Leitner Christian

09.10.2014

GOLD CATALYSED REACTIONS IN TOTAL SYNTHESIS

Abstract

1. Introduction

2. Gold catalysis in Total synthesis

   2.1 „Lewis acid“ gold catalysis

   2.2 „Carbenoid“ gold catalysis

   2.3 Gold catalysis of propargylic alcohols

3. Summary/ Conclusions

Introduction

Properties of Gold:

- **Atomic weight:** 196,97 g/mol
- **Electron configuration:** [Xe] $4f^{14}$ $5d^{10}$ $6s^{1}$
- **Oxidation states:** +1, +3, (-1, +2, +5)
- **Redox potentials:** Au/Au^{+} = +1,69 V; Au/Au^{3+} = 1,50 V
- **Electronegativity** (Pauling)**:** 2,4

- **Crystall structure:** Lattice face centered cubic
- **Density:** 19,32 g/cm^{3}
- **Melting Point:** 1064°C
- **Mohs hardness:** 2,5

Introduction

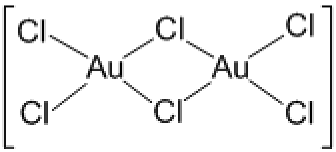
Preperation of Au salts:

- Using aqua regia: $Au^0 + \textit{aqua regia} \longrightarrow [AuCl_4]^{\ominus}$

- Oxidative with KCN: $Au^0 + KCN \xrightarrow{O_2} [Au(CN)_2]^{\ominus}$

- Oxidative solvent free: $2\ Au^0 + 3\ Cl_2 \xrightarrow{180°C} 2\ AuCl_3 \xrightarrow{250°C} 2\ AuCl + 2\ Cl_2$

(red needles) (pale yellow powder)

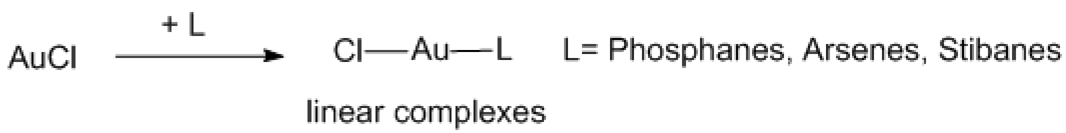


dimer
square planar complex

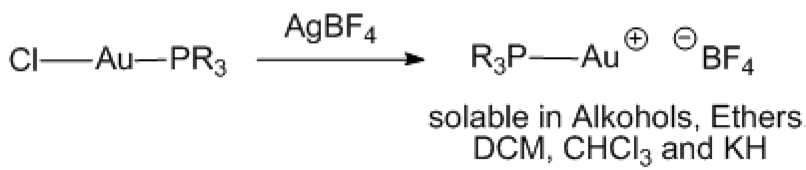
Introduction

Preperation of Au complexes:

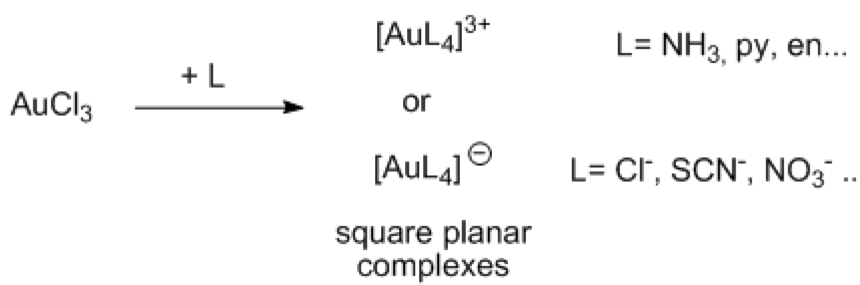
- Au(I) complexes:



- Good complexes for Auraration:



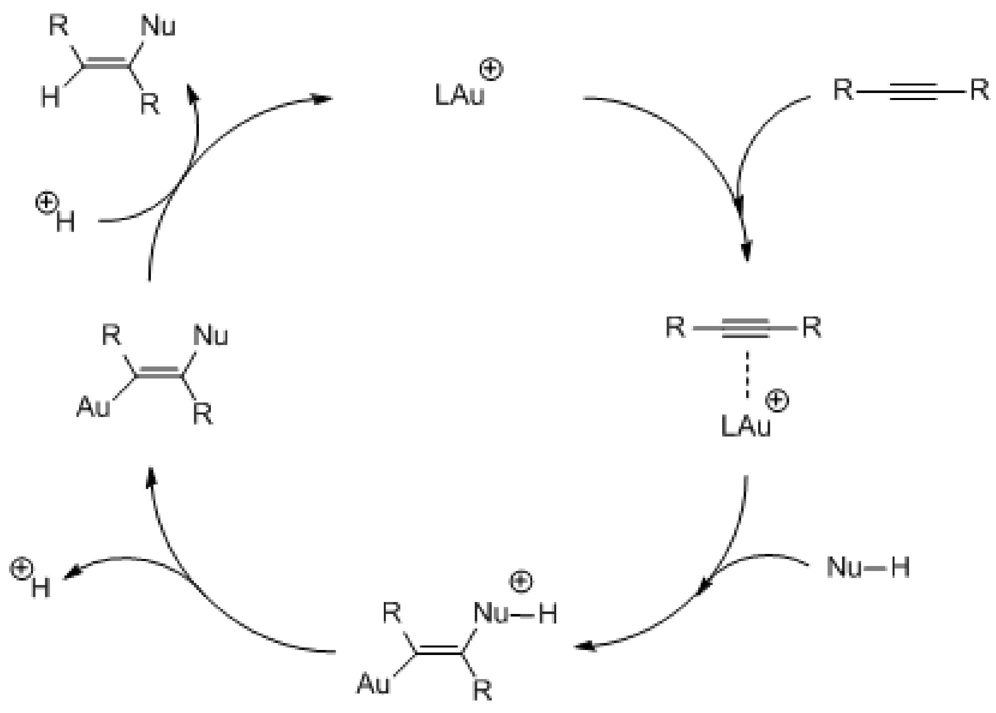
- Au(III) complexes:



„Lewis acid“ Gold catalysis

Typical catalytic Cycle:

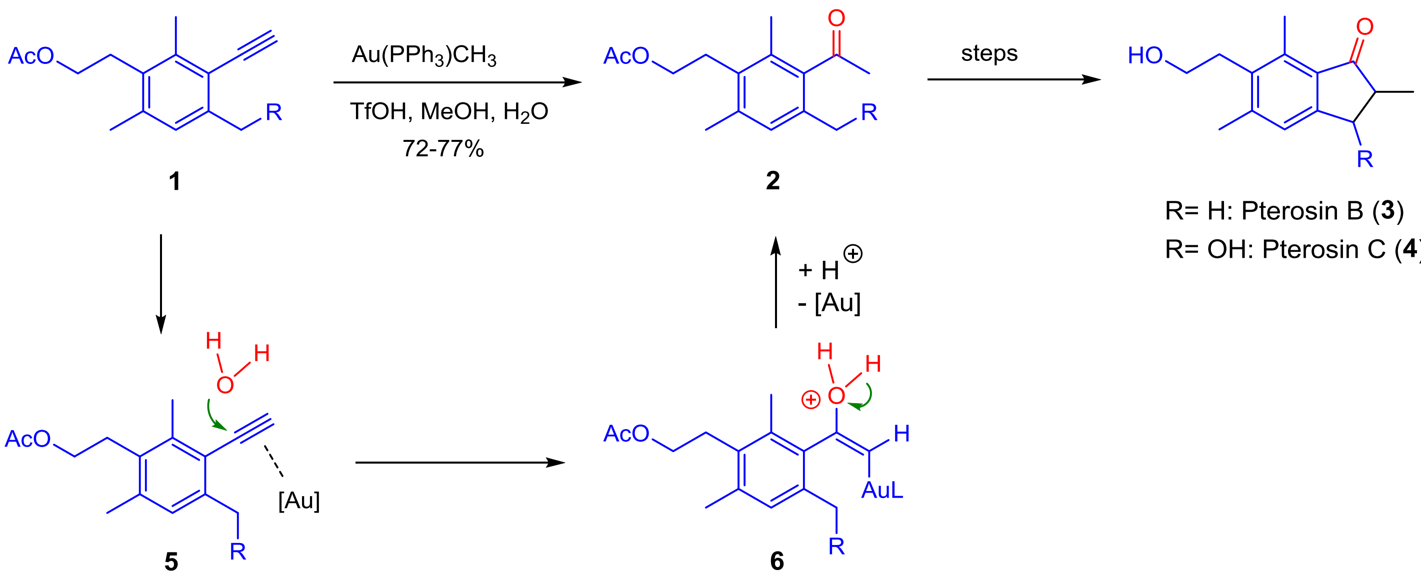
For gold(I)- catalysed addition of protic nukleophiles to alkynes



„Lewis acid“ Gold catalysis

Hydration of triple bonds:

- Synthesis of Pterosin B and C
- Isolatet from *Pteridium aquilinum*
- Total synthesis by Wessig P. *et al* [1]

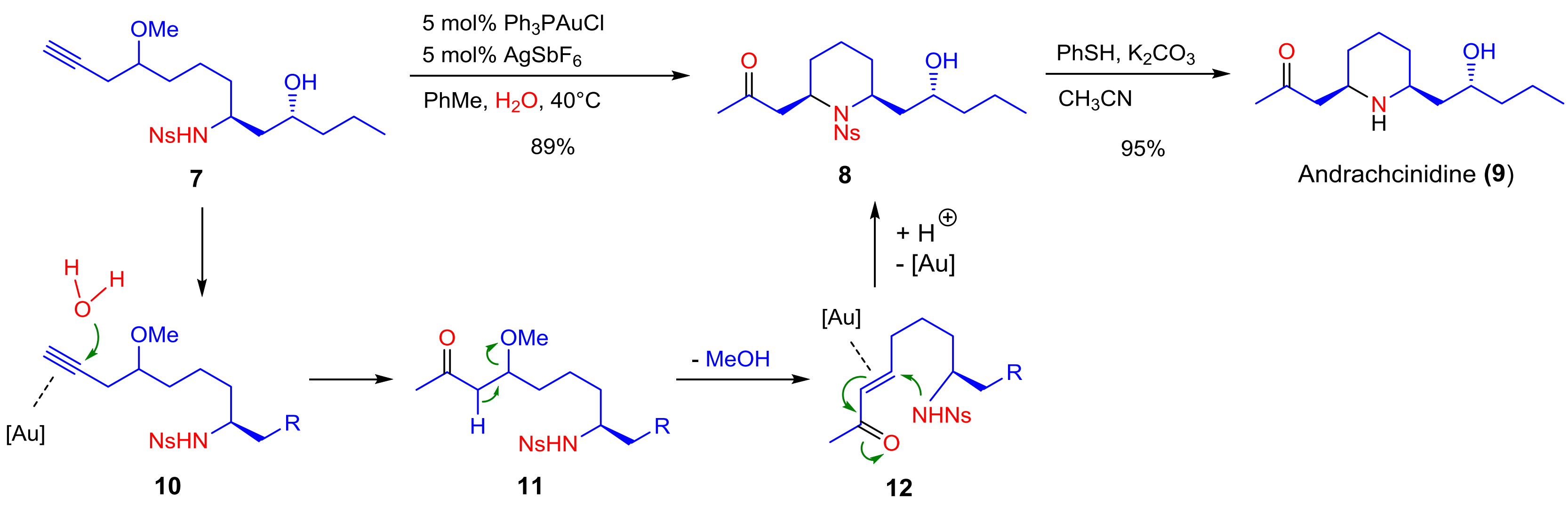


[1] P. Wessig *et al*, *Synlett* **2006**, *No. 10*, 1543

„Lewis acid“ Gold catalysis

Hydration of triple bonds:

- Synthesis of (+)-Andrachcinidine
- Isolatet from *Andrachne aspera* [2]
- Total synthesis by P. Floreancig *et al* [3]



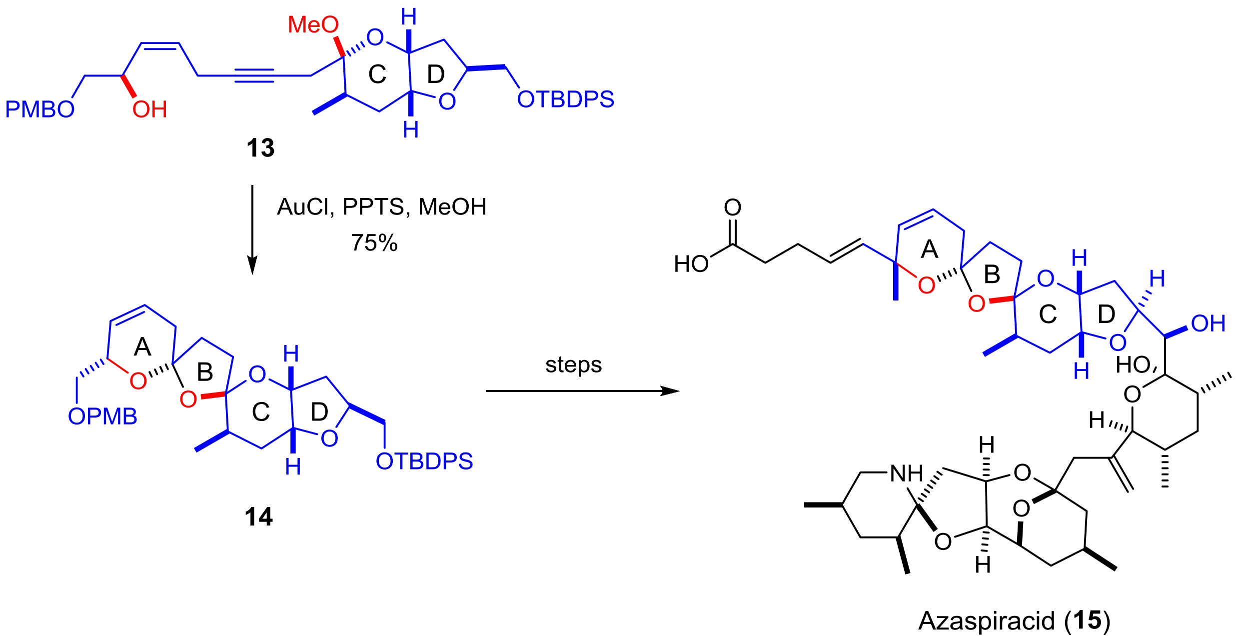
[2] C. Hootele *et al*, *J. Nat. Prod.* **2000,** *63,* 762

[3] E. Floreancig *et al*, *J. Org. Chem.* **2007**, *72*, 7359

„Lewis acid“ Gold catalysis

Spiroketalisation of alkynes:

- Synthesis of Azaspiracid
- Isolatet from *Mytilus edulis* [4]
- Spiroketalisation by Craig J. Forsyth *et al* [5]



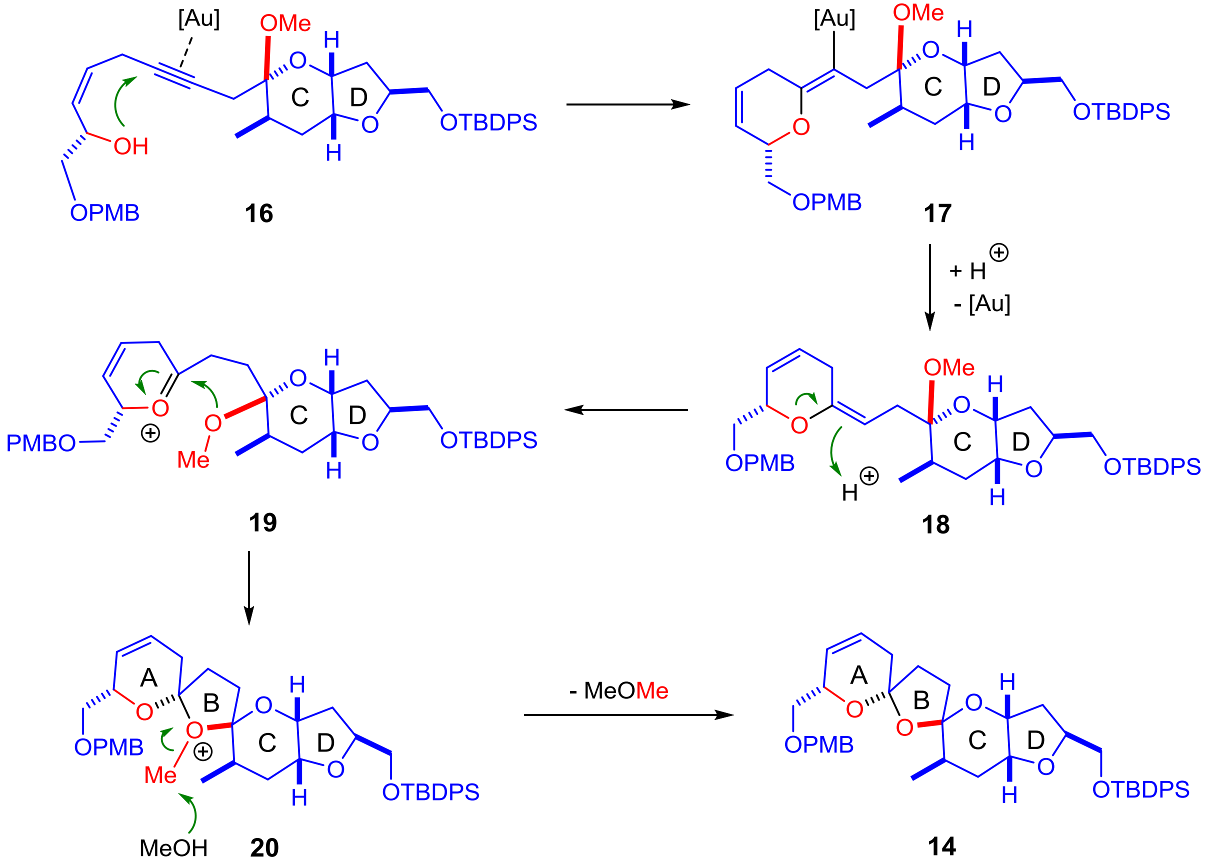
[4] T. Yasumoto *et al*, *J. Am. Chem. Soc.*, **1998,** *120,* 9967

[5] C. J. Forsyth *et al*, *Angew. Chem. Int. Ed.,* **2007**, 46, 279

„Lewis acid“ Gold catalysis

Spiroketalisation of alkynes:

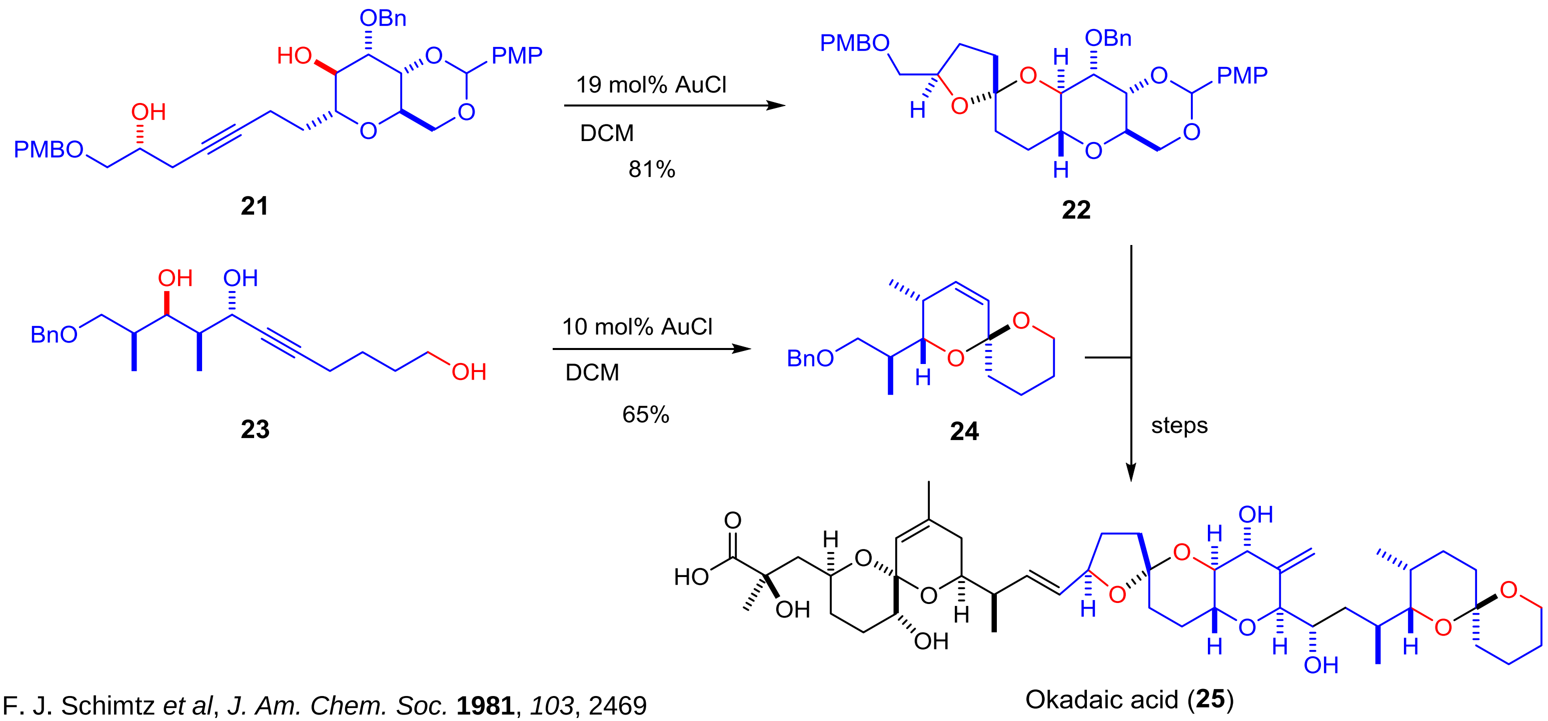
Mechanism:



„Lewis acid“ Gold catalysis

Spiroketalisation of alkynes:

- Synthesis of Okadaic Acid
- Isolatet from *Halichondria okadai* [6]
- Spiroketalisation by Craig J. Forsyth *et al* [7]



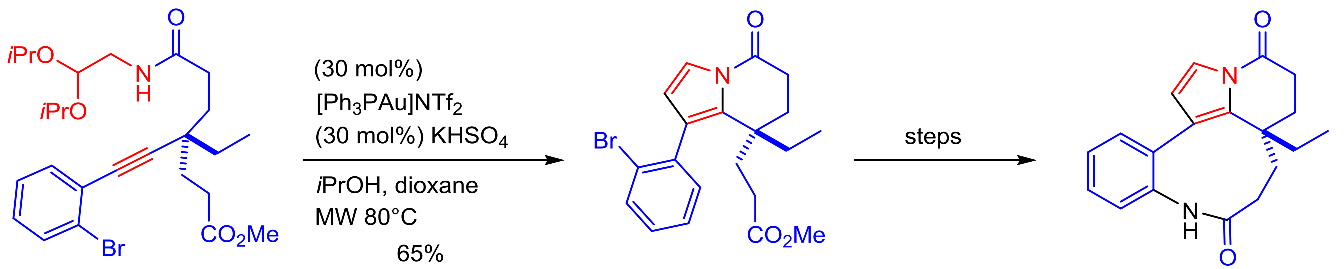
[6] F. J. Schimtz *et al*, *J. Am. Chem. Soc.* **1981**, *103*, 2469

[7] C. J. Forsyth *et al*, *Org. Lett.*, **2010**, *No. 20*, 4528

„Lewis acid“ Gold catalysis

Nu- addition at alkynes:

- Synthesis of (-)-Rhazinicine
- Isolatet from *Rhazya stricta* [8]
- Total synthesis by Hidetoshi Tokuyama *et al* [9]



26 **27** (-)-Rhazinicine (**28**)

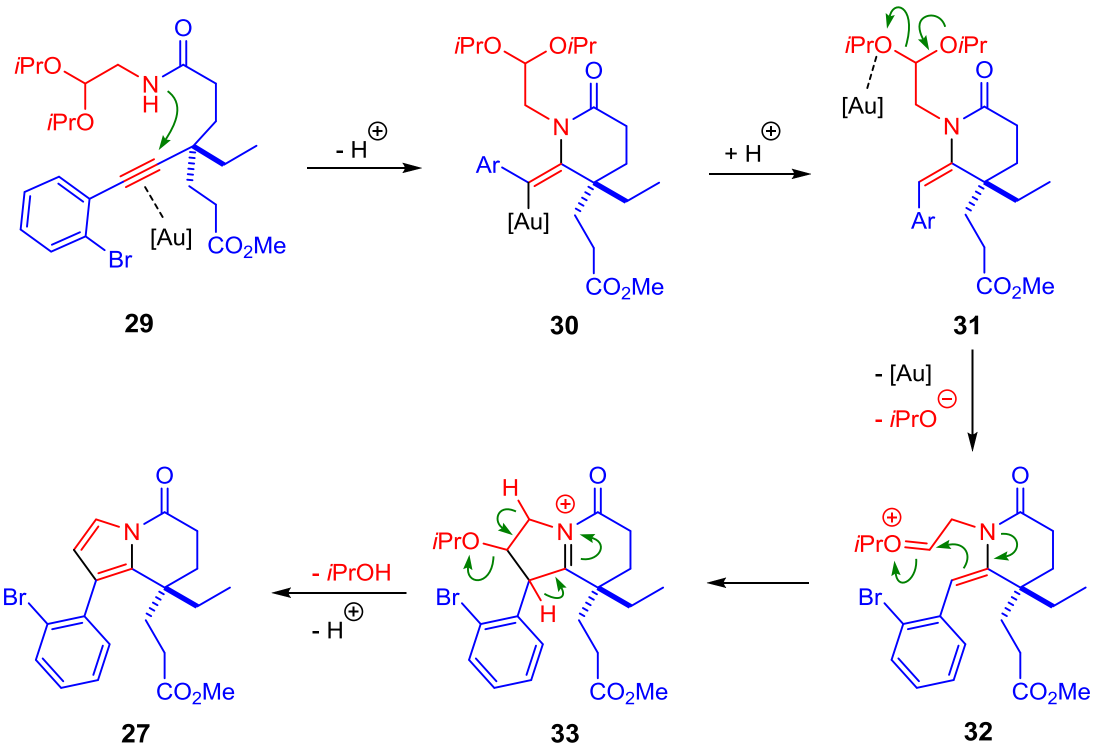
[8] I. Gerasimenko *et al*, *J. Nat. Prod.* **2001**, *64*, 114

[9] H. Tokuyama *et al, Angew. Chem., Int. Ed.* **2013**, *52*, 7168

„Lewis acid“ Gold catalysis

Nu- addition at alkynes:

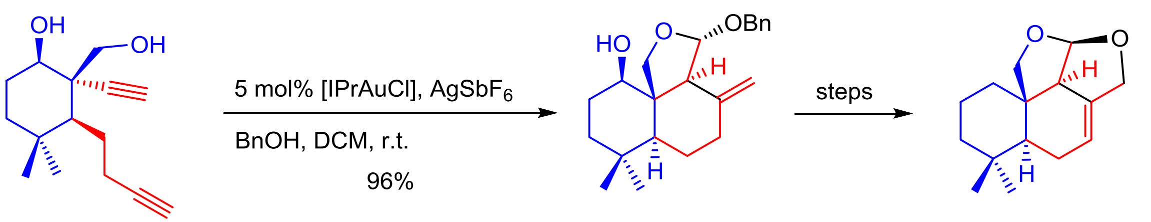
Mechanism:



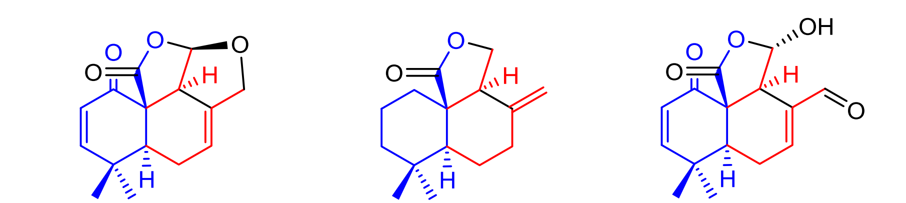
„Lewis acid“ Gold catalysis

Acetalisation, Nu- addition cascade:

- Synthesis of Marasmene
- Isolatet from *Marasmius oreades*
- Total synthesis by Z. Yang *et al* [10]



34 **35** Marasmene (**36**)



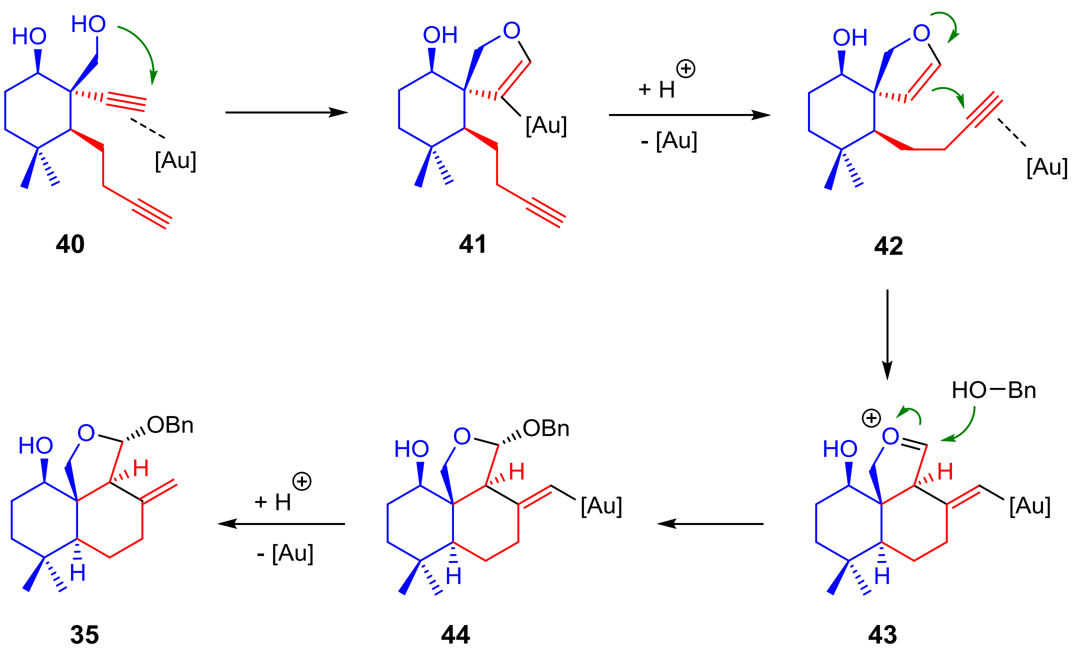
Anhydromarasmone (**37**) Antrocin (**38**) Kuehneromycin A (**39**)

[10] Z. Jang *et al*, *J. Am. Chem. Soc.*, **2011**, *133*, 14944

„Lewis acid“ Gold catalysis

Acetalisation, Nu- addition cascade:

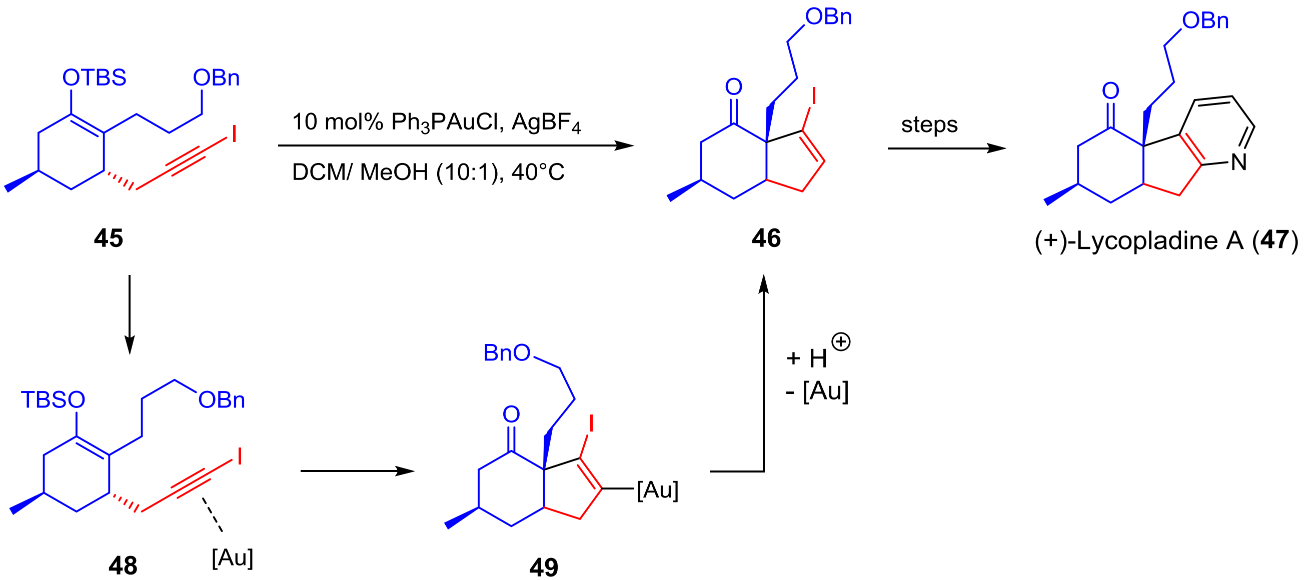
Mechanism:



„Lewis acid“ Gold catalysis

Gold catalysed Conia- ene like reactions:

- Synthesis of (+)-Lycopladine A
- Isolatet from *Lycopodium complanatum* [11]
- Total synthesis by Dean F. Toste *et al* [12]



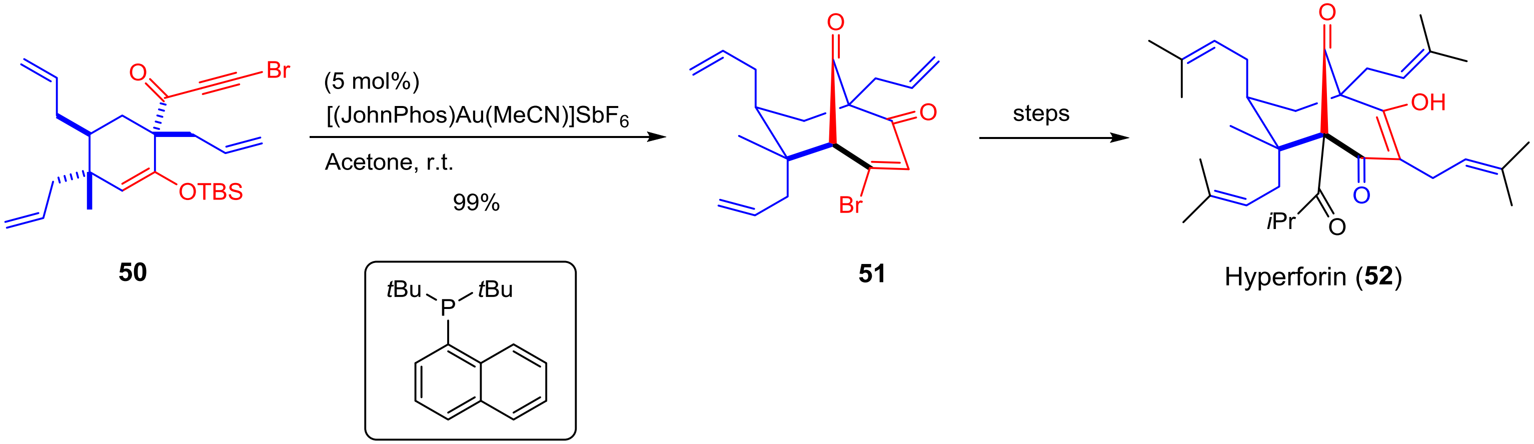
[11] Kobayashi *et al*, *Tetrahedron Lett.* **2006**, *47*, 3287

[12] F. D. Toste *et al*, *Angew. Chem., Int. Ed.* **2006**, *45*, 5991

„Lewis acid“ Gold catalysis

Gold catalysed Conia- ene like reactions:

- Synthesis of Hyperforin
- Isolatet from *Guttiferae* [13]
- Total synthesis by L. Barriault *et al* [14]



50

51

Hyperforin (**52**)

JohnPhos

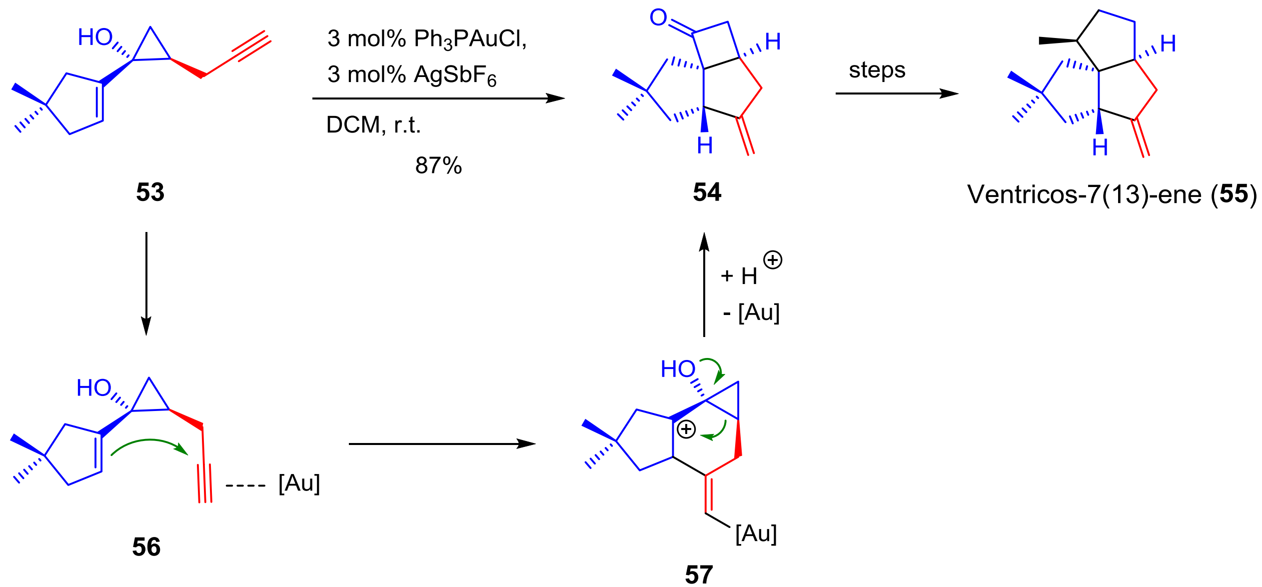
[13] I. Pal Singh, S. B. Bharate, *Nat. Prod. Rep*. **2006**, *23*, 558

[14] G. Bellavance, L. Barriault, *Angew. Chem., Int. Ed.* **2014**, *53*, 6701

„Lewis acid“ Gold catalysis

Nu- addition, ring expansion cascade:

- Synthesis of Ventricos-7(13)-ene
- Isolatet from *Lophozia ventricosa* [14]
- Total synthesis by F. Dean Toste *et al* [15]



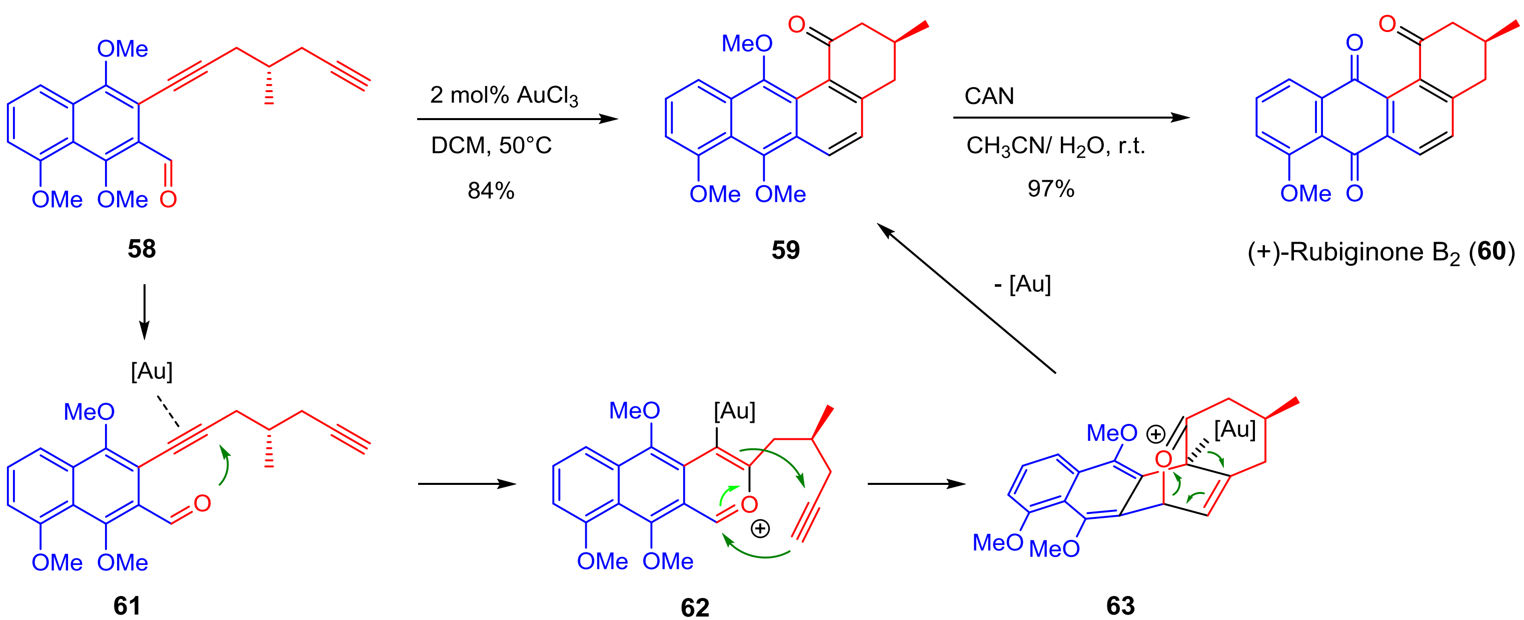
[14] C. Paul, R. Lu, *Tetrahedron: Asymm.* **2005**, *16*, 883

[15] F. D. Toste *et al*, *Org. Lett.,* **2008**, *No. 19*, 4315

„Lewis acid“ Gold catalysis

Generation of pyrylium intermediates:

- Synthesis of (+)-Rubiginone B_2
- Isolatet from *Streptomyces* [16]
- Total synthesis by Asao N. *et al* [17]



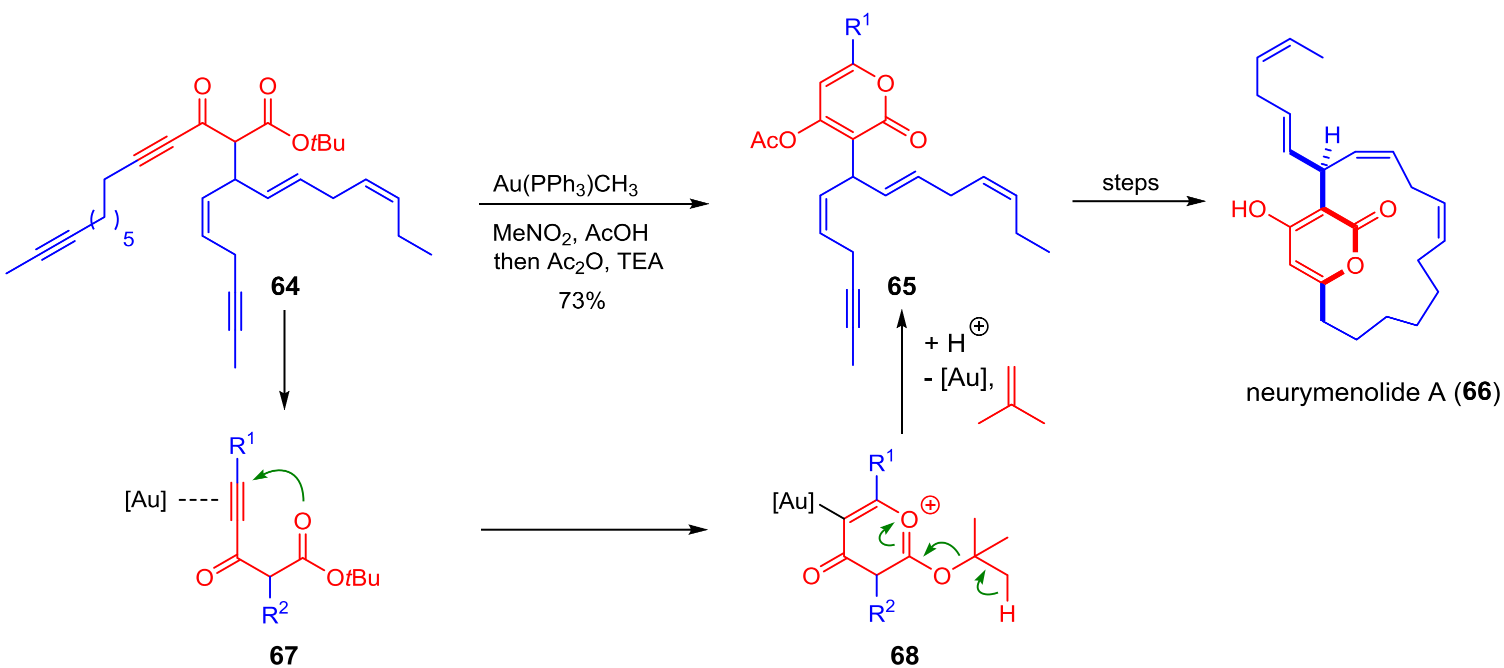
[16] A. W. Johnson *et al*, *Tetrahedron Lett*. **1967**, *16*, 1449

[17] Naoki Asao *et al*, *J. Org. Chem.* **2005**, *70*, 8977

„Lewis acid“ Gold catalysis

Synthesis of 4-Hydroxy 2-pyrones:

- Synthesis of Neurymenolide A
- Isolatet from *Neurymenia fraxinifolia* [18]
- Total synthesis by Alois Fürstner *et al* [19]



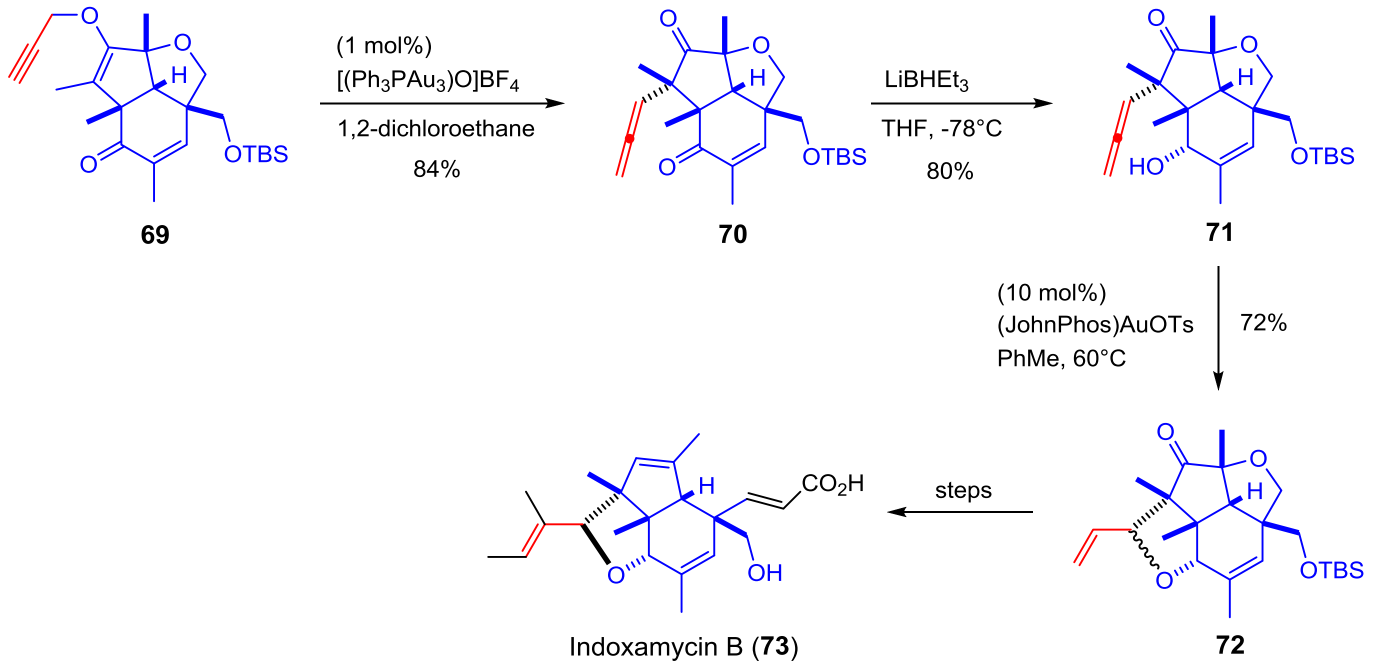
[18] E. P. Stout *et al*, *Org. Lett.* **2009**, *11*, 225

[19] A. Fürstner *et al*, *Angew. Chem. Int. Ed.* **2012**, *51*, 6929

„Lewis acid“ Gold catalysis

Propargylic Claisen-type rearrangement:

- Synthesis of Indoxamycin B
- Isolatet from *Streptomyces* [20]
- Total synthesis by Erick Carreira *et al* [21]



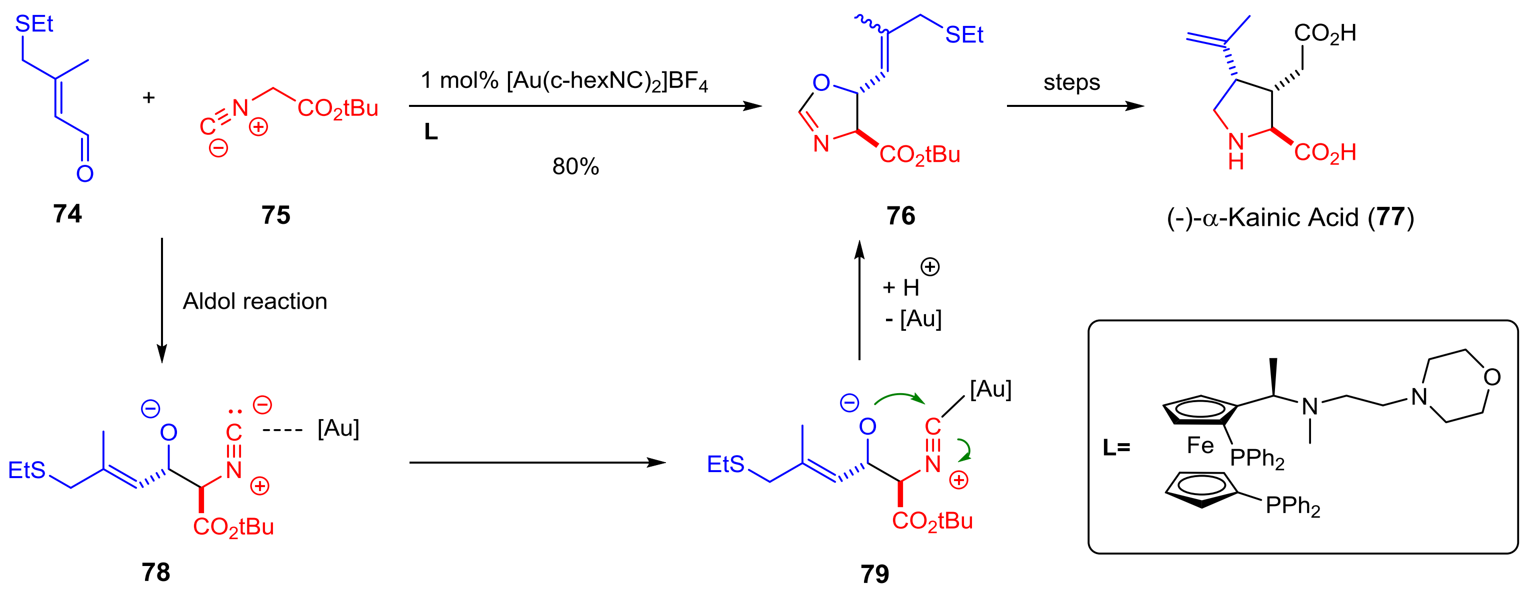
[20] S. Sato *et al*, *J. Org. Chem.* **2009**, *74*, 5502

[21] O. E. Jeker, E. M. Carreira, *Angew. Chem. Int Ed.* **2012**, *51*, 3474

„Lewis acid“ Gold catalysis

Activation of isonitriles:

- Synthesis of (–)-α-Kainic Acid
- Isolatet from *Digenea simplex* [22]
- Total synthesis by Mario D. Bachi *et al* [23]

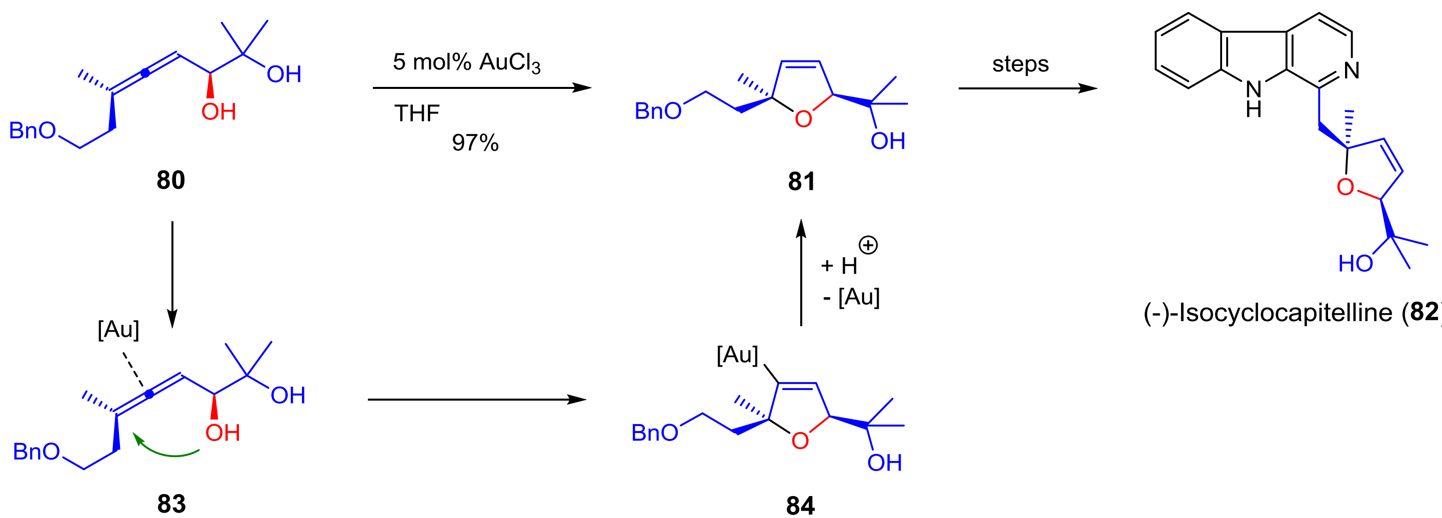


[22] G. Impellizzeri *et al*, *Phyrochemisrry* , **1975,** *14,* 1549
[23] M. D. Bachi *et al*, *J. Org. Chem.* **1997,** *62,* 1896

„Lewis acid“ Gold catalysis

Nu- addition at allenes:

- Synthesis of (–)-Isocyclocapitelline
- Isolatet from *Hedyotis capitellata* [24]
- Total synthesis via gold-catalysed allene cyclomerisation by Volz F., Krause N. *et al* [25]



(-)-Isocyclocapitelline (**82**)

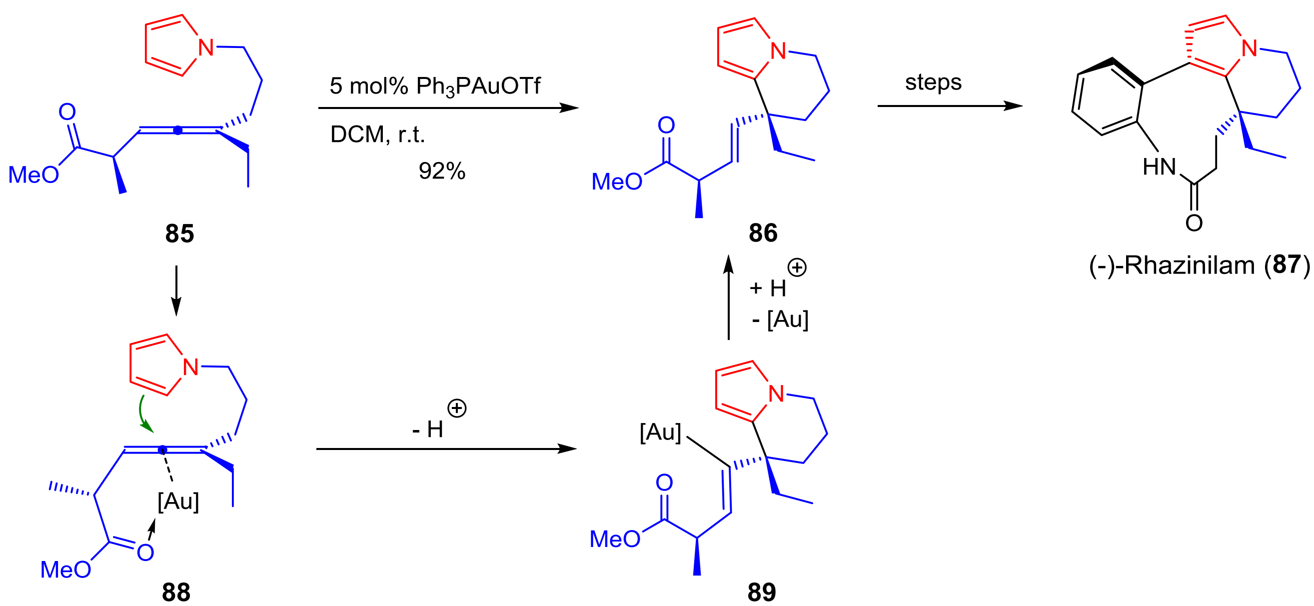
[24] N. M. Phuong *et al*, *Phytochemistry,* **1999**, *52*, 1725

[25] N. Krause *et al*, *Org. Biomol. Chem.*, **2007**, *5*, 1519

„Lewis acid“ Gold catalysis

Nu- addition at allenes:

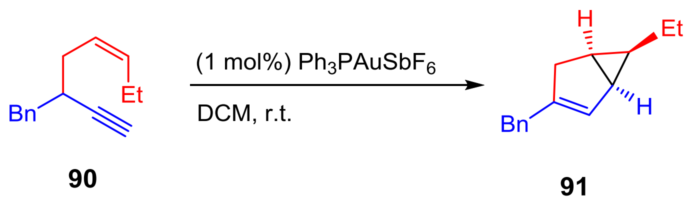
- Synthesis of (–)-Rhazinilam
- Isolatet from *Melodinus australis* [26]
- Total synthesis by Scott G. Nelson *et al* [27]



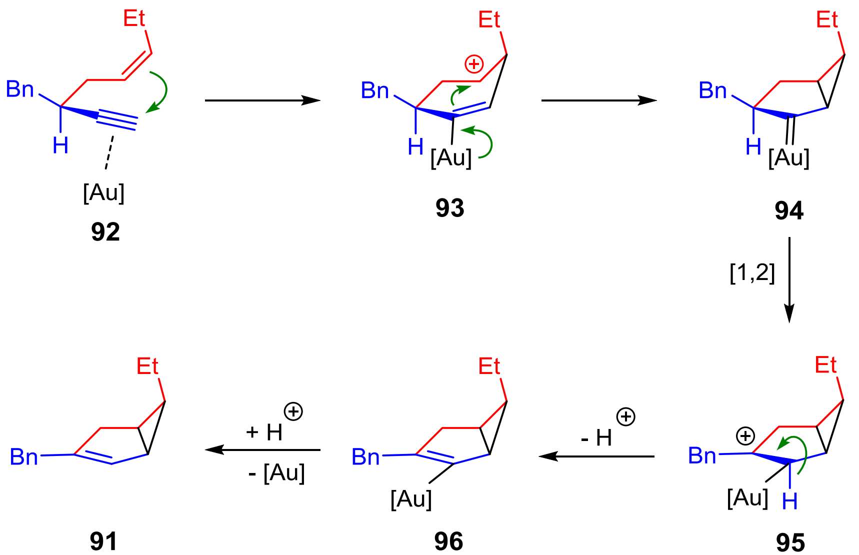
[26] P. Magnus *et al*, *Tetrahedron* **2001**, *57*, 8647
[27] S. G. Nelson *et al*, *J. Am. Chem. Soc.* **2006**, *128*, 10352

„Carbenoid“ Gold catalysis

Gold- catalysed cyclopropanation reaction: [28]



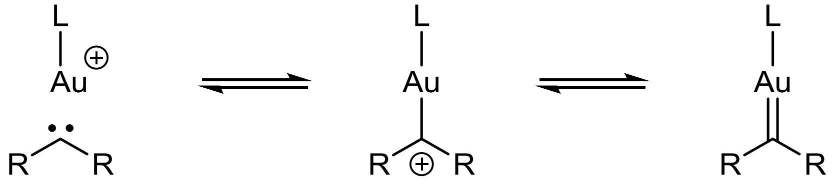
Mechanism:



[28] F. D. Toste *et al*, *J. Am. Chem. Soc.* **2004**, *126*, 10858

„Carbenoid“ Gold catalysis

Bonding Model for Gold(I)- carbene complexes:



Binding order: (**0**) Carbene (**1**) Carbenium (**2**) Back bonding

Natural bond order of Gold(I) carbenes: ≤ 1 [29]

⇒ Weak carbene-metal bonding

⇒ **Reactive gold carbenes composed mainly of π-type bonding** [30]

[29] F. Bernd Straub *et al*, *Angew. Chem.* **2014**, *126*, 9526
[30] F. Dean Toste *et al*, *Nature Chemistry* **2009**, 482

„Carbenoid“ Gold catalysis

Reactivity of Gold(I)- carbene complexes increases:

⇒ By an increase of gold to carbene π-bonding

⇒ And by a decreasing carbon to gold σ-bonding

- Substrate effects:

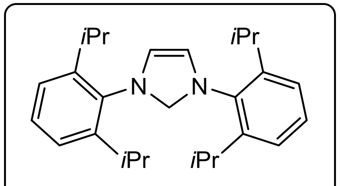
⇒ Heteroatoms or conjugation are stabalising the carbene

- Ligand effects:

⇒ Strong σ- donors are weakening the Au-C bond (*trans*-Effect)

⇒ Weak π-acceptor ligands increasing the Au-C π-bond interaction

N-Heterocyclic **C**arbene (**NHC**)

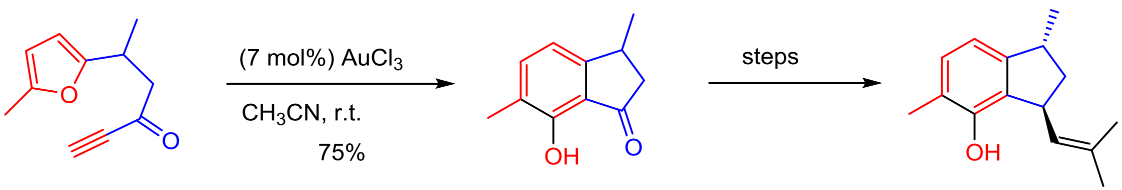


IPr

„Carbenoid“ Gold catalysis

Synthesis of annulated phenols:

- Synthesis of Jungianol
- Isolatet from *Jungia malvaefolia* [31]
- Total synthesis by Stephen Hashmi *et al* [32]



97 **98** Jungianol (**99**)

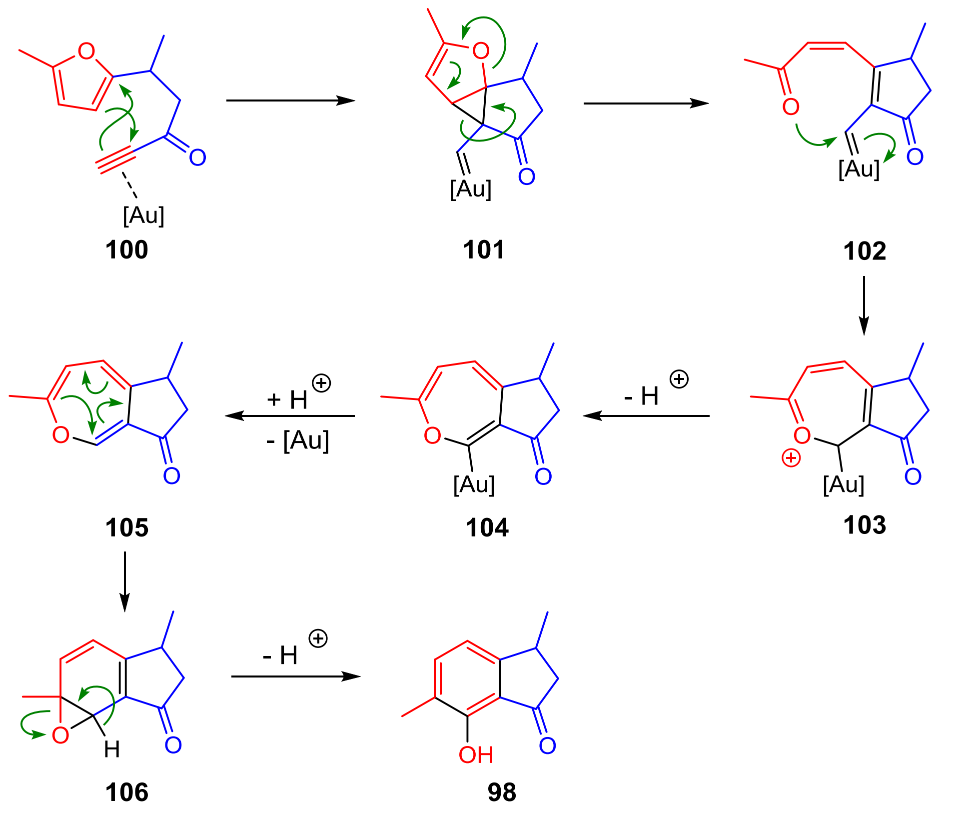
[31] F. Bohlmann, C. Zdero, *Phytochemistry* **1977**, *16*, 239

[32] S. K. Hashmi *et al*, *Chem. Eur. J.* **2003**, *9*, 4339

„Carbenoid“ Gold catalysis

Synthesis of annulated phenols:

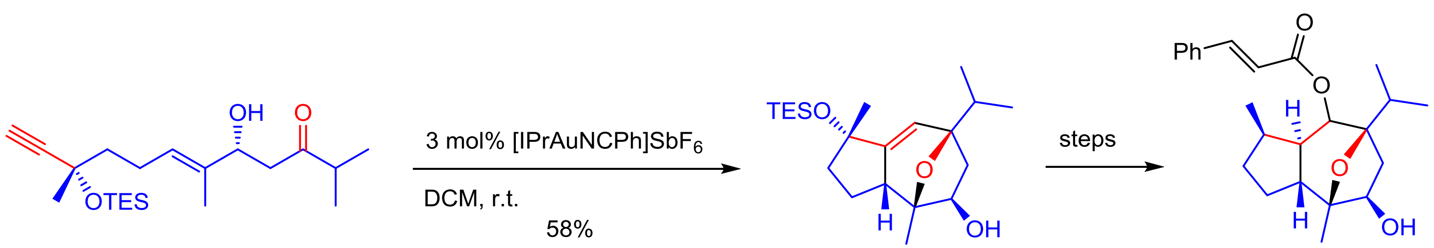
Mechanism:



„Carbenoid“ Gold catalysis

Synthesis of polycyclic systems:

- Synthesis of (–)-Englerine B
- Isolatet from *Phylanthus engleri*
- Total synthesis by Antonio Echavarren *et al* [33]



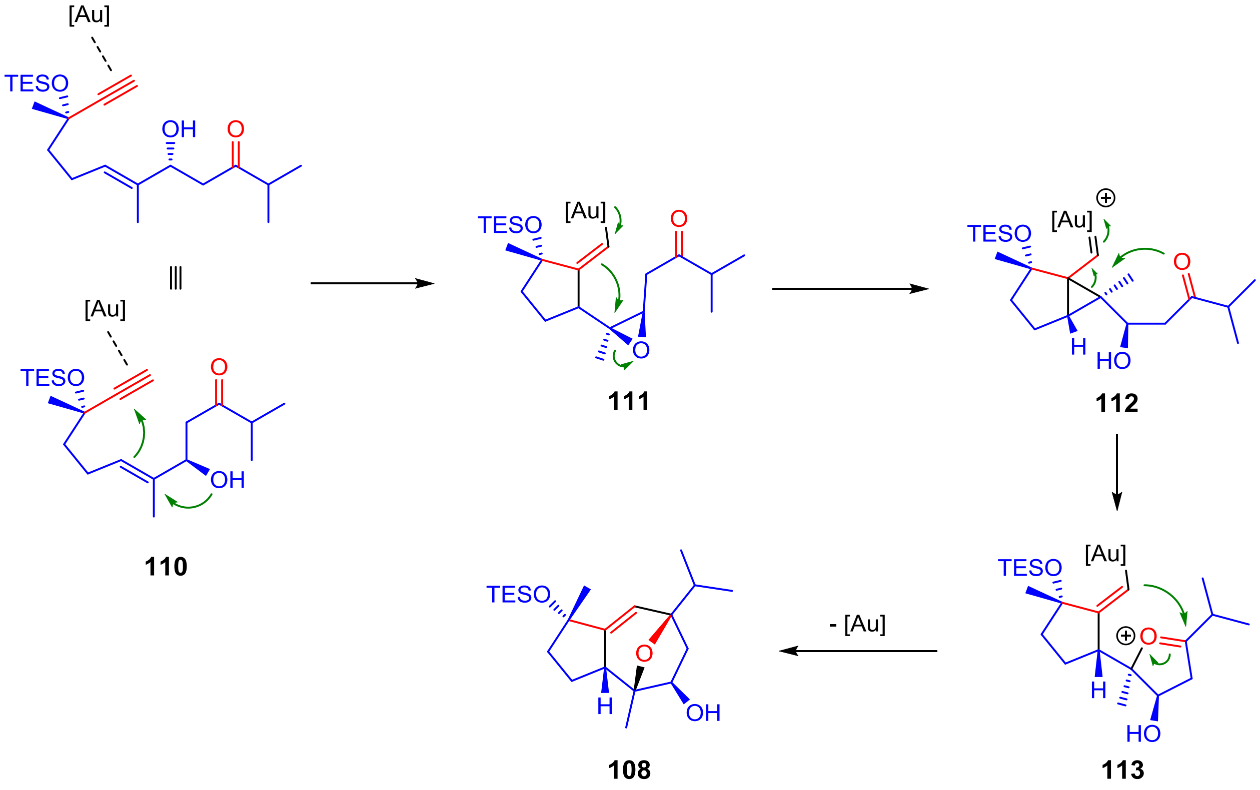
107 **108** (-)-Englerine B (**109**)

[33] A. M. Echavarren *et al*, *Angew. Chem. Int. Ed.*, **2010**, *49*, 3517

„Carbenoid“ Gold catalysis

Synthesis of polycyclic systems:

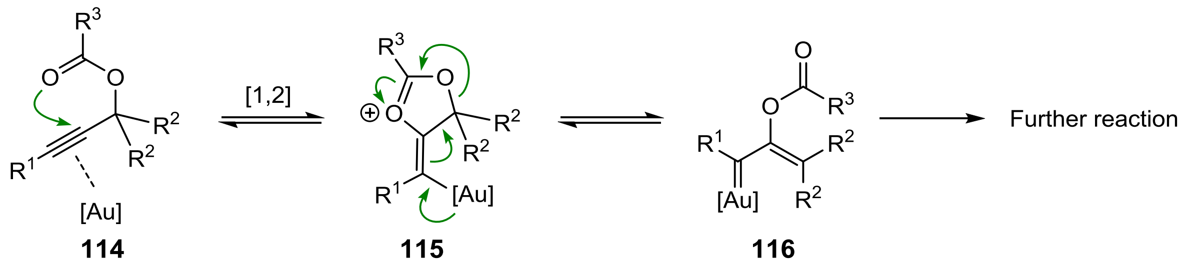
Mechanism:



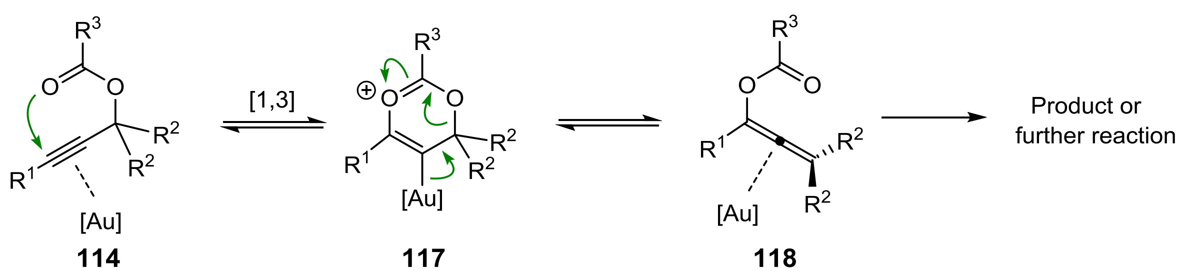
Gold catalysis of propargylic alcohols

Competing Acyloxy- migration mechanisms:

- [1,2]- Migration:



- [1,3]- Migration:



Rule of thumb for Acyloxy migration**:** [34]

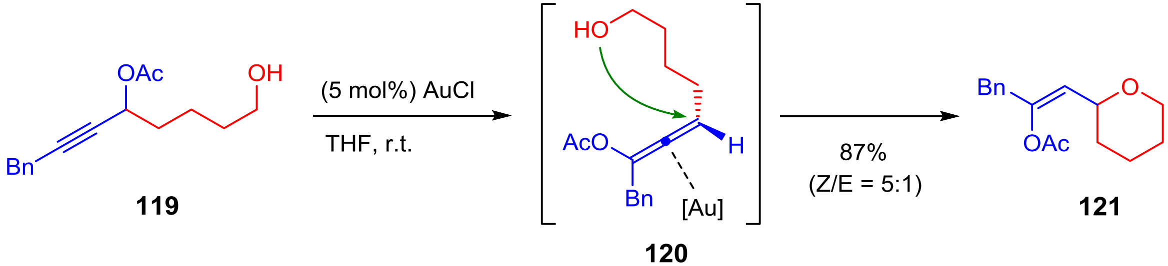
- Sterical and/or ele. balanced moieties (R^1~R^2) undergo [1,3]-M.
- Sterical and/or ele. unbalanced moieties ($R^1 \neq R^2$) undergo [1,2]-M.

[34] S. Wang *et al*, *Synlett* **2010**, *5*, 692

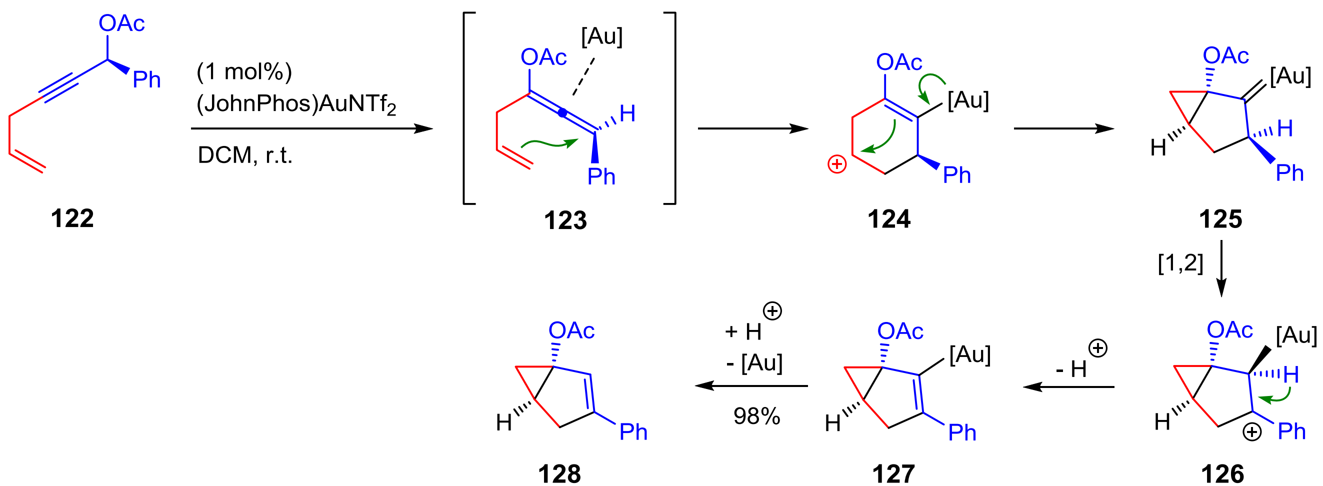
Gold catalysis of propargylic alcohols

Examples for a [1,3]-Acyloxy migration:

- Migration and Nu- addition cascade: [35]



- Migration and cyclopropanation cascade: [36]

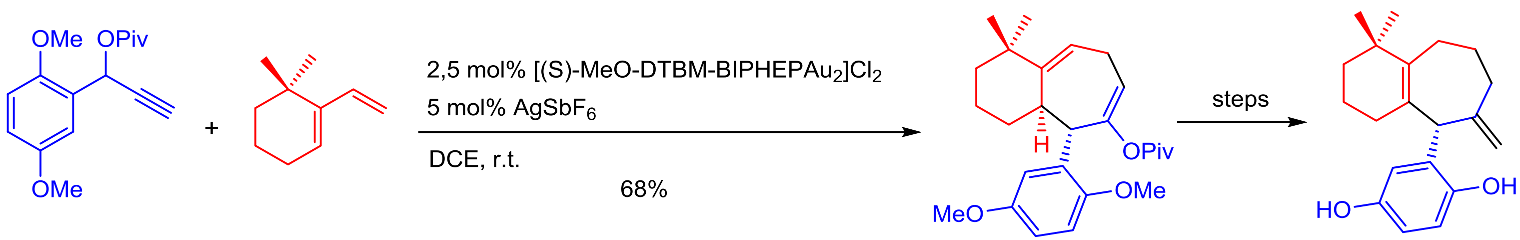


[35] A. Buzas, F. Gagosz, *J. Am. Chem. Soc.* **2006**, *128* , 12614
[36] J. K. Brabander *et al*, *Org. Lett.* **2008**, *10*, 2533

Gold catalysis of propargylic alcohols

Synthesis of 7-membered rings:

- Synthesis of (–)-Frondosin A
- Isolatet from *Dysidea Frondosa* [37]
- Gold catalysed cascade reaktion by Cristina Nevado *et al* [38]



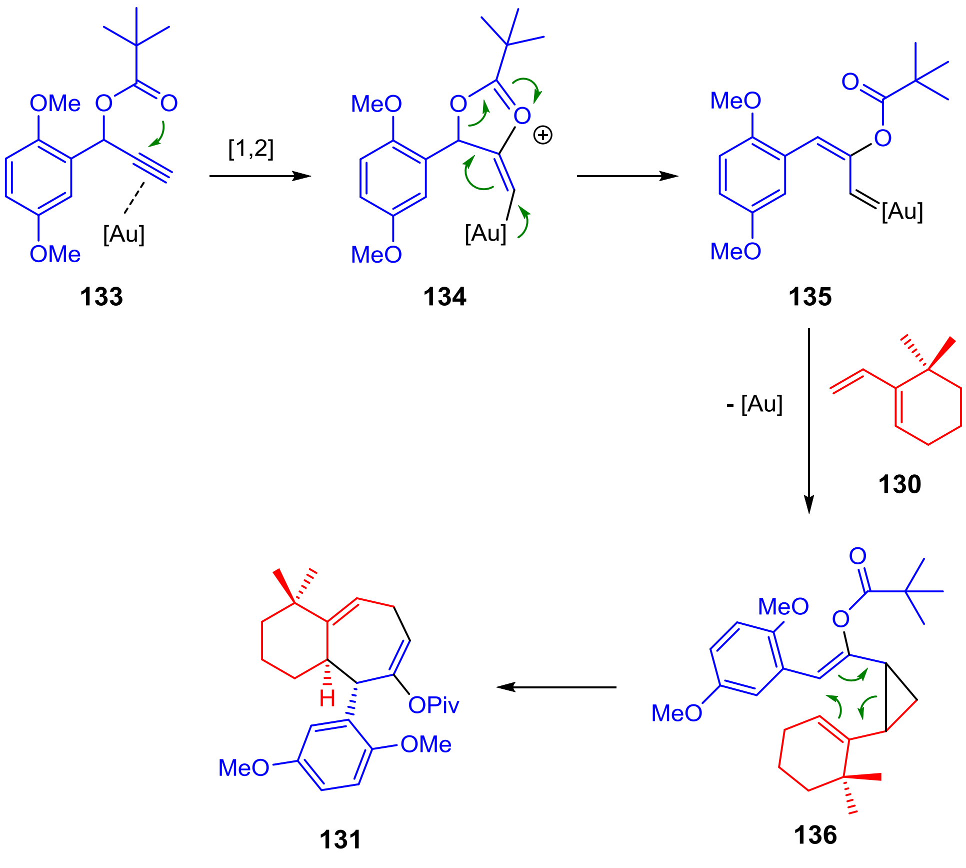
129 **130** **131** (-)-Frondosin A (**132**)

[37] R. K. Johnson *et al*, *Tetrahedron* **1997**, *53*, 5047
[38] C. Nevado *et al*, *Angew. Chem. Int. Ed.* **2011**, *50*, 911

Gold catalysis of propargylic alcohols

Synthesis of 7-membered rings:

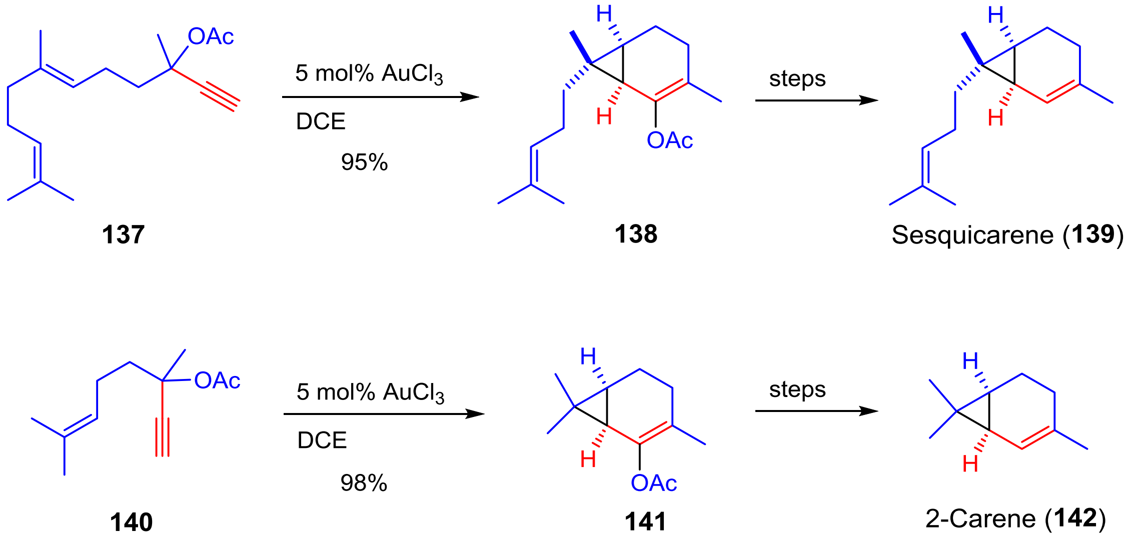
Mechanism:



Gold catalysis of propargylic alcohols

Synthesis of bicyclo [4.1.0] heptan skeletons:

- Synthesis of Carene Terpenoids
- Using propargylic alcohols as α-diazo keton surrogates
- Synthesis by Alois Fürstner *et al* [39]

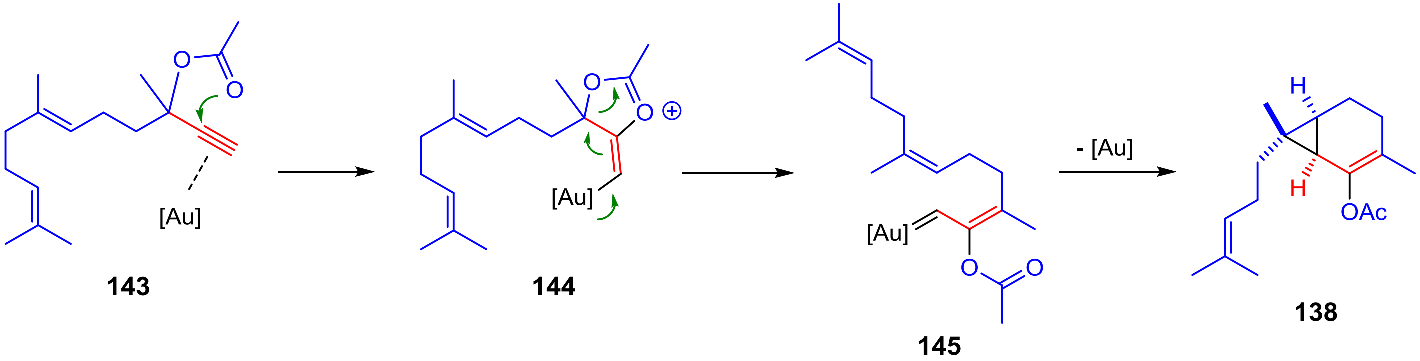


[39] A. Fürstner *et al*, *Chem. Commun.* **2004**, 2546

Gold catalysis of propargylic alcohols

Synthesis of carenes and sesquicarenes:

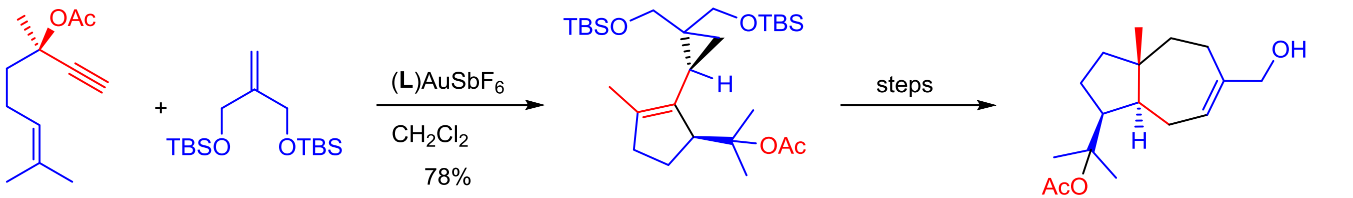
Mechanism:



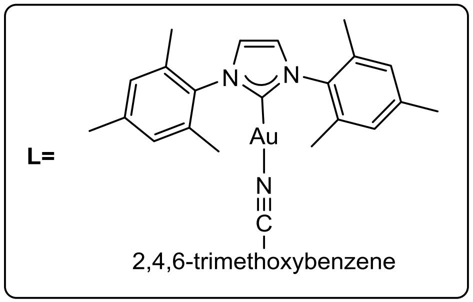
Gold catalysis of propargylic alcohols

Nu- addition, cyclopropanation cascade:

- Synthesis of (+)-Schisanwilsonene A
- Isolatet from *Schisandra wilsoniana* [40]
- Total synthesis by Antonio Echavarren *et al* [41]



140 **146** **147** (+)-Schisanwilsonene A (**148**)



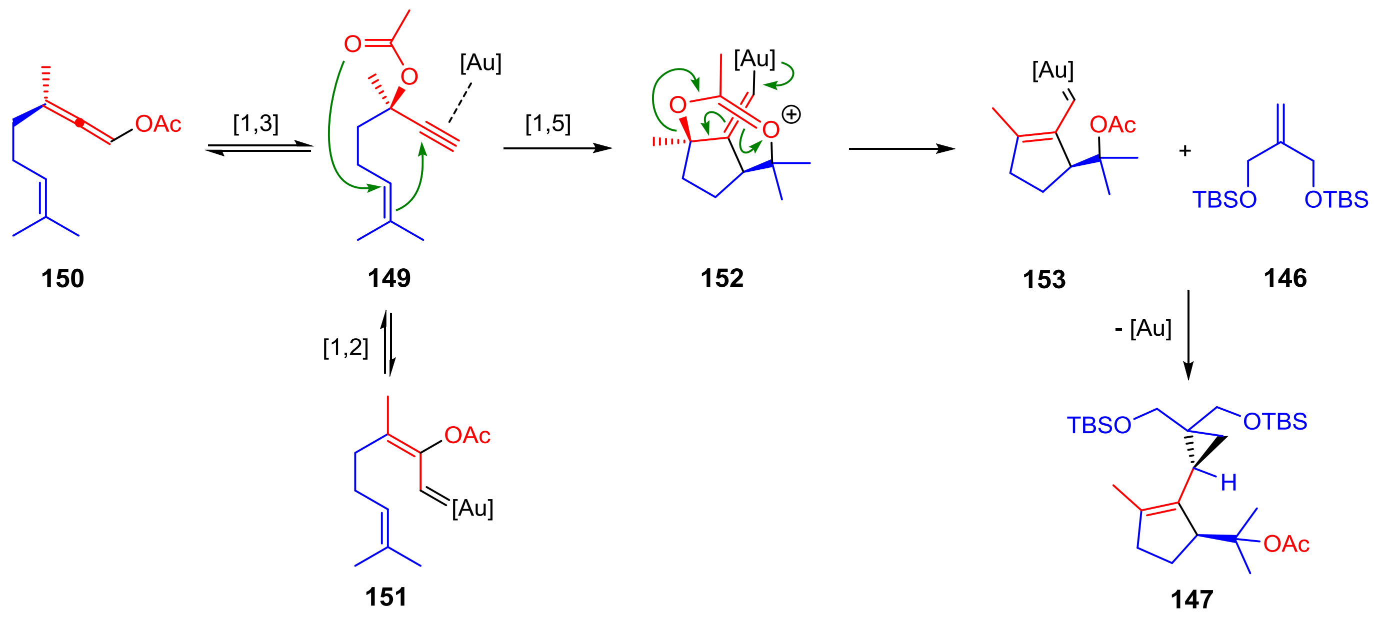
[40] W.-H. Ma, H. Huang, *J. Nat. Prod*. **2009**, *72*, 676

[41] A. M. Echavarren *et al*, *Angew. Chem. Int. Ed.* **2013**, *52*, 6396

Gold catalysis of propargylic alcohols

Nu- addition, cyclopropanation cascade:

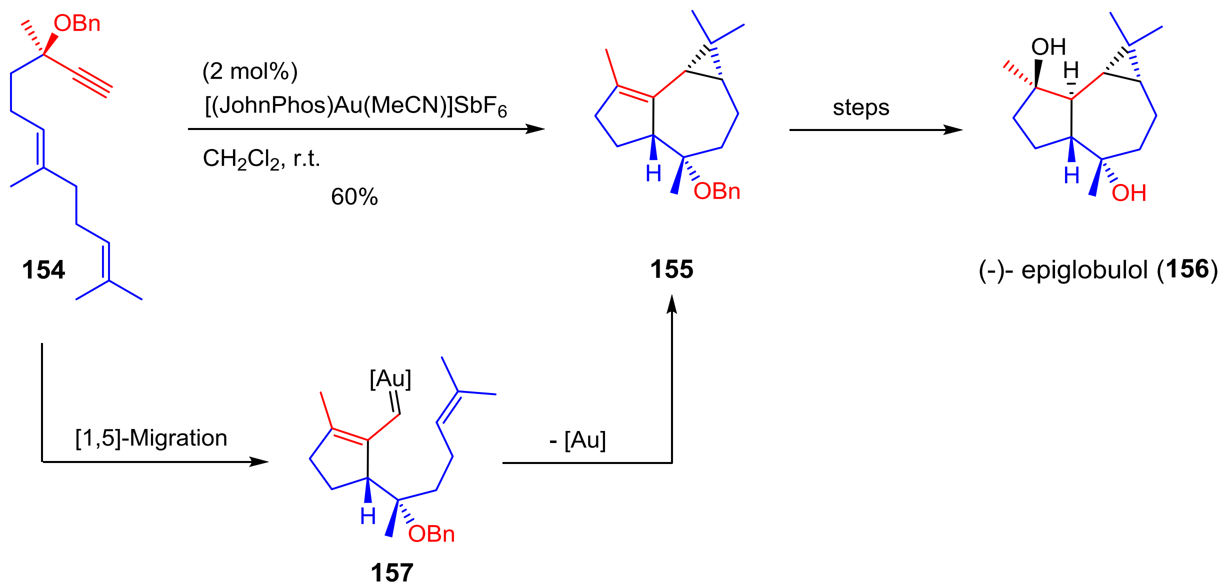
Mechanism:



Gold catalysis of propargylic alcohols

Nu- addition, cyclopropanation cascade:

- Synthesis of (-)-epiglobulol
- Isolatet from *Eucaliptus* trees [42]
- Total synthesis by Antonio Echavarren *et al* [43]



[42] H. J. M. Gijsen *et al*, *Prog. Chem. Org. Nat. Prod.* **1995**, *64*, 149
[43] A. M. Echavarren *et al*, *Angew. Chem. Int. Ed.* **2013**, *52*, 6396