Efficient Synthesis of Cyclopentenones from Enynyl Acetates via Tandem Au (I)-Catalyzed 3,3-Rearrangement and the Nazarov Reaction

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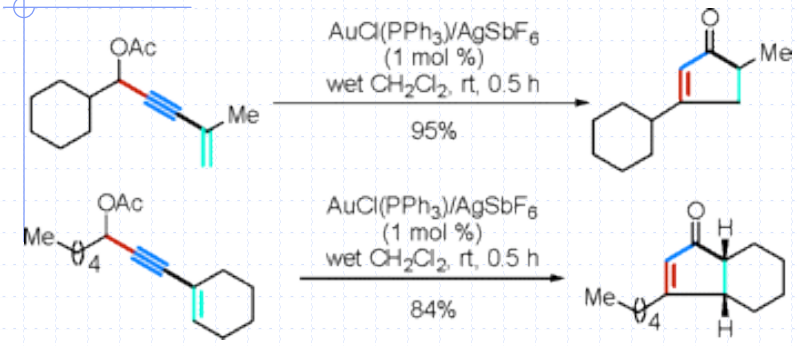
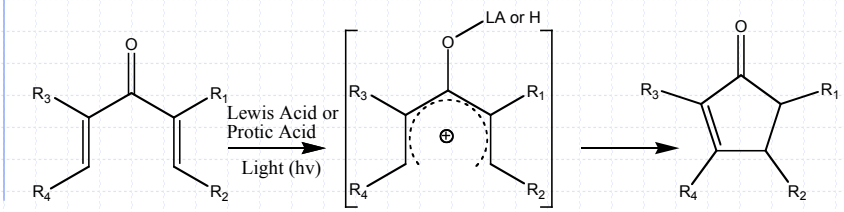
Synthesis of Cylopentenones

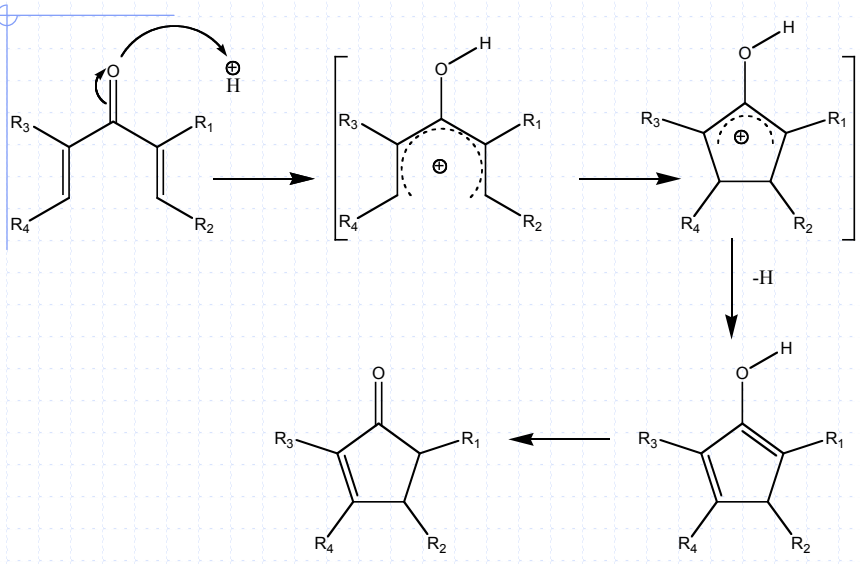


Classical Nazarov Reaction



- Vorlander & Schroeter (1903)
- Nazarov (1940 & 1950)
- Conversion of Divinyl Ketones to Cyclopentenones via pentadienylic cation

Mechanism



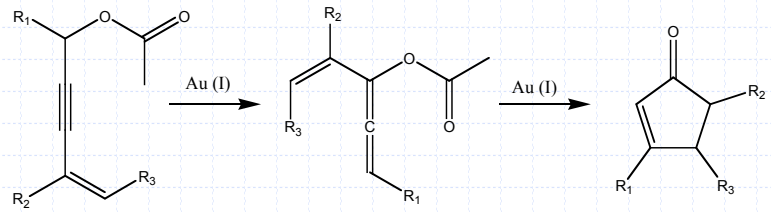
Summary of Problems

- Stereochemistry of substituents
- Source of proton loss
- Location of double bond formation
  - Silicon Groups will leave preferential in place of a proton to direct double bond formation
- Accessibility of Starting Materials

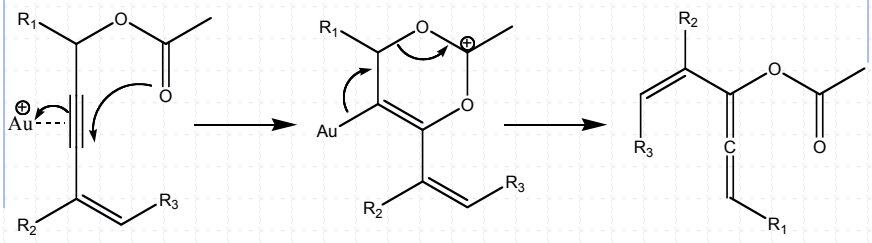
Summary of Positives

- Can make highly substituted fused bicyclic ring systems
- A lot of synthetic versatility
  - Cyclopentenones
  - Attack by nucleophiles to form cyclopentanones

Synthesis of Cylopentenones



3,3 Rearrangement



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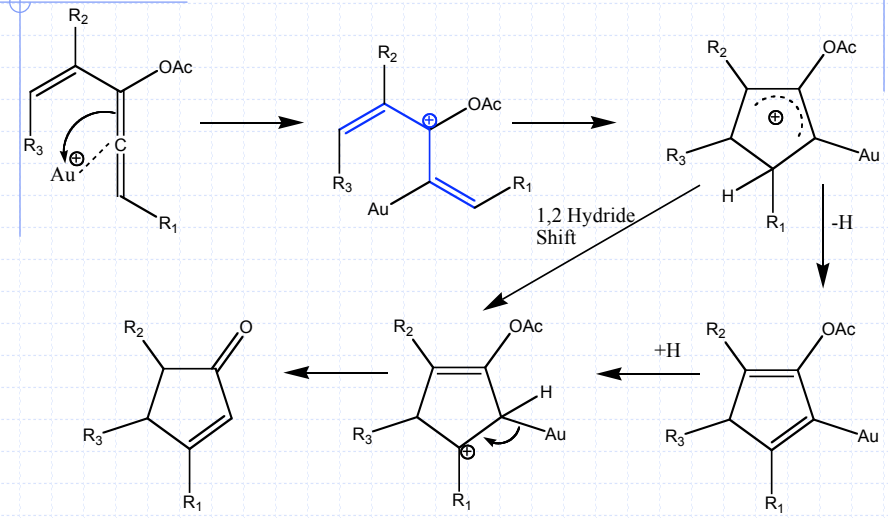
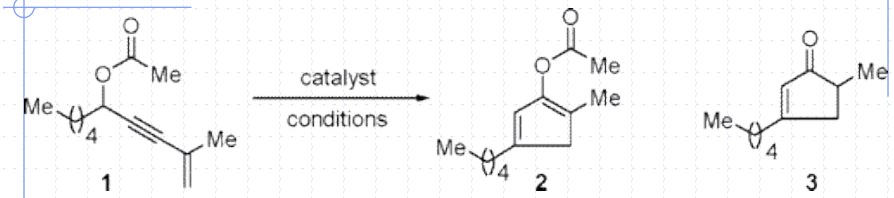
Nazarov Cyclization

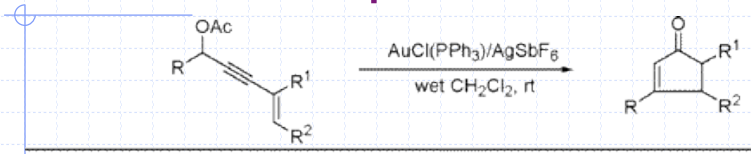


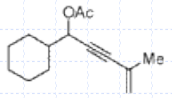
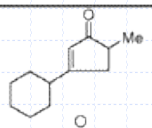
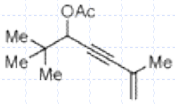
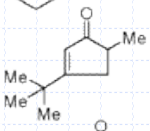
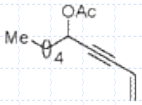
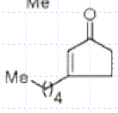
Reaction Optimization



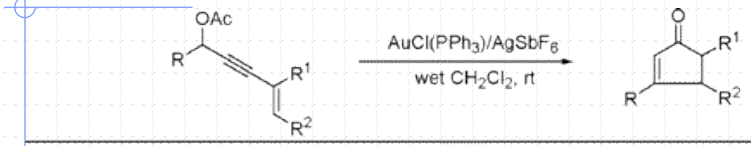
Entry	Catalyst	Conditions	Time (h)	Conv. (%)	yield (%) 2	3
1	1% $AuCl(PPh_3)/AgSbF_6$	dry CH_2Cl_2, rt	0.5	>99	65	8
2	1% $AuCl(PPh_3)/AgSbF_6$	wet CH_2Cl_2, rt	0.5	>99	<1	92
3	5% $AuCl_3$	dry CH_2Cl_2, rt	0.5	48	31	<1
4	5% $AuCl_3$	wet CH_2Cl_2, rt	0.5	96	5	64
5	5% $PtCl_2$	dry toluene, 80 ° C	4	41	32	<1
6	5% $AgSbF_6$	wet CH_2Cl_2, rt	0.5	<1	<1	<1
7	5% TfOH	dry CH_2Cl_2, rt	0.5	62[d]	<1	<1

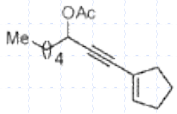
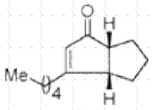
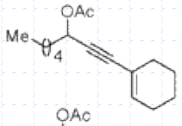
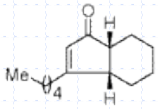
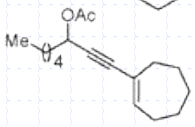
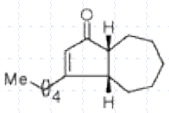
Reaction Scope



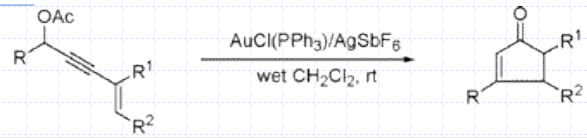
Entry	Enynyl acetate	Catalyst (mol %)	Time (h)	Cyclopentenone	Yield[b] (%)
1	 **4**	1	0.5	 **5**	95
2	 **6**	1	0.5	 **7**	88
3	 **8**	1	0.5	 **9**	79

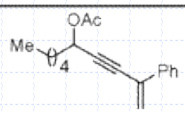
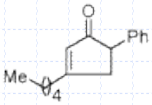
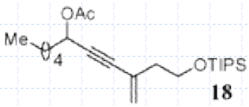
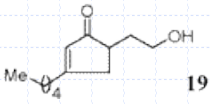
Reaction Scope



Entry	Enynyl acetate	Catalyst (mol %)	Time (h)	Cyclopentenone	Yield[b] (%)
4	 **10**	1	0.5	 **11**	57
5	 **12**	1	0.5	 **13**	84
6	 **14**	1	0.5	 **15**	90[c]

Reaction Scope

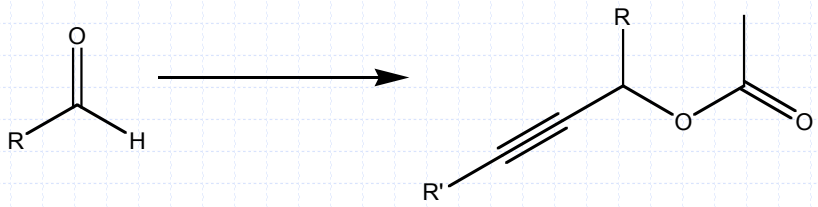


Entry	Enynyl acetate	Catalyst (mol %)	Time (h)	Cyclopentenone	Yield[b] (%)
7	 **16**	5	2	 **17**	74
8	 **18**	5	0.5	 **19**	81[d]

Aspects of Innovation

- Au (I) versus Classical Nazarov
  - Accessibility of complex structures is greater
    - Availability of diverse starting materials
  - Greater control over double bond placement
    - Assisted by catalyst
  - Conditions are mild
    - Room temperature and modest pH

Versatility of Propargyl Esters



- Prepared from Aldehyde and Enyne
- Prepared from Aldehyde, Acetylene, and Alkenyl Halide

State-Of-The-Art Analysis

- Raises the bar for catalysis
  - Multitasking Metals
    - Two different reactions mediated by a single catalysis
  - Immunity to water
    - Reaction is aided by the presence of water

Future Outlook

- Application of this methodology to complex molecules
  - Fused bicyclic systems-5,5; 5,6; 5,7 ring systems
- Further examination of this catalysis

References

- Zhang, L.; Wang, S. *J. Am. Chem. Soc.* **2006**, 128, 1442.
- Zhang, L. *J. Am. Chem. Soc.* **2005**, 127, 16804.
- Kurti, L.; Czako, B. *Strategic Applications of Named Reactions in Organic Chemistry*; Elsevier Academic Press: Burlington, MA, **2005**; pp 304-305.