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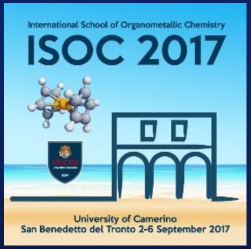
DI MILANO



Catalytic carbophilic activation in synthetic organic chemistry: catalysis by gold π acids

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Activation of π-systems (alkenes, alkynes and allenes)
towards nucleophilic additions

↑

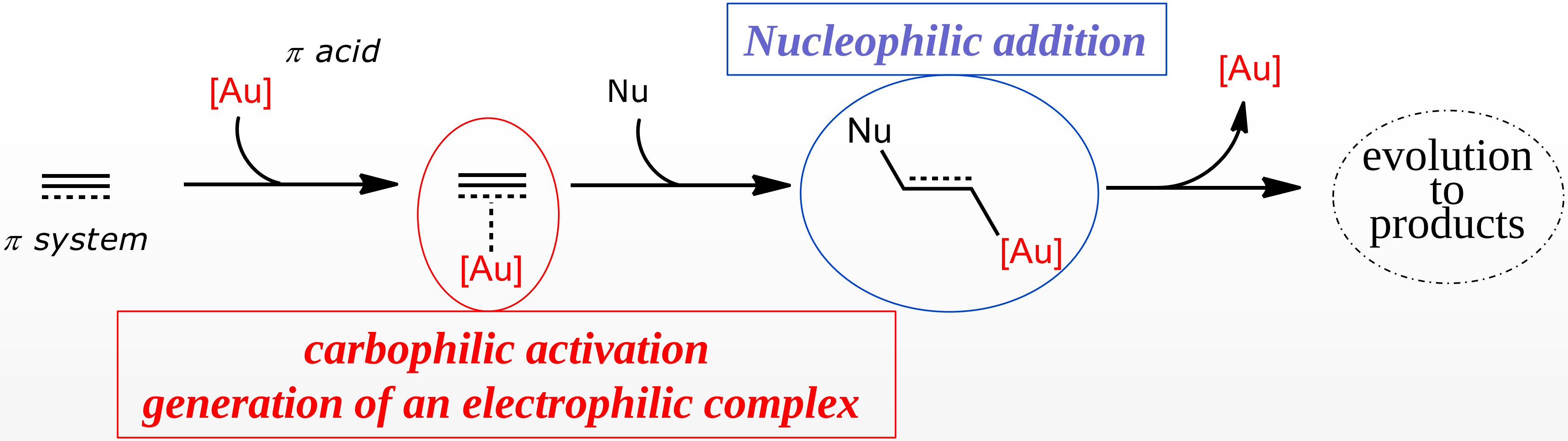
Catalytic ***carbophilic activation*** in synthetic organic chemistry:
catalysis by ***gold π acids***

↓

AuX_3 $L{-}Au^{+}\,X^{-}$

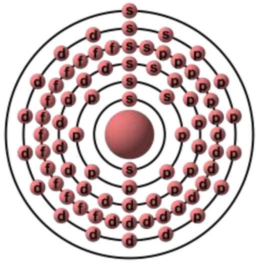
X^{-} = non-coordinating counterion

Catalytic **carbophilic activation** in synthetic organic chemistry: catalysis by **gold π acids**



Basic mechanism of π acid catalysis exemplified by the addition of a generic nucleophile across a π system

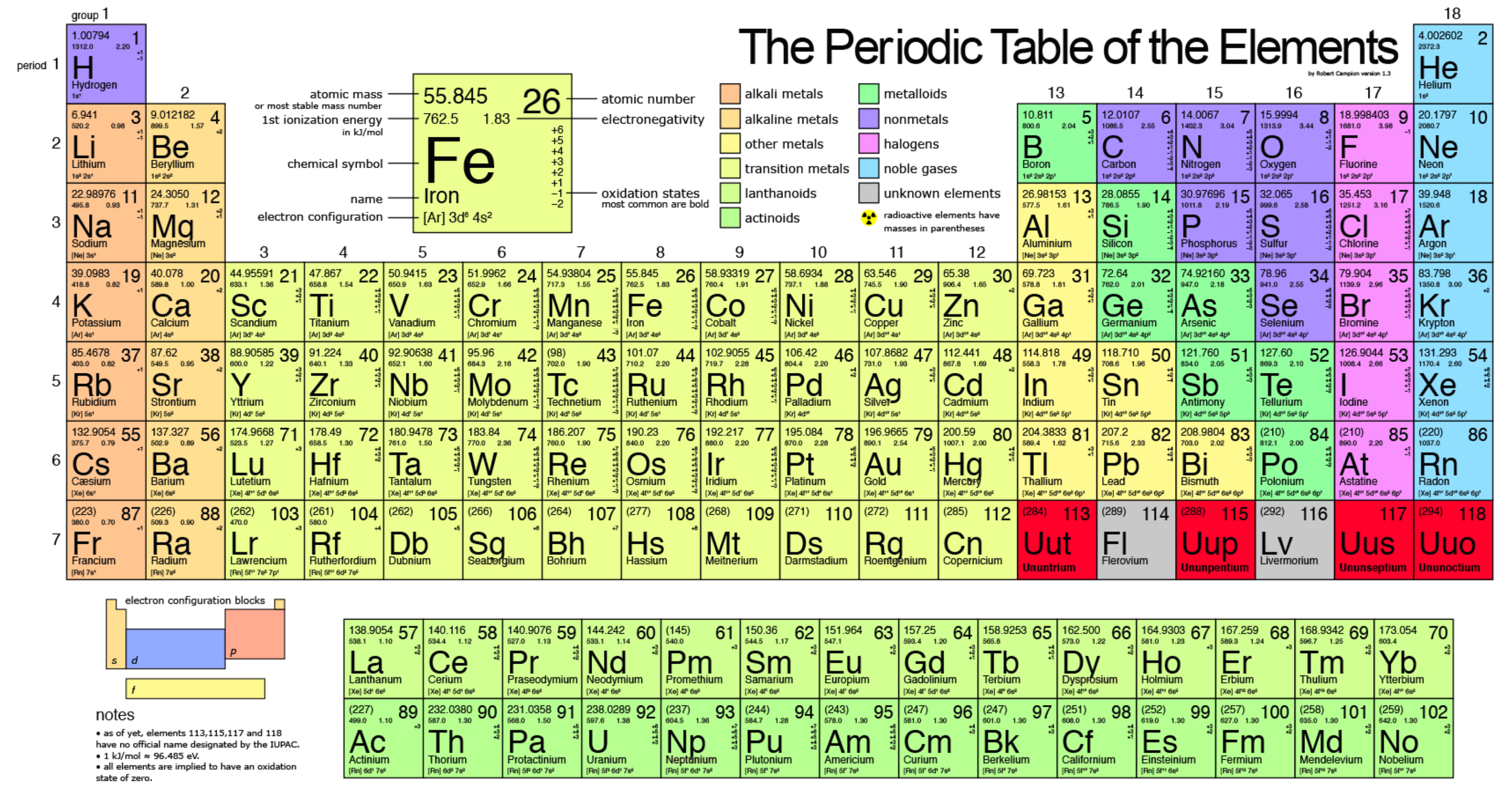
Gold as element



electronic configuration [Xe] $4f^{14}5d^{10}6s^{1}$

atomic number 79

atomic weight 197



The Periodic Table of the Elements

by Robert Campion version 1.3

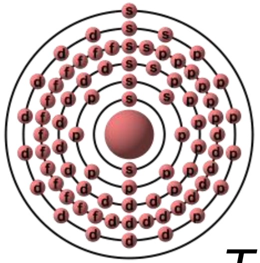
period	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
1	1.00794 1 H Hydrogen																	4.002602 2 He Helium
2	6.941 3 Li Lithium	9.012182 4 Be Beryllium											10.811 5 B Boron	12.0107 6 C Carbon	14.0067 7 N Nitrogen	15.9994 8 O Oxygen	18.998403 9 F Fluorine	20.1797 10 Ne Neon
3	22.98976 11 Na Sodium	24.3050 12 Mg Magnesium											26.98153 13 Al Aluminium	28.0855 14 Si Silicon	30.97696 15 P Phosphorus	32.065 16 S Sulfur	35.453 17 Cl Chlorine	39.948 18 Ar Argon
4	39.0983 19 K Potassium	40.078 20 Ca Calcium	44.95591 21 Sc Scandium	47.867 22 Ti Titanium	50.9415 23 V Vanadium	51.9962 24 Cr Chromium	54.93804 25 Mn Manganese	55.845 26 Fe Iron	58.93319 27 Co Cobalt	58.6934 28 Ni Nickel	63.546 29 Cu Copper	65.38 30 Zn Zinc	69.723 31 Ga Gallium	72.64 32 Ge Germanium	74.92160 33 As Arsenic	78.96 34 Se Selenium	79.904 35 Br Bromine	83.798 36 Kr Krypton
5	85.4678 37 Rb Rubidium	87.62 38 Sr Strontium	88.90585 39 Y Yttrium	91.224 40 Zr Zirconium	92.90638 41 Nb Niobium	95.96 42 Mo Molybdenum	(98) 43 Tc Technetium	101.07 44 Ru Ruthenium	102.9055 45 Rh Rhodium	106.42 46 Pd Palladium	107.8682 47 Ag Silver	112.441 48 Cd Cadmium	114.818 49 In Indium	118.710 50 Sn Tin	121.760 51 Sb Antimony	127.60 52 Te Tellurium	126.9044 53 I Iodine	131.293 54 Xe Xenon
6	132.9054 55 Cs Cæsium	137.327 56 Ba Barium	174.9668 71 Lu Lutetium	178.49 72 Hf Hafnium	180.9478 73 Ta Tantalum	183.84 74 W Tungsten	186.207 75 Re Rhenium	190.23 76 Os Osmium	192.217 77 Ir Iridium	195.084 78 Pt Platinum	196.9665 79 Au Gold	200.59 80 Hg Mercury	204.3833 81 Tl Thallium	207.2 82 Pb Lead	208.9804 83 Bi Bismuth	(210) 84 Po Polonium	(210) 85 At Astatine	(220) 86 Rn Radon
7	(223) 87 Fr Francium	(226) 88 Ra Radium	(262) 103 Lr Lawrencium	(261) 104 Rf Rutherfordium	(262) 105 Db Dubnium	(266) 106 Sg Seaborgium	(264) 107 Bh Bohrium	(277) 108 Hs Hassium	(268) 109 Mt Meitnerium	(271) 110 Ds Darmstadium	(272) 111 Rg Roentgenium	(285) 112 Cn Copernicium	(284) 113 Uut Ununtrium	(289) 114 Fl Flerovium	(288) 115 Uup Ununpentium	(292) 116 Lv Livermorium	117 Uus Ununseptium	(294) 118 Uuo Ununoctium

138.9054 57 La Lanthanum	140.116 58 Ce Cerium	140.9076 59 Pr Praseodymium	144.242 60 Nd Neodymium	(145) 61 Pm Promethium	150.36 62 Sm Samarium	151.964 63 Eu Europium	157.25 64 Gd Gadolinium	158.9253 65 Tb Terbium	162.500 66 Dy Dysprosium	164.9303 67 Ho Holmium	167.259 68 Er Erbium	168.9342 69 Tm Thulium	173.054 70 Yb Ytterbium
(227) 89 Ac Actinium	232.0380 90 Th Thorium	231.0358 91 Pa Protactinium	238.0289 92 U Uranium	(237) 93 Np Neptunium	(244) 94 Pu Plutonium	(243) 95 Am Americium	(247) 96 Cm Curium	(247) 97 Bk Berkelium	(251) 98 Cf Californium	(252) 99 Es Einsteinium	(257) 100 Fm Fermium	(258) 101 Md Mendelevium	(259) 102 No Nobelium

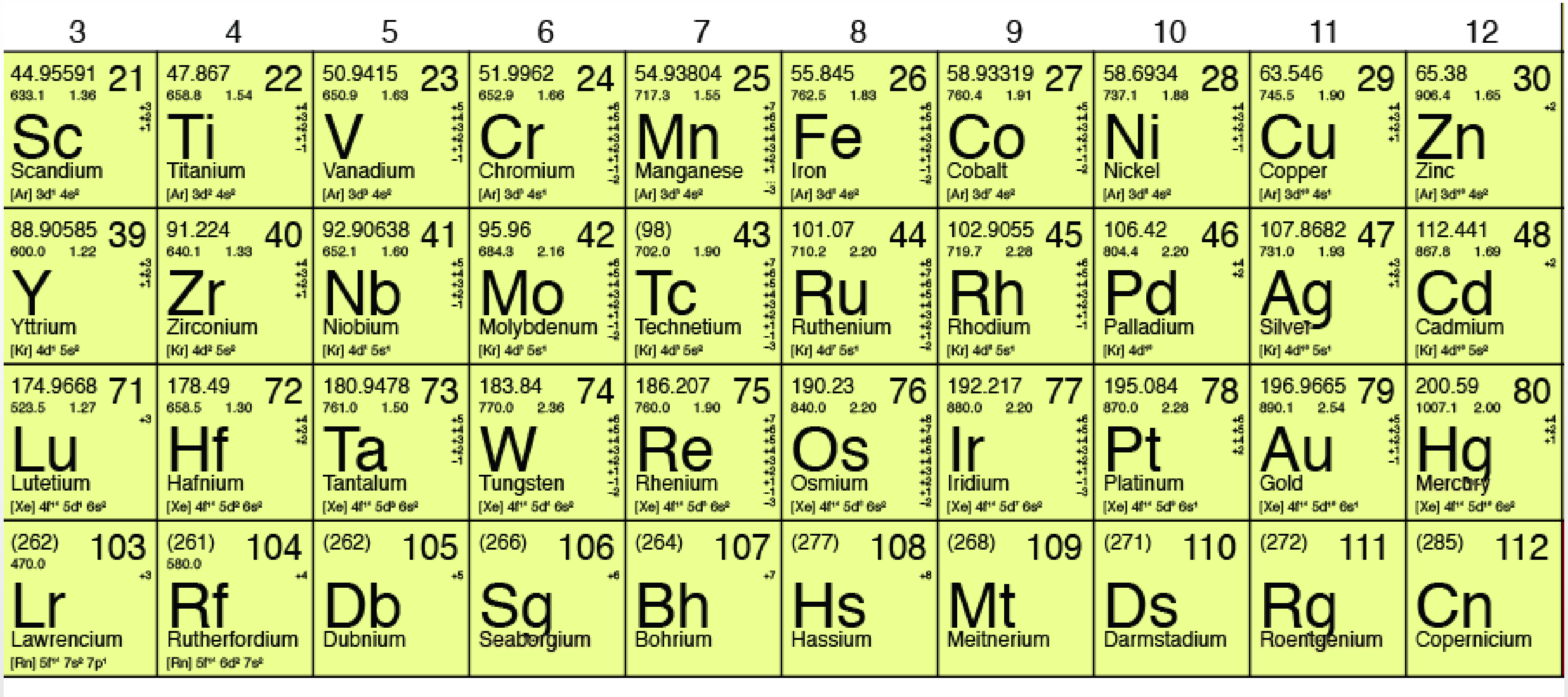
notes

- as of yet, elements 113,115,117 and 118 have no official name designated by the IUPAC.
- 1 kJ/mol ≈ 96.485 eV.
- all elements are implied to have an oxidation state of zero.

Gold as element: valence electron configuration $5d^{10}6s^1$

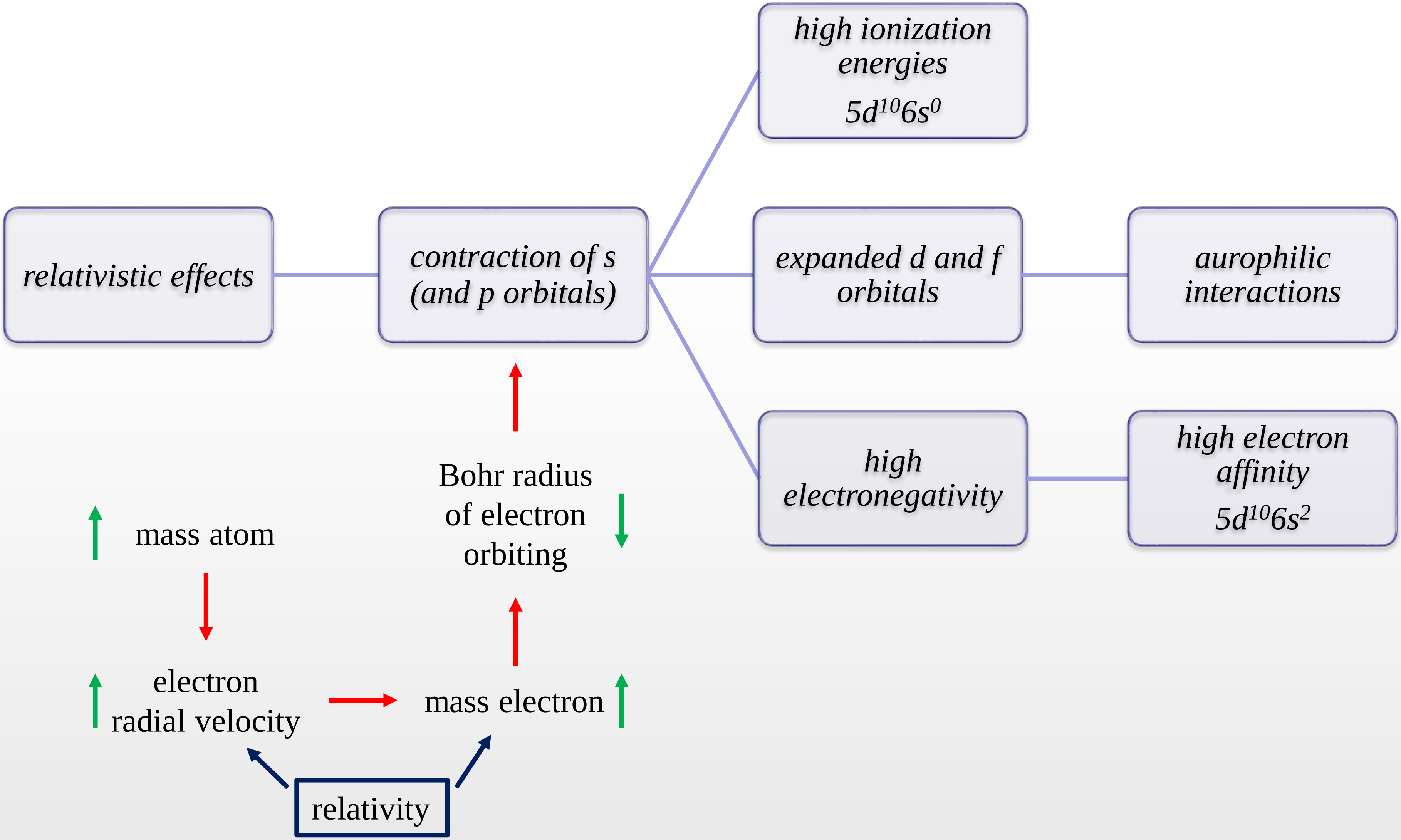


TM properties (ionization potential, electronegativity)



3	4	5	6	7	8	9	10	11	12
44.95591 21 633.1 1.36 Sc Scandium [Ar] $3d^1 4s^2$	47.867 22 658.8 1.54 Ti Titanium [Ar] $3d^2 4s^2$	50.9415 23 650.9 1.63 V Vanadium [Ar] $3d^3 4s^2$	51.9962 24 652.9 1.66 Cr Chromium [Ar] $3d^5 4s^1$	54.93804 25 717.3 1.55 Mn Manganese [Ar] $3d^5 4s^2$	55.845 26 762.5 1.83 Fe Iron [Ar] $3d^6 4s^2$	58.93319 27 760.4 1.91 Co Cobalt [Ar] $3d^7 4s^2$	58.6934 28 737.1 1.88 Ni Nickel [Ar] $3d^8 4s^2$	63.546 29 745.5 1.90 Cu Copper [Ar] $3d^{10} 4s^1$	65.38 30 906.4 1.65 Zn Zinc [Ar] $3d^{10} 4s^2$
88.90585 39 600.0 1.22 Y Yttrium [Kr] $4d^1 5s^2$	91.224 40 640.1 1.33 Zr Zirconium [Kr] $4d^2 5s^2$	92.90638 41 652.1 1.60 Nb Niobium [Kr] $4d^4 5s^1$	95.96 42 684.3 2.16 Mo Molybdenum [Kr] $4d^5 5s^1$	(98) 43 702.0 1.90 Tc Technetium [Kr] $4d^5 5s^2$	101.07 44 710.2 2.20 Ru Ruthenium [Kr] $4d^7 5s^1$	102.9055 45 719.7 2.28 Rh Rhodium [Kr] $4d^8 5s^1$	106.42 46 804.4 2.20 Pd Palladium [Kr] $4d^{10}$	107.8682 47 731.0 1.93 Ag Silver [Kr] $4d^{10} 5s^1$	112.441 48 867.8 1.69 Cd Cadmium [Kr] $4d^{10} 5s^2$
174.9668 71 523.5 1.27 Lu Lutetium [Xe] $4f^{14} 5d^1 6s^2$	178.49 72 658.5 1.30 Hf Hafnium [Xe] $4f^{14} 5d^2 6s^2$	180.9478 73 761.0 1.50 Ta Tantalum [Xe] $4f^{14} 5d^3 6s^2$	183.84 74 770.0 2.36 W Tungsten [Xe] $4f^{14} 5d^4 6s^2$	186.207 75 760.0 1.90 Re Rhenium [Xe] $4f^{14} 5d^5 6s^2$	190.23 76 840.0 2.20 Os Osmium [Xe] $4f^{14} 5d^6 6s^2$	192.217 77 880.0 2.20 Ir Iridium [Xe] $4f^{14} 5d^7 6s^2$	195.084 78 870.0 2.28 Pt Platinum [Xe] $4f^{14} 5d^9 6s^1$	196.9665 79 890.1 2.54 Au Gold [Xe] $4f^{14} 5d^{10} 6s^1$	200.59 80 1007.1 2.00 Hg Mercury [Xe] $4f^{14} 5d^{10} 6s^2$
(262) 103 470.0 +3 Lr Lawrencium [Rn] $5f^{14} 7s^2 7p^1$	(261) 104 580.0 +4 Rf Rutherfordium [Rn] $5f^{14} 6d^2 7s^2$	(262) 105 +5 Db Dubnium	(266) 106 +6 Sg Seaborgium	(264) 107 +7 Bh Bohrium	(277) 108 +8 Hs Hassium	(268) 109 Mt Meitnerium	(271) 110 Ds Darmstadium	(272) 111 Rg Roentgenium	(285) 112 Cn Copernicium

Gold as element: relativistic effects



relativistic effects

contraction of s (and p orbitals)

high ionization energies
$5d^{10}6s^{0}$

expanded d and f orbitals

aurophilic interactions

high electronegativity

high electron affinity
$5d^{10}6s^{2}$

Bohr radius of electron orbiting ↓

↑ mass atom

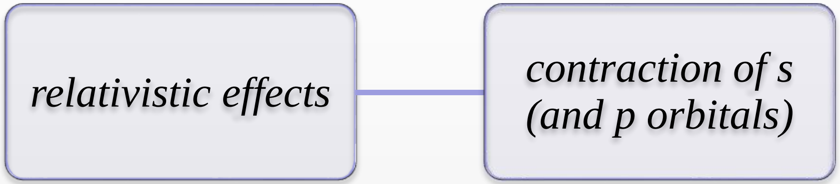
↑ electron radial velocity

mass electron ↑

relativity

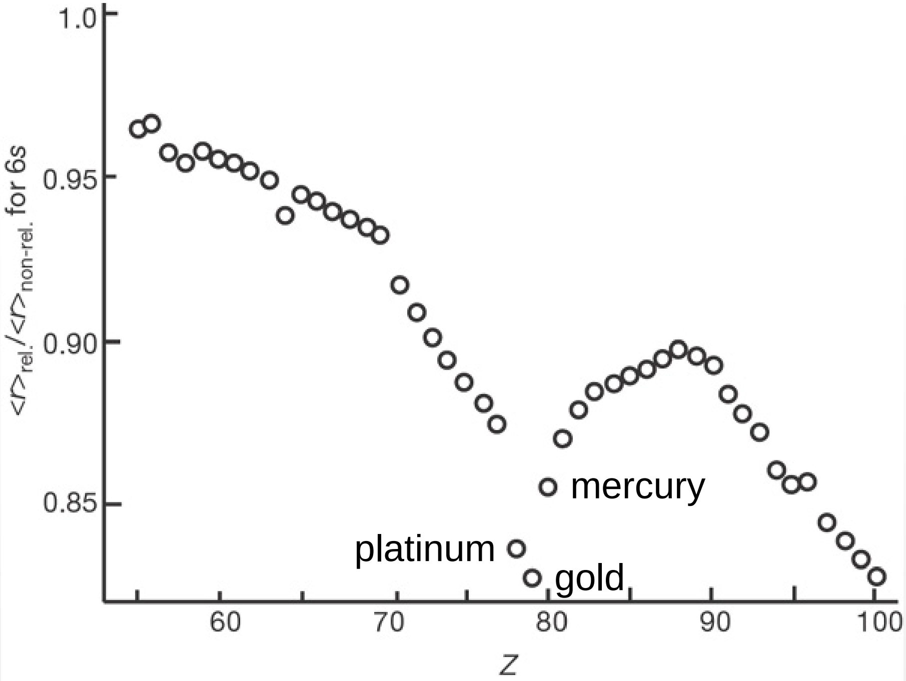
S. Kramer, F. Gagosz in “Gold Catalysis An Homogeneous Approach“, Eds. F. D. Toste, V. Michelet, 2014 World Scientific Publishing, ch. 1.
D. J. Gorin, F. D. Toste *Nature* **2007**, *446*, 395.
A. Fürstner, P. W. Davies *Angew. Chem. Int. Ed.* **2007**, *46*, 3410.

Gold as element: relativistic effects



relativistic effects

contraction of s (and p orbitals)



Calculated relativistic contraction of the 6s orbital.

R. Coquet, K. L. Howard, D. J. Willock *Chem. Soc. Rev*. **2008**, *37*, 2046.
E. Pyykko *Chem. Rev*. **1988**, *88*, 563.

Gold compounds and complexes

AuCl

$AuCl_3$ and $AuBr_3$

$NaAuCl_4$ and $KAuCl_4$

counterions

$[NTf_2]^-$, $[BF_4]^-$, $[SbF_6]^-$, $[OTf]^-$

$$AuCl_3 \xrightarrow{\text{Ligand(s)}} LAuCl_3 \text{ or } LL'AuCl_2$$

$$AuCl \xrightarrow{\text{Ligand}} LAuCl$$

A. Fürstner *Chem. Soc. Rev.* **2009**, *38*, 3208.
A. Fürstner, P. W. Davies *Angew. Chem. Int. Ed.* **2007**, *46*, 3410.
A. Fürstner *Acc. Chem. Res.* **2014**, *47*, 925.
B. Ranieri, I. Escofeta, A. M. Echavarren *Org. Biomol. Chem.* **2015**, *13*, 7103.
A. S. K. Hashmi *Chem. Rev.* **2007**, *107*, 3180.
A. S. K. Hashmi, G. J. Hutchings *Angew. Chem. Int. Ed.* **2006**, *45*, 7896.
C. Obradorsa, A. M. Echavarren *Chem. Commun.* **2014**, *50*, 16.
D. J. Gorin, B. D. Sherry, F. D. Toste *Chem. Rev.* **2008**, *108*, 3351.
A. Arcadi *Chem. Rev.* **2008**, *108*, 3266

gold(I) and gold(III) salts, aurous and auric compounds

$AuCl_3$ and $AuBr_3$

$$AuCl_3 + 3AgX \longrightarrow Au^{3+} + 3X^-$$

Less coordinating X
More electrofilic Au

counterions

$[NTf_2]^-$, $[BF_4]^-$, $[SbF_6]^-$, $[OTf]^-$

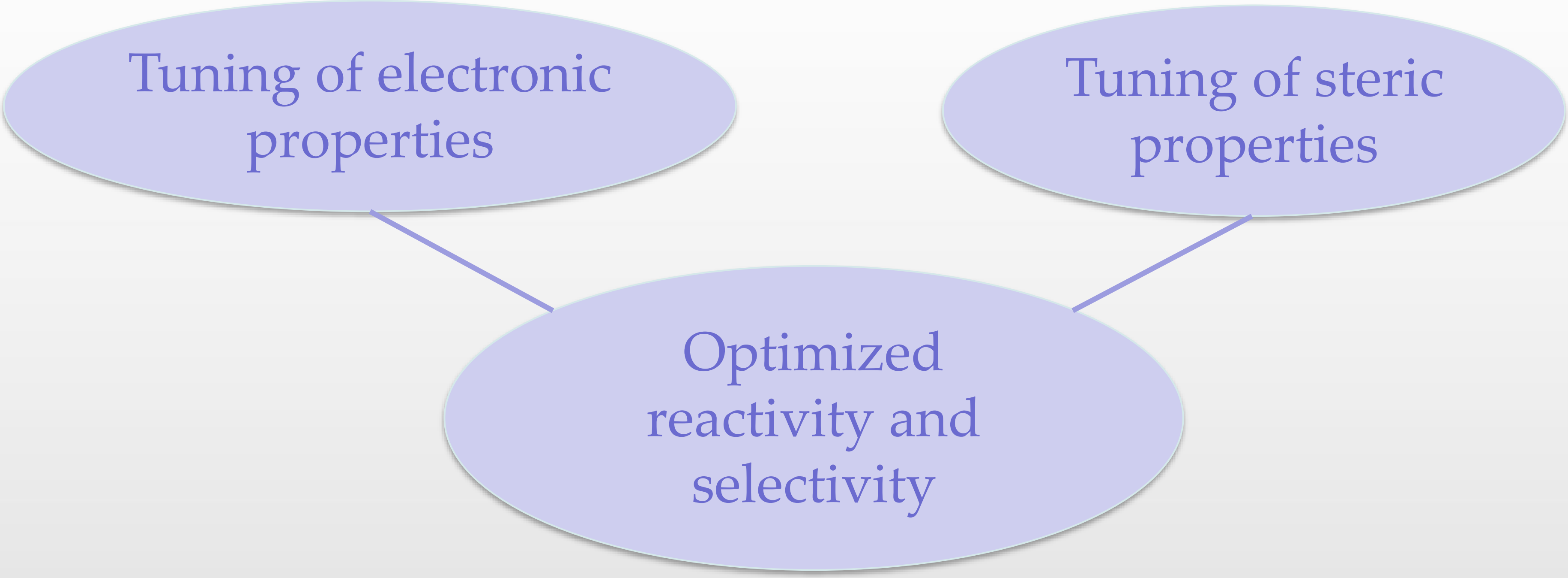
$NaAuCl_4$ and $KAuCl_4$

AuCl

gold(I) complexes

L Au Cl

ligand Gold(I) counterion



Tuning of electronic properties

Tuning of steric properties

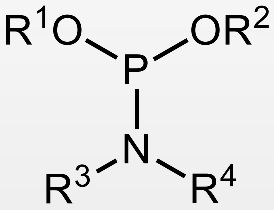
Optimized reactivity and selectivity

gold(I) complexes

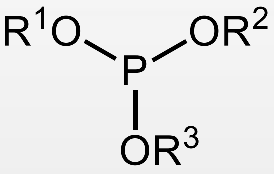
$$AuCl(SMe_2) \xrightarrow[\textit{solvent}]{\textit{Ligand}} \textbf{\textit{L}}AuCl$$

gold chloride complex *gold chloride complex*

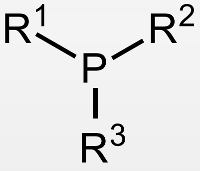
General structure of most commonly used ligands



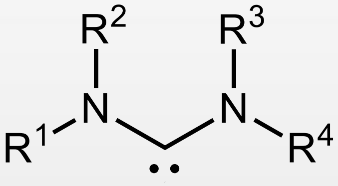
phosphoroamidite



phosphite



phosphine



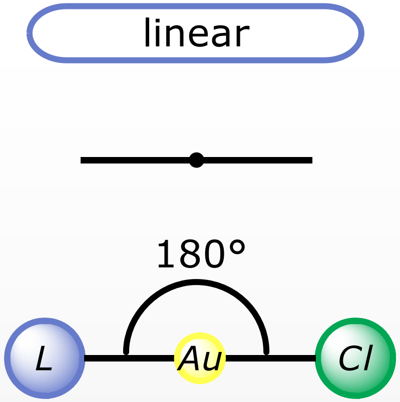
carbene

electrodonor properties

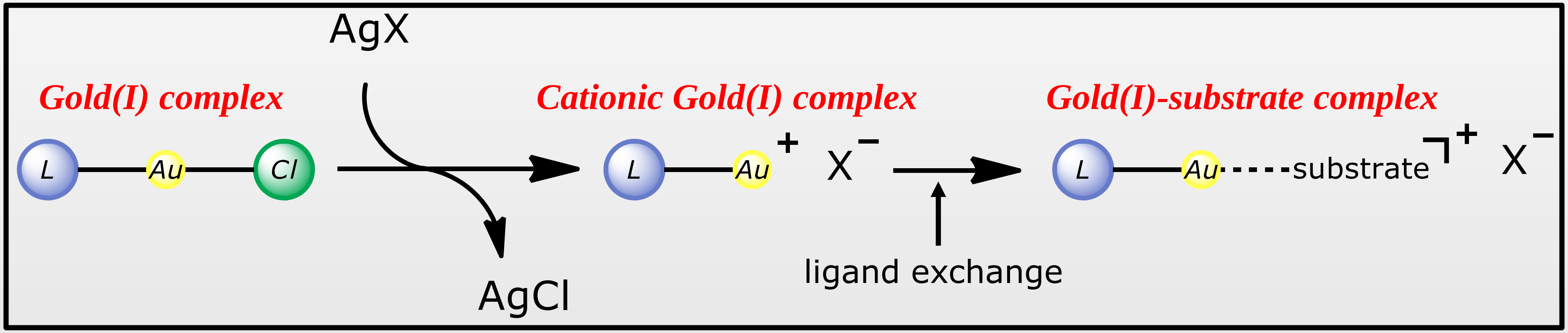
Gold compounds and complexes

gold(I) complexes

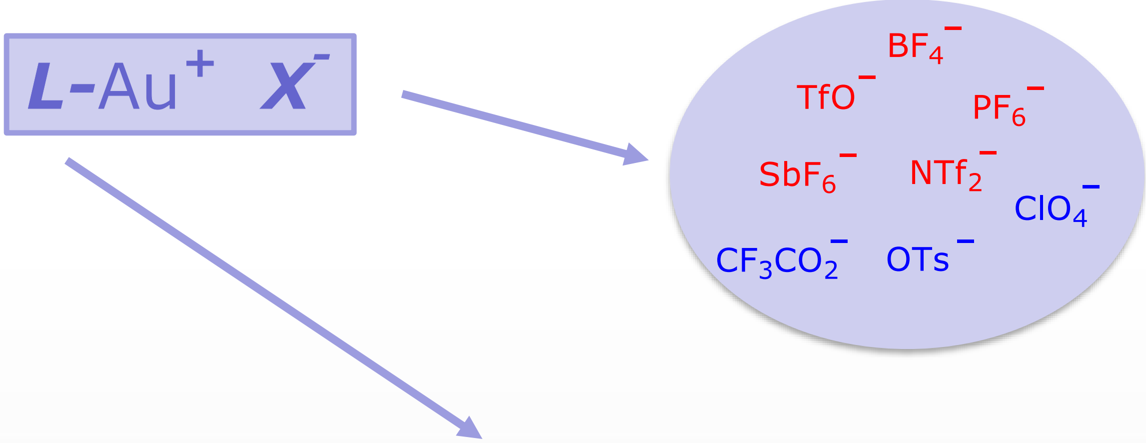
***L*AuCl**



Gold(I) complexes are *d^{10}* complexes and present a linear, bi-coordinated geometry comprising the metal center within the ligand and the chloride atom.



Gold compounds and complexes



$L\text{-}Au^{+}\ X^{-}$

BF_4^-

TfO^-

PF_6^-

SbF_6^-

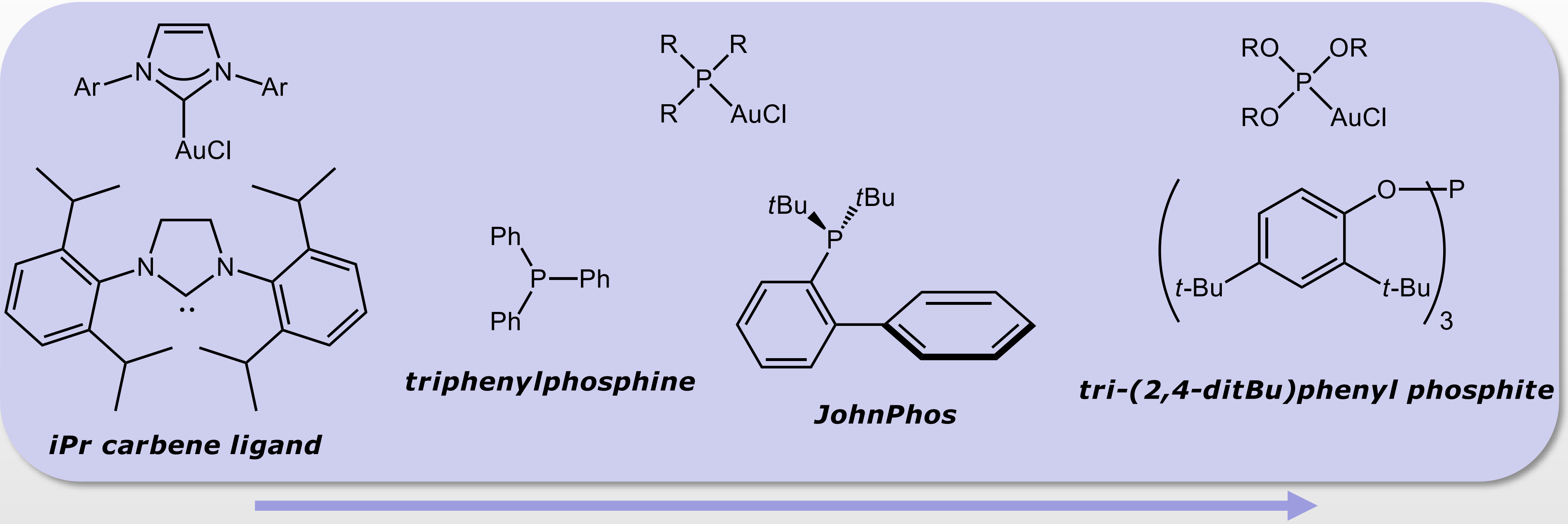
NTf_2^-

ClO_4^-

$CF_3CO_2^-$

OTs^-

Less and more coordinating ions



iPr carbene ligand

triphenylphosphine

JohnPhos

tri-(2,4-ditBu)phenyl phosphite

electrophilicity

Properties of cationic gold(I) species

$L\text{-Au}^{+}\quad X^{-}$

- ✓ strength of the *L*-Au bond
- ✓ Lewis acidity, π acids
- ✓ do not tend to undergo oxidative addition
- ✓ act as big soft proton

P. Schwerdtfeger, H. L. Hermann, H. Schmidbaur *Inorg. Chem.* **2003**, *42*, 1334.

Properties of cationic gold(I) species

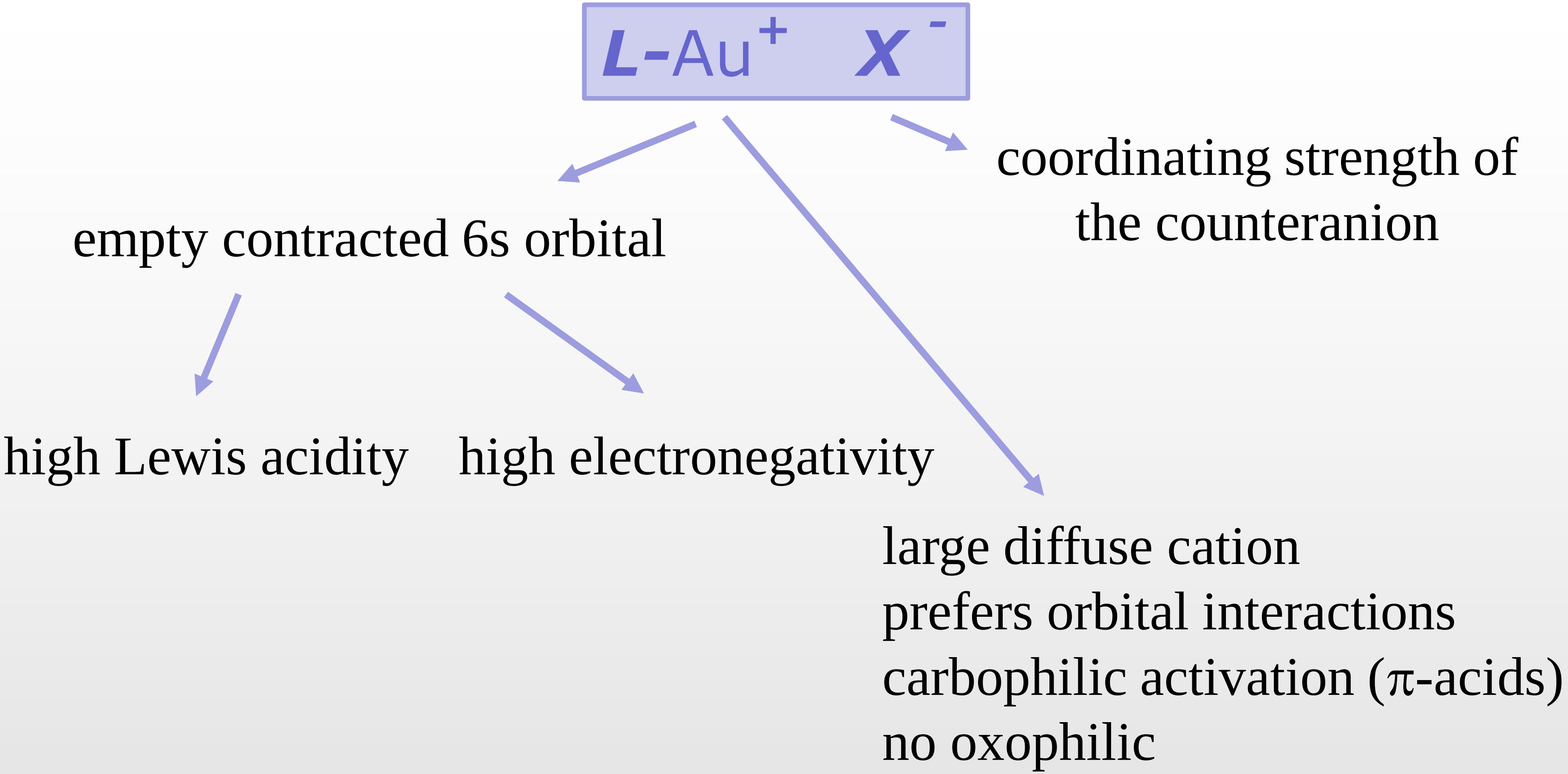
$L\text{-}Au^{+} \quad X^{-}$

- ✓ the strength of the L-Au bond depends on relativistic contraction of the 6s orbital
- ✓ the strength of the L-Au bond is greater than in Ag and Cu
- ✓ ligand exchange in solution is not observed

P. Schwerdtfeger, H. L. Hermann, H. Schmidbaur *Inorg. Chem.* **2003**, *42*, 1334.

Properties of cationic gold(I) species

✓ Lewis acidity, ‘soft’ Lewis acid, preferring ‘soft’ electrophiles



$L\text{-}Au^{+}\quad X^{-}$

empty contracted 6s orbital

coordinating strength of
the counteranion

high Lewis acidity

high electronegativity

large diffuse cation
prefers orbital interactions
carbophilic activation (π-acids)
no oxophilic

Properties of cationic gold(I) species

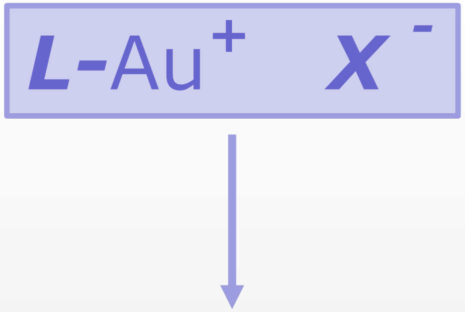
✓ do not tend to undergo oxidative addition

$L\text{-}Au^{+} \quad X^{-}$

✓ not particularly nucleophilic,
✓ do not tend to undergo oxidative addition,
✓ tolerant to oxygen.

Properties of cationic gold(I) species

- ✓ big soft proton

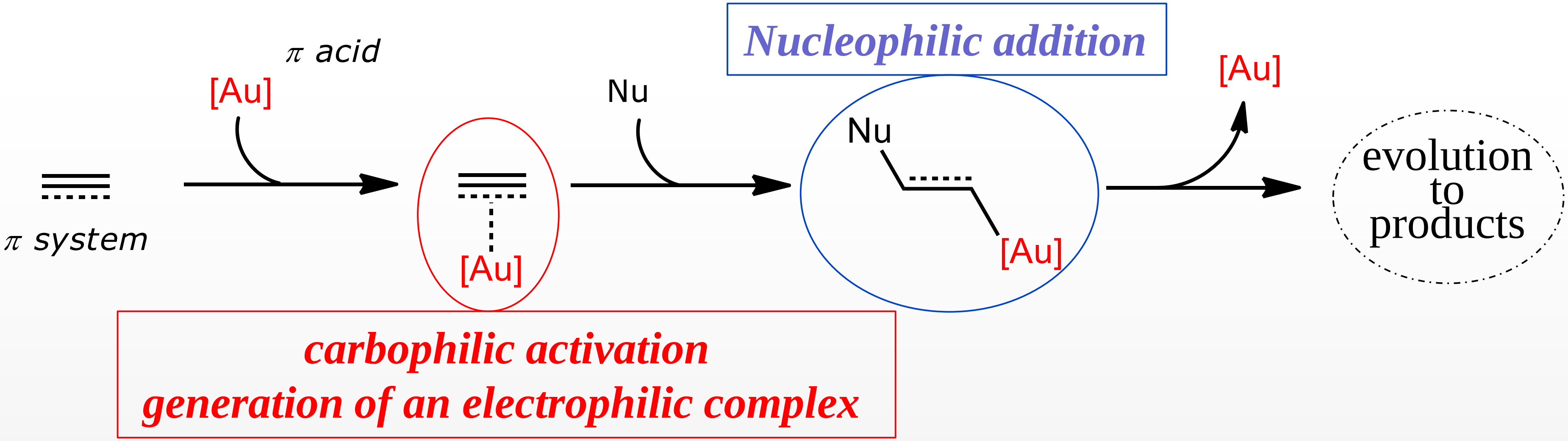


$L\text{-}Au^{+} \quad X^{-}$

- ✓ isolobal to H^+
- ✓ catalysis under “acidic” conditions

cfr Pt(II) and Hg(II)

*Catalytic **carbophilic activation** in synthetic organic chemistry: catalysis by **gold π acids***



Nucleophilic addition

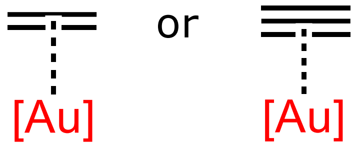
carbophilic activation
generation of an electrophilic complex

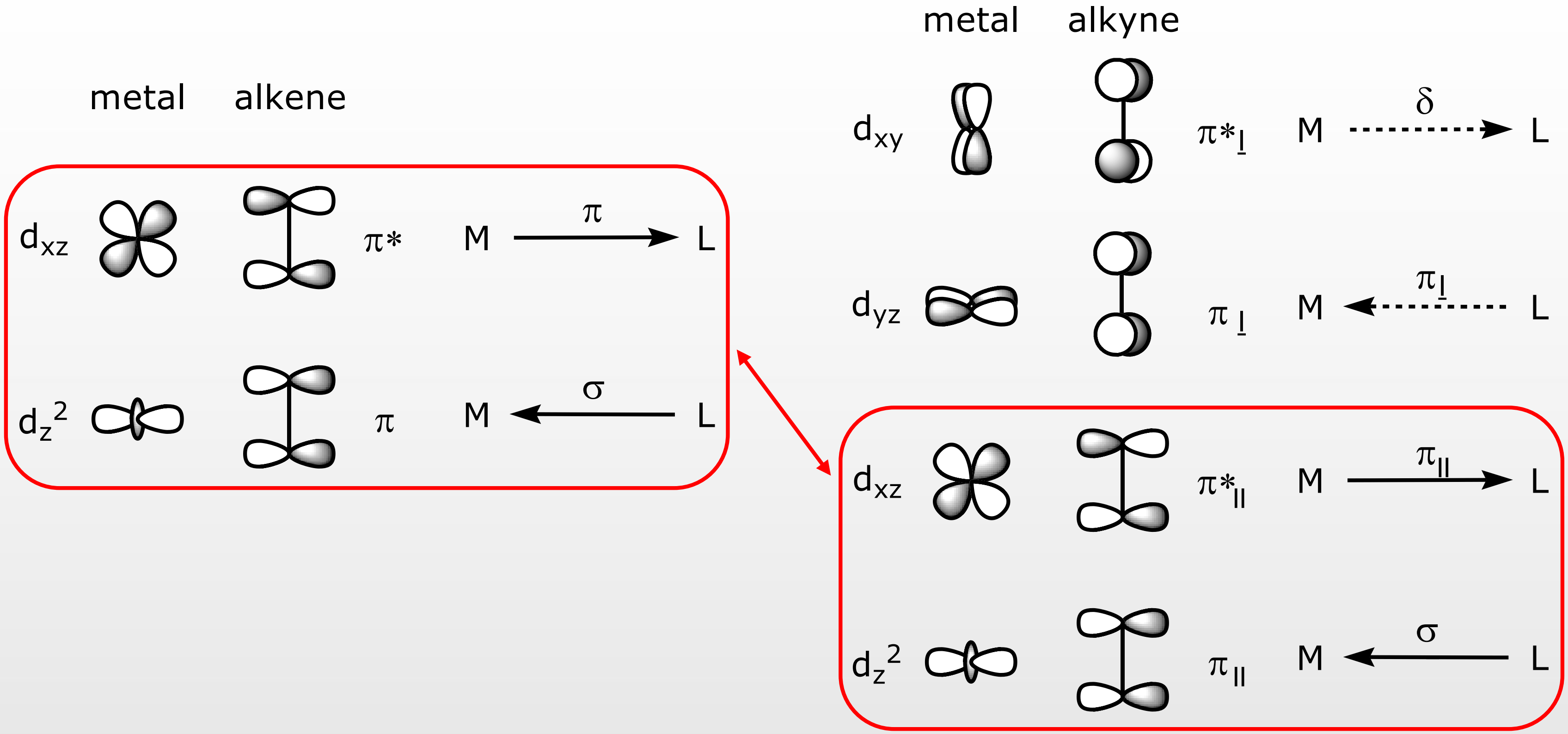
Basic mechanism of π acid catalysis exemplified by the addition of a generic nucleophile across a π system

*Catalytic **carbophilic activation** in synthetic organic chemistry: catalysis by **gold π acids***

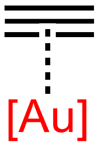
carbophilic activation
generation of an electrophilic complex

π acid coordination to unsaturated systems

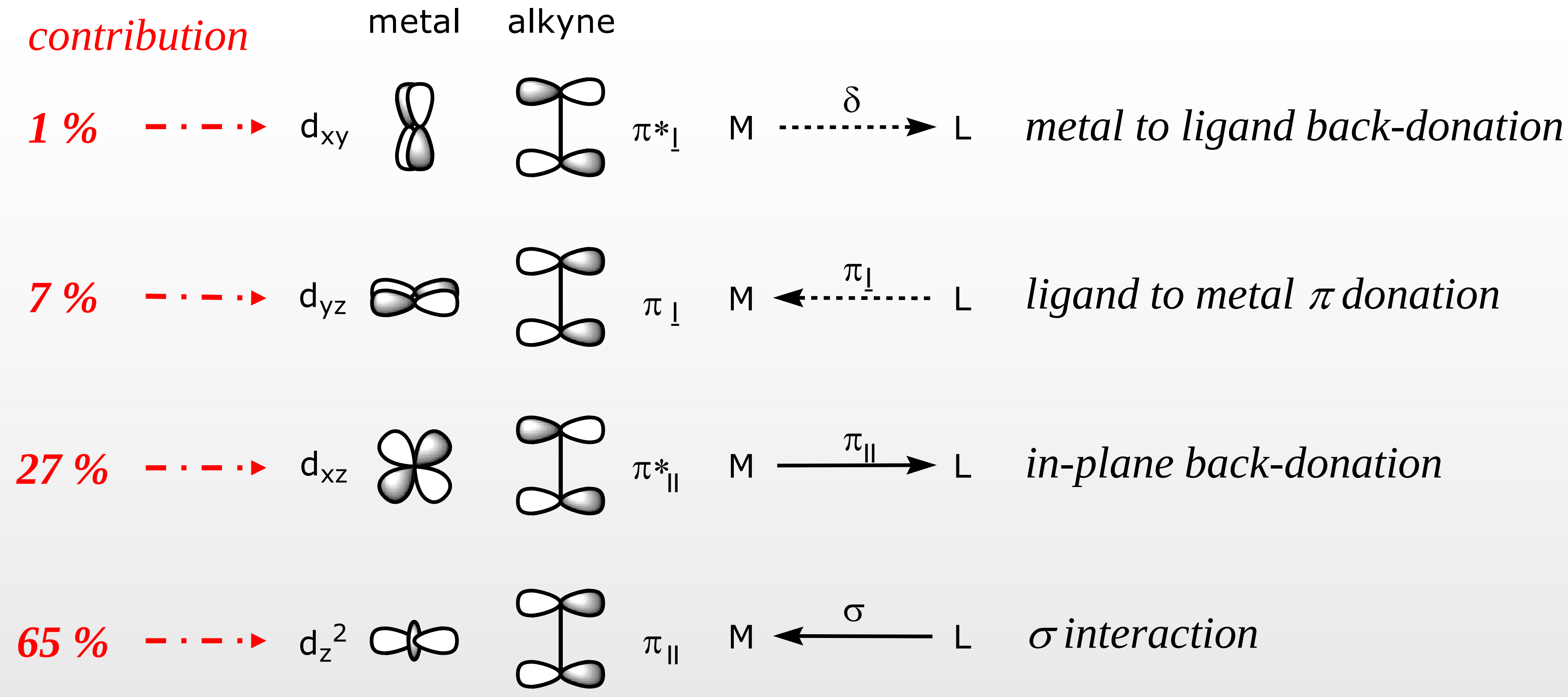




*Catalytic **carbophilic activation** in synthetic organic chemistry: catalysis by **gold π acids***

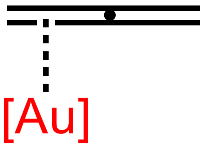


Au^+ acetylene complex

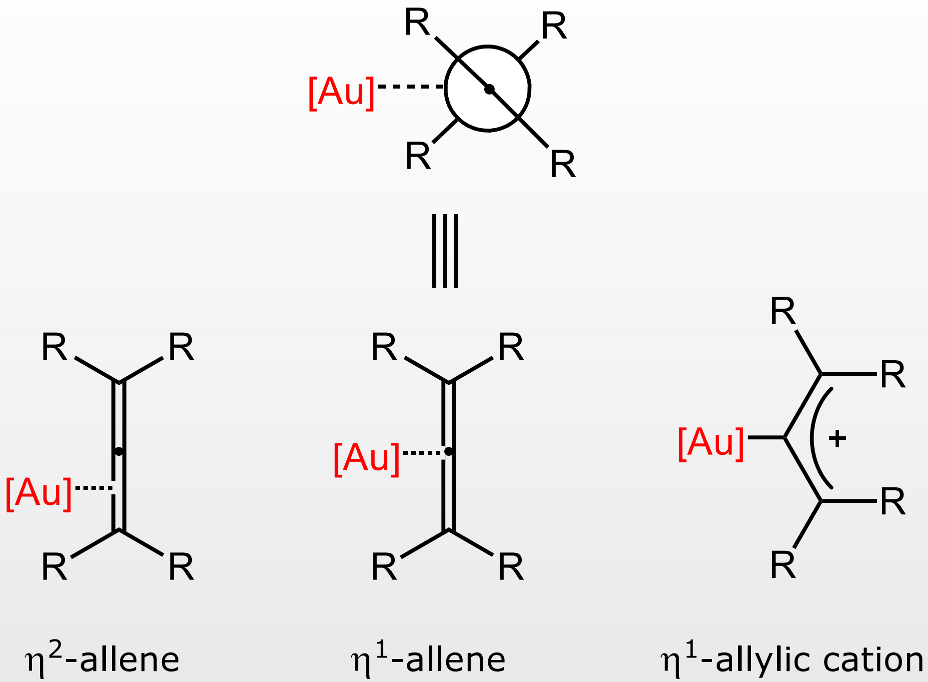


contribution		metal	alkyne			
1 %	d_{xy}			$\pi^*_{\perp}$	$M \xrightarrow{\delta} L$	*metal to ligand back-donation*
7 %	d_{yz}			$\pi_{\perp}$	$M \xleftarrow{\pi_{\perp}} L$	*ligand to metal π donation*
27 %	d_{xz}			$\pi^*_{\parallel}$	$M \xrightarrow{\pi_{\parallel}} L$	*in-plane back-donation*
65 %	d_{z^2}			$\pi_{\parallel}$	$M \xleftarrow{\sigma} L$	*σ interaction*

π acid coordination to unsaturated systems

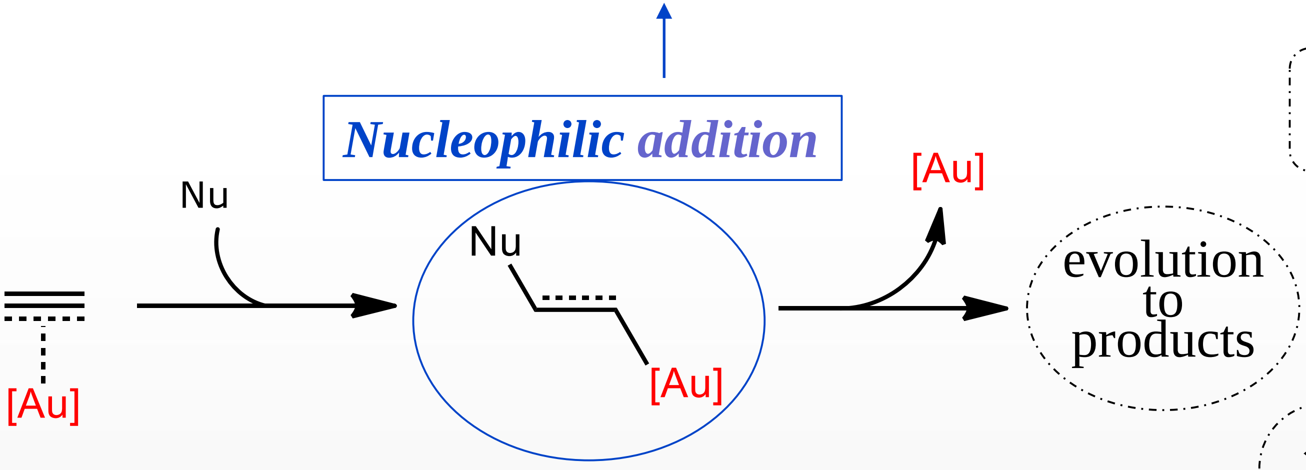


Potential coordination mode for gold π allene complexes



T. J. Brown, A. Sugie, M. G. Dickens, R. A. Widenhoefer, *Organometallics* **2010**, *29*, 4207.
T. J. Brown, A. Sugie, M. G. Dickens, R. A. Widenhoefer, *Chem. Eur. J.* **2012**, *18*, 6959.

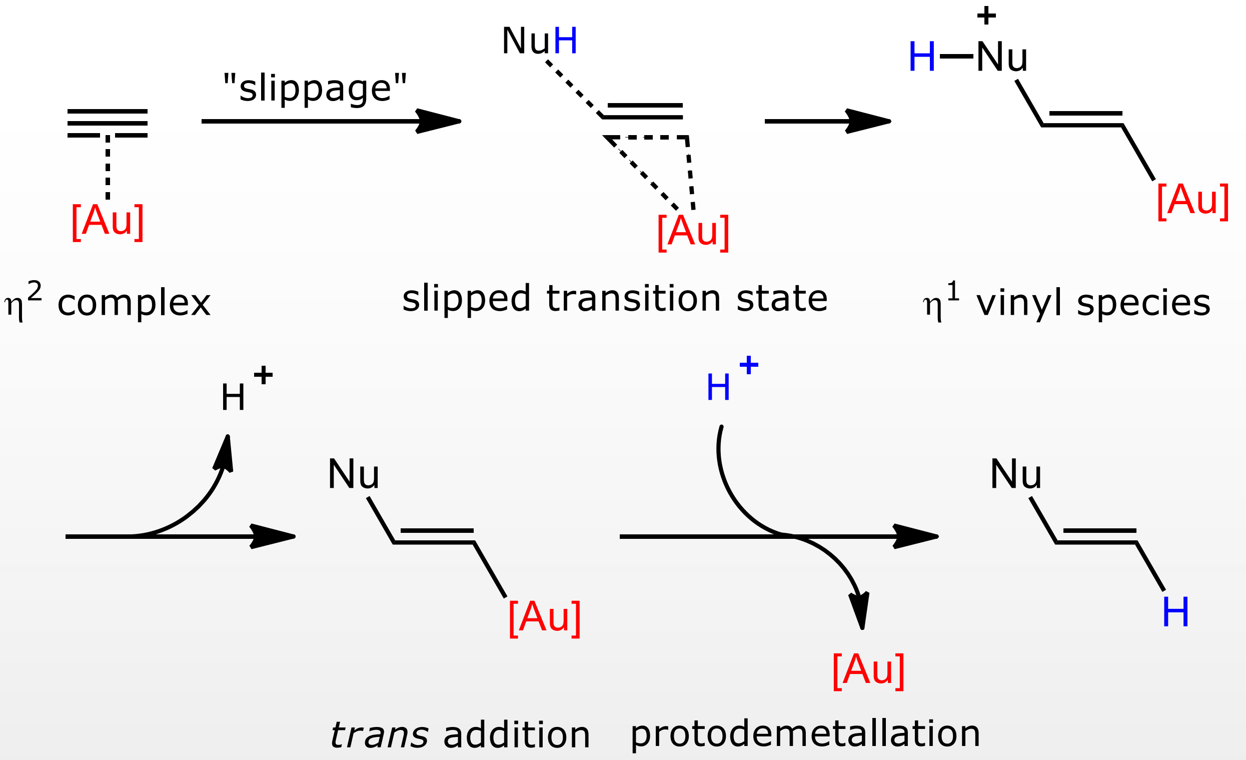
formation of carbon-heteroatom and carbon-carbon bonds



addition across the π system

- ✓ enyne cycloisomerization
- ✓ C-H functionalization
- ✓ cycloaddition
- ✓ cascade reactions
- ✓ rearrangements
- ✓ multicomponent reactions

Nucleophilic addition to π activated carbon-carbon triple bonds, synthesis of heterocycles



η^2 complex

slipped transition state

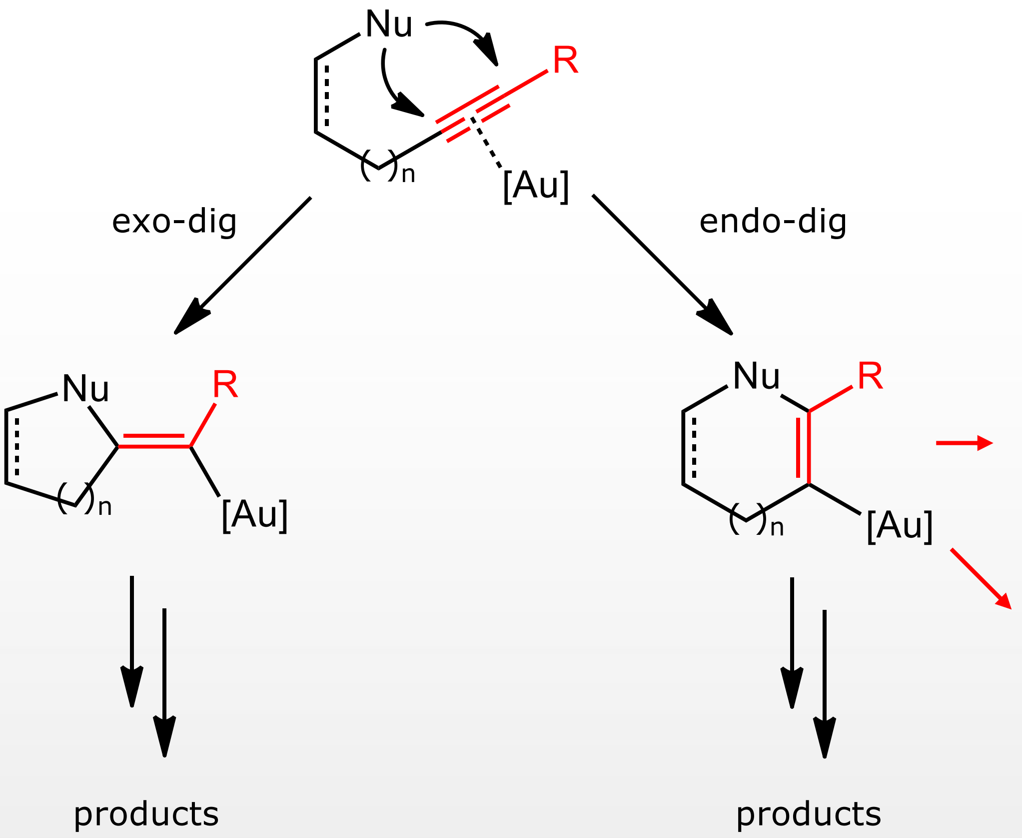
η^1 vinyl species

trans addition

protodemetallation

R. Dorel, A. M. Echavarren *Chem. Rev.* **2015**, *115*, 9028.
W. Debrouwer, T. S. A. Heugebaert, B. I. Roman, C. V. Stevens *Adv. Synth. Catal*. **2015**, *357*, 2975.

Nucleophilic addition to π activated carbon-carbon triple bonds, synthesis of heterocycles

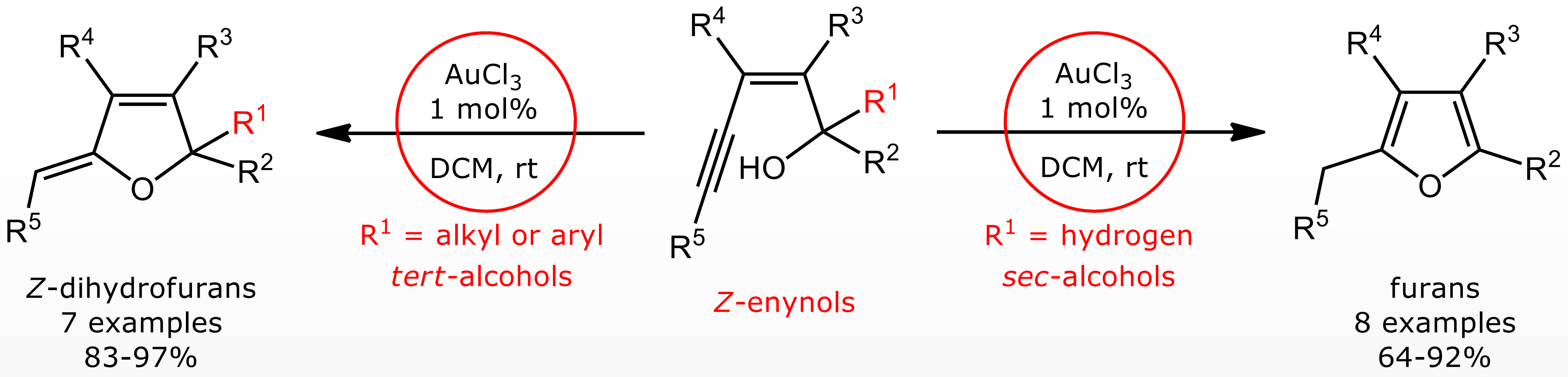


"formal" proposed intermediates

"omitted" ligands
"neutral" gold atom

R. Dorel, A. M. Echavarren *Chem. Rev.* **2015**, *115*, 9028.
W. Debrouwer, T. S. A. Heugebaert, B. I. Roman, C. V. Stevens *Adv. Synth. Catal*. **2015**, *357*, 2975.

gold-catalyzed 5-exo-dig cyclization of (Z)-enynols



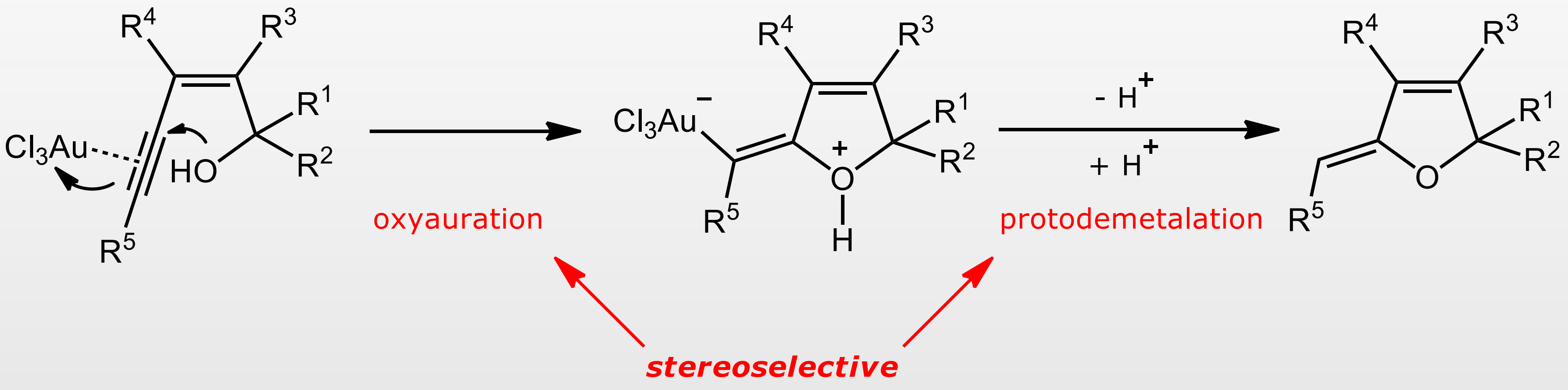
Z-dihydrofurans
7 examples
83-97%

R^1 = alkyl or aryl
tert-alcohols

Z-enynols

R^1 = hydrogen
sec-alcohols

furans
8 examples
64-92%



oxyauration

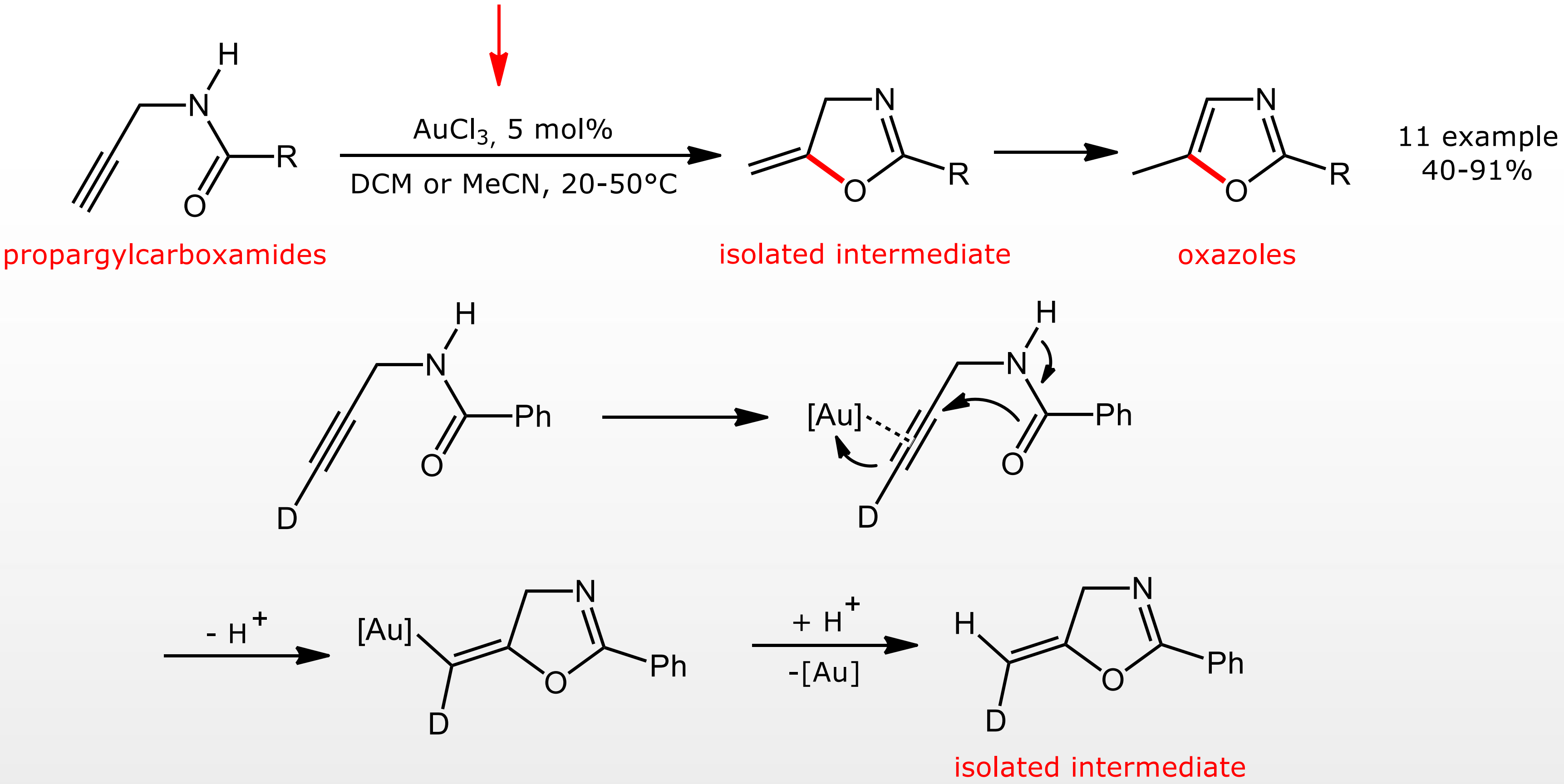
protodemetalation

stereoselective

A. S. K. Hashmi, L. Schwarz, J. H. Choi, T. M. Frost *Angew. Chem., Int. Ed*. **2000**, *39*, 2285.
Y. Liu, F. Song, Z. Song, M. Liu, B. Yan *Org. Lett*. **2005**, *7*, 5409.

Nucleophilic addition to π activated carbon-carbon triple bonds, synthesis of heterocycles

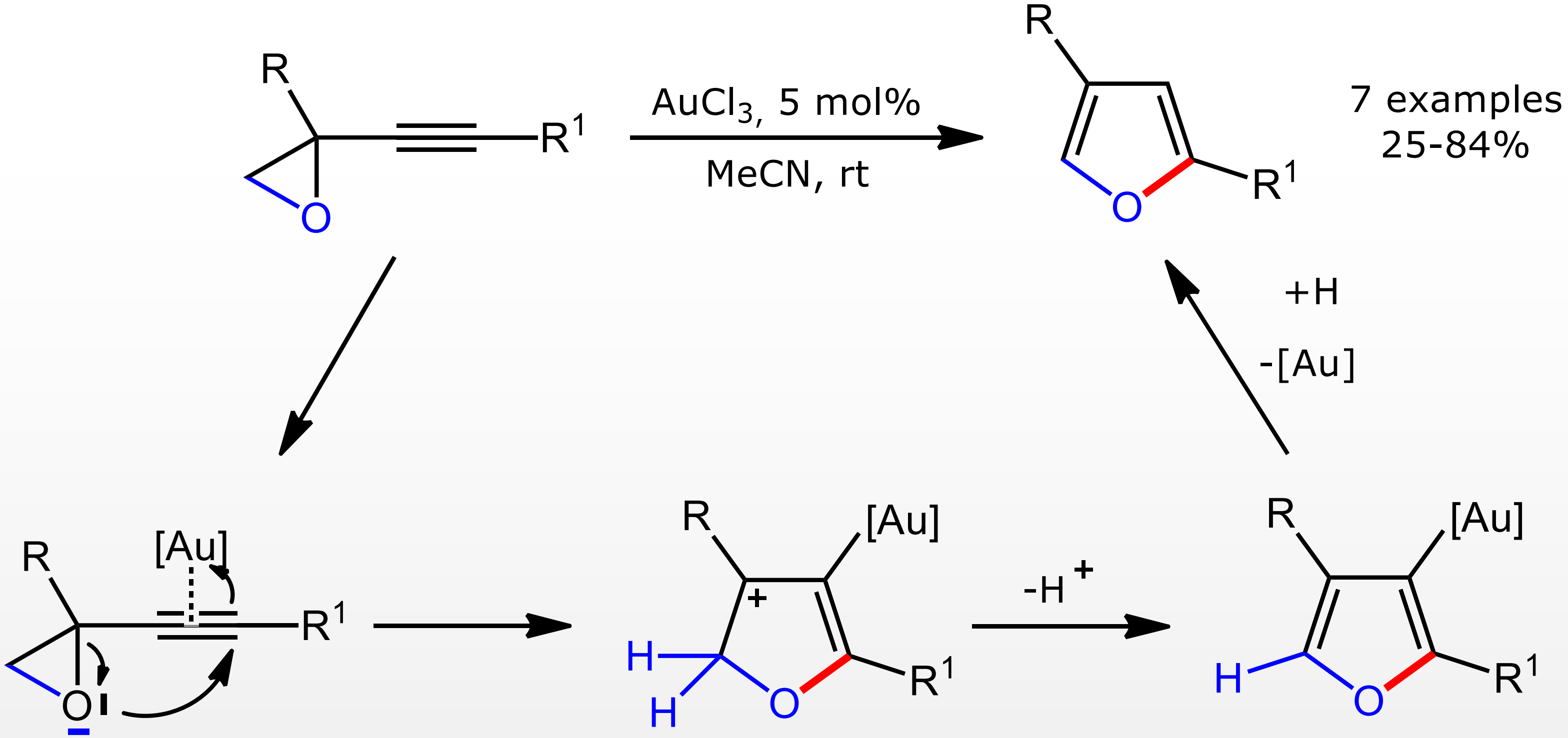
gold-catalyzed 5-exo-dig cyclization of propargylcarboxamides.



Alternative methodologies: basic conditions, Pt(II) or Hg(II) salts in stoichiometric amount at high temperature

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

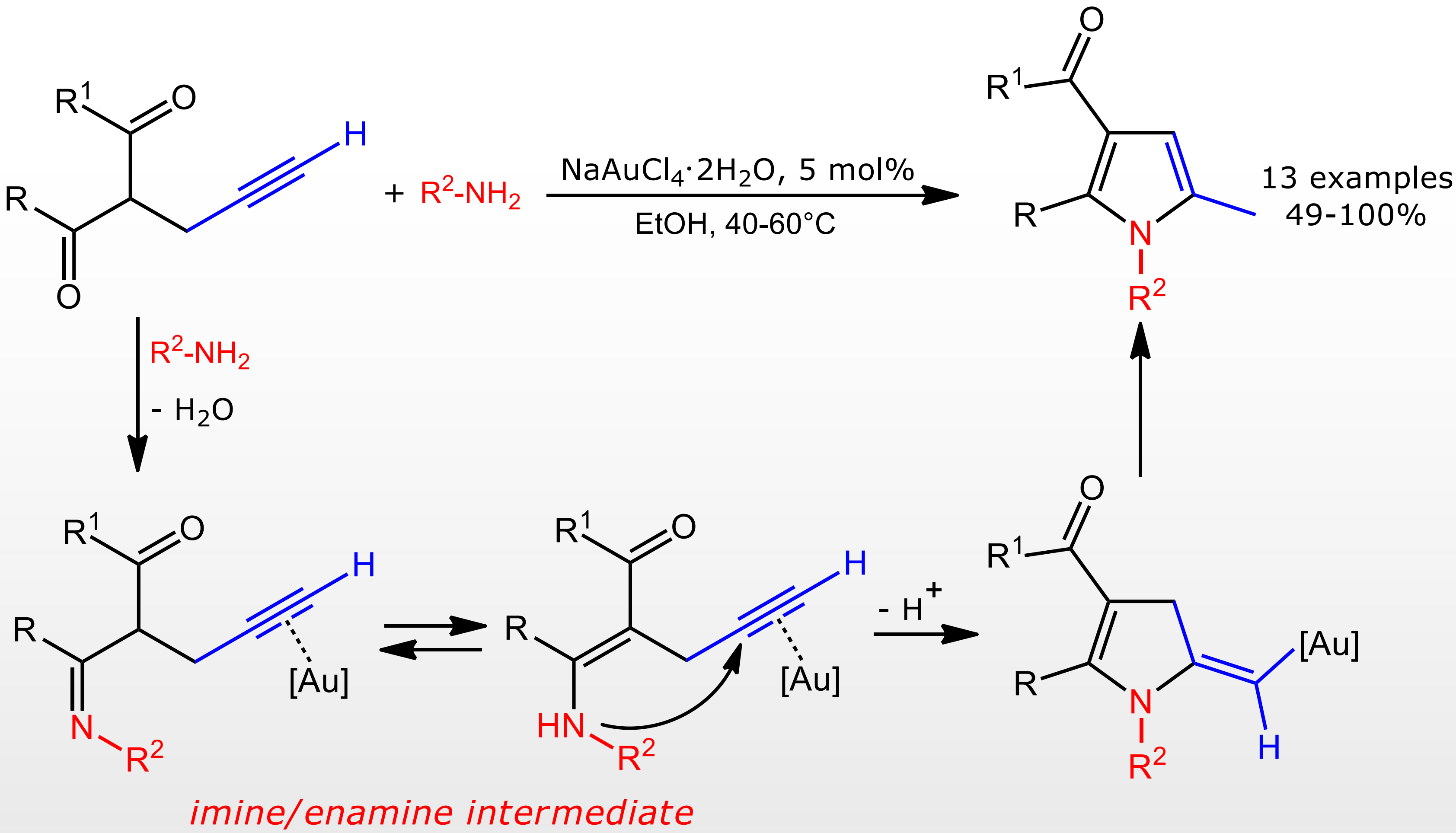
isomerization of alkynyl epoxides to furans



Alternative promoters: mercury salts *toxic*,
bases, *R = H*
molybdenum and ruthenium, *R¹ = H*

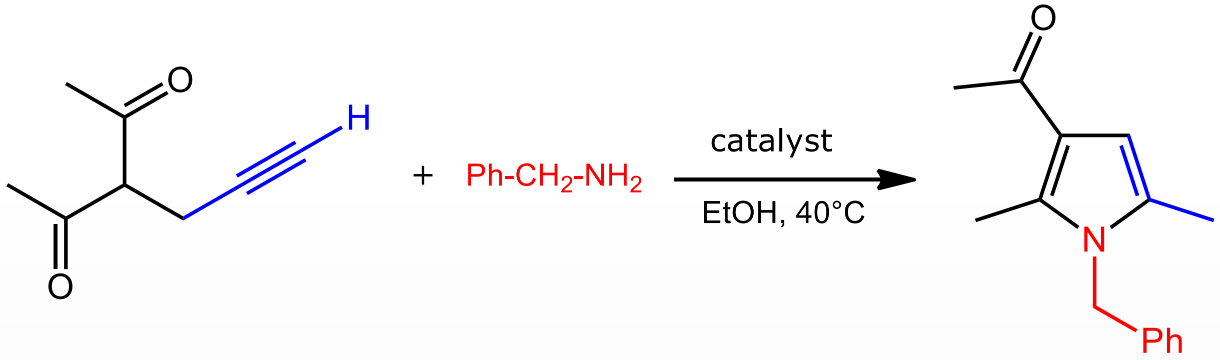
A. S. K. Hashmi, P. Sinha *Adv. Synth. Catal*. **2004**, *346*, 432.

Domino addition/annulation reaction for the synthesis of pyrroles



A. Arcadi, S. Di Giuseppe, F. Marinelli, E. Rossi *Adv. Synth. Catal*. **2001**, *343*, 443.
A. Arcadi, S. Di Giuseppe, F. Marinelli, E. Rossi *Tetrahedron: asymmetry* **2001**, *12*, 2715.
A. Arcadi, G. Abbiati, E. Rossi *J. Organomet. Chem*. **2011**, *696*, 87.

Domino addition/annulation reaction for the synthesis of pyrroles



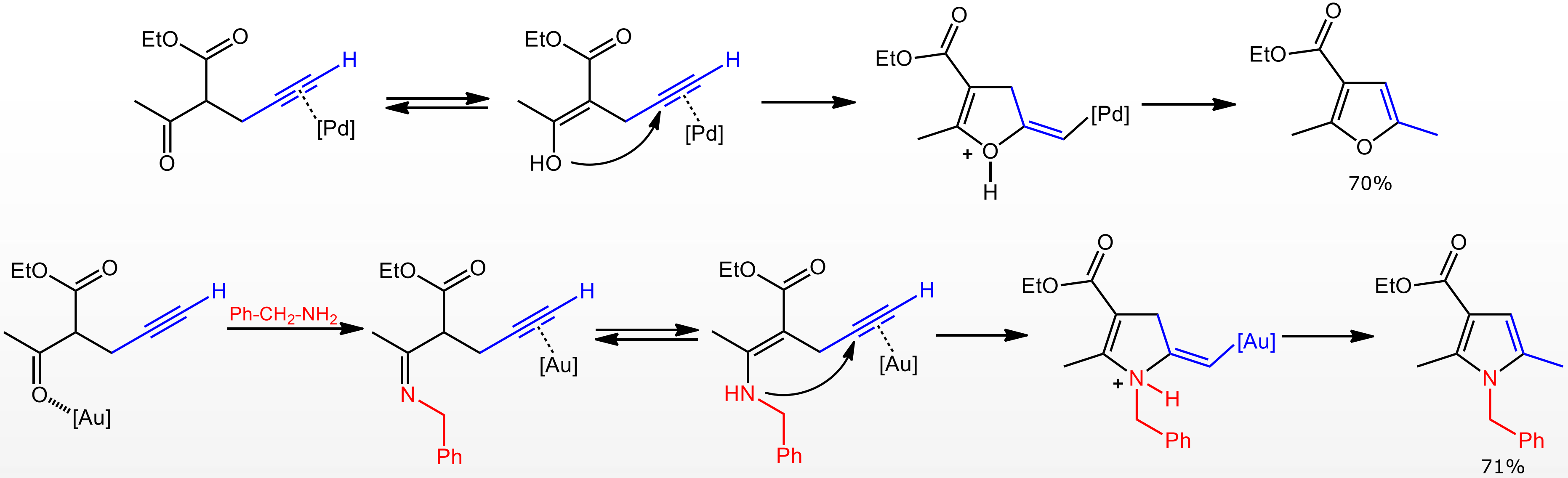
catalyst (mol%)	*time (h)*	*yield (%)*
$NaAuCl_4$ (5)	1	100
CuI (5)	24	100
$ZnCl_2$ (5)	24	34
Na_2PdCl_4 (5)	1	100
$AgNO_3$ (5)	6	71

→ Strictly anaerobic conditions

→ Poorly selective

A. Arcadi, S. Di Giuseppe, F. Marinelli, E. Rossi *Adv. Synth. Catal*. **2001**, *343*, 443.
A. Arcadi, S. Di Giuseppe, F. Marinelli, E. Rossi *Tetrahedron: asymmetry* **2001**, *12*, 2715.
A. Arcadi, G. Abbiati, E. Rossi *J. Organomet. Chem*. **2011**, *696*, 87.

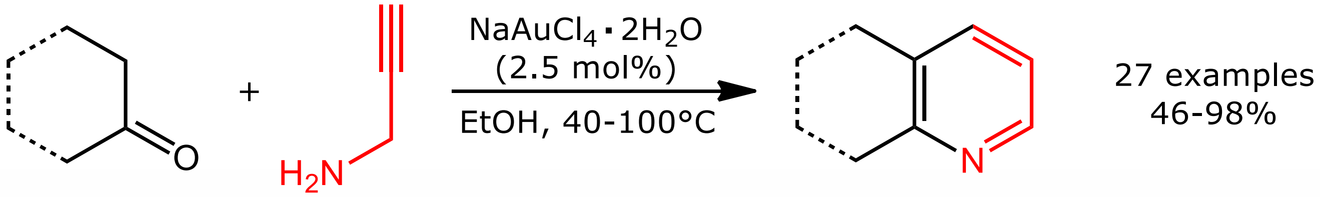
Domino addition/annulation reaction for the synthesis of pyrroles

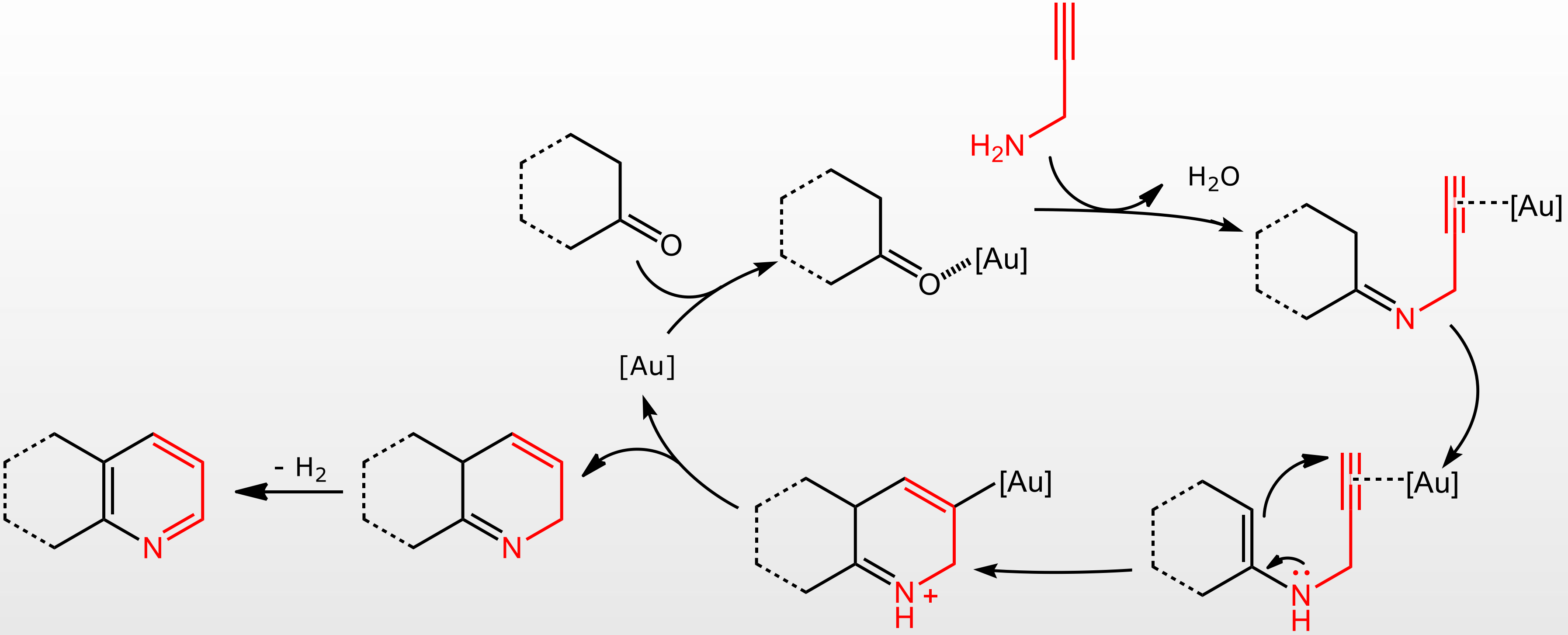


Reaction performed with β-ketoesters
selectivity could be related to the σ-philic property of gold(III) salts

A. Arcadi, S. Di Giuseppe, F. Marinelli, E. Rossi *Adv. Synth. Catal*. **2001**, *343*, 443.
A. Arcadi, S. Di Giuseppe, F. Marinelli, E. Rossi *Tetrahedron: asymmetry* **2001**, *12*, 2715.
A. Arcadi, G. Abbiati, E. Rossi *J. Organomet. Chem*. **2011**, *696*, 87.

Domino addition/annulation reaction for the synthesis of pyridines

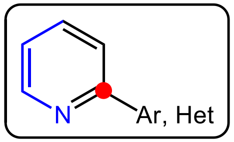




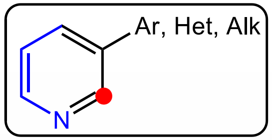
G. Abbiati, A. Arcadi, G. Bianchi, S. Di Giuseppe, F. Marinelli, E. Rossi *J. Org. Chem.* **2003**, *68*, 6959.

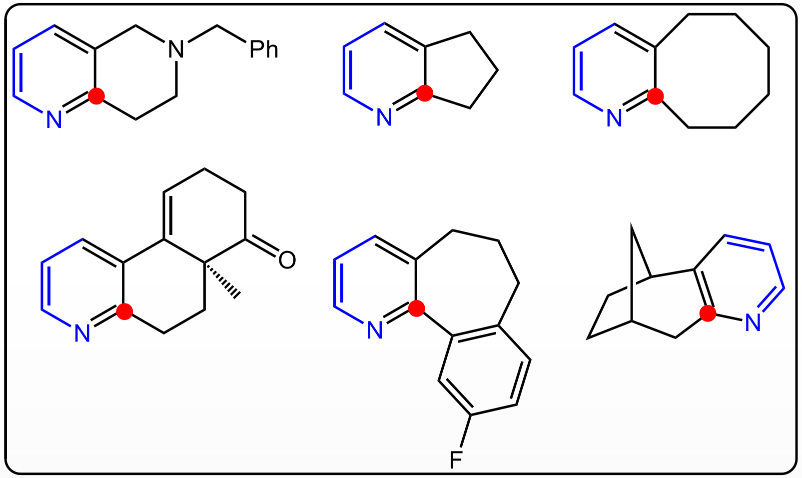
Nucleophilic addition to π activated carbon-carbon triple bonds, synthesis of heterocycles

from methyl ketones

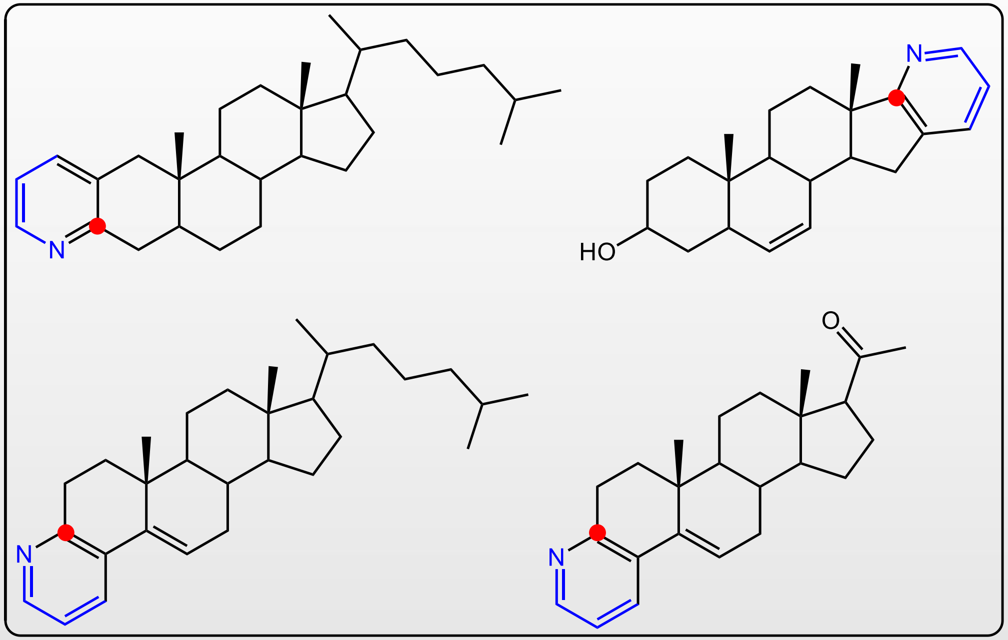


from aldehydes





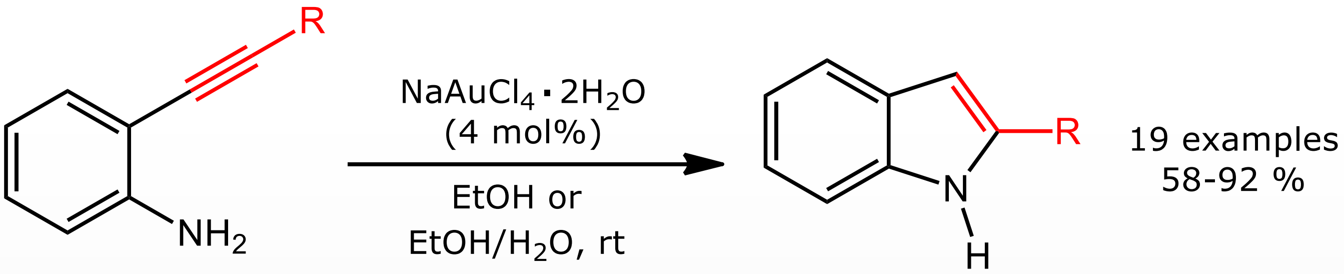
from cyclic ketones



linear or angular steroidal derivatives

G. Abbiati, A. Arcadi, G. Bianchi, S. Di Giuseppe, F. Marinelli, E. Rossi *J. Org. Chem*. **2003**, *68*, 6959.

annulation of 2-alkynylanilines

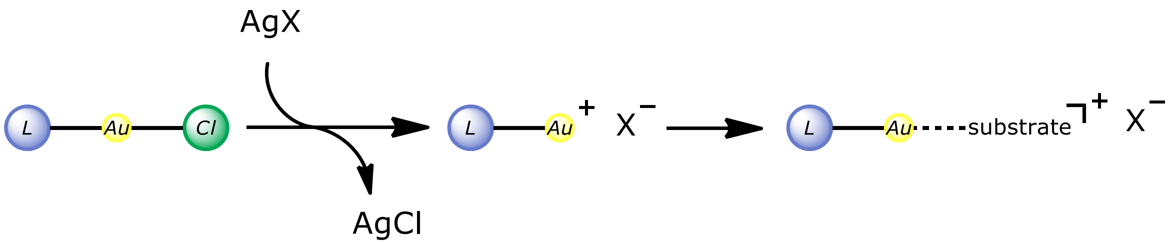


R = Ph

catalyst (mol%)	***solvent***	***yield (%)***
$NaAuCl_4$ (4)	EtOH	83
AuCl (4)	EtOH	50
Na_2PdCl_4 (5)	EtOH	7
$PdCl_2$ (5)	EtOH	6
$Pd(OAc)_2$ (5)	EtOH	8
$Cu(OTf)_2$ (5)	EtOH	10
$Cu(OAc)_2$ (5)	EtOH	0

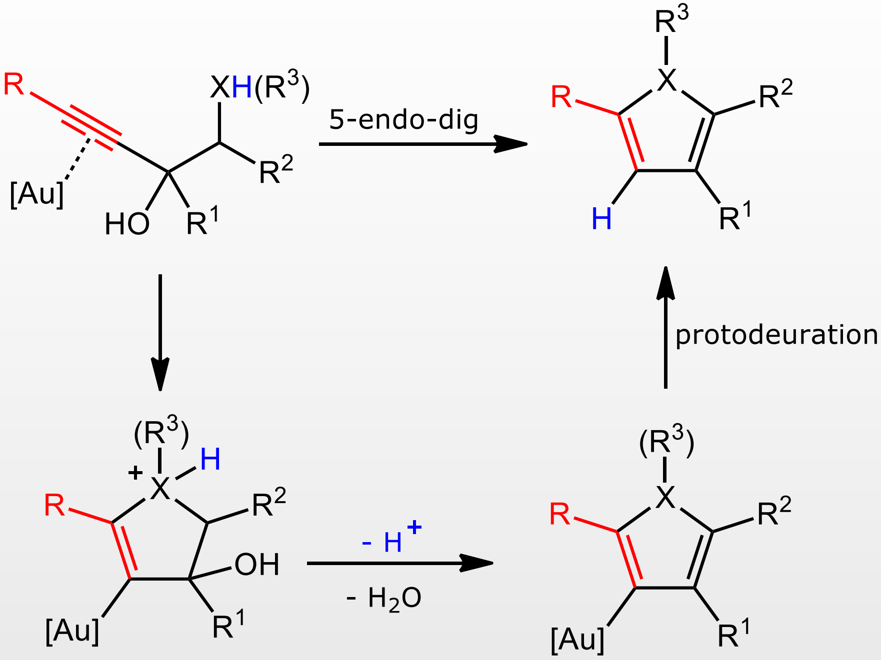
A. Arcadi, G. Bianchi, F. Marinelli *Synthesis* **2004**, 610.

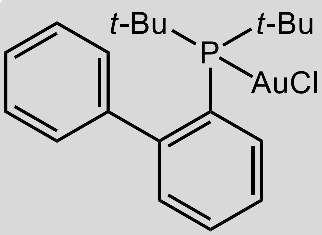
Nucleophilic addition to π activated carbon-carbon triple bonds, synthesis of heterocycles



Cationic Gold(I) complexes

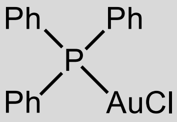
Synthesis of pyrroles, furans and thiophens from 2-hydroxyhomopropargylic alcohols, amines or sulphides





(JohnPhos)AuCl

Aponick
(JohnPhos)AuCl/AgOTf (2 mol%)
THF, 0°C
12 examples, 85-99%

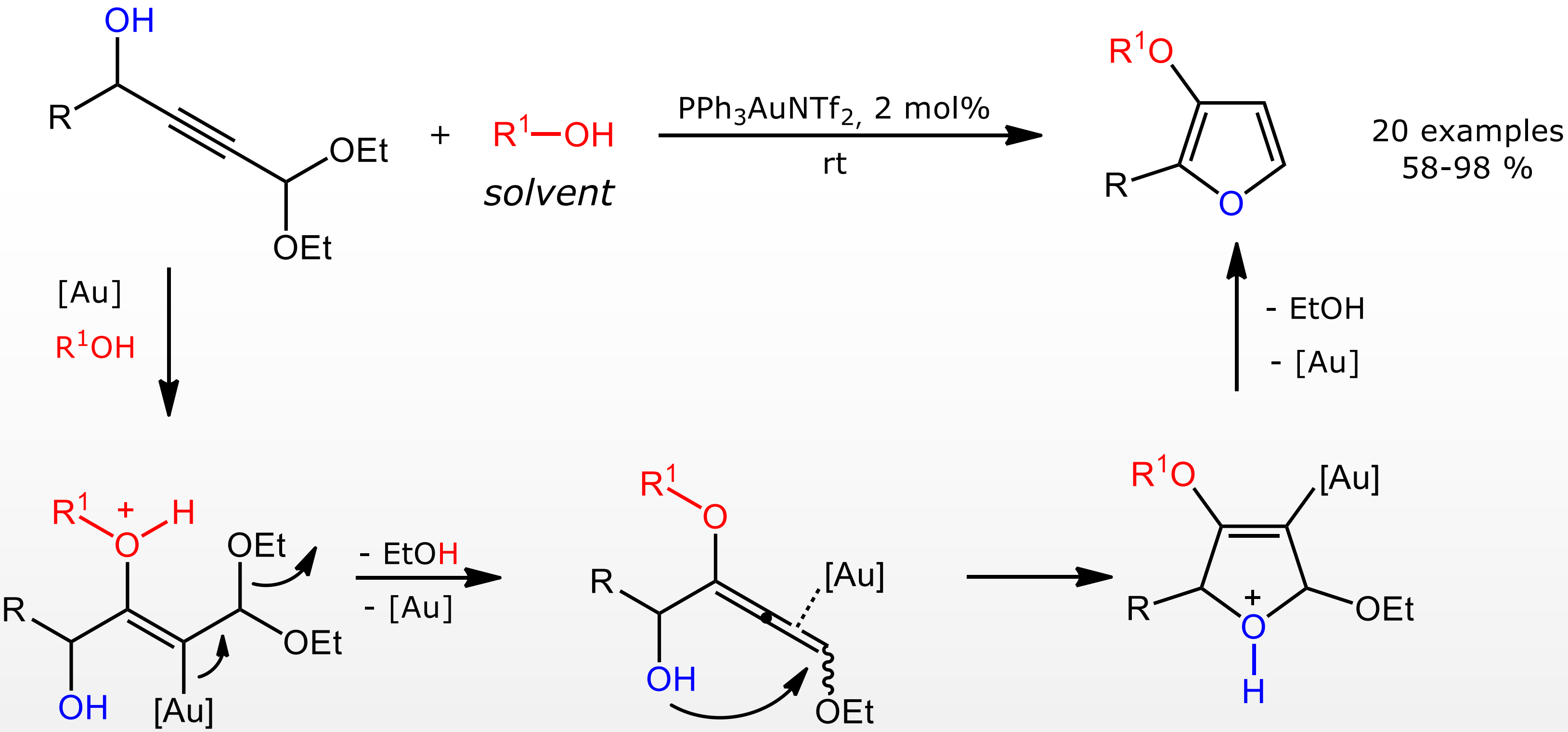


PPh_3AuCl

Akai
PPh_3AuCl/AgOTf (0.1%)
toluene, rt
13 examples, 73^{-97}%

A. Aponick, C.-Y. Li, J. Malinge, E. F. Marques *Org. Lett*. **2009**, *11*, 4624.
M. Egi, K. Azechi, S. Akai *Org. Lett*. **2009**, *11*, 5002.

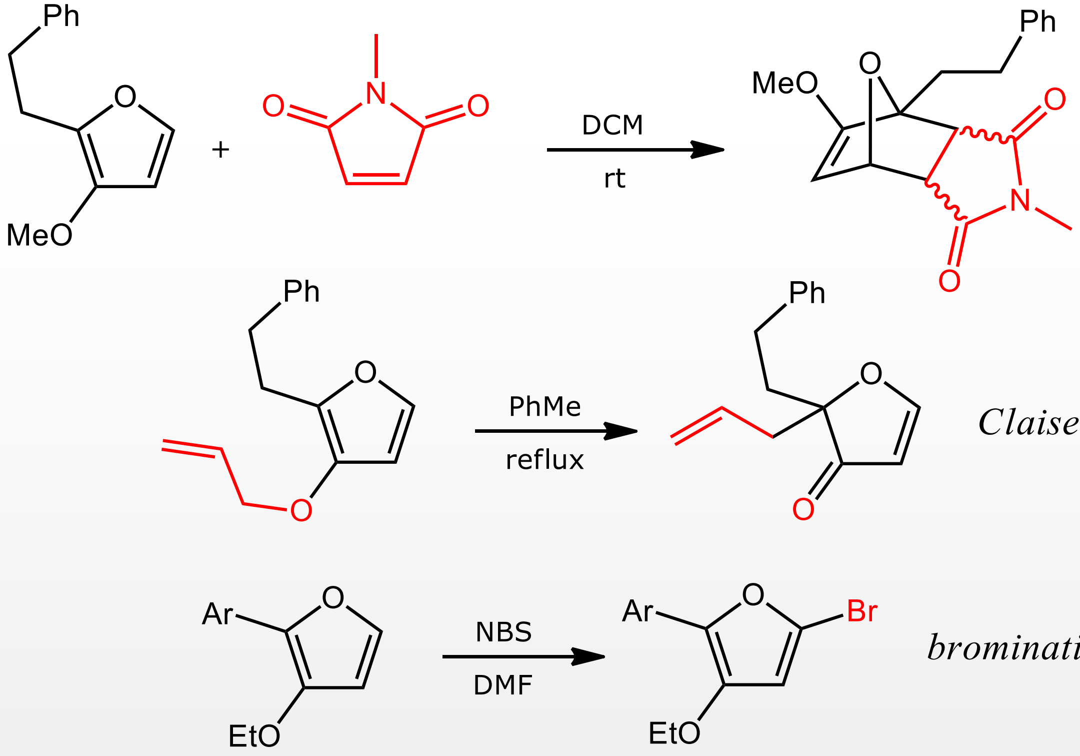
Synthesis of 3-alkoxyfurans from propargylic alcohols containing an acetal moiety



It is worth to underline that firm guidelines are not yet available for the optimum choice of ligands and counterions used in these processes, and so a certain degree of screening for the best reaction conditions (ligands, counterions, solvent, temperature) may be necessary.

M. N. Pennell, R. W. Foster, P. G. Turner, H. C. Hailes, C. J. Tame, T. D. Sheppard *Chem. Commun*. **2014**, *50*, 1302.

Nucleophilic addition to π activated carbon-carbon triple bonds, synthesis of heterocycles



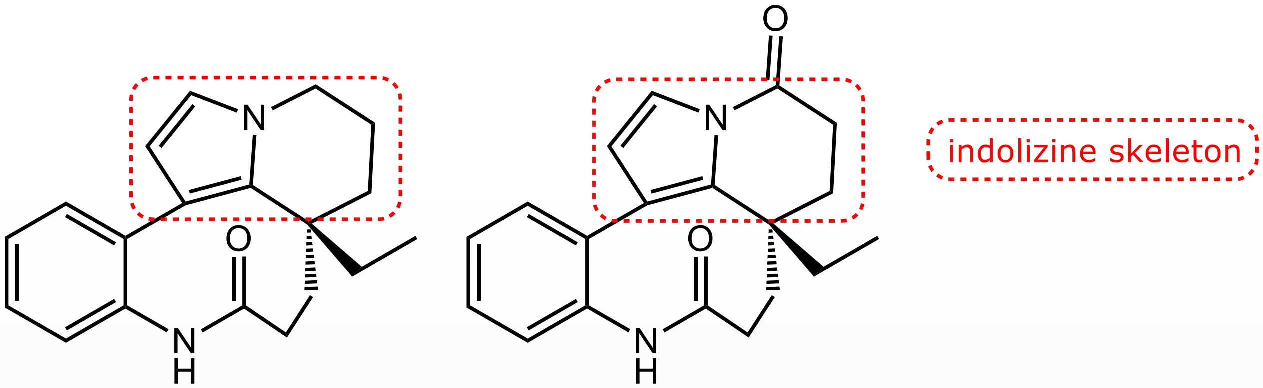
Diels-Alder cycloaddition

Claisen rearrangement

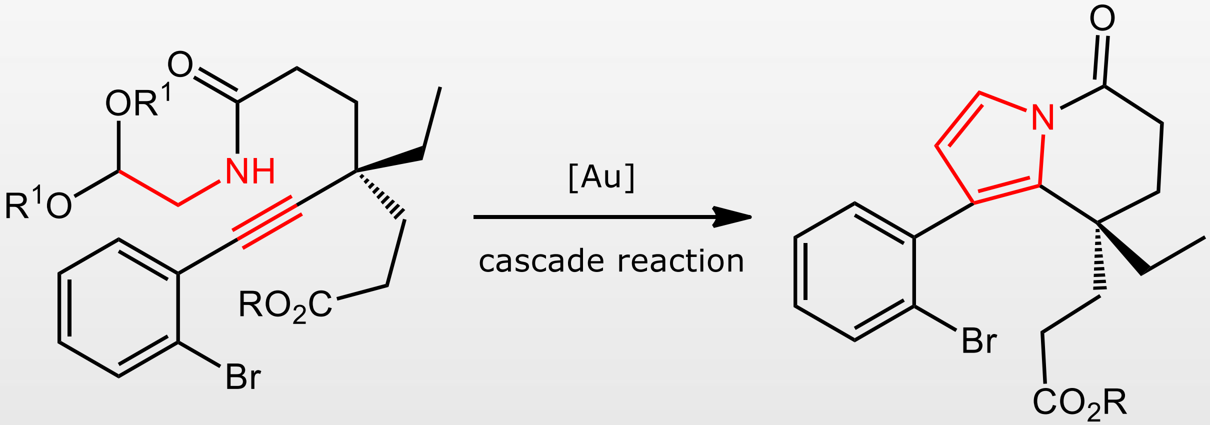
bromination reaction

M. N. Pennell, R. W. Foster, P. G. Turner, H. C. Hailes, C. J. Tame, T. D. Sheppard *Chem. Commun*. **2014**, *50*, 1302.

total syntheses of (-)-Rhazinilam and (-)-Rhazinicine



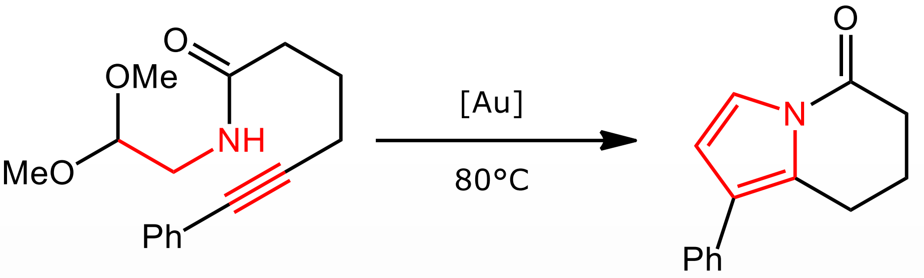
construction of indolizine skeleton from linear intermediates



K. Sugimoto, K. Toyoshima, S. Nonaka, K. Kotaki, H. Ueda, H. Tokuyama *Angew. Chem. Int. Ed.* **2013**, *52*, 7168.
H. Ueda, M. Yamaguchi, H. Kameya, K. Sugimoto, H. Tokuyama *Org. Lett*. **2014**, *16*, 4948.

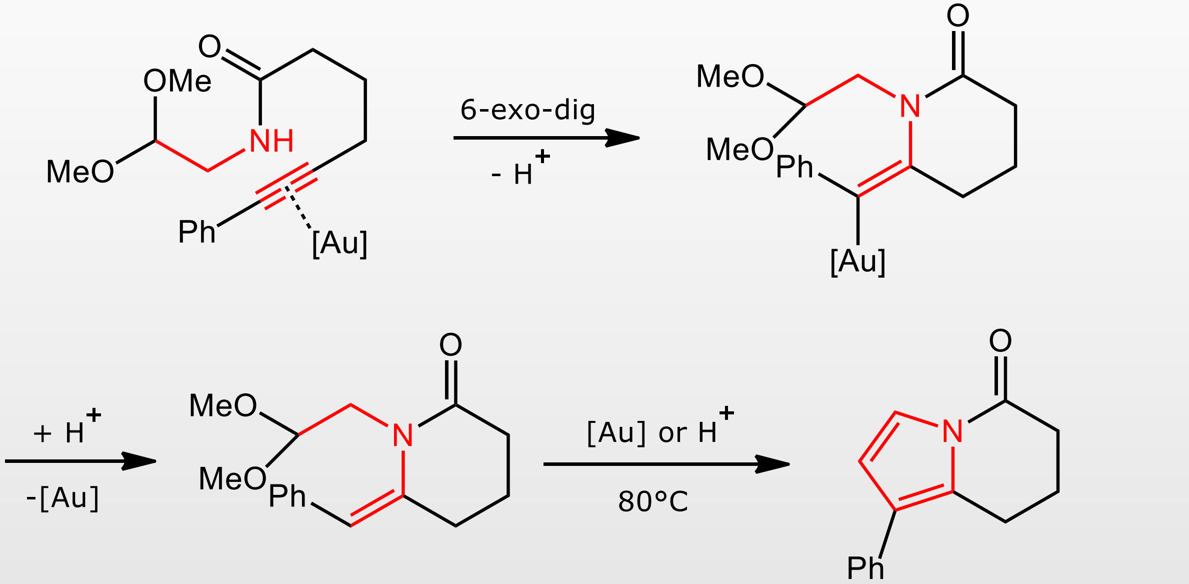
Nucleophilic addition to π activated carbon-carbon triple bonds, synthesis of heterocycles

model reaction



catalyst (mol%)	*solvent*	*yield (%)*
AuCl (10)	DCE	-
$AuCl_3$ (10)	DCE	-
$Au(PPh_3)Cl$ (10)	DCE	-
AuCl/AgOTf (10)	DCE	-
$Au(PPh_3)Cl$/AgOTf (10)	DCE	20
$Au(PPh_3)Cl/AgNTf_2$ (10)	DCE	20
$Au(PPh_3)NTf_2$ (10)	DCE	50
$Au(PPh_3)NTf_2$ (10)	1,4-dioxane	69

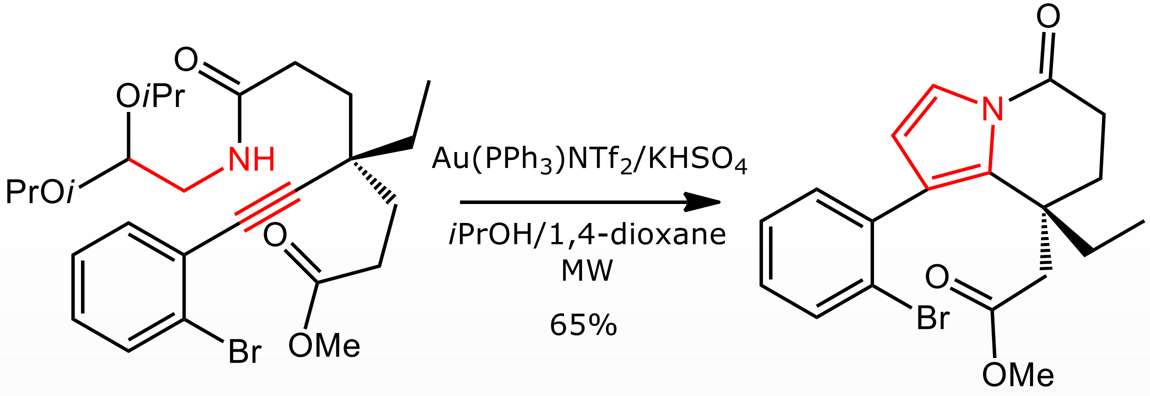
proposed reaction mechanism



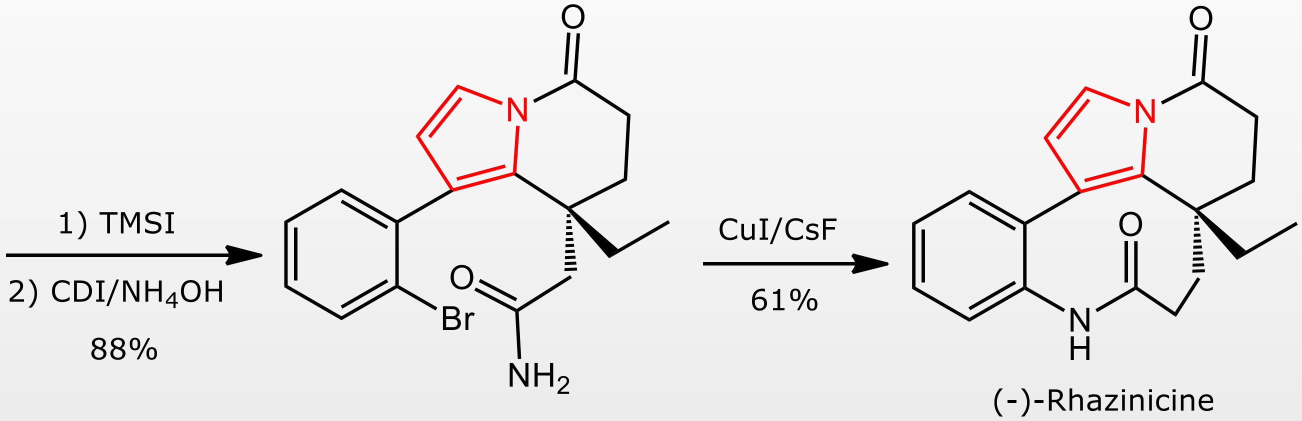
K. Sugimoto, K. Toyoshima, S. Nonaka, K. Kotaki, H. Ueda, H. Tokuyama *Angew. Chem. Int. Ed.* **2013**, *52*, 7168.
H. Ueda, M. Yamaguchi, H. Kameya, K. Sugimoto, H. Tokuyama *Org. Lett*. **2014**, *16*, 4948.

Nucleophilic addition to π activated carbon-carbon triple bonds, synthesis of heterocycles

application of the selected conditions to the synthesis of (-)-Rhazinicine



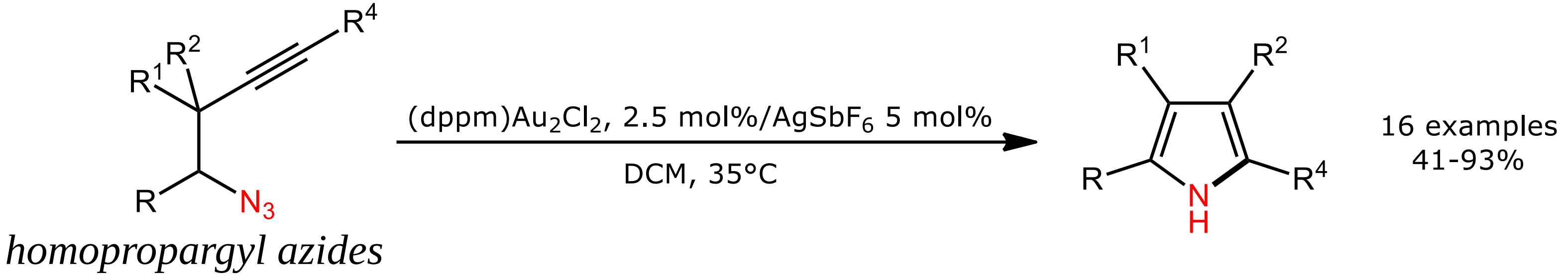
formation of indolizine skeleton



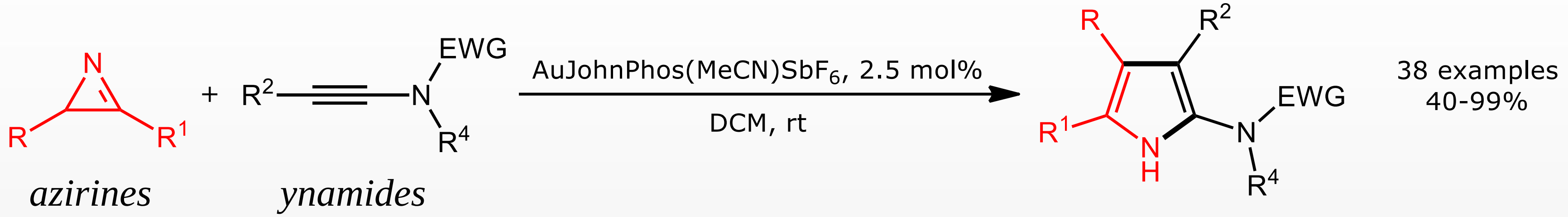
formation of the lactam ring

K. Sugimoto, K. Toyoshima, S. Nonaka, K. Kotaki, H. Ueda, H. Tokuyama *Angew. Chem. Int. Ed.* **2013**, *52*, 7168.
H. Ueda, M. Yamaguchi, H. Kameya, K. Sugimoto, H. Tokuyama *Org. Lett*. **2014**, *16*, 4948.

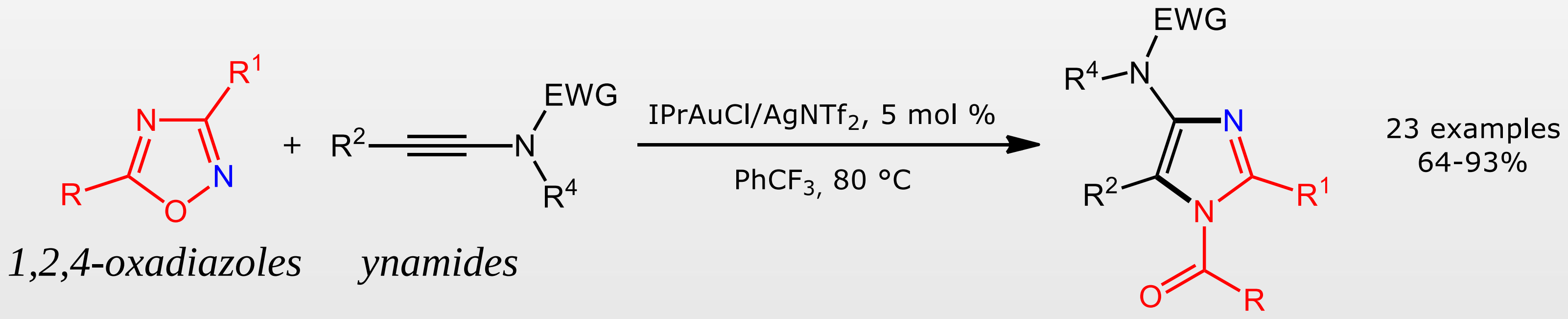
Nucleophilic addition to π activated carbon-carbon triple bonds, synthesis of heterocycles



D. J. Gorin, N. R. Davis, F. D. Toste *J. Am. Chem. Soc*. **2005**, *127*, 11260.

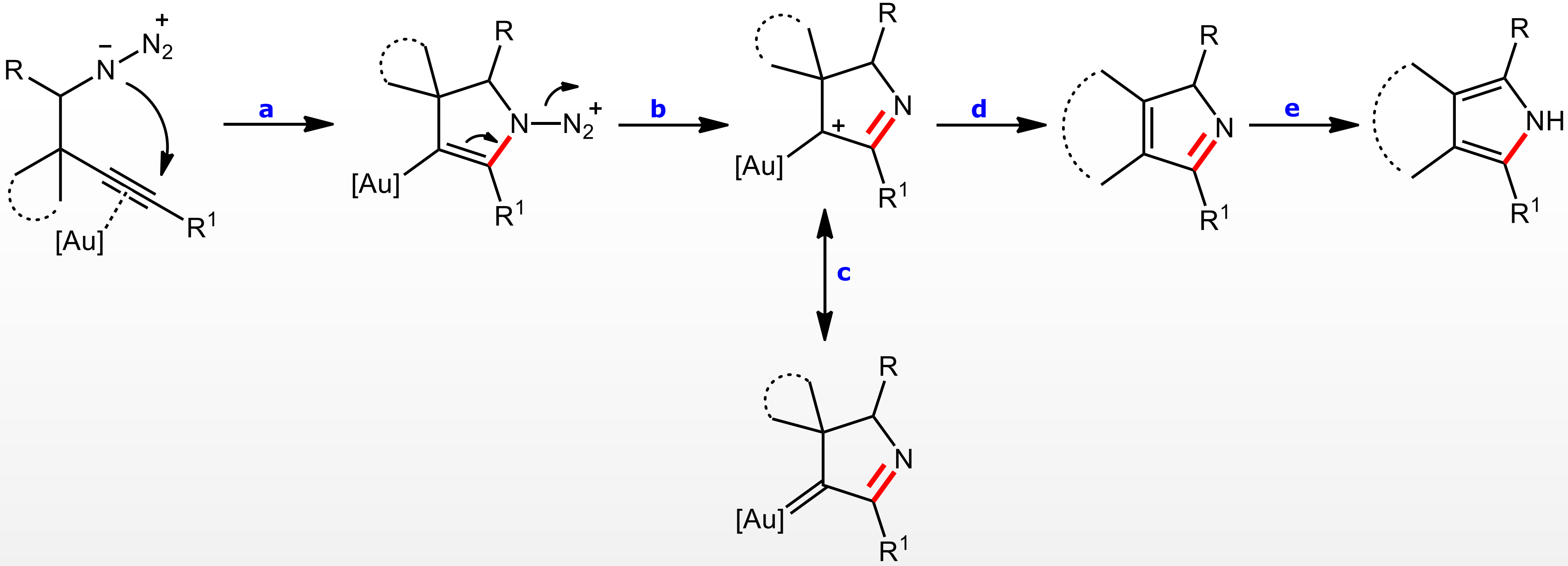


L. Zhu, Y. Yu, Z. Mao, X. Huang *Org. Lett*. **2015**, *17*, 30.



Z. Zeng, H. Jin, J. Xie, B. Tian, M. Rudolph, F. Rominger, A. S. K. Hashmi *Org. Lett*. **2017**, *19*, 1020.

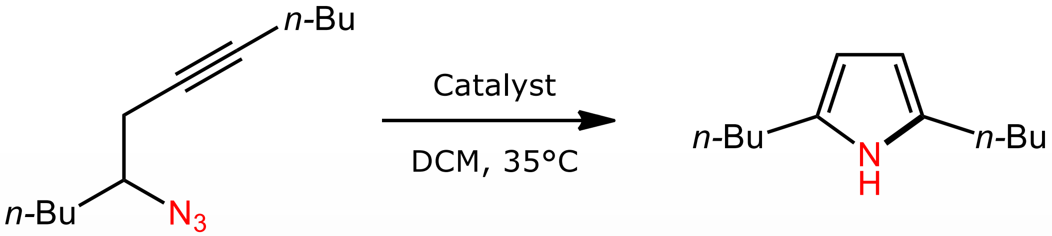
intramolecular Au(I)-catalyzed Schmidt reaction
reaction mechanism



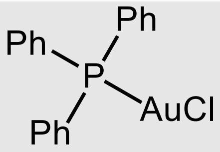
a) attack of the proximal *N*-atom of the azide on gold(I) activated triple bond,
b) loss of nitrogen, production of a cationic intermediate,
c) stabilization by electron donation from gold(I),
d) formal 1,2-shift and regeneration of the cationic gold(I) catalyst and produces a 2*H*-pyrrole,
e) tautomerization to the 1*H*-pyrrole.

D. J. Gorin, N. R. Davis, F. D. Toste *J. Am. Chem. Soc*. **2005**, *127*, 11260.

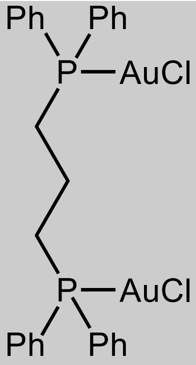
intramolecular Au(I)-catalyzed Schmidt reaction
reaction conditions



catalyst (mol%)	***yield (%)***
$Au(PPh_3)Cl$ (5), $AgSbF_6$ (5)	72
$(dppm)Au_2Cl_2$ (2.5), $AgSbF_6$ (5)	93
$(dppp)Au_2Cl_2$ (2.5), $AgSbF_6$ (5)	86
$AuCl_3$ (5)	-
CuI (5)	-
$AgSbF_6$ (5)	trace

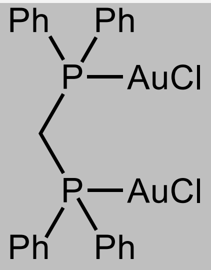


triphenylphosphinegoldchloride



$(dppp)Au_2Cl_2$

dppp = 1,1-Bis(diphenylphosphino)propane



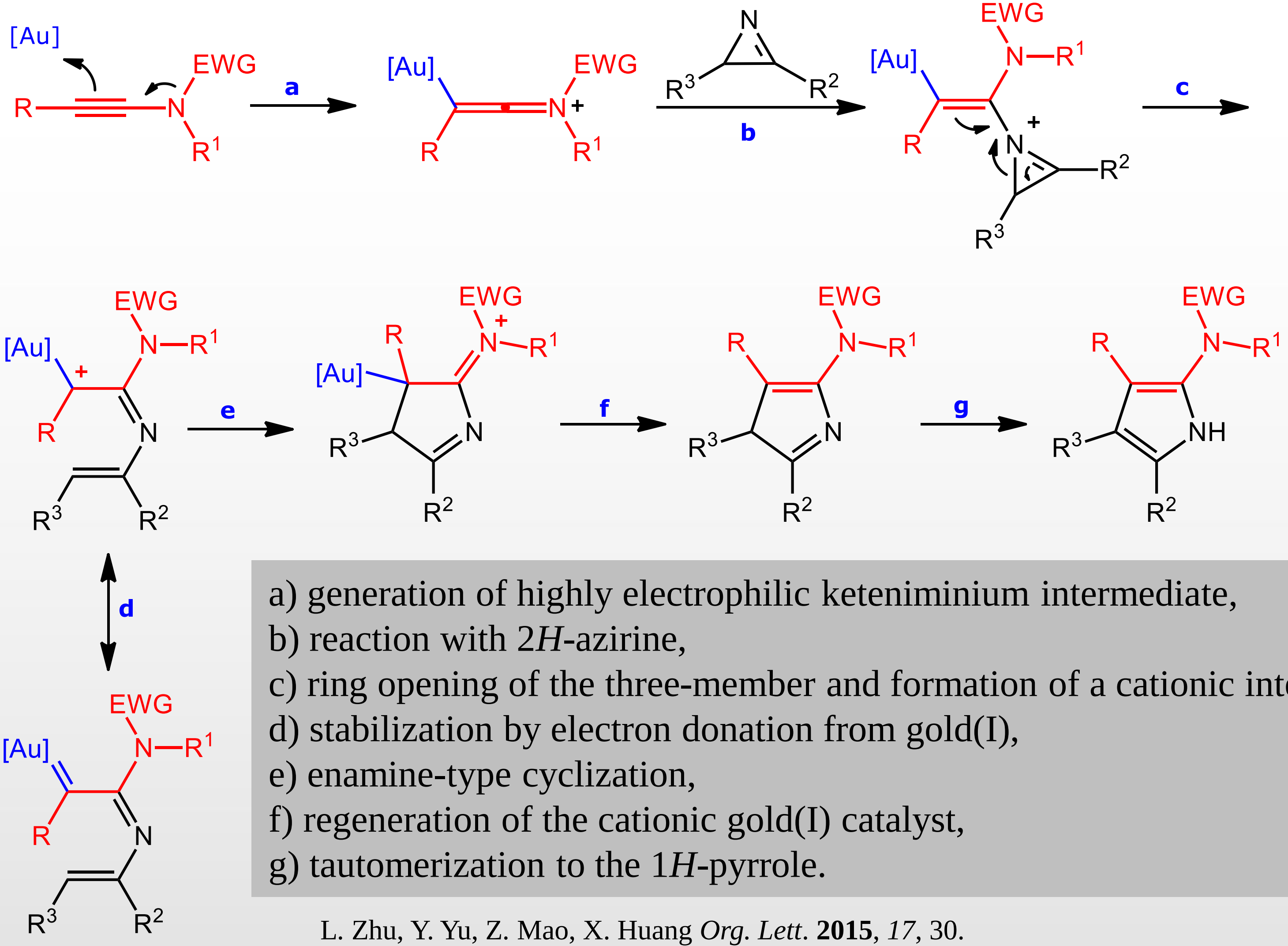
$(dppm)Au_2Cl_2$

dppm = 1,1-Bis(diphenylphosphino)methane

D. J. Gorin, N. R. Davis, F. D. Toste *J. Am. Chem. Soc.* **2005**, *127*, 11260.

Nucleophilic addition to π activated carbon-carbon triple bonds, synthesis of heterocycles

substituted pyrroles in via formal [3 + 2] cycloaddition
reaction mechanism

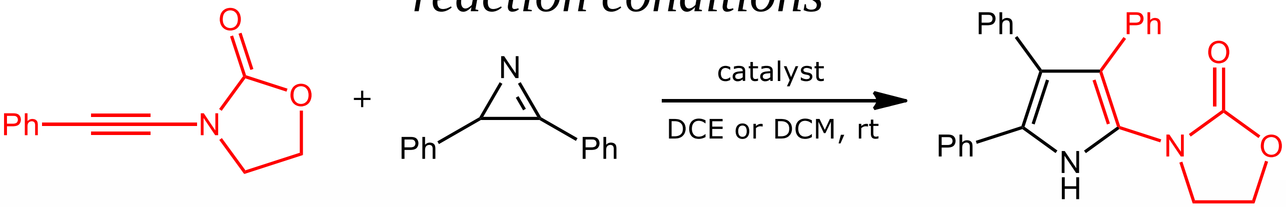


a) generation of highly electrophilic keteniminium intermediate,
b) reaction with 2*H*-azirine,
c) ring opening of the three-member and formation of a cationic intermediate,
d) stabilization by electron donation from gold(I),
e) enamine-type cyclization,
f) regeneration of the cationic gold(I) catalyst,
g) tautomerization to the 1*H*-pyrrole.

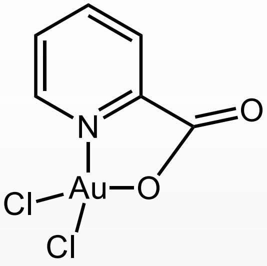
L. Zhu, Y. Yu, Z. Mao, X. Huang *Org. Lett*. **2015**, *17*, 30.

substituted pyrroles in via formal [3 + 2] cycloaddition

reaction conditions

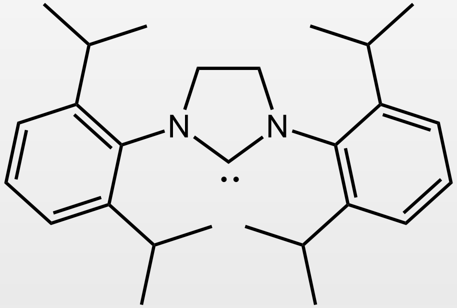


$AuCl_3$



gold(III) salt and complex

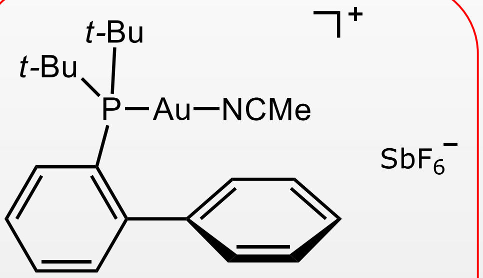
no reaction



*i*Pr carbene ligand

yield 55%

electrophilicity of the corresponding gold(I) complex with chloride as counterion

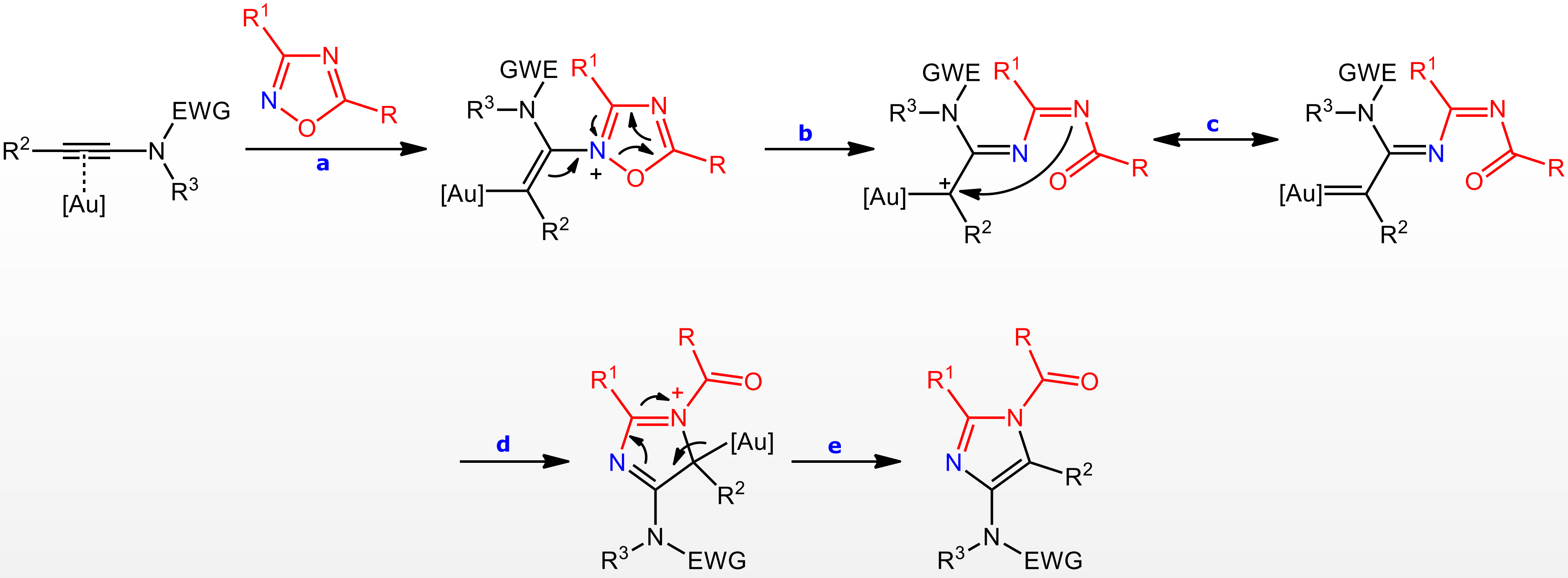


catalyst, 3 mol%
yield 99%

optimized reaction conditions

L. Zhu, Y. Yu, Z. Mao, X. Huang *Org. Lett.* **2015**, *17*, 30.

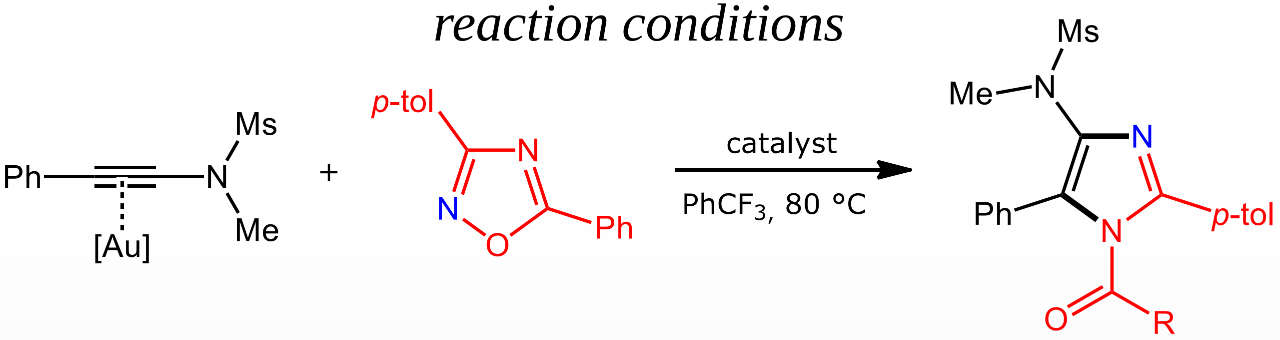
4-aminoimidazoles in via formal [3 + 2] cycloaddition reaction mechanism



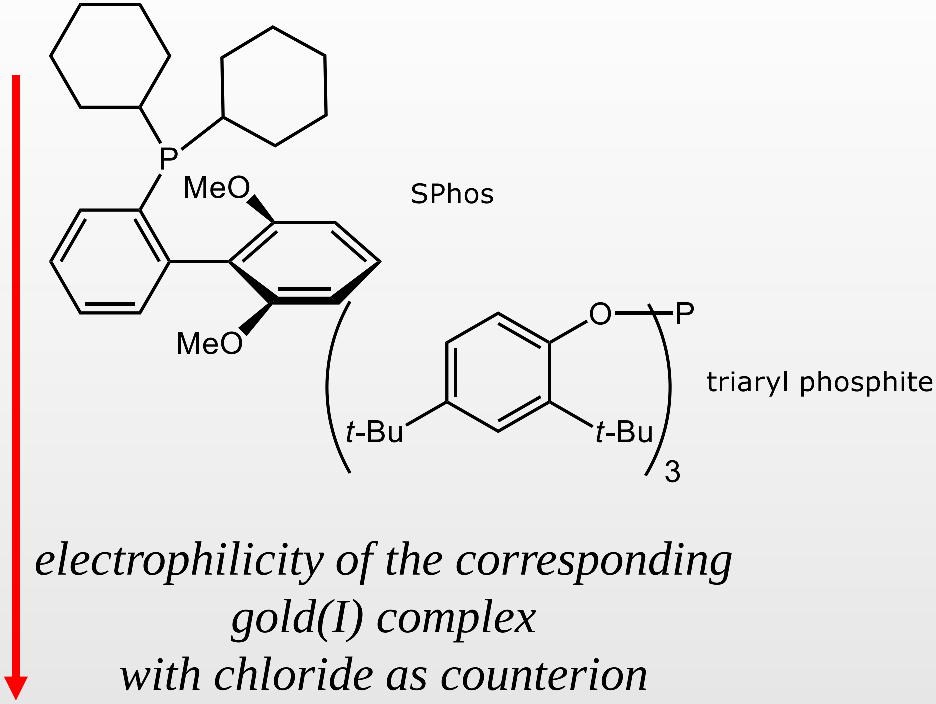
a) regioselective addition to gold-activated ynamide,
b) ring opening of the oxadiazole, formation of a cationic intermediate,
c) stabilization by electron donation from gold(I),
d) imine-type cyclization,
e) regeneration of the catalyst.

Z. Zeng, H. Jin, J. Xie, B. Tian, M. Rudolph, F. Rominger, A. S. K. Hashmi *Org. Lett*. **2017**, *19*, 1020.

4-aminoimidazoles in via formal [3 + 2] cycloaddition
reaction conditions



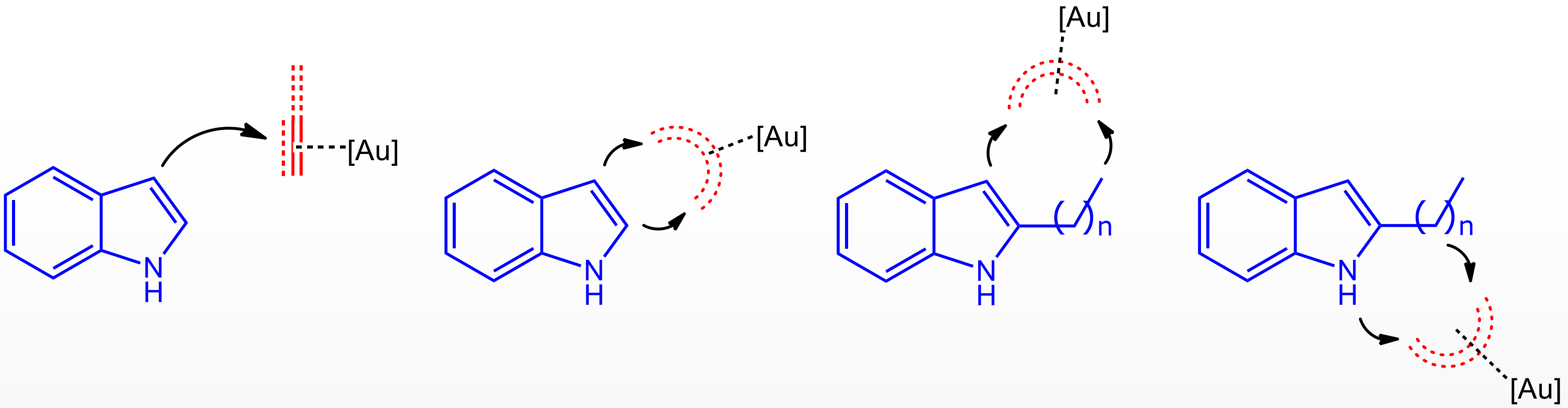
catalyst (mol%)	***imidazole (%)***
IPrAuCl/AgNTf$_2$ (5)	95
IPrAuCl/AgOTf (5)	67
PPh$_3$AuNTf$_2$ (5)	52
SPhosAuNTf$_2$ (5)	48
KAuBr$_4$	39
(2,4-*t*Bu$_2$PhO)$_3$PAuCl/AgNTf$_2$ (5)	30

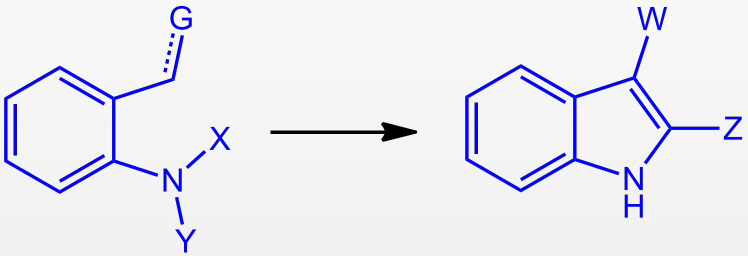


electrophilicity of the corresponding gold(I) complex
with chloride as counterion

Z. Zeng, H. Jin, J. Xie, B. Tian, M. Rudolph, F. Rominger, A. S. K. Hashmi *Org. Lett*. **2017**, *19*, 1020.

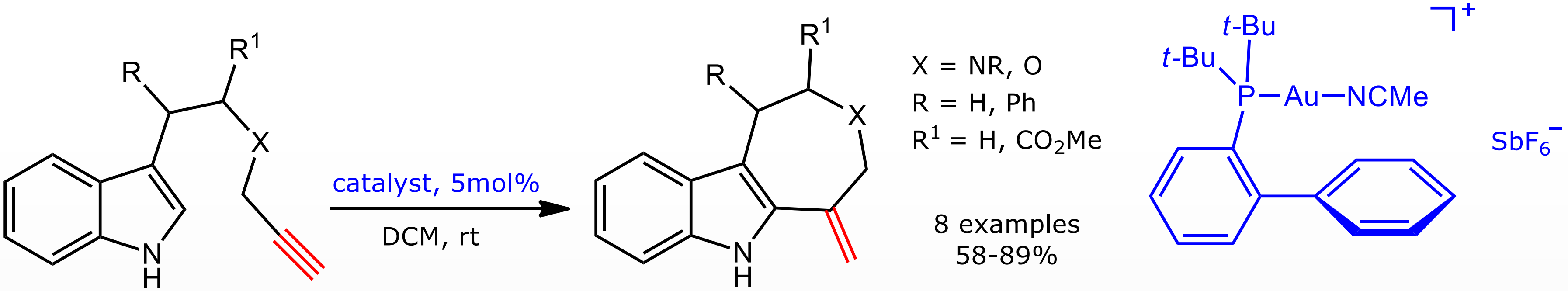
indoles as nucleophilic partners in reactions with activated π-systems





alkynes and allenes in functionalization, cyclization and cycloaddition reactions

intramolecular hydroarylations of alkyne tethered indoles



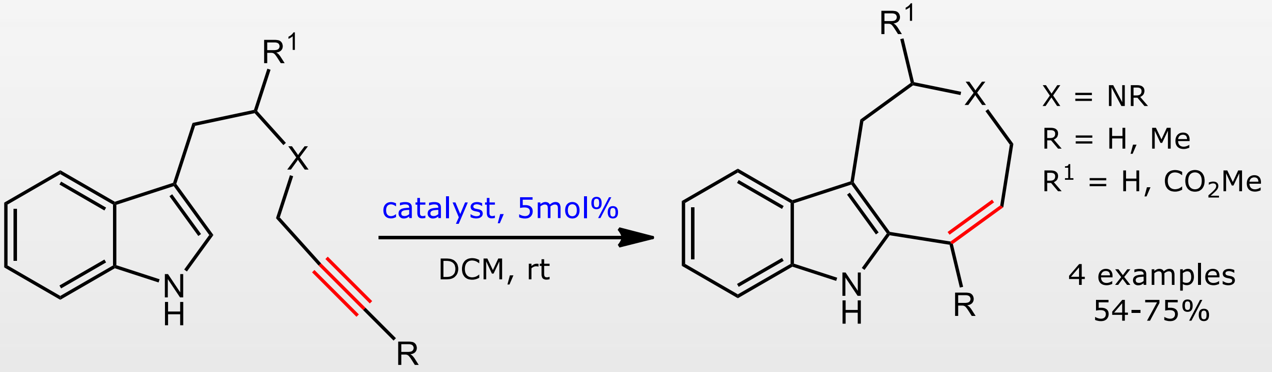
X = NR, O
R = H, Ph
R^1 = H, CO_2Me

8 examples
58-89%

same substrate
different catalyst!

formal 7-exo-dig cyclization

formal 8-endo-dig cyclization



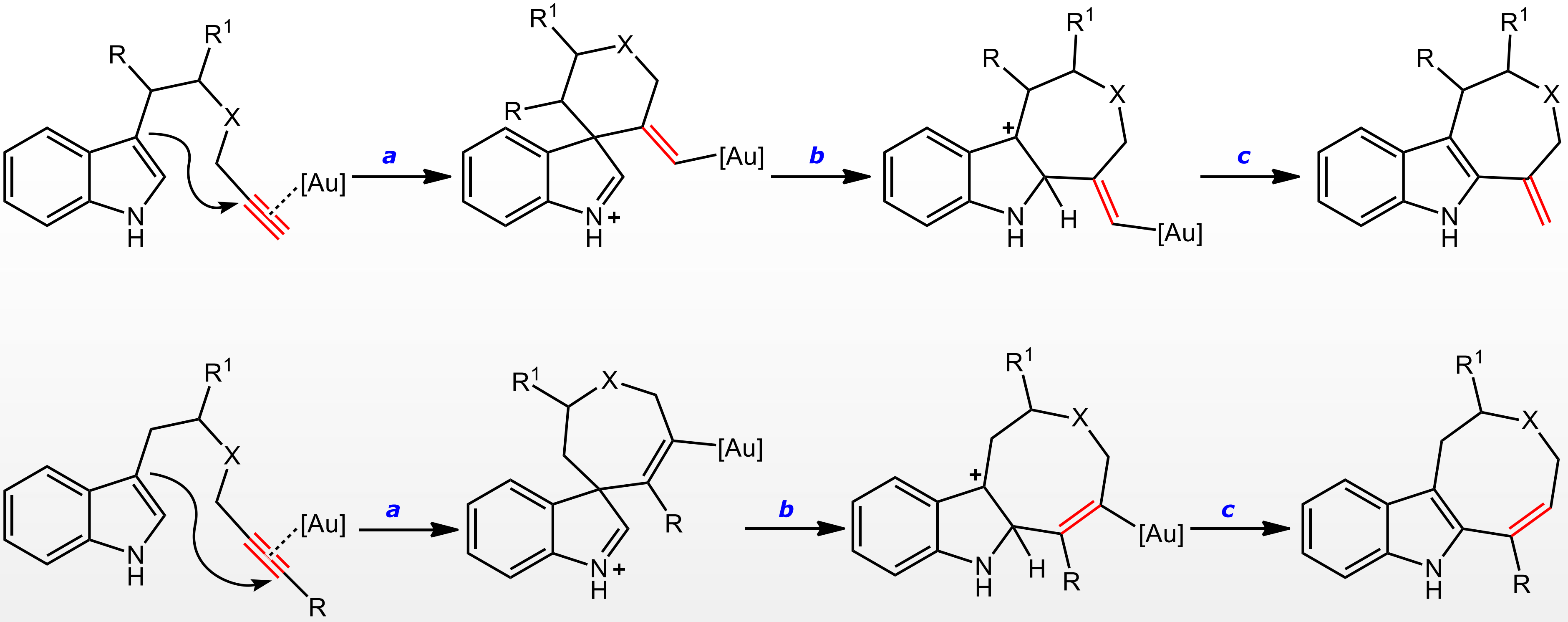
X = NR
R = H, Me
R^1 = H, CO_2Me

4 examples
54-75%

$AuCl_3$

C. Ferrer, A. M. Echavarren *Angew. Chem., Int. Ed.* **2006**, *45*, 1105.
C. Ferrer, C. H. M. Amijs, A. M. Echavarren *Chem. Eur. J.* **2007**, *13*, 1358.

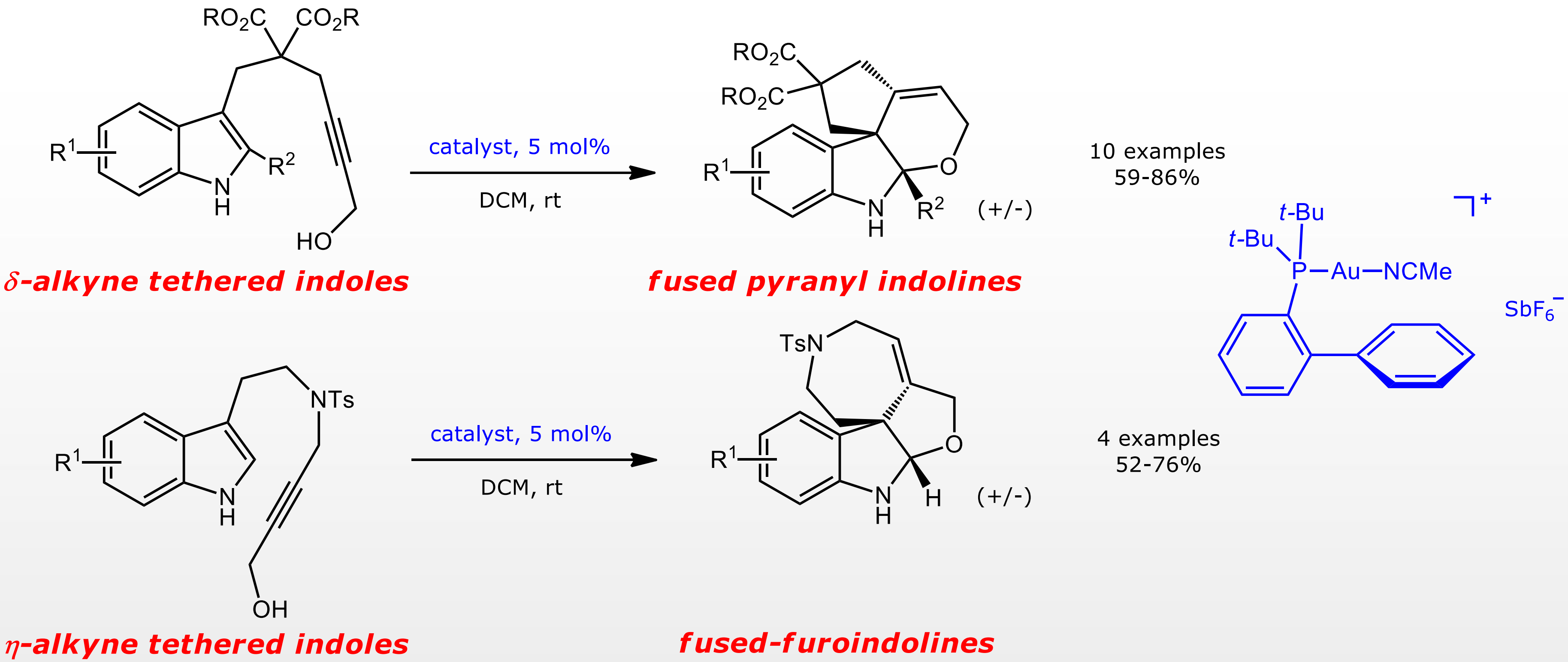
intramolecular hydroarylations of alkyne tethered indoles



a) intramolecular hydroarylation
b) 1,2 migration
c) aromatization, protodeauration

C. Ferrer, A. M. Echavarren *Angew. Chem., Int. Ed*. **2006**, *45*, 1105.
C. Ferrer, C. H. M. Amijs, A. M. Echavarren *Chem. Eur. J*. **2007**, *13*, 1358.

Cascade reactions of δ- and η-alkyne tethered indoles



δ-alkyne tethered indoles

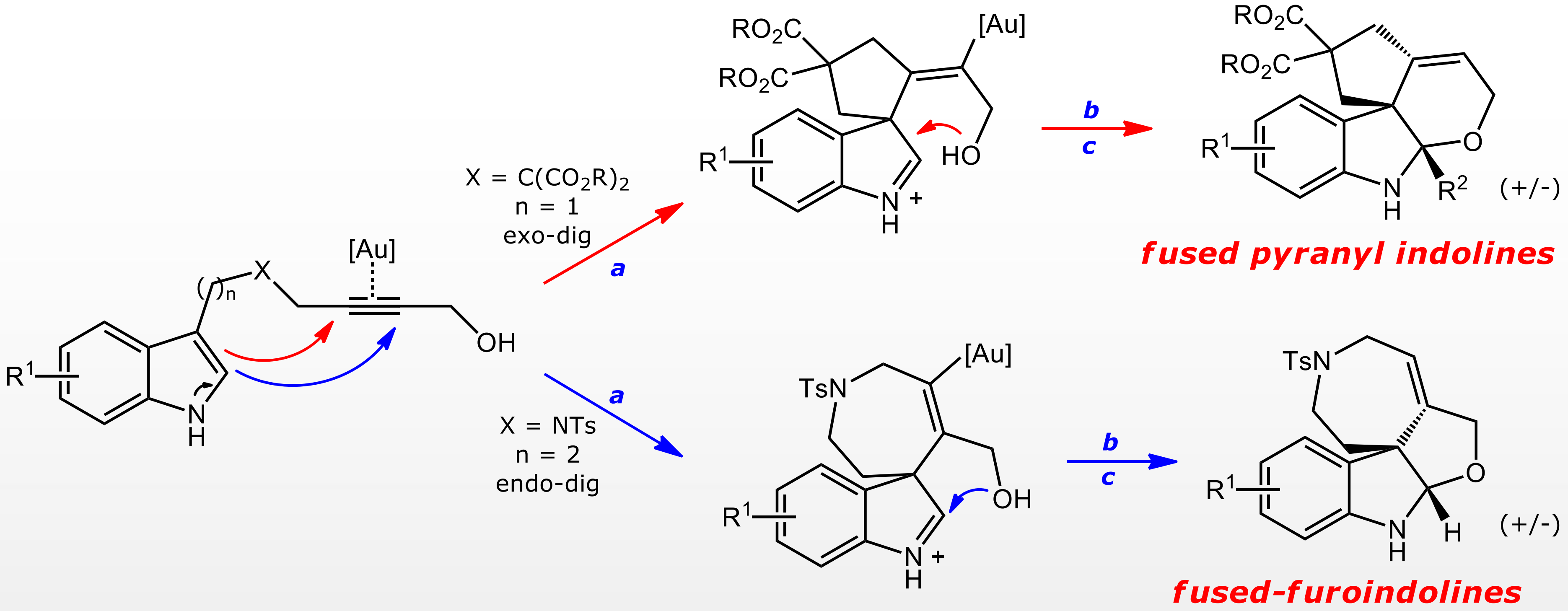
fused pyranyl indolines

η-alkyne tethered indoles

fused-furoindolines

G. Cera, P. Crispino, M. Monari, M. Bandini *Chem. Commun*. **2011**, *47*, 7803.
G. Cera, P. Crispino, M. Chiarucci, A. Mazzani, M. Mancinelli, M. Bandini *Org. Lett*. **2012**, *14*, 1350.

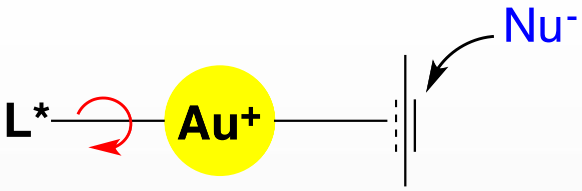
Cascade reactions of alkyne tethered indoles reaction mechanism



a) Intramolecular hydroarylation
b) trapping of the iminium group by the hydroxyl group
c) protodeauration

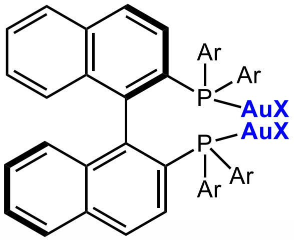
G. Cera, P. Crispino, M. Monari, M. Bandini *Chem. Commun*. **2011**, *47*, 7803.
G. Cera, P. Crispino, M. Chiarucci, A. Mazzani, M. Mancinelli, M. Bandini *Org. Lett*. **2012**, *14*, 1350.

Gold catalysis and indole chemistry

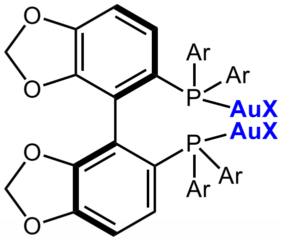


linear two-coordination mode
out-of-sphere π-activation

Bidentate catalyst

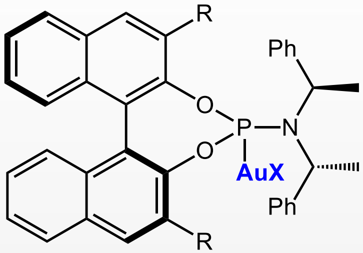


BINAP phosphines

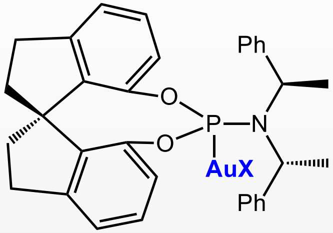


SEGPHOS phosphines

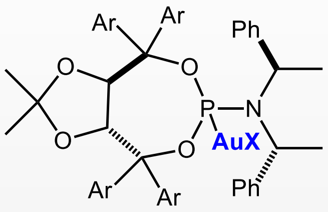
Monodentate catalyst



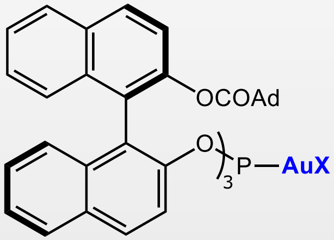
BINOL phosphoramidites



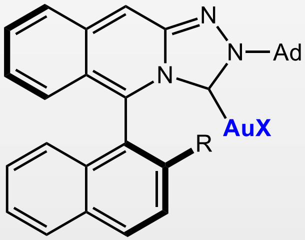
SPIINOL phosphoramidites



TADDOL phosphoramidites



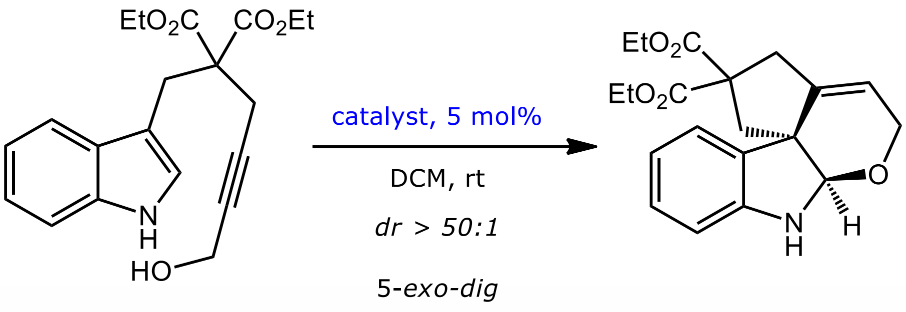
BINOL phosphites



Chiral NHCs

F. López, J. L. Mascareñas *Beilstein J. Org. Chem.* **2013**, *9*, 2250

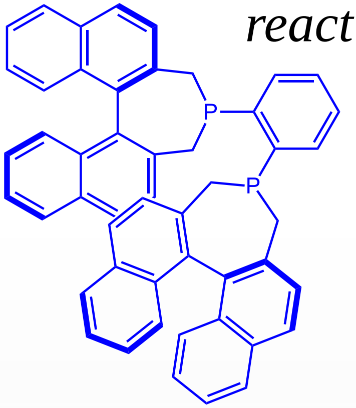
Gold catalysis and indole chemistry



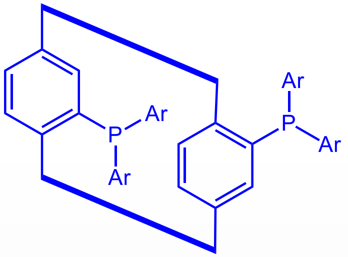
enantioselective cascade reaction

reaction conditions

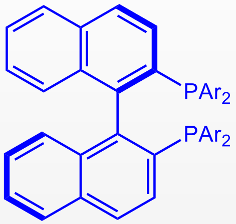
Catalyst (5 mol%)	***AgX***	***Yield (%)***	***ee (%)***
(*R*,*R*)-**L1**	AgSbF$_6$	21	46 (+)
(*S*)-**L2**	AgSbF$_6$	26	20 (-)
(*R*)-**L3**	AgSbF$_6$	65	56 (-)
(*S*)-**L4**	AgSbF$_6$	36	14 (-)
(R)-**L5**	AgSbF$_6$	61	0
(*S*)-**L6**	AgSbF$_6$	65	17 (-)
(*R*)-**L3**	AgOTf	59	72 (-)
(*R*)-**L3**	AgNTf$_2$	80	27 (-)
(*R*)-**L3**	AgBF$_4$	60	74 (-)
(*R*)-**L3**	AgPF$_6$	70	70 (-)
(*R*)-L3 0°C + 4A MS	**AgBF$_4$**	**89**	**86 (-)**



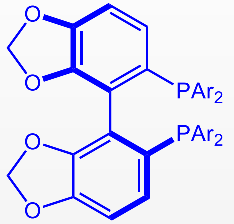
(*R*,*R*)-L1: binaphane



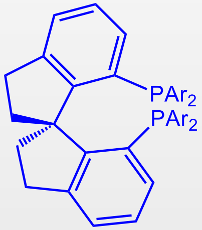
(*S*)-L2: Ar = 3,5-Me$_2$-Ph



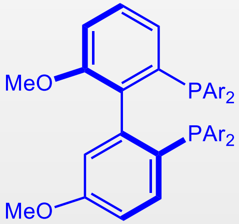
(*R*)-L3: Ar = 3,5-Me$_2$-Ph



(*S*)-L4: Ar = 3,5-(*t*Bu)$_2$-4-OMe-Ph



(*R*)-L5: Ar = 3,5-Me$_2$-Ph

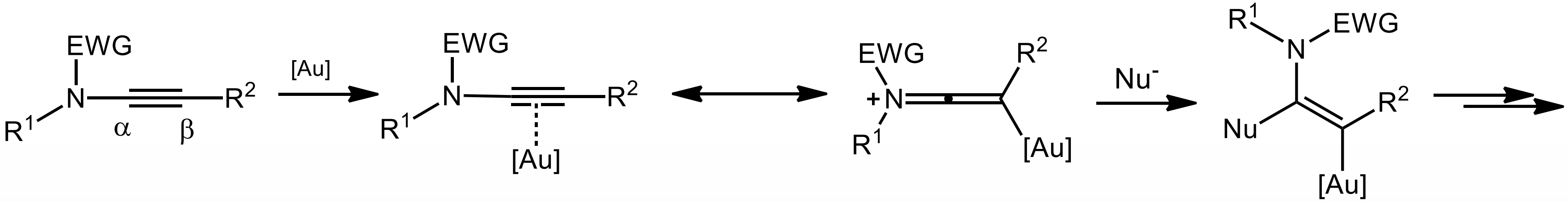


(*S*)-L6: Ar = 3,5-(*t*Bu)$_2$-4-OMe-Ph

9 examples
50-89%, ee 75-87%

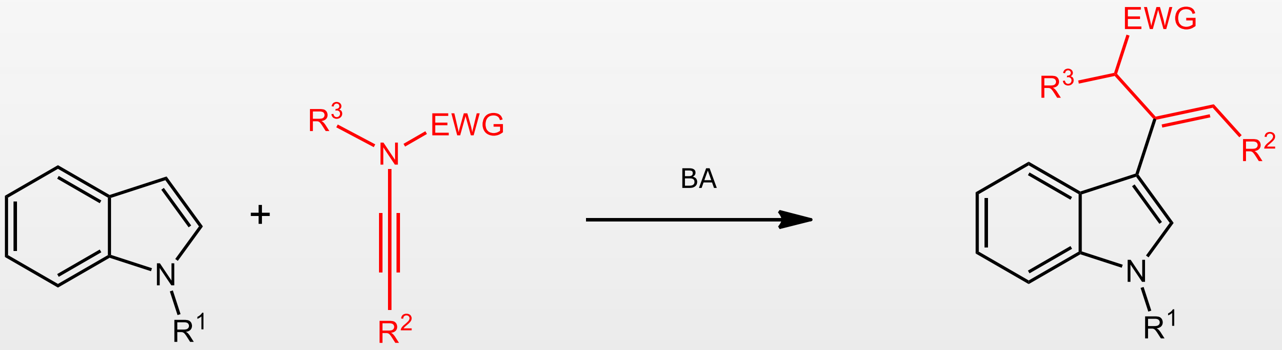
G. Cera, P. Crispino, M. Monari, M. Bandini *Chem. Commun*. **2011**, *47*, 7803.
G. Cera, P. Crispino, M. Chiarucci, A. Mazzani, M. Mancinelli, M. Bandini *Org. Lett*. **2012**, *14*, 1350.

ynamides and gold catalysis



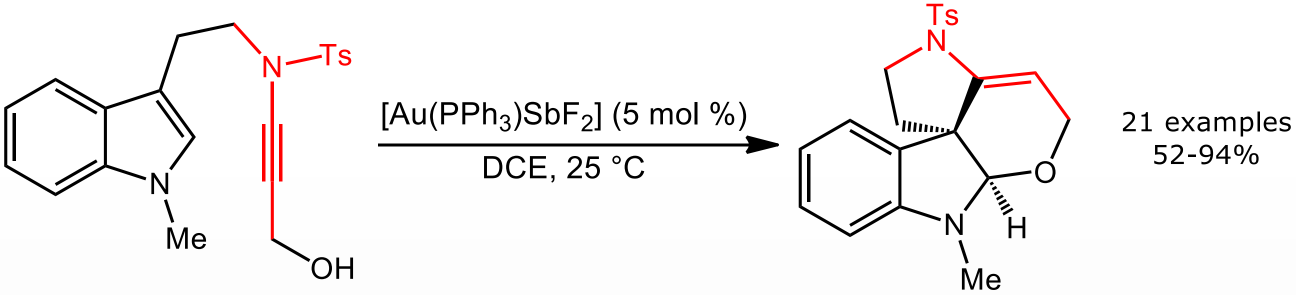
S. Nayak, B. Prabagar, A. K. Sahoo *Org. Biomol. Chem.* **2016**, *14*, 803.
C. Theunissen, M. Lecomte *Aldrichimica Acta* **2015**, *48*, 59.

reaction of indoles with ynamides under Broensted acid catalysis



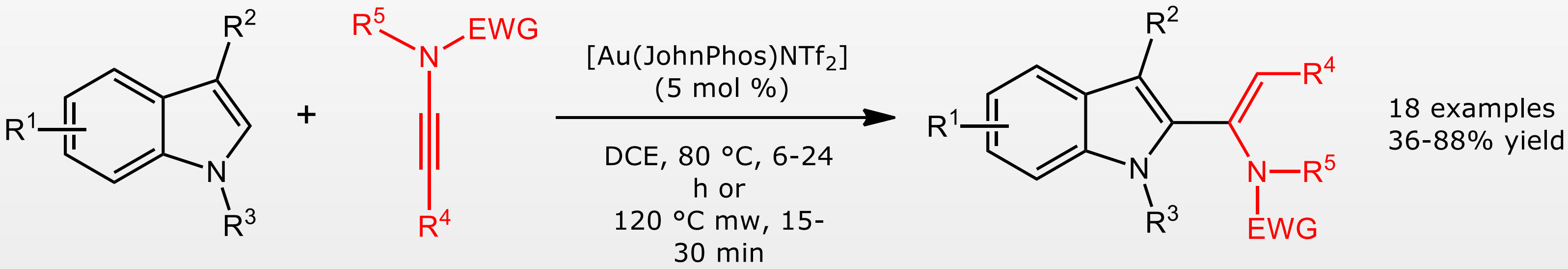
Y. Zhang *Tetrahedron* **2006**, *62*, 3917.

intra- and intermolecular reactions of ynamides and indoles under gold catalysis



spirocyclic pyrrolidinoindolines

N. Zheng, Y.-Y. Chang, L.-J. Zhang, J.-X. Gong, Z. Yang *Chem. Asian J*. **2016**, *11*, 371.

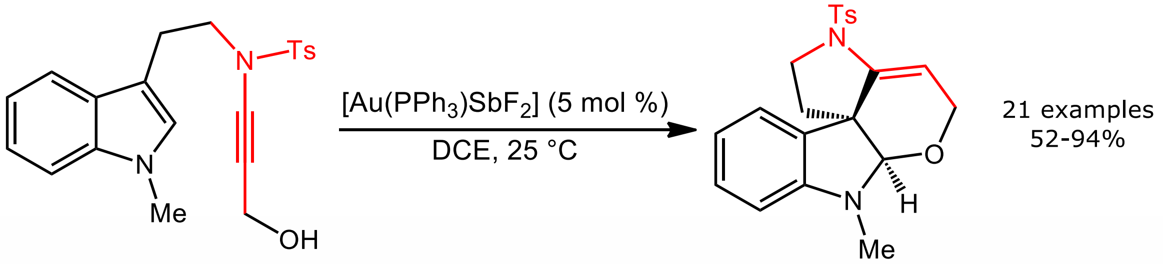


2-vinylindoles

V. Pirovano, M. Negrato, G. Abbiati, M. Dell’Acqua, E. Rossi *Org. Lett*. **2016**, *18*, 4798.

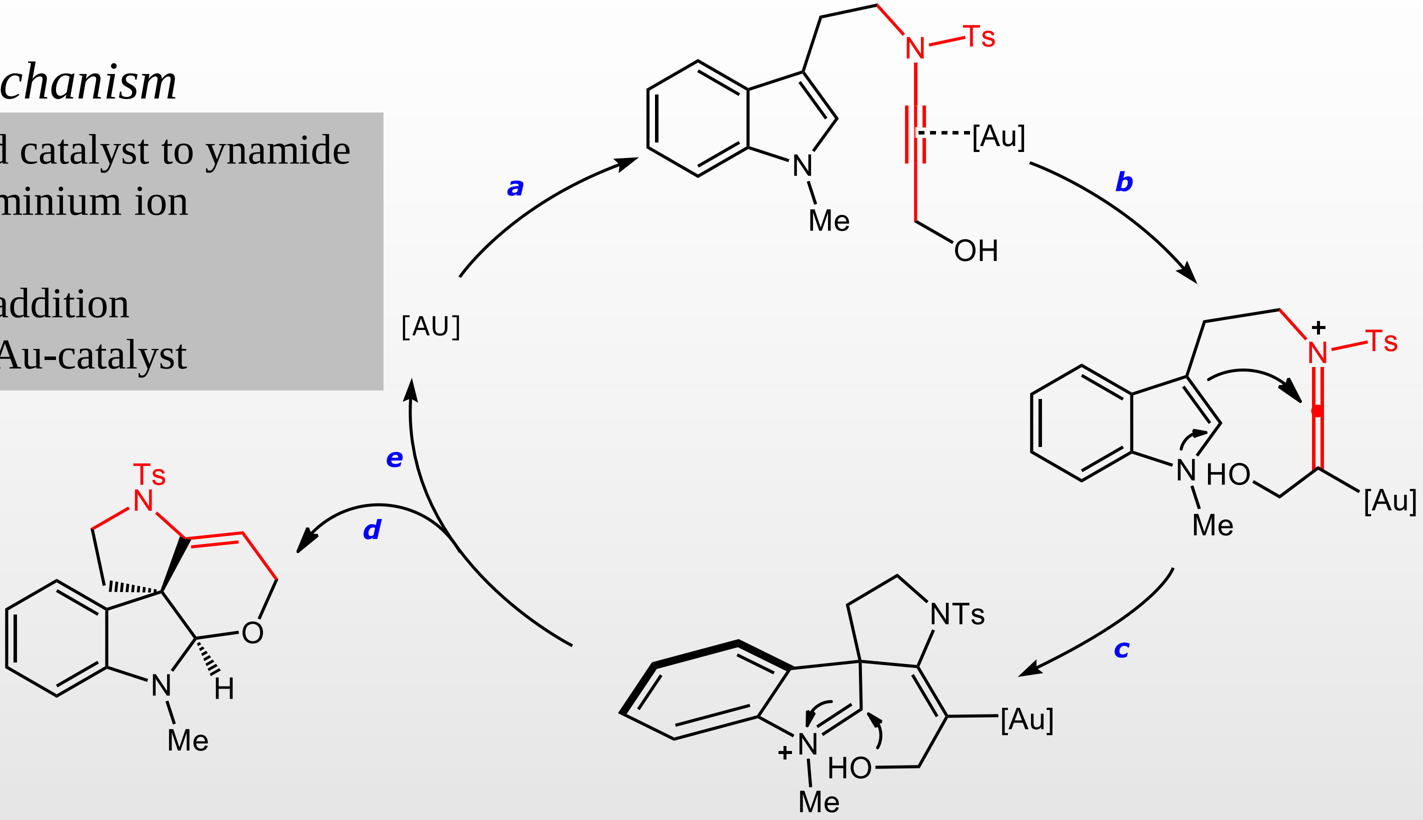
Gold catalysis and indole chemistry

synthesis of spirocyclic pyrrolidinoindolines



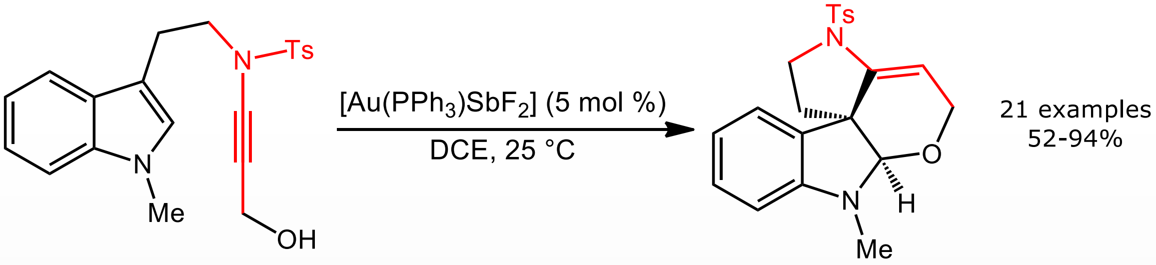
reaction mechanism

- a) coordination of gold catalyst to ynamide
- b) formation of keteniminium ion
- c) 5-endo cyclization
- d) 6-exo nucleophilic addition
- e) regeneration of the Au-catalyst



N. Zheng, Y.-Y. Chang, L.-J. Zhang, J.-X. Gong, Z. Yang *Chem. Asian J.* **2016**, *11*, 371.

synthesis of spirocyclic pyrrolidinoindolines
reaction conditions

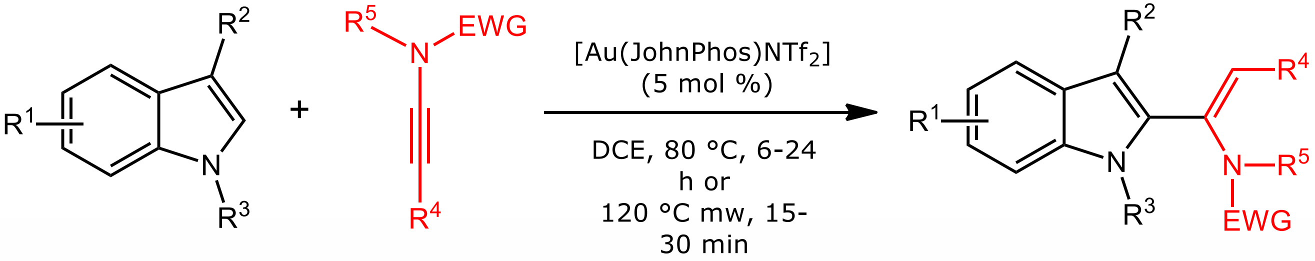


catalyst (mol%)	***Yield (%)***
TsOH (5)	-
TfOH (5)	13
Tf_2OH (5)	14
AgOTf (5)	-
$AuCl_3$ (5)	-
$PtCl_2$ (5)	-
iPrAuCl (5), $AgNTf_2$ (5)	60
iPrAuCl (5), $AgSbF_6$ (5)	76
PPh_3AuCl (5), $AgNTf_2$ (5)	77
PPh_3AuCl (5), $AgSbF_6$ (5)	94

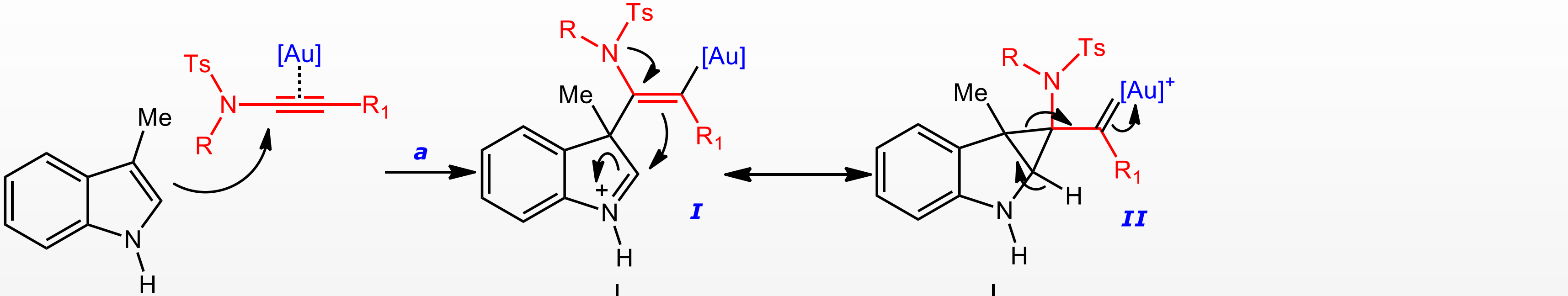
N. Zheng, Y.-Y. Chang, L.-J. Zhang, J.-X. Gong, Z. Yang *Chem. Asian J.* **2016**, *11*, 371.

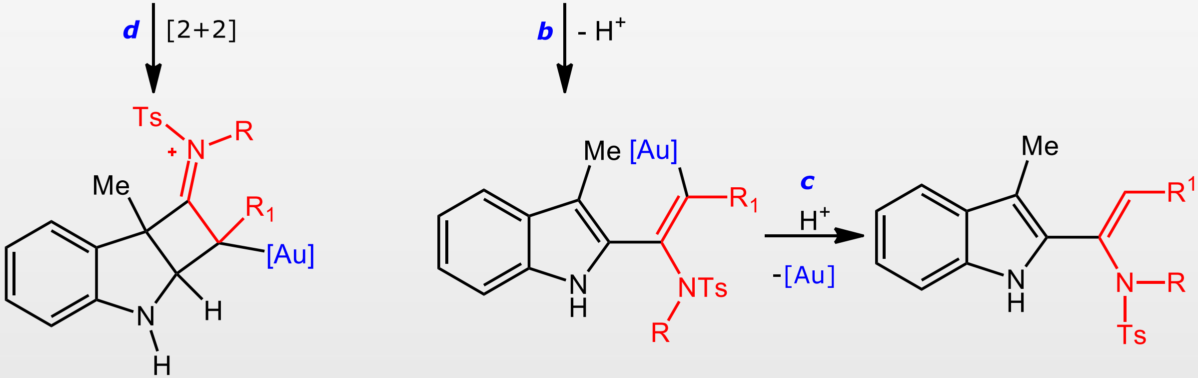
Gold catalysis and indole chemistry

synthesis of 2-vinylindoles



18 examples
36-88% yield





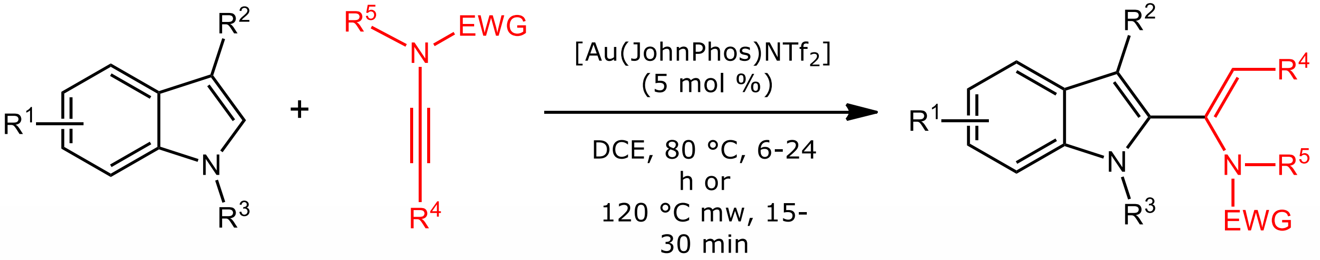
reaction mechanism

a) formation of intermediates I and II
b) loss of proton and ring opening
c) protodeauration step
d) formation of [2+2] cycloadduct

V. Pirovano, M. Negrato, G. Abbiati, M. Dell’Acqua, E. Rossi *Org. Lett*. **2016**, *18*, 4798.

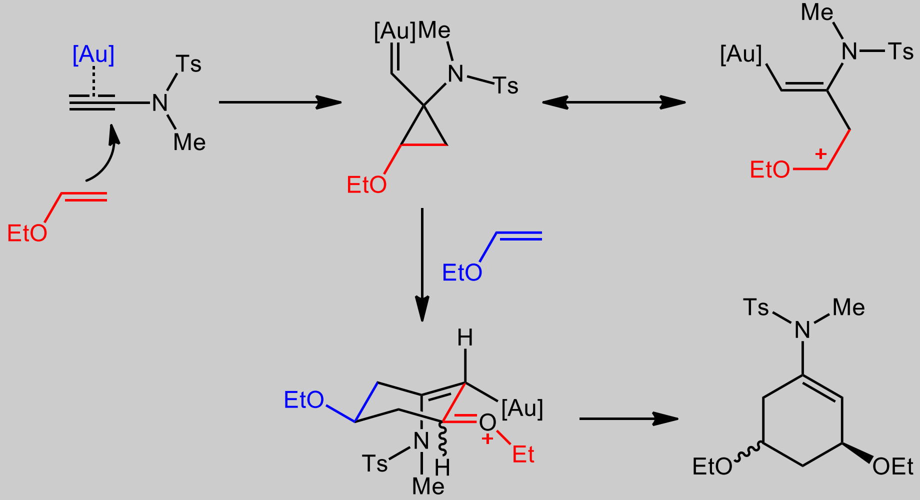
Gold catalysis and indole chemistry

synthesis of 2-vinylindoles



18 examples
36-88% yield

reaction mechanism



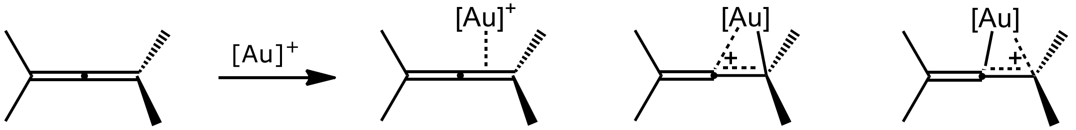
R. B. Dateer, B. S. Shaibu, R.-S. Liu *Angew. Chem. Int. Ed.* **2012**, *51*, 113.

reaction conditions

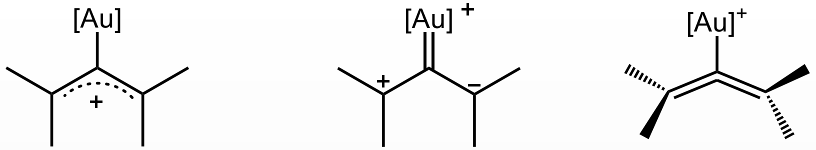
catalyst (mol%)	***Yield (%)***
$HNTf_2$ (5)	59
$AgNTf_2$ (5)	15
$AuCl_3$	5
$PtCl_2$	-
$iPrAuNTf_2$ (5)	57
PPh_3AuNTf_2 (5)	58
$JohnPhosAuNTf_2$ (5), 80°C	65
$JohnPhosAuNTf_2$ (5), mw, 120°C	70

V. Pirovano, M. Negrato, G. Abbiati, M. Dell’Acqua, E. Rossi *Org. Lett.* **2016**, *18*, 4798.

Allenes and gold catalysis



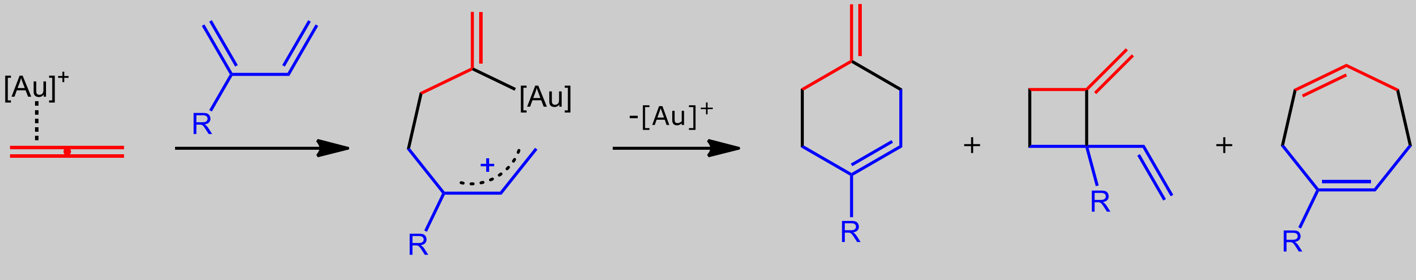
η^2 complexes
Au-coordinated allene



planar σ-allyl cations

carbenoid species

η^1 bent allenes



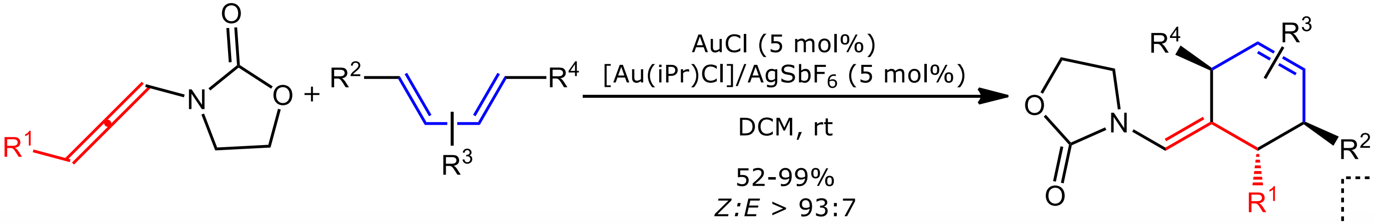
[4+2] [2+2] and [4+3] cycloadditions

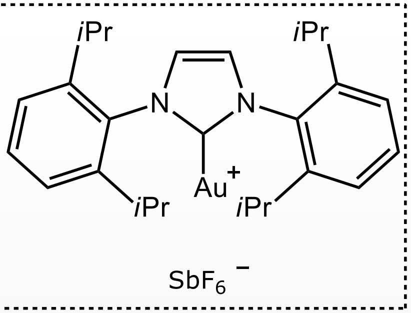
Selectivity?

F. López, J. L. Mascareñas *Beilstein J. Org. Chem.* **2013**, *9*, 2250
S. Montserrat, G. Ujaque, F. López, J. L. Mascareñas, A. Lledós *Top. Curr. Chem.* **2011**, *302*, 225

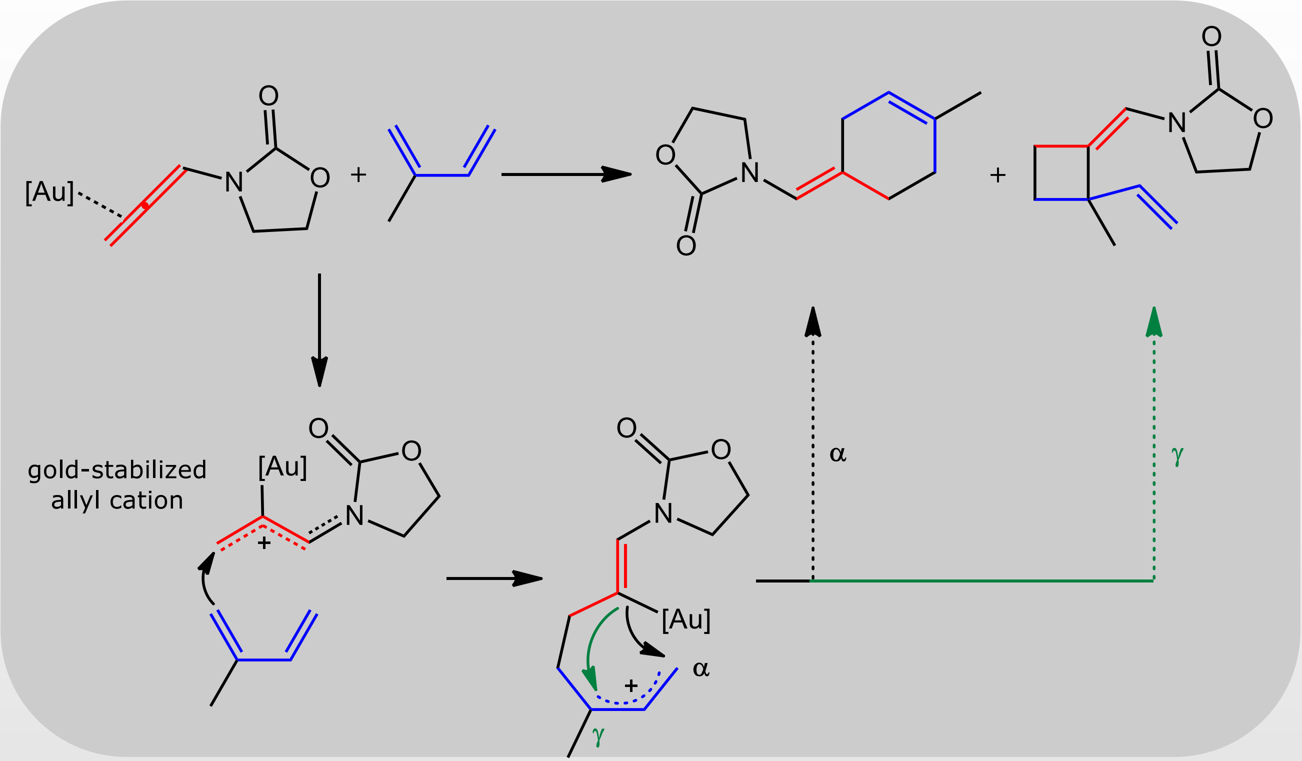
Intramolecular processes
P. Mauleón, R. M. Zeldin, A. Z. González, F. D. Toste *J. Am. Chem. Soc.*, **2009**, *131*, 6348
B. Trillo, F. López, S. Montserrat, G. Ujaque, L. Castedo, A. Lledós, J. L. Mascareñas *Chem.–Eur. J.*, **2009**, *15*, 3336
B. Trillo, F. López, M. Gulías, L. Castedo, J. L. Mascareñas *Angew. Chem., Int. Ed.*, **2008**, *47*, 951
H. Teller, S. Flügge, R. Goddard, A. Fürstner *Angew. Chem., Int. Ed.*, **2010**, *49*, 1949
I. Alonso, B. Trillo, F. López, S. Montserrat, G. Ujaque, L. Castedo, A. Lledós, J. L. Mascareñas *J. Am. Chem. Soc.*, **2009**, *131*, 13020

intermolecular [4+2] cycloaddition reactions involving allenes



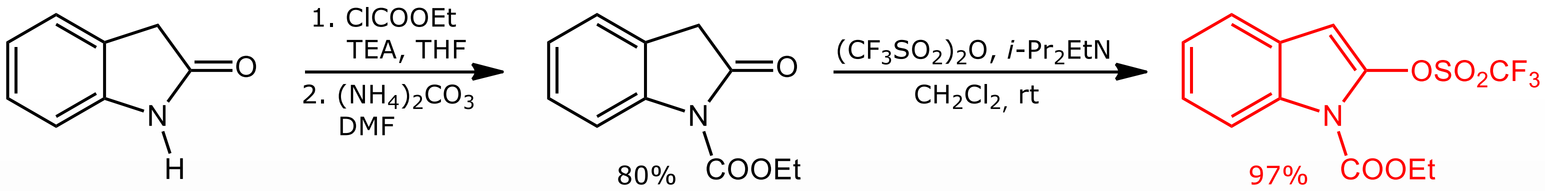


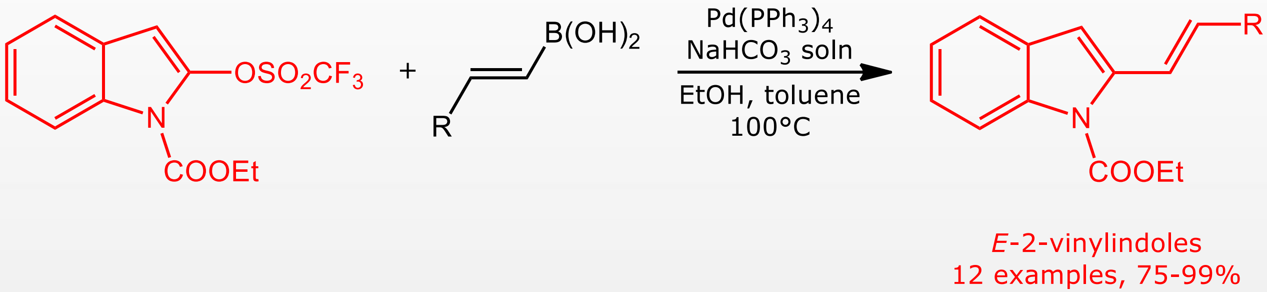
reaction mechanism



H. Faustino, F. López, L. Castedo, J. L. Mascareñas *Chem. Sci.* **2011**, *2*, 633

stereospecific synthesis of 2-vinylindoles

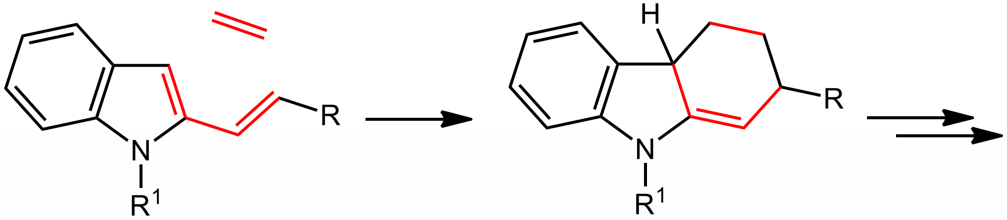




Suzuki-Miyaura coupling, high yield, stereospecific reaction

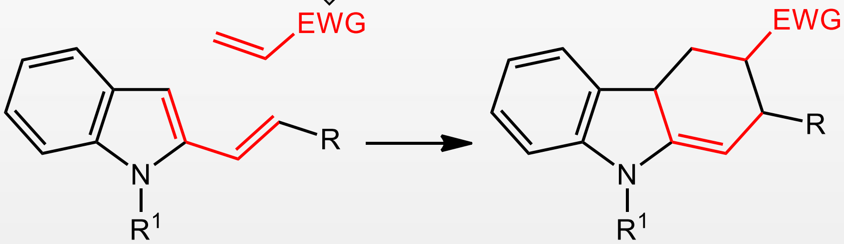
E. Rossi, G. Abbiati, V. Canevari, G. Celentano, E. Magri *Synthesis*, **2006**, 299
V. Pirovano, L. Decataldo, E. Rossi, R. Vicente *Chem. Commun.* **2013**, *49*, 3594

2-vinylindoles as 4π-component in cycloaddition reactions

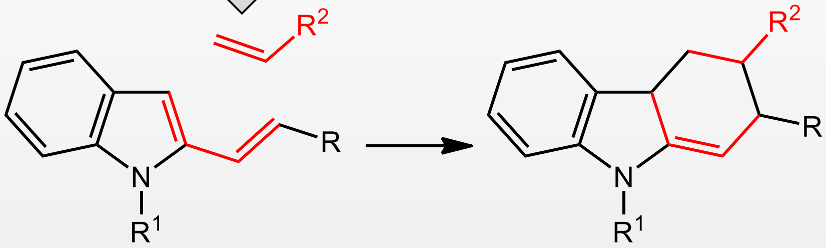


- ✓ Diels-Alder cycloaddition
- ✓ [4+2] cycloaddition
- ✓ [4+2] cyclization

σ-activation by *Lewis acids*



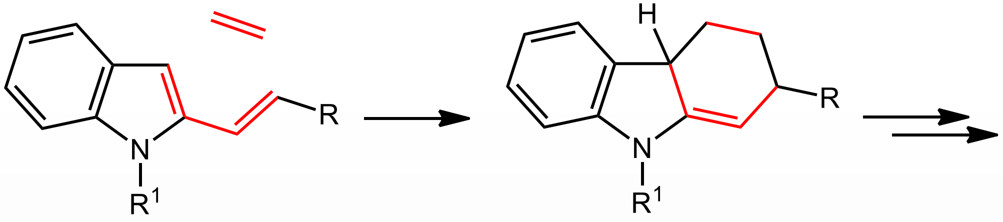
π-activation by *transition metals*



- ✓ Substrates
- ✓ Catalysts
- ✓ Reaction conditions

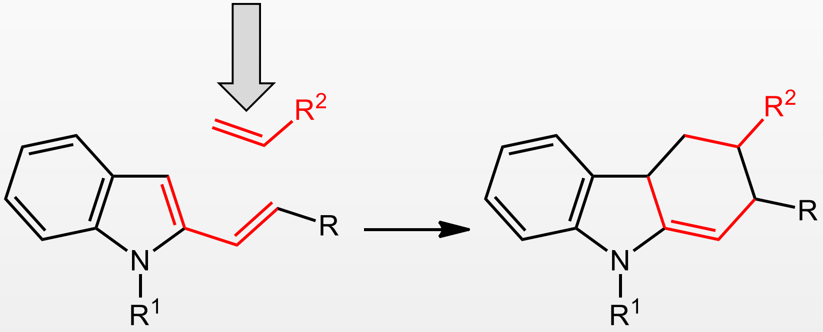
⇨ ***Selectivity***

2-vinylindoles as 4π-component in cycloaddition reactions

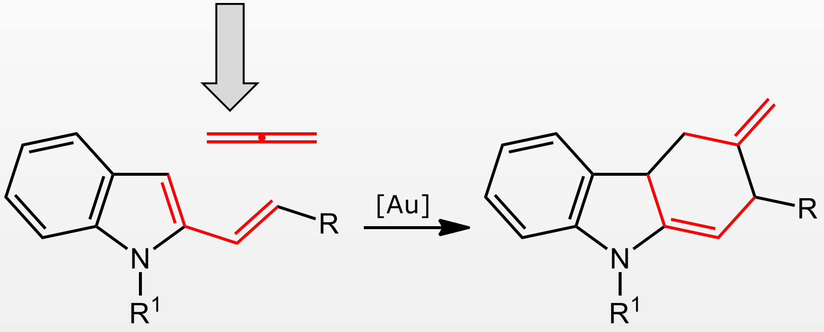


- ✓ Diels-Alder cycloaddition
- ✓ [4+2] cycloaddition
- ✓ [4+2] cyclization

π-activation by *transition metals*



π-activation by *gold catalysis*

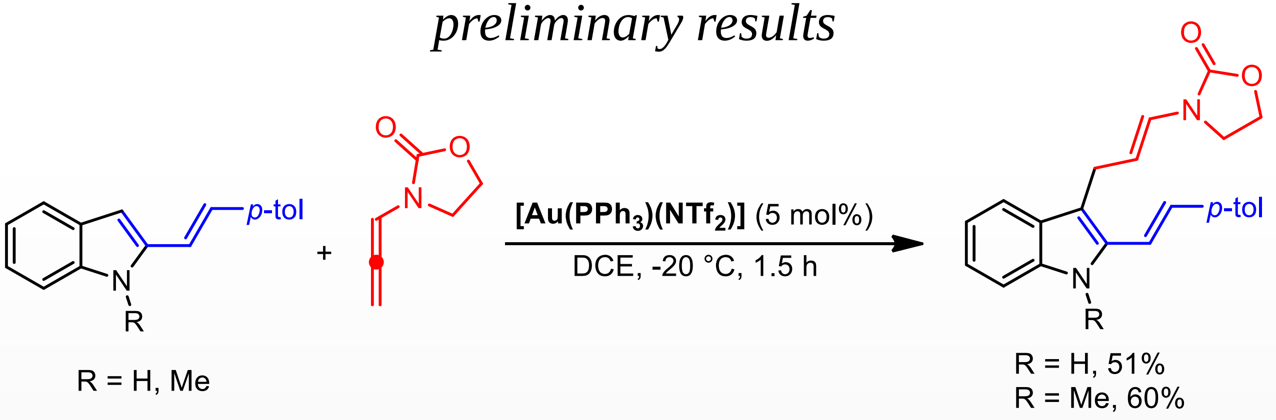


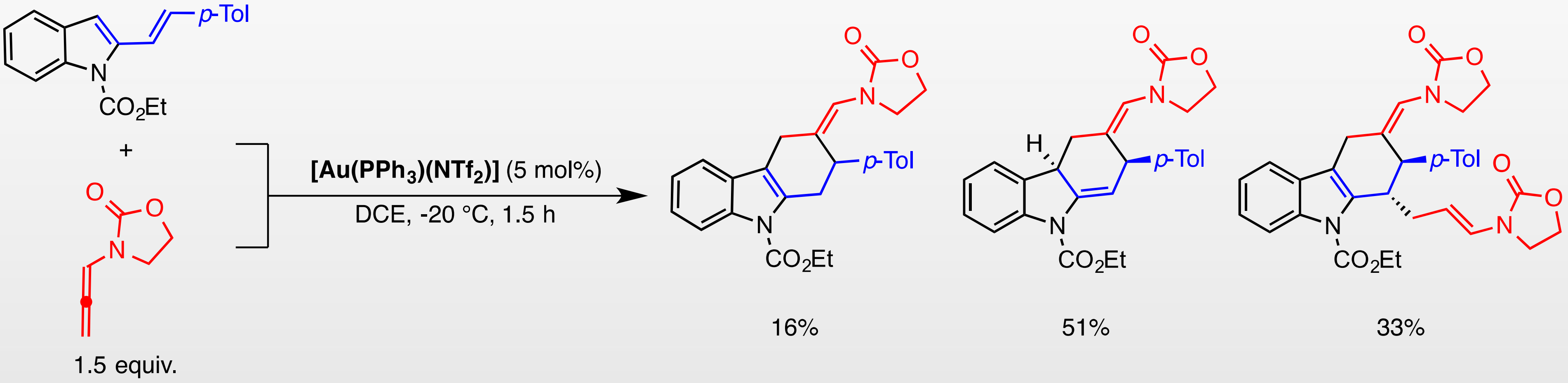
- ✓ Substrates
- ✓ Catalysts
- ✓ Reaction conditions

⇨ ***Selectivity***

Gold catalysis and indole chemistry

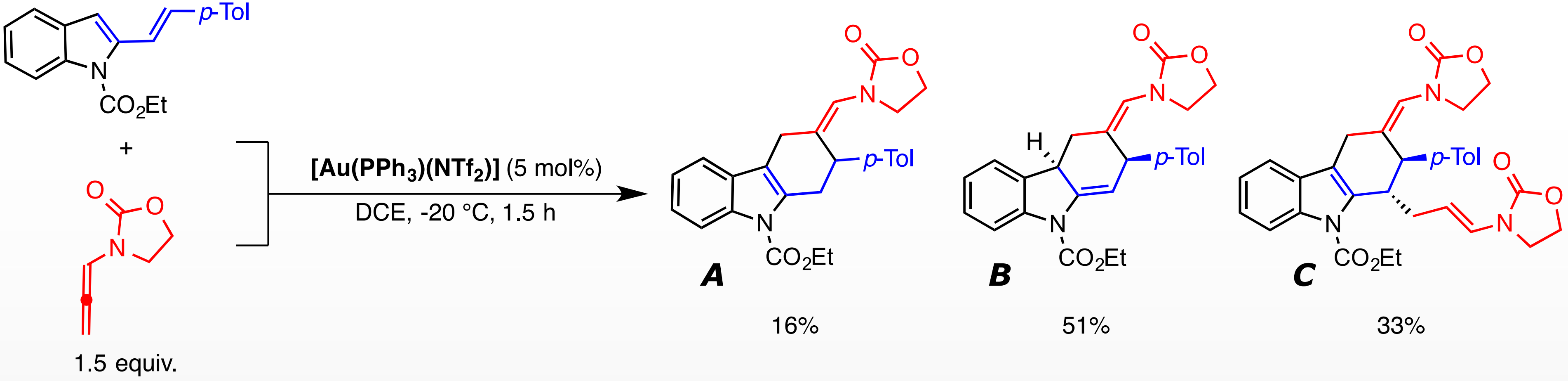
2-vinylindoles and allenamides preliminary results

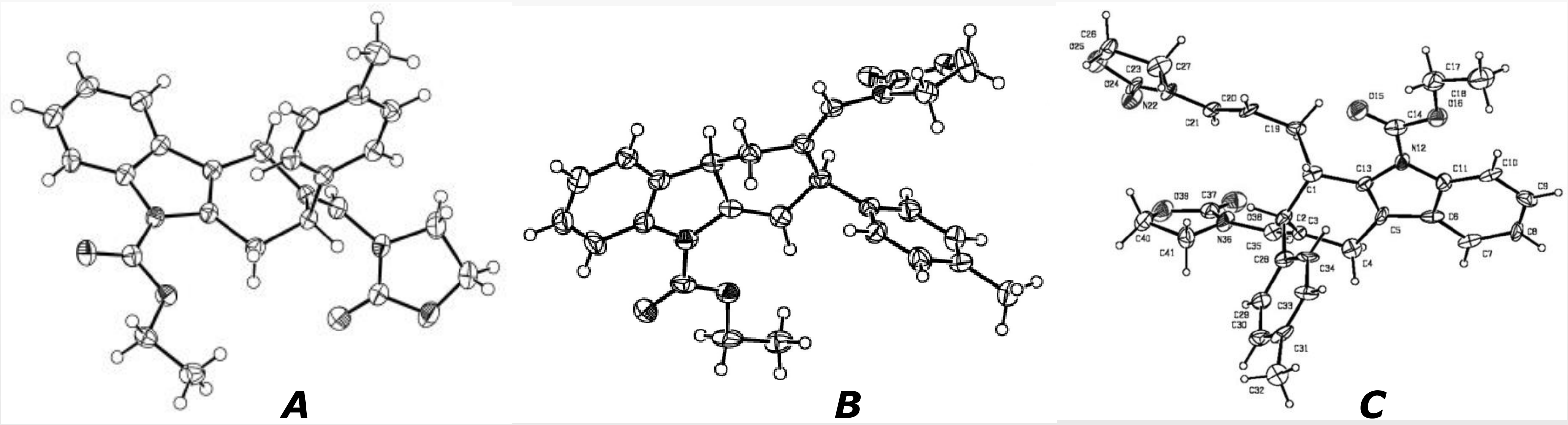




V. Pirovano, L. Decataldo, E. Rossi, R. Vicente *Chem. Commun.* **2013**, *49*, 3594

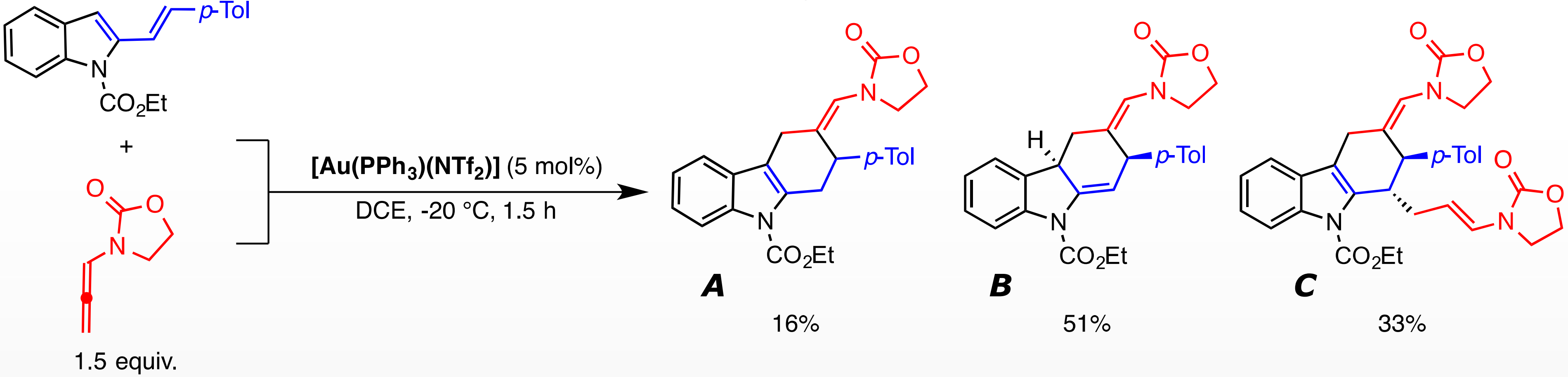
2-vinylindoles and allenamides

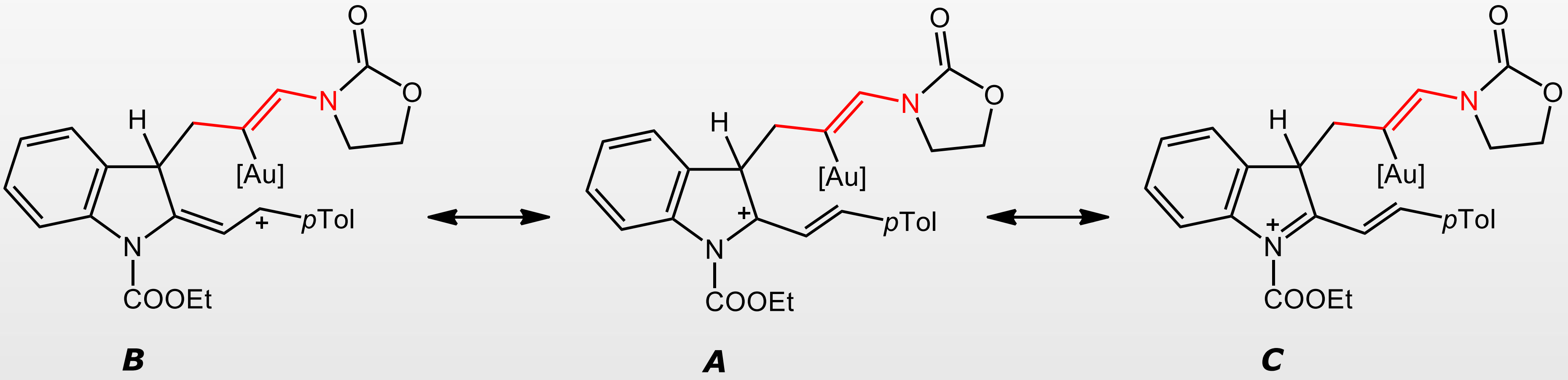




V. Pirovano, L. Decataldo, E. Rossi, R. Vicente *Chem. Commun.* **2013**, *49*, 3594

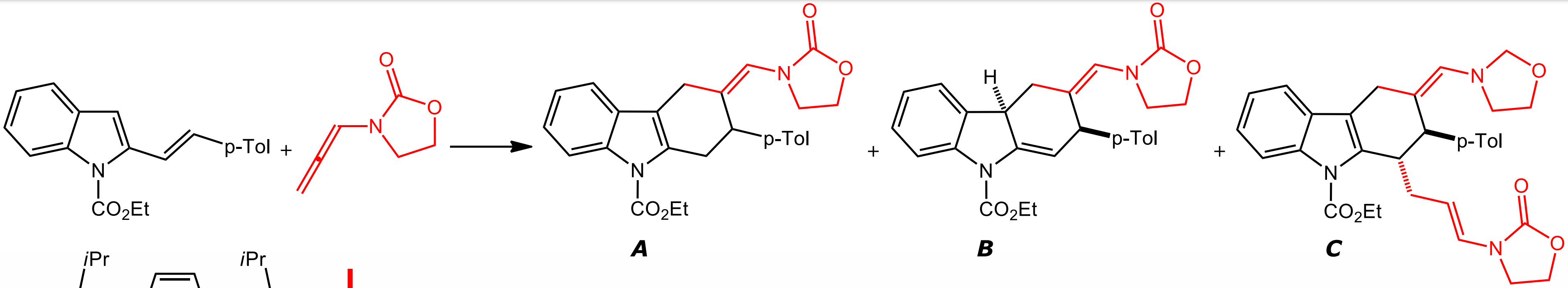
2-vinylindoles and allenamides preliminary results

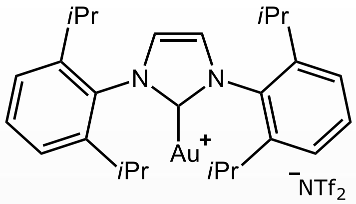




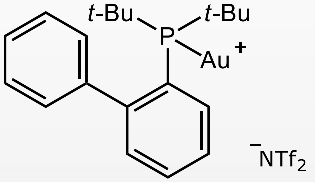
V. Pirovano, L. Decataldo, E. Rossi, R. Vicente *Chem. Commun.* **2013**, *49*, 3594

Gold catalysis and indole chemistry

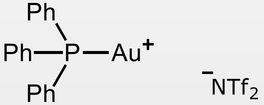




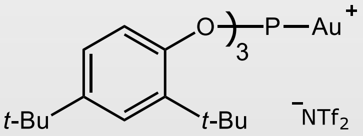
[Au(IPr)(NTf_2)]



[Au(JohnPhos)(NTf_2)]



[Au(PPh_3)(NTf_2)]



[Au($(ArO)_3P$)(NTf_2)]

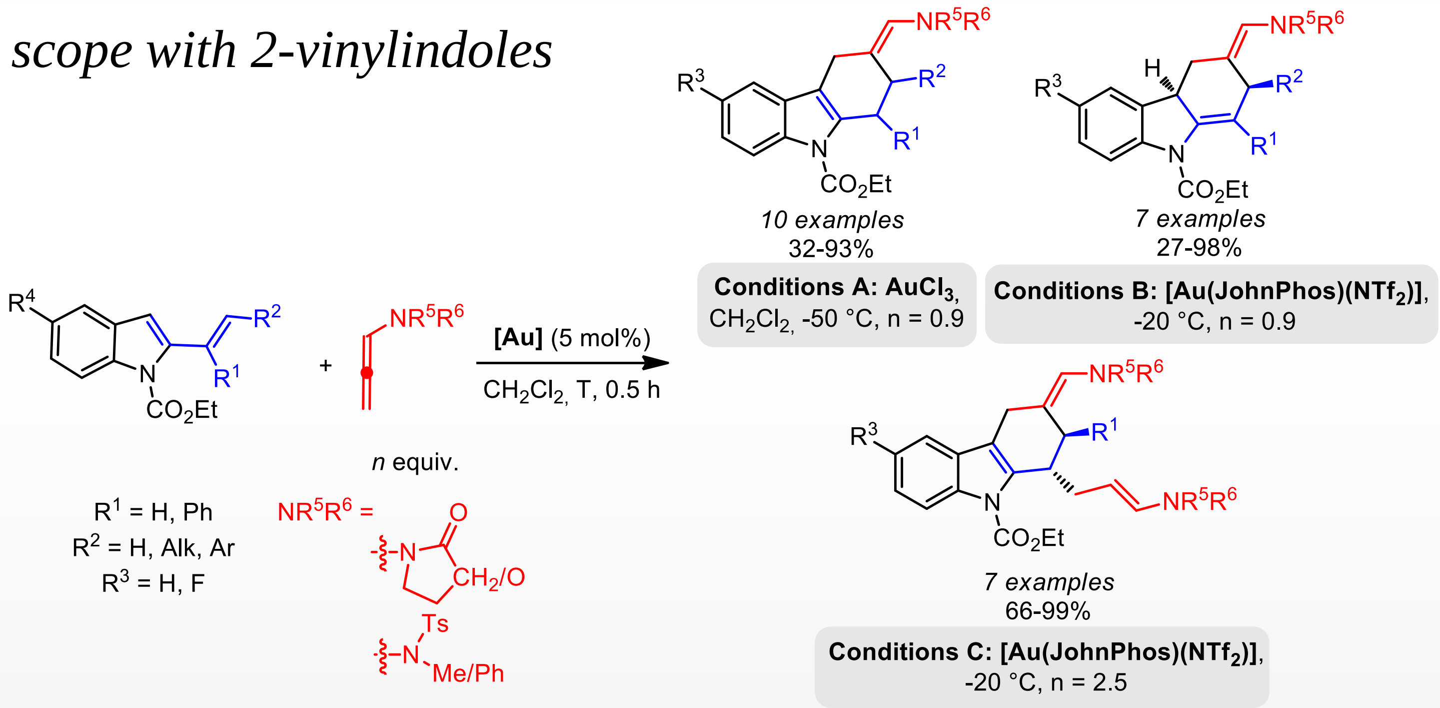
reaction conditions

entry	**allene equiv.**	**Catalyst (5 mol%)**	**solvent**	**T (°C)**	**[M]**	**A**	**B**	**C**
1	0.9	[Au(IPr)(NTf_2)]	DCE	-20	0.1	5	75	-
2	0.9	[Au(JohnPhos)(NTf_2)]	DCE	-20	0.1	-	81	8
3	0.9	[Au(PPh_3)(NTf_2)]	DCE	-20	0.1	54	-	9
4	0.9	[Au($(ArO)_3P$)(NTf_2)]	DCE	-20	0.1	65	18	-
5	0.9	[Au(JohnPhos)(NTf_2)]	DCM	-20	0.05	-	80	-
6	2.5	[Au(JohnPhos)(NTf_2)]	DCM	-20	0.05	-	-	95
7	0.9	$AuCl_3$	DCM	-50	0.1	83	-	-

V. Pirovano, L. Decataldo, E. Rossi, R. Vicente *Chem. Commun.* **2013**, *49*, 3594

Gold catalysis and indole chemistry

reaction scope with 2-vinylindoles



R^1 = H, Ph
R^2 = H, Alk, Ar
R^3 = H, F

10 examples
32-93%

Conditions A: $AuCl_3$, CH_2Cl_2, -50 °C, n = 0.9

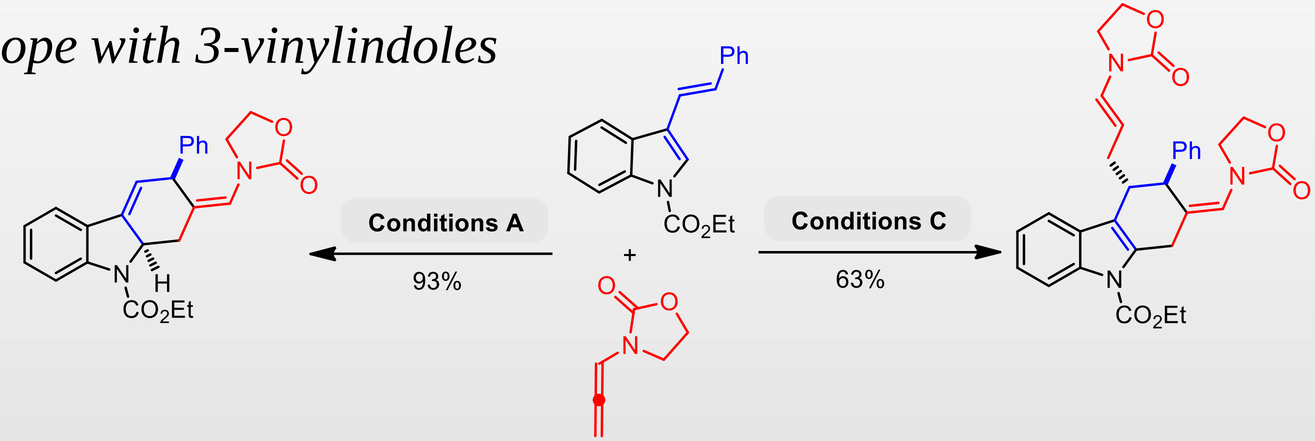
7 examples
27-98%

Conditions B: [Au(JohnPhos)(NTf_2)], -20 °C, n = 0.9

7 examples
66-99%

Conditions C: [Au(JohnPhos)(NTf_2)], -20 °C, n = 2.5

reaction scope with 3-vinylindoles



Conditions A

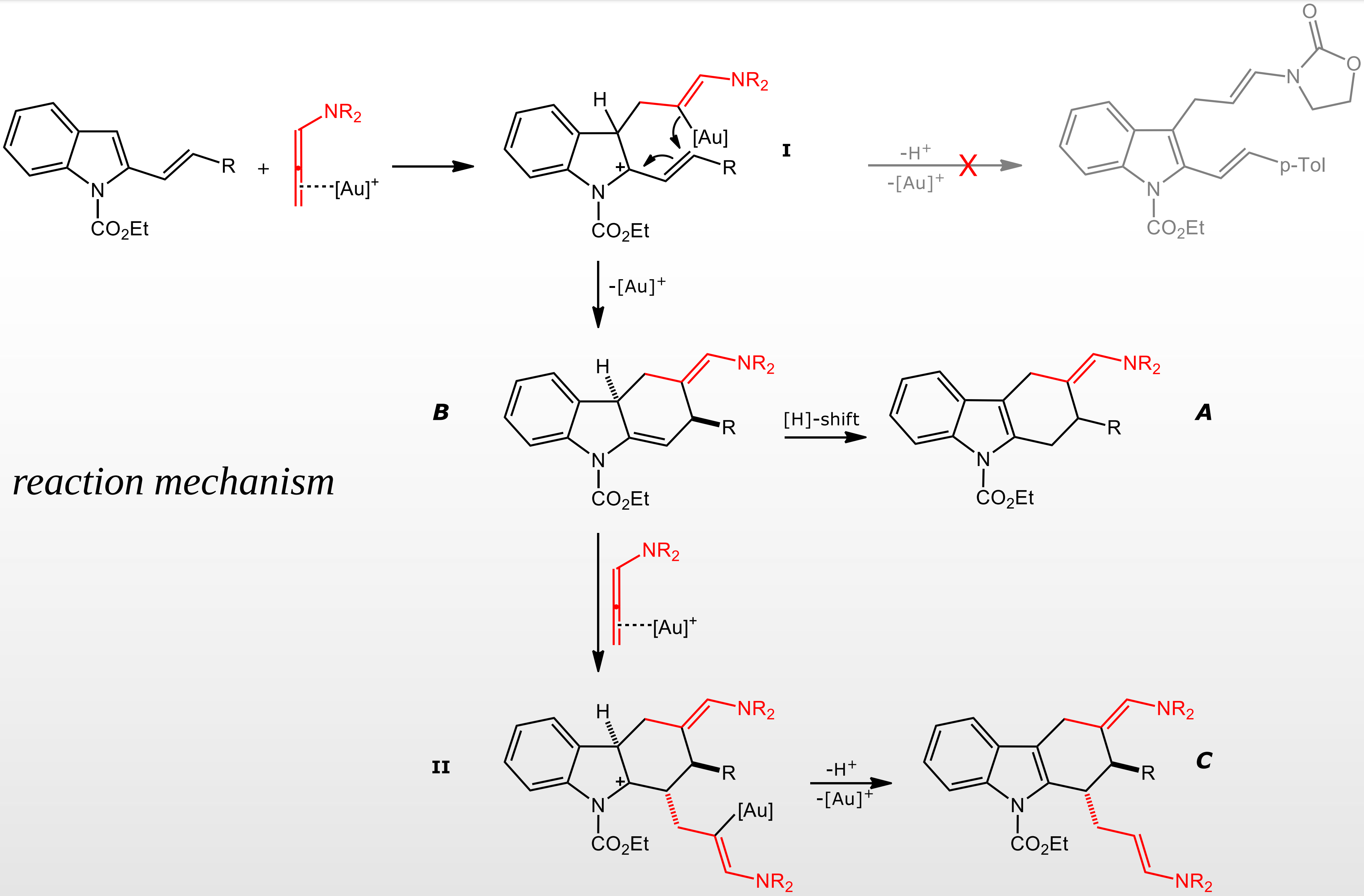
93%

Conditions C

63%

V. Pirovano, L. Decataldo, E. Rossi, R. Vicente *Chem. Commun.* **2013**, *49*, 3594

Gold catalysis and indole chemistry

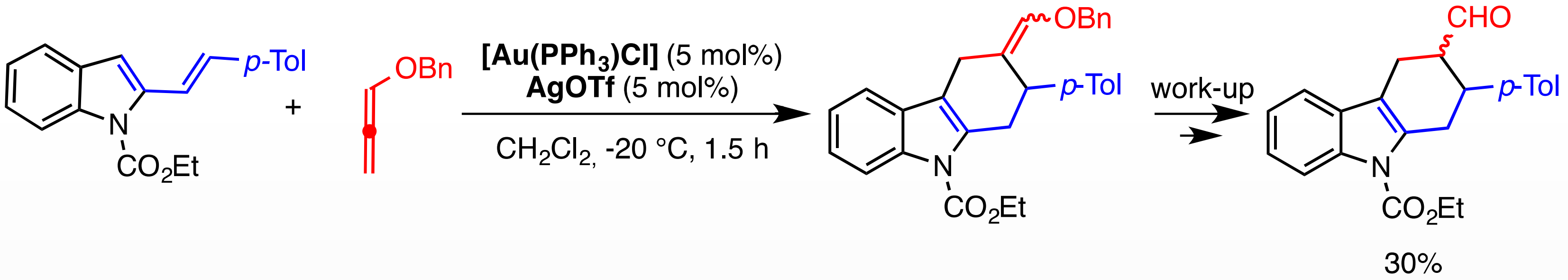


reaction mechanism

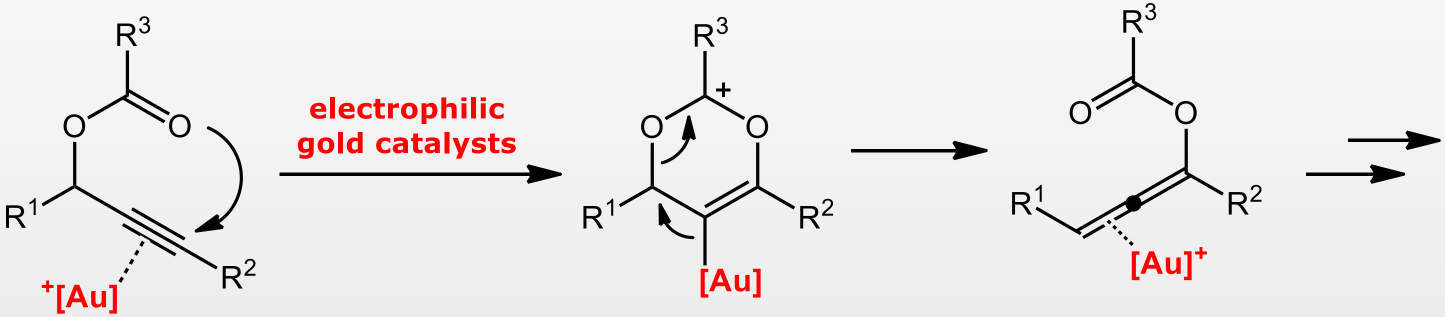
V. Pirovano, L. Decataldo, E. Rossi, R. Vicente *Chem. Commun.* **2013**, *49*, 3594

Gold catalysis and indole chemistry

2-vinylindoles and allenylethers



gold catalyzed propargylic esters rearrangement



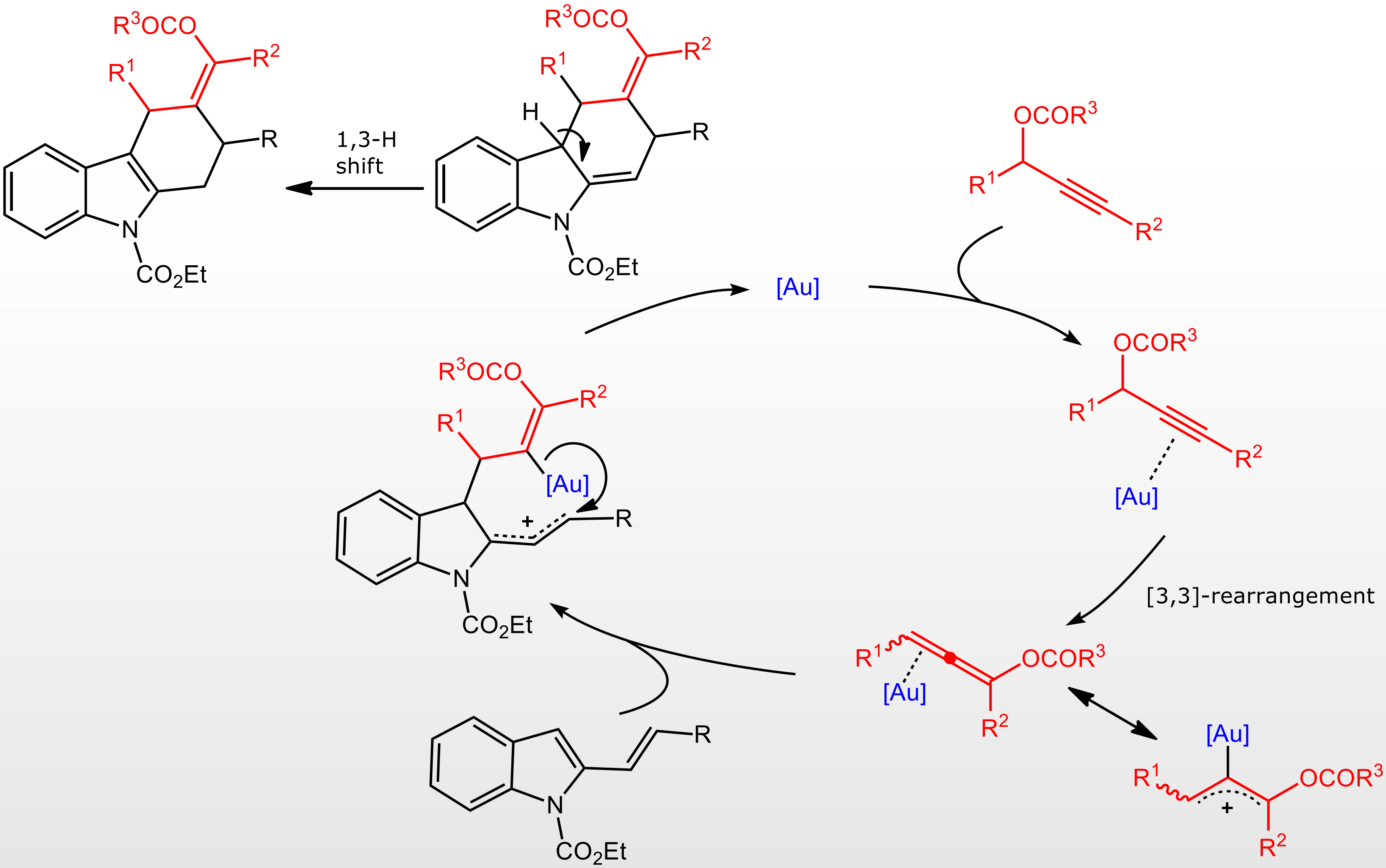
e.g.: [2,2]-cycloaddition,
Nazarov cyclization,
Myers-Sato cyclization,
nucleophilic attack,
electrophilic trapping,
ring expansion

1,3-migration

Au-coordinated allenyl ester

P. Mauleón, F. D. Toste in “Modern Gold Catalyzed Synthesis”, A. S. K. Hashmi, F. D. Toste Eds (2012) Wiley-WCH, Weinheim

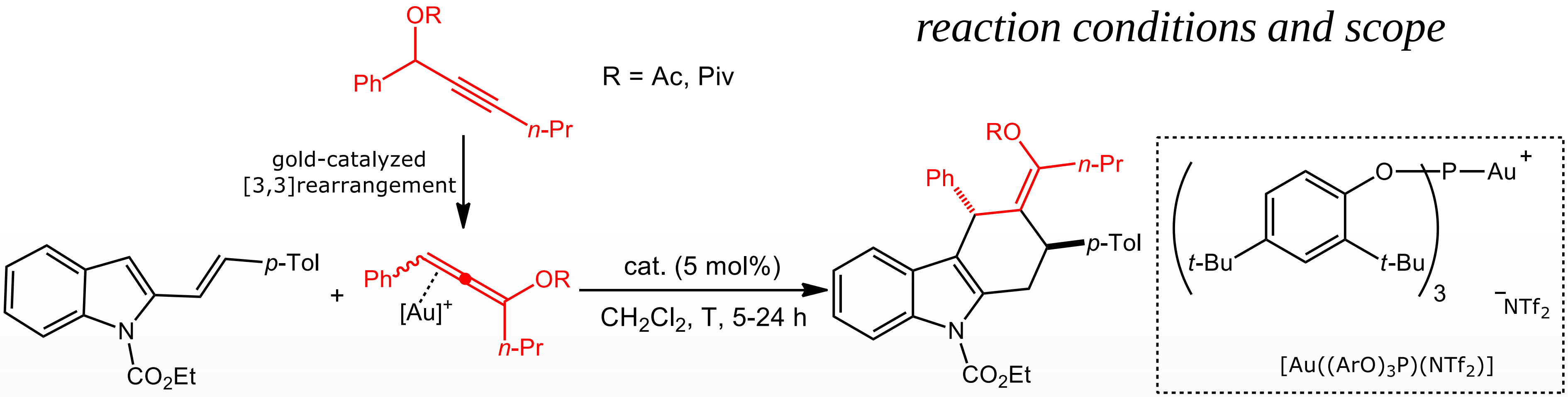
2-vinylindoles and allenylesters, cascade reaction



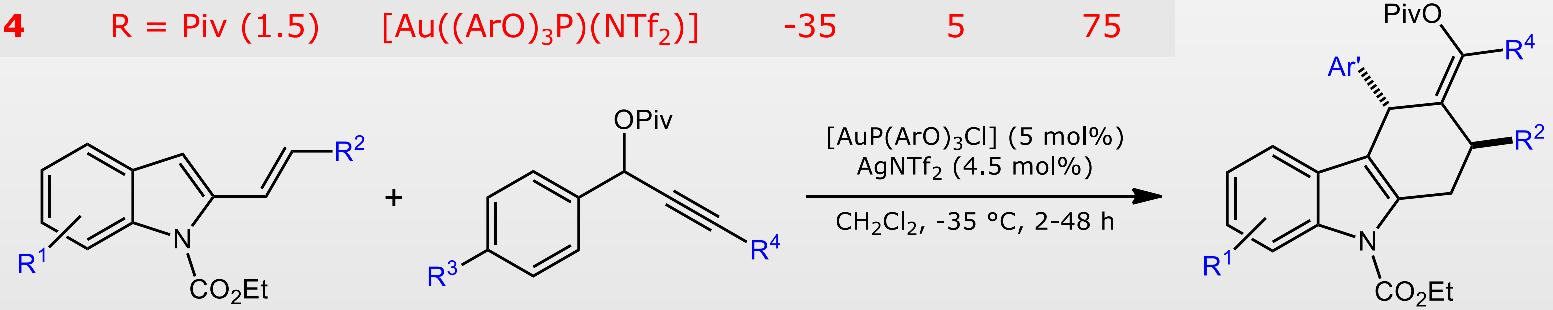
V. Pirovano, E. Arpini, M. Dell’Acqua, R. Vicente, G. Abbiati, E. Rossi *Adv. Synth. Catal.* **2016**, *358*, 403

Gold catalysis and indole chemistry

reaction conditions and scope



entry	*allene (equiv.)*	*Catalyst (5 mol%)*	*T (°C)*	*t [h]*	*Yield [%]*
1	R = Ac (1.1)	$[Au((ArO)_3P)(NTf_2)]$	-20	24	31
2	R = Ac (1.1)	$[Au((ArO)_3P)(NTf_2)]$	-20	24	52
3	R = Ac (1.1)	$[Au((ArO)_3P)(NTf_2)]$	-35	24	64
4	R = Piv (1.5)	$[Au((ArO)_3P)(NTf_2)]$	-35	5	75

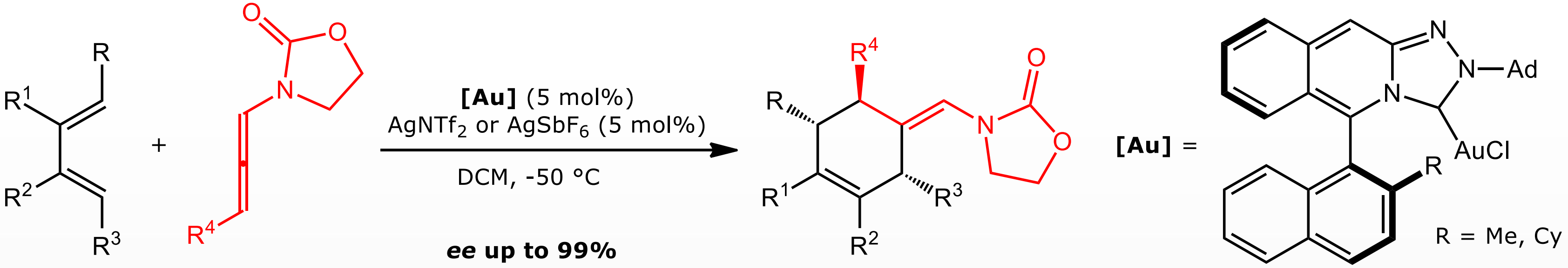


8 examples
35-86%

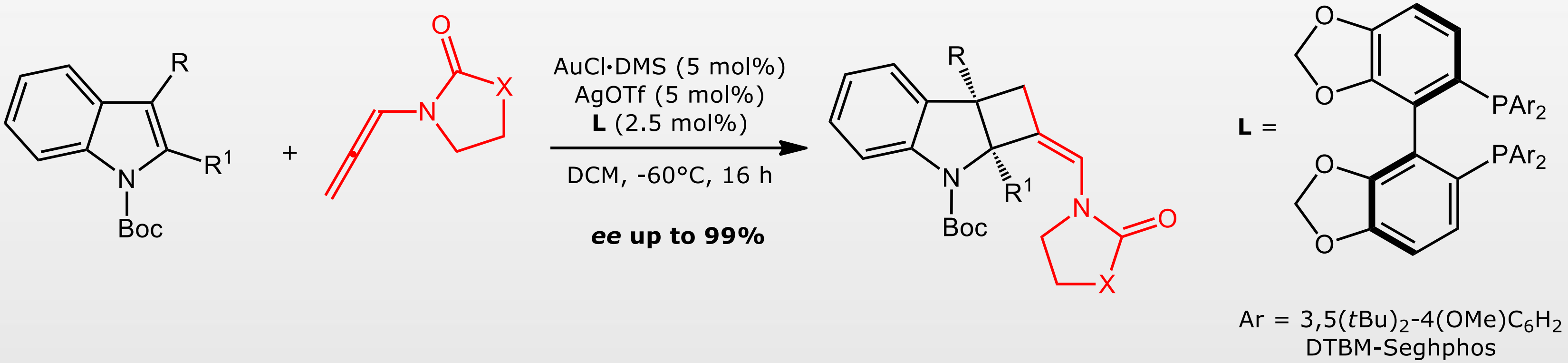
V. Pirovano, E. Arpini, M. Dell'Acqua, R. Vicente, G. Abbiati, E. Rossi *Adv. Synth. Catal.* **2016**, *358*, 403

Gold catalysis and indole chemistry

enantioselective cycloaddition reactions with allenamides

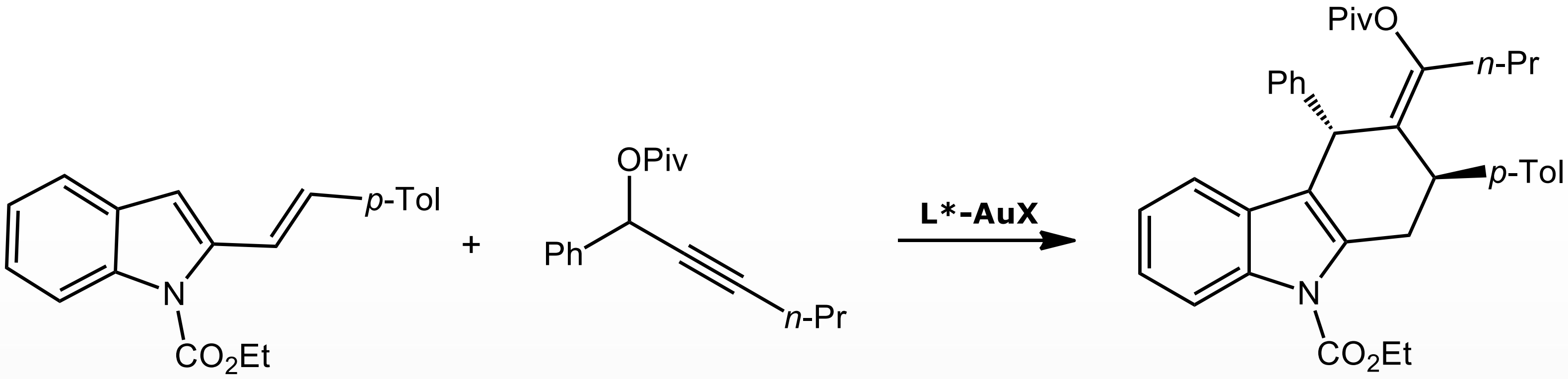


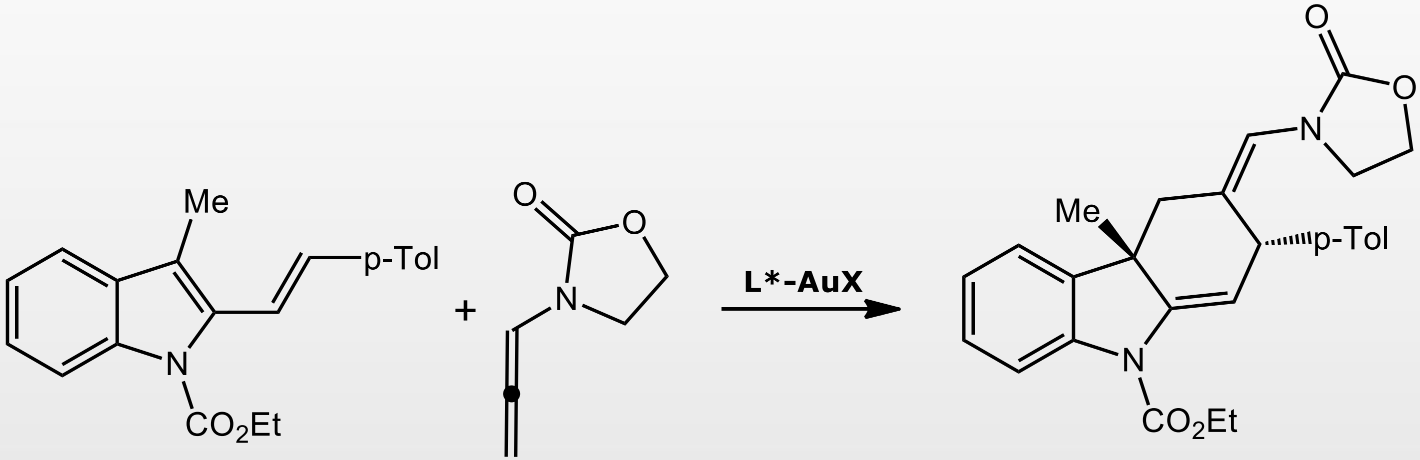
J. L. Mascareñas, *J. Am. Chem. Soc.* **2012**, *134*, 14322.



M. Jia, M. Monari, Q.-Q. Yang, M. Bandini *Chem. Commun.* **2015**, *51*, 2320

enantioselective cycloaddition reactions of 2-vinylindoles and allenes

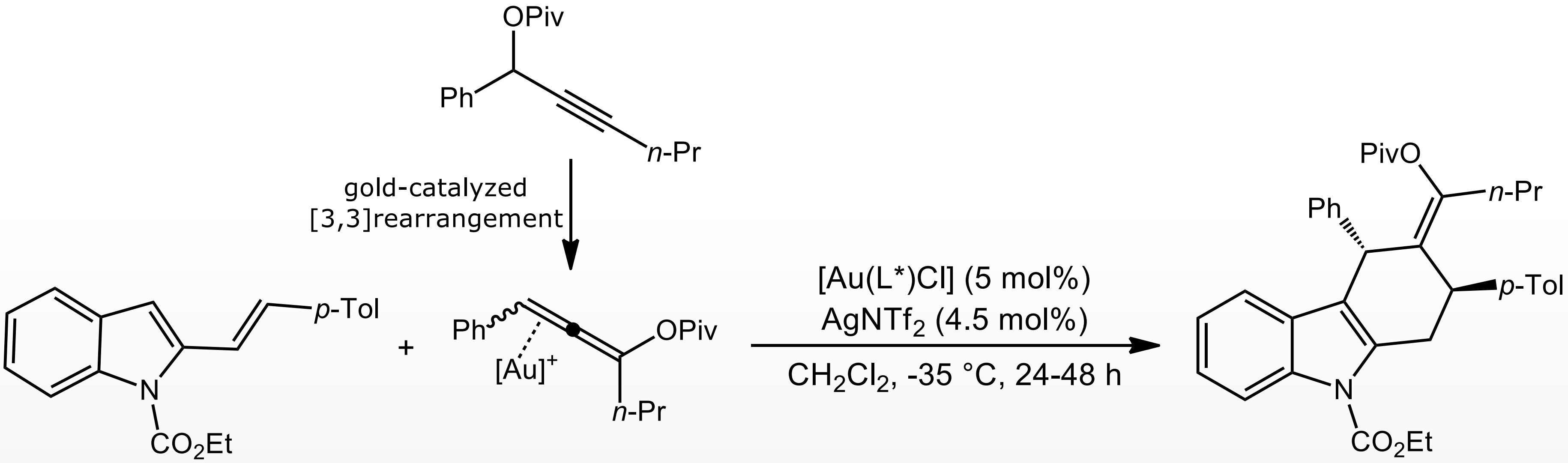




V. Pirovano, E. Arpini, M. Dell'Acqua, R. Vicente, G. Abbiati, E. Rossi *Adv. Synth. Catal.* **2016**, *358*, 403 – *VIP.*
V. Pirovano, M. Borri, S. Rizzato, G. Abbiati, E. Rossi *Adv. Synth. Catal.* **2017**, *359*, 1912.

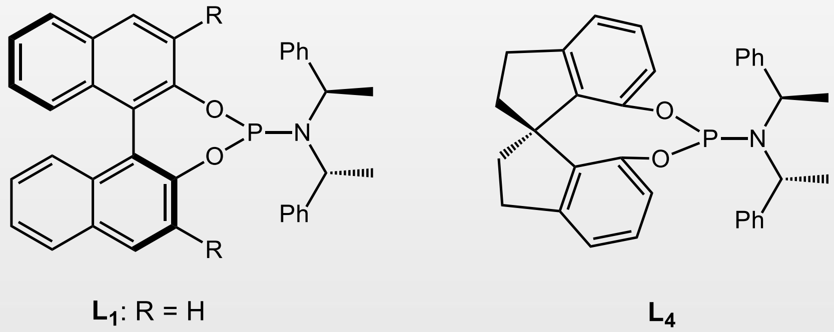
Gold catalysis and indole chemistry

enantioselective cycloaddition reactions of 2-vinylindoles and allenylesters



reaction conditions

entry	*L**	*Additive*	*t [h]*	*Yield [%]*	*e.r.*
1	L1	-	24	90	40:60
2	L2	-	24	42	80:20
3	L3	-	48	47	81:19
4	L4	-	48	42	84:16
5	L4	4 Å ms	48	62	85:15



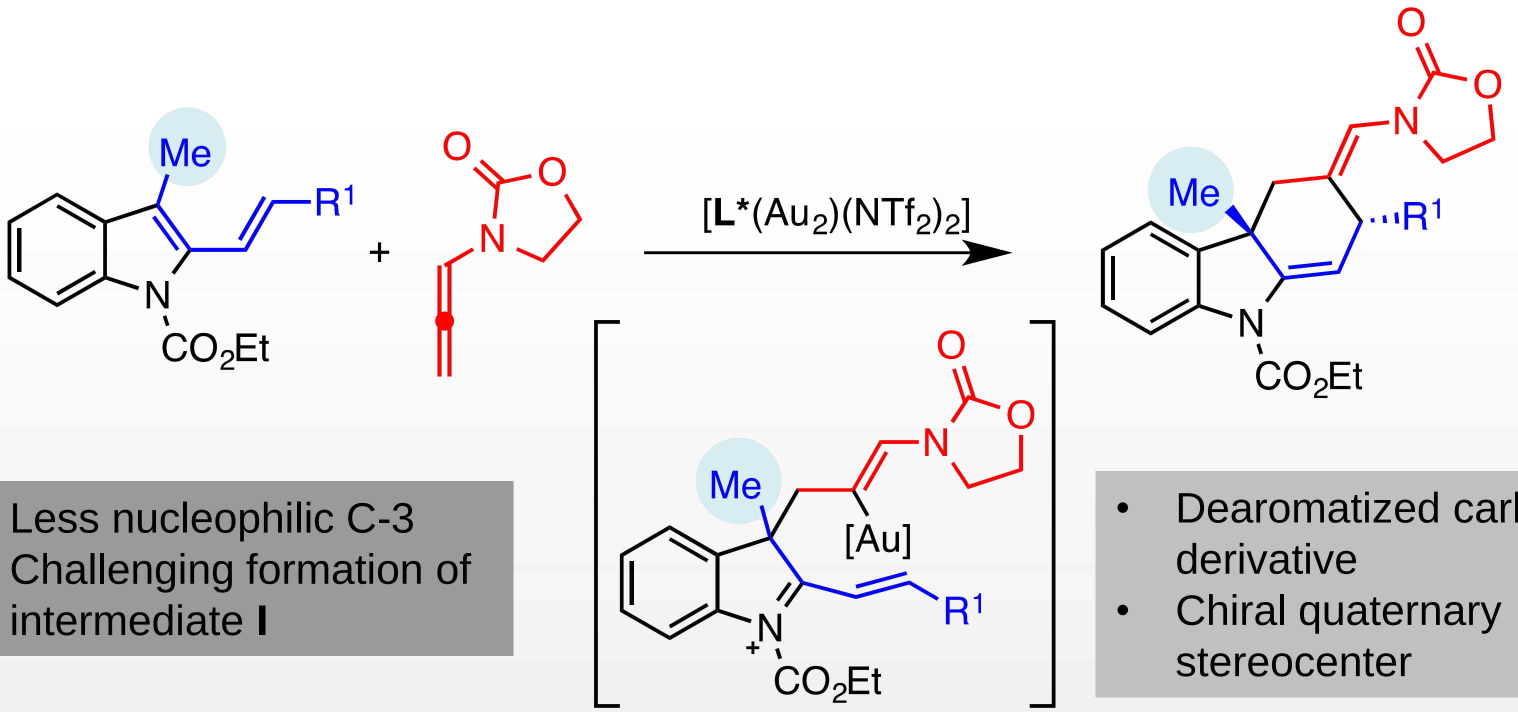
L_1: R = H
L_2: R = naphthyl
L_3: R = pyrenyl

L_4

V. Pirovano, E. Arpini, M. Dell'Acqua, R. Vicente, G. Abbiati, E. Rossi *Adv. Synth. Catal.* **2016**, *358*, 403 - *VIP*

Gold catalysis and indole chemistry

enantioselective cycloaddition reactions of 2-vinyl-3-methylindoles and allenamides



I

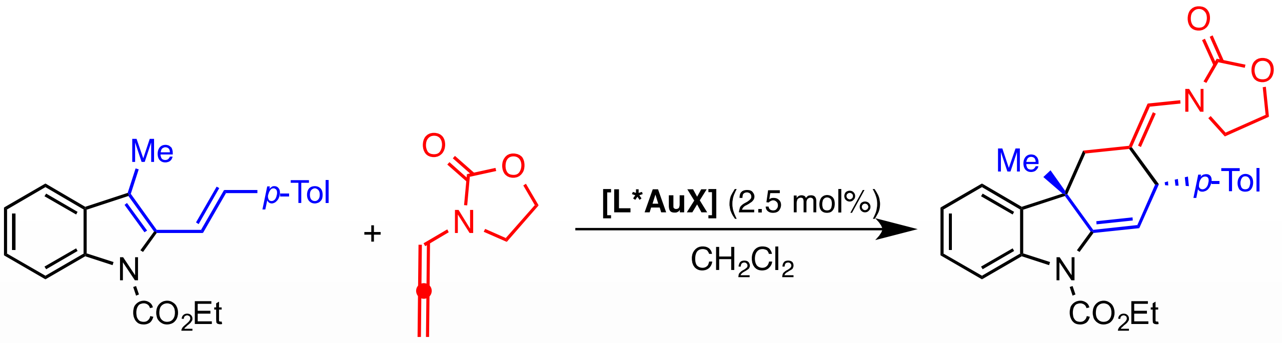
- Less nucleophilic C-3
- Challenging formation of intermediate **I**

- Dearomatized carbazole derivative
- Chiral quaternary stereocenter

L* = dinuclear chiral gold(I) catalyst

V. Pirovano, M. Borri, S. Rizzato, G. Abbiati, E. Rossi *Adv. Synth. Catal.* **2017**, *359*, 1912.

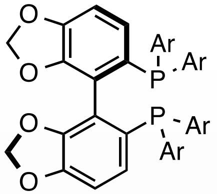
enantioselective cycloaddition reactions of 2-vinyl-3-methylindoles and allenamides



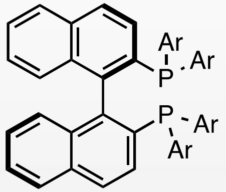
reaction conditions

Entry	*allene equiv.*	*Catalyst*	*T (°C)*	*t (h)*	*Yield (%)*	*e.r.*
1	0.9	$[L_1Au_2Cl_2]/AgNTf_2$	-20	1	72	7:93
2	1.2	$[L_1Au_2(NTf_2)_2]$	-40	18	75	4:96
3	1.2 (0.05 M)	$[L_1Au_2(NTf_2)_2]$	-40	18	79	4:96*
4	0.9	$[L_2Au_2Cl_2]/AgNTf_2$	-20	1	54	27:73
5	0.9	$[L_3Au_2Cl_2]/AgNTf_2$	-20	1	52	37:63
6	0.9	$[L_4Au_2Cl_2]/AgNTf_2$	-20	1	75	20:80
7	0.9	$[L_5Au_2Cl_2]/AgNTf_2$	-20	1	48	12:88

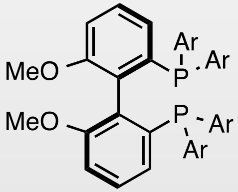
*: increased to 1:99 after a single recrystallization from CH_2Cl_2/pentane



L_1, Ar = 3,5-di-tert-butyl-4-methoxyphenyl;
(R)-DTBM-Segphos
L_2, Ar = 3,5-dimethylphenyl;
(R)-DM-Segphos



L_3, Ar = Ph;
(R)-BINAP)
L_4, Ar = 3,5-dimethylphenyl;
(R)-DM-BINAP

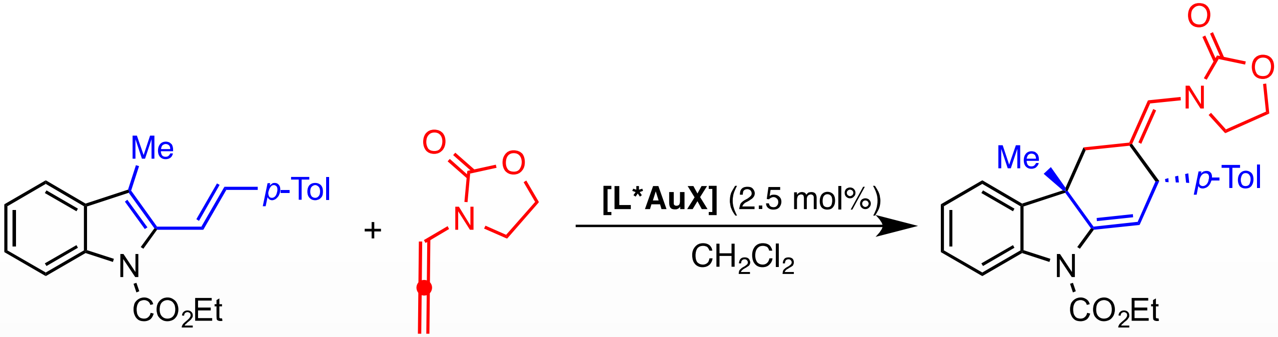


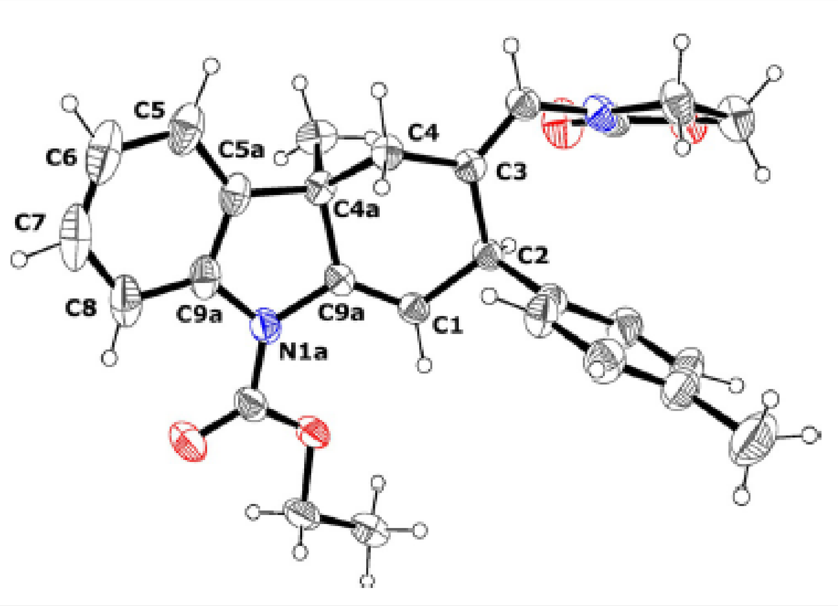
L_5, Ar = 3,5-di-tert-butyl-4-methoxyphenyl

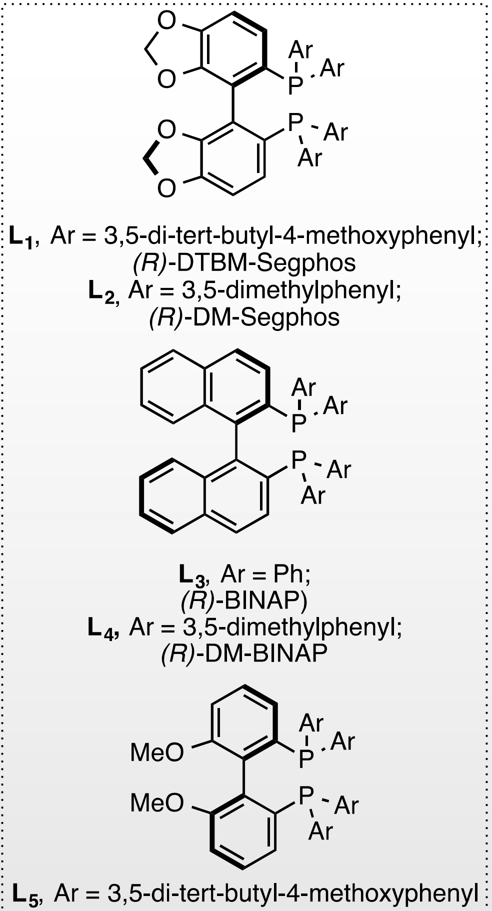
V. Pirovano, M. Borri, S. Rizzato, G. Abbiati, E. Rossi *Adv. Synth. Catal.* **2017**, *359*, 1912.

Gold catalysis and indole chemistry

enantioselective cycloaddition reactions of 2-vinyl-3-methylindoles and allenamides







L$_1$, Ar = 3,5-di-tert-butyl-4-methoxyphenyl; *(R)*-DTBM-Segphos
L$_2$, Ar = 3,5-dimethylphenyl; *(R)*-DM-Segphos

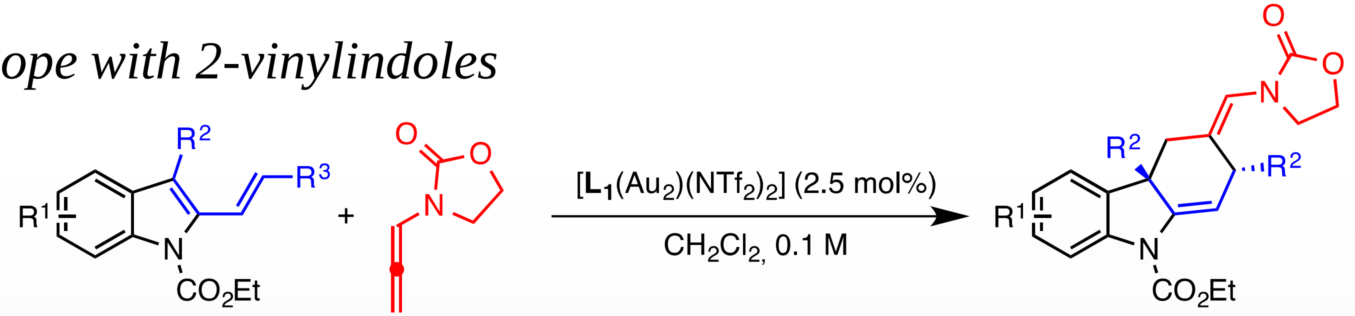
L$_3$, Ar = Ph; *(R)*-BINAP)
L$_4$, Ar = 3,5-dimethylphenyl; *(R)*-DM-BINAP

L$_5$, Ar = 3,5-di-tert-butyl-4-methoxyphenyl

V. Pirovano, M. Borri, S. Rizzato, G. Abbiati, E. Rossi *Adv. Synth. Catal.* **2017**, *359*, 1912.

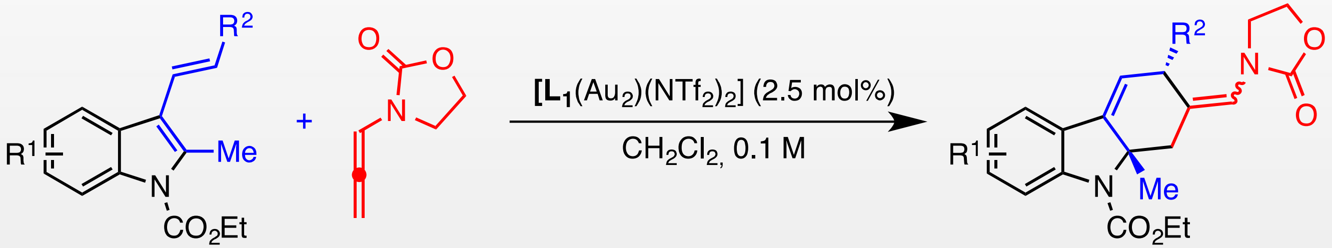
enantioselective cycloaddition reactions of 2-vinyl-3-methylindoles and allenamides

reaction scope with 2-vinylindoles



8 examples
40-90%
e.r. up to 97:3

reaction scope with 3-vinylindoles

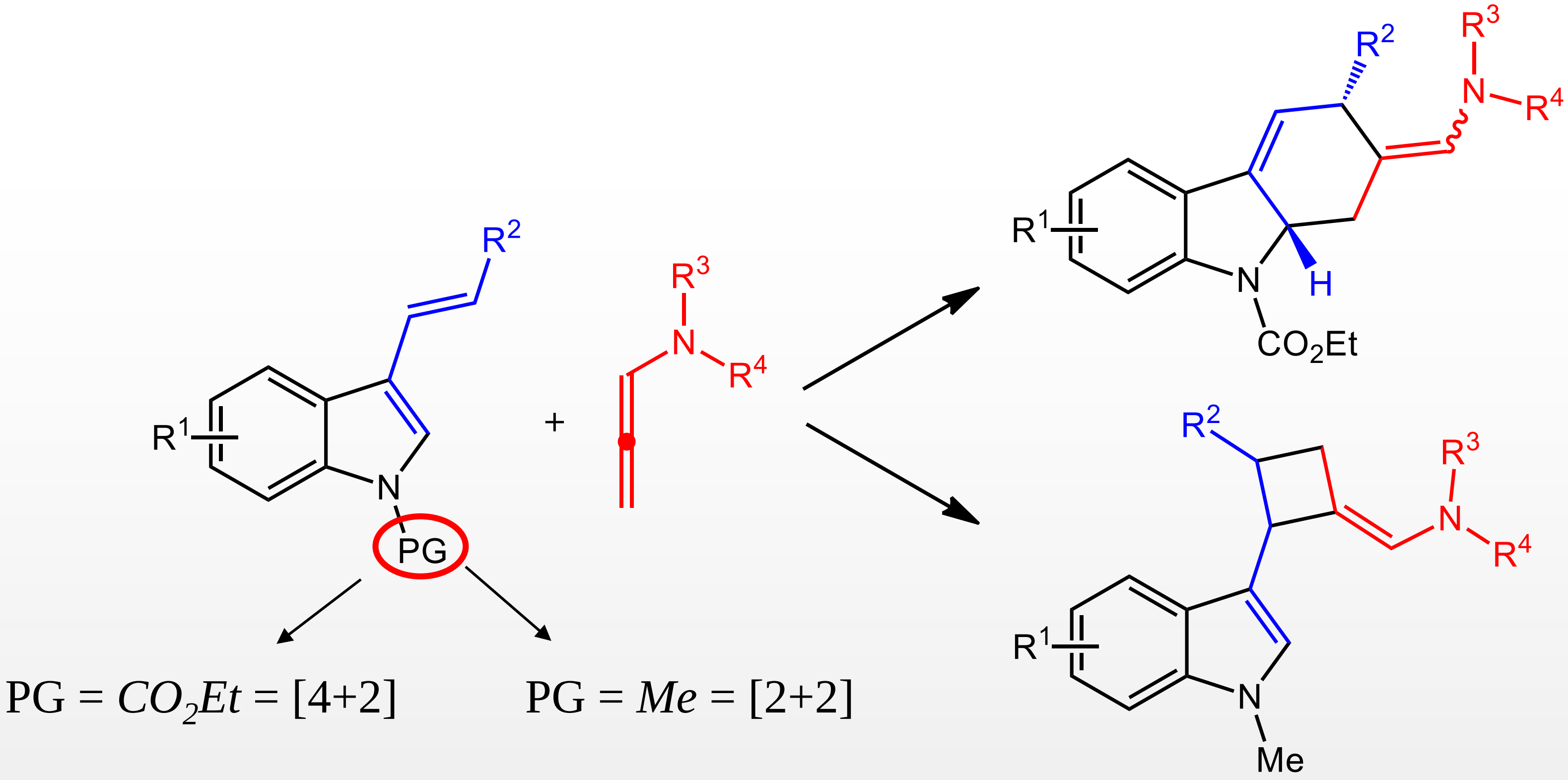


4 examples
80-97%
(*E*)/(*Z*) up to 20:1
e.r. (*E*) up to 98:2
e.r (*Z*) up to 99:1

V. Pirovano, M. Borri, S. Rizzato, G. Abbiati, E. Rossi *Adv. Synth. Catal.* **2017**, *359*, 1912.

Gold catalysis and indole chemistry

enantioselective cycloaddition reactions of 3-vinylindoles and allenamides



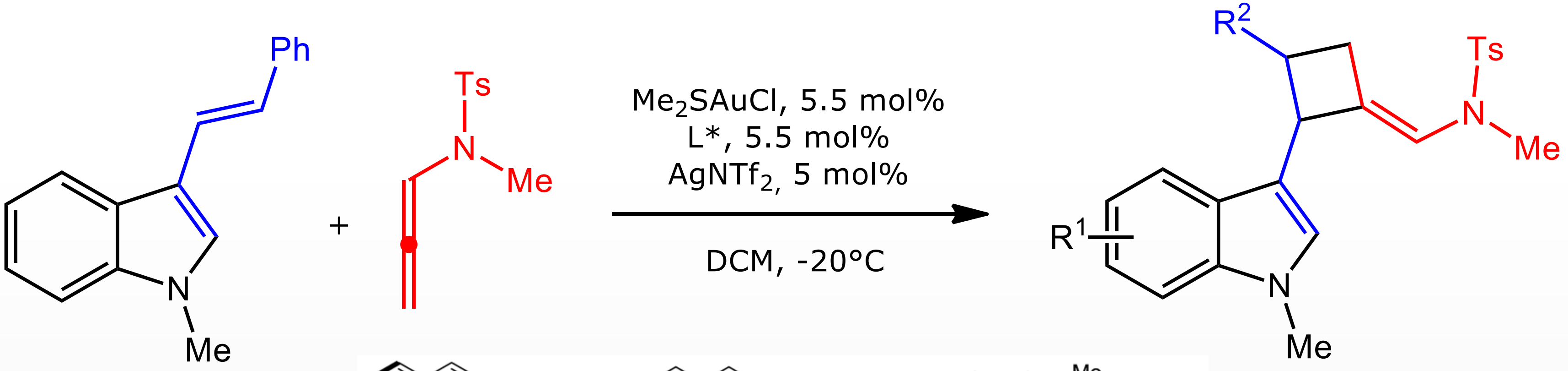
PG = *CO_2Et* = [4+2]

PG = *Me* = [2+2]

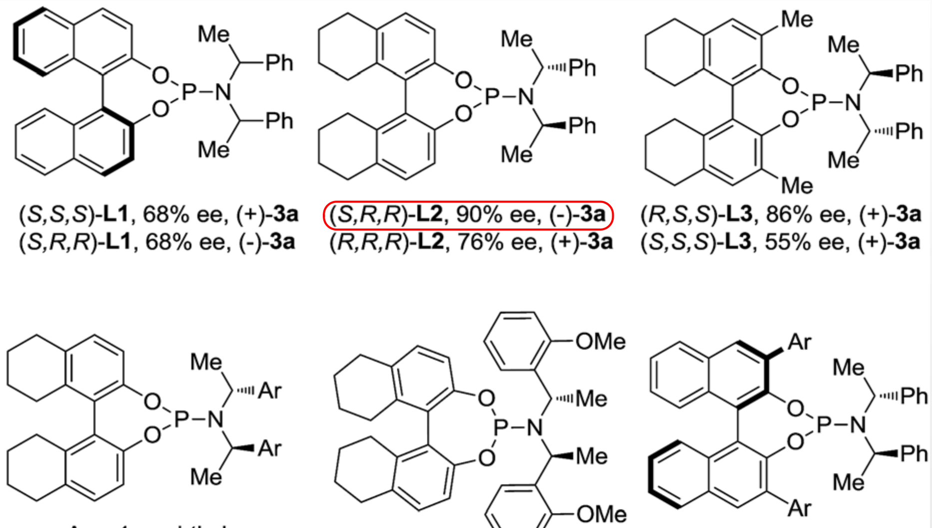
Y. Wang, P. Zhang, Y. Liu, F. Xia, J. Zhang *Chem. Sci*. **2015**, *6*, 5564.
H. Hu, Y. Wang, D. Qian, Z.-M. Zhang, L. Liu, J. Zhang *Org. Chem. Front*. **2016**, *3*, 759.

Gold catalysis and indole chemistry

enantioselective cycloaddition reactions of 3-vinylindoles and allenamides



reaction conditions



(*S*,*S*,*S*)-**L1**, 68% ee, (+)-**3a**
(*S*,*R*,*R*)-**L1**, 68% ee, (-)-**3a**

(*S*,*R*,*R*)-**L2**, 90% ee, (-)-**3a**
(*R*,*R*,*R*)-**L2**, 76% ee, (+)-**3a**

(*R*,*S*,*S*)-**L3**, 86% ee, (+)-**3a**
(*S*,*S*,*S*)-**L3**, 55% ee, (+)-**3a**

Ar = 1-naphthyl

(*R*,*R*,*R*)-**L4**, 52% ee, (+)-**3a**
(*S*,*R*,*R*)-**L4**, 52% ee, (-)-**3a**

(*S*,*S*,*S*)-**L5**, 43% ee, (+)-**3a**
(*R*,*S*,*S*)-**L5**, 47% ee, (-)-**3a**

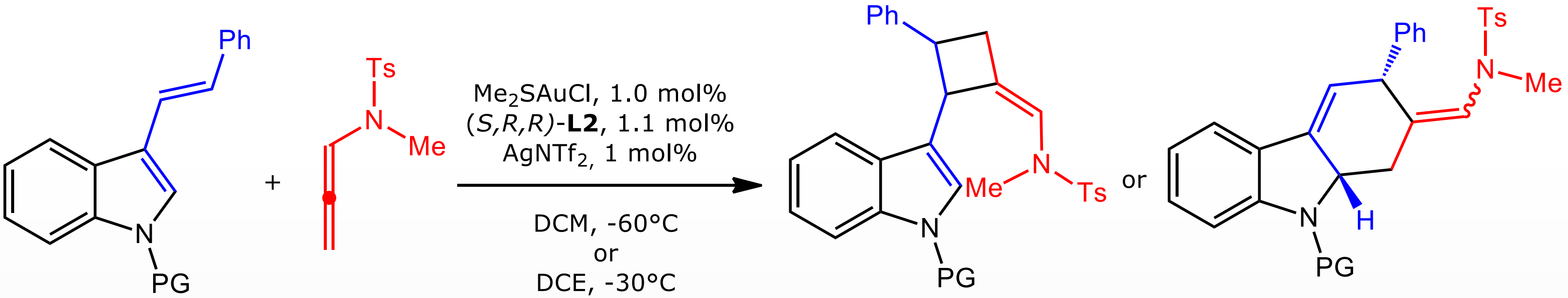
Ar = anthracenyl

(*R*,*R*,*R*)-**L6**, 72% ee, (-)-**3a**

Y. Wang, P. Zhang, Y. Liu, F. Xia, J. Zhang *Chem. Sci*. **2015**, *6*, 5564.
H. Hu, Y. Wang, D. Qian, Z.-M. Zhang, L. Liu, J. Zhang *Org. Chem. Front*. **2016**, *3*, 759.

Gold catalysis and indole chemistry

enantioselective cycloaddition reactions of 3-vinylindoles and allenamides



Me_2SAuCl, 1.0 mol%
(*S*,*R*,*R*)-**L2**, 1.1 mol%
$AgNTf_2$, 1 mol%

DCM, -60°C
or
DCE, -30°C

reaction conditions and scope

PG	*[ ]*	*condition*	*yield (%)*	*Z/E*	*ee (%)*
Me	[2+2]	A	99	1:0	96
Bn	[2+2]	A	94	1:0	92
Allyl	[2+2]	A	93	1:0	91
H	[2+2]	A	95	1:0	72
CO_2Et	[4+2]	B	95	5.3:1	95
Ts	[4+2]	B	86	4.2:1	91
Ac	[4+2]	B	67	7.3:1	94

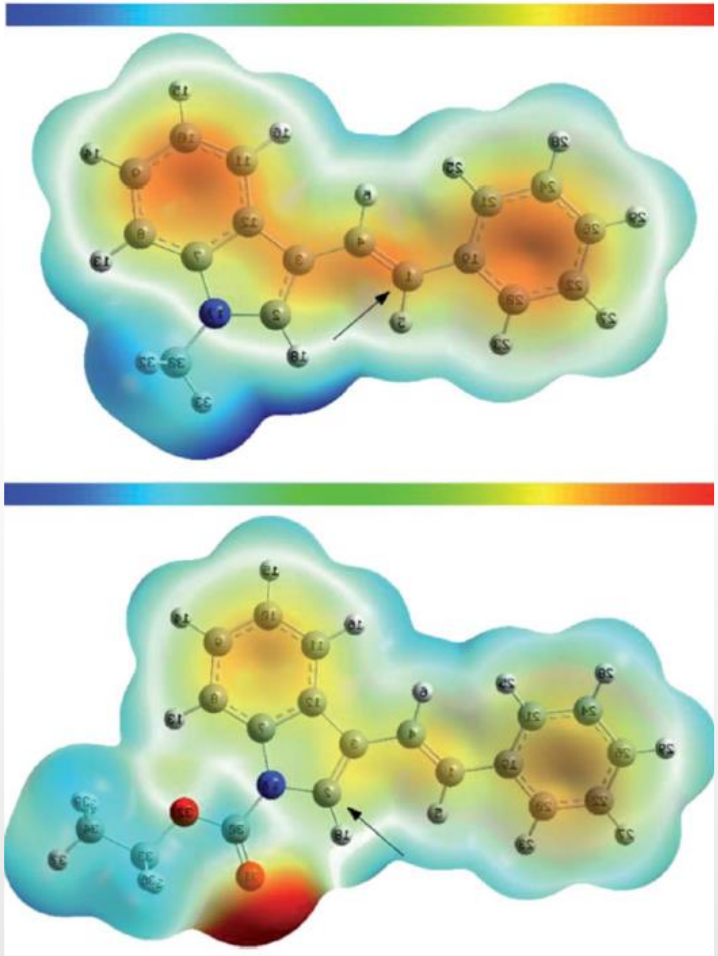
13 examples
58-99%
Z/E 1:0
ee 82-96%

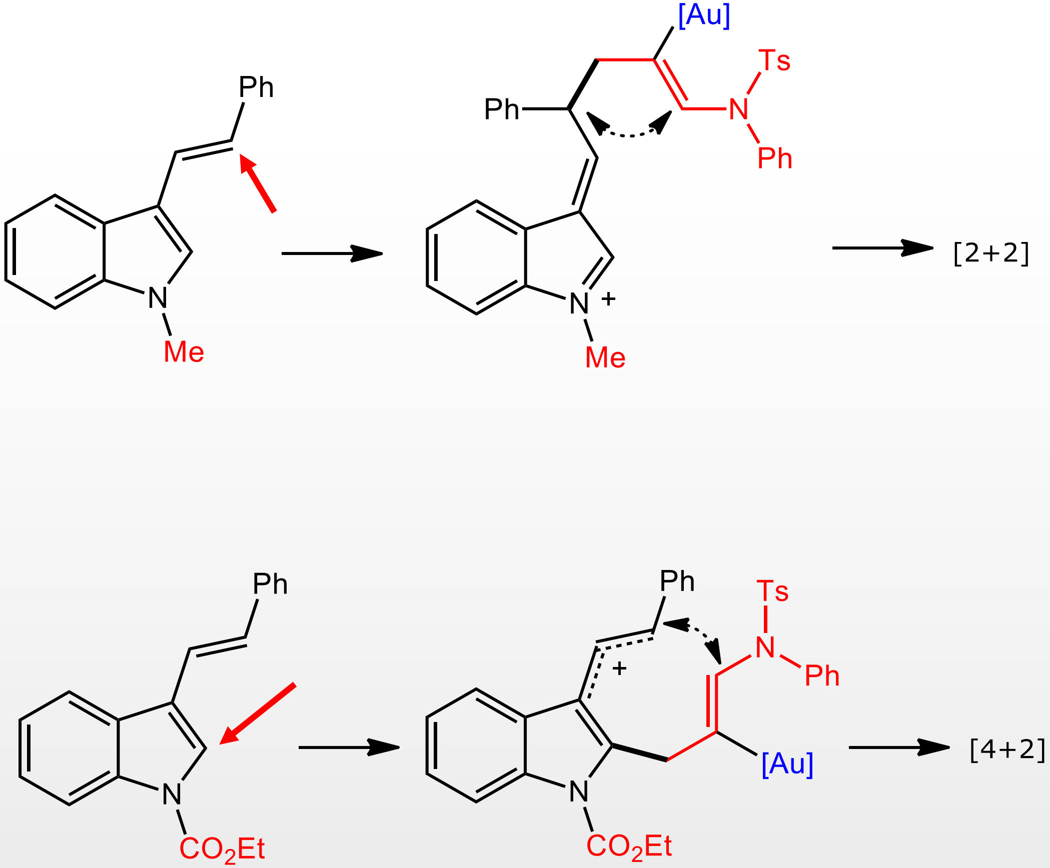
12 examples
82-99%
Z/E 3-6.1:1
ee (Z) 89-97% *ee (E)* 88-92%

Y. Wang, P. Zhang, Y. Liu, F. Xia, J. Zhang *Chem. Sci.* **2015**, *6*, 5564.
H. Hu, Y. Wang, D. Qian, Z.-M. Zhang, L. Liu, J. Zhang *Org. Chem. Front.* **2016**, *3*, 759.

Gold catalysis and indole chemistry

enantioselective cycloaddition reactions of 3-vinylindoles and allenamides





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