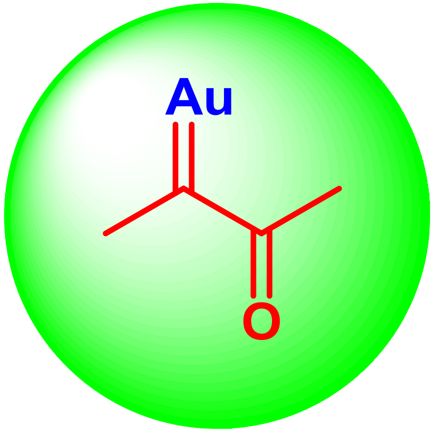
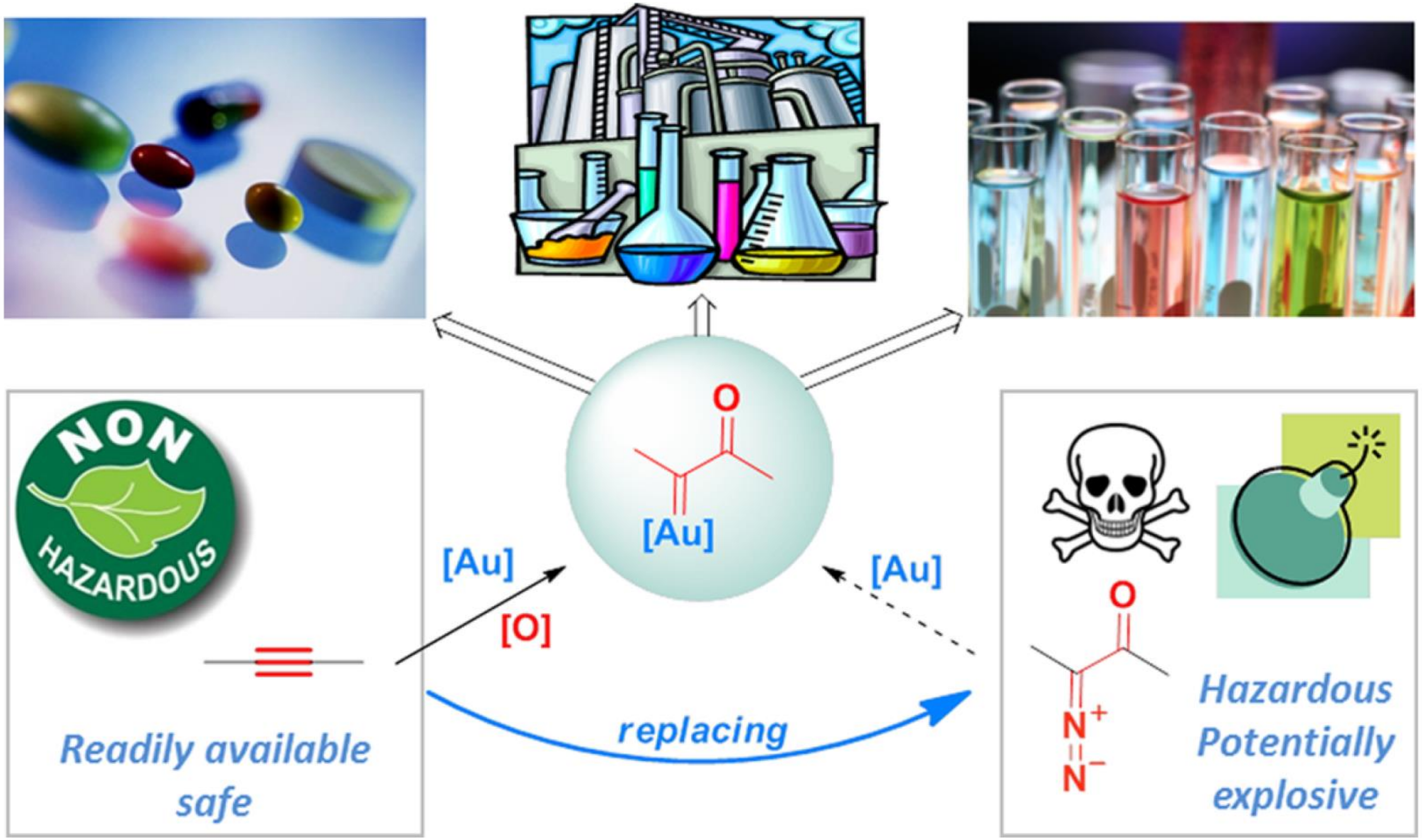
A NON-DIAZO APPROACH TO α-OXO GOLD CARBENES VIA ALKYNE OXIDATION BY S-O OR N-O OXIDANTS



Rong Zeng
Dong Group Seminor
2014/4/23

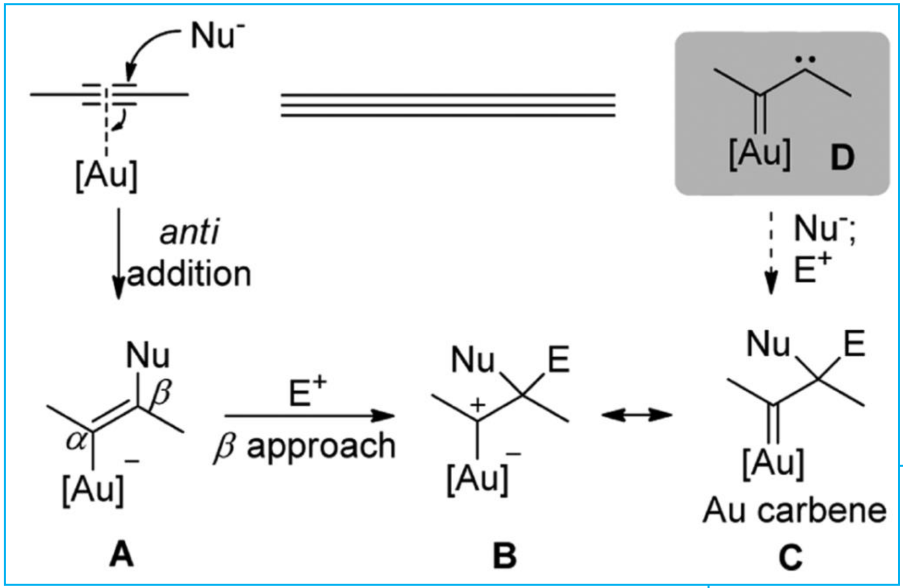


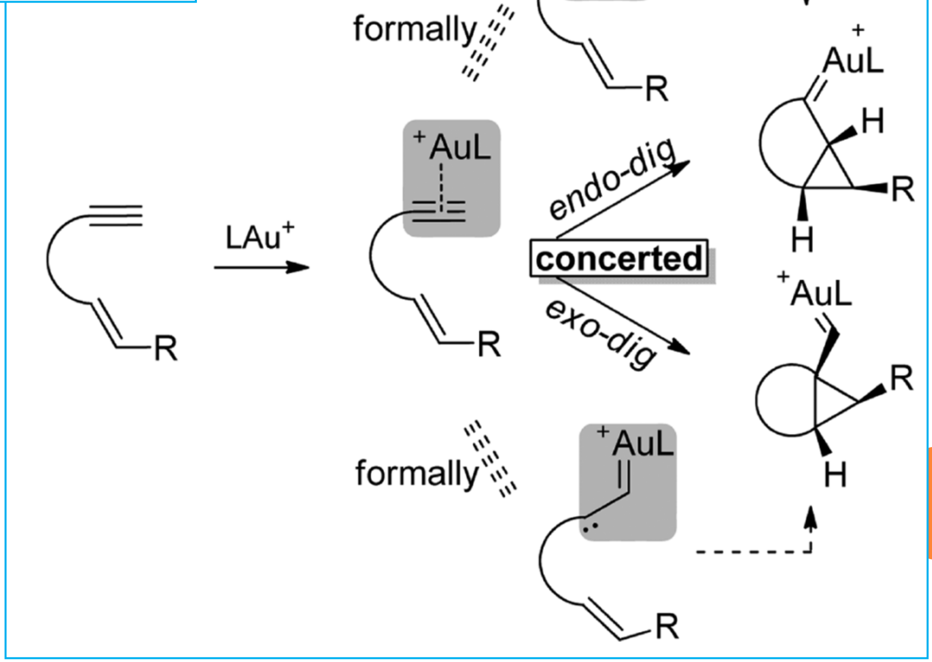
Zhang, L. *Acc. Chem. Res.* **2014**, *47*, 877.
Yeom, H.-S.; **Shin, S.** *Acc. Chem. Res.* **2014**, *47*, 966.

Pic comes from Zhang's *Acc. Chem. Res.*

CONTENTS

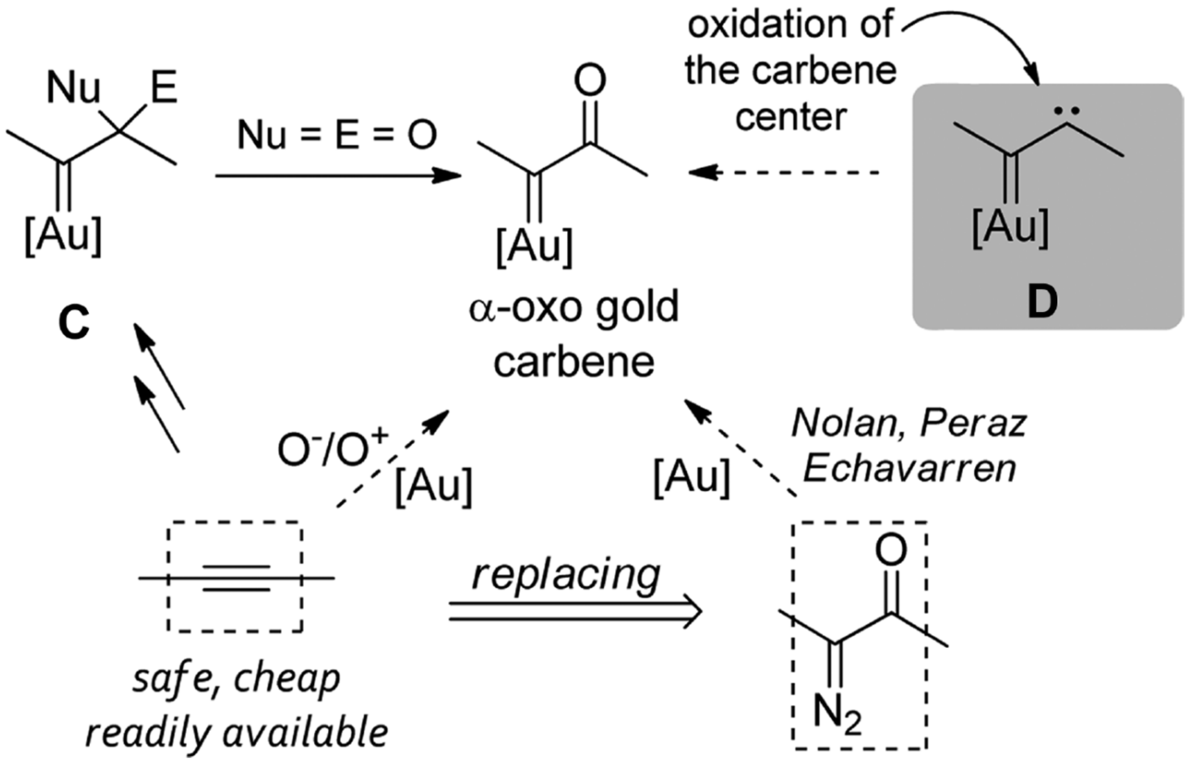
Introduction: Generation of Gold Carbenes from Alkynes

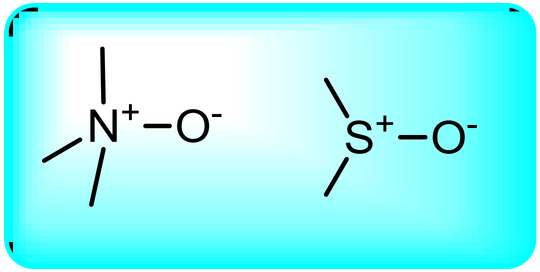


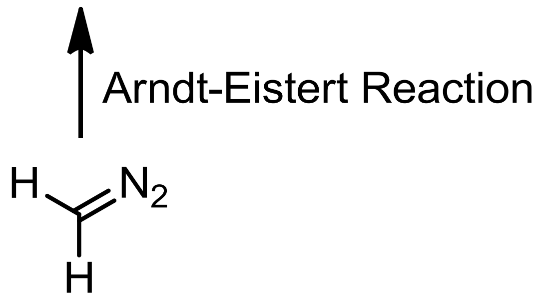


For Gold-Catalyzed Cycloisomerizations of Enynes, see:

a) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal*. **2006**, *348*, 2271.
b) Jimenez-Nunez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326–3350.



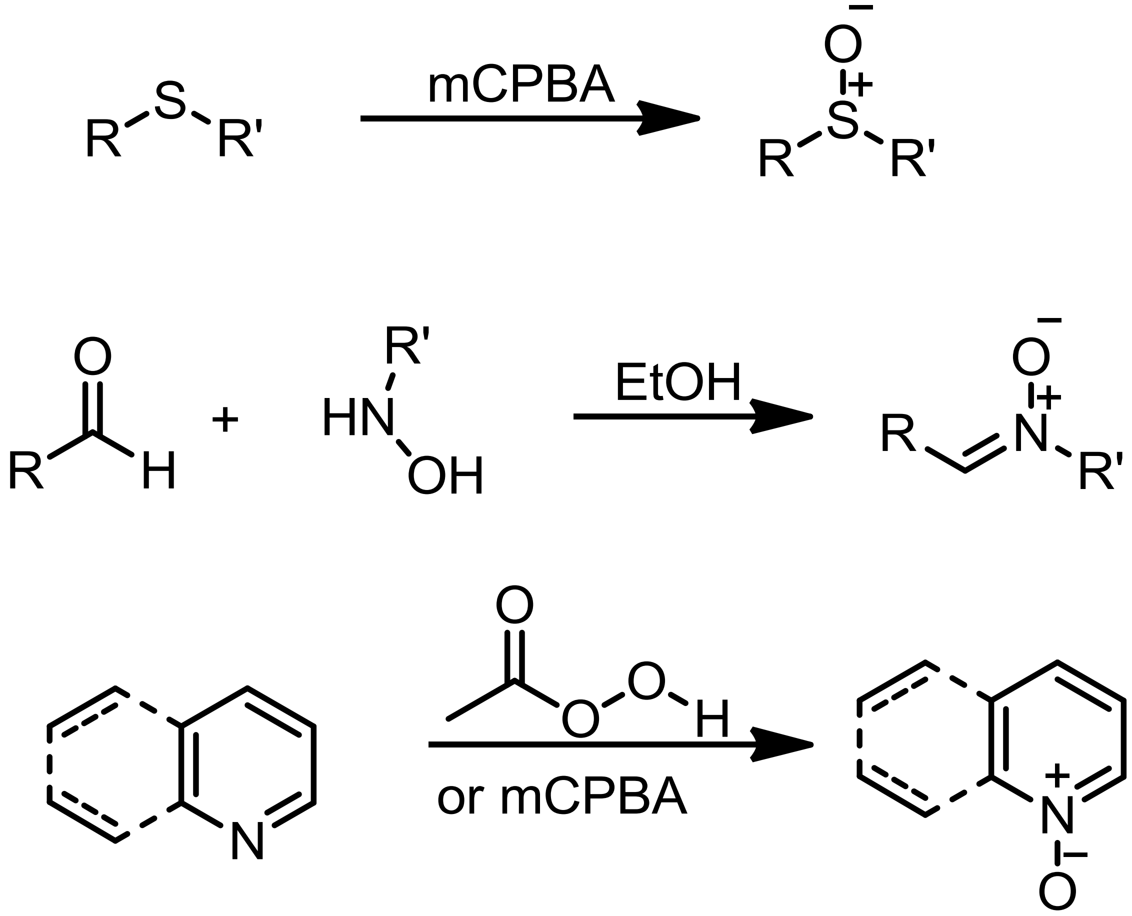




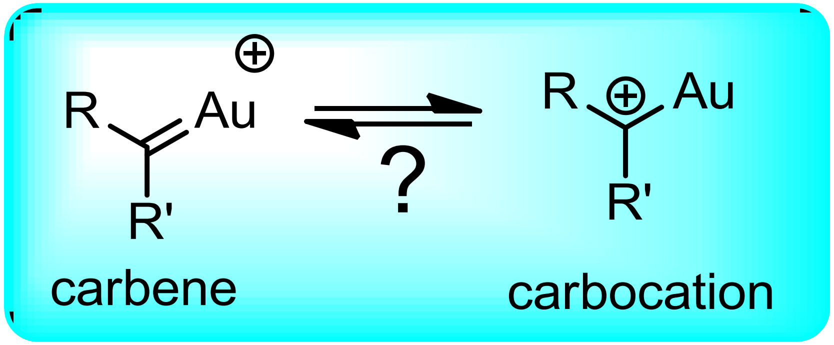
1) Low explosive limit (3.9% v/v in Air; 14.7% in N_2)

2) 60 Tons are produced (Mw is 42).

Preparation of S-O or N-O oxidants.



Controversy: Carbenes or Gold-stabilized Carbocations?



…gold intermediates involved are more appropriately described as gold-stabilized carbocations rather than "gold carbenes"…

Fürstner, A.; Morency, L. *Angew. Chem. Int. Ed.* **2008**, *47*, 5030.

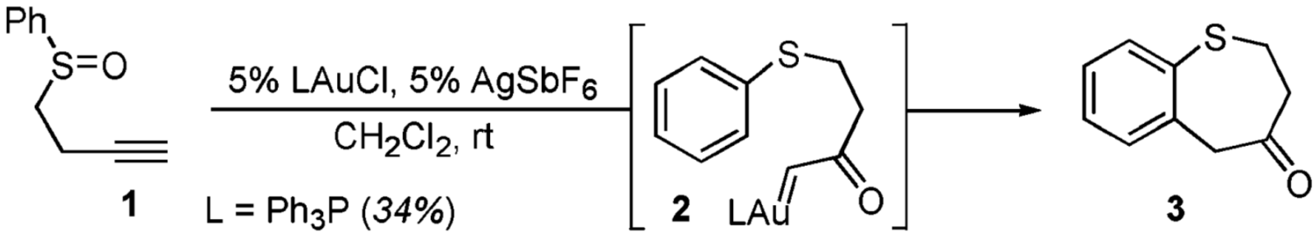
…a continuum ranging from a metal-stabilized singlet carbene to a metal-coordinated carbocation. The position…is largely determined by the carbene substituents and the ancillary ligand…

Toste, D. F. *et al* *Nat. Chem.* **2009**, *1*, 482

More discussion, see:
Seidel, G.; **Fürstner, A.** *Angew. Chem. Int. Ed.* **2014**, *53*, Early View.
Echavarren, A. M. *Nat. Chem.* **2009**, *1*, 431.
Hashimi, A. S. K. *Angew. Chem. Int. Ed.* **2008**, *47*, 6754.

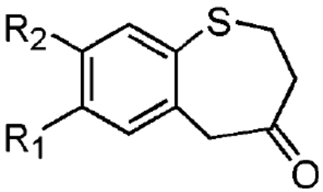
- Intramolecular Alkyne Oxidation

Intramolecular Alkyne Oxidation



1 **2** **3**

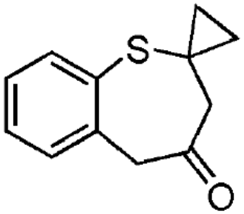
L = Ph_3P (*34%*)
= (p-$CF_3C_6H_4)_3P$ (*25%*)
= IMes (*94%*)



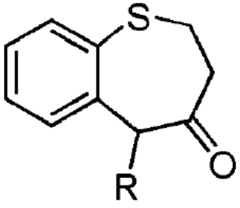
4 $R_1=NO_2$, $R_2=H$

6 $R_1=R_2=OMe$

5	71%
7	87%



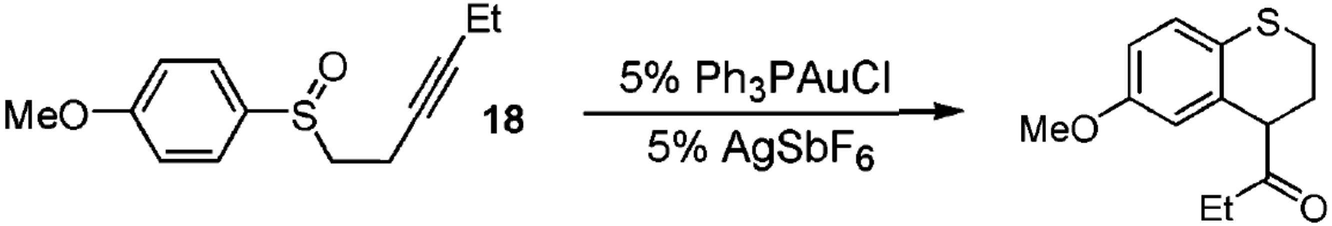
9 71%



15	63%
17	91%[c]

R=4-NO_2-C_6H_4

R=CO_2Et



18

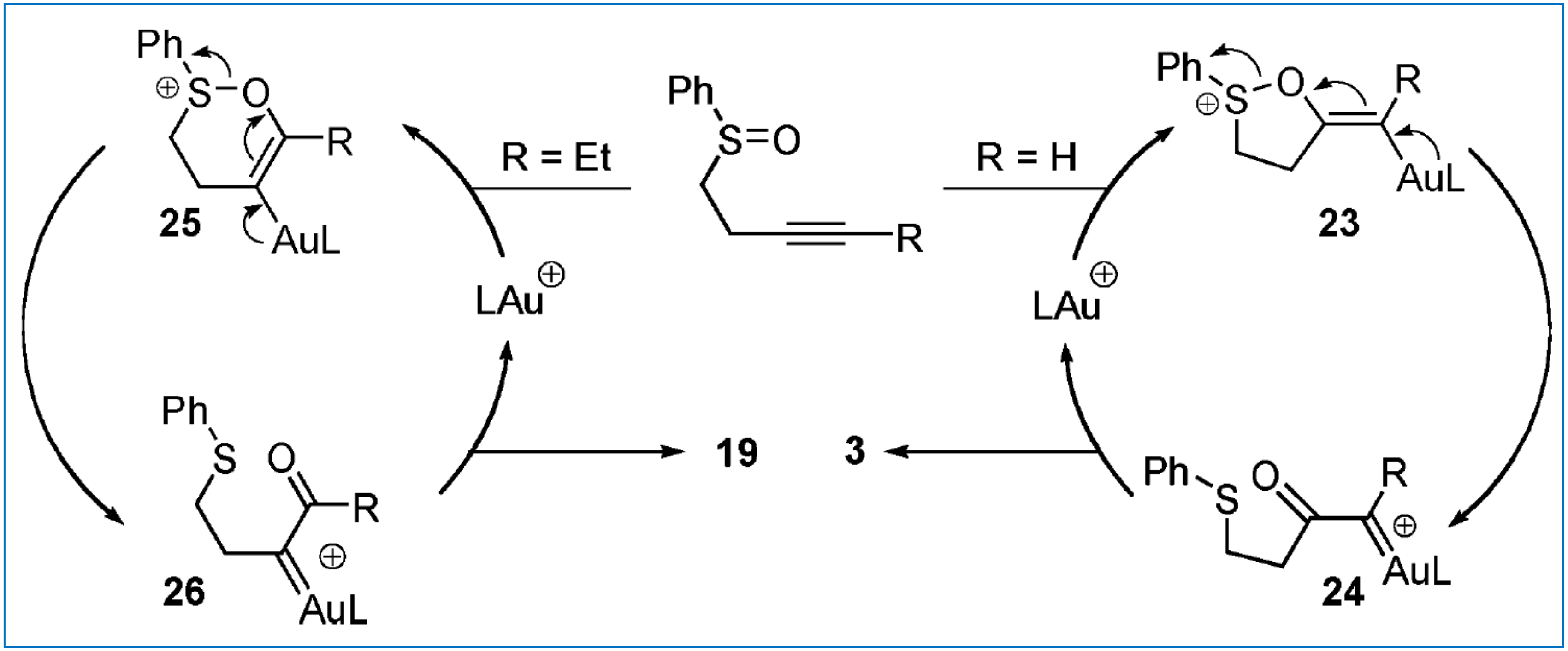
19 64%

Shapiro, N. D.; **Toste, F. D.*** *J. Am. Chem. Soc.* **2007**, *129*, 4160.

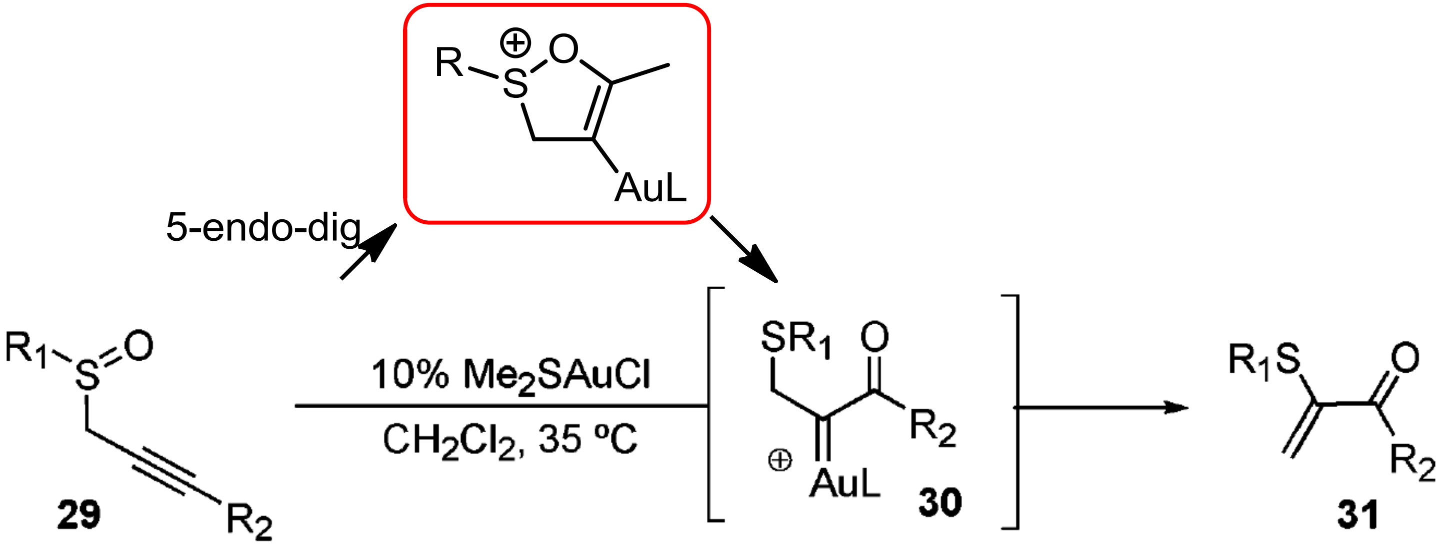
Proposed mechanism

6-endo-dig

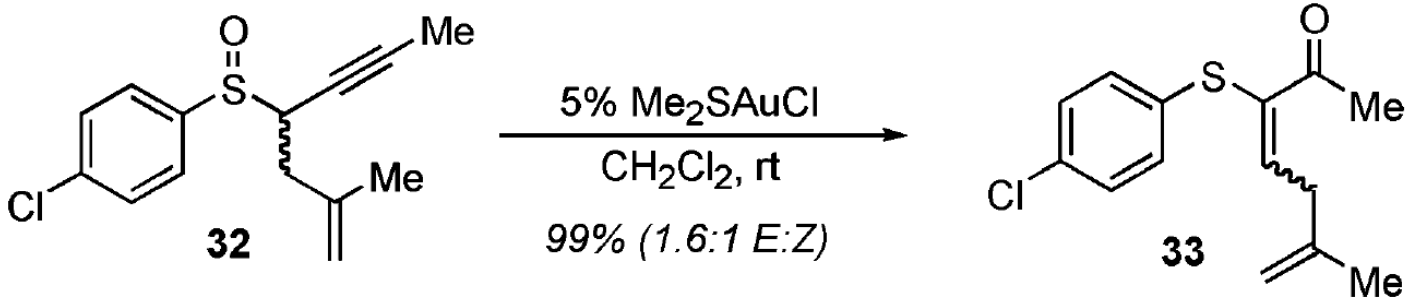
5-exo-dig



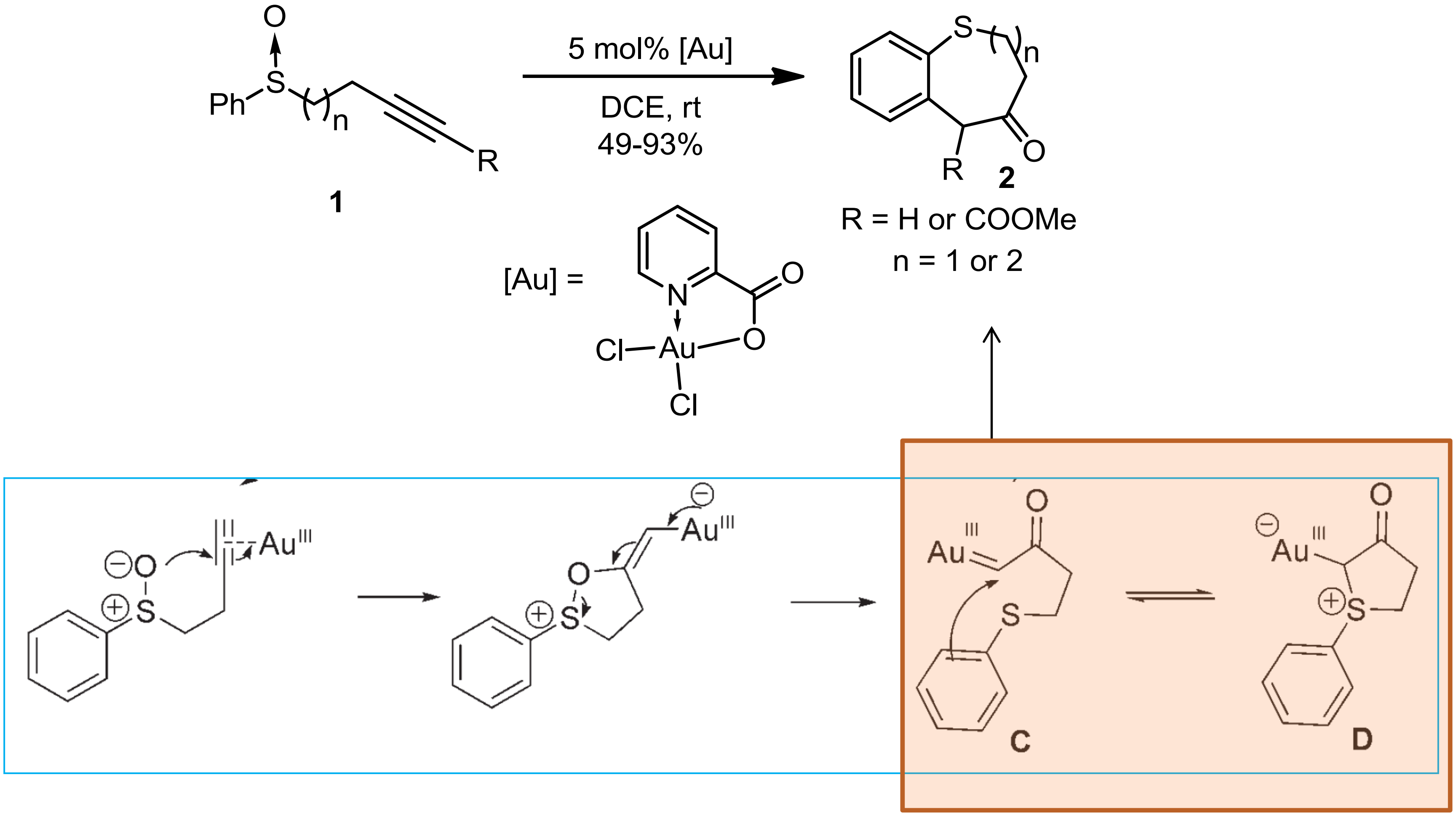
Shapiro, N. D.; **Toste, F. D.*** *J. Am. Chem. Soc.* **2007**, *129*, 4160.



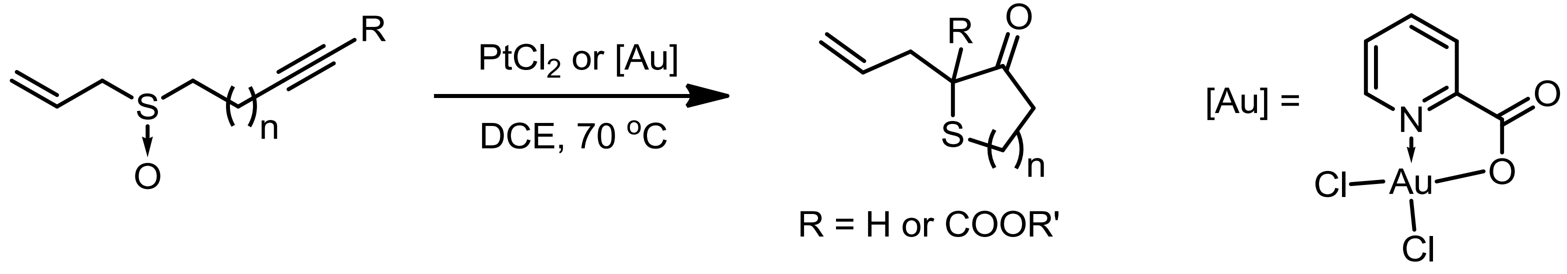
a R_1 = 4-MeO-C_6H_4, R_2 = Ph *(67%)*
b R_1 = 4-NO_2-C_6H_4, R_2 = Et *(91%)*
c R_1 = 4-Cl-C_6H_4, R_2 = Me *(89%)*
d R_1 = Ph, R_2 = H *(51%)*

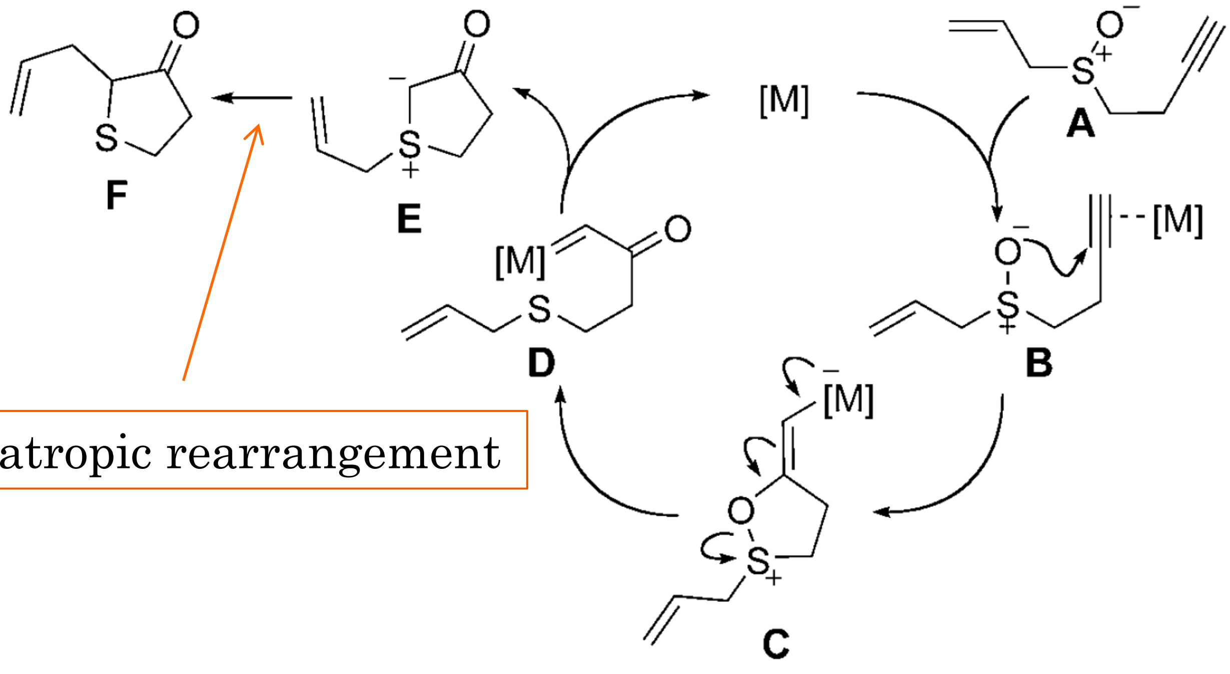


Shapiro, N. D.; **Toste, F. D.*** *J. Am. Chem. Soc.* **2007**, *129*, 4160.



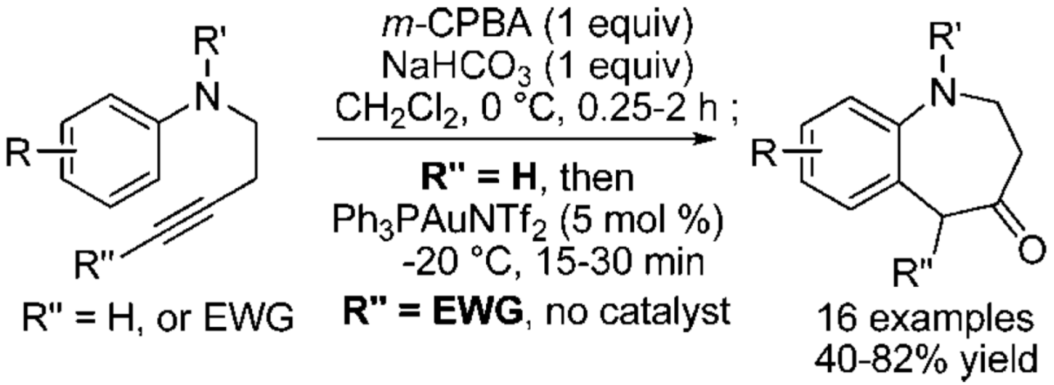
Li, G.; **Zhang, L.*** *Angew. Chem. Int. Ed.* **2007**, *46*, 5156.

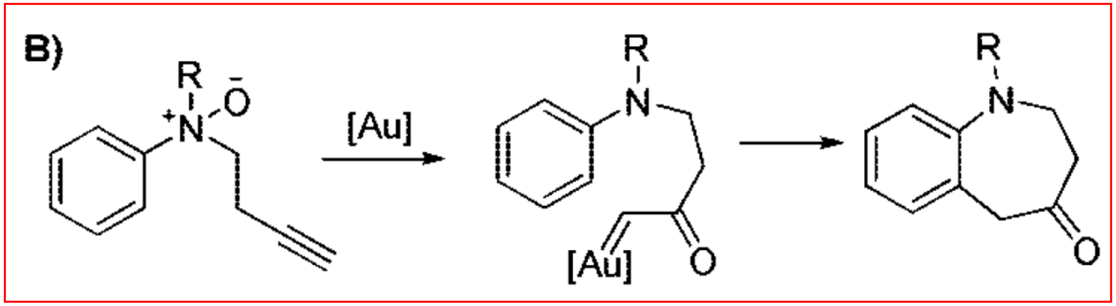




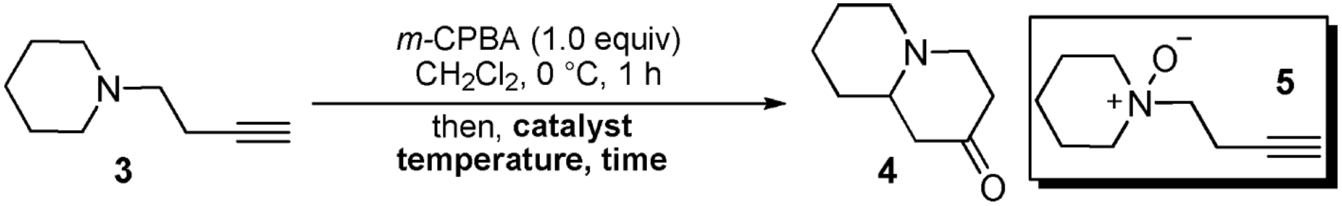
2,3-sigmatropic rearrangement

Davies, P. W.;* Albrecht, S. J.-C. *Angew. Chem. Int. Ed.* **2009**, *48*, 8372.



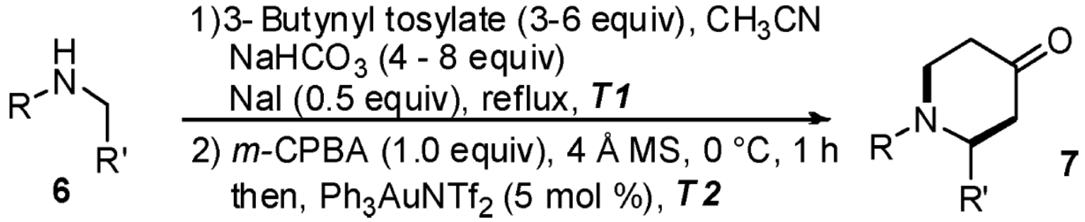


Cui, L.; Zhang, G.; Peng, Y.; **Zhang, L.** *Org. Lett.* **2009**, *11*, 1225.

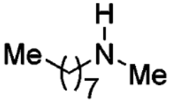
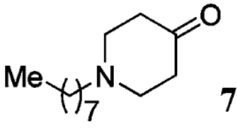
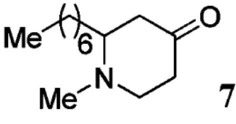


entry[a]	catalyst (5 mol %)	*T* (°C)	time (h)	yield (%)[b]
1	$Ph_3PAuNTf_2$	0	1	87

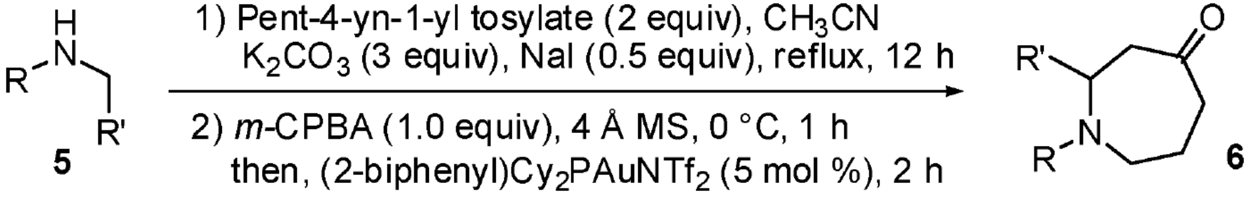
Cui, L.; Peng, Y.; **Zhang, L.*** *J. Am. Chem. Soc.* **2009**, *131*, 8394.



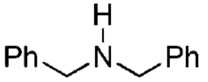
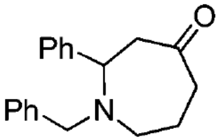
1) 3- Butynyl tosylate (3-6 equiv), CH_3CN
$NaHCO_3$ (4 - 8 equiv)
NaI (0.5 equiv), reflux, ***T1***
2) *m*-CPBA (1.0 equiv), 4 Å MS, 0 °C, 1 h
then, Ph_3AuNTf_2 (5 mol %), ***T2***

entry[a]	substrate	product		T1/T2	yield[b]
1	 **6a**	 **7a** 5	 **7a'** 1	20 h /1 h	70%

Cui, L.; Peng, Y.; **Zhang, L.*** *J. Am. Chem. Soc.* **2009**, *131*, 8394.

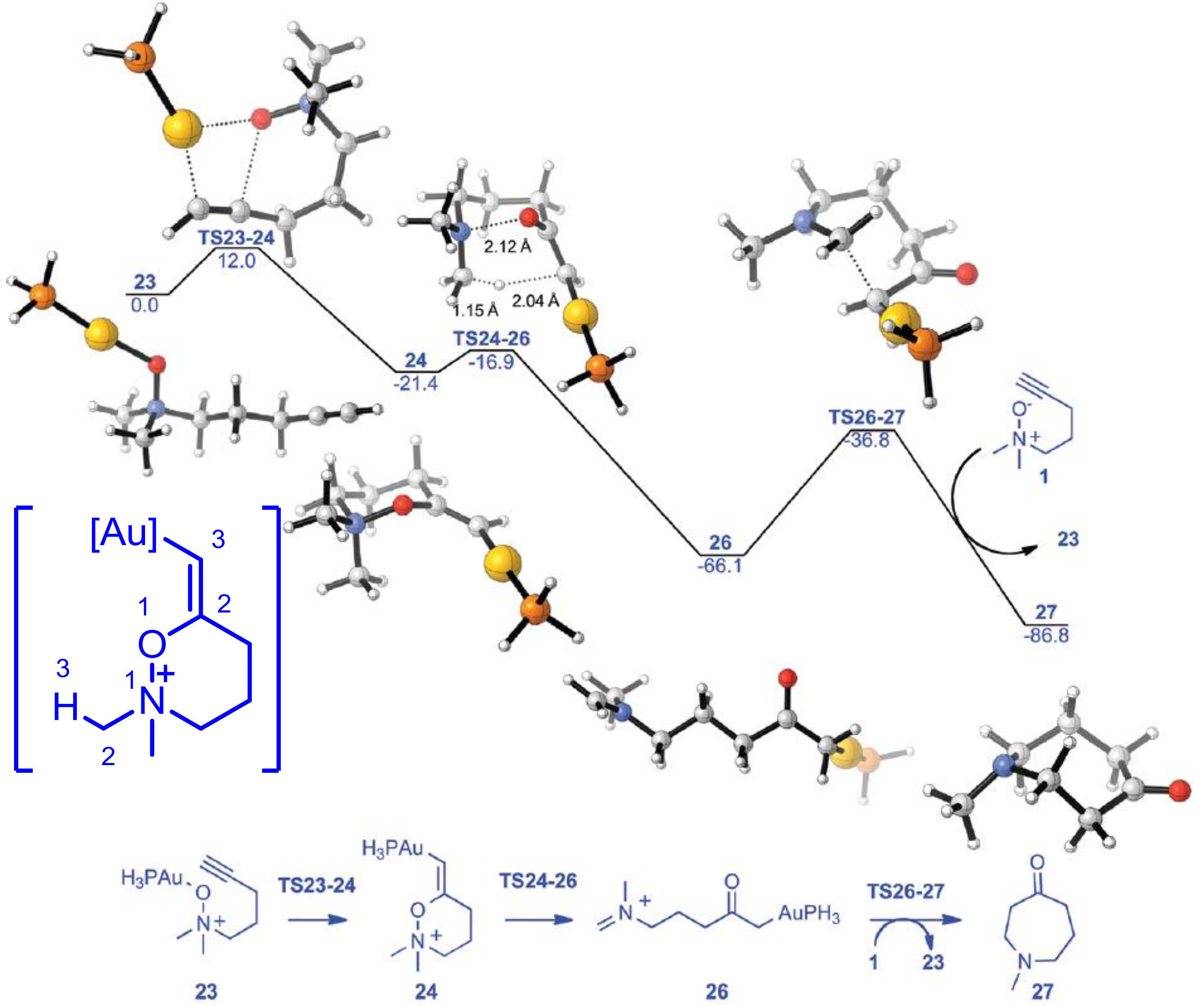


1) Pent-4-yn-1-yl tosylate (2 equiv), CH_3CN
K_2CO_3 (3 equiv), NaI (0.5 equiv), reflux, 12 h
2) *m*-CPBA (1.0 equiv), 4 Å MS, 0 °C, 1 h
then, (2-biphenyl)$Cy_2PAuNTf_2$ (5 mol %), 2 h

Entry[a]	Substrate	Product[b]	Yield (%) 1st step	Yield (%) 2nd step
1	 **5a**	 **6a**	99	87

Cui, L.; Ye, L.; **Zhang, L.*** *Commun. Chem.* **2010**, *46*, 3351.

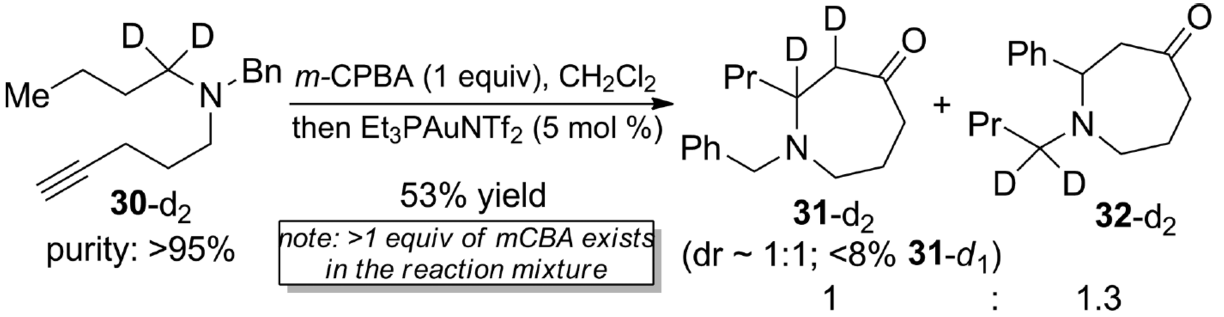
Different mechanism:



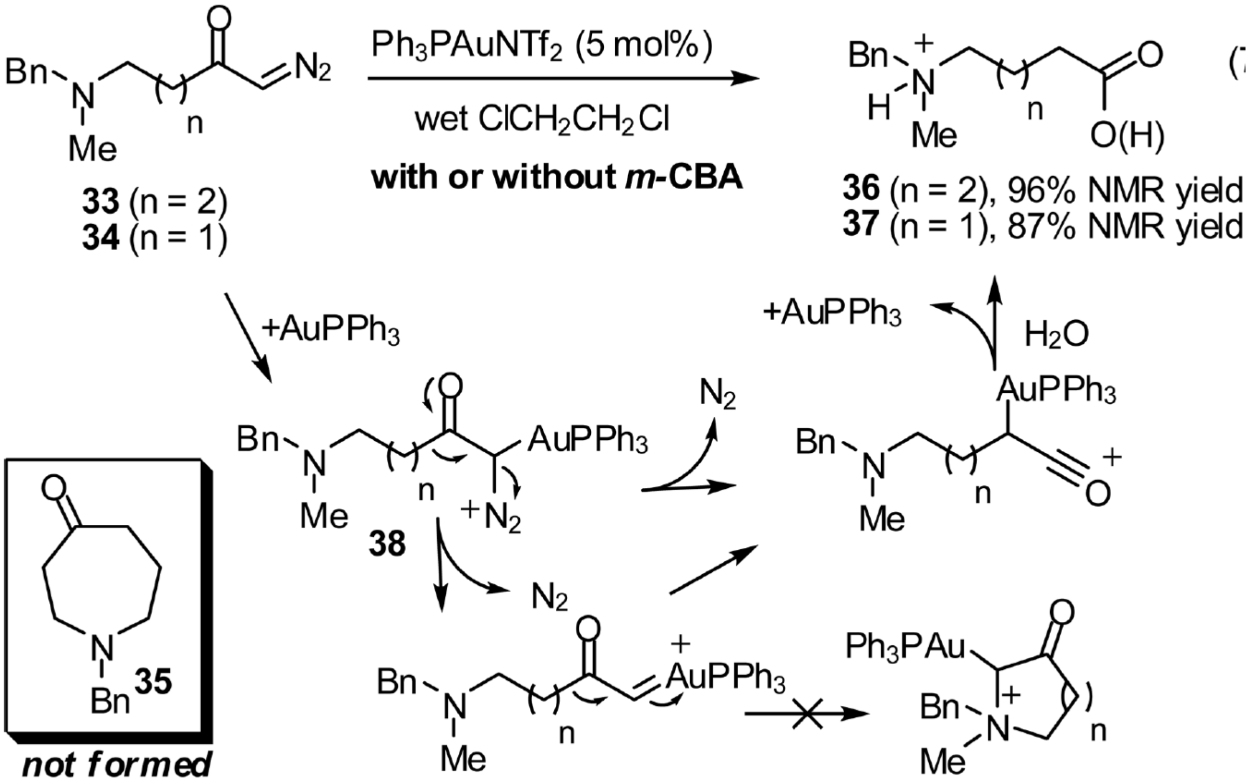
Noey, E. L.; Luo, Y.; **Zhang, L.;* Houk, K. N.*** *J. Am. Chem. Soc.* **2012**, *134*, 1078.

Experimental studies

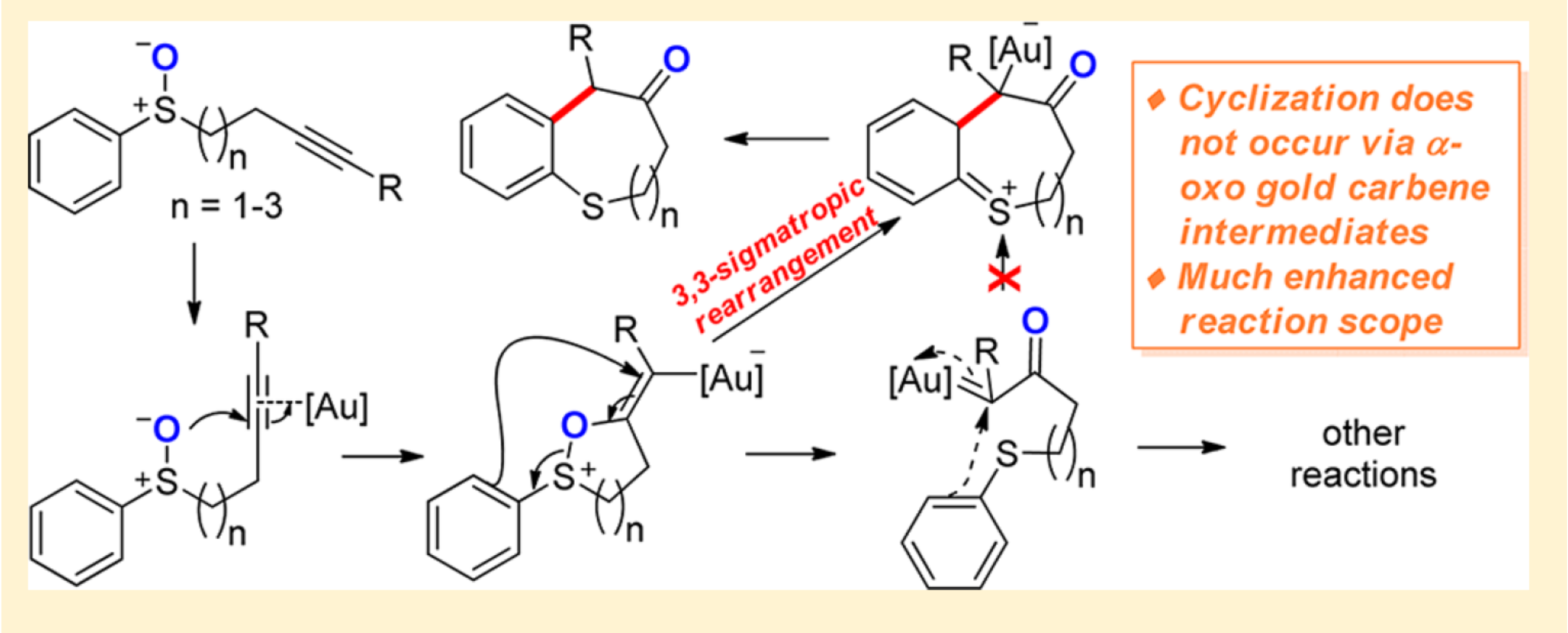
1)



2)



Noey, E. L.; Luo, Y.; **Zhang, L.;*** **Houk, K. N.*** *J. Am. Chem. Soc.* **2012**, *134*, 1078.



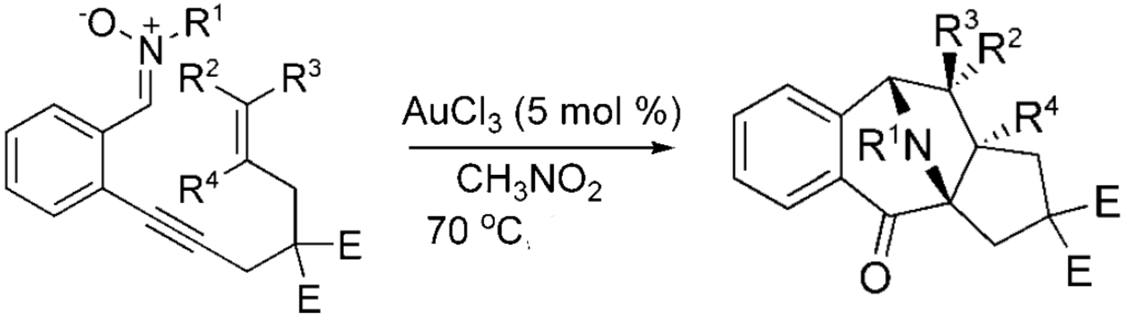
- Cyclization does not occur via α-oxo gold carbene intermediates
- Much enhanced reaction scope

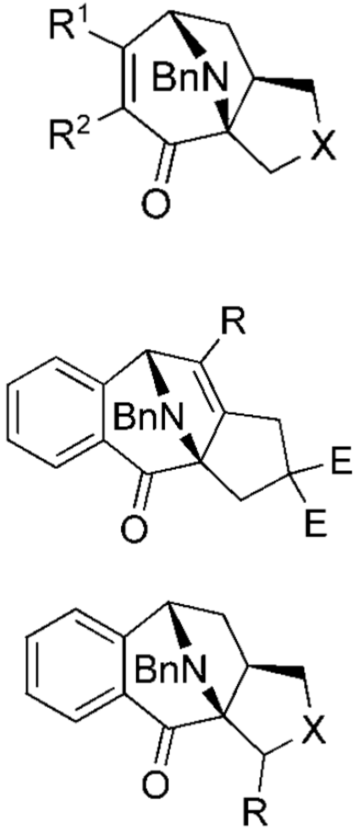
Liu, B.; Li, Y.; Wang, Y.; Aue, D. H.; Luo, Y.; **Zhang, L.*** *J. Am. Chem. Soc.* **2013**, *135*, 8512

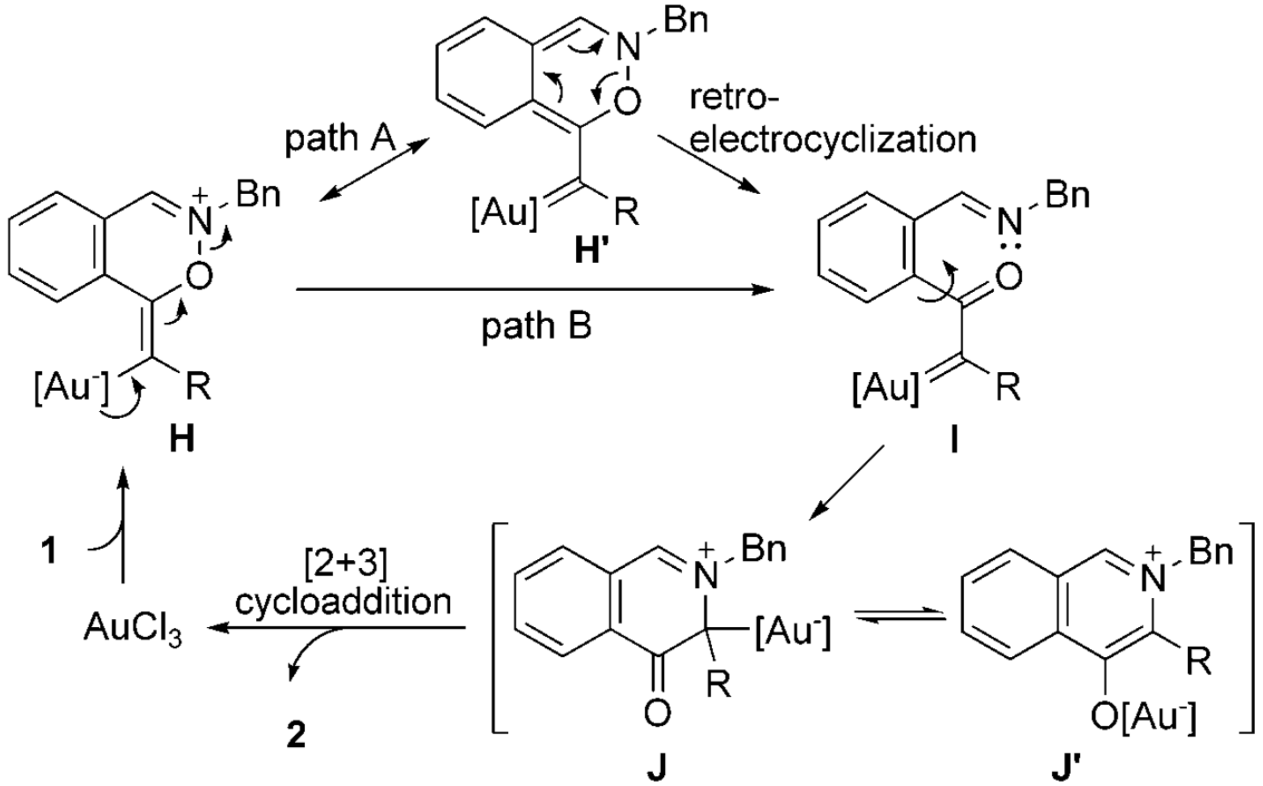
This mechanistic twist, however, needs not to be generalized and is likely limited to the cases where other facile processes could interfere. It does not necessarily invalidate the general strategy.

Zhang, L.

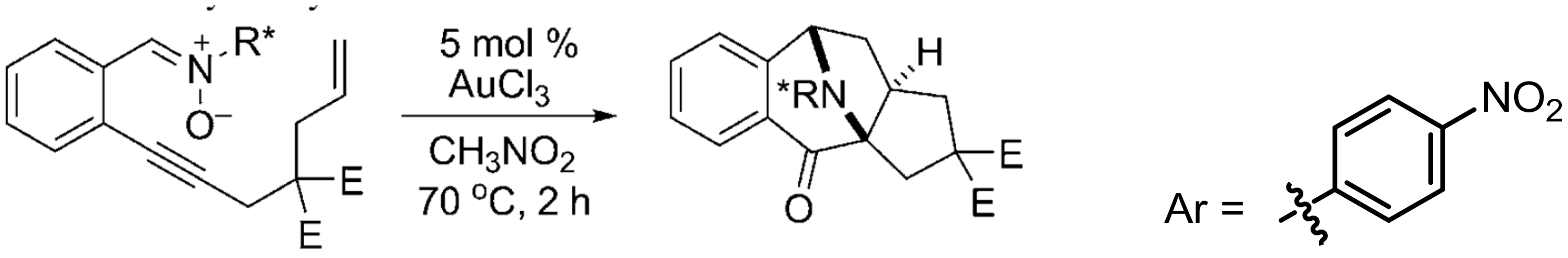
Cyclization of nitrone-containing enynes





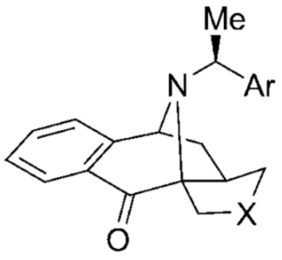


Yoem, H.-S.; Lee, J.-E.; **Shin, S.** *Angew. Chem., Int. Ed.* **2008**, *47*, 7040.

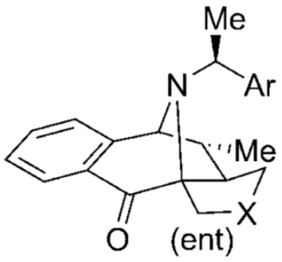


2aa–2ai (E = CO_2Et)

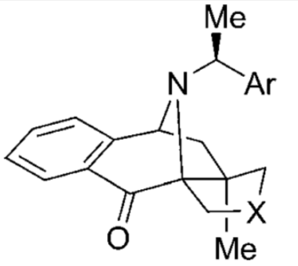
3aa–3ai



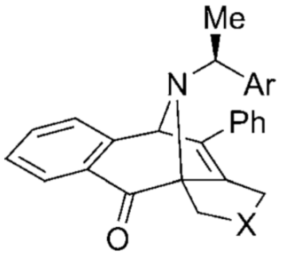
3ai 78 %
(98.5 % *ee*)



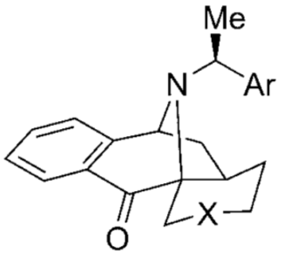
3bi 78 %
(96.4 % *ee*)[c]



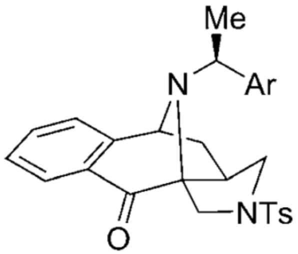
3ci 70 %
(95.4 % *ee*)



3ei 60 %
(98.6 % *ee*)

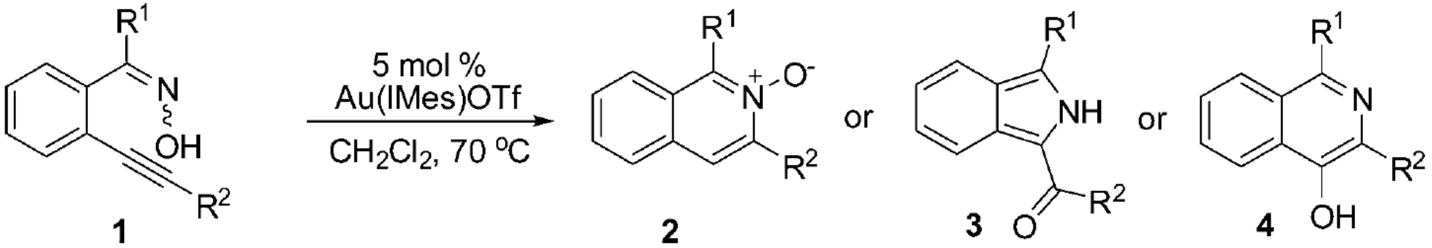


3fi 79 %
(97.6 % *ee*)



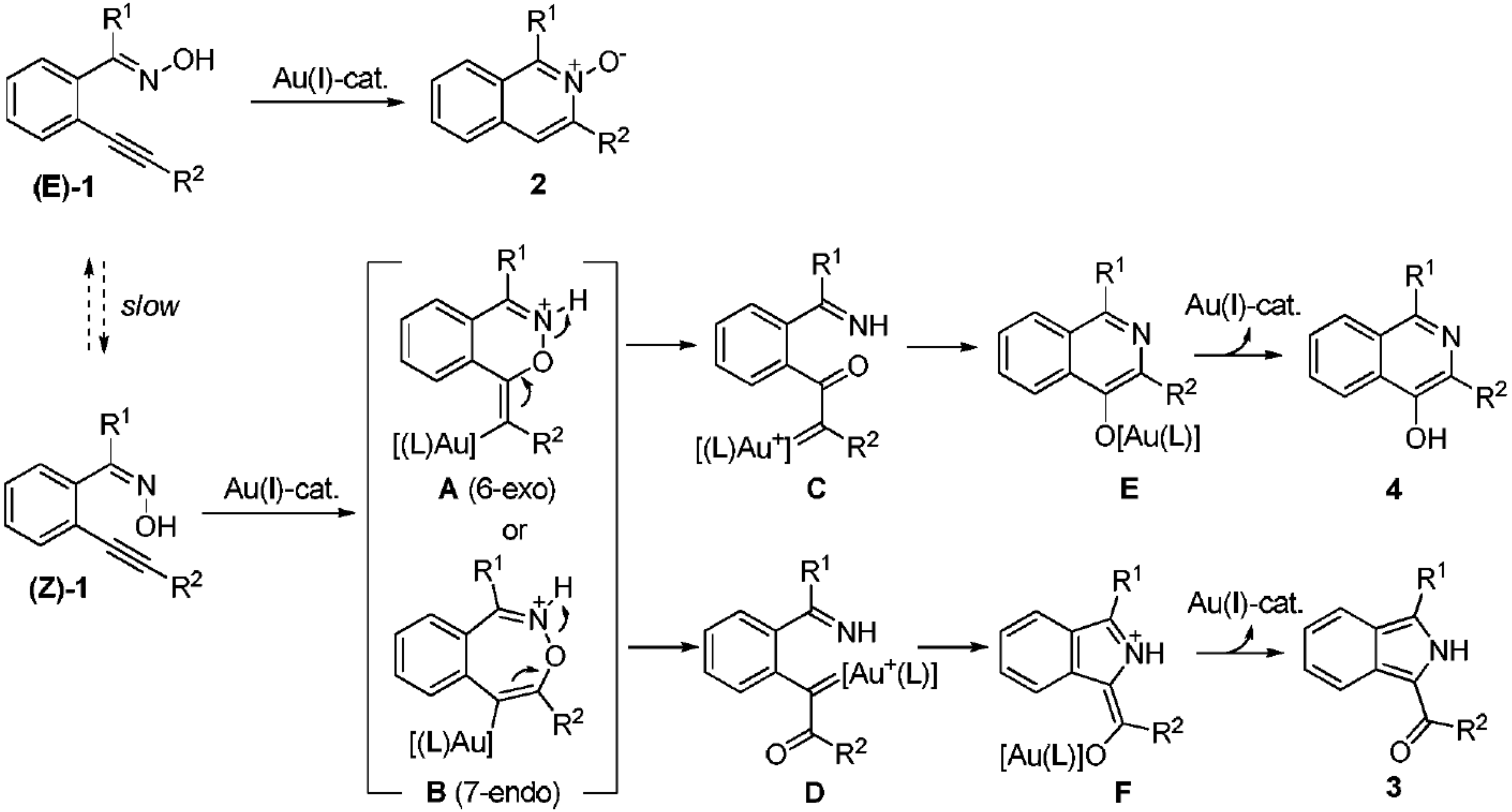
3gi 75 %
(97.5 % *ee*)

Jeong, J.; Yeom, H.-S.; Kown, O.; **Shin, S.*** *Chem.;Asian J.* **2011**, *6*, 1977



Entry	Oxime	R^1, R^2	Time/h	**2**/**3**/**4** (%)^b
1	(*E*)-**1a**	Me, Me	2	**2a**, 83
2	(*Z*)-**1a**		1	**3a**, 66
3	(*E*)-**1b**	Me, *n*-Bu	2	**2b**, 91
4	(*Z*)-**1b**		0.5	**3b**, 42
5	(*E*)-**1c**	Me, Ph	2	**2c**, 46
6	(*Z*)-**1c**		12	**3c**, 30/**4c**, 41

Yeom, H.-S.; Lee, Y.; Lee, J.-E.; **Shin, S.** *Org. Biomol. Chem.* **2009**, *7*, 4744

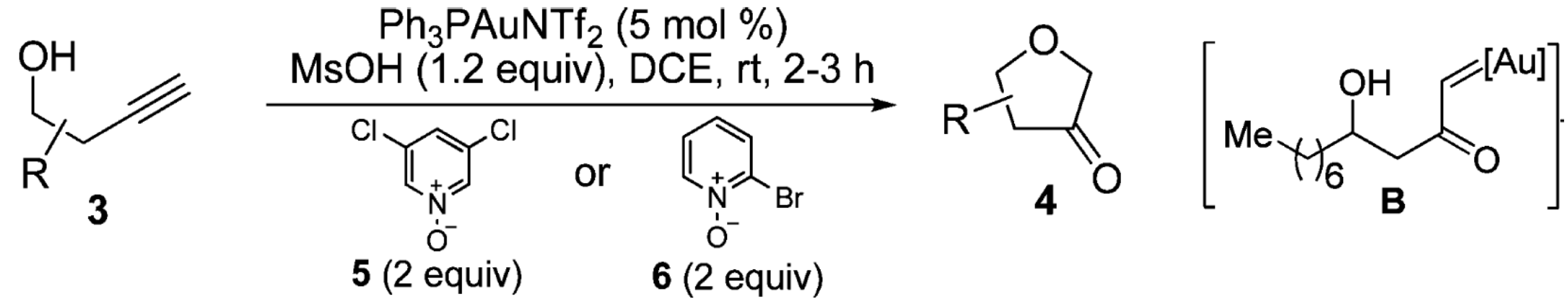

(E)-1
Au(I)-cat.
2
slow
(Z)-1
Au(I)-cat.
A (6-exo)
or
B (7-endo)
C
D
E
F
Au(I)-cat.
4
Au(I)-cat.
3

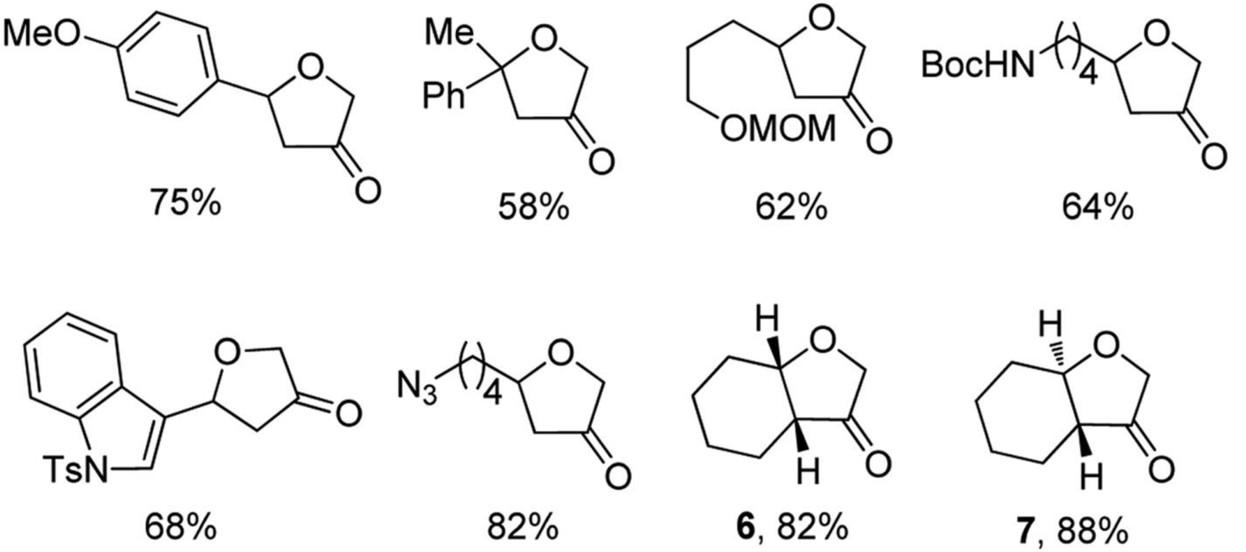
- Intermolecular Alkyne Oxidation

  Intramolecular Trapping

  Intermolecular Trapping

Cyclization of homopropargylic alcohol:

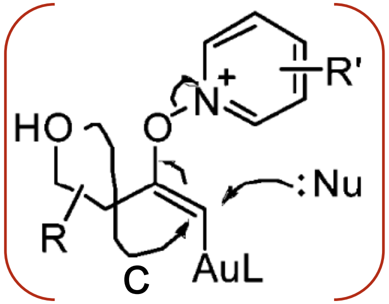




Ye, L.; Cui, Y. Zhang, G.; **Zhang, L.** *J. Am. Chem. Soc.* **2010**, *132*, 3258.

Mechanism:

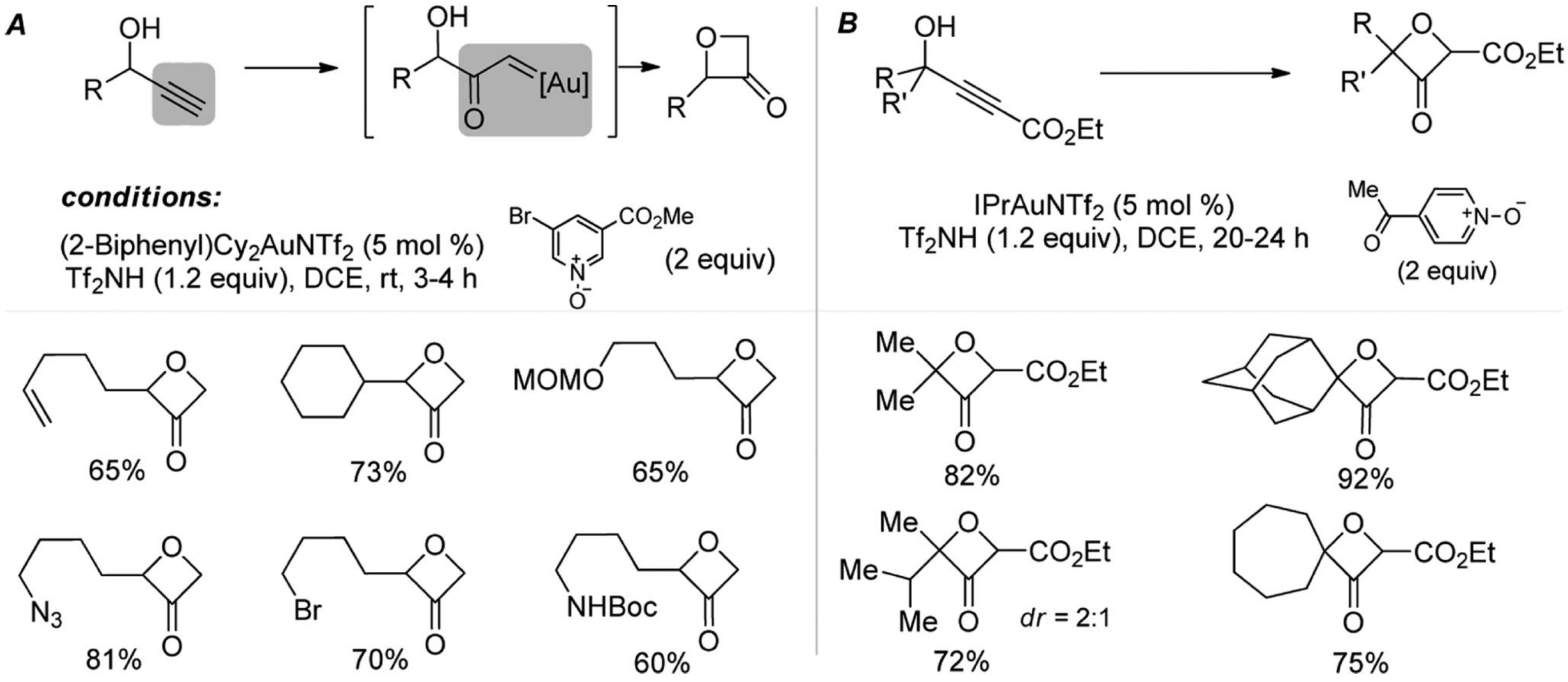
or

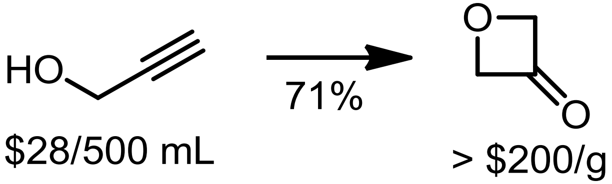


Observed:

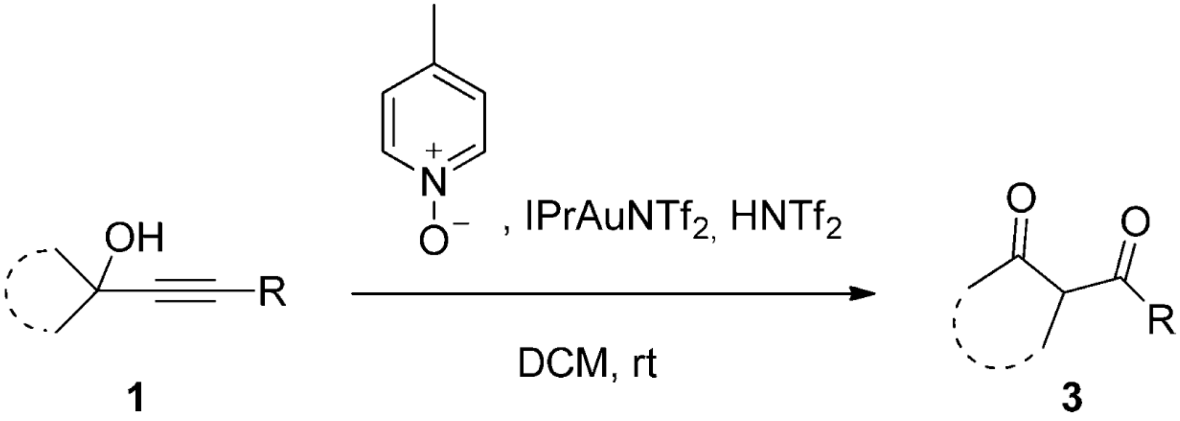
disfavored 5-endo-trig cyclization

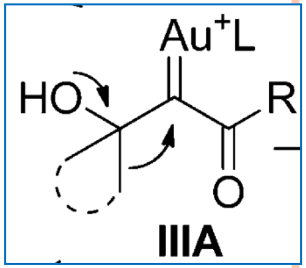
Cyclization of propargylic alcohol:



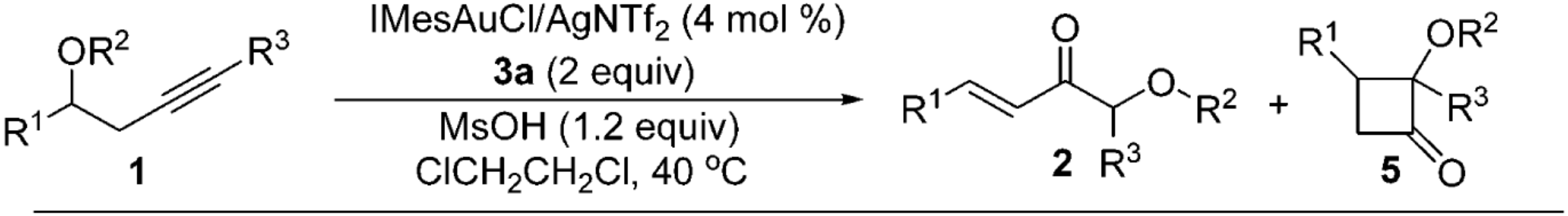


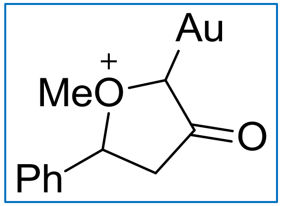
Ye, L.; He, W.; **Zhang, L.*** *J. Am. Chem. Soc.* **2010**, *132*, 8550





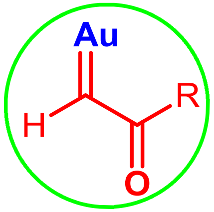
Hashimi, A. S. K.; Wang, T.; Shi, S.; Rudolph, M. *J. Org. Chem.* **2012**, *77*, 7761

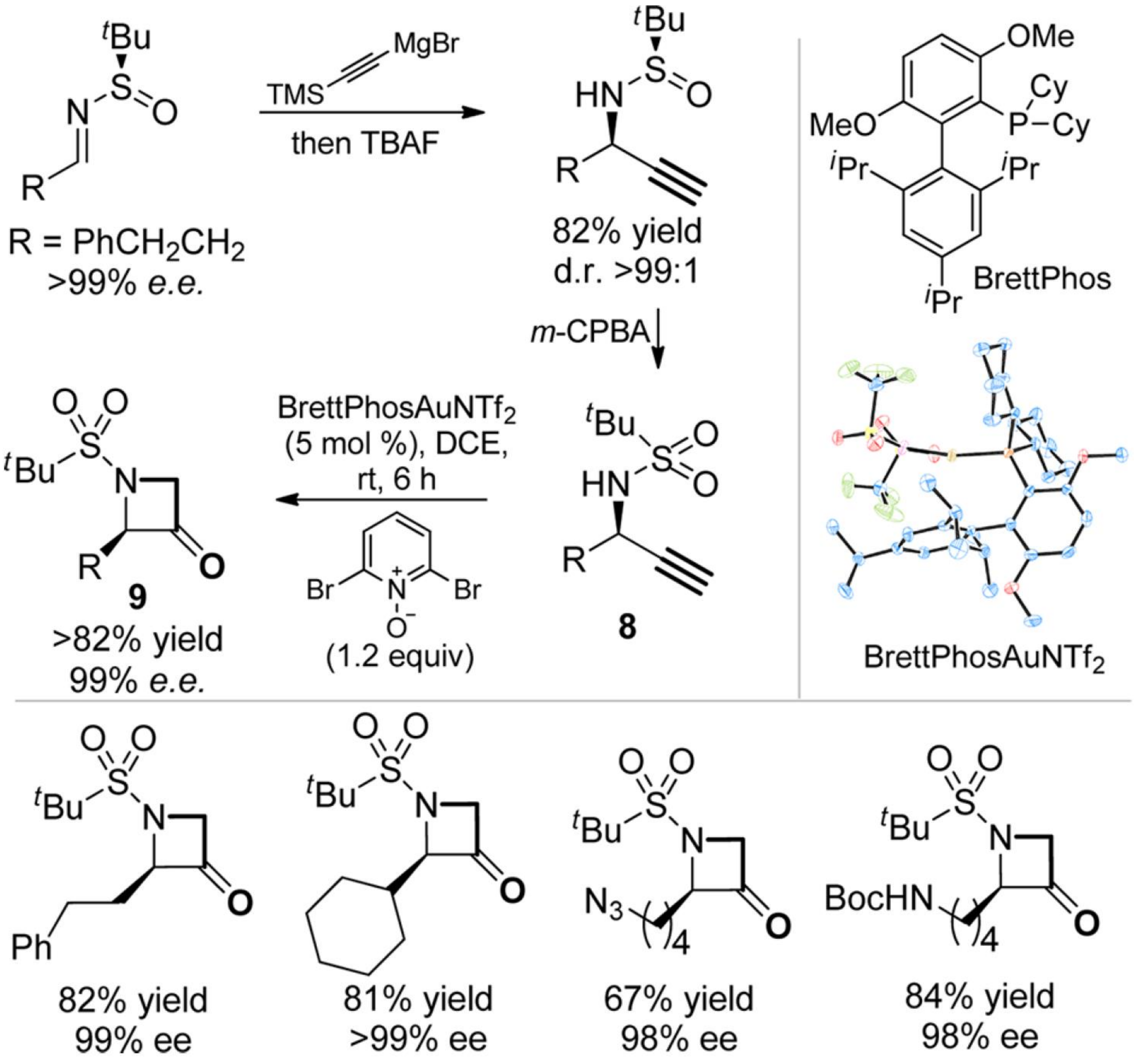




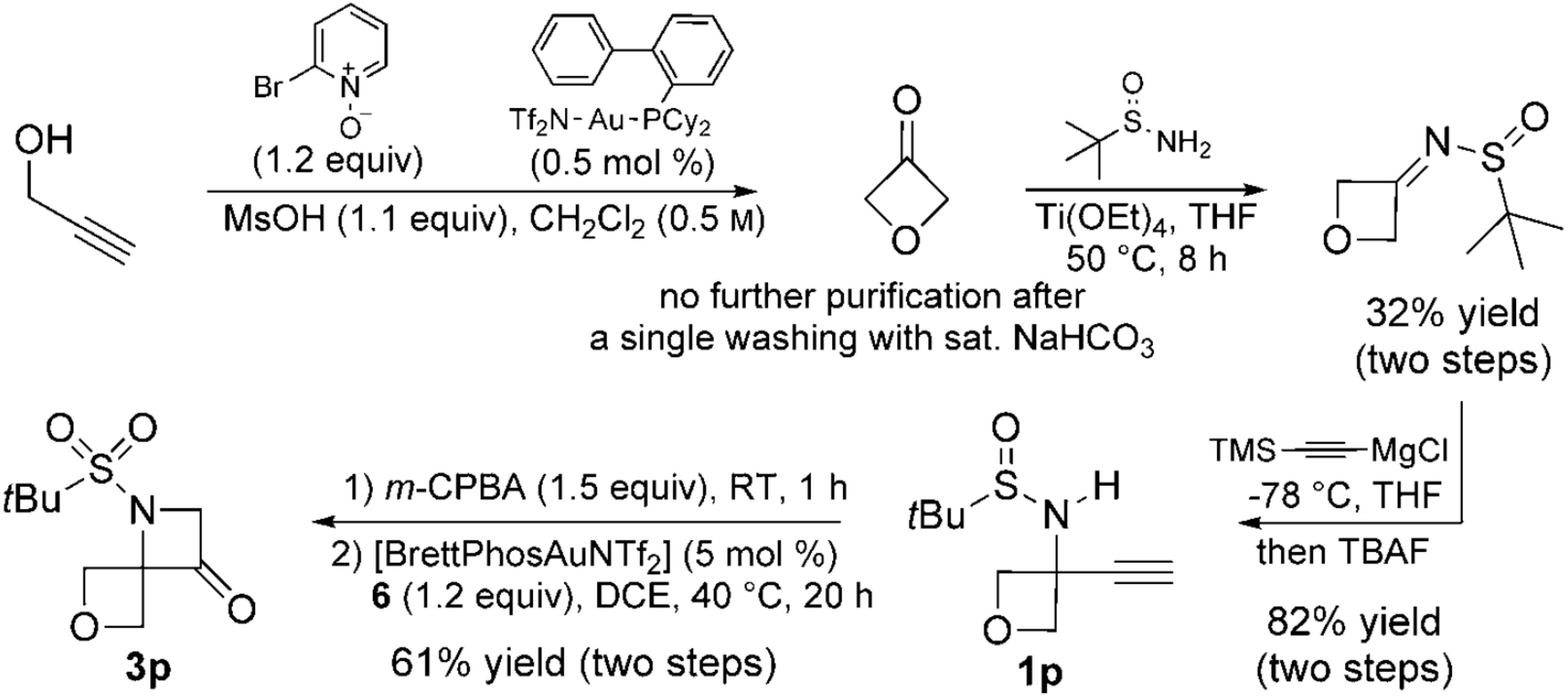
Xu, M.; Ren, T.-T.; **Li, C.-Y.** *Org. Lett.* **2012**, *14*, 4902

Cyclization of propargylic amine:



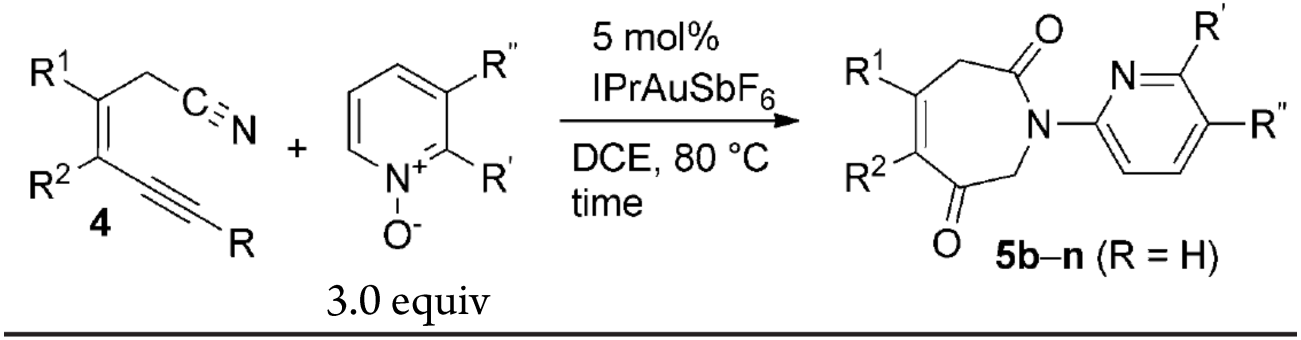


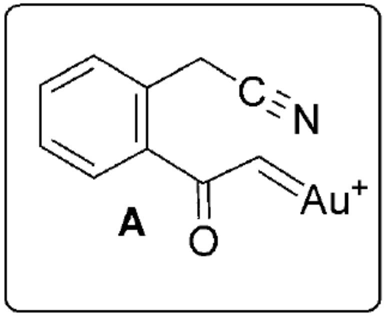
Ye, L.; He, W.; **Zhang, L.** *Angew. Chem., Int. Ed.* **2011**, *50*, 3236.

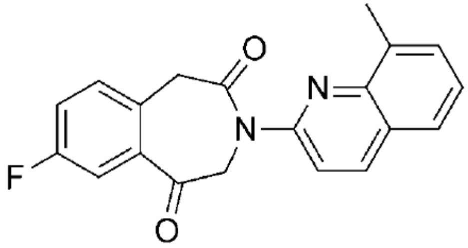


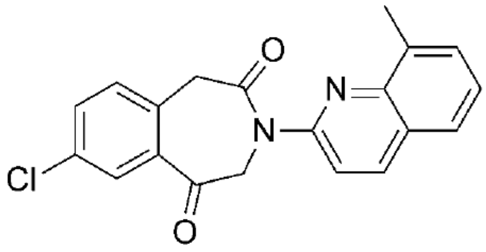
building blocks in medicinal chemistry?

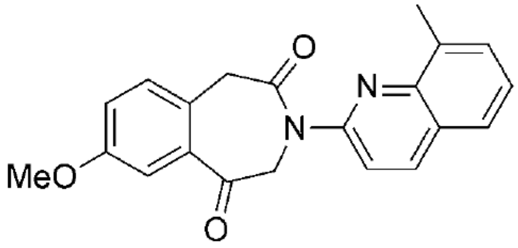
Ye, L.; He, W.; **Zhang, L.** *Angew. Chem., Int. Ed.* **2011**, *50*, 3236.

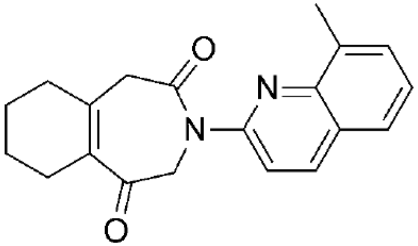


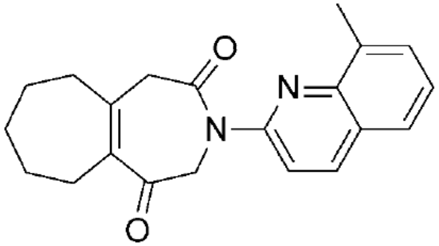


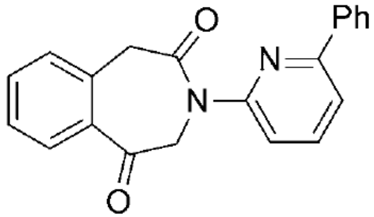

5e (12 h, 75 %)


5f (7.5 h, 72 %)

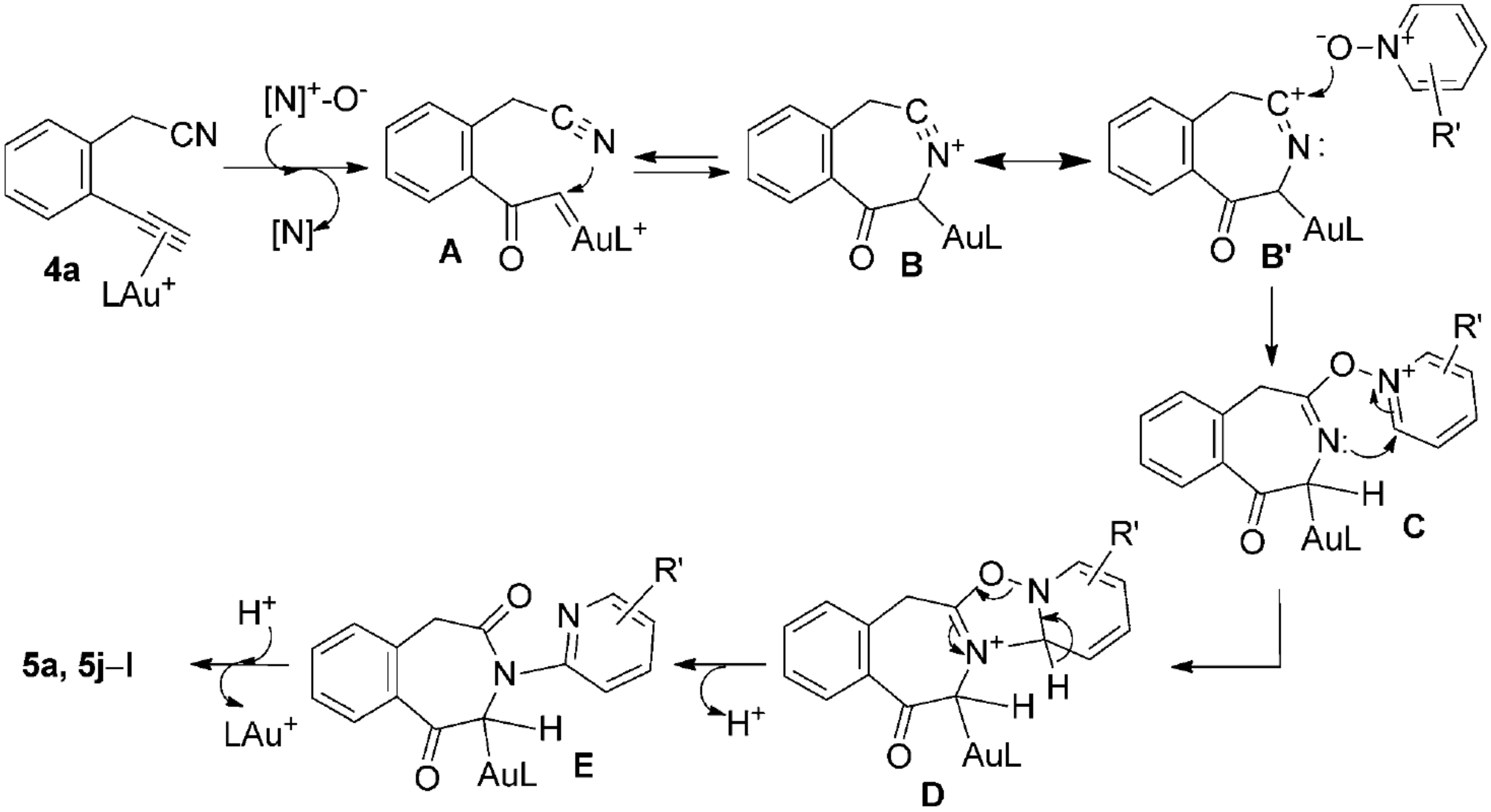

5g (10.5 h, 85 %)


5h (2.5 h, 84 %)


5i (7 h, 62 %)

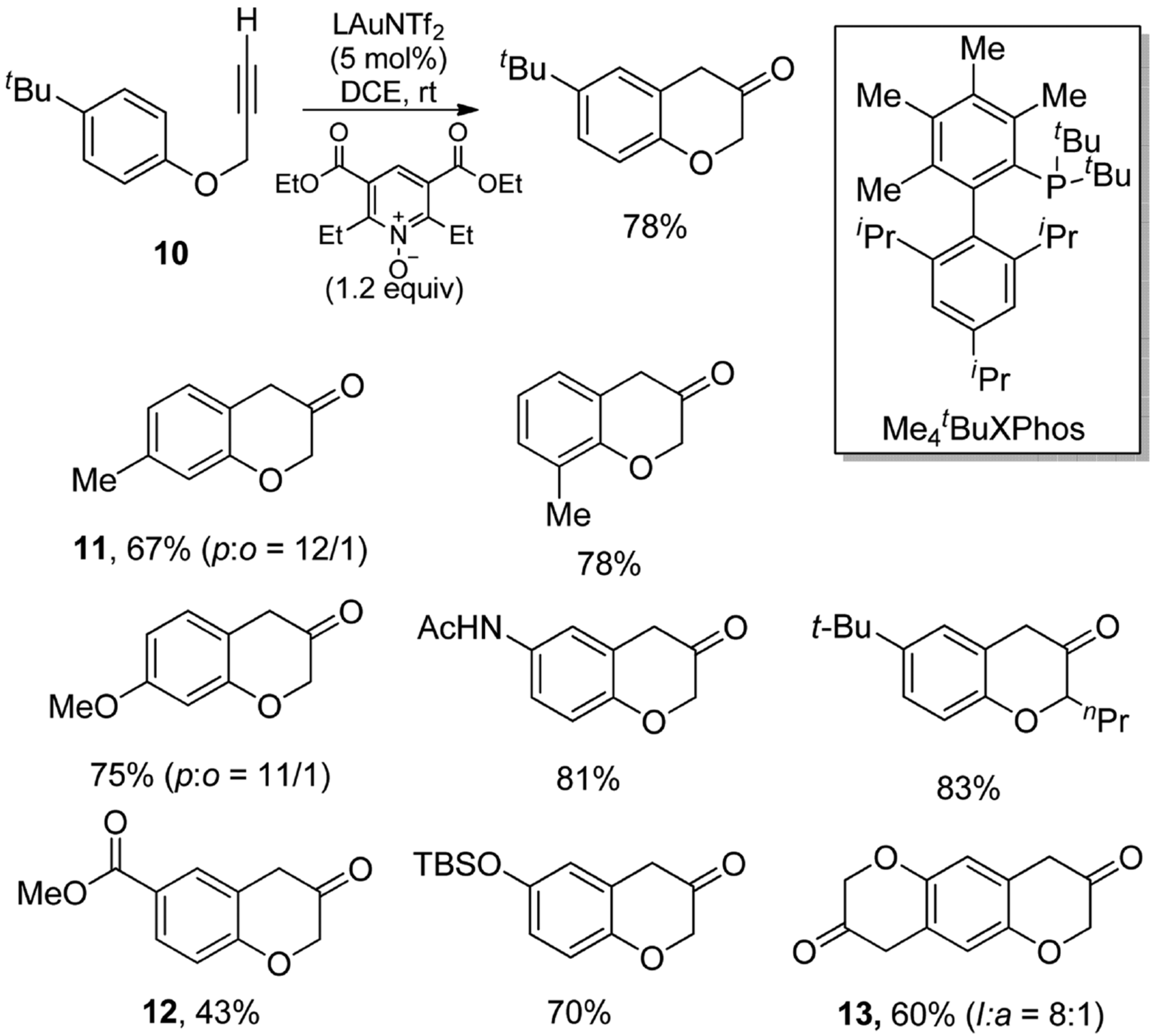

5j (12 h, 41 %)

Karad, S. N.; **Liu,R.-S.** * *Angew. Chem. Int. Ed.* **2014**, *53*, early view.

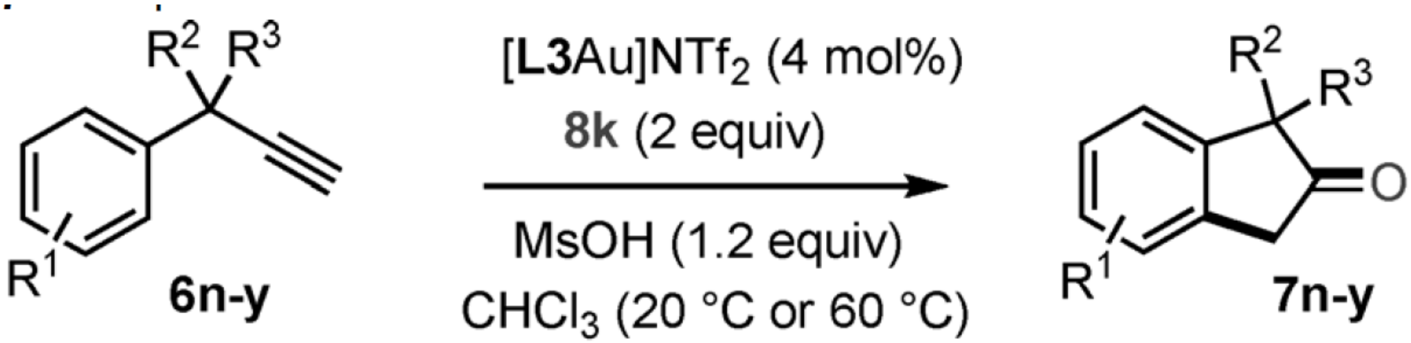


CN
4a
LAu+
[N]+-O-
[N]
C
N
A
O
AuL+
N+
B
AuL
-O-N+
C+
N:
R'
B'
O-N+
H
C
R'
O
N
N+
H
AuL
D
O
N
R'
H
E
H+
5a, 5j–l
H+
LAu+

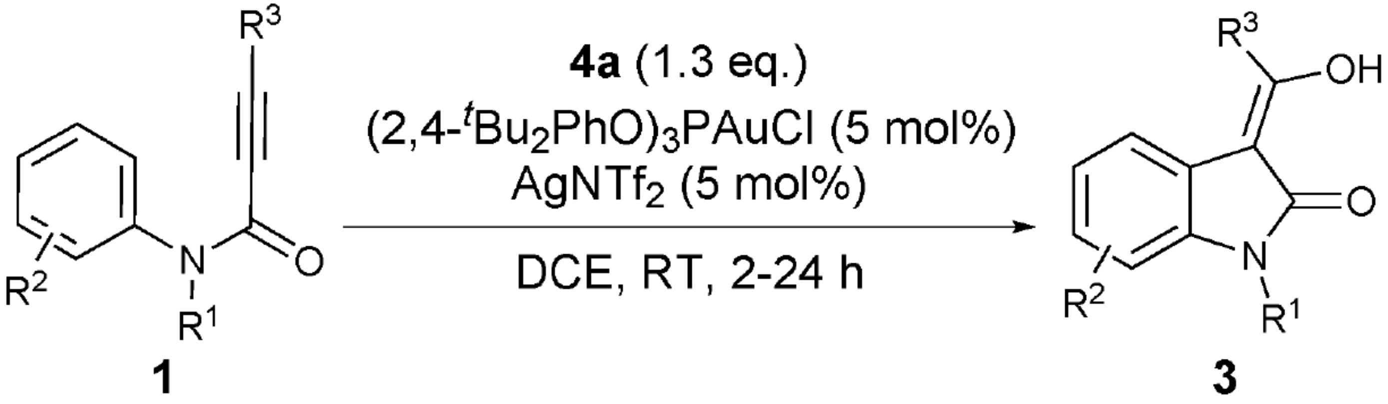
Insertion of aryl C-H bond:



Wang, Y.; Ji, K.; Lan, S.; **Zhang, L.** *Angew. Chem., Int. Ed.* **2012**, *51*, 1915

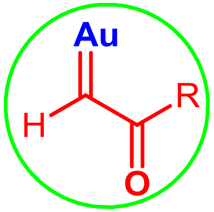


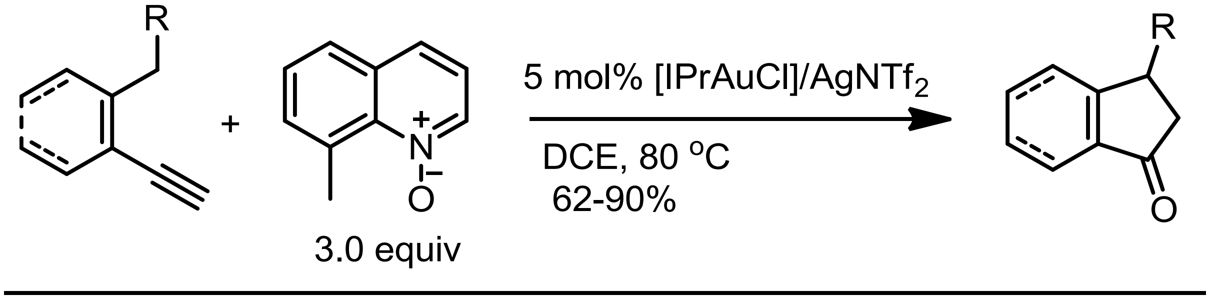
Henrion, G.; Chavas, T. E. J.; Le Goff, X.; **Gagosz, F.** *Angew. Chem., Int. Ed.* **2013**, *52*, 6277

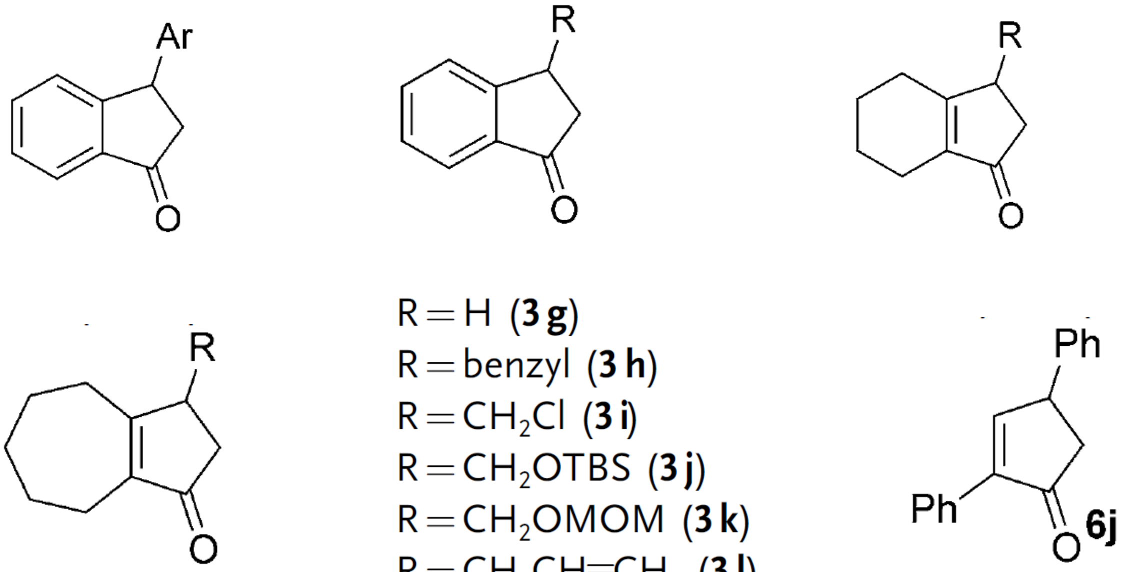


Qian, D.; **Zhang, J.** *Chem. Commun*. **2012**, *48*, 7082–7084.

Insertion of benzylic C-H bond:





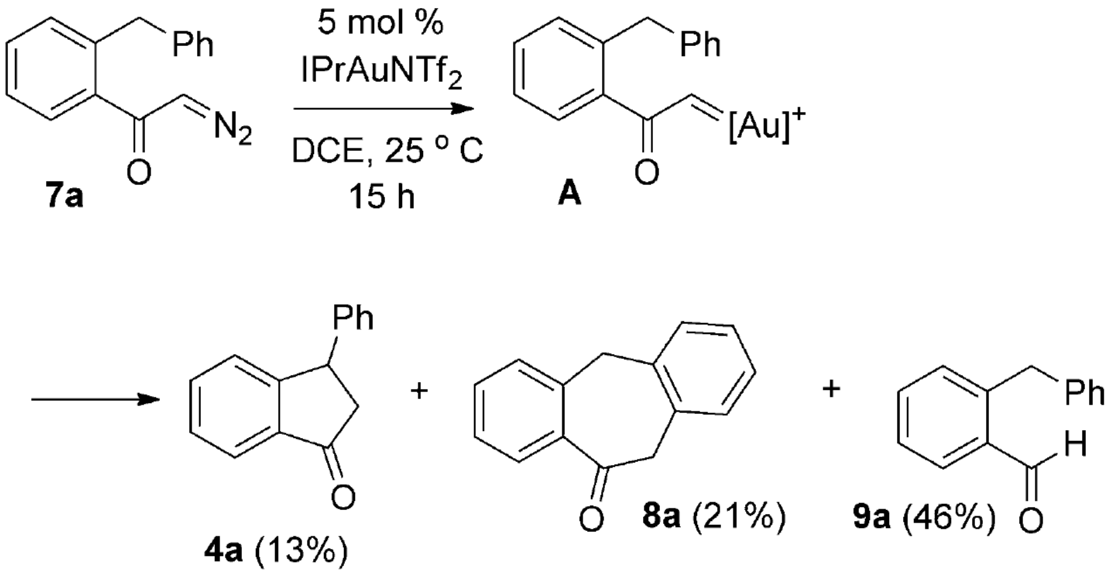


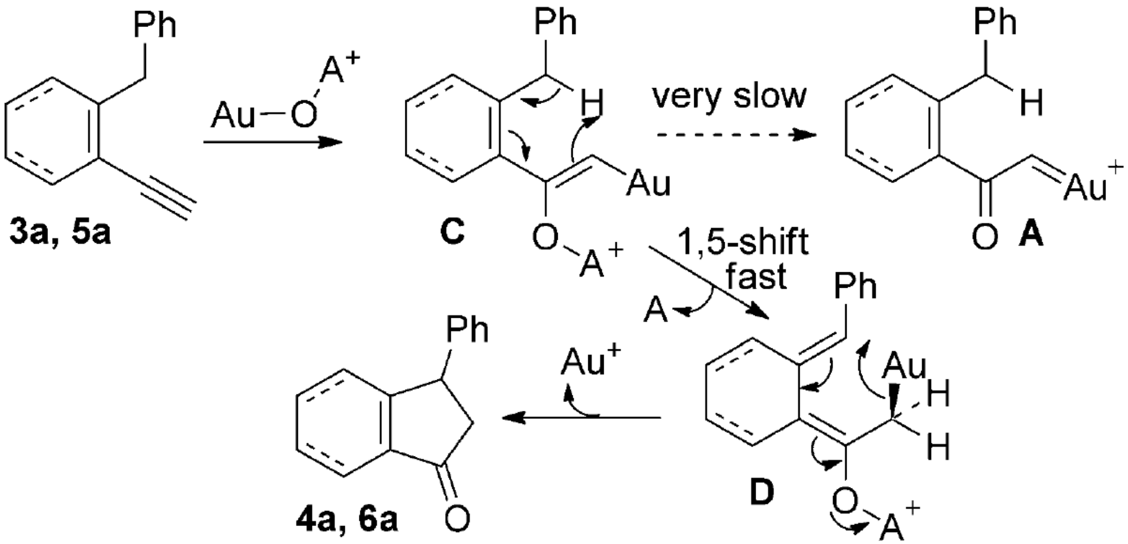
R = H (**3 g**)
R = benzyl (**3 h**)
R = CH_2Cl (**3 i**)
R = CH_2OTBS (**3 j**)
R = CH_2OMOM (**3 k**)
R = $CH_2CH{=}CH_2$ (**3 l**)

6j

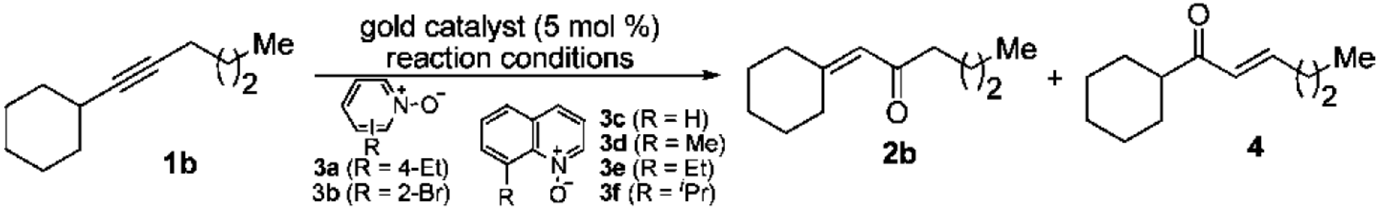
Bhunia, S.; Ghorpade, S.; Huple, D. B.; **Liu, R.-S.** *Angew. Chem. Int. Ed.* **2012**, *51*, 2939

Mechanism:


Ph
N2
O
7a
5 mol %
IPrAuNTf2
DCE, 25 ° C
15 h
Ph
[Au]+
O
A
Ph
O
4a (13%)
+
O
8a (21%)
+
Ph
H
9a (46%)
O


Ph
3a, 5a
Au–O
A+
Ph
H
Au
C
O
A+
very slow
Ph
H
Au+
O
A
1,5-shift
fast
A
Ph
Au
H
H
D
O
A+
Au+
Ph
4a, 6a
O

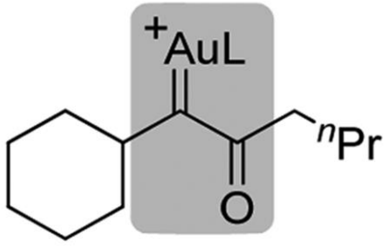
1,2-C-H insertion



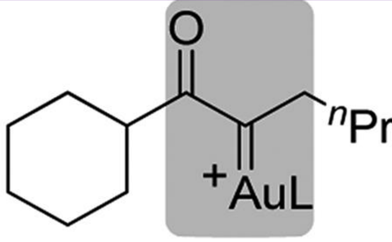
entry	catalyst	*N*-oxide (equiv)	MsOH (equiv)	reaction conditions	yield % (% **1b** left)[b]	**2b/4**
1	$Ph_3PAuNTf_2$	**3a** (2)	1.2	DCE, rt, 12 h	45 (50)	2.1
2	$Ph_3PAuNTf_2$	**3b** (2)	1.2	DCE, rt, 12 h	53 (37)	2.6
3	$Ph_3PAuNTf_2$	**3c** (2)	1.2	DCE, rt, 18 h	46 (20)	2.3
4	$Ph_3PAuNTf_2$	**3d** (2)	1.2	DCE, rt, 40 min	88	2.8
5	$Ph_3PAuNTf_2$	**3e** (2)	1.2	DCE, rt, 40 min	82	3.1
6	$Ph_3PAuNTf_2$	**3f** (2)	1.2	DCE, rt, 40 min	85	3.4
7	$Ph_3PAuNTf_2$	**3f** (1.2)	no	DCE, rt, 40 min	87	3.2
8	$Et_3PAuNTf_2$	**3f** (1.2)	no	DCE, rt, 40 min	71	3.8
9	$LAuNTf_2$[c]	**3f** (1.2)	no	DCE, rt, 40 min	83	3.1
10	$IPrAuNTf_2$	**3f** (1.2)	no	DCE, rt, 15 min	85	6.4
11	$IPrAuNTf_2$	**3f** (1.2)	no	DCE, −20 °C, 14 h	89	9.1
12	$IPrAuNTf_2$	**3f** (1.2)	no	toluene, −20 °C, 14 h	80	12
13	$IPrAuNTf_2$	**3f** (1.2)	no	THF, −20 °C, 14 h	90[d]	13

[a] In vial; [**1b**] = 0.1 M. [b] Estimated by ^1H NMR using diethyl phthalate as internal reference. [c] L = $(4\text{-}CF_3Ph)_3P$. [d] 83% isolated yield.

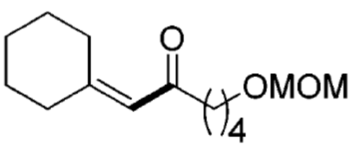
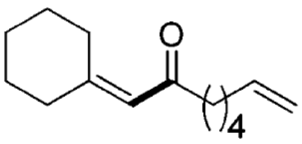
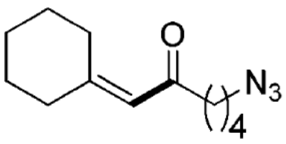
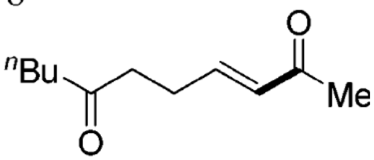
Lu, B.; Li, C.; **Zhang, L.** *J. Am. Chem. Soc*. **2010**, *132*, 14070



N



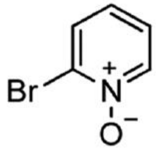
O

5	6	7	8
			
2f, 84% (11:1) -20 °C; 24 h	**2g**, 78%, (10:1) 0 °C; 48 h	**2h**, 88% (16:1) -20 °C; 24 h	**2i**, 83% (17:1) -20 °C; 36 h

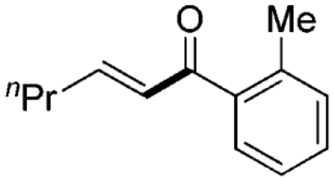
Conjugated Alkynes (aryl alkynes and enynes):

The regioselectivities were opposite to those of alphatic alkynes.

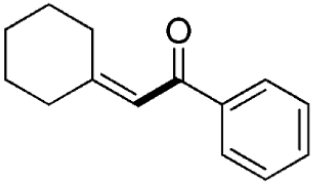
$(RO)_3PAuNTf_2$
(R = 2,4-^{t}Bu$_2$Ph)
(5 mol %)



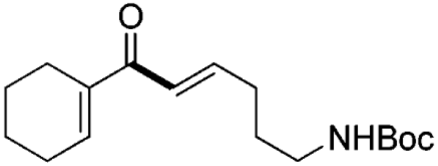
(1.2 equiv)



2n, 72% (16:1)
rt; 26 h



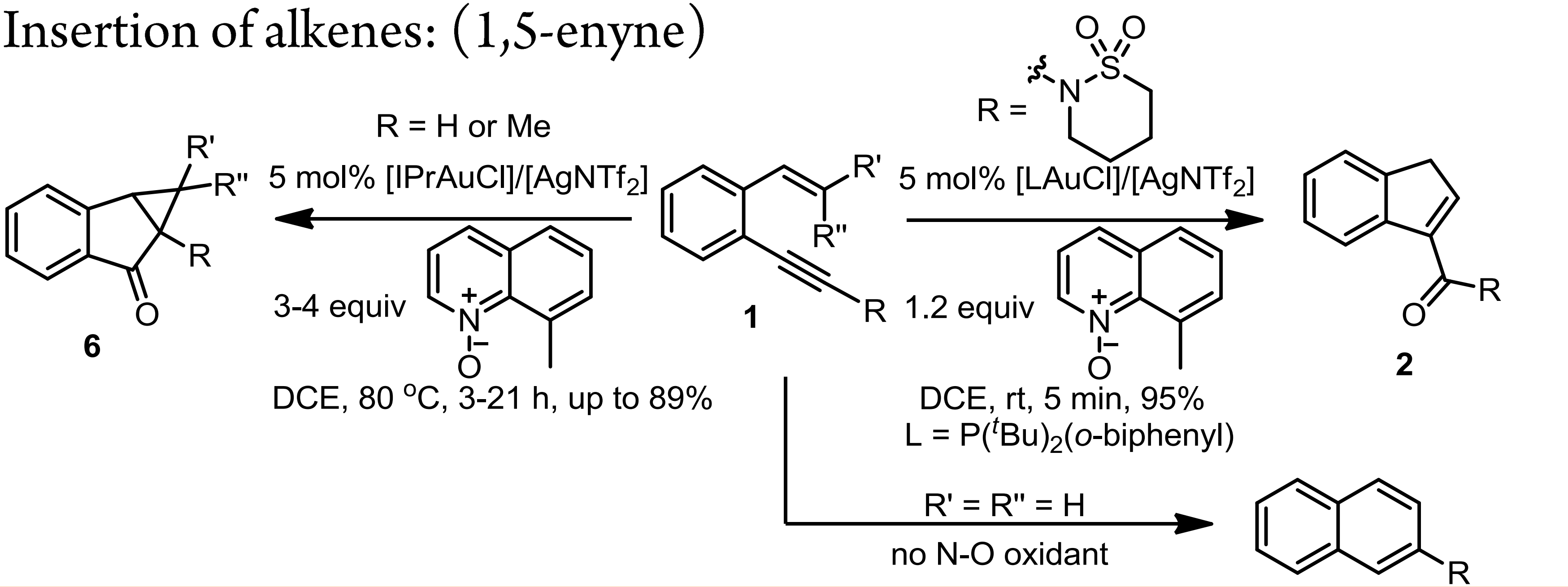
2q, 85% (>50:1)
rt; 26 h

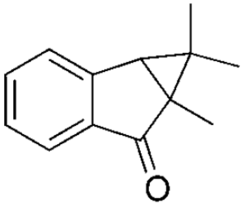


2v, 87% (>50:1)
rt; 1 h

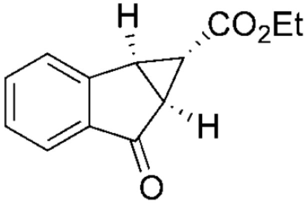
Lu, B.; Li, C.; **Zhang, L.** *J. Am. Chem. Soc*. **2010**, *132*, 14070

Insertion of alkenes: (1,5-enyne)

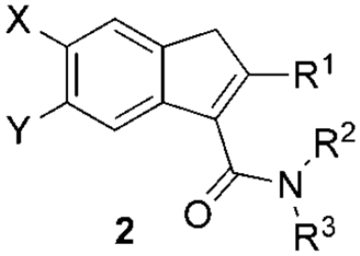




6o (76%)



6p (67%)



$R^2 = Ms$, $R^3 = n$Bu (**1d**)

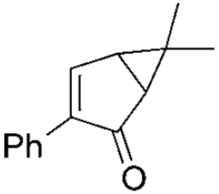
$R^2 = Ts$, $R^3 = Me$ (**1e**)

$R^2 = Ts$, $R^3 = Ph$ (**1f**)

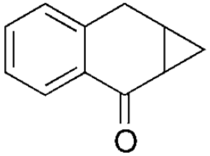
R^2, $R^3 = \text{-}(CH_2)_3SO_2\text{-}$ (**1g**)

X = H, Y = Cl (**1j**)

X = OMe, Y = H (**1k**)



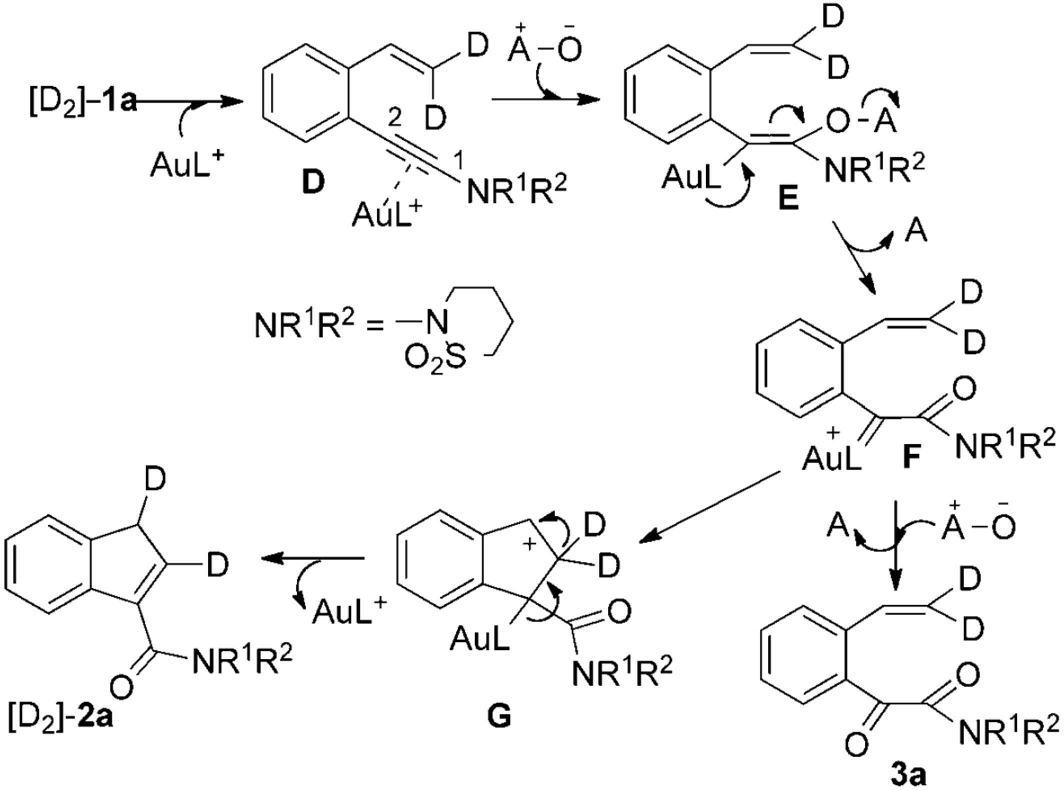
6j (84 %)



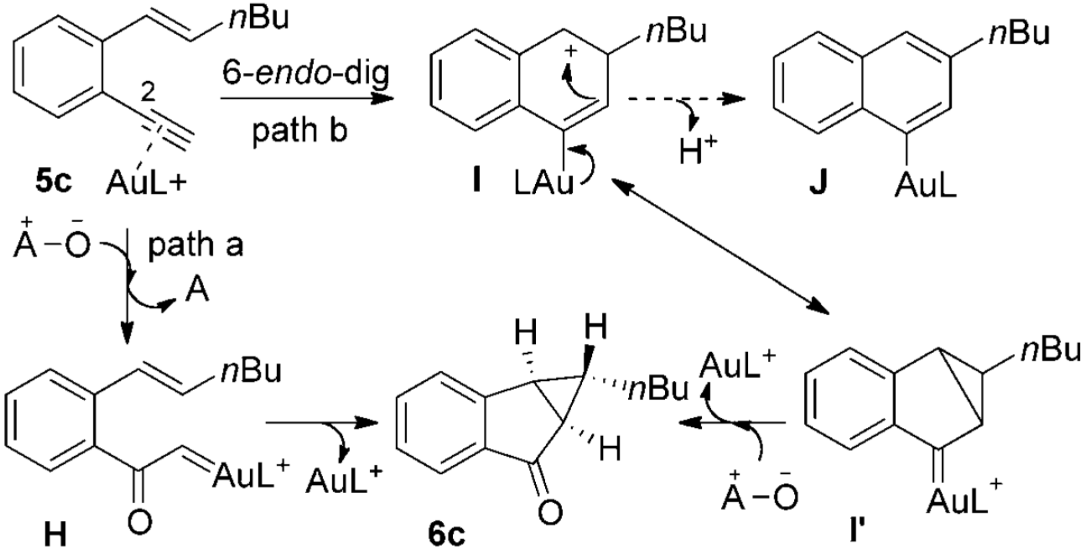
8 (61%)

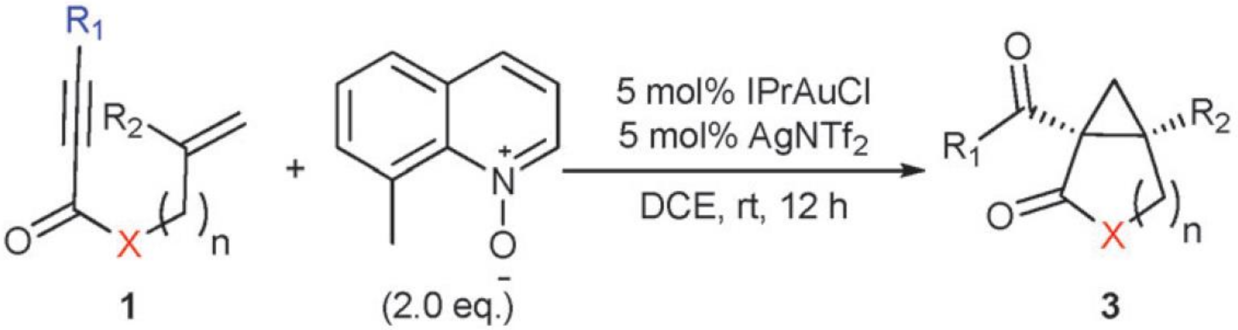
Liu, R.-S.* et al. *Angew. Chem. Int. Ed.* **2011**, *50*, 6911

Indene synthesis:

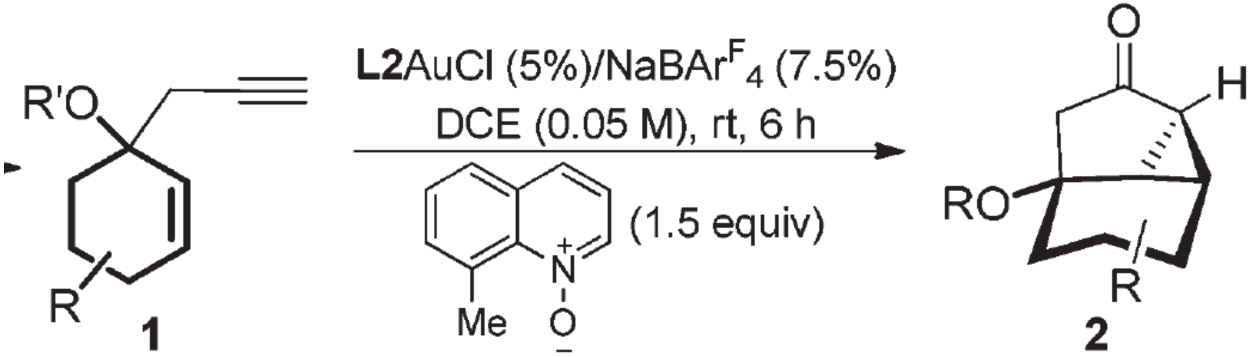


cyclopropanation:



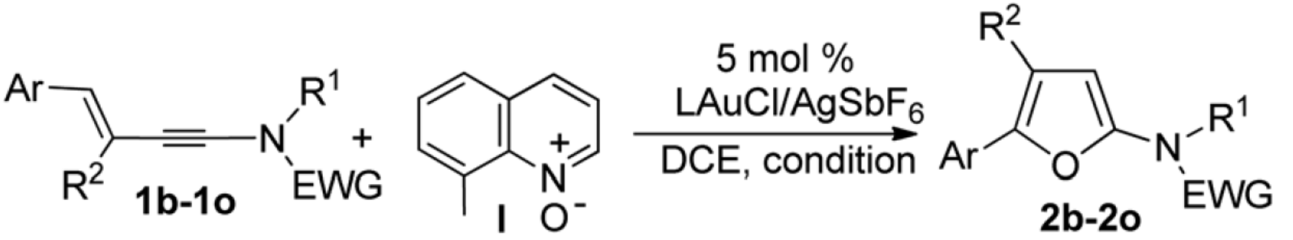


Qian, D.; **Zhang, J.** *Chem. Commun.* **2011**, *47*, 11152



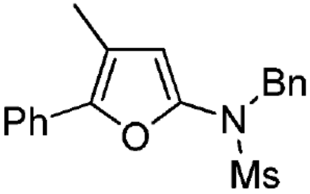
Ji, K.; **Zhang, L.** *Org. Chem. Front.*, **2014**, *1*, 34

(1,3-enyne)

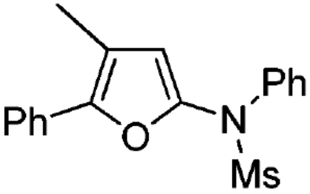


L = P(t-Bu)$_2$(o-biphenyl)

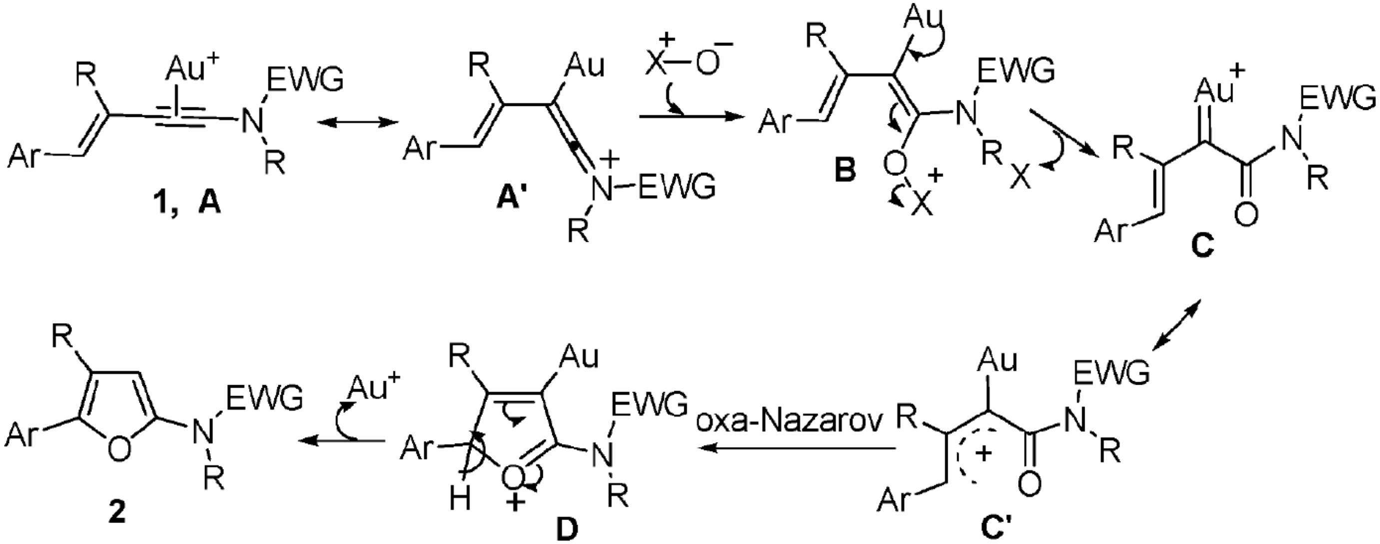
(1) **2b** (81%)
60 °C, 8 h



(2) **2c** (86%)
60 °C, 8 h

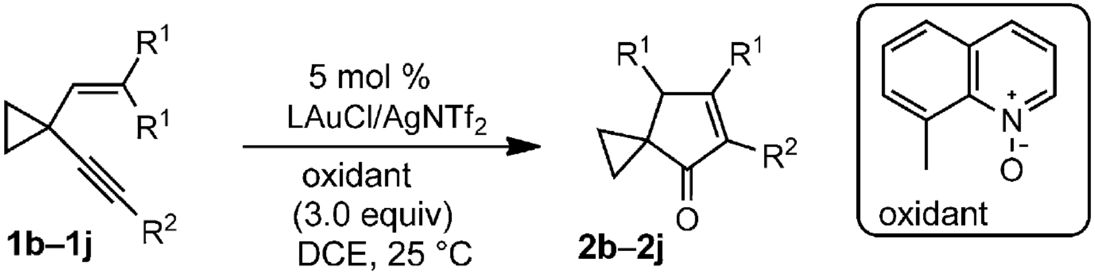


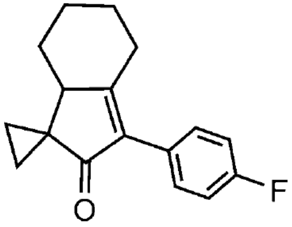
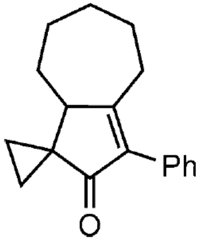
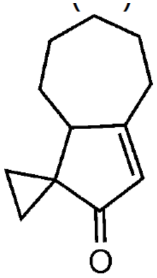
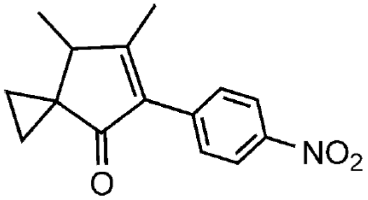
(3) **2d** (78%)
28 °C, 12 h



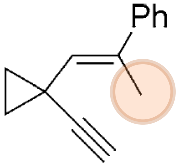
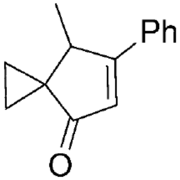
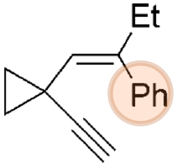
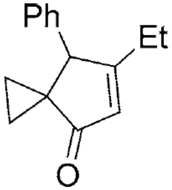
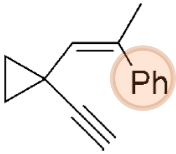
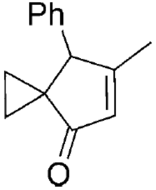
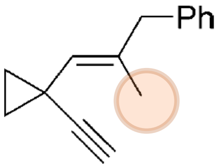
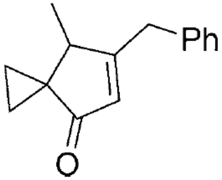
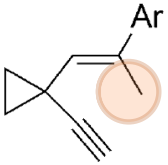
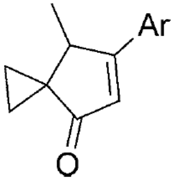
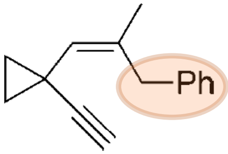
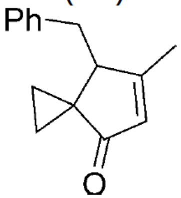
Dateer, R. B.; Pati, K.; **Liu, R.-S.** *Chem. Commun.* **2012**, *48*, 7200

(1,4-enyne): oxidation/cyclization/migration



Entry	2 (yield [%])[b]	*t* [h]	Entry	2 (yield [%])[b]	*t* [h]
1	 **2b** (83)	6.5	6	 **2g** (72)	12
4	 **2e** (78)	0.5	9	 **2j** (86)	3

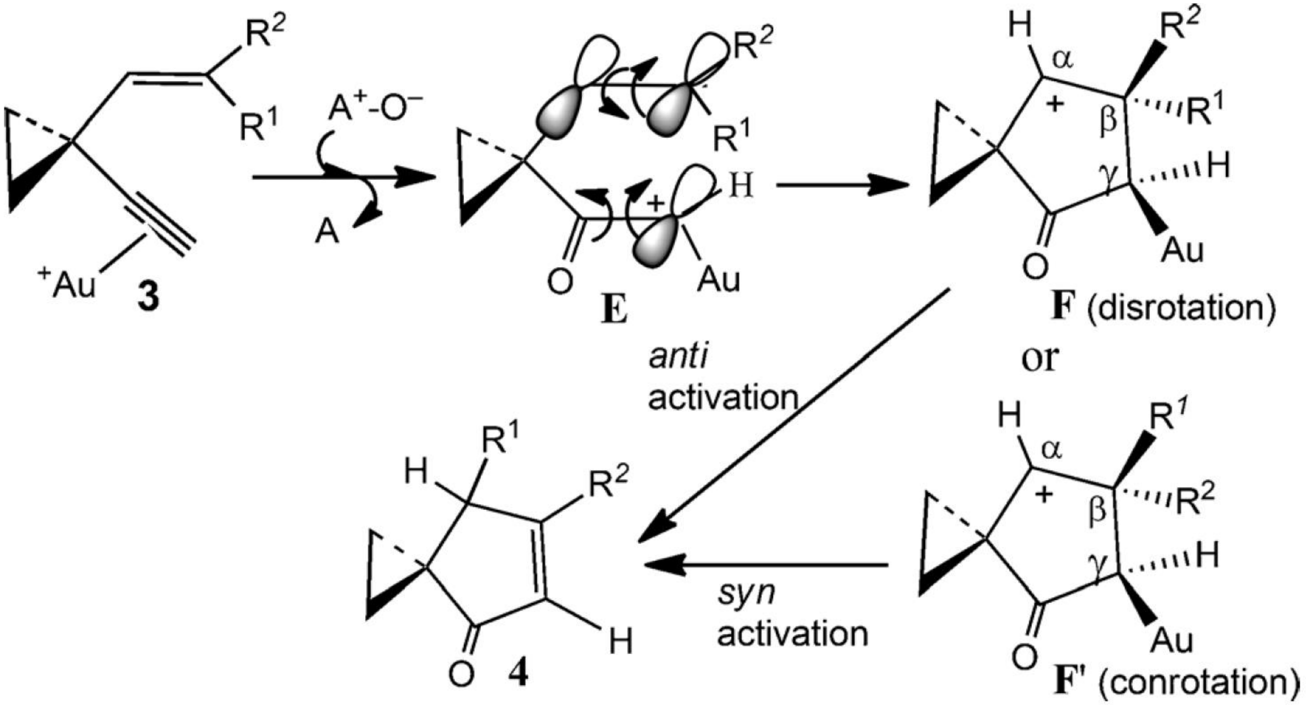
Ghorpade, S.; Su, M.-D.; **Liu, R.-S.** *Angew. Chem., Int. Ed.* **2013**, *52*, 4229

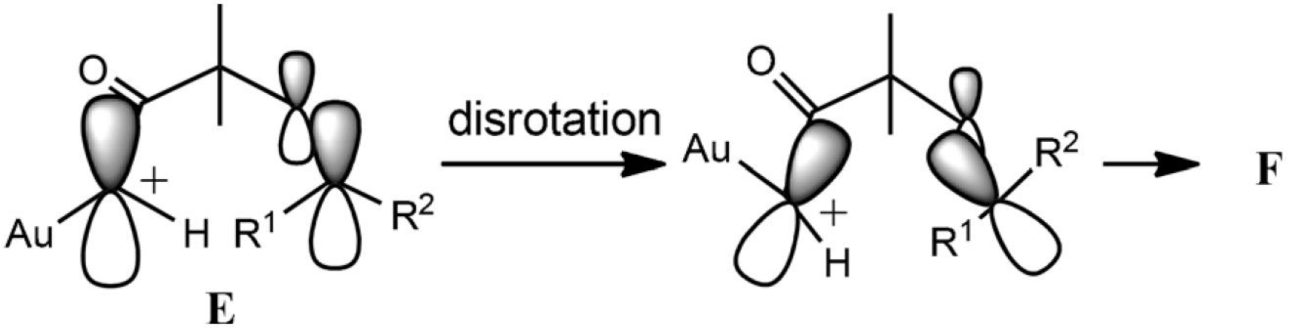
Entry	3	4 (yield [%])[b]	t [h]	Entry	3	4 (yield [%])[b]	t [h]
1	 ***E*-3 a**[a]	 **4 a** (78)	0.5	10	 ***Z*-3 e**	 **4 e’** (71)	5
2	 ***Z*-3 a**	 **4 a′** (81)	2	11	 ***E*-3 f**	 **4 f** (71)	7
3	 ***E*-3 b** Ar = $4\text{-ClC}_6\text{H}_4$	 **4 b** (72)	0.5	12	 ***Z*-3 f**	 **4 f’** (73)	10
4	***Z*-3 c** Ar = $4\text{-MeOC}_6\text{H}$	**4 c** (79)	0.5				

Always alkenyl *cis*-substituents migration happened.

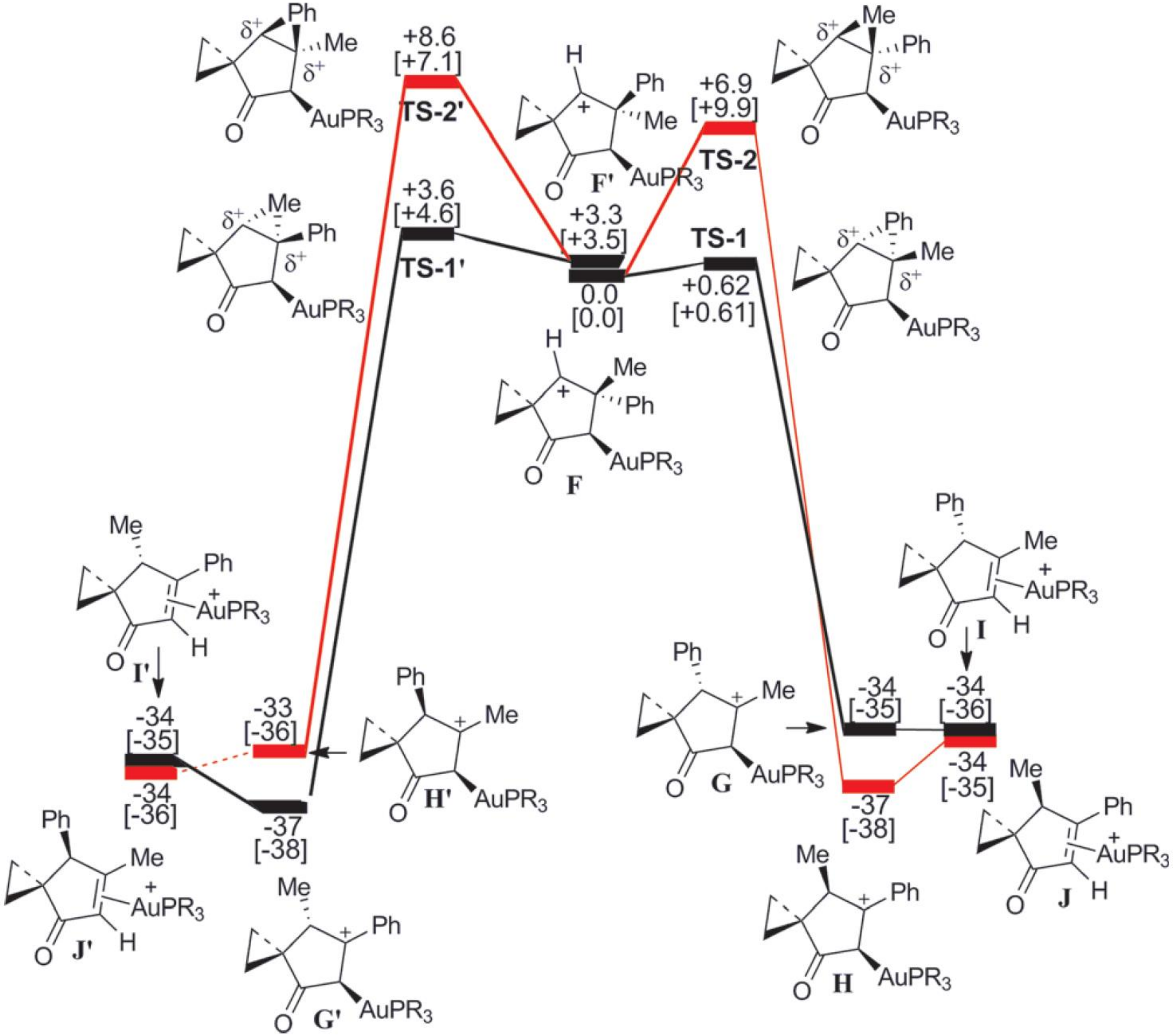
the reactions rates: E-configured olefins > Z-isomers

Mechanism:

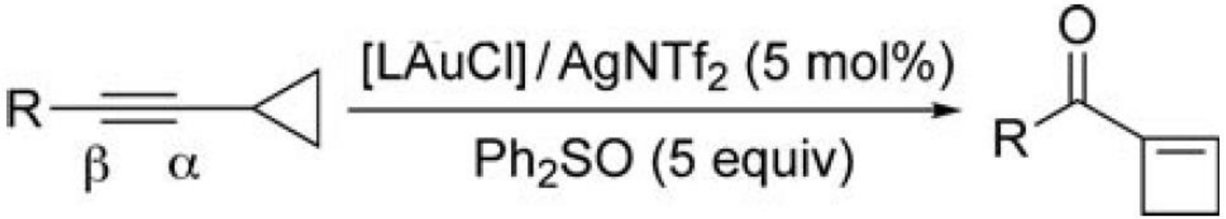




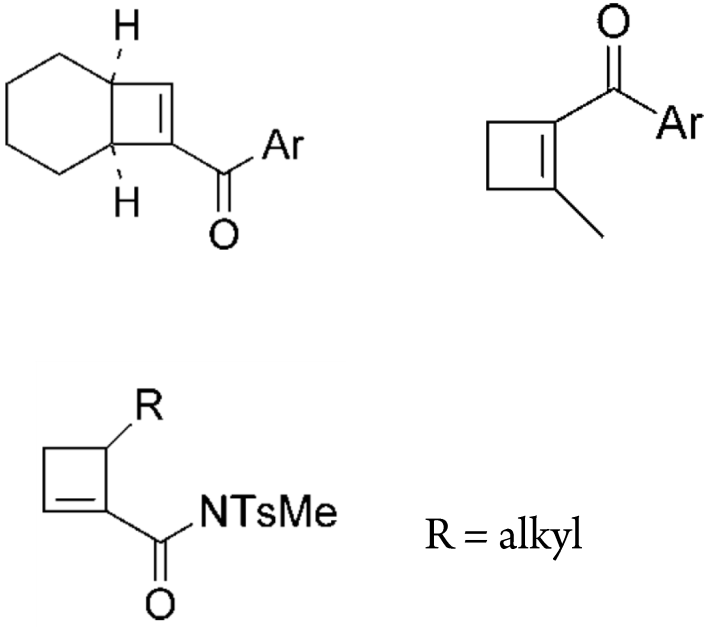
disrotation route allows an efficient overlap between two interacting p orbitals


+8.6
[+7.1]
TS-2'
+6.9
[+9.9]
TS-2
F'
+3.6
[+4.6]
TS-1'
+3.3
[+3.5]
TS-1
0.0
[0.0]
+0.62
[+0.61]
F
I'
-34
[-35]
-33
[-36]
-34
[-36]
-37
[-38]
J'
H'
G'
G
I
-34
[-35]
-34
[-36]
-34
[-35]
-37
[-38]
H
J
Ph
Me
δ+
AuPR3
O
H
+

C-C insertion: (Ring expansion of Alkynylcyclopropanes)



R = 4-MeC_6H_4 (**1b**)
R = 4-$MeOC_6H_4$ (**1c**)
R = 4-FC_6H_4 (**1d**)
R = 4-ClC_6H_4 (**1e**)
R = 4-BrC_6H_4 (**1f**)
R = 4-$MeO_2CC_6H_4$ (**1g**)
R = 3-$MeOC_6H_4$ (**1h**)
R = 3-FC_6H_4 (**1i**)
R = 3-ClC_6H_4 (**1j**)
R = 3,5-$(MeO)_2C_6H_3$ (**1k**)
R = 3,4-$(OCH_2O)C_6H_3$ (**1l**)
R = 2-naphthyl (**1m**)
R = TsNMe (**1n**)
R = TsN(*n*Pr) (**1o**)
R = MsNMe (**1p**)
R = MsNBn (**1q**)

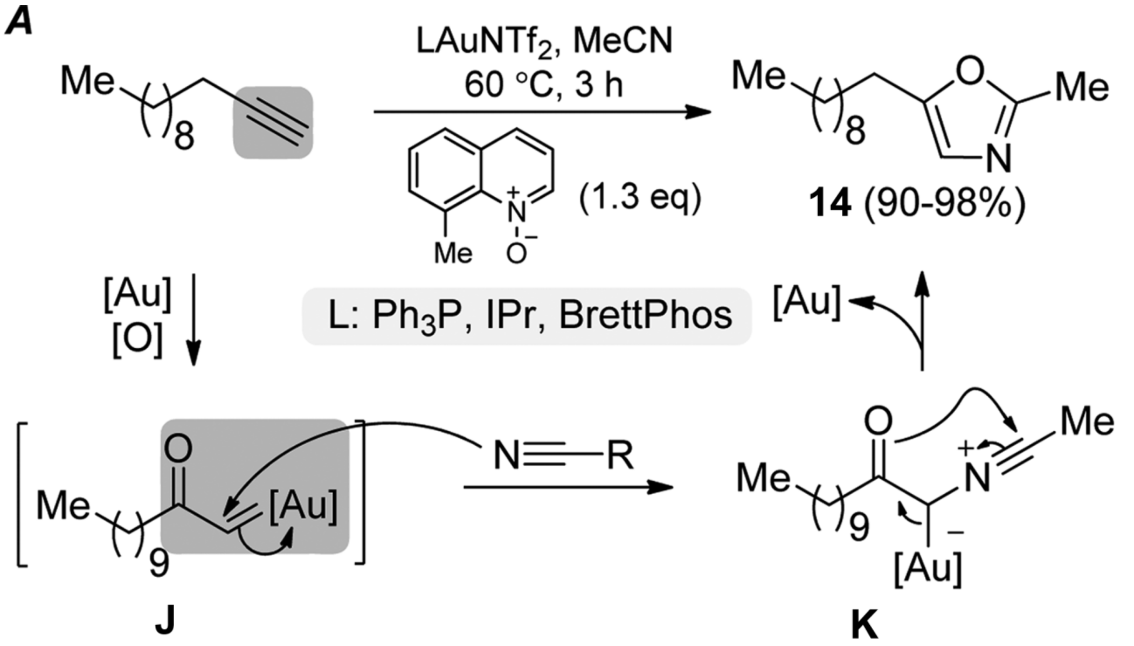


R = alkyl

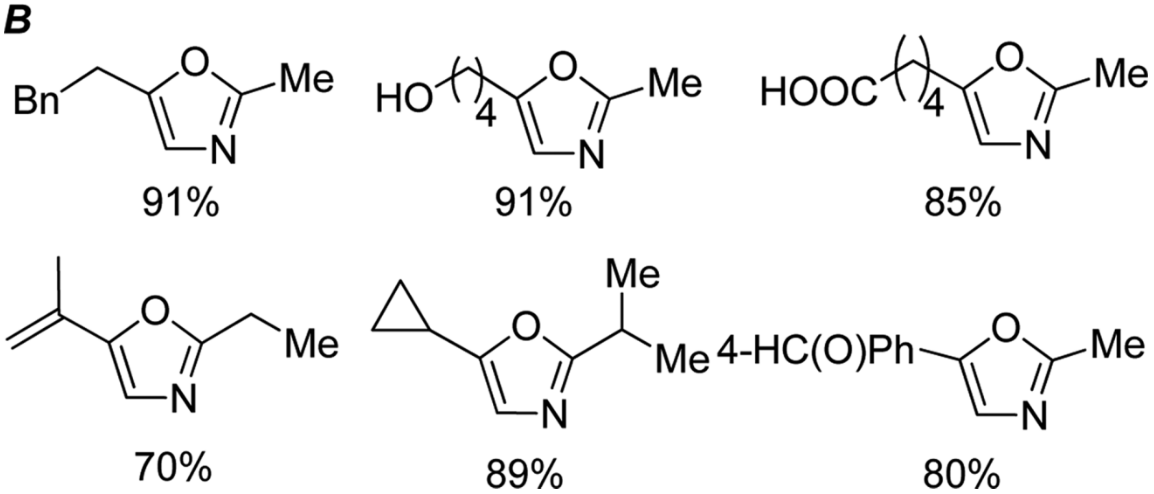
Li, C.-W.; Pati, K.; Lin, G.-Y.; Sohel, S. M. A.; Hung, H.-H.; **Liu, R.-S.*** *Angew. Chem., Int. Ed.* **2010**, *49*, 9891

- Intermolecular Alkyne Oxidation
    - Intramolecular Trapping
    - Intermolecular Trapping

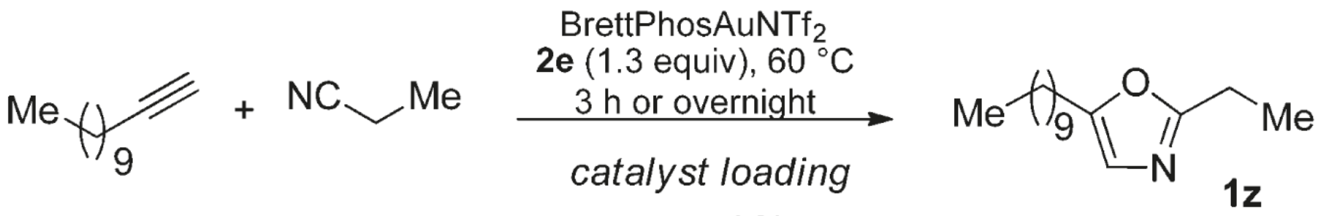
Intermolecular trapping



nitriles as both the reacting partner and the reaction solvent

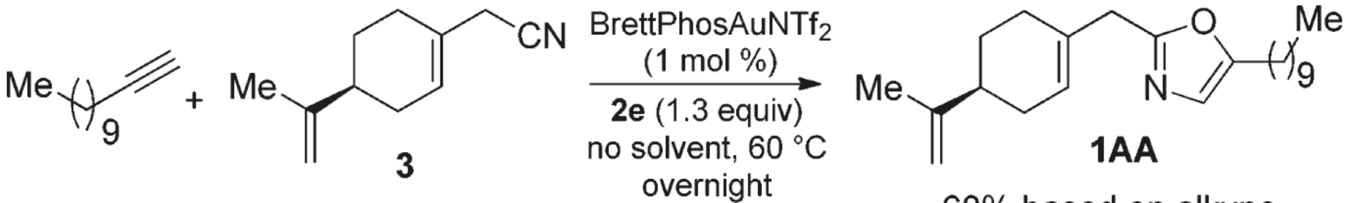


He, W.; Li, C.; **Zhang, L.** *J. Am. Chem. Soc.* **2011**, *133*, 8482.



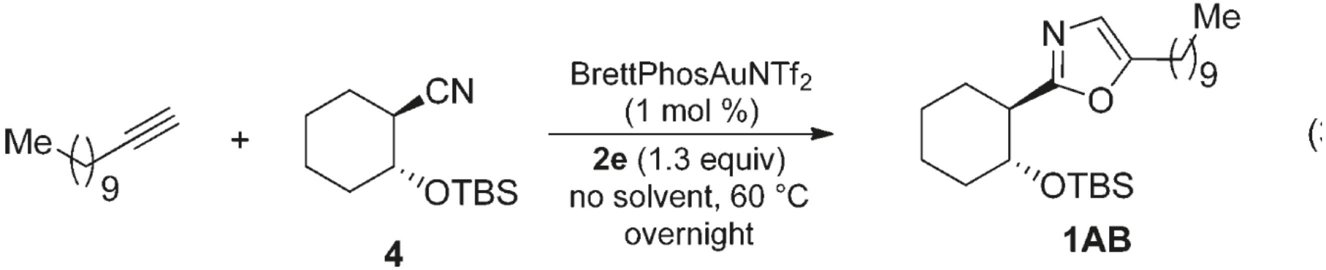
1z

	catalyst loading	
solvent (0.1 M)	5 mol %	85%
3 equiv (6 equiv of PhCl as solvent)	5 mol %	50%
3 equiv (no solvent)	5 mol %	60%
3 equiv (no solvent)	1 mol %	59%



3
(3 equiv)

1AA
60% based on alkyne
68% based on recovered nitrile

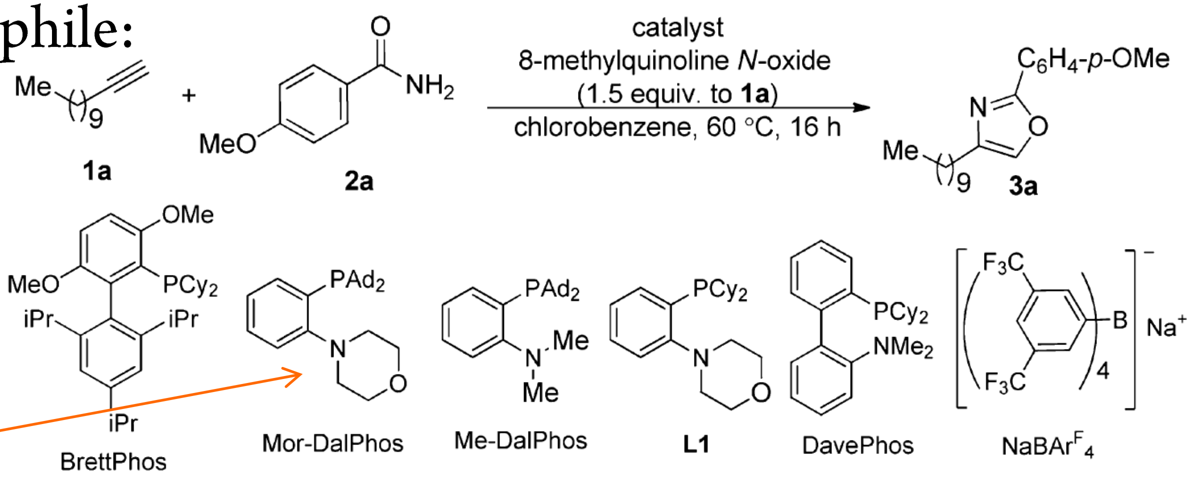


4
(3 equiv)

1AB
64% based on alkyne
81% based on recovered nitrile

He, W.; Li, C.; **Zhang, L.** *J. Am. Chem. Soc.* **2011**, *133*, 8482.

Amides as nucleophile:

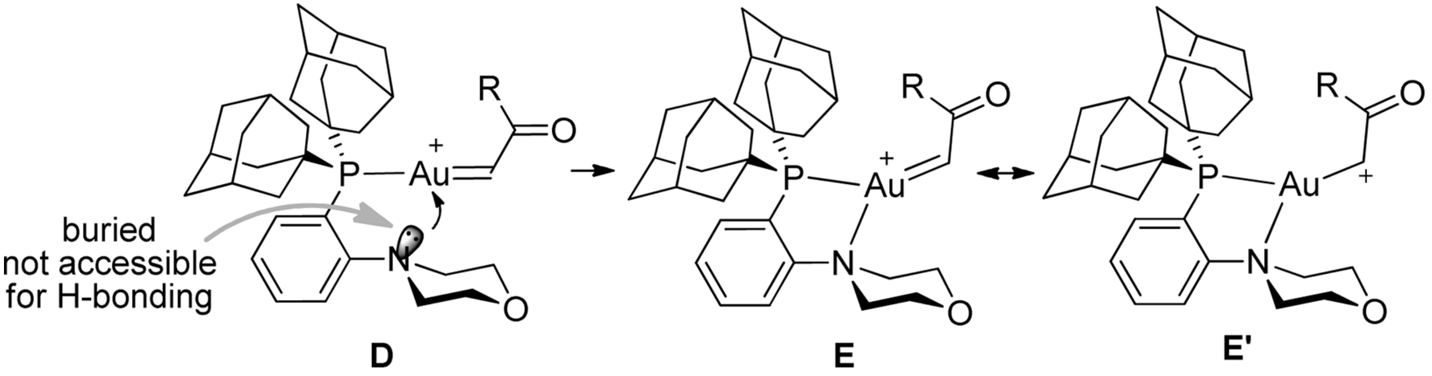


neighboring amino group was crucial.

entry	**1a/2a**	catalyst	yield^b
1	1:1.2	$\mathrm{Ph_3PAuNTf_2}$ (5 mol %)	0^c
2	1:1.2	Cy-JohnPhosAuNTf$_2$ (5 mol %)	0^c
3	1:1.2	IPrAuNTf$_2$ (5 mol %)	0^c
4	1:1.2	$\mathrm{(4\text{-}CF_3Ph)_3PAuNTf_2}$ (5 mol %)	0^c
5	1:1.2	BrettPhosAuNTf$_2$ (5 mol %)	$4\%^c$
6	1:1.2	Mor-DalPhosAuNTf$_2$ (5 mol %)	58%
7	1:1.2	Mor-DalPhosAuCl (5 mol %)/AgSbF$_6$ (5 mol %)	37%
8	1:1.2	Mor-DalPhosAuCl (5 mol %)/AgOTf (5 mol %)	30%
9	1:1.2	Mor-DalPhosAuCl (5 mol %)/NaBAr$^F{}_4$ (10 mol %)	64%
10	1:1.2	Me-DalPhosAuCl (5 mol %)/NaBAr$^F{}_4$ (10 mol %)	64%
11	1:1.2	**L1**AuCl (5 mol %)/NaBAr$^F{}_4$ (10 mol %)	52%
12	1:1.2	DavePhosAuCl (5 mol %)/NaBAr$^F{}_4$ (10 mol %)	0^c
13	1.5:1	Mor-DalPhosAuCl (5 mol %)/NaBAr$^F{}_4$ (10 mol %)	$87\%^d$
14	1.5:1	Mor-DalPhosAuCl (5 mol %)/NaBAr$^F{}_4$ (10 mol %)	$59\%^e$
15	1.5:1	Mor-DalPhosAuCl (5 mol %)/NaBAr$^F{}_4$ (10 mol %)	$78\%^f$

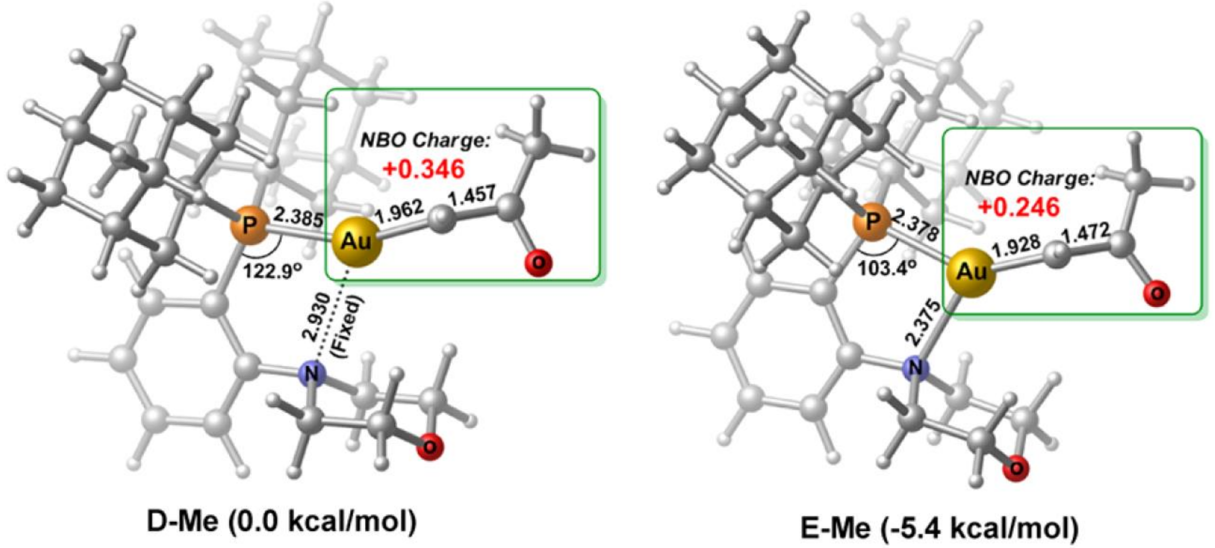
The role of neighboring amino group:

a)



the carbene center would be less cationic!

b) supported by DFT calculations



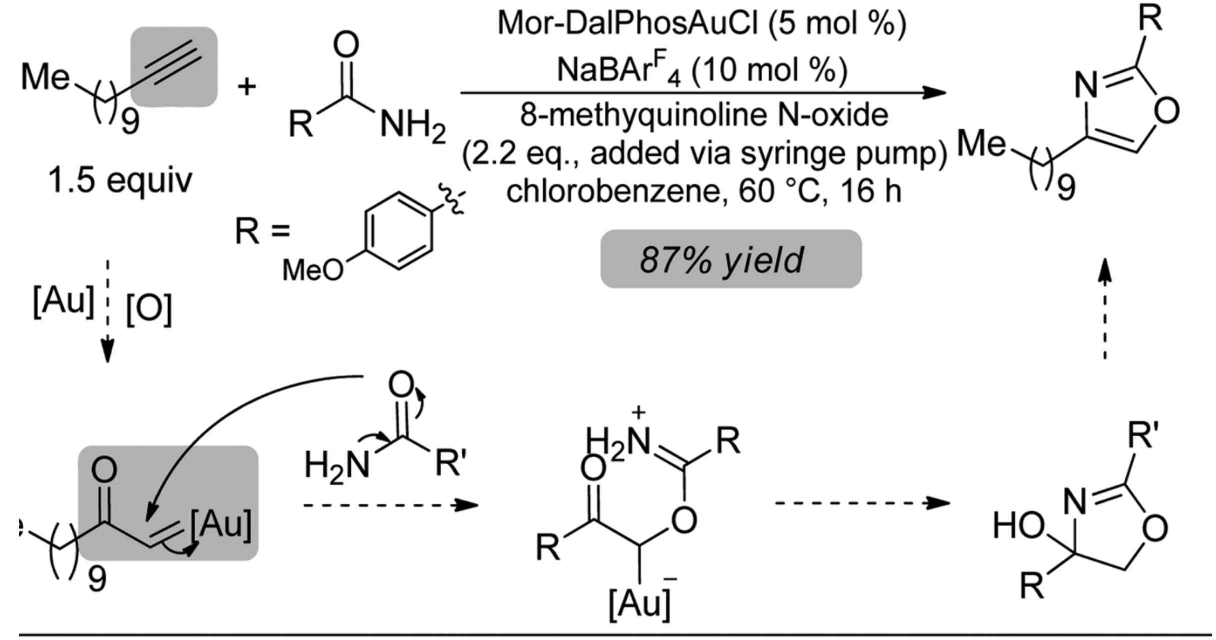
D-Me (0.0 kcal/mol)

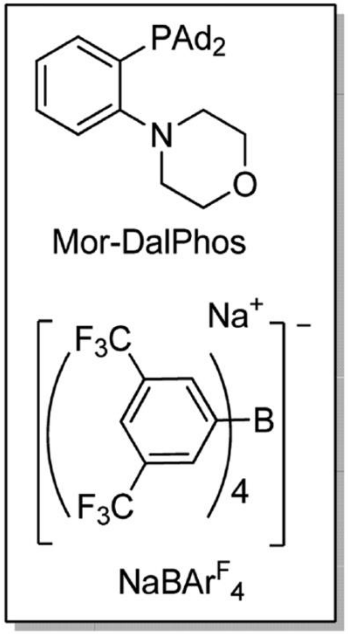
E-Me (-5.4 kcal/mol)

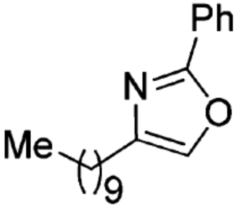
electrophilicity of the carbene center might be attenuated

Luo, Y.; Ji, K.; Li, Y.; **Zhang, L.** *J. Am. Chem. Soc.* **2012**, *134*, 17412.

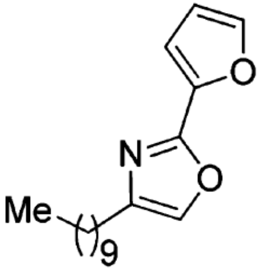
Amides as nucleophile:



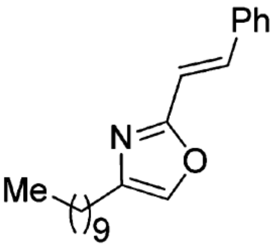




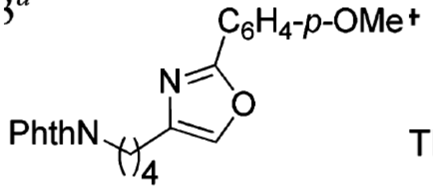
3c, 72%



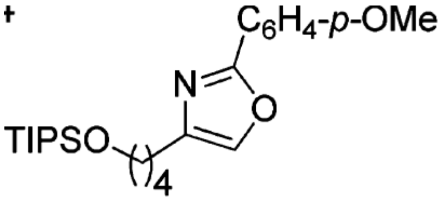
3g, 73%



3i, 79%



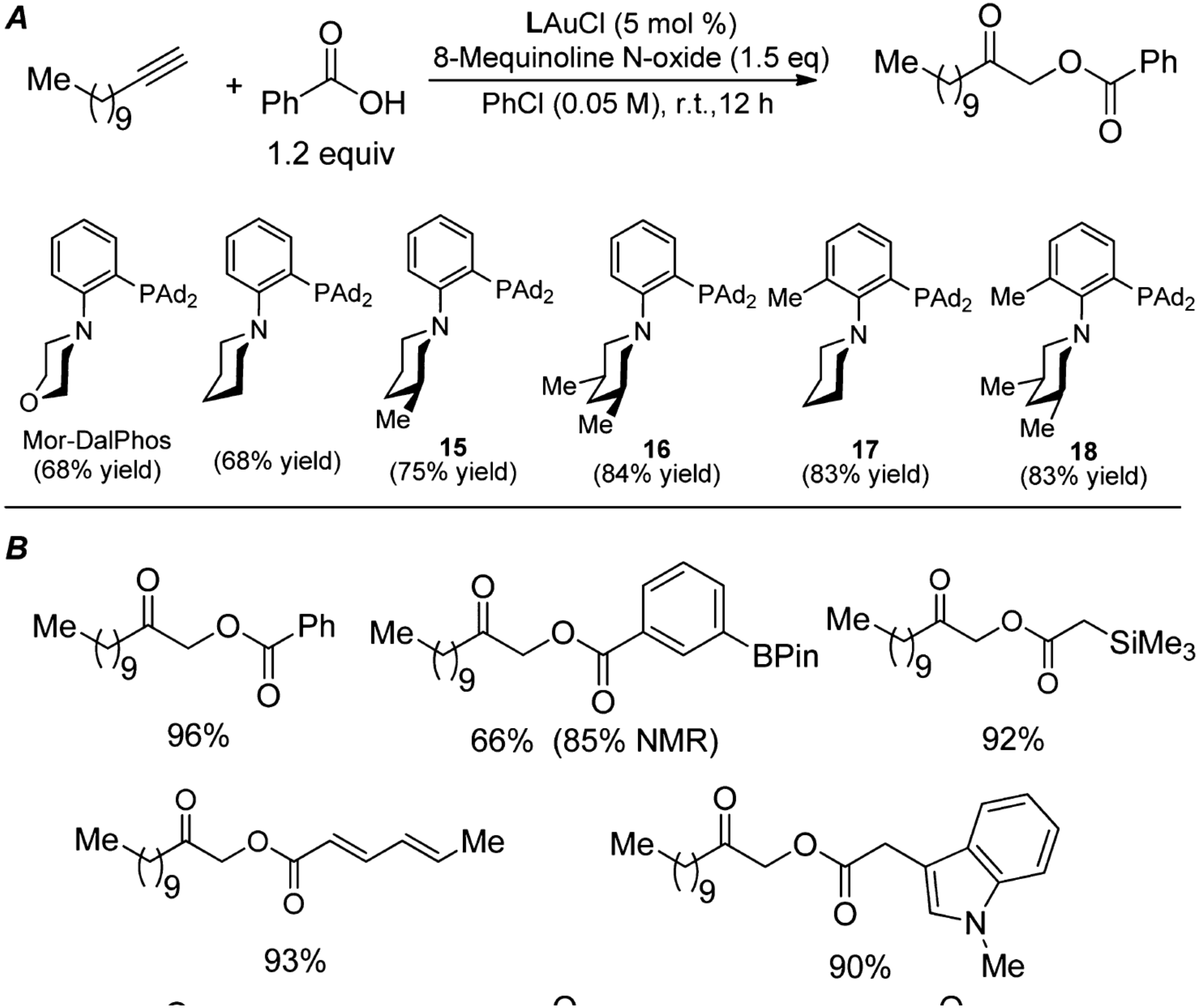
3n, 82%



3o, 71%

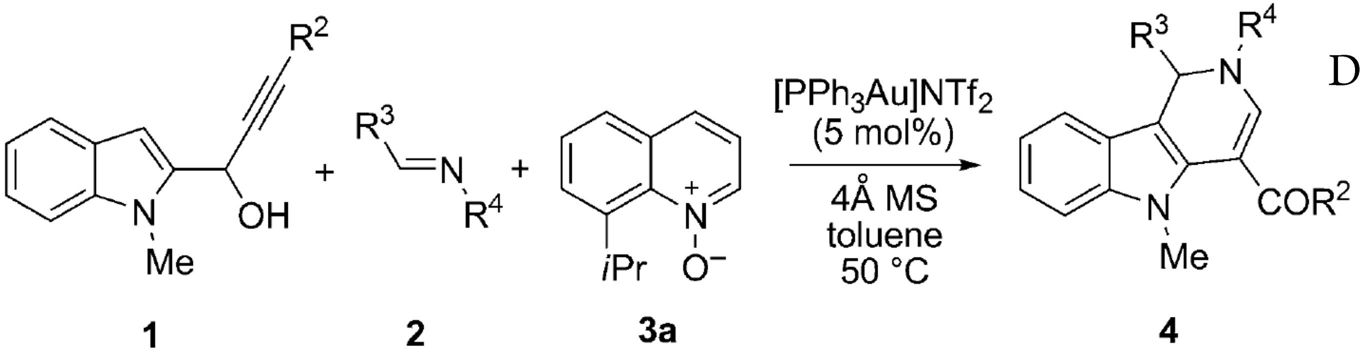
Luo, Y.; Ji, K.; Li, Y.; **Zhang, L.** *J. Am. Chem. Soc.* **2012**, *134*, 17412.

Carboxylic acid as nucleophile:

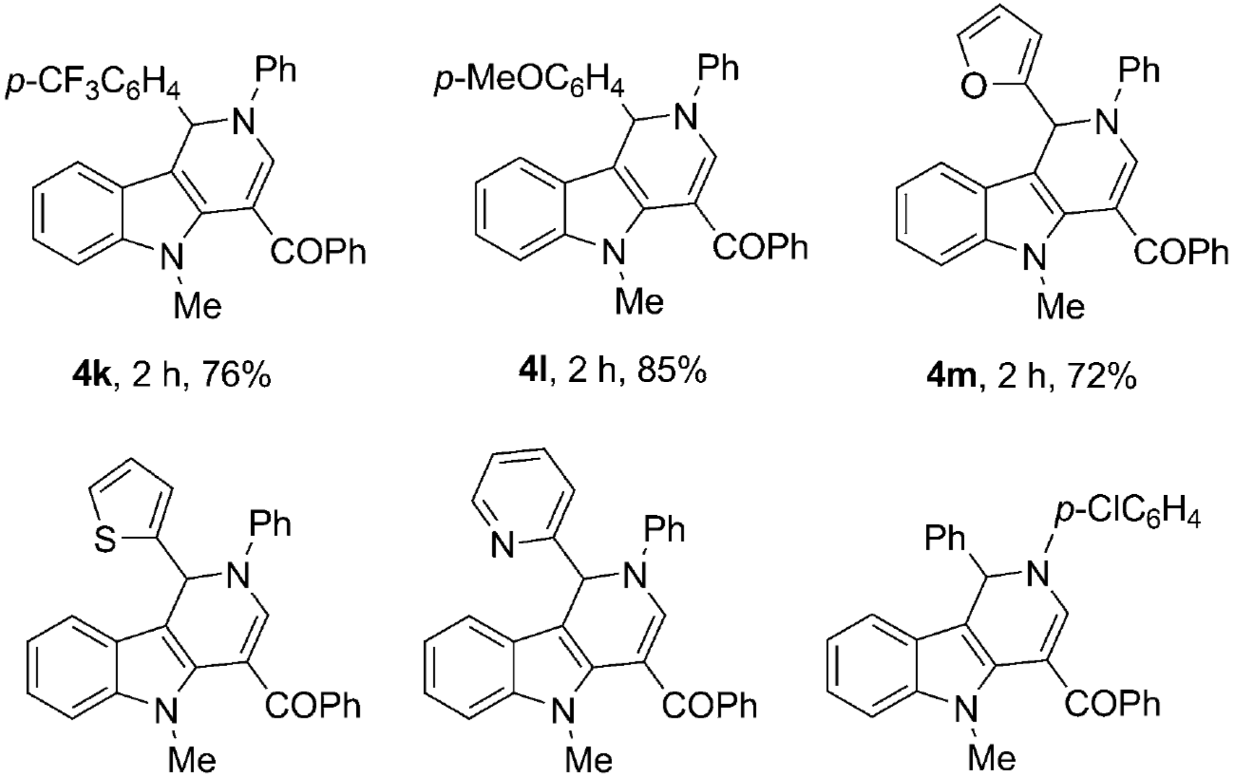


Ji, K.; Zhao, Y.; **Zhang, L.** *Angew. Chem., Int. Ed.* **2013**, *52*, 6508.

Dihydro-gama-Carbolines



1 **2** **3a** **4**



4k, 2 h, 76%

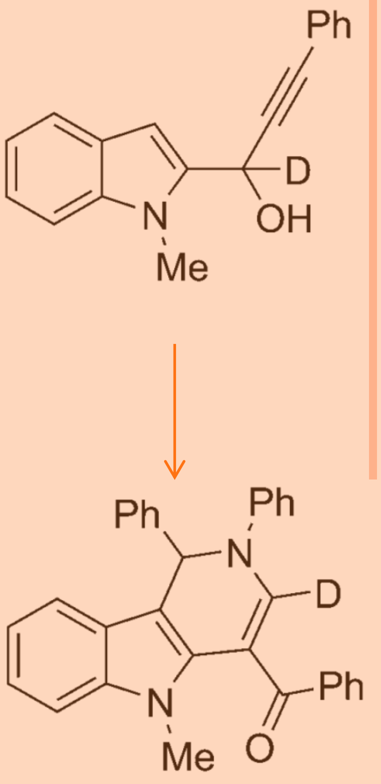
4l, 2 h, 85%

4m, 2 h, 72%

4n, 2 h, 78%

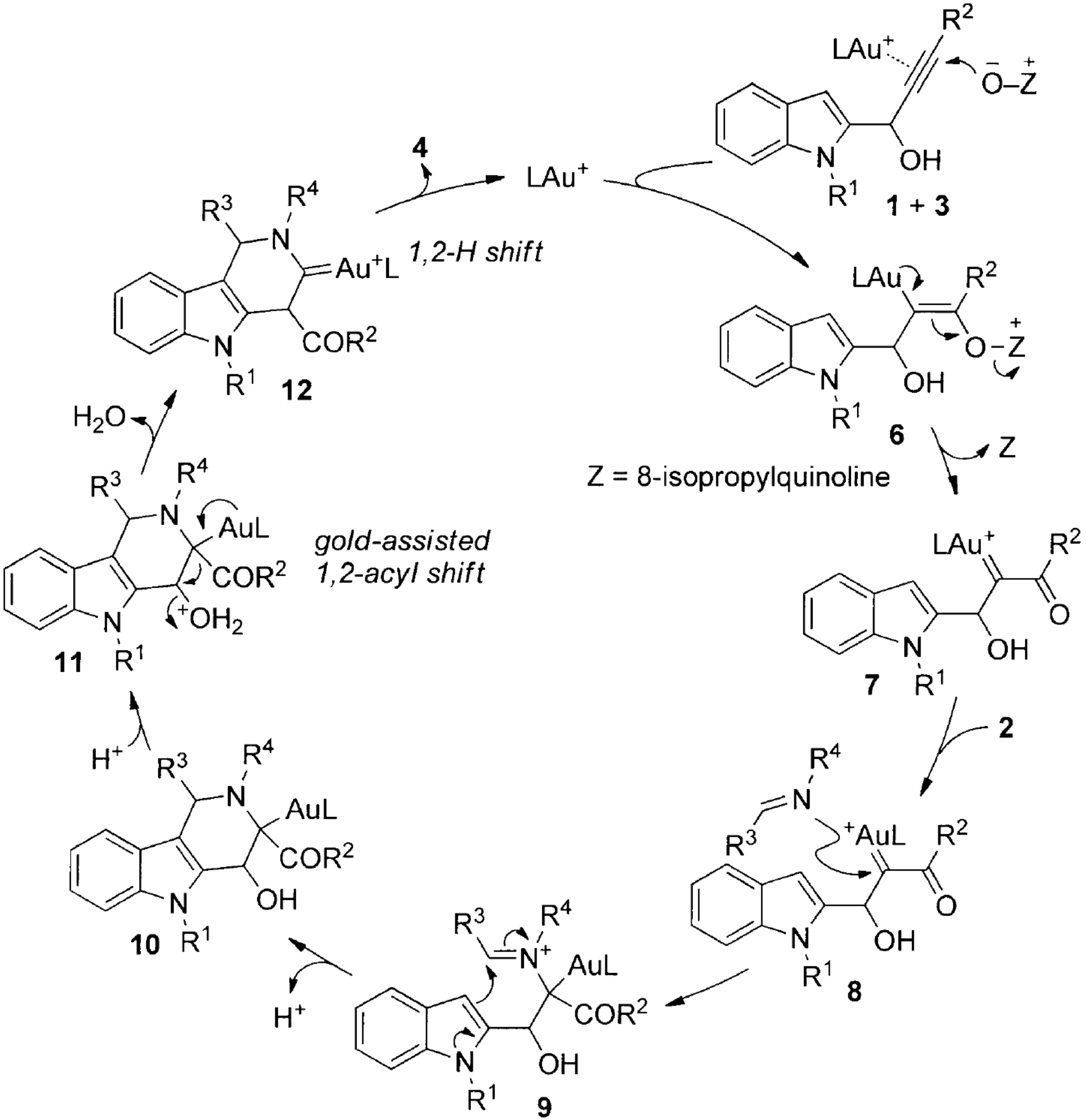
4o, 4 h, 79%

4p, 2 h, 88%

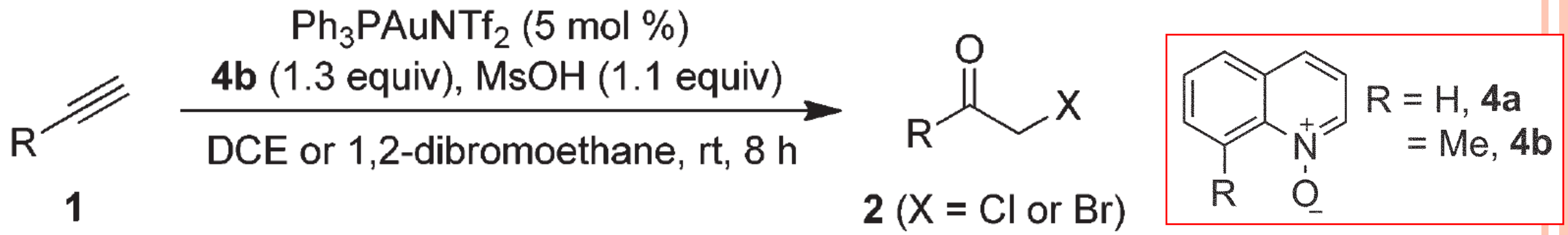


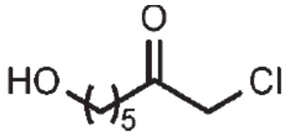
[D]**4a**, 86%; D = 96%

Wang, L.; Xie, X.; **Liu, Y.** *Angew. Chem., Int. Ed.* **2013**, *52*, 13302

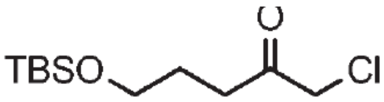


Z = 8-isopropylquinoline

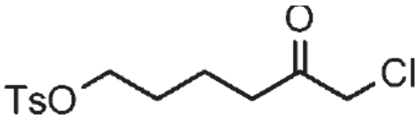




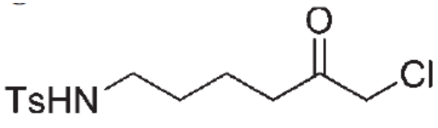
2b, 58%



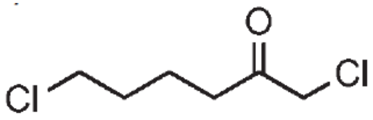
2c, 42%



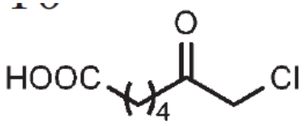
2f, 65%



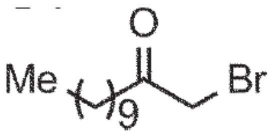
2i, 56%



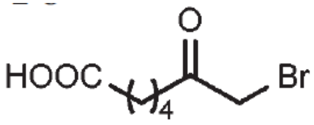
2h, 51%



2k, 60%



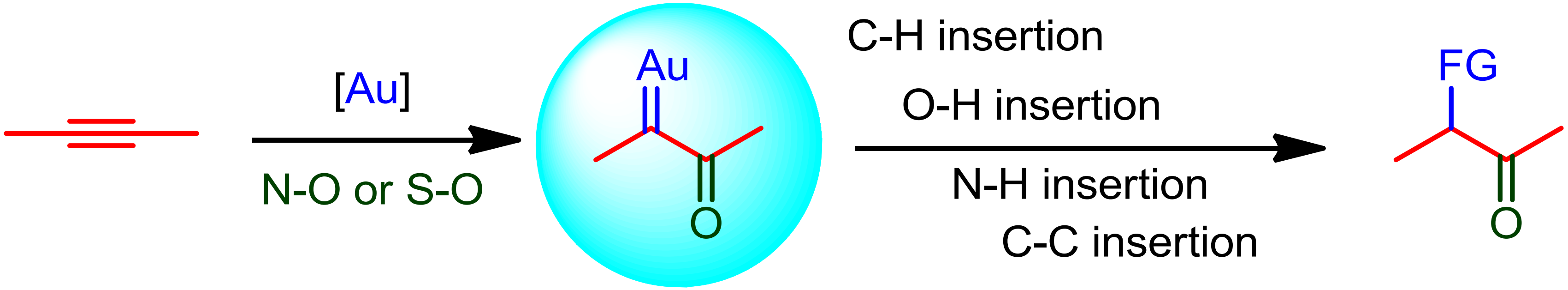
2o, 68%



2q, 56%

He, W.; Xie, L.; Xu, Y.; **Xiang, J.;*** **Zhang, L.*** *Org. Biomol. Chem.*, **2012**, *10*, 3168

Summary:

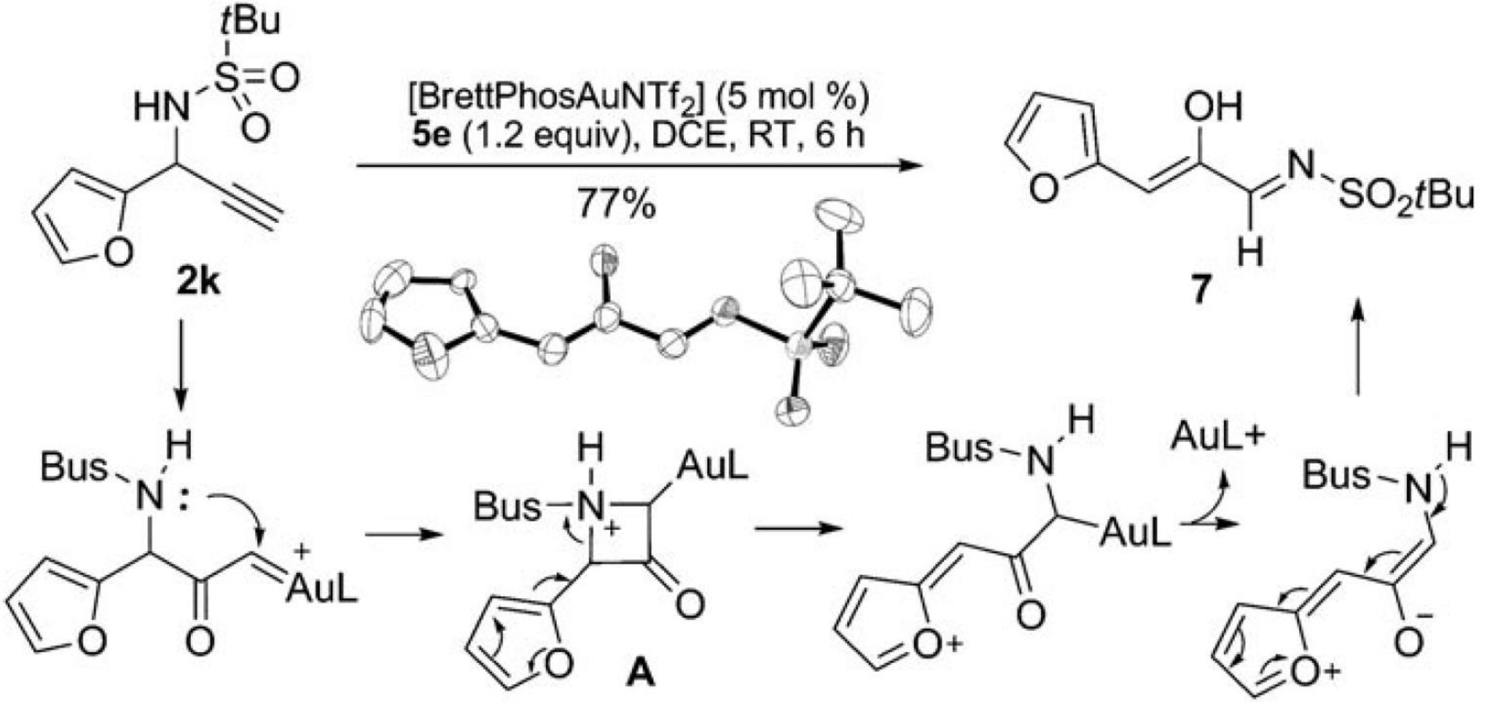


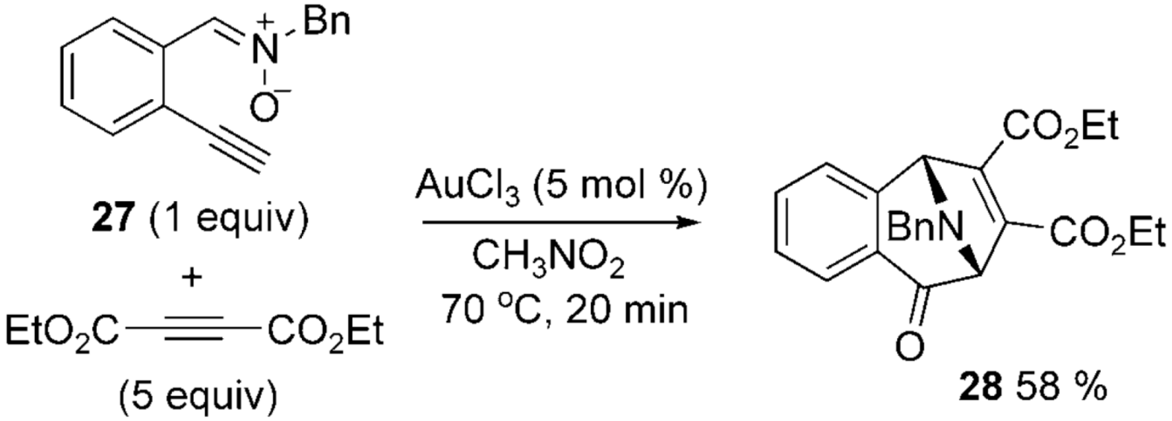
Prospects:

1) more atom-economic and greener oxidants;
2) a broad range of nucleophiles as trapping partners;
3) More details of the mechanism;
4) lowering the catalyst loading

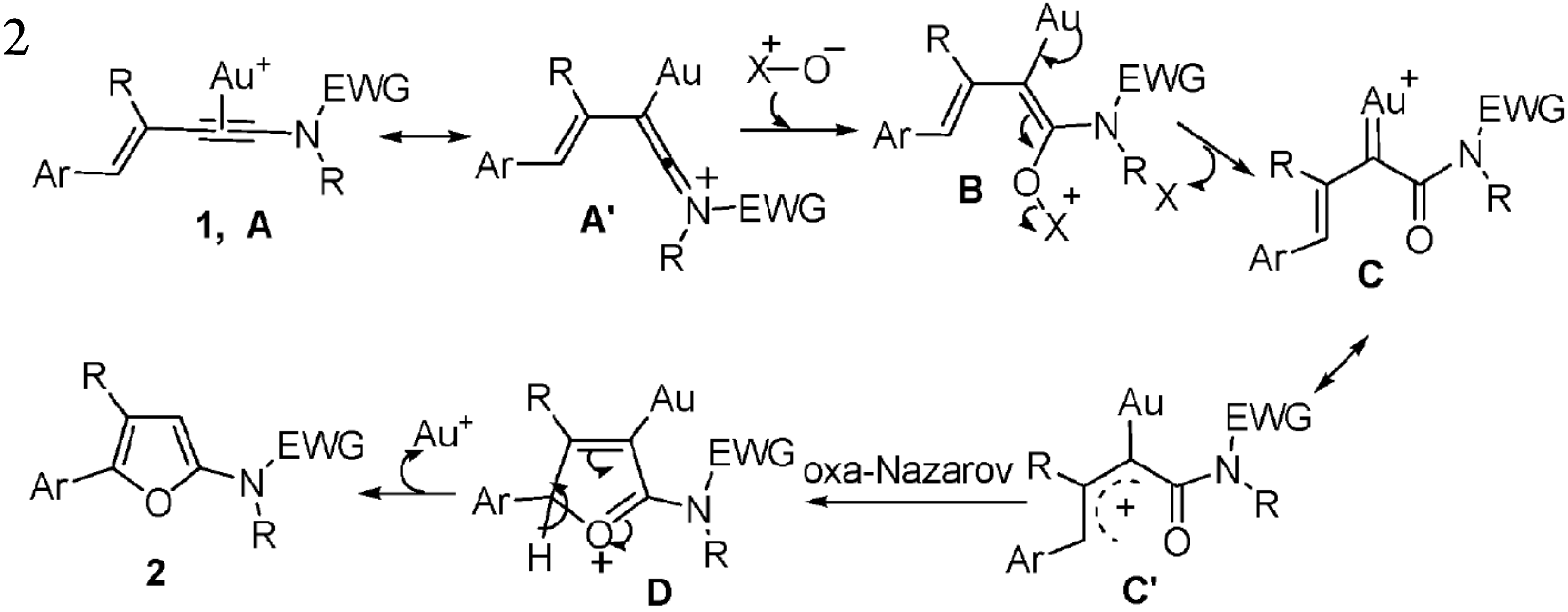
Thank you!

1

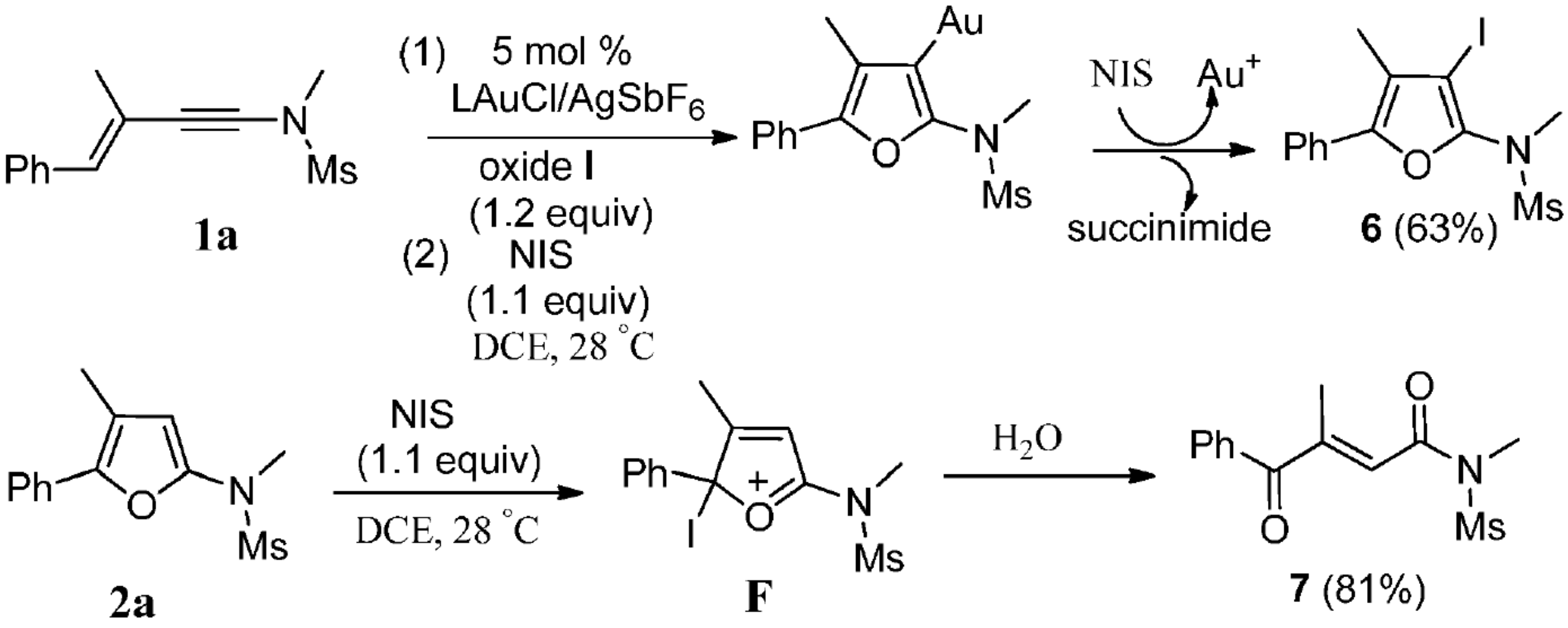

tBu
HN
S
O
O
[BrettPhosAuNTf2] (5 mol %)
5e (1.2 equiv), DCE, RT, 6 h
77%
OH
N
SO2tBu
H
O
2k
7
Bus
N
H
AuL
+
A
AuL+
O+
O-


+
N
Bn
O−
27 (1 equiv)
+
EtO2C
CO2Et
(5 equiv)
AuCl3 (5 mol %)
CH3NO2
70 °C, 20 min
CO2Et
CO2Et
BnN
O
28 58 %

2

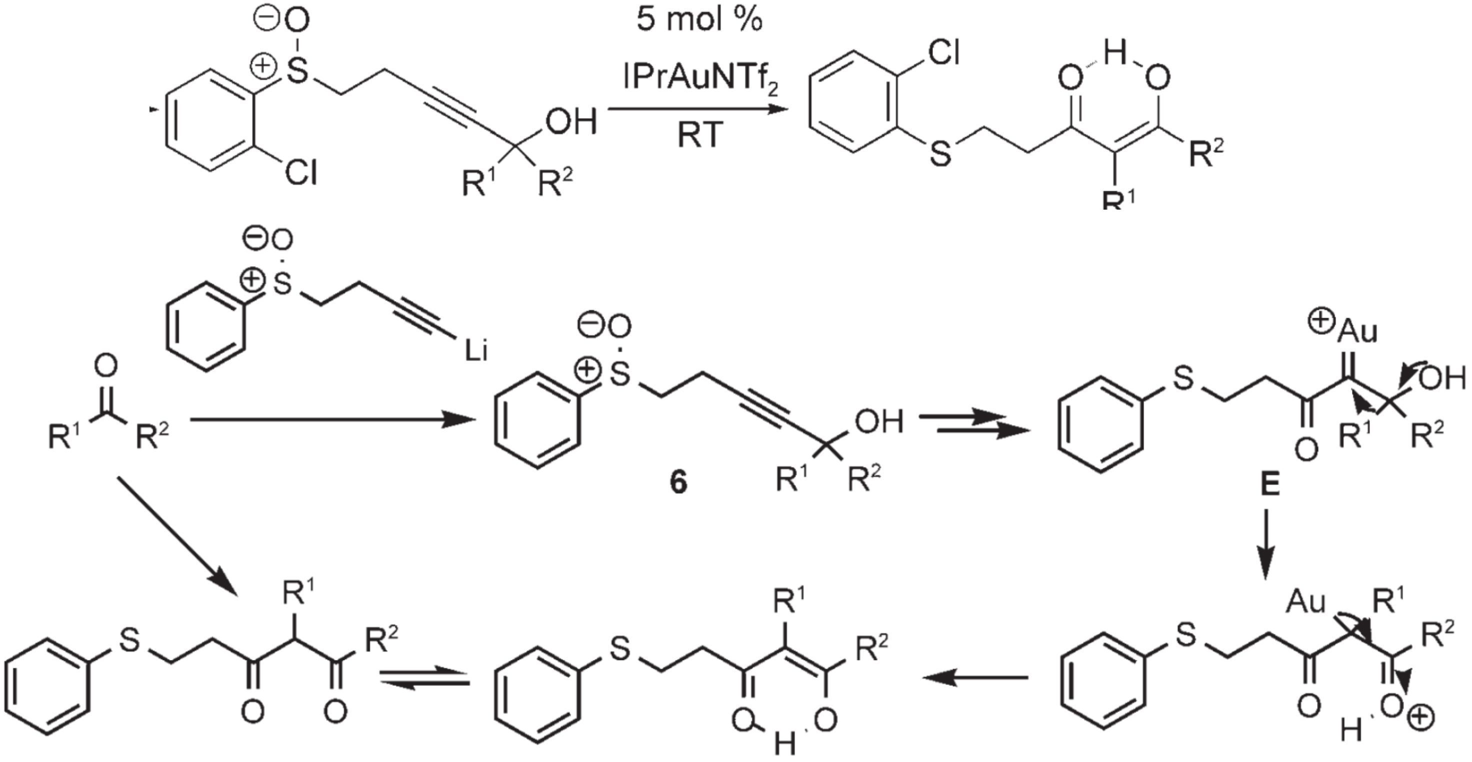


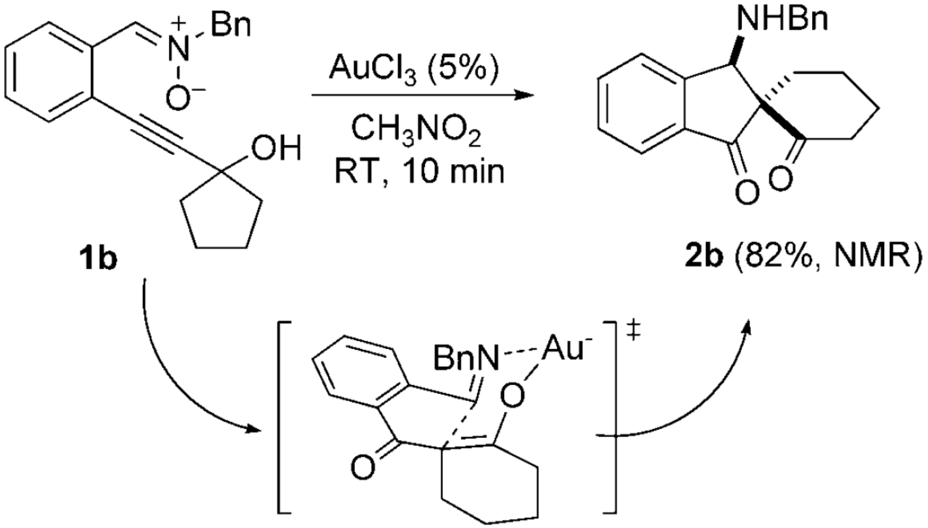
1, A
A'
B
C
C'
D
2
oxa-Nazarov
Au⁺
EWG
Ar
R



1a
(1) 5 mol % LAuCl/AgSbF$_6$
oxide I (1.2 equiv)
(2) NIS (1.1 equiv)
DCE, 28 °C
NIS
Au⁺
succinimide
6 (63%)
2a
NIS (1.1 equiv)
DCE, 28 °C
F
H_2O
7 (81%)

3


5 mol %
IPrAuNTf$_2$
RT
Cl
OH
R^1
R^2
Li
6
E
$^{\oplus}$Au
Au
H


Bn
OH
1b
AuCl$_3$ (5%)
CH$_3$NO$_2$
RT, 10 min
NHBn
2b (82%, NMR)
BnN
Au$^-$
‡