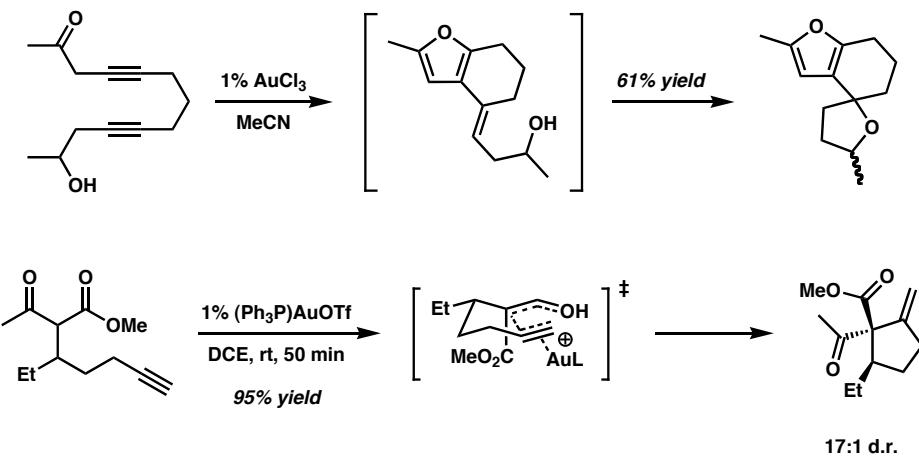


Homogeneous Gold Catalysis

Highly Efficient Functionalization of C–C Multiple Bonds and Electron-Rich C–H Bonds



Michael R. Krout
Stoltz Group Literature Talk
May 30, 2005

8pm, 147 Noyes

Outline

1. Introduction
 - a. History
 - b. A few basics of Au chemistry
 - c. Some Au(I) and Au(III) organometallic complexes
2. Additions of carbon nucleophiles to activated C–C multiple bonds
 - a. Catalytic asymmetric aldol
 - b. Stabilized carbon nucleophiles
 - c. Rearrangements/cycloisomerization
 - d. Phenol synthesis
 - e. Arene nucleophilic additions (C–H functionalization)
3. Heteroatom nucleophiles (also assisted)
 - a. Hydration/hydroamination
 - b. Heterocycle synthesis
 - c. Annulation/naphthylketone synthesis

Select Au background references:

- Puddephatt, R. *The Chemistry of Gold*; E. L. Sevier Scientific Publication Co., Amsterdam, 1978.
 Hashmi, A. S. K. *Gold Bulletin* 2004, 37, 51-65.
 Parish, R. V. *Gold Bulletin* 1997, 30, 3-12.
 Parish, R. V. *Gold Bulletin* 1997, 30, 55-61.
 Parish, R. V. *Gold Bulletin* 1998, 31, 14-21.
 Gimeno, M. C.; Laguna, A. *Chem. Rev.* 1997, 97, 511-522.
 Grohmann, A.; Schmidbaur, H. *Comprehensive Organometallic Chemistry II*, 1995; vol. 3 pp 1-56.

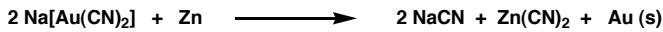
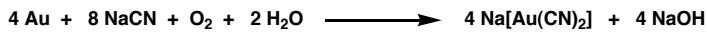
Introduction

Brief History of Gold (circa. 3000 BC)

Gold is found in many minerals, including: quartz, nagyagite, calaverite, sylvanite, krennerite, pyrite and other sulfides (tellurides). Also found in veins in rocks or by sifting river beds.



Elemental Gold is purified by extractive metallurgy (using Cl₂ sources) or by cyaniding:



Gold is stable to oxygen and most corrosives, but is readily oxidized by Cl₂ or dissolved in aqua regia, forming one of the most common gold complexes, HAuCl₄ (chlorauric acid).

The most malleable element: 1 g can be beaten into a 1 m² sheet (~ 230 atoms thick)

Used in jewelry, dentistry, electronics, photography, coins, etc.



Introduction

Basic Principles of Gold Chemistry

Au(I) and Au(III) are the most common oxidation states of Gold, with Au(III) being most prevalent

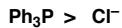
Au is a soft metal, and therefore prefers soft ligands (e.g. R₃P and carbanions):



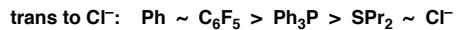
hard ← → soft

Propensity for strong trans effect and trans influence

trans effect: ability of L to stabilize L trans to itself, directing incoming ligands to the trans position (kinetic effect)



trans influence: ability of a L to weaken the M–L bond trans to itself in the ground state of the complex (thermodynamic effect)

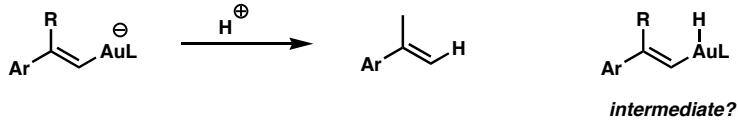


Introduction

Basic Principles of Gold Chemistry

Au organometallic complexes have a very low tendency to undergo β -H elimination; Au–H complexes are very rare.

Protodemetallation extremely fast; it is proposed that the Au-ate complex is protonated by acid, followed by reductive elimination. Weaker acids react more slowly for protonolysis of the Au–C intermediate.



Au(I) and Au(III) ligand exchange reactions are associative, and can occur at extremely high rates.

Although Au complexes can undergo oxidative addition/reductive elimination, these processes are rare except for a few well defined cases. The lack of oxidation state change makes coupling chemistry (think Pd) difficult.

Many mechanisms proposed with the following chemistry, but it is important to note that in many cases the mechanism, and even the oxidation state of the catalytically active species are not known.

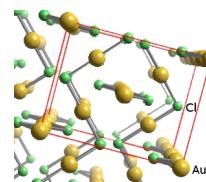
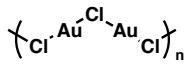
Au(I) Complexes

Au(I) complexes are d^{10} and prefer to be linear, two-coordinate

- can be 3-coordinate trigonal planar
- can be 4-coordinate tetrahedral

AuCl

– commercially available source of Au(I); exists as a polymeric chain with μ -Cl L's



– bench stable, but can reduce to Au(0) slowly:



– R_3P can dissociate to form monomeric $(\text{R}_3\text{P})\text{AuCl}$



Au(I) Complexes

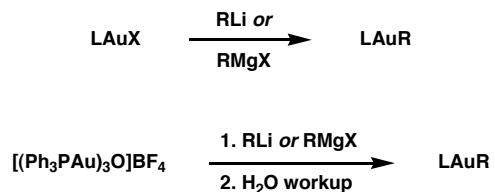
$[(\text{Ph}_3\text{PAu})_3\text{O}]\text{BF}_4$

- common source of electrophilic Au(I); useful in organometallic synthesis
- air and moisture stable



LAuR

- readily prepared from L-stabilized Au(I) halide; bench stable complexes



Inorg. Chem. **1993**, *32*, 1946
J. Organomet. Chem. **1989**, *369*, 267

Cationic Au(I) Complexes

Common methods for generation of LAu^\oplus :

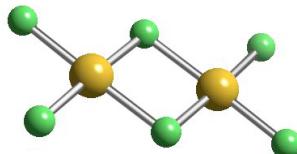
1. AgX , where $\text{X} = \text{non-coordinating anion}$
2. $\text{LAuCH}_3 + \text{strong acid}$ (e.g. H_2SO_4 , MsOH , HBF_4)
3. $\text{LAuX} + \text{BF}_3\cdot\text{Et}_2\text{O}$
4. $[(\text{LAu})_3\text{O}]\text{BF}_4 + \text{BF}_3\cdot\text{Et}_2\text{O}$

Au(III) Complexes

Au(III) complexes are d⁸ and prefer to be square planar, four-coordinate; best known oxidation state

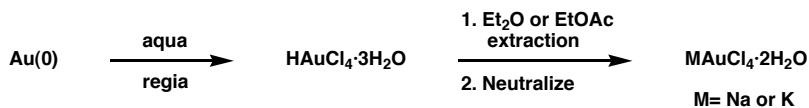
AuCl₃

– commercially available source of Au(III); exists as a dimer(Au₂Cl₆) with μ -Cl L's



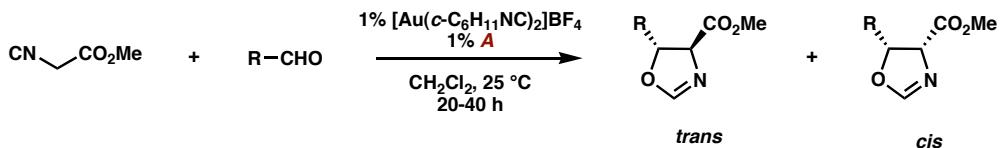
HAuCl₄·3H₂O and NaAuCl₄·2H₂O

– the cheapest available source of Au(III)

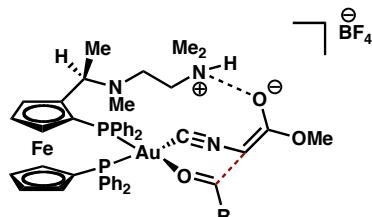
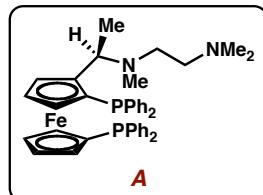


C–C Bond Forming Reactions

Catalytic, Asymmetric Aldol



R	% yield	trans/cis ratio	%ee trans
Ph	98	89/11	96
Me	100	84/16	72
c-Hex	95	97/3	90
t-Bu	100	100/0	97

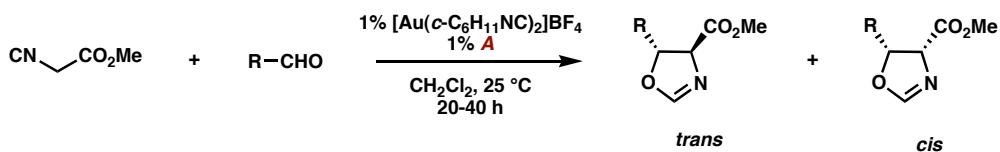


Proposed Transition State Model

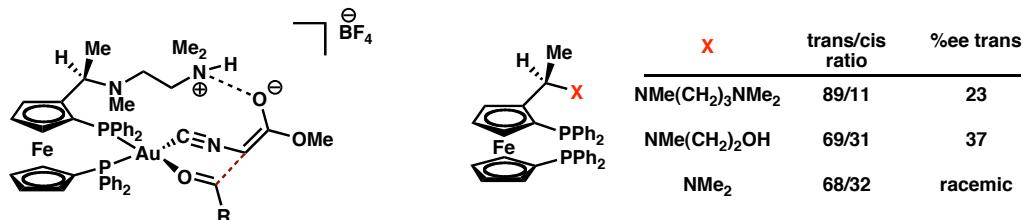
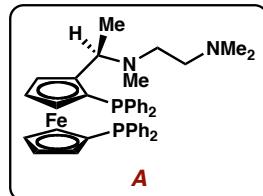
Ito, Y.; Hayashi, T. *JACS* **1986**, *108*, 6405
Ito, Y. *Chem. Rev.* **1992**, *92*, 857

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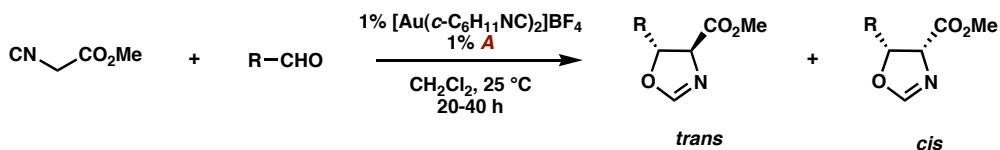


Proposed Transition State Model

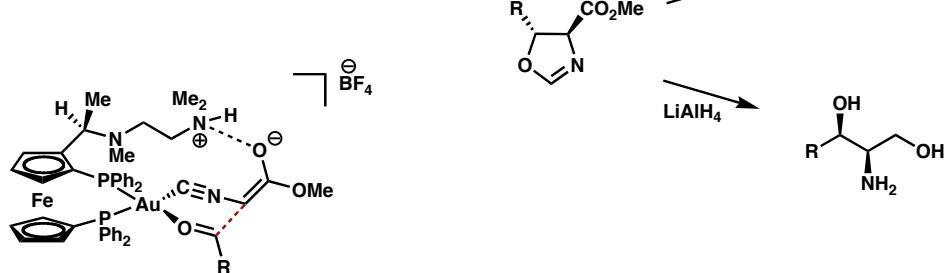
Ito, Y.; Hayashi, T. *JACS* **1986**, *108*, 6405
Ito, Y. *Chem. Rev.* **1992**, *92*, 857

C–C Bond Forming Reactions

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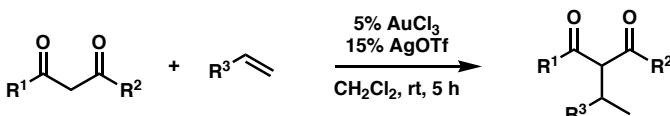


Proposed Transition State Model

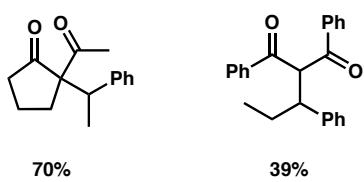
also see: Ito, Y.; Hayashi, T. *Tet. Lett.* **1988**, *29*, 235
Lin, Y.-R. *Tet. Asymm.* **1999**, *10*, 855

C–C Bond Forming Reactions

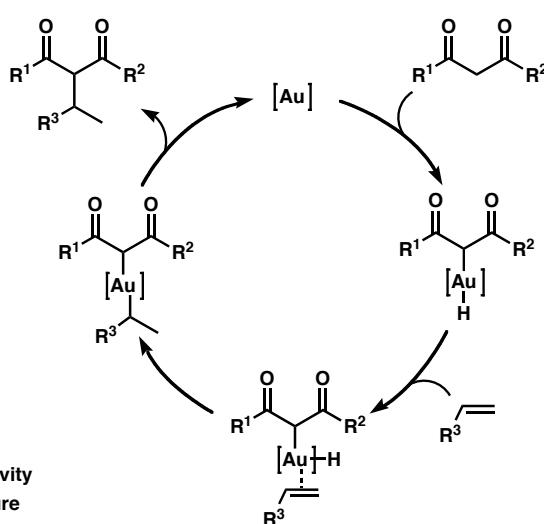
Stabilized Nucleophilic Additions to Alkenes



R ¹	R ²	R ³	% yield
Me	Me	Ph	89
Me	Me	p-MeOC ₆ H ₅	62
Ph	Me	m-ClC ₆ H ₅	67
Ph	Ph	Ph	93



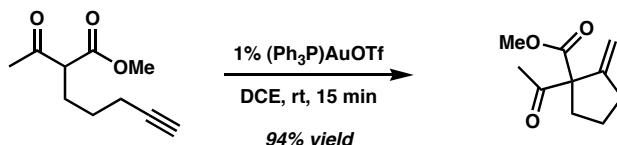
- (Ph₃P)AuCl or (c-HexNC)AuCl showed decreased reactivity
- β -ketoesters reacted but gave a complex reaction mixture
- alkene added by syringe pump



Li, C.-J. *JACS* 2004, 126, 6884

C–C Bond Forming Reactions

Conia-Ene 5-exo-dig Cyclization



- 1% [(Ph₃PAu)₃O]BF₄ + 5% TfOH same result; AgOTf gave no reaction
- no precaution to exclude air or moisture necessary

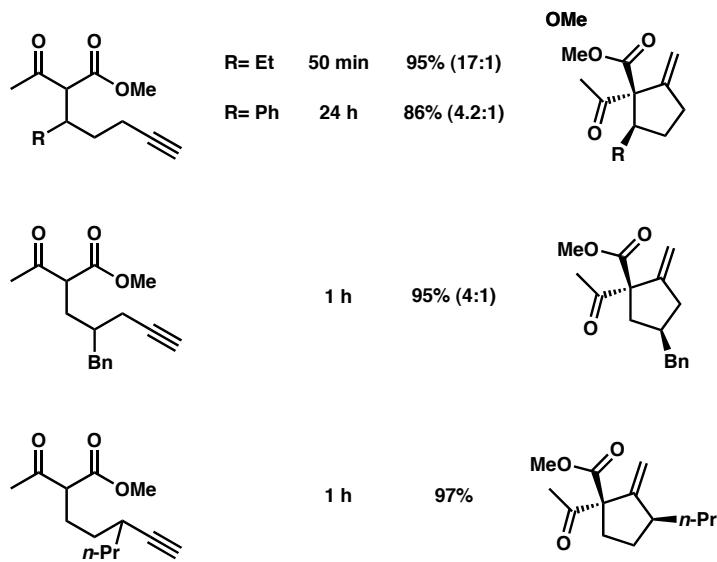
substrate	time	product	yield
 X = CH ₂	n = 1 1 h		90%
	2 18 h		90% ^a
	1 16 h		88%
	8 h		83%
	5 min		99%

^a 5% catalyst used

Toste, F.D. *JACS* 2004, 126, 4526

C–C Bond Forming Reactions

Conia-Ene 5-exo-dig Cyclization

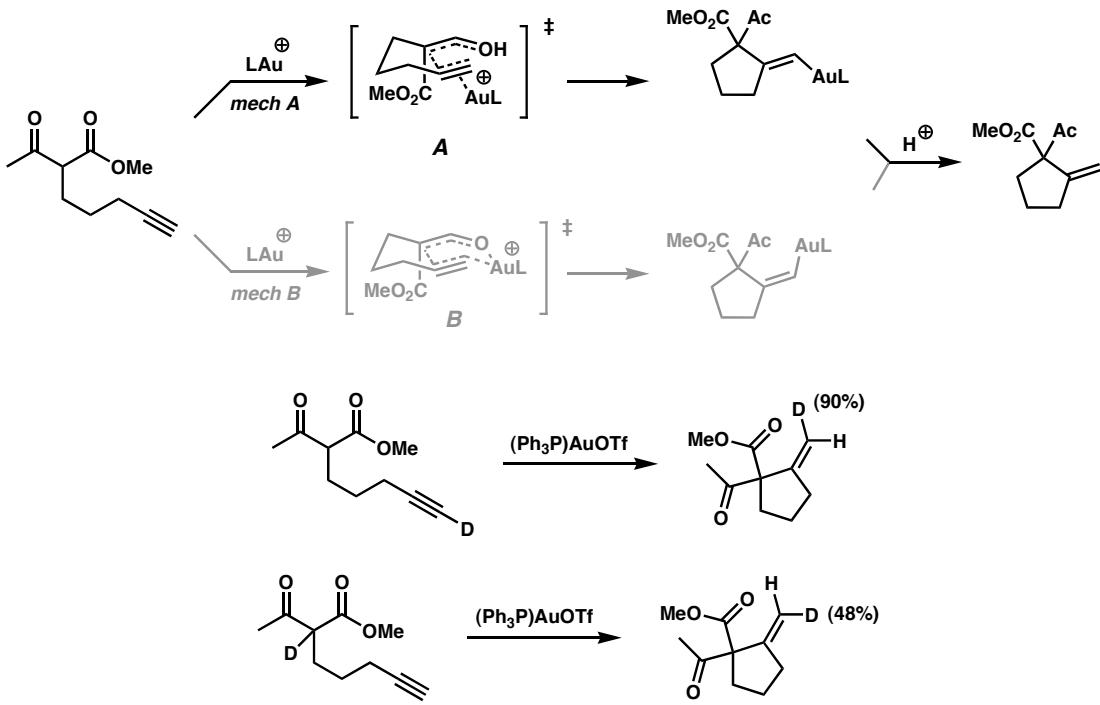


diastereoselectivity implies some degree of ordering in the transition state

Toste, F.D. *JACS* 2004, 126, 4526

Conia-Ene 5-exo-dig Cyclization

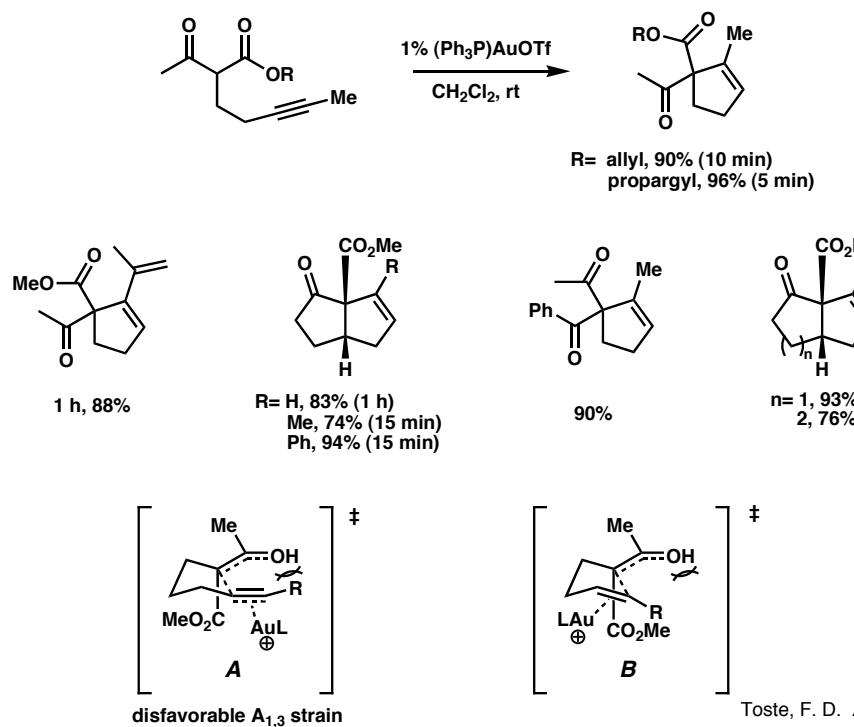
Mechanistic Considerations



Toste, F.D. *JACS* 2004, 126, 4526

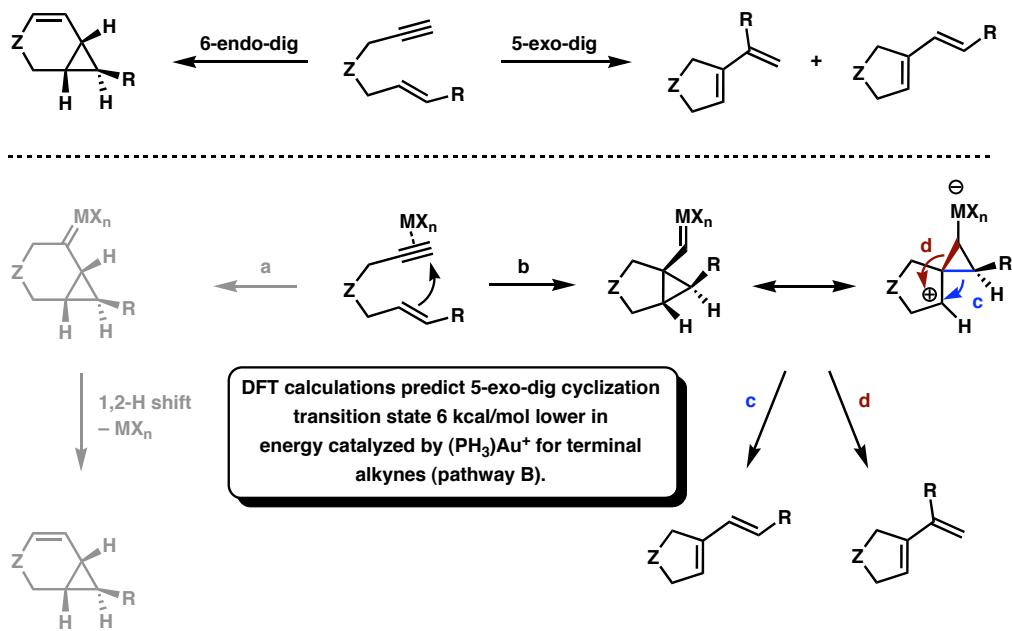
C–C Bond Forming Reactions

5-endo-dig Carbocyclization



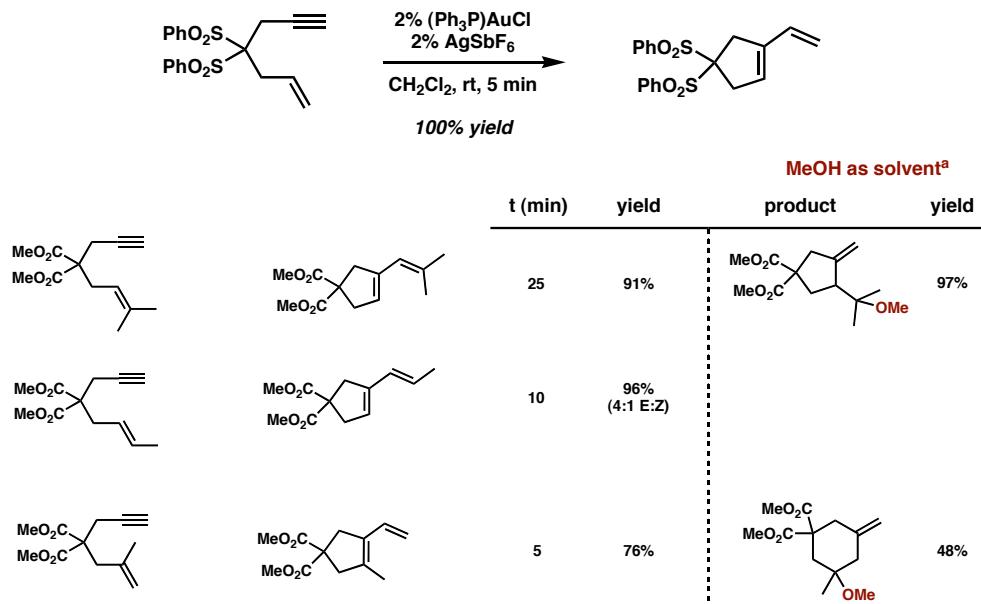
C–C Bond Forming Reactions

Enyne Cycloisomerization- Theoretical Predictions



C–C Bond Forming Reactions

Enyne Cycloisomerization- Experimental Observations

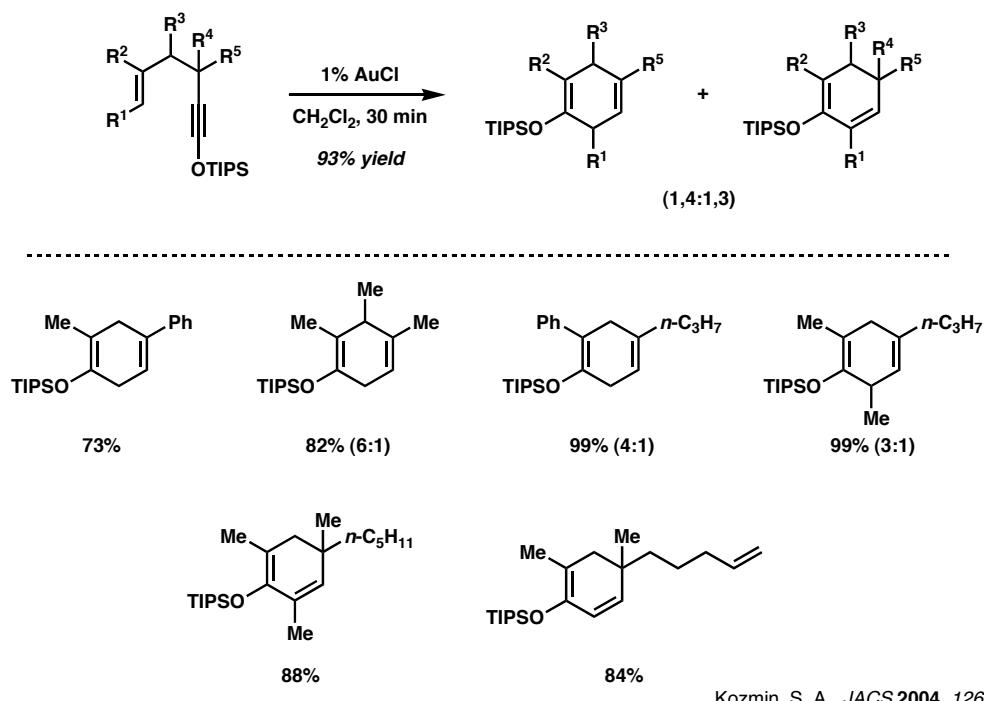


Echavarren, A. M. *ACIE* 2004, 43, 2402
Echavarren, A. M. *JACS* 2001, 123, 10511

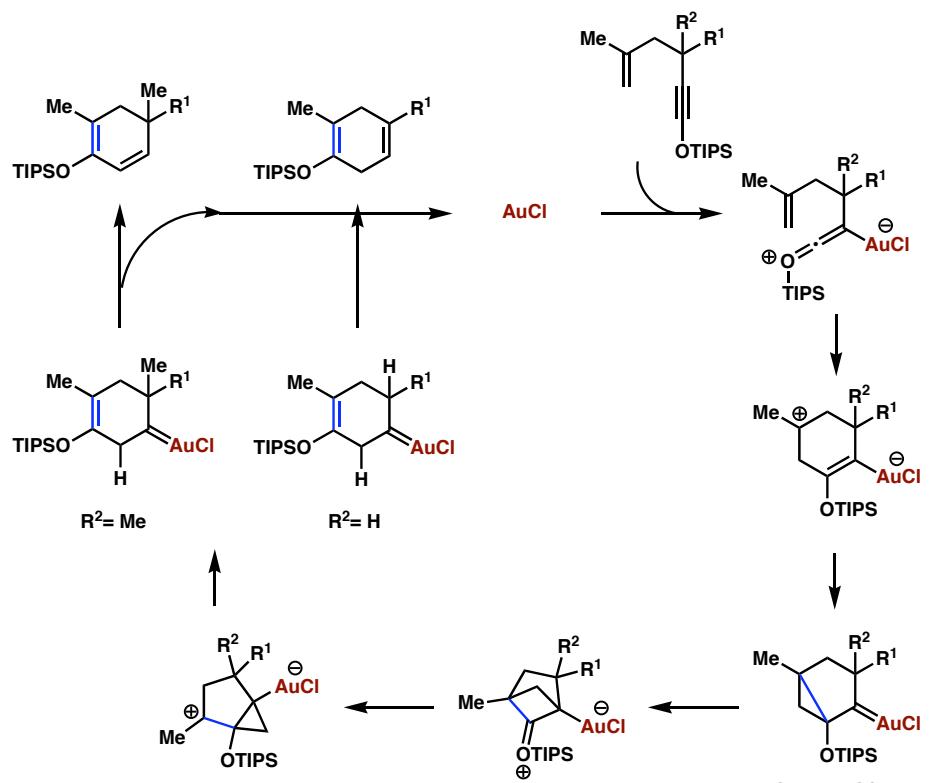
^a Reaction run with 3% (Ph₃P)AuCH₃ with acid co-catalyst (HBF₄ or H₃PW₁₂O₄₀). Reaction times are 4 and 12 h.

C–C Bond Forming Reactions

Enyne Cycloisomerization- Synthesis of 1,3- and 1,4-dienes



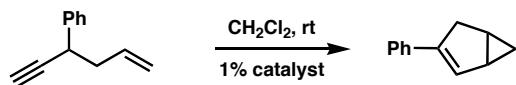
Proposed Mechanism for Enyne Cycloisomerization for the Synthesis of 1,3- and 1,4-dienes



Kozmin, S. A. *JACS* 2004, 126, 11806

C–C Bond Forming Reactions

Catalyst Optimization for Enyne Cycloisomerization



catalyst	conversion
$(\text{MeCN})\text{PdCl}_2$, 24 h	~ 4%
PtCl_2 , 24 h	~ 4%
$\text{PtCl}_2, \text{AgBF}_4$, 24 h	~ 5%
AgBF_4 , 24 h	trace
$(\text{Ph}_3\text{P})\text{AuCl}, \text{AgBF}_4$, 5 min	100%
$(\text{Ph}_3\text{P})\text{AuCl}$, 24 h	0%
AuCl_3 , 3 h	50%

5% AuCl_3 , 15% AgOTf gave complete conversion but substantial decomposition

Toste, F. D. *JACS* 2004, 126, 10858

C–C Bond Forming Reactions

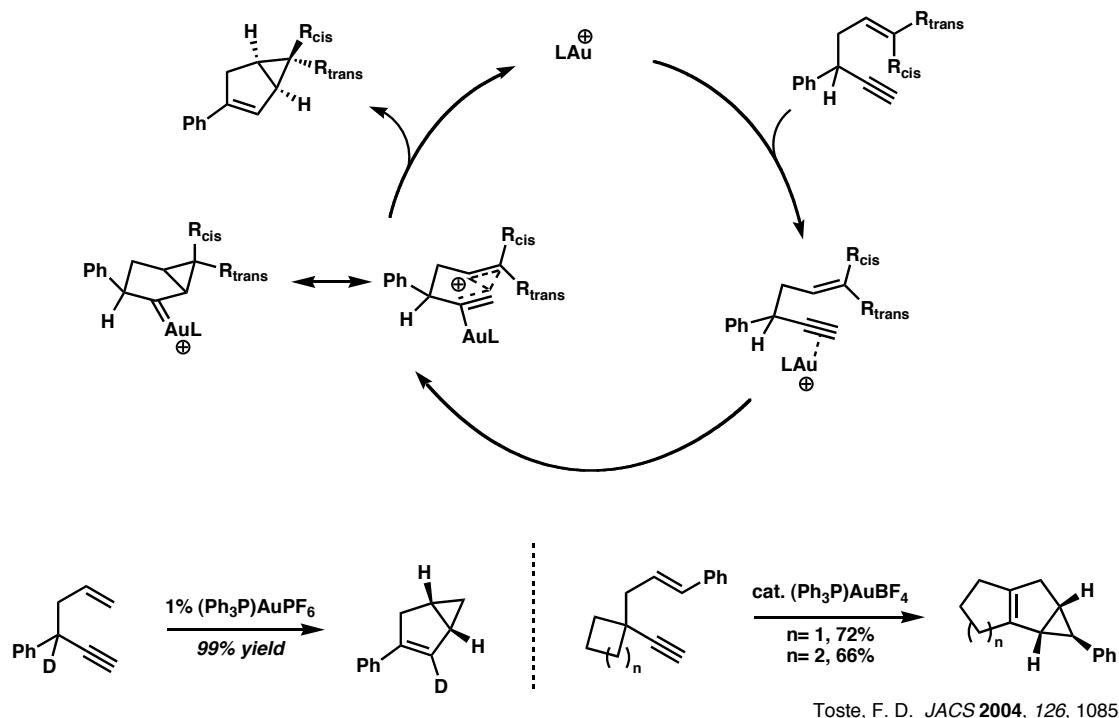
Substrates for Enyne Cycloisomerization

substrate	catalyst	product	yield (d.r.)
	1% (Ph_3P) AuSbF_6		95%
	1% (Ph_3P) AuSbF_6		94%
	1% (Ph_3P) AuSbF_6		98% (>99:1)
	1% (Ph_3P) AuSbF_6		96% (97:3)
	3% (Ph_3P) AuPF_6		99% (>99:1) 91% ee

Toste, F. D. *JACS* 2004, 126, 10858

C–C Bond Forming Reactions

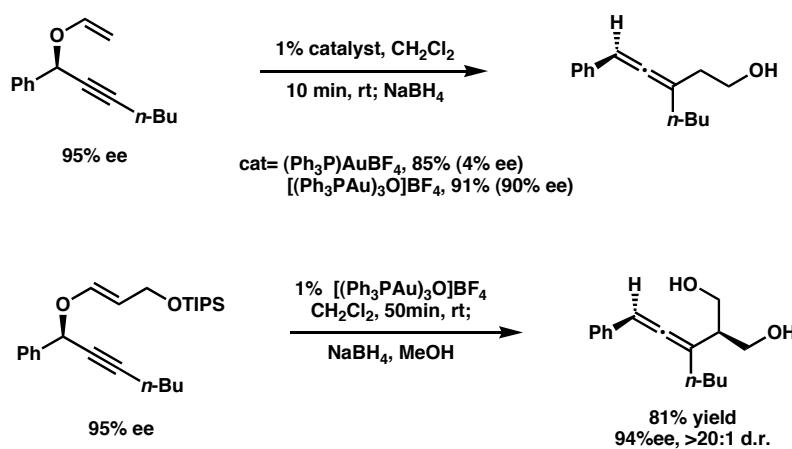
Proposed Mechanistic Hypothesis



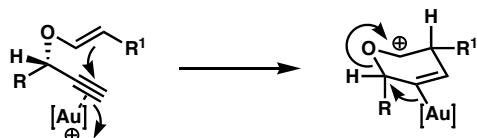
Toste, F. D. *JACS* 2004, 126, 10858

C–C Bond Forming Reactions

Cationic Au(I) Propargyl-Claisen Rearrangement



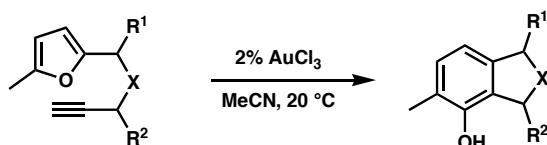
specificity occurs when pseudoaxial R avoids $\text{A}_{1,2}$ interaction with vinyl Au



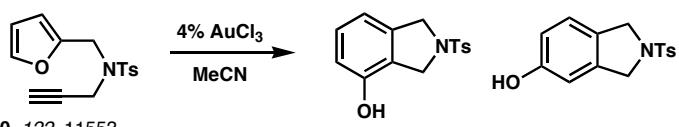
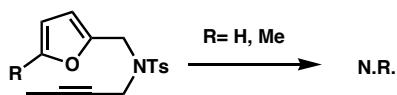
Toste, F. D. *JACS* 2004, 126, 15978

C–C Bond Forming Reactions

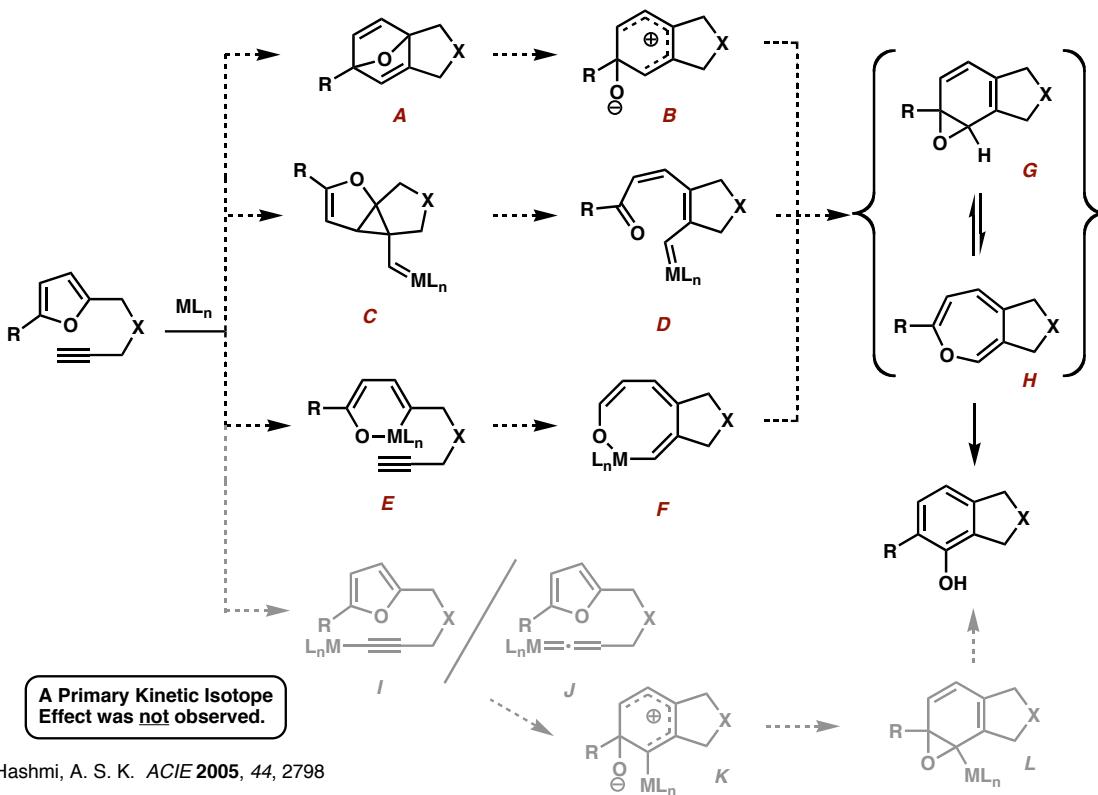
Phenol Synthesis



X	R ¹	R ²	% yield	
CH ₂	H	H	65	
NTs	H	H	97	– Pd(II), Pt(II) work, but very slowly
NTs	Me	H	94	– rxn not sensitive to O ₂ or H ₂ O
NTs	H	Me	93	– up to 5 equiv ¹⁸ OH ₂ gave < 1% ¹⁸ O incorporation
C(CO ₂ Me) ₂	H	H	88	
N(Ts)CH ₂	H	H	81	

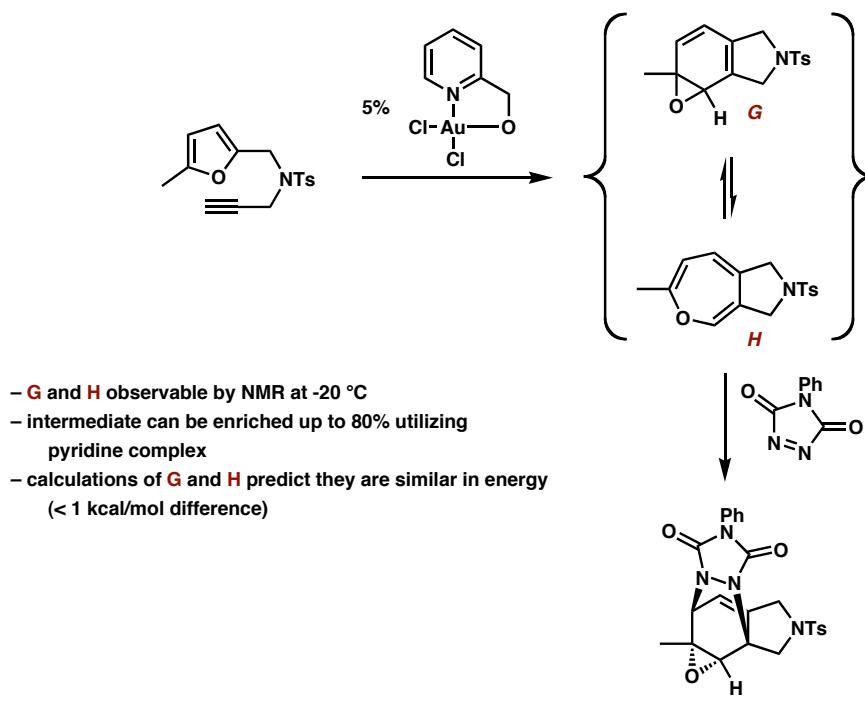


Hashmi, A. *JACS* 2000, 122, 11553
Hashmi, A. *Org. Lett.* 2001, 3, 3769



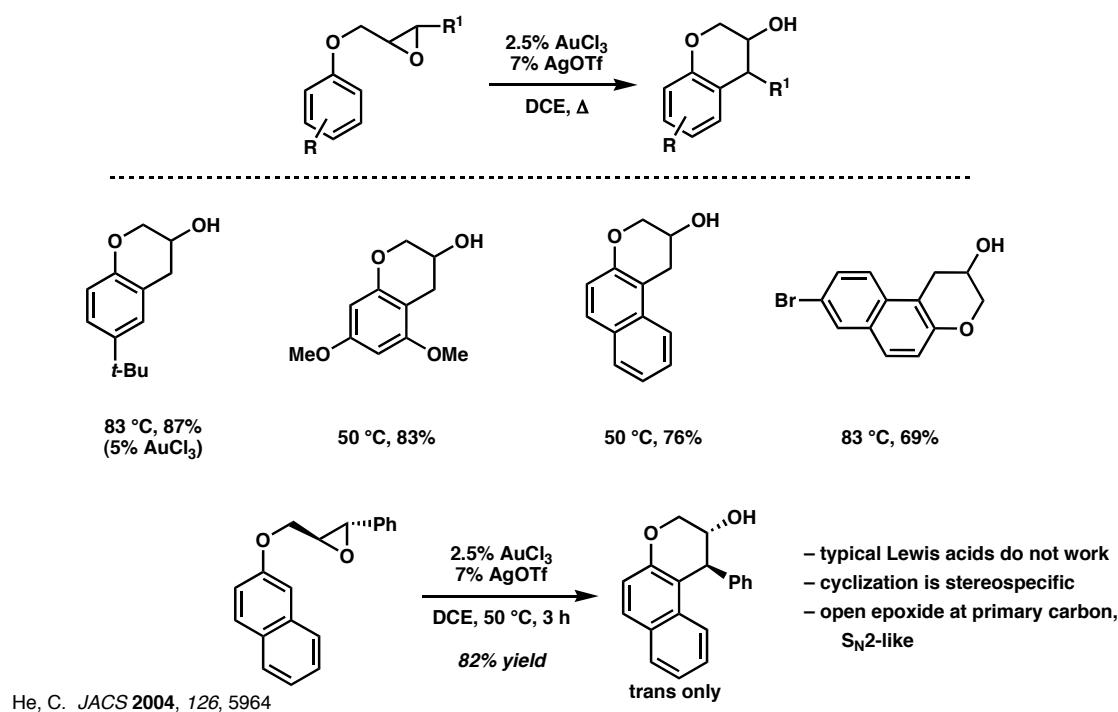
C–C Bond Forming Reactions

Phenol Synthesis



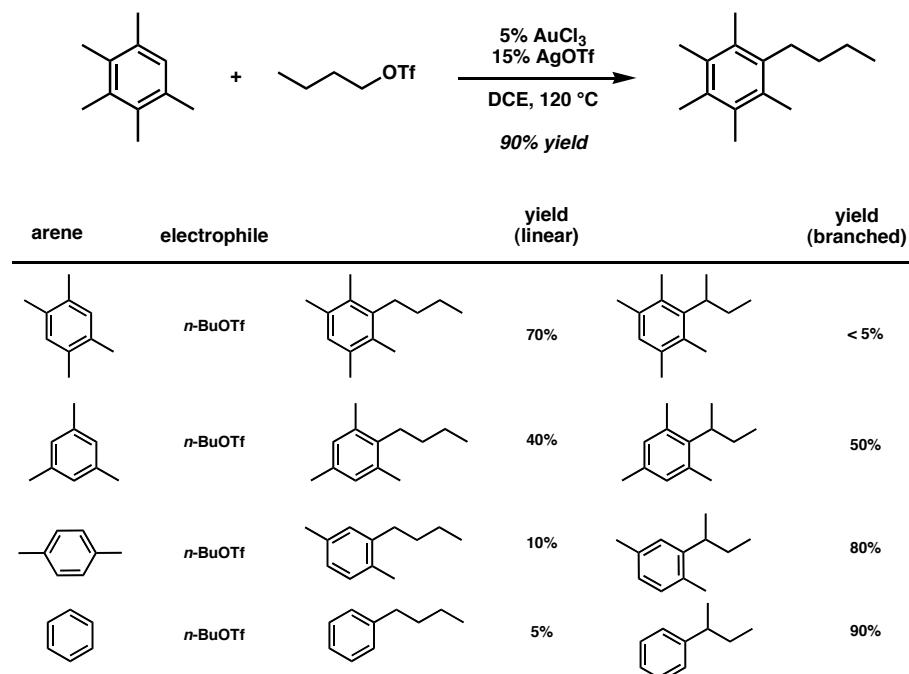
C–C Bond Forming Reactions

Arene Functionalization



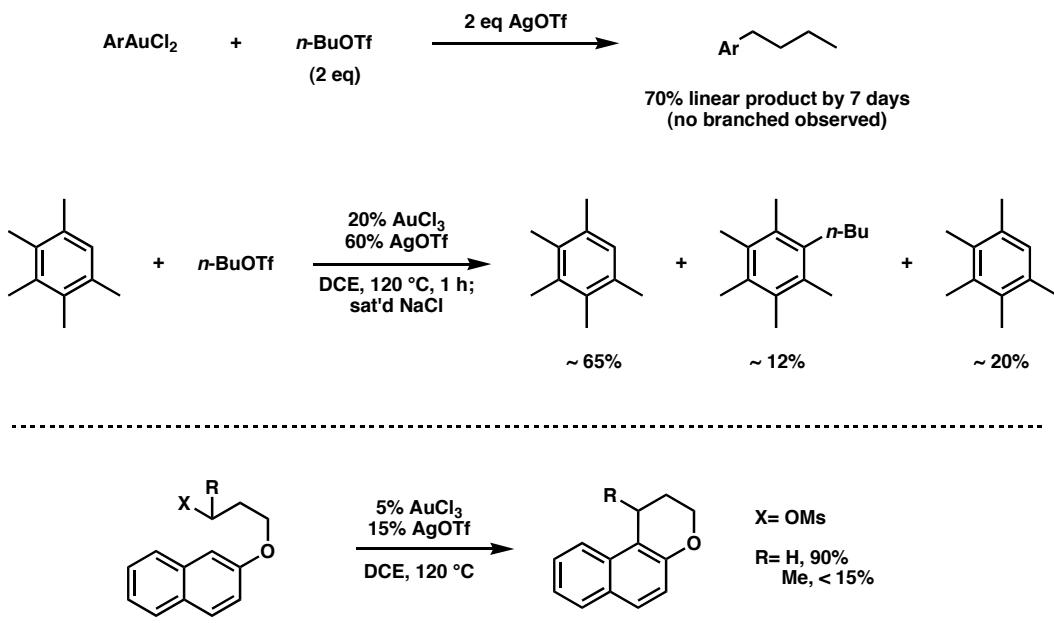
C–C Bond Forming Reactions

Electron-rich Arene Functionalization



C–C Bond Forming Reactions

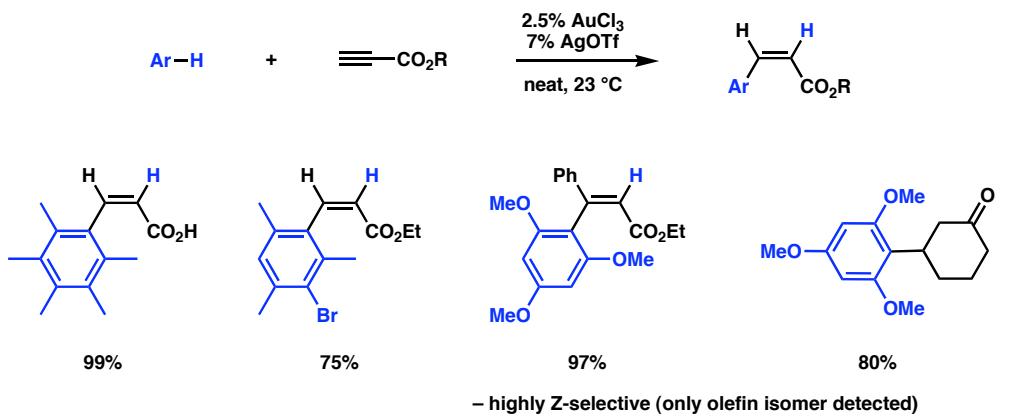
Electron-rich Arene Functionalization- Mechanistic Insight



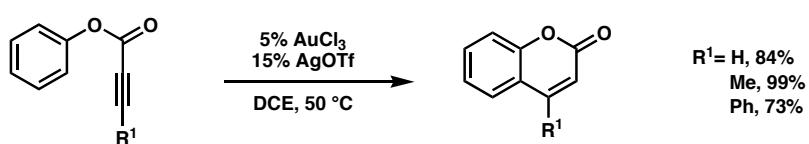
He, C. *JACS* **2004**, *126*, 13596

C–C Bond Forming Reactions

Arene Addition to Electron-deficient Alkynes



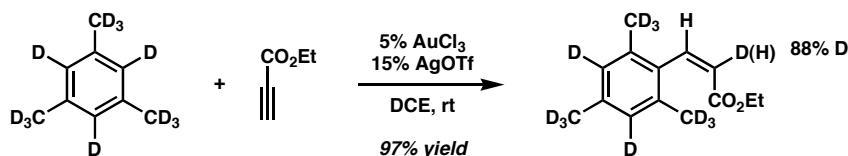
– immediate color change when arene and cationic complex mixed



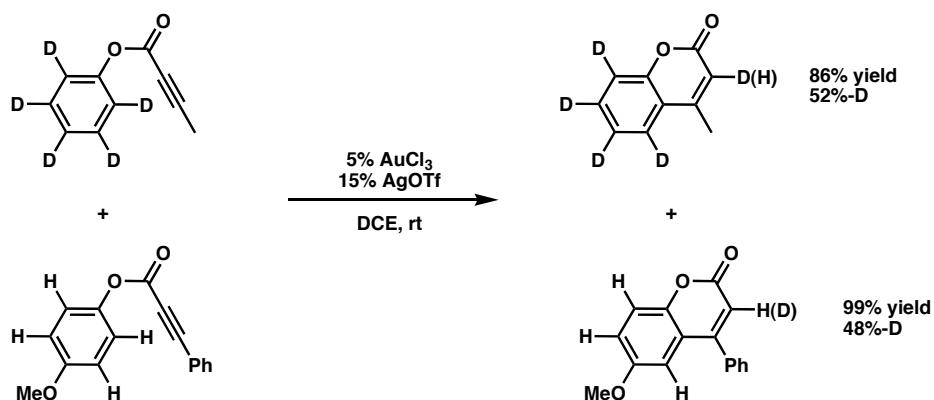
He, C. *JOC* **2004**, *69*, 3669

C–C Bond Forming Reactions

Labeling and Crossover Experiments



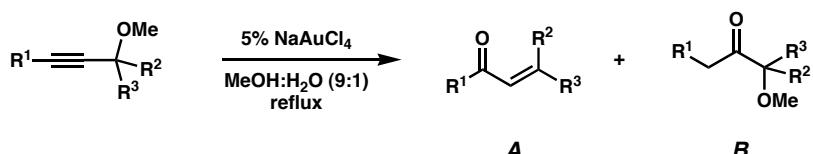
Crossover Experiment



He, C. *JOC* 2004, 69, 3669

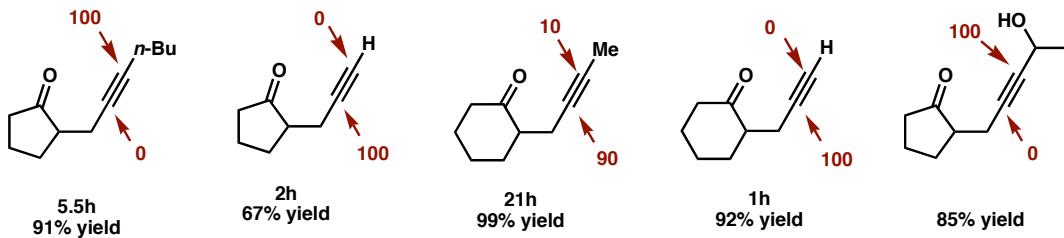
C–O Bond Forming Reactions

Directed Hydration of Alkynes



R ¹	R ²	R ³	time (h)	product	% yield
n-C ₅ H ₁₁	H	n-C ₄ H ₉	2	A ^a	79
CH ₃	H	n-C ₅ H ₁₁	2	A ^a	75
n-C ₆ H ₁₃	CH ₃	CH ₃	10	A	70
H	H	n-C ₅ H ₁₁	1	B	91

^a Product isolated as a single olefin isomer (E).

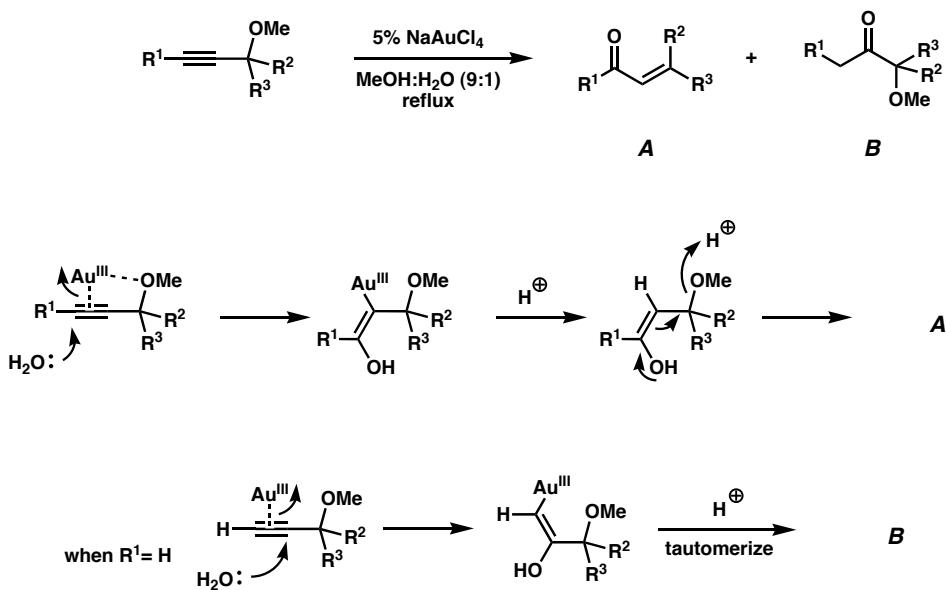


conditions: 3% NaAuCl₄·2H₂O, MeOH:H₂O (10:1), ultrasound

Utimoto, K. *Bull. Chem. Soc. Jpn.* 1991, 64, 2013
Utimoto, K. *Tet. Lett.* 1997, 28, 3127

C–O Bond Forming Reactions

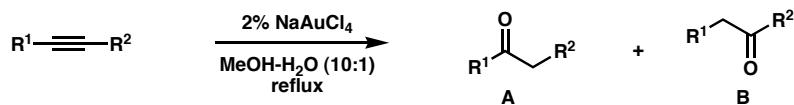
Directed Hydration of Alkynes - Mechanistic Hypothesis



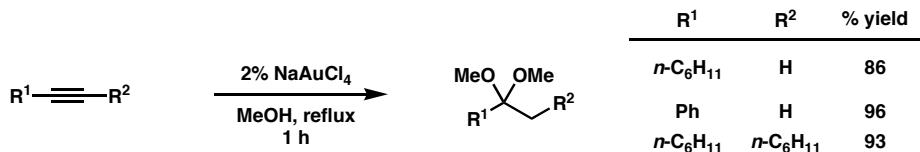
Utimoto, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2013

C–O Bond Forming Reactions

Hydration of Alkynes



R ¹	R ²	time (h)	product	% yield
n-C ₆ H ₁₃	H	1	A	91
HO(CH ₂) ₉	H	1	A	91
n-C ₆ H ₁₃	CH ₃	5	A:B (40:60)	94
Ph	C ₂ H ₅	10	A:B (57:43)	28



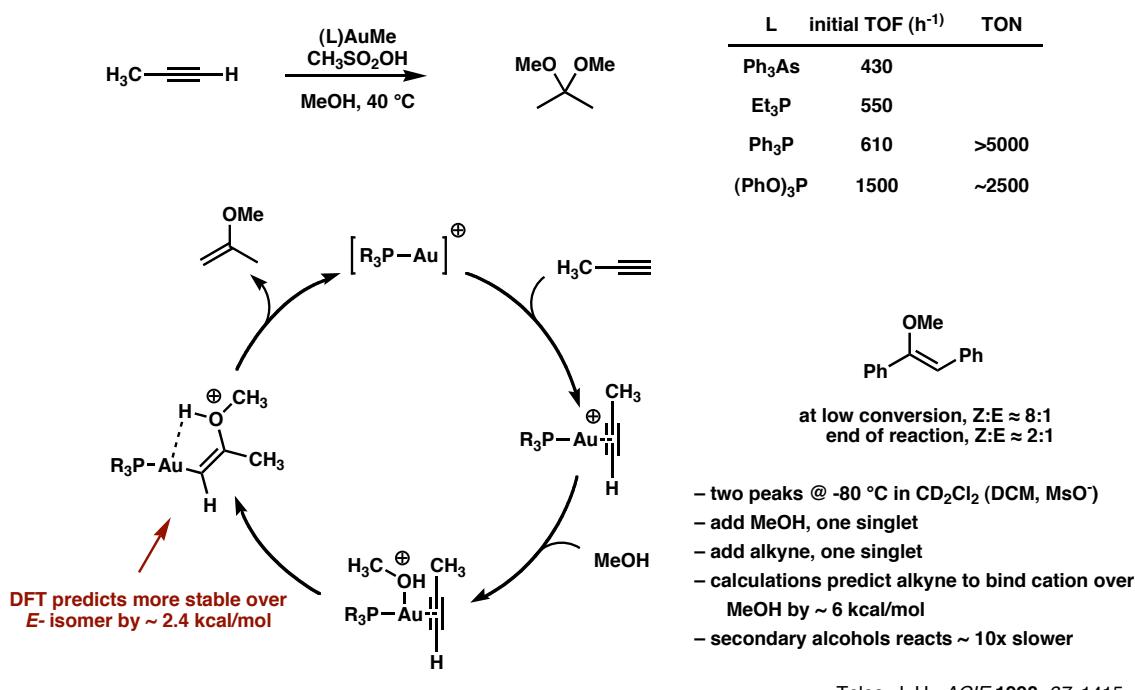
– reproducible on gram scale

– reduced to Au(0) during reaction, preventing lower catalyst loadings

Utimoto, K. *J. Org. Chem.* **1991**, *56*, 3729

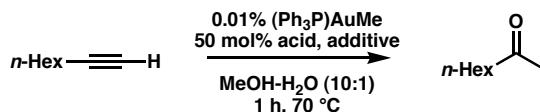
C–O Bond Forming Reactions

Efficient Hydration of Propyne



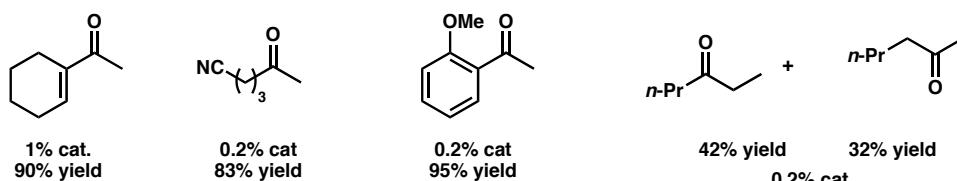
C–O Bond Forming Reactions

Efficient Hydration of Alkynes



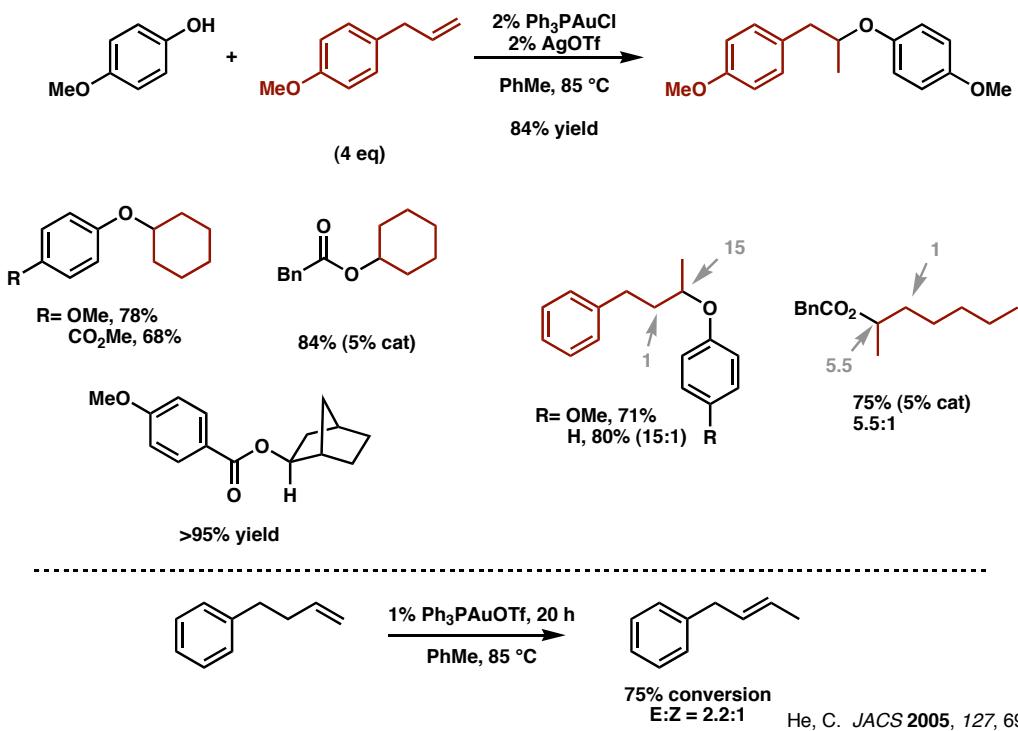
acid	additive	% yield
H_2SO_4	–	35
H_2SO_4	CO (1atm)	99
$\text{CH}_3\text{SO}_3\text{H}$	–	77
$\text{H}_3\text{PW}_{12}\text{O}_{40}$	–	80

- w/o additional L, catalyst decomposition observed (particles)
- H_2SO_4 conditions w/o added L



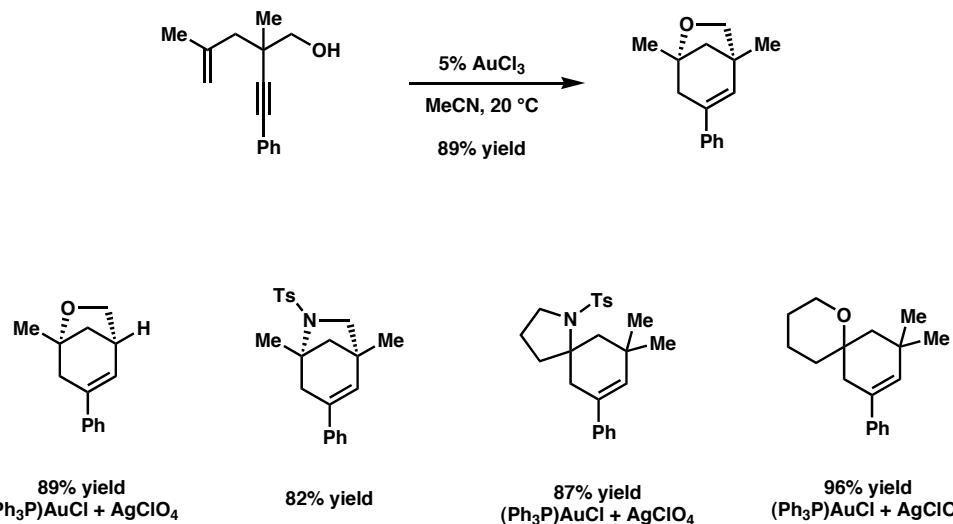
C–O Bond Forming Reactions

Alcohol Addition onto Unactivated Terminal Olefins



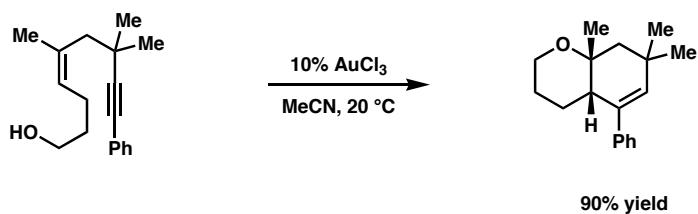
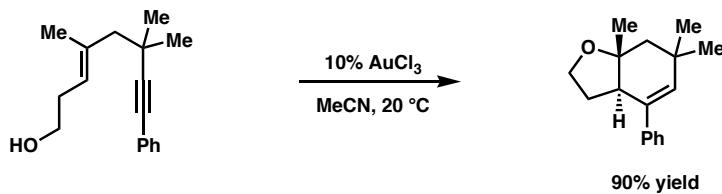
C–X Bond Forming Reactions

Intramolecular Trapping of Enyne Cycloisomerization Adduct with Heteroatom Nucleophile



C–X Bond Forming Reactions

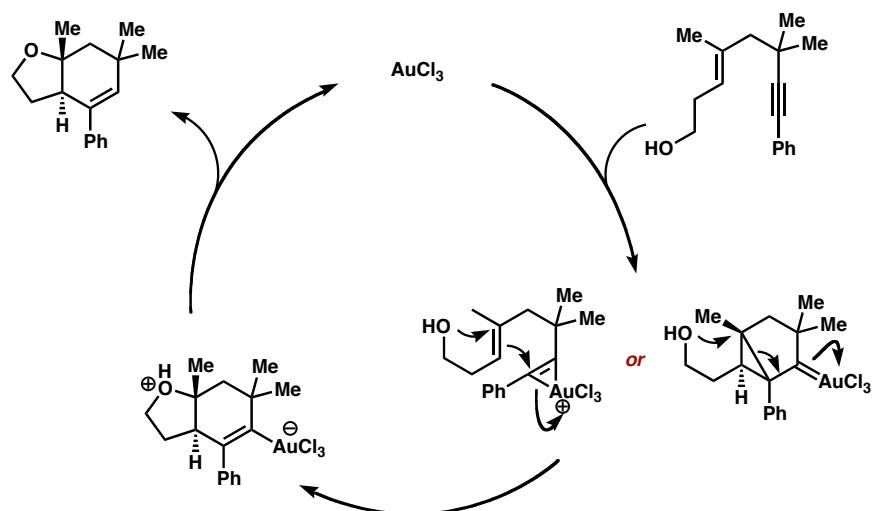
Intramolecular Trapping of Enyne Cycloisomerization Adduct with Heteroatom Nucleophile



Kozmin, S. A. *JACS* **2005**, 127, 6962

C–X Bond Forming Reactions

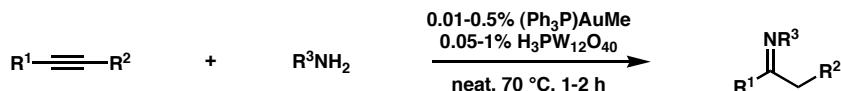
Mechanistic Rationale



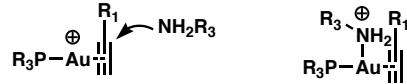
Kozmin, S. A. *JACS* **2005**, 127, 6962

C–N Bond Forming Reactions

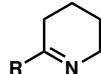
Hydroamination of Alkynes



R^1	R^2	R^3	% yield
C_6H_5	H	4-BrC ₆ H ₄	94
C_6H_5	H	4-NCC ₆ H ₄	90
2-C ₄ H ₃ S	H	C ₆ H ₅	87
<i>n</i> -C ₃ H ₇	CH ₃	4-BrC ₆ H ₄	32 + 29
C ₆ H ₅	H	C ₆ H ₅ NH	99



- internal alkynes less reactive (sterics?)
- reaction proceeds more smoothly if
 1. amine is more electron withdrawing
 2. alkyne is more electron donating
- Au(I) calculations predict B
- Attack by mode of A used to rationalize Au(III) amine additions (tetrahydropyridine synthesis)
- EWD amine as a better reactant supports B

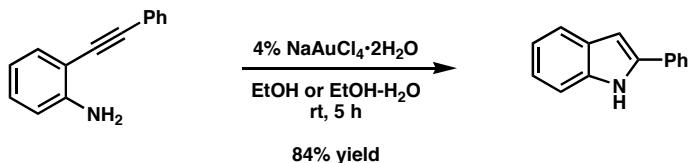


Utimoto, K. *Heterocycles* **1987**, *25*, 297
Utimoto, K. *Synthesis* **1991**, 975

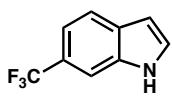
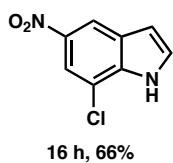
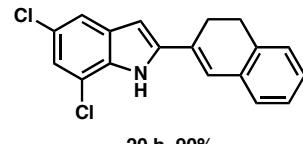
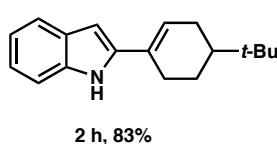
Tanaka, M. *Org. Lett.* **2003**, *5*, 3349

C–N Bond Forming Reactions

Indole Synthesis



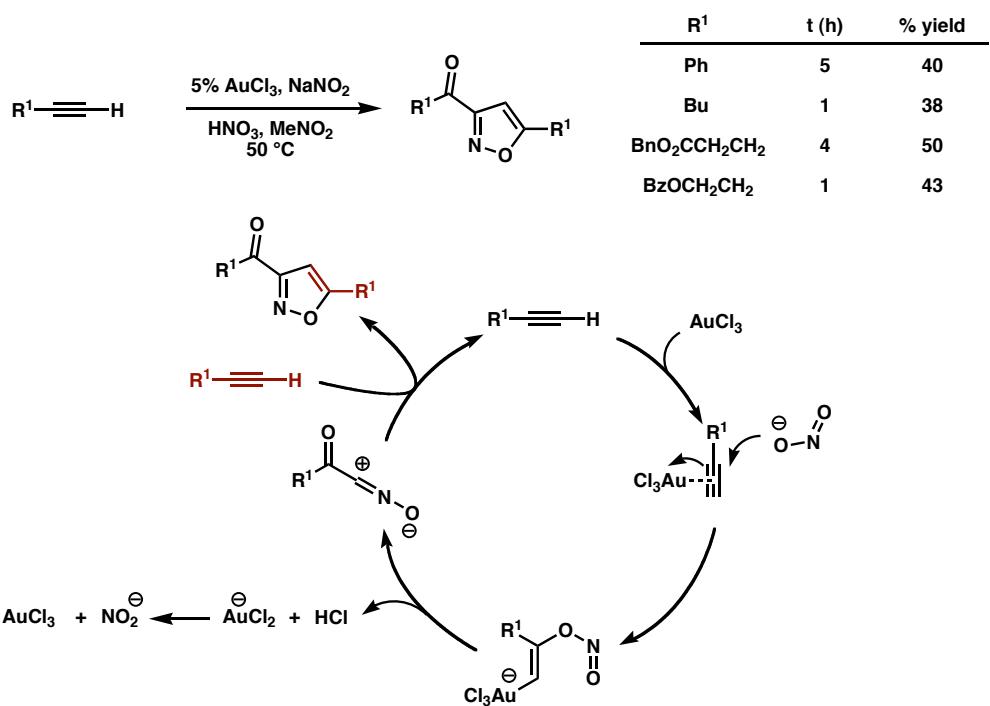
Au(III) salts gave best yields, AuCl (50%), PtCl₄ (20%), various Pd(II) and Cu(II) gave < 10%.



Marinelli, F. *Synthesis* **2004**, *4*, 610

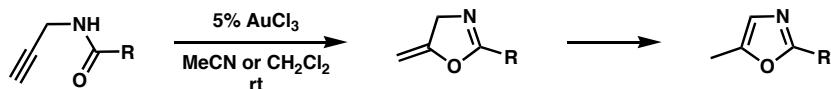
C–N,O Bond Forming Reactions

Isoxazole Synthesis

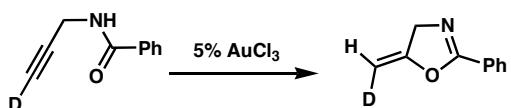


C–O Bond Forming Reactions

Oxazole Synthesis

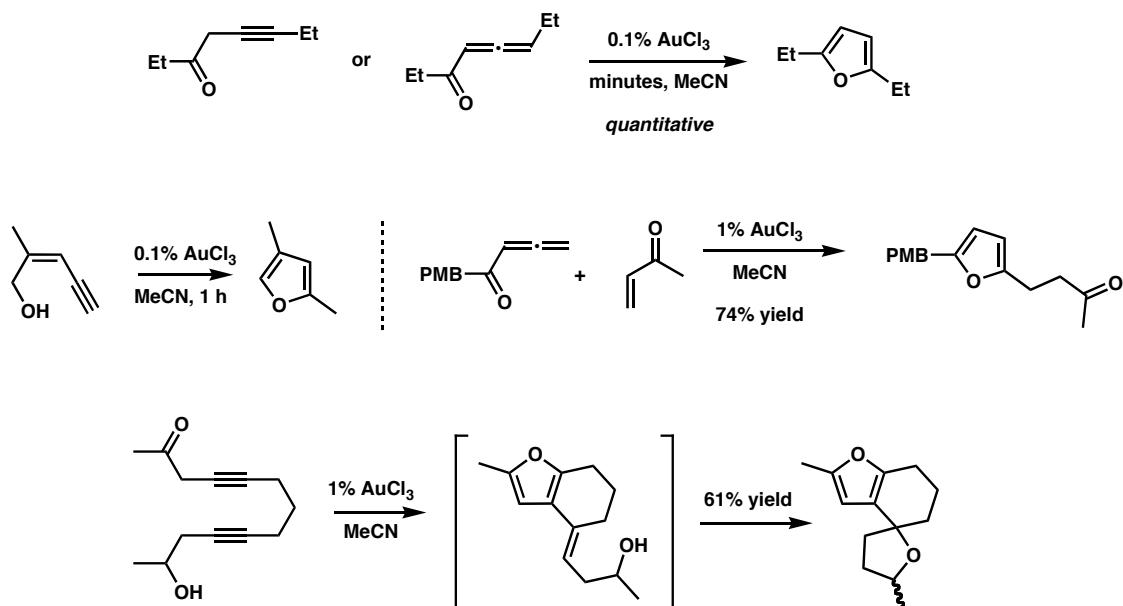


R	t (h)	% yield	
Me	12	>95	stereospecific addition of oxygen to activated alkyne
Ph	12	>95	
	20	>95	
	12	73	<ul style="list-style-type: none"> - can be enriched up to 95% before isomerization to oxazole - stable for weeks at -25 °C
	2	86	



C–O Bond Forming Reactions

Furan Synthesis

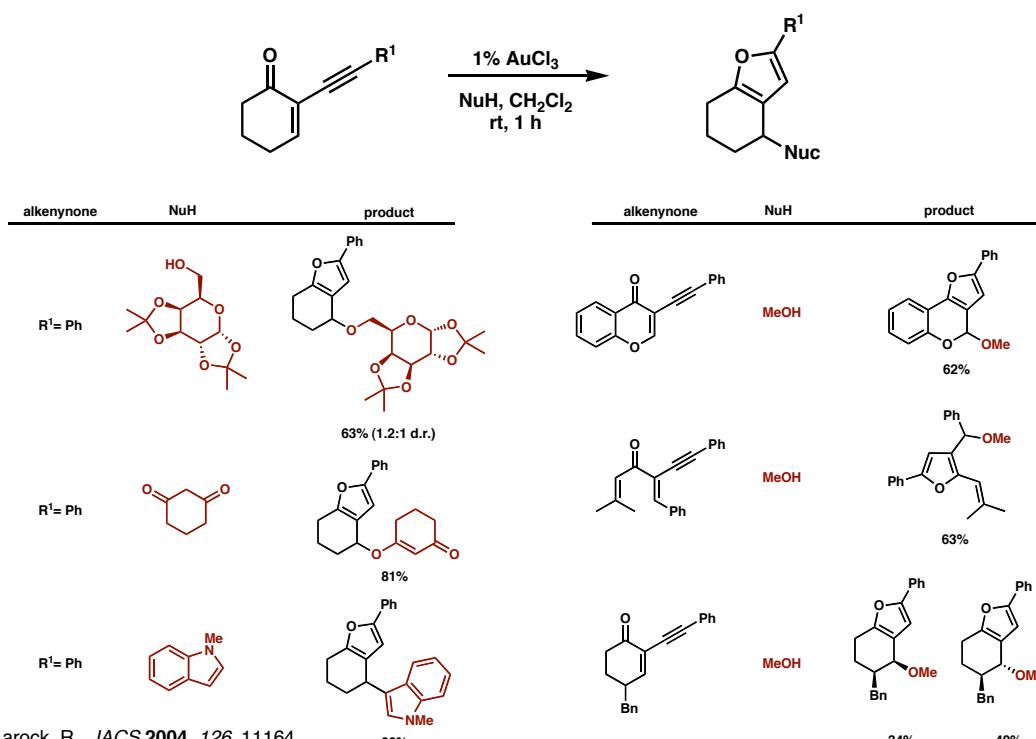


– Ag(I) very slow reaction, $\text{PdCl}_2(\text{MeCN})_2$ took about an hour

Hashmi, A. S. K. *ACIE* 2000, 39, 2285

C–O Bond Forming Reactions

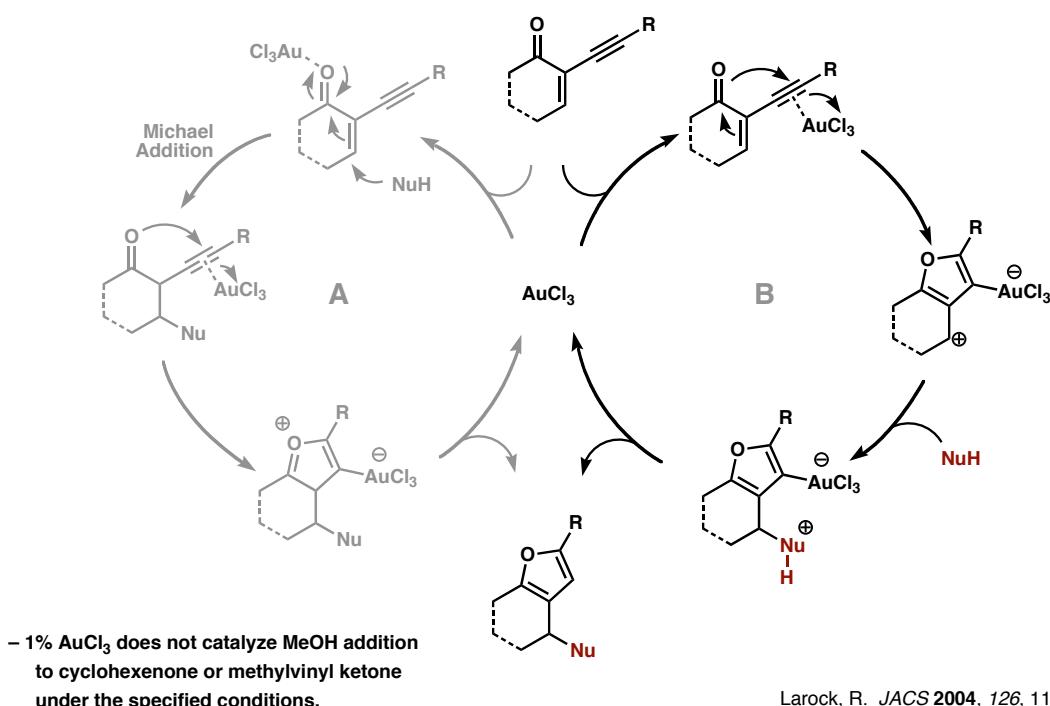
Furan Synthesis



Larock, R. *JACS* 2004, 126, 11164

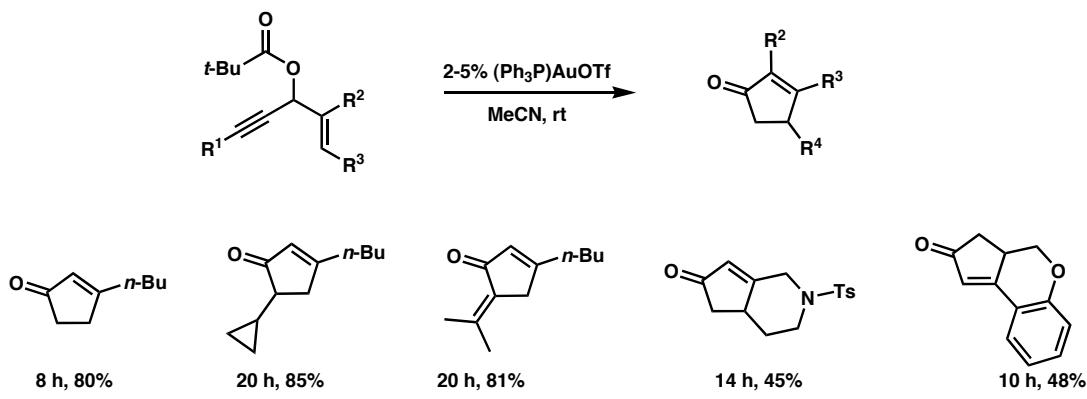
C–O Bond Forming Reactions

Furan Synthesis Mechanistic Rationale



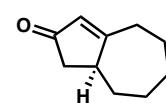
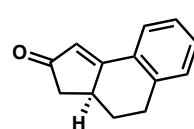
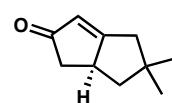
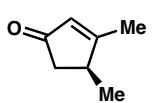
O-Assisted Bond Forming Reactions

Cyclopentanone Synthesis



conditions:
5% $(\text{Ph}_3\text{P})\text{AuSbF}_6$
MeCN, -20 °C

% yield
SM % ee
Product % ee

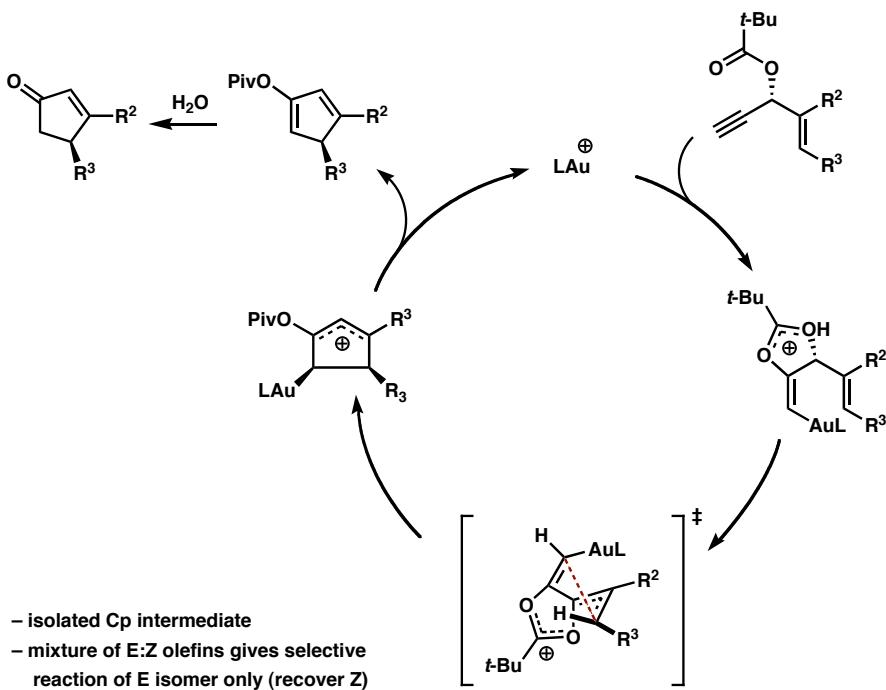


Toste, F. D. *JACS* 2005, 127, 5802

84	80	88	82
88	79	98	92
82	77	96	83

O-Assisted Bond Forming Reactions

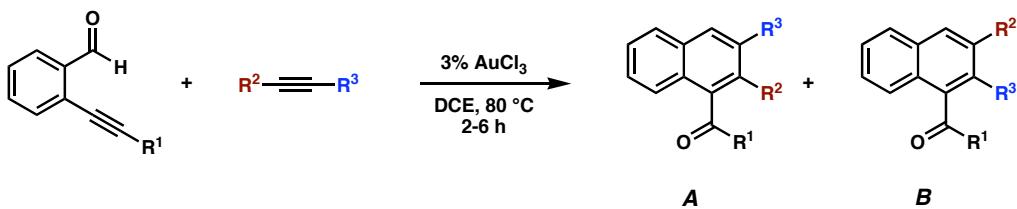
Cyclopentanone Synthesis



Toste, F. D. *JACS* **2005**, 127, 5802

O-Assisted Bond Forming Reactions

Naphthylketone Synthesis

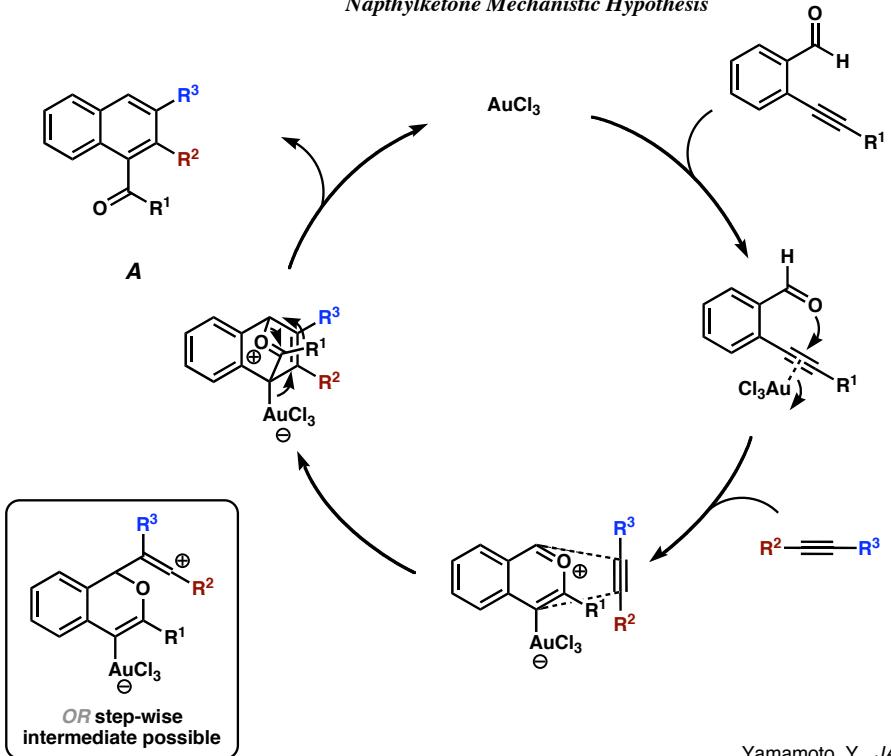


R^1	R^2	R^3	A:B ratio	% yield	
Ph	$n\text{-C}_3\text{H}_7$	H	92:8	91	
Ph	Ph	H	99:<1	96	\Rightarrow when $\text{R}^3 = \text{D}$
Ph	SiMe_3	H	16:84	82	
Ph	COCH_3	H	<1:99	75	NMR evidence for substitution pattern
Ph	Ph	SiMe_3	99:<1	92	
$n\text{-C}_6\text{H}_{13}$	Ph	H	92:8	91	- other solvents work (EtOAc, dioxane, MeCN) - no reaction w/o AuCl_3

Yamamoto, Y. *JACS* **2002**, 124, 12650

O-Assisted Bond Forming Reactions

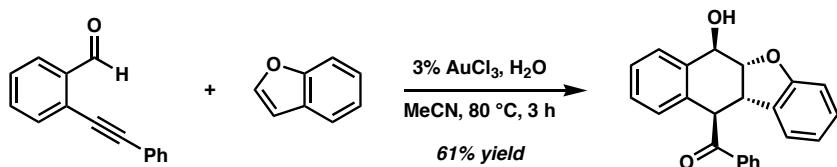
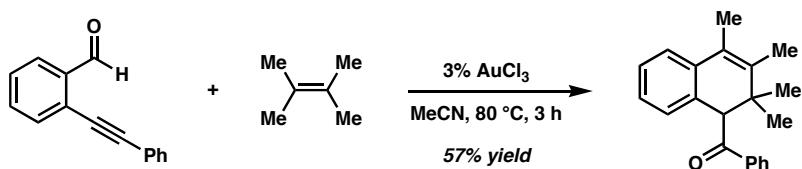
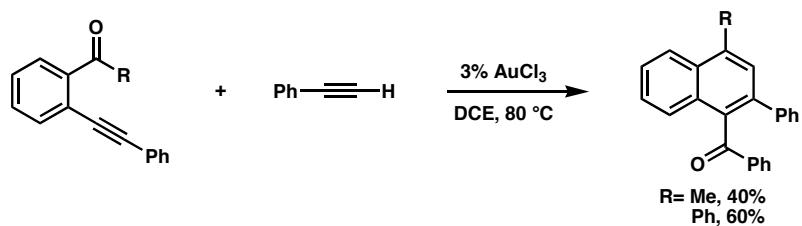
Naphthylketone Mechanistic Hypothesis



Yamamoto, Y. *JACS* 2002, 124, 12650

O-Assisted Bond Forming Reactions

Naphthylketone Mechanistic Hypothesis



Yamamoto, Y. *JACS* 2002, 124, 12650
Dyker, G. *ACIE* 2003, 42, 4399