GOLD-CATALYZED INTRAMOLECULAR CYCLIZATIONS OF ENYNES

Reported by Chloe Wendell September 26th 2016

INTRODUCTION

In recent years, gold catalysis has undergone significant development, an exceptionally selective and reactive method for the cycloisomerizations of enynes. This utility is derived from the fundamental properties of gold. Gold does not readily undergo either β-hydride elimination or oxidative addition, though gold-carbon bonds do protonolyze; its high electronegativity makes it extremely alkynophilic.[1] This pattern of reactivity excludes alder-ene type cyclization common with other metals.[2] While gold only precedes via a few key intermediates, these are extremely versatile, and tuning the conditions and substrates can selectively produce an incredible variety of extremely complex products from these mechanistic keystones.

1,5-ENYNES

1,5-Enynes most readily undergo 5-endo-dig type cyclizations. These cyclizations form key cyclopropyl carbene intermediate **2**, which may be better represented as carbocation **2'**.[3, 2] These intermediates may demetallate immediately (**7**), undergo various skeletal rearrangements (**3**, **4**), or react with oxygen and nitrogen nucleophiles intermolecularly and intramolecularly (**Fig. 1**).[1, 4, 5, 6] Nucleophiles generally add at C6 (**6**), but can also add at C5 if tethered (**5**) (**Fig 1**).[2]

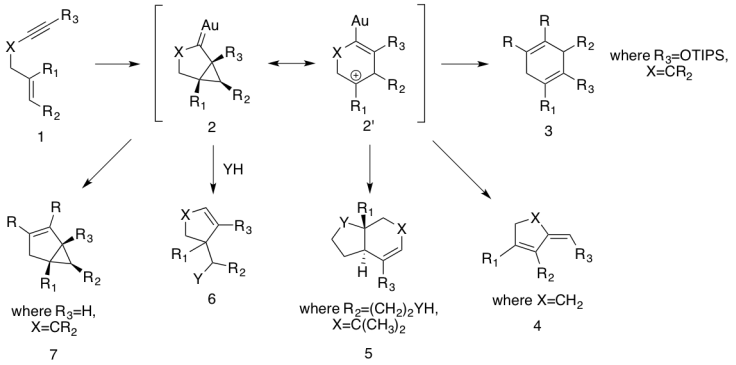

Figure 1. *Skeletal rearrangements and nucleophile additions of 1,5-enynes*.

1,6-ENYNES

1,6-Enynes most readily undergo 5-exo-dig type cyclizations. This leads to common cyclopropyl intermediate **9** which may also be represented as carbocation **9'**.[3] This common intermediate leads to a great variety of products, through skeletal rearrangements (**11**, **13**), nucleophile trapping (**14**, **15**, **16**), and formal [4+2] rearrangements (**20**) (**Fig 2, Fig 3**). Skeletal rearrangements are either single

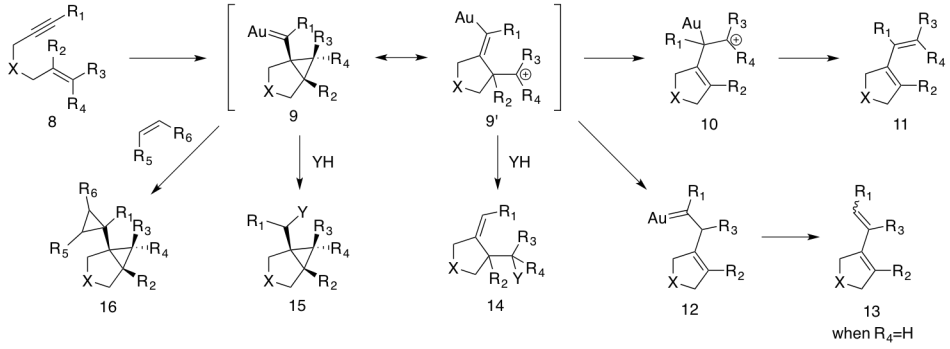

Figure 2. *Skeletal Rearrangements and nucleophile additions of 1,6-enynes*.

cleavage (**11**) or double cleavage (**13**).[2] Monosubstituted alkenes generally favor double cleavage mechanisms due to the lack of stabilizing groups necessary to generate carbocation **10** and to steric factors in the 1,2-alkyl shift necessary to generate carbene **12** (**Fig 2**).[7]

Intermediate **9** has also been trapped with various carbon, oxygen, and nitrogen nucleophiles at both C1 (**15**) and C7 (**14**).[7] Phosphine or phosphite ligands tend to lead to a more electrophilic gold, which decreases its carbene character and shifts the structure of intermediate **9** further towards the carbocation **9'**.[7] Therefore, under these conditions nucleophiles generally attack at C7, producing **14** (**Fig 4**).[7] More electron-rich NHC ligands decrease the electrophilicity of the gold and stabilize the carbene, shifting the structure closer to carbene **9**.[7] This increases the selectivity for attack at C1, yielding mostly product **15**.[7]

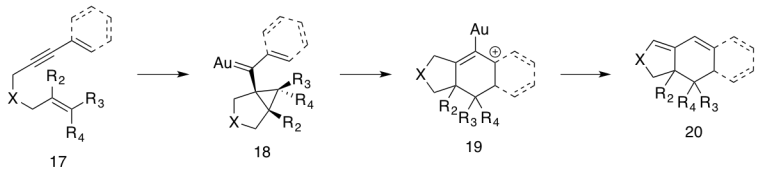

Figure 3. *Formal [4+2] cyclizations of 1,6-enynes.*

The carbene intermediate **9** can also cyclopropanate another olefin inter- or intra-molecularly to produce adduct **16** (**Fig 2**).[8, 4] Additionally, when R_1 is a vinyl or aryl group, a formal [4+2] cyclization takes place from intermediate **18** to form bi- or tri-cycle **20** through carbocation intermediate **19**.[1]

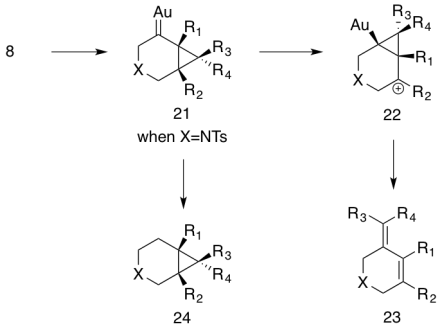

Figure 4. *6-Endo dig cyclizations of 1,6-enynes.*

1,6-Enynes can also undergo 6-endo-dig cyclizations, particularly when X=NTs or when there is hyperconjugative stabilization of the resulting carbocation **22**.[9, 10] The resulting intermediate **21** can undergo a single cleavage skeletal rearrangement to produce product **23** or can protodemetallate immediately to form **24**.[9, 1]

CONCLUSION

Gold catalysis is unique in its ability to produce a wide variety of complex skeletons from a small number of mechanistic intermediates under mild conditions.

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