Gold(I)-catalyzed Tandem Cyclization of 3-(*tert*-Butoxycarbonyloxy)-1,6-enynes

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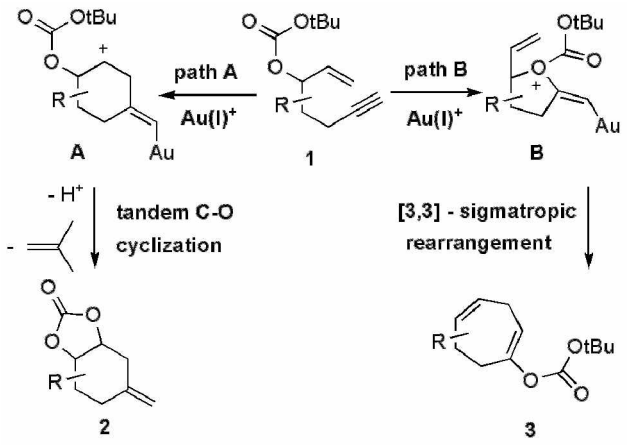
Over the past decade, there has been explosive interest in the area of new homogeneous gold-catalyzed reactions.[1] The capability of cationic gold(I) species that activates alkynes towards heteroatom and carbon nucleophiles led to the discovery of numerous novel catalytic transformations. Diverse structures generated by these reactions make this process a very powerful strategy for organic synthesis. Tandem reactions of 1,n-enyne substrates are particularly interesting in this regard.[2] Our interest in this area has focused on the divergent reactivity of 3-alkoxy-1,6-enynes. A salient feature of these types of substrates is that oxygen atom and the olefin can compete in the addition to the gold-bound alkynes. This competition may lead to synthetically important structural motifs *via* catalytic tandem reactions.

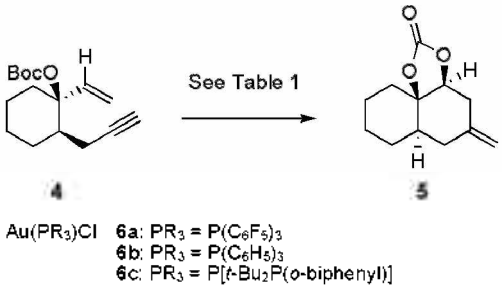
Recently, we discovered gold(I)-catalyzed cycloisomerization of 3-methoxy-1,6-enynes, invoking heterocyclization and the subsequent [3,3]-sigmatropic rearrangement as the key mechanism.[3] Further investigation of 3-siloxy-1,6-enynes led to the development of unprecedented gold(I)-catalyzed divergence between pinacol-terminated *vs.* Claisen-terminated cyclization cascades.[4] These examples indeed illustrate that the reactivity of 3-alkoxy-1,6-enynes in the divergent pathway can be controlled by the subtle variation of the substituents on the alkoxy group. In an effort to expand the scope of the catalytic reactions associated with the 3-alkoxy-1,6-enynes, we pursued further variation of the alkoxy moiety. In particular, we considered using 3-(*t*-butyloxycarbonyl)oxy-1,6-enynes **1** (Scheme 1), based on the recent reports on the use of *t*-butyloxycarbonyl (*t*-Boc) group in gold(I)-catalyzed domino processes.[5]



Scheme 1. Competing tandem pathways for 3-(*t*-butyloxycarbonyl)-oxy-1,6-enynes

We first reasoned that the introduction of this substituent onto the oxygen would suppress the formation of **3** (path B, Scheme 2), because of the reduced bacisity of *t*-Boc group. Unlike our previous studies,[3,4] pathway A would prevail in this case. Moreover, this new catalytic reaction will provide synthetically useful cyclohexane-1,2-diol compounds possessing exo-olefins at the 4-position (**2**, in Scheme 1).

Our rationalization in terms of the competing pathways was justified when we examined substrate **4**. Using electron poor ligand **6a** (5 mol%) with $AgSbF_6$ (5 mol%) provided the product **5** in only 32% NMR yield, although the starting material was completely consumed within 10 min (entry 1). In this preliminary study, no apparent formation of the cycloheptene product **3** generated *via* path B was observed. Using a more electron-donating ligand **6b** (5 mol%) somewhat improved the yield of **5** (entry 2). A significant increase of the yield arises when more electron-donating ligand **6c** (5 mol%) was employed (entry 3) In this case, the product was obtained in 76% isolated yield after 10 min. Delightedly, reducing the catalyst loading to 2 mol% still maintained the catalytic activity with slight decrease in the yield of the desired transformation



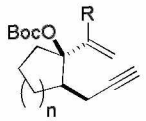
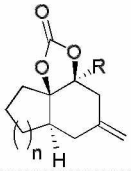
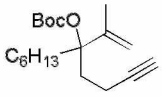
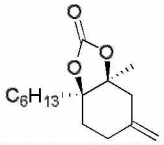
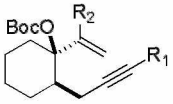
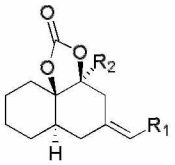
(1)

Table 1. Optimization of the reaction condition

Entry	Catalyst	Time	Yield[a]
1	**6a** (5 mol%) / $AgSbF_6$ (5 mol%)	10 min	32
2	**6b** (5 mol%) / $AgSbF_6$ (5 mol%)	30 min	52
3	**6c** (5 mol%) / $AgSbF_6$ (5 mol%)	10 min	79 (76[b])
4	**6c** (2 mol%) / $AgSbF_6$ (2 mol%)	20 min	76
5	**6c** (1 mol%) / $AgSbF_6$ (1 mol%)	30 min	67
6	**6c** (5 mol%) / AgOTf (5 mol%)	30 min	trace
7	**6c** (5 mol%) / $AgClO_4$ (5 mol%)	30 min	trace

[a]NMR yield determined using 1,3,5-trimethoxybenzene as an internal standard. [b]Isolated yield.

Table 2. Examples of gold(I)-catalyzed tandem cyclization

Entry	Substrate		Method[a]	Time	Product		Yield
1		**7** (n = 2, R = CH_3)	B	10 min		**8**	90%
2		**9** (n = 3, R = H)	B	10 min		**10**	68%
3		**11** (n = 3, R = CH_3)	A	5 min		**12**	74%
4		**13** (n = 1, R = CH_3)	A	10 min		**14**	84%
5		**15** (n = 1, R = H)	A	6 h		**16**	---[c]
6		**17**	A	3 h		**18**	58%
7		**19** (R_1 = Ph, R_2 = H)	A	20 h		**20**	60%
8		**21** (R_1 = (*p*-OMe)Ph, R_2 = H)	A	20 h		**22**	63%

[a]Method A: Catalyst **6c** (5%) and $AgSbF_6$ (5%) was used. Method B: Catalyst **6c** (2%) and $AgSbF_6$ (2%) was used. [b]Isolated yield. [c]No reaction.

(entry 4). However, using 1 mol% catalyst significantly reduced the yield of **5** (entry 5). Changing the counteranions (entries 6 and 7) led to the decomposition of the starting material **4**.[6,7] Using the optimized conditions described in Table 1, an array of the substrates was tested for the gold(I)-catalyzed tandem cyclization process. As can be seen in Table 2, substrate **7** possessing a methyl substituent at the internal position of the olefin significantly increased the yield for the desired transformation, furnishing the tricyclic carbonate **8** in 90% yield (entry 1). Substrates **9** and **11** generated from cycloheptanone also worked efficiently to give the products in good yield (entries 2 and 3). On the other hand, substrates generated from cyclopentanone showed interesting discrepancy from larger-sized ring homologues (entries 4 and 5). The substrate **13** possessing methyl substitution at the internal position of the olefin gave the product in good yield (entry 4), whereas, substrate **15** lacking the methyl group proved unreactive (entry 5). Acyclic substrate **17** produced the bicyclic carbonate **18** in moderate 58% yield (entry 6). Internal alkynes were also efficient substrates for the transformation, although the reaction was somewhat slower (enties 7 and 8). For example, phenyl-substituted alkyne **19** gave the product **20** in 60% yield after 20 h. In this case, the product was obtained as single diastereomer (entry 7), whose structure was unambiguously determined by nOe analysis. Introducing (*p*-methoxy)phenyl group gave the product **22** in comparable yield as a mixture of two olefin isomers (entry 8).

In summary, we have developed a highly efficient tandem gold(I)-catalyzed cyclization reaction of 3-*t*-butoxycarbonyloxy-1,6-enynes. Noteworthy is the complete selectivity in the initial cyclization. This result well complements our previous studies on the tandem cyclization of various 3-alkoxy-1,6-enynes. Application of this method to the synthesis of bioactive natural products as well as the investigation of other 3-alkoxy-1,6-enynes are currently under investigation.

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References

1. For recent reviews on the recent advances on the gold(I)-catalyzed reactions, see: (a) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351. (b) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (c) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266. (d) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395.
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5. Lim, C.; Kang, J.-E.; Lee, J.-E.; Shin, S. *Org. Lett.* **2007**, *9*, 3539, and see the references therein.
6. Under the identical condition, neither $AgSbF_6$ alone nor HF showed any catalytic activity.
7. In more polar solvents (such as DMF and THF), the yield significantly dropped (below 20%).