UNIVERSITY OF OXFORD

Gold-catalysis:

Applications to Natural Product Synthesis

Steve Mansfield
16/03/17

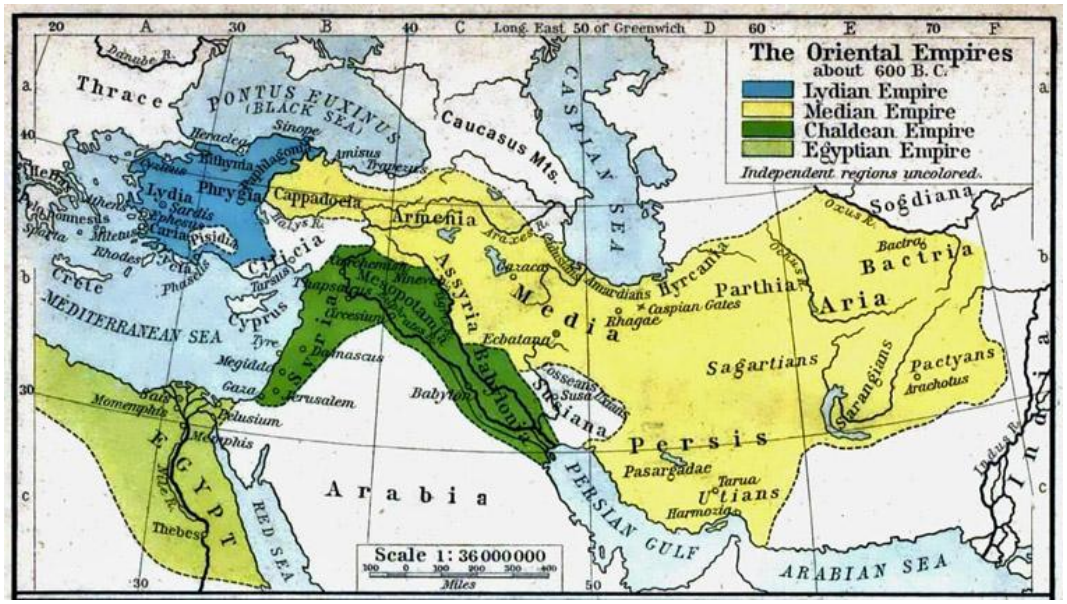
SBM

Lure, Lore of Gold

Aurum (latin) means "shining dawn", relating to the Goddess of dawn, Aurora.

Recorded discovery circa 6000 B.C. Used by pharaohs and temple priests in ancient Egypt circa 3000 B.C. Became a symbol of immortality and power due to its rarity and aesthetics.

Archaeologists found natural gold in Spanish caves used by Paleolithic Man circa 40,000 B.C.



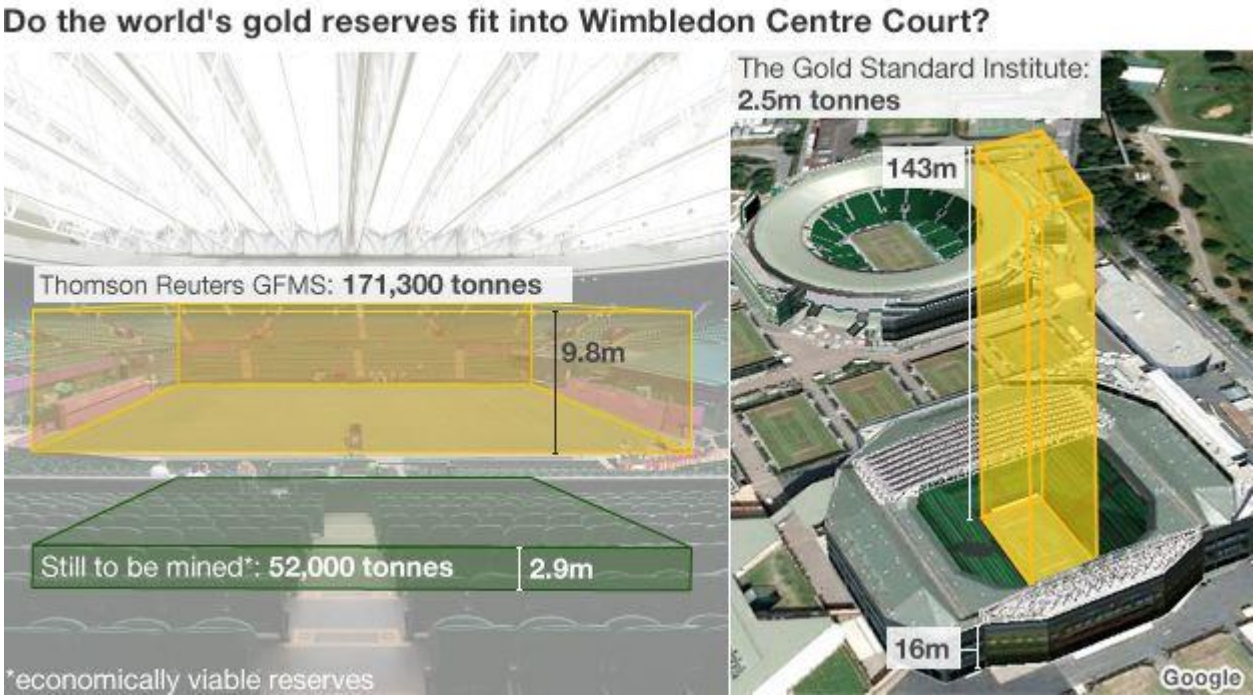
First use of gold as money in 700 B.C. is claimed by the citizens of the Kingdom of Lydia.

Egyptians produced the first known currency exchange rate which mandated 1 piece of gold is equal to 2.5 parts of silver. Also the first recorded valuation of silver to be lower than that of gold.

Lure, Lore of Gold

Natural abundance in Earth's crust only 0.004pm (cf. Cu 68 ppm, Ag 0.08 pm)

World's holdings accumulated during all recorded history to present is estimated to be between 171,000 and 2.5 million tonnes. This has a value between 8.8 and 124 trillion US dollars.



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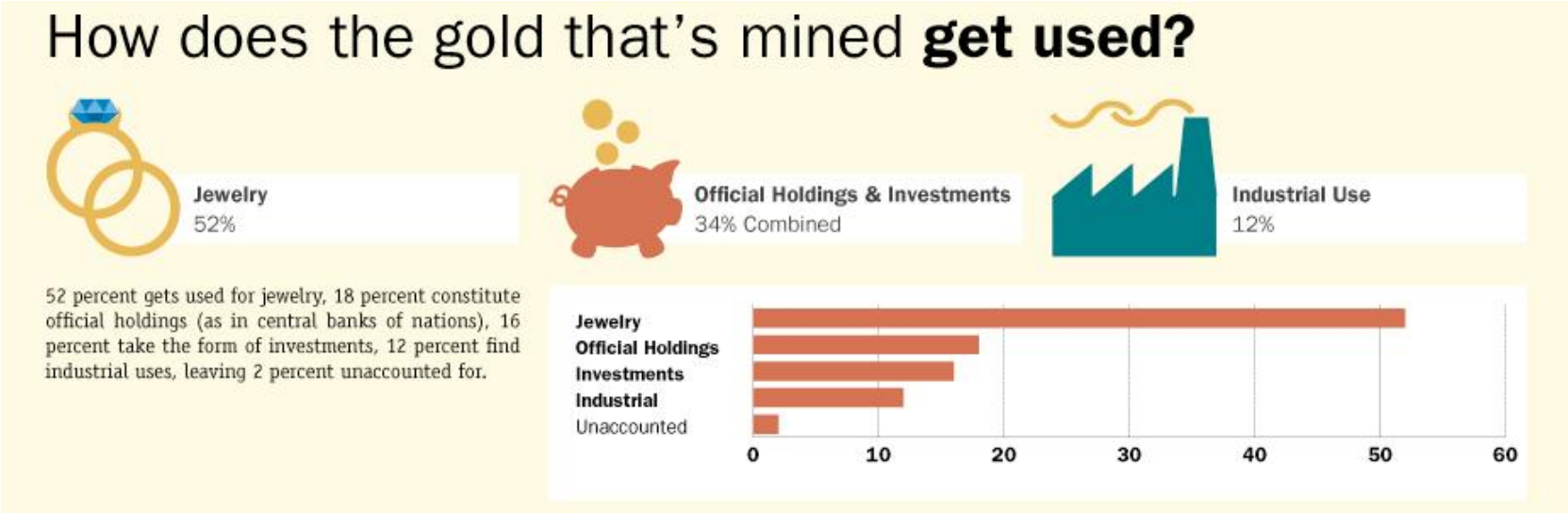


An Inorganic Introduction

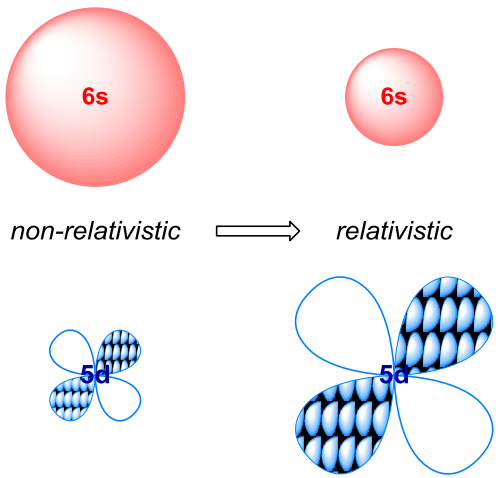
Relativistic effects: relevant when considering velocity as significant relative to the speed of light:

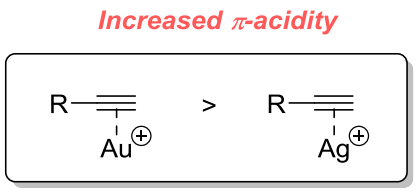
$$m = m_0 / \sqrt{(1-(v/c)^2}$$

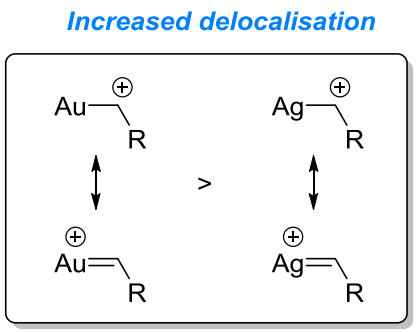
Relativistic mass increases as $v \rightarrow c$

Bohr radius decreases: $a_0 = 137\hbar / mc$

Consequences:







-Contracted 6s/6p => increased shielding of 5d.
-Greater electronegativity of Au, small ionic radii. r(Au)$^+$ = 125 pm, r(Ag)$^+$ = 133pm.
-Leads to greater lewis acidity, poorer nucleophilicity. Stronger M-L bonds.
-Destabilisation 5d => easier formation of Au(III). Stabilisation of 6s explains Au(-I)

Toste *et al*, Nature, **2007**, *446*, 395

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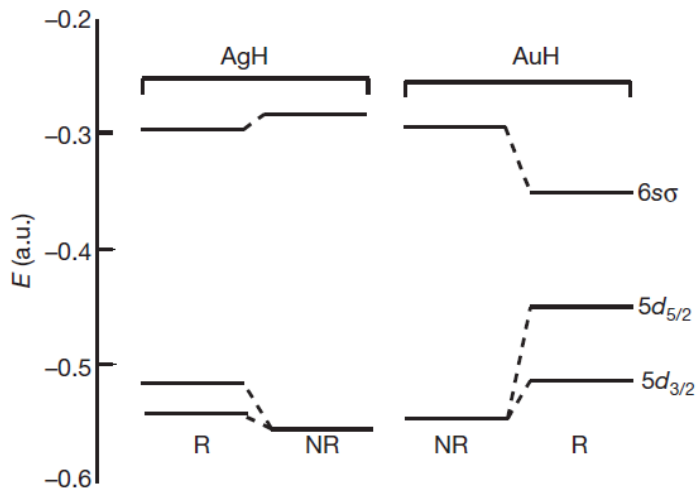

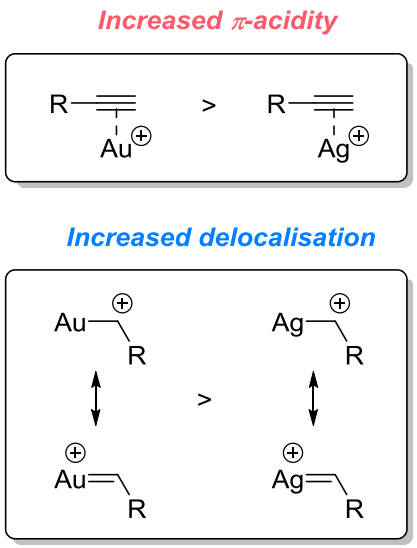

-Au(I) complexes tend to be linear due to significant 6s/6p contribution to bonding (3c4e).
-Au(III) complexes adopt square planar arrangements as expected for d^8.
-"Bending energy" renders Au(I)/Au(III) redox-cycles difficult.

Toste *et al*, Nature, **2007**, *446*, 395

An Inorganic Introduction

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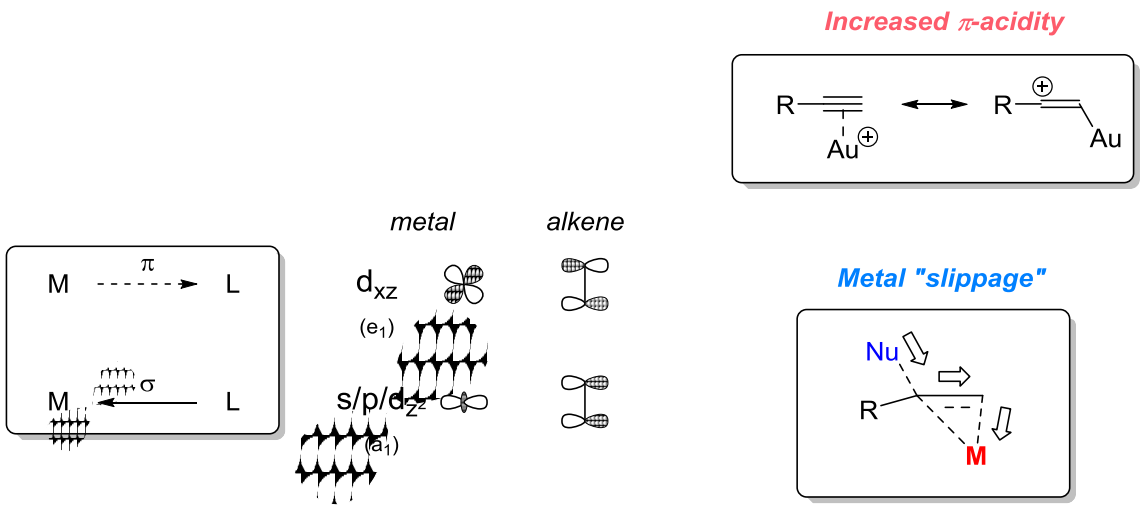


- More electron density is lost than is gained. Increases the electrophilicity of bound ligands.
- Over half the bonding force is electrostatic in nature.

Toste *et al*, Nature, **2007**, *446*, 395

An Inorganic Introduction

A note on catalysts:

-Gold catalysts range from simple halides of Au(I) and Au(III), to cationic catalysts typically employing phosphine or NHC ligands.

-Au(I) complexes are soft, Au(III) complexes are hard.

-A consequence of linearity of neutral Au(I) is the requirement to activate by ligand abstraction (AgX for halide, HBF_4 for LAuMe complex). Difficult to chelate bidentate ligands to a single gold atom – difficult to induce asymmetry in transformations.

-Redox stability => air compatible, operationally simple and practical to use.

-Price per gram of metal (as of 10th March 2017):

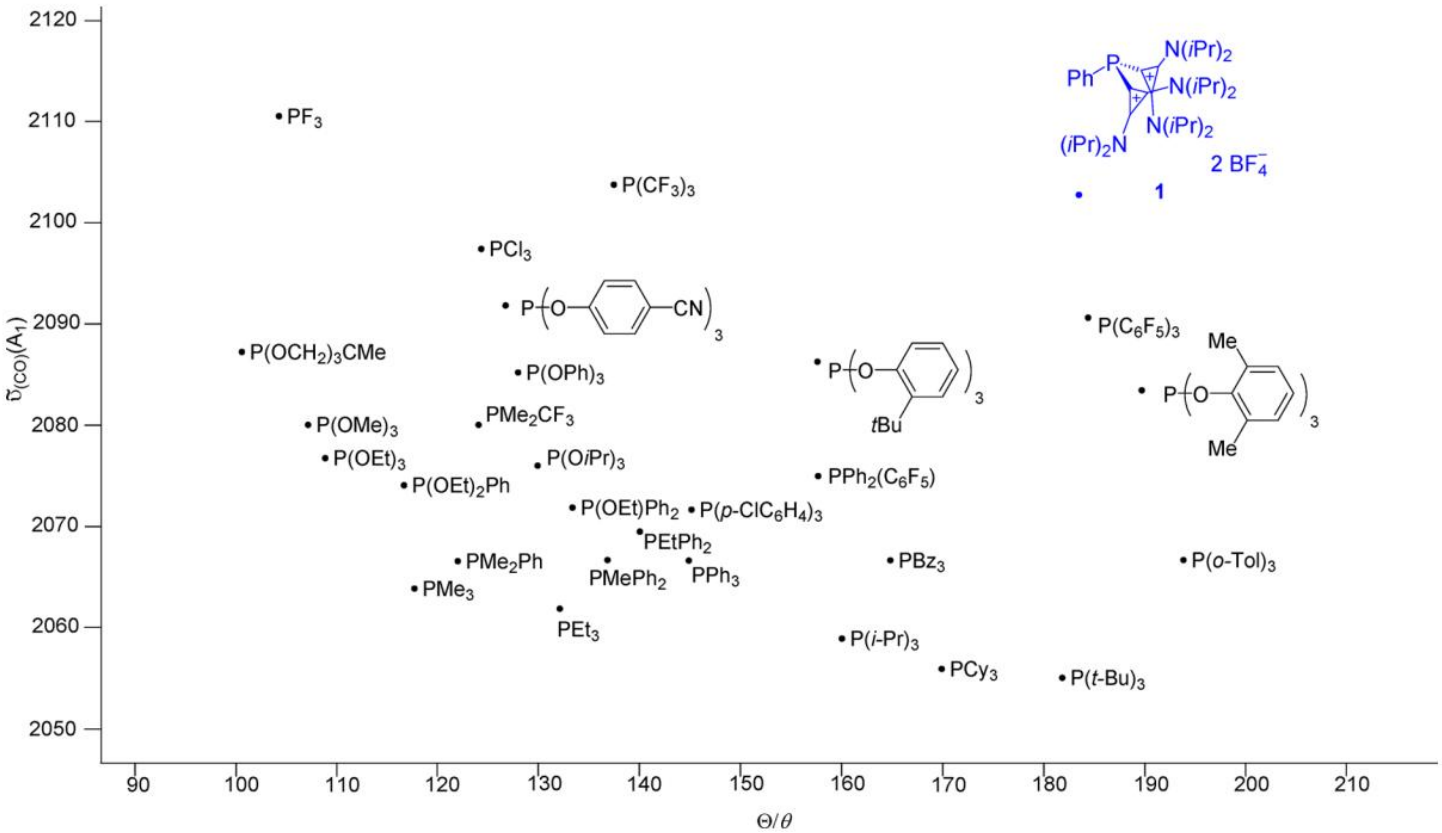
Au: £31.80
Pt: £24.90
Rh: £24.71
Ir: £20.06
Pd: £19.88
Ru: £1.06
Ag: £0.45

Despite metal prices, Rh, Ir, Pd catalysts are generally more expensive (fancy ligands are expensive).

Echavarren *et al*, Org. Biomol. Chem., **2015**, *13*, 7103

An Inorganic Introduction

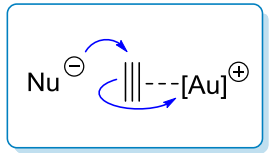
Phosphine ligand tuning: Tolman stereoelectronic map



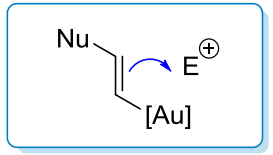
NHCs are stronger σ-donors and weaker π-acceptors than phosphines. Thus a given metal will be more electron rich as a NHC-metal complex as compared to the corresponding phosphine complex.

Tolman, Chem. Rev. **1977**, *77*, 313
Dutton *et al*, Inorg. Chem., **2012**, *51*, 7657
Alcarazo *et al*, J. Am. Chem. Soc., **2013**, *135*, 18815

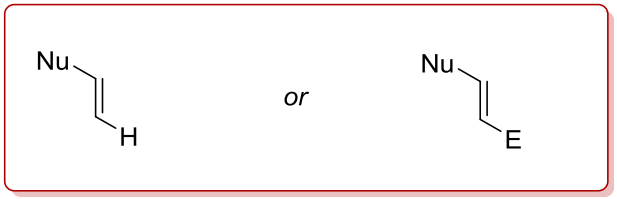
Modes of Reactivity



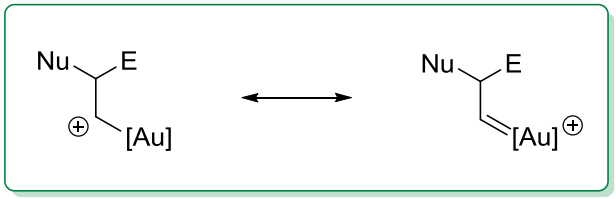
trans-addition



Deauration



Au backbonding



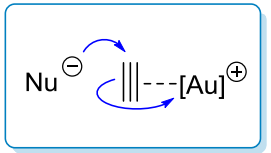
Lewis acid-derived products

Hydroamination/alkoxylation,
Hydroacyloxylation,
Ketalisation,
Carbocylisation

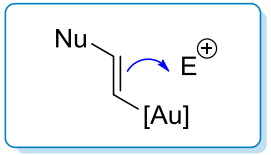
Carbene–derived products

Cyclisations/rearrangements,
C-H insertion, cyclopropanation

Modes of Reactivity



trans-addition



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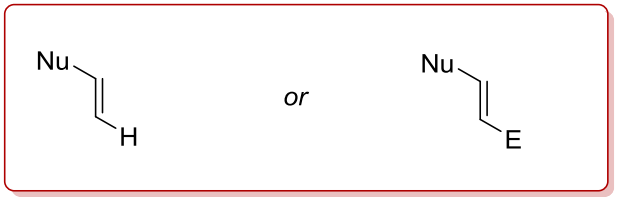

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Hydroamination/alkoxylation,
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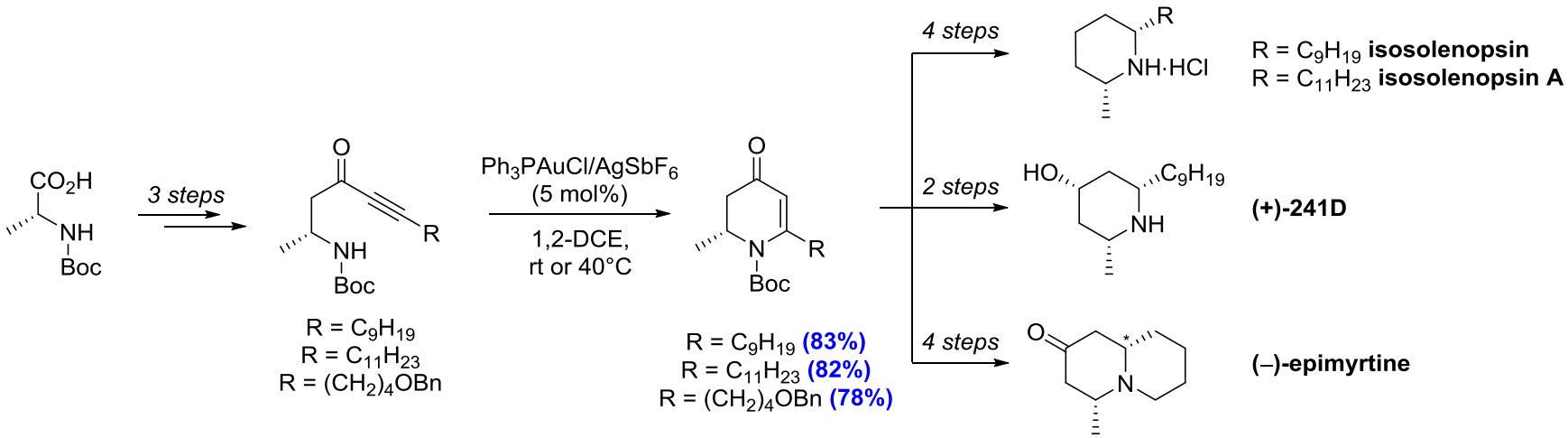
Heterofunctionalisation

Hydroamination and the synthesis of alkaloids – death and delight!

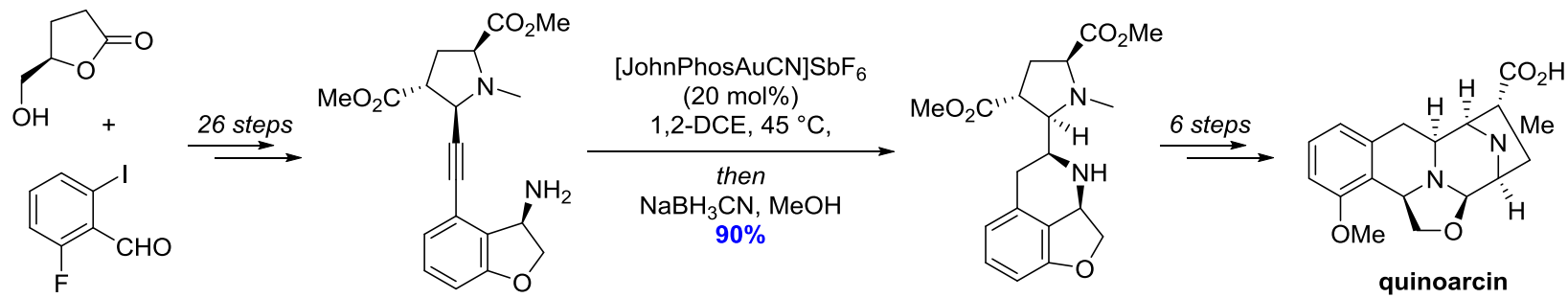
Solenopsins = fire ant venom.
241D = poison frog toxin.
Myrtine/epimyrtine = potential anticancer, antibacterial, antiviral and anti-inflammation.

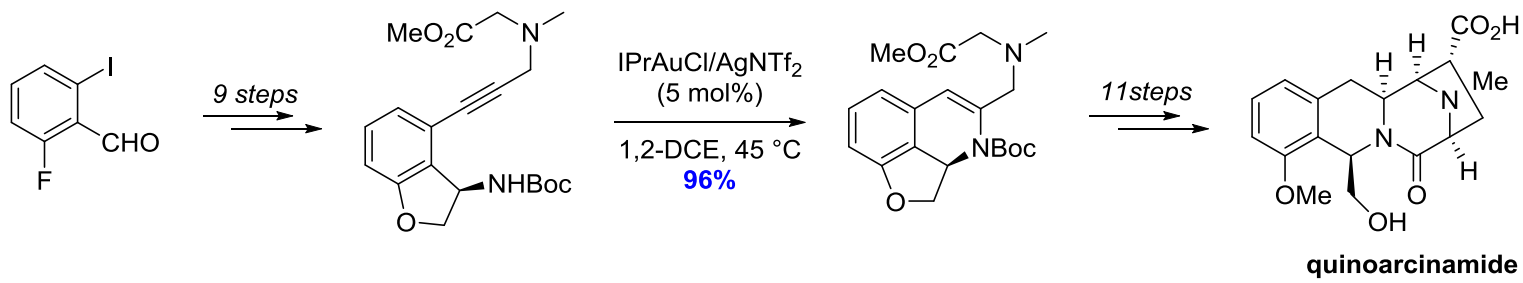


Hootelé et al, Tetrahedron Lett., **1978**, *19*, 397
Daly *et al*, J. Nat. Prod., **1988**, *51*, 1188
Braekman *et al*, Org. Prep. Proced. Int., **1996**, *28*, 499
Gouault *et al*, Org. Biomol. Chem., **2012**, *10*, 5541
Gouault *et al,* Beilstein J. Org. Chem., **2013**, *9*, 2042

Hydroamination:

Potent broad-spectrum antitumor activity.



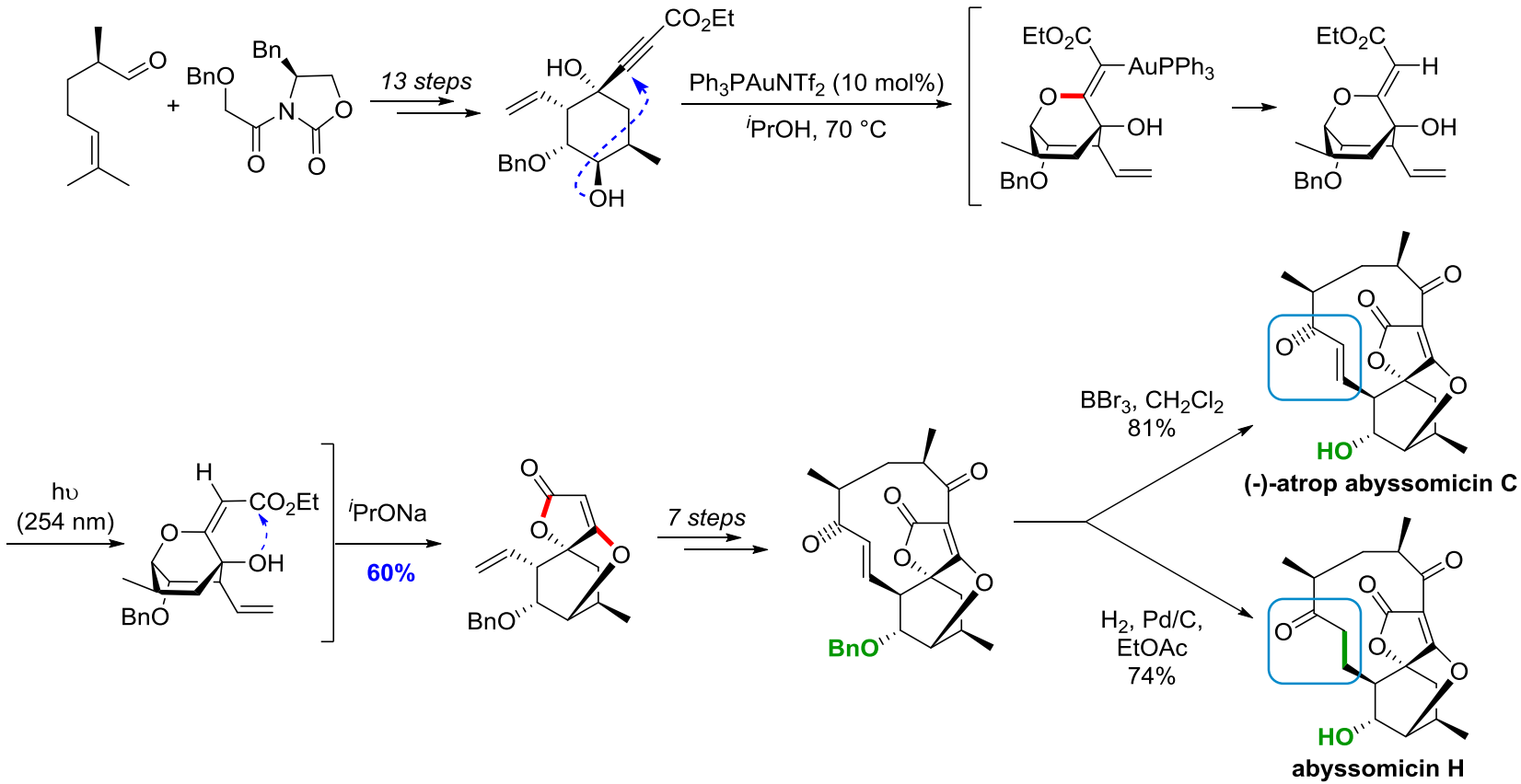


Williams *et al*, J. Org. Chem., **1995**, *60*, 6791
Ohno *et al,* Angew. Chem. Int. Ed. **2012**, *51*, 9169
Ohno *et al*, Tetrahedron Lett., **2012**, *53*, 6273

Heterofunctionalisation

Hydroalkoxylation:

Abyssomicins show antibacterial activity.

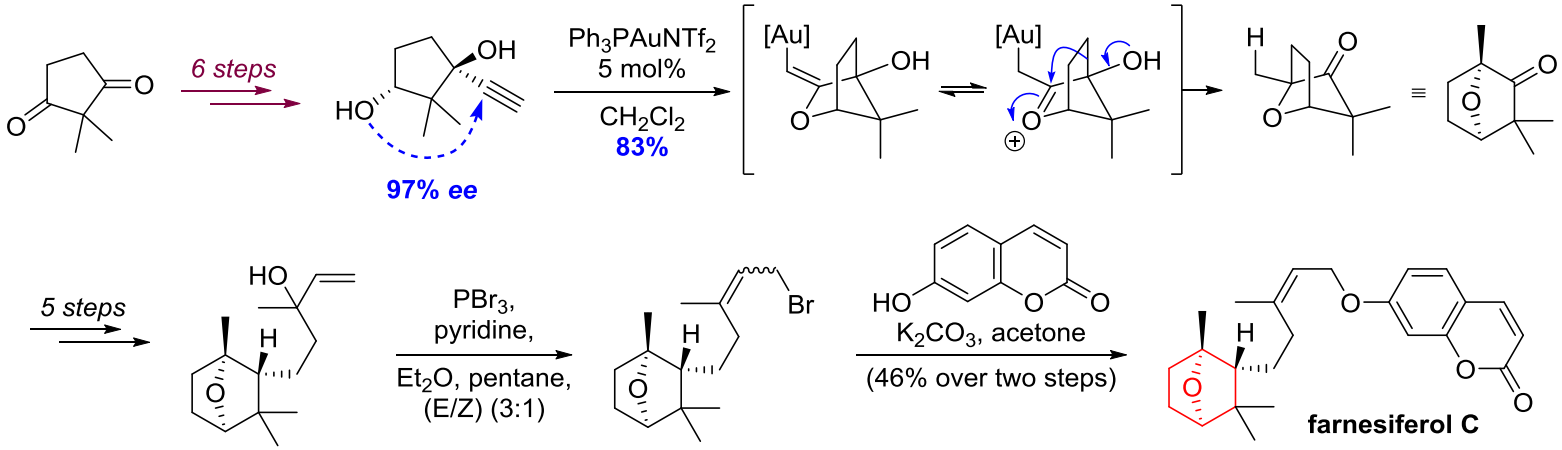


Saicic *et al*, Org. Biomol. Chem., **2013**, *11*, 5413
Saicic *et al* , Angew. Chem., Int. Ed., **2012**, *51*, 5687

Heterofunctionalisation

Hydroalkoxylation:

Farnesiferol C and cortistatins show anti-angiogenesis and antitumor activity.



Yang *et al*, Adv. Synth. Catal., **2016**, *358*, 1392
Yang *et al*, Nat. Commun., **2015**, *6*, 8617

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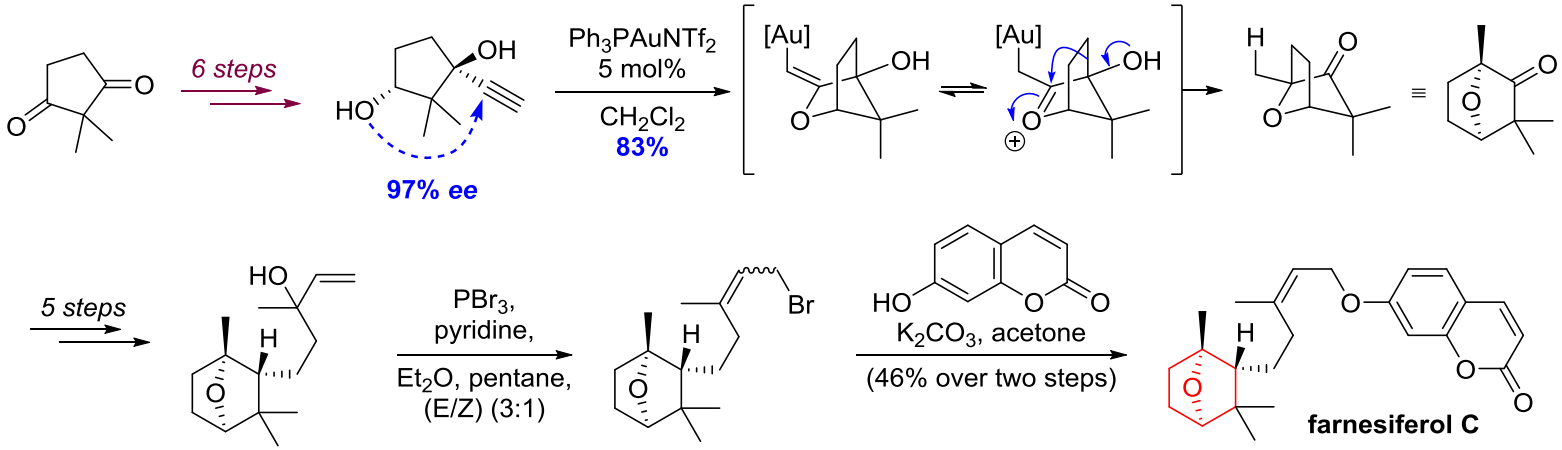
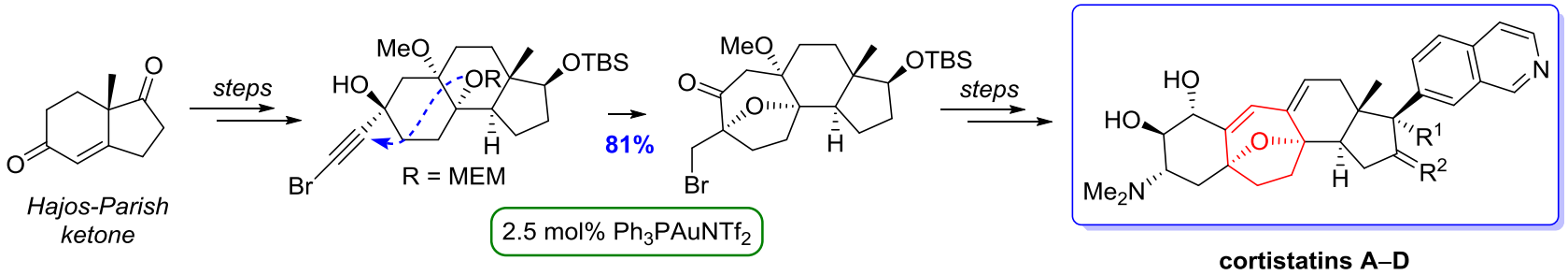




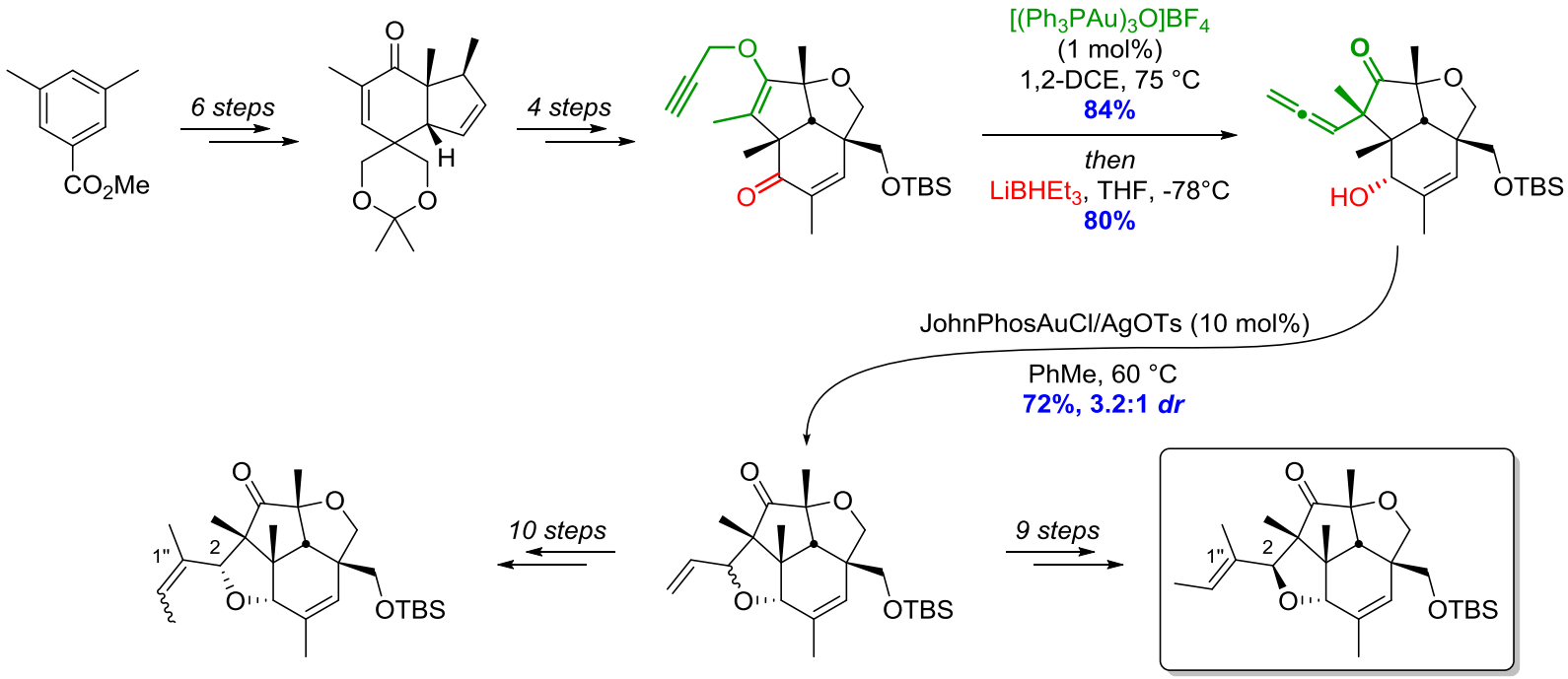
cortistatins A–D

Yang *et al*, Adv. Synth. Catal., **2016**, *358*, 1392
Yang *et al*, Nat. Commun., **2015**, *6*, 8617

Heterofunctionalisation

Saucy-Marbet/ Hydroalkoxylation :

Indoxamycin shows antitumor activity.

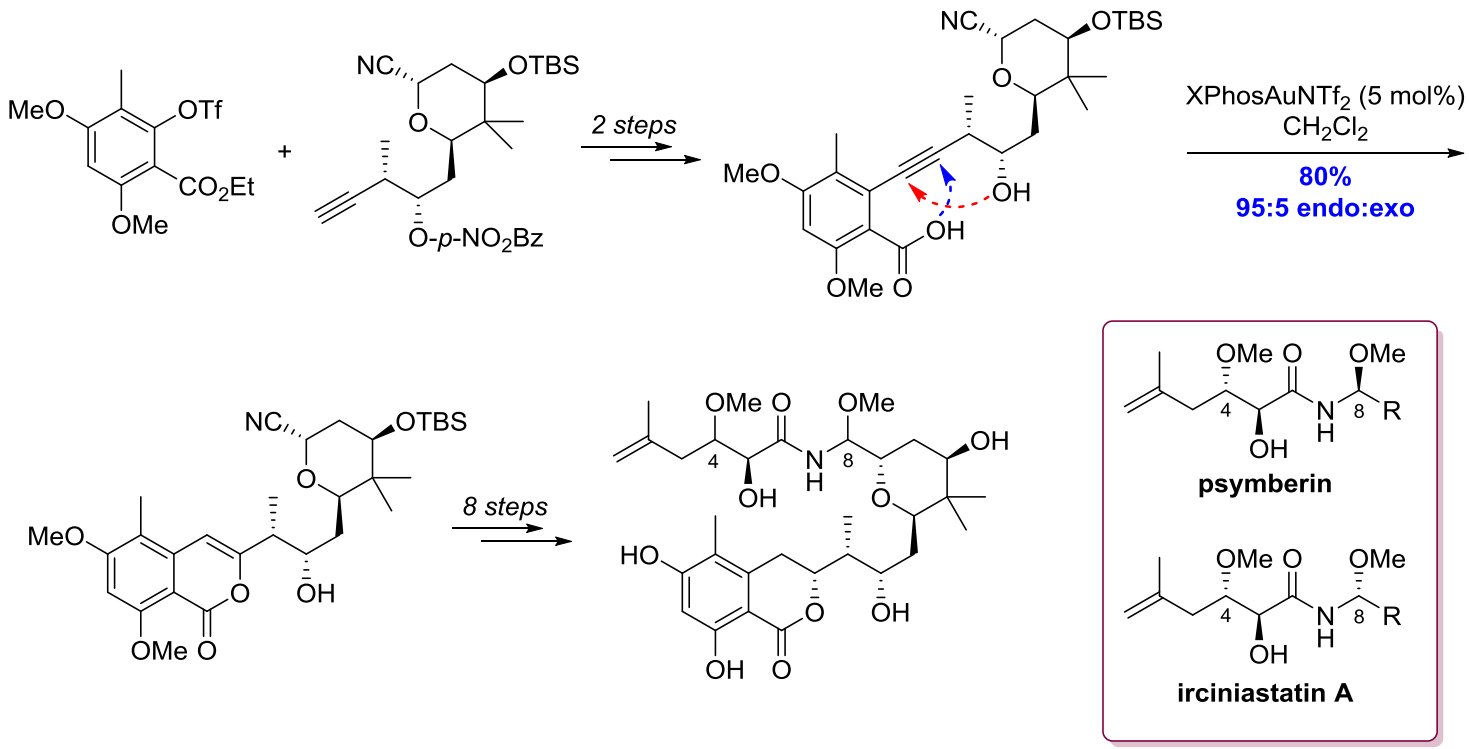


Carreira *et al*, Angew. Chem., Int. Ed., **2012**, *51*, 3474

Heterofunctionalisation

Hydroacyloxylation:

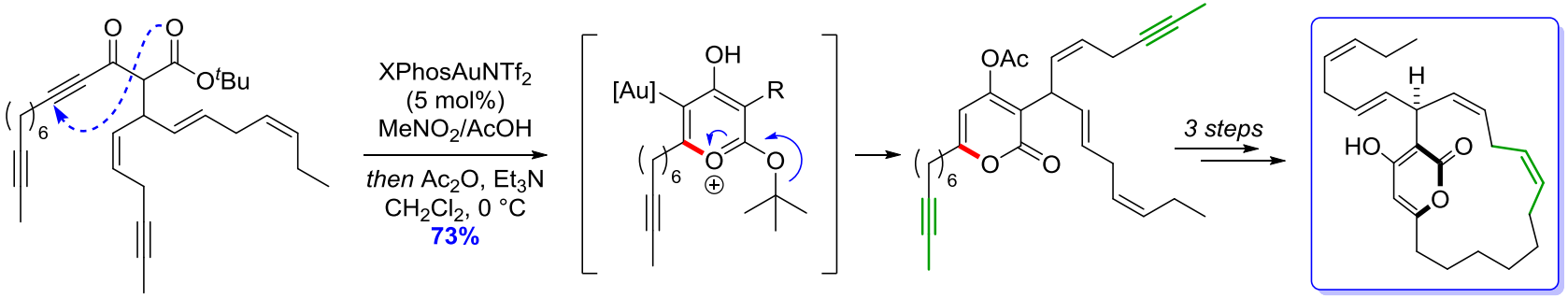
Psymberin and irciniastatin are cytotoxins – determination of C4 and C8 stereochemestry.

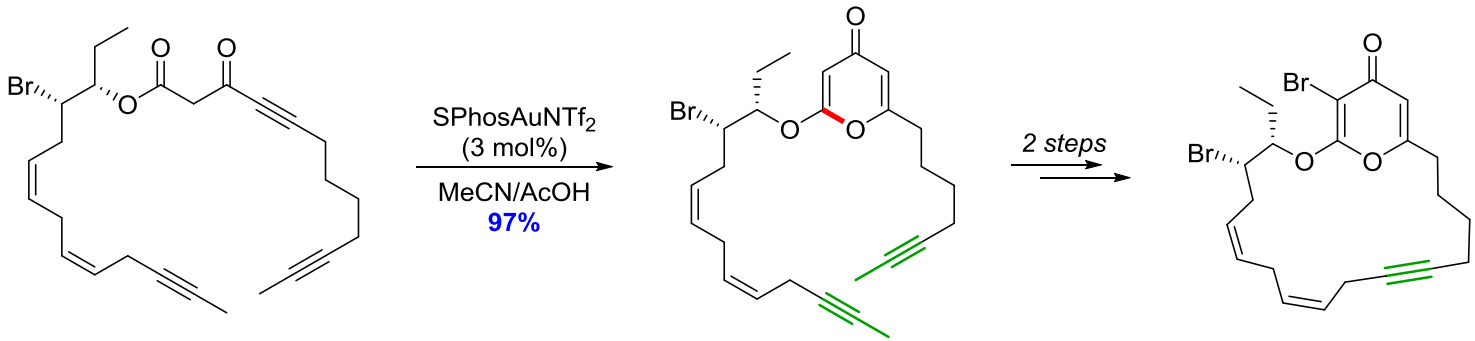


Brabander *et al*, J. Am. Chem. Soc., **2012**, *134*, 17083

Hydroacyloxylation:

Neurymenolide A shows appreciable antibacterial activity against methicillin and vancomycin resistant bacteria.





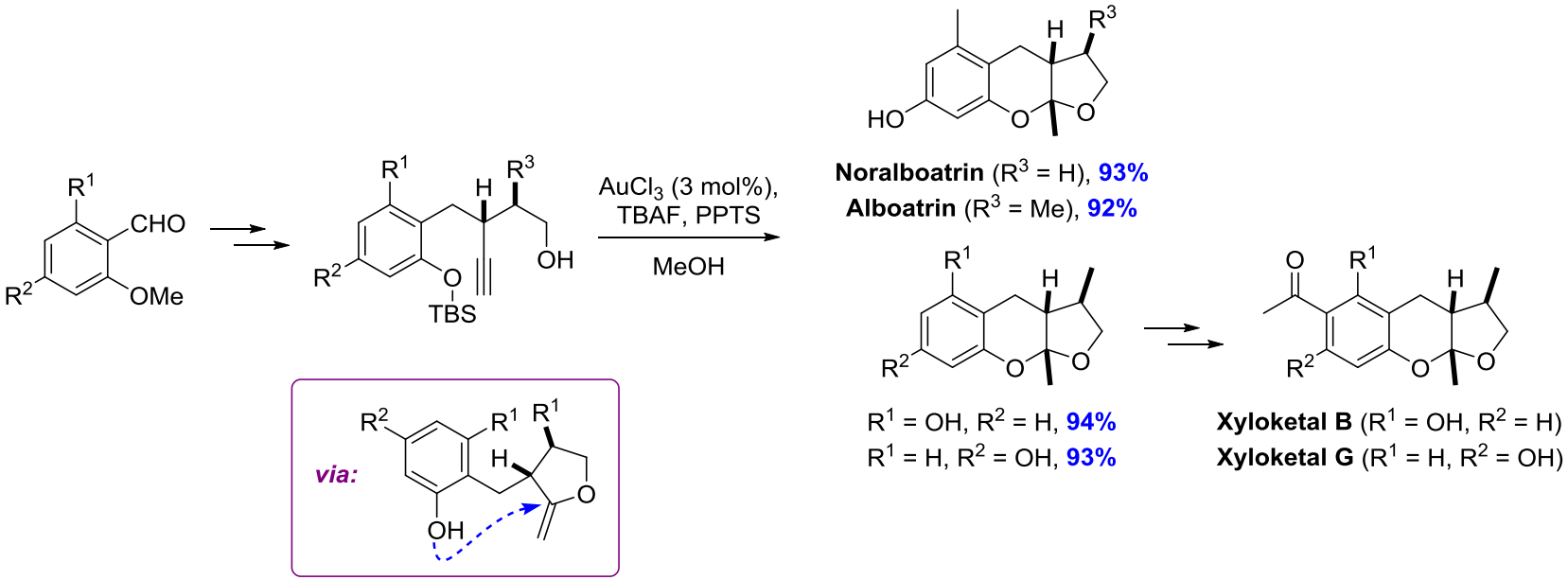
***Phacelocarpus labillardieri* metabolite**

Fürstner *et al*, Angew. Chem., Int. Ed., **2012**, *51*, 6929
Fürstner *et al*, Chem. Eur. J., **2015**, *21*, 4529

Heterofunctionalisation

Ketalisation:

Xyloketals are potential lead compounds for neurological disorders such as Alzheimers disease. Alboatrin demonstrates herbicidal properties.

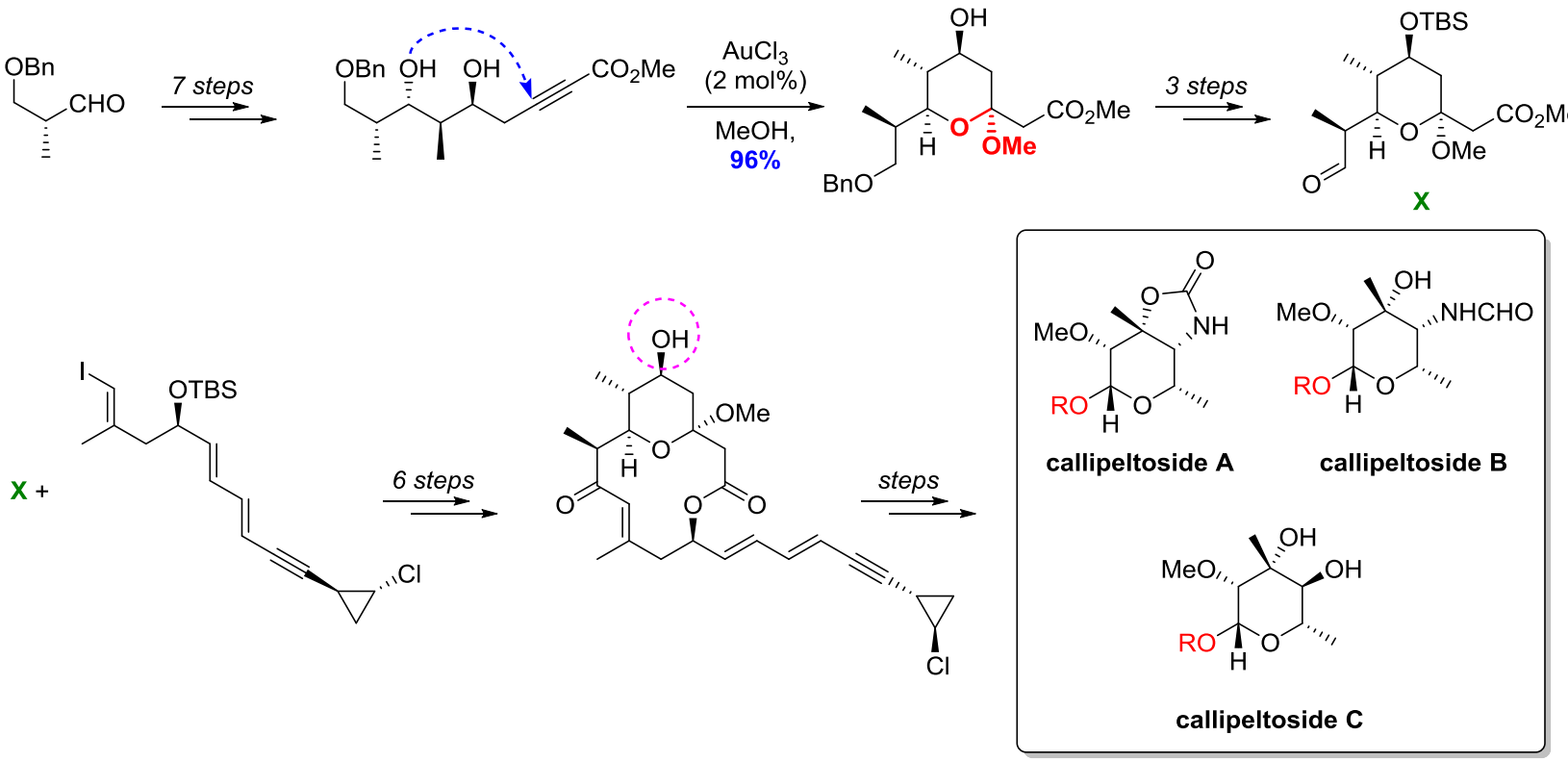


Sarkar *et al*, J. Org. Chem., **2013**, *78*, 2413

Heterofunctionalisation

Ketalisation:

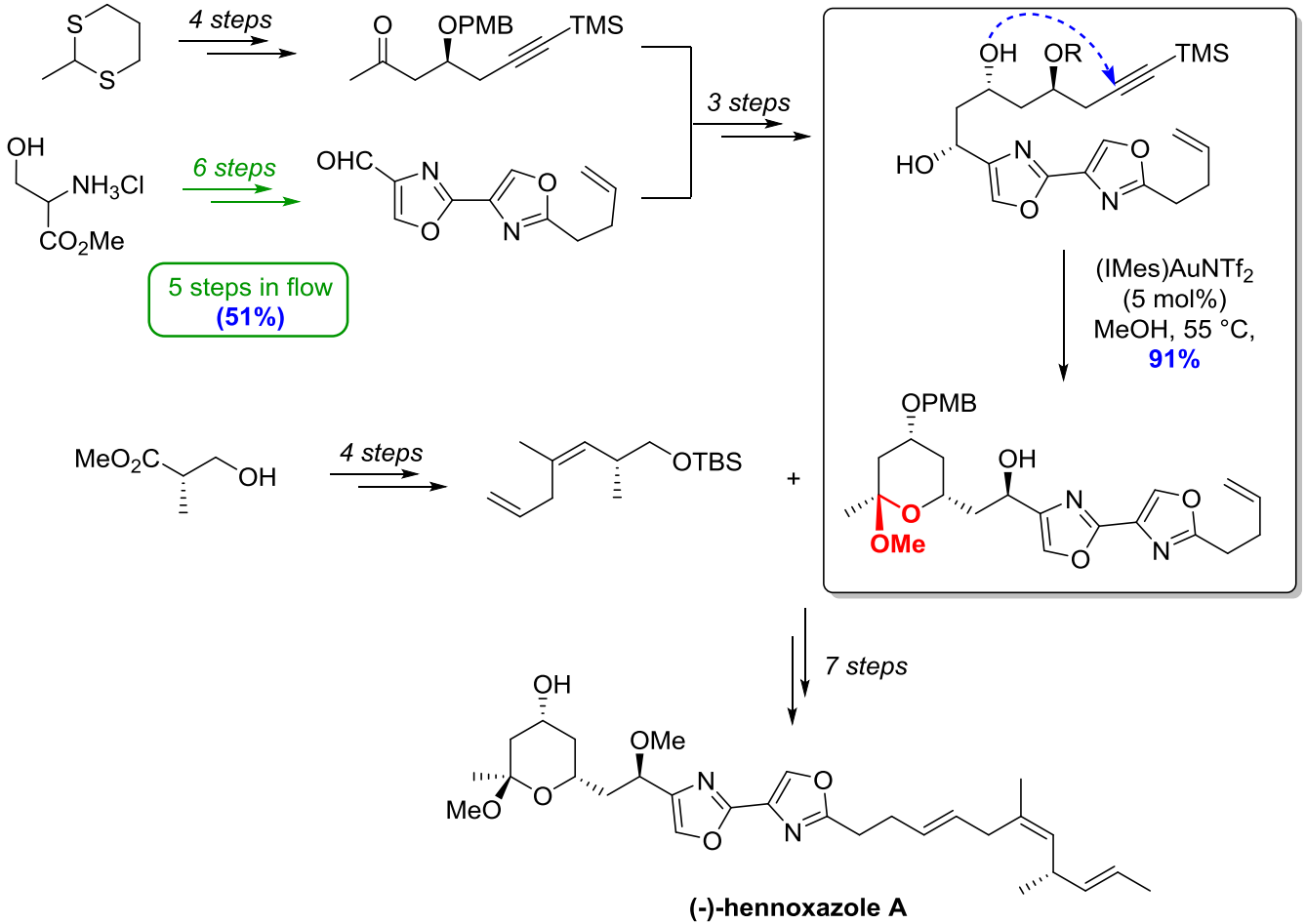
Callipeltosides exhibit moderate cytotoxicity.



Ley *et al*, Angew. Chem. Int. Ed. **2012**, *51*, 9366

Heterofunctionalisation

Integrating batch and flow chemistry methods:

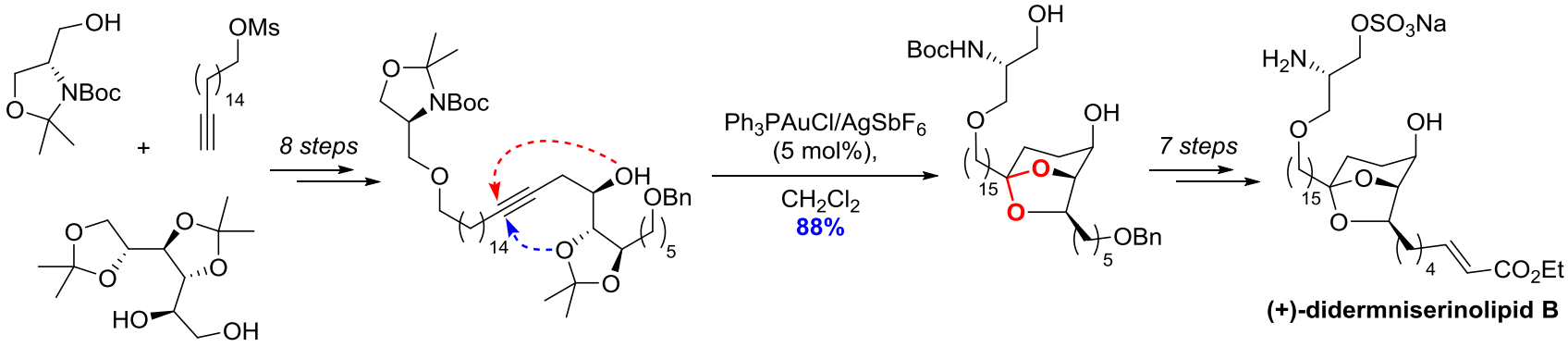


Ley *et al*, Synlett, **2013**, 514

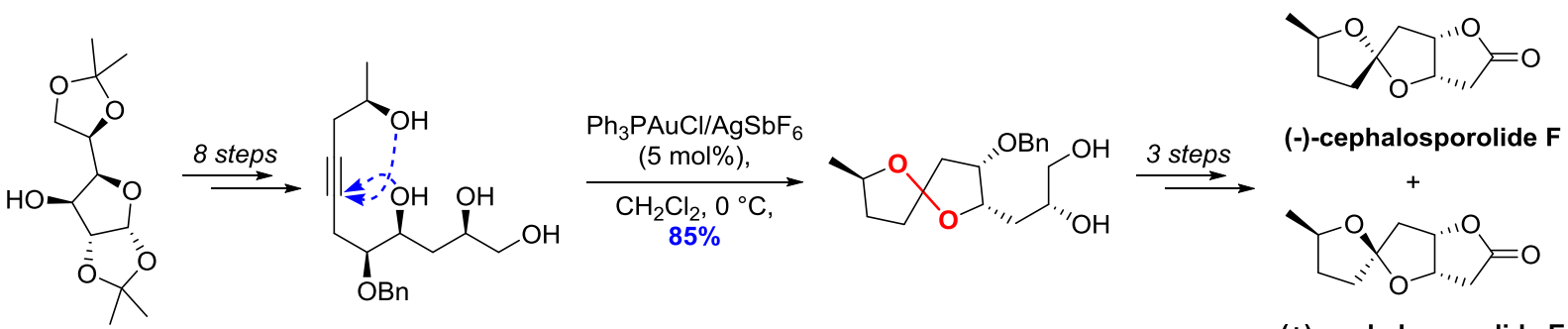
Heterofunctionalisation

Ketalisation:

Diderminserinolipids show anti-HIV activity.
Cephalosporolides less exciting: thought to be isolation artifacts.



(+)-didermniserinolipid B



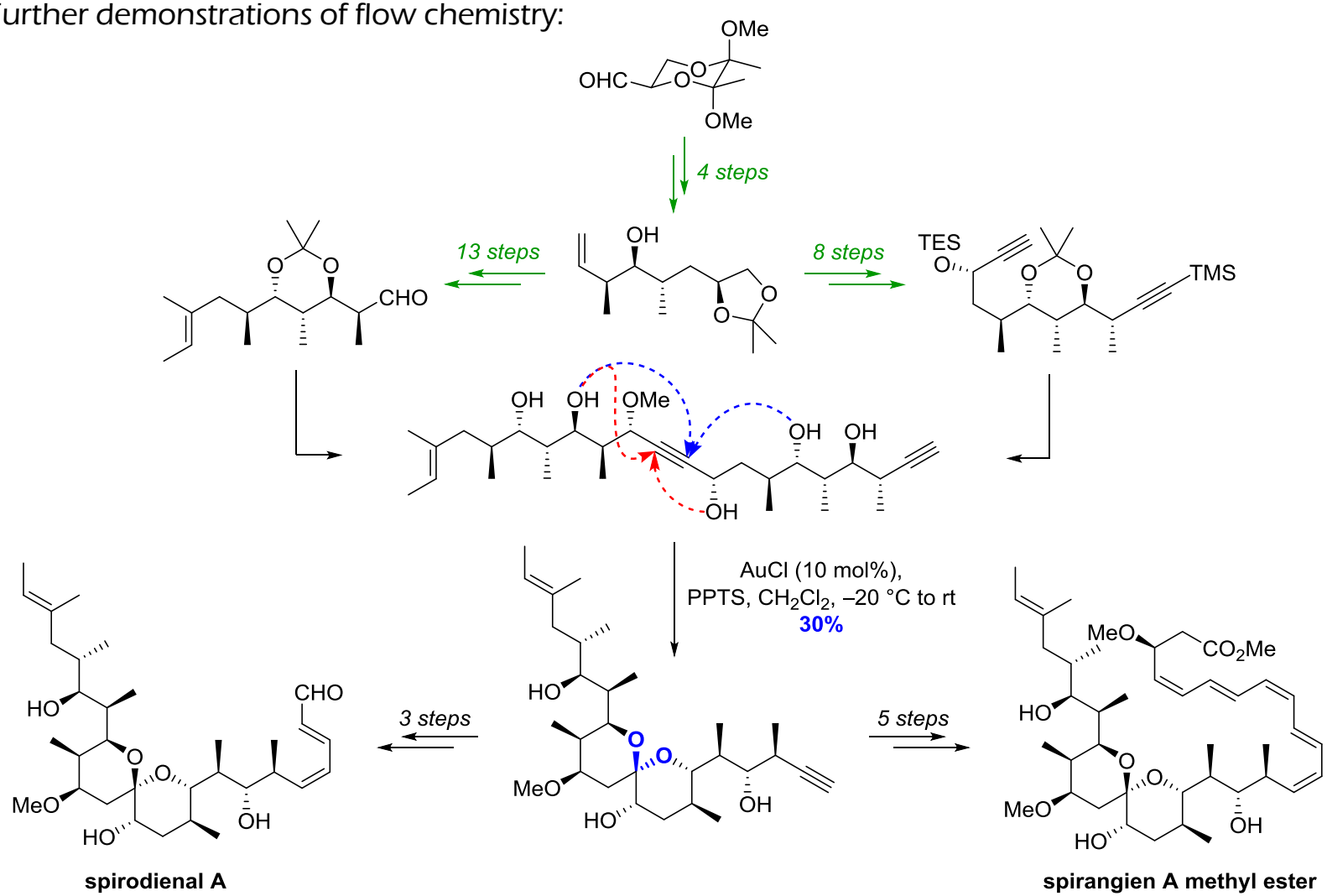
(-)-cephalosporolide F

(+)-cephalosporolide E

Ramana *et al*, Tetrahedron, **2013**, *69*, 1881
Ramana *et al*, Tetrahedron, **2014**, *70*, 3653

Heterofunctionalisation

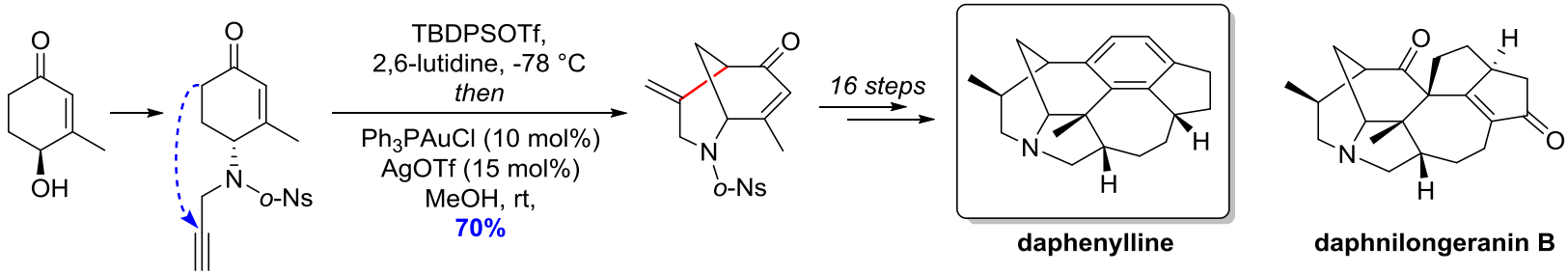
Further demonstrations of flow chemistry:

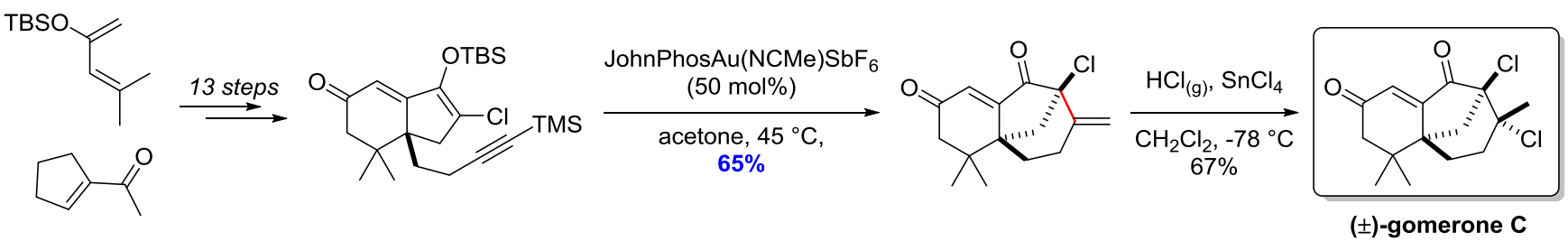


Ley *et al*, Angew. Chem., Int. Ed., 2014, 53, 4915

Carbocyclisations

***Daphniphyllum* alkaloids**: large class of natural products from plants widely used in Chinese herbal medicine. Remarkable range of biological activities, including anticancer, antioxidant, and vasorelaxation properties.

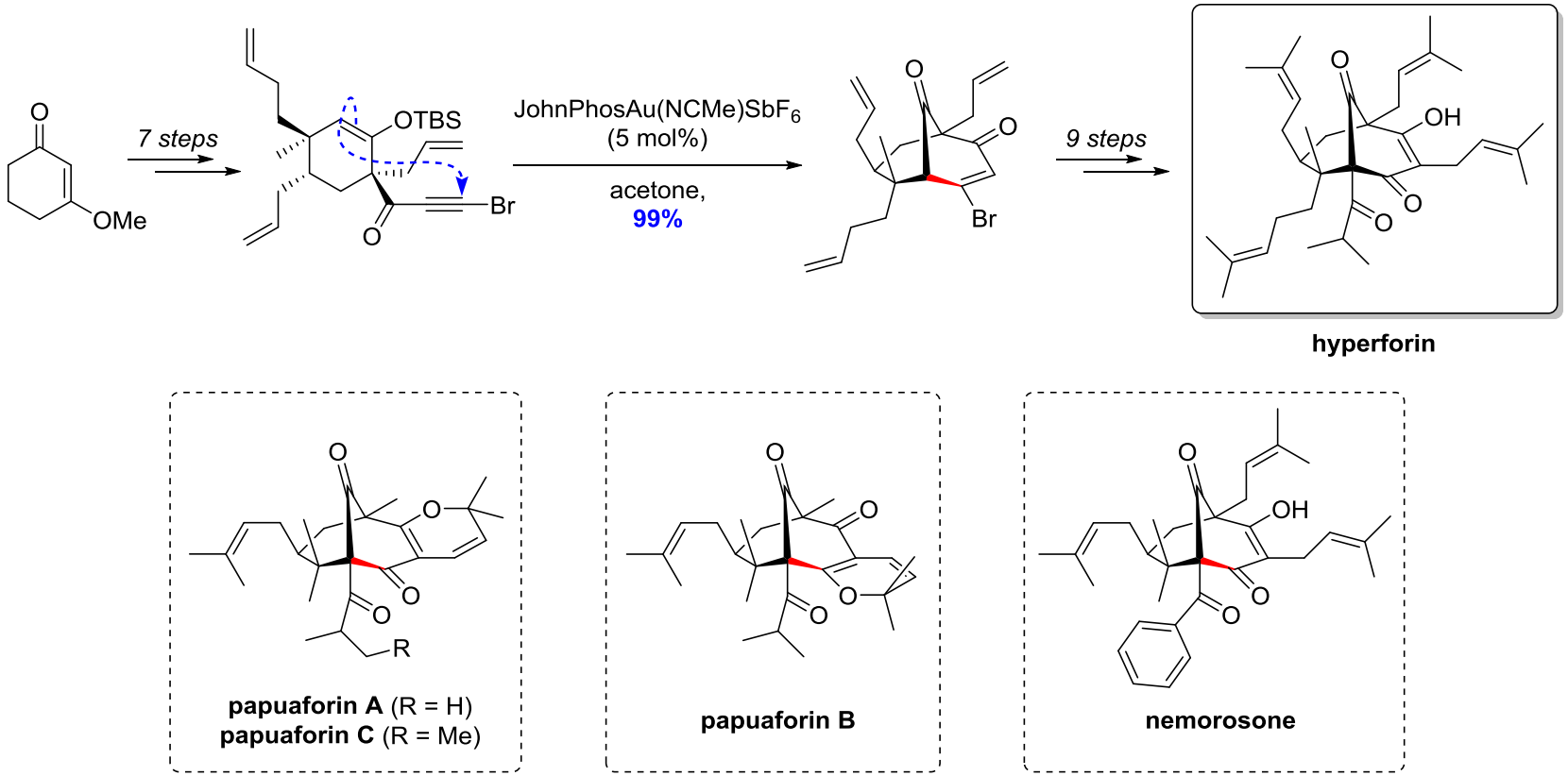




Carreira *et al*, Angew. Chem. Int. Ed. **2012**, *51*, 13066
Li *et al*, Nature Chem., **2013**, *5*, 679

Carbocyclisations

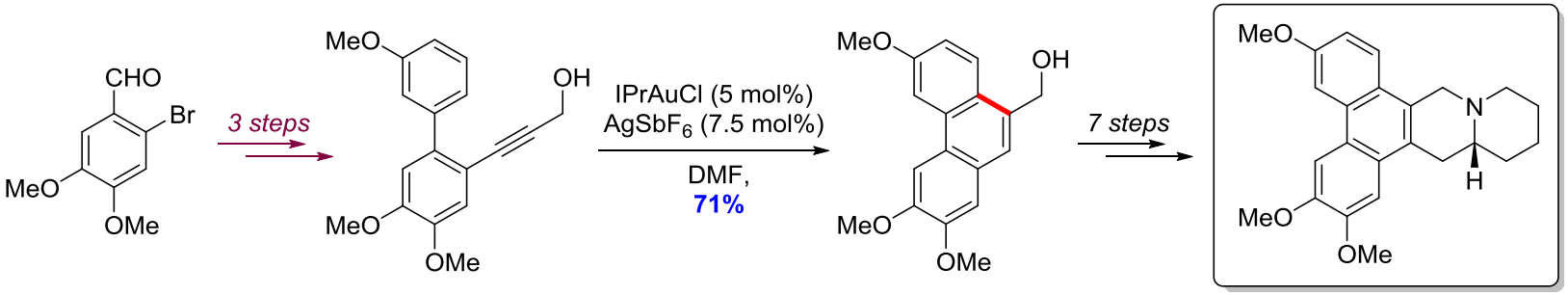
Hyperforin has been long known as an antidepressant. This, and other analogues, also display antibacterial and inflammatory properties.



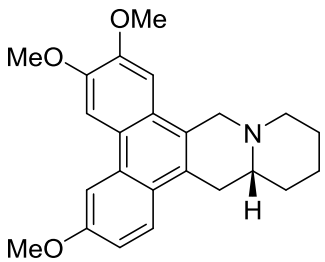
Barriault *et al*, Angew. Chem., Int. Ed., **2014**, *53*, 6701

Carbocyclisations

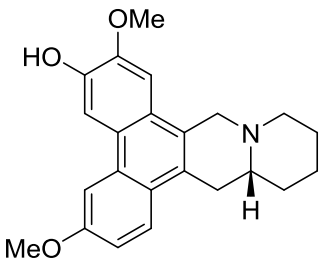
Phenanthroquinolizidines show potent antiviral, anti-inflammatory and anticancer activities. (-)-Boehmeriasin A is more potent than taxol in vitro.



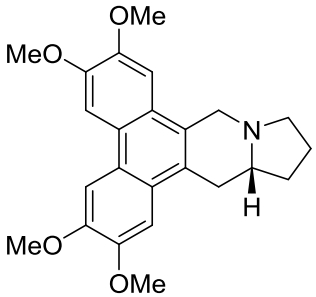
(–)-cryptopleurine



(–)-boehmeriasin A



(–)-boehmeriasin B

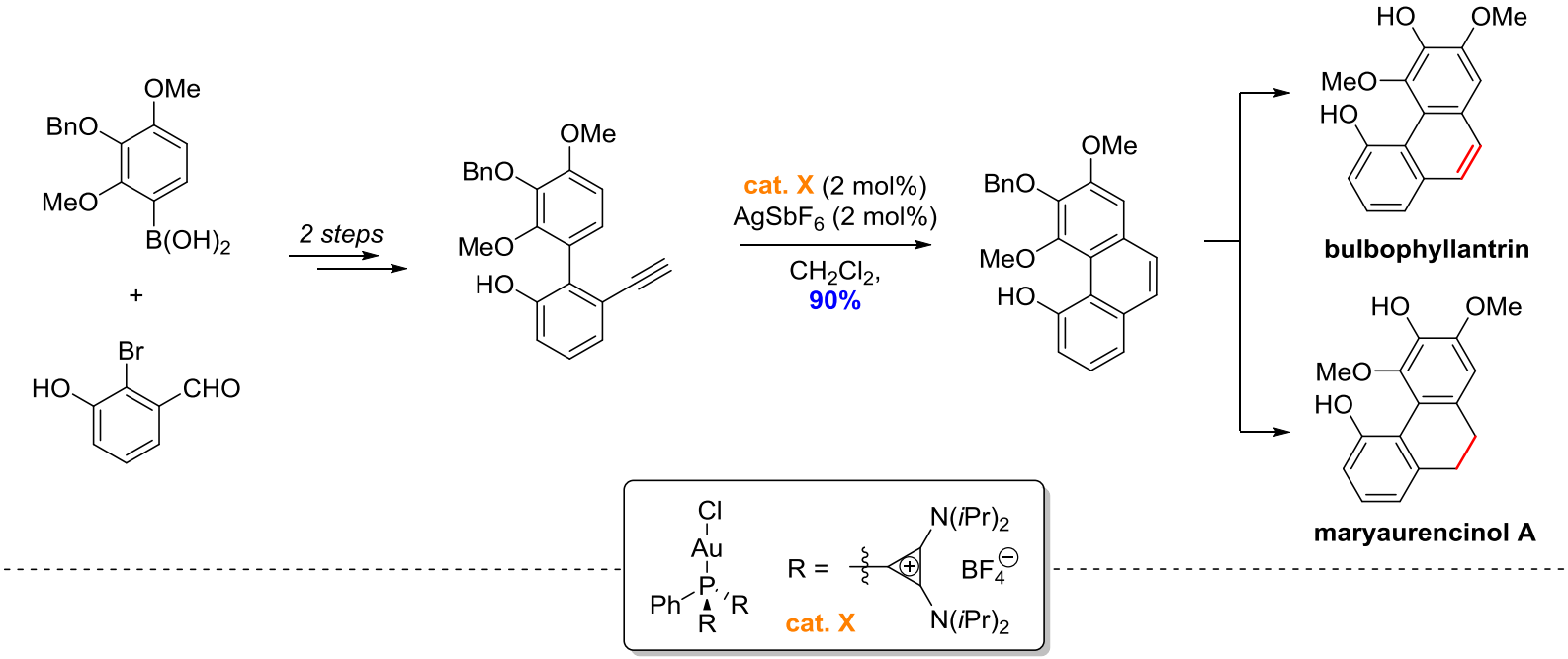


(–)-tylophorine

Opatz *et al*, Eur. J. Org. Chem., **2015**, 2149

Carbocyclisations

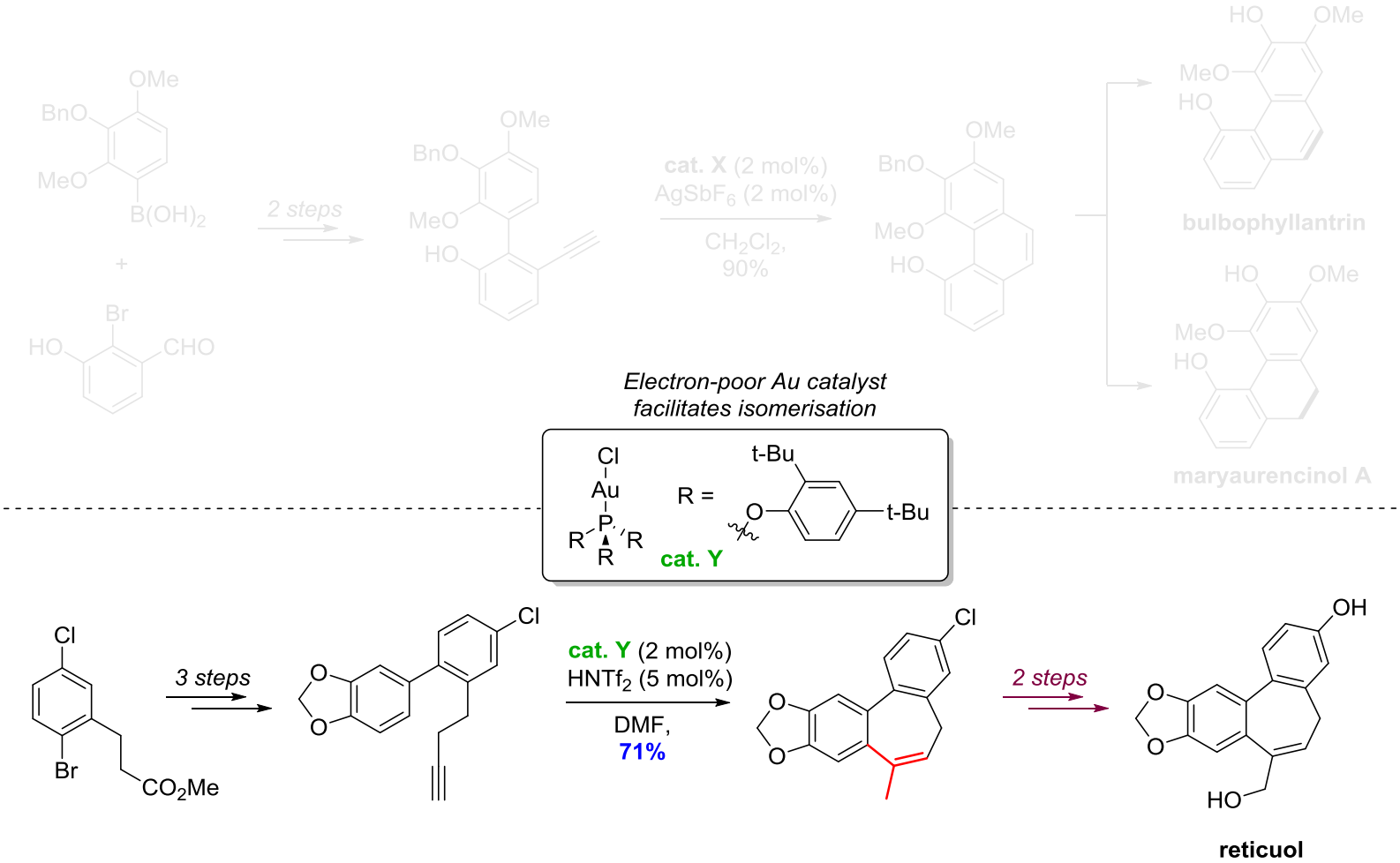
Bulbophyllantrin component of cell walls, maryaurencinol shows weak anti-biotic properties.



Alcarazo *et al*, J. Am. Chem. Soc., **2013**, *135*, 18815
Hashmi *et al*, Chem. Eur. J., **2014**, *20*, 6752

Carbocyclisations

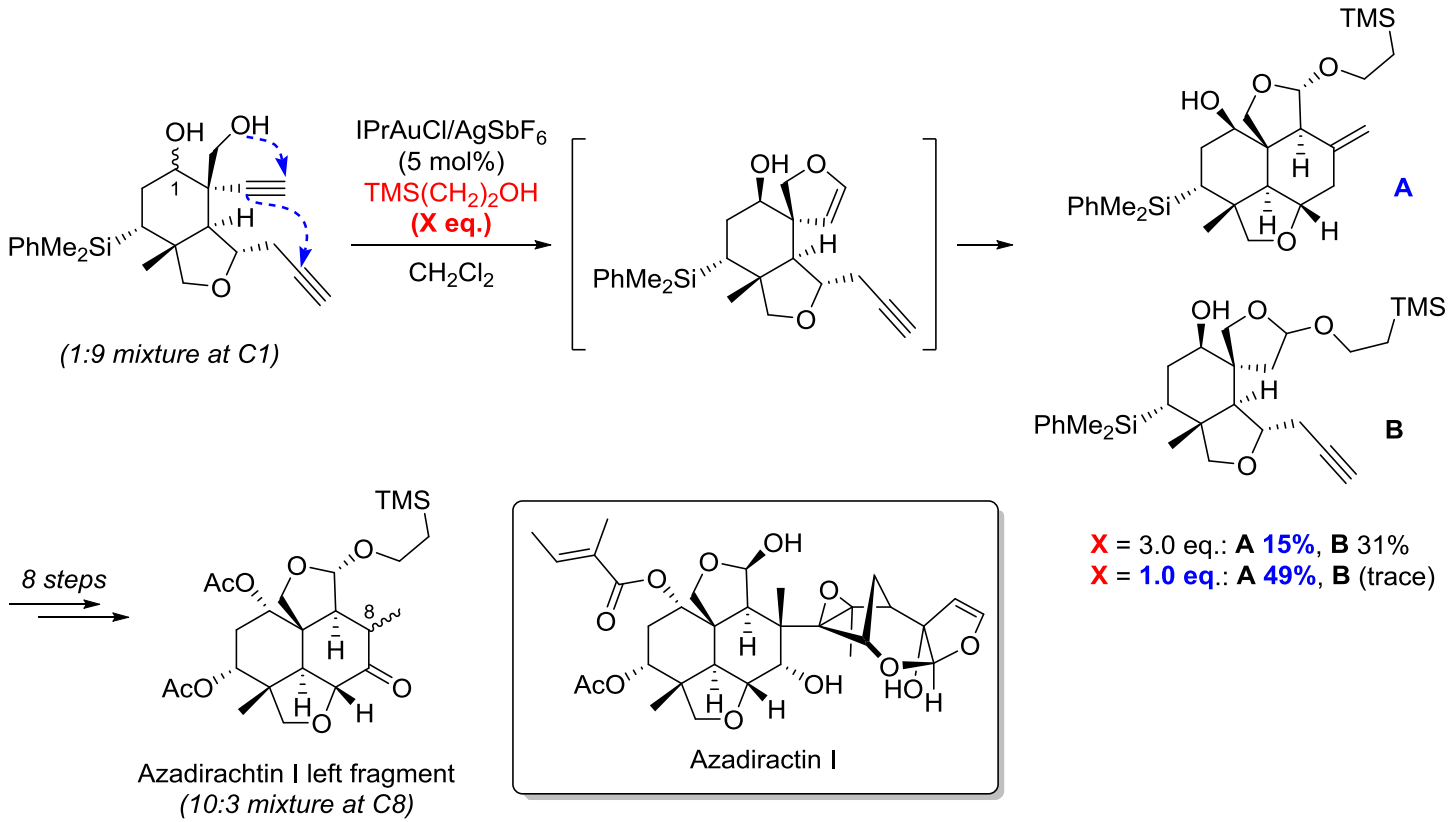
Reticuol sesquiterpenoids display insecticidal, anti-inflammatory and antimicrobial activities.



Alcarazo *et al*, J. Am. Chem. Soc., **2013**, *135*, 18815
Hashmi *et al*, Chem. Eur. J., **2014**, *20*, 6752

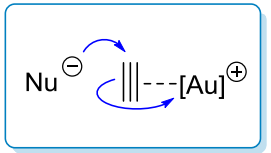
Carbocyclisations

Azadirachtins are potent insecticides by acting as a feeding inhibitor.

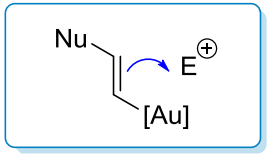


Yang *et al*, J. Org. Chem. **2016**, *81*, 751
Ley *et al*, Angew. Chem. Int. Ed. Engl., **2007**, 46, 7629

Modes of Reactivity

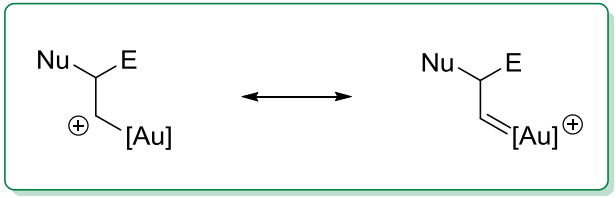


trans-addition



Deauration

Au backbonding



Lewis acid-derived products

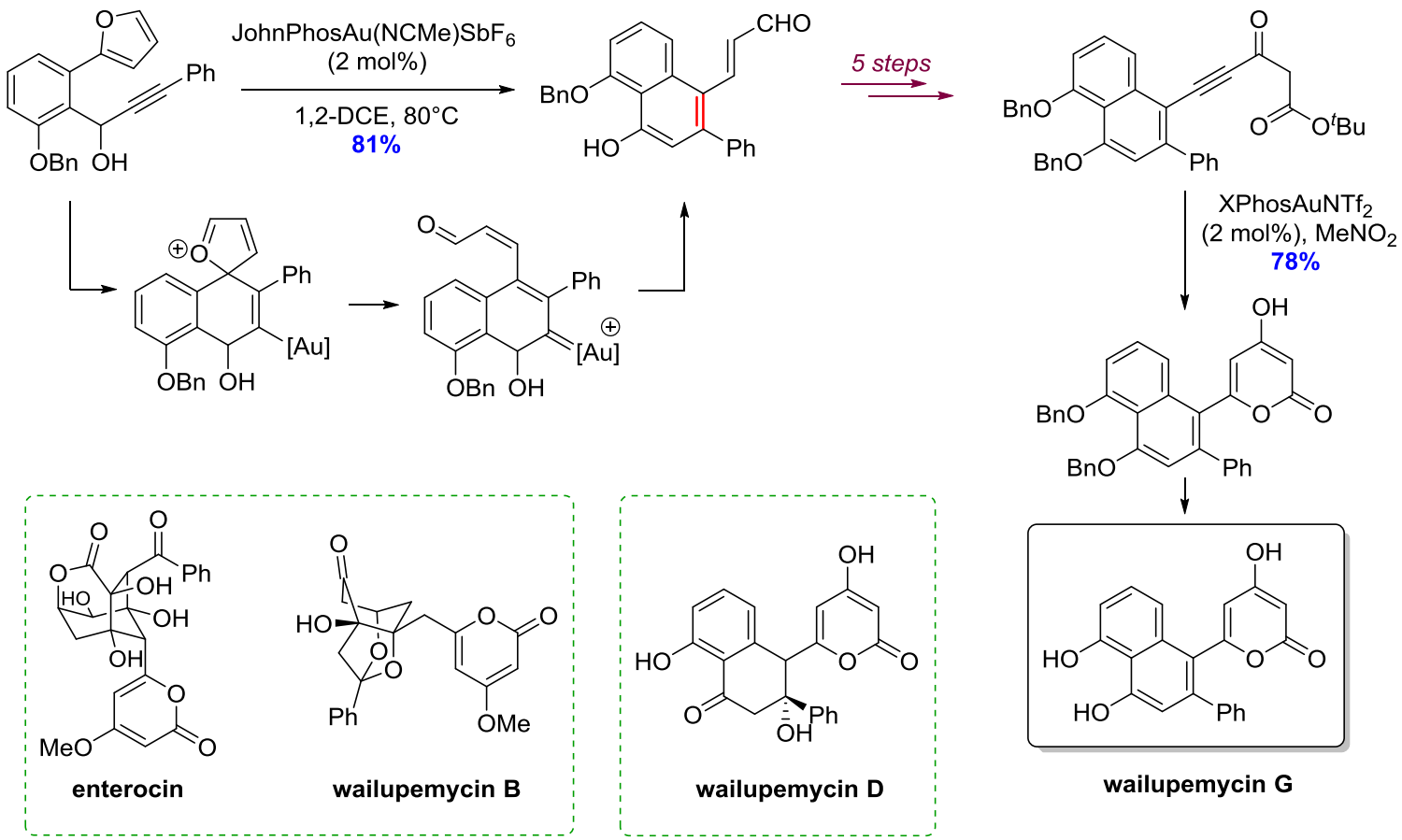
Hydroamination/alkoxylation,
Hydroacyloxylation,
Ketalisation,
Carbocylisation

Carbene–derived products

Cyclisations/rearrangements,
C-H insertion, cyclopropanation

Carbenoid Intermediates

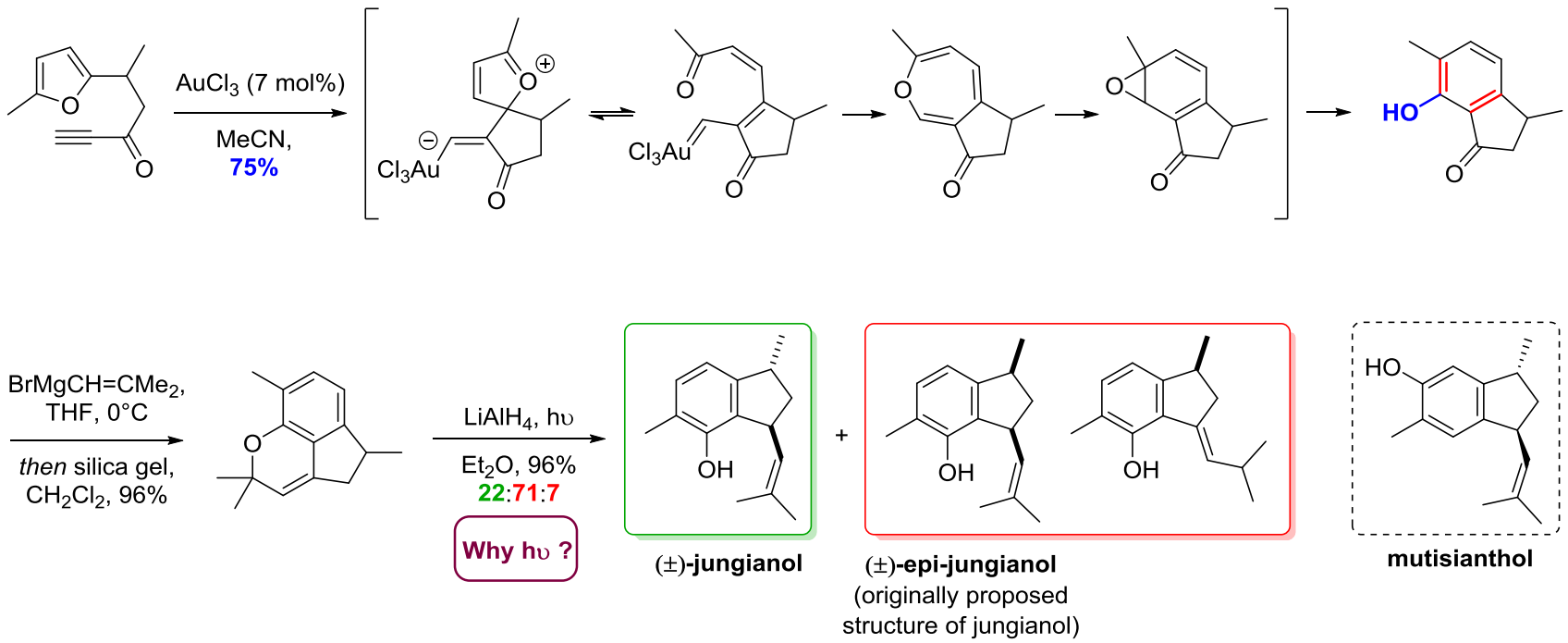
Enterocins and wailupemycins are biostatic agents – vast structural diversity.



Liu *et al*, Chem. Eur. J., **2014**, *20*, 12015
Moore *et al*, J. Am. Chem. Soc., **2000**, *122*, 5415

Carbenoid Intermediates

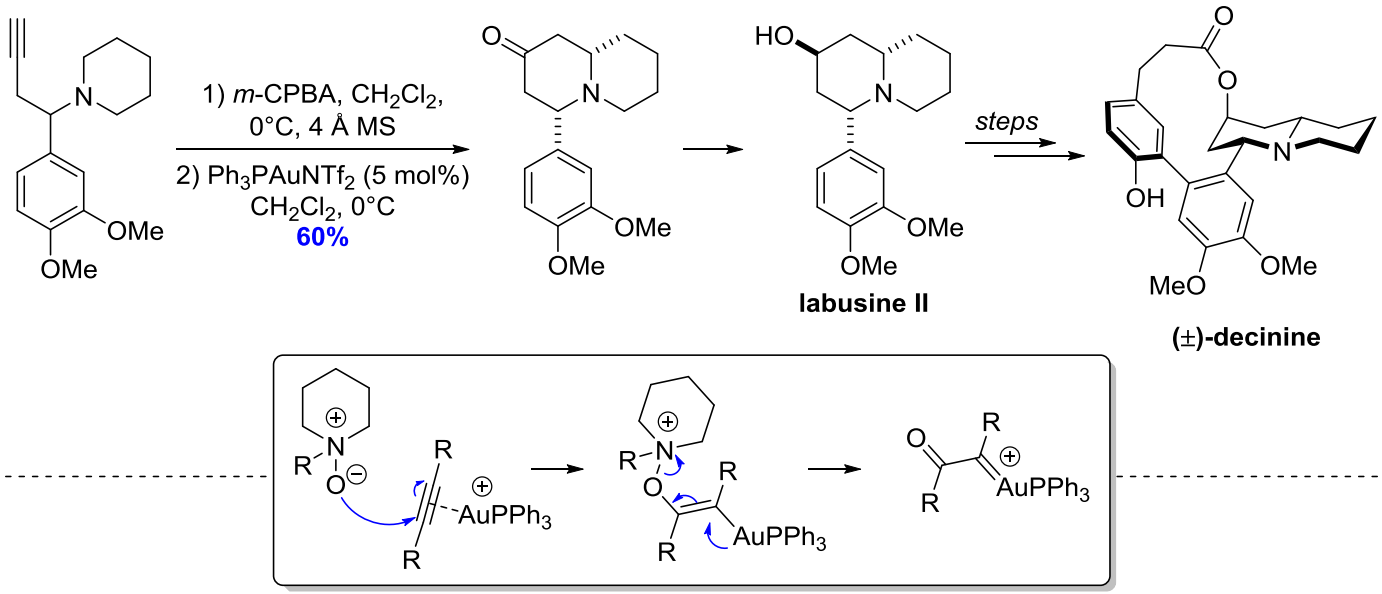
Jungianol has unknown biological activity. Its isomer, mutisianthol, shows anti-tumor activity.



Hashmi *et al*, Chem. Eur. J., **2003**, *9*, 4339

Carbenoid Intermediates

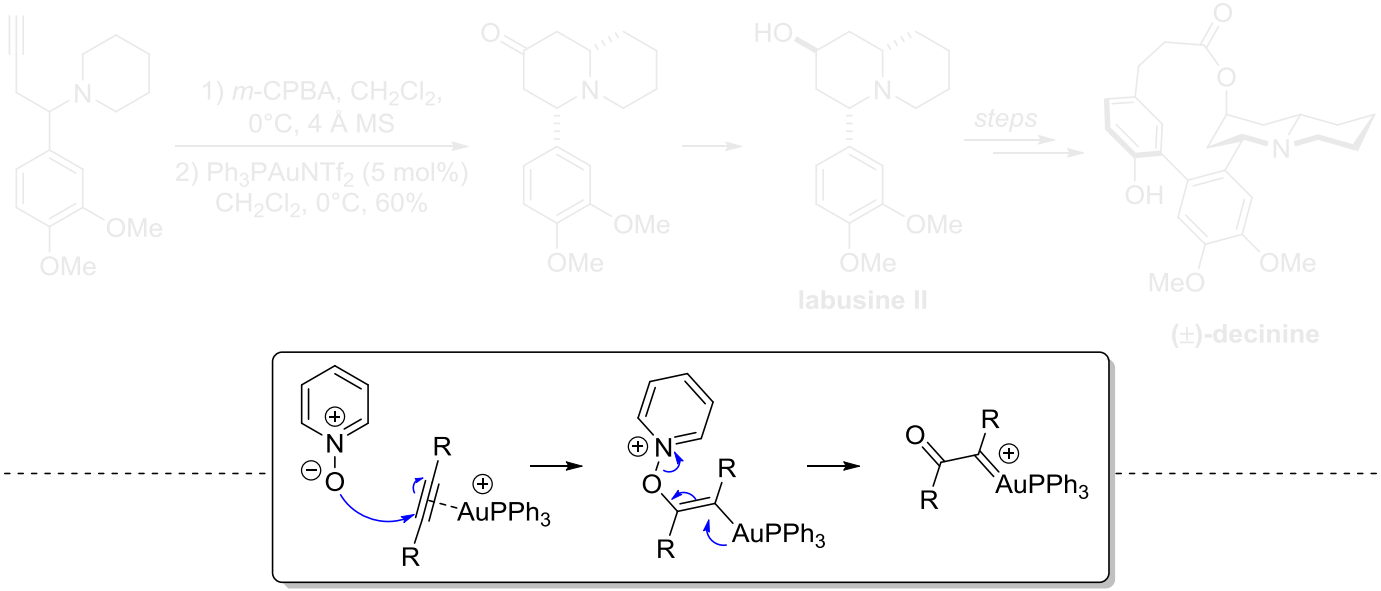
Lythraceae family shows a range of activities, including anti-inflammatory and diuretic properties.

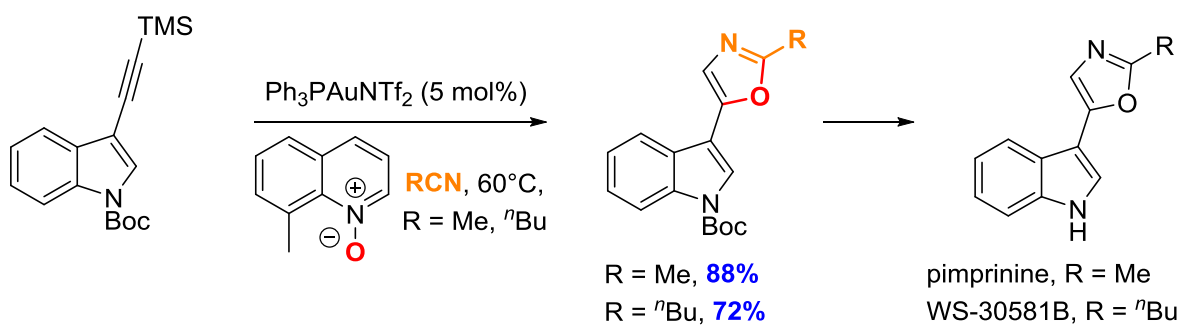


Yang et al, Org. Lett., ***2012***, *14*, 3712
Zhang *et al*, J. Am. Chem. Soc., **2009**, *131*, 8394

Carbenoid Intermediates

Pimprinine is a potent inhibitor of monoamine oxidase. Has anti-epileptic effects and also inhibits platelet aggregation.

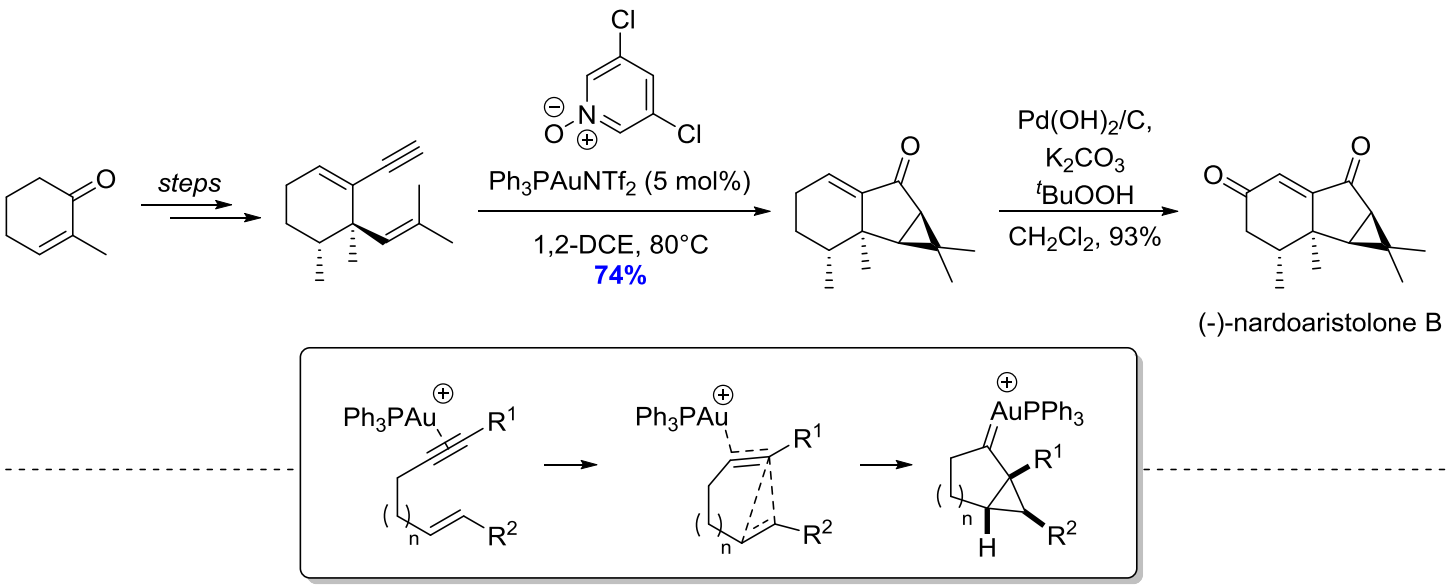




Jiannan *et al*, Acta Chim. Sin., **2012**, *70*, 1367

Carbenoid Intermediates

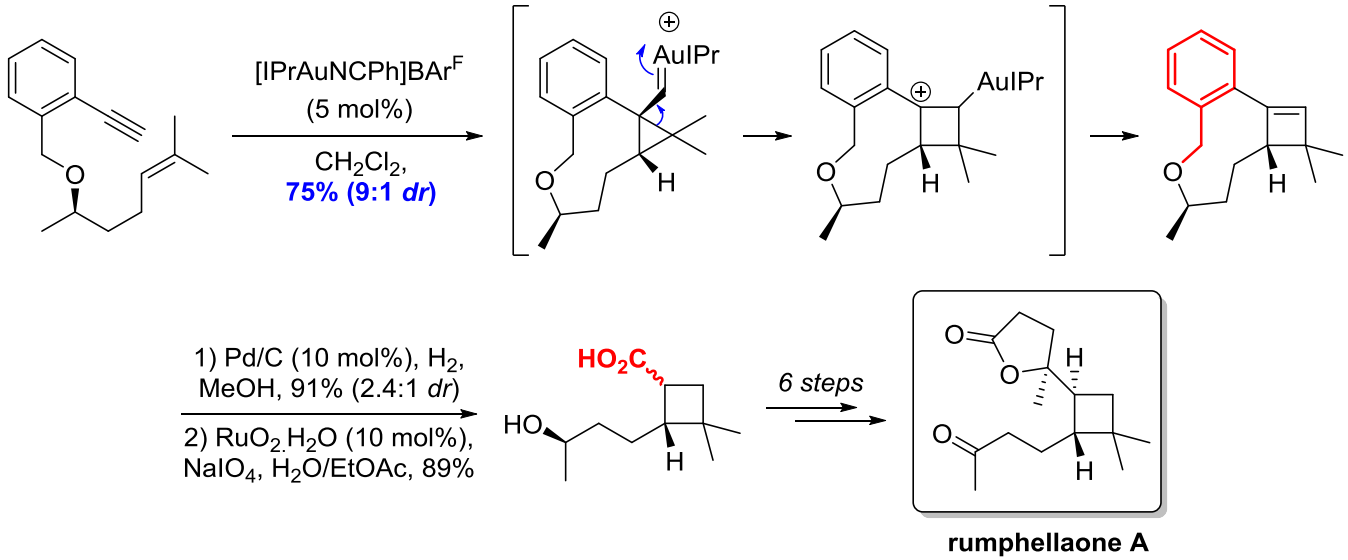
Nardoaristolone B exhibits protective activity on the injury of neonatal rat cardiomyocytes.

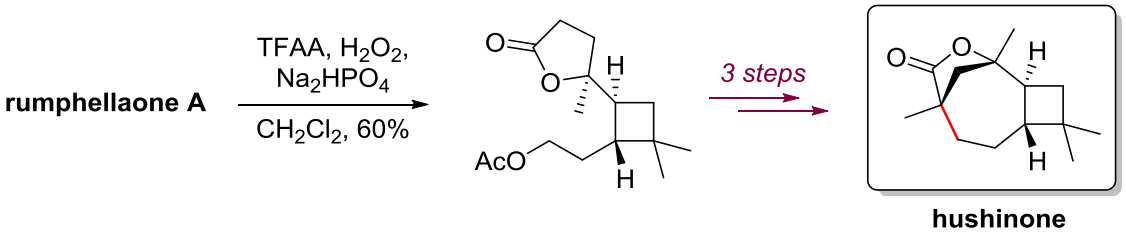


Echavarren *et al*, Org. Lett., **2015**, *17*, 461

Carbenoid Intermediates

Rumphellaone shows cytotoxicity to Leukaemia tumour cells. Hushinone isolated from tree buds.

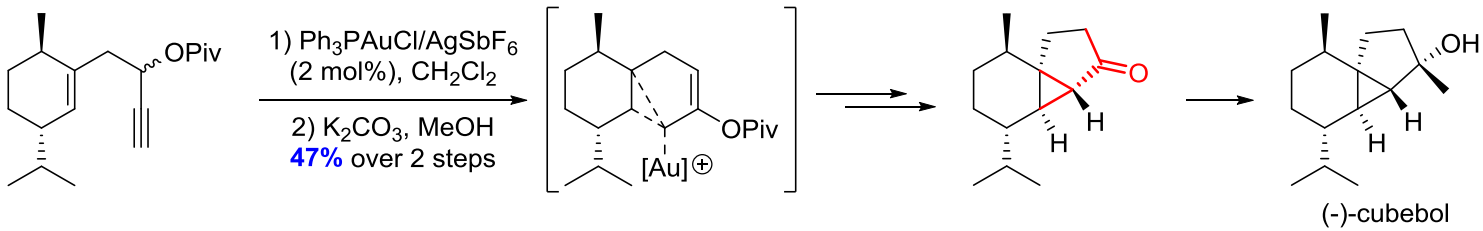


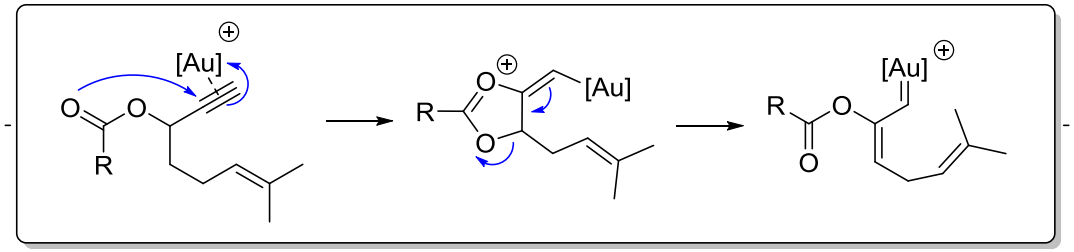


Echavarren *et al*, Org. Lett., **2016**, *18*, 1614

Carbenoid Intermediates

Cycloisomerisations are very dependant on substrate, and catalyst choice!





Echavarren *et al*, Angew. Chem. Int. Ed. **2013**, *52*, 6396
Fehr *et al*, Angew. Chem. Int. Ed. **2006**, *45*, 2901

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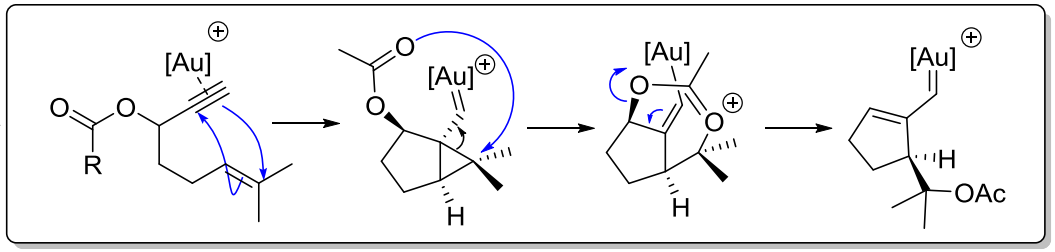

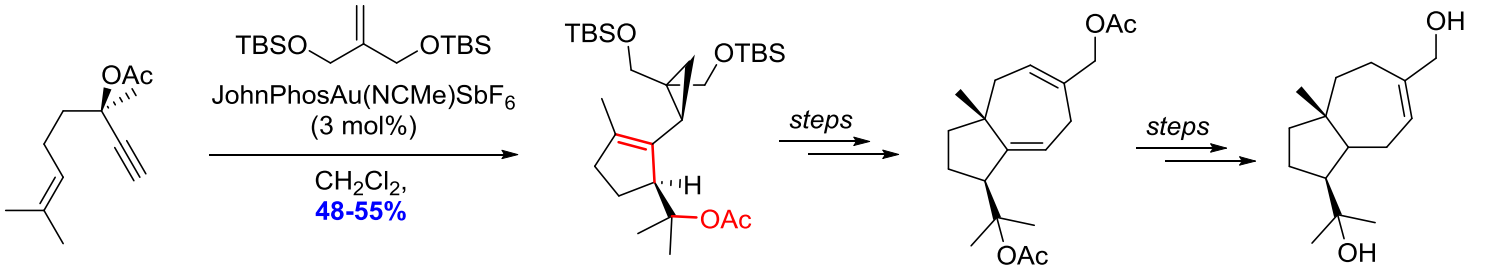

(+)-schisanwilsonene A

Echavarren *et al*, Angew. Chem. Int. Ed. **2013**, *52*, 6396
Fehr *et al*, Angew. Chem. Int. Ed. **2006**, *45*, 2901

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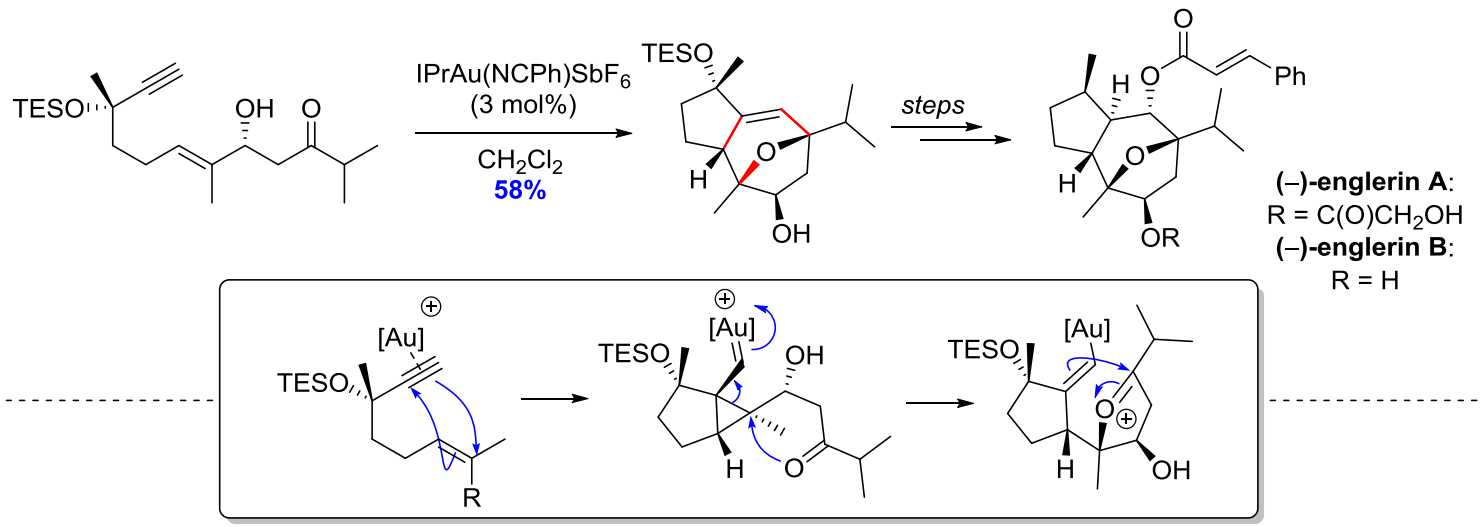
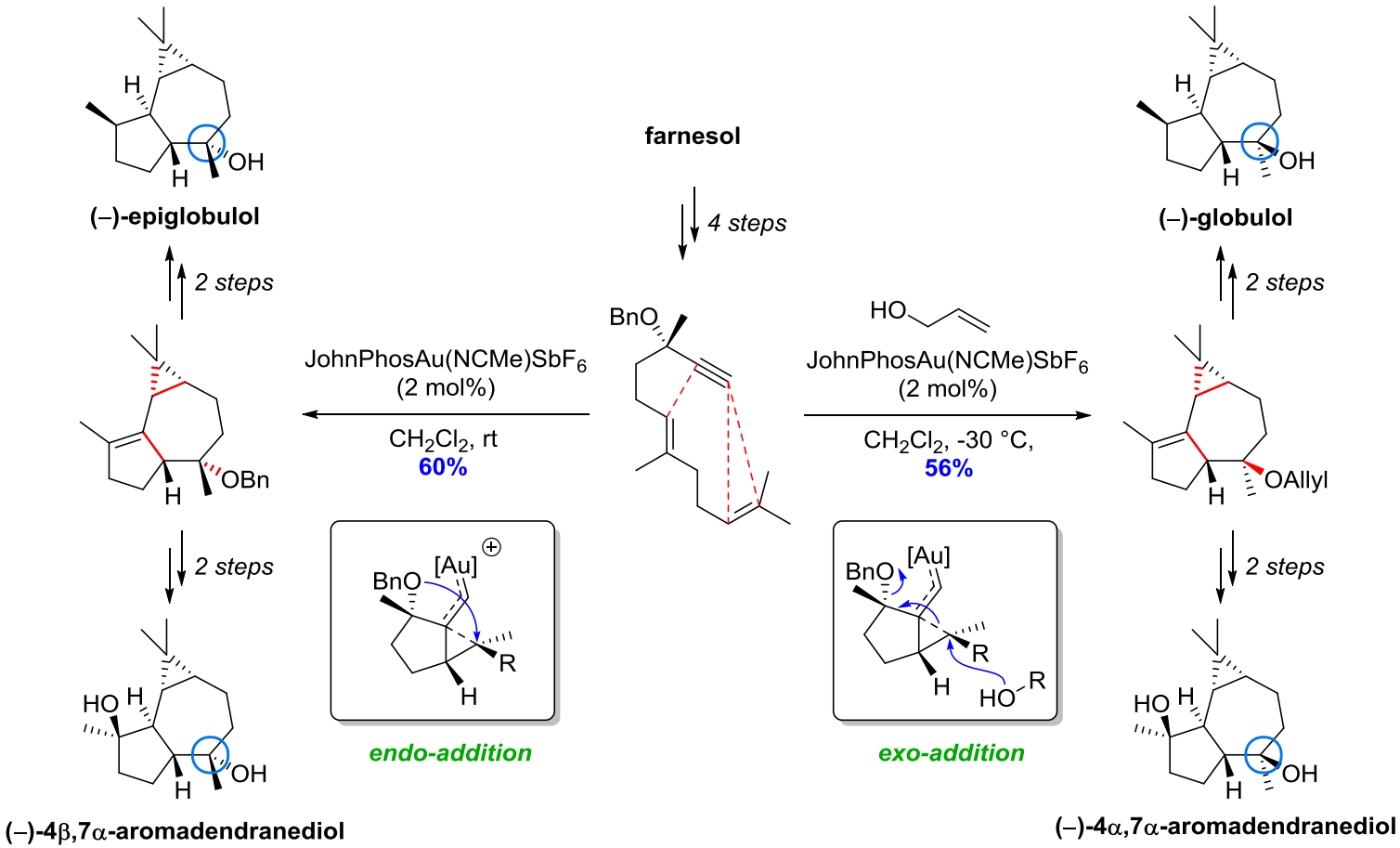


Echavarren *et al*, Angew. Chem. Int. Ed., **2010**, *49*, 3517

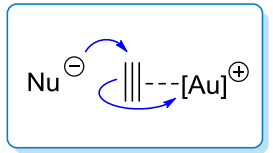
Carbenoid Intermediates

The following sesquiterpenoids display a range of antifungal, antibacterial and antiviral activities.

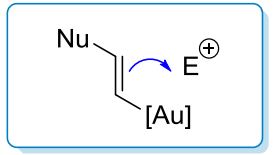


Echavarren *et al*, Angew. Chem. Int. Ed., **2014**, *53*, 4896

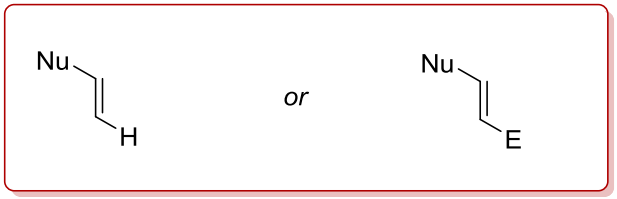
Conclusions



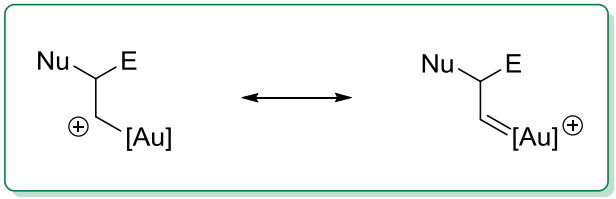
trans-addition



Deauration



Au backbonding



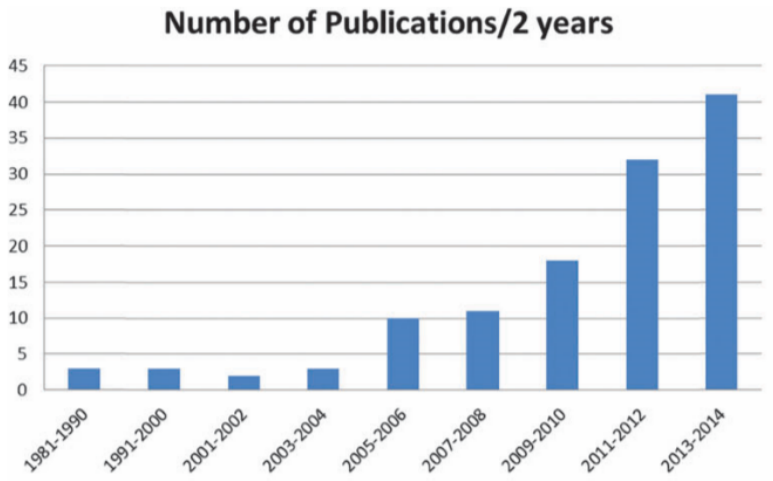
Lewis acid-derived products

Hydroamination/alkoxylation,
Hydroacyloxylation,
Ketalisation,
Carbocylisation

Carbene–derived products

Cyclisations/rearrangements,
C-H insertion, cyclopropanation

Conclusions



Deauration

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Conclusions

Applicability?

New Reactivity?

Deauration

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Carbene–derived products

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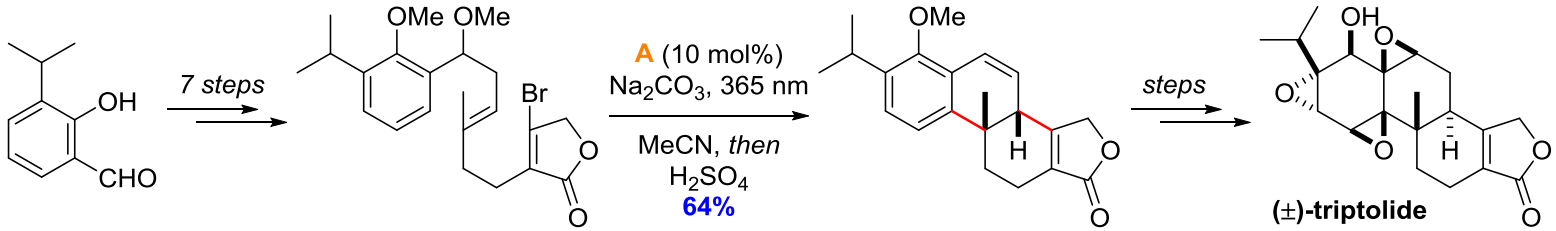
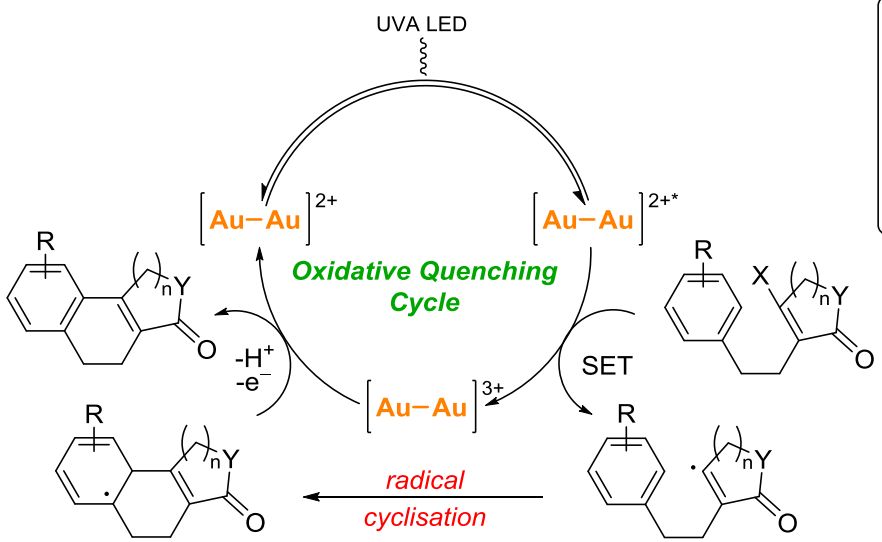
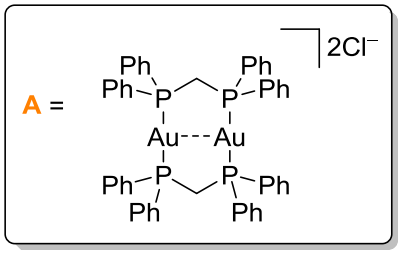
Photoredox-Catalysis

Formal synthesis of (±)-triptolide:







Barriault *et al*, Org. Lett. **2016**, *18*, 2592
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“Our fascination with gold is related to the erotic fantasies of early childhood." – Sigmund Freud

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