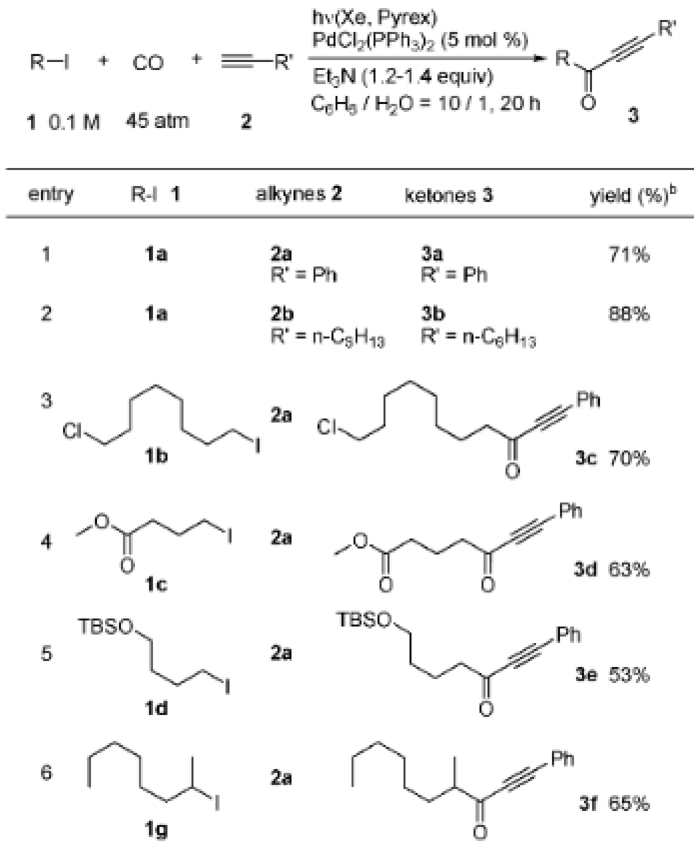
Wu, X.-F., Sundararaju, B., Neumann, H., Dixneuf, P.H., Beller, M., *Chem. Eur. J.*, **2011**, *17*, 106.

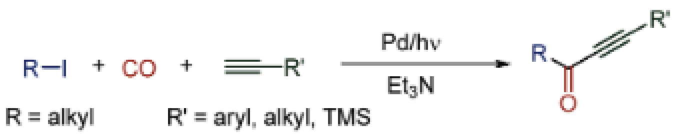
N-Heterocyclic Ynone Synthesis

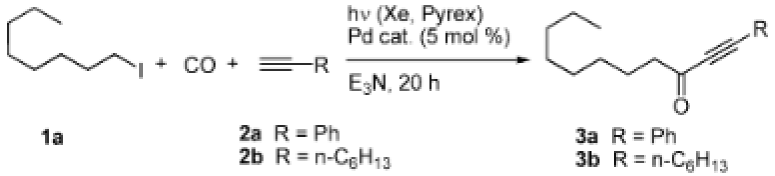


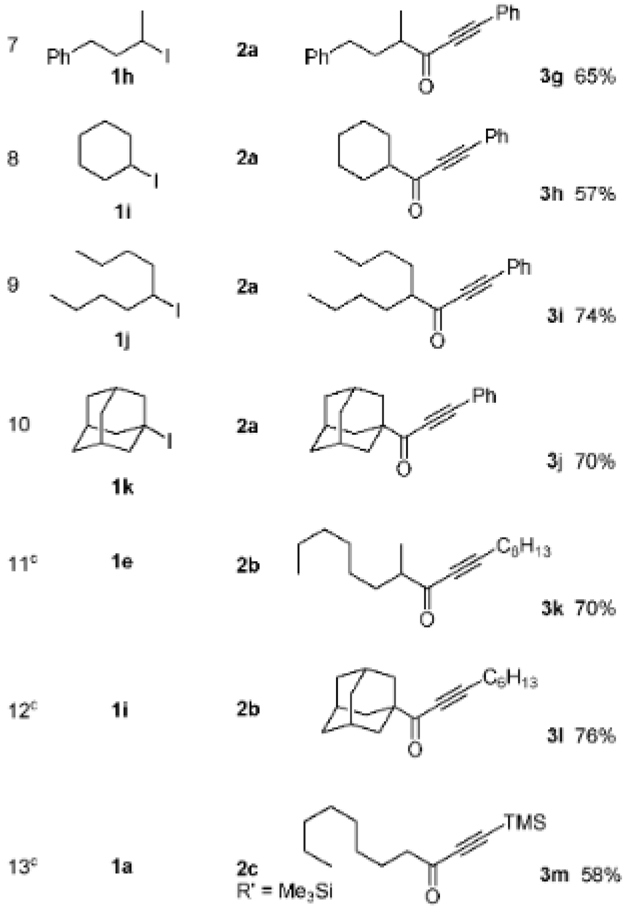
Boersch, C., Merkul, E., Muller, T.J.J., *Angew. Chem. Int. Ed.*, **2011**, *50*, 10448.

Palladium/hv-Alkyl Halides Possible



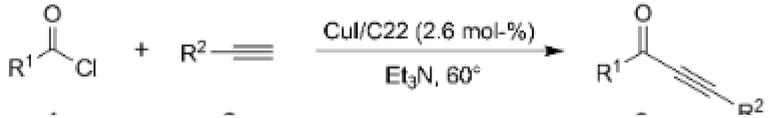


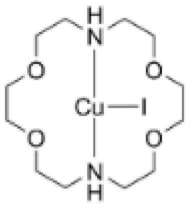




Fusano, A., Fukuyama, T., Nishitani, S., Inouye, T., Ryu, I., *Org. Lett.*, **2010**, *12*, 2410.

Palladium Free-Cu(I) Catalyzed





CuI/C22 Cat.

Table 3. *Comparison of Different Catalytic Systems for the Coupling Reaction of Benzoyl Chloride* (**1a**) *with Phenylacetylene* (**2a**)

Entry	Catalyst	Conditions	Time [h]	Yield [a]) [%]	Ref.
1	$Pd(OAc)_2$	Neat, r.t., Ar	0.17	93	[10c]
2	$Pd(OAc)_2$	Toluene, 110°	1	70	[16]
	Palladacycle	Toluene, 110°	1	75	[16]
3	$PdCl_2(PPh_3)$/CuI	H_2O, 65°	4	98	[11a]
4	$PdCl_2(PPh_3)$/CuI	THF, r.t.	0.17	96	[11b]
5	NS-MCM-41-Pd/CuI	Et_3N, 50°, N_2	36	93	[17]
6	CuI	Neat, r.t., Ar	30	78	[14a]
7	CuI/C22	Neat, 60°	0.5	93	[b])

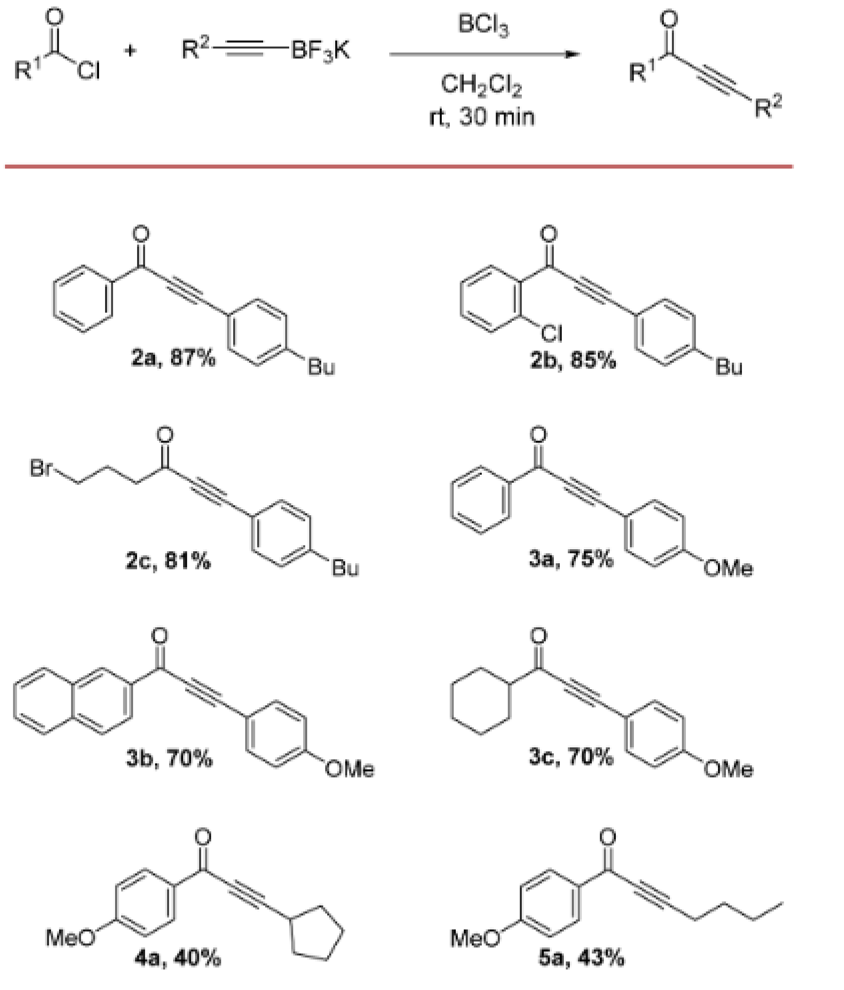
[a]) Yield of isolated product. [b]) This work.

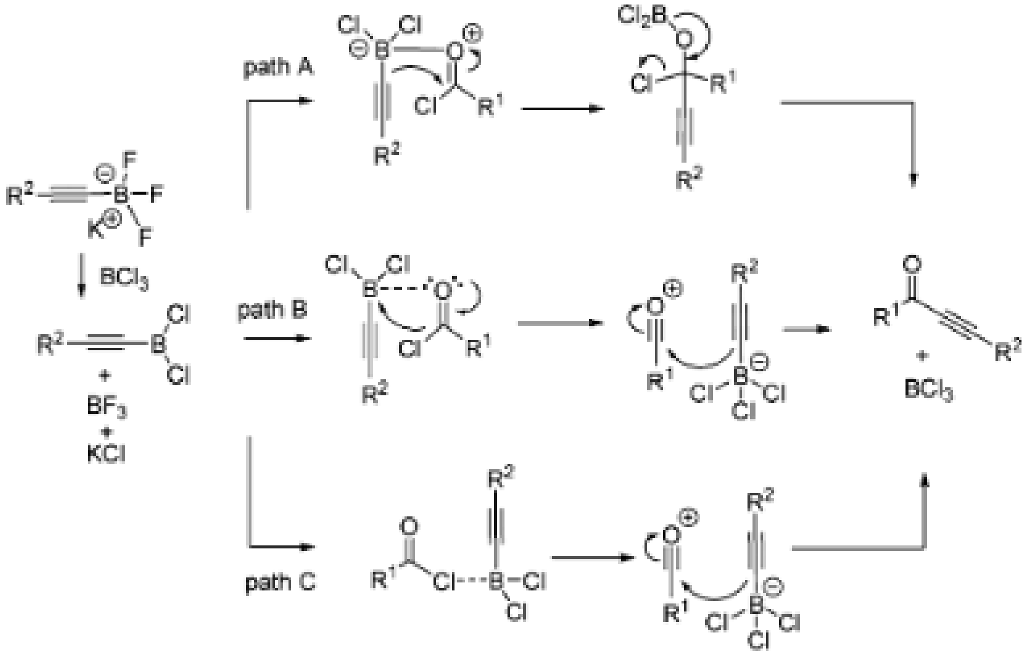
13	**1k**	4-MeO–C_6H_4	**2b**	Bu	**3m**	3	35
14	**1a**	Ph	**2c**	Hexyl	**3n**	5.3	52

[a]) Reaction conditions: 1.0 mmol of **2**, 1.4 mmol of **1**, 1.2 mmol of Et_3N, 60°, aerobic condition. [b]) Yields of isolated products.

Mohammadi, E., Movassagh, B., Navidi, M., *Helvetica Chimica Acta*, **2014**, *97*, 70.

Lewis Acid Catalysis- Organotrifluoroborate Salts

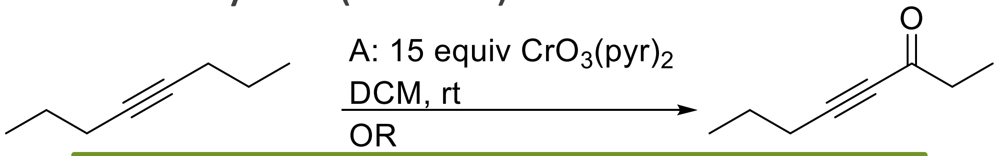




Taylor, C., Bolshan, Y., *Org. Lett.*, **2014**, *16*, 488.

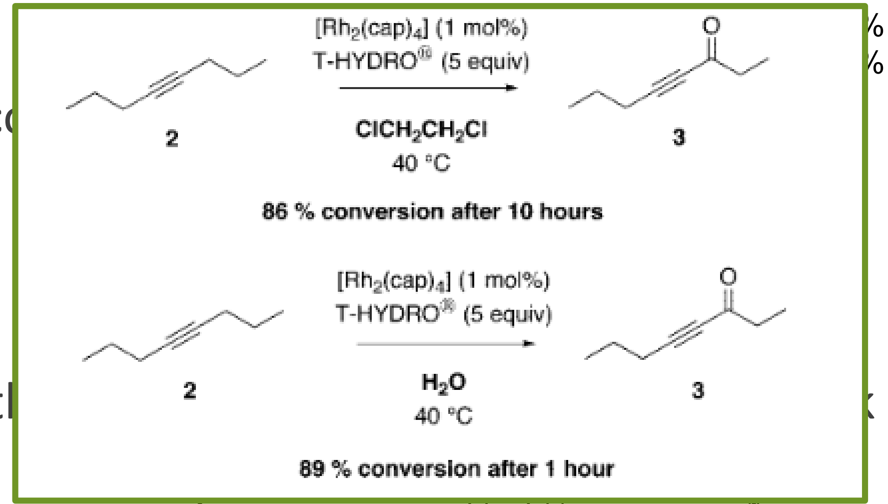
Oxidative Methods

- Chromium first found to oxidize alkynes (Harsh!)



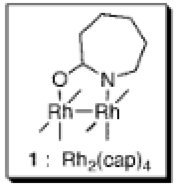
Shaw, J.E., Sherry, J.J., *Tetrahedron Lett.*, **1971**, 4379.

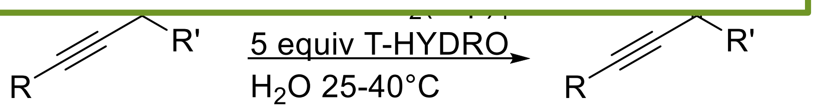
- Williams found more mild c



Li, P., Fong, W.M., Chao, L.C.F., Fung, S.H.C., Williams, I.D., *J. Org. Chem.*, **2001**, *66*, 4087.

- More recently, rhodium in t



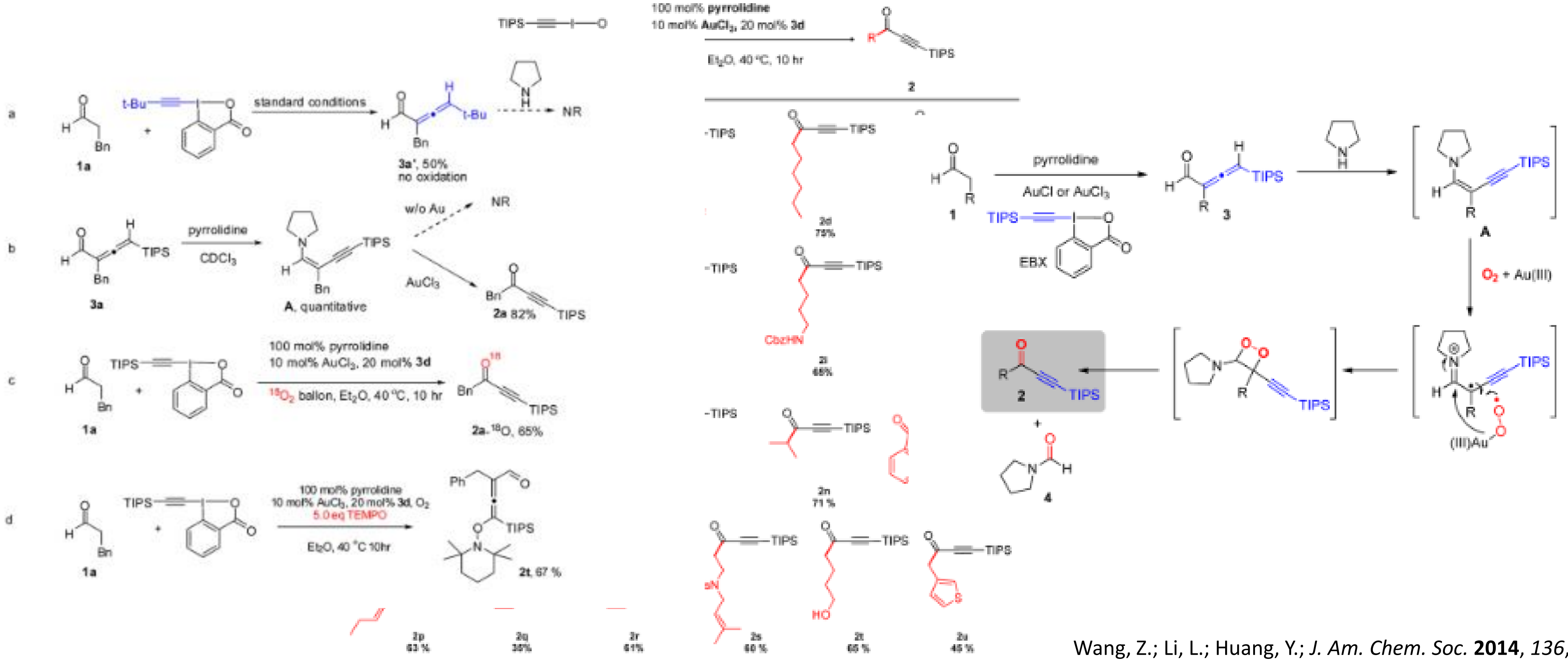


R= H, alkyl, Ph, TMS
R'= alkyl
T-HYDRO: 70% w/w aq tBuOOH

42-80%

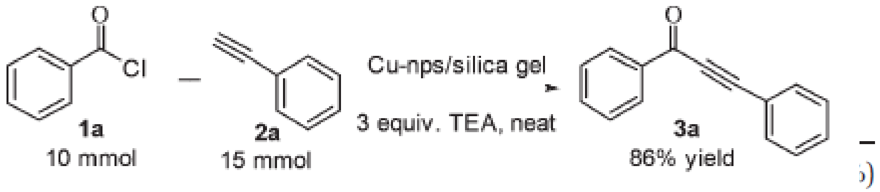
McLaughlin, E.C., Doyle, M.P., *J. Org. Chem.*, **2008**, *73*, 4317.

Oxidative Methods-Oxidative C-C Bond Cleavage of Aldehydes



Wang, Z.; Li, L.; Huang, Y.; *J. Am. Chem. Soc.* **2014**, *136*, 12233.

"Green" Methods-Recyclable Copper Nanoparticles



1	Cu-nps (5)	Toluene	TEA (3)	82
2	Cu-nps (5)	DCM	TEA (3)	12
3	Cu-nps (5)	MeCN	TEA (3)	49

Entry	Supporter	First run yield[b] (%)	Second run yield[b] (%)	Third run yield[b] (%)
1	γ-Al_2O_3	89	83	78
2	Silica gel	95	90	84
3[c]	Silica gel	92	88	85

[a] Reaction conditions: alkyne (0.5 mmol), acyl chloride (1.5 equiv.), Et_3N (3 equiv.), 40 °C overnight, supported Cu-nps (1 mol%). [b] Yield determined by GC using dimethyl phthalate as an internal standard. [c] Reaction in the 2 mmol scale.

20	Cu-nps/silica gel (1)	Free	TEA (3)	95

Sun, W., Wang, Y., Wu, X., Yao, X., *Green Chem.*, **2013**, *15*, 2356.

Applications of Ynones

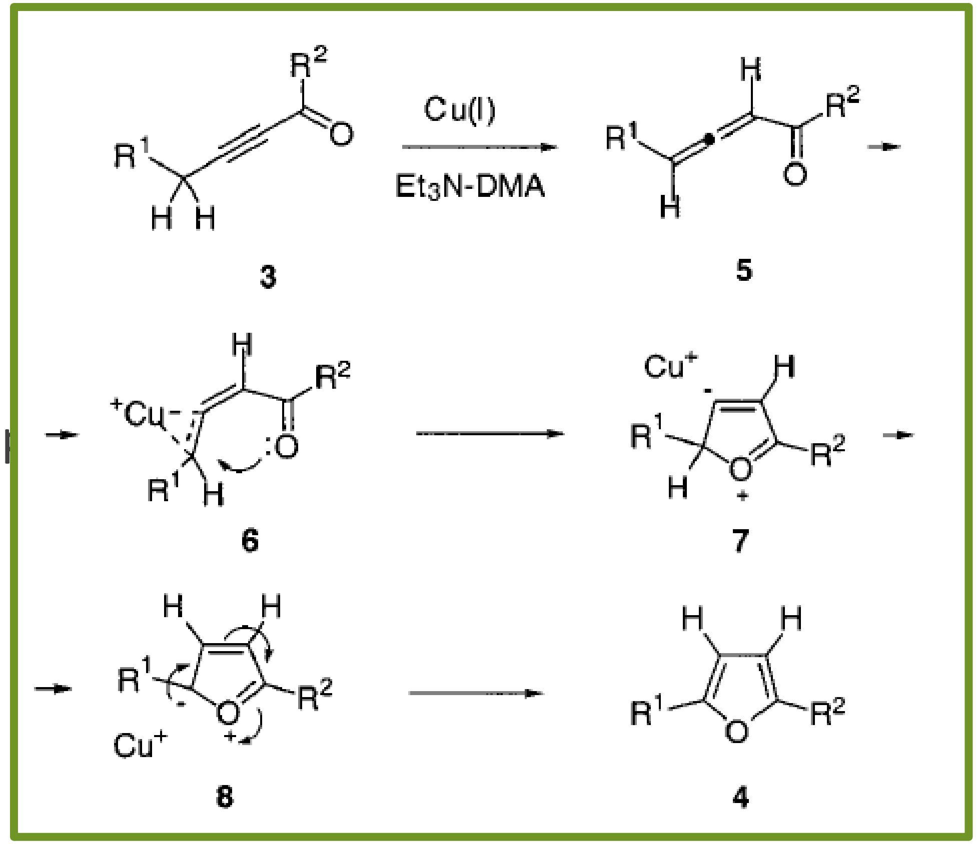
- Cyclization Methodologies

- Use in Total Synthesis (Generally through Cyclizations)

- Others Applications

Furan Formation

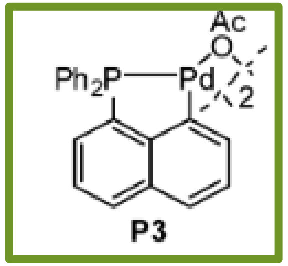
- First reported with palladium in 1986

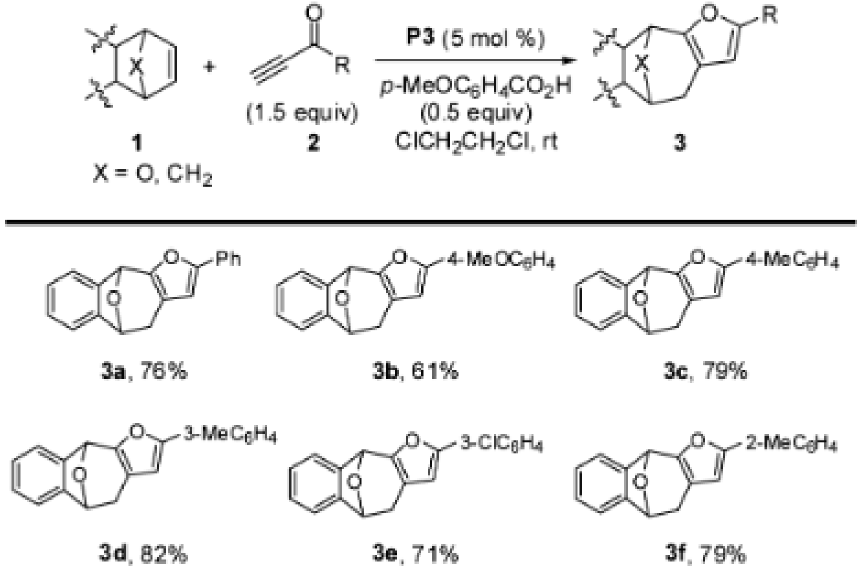


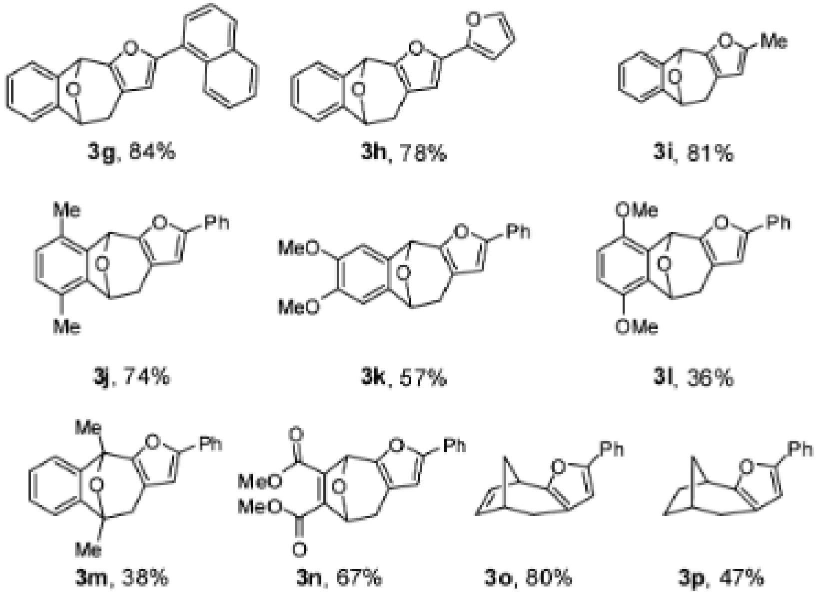
- Later reported with copp

Sheng, H., Lin, S., Huang, Y.Z., *Tetrahedron Letters*, **1986**, *27*, 4893.
Kel'in, A., Gevorgyan, V., *Journal of Organic Chemistry*, **2002**, *67*, 95.

Bicyclic Alkenes to Furans



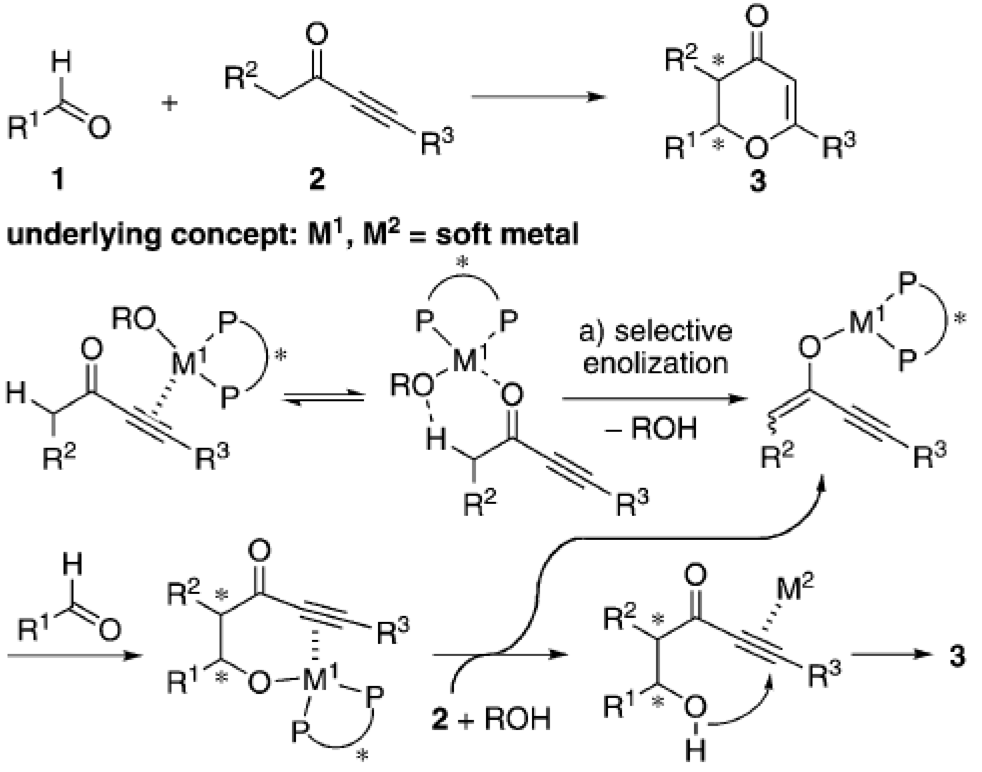


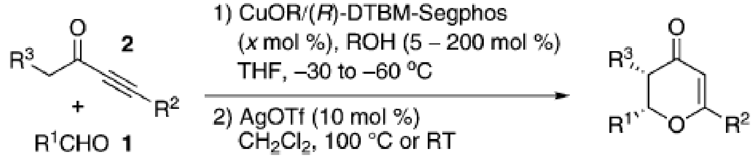


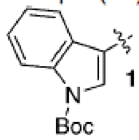
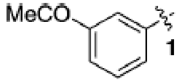
Ge, G-C., Mo, D-L., Ding, C-H., Dai, L-X., Hou, X-L., *Org. Lett.*, **2012**, *14*, 5756.

Asymmetric Synthesis of Dihydropyranones

CuOR = $CuOCH_2CF_3$ (3-5 mol%)
ROH = CF_3CH_2OH



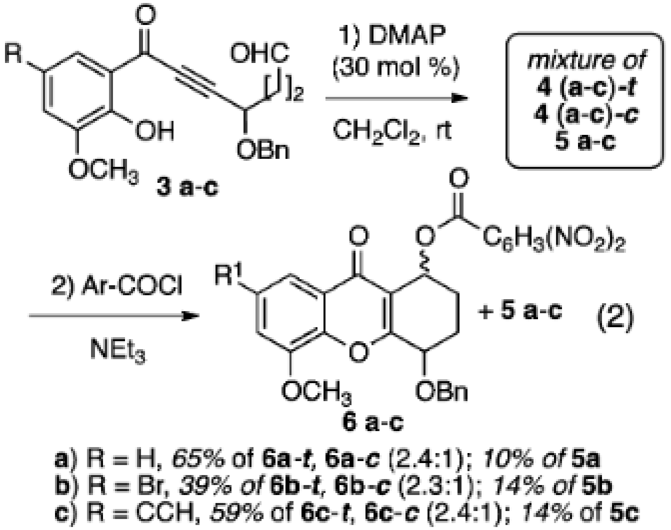


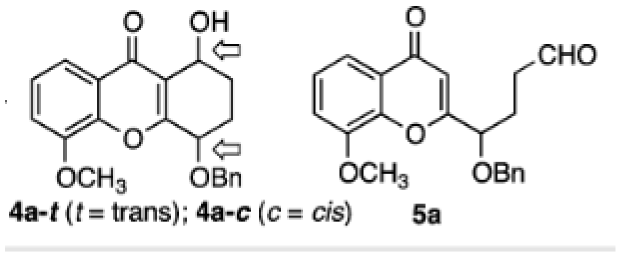
Entry	Aldehyde: R^1	Ynone: R^2, R^3	*x*	Cond.[a]	Prod.	Yield [%][b]	*ee* [%]
1	*i*Pr (**1a**)	Et, H (**2a**)	5	A[c]	**4aa**	81	88
2	*c*Hex (**1b**)	Et, H (**2a**)	5	A[c]	**4ba**	75	88
3[d]	*t*Bu (**1c**)	Et, H (**2a**)	3	A	**4ca**	88	93
4	$Ph(CH_2)_2$ (**1d**)	Et, H (**2a**)	3	A[e]	**4da**	55	75
5	*t*Bu (**1c**)	Ph, H (**2b**)	3	A[f]	**4cb**	65	95
6	*t*Bu (**1c**)	$(CH_2)_2OH$, H (**2c**)	3	A[f]	**4cc**	73	93
7	Ph (**1e**)	Et, H (**2a**)	5	B	**4ea**	99	91
8[g]	Ph (**1e**)	Me, H (**2d**)	5	B	**4ed**	94	90
9	2-naph (**1f**)	Et, H (**2a**)	5	B	**4fa**	89	88
10	 **1g**	Et, H (**2a**)	5	B[h]	**4ga**	75	83
11	 **1h**	Et, H (**2a**)	3	B[i]	**4ha**	56	87

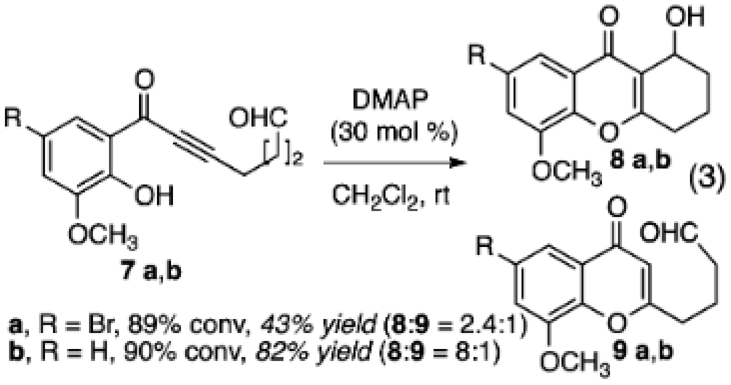
Shi, S-L., Kanai, M., Shibasaki, M., *Angew. Chem., Int. Ed.*, **2012**, *51*, 3932.

DMAP-Promoted Formation of THX

- Tetrahydroxanthones are xanthone derivatives that have proved difficult to synthesize, but show interesting biological properties

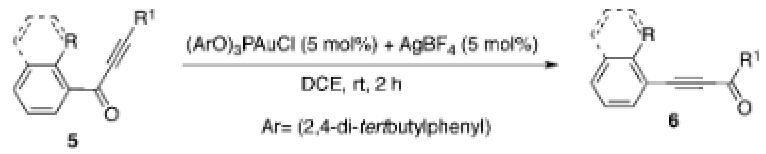


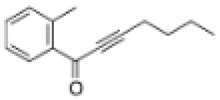
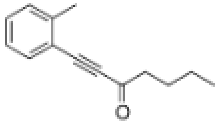
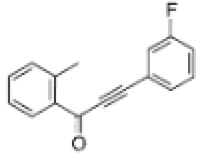
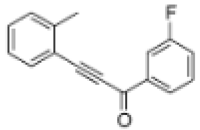
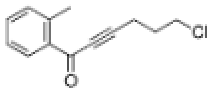
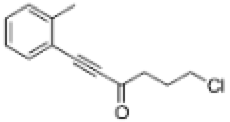
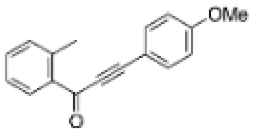
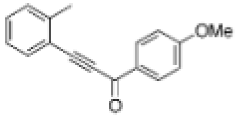
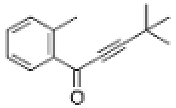
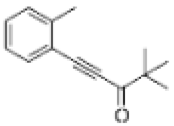
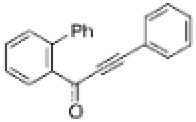
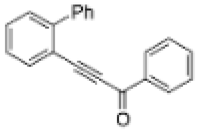
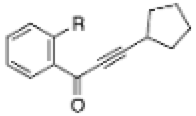
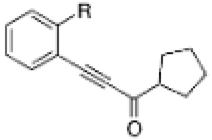
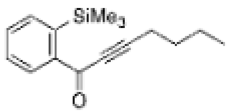
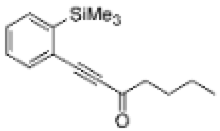




Castillo-Contreras, E.B., Dake, G.R., *Org. Lett.*, **2014**, *16*, 1642.

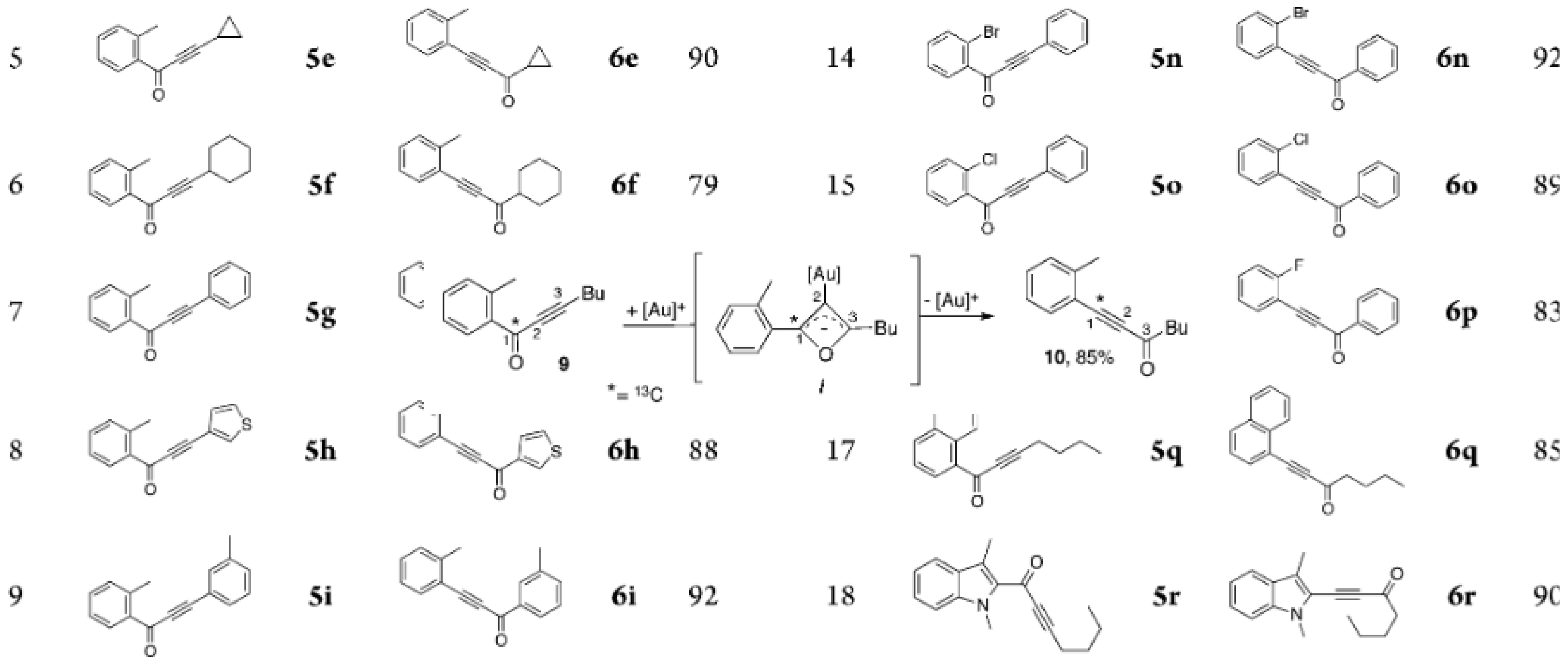
1,3 Transposition With Gold



entry	5		6		Yield %[a]	entry	5		6		Yiel %[
1		**5a**		**6a**	95	10		**5j**		**6j**	97
2		**5b**		**6b**	90	11		**5k**		**6k**	81
3		**5c**		**6c**	98	12		**5l**		**6l**	91
4		R=H **5d** R=Me **5d’**			R=H, 89 **6d:5d**=38:62[b,c] R= Me, 91 **6d’** only	13		**5m**		**6m**	91

Shiroodi, R.K., Soltani, M., Gevorgyan, V., *J. Am. Chem. Soc.*, **2014**, *136*, 9882.

1,3 Transposition With Gold



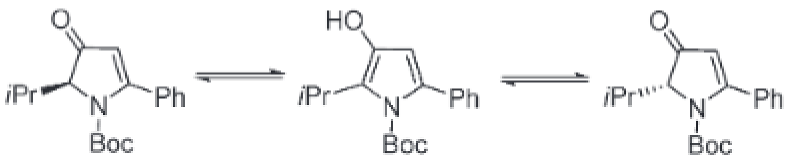
Shiroodi, R.K., Soltani, M., Gevorgyan, V., *J. Am. Chem. Soc.*, **2014**, *136*, 9882.

Pyrrolin-4-ones

- Uriac showed gold catalysis could allow for quick synthesis under mild conditions

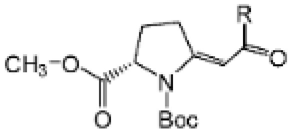
entry	catalyst	base (2 equiv)	temp (°C)	time (h)	yield (%)	ee (%)[a]
1	AuCl		rt	1	96	0
2	AuCl	K_2CO_3	rt	1	90	60
3	AuCl	DBP[b]	rt	1	85	70
4	AuCl	amylene	rt	1	82	10
5	PPh_3AuCl $AgSbF_6$		rt	1	90	10
6	Au_2O_3		rt	48	91	82
7	Au_2O_3		60	1.5	95	99
8	$Au(OH)_3$		rt	5	nr[c]	
9	$Au(OH)_3$		60	24	80	99
10	$Au(OAc)_3$		rt	5	nr[c]	
11	$Au(OAc)_3$		60	24	42	25

[a] Determined by chiral HPLC. [b] 2,6-Di-*tert*-butylpyridine. [c] No reaction.



Gouault, N., Le Roch, M., Cornee, C., David, M., Uriac, P., *J. Org. Chem.*, **2009**, *74*, 5614.

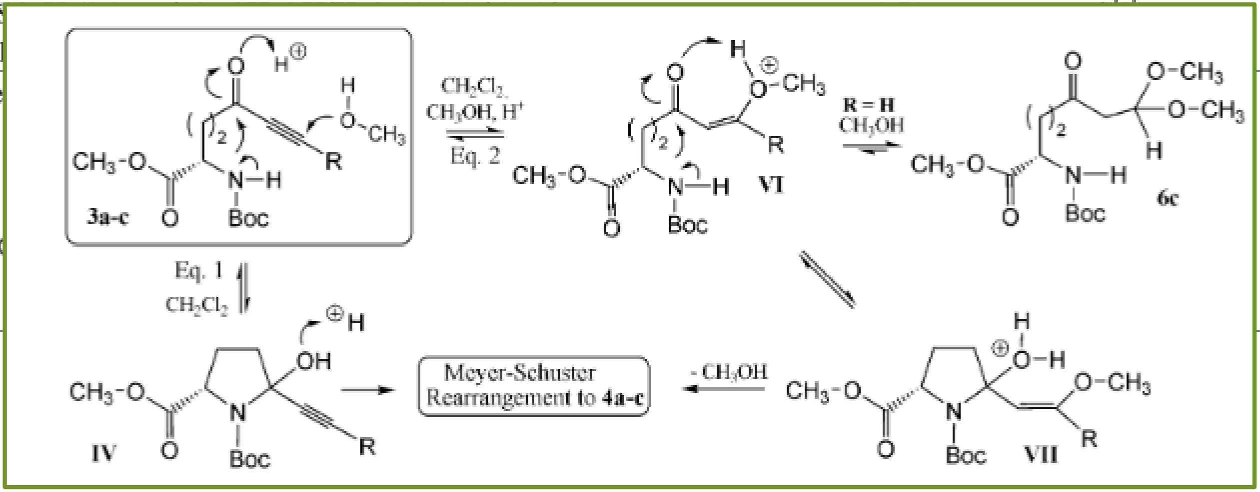
Enantiopure Pyrrolidine from γ-Amino-ynones



4a: R = $(CH_2)_2CH_3$
4b: R = Ph
4c: R = H

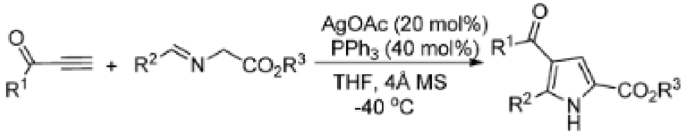
Entry	Conditions	3a/4a	3b/4b	3c/4c
1	CH_2Cl_2/CH_3OH 9:1, 12 h, r.t.	100:0	n.d.[a]	n.d.[a] .
2	CH_3SO_3H (0.2 equiv.), CH_2Cl_2, 4 h, r.t.	80:20	70:0	0:90[b]
3	CH_3SO_3H (0.8 equiv.), CH_2Cl_2, 4 h, r.t.	55:10	15:0	0:90[b]
4	CH_3SO_3H (0.8 equiv.), CH_2Cl_2/CH_3OH 9:1, 4 h, r.t.	0:90	0:85	0:50
5	CH_3SO_3H (0.8 equiv.), CH_3OH, 4 h, r.t.	0:90	0:90	0:5
6	CH_3SO_3H (0.8 equiv.), CH_2Cl_2, H_2O (50 µL), 4 h, r.t.	95:0	100:0	90:5
7	CH_3S			n.d.[a]
8	Cam			n.d.[a]

[a] n.d: not done



Vu, H-D., Renault, J., Roisnel, T., Gouault, N., Uriac, P., *Eur. J. Org. Chem.*, **2014**, 4506.

1,3 Dipolar Cycloaddtion to Pyrroles



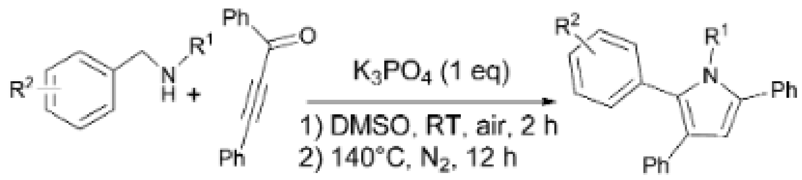
1 2 3

Entry	R^1	R^2/R^3	Yield[b] (%)	*t* (h)
1	C_6H_5 (**1a**)	4-ClC_6H_4/Me (**2a**)	73	30
2	4-ClC_6H_4 (**1b**)	4-ClC_6H_4/Me (**2a**)	63	20
3	4-$NO_2C_6H_4$ (**1c**)	4-ClC_6H_4/Me (**2a**)	71	20
4	3-BrC_6H_4 (**1d**)	4-ClC_6H_4/Me (**2a**)	69	20
5	2-FC_6H_4 (**1e**)	4-ClC_6H_4/Me (**2a**)	67	20
6	2-MeC_6H_4 (**1f**)	4-ClC_6H_4/Me (**2a**)	62	48
7	2,4-MeC_6H_3 (**1g**)	4-ClC_6H_4/Me (**2a**)	53	48
8	4-$MeOC_6H_4$ (**1h**)	4-ClC_6H_4/Me (**2a**)	80	48
9[c]	4-$MeOC_6H_4$ (**1h**)	4-ClC_6H_4/Me (**2a**)	51	48
10	4-MeC_6H_4 (**1i**)	4-ClC_6H_4/Me (**2a**)	65	48
11	2-Furyl (**1j**)	4-ClC_6H_4/Me (**2a**)	68	20
12	C_6H_5 (**1a**)	4-ClC_6H_4/Et (**2b**)	69	12
13	C_6H_5 (**1a**)	4-ClC_6H_4/*t*-Bu (**2c**)	69	12
14	C_6H_5 (**1a**)	C_6H_5/Me (**2d**)	82	20
15[c]	C_6H_5 (**1a**)	C_6H_5/Me (**2d**)	61	20
16	C_6H_5 (**1a**)	4-BrC_6H_4/Me (**2e**)	79	20
17	C_6H_5 (**1a**)	2-ClC_6H_4/Me (**2f**)	89	20
18[c]	C_6H_5 (**1a**)	2-ClC_6H_4/Me (**2f**)	79	20
19	C_6H_5 (**1a**)	3-BrC_6H_4/Me (**2g**)	72	20
20	C_6H_5 (**1a**)	4-MeC_6H_4/Me (**2h**)	76	30
21	C_6H_5 (**1a**)	2-MeC_6H_4/Me (**2i**)	82	30
22[c]	C_6H_5 (**1a**)	2-MeC_6H_4/Me (**2i**)	63	30
23	C_6H_5 (**1a**)	Cy/Me (**2j**)	31	30

[a] Conditions: AgOAc (20 mol%), PPh_3 (40 mol%), THF, 4 Å MS, −40 °C.
[b] Isolated yields. [c] 10 mol% AgOAc and 20 mol% PPh_3 were used.

Wang, Z., Shi, Y., Luo, X., Han, D-M., Deng, W-P., *New J. Chem.*, **2013**, *37*, 1742.

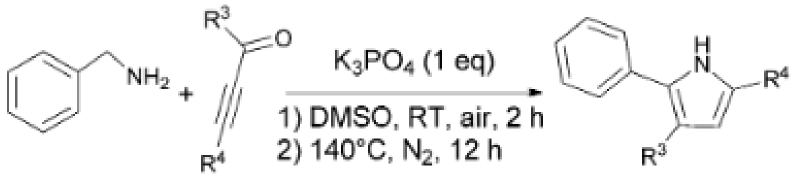
Metal-Free Synthesis Pyrroles



2a-2j **3a** **4aa-4ja**

Entry	2	R^1	R^2	4	Yield[b] (%)
1	**2a**	H	H	**4aa**	88
2	**2b**	H	4-Me	**4ba**	82
3	**2c**	H	2-Me	**4ca**	84
4	**2d**	H	4-OMe	**4da**	75
5	**2e**	H	4-*t*Bu	**4ea**	81
6	**2f**	H	4-Cl	**4fa**	85
7	**2g**	H	4-CF_3	**4ga**	79
8	**2h**	H	3,4-OMe	**4ha**	82
9	**2i**	Me	H	**4ia**	91
10	**2j**	*n*Bu	H	**4ja**	55[c]

[a] Reaction conditions: benzylamines **2a–2j** (1 mmol), 1,3-diphenylprop-2-yn-1-one **3a** (1 mmol), K_3PO_4 (1 mmol) and DMSO (2.0 mL) at a 140 °C under N_2 atmosphere. [b] Isolated yields based on 1,3-diphenylprop-2-yn-1-one **3a**. [c] 80% yield was obtained from the corresponding *N*-*n*butyl enaminone.



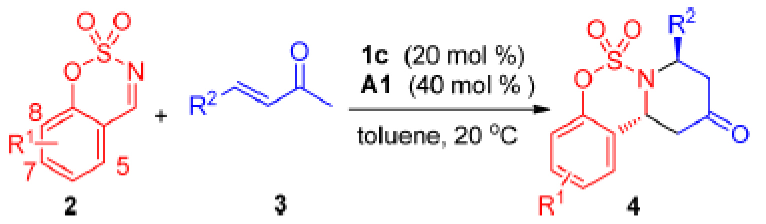
2a **3b-3p** **4ab-4ap**

Entry	3	R^3	R^4	4	Yield[b] (%)
1	**3b**	2-MeC_6H_4-	Ph	**4ab**	89
2	**3c**	4-MeC_6H_4-	Ph	**4ac**	86
3	**3d**	3-$MeOC_6H_4$-	Ph	**4ad**	82
4	**3e**	4-*t*BuC_6H_4-	Ph	**4ae**	81
5	**3f**	4-ClC_6H_4-	Ph	**4af**	64
6	**3g**	4-FC_6H_4-	Ph	**4ag**	85
7	**3h**	Thiophen-2-	Ph	**4ah**	87
8	**3i**	Cyclohexyl-	Ph	**4ai**	91
9	**3j**	Isopropyl-	Ph	**4aj**	40
10	**3k**	Ph	4-MeC_6H_4-	**4ak**	88
11	**3l**	Ph	3-MeC_6H_4-	**4al**	81
12	**3m**	Ph	2-MeC_6H_4-	**4am**	49
13	**3n**	Ph	4-$MeOC_6H_4$-	**4an**	83
14	**3o**	Ph	4-ClC_6H_4-	**4ao**	70
15	**3p**	Ph	4-FC_6H_4-	**4ap**	82
16	**3q**	Ph	*n*Bu	**4aq**	74
17	**3r**	Ph	*t*Bu	**4ar**	70

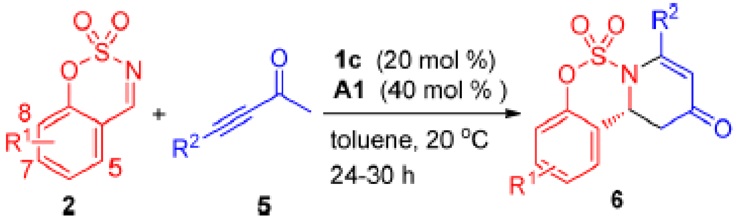
[a] Reaction conditions: benzylamine **2a** (1 mmol), ynone **3** (1 mmol), K_3PO_4 (1 mmol), DMSO (2.0 mL) at 140 °C under N_2 atmosphere. [b] Isolated yields based on ynone **3**.

Shen, J., Cheng, G., Cui, X., *Chem. Commun.*, **2013**, *49*, 10641.

[4+2] With Cyclic *N*-Sulfimines

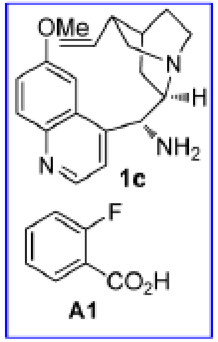


entry	R^1	R^2	4	yield[b] (%)	dr[c]	ee[d] (%)
1	H	C_6H_5	**4a**	80	>19:1	97
2	H	$4\text{-}MeC_6H_4$	**4b**	81	19:1	94
3	H	$4\text{-}MeOC_6H_4$	**4c**	75	19:1	95
4	H	$4\text{-}ClC_6H_4$	**4d**	85	19:1	92
5	H	$4\text{-}BrC_6H_4$	**4e**	80	19:1	91
6	H	$4\text{-}CF_3C_6H_4$	**4f**	70	18:1	94
7	H	$4\text{-}FC_6H_4$	**4g**	73	19:1	92
8	H	$3\text{-}MeC_6H_4$	**4h**	83	>19:1	95
9	H	$3\text{-}MeOC_6H_4$	**4i**	81	19:1	92
10	H	$3\text{-}ClC_6H_4$	**4j**	85	>19:1	97
11	H	$3\text{-}BrC_6H_4$	**4k**	82	>19:1	97
12[e]	H	$2\text{-}BrC_6H_4$	**4l**	61	18:1	90
13	H	2-furyl	**4m**	80	19:1	95



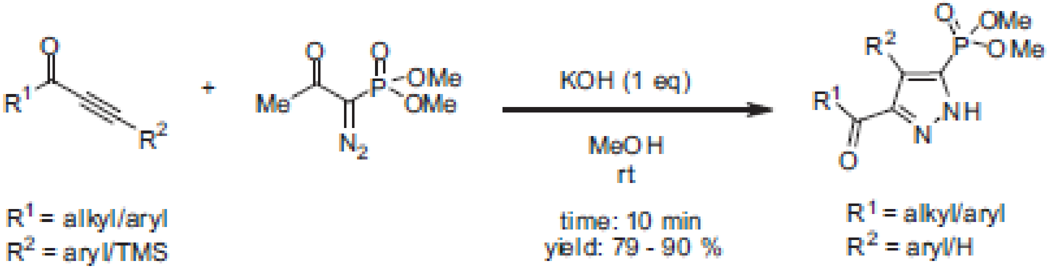
entry	R^1	R^2	6	yield[b] (%)	ee[c] (%)
1	H	C_6H_5	**6a**	80	91
2	7-MeO	C_6H_5	**6b**	70	90
3	6-Cl	C_6H_5	**6c**	64	87
4	6-MeO	C_6H_5	**6d**	65	90
5	6,8-tBu	C_6H_5	**6e**	60	87
6	H	Et	**6f**	65	94

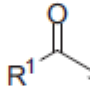
[a] General conditions: cyclic *N*-sulfonylimines **2** (0.1 mmol), ynones **5** (0.15 mmol), catalyst **1c** (20 mol %), and **A1** (40 mol %) in 0.5 mL of toluene at 20 °C for 24–30 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis.



Liu, Y., Kang, T-R., Liu, Q-Z., Chen, L-M., Wang, Y-C., Liu, J., Xie, Y-M., Yang, J-L., He, L., *Org. Lett.*, **2013**, *15*, 6090.

1,3 Cycloaddition With Ohira-Bestmann





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Entry
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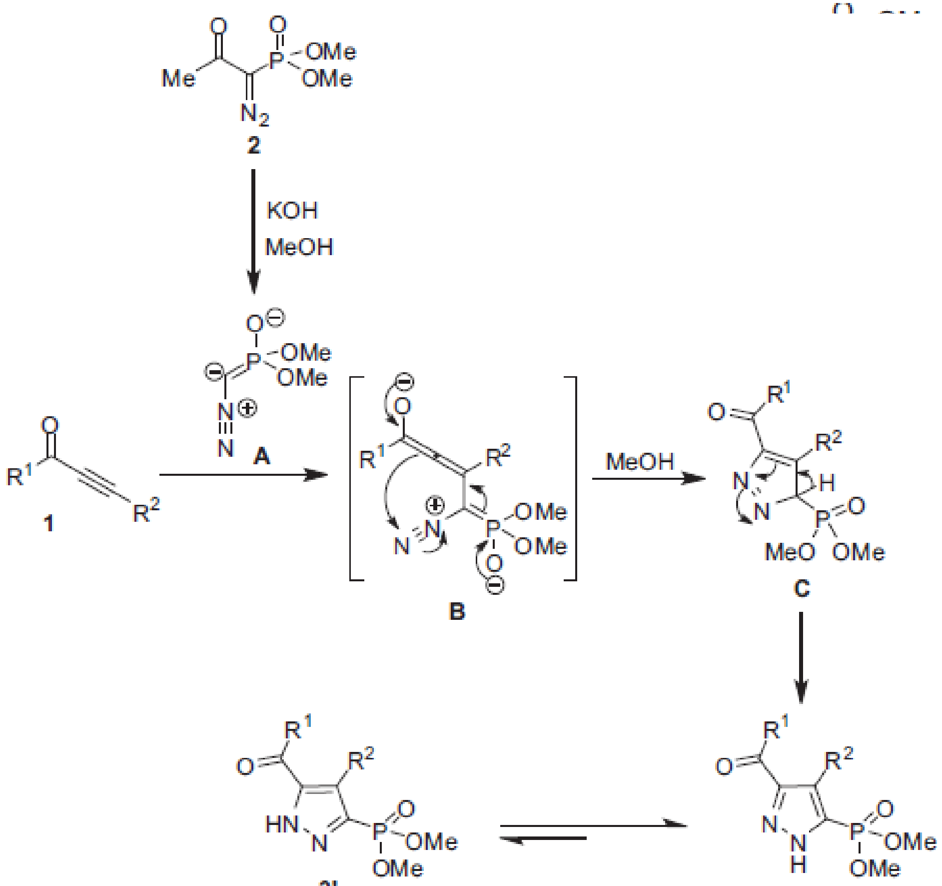
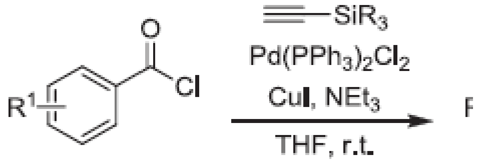


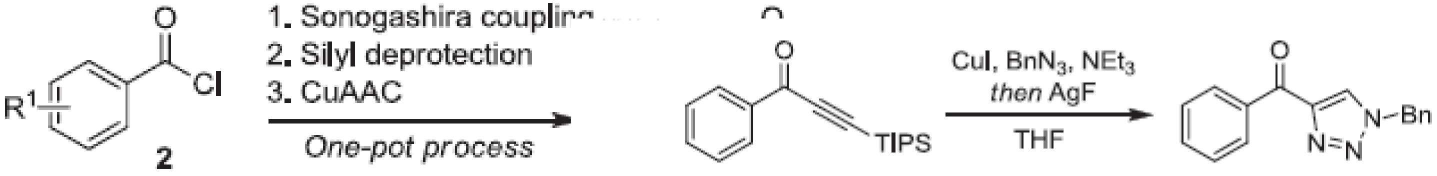
Pramanik, M.M.D., Kant, R., Rastogi, N.,
Tetrahedron, **2014**, *70*, 5214.

Click Chemistry

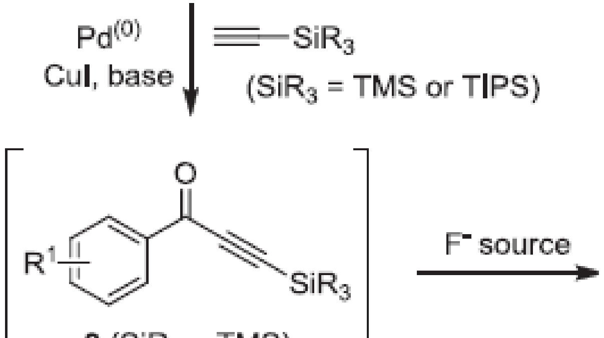


2a–c

Entry[a,b]	2a–c (R[1])	Acetylene (SiR$_3$)
1	**2a** (4-OMe)	TMS
2	**2b** (4-NO$_2$)	TMS
3	**2a** (4-OMe)	TIPS
4	**2a** (4-OMe)	TIPS
5	**2a** (4-OMe)	TIPS
6	**2b** (4-NO$_2$)	TIPS
7	**2b** (4-NO$_2$)	TIPS
8	**2b** (4-NO$_2$)	TIPS
9	**2c** (H)	TIPS
10	**2c** (H)	TIPS
11	**2c** (H)	TIPS



2 4c 1c



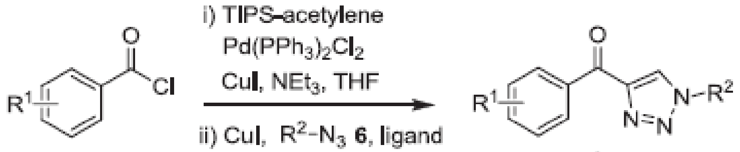
3 (SiR$_3$ = TMS)
4 (SiR$_3$ = TIPS)

Entry	CuI (equiv)	Temperature	Time (h)	Triazole **1c** (yield, %)[b]
1	1.0	rt	13	64
2	1.0	60 °C	13	92
3	0.5	60 °C	13	89
4[c]	0.1	rt	5	91

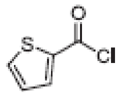
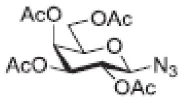
[a] Reaction conditions: 1.0 equiv of ynone **4c** (1.0 mmol), 1.5 equiv of BnN$_3$, CuI (0.1, 0.5 or 1.0 equiv), 3.0 equiv of NEt$_3$, and 1.5 equiv of AgF, THF (10 mL/mmol ynone **4c**).
[b] Isolated yield.
[c] 1,10-Phenanthroline of 0.02 equiv was used as a ligand.

Hwang, S., Bae, H., Kim, S., Kim, S., *Tetrahedron*, **2012**, *68*, 1460.

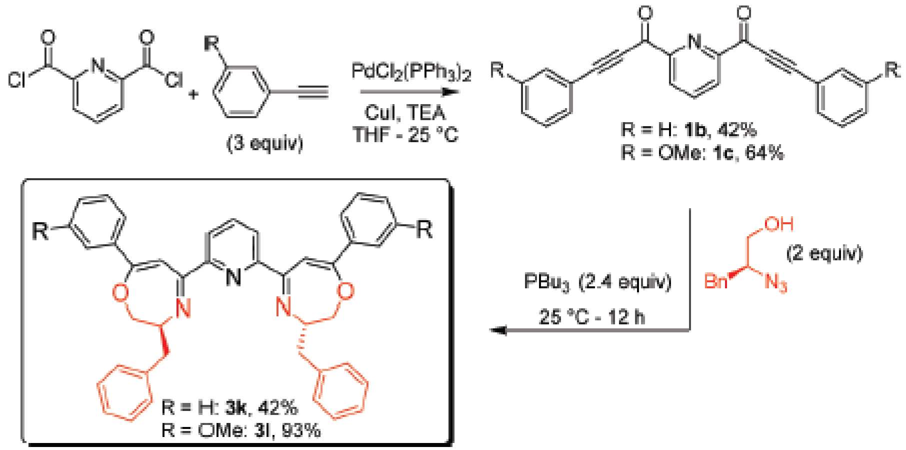
Click Chemistry



2 1

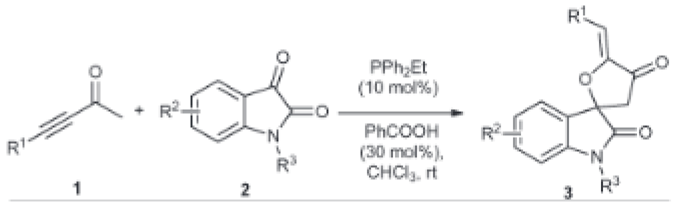
Entry	2 (R^1)	6 (R^2)	Method A[a] 1 (yield, %)	Method B[b] 1 (yield, %)
1	H	Benzyl	**1c** (83)	**1c** (85)
2	4-OMe	Benzyl	**1a** (81)	**1a** (86)
3	4-NO_2	Benzyl	**1b** (68)	**1b** (65)
4	4-F	Benzyl	**1d** (84)	**1d** (83)
5		Benzyl	**1e** (82)	**1e** (84)
6	H	4-Methoxybenzyl	**1f** (83)	**1f** (82)
7	H	4-Nitrobenzyl	**1g** (82)	**1g** (80)
8	H	*n*-Octyl	**1h** (81)	**1h** (86)
9	H	2-Thienylmethyl	**1i** (82)	**1i** (83)
10	H		**1j** (82)	**1j** (85)
11	H	Phenyl	**1k** (79)	**1k** (78)
12	H	4-Methoxyphenyl	**1l** (81)	**1l** (80)
13	H	2,6-Diethylphenyl	**1m** (84)	**1m** (84)
14	H	4-Nitro	—[c]	—[c]

1,4 Oxazepines/1,3-Oxazines

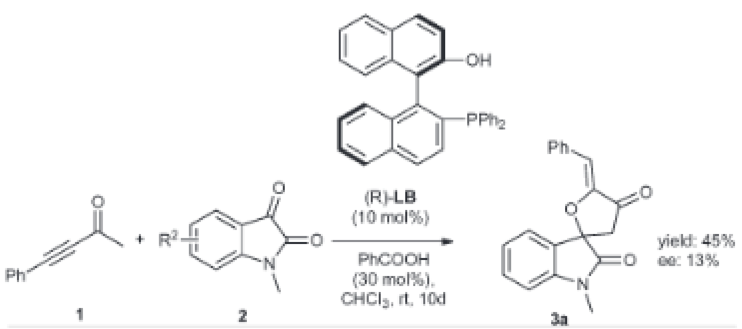


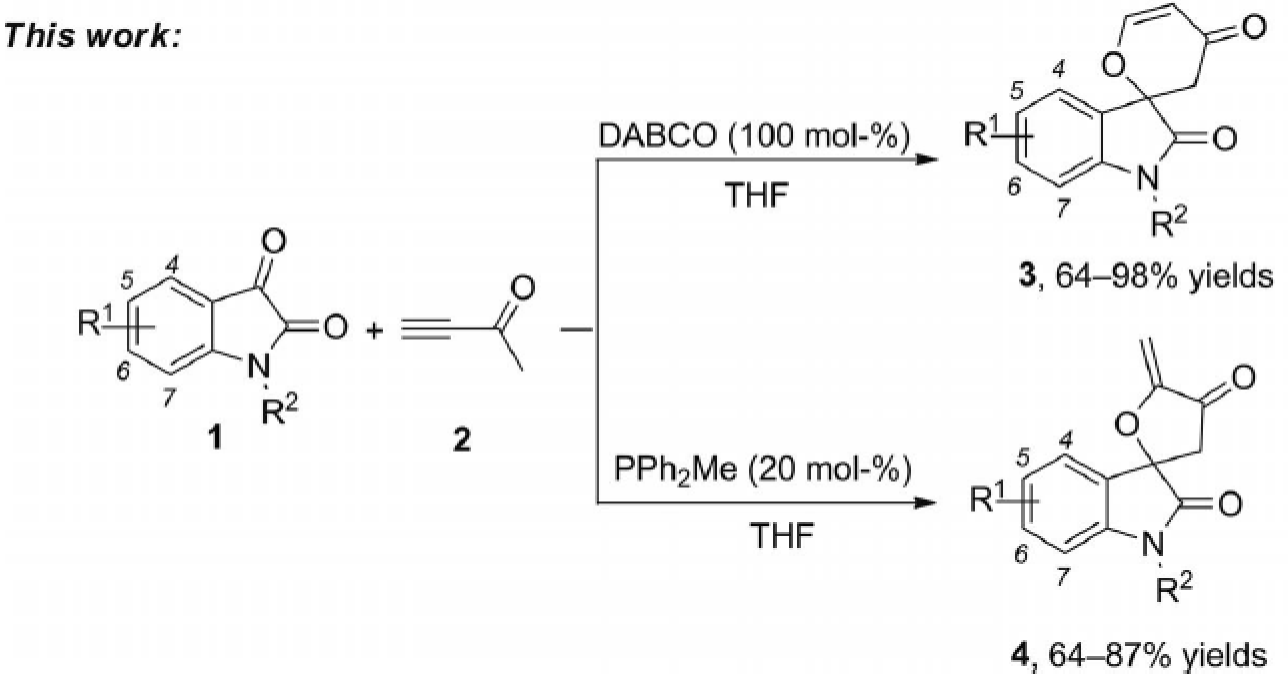
Francois-Endelmond, C., Carlin, T., Thuery, P., Loreau, O., Taran, F., *Org. Lett.*, **2010**, *12*, 40.

[3+2] Annulations



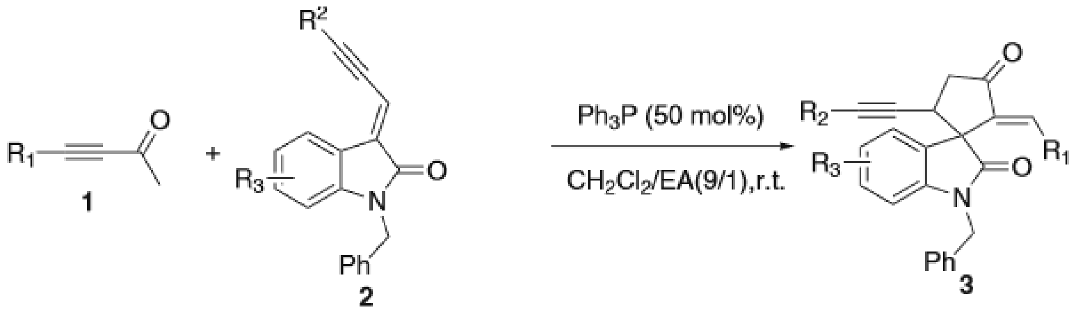
Entry	R^1	R^2	R^3	t/h	Yield[b] (%)
1					
2					
3					
4					
5					
6					
7					
8					
9					
1					
1					
1					
13	p-MeC_6H_4	o-Cl	CH_3	5.5	77 (3m)
14	p-FC_6H_4	H	CH_3	5	81 (3n)
15	p-FC_6H_4	p-CH_3	CH_3	5.5	87 (3o)
16	p-FC_6H_4	p-Cl	CH_3	5	72 (3p)
17	p-FC_6H_4	o-Cl	CH_3	5	85 (3q)





Lian, Z., Shi, M., *Eur. J. Org. Chem.*, **2012**, 581.
Yang, L., Xie, P., Li, E., Li, X., Hunag, Y., Chen, R., *Org. Biomol. Chem.*, **2012**, *10*, 7628.
Zhou, Q-F., Chu, X-P., Ge, F-F., Li, C., Lu, T., *Mol. Divers.*, **2013**, *17*, 563.

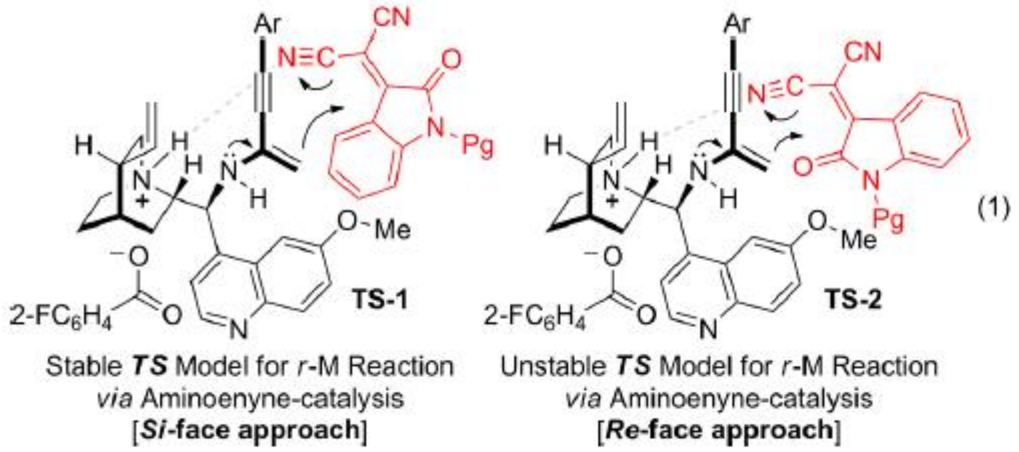
[3+2] Annulations

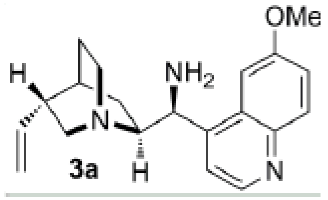


Entry	R^1	R^2	R^3	Product	Yield (%)[b]	dr (%)[c]
1	Ph	Ph	H	**3a**	63	>99/1
2	Ph	4-Me–Ph	H	**3b**	43	87/13
3	Ph	4-MeO–Ph	H	**3c**	36	>99/1
4	Ph	$3,4-(MeO)_2$–Ph	H	**3d**	17	89/11
5	Ph	4-F–Ph	H	**3e**	50	85/15
6	Ph	4-Cl–Ph	H	**3f**	37	90/10
7	Ph	3-Cl–Ph	H	**3g**	35	96/4
8	Ph	2-Cl–Ph	H	**3h**	61	84/16
9	Ph	2-Naphthyl	H	**3i**	19	88/12
10	Ph	*n*-Propyl	H	–[a]		
11	Ph	Ph	5-Me	**3j**	26	90/10
12	Ph	Ph	5-F	**3k**	58	>99/1
13	Ph	Ph	5-Cl	**3l**	72	>99/1
14	4-MeO–Ph	Ph	H	**3m**	44	89/11
15	4-F–Ph	Ph	H	**3n**	43	91/9
16	H	Ph	H	–[a]		
17	Et	Ph	H	–[a]		

, *Org. Biomol. Chem.*, **2012**, *10*, 7628.
. *Divers.*, **2013**, *17*, 563.

Amino Enyne Catalysis to Spirooxindoles

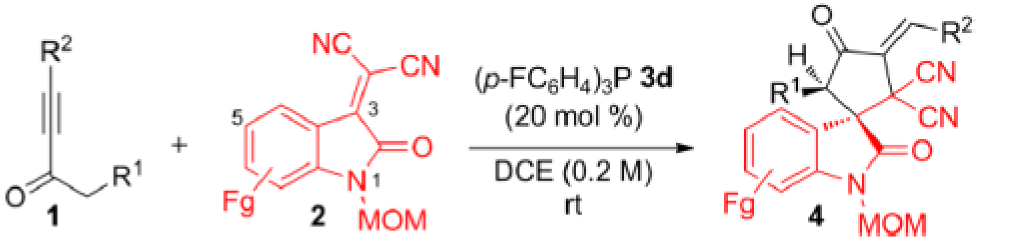




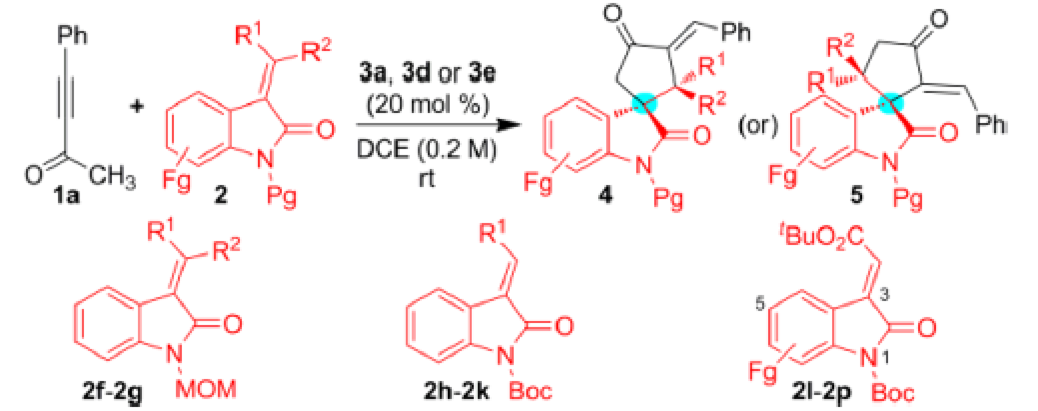
o-$FC_6H_4CO_2H$ **4b**

Ramachary, D.B., Venkaiah, C., Madhavachary R., *Org. Lett.* **2013**, *15*, 3042.

5-Membered Spirooxindoles via Tomita Zipper



entry	ynone 1	olefin 2	T (h)	yield[a–c] (%)
1	1b: R^2, R^1 = 4-MeC$_6$H$_4$, H	2a: Fg = H	36	65 (4ba)
2	1c: R^2, R^1 = 4-MeOC$_6$H$_4$, H	2a	72	66 (4ca)
3	1d: R^2, R^1 = 4-MOMOC$_6$H$_4$, H	2a	48	60 (4da)
4	1e: R^2, R^1 = 4-FC$_6$H$_4$, H	2a	24	65 (4ea)
5	1f: R^2, R^1 = 4-ClC$_6$H$_4$, H	2a	36	65 (4fa)
6[d]	1g: R^2, R^1 = Ph, Me	2a	48	66 (4ga)[e]
7	1h: R^2, R^1 = Ph, Et	2a	48	78 (4ha)[f]
8[d]	1i: R^2, R^1 = 2-Thiophenyl, H	2a	48	64 (4ia)
9[g]	1j: R^2, R^1 = Ph, OMOM	2a	12	60 (4ja)[h]
10	1a: R^2, R^1 = Ph, H	2q: Fg = 5-F	24	60 (4aq)
11	1a	2r: Fg = 5-Cl	48	60 (4ar)
12	1a	2s: Fg = 5-Br	36	60 (4as)
13	1a	2t: Fg = 5-I	24	60 (4at)
14	1a	2u: Fg = 5,7-Me$_2$	36	80 (4au)

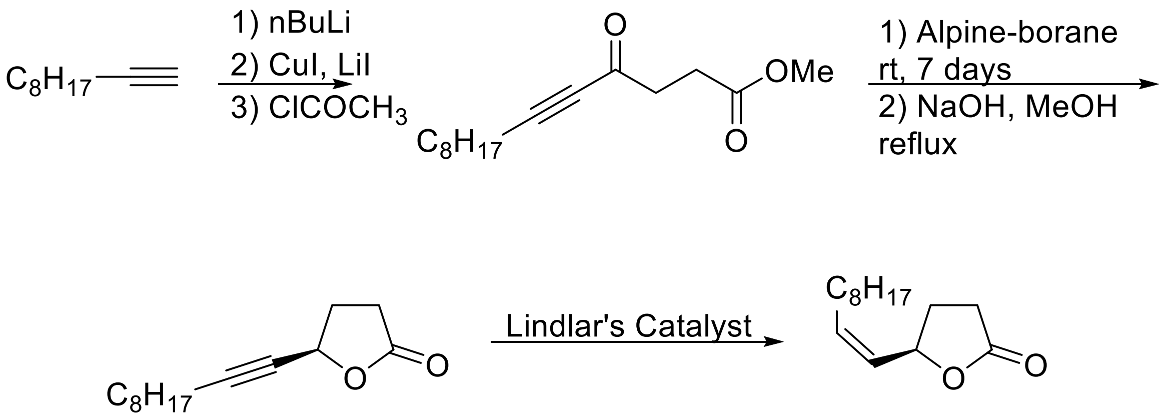


entry	olefin 2	catalyst 3	time (h)	yield[a] (%)	dr[b,c]
1[d]	2f: R^1, R^2 = CO$_2$Et	3a or 3d	72	40 (4af)	–
2[d]	2f: R^1, R^2 = CO$_2$Et	3e	72	60 (4af)	–
3	2g: R^1, R^2 = CN, CO$_2$Et	3a	24	60 (4ag)	1.3:1
4	2g: R^1, R^2 = CN, CO$_2$Et	3d	36	75 (4ag)	1.3:1
5	2h: R^1 = Ph	3e	72	<10 (5ah)	–
6	2i: R^1 = CO$_2$Me	3a	24	50 (5ai)	4:1
7	2j: R^1 = CO$_2$Et	3a	48	70 (5aj)	6:1
8	2j: R^1 = CO$_2$Et	3d or 3e	72	<10 (5aj)	–
9	2k: R^1 = CO$_2{}^t$Bu	3a	24	70 (5ak)	6:1
10	2l; Fg = 5-F	3a	24	60 (5al)	9:1
11	2m: Fg = 5-Cl	3a	12	55 (5am)	9:1
12	2n: Fg = 5-Br	3a	12	50 (5an)	17:1
13	2o: Fg = 5-I	3a	12	50 (5ao)	17:1
14	2p: Fg = 5,7-Me$_2$	3a	12	50 (5ap)	9:1

., Krishna,
14.

Beetle Sex Pheromone

- Synthesized by Nguyen is the early 1980’s

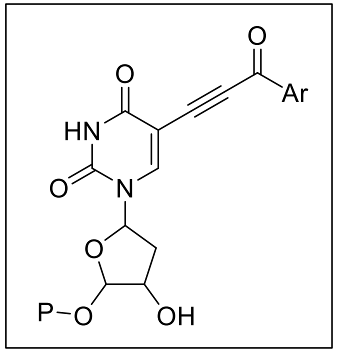


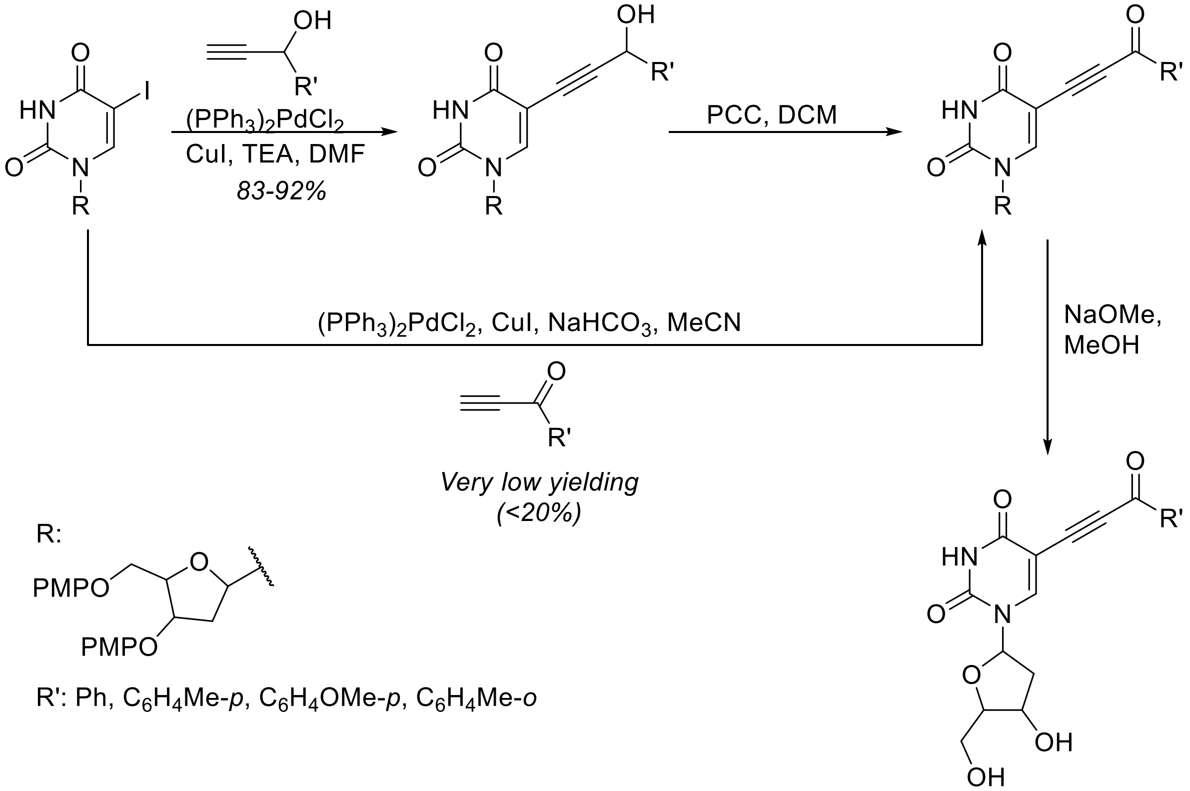
(R)-(-)-(Z)-5-tetradecen-4-olide

Midland, M.M., Nguyen, N.H., *J. Org. Chem.*, **1981**, *46*, 4107.

Synthesis of 5-(Acylethynyl)uracils

- Substituted uracil derivatives can function as enzyme inhibitors





Kundu, N.G.; Chaudhuri, L.N.; *J. Chem. Soc. Perkin Trans. 1*, **1991**, 1677.
Kundu, N.G.;Dasgupta, S.K.; *J. Chem. Soc. Perkin Trans. 1*, **1993**, 2657.

Synthesis of 5-(Acylethynyl)uracils

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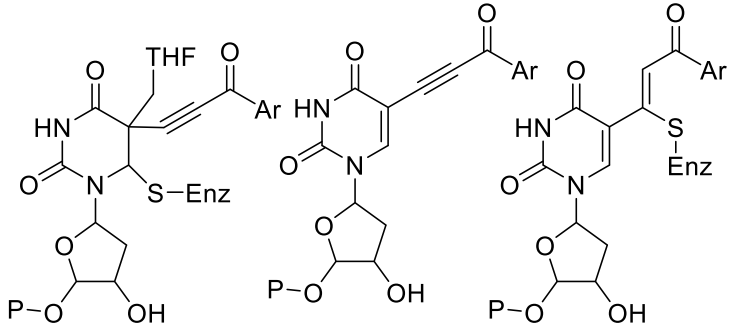
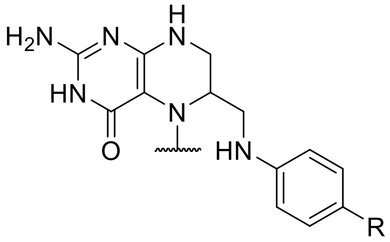
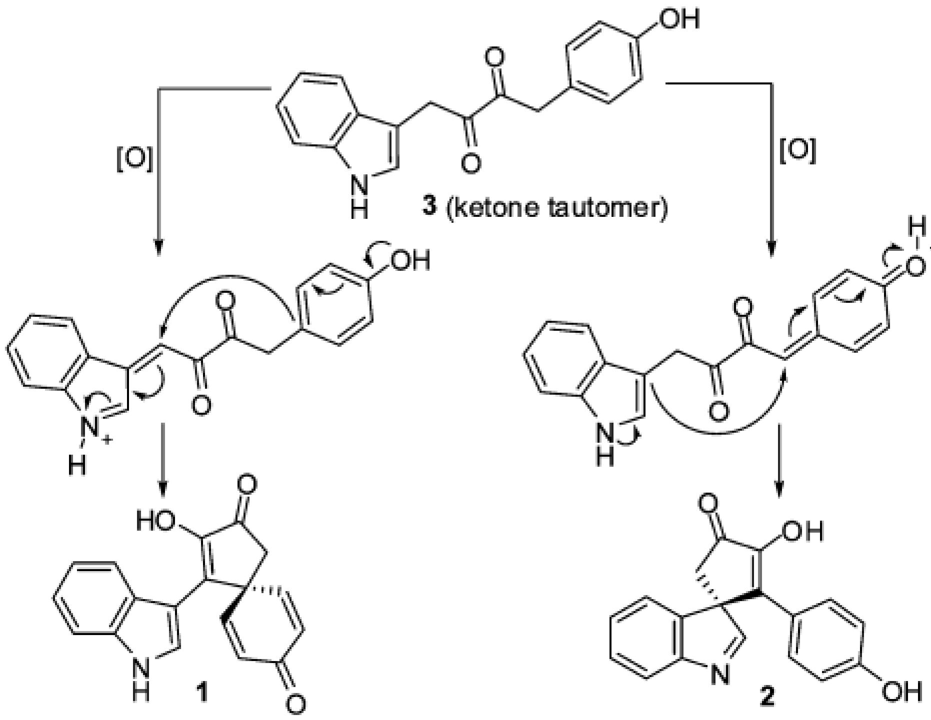


THF = Tetrahydrofolate

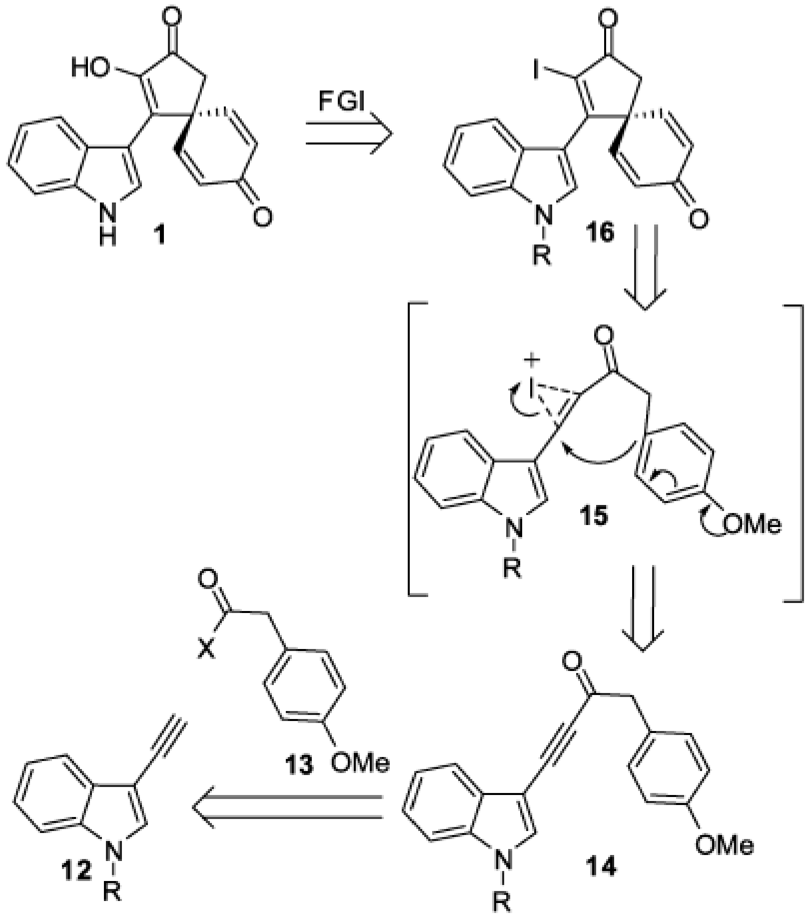


Kundu, N.G.; Chaudhuri, L.N.; *J. Chem. Soc. Perkin Trans. 1*, **1991**, 1677.
Kundu, N.G.;Dasgupta, S.K.; *J. Chem. Soc. Perkin Trans. 1*, **1993**, 2657.

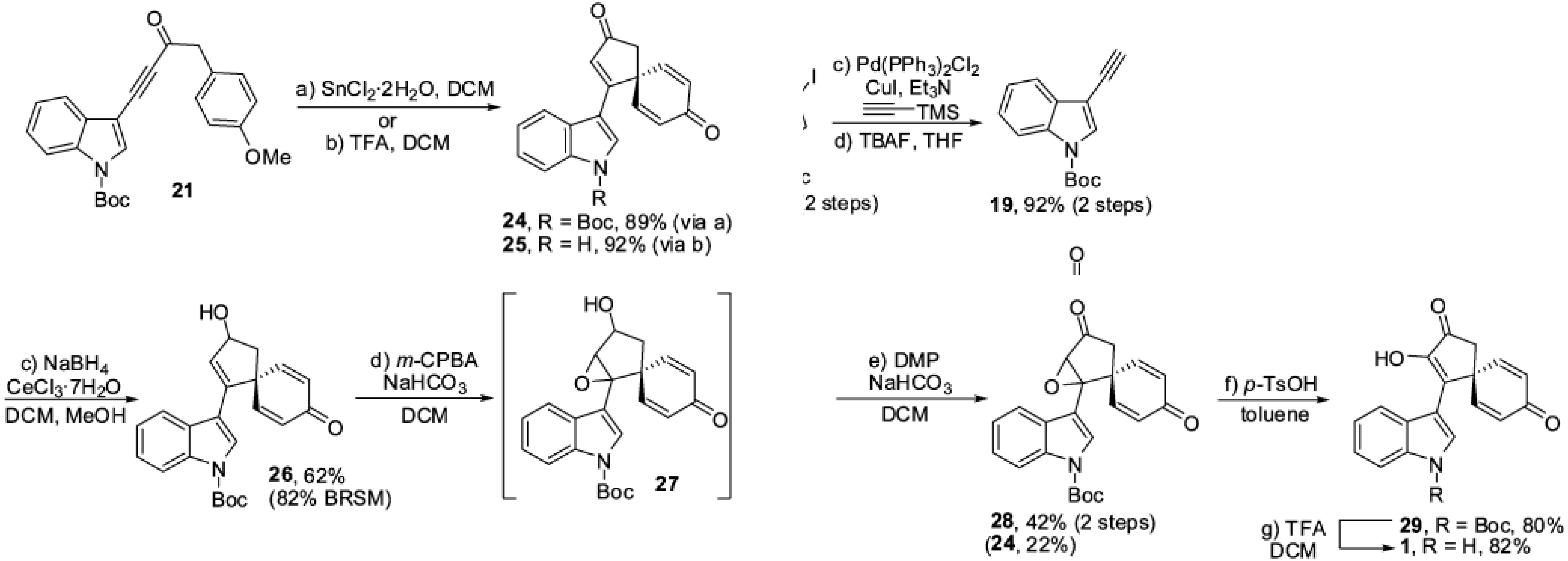
Total Synthesis of Spirobacillene A



Unsworth, W.P., Cuthbertson, J.D., Taylor, R.J.K., *Org. Lett.*, **2013**, *15*, 3306.

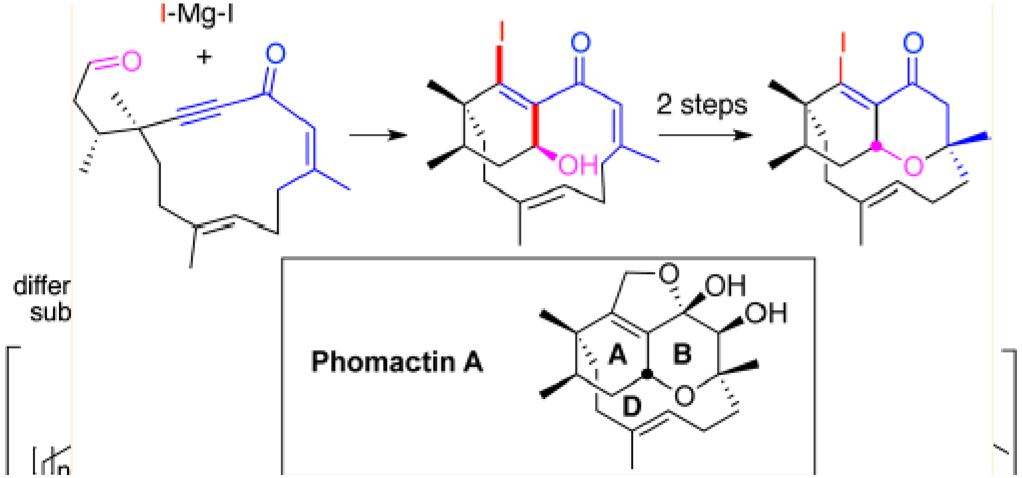


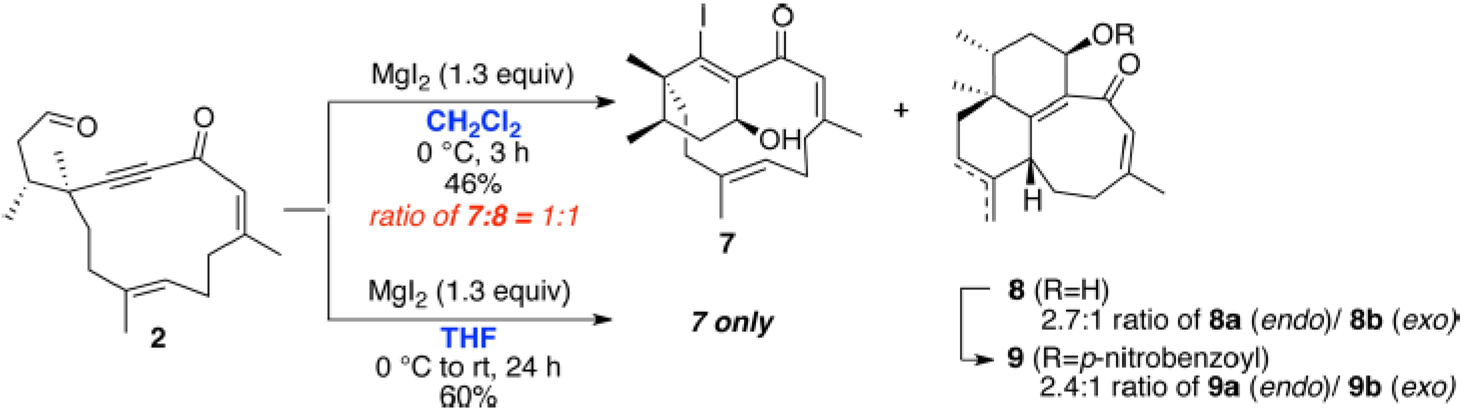
Spirobacillene A-Key Step!



Unsworth, W.P., Cuthbertson, J.D., Taylor, R.J.K., *Org. Lett.*, **2013**, *15*, 3306.

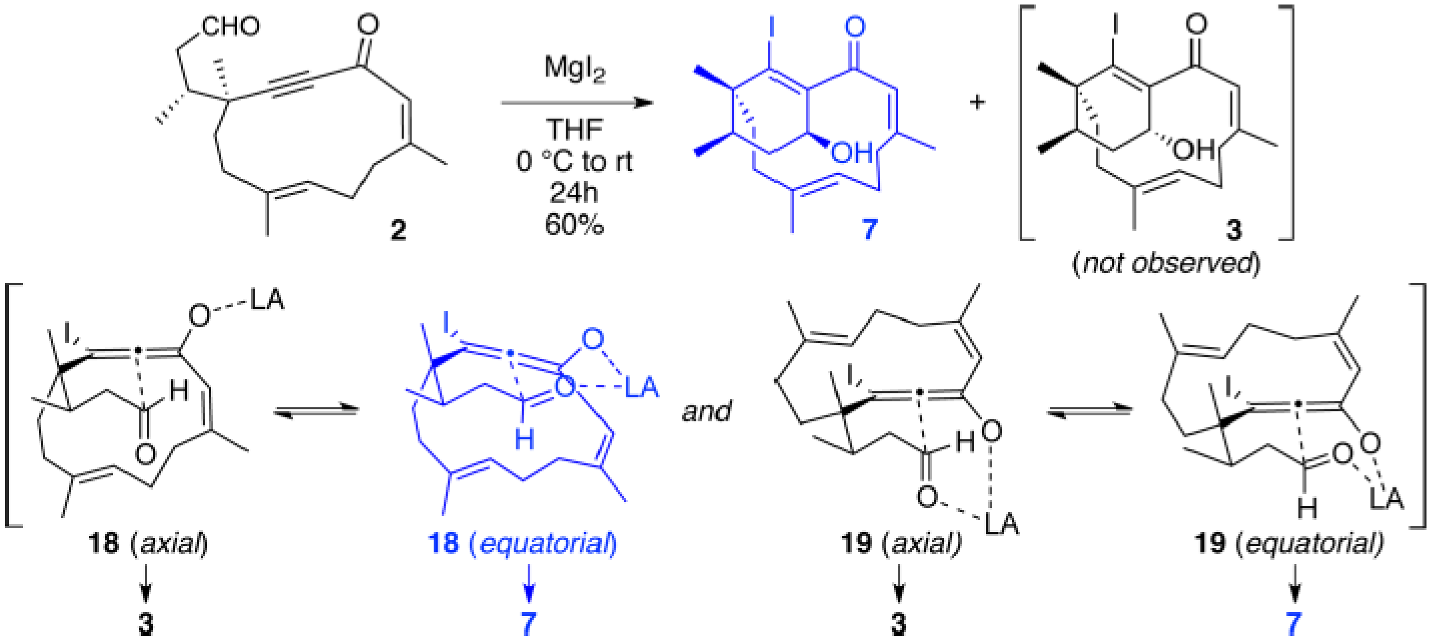
Cascade Cyclization Toward Phomactin A





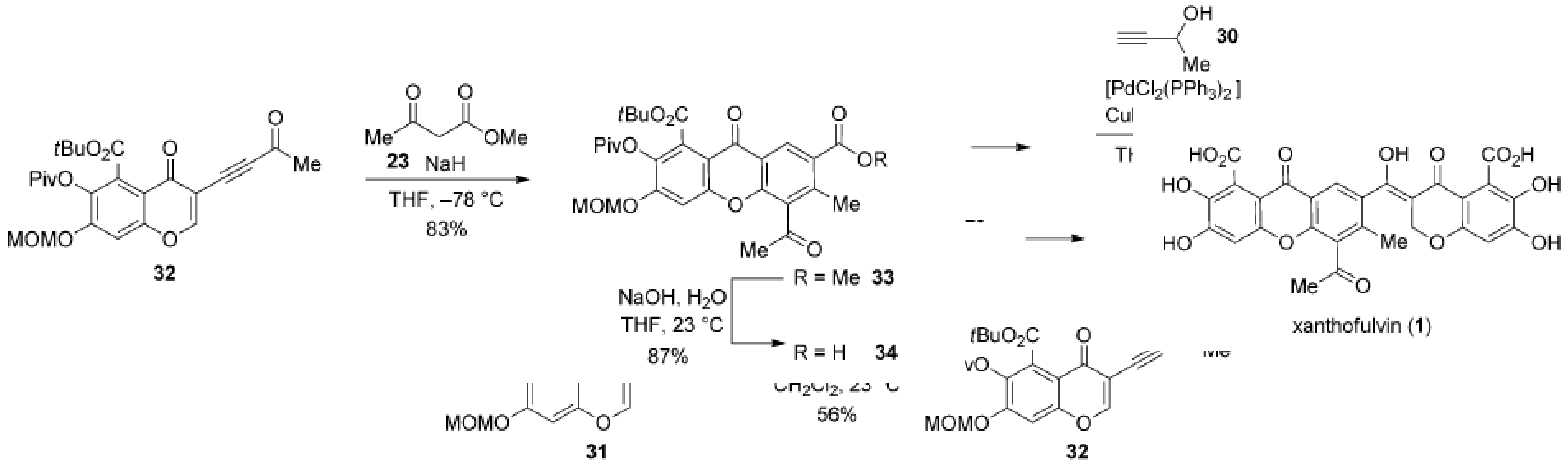
Ciesielski, J., Gandon, V., Frontier, A.J., *J. Org. Chem.*, **2013**, *78*, 9541.

Cascade Cyclization Toward Phomactin A



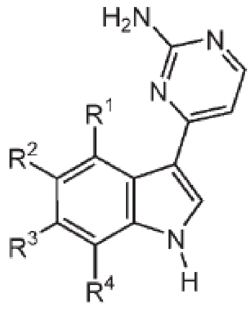
Ciesielski, J., Gandon, V., Frontier, A.J., *J. Org. Chem.*, **2013**, *78*, 9541.

Synthesis of Xanthofulvin



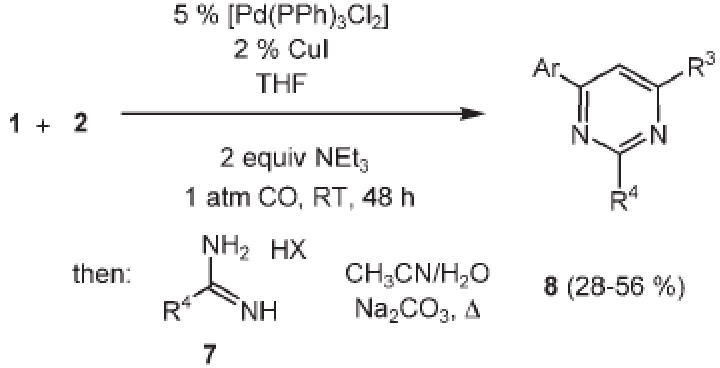
Axelrod, A., Eliasen, A.M., Chin, M.R., Zlotkowski, K., Siegel, D., *Angew. Chem., Int. Ed.*, **2013**, *52*, 3421.

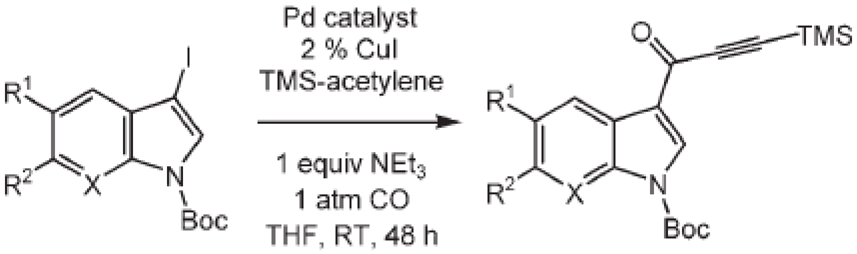
Meridianins Syntheses



meridianins

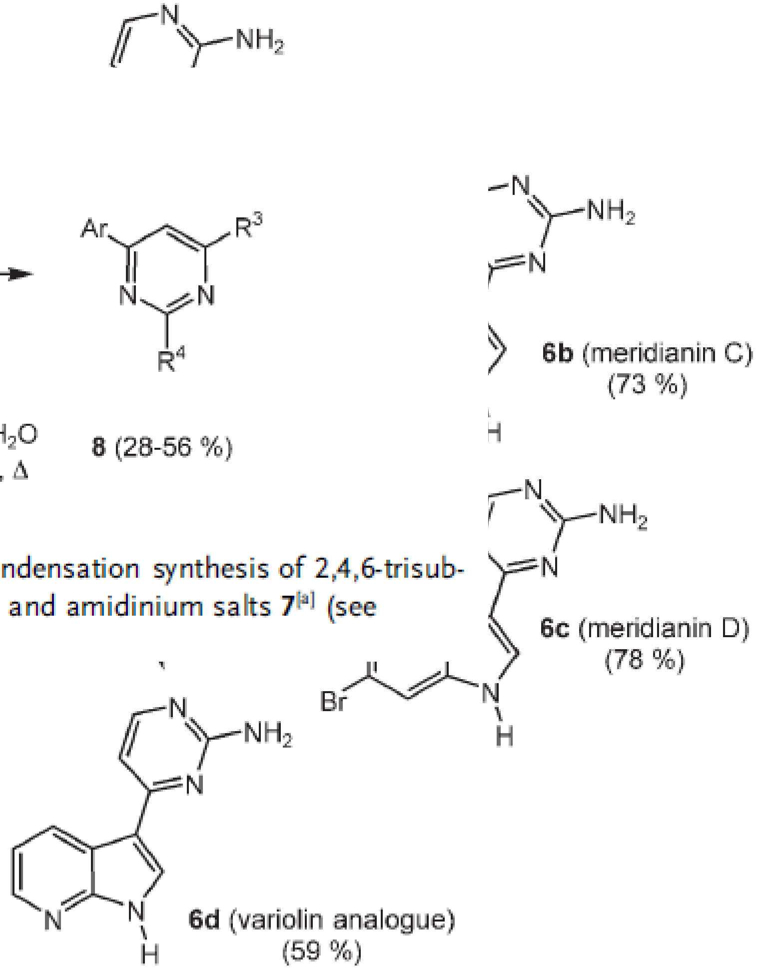
A: R^1 = OH, R^2 = H, R^3 = H, R^4 = H
B: R^1 = OH, R^2 = H, R^3 = Br, R^4 = H
C: R^1 = H, R^2 = Br, R^3 = H, R^4 = H
D: R^1 = H, R^2 = H, R^3 = Br, R^4 = H
E: R^1 = OH, R^2 = H, R^3 = H, R^4 = Br
F: R^1 = H, R^2 = Br, R^3 = Br, R^4 = H
G: R^1 = H, R^2 = H, R^3 = H, R^4 = H



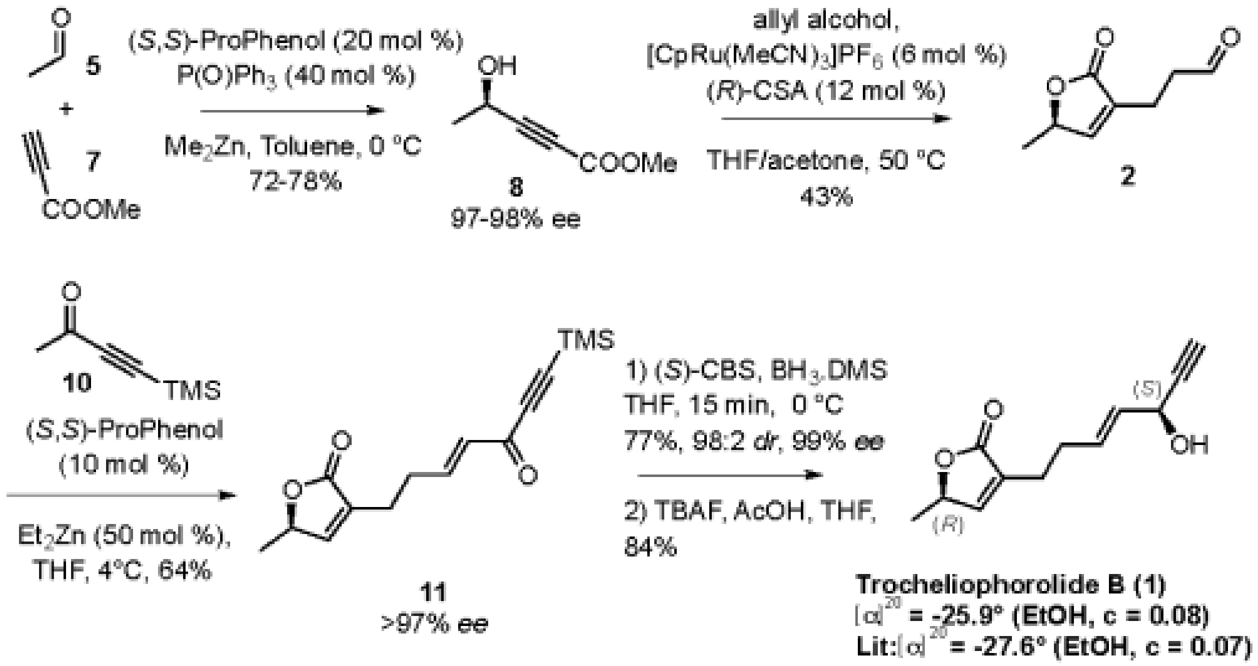


4 5

ent carbonylative coupling–cyclocondensation synthesis of 2,4,6-trisub-
yl iodides ArI 1, alkynes HC≡CR³ 2, and amidinium salts 7[a] (see

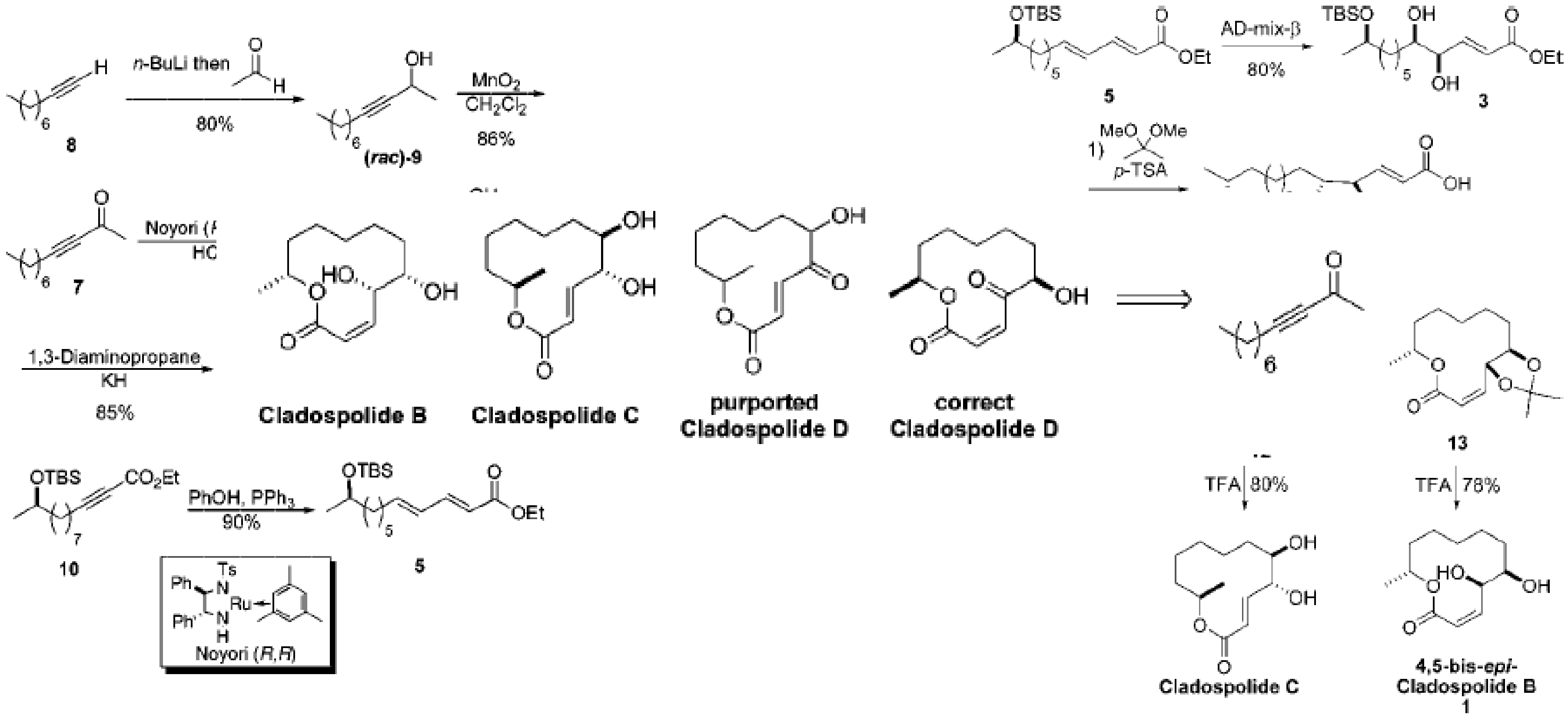


Aldol Condensation to Trocheliophorolide B



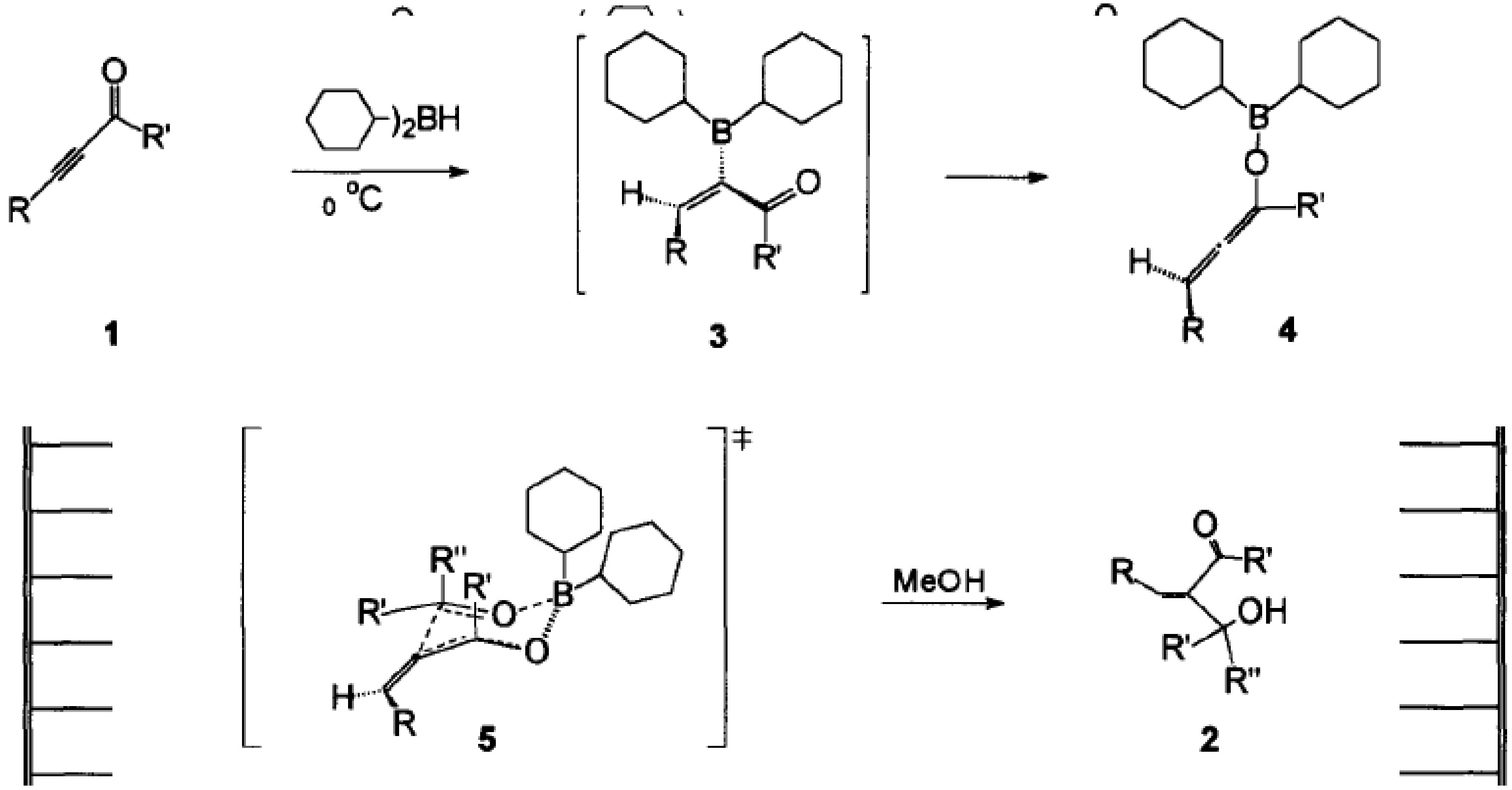
Trost, B.M., Quintard, A., *Org. Lett.*, **2012**, *14*, 4698.

Cladospolide B-D



Xing, Y., O'Doherty, G.A., *Org. Lett.*, **2009**, *11*, 1107.

Other Applications-Stereodefined Trisubstituted Olefin Synthesis

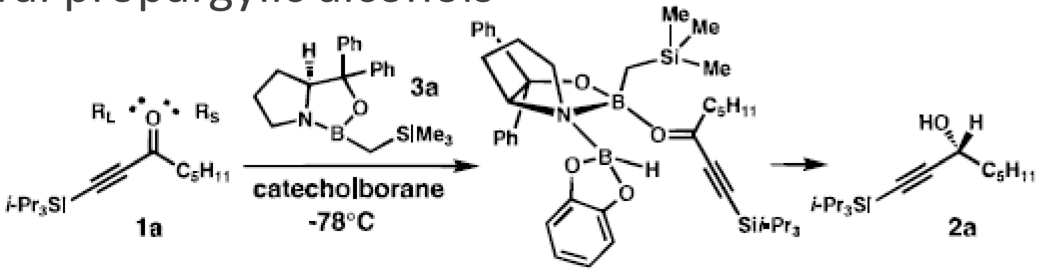


R'' = RC≡C

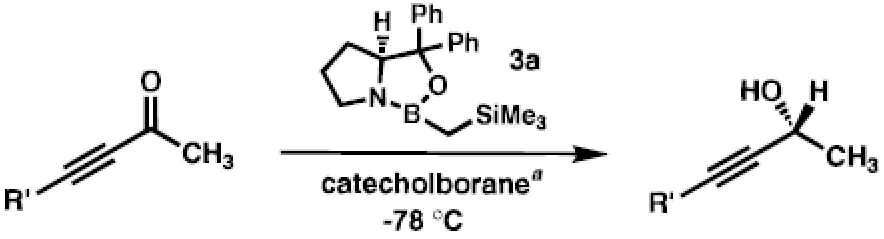
Kabalka, G.W., Yu, S., Li, N., Lipprandt, U., *Tetrahedron Lett.*, **1999**, *40*, 37.

Enantioselective Reduction

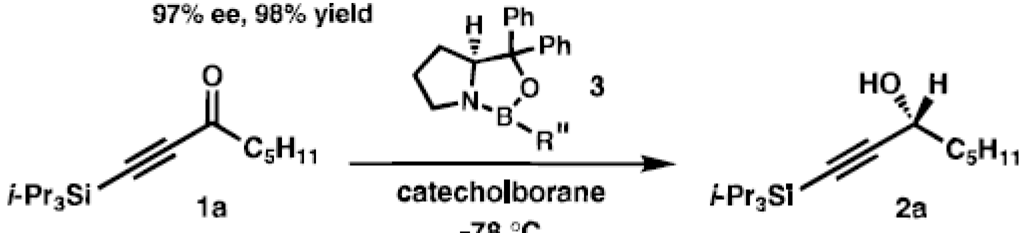
- Direct formation of chiral propargylic alcohols



97% ee, 98% yield



entry	R′	ee (in %) (er)[b]	yield (%)
a	$CH_3(CH_2)_3CH_2$	68[c] (5:1)	93
b	Ph	87[d] (14:1)	100
c	Me_3Si	87[e] (14:1)	92
d	*i*-Pr_3Si	96[f] (49:1)	95



91-98% yield

		ee[b] (in %) (er)	
entry	R″[a]	CH_2Cl_2	toluene
a	CH_2SiMe_3	97 (66:1)	95 (39:1)
b	n-Bu	92 (24:1)	72 (6:1)
c	Me	60 (4:1)	46 (1:3)[c]

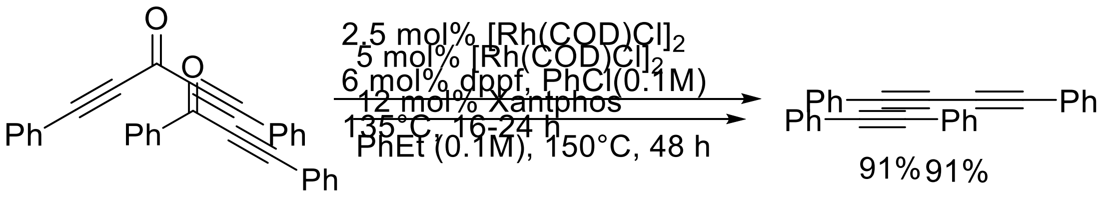
Helal, C.J., Magriotis, P.A., Corey, E.J., *J. Am. Chem. Soc.*, **1996**, *118*, 10938.

Decarbonylation!

- Mueller demonstrated stoichiometric reaction

Muller, E., *Tetrahedron Letters*, **1969**, 1129.
Mueller, E. *Justus Liebigs Ann. Chem.***1973**, *9*, 1583.

- Our group has made the transformation catalytic



Dermenci, A., Whittaker, R.E., Dong, G. *Organic Letters*, **2013**, *15*, 2242.

Conclusions

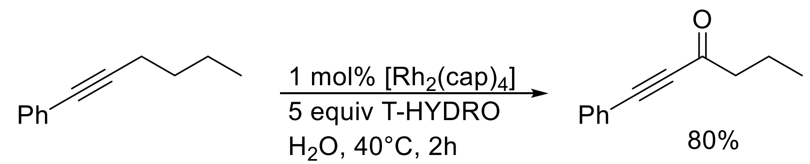
- Ynones have a rich history
  - Have been synthesized in a variety of ways
  - Mostly through carbonylative Songashira or metal acetylide addition

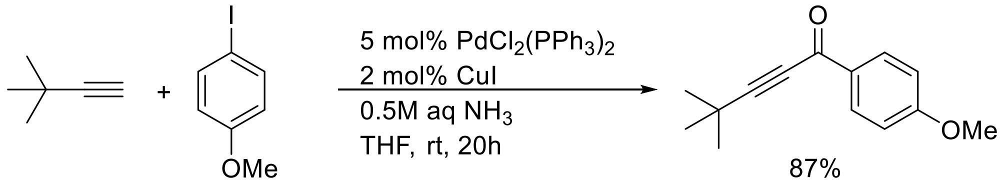
- Ynones are prime candidates for a variety of cyclization reactions
  - This makes them interesting starting materials and intermediates for both natural product synthesis and methodology
  - Very popular motifs in the literature

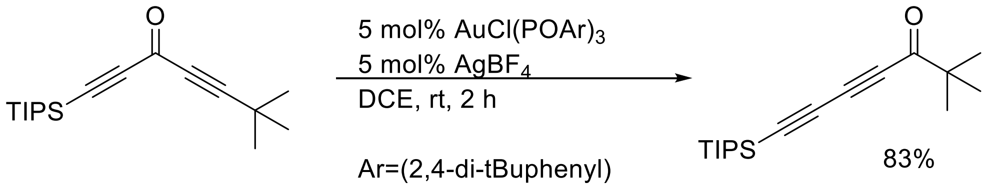
Thanks!

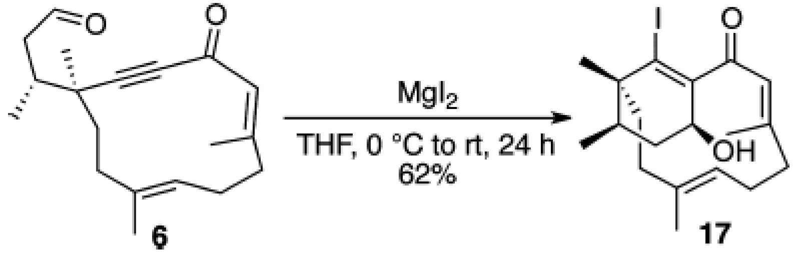
Any questions or comments?

1)

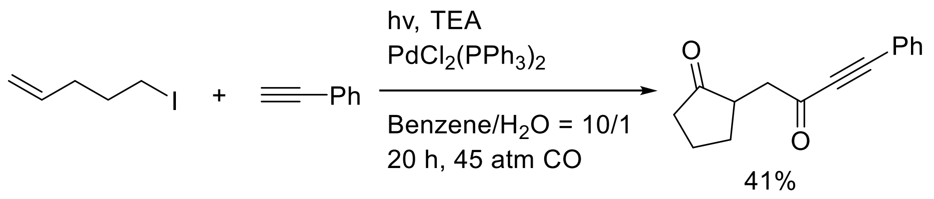

Ph
1 mol% [Rh2(cap)4]
5 equiv T-HYDRO
H2O, 40°C, 2h
O
Ph
80%


I
+
OMe
5 mol% PdCl2(PPh3)2
2 mol% CuI
0.5M aq NH3
THF, rt, 20h
O
OMe
87%

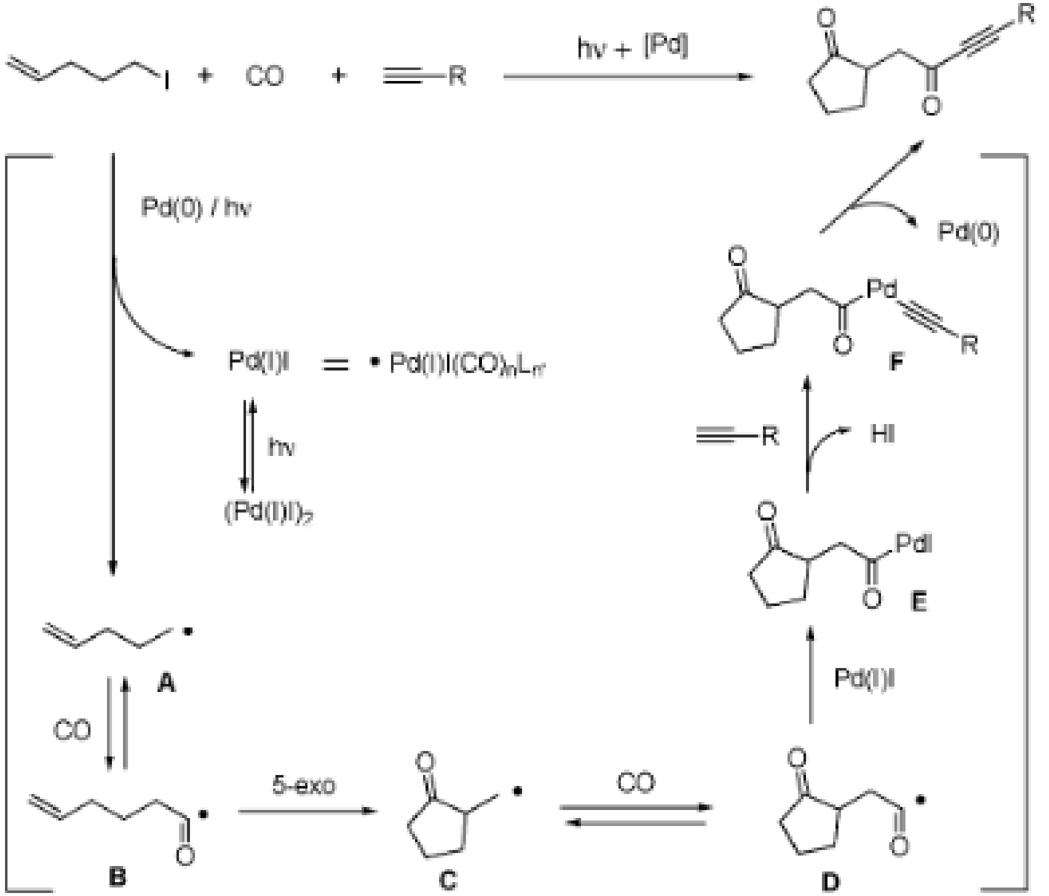

O
TIPS
5 mol% AuCl(POAr)3
5 mol% AgBF4
DCE, rt, 2 h
Ar=(2,4-di-tBuphenyl)
O
TIPS
83%


O
O
6
MgI2
THF, 0 °C to rt, 24 h
62%
I
O
OH
17

2)



hv, TEA
PdCl2(PPh3)2
Ph
Ph
O
O
Benzene/H2O = 10/1
20 h, 45 atm CO
41%



CO
R
hv + [Pd]
O
R
O
Pd(0) / hv
Pd(0)
Pd(I)I
Pd(I)I(CO)nLm
hv
(Pd(I)I)2
Pd
R
F
HI
PdI
E
A
Pd(I)I
CO
5-exo
CO
B
C
D

3)