

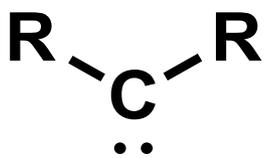
sp^3 C-H insertion by α -Oxo Gold Carbene

B4 Kei Ito

2016. 1. 30

1. Introduction

About Carbene

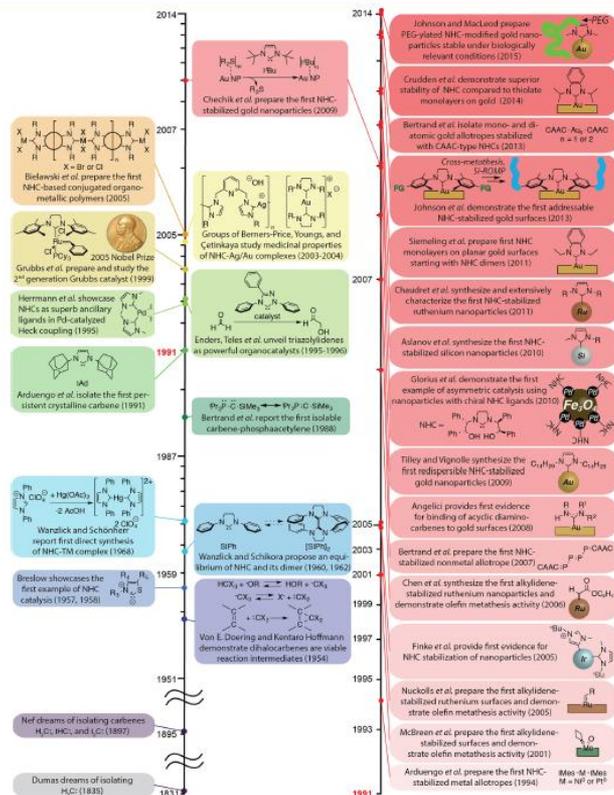


Brief history of carbene (~2000)

Carbene ... Neutral compounds featuring a divalent carbon atom with only six electrons in its valence shell

Chem. Rev. 2000, 100, 39

- 1835 Dumas firstly proposed to prepare carbene CH₂ :
- 1925 Chugaev firstly synthesized carbene metal complex
- 1954 Discovery of cyclopropanation reaction
- 1957 Appearance of NHC catalysts
- 1988 Bertland firstly reported isolable carbene
- 1999 2nd generation Grubbs catalyst (Nobel Prize 2005) etc.



Chem. Rev., 2015, 115, 11503

Figure 1. Timelines depicting major milestones in the development of carbene chemistry and its major applications. Key examples of carbenes at surface chemistry from 1994 to 2015 are shown at right.

Singlet carbene and Triplet carbene

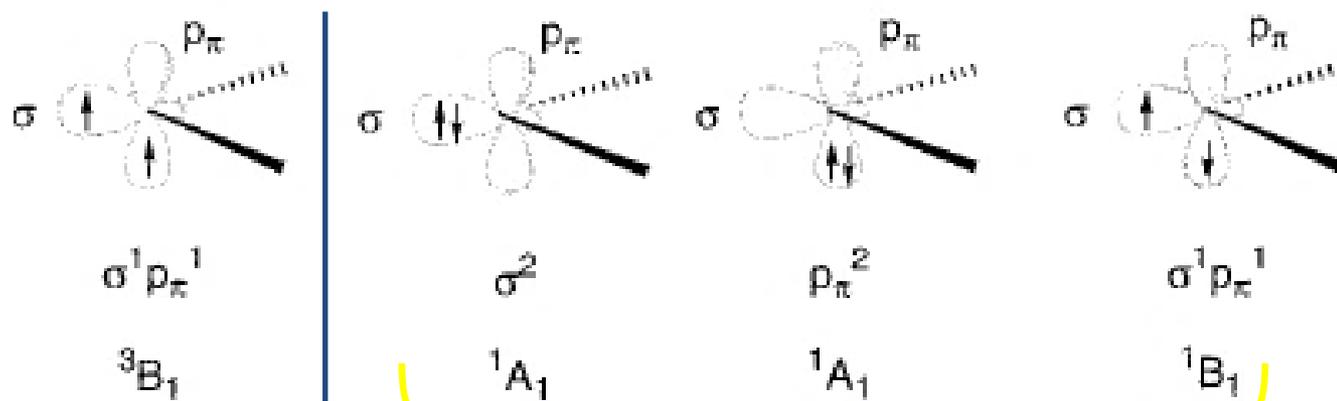
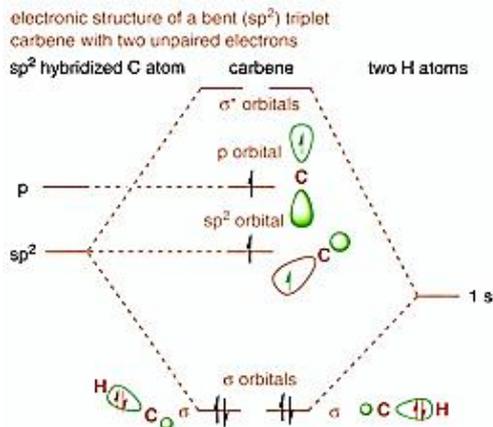


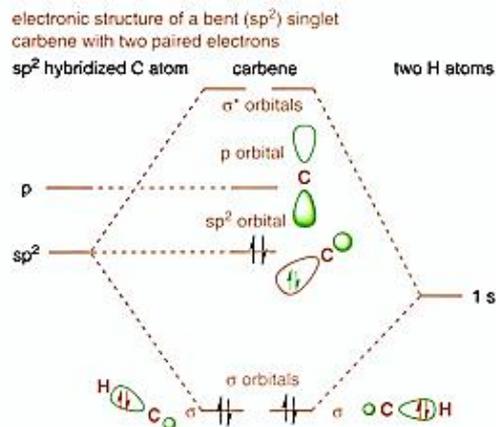
Figure 3. Electronic configurations of carbenes.

Chem. Rev., 2000, 100, 39

Triplet carbene

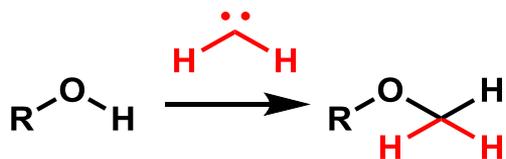


Singlet carbene

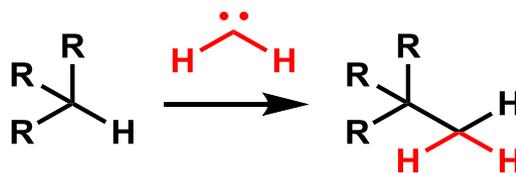


Representative reactions of carbene

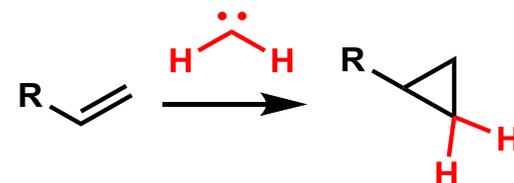
O-H insertion



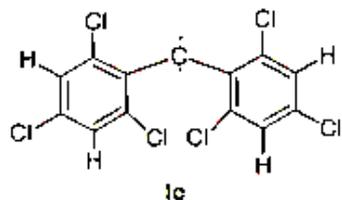
C-H insertion



C=C insertion (Cyclopropanation)

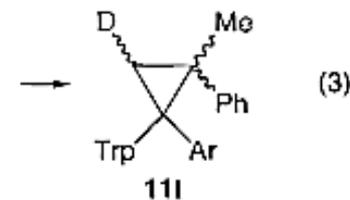
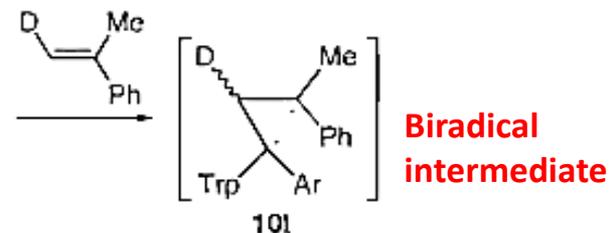
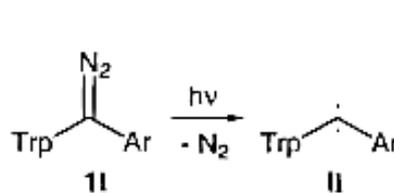


• Triplet carbene reacts radically



Acta.Chem.Scand., 1992, 46, 680

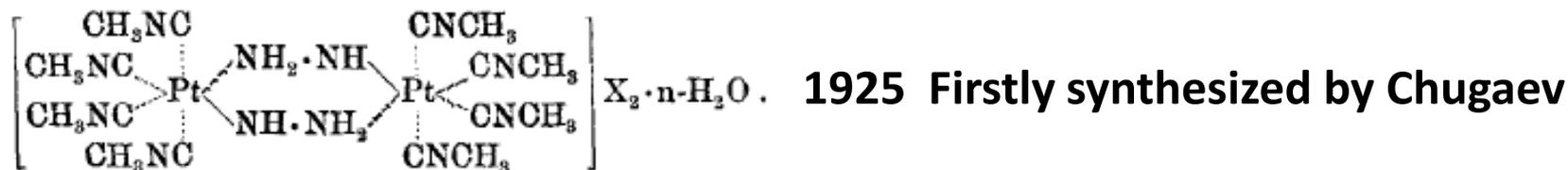
Dimerization



JACS, 1995, 117, 11355

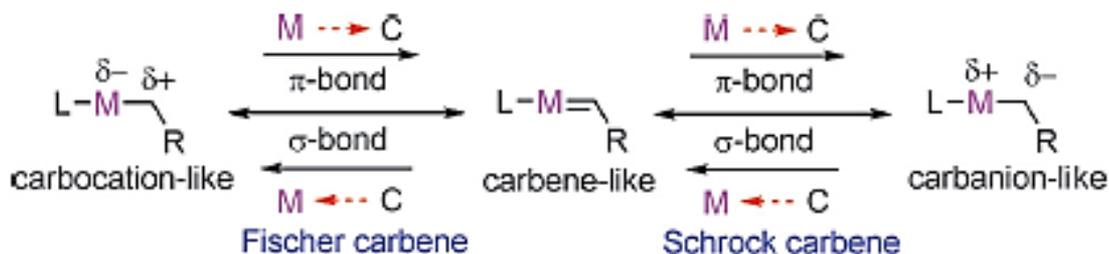
Cyclopropanation with loss of stereochemistry

Carbene metal complex

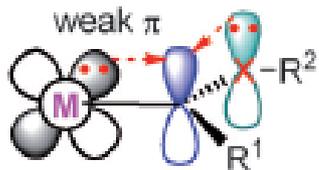


Anorg. Allg. Chem., **1925**, 148, 37

▪ Fischer carbene and Schrock carbene

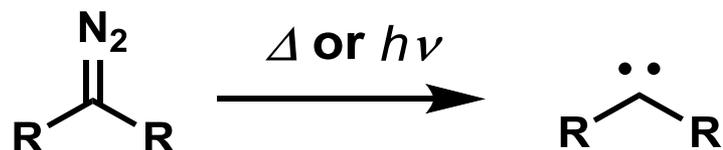


Fischer carbene	Schrock carbene
Carbocation-like (electrophilic)	Carbanion-like (nucleophilic)
weak π back-donation	strong π back-donation
adjacent to heteroatom (stabilization by π donation)	adjacent to C or H atom (no stabilization)



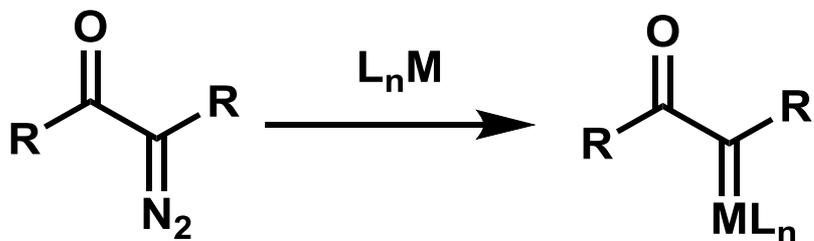
Fischer metal carbene

Generation of carbene from diazo compound

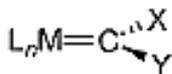


Thermally or photochemically generated carbenes \longrightarrow Unselective

Metal carbene from α -diazo carbonyl compound



M = Ag, Au, Co,
Cu, Fe, Rh,
Ru



X or Y = H, R, Ar,
COR, COOR,
CONR₂, SO₂R,
P(O)(OR)₂

*Electron withdrawal by L, Y, or X
increases reactivity, decreases selectivity.*

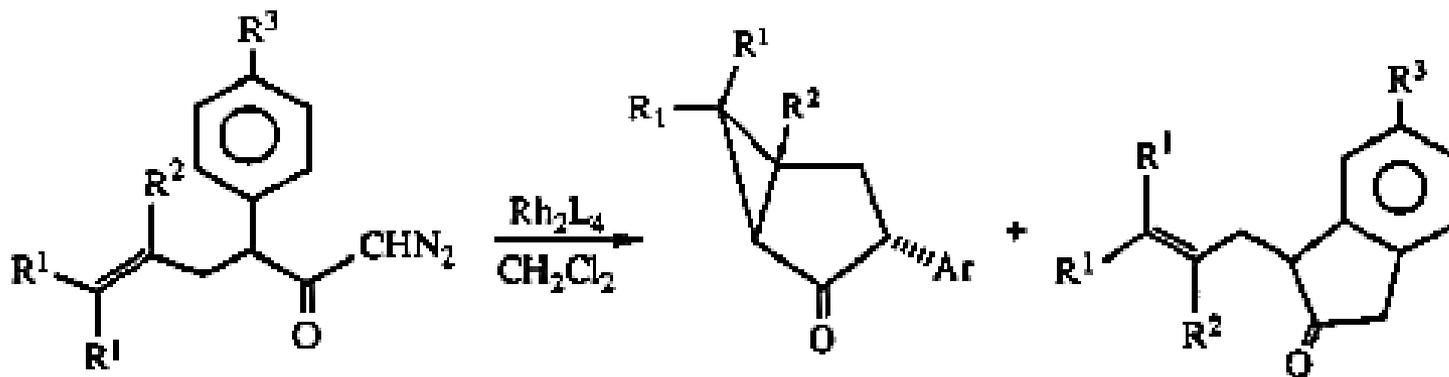
*Steric influences by L, Y, or X changes
stereoselectivity*

M (Rh, Ru, Cu, Au etc.) and L control the reactivity and selectivity of carbene center

Reactivity (electrophilicity) is depend on the metal(+ligand) and substituent of carbene center

Ligands affect the reactivity and selectivity(1)

ex.1 Chemoselectivity

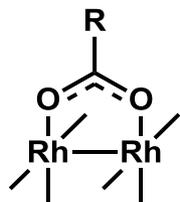


1a: $\text{R}^1 = \text{R}^3 = \text{H}$, $\text{R}^2 = \text{Me}$

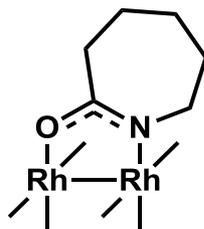
1b: $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Me}$, $\text{R}^3 = \text{OMe}$

1c: $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{R}^3 = \text{H}$

1d: $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$



$\text{R} = \text{C}_3\text{F}_7$ $\text{Rh}_2(\text{pfb})_4$

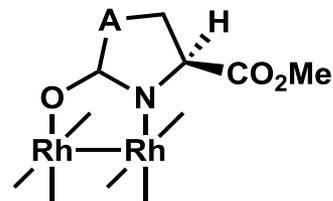
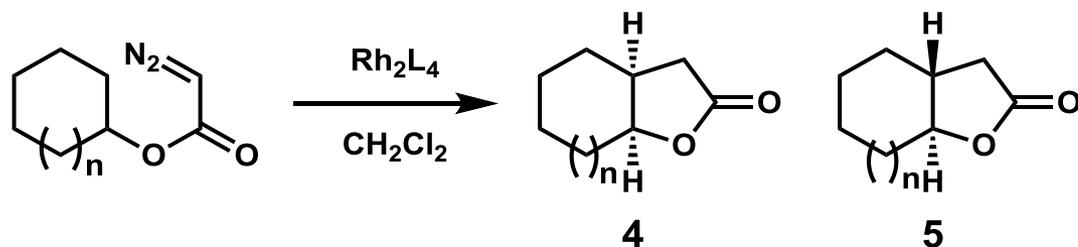


$\text{Rh}_2(\text{cap})_4$

compd	R^1	R^2	R^3	Rh_2L_4	isolated yield, %	rel yield, %	
						2	3
a	H	Me	H	$\text{Rh}_2(\text{OAc})_4$	92	48	52
				$\text{Rh}_2(\text{pfb})_4$	86	0	100
				$\text{Rh}_2(\text{cap})_4$	75	100	0
b	H	Me	OCH ₃	$\text{Rh}_2(\text{OAc})_4$	83	60	40
				$\text{Rh}_2(\text{pfb})_4$	80	0	100
				$\text{Rh}_2(\text{cap})_4$	80	100	0
c	Me	H	H	$\text{Rh}_2(\text{OAc})_4$	88	45	55
				$\text{Rh}_2(\text{pfb})_4$	82	0	100
				$\text{Rh}_2(\text{cap})_4$	97	100	0
d	H	H	H	$\text{Rh}_2(\text{OAc})_4$	99	67	33
				$\text{Rh}_2(\text{pfb})_4$	95	0	100
				$\text{Rh}_2(\text{cap})_4$	72	100	0

Ligands affect the reactivity and selectivity(2)

ex.2 Stereoselectivity



A=CH₂: Rh₂(5S-MEPY)₄

A=O: Rh₂(4S-MEOX)₄

A=NAc: Rh₂(4S-MACIM)₄

diazoacetate	catalyst	isolated yield, %	4:5	% ee	
				4 ^b	5 ^b
cyclohexyl	Rh ₂ (4S-MACIM) ₄	70	99:1	97	65
	Rh ₂ (5R-MEPY) ₄ ^c	65	75:25	97	91
	Rh ₂ (4S-MEOX) ₄	50	55:45	96	95
	Rh ₂ (OAc) ₄	46	40:60		
cycloheptyl	Rh ₂ (4S-MACIM) ₄	75	99:1	96	61
	Rh ₂ (5R-MEPY) ₄ ^c	80	71:29	96	85
	Rh ₂ (4S-MEOX) ₄	68	58:42	97	94
	Rh ₂ (OAc) ₄	29	30:70		
cyclooctyl	Rh ₂ (4S-MACIM) ₄	62	99:1	97	59
	Rh ₂ (5R-MEPY) ₄ ^c	80	72:28	97	95
	Rh ₂ (4S-MEOX) ₄	60	57:43	99	95
	Rh ₂ (OAc) ₄	33	29:71		

2. Gold carbene

Characteristics of Gold

79Au

Group 11, 6th period

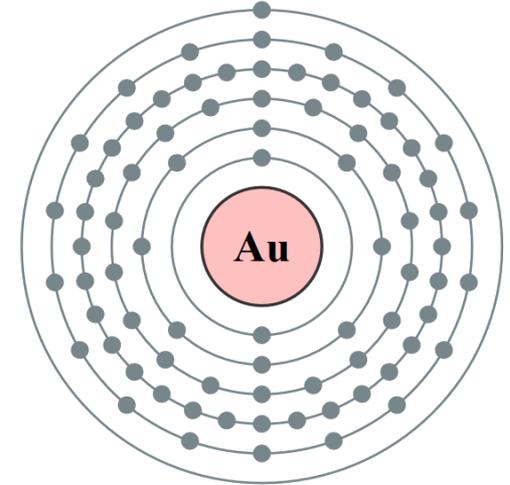
Electron configuration [Xe], 4f¹⁴, 5d¹⁰, 6s¹

Oxidation state 5, 4, 3, 2, 1, -1
especially Au(III) and Au(I) are stable
(work as soft Lewis acid)

Most electronegative transition metal in the **Pauling's scale**

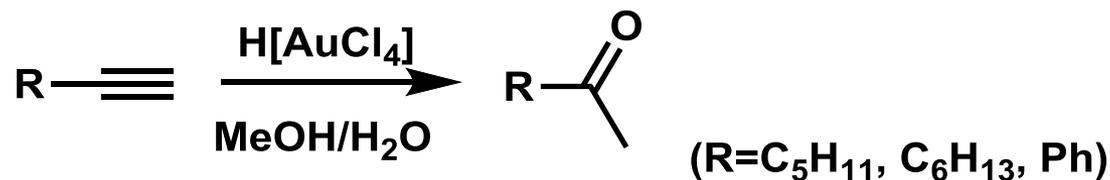


Gold carbene exhibits special characteristics

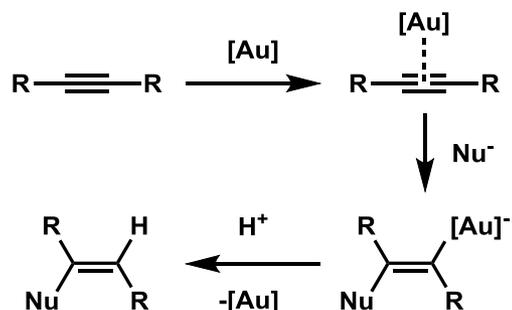


Gold catalysts can activate alkyne(1)

Soft Lewis acidities → Activate alkyne, allene, alkene for attack of nucleophile

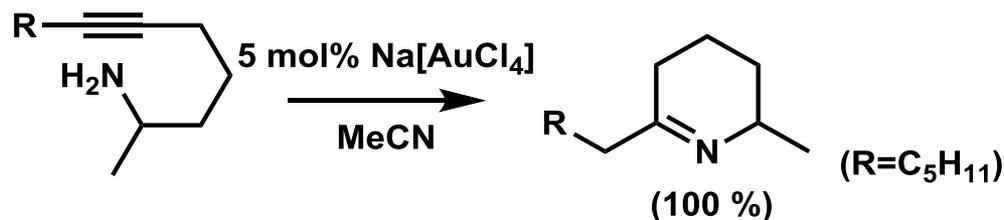


J. Chem. Soc. Perkin. Trans.1., 1976, 29, 123



Gold coordinated intermediates are trapped by various types of nucleophile

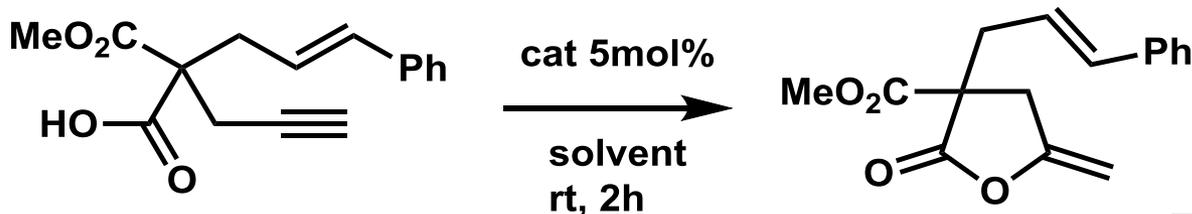
▪ Alkyne + amine



Heterocycles, 1987, 25, 297

Gold catalysts can activate alkyne(2)

Alkyne+Carboxylic acid

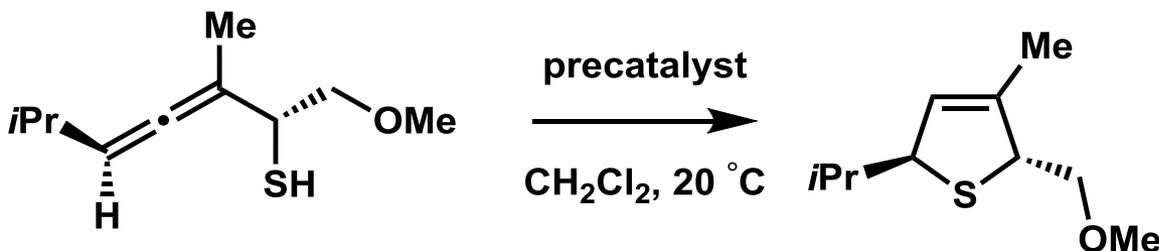


entry	catalyst ^a	solvent	yield (%) ^b
1	AuCl	CH ₃ CN	90
2	AuCl ₃	CH ₃ CN	84
3	AgOTf	CH ₃ CN	10 ^c
4	Sc(OTf) ₃	CH ₃ CN	0
5	HCl	CH ₃ CN	0
6	AuCl	toluene	60
7	AuCl	CH ₂ Cl ₂	63
8	AuCl	C ₂ H ₄ Cl ₂	57

^a 5 mol %. ^b Isolated yield. ^c Conversion.

JACS, 2006, 128, 3112

Allene+Thiol

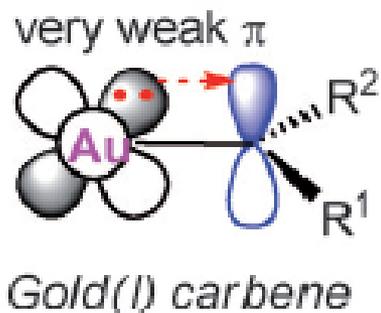


Entry	Precatalyst (mol%)	t	Yield (2a) [%]
1	AuCl ₃ (5)	3 h	58 ^[a]
2	AuBr ₃ (5)	20 min	56 ^[a]
3	AuCl (5)	1.5 h	88
4	AuI (5)	5 min	88
5	AuI (1)	1.5 h	64
6	[Ph ₃ PAuCl] (5)	7 days	trace
7	[Ph ₃ PAuCl] (5)/ AgBF ₄ (10)	4 h	52
8	AgBF ₄ (15)	2 days	trace
9	AgCl (15)	2 days	no reaction
10	CuCl (20)	1 h	trace
11	CuI (20)	2 days	no reaction

Angew. Chem. Int. Ed., 2006, 45, 1897

Gold is less effective in π -back donation than Rh(1)¹⁴

π -back donation ability depends on the electronegativity



Most electronegative transition metal
 \Rightarrow weak π -back donation
 π -back donation from metal stabilizes the carbene center
 \Rightarrow weak π -back donation makes more reactive (electrophilic)

Gold-coordinated
carbocation

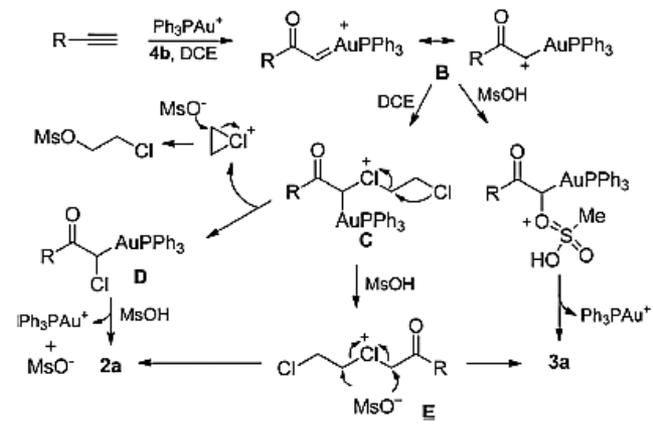
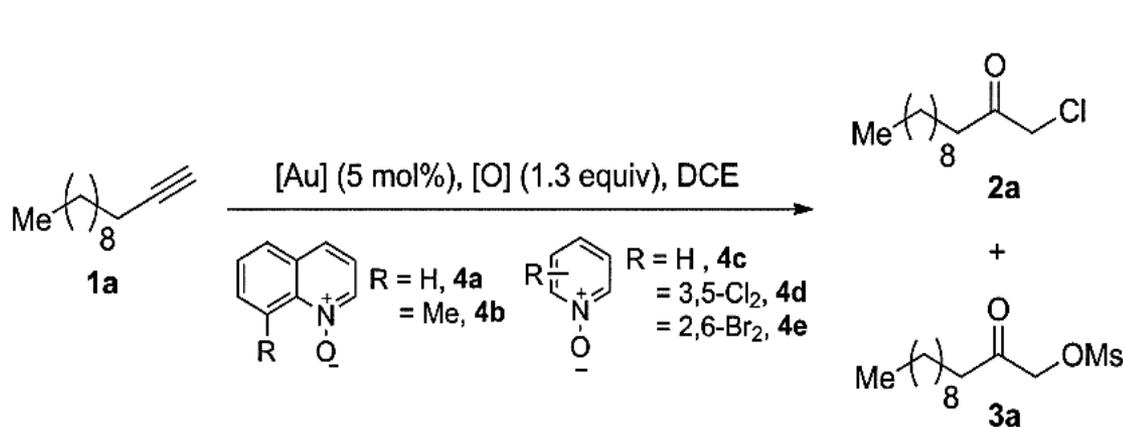


Gold-stabilized
singlet carbene

←
Electrophilicity

Gold is less effective in π -back donation than Rh(2)¹⁵

- Gold carbene is so electrophilic that it can abstract Cl from solvent



Scheme 2 Proposed reaction mechanism.

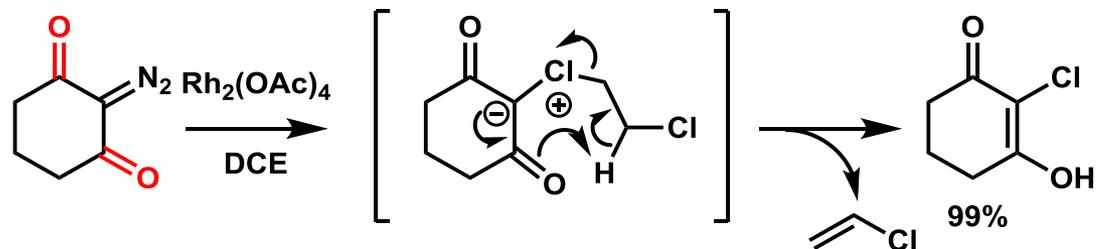
Entry	Gold catalyst	Oxidant	Acid (1.1 eq)	Reaction conditions	Yield ^b [%]	
					2a	3a
1	Ph ₃ PAuNTf ₂	4b	—	60 °C, 8 h	8	0
2	Ph ₃ PAuNTf ₂	4b	MsOH	60 °C, 8 h	39	6
3	Ph ₃ PAuNTf ₂	4b	MsOH	RT, 8 h	63^{cd}	5
4 ^e	Ph ₃ PAuNTf ₂	4b	MsOH	RT, 8 h	41	6
5	Ph ₃ PAuNTf ₂	4a	MsOH	RT, 8 h	60	5
6	Ph ₃ PAuNTf ₂	4c	MsOH	RT, 8 h	21	11
7	Ph ₃ PAuNTf ₂	4d	MsOH	RT, 8 h	24	15
8	Ph ₃ PAuNTf ₂	4e	MsOH	RT, 8 h	39	14
9	IPrAuNTf ₂	4b	MsOH	RT, 8 h	19	11
10	(RO) ₃ PAuNTf ₂ ^f	4b	MsOH	RT, 8 h	51	13
11	Au(III) ^g	4b	MsOH	RT, 8 h	4	13

^a In vial; [1a] = 0.1 M. ^b Estimated by ¹H NMR spectroscopy using diethyl phthalate as an internal reference. ^c Isolated yield of 63%.

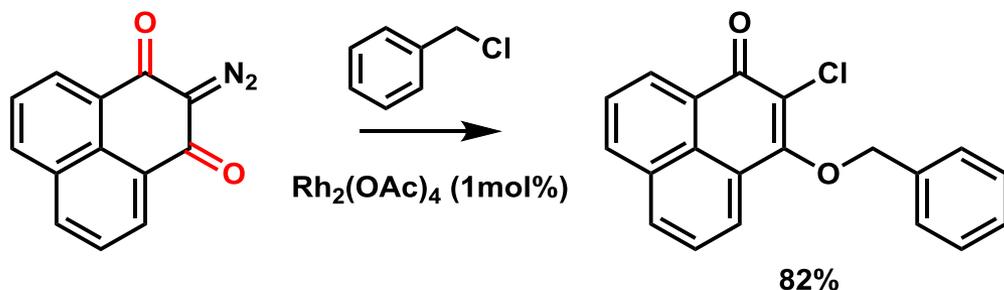
^d MsOCH₂CH₂Cl was formed in 46% yield. ^e CH₂Cl₂ as solvent. ^f R = 2,4-(*t*-Bu)₂Ph. ^g Dichloro(2-picolinato)gold(III).

Gold is less effective in π -back donation than Rh(3)¹⁶

- In the case of Rh carbene



J. Org. Chem., 1995, 60, 2112



Tetrahedron, 2003, 59, 9333

Rh carbene intermediates are flanked by two electro-withdrawing carbonyl groups

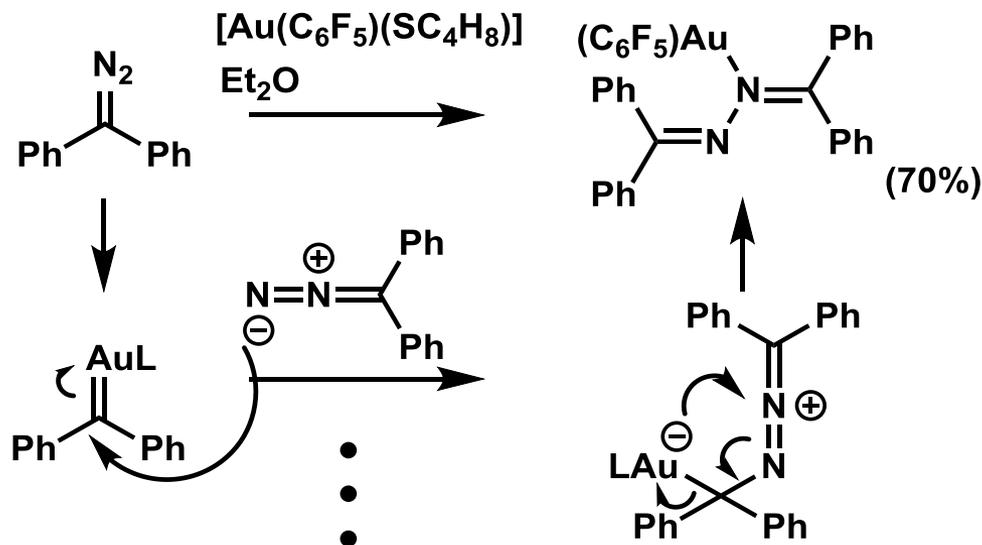


Electrophilicity

Au carben intermediates with one electro-withdrawing carbonyl groups

Gold is less effective in π -back donation than Rh(4)¹⁷

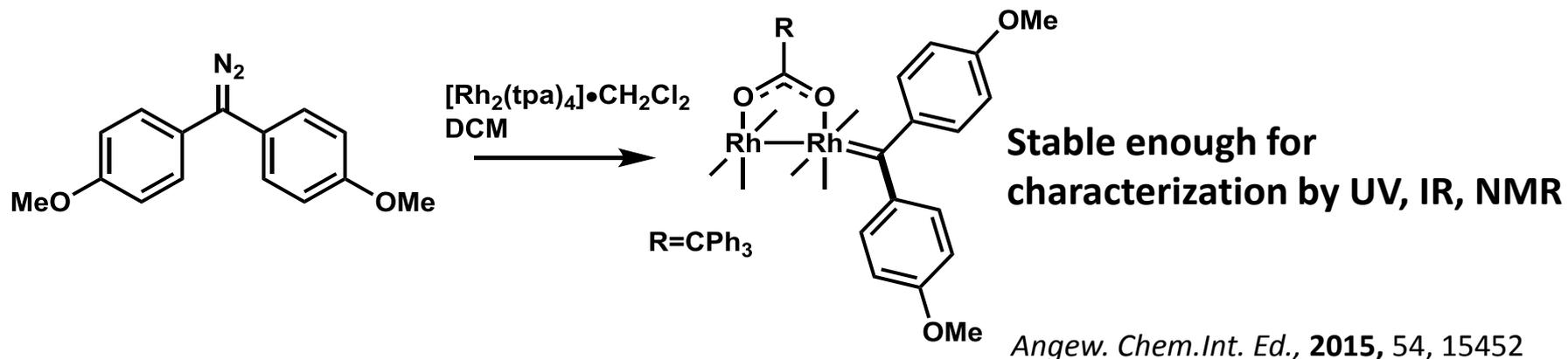
- Diazo compound and gold catalysts give azine compound



Inorganica. Chimica. Acta., 1994, 222, 267

So electrophilic to be attacked by diazo compound

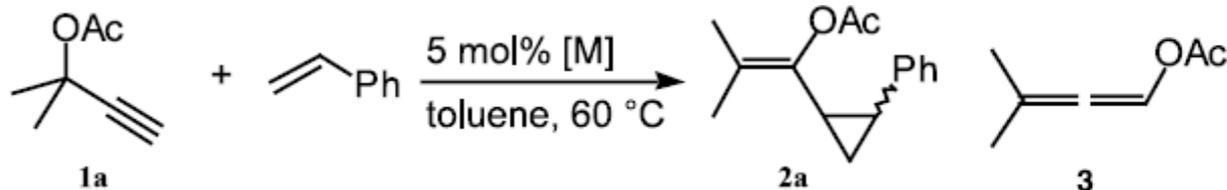
cf.



Angew. Chem. Int. Ed., 2015, 54, 15452

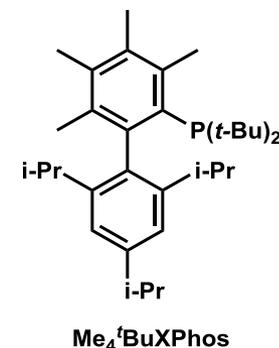
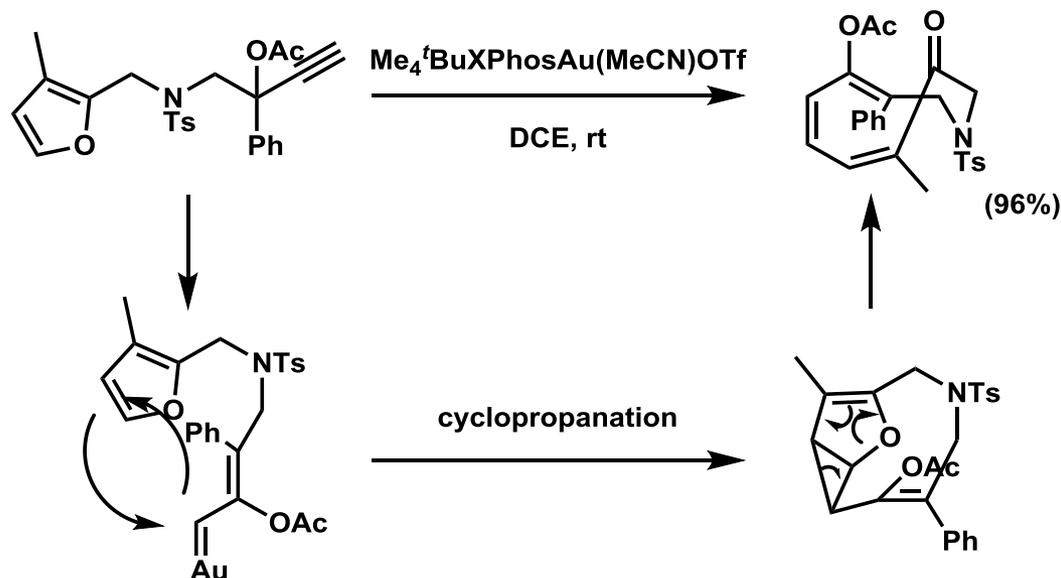
Gold is less effective in π -back donation than Rh(5)¹⁸

Intermediates as gold carbene



Entry	[M]	Time	Yield (%) ^b	
			2a (cis:trans) ^c	Allene 3
1	$[\text{RuCl}_2(\text{CO})_3]_2^{\text{d}}$	18 h	83 (84:16)	5
2	$[\text{RuCl}_2(\text{CO})_3]_2$	15 h	90 (86:14)	0
3	$[\text{Rh}(\text{OCOCF}_3)_2]_2^{\text{d}}$	30 min	Trace	99
4	$[\text{IrCl}(\text{cod})]_2^{\text{d}}$	18 h	37 (70:30)	7
5	AuCl_3	10 min	54 (76:24)	39
6 ^e	AuCl_3	10 min	63 (79:21)	26
7	PtCl_2	1 h	91 (68:32)	9
8	GaCl_3^{f}	28 h	26 (65:35)	0

Tetrahedron. Let., **2003**, 44, 2019



Chem. Commun., **2015**, 51, 13937

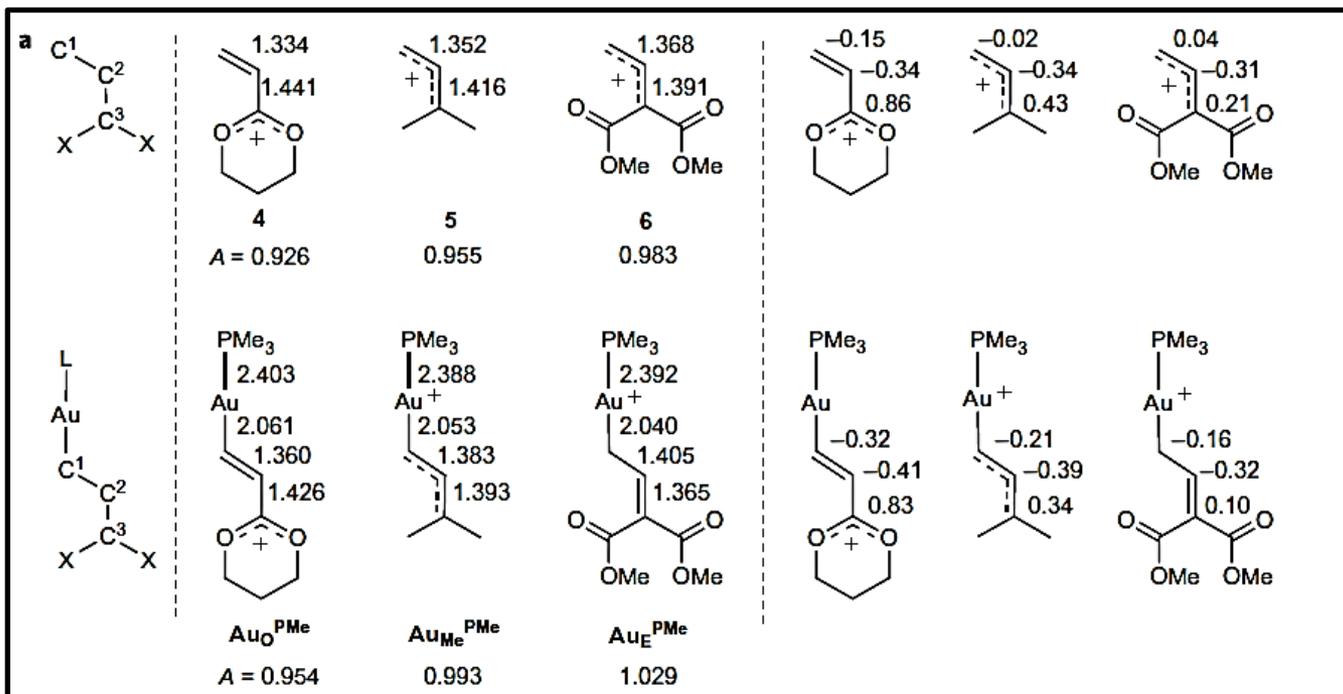
Gold carbene and Gold stabilized carbocation(1)

What decides the character of carbene center?

- Computational and experimental analysis → Focusing on ligand and substituent (By Toste's group)

① Substituent

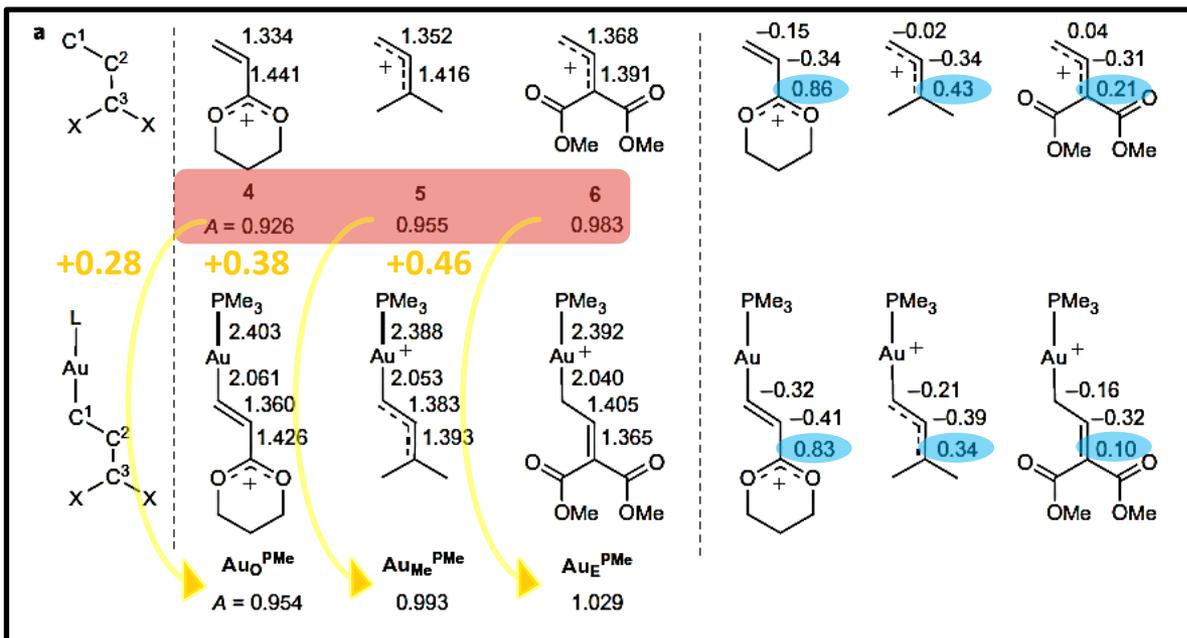
Structural and electronic comparison of cationic metal-free and $[\text{AuPMe}_3]^+$ substituted substrates



Gold carbene and Gold stabilized carbocation(2)

Bond length

Natural atomic charge



$$A = (C^1 - C^2) / (C^2 - C^3)$$

Lower A ... Positive charge is stabilized by C^3 substituent

Higher A ... Positive charge is stabilized by C^1 substituent (AuL)

◆ A increases with less-donating C^3 substituent (O \rightarrow Me \rightarrow ester)

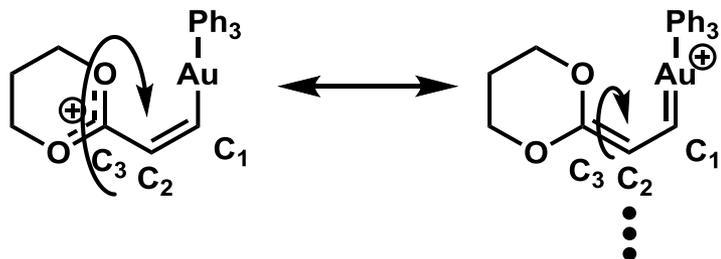
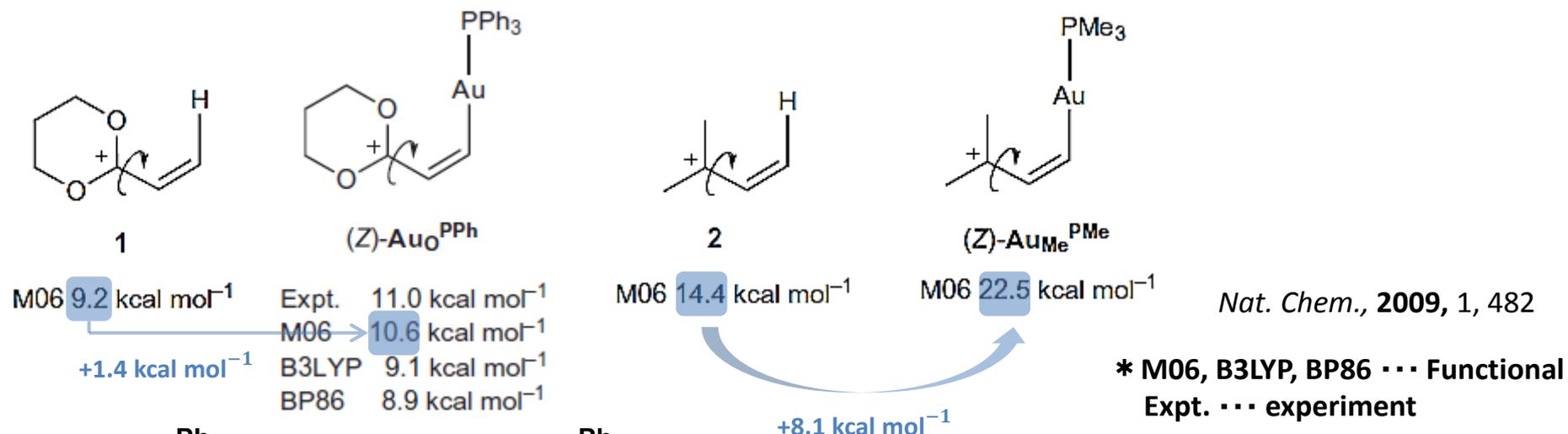
◆ A increases by the stabilization of positive charge at C^1 from AuL

Au \rightarrow C^1 stabilization grows with increasing electrophilicity of the allyl cation

◆ Effect on natural atomic charge at C^3 grows with increasing electrophilicity of the allyl cation (0.86 \rightarrow 0.83, 0.43 \rightarrow 0.34, 0.21 \rightarrow 0.10)

Gold carbene and Gold stabilized carbocation(3)

The effect of AuL on rotational barrier with different substituents



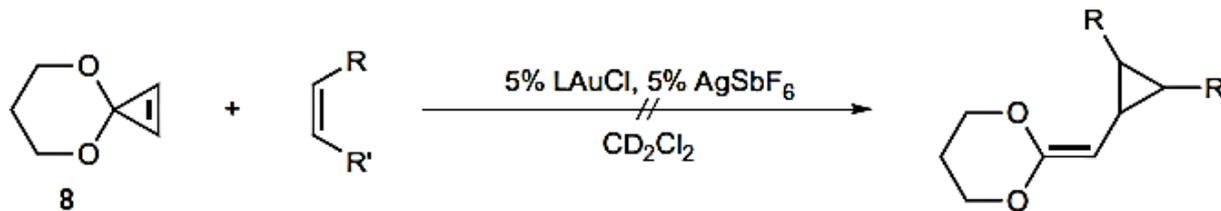
C^2-C^3 bond of carbene resonance extreme has double bond character \Rightarrow High rotation barrier indicates character of carbene intermediate

AuL \rightarrow C stabilization (carbene character) is dependent on carbene substituent!!

Gold carbene and Gold stabilized carbocation(4)

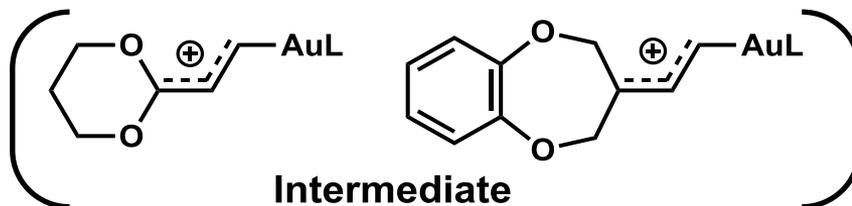
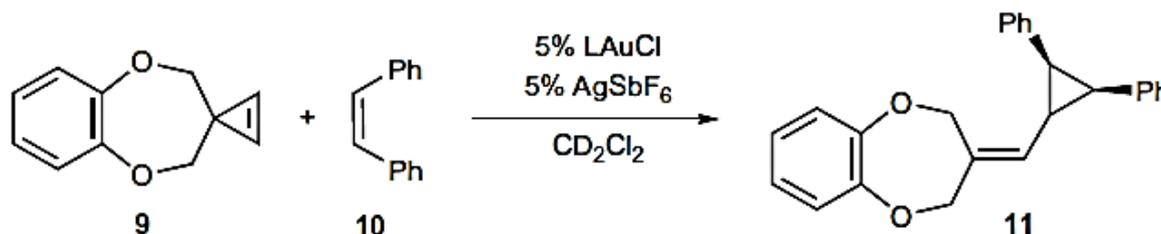
Experiment analysis

a



Never
observed

b



Ligand (L)	Yield (d.r.)
P(OMe) ₃	0%
P(OPh) ₃	11% (4:1)
PMe ₃	56% (1.4:1)
PPh ₃	52% (1.7:1)
IPr	80% (11:1)

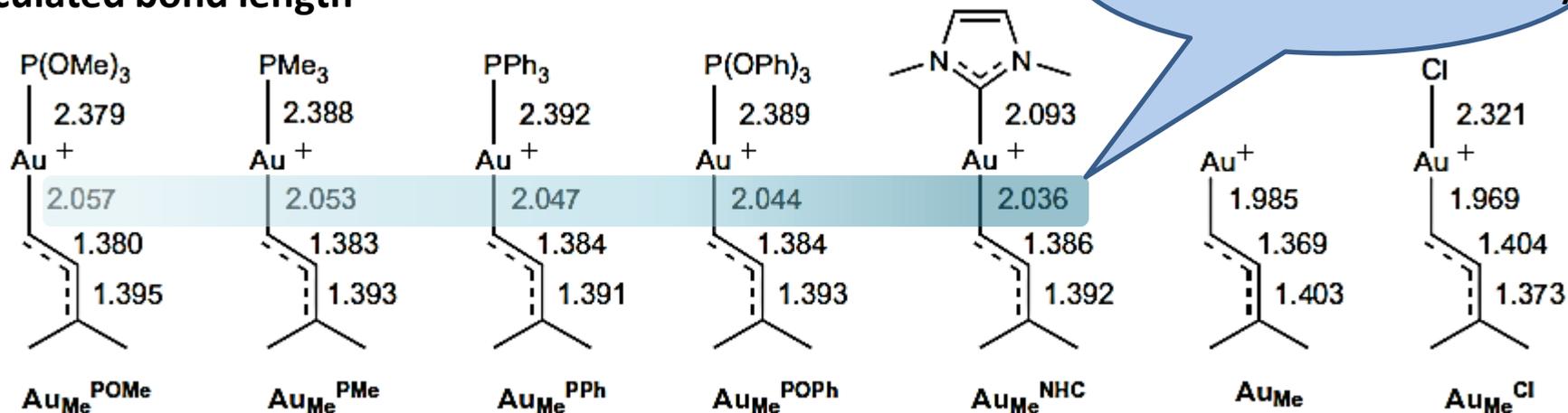
Experimental analysis also shows electron-donating substituent decrease carbene character!!

Ligand effect is important?

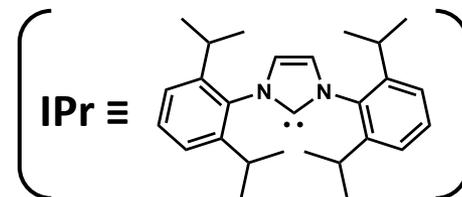
Gold carbene and Gold stabilized carbocation(5)

② Ligand

Calculated bond length



Ligand (L)	Yield (d.r.)	Product	Reactivity
P(OMe)_3	0%	Polymerized product	carbocation-like reactivity
P(OPh)_3	11% (4:1)		
PMe_3	56% (1.4:1)	Cyclopropanation	carbene-like reactivity
PPh_3	52% (1.7:1)		
IPr	80% (11:1)		

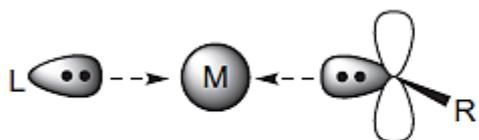
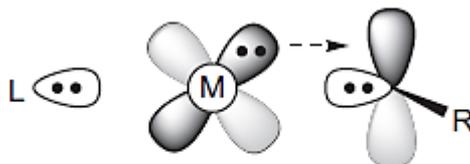
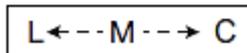
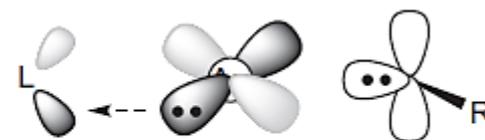
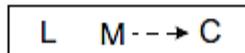
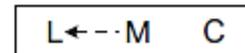


Computational and experimental analyses are consistent with each other !!

What difference is deciding ligand effect?

Representative bond of metal carbene

Representative bond of carbene

3 centre-4 electron σ -bondMetal \rightarrow alkylidene π -bondMetal \rightarrow ligand π -bond

$L \rightarrow M$ σ donation

$M \leftarrow :C$ σ donation

$C : \leftarrow M$ π donation

$M \rightarrow L$ π donation

• High \longleftrightarrow • Low

(weak σ bonding)

• High \longleftrightarrow • Low

(strong π bonding)

π -acidic

weak



strong

Carbene-like reactivity

Ligand

Carbocation-like reactivity

strong



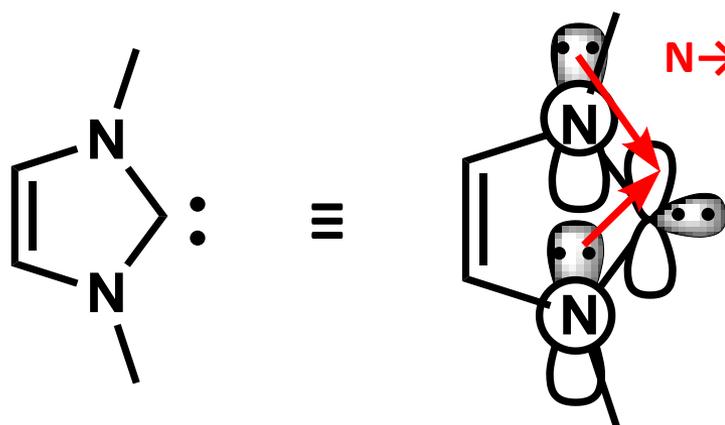
weak

σ -donating

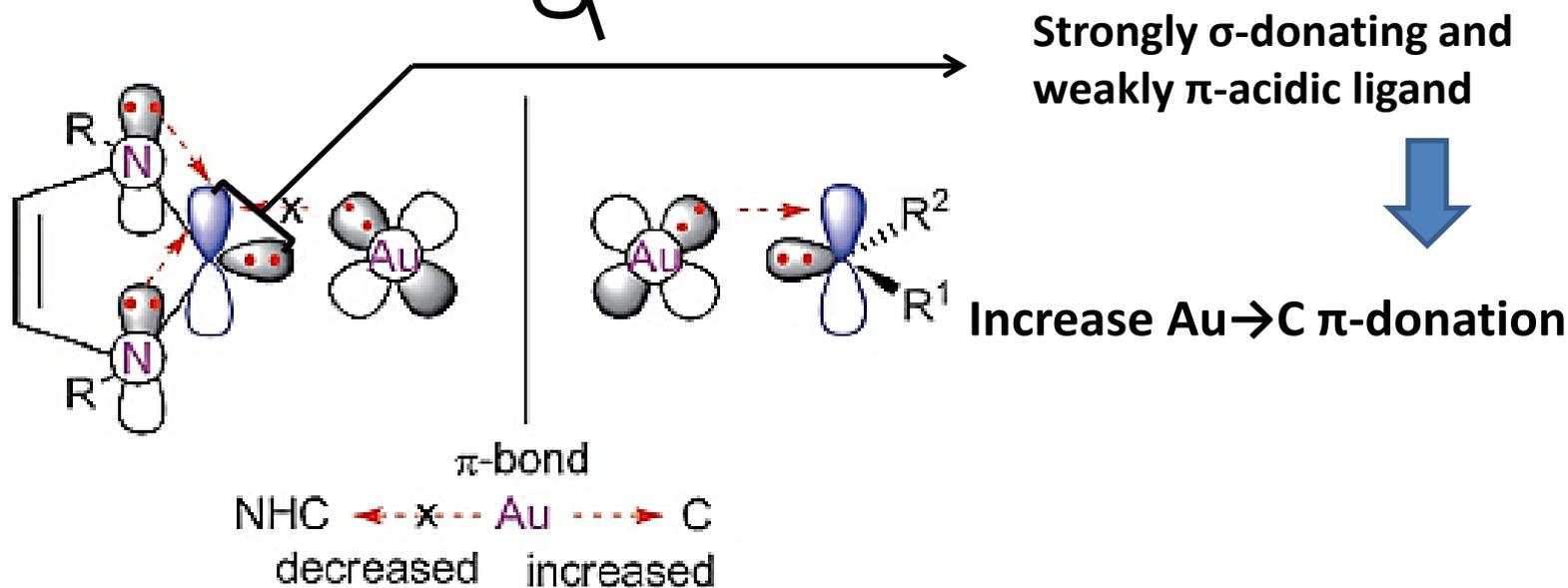
NHC ligand

NHC··· N- Heterocyclic Carbene

Stable singlet carbene

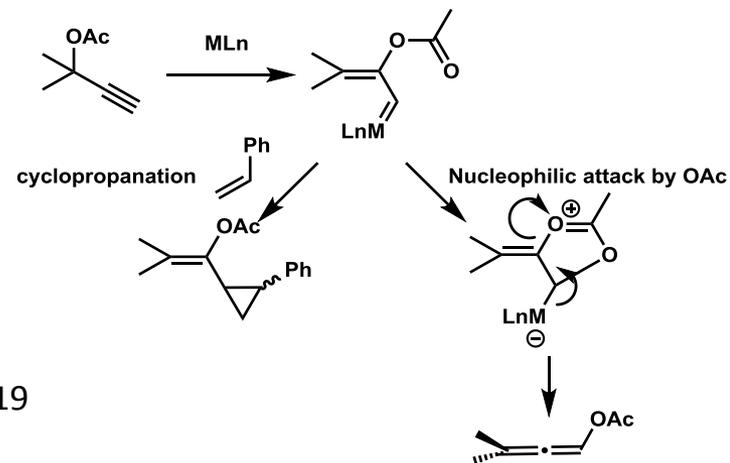
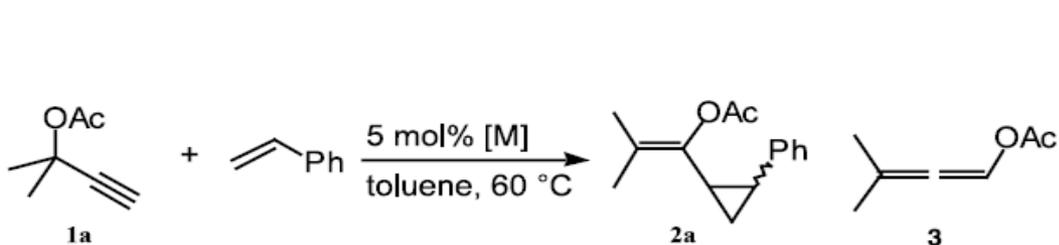


N→C π donation stabilize carbene center



Gold is less effective in π -back donation than Rh(5¹⁸)

Intermediates as gold carbene



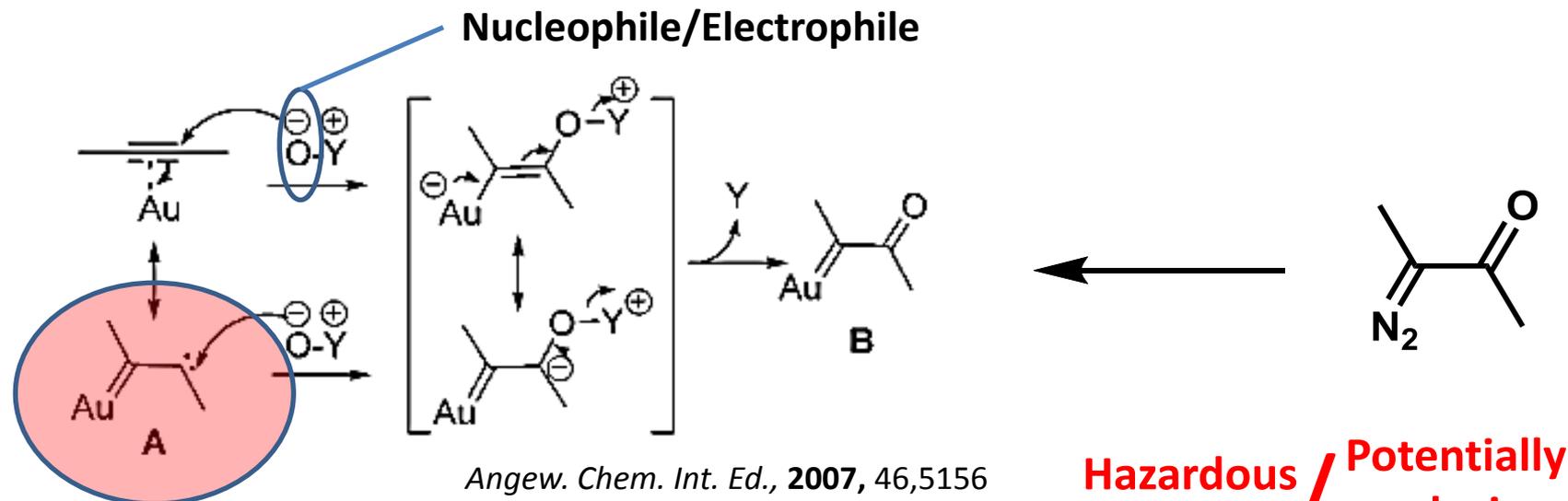
Tetrahedron. Let., **2003**, 44, 2019

Entry	[M]	Time	Yield (%) ^b	
			2a (<i>cis:trans</i>) ^c	Allene 3
1	$[RuCl_2(CO)_3]_2$ ^d	18 h	83 (84:16)	5
2	$[RuCl_2(CO)_3]_2$	15 h	90 (86:14)	0
3	$[Rh(OCOCF_3)_2]_2$ ^d	30 min	Trace	99
4	$[IrCl(cod)]_2$ ^d	18 h	37 (70:30)	7
5	$AuCl_3$	10 min	54 (76:24)	39
6 ^e	$AuCl_3$	10 min	63 (79:21)	26
7	$PtCl_2$	1 h	91 (68:32)	9
8	$GaCl_3$ ^f	28 h	26 (65:35)	0

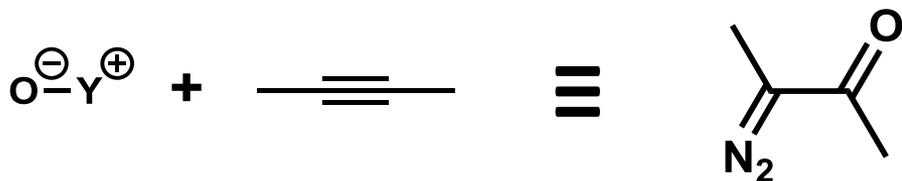
**Less donating catalysts give allene
(Reaction time is very short)**

3. α -oxo gold carbene

α -oxo gold carbene (By Zhang's group)



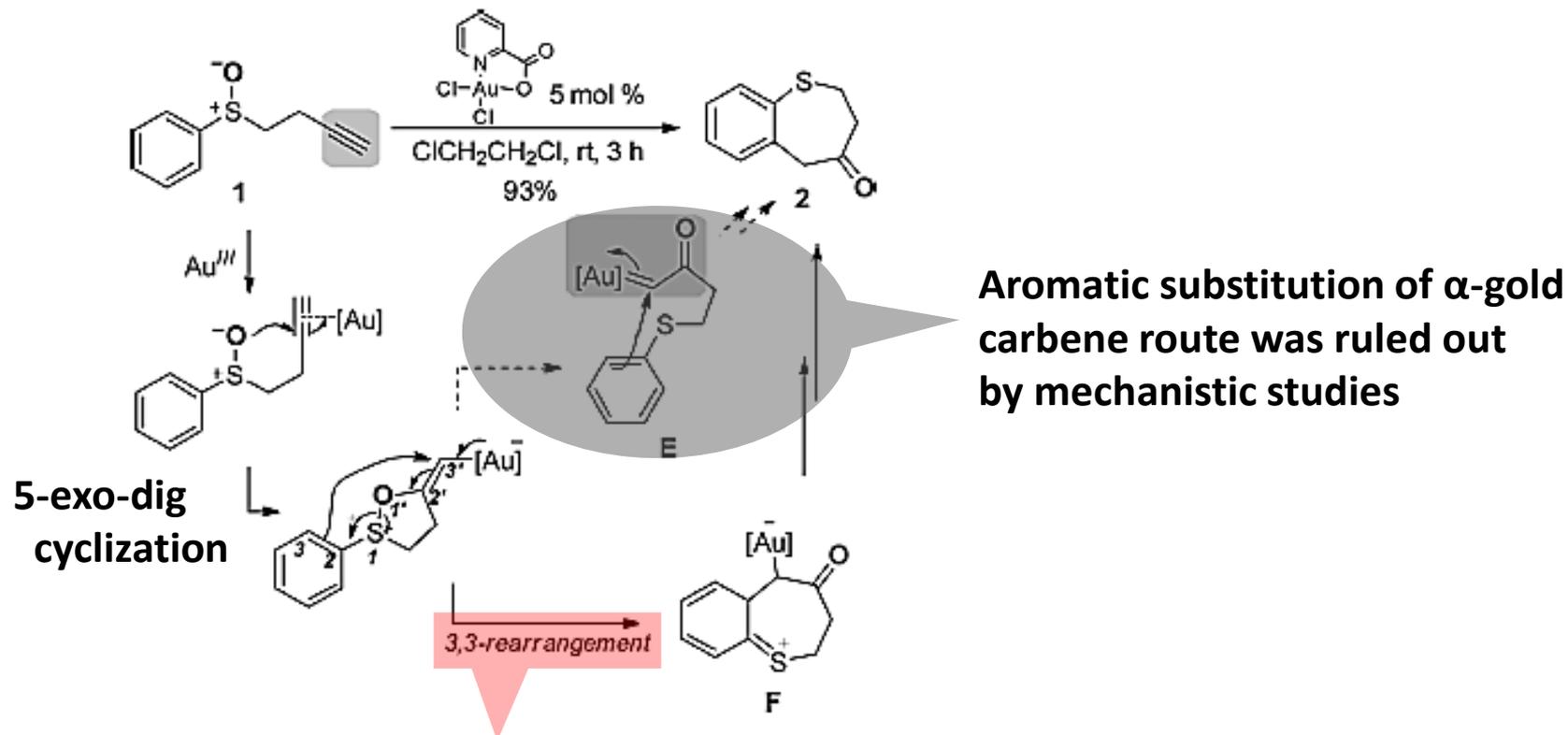
α -carbene gold carbene



$\text{O}^{\ominus} - \text{Y}^{\oplus} + \text{alkyne}$ is equivalent of
diazo carbonyl compounds

Intramolecular oxidation (1)

Intramolecular oxidation ··· Using **sulfoxide** as oxidant



Facile 3,3-sigmatropic rearrangement is favorable

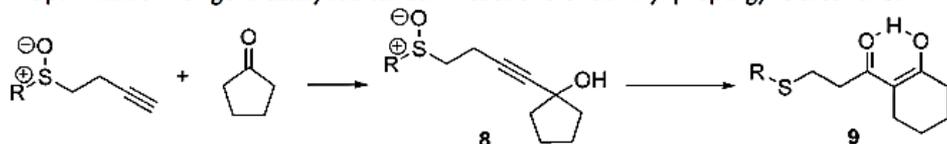
α -oxo gold carbene can't be generated?

Intramolecular oxidation (2)

Evidence of α -oxo gold carbene formation

Pinacol-type rearrangement

Table 1: Optimization for gold-catalyzed tandem reactions of sulfinyl propargylic alcohol **8**.^[a]



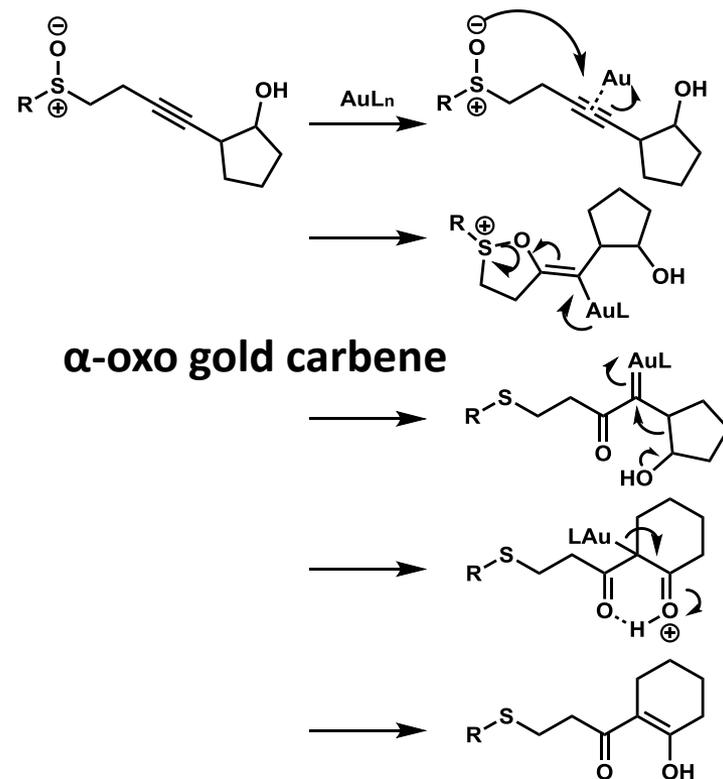
Entry ^[a]	R		Reaction conditions	Yield of 9 [%] ^[b]
1			5 mol % 3 , (ClCH ₂) ₂ , RT, 3 h	36
2	Ph	8a	5 mol % Ph ₃ PAuNTf ₂ , (ClCH ₂) ₂ , RT, 5 h	11
3		8a	5 mol % IMesAuNTf ₂ , (ClCH ₂) ₂ , RT, 3 h	22
4		8a	5 mol % IPrAuNTf ₂ , (ClCH ₂) ₂ , RT, 3 h	53
5	2,6-Me ₂ C ₆ H ₃	8b	5 mol % IPrAuNTf ₂ , (ClCH ₂) ₂ , RT, 12 h	37
6	2,6-Cl ₂ C ₆ H ₃	8c	5 mol % IPrAuNTf ₂ , (ClCH ₂) ₂ , RT, 24 h	44
7	2-ClC ₆ H ₄	8d	5 mol % IPrAuNTf ₂ , (ClCH ₂) ₂ , RT, 3 h	63
8	2-ClC ₆ H ₄ ^[c]	8d	5 mol % IPrAuNTf ₂ , (ClCH ₂) ₂ , RT, 3 h	77^[d]
9	<i>t</i> Bu	8e	5 mol % IPrAuNTf ₂ , (ClCH ₂) ₂ , RT, 3 h	— ^[e]
10	<i>n</i> Bu	8f	5 mol % IPrAuNTf ₂ , (ClCH ₂) ₂ , RT, 2 h	15 ^[f]

[a] The substrate concentration was 0.02 M. [b] Estimated by ¹H NMR spectroscopy using diethyl phthalate as an internal standard. [c] The substrate concentration was 0.005 M. [d] Yield of isolated product. [e] 53% of **10** was isolated. [f] 18% of **11** was isolated.



4 ... IPr(NHC) ligand is suitable

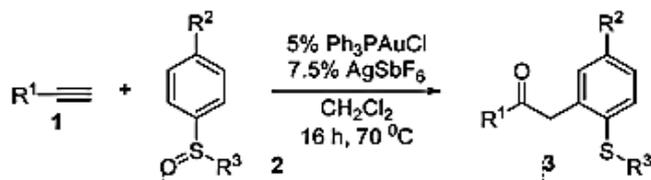
8 ... *o*-chlorinated benzene ring is good substrate to inhibit competitive 3,3-sigmatropic rearrangement



Intermolecular oxidation (1)

Intermolecular oxidation

Aryl sulfoxide as oxidant



	1		2		3	yield (%)
	R ¹	R ²	R ³			
1a	C ₆ H ₅	2a	OCH ₃	CH ₃	3aa	87
1a	C ₆ H ₅	2b	H	CH ₂ C ₆ H ₅	3ab	83
1a	C ₆ H ₅	2c	Br	CH ₃	3ac	49
1b	<i>p</i> -ClC ₆ H ₄	2a	OCH ₃	CH ₃	3ba	71
1c	<i>n</i> -C ₄ H ₉	2a	OCH ₃	CH ₃	3ca	84
1d	(CH ₃) ₃ C	2a	OCH ₃	CH ₃	3da	20
1e	CH ₃ CH ₂ O	2a	OCH ₃	CH ₃	3ea	50

Reaction at the position adjacent to C-S=O was only observed



More activated C5 position didn't occur aromatic substitution

Apparently good result

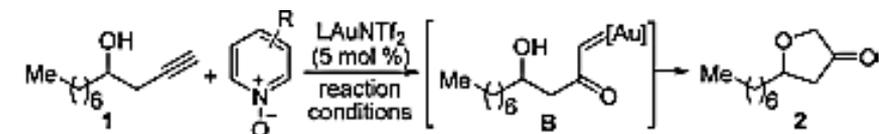
Org. Lett., 2009, 11, 4906

Formation of α -oxo gold carbene < 3,3-sigmatropic rearrangement

Sulfoxide isn't suitable for intermolecular oxidation

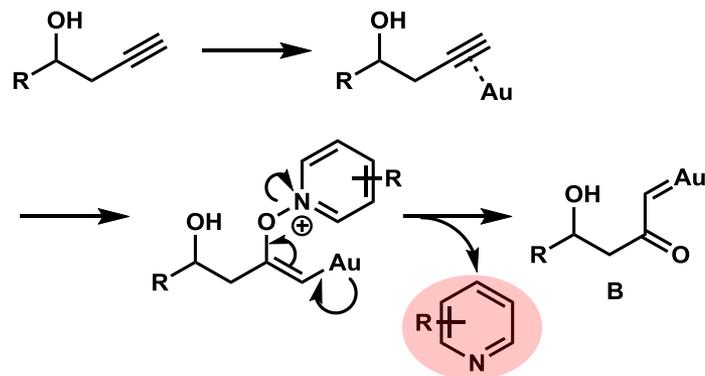
Intermolecular oxidation (2)

Pyridine N-oxide as oxidant → Avoid 3,3-sigmatropic rearrangement



entry	L	R ^b	acid ^b	conditions	yield ^f
1	IPr	H	—	DCE, 60 °C, 10 h	9% ^d
2	IPr	H	Cl ₃ CCO ₂ H	DCE, 60 °C, 10 h	32% ^e
3	IPr	H	F ₃ CCO ₂ H	DCE, 60 °C, 5.5 h	56%
4	IPr	H	F ₃ CCO ₂ H	DCE, rt, 8 h	53%
5	IPr	H	MsOH	DCE, rt, 4.5 h	51%
6	IPr	H	TfOH	DCE, rt, 2 h	54%
7	IPr	3-Br	MsOH	DCE, rt, 2.5 h	64%
8	IPr	3,5-Cl ₂	MsOH	DCE, rt, 2.5 h	68%
9	IPr	2-Br	MsOH	DCE, rt, 3.5 h	68%
10	IPr	4-Ac	MsOH	DCE, rt, 8 h	52%
11	IPr	2-Br	MsOH ^f	DCE, rt, 3.5 h	65%
12	Et ₃ P	2-Br	MsOH ^f	DCE, rt, 3.5 h	64%
13	Ph ₃ P	2-Br	MsOH ^f	DCE, rt, 2.5 h	78% ^g
14	Ph ₃ P	3,5-Cl ₂	MsOH ^f	DCE, rt, 2.5 h	75%

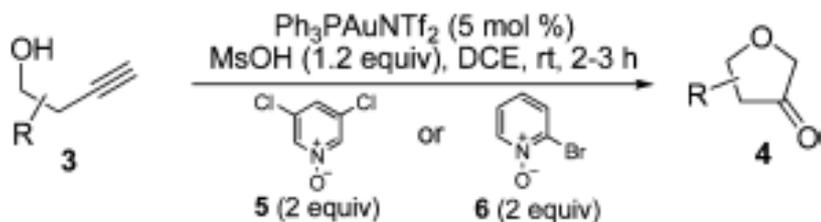
^a [1] = 0.05 M; DCE = 1,2-dichloroethane. ^b Unless otherwise specified, 2 equiv was used. ^c Estimated by ¹H NMR analysis using diethyl phthalate as an internal reference. ^d 75% conversion. ^e 68% conversion. ^f 1.2 equiv. ^g 76% isolated yield.



Acidic condition is needed
(Pyridine deactivate catalyst?)

Phosphine ligand is better
than NHC ligand

Intermolecular oxidation (3)



en-	<i>N</i> -try oxide	product	4/ yield ^b
5	5		4e 62%
6	5		4f 64%
17 ^d	5		4q 82%
18 ^e	5		4r ^d 88%

Less stable trans-fused ring

The condition is so mild MOM and Boc can tolerate

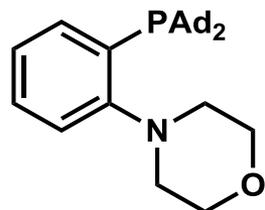
Highly reactive intermediate



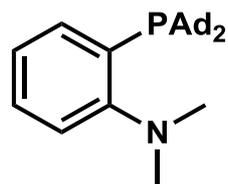
Reaction efficiency depends on kinetics of OH trapping

Other type of Ligand (1)

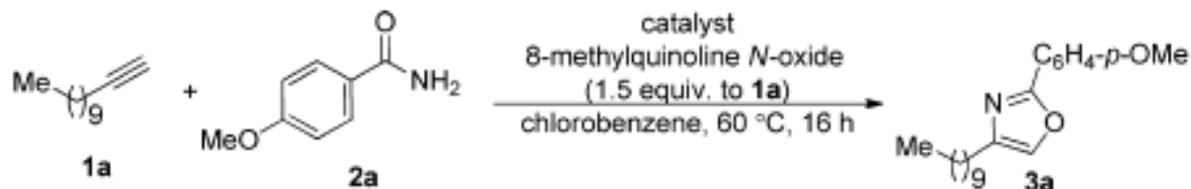
P,N-bidentate ligand



Mor-DalPhos

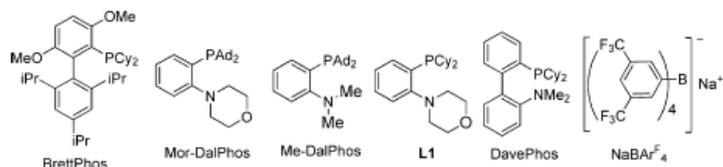


Me-DalPhos



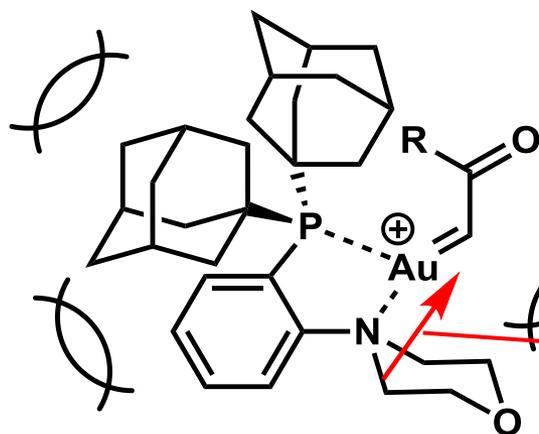
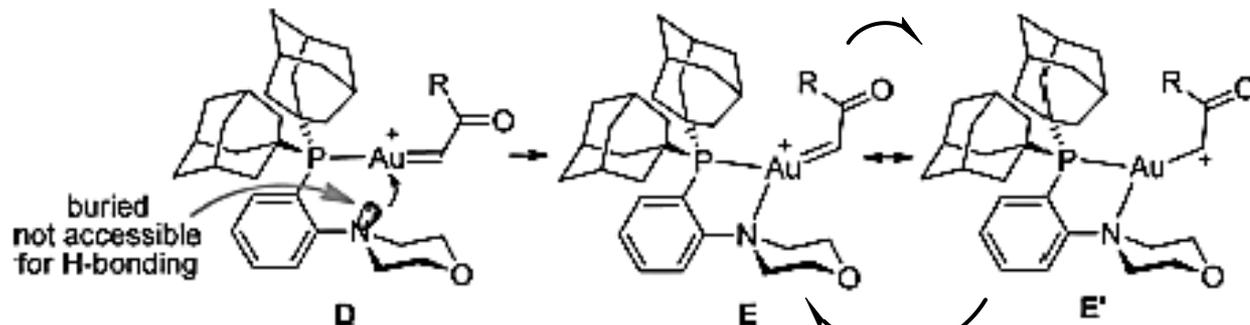
entry	1a/2a	catalyst	yield ^b
1	1:1.2	Ph ₃ PAuNTf ₂ (5 mol %)	0 ^c
2	1:1.2	Cy-JohnPhosAuNTf ₂ (5 mol %)	0 ^c
3	1:1.2	IPrAuNTf ₂ (5 mol %)	0 ^c
4	1:1.2	(4-CF ₃ Ph) ₃ PAuNTf ₂ (5 mol %)	0 ^c
5	1:1.2	BrettPhosAuNTf ₂ (5 mol %)	4% ^c
6	1:1.2	Mor-DalPhosAuNTf ₂ (5 mol %)	58%
7	1:1.2	Mor-DalPhosAuCl (5 mol %)/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	L1AuCl (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

^aThe reaction was run with everything except the oxidant in a vial capped with a septum, and the oxidant was introduced into the reaction mixture slowly using a syringe pump. Initially, [1a] = 0.1 M. ^bMeasured by ¹H NMR analysis using diethyl phthalate as the internal standard. ^c<20% of 1-dodecyne was left, and the crude ¹H NMR spectrum was mostly messy. ^d81% isolated yield. ^eDCE was used as the solvent. ^fToluene was used as the solvent.



Other type of Ligand (2)

The role of ligand



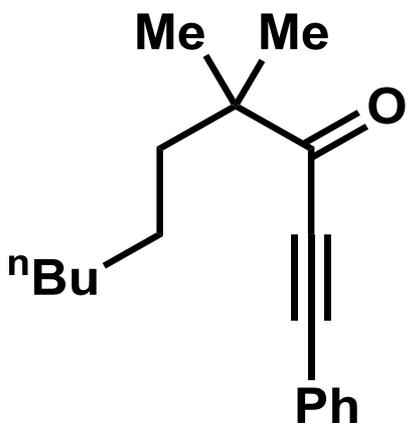
① Steric shield on carbene center by rigid conformation

② N→Au donation increase Au→:C donation
(Carbene like \gg Carbocation like)

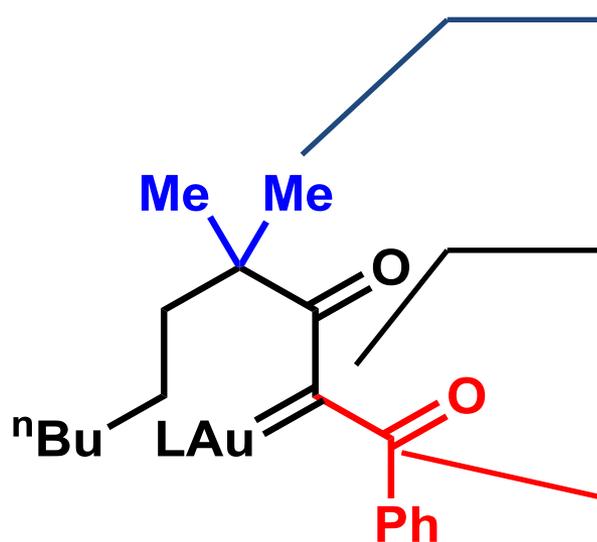
①,② \longrightarrow Decrease electrophilicity (= Increase selectivity)

α -oxo gold carbene to C-H insertion (1)

sp^3 C-H insertion (\rightarrow cyclopentanone)



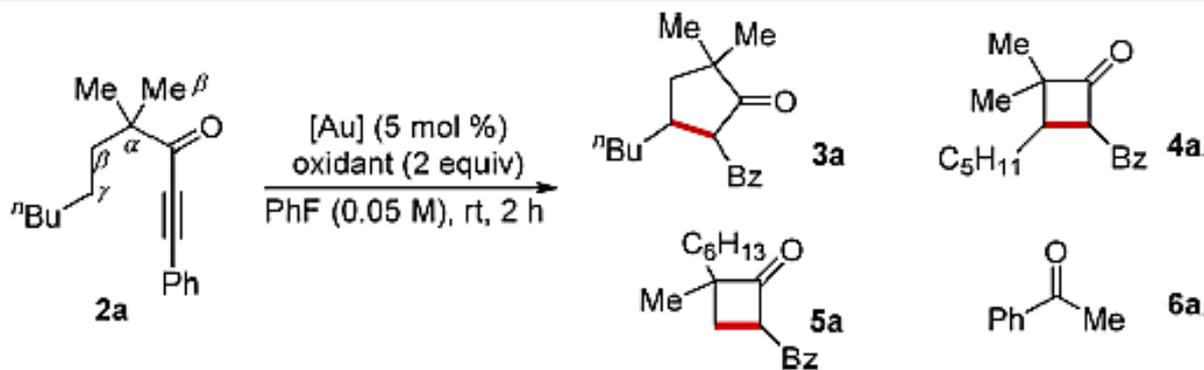
Outset substrate



Intermediate

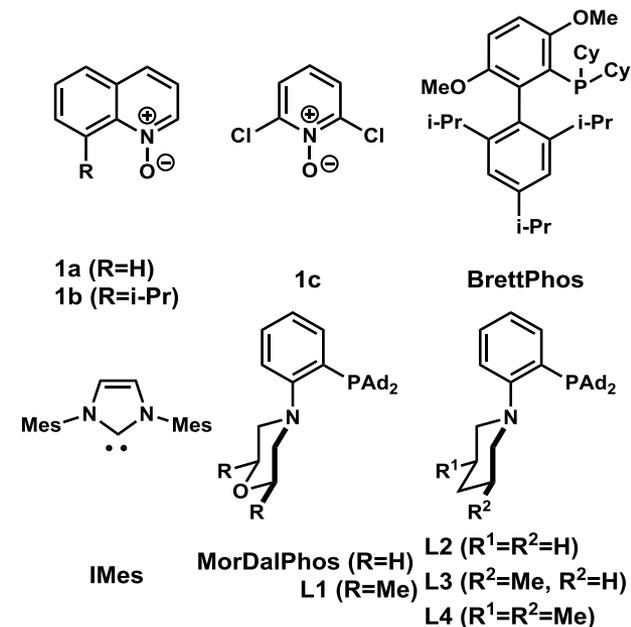
- ① Conformation control by Thorpe-Ingold effect
- ② β -diketone- α -gold carbene (more electrophilic = more reactive to C-H insertion)
- ③ Bulky acyl group to hinder intermolecular side reactions

α -oxo gold carbene to C-H insertion (2)



entry	catalyst (5 mol %)	N-oxide	yield ^b	
			3a/4a/5a ^c	6a
1	Ph ₃ PAuNTf ₂	Ia	30% (9.5/1/1.1)	7%
2	BrettPhosAuNTf ₂	Ia	61% (1.1/1/1)	20%
3	IPrAuNTf ₂	Ia	63% (7.9/1/0)	11%
4	IMesAuCl/AgNTf ₂	Ia	57% (15.7/1/0)	7%
5	MorDalPhosAuNTf ₂	Ia	70% (6.7/1/0)	12%
6	L1AuCl/AgNTf ₂	Ia	59% (7.7/1/0)	7%
7	L2AuCl/AgNTf ₂	Ia	65% (10.0/1/0)	10%
8	L3AuCl/AgNTf ₂	Ia	68% (11.0/1/0)	8%
9	L4AuCl/AgNTf ₂	Ia	72% (13.2/1/0)	7%
10	L4AuCl/AgOTf	Ia	67% (12.8/1/0)	12%
11	L4AuCl/AgSbF ₆	Ia	67% (12.2/1/0)	10%
12 ^d	L4AuCl/NaBAR ^F ₄ (10 mol %)	Ia	71% (9.5/1/0)	5%
13	L4AuCl/AgNTf ₂	Ib	84% ^e (13.7/1/0)	8%
14 ^f	L4AuCl/AgNTf ₂	Ic	75% (13.0/1/0)	6%
15	IMesAuCl/AgNTf ₂	Ib	74% (13.8/1/0)	10%

^a[2a] = 0.05 M. ^bEstimated by ¹H NMR using diethyl phthalate as the internal reference. ^cAs mixtures of tautomers and diastereomers. ^d12 h; isolated yield. ^e77% isolated yield. ^fOvernight.

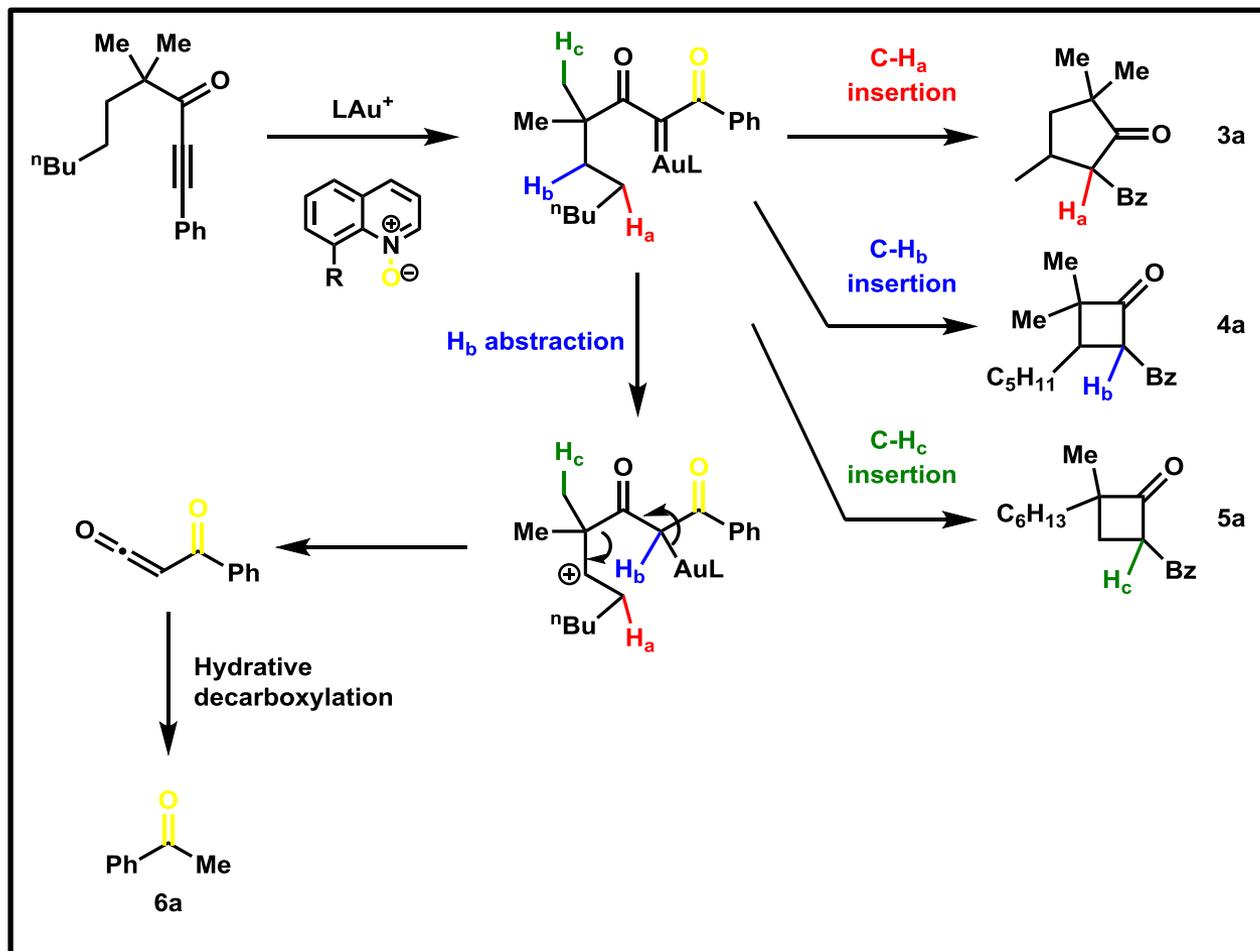


⑨ L4 ligand (Most bulky P,N-bidentate ligand) is the most favorable for reactivity and selectivity

⑬ More hindered oxidant and NTf₂ as counteranion are the most suitable

α -oxo gold carbene to C-H insertion (3)

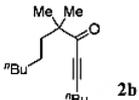
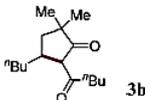
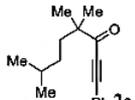
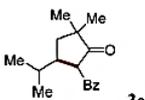
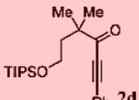
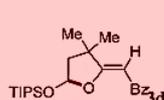
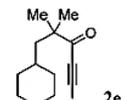
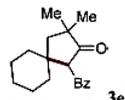
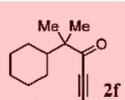
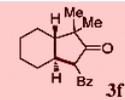
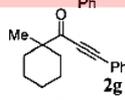
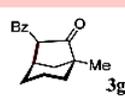
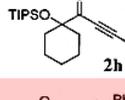
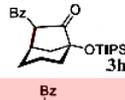
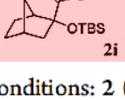
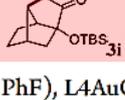
Proposed mechanism of the reaction

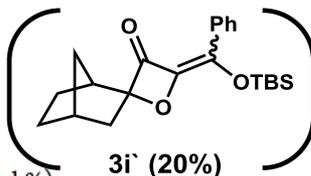
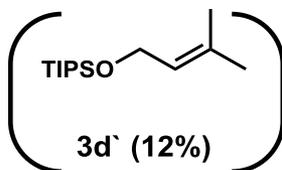


α -oxo gold carbene to C-H insertion (4)

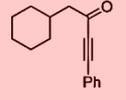
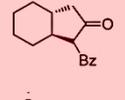
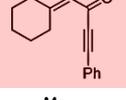
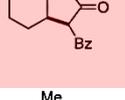
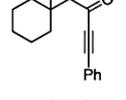
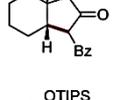
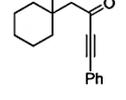
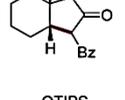
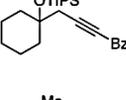
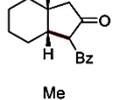
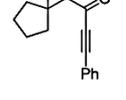
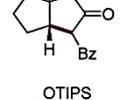
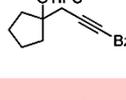
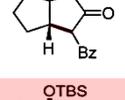
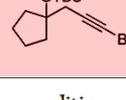
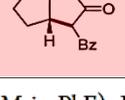
Substrate scope with Yrones

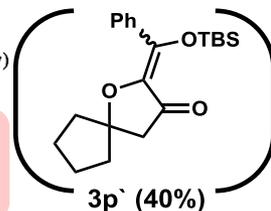
A

entry	substrate 2	product 3	yield ^b
1	 2b	 3b	94% (>25/1) ^c
2 ^{d,e}	 2c	 3c	78% (15/1) ^c
3 ^f	 2d	 3d	60%
4	 2e	 3e	96% (18.2/1) ^c
5	 2f	 3f	72% (trans/cis : >20/1)
6	 2g	 3g	85%
7	 2h	 3h	75%
8 ^f	 2i	 3i	76%



B

entry	substrate 2	cyclopentanone 3	yield ^b
1 ^c	 2j	 3j	40% (trans/cis : >8/1)
2	 2k	 3k	48%
3 ^d	 2l	 3l	83% (cis/trans : 3.5/1)
4 ^d	 2m	 3m	75% (cis only)
5 ^d	 2m'	 3m	75% (cis only)
6	 2n	 3n	67% (cis only)
7	 2o	 3o	67% (cis only)
8	 2p	 3p	40%



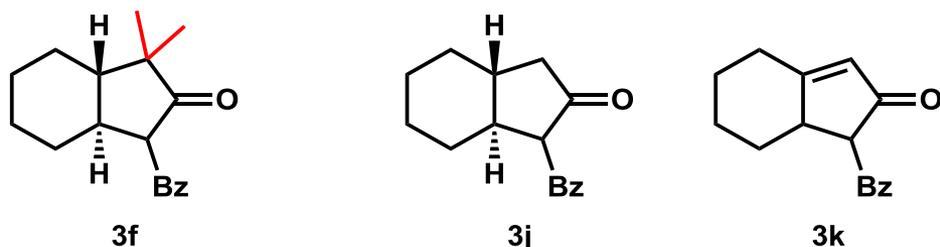
^aReaction conditions: 2 (0.05 M in PhF), L4AuCl/AgNTf₂ (5 mol %), 1b (2 equiv), rt, 2 h. ^bIsolated yield. ^cRatio of 3/4. ^dMeAuCl/AgNTf₂ (5 mol %) as catalyst. ^e58% yield and 3/4 = 2/1 with L4AuCl/AgNTf₂ as catalyst. ^fIPrAuNTf₂ (5 mol %) as catalyst.

^aReaction conditions: 2 (0.05 M in PhF), IPrAuNTf₂ (5 mol %), 1b (2 equiv), rt, 2 h. ^bIsolated yield. ^cDCE as solvent. ^d1.5 equiv of 1b.

α -oxo gold carbene to C-H insertion (5)

Key points for control of reactivity

①

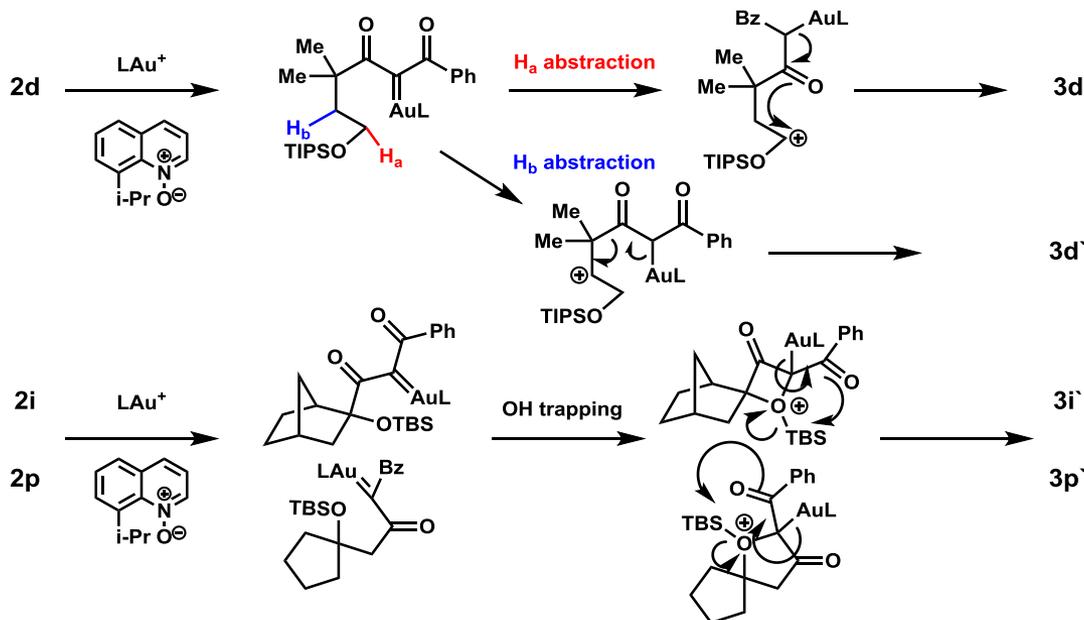


Higher yield and selectivity

Lower yield and selectivity (3j)

Thorpe-Ingold effect
is important !

②



Masking of competing
nucleophile is important !

Summary

Carbocation-like ← Gold carbene → Carbene-like

▪ More electrophilic	Reactivity	▪ Less electrophilic
▪ Less donating ligand (Phosphine ligand)	Ligand	▪ More donating ligand (NHC, P,N bidentate ligand)

α -oxo gold carbene

- Prepared from alkyne + AuL + pyridine N-oxide
(Safe method without hazardous α -diazo carbonyl compounds)
- For C-H insertion
NHC or P,N bidentate ligand is suitable
Thorpe-Ingold effect is important (cyclization)
Blocking of competing nucleophile is required