Gold(I)-Catalyzed Polycyclization of Linear Dienediynes to Seven-Membered Ring Containing Polycycles via Tandem Cyclopropanation/Cope Rearrangement/C-H Activation

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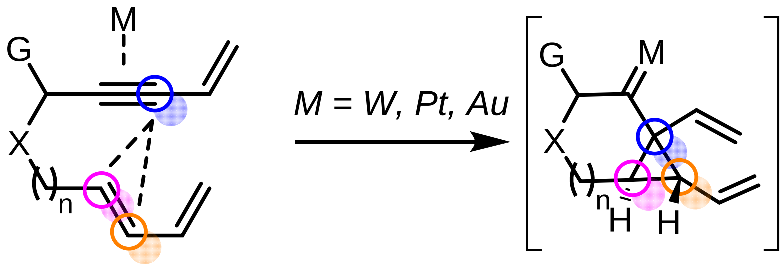
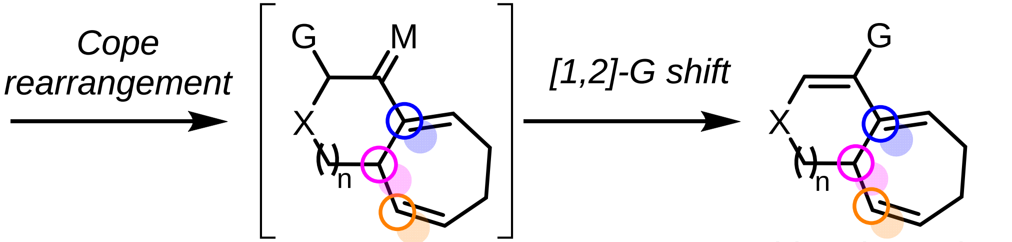
Maxime Dousset
06/01/15

Previous work

- Tandem cyclopropanation / Cope rearrangement / [1,2]-G shift of migratory group



linear trienyne (n = 0,1)
G = OAc or H

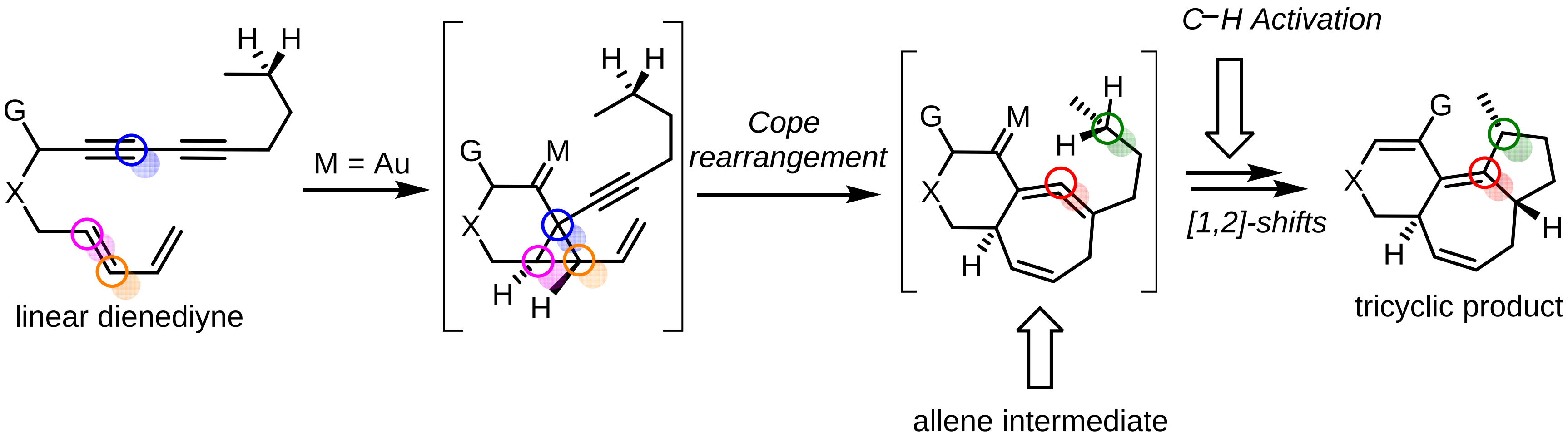


bicyclic product

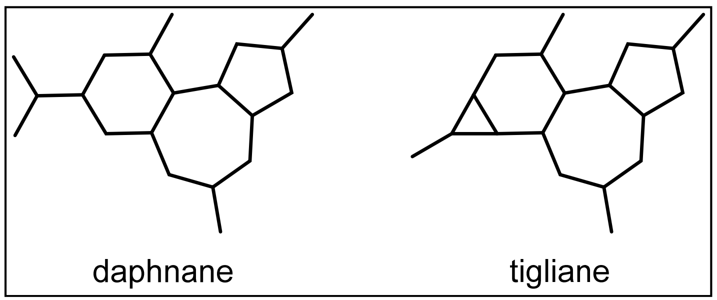
M = W: Iwasawa, N. *J. Am. Chem. Soc.* **2006**, *128*, 16500.
M = Pt: Chung, Y. K. et al. *Angew. Chem.* **2010**, *49*, 415.
M = Au: Gagosz, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 9014.

This Work

- Tandem cyclopropanation / Cope rearrangement / C-H activation

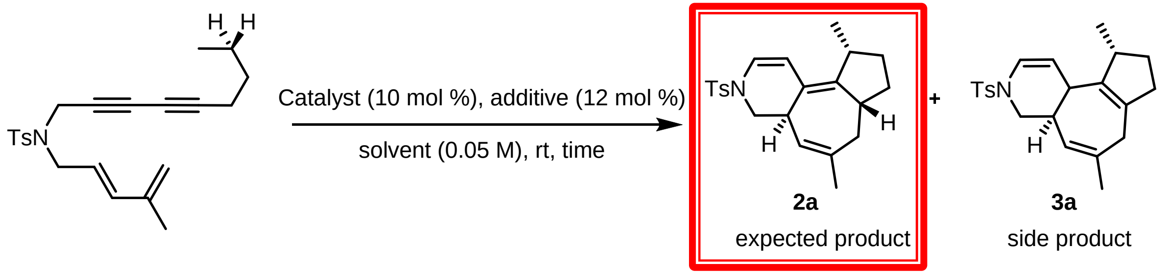


Acces to diterpenes:



Allene intermediate: Johnson, R. P. *Chem. Rev.* **1989**, *89*, 1111.
C-H activation: Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2013**, *52*, 2593.

Optimization Studies on the Gold(I)-Catalyzed Polycyclization



Entry	Catalyst	Additive	Solvent	Time (h)	Isolated yield of **2a**	Isolated yield of **3a**
1	$(2,4\text{-}^{t}Bu_2\text{-}C_6H_3O)_3PAuCl$	$AgSbF_6$	CH_2Cl_2	5.5	34 %	18 %
2	Ph_3PAuCl	$AgSbF_6$	CH_2Cl_2	14	19 %	20 %
3	IPrAuCl	$AgSbF_6$	CH_2Cl_2	6	30 %	34 %
4	JohnPhosAuCl	$AgSbF_6$	CH_2Cl_2	2	72 %	trace
5	JohnPhosAuCl	$AgBF_4$	CH_2Cl_2	2	77 %	trace
6	JohnPhosAuCl	AgOTf	CH_2Cl_2	2	trace	69 %
7	$[JohnPhosAu(NCMe)]SbF_6$	none	CH_2Cl_2	2	71 %	trace
8	$[JohnPhosAu(NCMe)]SbF_6$	none	DCE	2	79 %	trace

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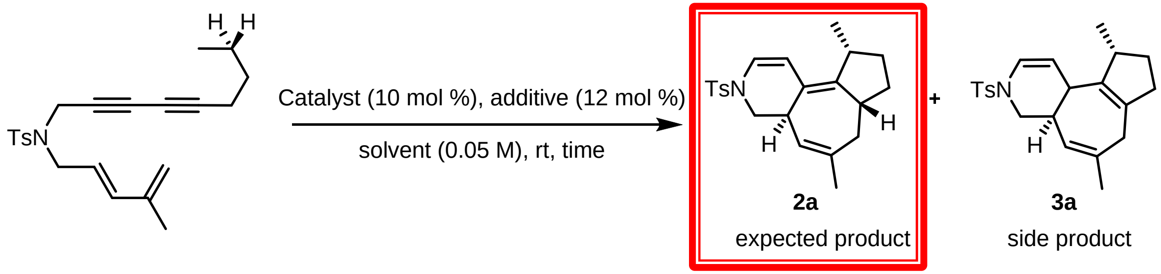

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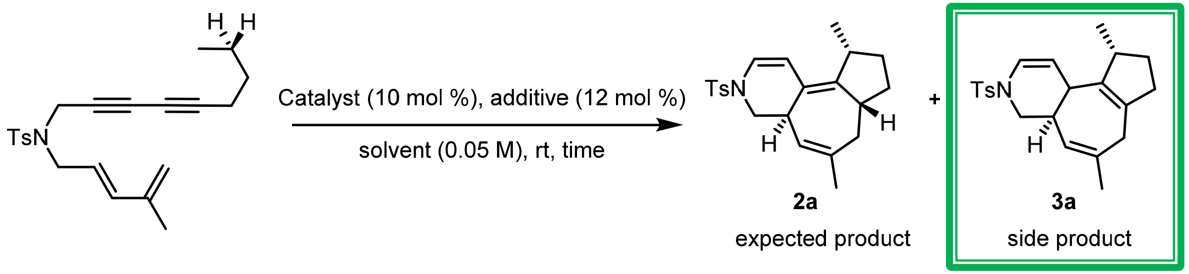

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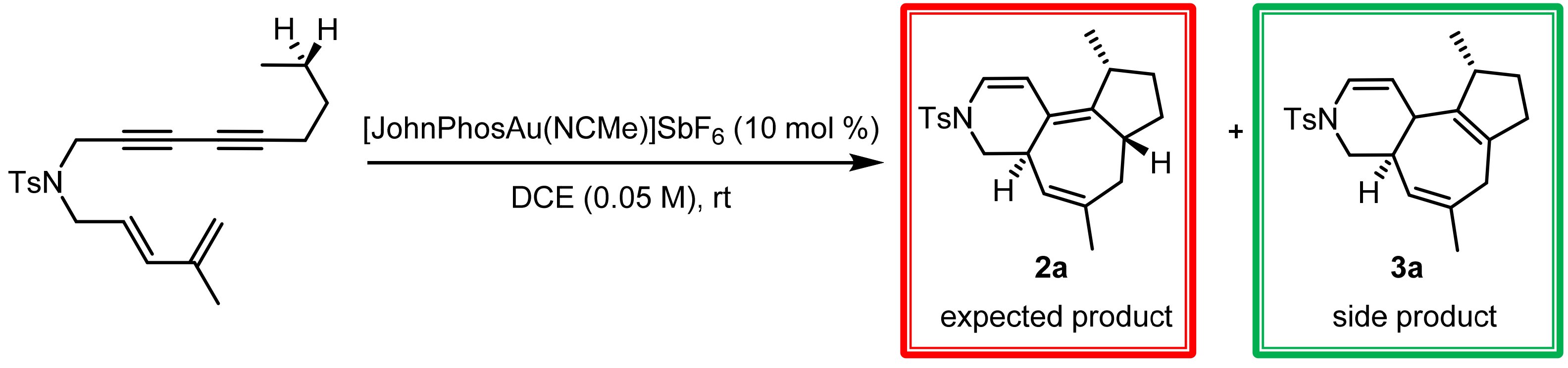
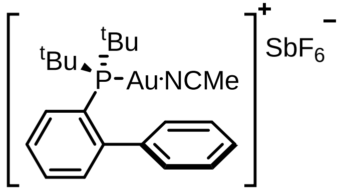
Optimization Studies on the Gold(I)-Catalyzed Polycyclization



- To obtained the expected product **2a**
  - Use Echavarren gold(I) complex
  - DCE as solvent

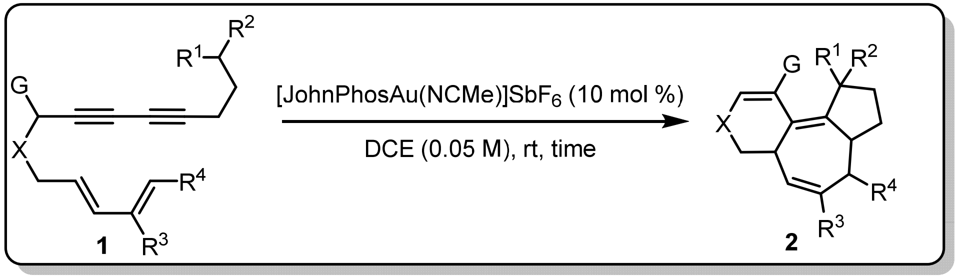
- To obtained the side product **3a**
  - Use basic counteranions triflate or water in the reaction

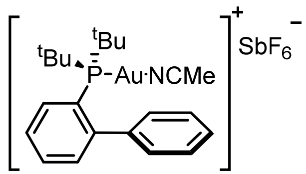
catalyst



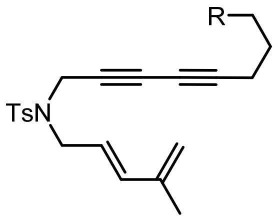
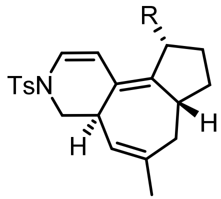
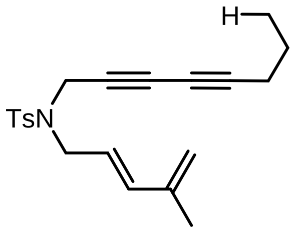
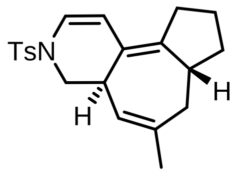
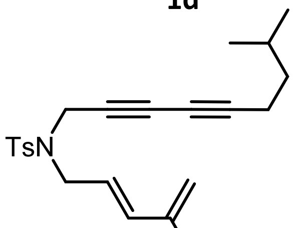
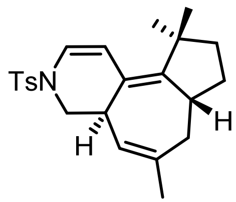
[JohnPhosAu(NCMe)]SbF_6

Polycyclization Reaction Scope

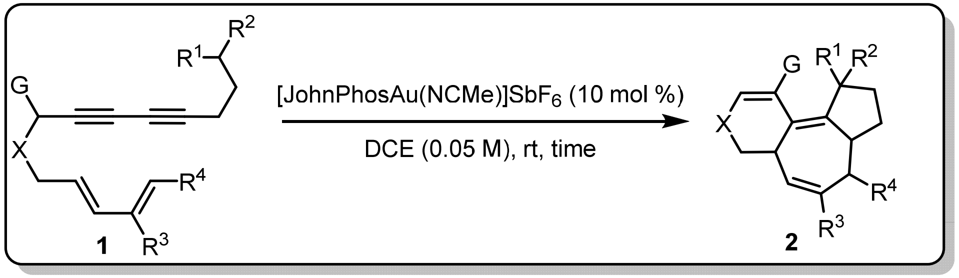


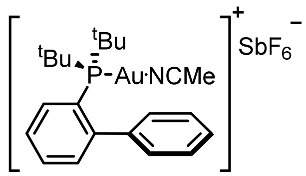


[JohnPhosAu(NCMe)]SbF_6

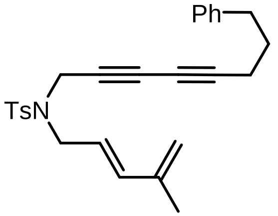
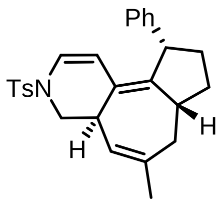
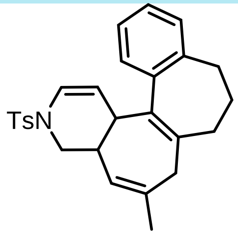
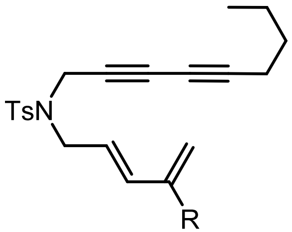
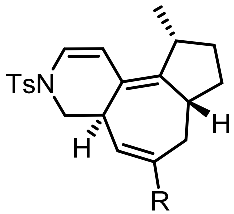
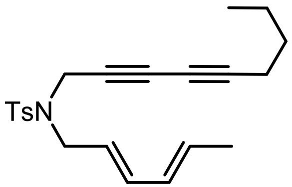
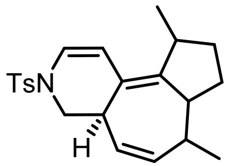
Entry	Dienediyne **1**	Product **2**	Yield (dr), time
1	 **1a** (R = Me) **1b** (R = $^{n}C_5H_{11}$) **1c** (R = CH_2OTBS)	 **2a** (R = Me) **2b** (R = $^{n}C_5H_{11}$) **2c** (R = CH_2OTBS)	79 % (15:1), 2 h 70 % (>20:1), 2 h 47 % (7:1), 4 h
2	 **1d**	 **2d**	24 % (>20:1), 24 h
3	 **1e**	 **2e**	56 % (>20:1), 24 h

Polycyclization Reaction Scope

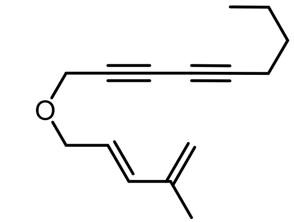
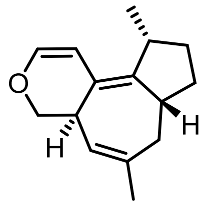
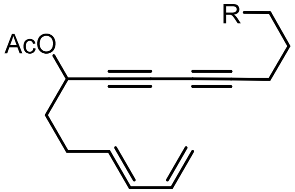
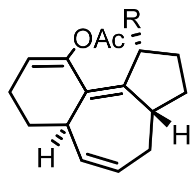




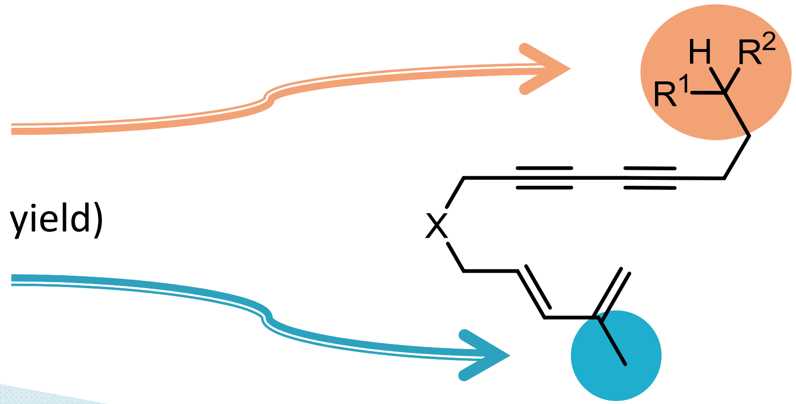
[JohnPhosAu(NCMe)]SbF_6

Entry	Dienediyne **1**	Product **2**	Yield (dr), time
1	 **1f**	 **2f**, 30 % (>20:1) +	 **4f**, 39 % 14 h
2	 **1g** (R = Bn) **1h** (R = ^{i}Pr) **1i** (R = H)	 **2g** (R = Bn) **2h** (R = ^{i}Pr) **2i**(R = H)	77 % (12:1), 12 h 94 % (10:1), 6 h 87 % (8:1), 11 h
3	 **1j**	 **2j**	67 % (3:1), 10 min

Polycyclization Reaction Scope

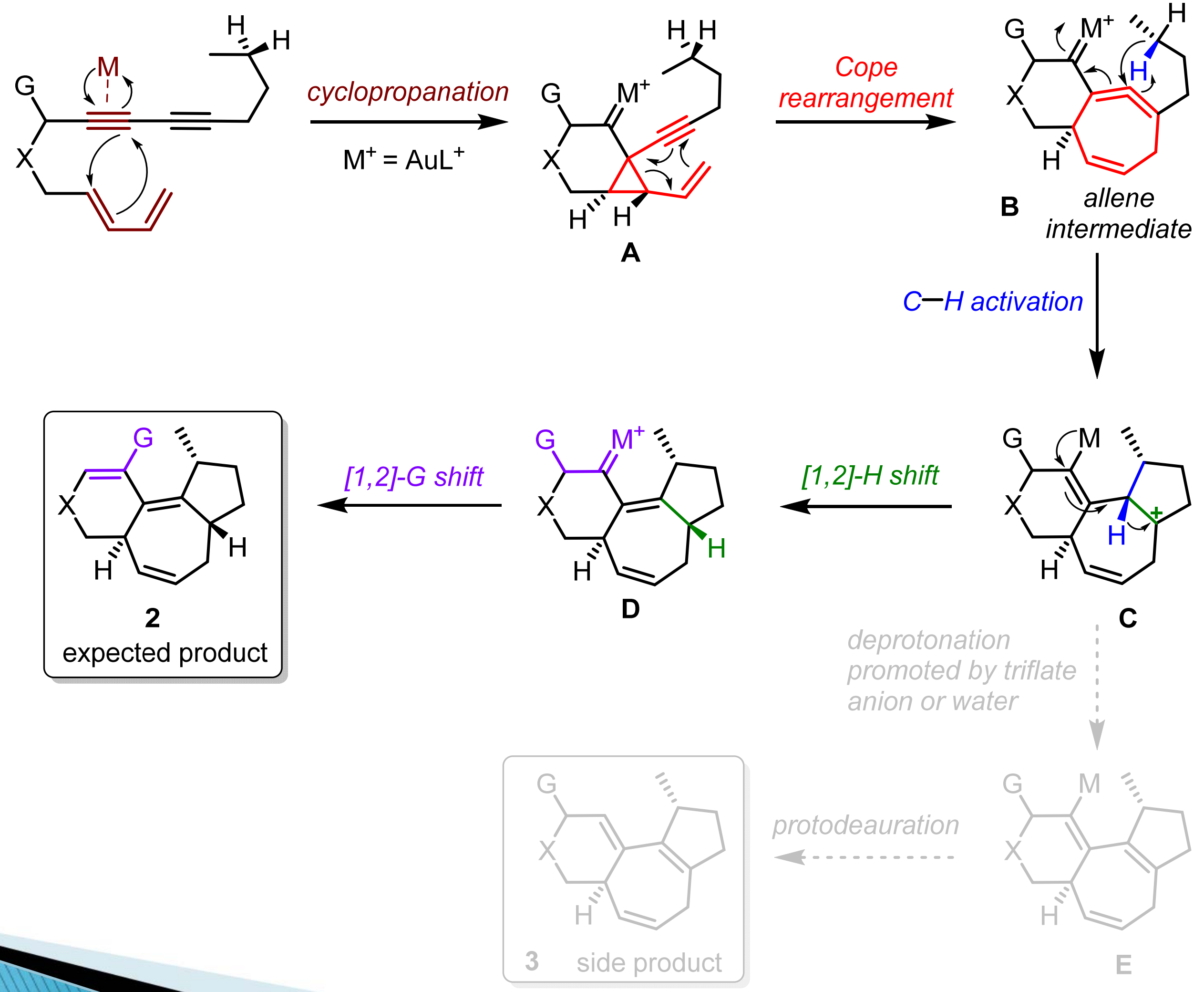
Entry	Dienediyne **1**	Product **2**	Yield (dr), time
1	 **1k**	 **2k**	74 % (>20:1), 0.5 h
2 20 mol % cat, 4Å MS	 **1l** (R = Me) **1m** (R = Et)	 **2l** (R = Me) **2m** (R = Et)	66 % (20:2:1), 4.5 h 76 % (27:2:2:1), 4 h

- The reaction works better with:
  - secondary and tertiary γ carbon
  - Methyl in γ position of diene (better yield)



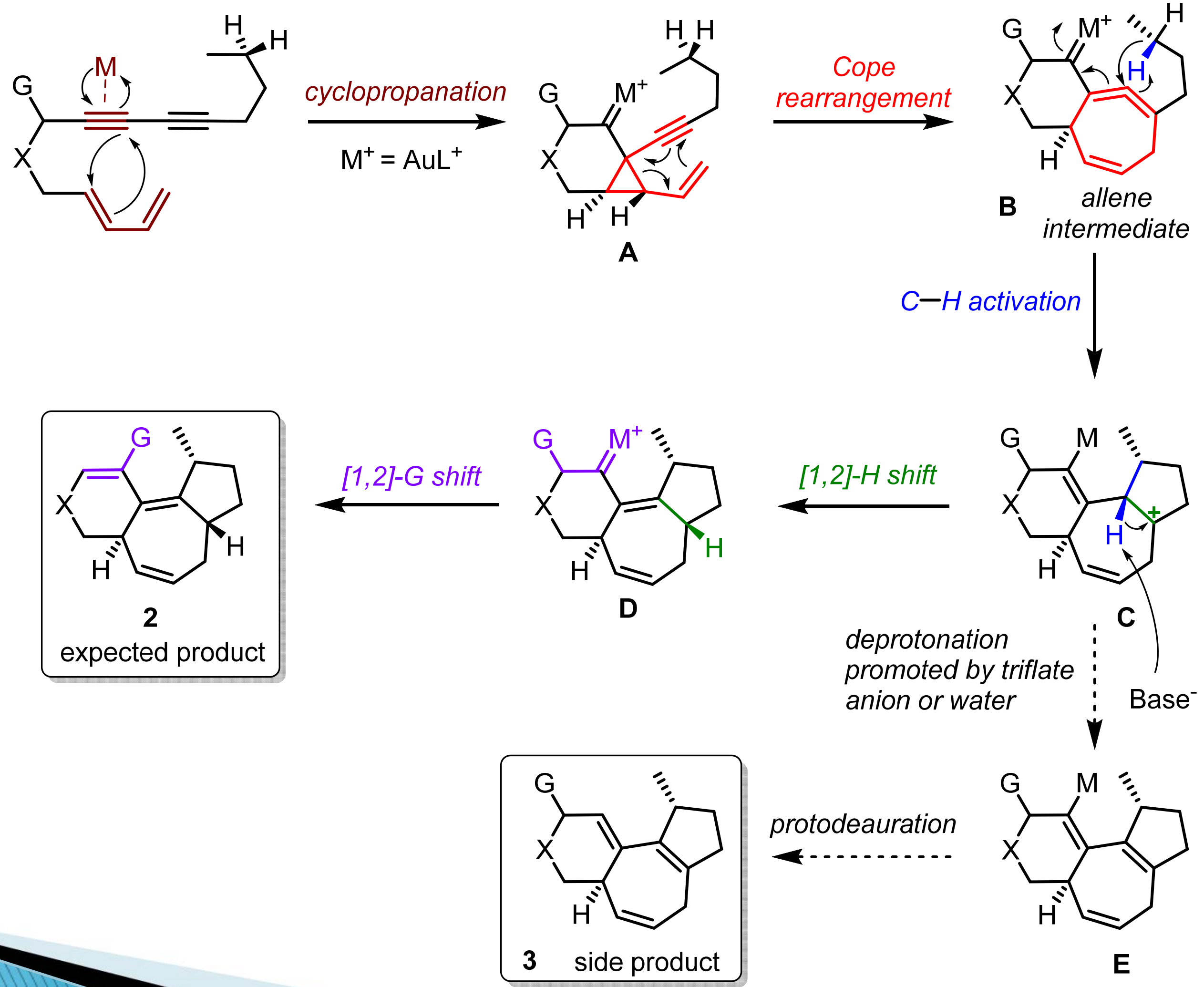
Proposed Mechanism

- Preliminary DFT studies supported the following mechanism.



Proposed Mechanism

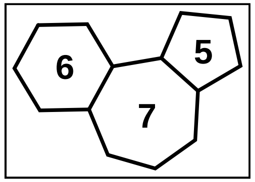
- For the side product 3, it is a hypothesis.



Conclusion

- First work on dienediynes which combines Cyclopropanation / Cope rearrangement/ Aliphatic C-H activation.

- An efficient gold(I)-catalyzed polycyclisation to get the fused 5,7,6-tricyclic ring system in one step with high diastereocontrol.



- Could potentially give access to a wide range of diversely functionalized ring system.

Thank you for your attention

SM Preparation