Gold Catalysis in Organic Synthesis

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Why use gold catalysis for organic synthesis?

- Gold catalysed reactions show several characteristics that render them synthetically attractive:
  - Significant increases in molecular complexity;
  - Diverse set of reactions;
  - Mild reaction conditions (often room temperature);
  - Au(I) generally tolerant of oxygen;
  - Minimal use of additives;
  - Excellent chemoselectivity;
  - Asymmetric control possible;
  - Straightforward work-ups;
  - Robust readily accessible precatalysts;
  - Orthogonal reactivity to many other TM catalysed processes;
  - Au(I), Au(III) do not readily cycle between oxidation states (though see final section).

Talk Overview

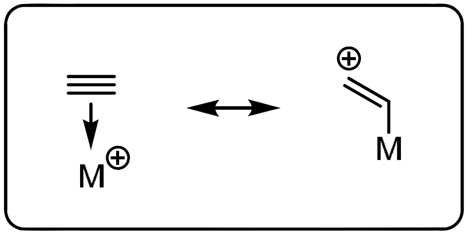
This talk is intended to give an overview of the breadth and depth of gold catalysis in the development of methodology for organic synthesis and its implementation.

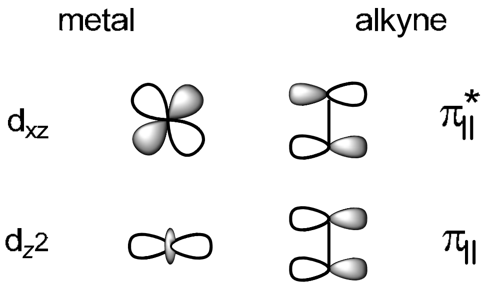
The talk is loosely broken down into sub-sections concerning particular types of overall reactivity:

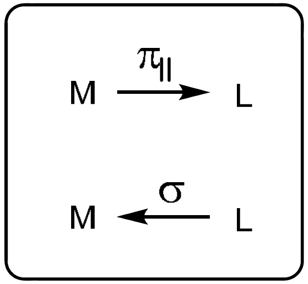
1. Gold as a π–acid
2. X-H addition across π–systems
3. Indirect X-H addition
4. C-H addition across π–systems
5. Gold Intermediates
6. C-X addition across π–systems
7. Cycloadditions
8. Enyne cycloisomerisations
9. Propargylic carboxylates
10. Preparation of gold carbenoids
11. Recent advances in gold redox cycles

Gold as a π-acid catalyst

- A diverse range of transformations have been developed based on the activation of alkynes by gold (and platinum) salts and complexes:





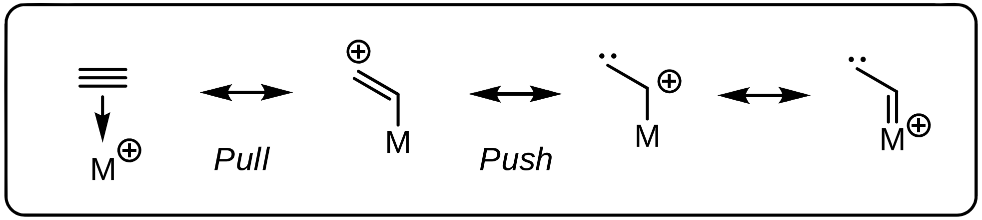


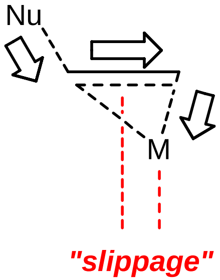
- π-acids:
  - Metal fragments that bind to a C-C multiple bond
  - Deprive multiple bonds of a part of their electron density
  - Induce positive charge onto multiple bonds
  - “soft” counterparts to conventional Lewis acids

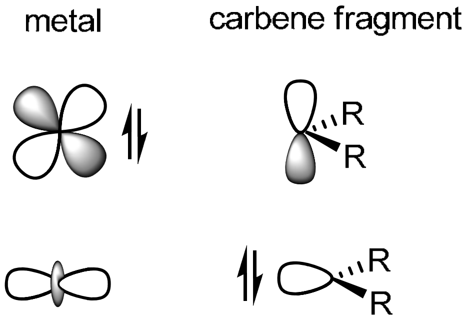
- More electron density is lost than is gained through back donation, rendering the π-system electrophilic

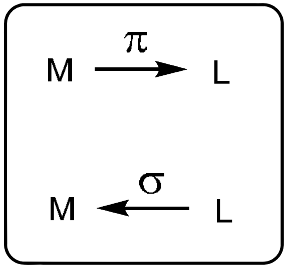
Reviews: Relativistic Effects: D. J. Gorin, F. D. Toste, Nature, **2007**, *446*, 395.
π-acids: A. Fürstner, P. W. Davies *Angew. Chem. Int. Ed.* **2007**, *46*, 3410.
Thematic issue of *Chem. Rev.* **2008**, Issue 108.

π-acids: post slippage carbenoids







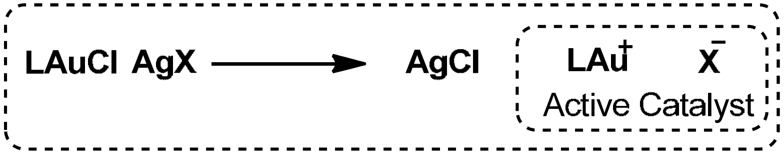


- After slippage an incipient carbene is stabilised by metal ligand back-bonding
- Calculations show carbene of 5d transition metals are distinguished by particularly high bond energies (peak at Pt)
- Prototype Fischer-carbene complexes of chromium, molybdenum or tungsten readily undergo carbene transfer on reaction with gold salts, thus indicating that gold carbene complexes are thermodynamically highly favorable.
- Metal d$_{xz}$ to ligand p$_z$ interaction is effective.
- Molecular structures in the solid state that such species show very little, if any, double bond character for the C-Au “carbene” bond

Reviews: Relativistic Effects: D. J. Gorin, F. D. Toste, Nature, **2007**, *446*, 395.
π-acids: A. Fürstner, P. W. Davies *Angew. Chem. Int. Ed.* **2007**, *46*, 3410.
Thematic issue of *Chem. Rev.* **2008**, Issue 108.

A note on the catalysts

- Gold catalysts range from simple Au(I) and Au(III) halides and cationic gold complexes employing spectator ligands such as phosphines an *N*-heterocyclic carbenes.
- Throughout this presentation these species will be denoted as [Au] (or $[\mathrm{Au}]^+$ for cationic gold systems) in catalytic cycles.



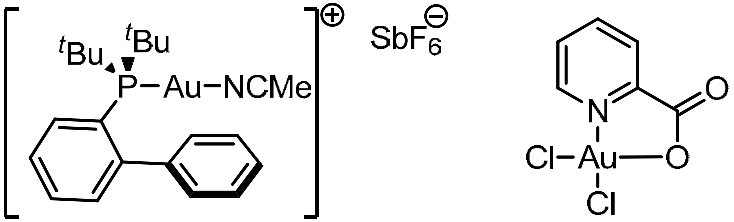
LAuCl AgX $\longrightarrow$ **AgCl** $\mathbf{LAu^+}$ $\mathbf{X^-}$

Active Catalyst

L = Phosphine, phosphite and *N*-heterocyclic carbenes

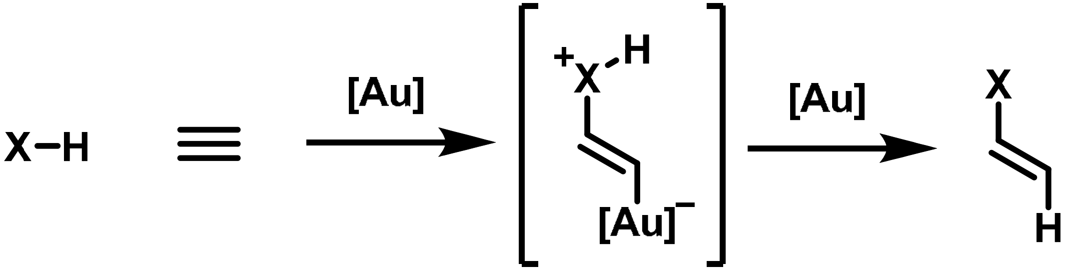
$\mathbf{Ph_3PAuNTf_2}$

Gagosz
(air/moisture stable silver free system)



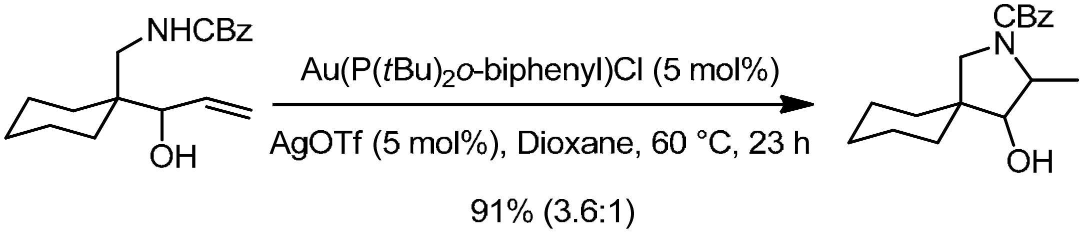
Review on ligand effects: D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351.

X-H addition across C-C π-systems



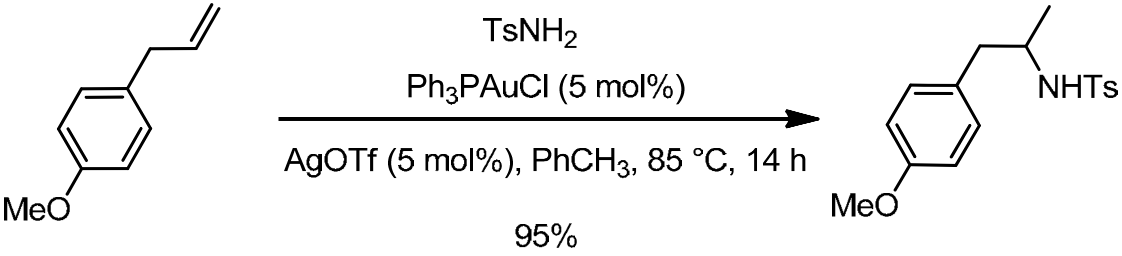
N-H addition to alkenes

- Intramolecular hydroamination



X. Han, R. A. Widenhoefer, *Angew. Chem. Int. Ed.* **2006**, *45*, 1747.

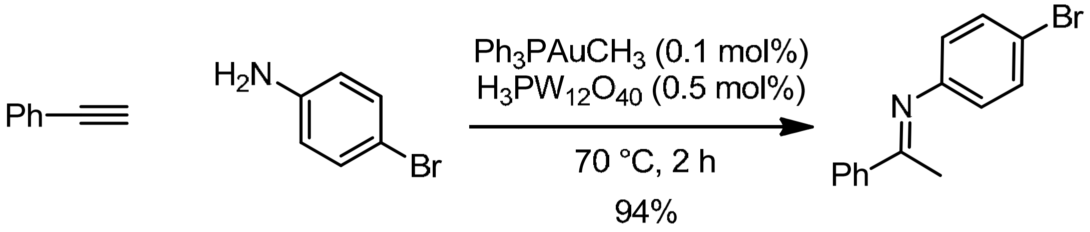
- Intermolecular hydroamination



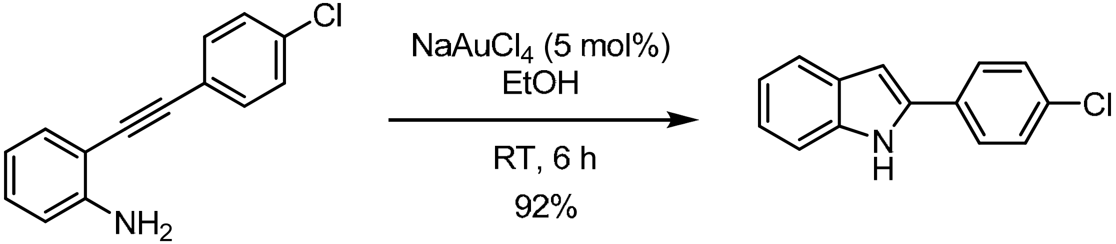
J. Zhang, C.-G. Yang, C. He, *J. Am. Chem. Soc.* **2006**, *128*, 1798.

N-H addition to alkynes

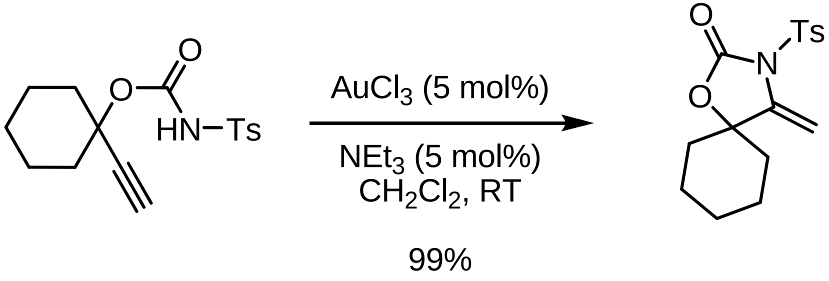
- Hydroamination



E. Mizushima, T. Hayashi, M. Tanaka, *Org. Lett.* **2003**, *5*, 3349.



A. Arcadi, G. Bianchi, F. Marinelli, *Synthesis* **2004**, 610.

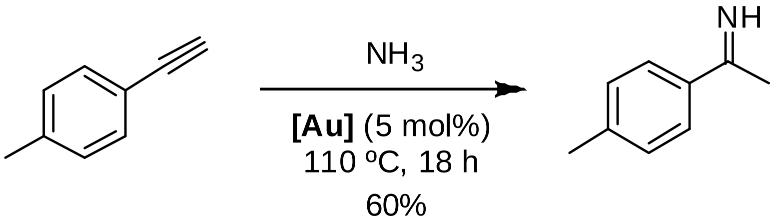


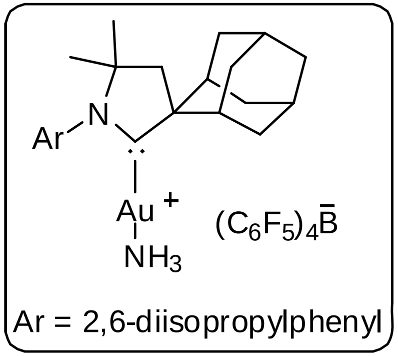
S. Ritter, Y. Horino, J. Lex, H.-G. Schmalz, *Synlett.* **2006**, 3309.

NH_3 addition to alkynes

- The inability to effectively employ ammonia as the amine source is a major limitation of hydroamination chemistry (due to supposed formation of inert ammonia-Lewis acid complexes). The use of ammonia in such reactions was identified as one of the ten greatest challenges for catalysis chemistry.

J. Haggin, *Chem. Eng. News* **1993**, *71*, 23.



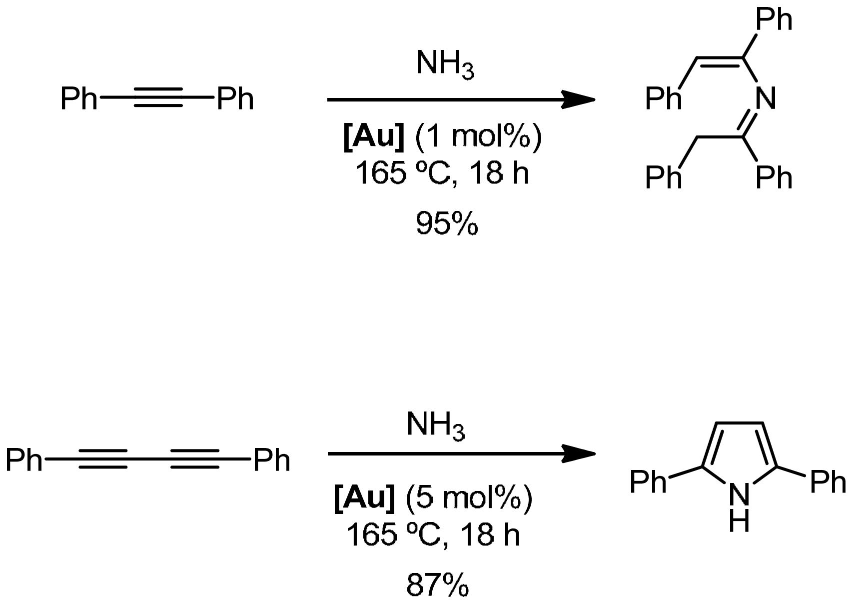


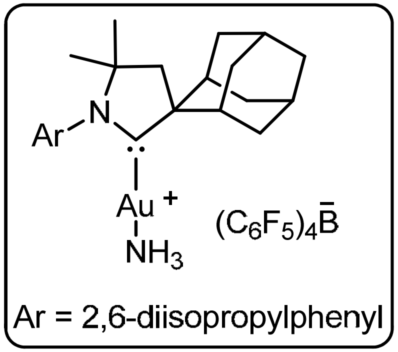
- A gold complex bearing a cyclic(alkyl)(amino)carbene (CAAC) ligand will readily catalyse the hydroamination of alkynes and allenes directly with ammonia to afford imine products.

V. Lavallo, G. D. Frey, B. Donnadieu, M. Soleilhavoup, G. Bertrand, *Angew. Chem. Int. Ed.* **2008**, *47*, 5224.

NH_3 addition to alkynes

- If the initial imine product contains an acidic α-hydrogen atom, enamine tautomerisation leads to a second hydramination and double alkyne insertion product.
- Use of a diyne, follows a similar protocol to afford a pyrrole.

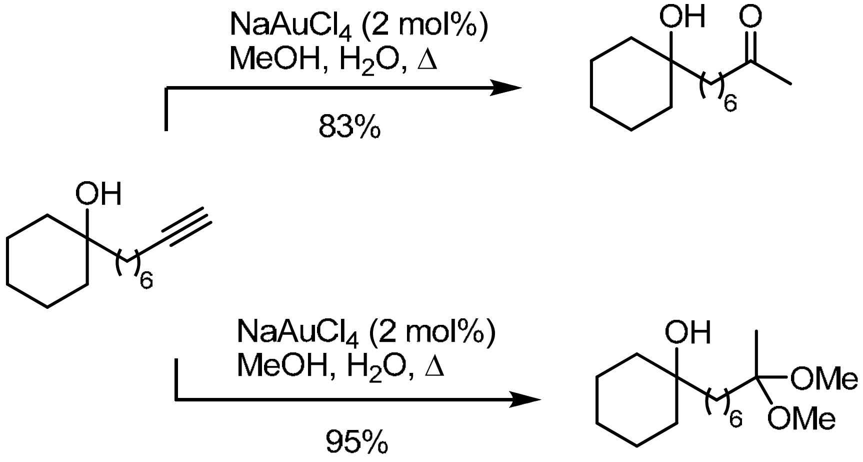




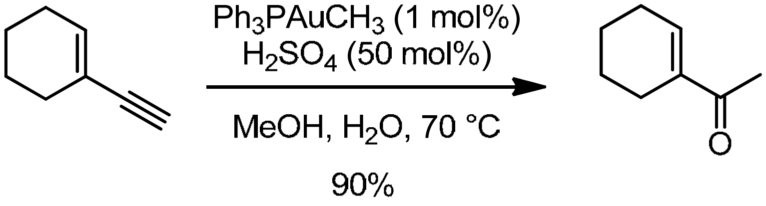
V. Lavallo, G. D. Frey, B. Donnadieu, M. Soleilhavoup, G. Bertrand, *Angew. Chem. Int. Ed.* **2008**, *47*, 5224.

Intermolecular O-H addition to alkynes

- Use of water leads to the ketones.
- Initial methyl enol ether products are readily transformed under the reaction conditions to acetals or hydrolysed to ketones.



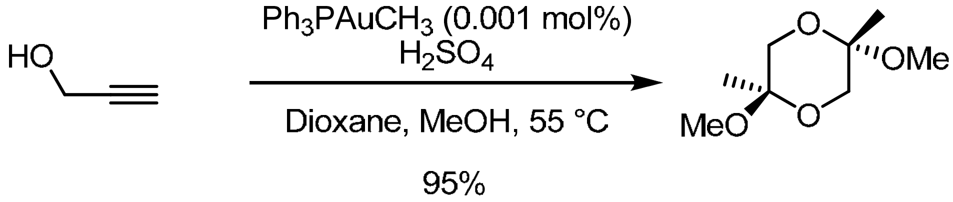
Y. Fukudu, K. Utimoto, *J. Org. Chem.* **1991**, *56*, 3729.



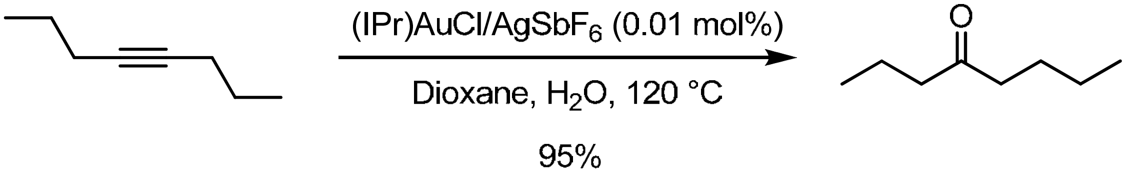
J. H. Teles, S. Brode, M. Chabanas, *Angew. Chem. Int. Ed.* **1998**, *37*, 1415.

O-H addition to alkynes

- Hydration – low catalyst loadings



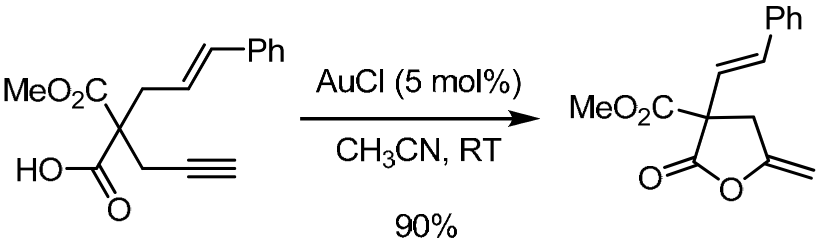
J. H. Teles, S. Brode, M. Chabanas, *Angew. Chem. Int. Ed.* **1998**, *37*, 1415.
Also: Mizushima, E.; Sato, K.; Hayashi, T.; Tanaka, M. *Angew. Chem. Int. Ed.* **2002**, *41*, 4563–4565



N. Marion, R. S. Ramon, S. P. Nolan, *J. Am. Chem. Soc.* **2009**, *131*, 448.
Hydration of Nitriles: R. S. Ramon, N. Marion, S. P. Nolan, *Chem. Eur. J.* **2009**, *15*, 8695.

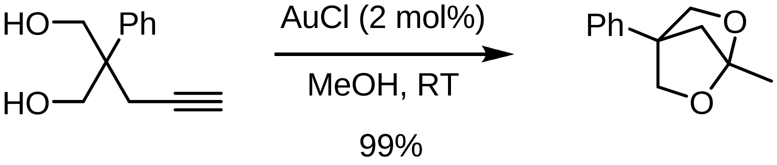
Intramolecular O-H addition to alkynes

- Cyclisation of a carboxylic acid leads to a lactone.



E. Genin, P. Y. Toullec, S. Antoniotti, C. Brancour, J.-P. Genêt, V. Michelet, *J. Am. Chem. Soc.* **2006**, *128*, 3112.

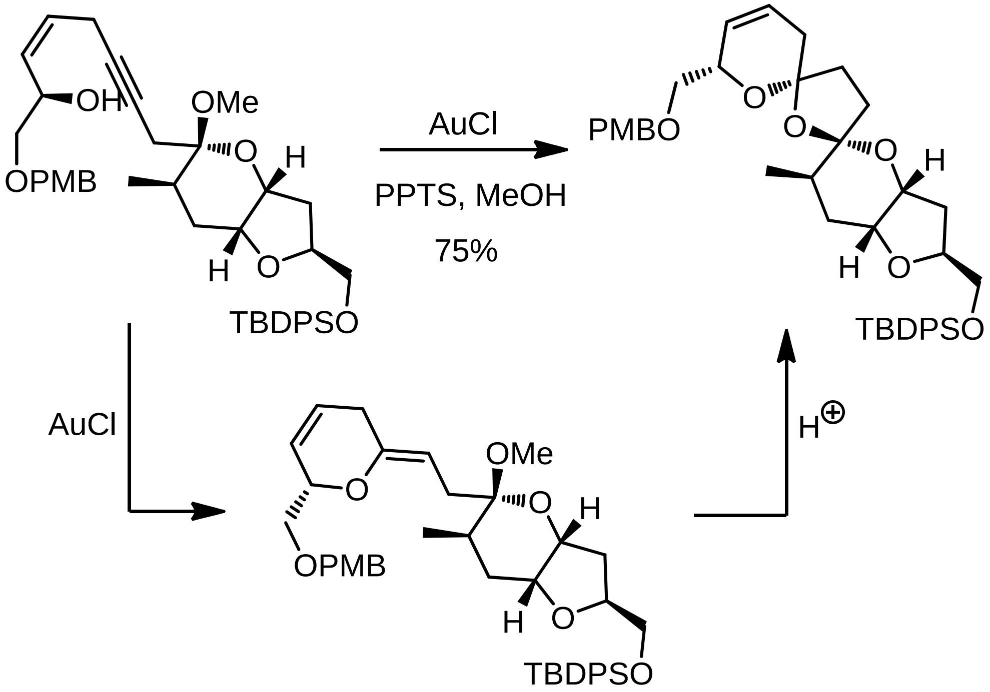
- Use of a diol leads to the acetal by trapping the intermediate enol ether.



S. Antoniotti, E. Genin, V. Michelet, J.-P. Genêt, *J. Am. Chem. Soc.* **2005**, *127*, 9976.

Intramolecular O-H addition to alkynes: Applications

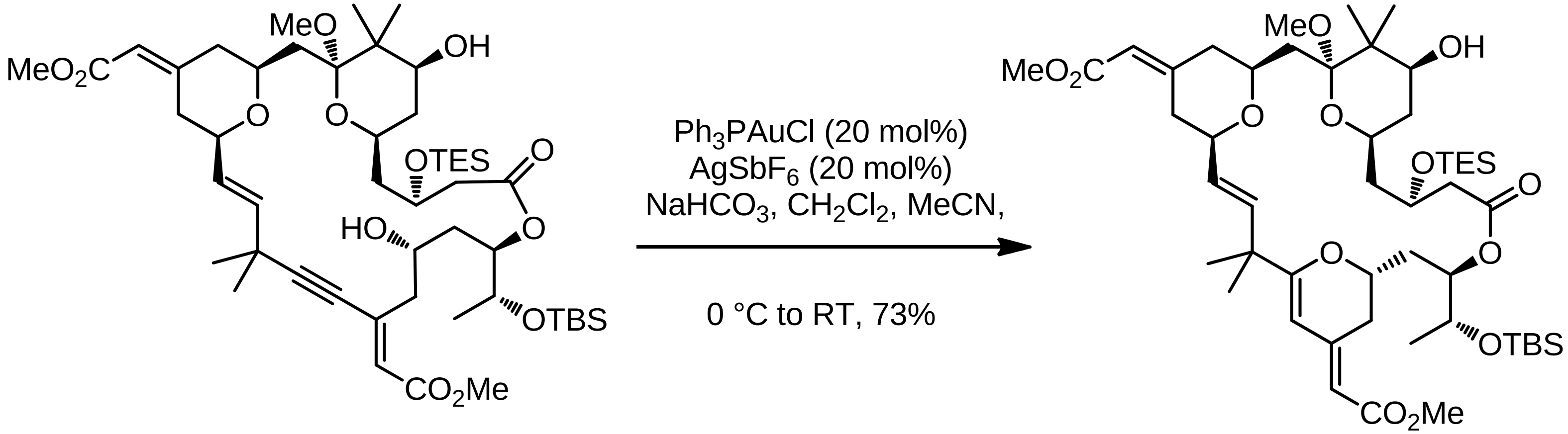
- Gold-catalysed bis-spiroketalisation was employed to construct the A and B rings of the marine toxin azaspiracid. Gold-mediated hydroalkoxylation of the alkyne affords an enol ether which further cyclises under protic conditions to the desired structure.



Y. Li, F. Zhou and C. J. Forsyth, *Angew. Chem. Int. Ed.* 2007, **46**, 279.

Intramolecular O-H addition to alkynes: Applications

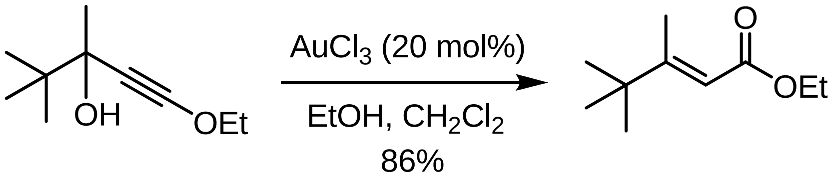
- Bryostatin 16. Cyclisation occurs in the presence of acetals, activated alkenes and unprotected alcohols



B. M. Trost, G. Dong, *Nature* **2009**, *456*, 485.

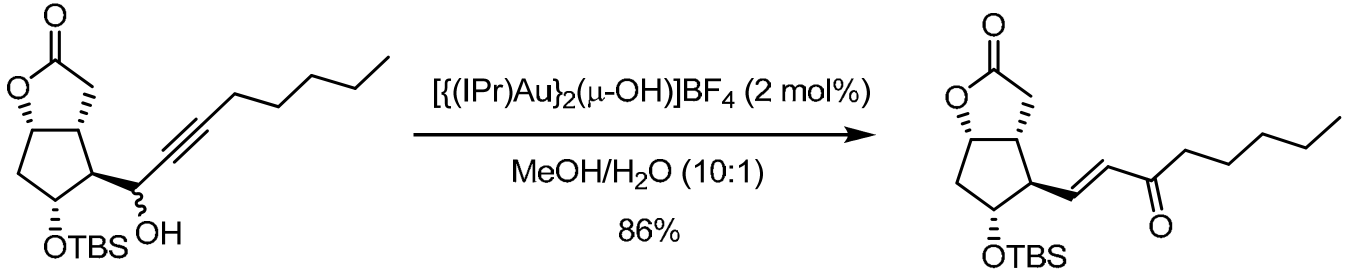
Meyer-Schuster reaction

- Transformation of a propargylic alcohol into an unsaturated carbonyl.
- Hydration and elimination process and/or Au-promoted elimination of the hydroxyl unit followed by hydrolysis of the propargylic system



Y. Fukada, K. Utimoto, *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2013;
D. A. Engel, G. B. Dudley, *Org. Lett.* **2006**, *8*, 4027.

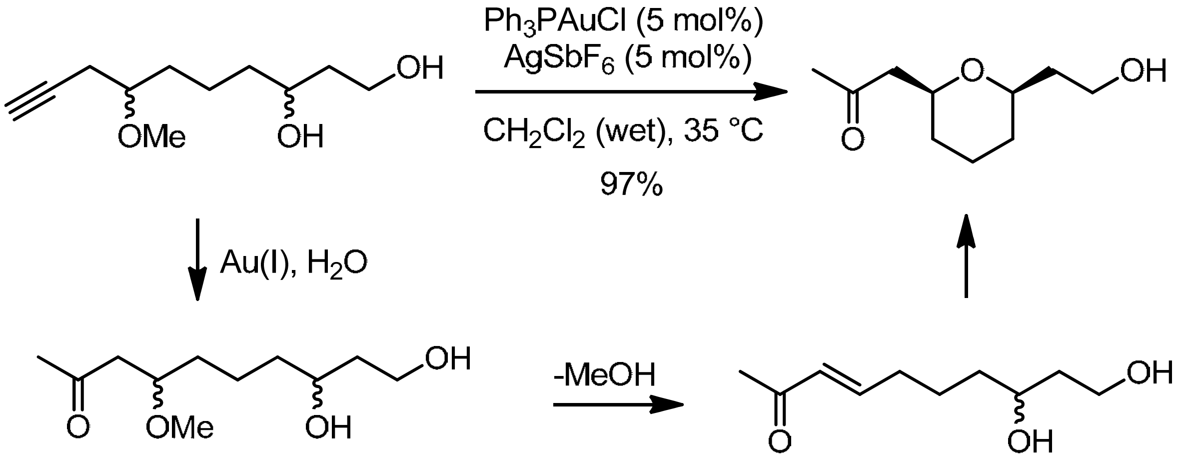
- Applied to a Prostaglandin synthesis ($PGF_{2\alpha}$):



R. S. Ramon, S. Gaillard, A. M. Z. Slavin, A. Porta, A. D'Alfonso, G. Zanoni, S. P. Nolan, *Organometallics* **2010**, *29*, 3665.

X-H addition to alkynes: Cascade reactions

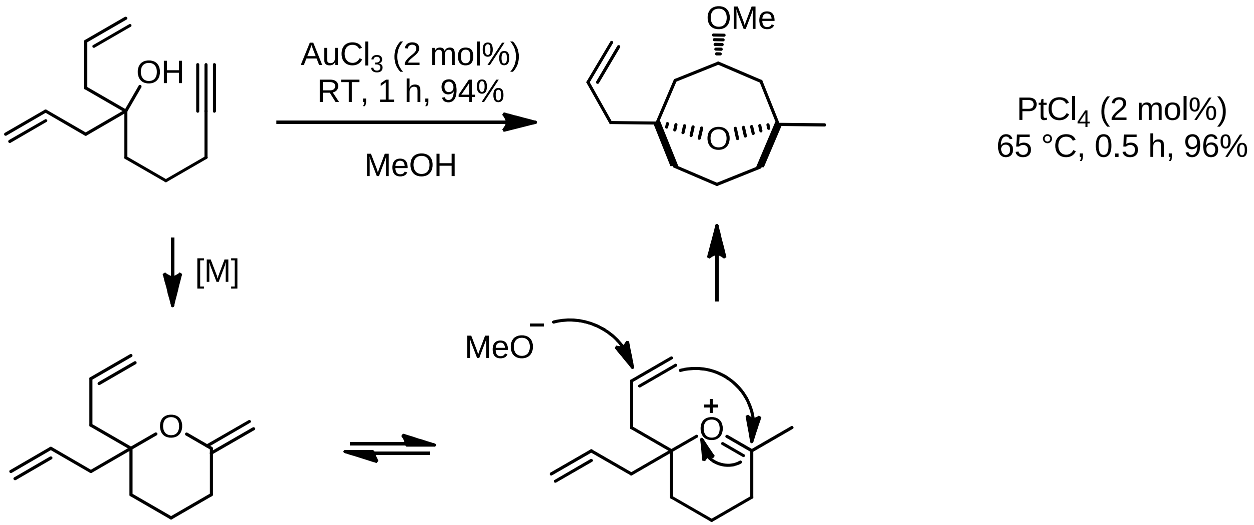
- With C-O bond formation.
  Alkyne hydration, followed by elimination and 1,4 addition.



H. H. Jung, P. E. Floreancig, *Org. Lett.* **2006**, *8*, 1949.

X-H addition to alkynes: Cascade reactions

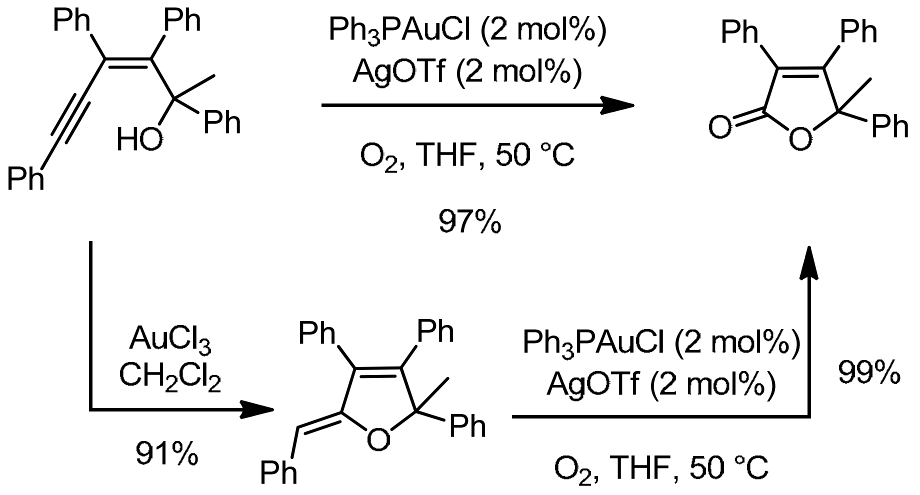
- Intramolecular hydroalkoxylation followed by Prins-type cyclisation.



J. Barluenga, A. Diéguez, A. Fernández, F. Rodríguez, F. Fañanás, *Angew. Chem. Int. Ed.* **2006**, *45*, 2091.

X-H addition to alkynes: Cascade reactions

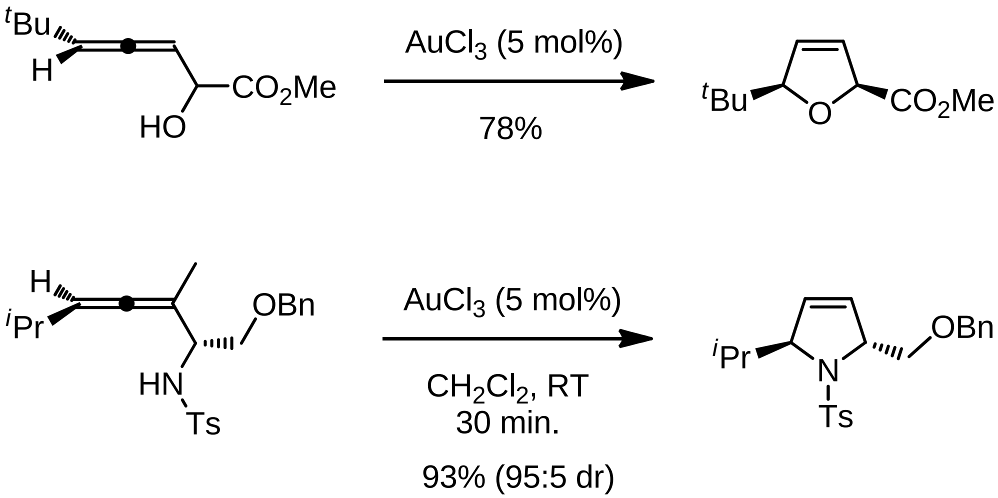
- In the presence of molecular oxygen, the intramolecular hydoalkoxylation products undergo gold-catalyzed aerobic oxidation to form butenolides



Liu, F. Song, Z. Song, M. Liu, B. Yan, *Org. Lett.* **2005**, *7*, 5409.

X-H addition to allenes

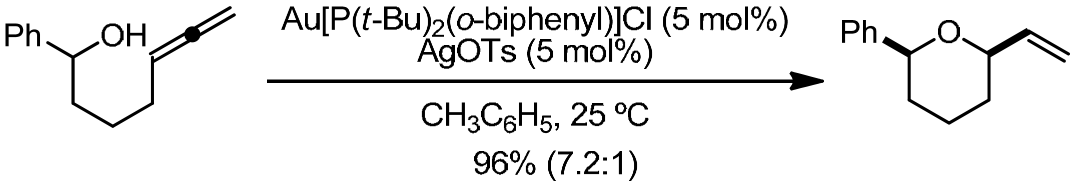
- Intramolecular X-H addition across allenes is also facile and results in the formation of a chiral product.
- α-hydroxyallene to dihydrofurans; α-aminoallenes to dihydropyrroles; β-hydroxyallene to dihydropyrans



A. Hoffman-Röder, N. Krause, *Org. Lett.* **2001**, *3*, 2537; B. Gockel, N. Krause, *Org. Lett.* **2006**, *8*, 4485; N. Morita, N. Krause, *Org. Lett.* **2004**, *6*, 4121.

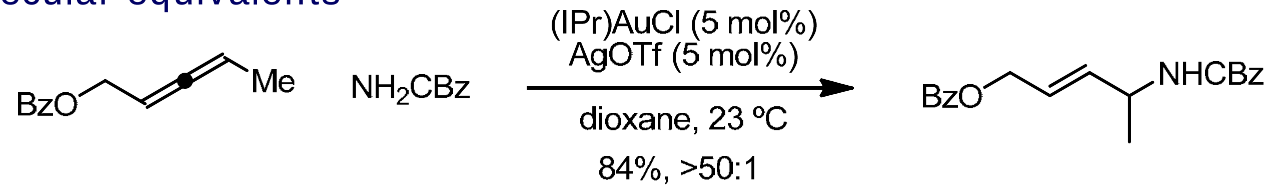
X-H addition to allenes

- Addition can take place at internal and terminal points of the allene

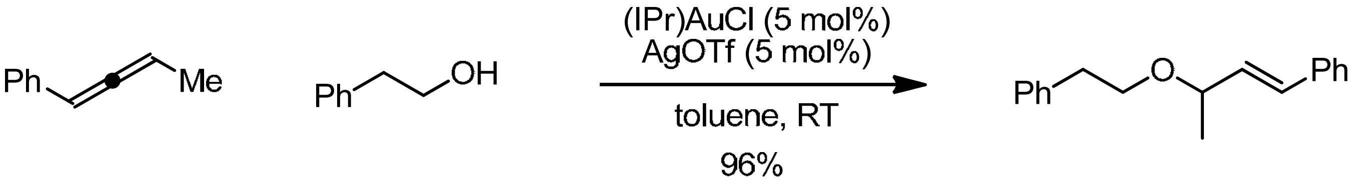


Z. Zhang, C. Liu, R. E. Kinder, X. Han, H. Qian, R. A. Widenhoefer, *J. Am. Chem. Soc*. **2006**, *128*, 9066.

- Intermolecular equivalents



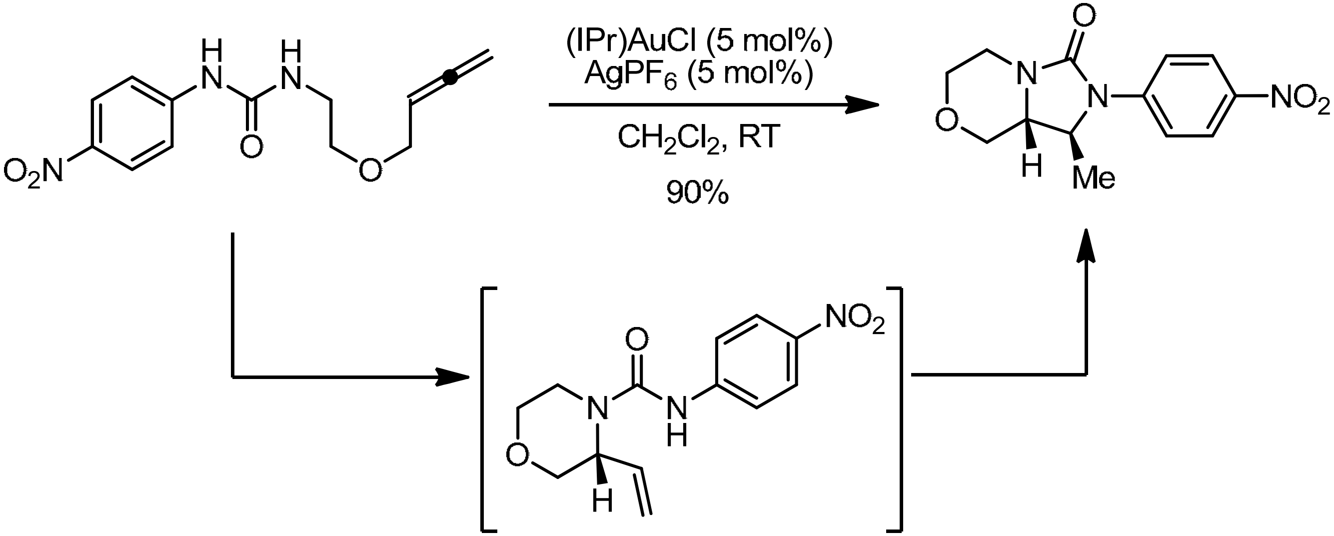
R. E. Kinder, Z. Zhang, R. A. Widenhoefer, *Org. Lett.* **2008**, *10*, 3157.



Z. Zhang, R. A. Widenhoefer, *Org. Lett.* **2008**, *10*, 2079.
Preparation of tertiary allylic ethers: M. S. Hadfield, A.-L. Lee, *Org. Lett.* **2010**, *12*, 484.

Dihydroamination of allenes

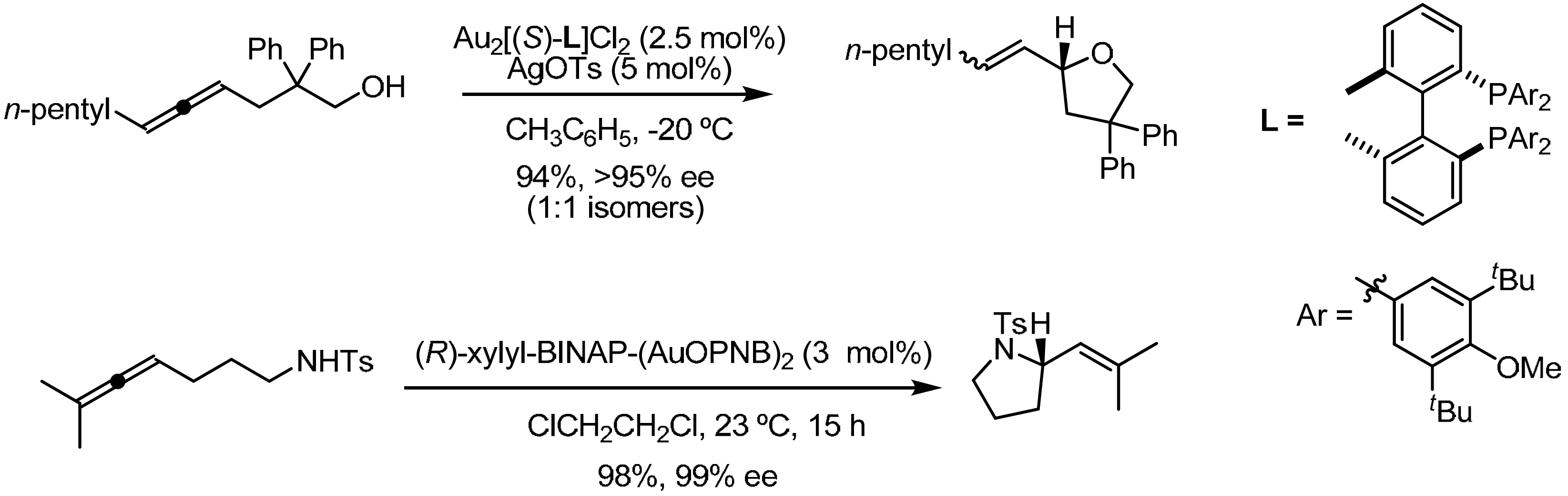
- When allenyl urea substrates are employed the intermediate alkene of the initial cyclisation can undergo a second hydroamination.



H. Li, R. A. Widenhoefer, *Org. Lett.* **2009**, *11*, 2671.

X-H addition across allenes: Asymmetric versions

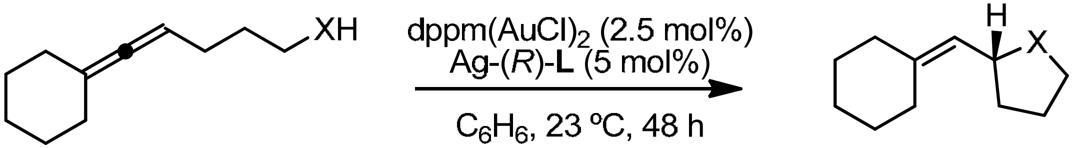
- Highly enantioselective hydroalkoxylation and hydroamination have been reported with bisgold complexes of chiral bisphosphines.



Z. Zhang, R. A. Widenhoefer, *Angew. Chem. Int. Ed.* **2007**, *46*, 283; R. LaLonde, B. D. Sherry, E. J. Kang, F. D. Toste, *J. Am. Chem. Soc.* **2007**, *129*, 2452; Z. Zhang, C. F. Bender, R. A. Widenhoefer, *Org. Lett.* **2007**, *9*, 2887; Z. Zhang, C. F. Bender, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2007**, *129*, 14148.

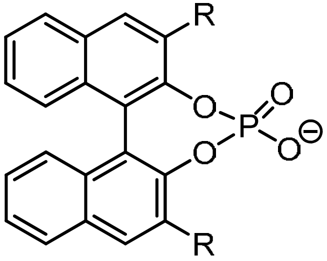
X-H addition across allenes: Asymmetric versions

- A chiral counterion strategy: Employing an achiral phosphine-gold chloride complex alongside the silver salt of a chiral binapthol-derived phosphate anion.
- Use of a chiral Ligand and counterion can be combined for enhanced asymmetric induction).



X = O, 90%, 97% ee
X = NSO$_2$Me, 97%, 96% ee

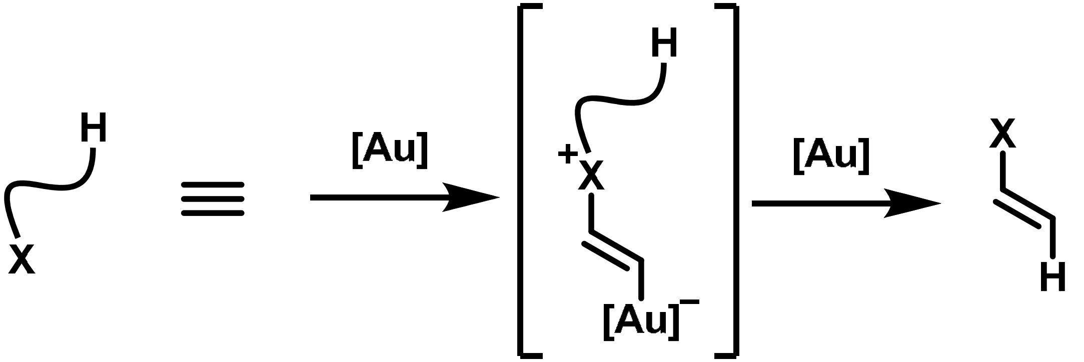
L =



R = 2,4,6-^{i}Pr$_3$-C$_6$H$_2$

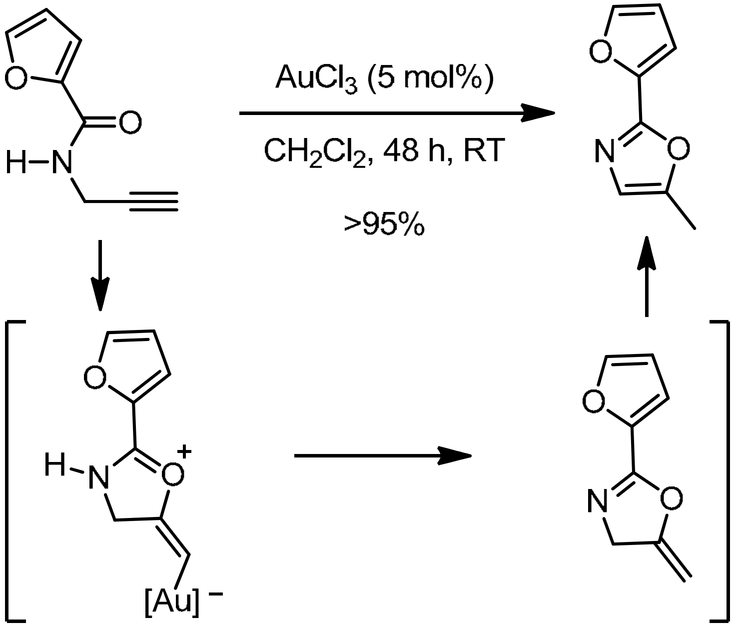
G. L. Hamilton, E. J. Kang, M. Mba, F. D. Toste, *Science*, **2007**, *317*, 496.

Indirect X-H addition

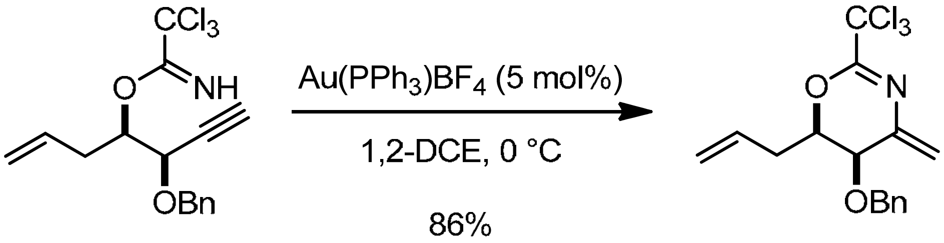


Intramolecular cyclisations

- sp^2-Hybridised heteroatoms in groups such as amides, carbonates and carbamates can also be employed as nucleophiles to gold activated π-systems to effect an overall X-H addition.



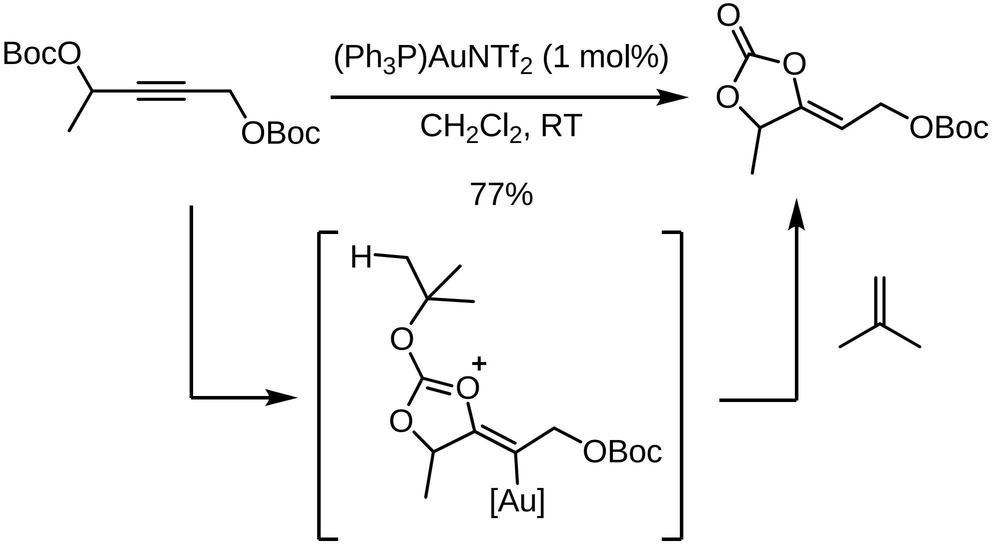
A. S. K. Hashmi, J. P. Weyrauch, W. Frey, J. W. Bats, *Org. Lett.* **2004**, *6*, 4391.



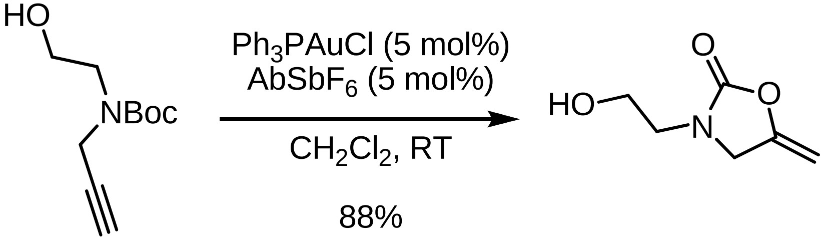
J.-E. Kang, H.-B. Kim, J.-W. Lee. S. Shin, *Org. Lett.* **2006**, *8*, 3537.

Intramolecular cyclisations

- After cyclisation, protodemetallation can arise either though direct proton transfer or by fragmentation, for instance with loss of isobutene.



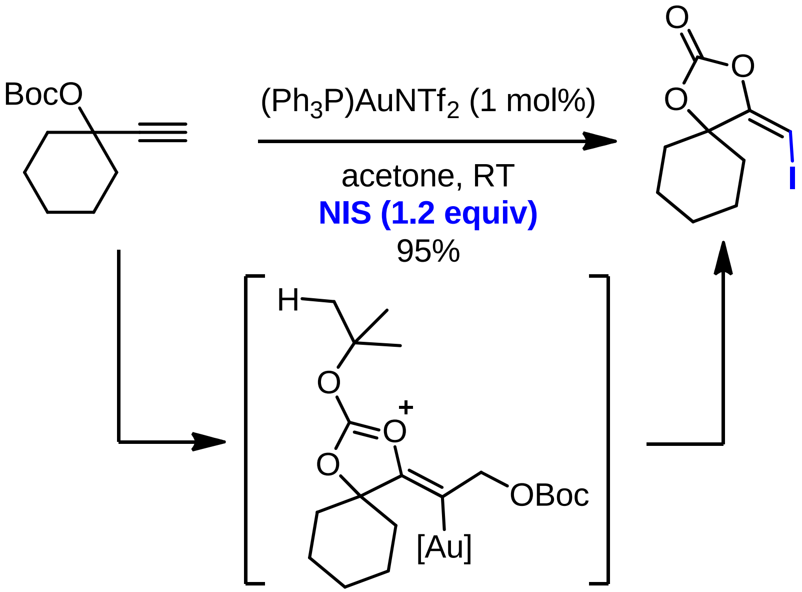
A. Buzas, F. Gagosz, *Org. Lett.* **2006**, *8*, 515.



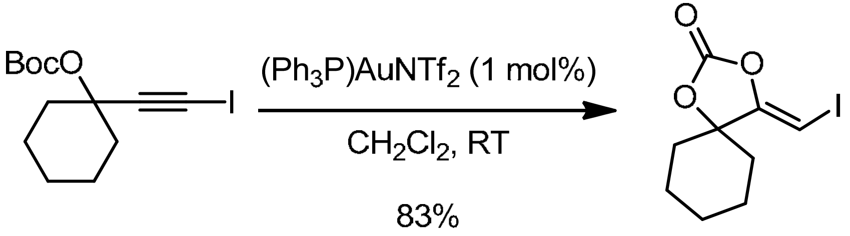
R. Robles-Machín, J. Adrio, J. C. Carretero, *J. Org. Chem.* **2006**, *71*, 5023.

Interrupted cyclisations

- In the presence of a stoichiometric quantity of an electrophilic iodine source, the catalytic cycle is completed by iododeauration.



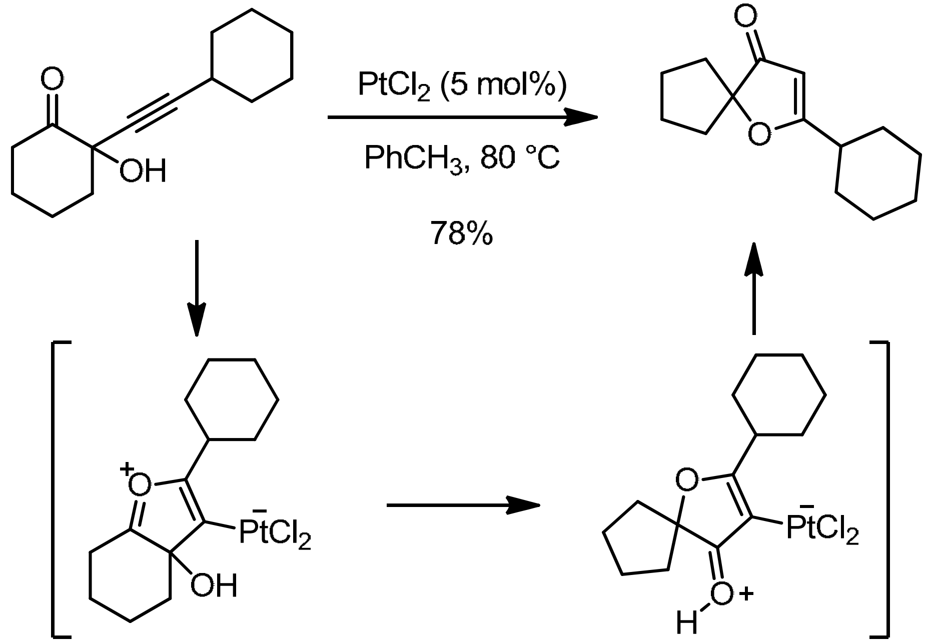
- The result is a stereodefined vinyl iodide. The complimentary geometric isomer can be prepared from the alkynyl iodide.



A. Buzas, F. Gagosz, *Org. Lett.* **2006**, *8*, 51.

Pinacol type reaction

- In the absence of an external nucleophile or proton transfer, skeletal rearrangement is viable.

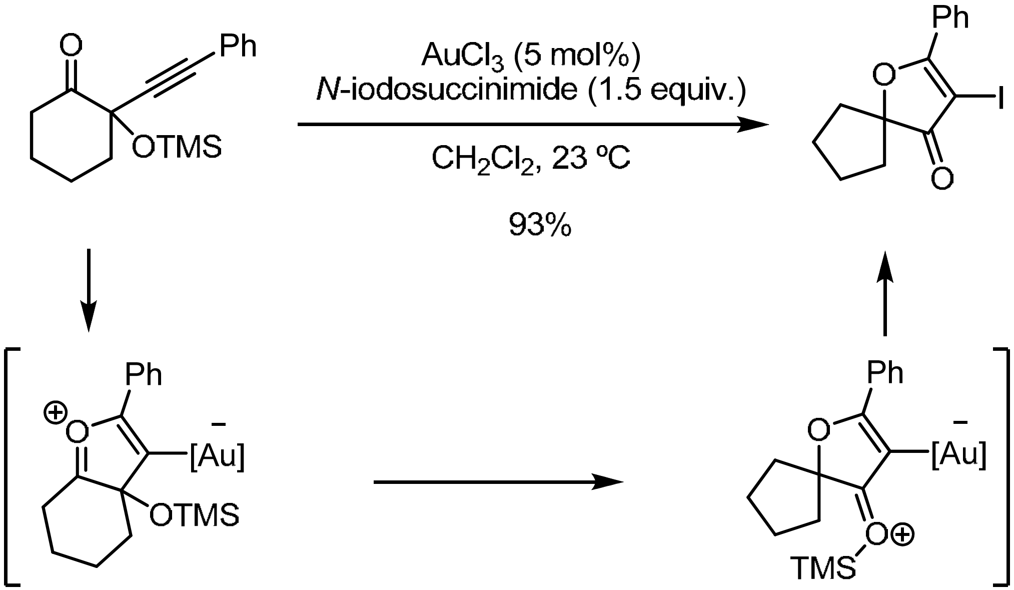


S. F. Kirsch, J. T. Binder, C. Liébert, H. Menz, *Angew. Chem. Int. Ed.* **2006**, *45*, 5878.

Review: B. Crone, S. F. Kirsch, *Chem.-Eur. J.* **2008**, *14*, 3514.

Pinacol type reaction II

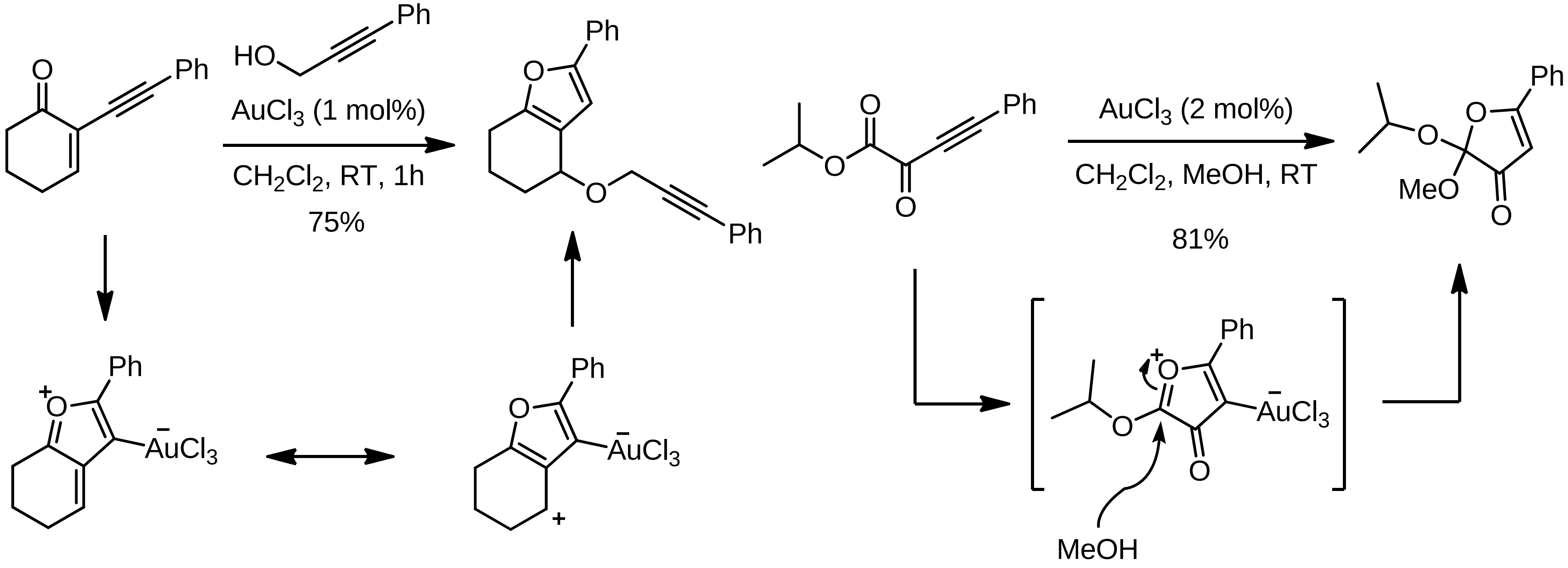
- In the absence of an external nucleophile or proton transfer, skeletal rearrangement can be coupled with iododemetallation.



B. Crone, S. F. Kirsch, *J. Org. Chem.* **2007**, *72*, 5435.

Trapping the intermediate with alcohol

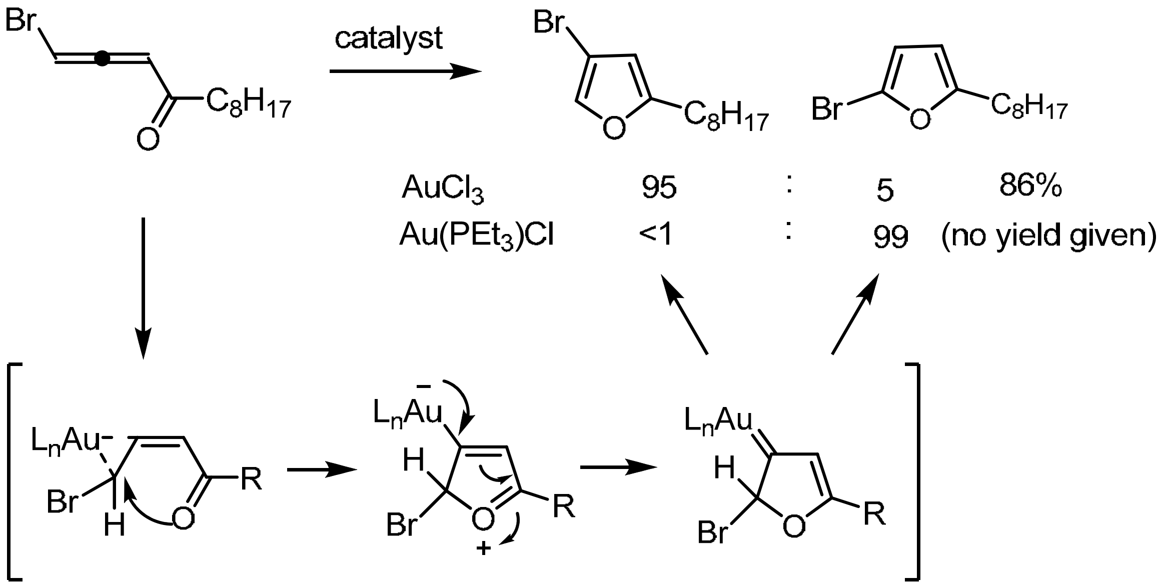
- The initial cyclisation of an sp^2-hybridised heteroatom provides significant opportunity for reaction development by capture of the carbocation by an external nucleophile.



T. Yao, X. Zhang, R. C. Larock, *J. Am. Chem. Soc.* **2004**, *126*, 11164;
X. Liu, Z. Pan, X. Shu, X. Duan, Y. Liang, *Synlett* **2006**, 1962.

Allenyl ketone cycloisomerisation

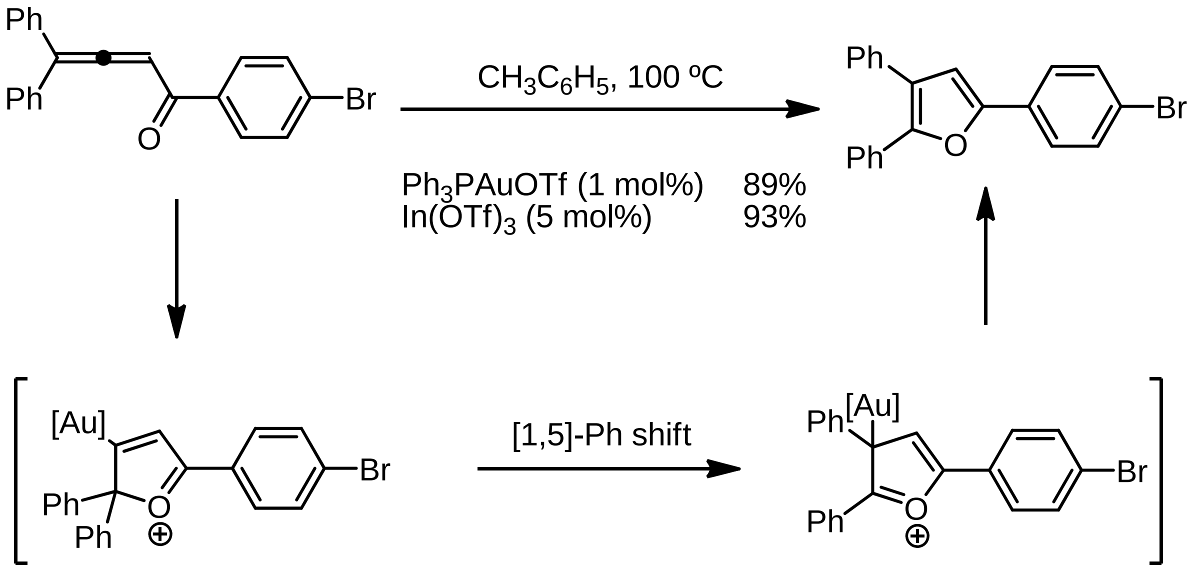
- Catalyst control over Br/H migration to a carbene intermediate.



W. Sromek, M. Rubina, V. Gevorgyan, *J. Am. Chem. Soc.* **2005**, *127*, 10500;
Y. Xia, A. S. Dudnik, V. Gevorgyan, Y. Li, *J. Am. Chem. Soc.* **2008**, *130*, 6940.

Allenyl ketone cycloisomerisation

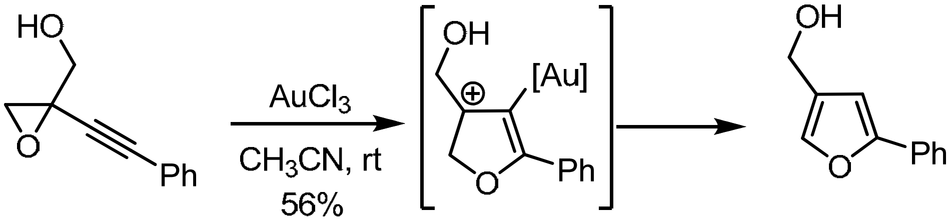
- 1,2-shift of diverse functional groups.



A. S. Dudnik, V. Gevorgyan, *Angew. Chem. Int. Ed.* **2007**, *46*, 5195.
A. S. Dudnik, A. W. Sromek, M. Rubina, J. T. Kim, A. V. Kel'in, V. Gevorgyan, *J. Am. Chem. Soc.* **2008**, **130**, 1440.

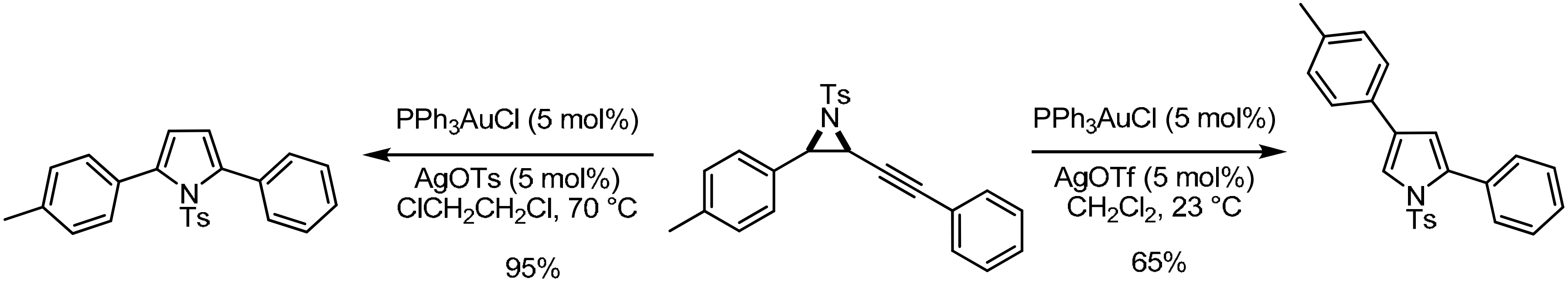
X-H additions by formal ring expansions

- Ring-expansion of alkynyl epoxides



A. S. K. Hashmi, P. Sinha, *Adv. Synth. Catal*. **2004**, *346*, 432.
Ring-opening/closing cascade: A. Blanc, K. Tenbrink, J.-M. Weibel, P. Pale, *J. Org. Chem.,* **2009**, *74*, 5342.

- Ring-expansion of alkynyl aziridines. Counterion (and solvent) effects dictate the outcome of the reaction with ring expansion competing against cascade ring-expansion and skeletal rearrangement.



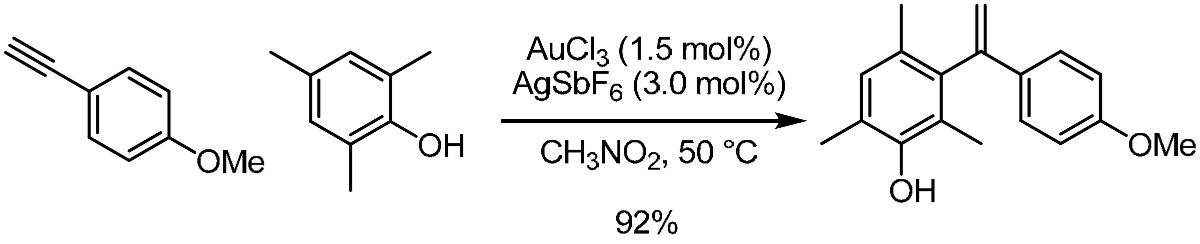
P. W. Davies, N. Martin, *Org. Lett.* **2009**, 2293.

Ring expansion, also see : M. Yoshida *et al. Synthesis* **2009**, 2454; X.-L. Hou *et al. Tetrahedron Lett.* **2009**, *50*, 6944.; Y. Liu *et al. J. Org. Chem.* **2010**, *75*, 510.

C-H addition across C-C π-systems

Arylation

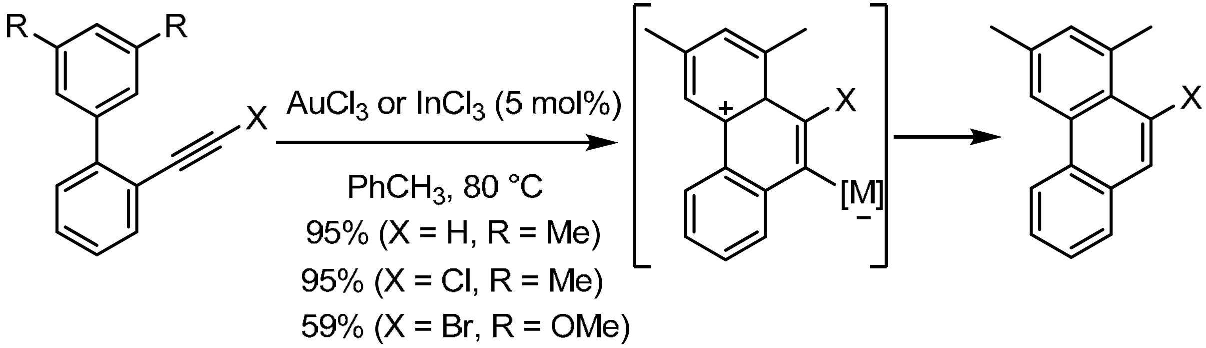
- Intermolecular

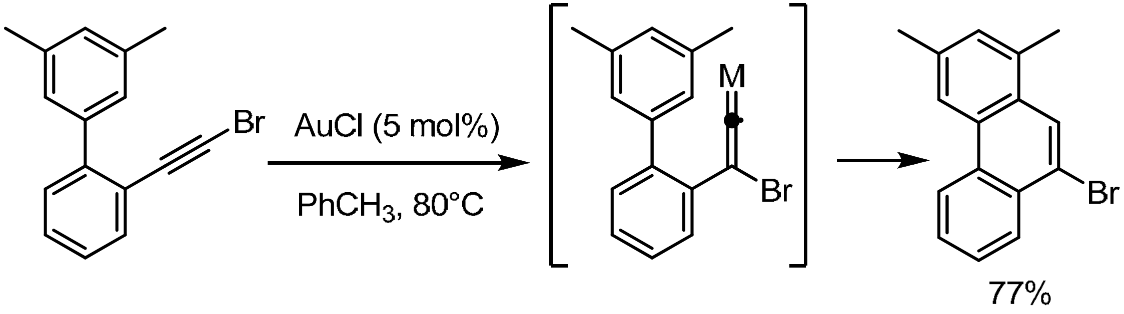


M. T. Reetz, K. Sommer, *Eur. J. Org. Chem.* **2003**, 3485.

- Intramolecular

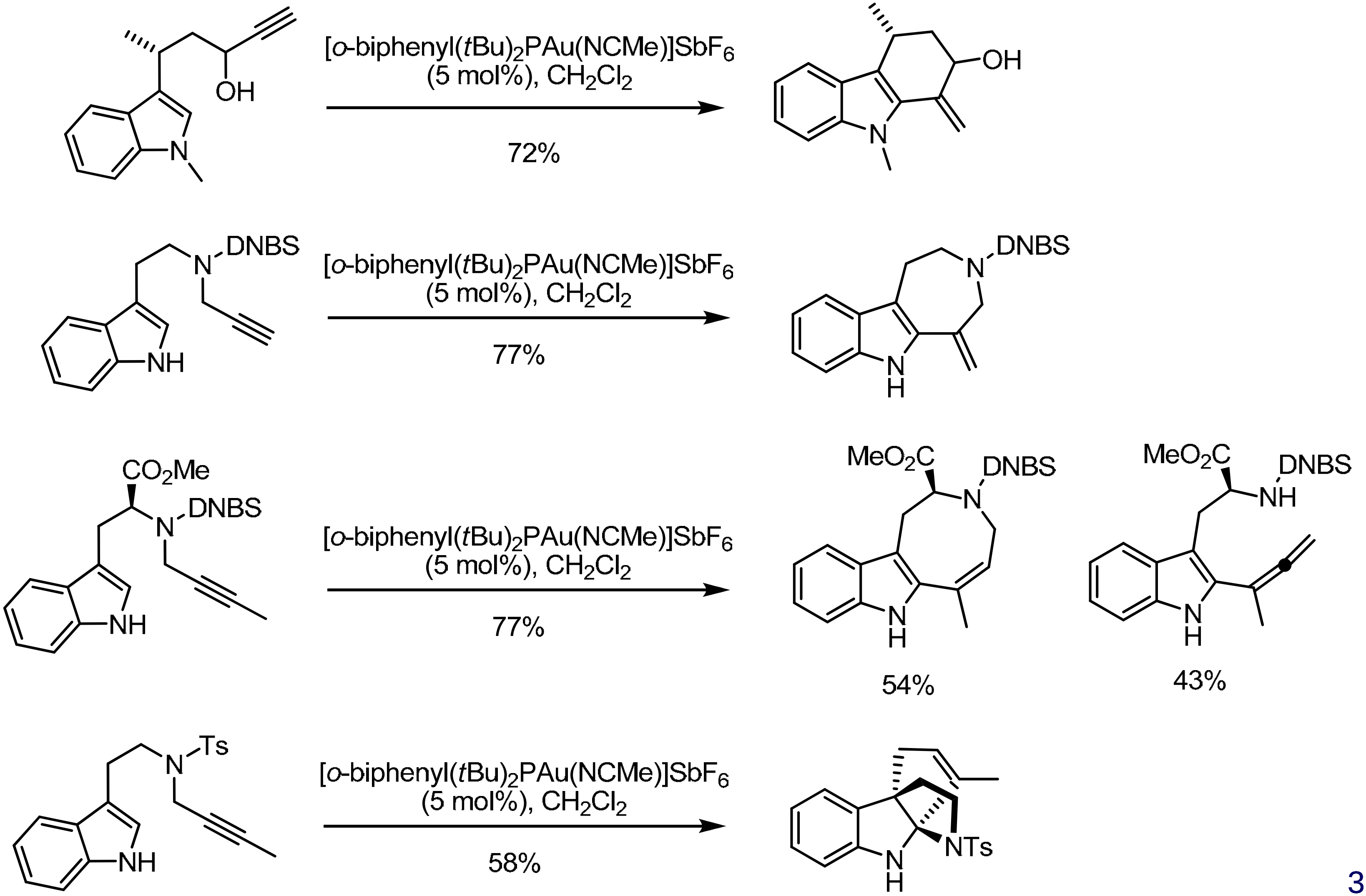
V. Mamane, P. Hannen, A. Fürstner, *Chem. Eur. J.* **2004**, *10*, 4556; A. Fürstner, V. Mamane, *J. Org. Chem.* **2002**, *67*, 6264. Theoretical studies: E. Soriano, J. Marco-Contelles, *Organometallics*, **2006**, *25*, 4542.





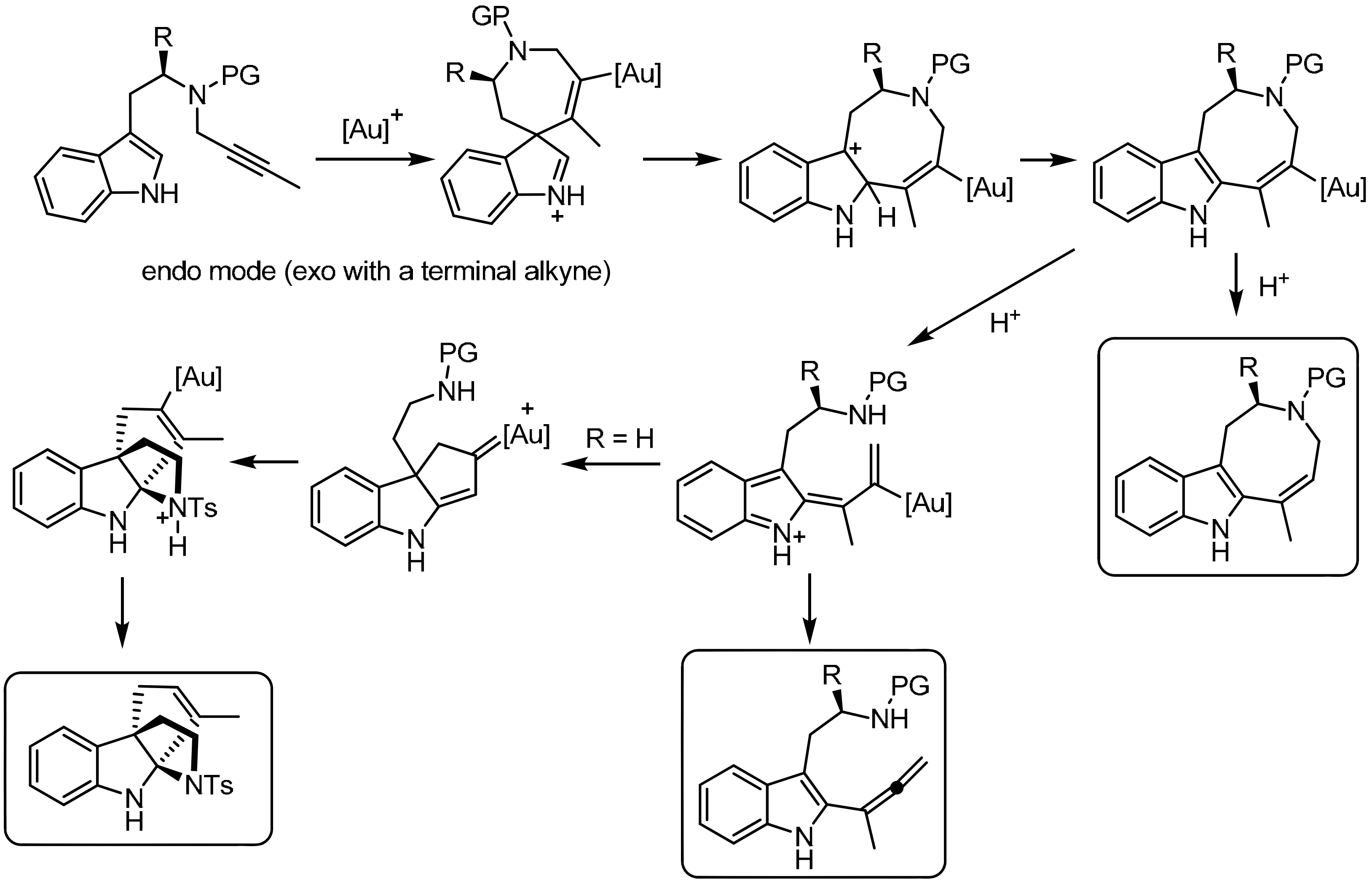
Arylation

- Structural diversity from a simple Friedel-Crafts reaction:



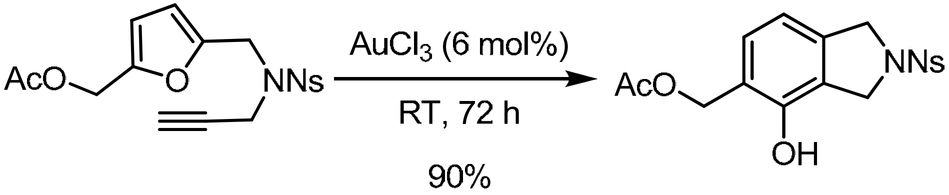
C. Ferrer, C. H. M. Amijs, A. M. Echavarren, *Chem. Eur. J.* **2007**, *13*, 1358.

Alkyne arylation with indoles

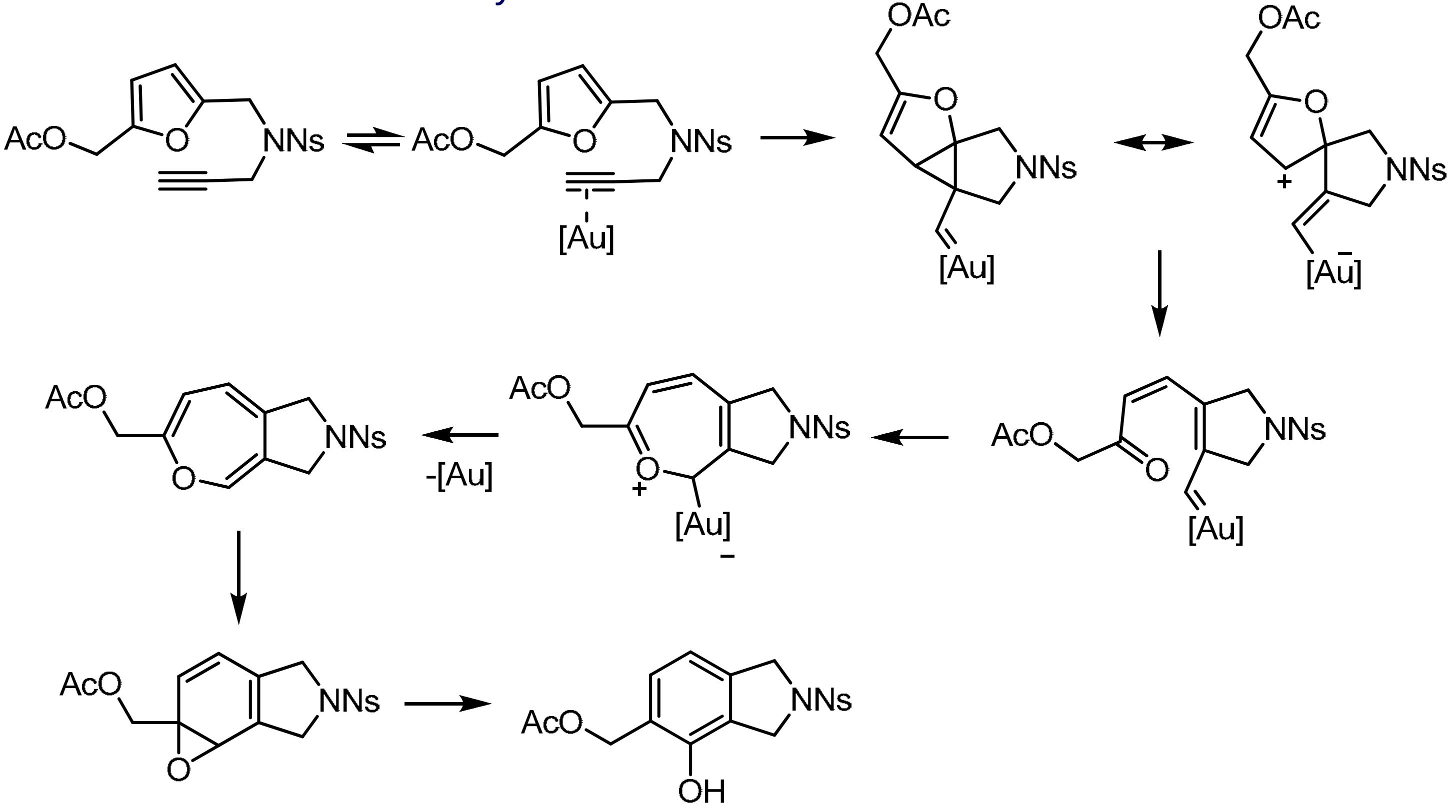


C. Ferrer, C. H. M. Amijs, A. M. Echavarren, *Chem. Eur. J.* **2007**, *13*, 1358.

Phenol synthesis



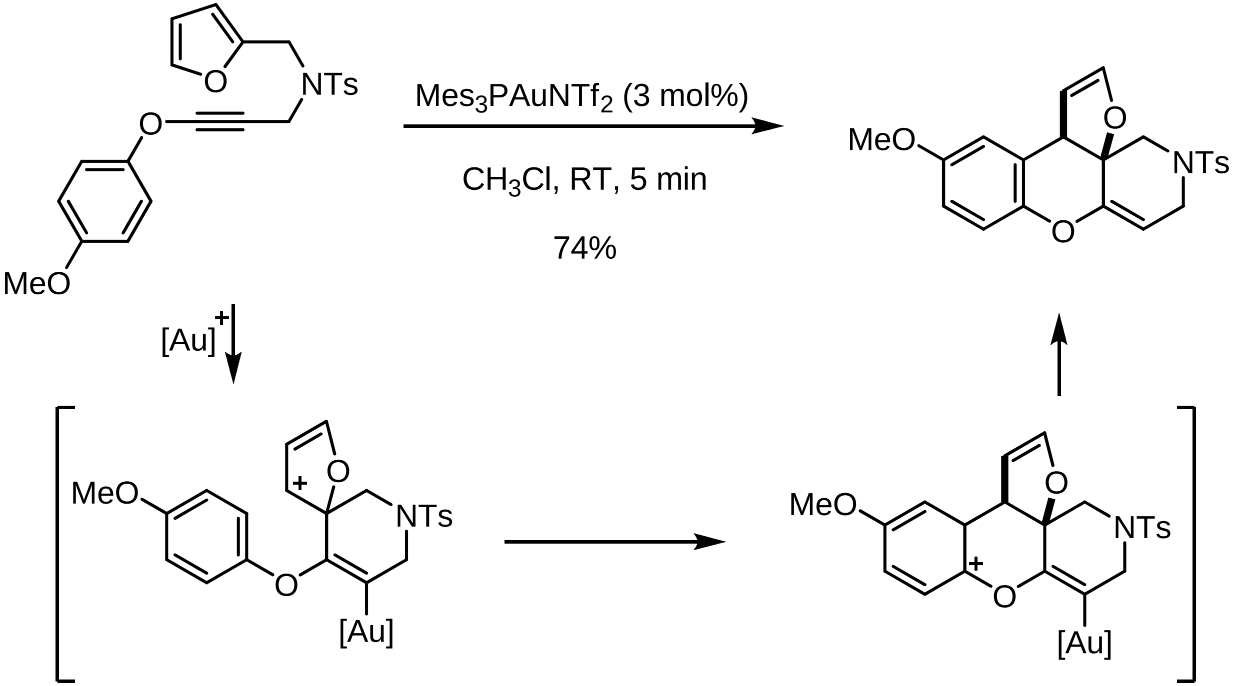
- Extensively-studied, robust and general reaction affords highly-substituted phenols by reaction of furans and alkynes.



A. S. K. Hashmi, *Pure Appl. Chem*. **2010**, *82*, 1517; A. S. K. Hashmi, R. Salathé, W. Frey, *Chem. Eur. J.* **2006**, *12*, 6991; A. S. K. Hashmi, L. Ding, J. W. Bats, P. Fischer, W. Frey, *Chem. Eur. J.* **2003**, *9*, 4339; B. Martín-Matute, D. J. Cárdenas, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2001**, *40*, 4754.

Divergence from the phenol synthesis

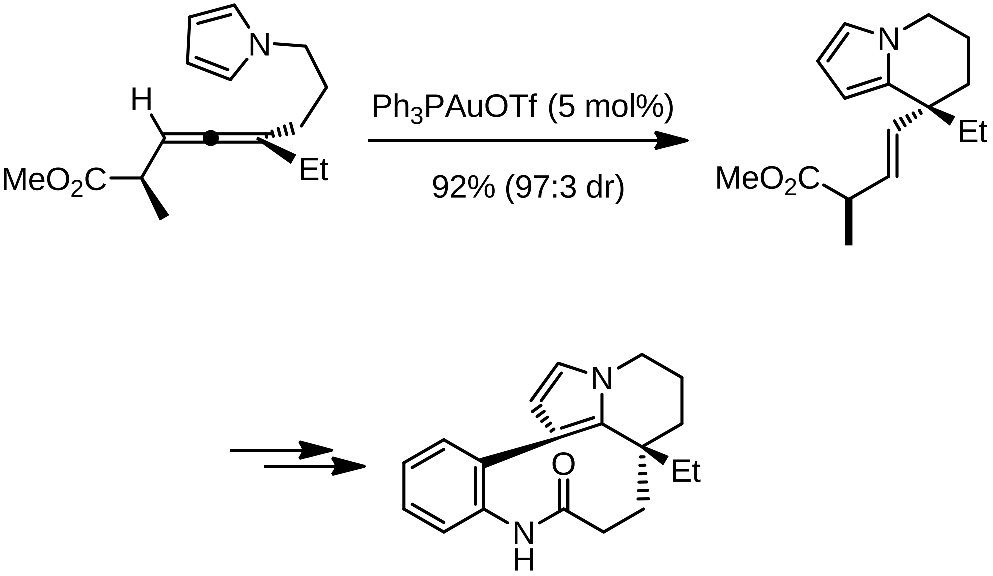
- The presence of an oxygen alters the cyclisation mode to divert the otherwise robust reaction and lead to a new class of tetracyclic system.



A. S. K. Hashmi, M. Rudolph, J. Huck, W. Frey, J. W. Bats, M. Hamzić, *Angew. Chem. Int. Ed.* **2009**, *48*, 5848.

Hydroarylation of allenes

- Gold-catalyzed reaction of an enantioenriched chiral allene with a tethered pyrrole constructs the key tetrahydroindolizidine structure of (-)-rhazininam and introduces the quaternary carbon centre with high diastereoselectivity.

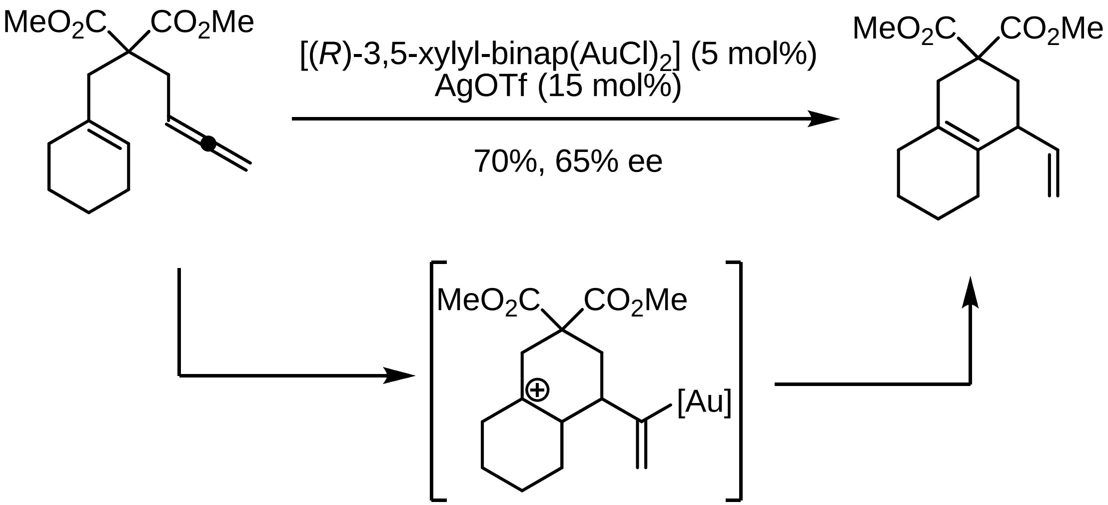


(–)-rhazilinam

Z. Liu, A. S. Wasmuth, S. G. Nelson, *J. Am. Chem. Soc.* **2006**, *128*, 10352.

Asymmetric addition of alkenes to allenes

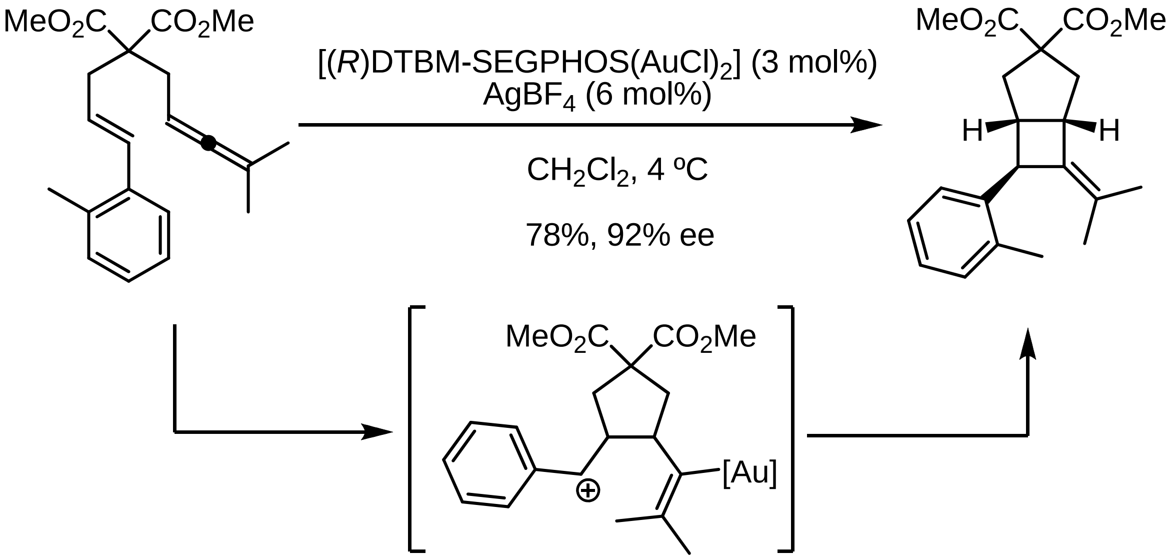
- As well as heteroatom and electron-rich aryl nucleophiles, alkenes have also been reacted with allenes under gold catalysis.
- 6-membered ring formation is favoured by stability of carbocationic intermediate



M. A. Tarselli, A. R. Chianese, S. J. Lee and M. R. Gagné, *Angew. Chem. Int. Ed.* **2007**, *46*, 6670.

Asymmetric addition of alkenes to allenes

- Formation of a five-membered ring can be favoured by varying alkene substitution, for instance, when cyclisation affords a benzylic cation.

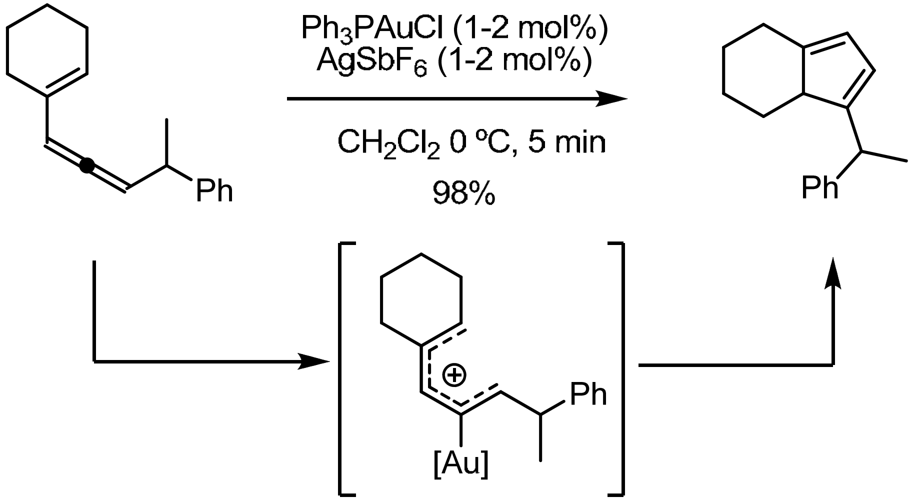


- The cation is trapped with a nucleophilic vinyl gold species – overall, a formal asymmetric [2+2] cycloaddition.

M. Luzung, P. Mauleón, F. D. Toste, *J. Am. Chem. Soc.* **2007**, *129*, 12402.

Nazarov varations

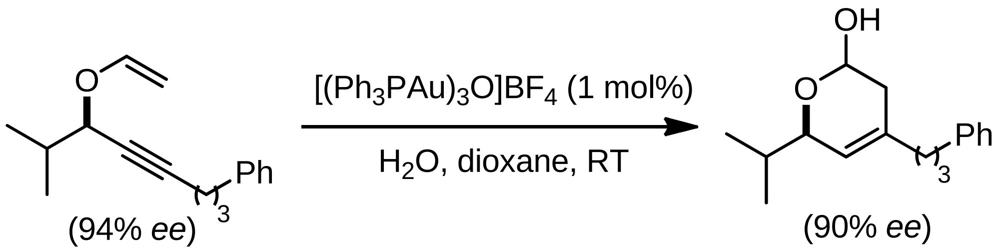
- When the alkene is in conjugation to the allene, electrophilic activation affords a cyclopentadienyl cation.
- Cyclopentadienes result from a Nazarov-type cyclisation.



J. H. Lee, F. D. Toste, *Angew. Chem. Int. Ed.* **2007**, *46*, 912.

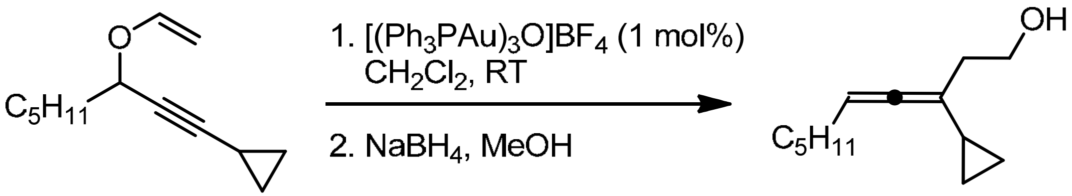
Cyclisation of allenes with enol ethers

- In the presence of alcohols cyclisation of an enol ether to an alkyne results in the formation of dihydropyran derivatives.

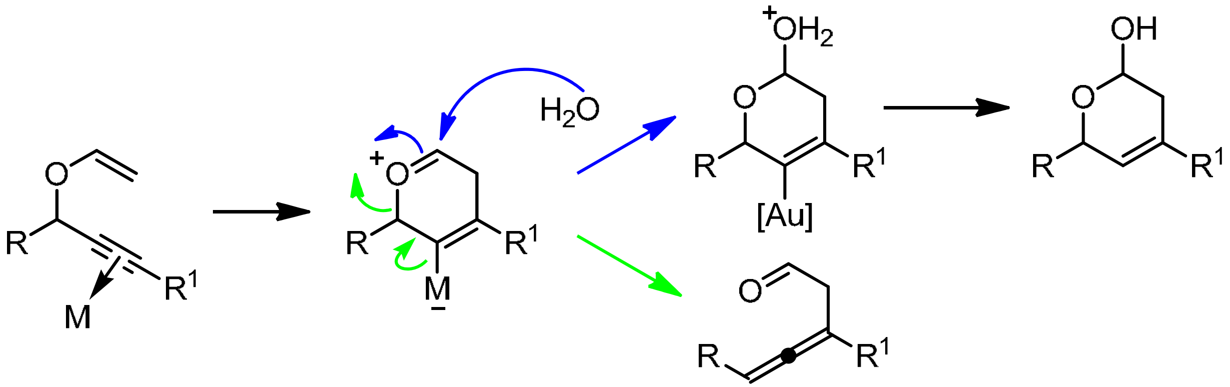


B. D. Sherry, L. Maus, B. N. Laforteza, F. D. Toste, *J. Am. Chem. Soc.* **2006**, *128*, 8132.

- In the absence of an external nucleophile, the same reaction affords allenols after reduction (substrates for further gold catalysed cyclisation).

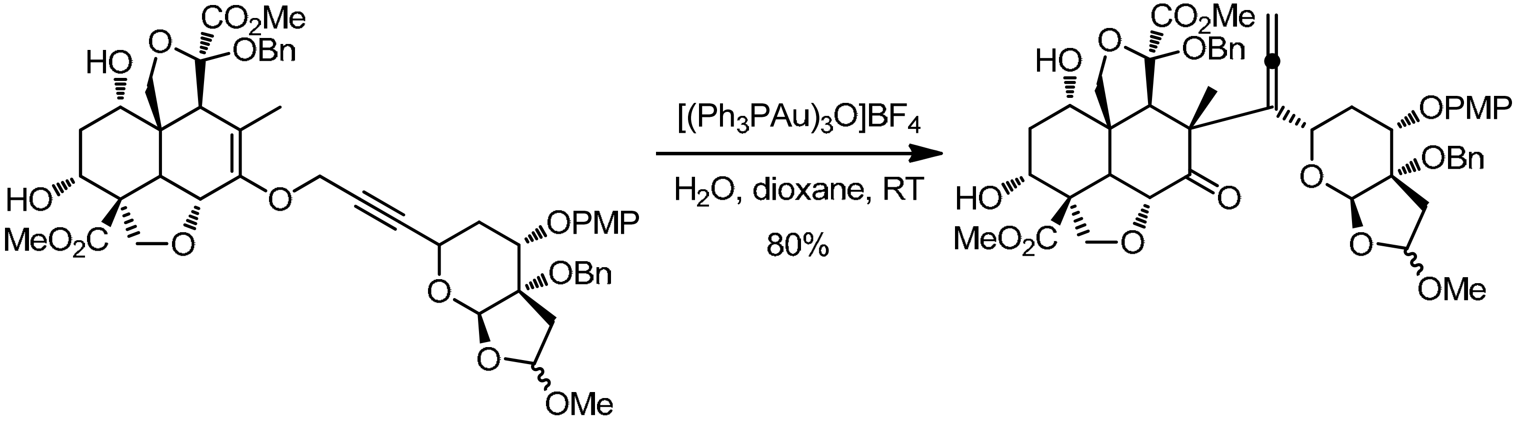


B. D. Sherry, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 15978.



Use in azadirachtin

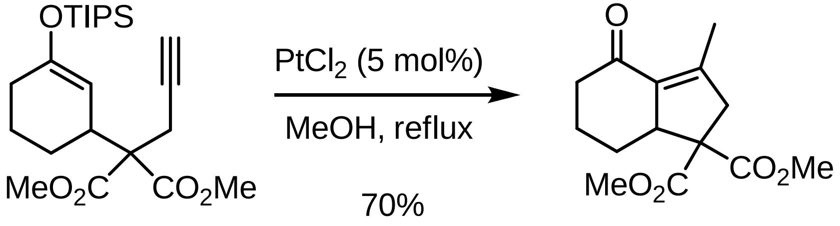
- The propargyl Claisen rearrangement can be applied to highly substituted and labile species.



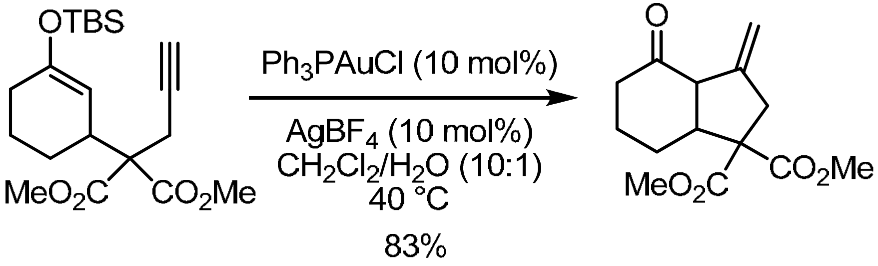
G. E. Veitch, E. Beckmann, B. J. Burke, A. Boyer, S. L. Masle, S. V. Ley, *Angew. Chem. Int. Ed.* **2007**, *46*, 7629.

Silyl enol ethers as nucleophiles

- The cyclisation of silyl enol ethers onto alkynes is a powerful methodology for the formation of C-C bonds, with O-Si cleavage in the presence of alcohol/water additives.



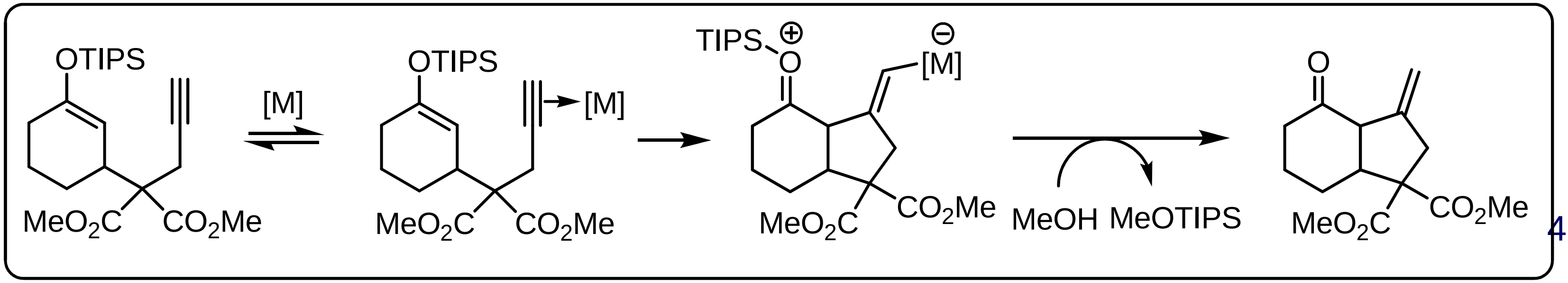
A. M. Echavarren *et al. Chem. Eur. J.* **2003**, *9*, 2627.



S. T. Staben, J. J. Kennedy-Smith, D. Huang, B. K.; Corkey, R. L. Lalonde, F. D. Toste, *Angew. Chem. Int. Ed.* **2006**, *45*, 5991.

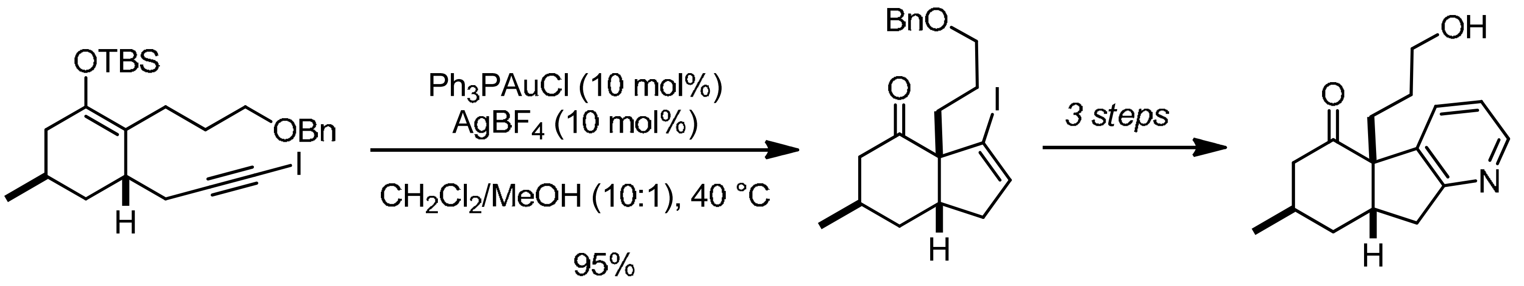
Silyl ketene amides: E. C. Minnihan, S. L. Colletti, F. D. Toste, H C. Shen, *J. Org. Chem.* **2007**, *72*, 6287.

7-membered rings: H. Ito, H. Ohmiya, M. Sawamura, *Org. Lett.* **2010**, *12*, 4380.



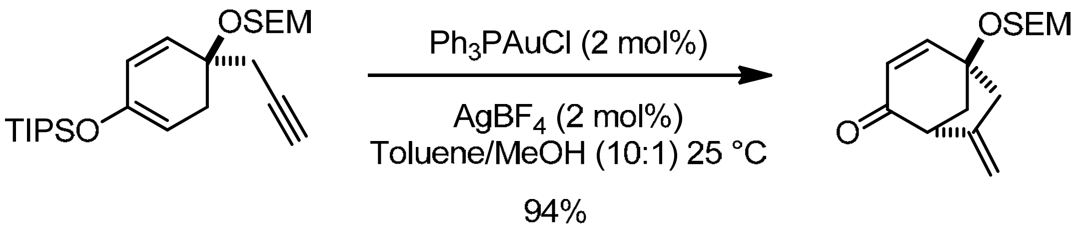
Silyl enol ethers as nucleophiles

- This process has been shown robust for application in the synthesis of natural products.

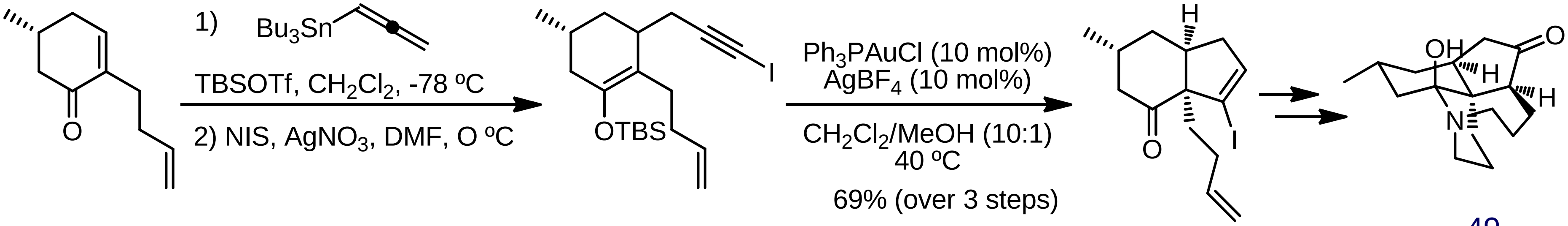


(+)-lycopladine A

lycopladine: S. T. Staben, J. J. Kennedy-Smith, D. Huang, B. K.; Corkey, R. L. Lalonde, F. D. Toste, *Angew. Chem. Int. Ed.* **2006**, *45*, 5991.



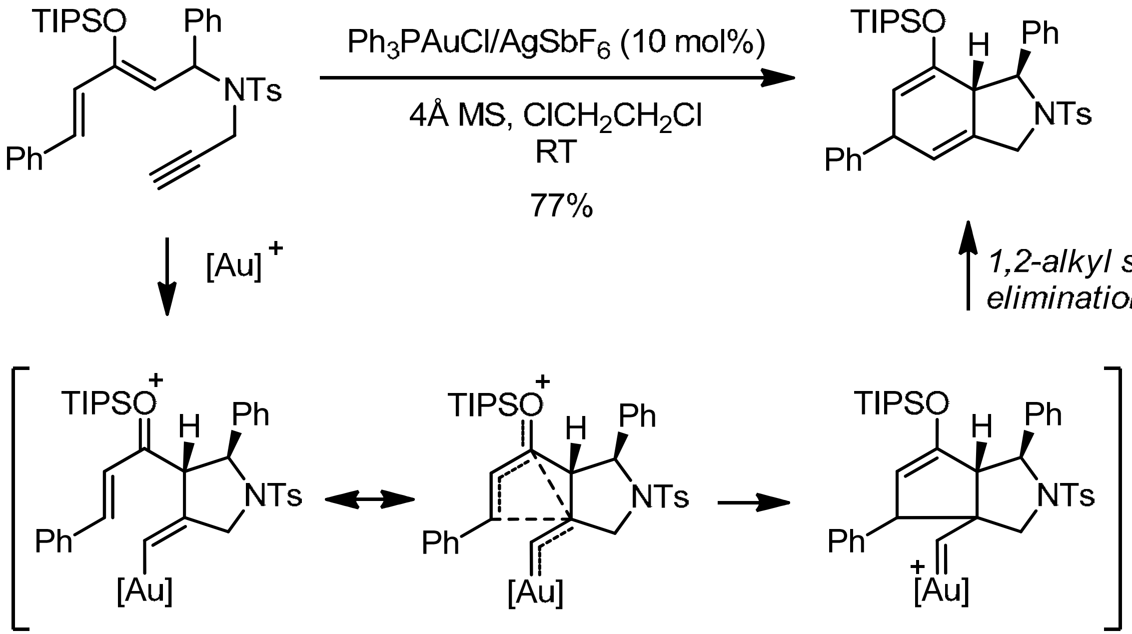
Platencin: K. C. Nicolaou *et al. Angew. Chem. Int. Ed.* **2008**, *47*, 1780.



fawcettimine X. Linghu, J. J. Kennedy-Smith and F. D. Toste, *Angew. Chem. Int. Ed.* **2007**, *46*, 7671.

Dienol silyl ethers as nucleophiles

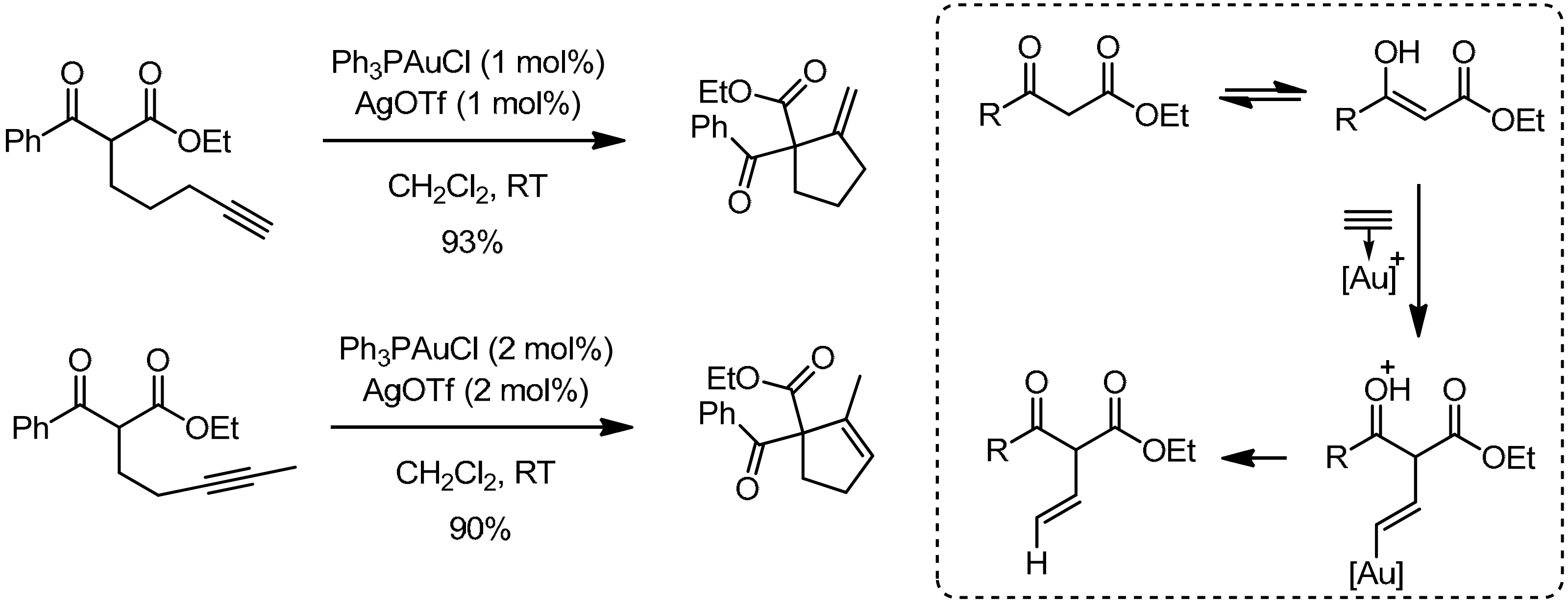
- A formal [4_2] cycloaddition is observed through use of dienol silyl enol ethers, thought to proceed through a stepwise process.
- Presence of molecular sieves reduces O-Si cleavage



H. Kusama, Y. Karibe, Y. Onizawa, N. Iwasawa, *Angew. Chem. Int. Ed.* **2010**, *49*, 4269.

Activated methylene units as nucleophiles

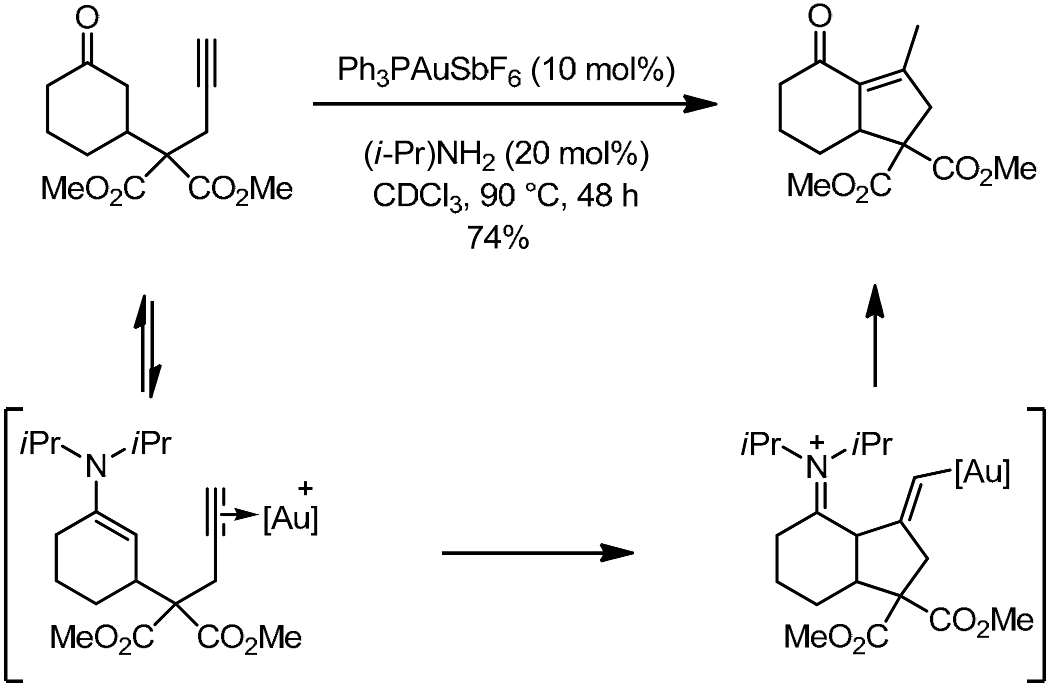
- The Gold-catalysed variant of the Conia-ene thermal pericyclic reaction allows both *exo* and *endo* cyclisations, with anti-addition across the alkyne.
- The electron withdrawing group is present to increase concentration of the *C*-nucleophilic enol tautomer.



J. J. Kennedy-Smith, S. T. Staben, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 4526.
S. T. Staben, J. J. Kennedy-Smith, F. D. Toste, *Angew. Chem. Int. Ed.* **2004**, *43*, 5350.

Gold-catalysed cyclisation of keto-alkynes

- Unactivated enolisable carbonyls can undergo α-functionalisation with alkynes under gold catalysis in the presence of an amine to access iminium-enamine tautomerisation.



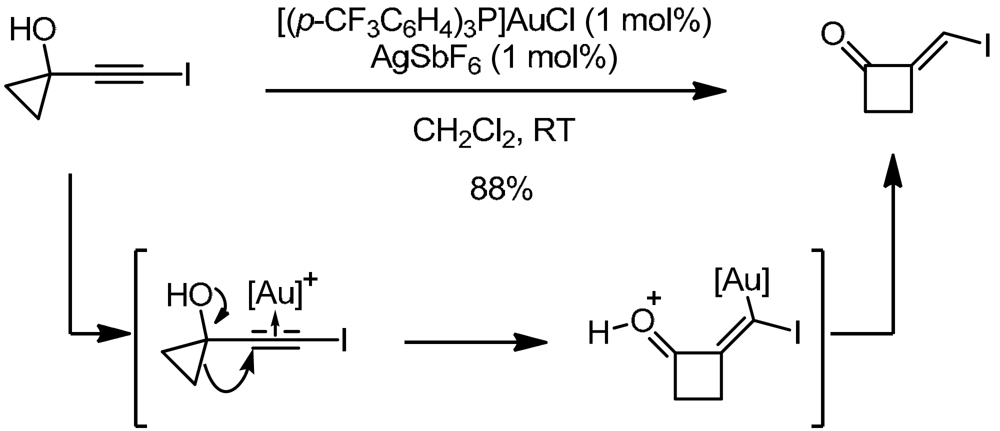
J. T. Binder, B. Crone, T. T. Haug, H. Menz, S. Kirsch, Org. Lett. **2008**, *10*, 1025.
Cu-catalysed Cascade Process: Dixon *et al*. *Chem. Commun.* **2008**, 2923.

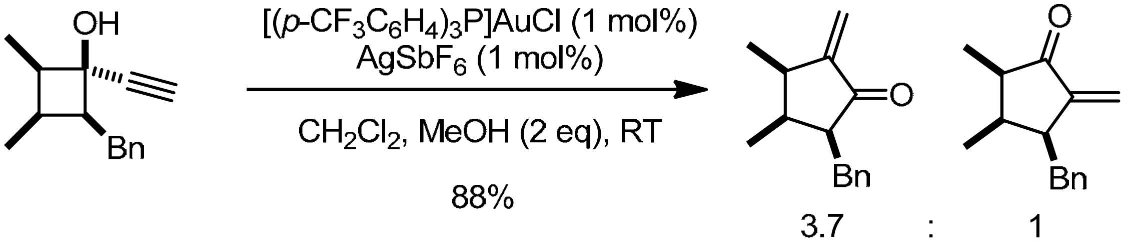
- Analogous cyclisations are observed in the absence of an amine at room temperature, but likely proceed *via* alkyne hydration/aldol dehydration processes.

P. W. Davies, C. Detty-Mambo, *Org. Biomol Chem.* **2010**, *8*, 2918.

Ring-expansion processes

- Addition of C H across an alkyne can also be achieved by ring expansion. Gold activation of the alkyne triggers a heteroatom assisted 1,2-shift in a ring expansion of cyclopropanols and cyclobutanols.



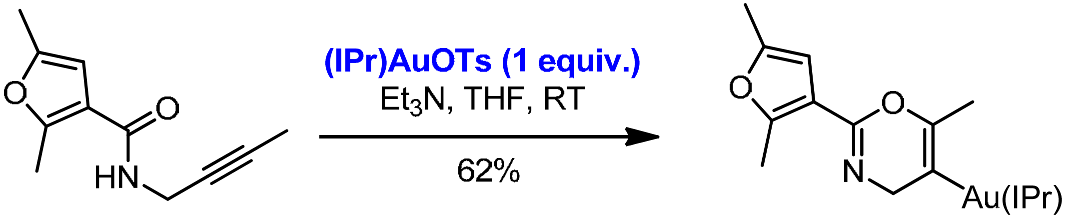


J. P. Markham, S. T. Staben, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 9708.

Gold Intermediates

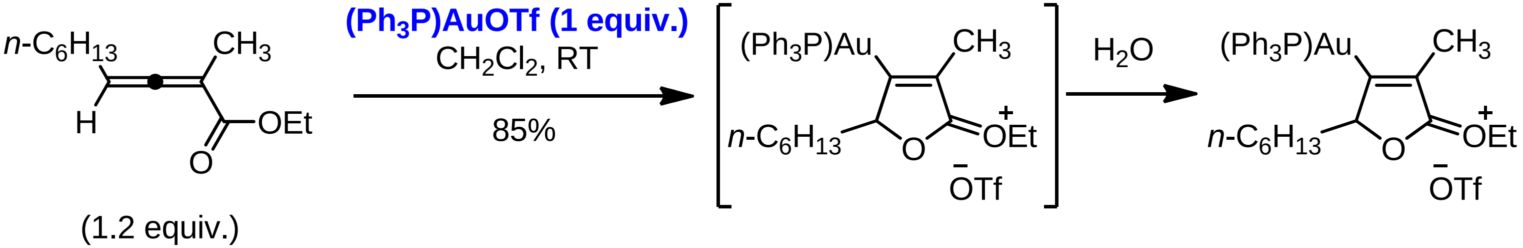
Isolation of Intermediates

- Vinyl gold species are implicated as the first intermediate from addition of nucleophilic addition to a gold-activated alkyne and in several cases have now been isolated form cyclisation processes.
- A base is required to sequester the proton which would otherwise be involved with protodemetallation and catalyst turnover.



A. S. K. Hashmi, A. M. Schuster, F. Rominger, *Angew. Chem. Int. Ed.* **2009**, *48*, 8247;
A. S. K. Hashmi, T. Dondeti Ramamurthi, F. Rominger, Adv. Synth. Catal. **2010**, *352*, 971.

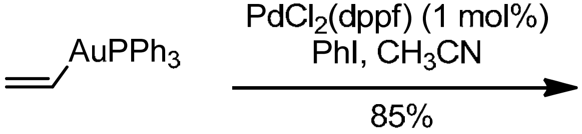
- Consistent with the complexes isolated from allenoate cyclisations (in the absence of base).

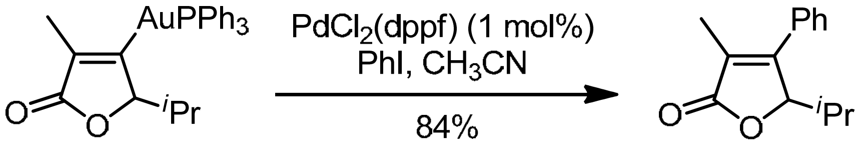


L.-P. Liu, B. Xu, M.S. Mashata, G. B. Hammond, *J. Am. Chem. Soc.* **2008**, *130*, 17642.

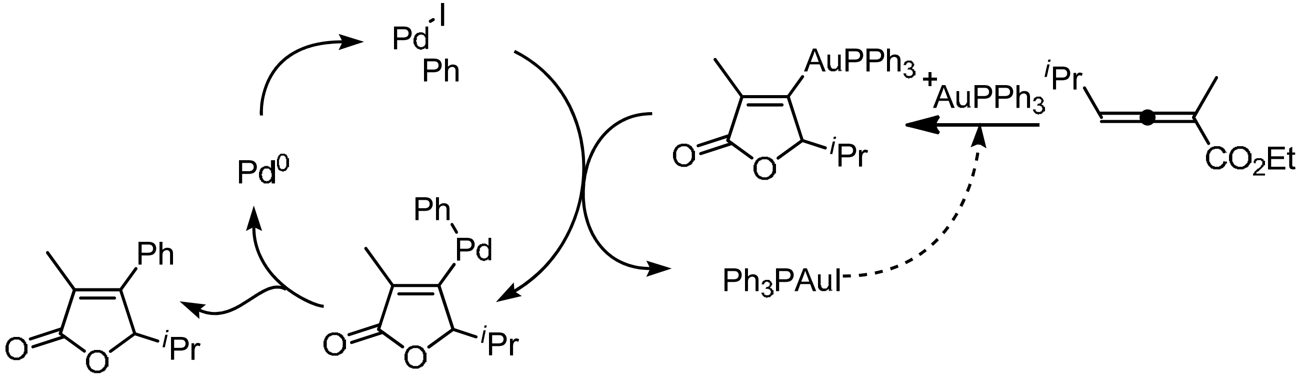
Use of vinyl-gold intermediates

- Vinyl, aryl or alkynyl gold(I) species can be productively cross-coupled to aryl halides by palladium without any requirement for further additives.





- Potential scope exists to combine two catalytic cycles.

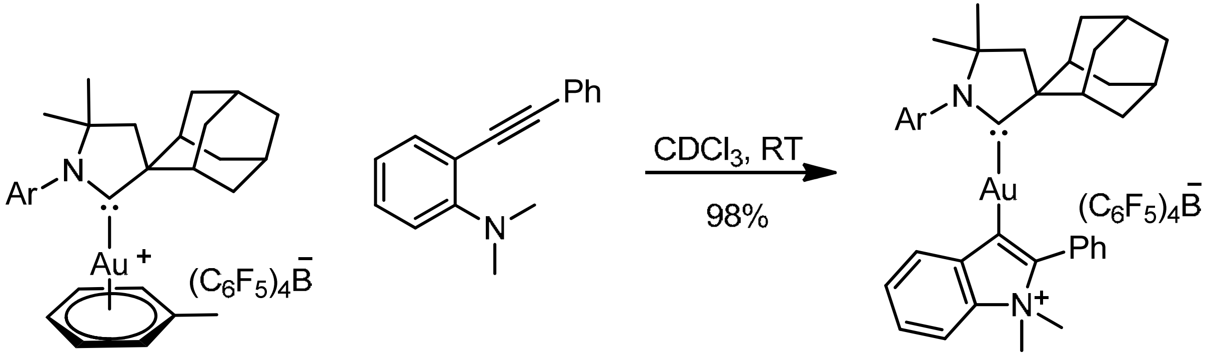


A. S. K. Hashmi, C. Lothschütz, R. Döpp, M. Rudolph, T. D. Ramamurthi, F. Rominger, *Angew. Chem. Int. Ed.* **2009**, *48*, 8247; A. S. K. Hashmi, R. Döpp, C. Lothschütz, M. Rudolph, D. Riegel, F. Rominger, *Adv. Synth. Catal.* **2010**, *352*, 1307.

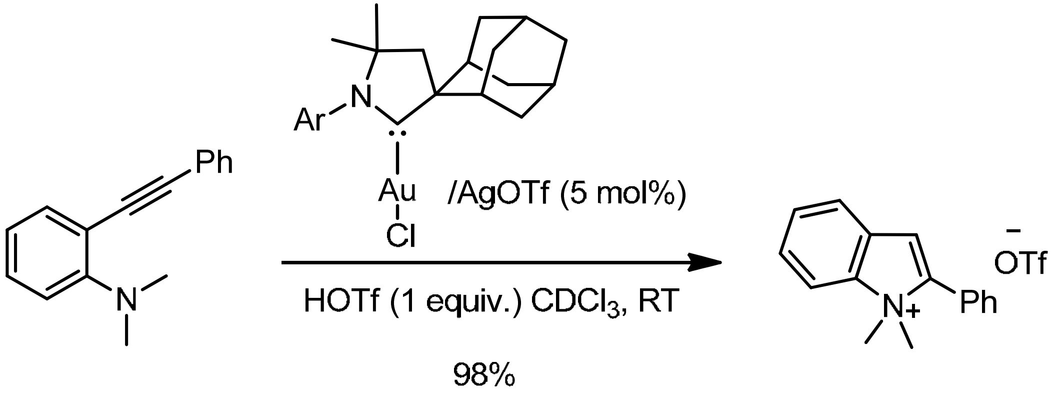
See also: Carboauration of alkynes, Y. Shi, S. D. Ramgren, S. A. Blum, *Organometallics* **2009**, *28*, 1275.

Gold intermediates

- Use of a CAAC allows capture of aryl gold intermediates in hydroamination and the gold-catalysed hydroammoniation of alkynes.



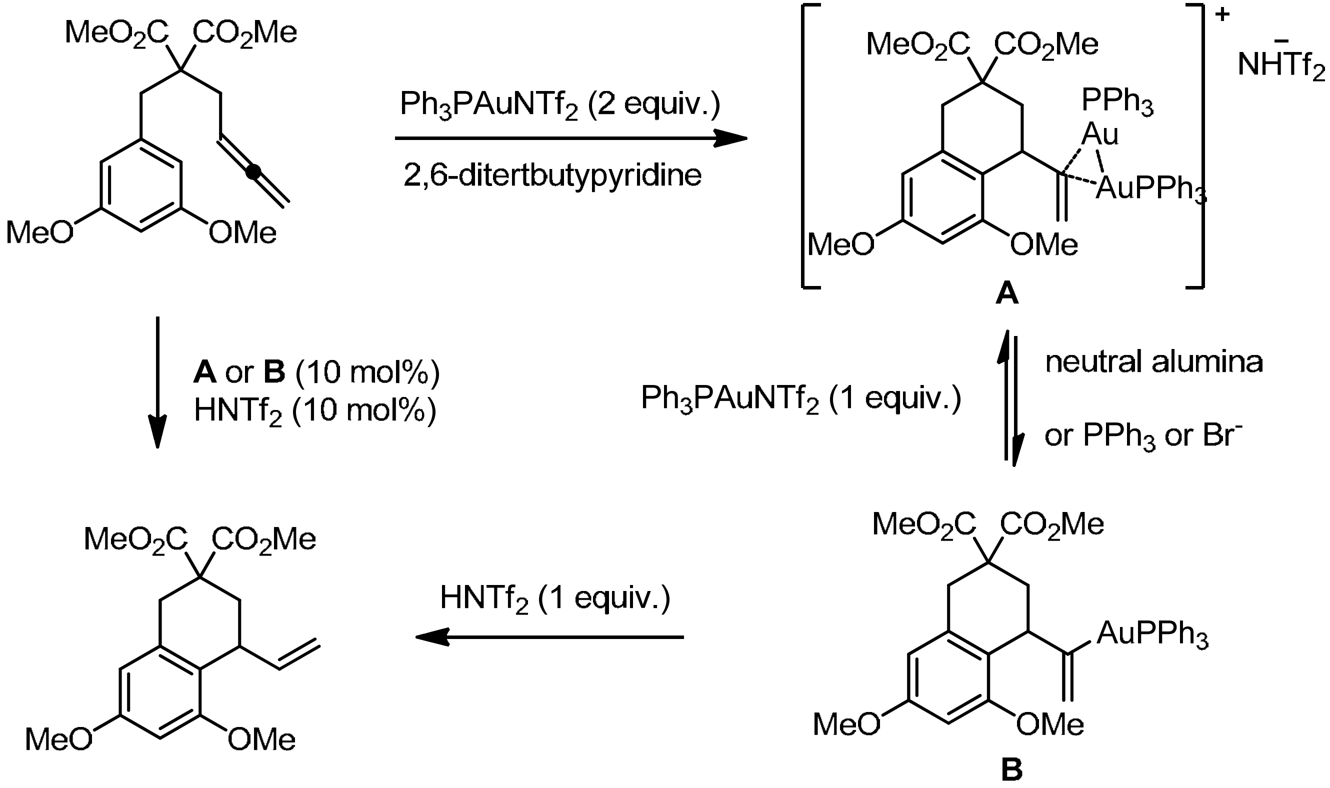
Ar = 2,6-diisopropylphenyl



X. Zeng, R. Kinjo, B. Donnadieu, G. Bertrand, *Angew. Chem. Int. Ed.* **2010**, *49*, 942.

Allenes: gem-diauration

- Hydroarylation of allenes led to the isolation and identification of a dimetallated species which appears to represent a resting state for the catalyst.
- Protodemetallation is retarded through use of an amine.

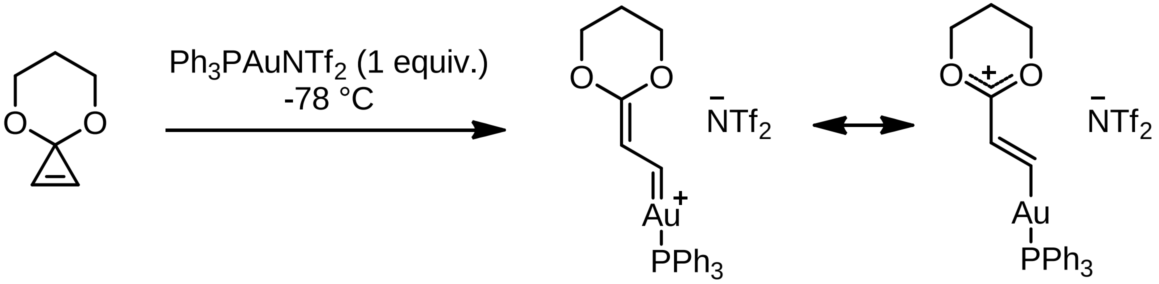


- **A** is stable to water and air. Purification techniques either led to the protodemetallation product, or (on alumina) the monometallic vinyl gold intermediate.
- **B** readily undergoes protodemetallation, **A** does not (stabilising Au-Au interaction).

D. Weber, M. A. Tarselli, R. Gagné, *Angew. Chem. Int. Ed.* **2009**, *48*, 5733;
G. Seidel, C. W. Lehmann, A. Furstner, *Angew. Chem. Int. Ed*. **2010**, *49*, 8466.

Organogold species: Carbene or delocalised carbocation?

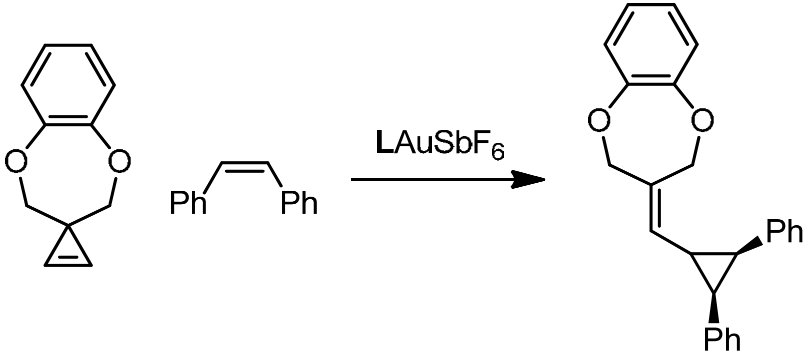
- NMR spectroscopy of these species supports the oxocarbenium cation in the electronically biased system.



- The carbon-gold bond is made up from varying degrees of σ and π-bonding.

- In gold-stabilized intermediates the nature of the bonding is dictated by the 'carbene' substituents and ligands on the gold.

- Experimental correlation between bonding and reactivity was studied looking at the the yield of gold-catalyzed cyclopropanation reactions.



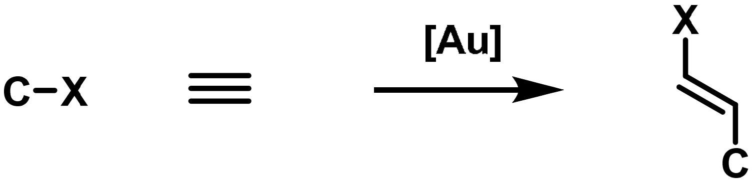
L = $(MeO)_3P$	0%	
$(PhO)_3P$	11%	(4:1)
Me_3P	56%	(1.4:1)
IPr	80%	(11:1)

G. Seidel, R. Mynott, A. Fürstner, *Angew. Chem. Int. Ed.* **2009**, *48*, 2510; D. Benitez, N. D. Shapiro, E. Tkatchouk, Y. Wang, W. A. Goddard, F. D. Toste, *Nat. Chem.* **2009**, *1*, 482.

Review of characterised intermediates: A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2010**, *49*, 5232.

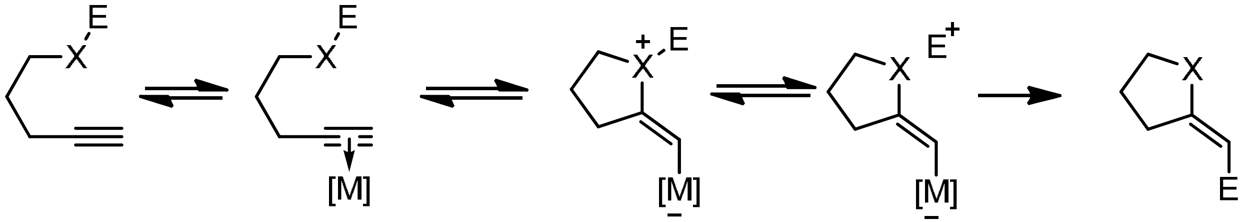
Cyclopropenes as precursors to gold carbenoids for synthesis: J. T. Bauer, M. S. Hadfield, A.-L. Lee, *Chem. Commun.* **2008**, 6405; Z.-B. Zhu, M. Shi, *Chem. Eur. J.* **2008**, *14*, 10219.

C-X addition across C-C π-systems



- Hydroamination and related reactions mimic classical π-activation chemistry, though gold can provide a greatly improved generality.

- However, valuable substituted heterocyclic scaffolds can be accessed by use of heteroatom nucleophiles not bonded to hydrogen.



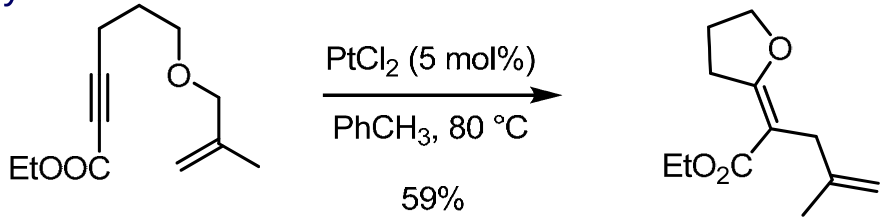
- Generally, an onium complex is formed after complexation of the nucleophilic heteroatom to the metal-activated alkyne.

- One of the heteroatom substituents transfers to the metallated position resulting in overall heteroatom→carbon shift.

- While the mechanism may vary depending on the exact process, the substituent best-able to stabilize a developing positive charge undergoes the shift.

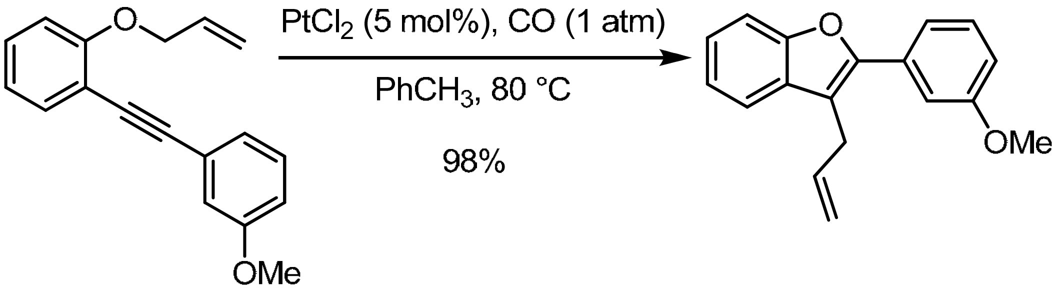
Carboalkoxylation with π-acids

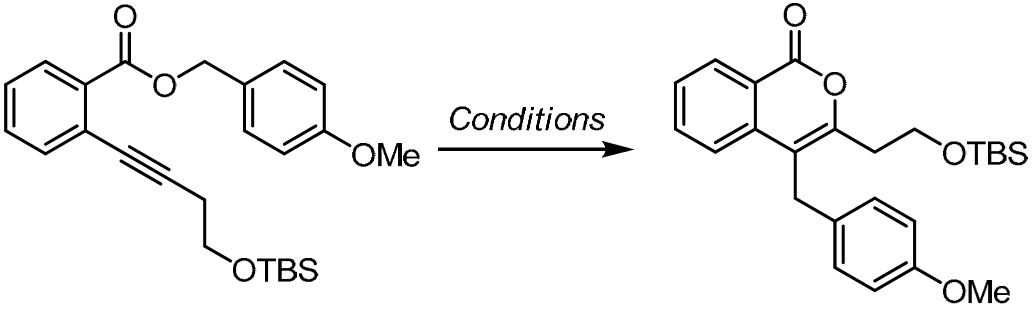
- C-O addition: allyl ethers



A. Fürstner, F. Stelzer, H. Szillat, *J. Am. Chem. Soc.* **2001**, *123*, 11863;
A. Fürstner, H. Szillat, F. Stelzer, *J. Am. Chem. Soc*. **2000**, *122*, 6785.

- C-O addition: acetals, allyl ethers, benzyl esters



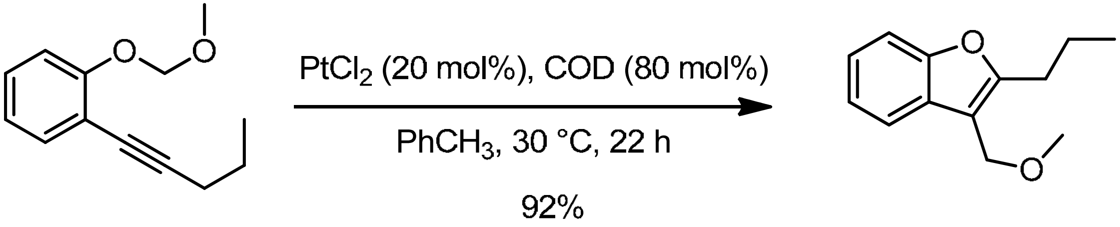


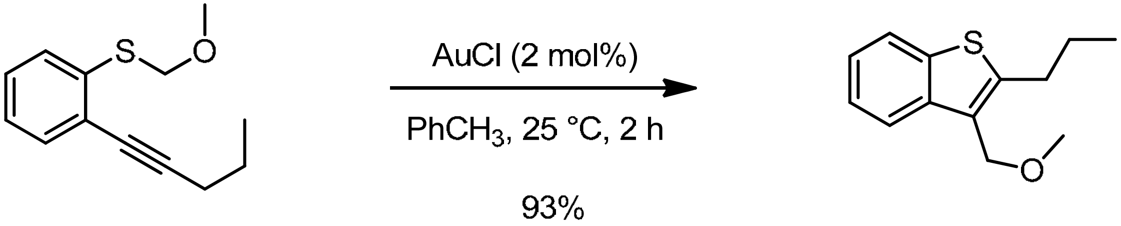
$PtCl_2$ (5 mol%), CO (1 atm), $PhCH_3$, 80 °C, 5 min	98%
AuCl (5 mol%), CH_2Cl_2, 25 °C, 1 h	98%

A. Fürstner, P. W. Davies, *J. Am. Chem. Soc.* **2005**, *127*, 15024; *Angew. Chem. Int. Ed.* **2007**, *46*, 3410.

C-N, C-O and C-S addition across alkynes

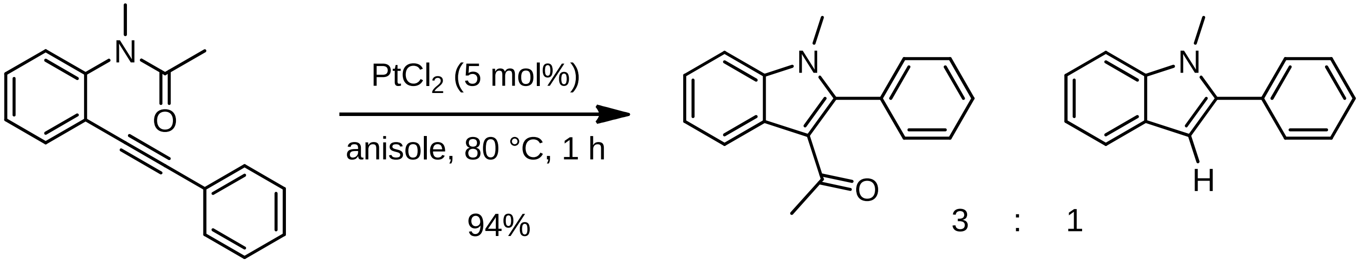
- C-O/C-S addition: mixed acetals, O,S-acetals





I. Nakamura, Y. Mizushima, Y. Yamamoto, *J. Am. Chem. Soc.* **2005**, *127*, 15022.
I. Nakamura, T. Sato, Y. Yamamoto, *Angew. Chem. Int. Ed.* **2006**, *45*, 4473.

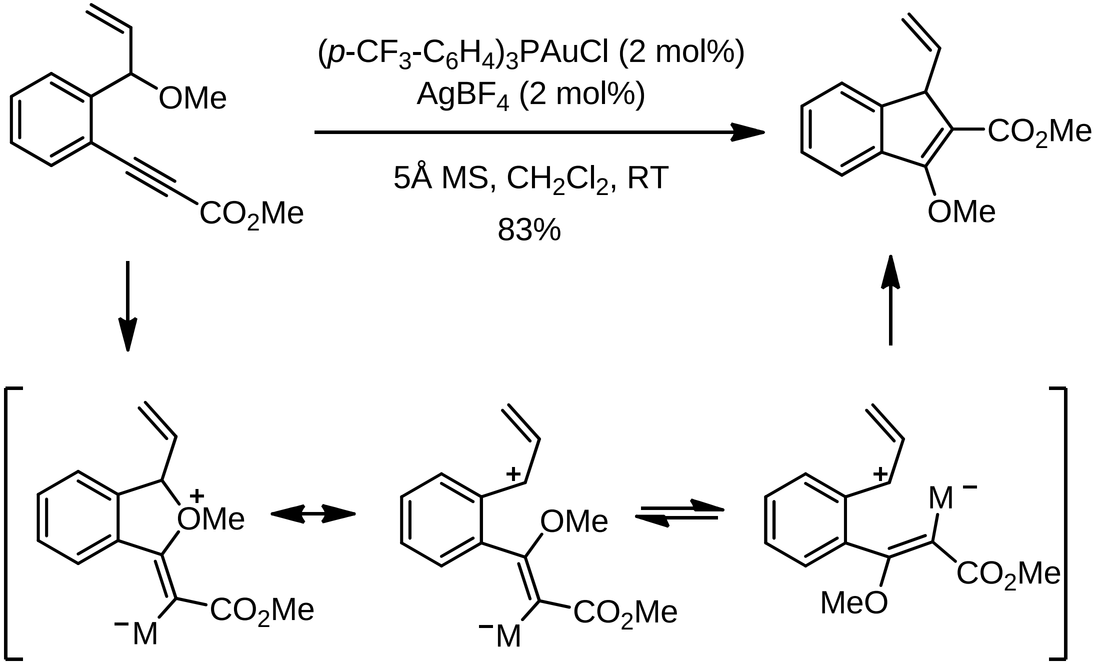
- C-N addition: amides



T. Shimada, I. Nakamura, Y. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 10546.

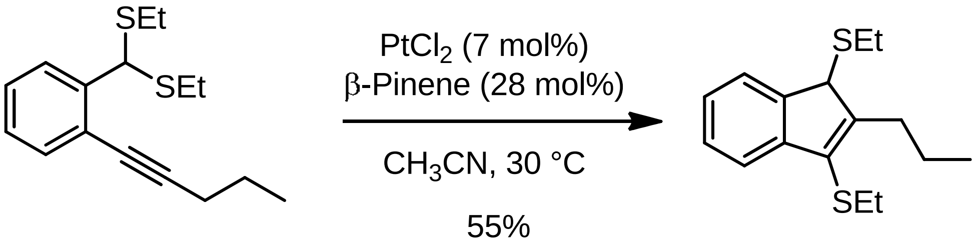
C-migrating groups within the tether

- C-O addition: Benzyl ethers
- The transferring group can be within the tether linking the oxygen nucleophile to the alkyne



P. Dubé, F. D. Toste, *J. Am. Chem. Soc.* **2006**, *128*, 12062.

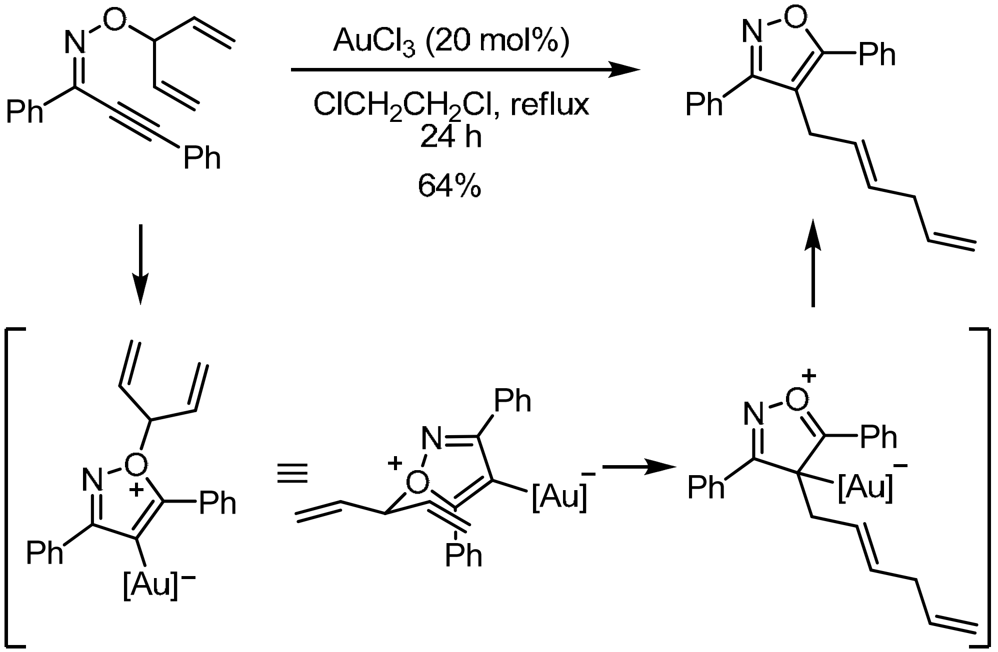
- C-S addition: benzyl acetals and thioacetals



I. Nakamura, G. B. Bajracharya, Y. Mizushima, Y. Yamamoto, *Angew. Chem. Int. Ed.* **2002**, *41*, 4328; I. Nakamura, G. B. Bajracharya, H. Wu, K. Oishis, Y. Mizushima, I. D. Gridnev, Y. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 15423.

C-O addition to form oxazoles

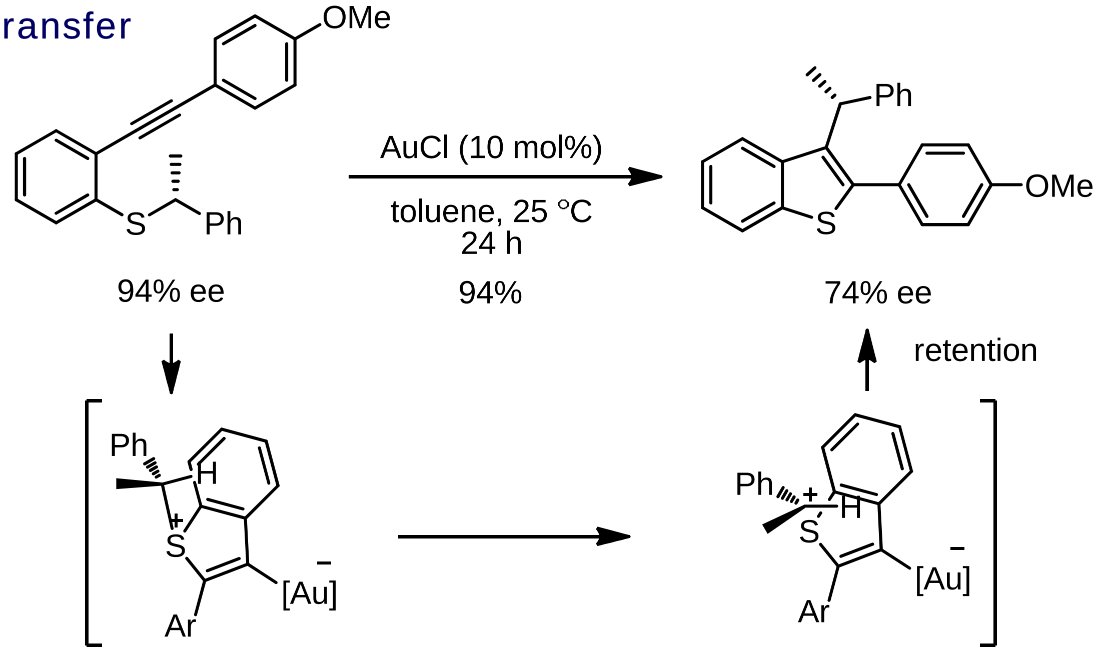
- C-O addition: Oxime ethers.



M. Ueda, A. Sato, Y. Ikeda, T. Miyoshi, T. Naito, O. Miyata, *Org. Lett.* **2010**, *12*, 2594.

C-S and S-Si addition to alkynes

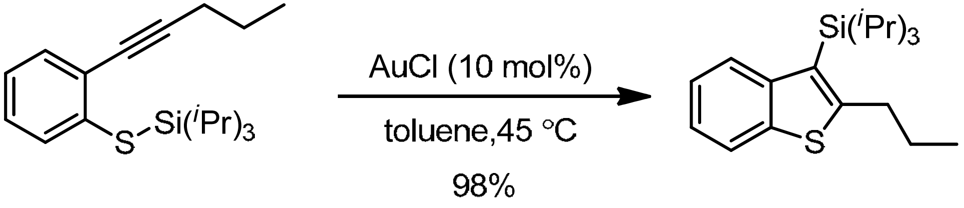
- C-S addition: Mechanistic study supports the generation of a contact ion pair prior to C-C bond formation
- 79% chirality transfer



I. Nakamura, T. Sato, M. Terada, Y. Yamamoto, *Org. Lett.* **2008**, *10*, 2649.

Benezoselenophenes: T. Sato, I. Nakamura, M. Terada, *Eur. J. Org. Chem.* **2009**, *5509*.

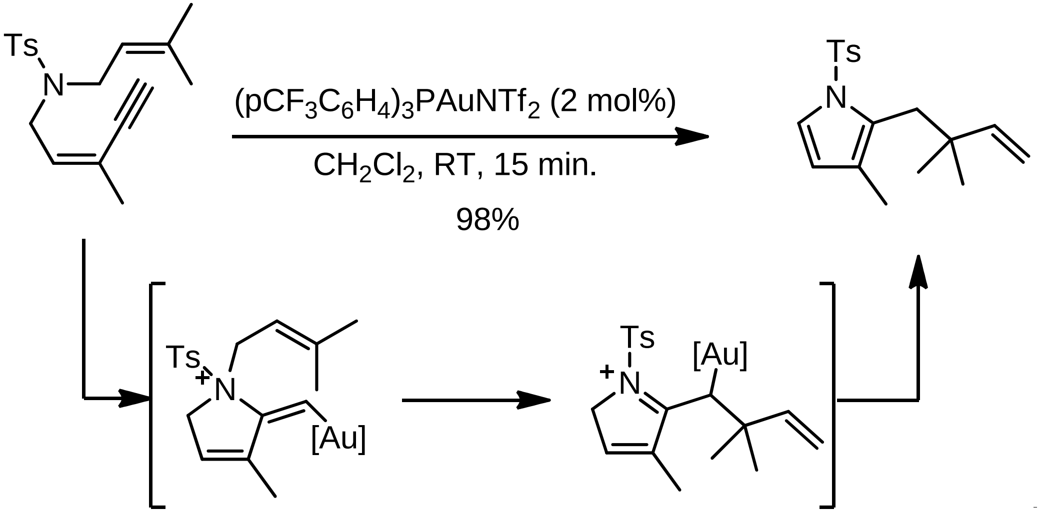
- S-Si bond formation by silyldemetallation



I. Nakamura, T. Sato, M. Terada, Y. Yamamoto, *Org. Lett.* **2007**, 9, 4081.

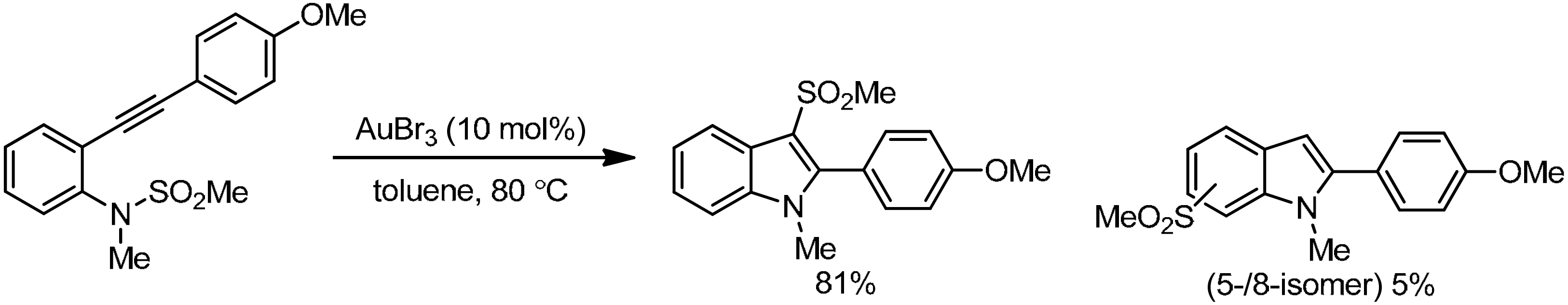
C-N and N-S addition to alkynes

- C-N addition: Pyrrole synthesis through an Aza-Claisen mechanism.



F. M. Istrate, F. Gagosz, *Org. Lett.* **2007**, 9, 3181.

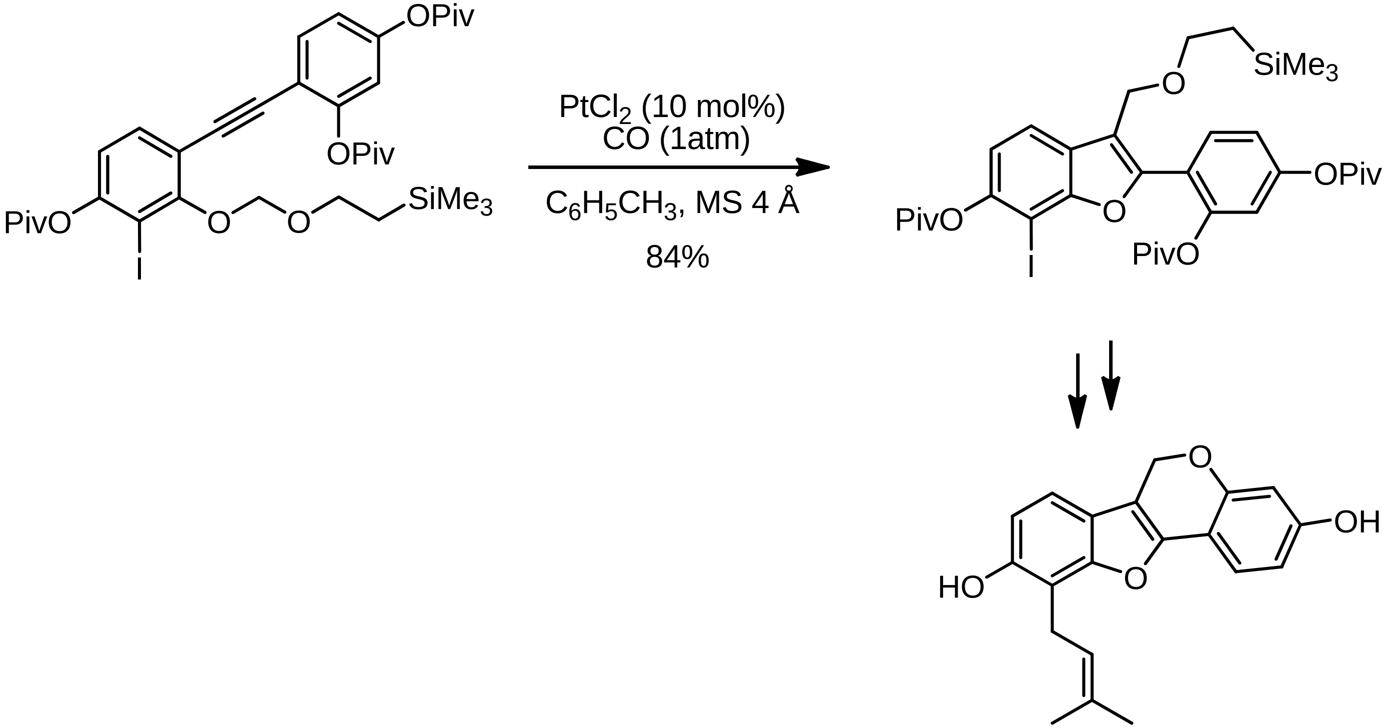
- N-S addition: Sulfonyl transfer: Use of $InBr_3$ as catalyst favours the alternative regiochemical outcome.



I. Nakamura, U. Yamagishi, D. Song, S. Konta, Y. Yamamoto, *Angew. Chem. Int. Ed.* **2007**, *46*, 2284.

Applications

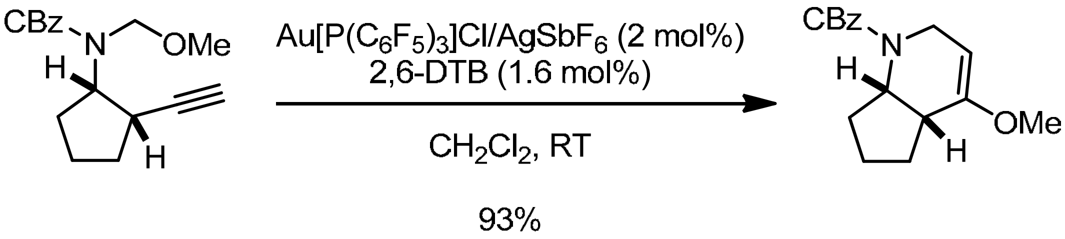
- C-O addition: Employed in the synthesis of the antibiotic erypoegin H and its cognates.
- Gold and platinum catalysis is orthogonal to other redox-based catalyst systems.



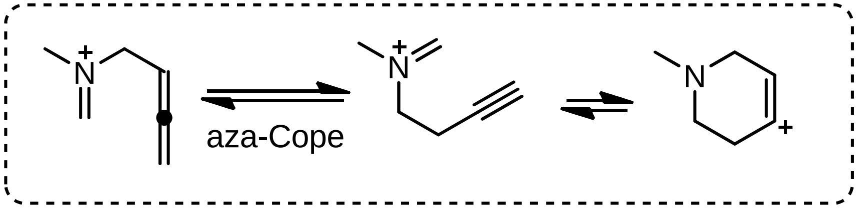
A. Fürstner, E. K. Heilmann, P. W. Davies, *Angew. Chem. Int. Ed.* **2007**, *46*, 4760.

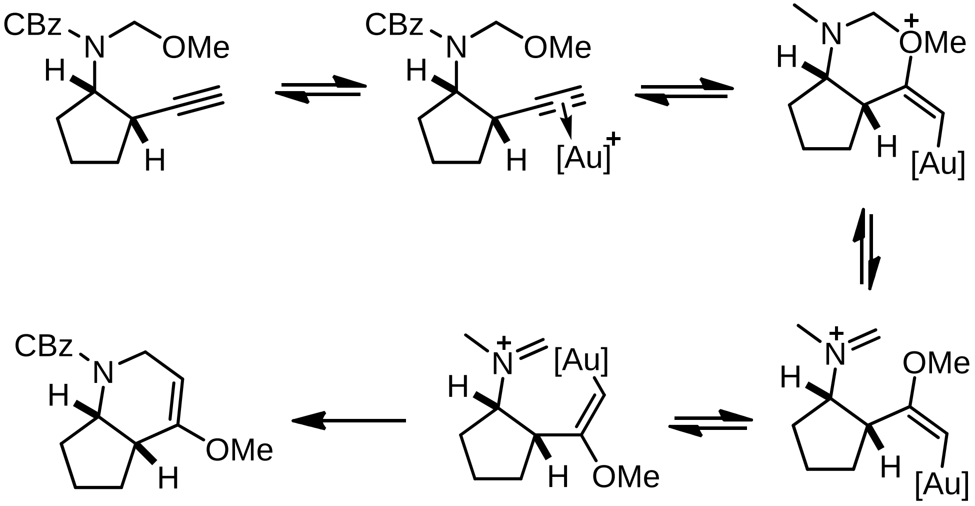
C-O additions across alkynes

- C-O addition: from mixed *N*,*O*-acetals for piperidine synthesis



- Variant on an aza-Cope approach which requires formation of a vinyl cation



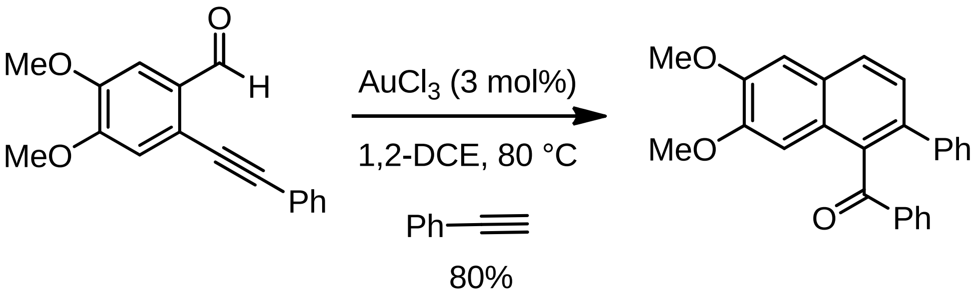


C. Kim, H. J. Bae, J. H. Lee, W. Jeong, H. Kim, V. Sampath, Y. H. Rhee, *J. Am. Chem. Soc.* **2009**, *131*, 14660.

Cycloadditions

Benzannulation reactions

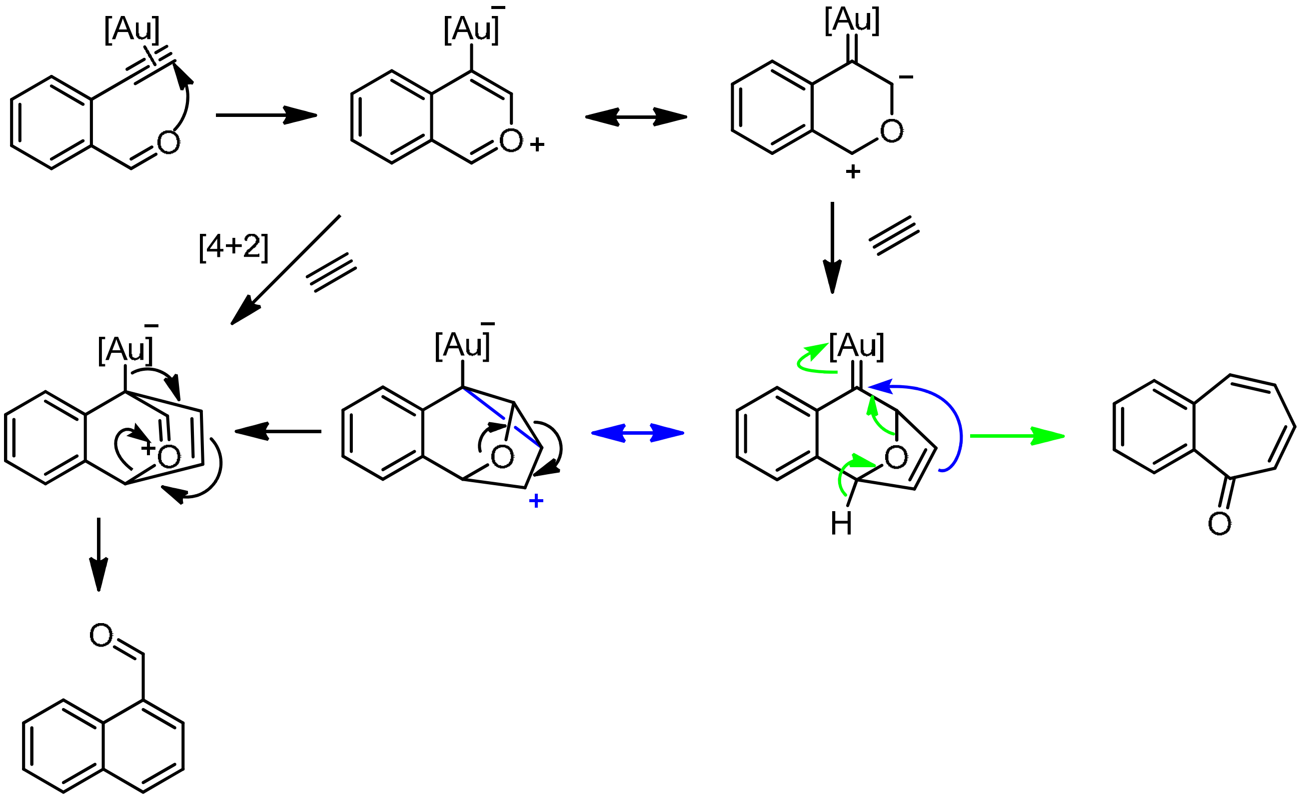
- Oxonium (or iminium) species generated from the nucleophilic attack of a carbonyl (imine) onto a metal activated alkyne may be employed in cycloaddition reactions as 1,3 (or 1,4) dipoles.
- Benzannulated products are formed after further rearrangement.



B. F. Straub, *Chem. Commun.* **2004**, 1726; N. Asao, H. Aikawa, Y. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 7458; N. Kim, Y. Kim, W. Park, D. Sung, A. K. Gupta, C. H. Oh, *Org. Lett.* **2005**, *7*, 5289; N. Asao, H. Aikawa, *J. Org. Chem.* **2006**, *71*, 5249; N. Asao, K. Takahashi, S. Lee, T. Kasahara, Y. Yamamoto, *J. Am. Chem. Soc.* **2002**, *124*, 12650; N. Asao, T. Nogami, S. Lee, Y. Yamamoto, *J. Am. Chem. Soc.* **2003**, *125*, 10921; N. Asao, K. Sato, Menggenbateer, Y. Yamamoto, *J. Org. Chem.* **2005**, *70*, 3682; D. Hildebrandt, W. Hüggenberg, M. Kanthak, T. Plöger, I. M. Müller, G. Dyker, *Chem. Commun.* **2006**, 2260.

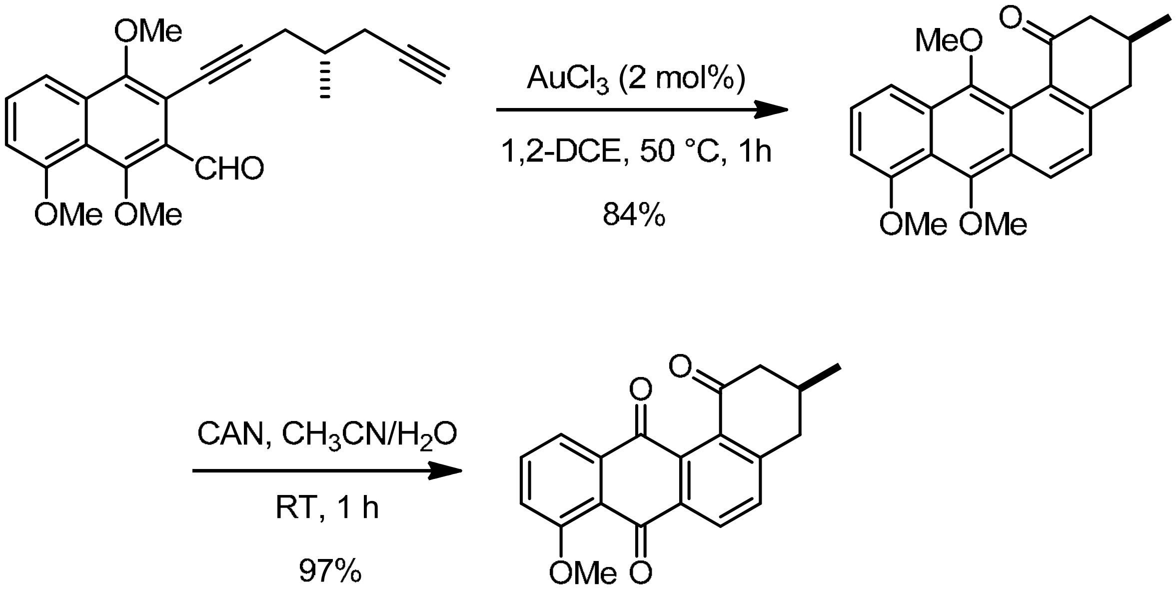
Mechanism

- [3+2]/rearrangement pathways are more likely than direct [4+2] cycloadditions though the processes are substrate- and catalyst dependent.
- Inter and intermolecular cycloaddition processes have been realised.



Benzannulation in synthesis

- Formal [4+2] benzannulation of *o*-alkynylbenzaldehydes is employed as the key step in the synthesis of (+)-rubiginone.

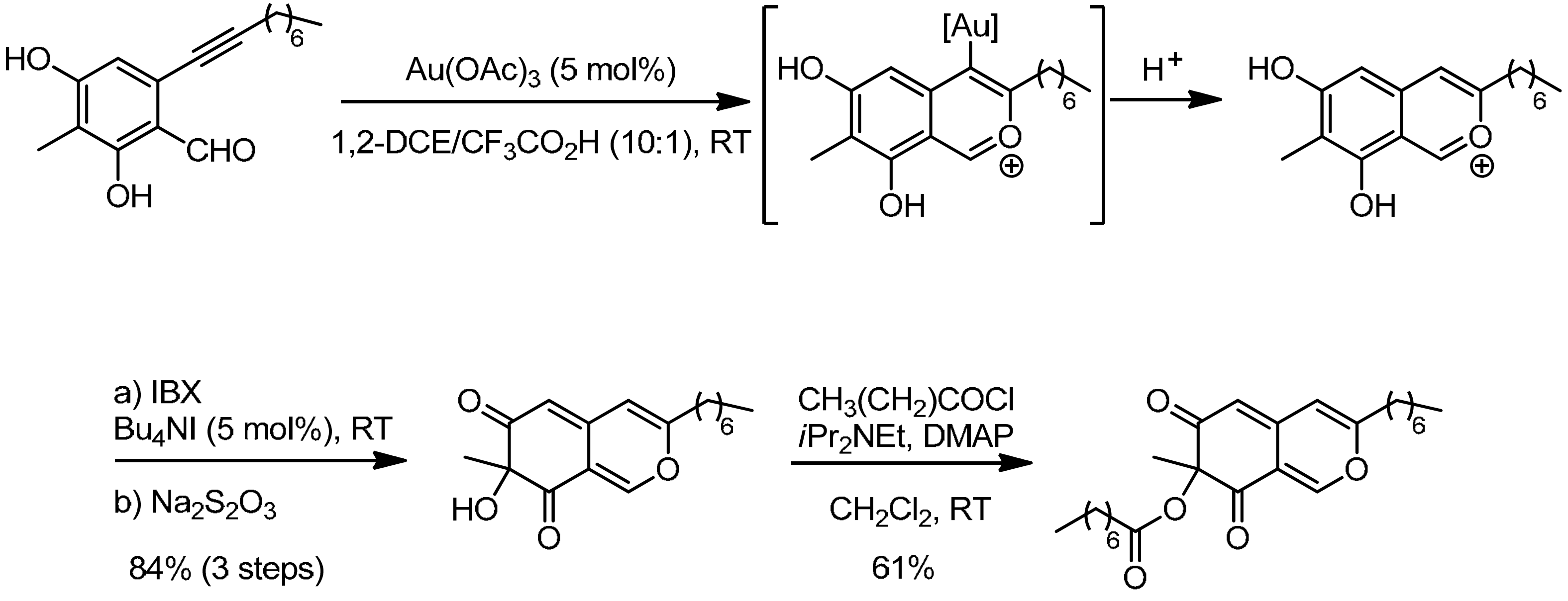


(+)-rubiginone B$_2$

K. Sato, N. Asao, Y. Yamamoto, *J. Org. Chem.* **2005**, *70*, 8977.

Oxonium formation in azaphilone synthesis

- Protodemetallation of the intermediate formed on cyclisation allows isolation of the oxonium species which can subsequently be oxidised to access the natural product structures.

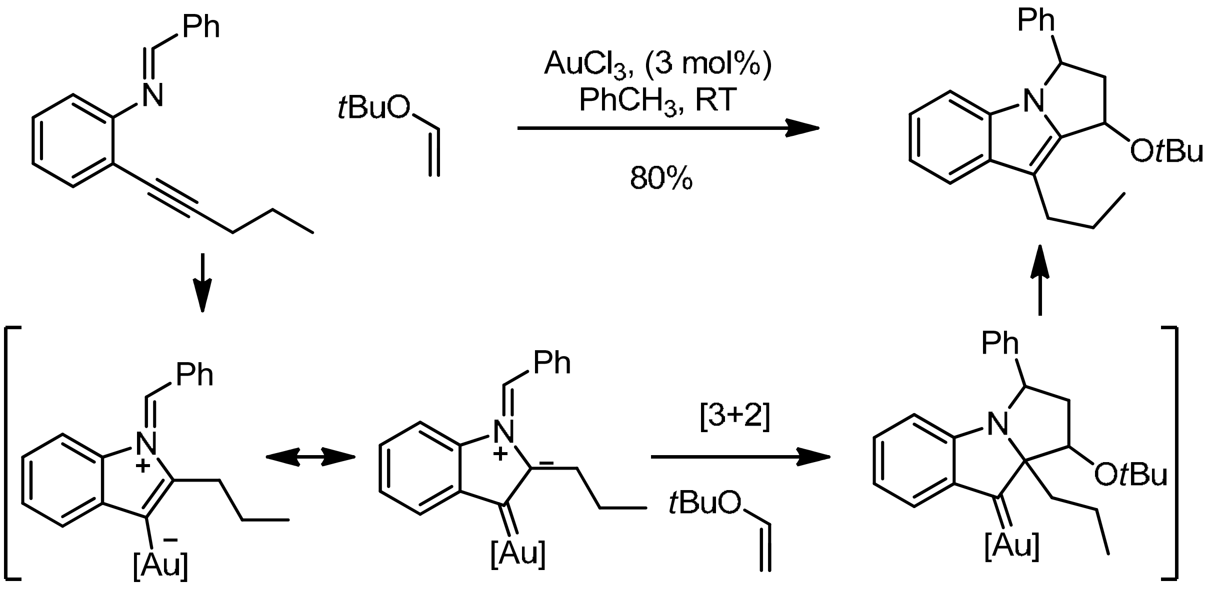


(±)-S-15183a

J. Zhu, A. R. Germain, J. A. Porco, Jr., *Angew. Chem. Int. Ed.* **2004**, *43*, 1239.

Azomethine ylides

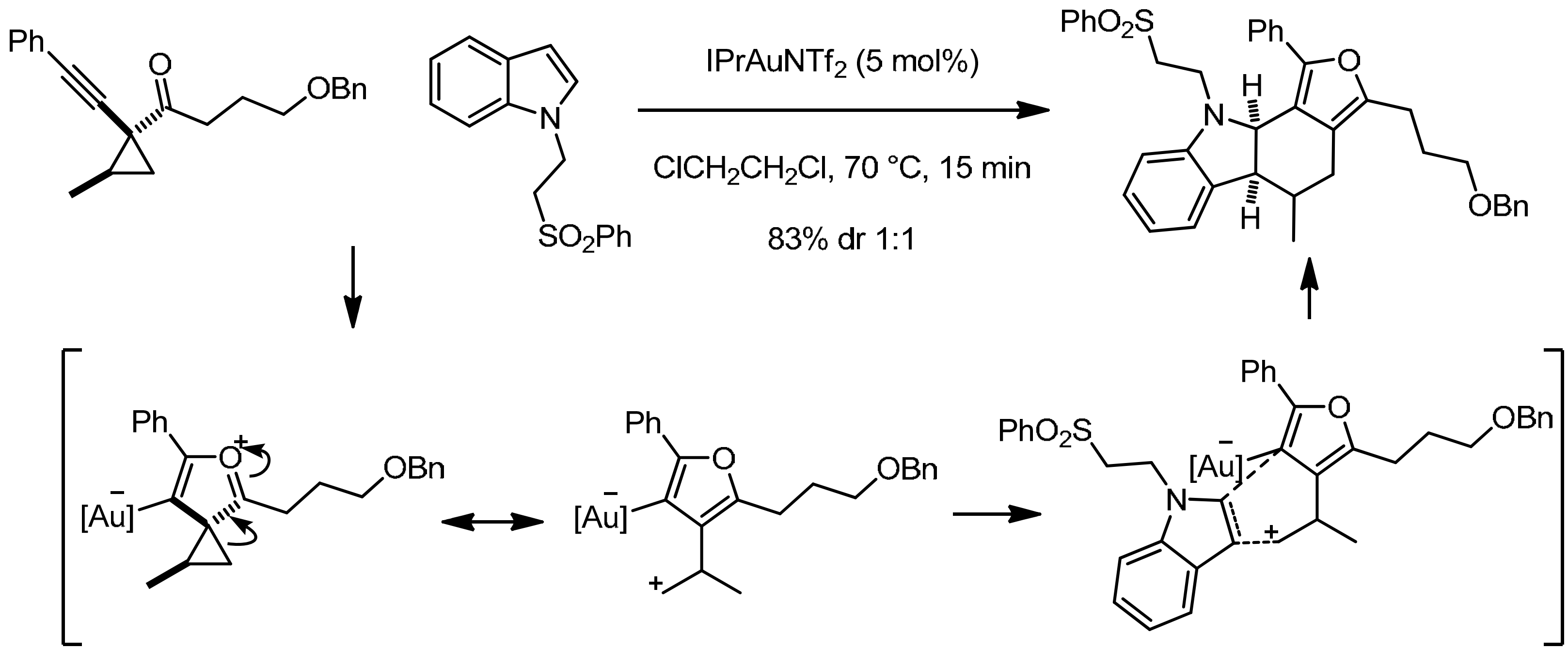
- A variation on the underlying theme of [3+2] cycloaddition employs imines with reversed orientation relative to the alkyne.
- An azomethine ylide is generated that can be trapped with a suitable dipolarophile followed by 1,2-alkyl shift and elimination.



H. Kusama, Y. Miyashita, J. Takaya, N. Iwasawa, *Org. Lett.* **2006**, *8*, 289.

Carbon 1,4-dipoles

- All-carbon 1,4-dipoles can also be accessed by cyclisation of a carbonyl unit onto an gold-activated alkyne.
- The resulting dipolar intermediate can ring-open at the cyclopropane to quench charge on the heteroatom and generate a furan containing an all-carbon dipole for [4+2] annelations.

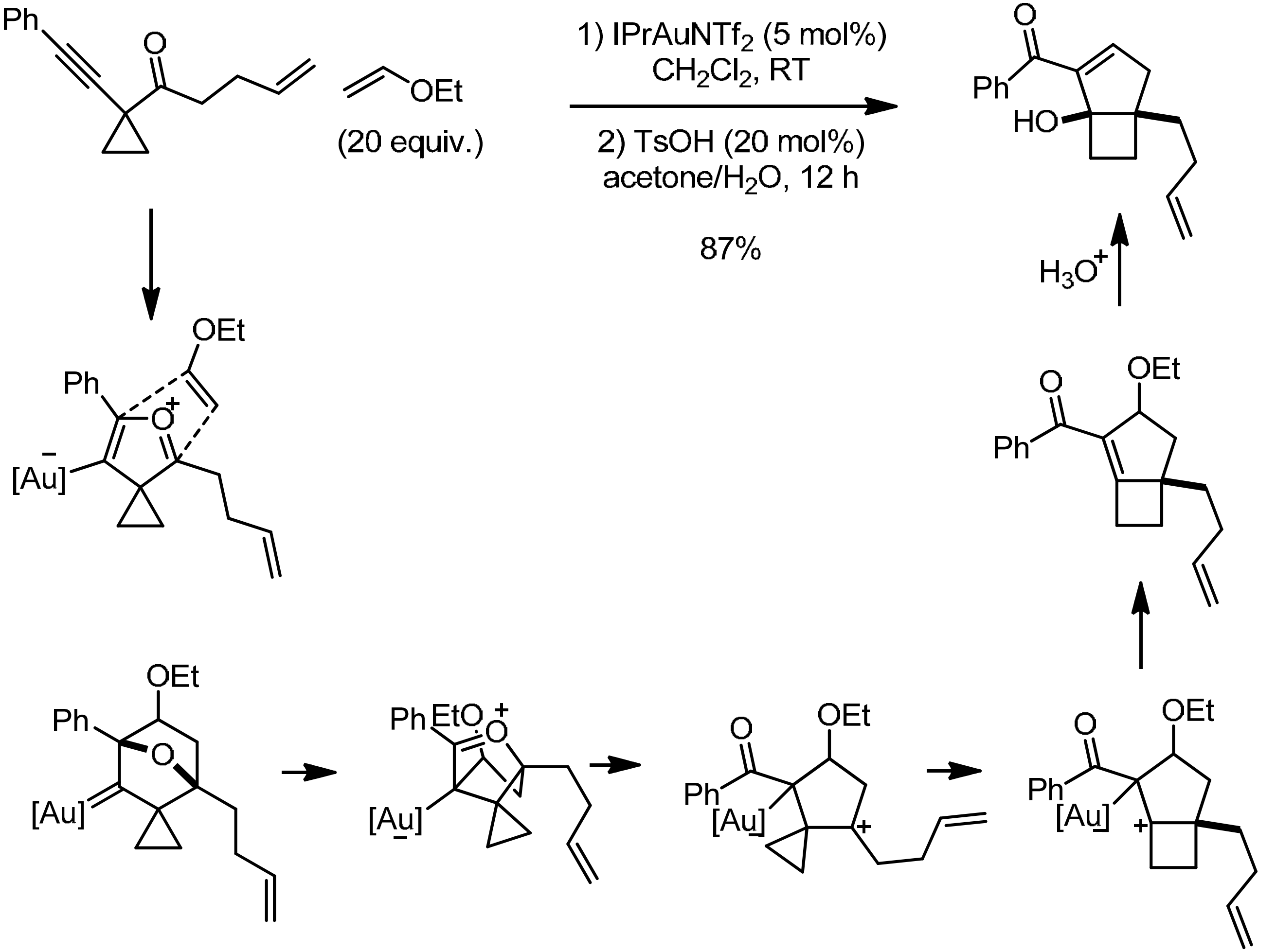


G. Zhang, X. Huang, G. Li and L. Zhang, *J. Am. Chem. Soc.* **2008**, *108*, 1815.

1,3-dipoles

- In the presence of excess enol ether the cyclopropyl containing keto-alkyne substrates react as 1,3-dipoles

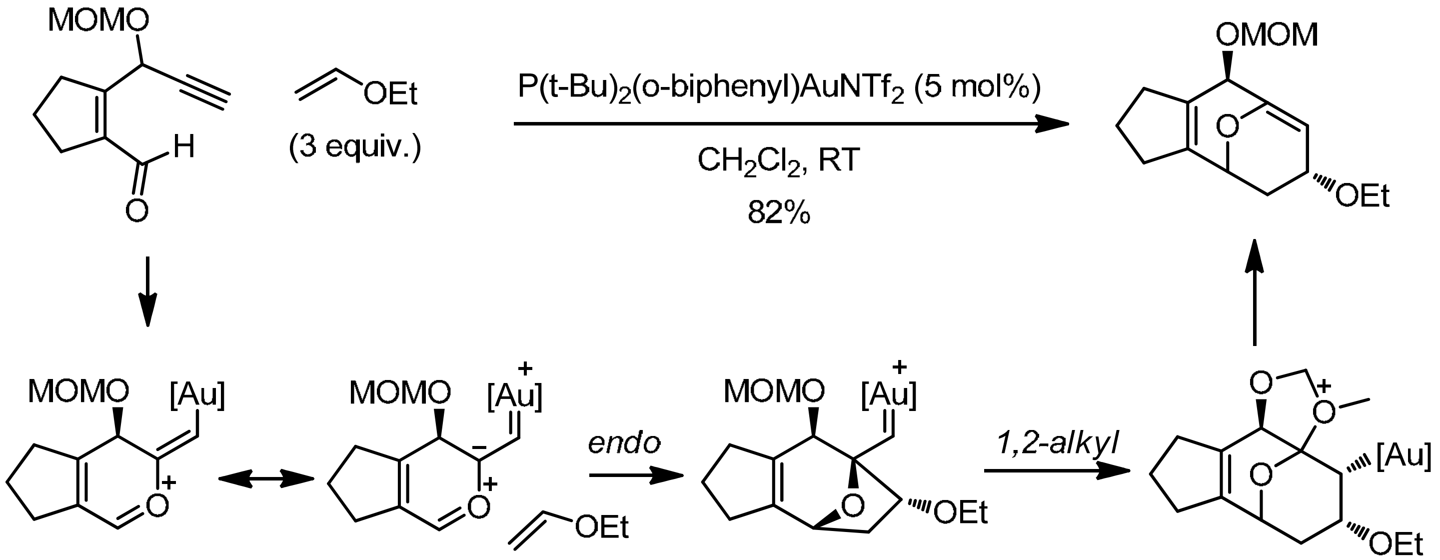
- After cycloaddition, a 1,2-alkyl shift affords bicycle[3.2.0]heptanes followed by 1,2-alkyl shift onto the carbenoid. Subsequently a ring-expansion of intermediate



G. Li, X. Huang, L. Zhang, *J. Am. Chem. Soc.* **2008**, *108*, 6945.

Oxonium species

- Anti-Bredt oxacycles from formal [4+2] cycloaddition proceeding via [3+2] cycloaddition and ring expansion.
- MOM protecting group aids the 1,2-alkyl shift process, stabilising the developing carbocation.

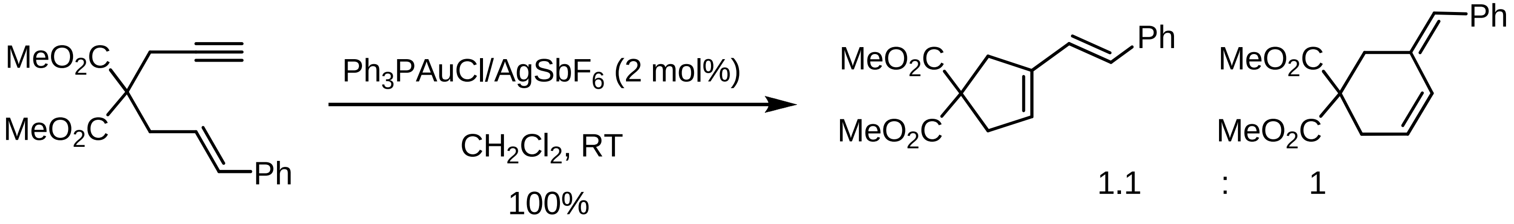


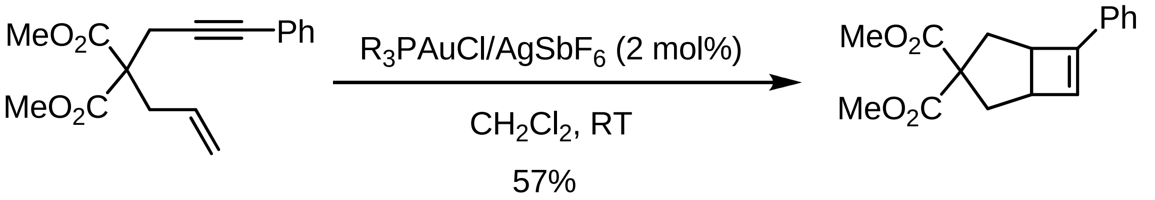
T.-M. Teng, A. Das, D. B. Huple, R.-S. Liu, *J. Am. Chem. Soc.* **2010**, *132*, 12565.

Enyne Cycloisomerisations

Enyne cycloisomerisations

- Enyne cycloisomerisations represent one of the most widely studied subfields of gold/π-acid catalysis.
- The reactions are fully atom economic by substrate.
- (Multiple) C-C bond forming processes are achieved under mild conditions with significant increase in molecular complexity.
- A diverse array of reactions are possible.



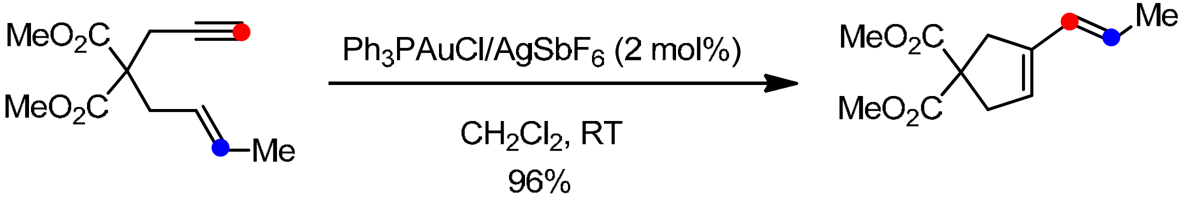


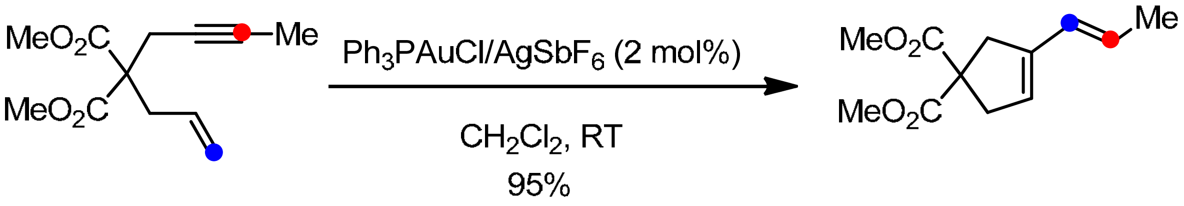
C. Nieto-Oberhuber, M. P. Muñoz, E. Buñuel, C. Nevado, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2003**, *43*, 2402; C. Nieto-Oberhuber, S. López, A. M. Echavarren, *J. Am. Chem. Soc.* **2005**, *127*, 6178.

Review of Au/enynes E. Jiménez-Nũńez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326.

Enyne cycloisomerisations

- Enyne cycloisomerisations can involve C-C σ-bond formation from π-systems as well as processes where the skeletal C-C connectivity is reconfigured through single (alkene) or double (alkene and alkyne) cleavages.



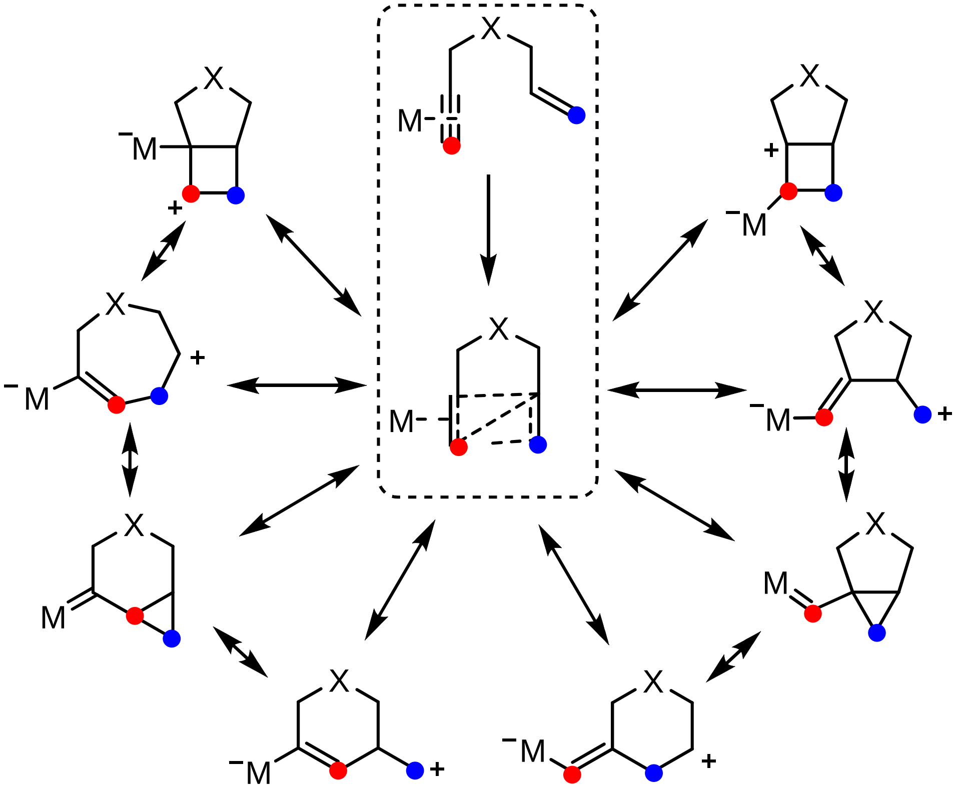


C. Nieto-Oberhuber, S. López, M. P. Muñoz, D. J. Cárdenas, E. Buñuel, C. Nevado, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2005**, *44*, 6146.

Review of Au/enynes E. Jiménez-Nũńez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326.

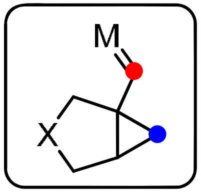
π-Acid activation of 1,6-enynes

- Intermediates (DFT) involved in enyne cyclisations are highly delocalised structures
- Many of the intermediates are drawn as gold carbenes, often for convenience.

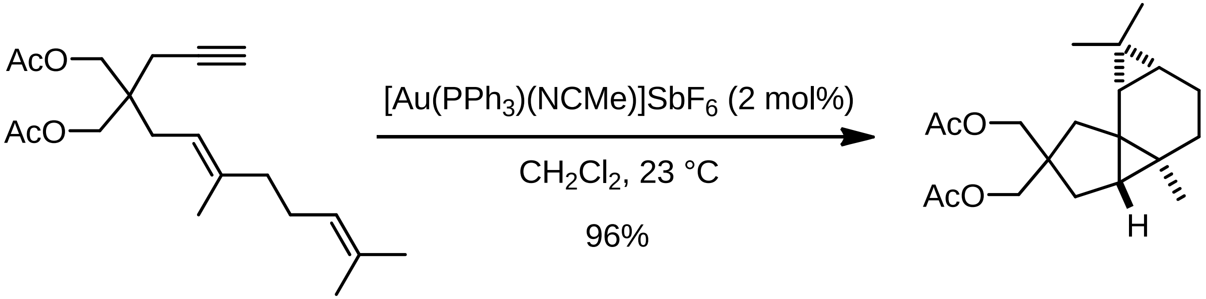


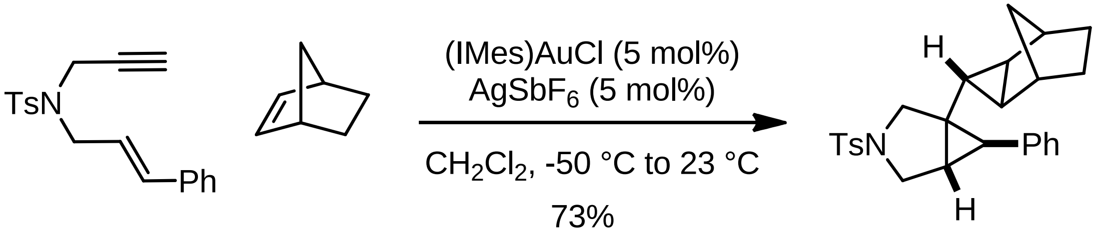
Non-classical carbocations: A. Fürstner, H. Szillat, B. Gabor, R. Mynott, *J. Am. Chem. Soc.* **1998**, *120*, 8305.
Reviews: A. Fürstner, P. W. Davies, *Angew. Chem. Int. Ed.* **2007**, *46*, 3410;
E. Jiménez-Nũńez and A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326.

π-Acid activation of enynes



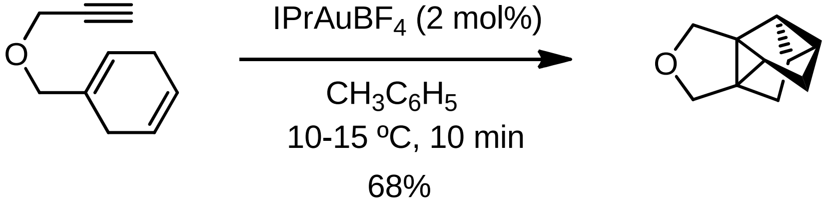
- The ‘carbenoid’ nature of alkynes activated by gold is particularly evident from polycyclization reactions.





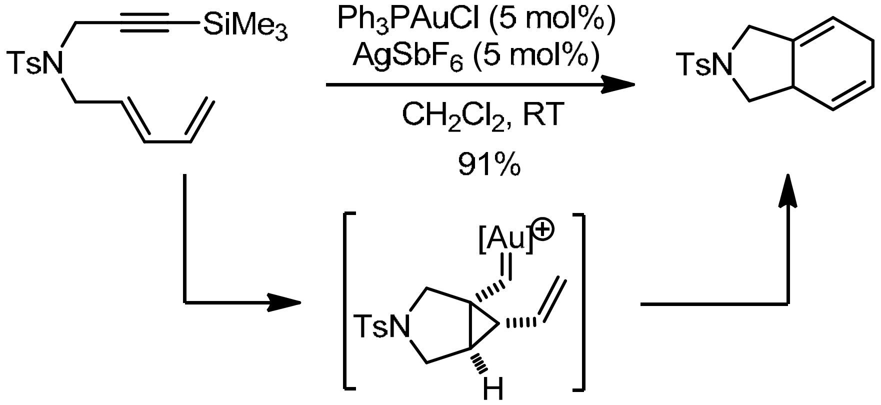
C. Nieto-Oberhuber, S. López, M. Paz Muñoz, E. Jiménez-Núñez, E. Buñuel, D. J. Cárdenas, A. M. Echavarren, *Chem. Eur. J.* **2006**, *12*, 1694; S. López, E. Herrero-Gómez, P. Pérez-Galán, C. Nieto-Oberhuber, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2006**, *45*, 6029; Kim *et al.*, *Angew. Chem. Int. Ed.* **2007**, *46*, 6172.

Yne-diene cycloisomerisations



S. M. Kim, J. H. Park, S. Y. Choi, Y. K. Chung, *Angew. Chem. Int. Ed.* **2007**, *46*, 6172.

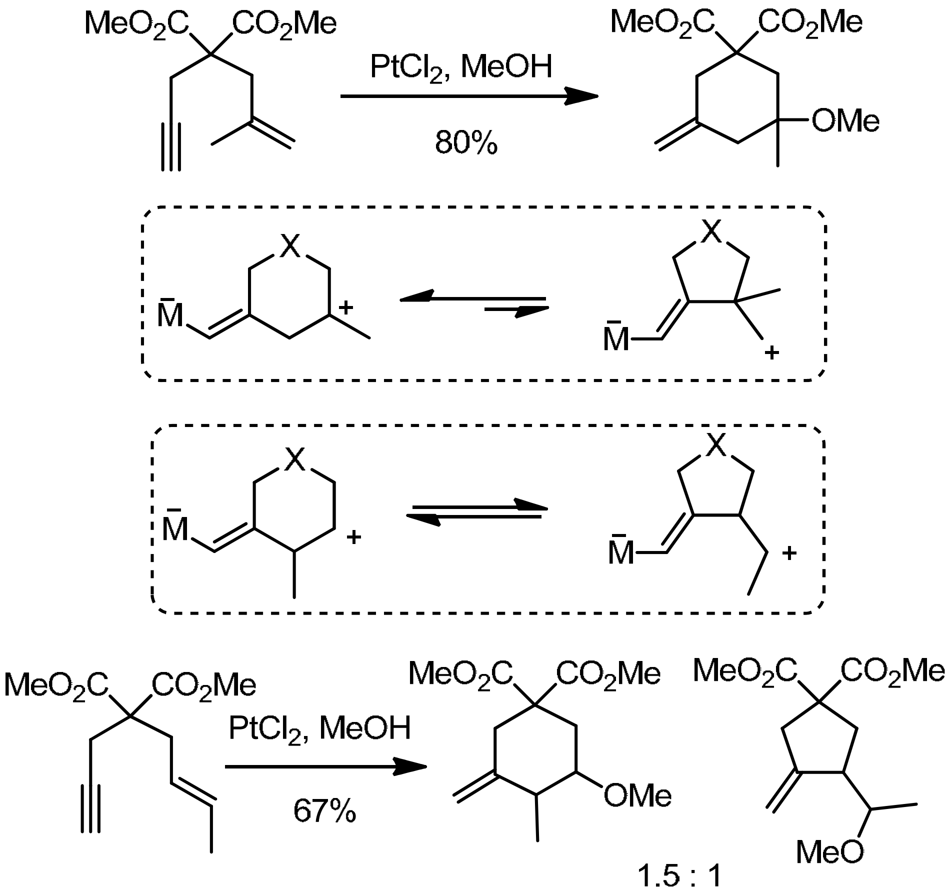
- When the alkenes are conjugated, gold-catalysed intramolecular Diels-Alder-like reaction occurs *via* a vinyl cyclopropyl carbene and subsequent metallo-Cope reaction
- Loss of the silyl end group occurs on work-up affording the bicyclic dienes such as Alkynyl stannanes can also be employed to access vinyl stannane products.



A. Fürstner, C. C. Stimson, *Angew. Chem. Int. Ed.* **2007**, *46*, 8845.

Carbocation considerations

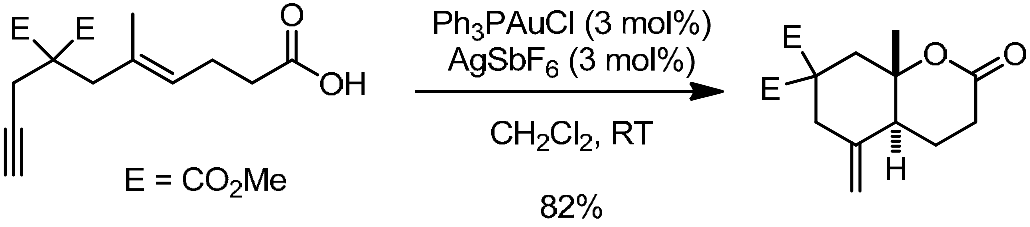
- However the mode of cyclisation can be rationalised by considering the most stable carbocationic form (the same is true with Au).



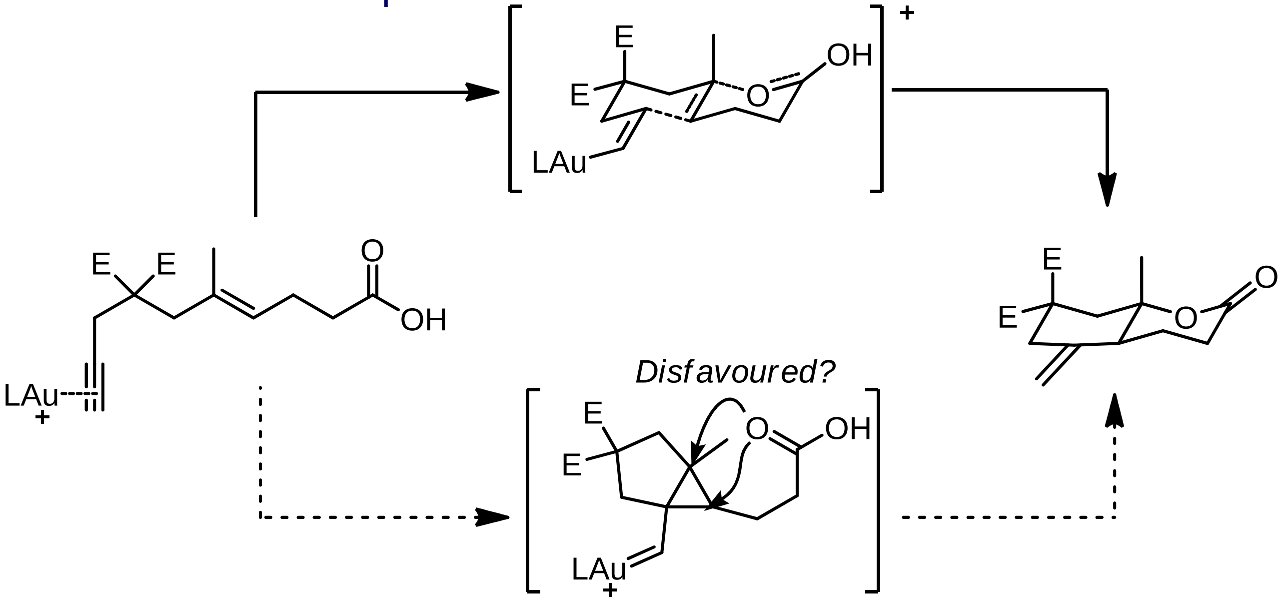
M. Méndez, M. P. Muñoz, A. M. Echavarren, *J. Am. Chem. Soc.* **2000**, *122*, 11549; C. Nieto-Oberhuber, M. P. Muñoz, E. Buñuel, C. Nevado, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2003**, *43*, 2402.

Carbene versus cationic forms

- When the metal carbene structures are employed in mechanistic discussion, the strongly electrophilic nature at carbon must always be borne in mind.



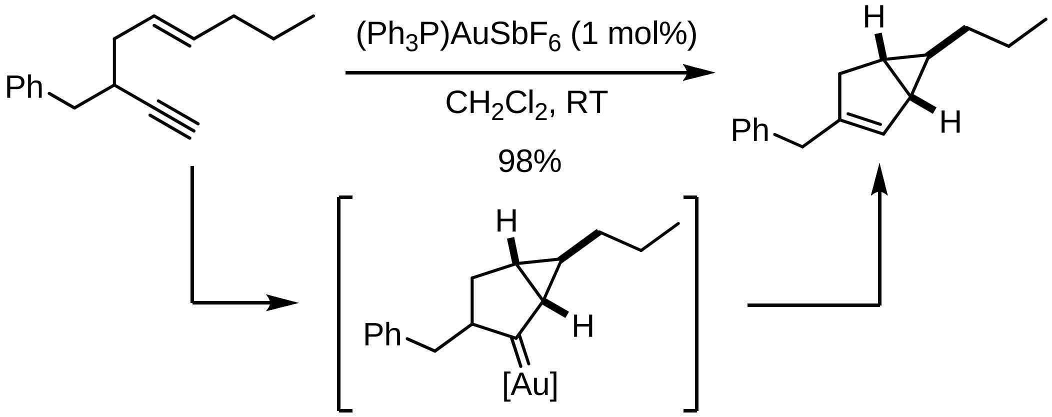
- The addition of the carboxylate to the cyclopropyl ring of carbene would be expected to proceed onto the least crowded carbon atom.
- Addition actually occurs at the more sterically encumbered site.
- The reaction occurs at the position which best stabilises cationic character.



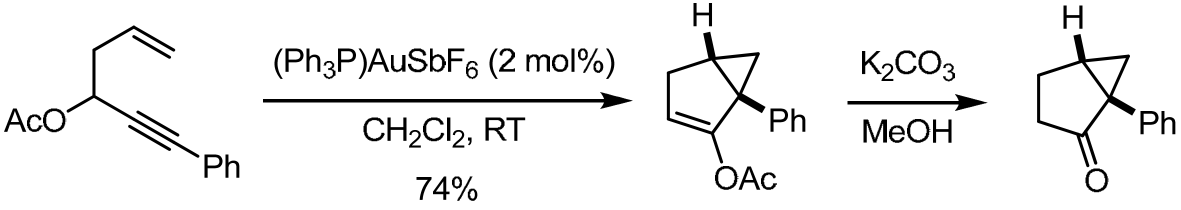
A. Fürstner, L. Morency, *Angew. Chem. Int. Ed.* **2008**, *47*, 5030.

1,5-Enynes

- 5-*endo-dig* cyclisation affords an internal cyclopropyl gold-carbenoid (bearing in mind the cationic character) which undergoes hydride or alkyl 1,2-shift.



- 1,2-Acetate shifts are observed (Rautenstrauch reaction). See section on propargylic carboxylates.

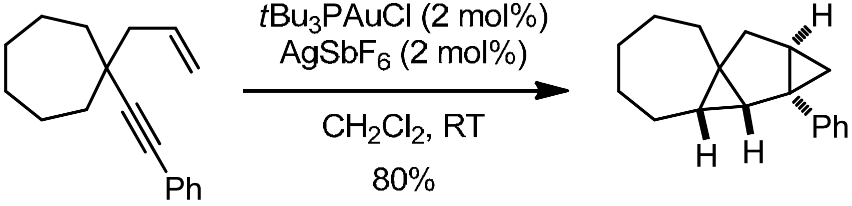


V. Mamane, T. Gress, H. Krause, A. Fürstner, *J. Am. Chem. Soc.* **2004**, *126,* 8654; Y. Harrak, C. Blaszykowski, M. Bernard, K. Cariou, E. Mainetti, V. Mouries, A. L. Dhimane, L. Fensterbank, M. Malacria, *J. Am. Chem. Soc.* **2004**, *126,* 8656*;* M. R. Luzung, J. P. Markham, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 10858; *1,4-enynes:* X. Shi, D. J. Gorin, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 15802.

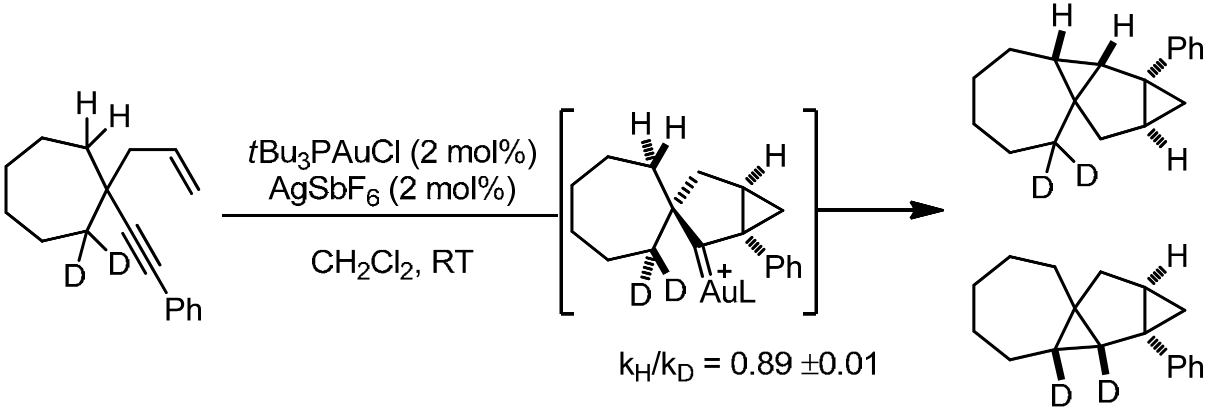
Review: E. Jiménez-Nũńez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326.

1,5-Enynes

- Cycloisomerisation of 1,5-enynes can be quenched by 1,3-C-H insertion to form a cyclopropane.



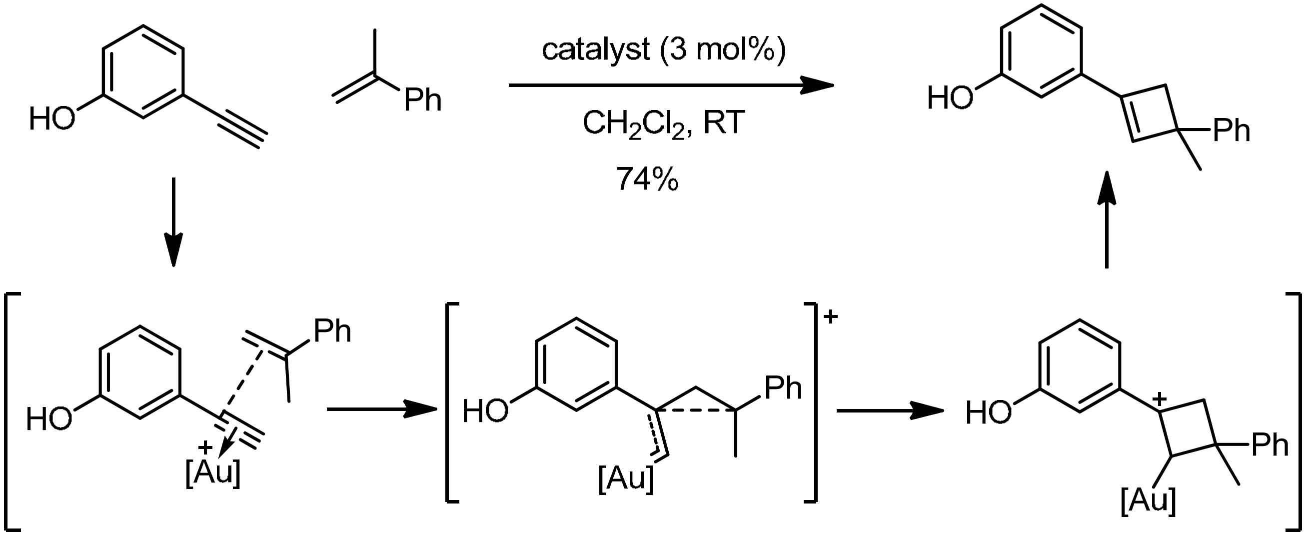
- Studies of the kinetic isotope effects are inconsistent with either a direct metal carbenoid insertion into C-H bond, or a hydride shift to a carbocation, and the formation of a σ-complex between the hydrogen atom and the cationic gold is proposed to precede the hydrogen transfer step.

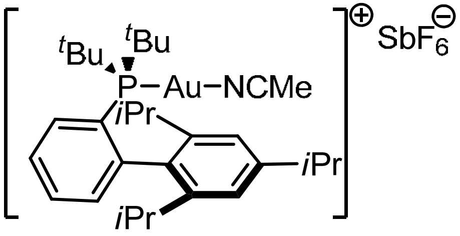


Y. Horino, T. Yamamoto, K. Ueda, S. Kuroda and F. D. Toste, *J. Am. Chem. Soc.* **2009**, *131*, 2809.

Intermolecular enyne reactions

- In the absence of the tethers commonly used to link alkene and alkyne, cyclobutenes are formed.

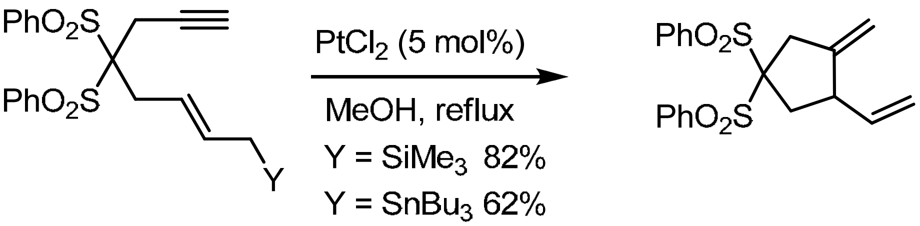




V. Lopez-Carrillo, A. M. Echavarren, *J. Am. Chem. Soc.* **2010**, *132*, 9292.

Use of allyl silanes as nucleophile

- Inter- and intramolecular hydroallylation of alkynes can be achieved using allyl silanes or stannanes in the presence of a noble metal catalyst and an alcohol additive.

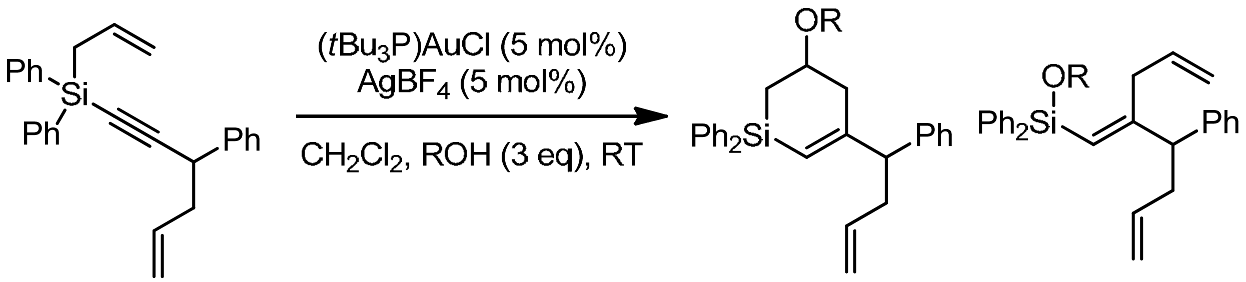


C. Fernández-Rivas, M. Méndez, A. M. Echavarren, *J. Am. Chem. Soc.* **2000**, *122*, 1221;
C. Fernández-Rivas, M. Méndez, C. Nieto-Oberhuber, A. M. Echavarren, *J. Org. Chem.* **2002**, *67*, 5197.

- The allyl silane can be incorporated within the tether, resulting in a stereoselective synthesis of vinyl silanes.

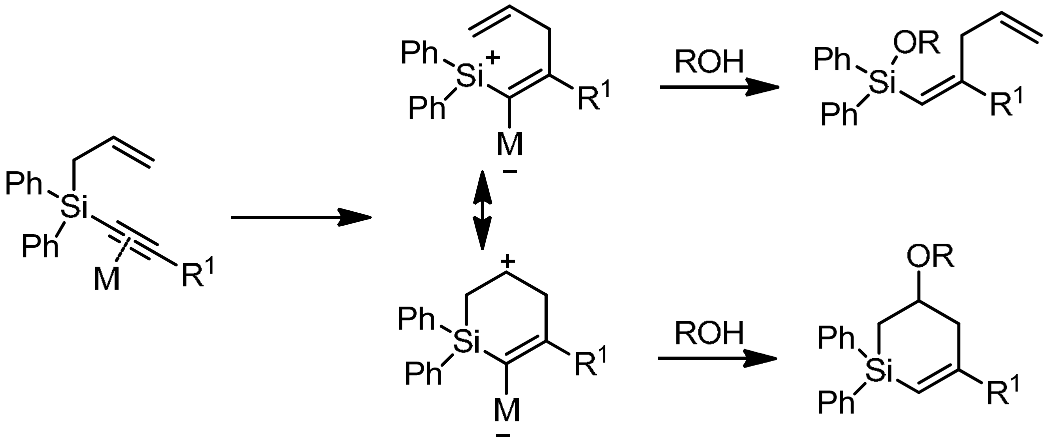
Use of allyl silanes as nucleophile

- Using a secondary alcohol or phenol results in silicon-carbon bond cleavage.
- Use of the more nucleophilic MeOH affords a silacycle by addition of the alcohol to the carbocation.



R = Me	68%	0%
R = Ph	0%	69%

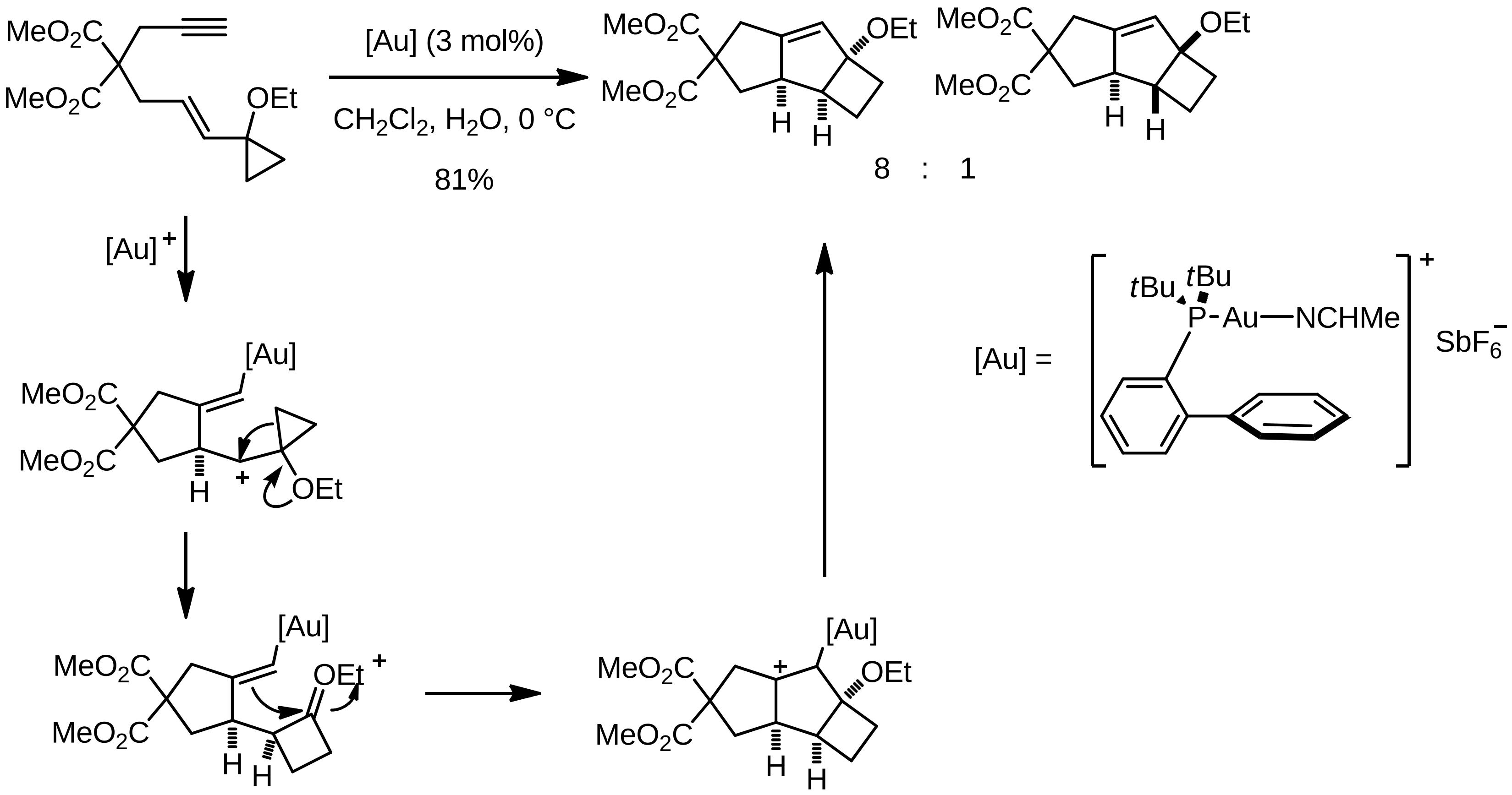
1:1 mix of diastereomers



S. Park, D. Lee, *J. Am. Chem. Soc.* **2006**, *128*, 10664;
Y. Horino, M. R. Luzung, F. D. Toste, *J. Am. Chem. Soc.* **2006**, *128*, 11364.

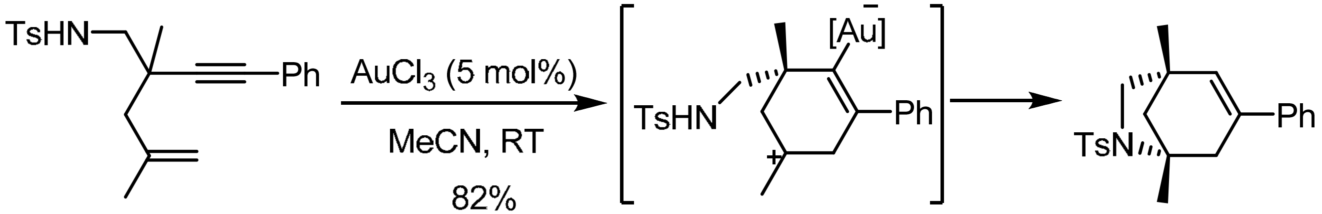
Enyne-cyclisation and ring-expansion cascade

- Cascade reactions build upon the carbocationic character of the intermediates. Cyclisation - ring expansion – nucleophilic addition leads to the formation of a tricyclic carbon skeleton.

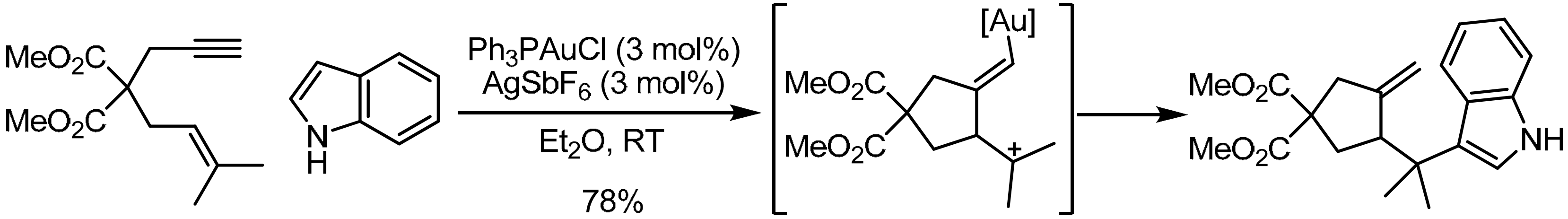


E. Jiménez-Núñez, C. K. Claverie, C. Nieto-Oberhuber, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2006**, *45*, 5452.

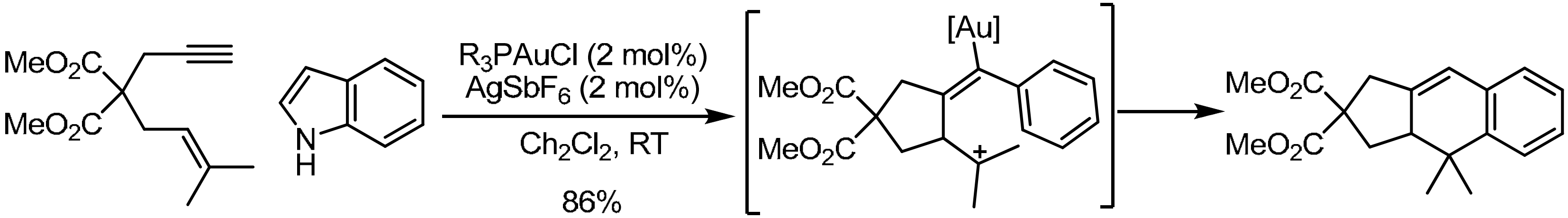
Trapping an intermediate carbocation



L. Zhang, S. A. Kozmin, *J. Am. Chem. Soc.* **2005**, *127*, 6962.



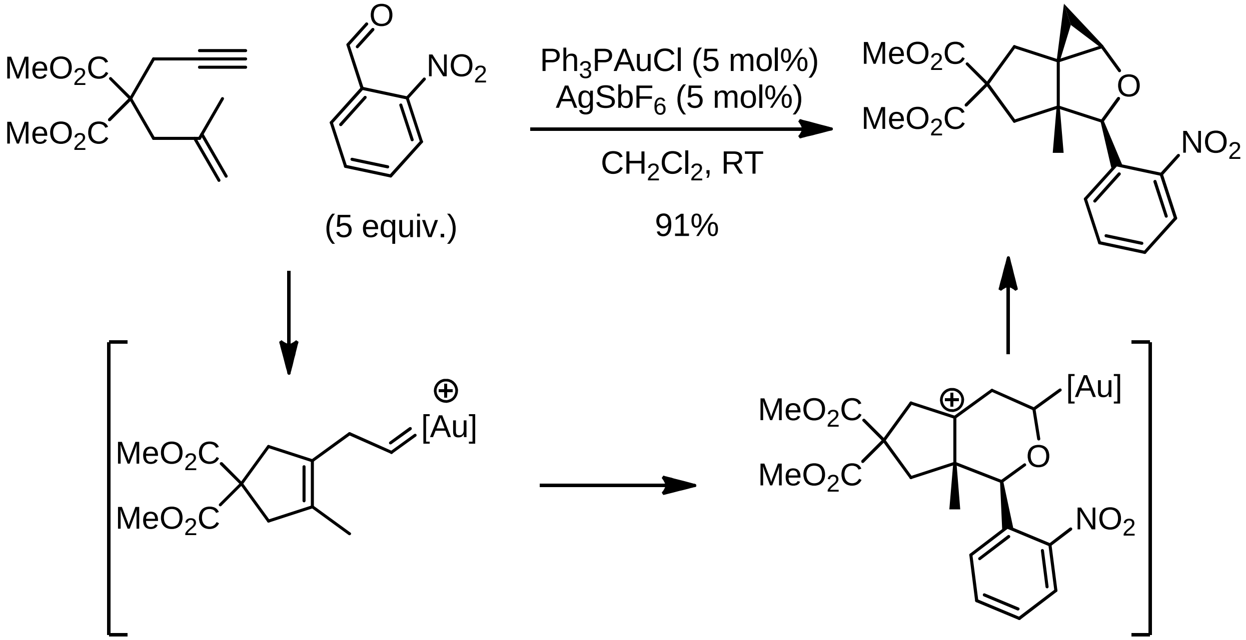
P. Y. Toulec, E. Genin, J.-P. Genêt, V. Michelet, *Angew. Chem. Int. Ed.* **2006**, *45*, 7427;
C. H. M. Amijs, C. Ferrer, A. M. Echavarren, *Chem. Commun.* **2007**, 698.



C. Nieto-Oberhuber, S. Lopez, A. M. Echavarren, *J. Am. Chem. Soc.* **2005**, *127*, 6178.

Intermolecular coupling of aldehydes and enynes

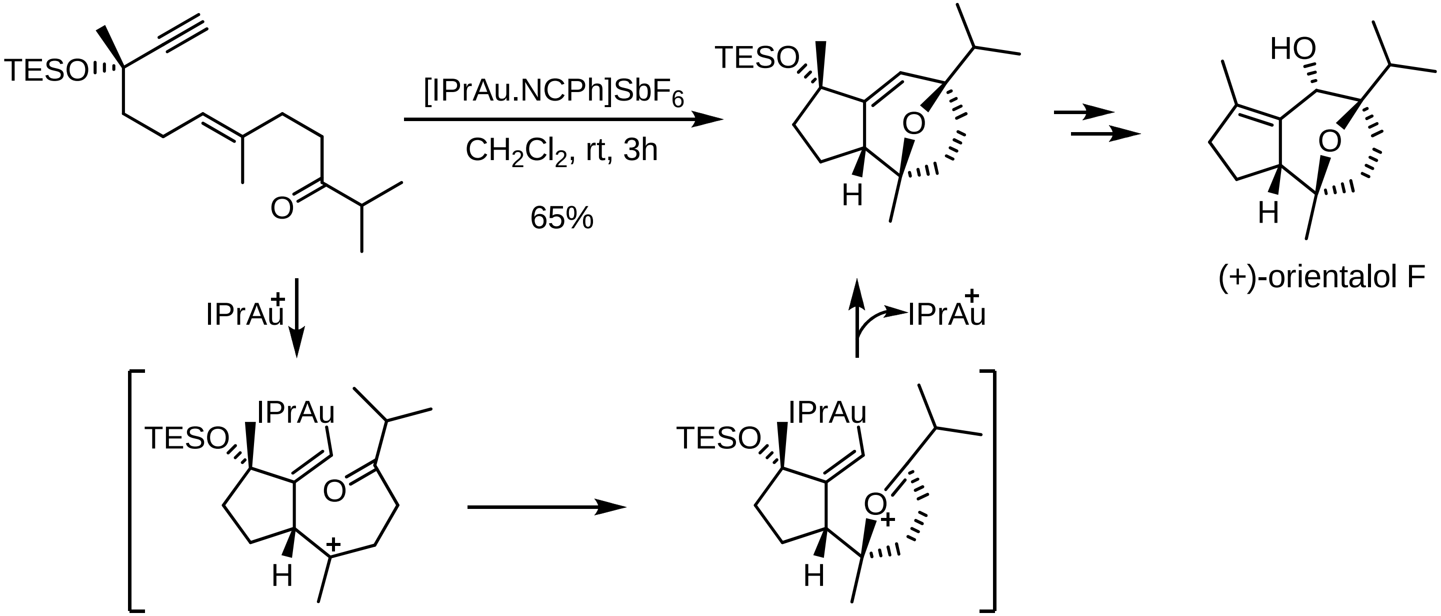
- Unusual tricyclic structures can be accessed by intermolecular capture of enyne intermediates acting as all-carbon 1,4-dipoles.
- Collapse of intermediate results in formation of the cyclopropane ring and release of the catalytic gold species.



M. Schelwies, A. L. Dempwolff, F. Rominger, G. Helmchen, *Angew. Chem. Int. Ed.* **2007**, *46*, 5598.

Applications in natural product synthesis

- A formal [2+2+2] cycloaddition reaction.
- Tertiary ether in the propargylic position – Potential for Meyer-Schuster rearrangement.
- Three manipulations required for the completion of the synthesis after the key step



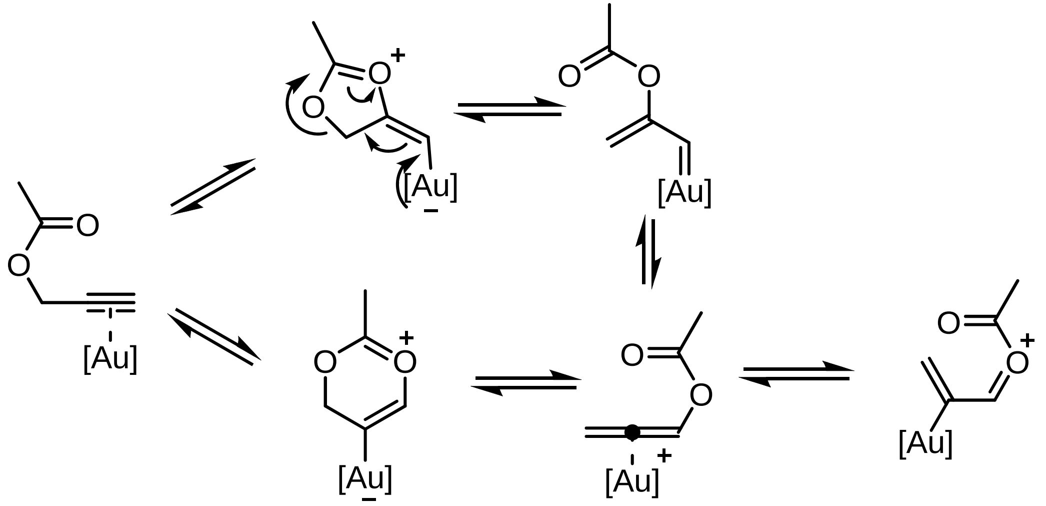
(+)-Orientalol F: E. Jiménez-Núñez, K. Molawi, A. M. Echavarren, *Chem. Commun.* **2009**, 7327.

(-)-Engelerins A + B: Q. Zhou, X. Chen, D. Ma, *Angew. Chem. Int. Ed.* 2010, *49*, 3513; K. Molawi, N. Delpont, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2010**, *49*, 3517.

Propargylic Carboxylates

Propargylic carboxylates activated by gold

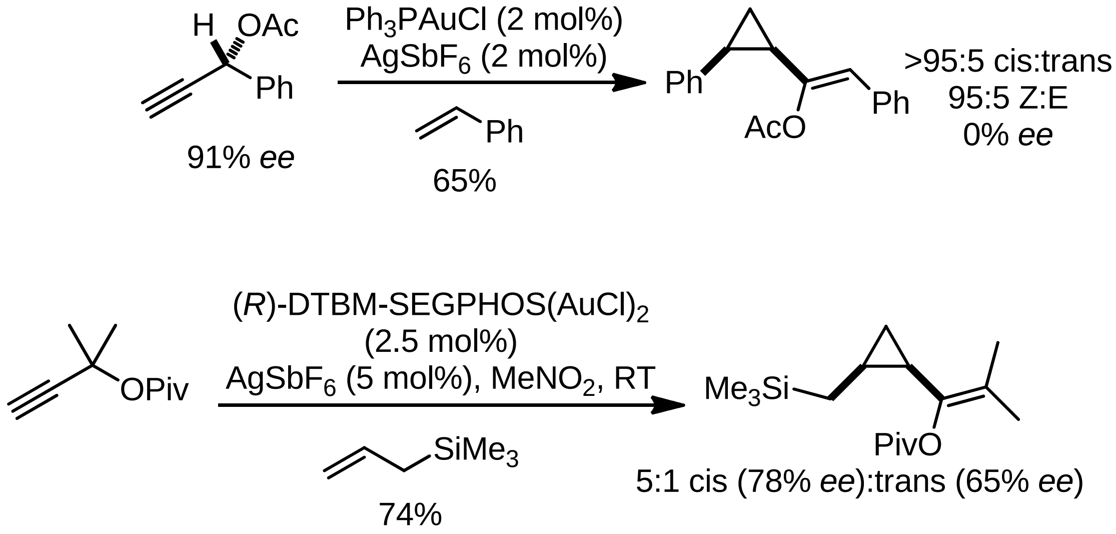
- These units readily undergo 1,2- or 1,3-acyl migration to afford gold carbenoid or gold allene species.
- Initially explored in intramolecular processes (Rautenstrauch/Ohloff cyclisations).
- Computational and experimental studies show these complexes to be in rapid equilibrium with interconversion occurring in any direction.
- The activation mode ultimately seen depends on the subsequent irreversible formation of products after reaction with other functionality.
- The substituents on the propargylic carboxylate, the reaction conditions and the nature of the catalyst used all play a role in determining the final outcome of these reactions.

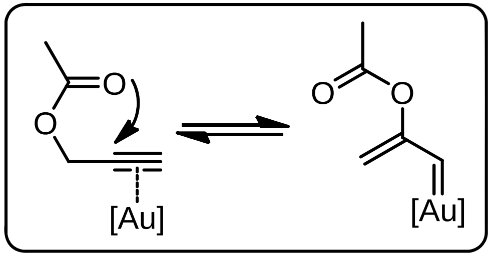


A. Correa, N. Marion, L. Fensterbank, M. Malacria, S. P. Nolan, L. Cavallo,
B. *Angew. Chem. Int. Ed.* **2007**, *46*, 718.

Propargylic carboxylates as carbenoid equivalents

- Intermolecular cyclopropanation occurs.
- There is no chirality transfer form the propargylic unit to the product, supporting the intermediacy of achiral intermediates.
- Use of a chiral gold complex allowed the first demonstration of uniformly good ee’s across a range of alkyne substrates.

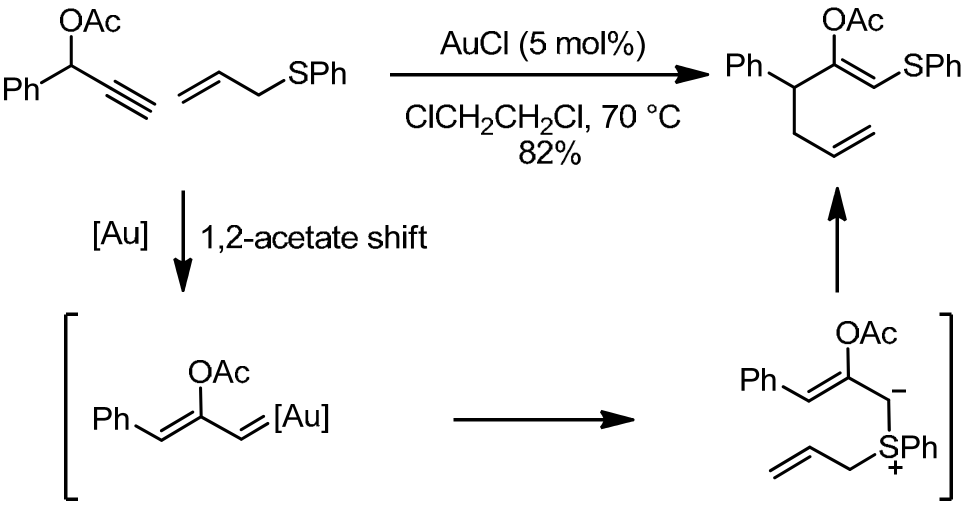




M. J. Johansson, D. J. Gorin, S. T. Staben, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 18002.

As ylide precursors

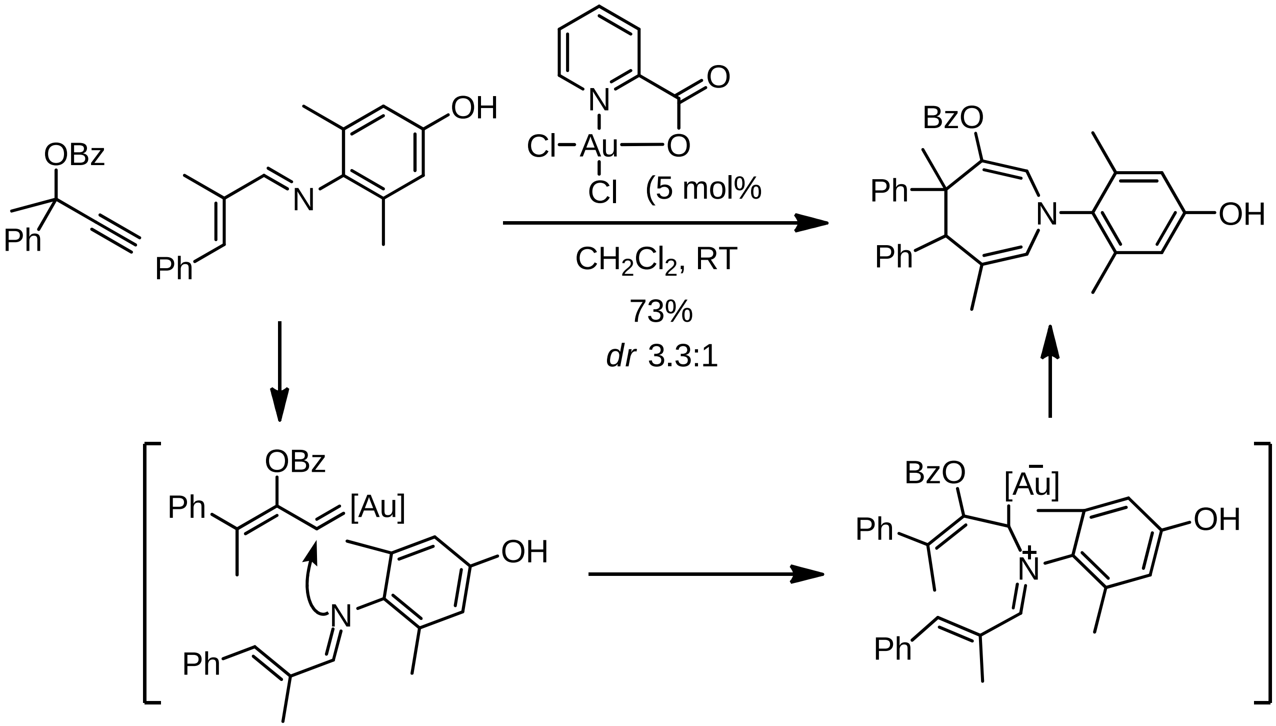
- Propargylic carboxylates can undergo intermolecular coupling reactions.
- Addition of a nucleophile to the vinylcarbenoid species formed by 1,2-acetate rearrangement affords a species with, demonstrating overall 1,3-carbon dipole nature.
- Sulfur Ylides:



P. W. Davies, S. J. C. Albrecht, *Chem. Commun.* **2008**, 238.

Use as all carbon 1,3-dipoles

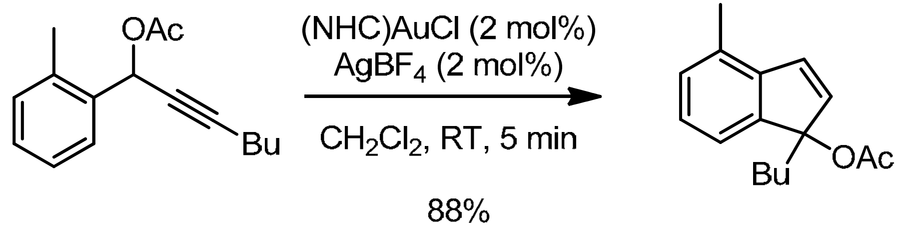
- Azepine synthesis by overall [4+3] annelation.



N. D. Shapiro, F. D. Toste, *J. Am. Chem. Soc.* **2008**, *108*, 9245.

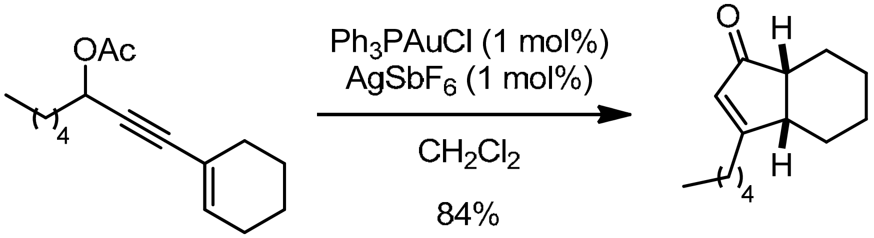
Intramolecular uses

- Reactions of the incipient allenyl acetates with an adjacent benzene ring explains the gold-catalyzed formation of substituted indenes.

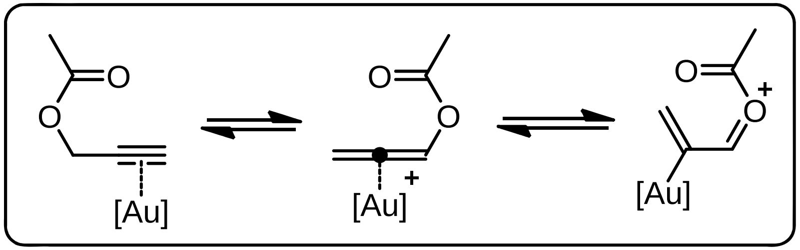


J. Zhao, C. O. Hughes, F. D. Toste, *J. Am. Chem. Soc.* **2006**, *128*, 7436.

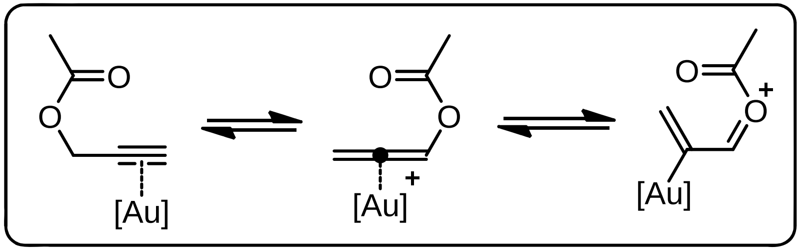
- Nazarov reaction:



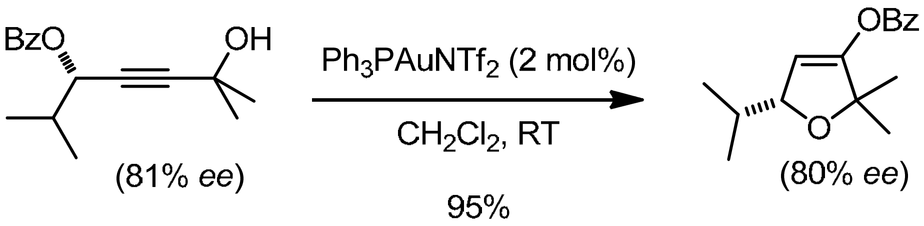
S. Wang, L. Zhang, *J. Am. Chem. Soc.* **2006**, *128*, 8414.



Intramolecular uses

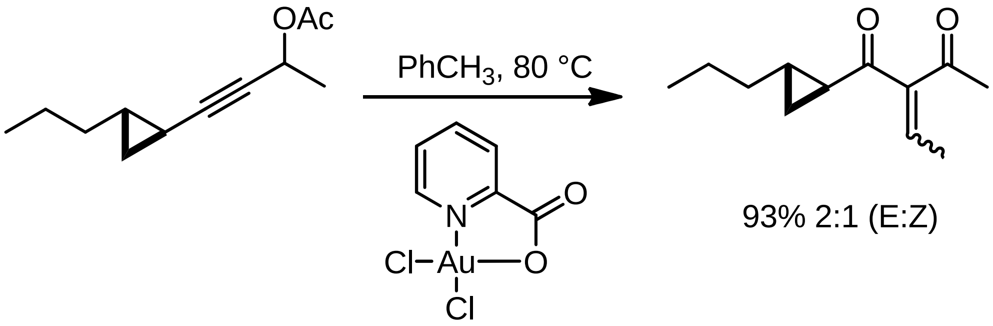


- The presence of alcohols afford dihydrofurans in a reaction reminiscent of the transformation of preformed allenes.



A. Buzas, F. Istrate, F. Gagosz, *Org. Lett.* **2006**, *8*, 1957.

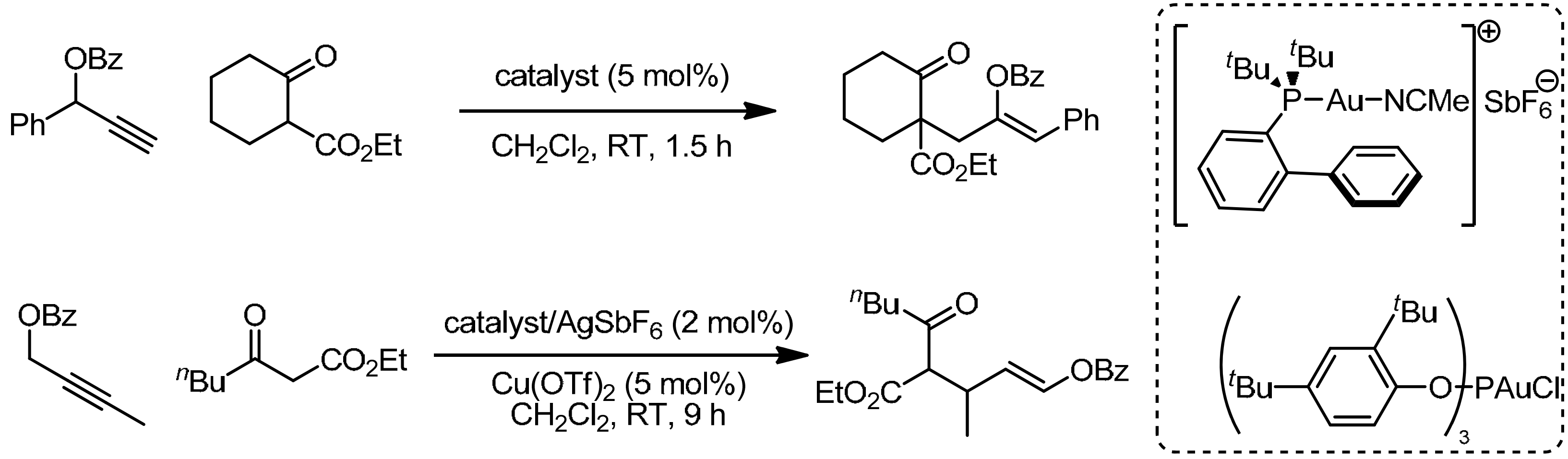
- Fission of the acetate unit:

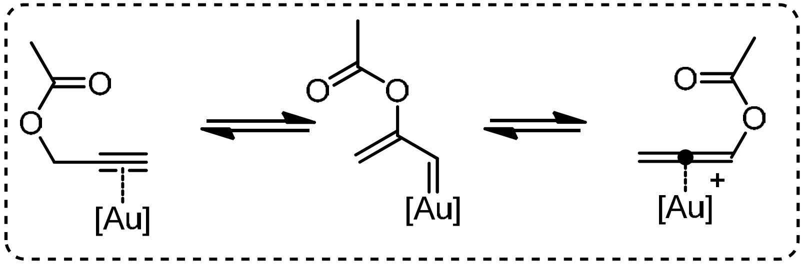


L. Zhang, S. Wang, *J. Am. Chem. Soc.* **2006**, *128*, 1442.

Addition of carbon nucleophiles

- Intermolecular trapping with activated methylene compounds shows the effect of substituent on reaction outcome.

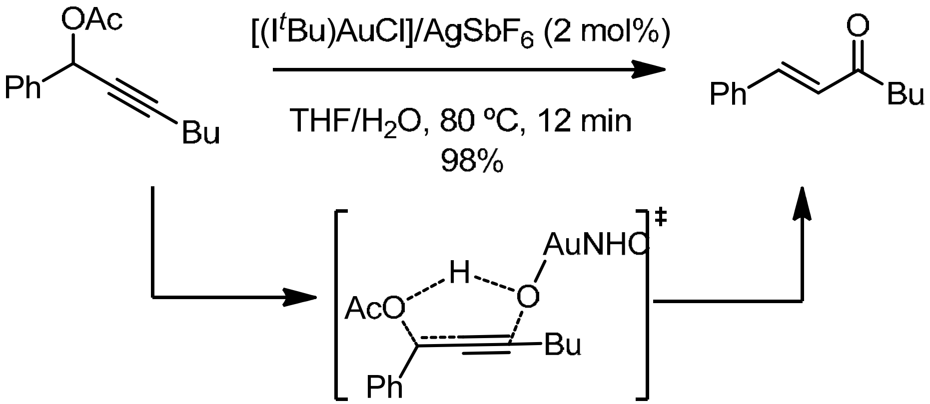




C. H. M. Amijs, V. López-Carrillo, A. M. Echavarren, *Org. Lett.* **2007**, *9*, 4021.

Substitutions

- Propargylic carboxylates can be transformed to α,β-unsaturated carbonyl compounds.
- Theoretical studies support the contention that the active catalyst is [(NHC)AuOH], formed *in situ* from reaction of the cationic gold species with water.



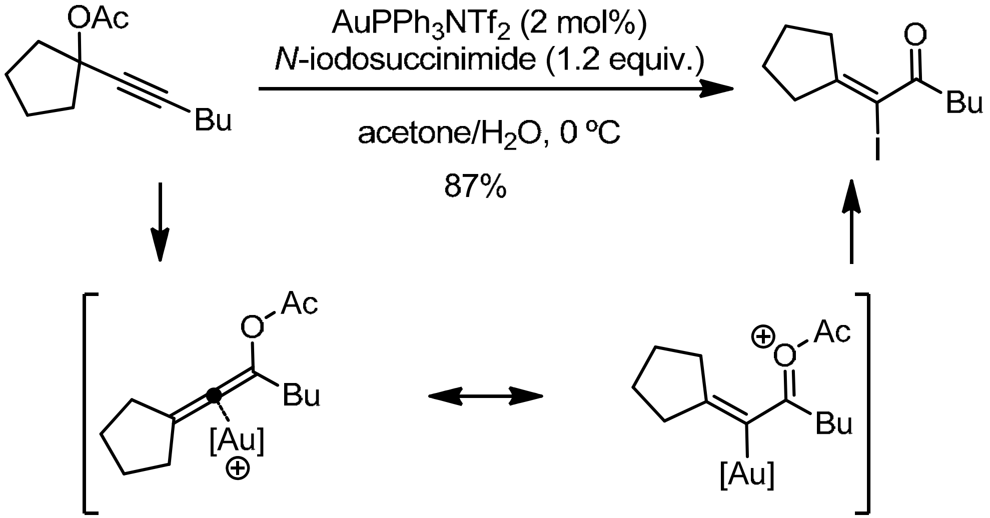
N. Marion, P. Carlqvist, R. Gealageas, P. De Fremont, F. Maseras, S. P. Nolan, *Chem. Eur. J.* **2007**, *13*, 6437; M. Yu, G. Li, S. Wang; L. Zhang, *Adv. Synth. Catal.* **2007**, *349*, 871.

- Isolation and utility of [(NHC)AuOH].

S. Gaillard, A. M. Z. Slawin, S. P. Nolan, *Chem. Commun.* **2010**, 2742.

Trapping intermediates with electrophiles

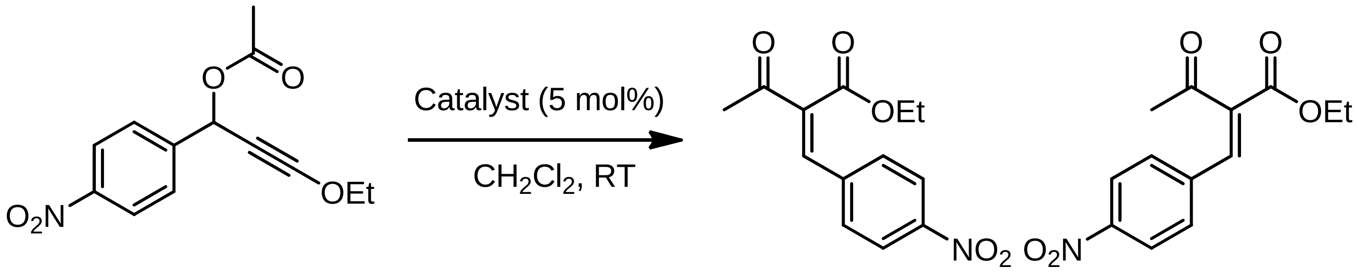
- In the presence of *N*-iodosuccinimide, propargylic carboxylate units react to give the α-iodo-α,β-unsaturated carbonyl compounds with hydrolysis of the acetate unit of the allenyl gold intermediate and iododemetallation of the carbon gold bond.



M. Yu, G. Zhang, L. Zhang, *Org. Lett.* **2007**, *9*, 2147.

Use of Pt or Cu catalysis

- The use of ethoxy alkyne derivatives of propargylic carboxylates led to the formation of ɑ-ylidene-β-keto and –malonate esters. Choice of catalyst effects which isomer is formed preferentially

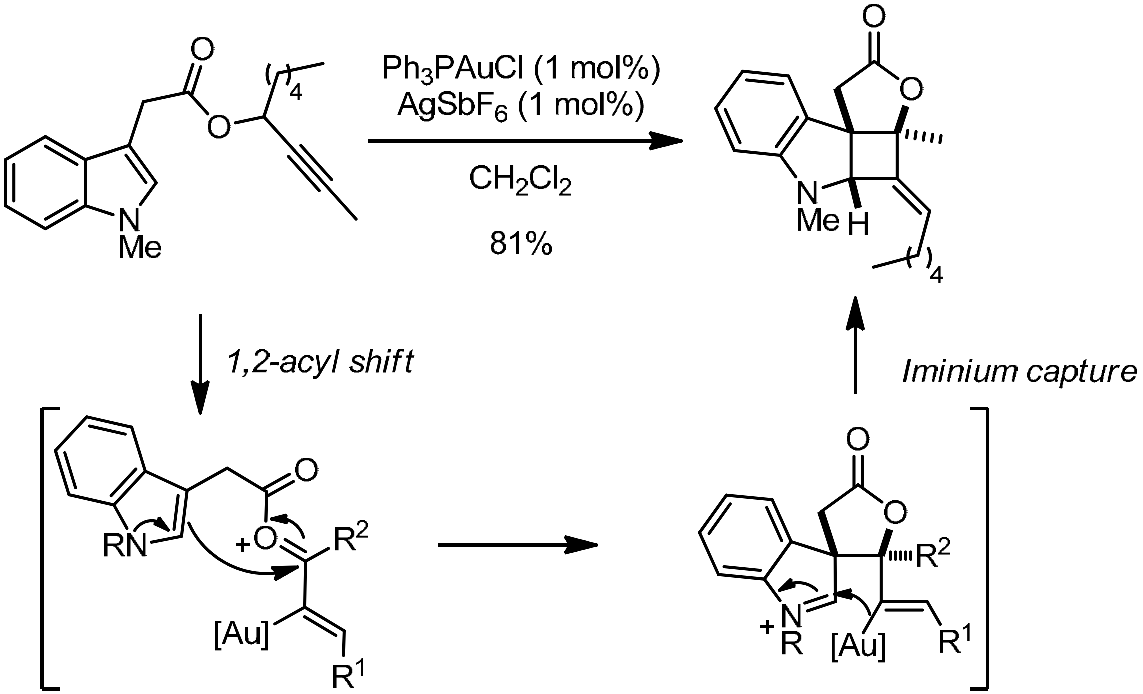


$PtCl_2$	75%	-
$[Cu(CH_3CN)_4][BF_4]$	-	50%

J. Barluenga, L. Riesgo, R. Vicente, L. A. López, M. Tomás *J. Am. Chem. Soc.* **2007**, *129*, 7772.

Cascade cyclisations

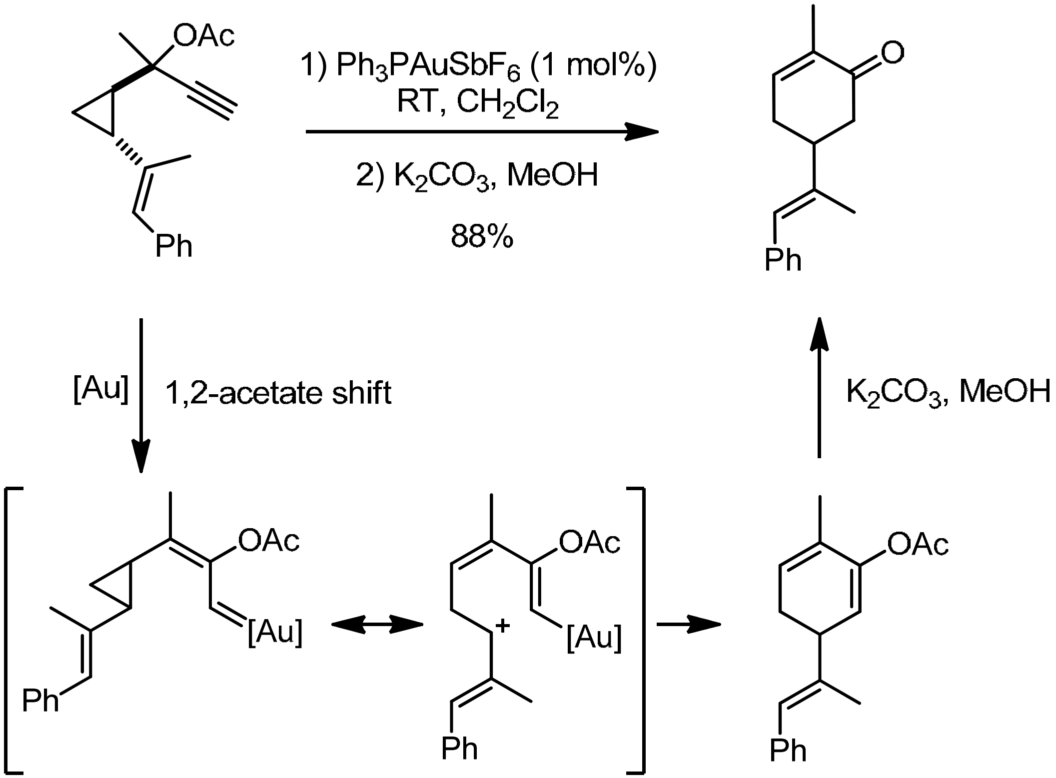
- In the absence of other nucleophiles, the allenyl acetates formed in situ react with gold affording vinyl-gold intermediate to undergo substrate specific reactions including formal [2+2] cycloadditions with indoles.
- This latter example provides an excellent illustration of the structural complexity that can be garnered via easily performed noble-metal catalysis.



L. Zhang, *J. Am. Chem. Soc.* **2005**, *127*, 16804.

Extension of the cationic intermediates

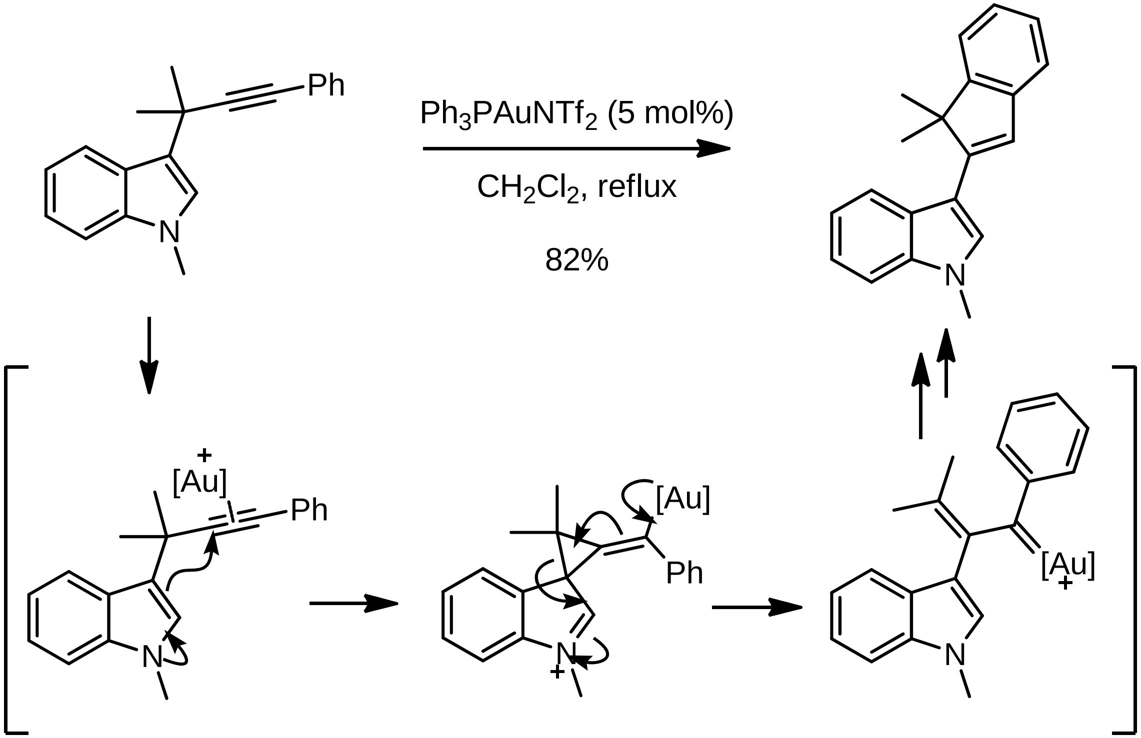
- Presence of a cyclopropane allows the charged canonical forms of the gold carbenoid formed on 1,2-acetate rearrangement, to be extended through the principle of nonclassical forms of the resulting carbocation.
- Ring-opening and closing affords cyclohexenone derivatives with significant levels of chirality transfer which supports the supposition that the gold-stabilised non-classical carbocations retain a degree of configurational stability.



Y. Zou, D. Garayalde, Q. Wang, C. Nevado, A. Goeke, *Angew. Chem. Int. Ed.* **2008**, *47*, 10110.
Cyclopropane modified structures have also been used to explore reversibility of the mechanism: P. Mauleon, J. L. Krinsky, F. D. Toste, *J. Am. Chem. Soc.* 2007, **129**, 7772.

Indole migration

- In analogous fashion 1,2-indole migrations can be employed.
- 3-substitution of the indole forms cyclopropane followed by generation of the metal carbenoid and the aromatic indole system. Subsequent Nazarov cyclisation accesses polycyclic systems.

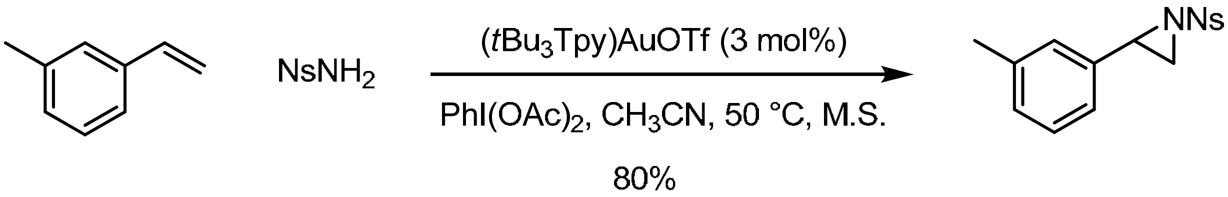


R. Sanz, D. Miguel, F. Rodríguez, *Angew. Chem. Int. Ed.* **2008**, *47*, 5224.

Preparation of gold carbenoids

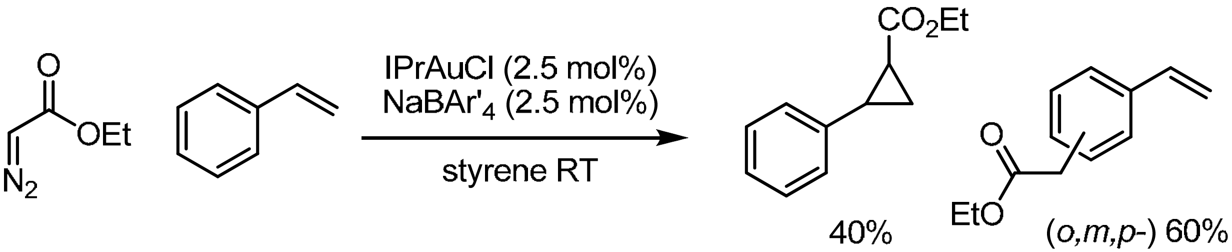
Gold carbenes from atom transfer reactions

- Atom transfer reactions catalysed by gold are known:
- Nitrenes:

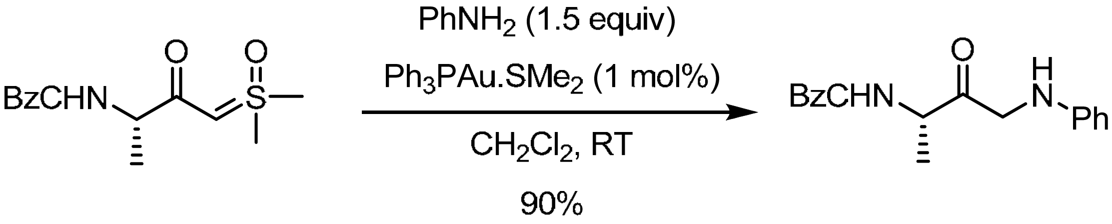


Z. Li, X. Ding, C. He, *J. Org. Chem.* **2006**, *71*, 5876.

- Carbenes:



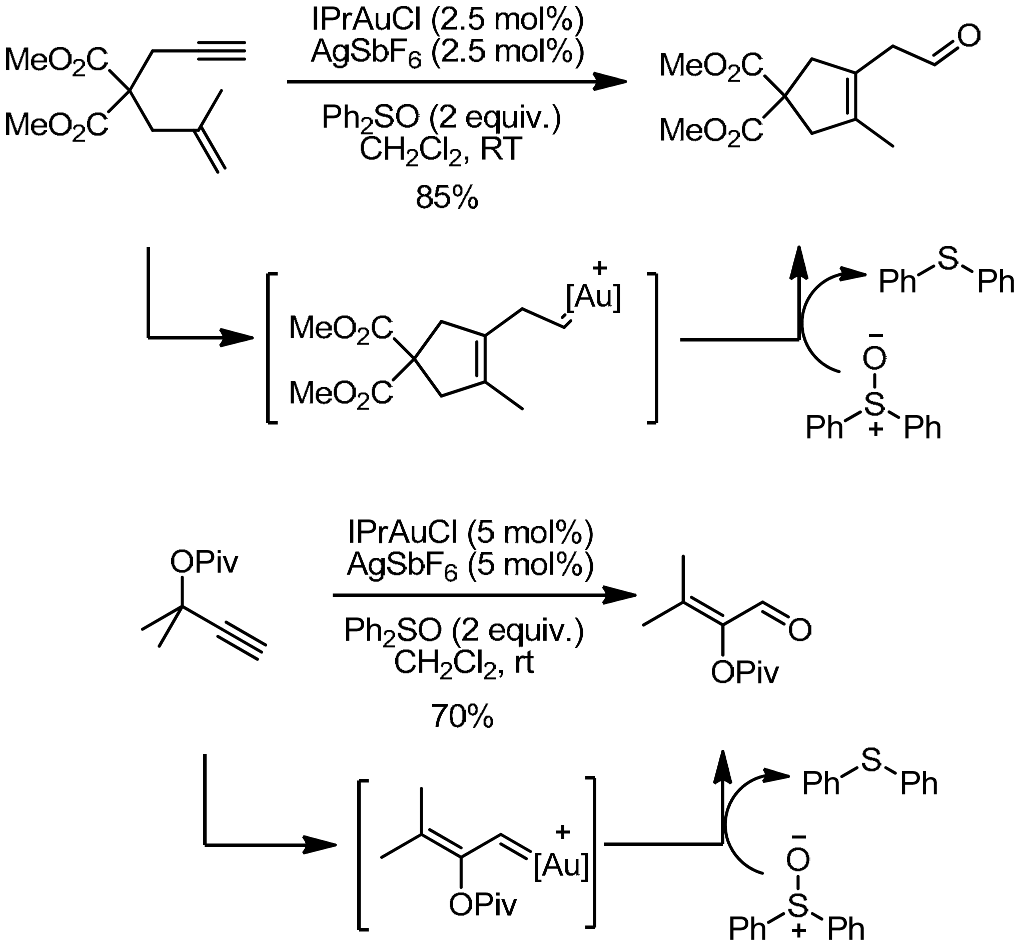
M. R. Fructos, T. R. Belderrain, P. de Fremont, N. M. Scott, S. P. Nolan, M. M. Diaz-Requejo, P. J. Perez, *Angew. Chem. Int. Ed.* **2005**, *44*, 5284.
Also: M. R. Fructos, M. M. Diaz-Requejo, P. J. Perez, *Chem. Comm.* **2009**, 5153.



Gas phase synthesis and reactivity of a gold carbene complex: A. Fedorov, M.-E. Moret, P. Chen, *J. Am. Chem. Soc.* **2008**, *130*, 8880.

Oxidation of incipient carbenoids

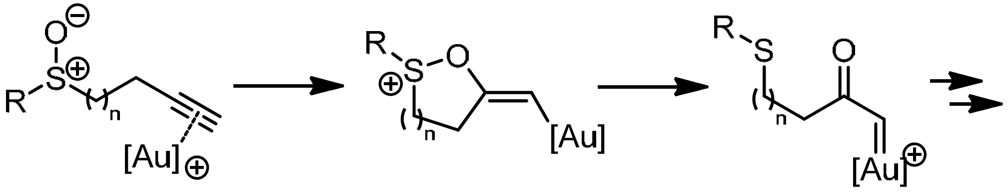
- Sulfoxide can be used as an external oxidizing agent for carbenes and has been employed in this manner in a variety of gold-catalysed processes.

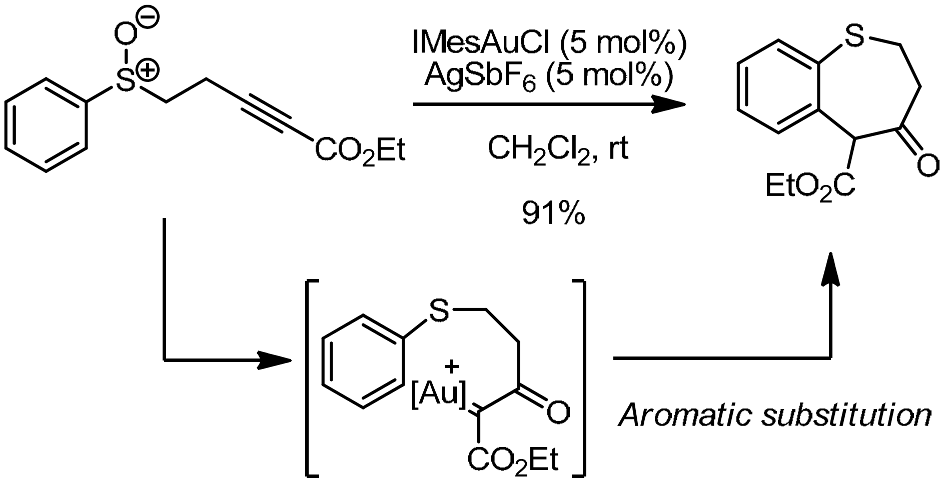


C. Witham, P. Mauleón, N. D. Shapiro, B. D. Sherry, F. D. Toste, *J. Am. Chem. Soc.* **2007**, *129*, 5838.

Internal redox processes: Sulfoxides

- Sulfoxides can also be used to trigger the formation of α-oxo gold carbenoids.

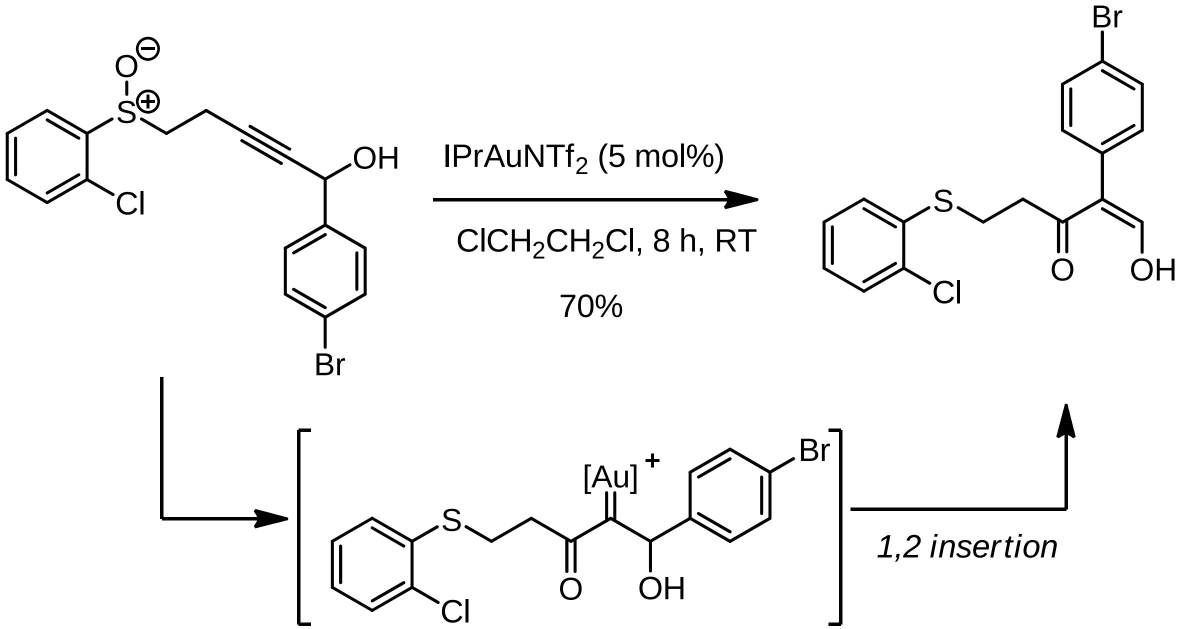




N. D. Shapiro, F. D. Toste, *J. Am. Chem. Soc.* **2007**, *129*, 4160.

Internal redox processes: Sulfoxides

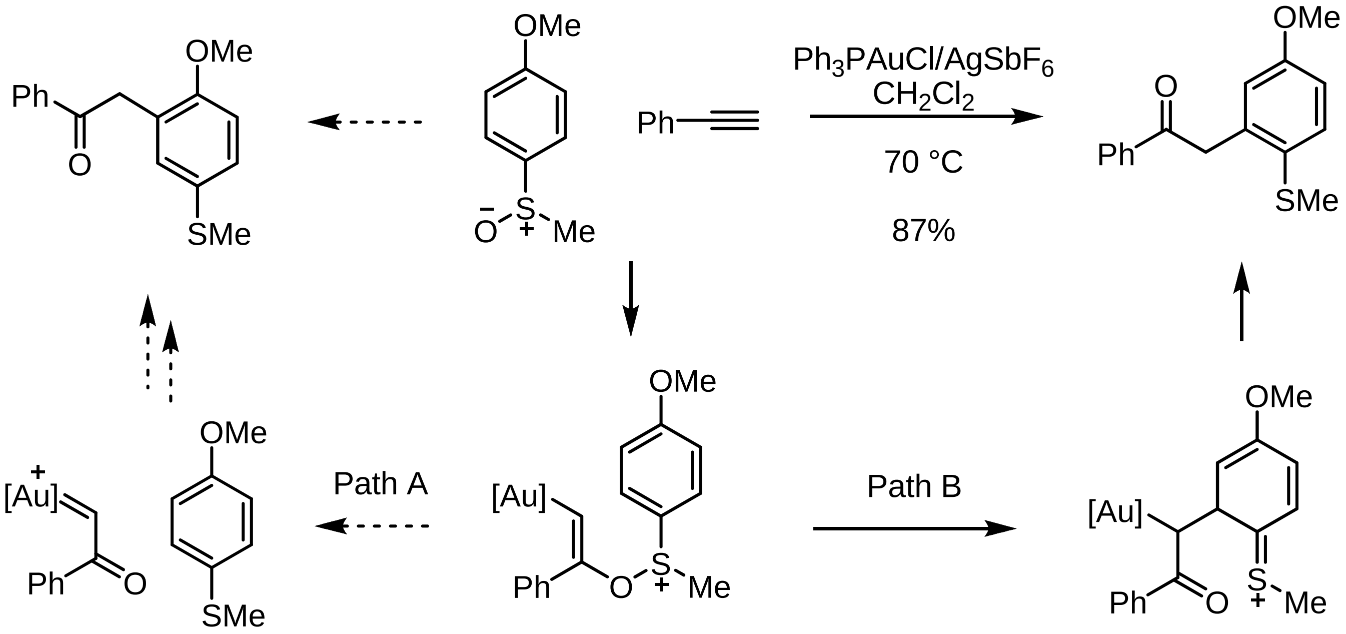
- Capture of the carbenoid by 1,2-insertion
- Use of *o*-chloroaryl reduces competing electrophilic aromatic substitution



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

Intermolecular redox processes: Sulfoxides

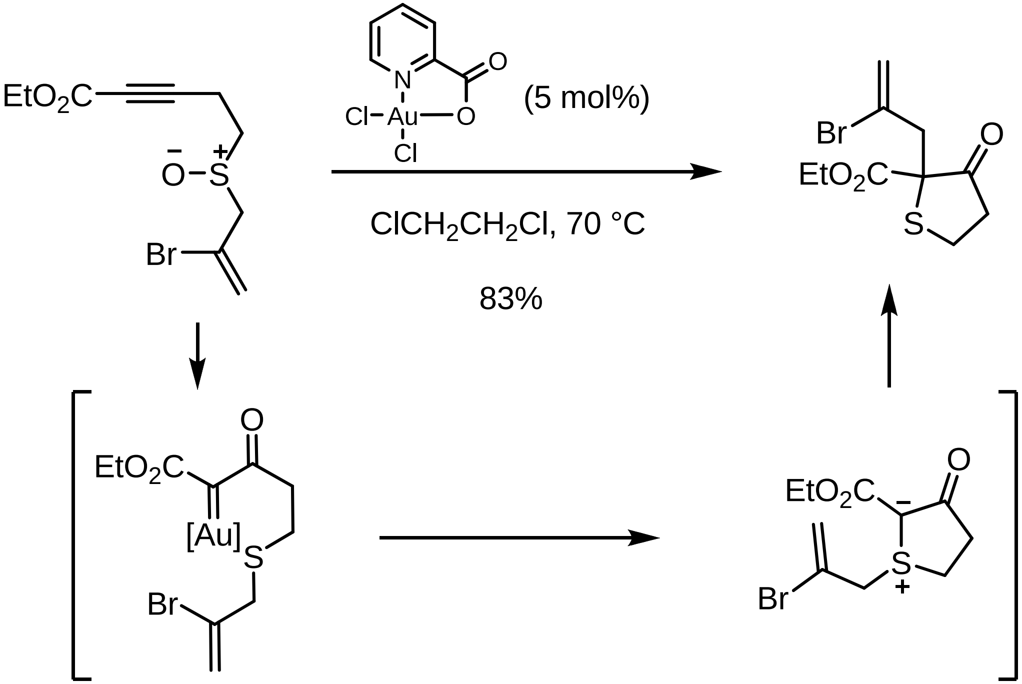
- The outcome expected from formation of a gold carbenoid by oxidation is not observed.
- 3,3-sigmatropic rearrangement occurs after intitial oxyauration of the alkyne.



A. B. Cuenca, S. Montserrat, K. M. Hossain, G. Mancha, A. Lledós, M. Medio-Simón, G. Ujaque, G. Asensio, *Org. Lett.* **2009**, *11*, 4906.

Internal redox processes: Sulfoxides

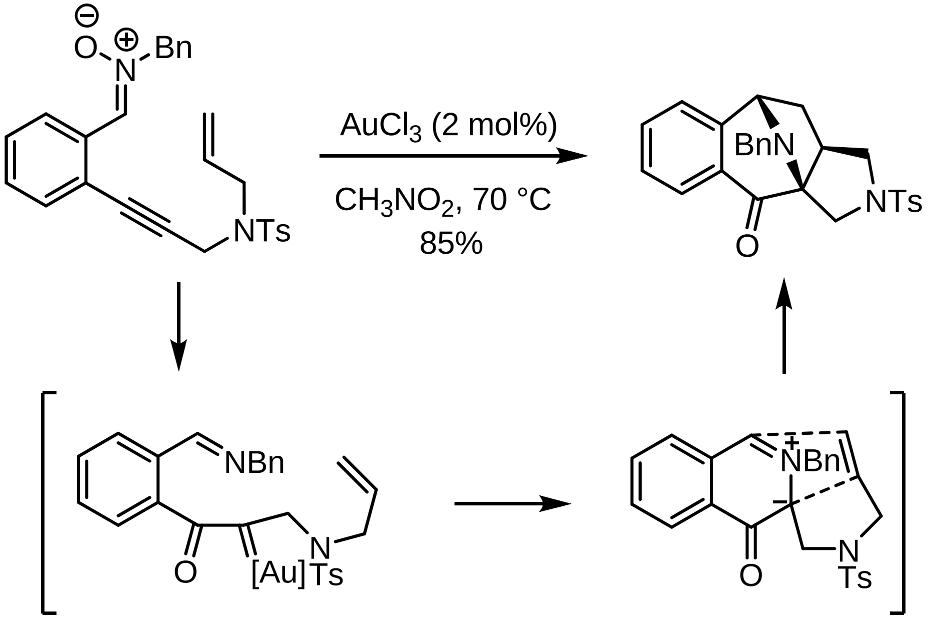
- Use as a diazo-free access to sulfur ylides for *S*-heterocycle synthesis.



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

Internal redox processes: Nitrones

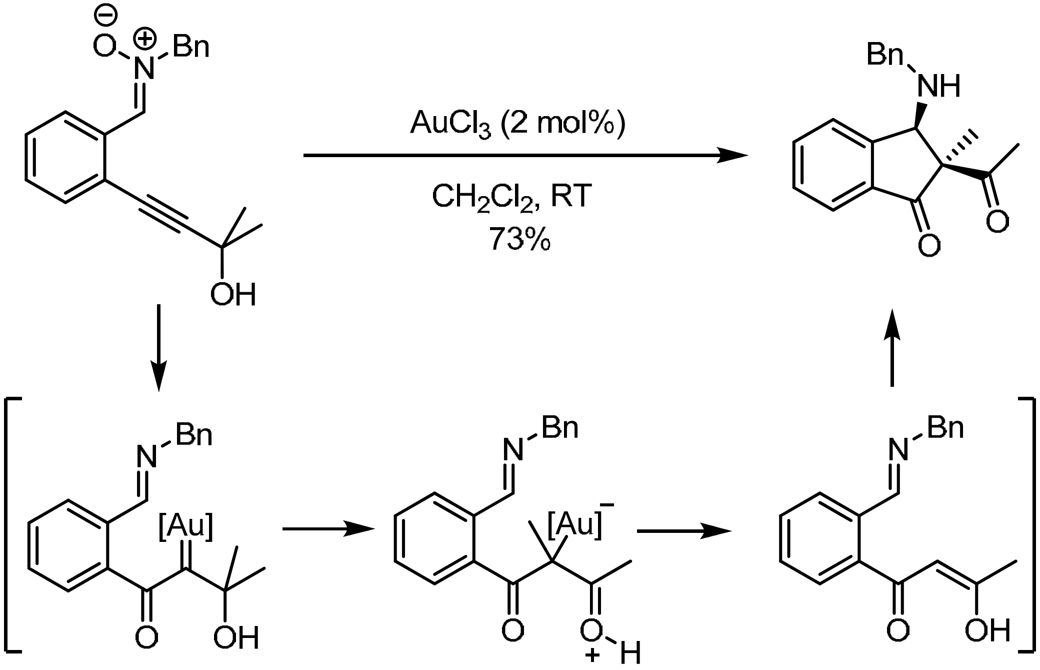
- Use of a nitrone results in the formation of a 1,3-dipole which is trapped by intermolecular cycloaddition.



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

Internal redox processes: Nitrones

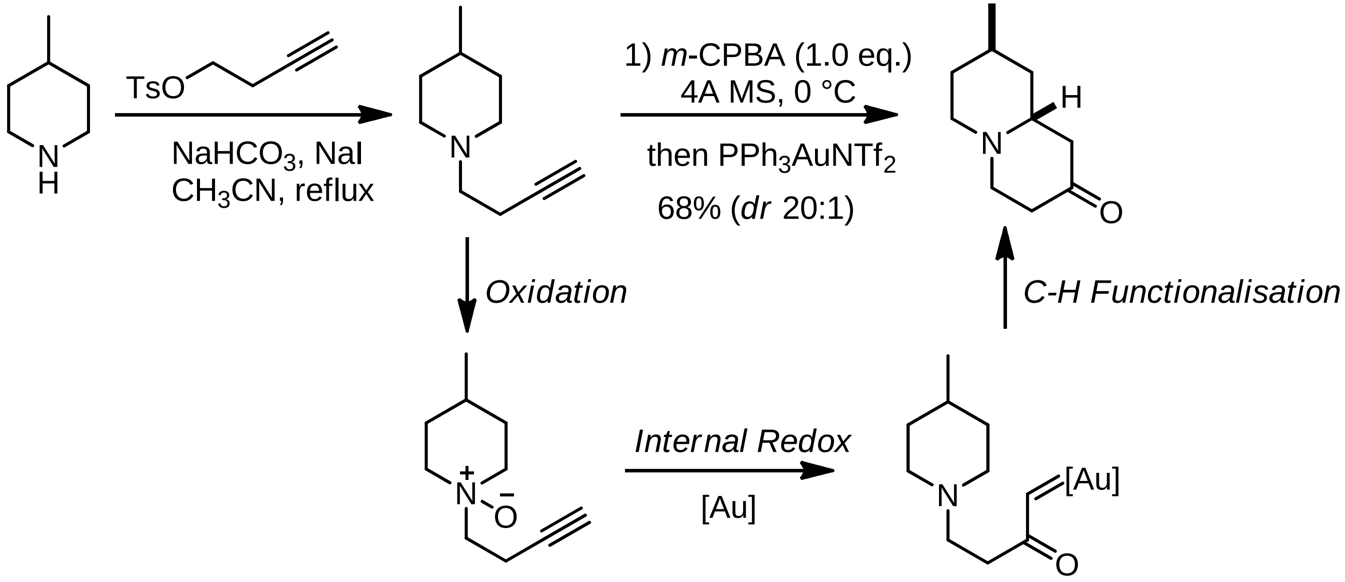
- A competing 1,2-alkyl shift is followed by a Mannich reaction.



H.-S. Yeon, Y. Lee, J. Jeong, E. So, S. Hwang, J.-E. Lee, S. S. Lee, S. Shin, *Angew. Chem. Int. Ed.* **2010**, *49*, 1611.

Internal redox processes: amine *N*-oxides

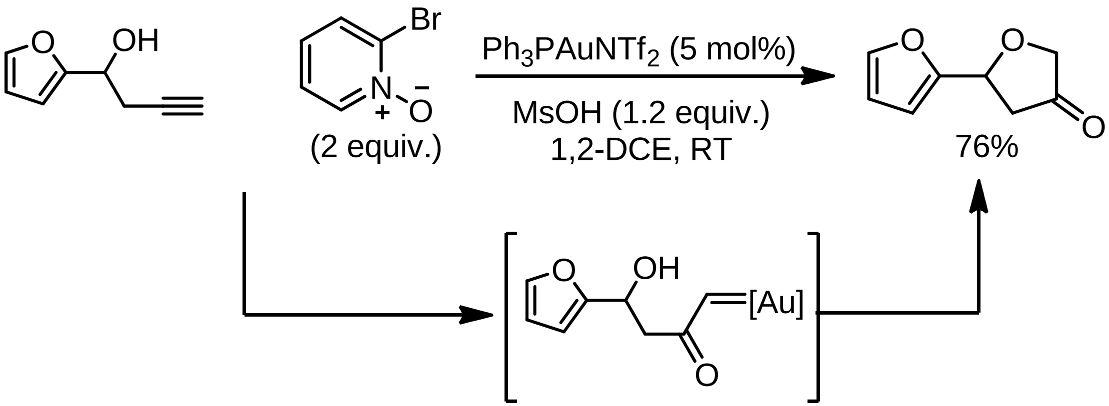
- Oxidation of an amine is followed immediately by gold catalysed reaction.



L. Cui, Y. Peng, L. Zhang, *J. Am. Chem. Soc.* **2009**, *131*, 8394.
L. Cui, G. Zhang, Y. Peng, L. Zhang, *Org. Lett.* **2009**, *11*, 1225.
L. Cui, L. We, L. Zhang, *Chem. Commun.* **2010**, 3351.

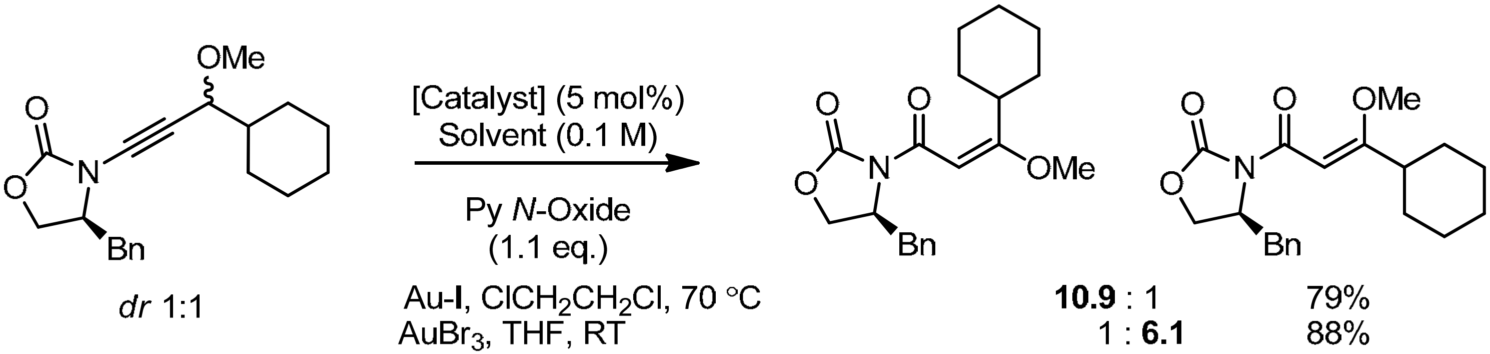
Intermolecular equivalents

- Pyridine *N*-oxides have been used to effect intermolecular oxidation of alkynes, followed by O-H insertion of the incipient carbenoid in the presence of stoichiometric acid.



L. Ye, L. Cui, G. Zhang, L. Zhang. *J. Am. Chem. Soc.* **2010**, *132*, 3258; L. Ye, W. He, L. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 8550; B. Lu, C. Li, L. Zhang, *J. Am. Chem. Soc.* DOI:10.1021/ja1072614.

- 1,2-insertions after oxidation of ynamides and ynol ethers in the absence of acid.

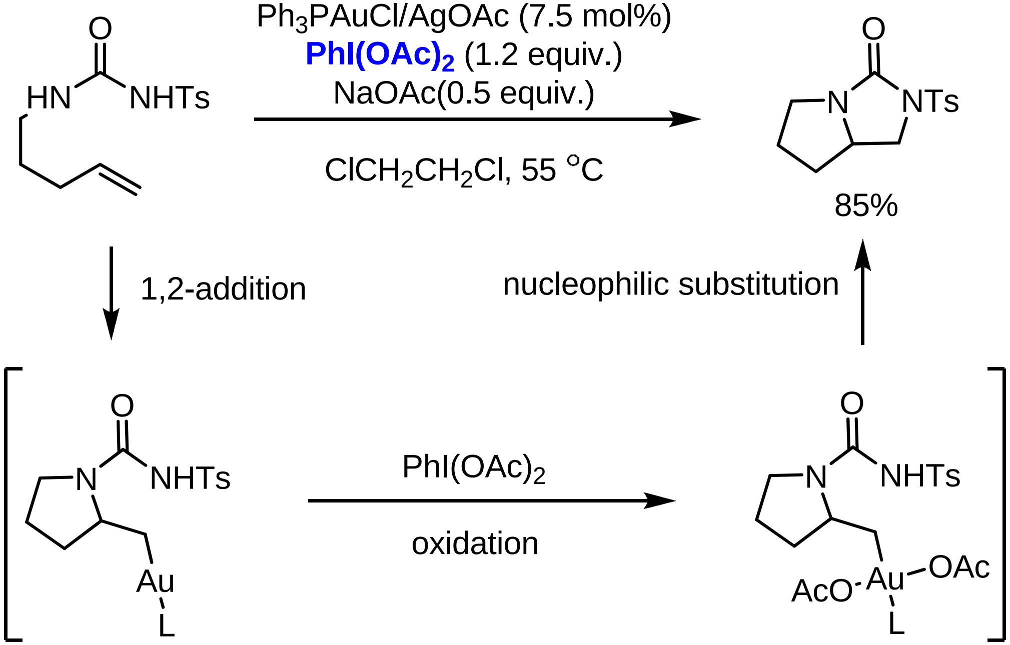


P. W. Davies, A. Cremonesi, N. Martin, *Chem. Commun.* DOI:10.1039/C0CC02736G.

Recent Developments in Gold Redox Cycles

Diamination of alkenes

- In analogy to palladium catalysed diamination of alkenes, use of a gold catalyst and a stoichiometric oxidant allow for intramolecular diamination through a Au(I)-Au(III) redox cycle.

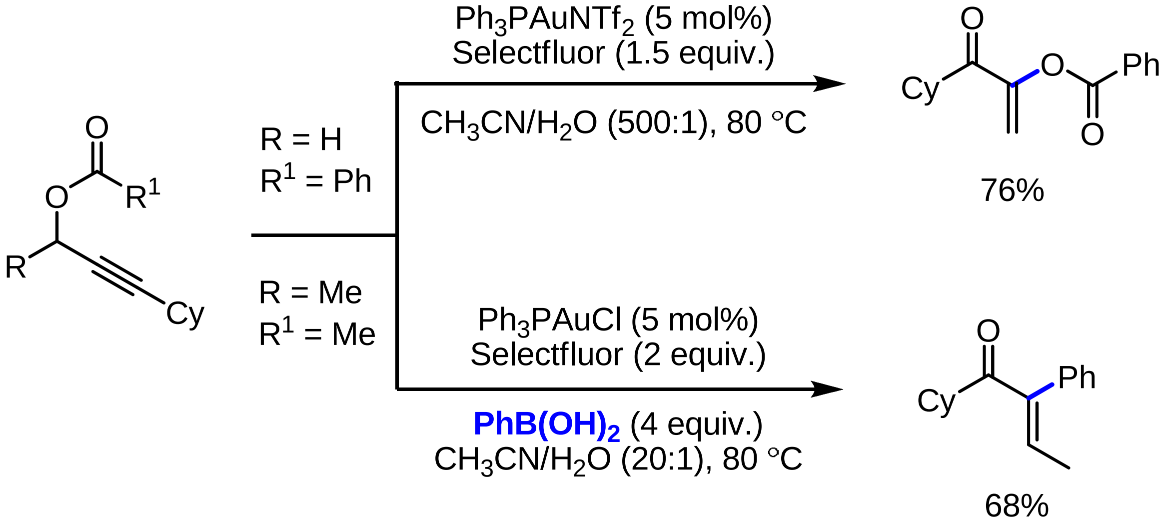


- Anti-aminometallation and anti-C-N bond formation process.

A. Iglesias, K. Muniz, *Chem. Eur. J.* **2009**, *15*, 10563.

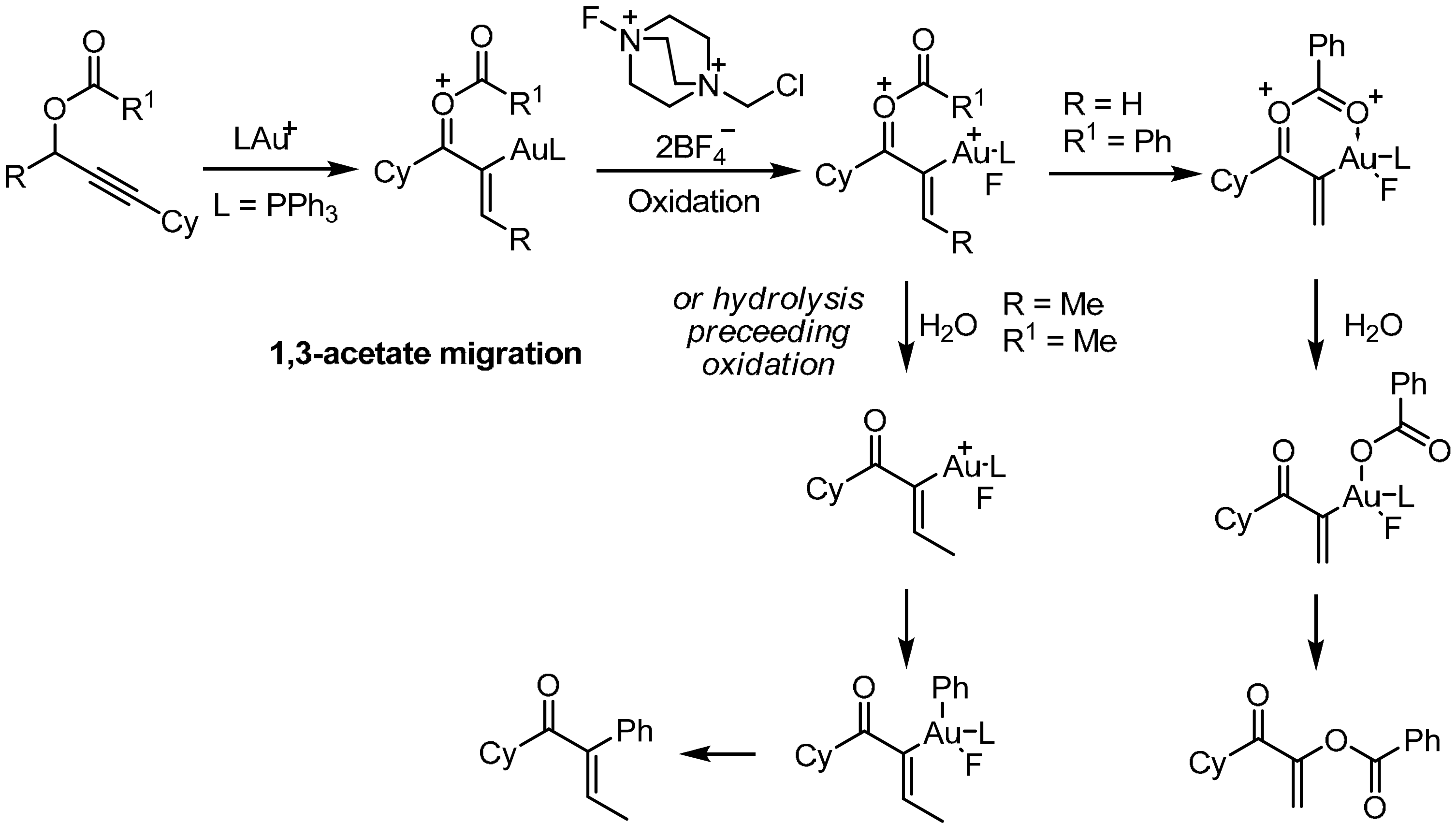
Oxidative use of propargylic carboxylates

- In the presence of the strong oxidising agent the established rearrangement of the propargylic carboxylate is diverted through to a gold(III) intermediate.
- Depending on the reaction conditions, additives and substrate structure: benzoxyinyl ketones are formed with formation of C-O bond.
- In the presence of an excess of boronic acid, transmetallation dominates leading to the cross-coupled product



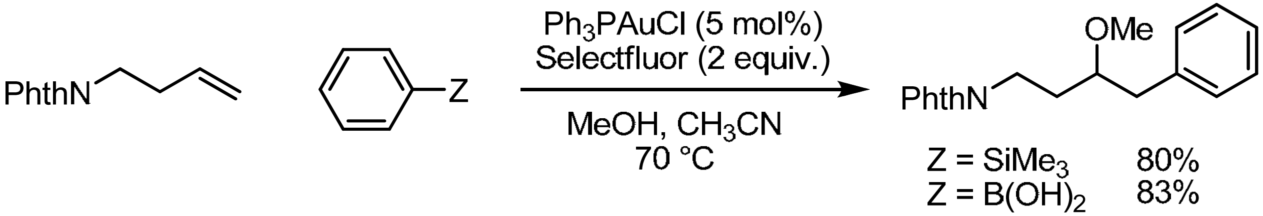
Y. Peng, L. Cui, G. Zhang and L. Zhang, *J. Am. Chem. Soc.* **2009**, *131*, 5062;
G. Zhang, Y. Peng, L. Cui and L. Zhang, *Angew. Chem. Int. Ed.* **2009**, *48*, 3112.

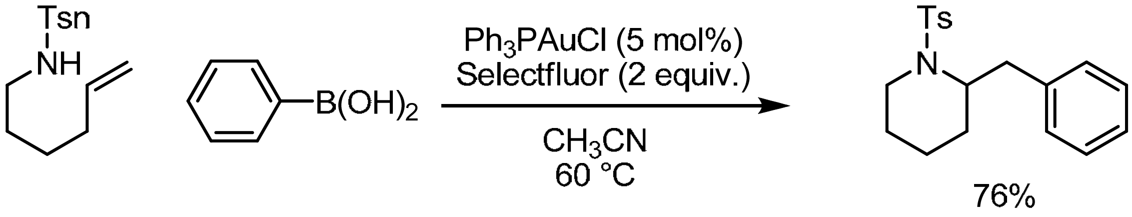
Oxidative use of propargylic carboxylates

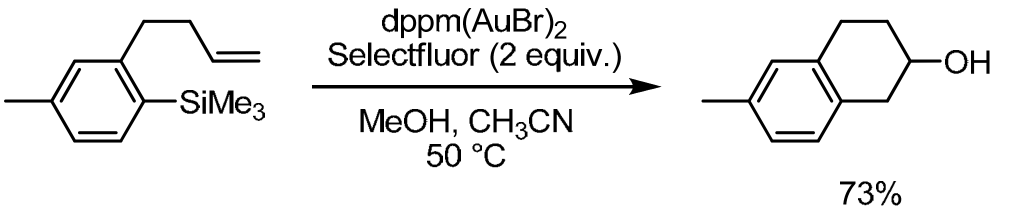


Y. Peng, L. Cui, G. Zhang, L. Zhang, *J. Am. Chem. Soc.* **2009**, *131*, 5062.
G. Zhang, Y. Peng, L. Cui, L. Zhang, *Angew. Chem. Int. Ed.* **2009**, *48*, 3112.

Amino/Oxyarylation of alkenes







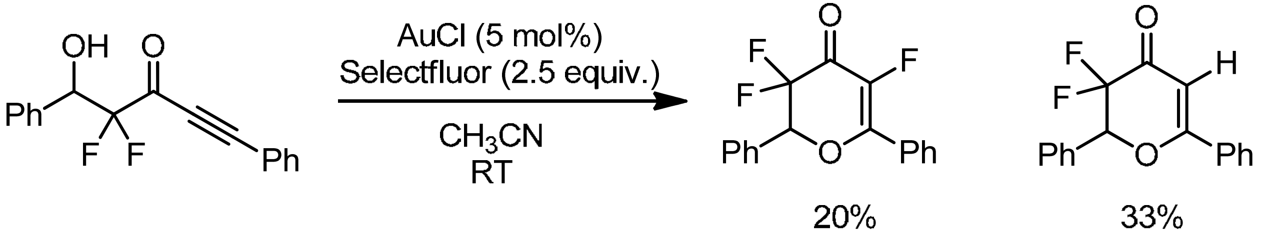
Guozhu Zhang, Li Cui, Yanzhao Wang, and Liming Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 1474; A. D. Melhado, W. E. Brenzovich, Jr., A. D. Lackner, F. D. Toste, *J. Am. Chem. Soc.* **2010**, *132*, 8885; L. T. Ball, M. Green, G. C. Lloyd-Jones, C. A. Russell, *Org. Lett.* **2010**, *12*, 4724; W. E. Brenzovich, Jr., J.-F. Brazeau, F. D. Toste, *Org. Lett.* **2010**, *12*, 4728.

- Experimental evidence for the cross-coupling of alkylgold(III)fluoride complexes with aryl boronic acids.

N. P. Mankad, F. D. Toste, *J. Am. Chem. Soc.* **2010**, *132*, 12859.

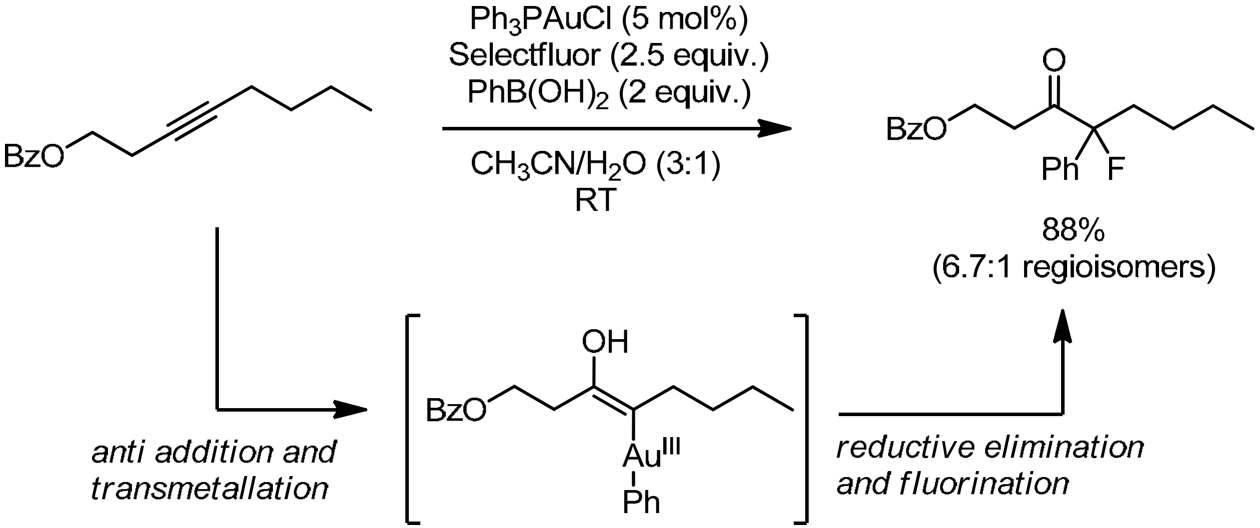
Fluorinations

- Combination of gold catalysis with electrophilic fluorinating reagents to prepare cationic gold systems and achieve C-F bond formation.
- For fluorinative cyclisations:



M. Schuler, F. Silva, C. Bobbio, A. Tessier, V. Gouverneur, *Angew. Chem.* **2008**, *120*, 8045.

- Synthesis of functionalised α-fluoro acetals and ketones



W. Wang, J. Jasinski, G. B. Hammond, B. Xu, *Angew. Chem. Int. Ed.* **2010**, *49*, 7247.
T. de Haro, C. Nevado, *Adv. Synth. Catal.* **2010**, *352*, 2767.

Conclusion

- The chemistry of gold catalysis is diverse and powerful and has advanced rapidly within a short period of time;
- There is great potential for application of gold catalysis in advanced organic synthesis: both in extending known reactivities and in developing novel transformations (including asymmetric variations);
- Understanding of control factors and mechanism in this young field is improving;
- The reactions developed all fit within the known activation modes of gold catalysis starting with electrophilic activation and the ability of gold to stabilise positive charge;
- There is potential for further use of gold-species generated *in situ* by coupling or cyclisation reactions.