Synthetic Methods

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Regioselective Cyclizations Utilizing a Gold-Catalyzed [3,3] Propargyl Ester Rearrangement**

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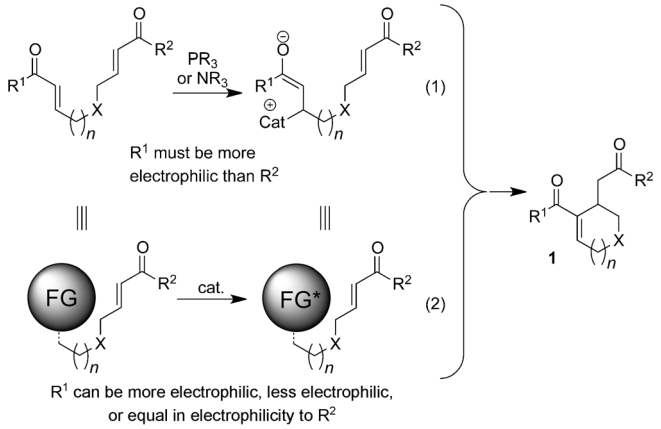
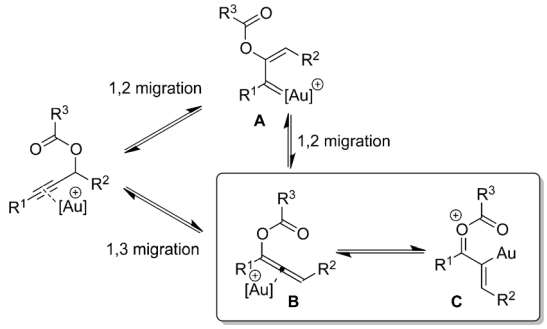
Unsaturated carbocycles of the general configuration **1** (Scheme 1) constitute a fundamental building block in organic synthesis owing to their inherent flexibility for further elaboration. Such compounds have traditionally been accessed through the intramolecular Rauhut–Currier (RC) reaction utilizing trialkyl-phosphine- and tertiary-amine-based catalysts [Eq. (1); Scheme 1].[1–3] The efficacy of this method has been demonstrated through its use as a key step in natural product syntheses by several groups.[4]



Scheme 1. Chemoselective formation of zwitterion surrogate.

However, utilization of this protocol can be hindered by the lack of regioselectivity demonstrated by the nucleophilic catalyst for unsymmetrical substrates where R^1 and R^2 differ. Although this problem can be overcome by ensuring a sufficient difference in electrophilicity between the two unsaturated systems, this feature inherently limits the reaction scope. Additionally, there remains no way of inducing the less reactive unsaturated carbonyl group to preferentially react with the catalyst to access the regioisomerically disfavored cycloadduct. Conceptually, we envisaged a solution to this problem might be found by introducing a surrogate functional group [FG; Eq. (2); Scheme 1] for one of the unsaturated carbonyl groups, capable of activation by an appropriate catalyst to reveal latent reactivity analogous to the nucleophilic zwitterionic intermediate proposed for the RC reaction [FG*; Eq. (2); Scheme 1].[5] Such an intermediate would then be primed for Michael addition to the second α,β-unsaturated carbonyl group, thus allowing either regioisomer to be cleanly accessed provided the catalyst possessed the necessary chemoselectivity to discriminate between the surrogate and the unmodified unsaturated carbonyl group.

Herein we report the successful utilization of the gold-catalyzed [3,3] rearrangement of propargyl esters for this purpose.[6,7] Propargyl carboxylates have been reported by several groups[8] to undergo a gold-catalyzed [2,3] rearrangement by a 1,2-acyl migration to give alkenyl gold carbenoids of type **A** (Scheme 2). Subsequently, Zhang[6] showed that



Scheme 2. Proposed gold-catalyzed propargyl ester rearrangements.

propargyl carboxylates can also undergo [3,3] rearrangment through either consecutive 1,2-acyl migrations or a 1,3-acyl migration to give the α-vinyl gold oxocarbenium intermediate **C** via allene **B**. Interconversion between the species is thought to be reversible[9] and the equilibrium is determined largely by the steric and electronic nature of the substituents.[10]

The interception of the intermediates **B** or **C** with various nucleophiles and electrophiles has since been reported.[7a,10,11] In particular, Zhang and co-workers have shown that the postulated α-vinyl gold intermediate **C** has sufficient nucleophilic character to undergo intermolecular addition to soft electrophiles such as NIS.[11h,12] As such, we hypothesized that the intermediates **C1** or **D1** (Scheme 3), could serve as a RC zwitterion equivalent and intramolecularly add to suitably appended α,β-unsaturated carbonyl groups, which as Michael acceptors, are also soft electrophiles.

Accordingly, we synthesized the propargyl pivolate **3a** (Scheme 4),[13] with the expectation that it would undergo rearrangement and cyclization to give the cyclic enone **4a**

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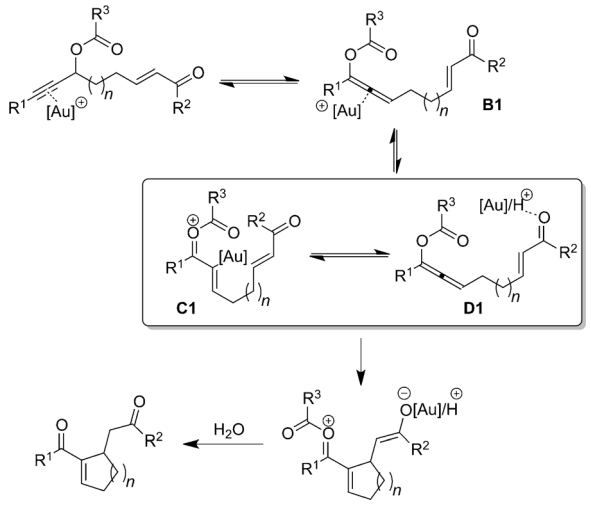
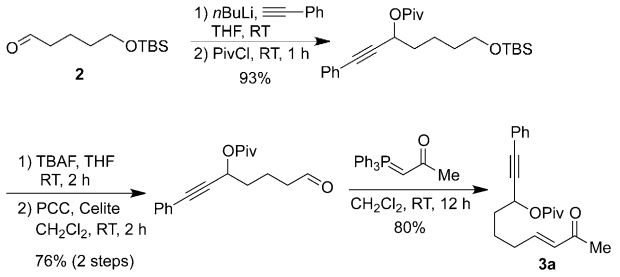


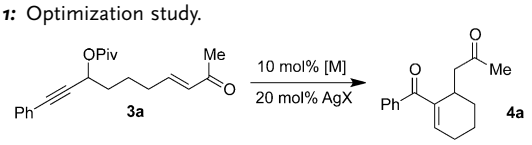
Scheme 3. Proposed mechanism for cyclic enone formation.



Scheme 4. Synthesis of substrate **3a**. PCC = pyridinium chlorochromate, Piv = pivaloyl, TBAF = tetra-*n*-butylammonium fluoride, TBS = *tert*-butyldimethylsilyl, THF = tetrahydrofuran.

(Table 1). To our satisfaction, subjecting **3a** to a range of commercially available gold and platinum catalysts revealed that the strategy was feasible (Table 1). Optimum reaction conditions were found by employing $AuClO_4$ (formed in situ from Au^I and $AgClO_4$) in dry $MeNO_2$ (entry 1). A 2:1 ratio of Ag/Au was found to give higher yields and shorter reaction times than a 1:1 ratio (entry 2). When using wet $MeNO_2$ virtually no product was formed (entry 3), thus suggesting that while exogenous water is presumably needed for release of the catalyst too much is detrimental for the reaction. $AuCl_3$ was also found to be an active catalyst although the conversion was not as clean as with AuCl (entry 6). AuCl without $AgClO_4$ was found to catalyze the reaction, although gold(III) formed from disproportionation might be the active catalyst (entry 5).[14] $AgClO_4$ was found to be inactive as a catalyst (entries 12 and 13), while $PtCl_2$[15] catalyzed the reaction, but at a slower rate (entry 8). Pivalic acid (entry 9), a reaction by-product formed through loss of the pivolate, was found to be inert, while the more acidic TsOH (entry 10) catalyzed the reaction but much less efficiently than gold. Employing $HClO_4$ (entry 11) resulted in considerable decomposition. The presence of a PPh_3 ligand on gold had no beneficial effect (entry 7), and the presence of an NHC ligand on gold rendered the catalyst insoluble in $MeNO_2$, thereby resulting in a low yield (entry 14). Surprisingly, the cationic gold(I) catalysts examined gave distinctly contrasting results (entries 15 and 16).

Table 1: Optimization study.

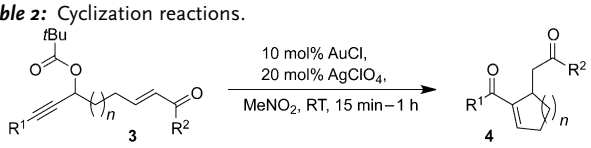


Entry	[M]	X	Solvent	*t* [min]	Yield [%][a]
1	AuCl	ClO_4	$MeNO_2$	10	89
2	AuCl	ClO_4 (10 mol%)	$MeNO_2$	10	71–86
3	AuCl	ClO_4	$MeNO_2$[b]	60	trace
4	AuCl	ClO_4	CH_2Cl_2	10	35
5	AuCl	–	$MeNO_2$	10	32
6	$AuCl_3$	–	$MeNO_2$	10	83[c]
7	PPh_3AuCl	ClO_4	$MeNO_2$	10	84
8	$PtCl_2$	ClO_4	$MeNO_2$	10	33
9	PivOH[d]	–	$MeNO_2$	180	0
10	TsOH[e]	–	$MeNO_2$	60	25
11	$HClO_4$	–	$MeNO_2$	10	46[c]
12	–	ClO_4	$MeNO_2$	10	0
13	–	ClO_4	$MeNO_2$	60	trace
14	NHCAuCl	ClO_4	$MeNO_2$	60	< 10
15	PPh_3AuNTf_2	–	$MeNO_2$	60	72[c]
16	$(Ph_3PAu)_3OBF_4$	–	$MeNO_2$	60	0

[a] Yield of isolated product. Unreacted starting material accounted for the majority of the mass balance. [b] 99% distilled $MeNO_2$ with 1% deionized water. [c] No starting material present. [d] Used 40 mol% catalyst. [e] Used 20 mol% catalyst. NHC = 1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene, Tf = trifluoromethanesulfonyl, Ts = 4-toluenesulfonyl.

With the optimized results in hand the reaction scope was studied (Table 2). In general, yields were high with the reactions complete in less than 1 hour. Significantly, it was found that alkyl substituents and electron-rich and electron-poor aryl substituents were tolerated at both the R^1 and R^2

Table 2: Cyclization reactions.

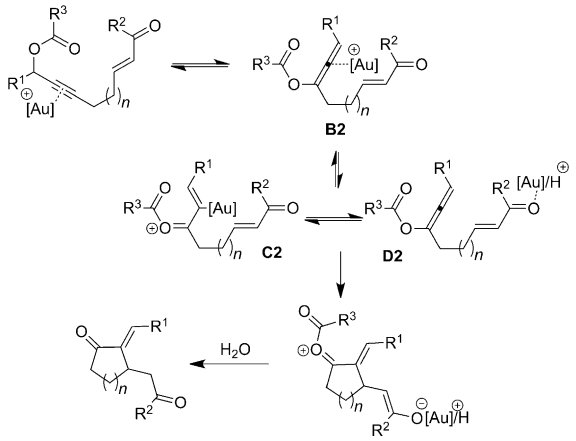


Entry	Substrate	*n*	R^1	R^2	Product	Yield [%][a]
1	**3b**	1	Ph	Me	**4b**	92
2	**3c**	1	Me	Ph	**4c**	93[b]
3	**3d**	1	Ph	Ph	**4d**	85
4	**3e**	1	*n*Bu	Me	**4e**	75
5	**3f**	1	*n*Bu	Ph	**4f**	79
6	**3g**	1	H	Me	**4g**	0[c]
7	**3a**	2	Ph	Me	**4a**	96
8	**3h**	2	Ph	Ph	**4h**	94
9	**3i**	2	*n*Bu	Me	**4i**	66[b]
10	**3j**	2	*n*Bu	Ph	**4j**	71
11	**3k**	2	H	Me	**4k**	0[c]
12	**3l**	1	*p*-$F_3CC_6H_4$	Me	**4l**	91
13	**3m**	2	*p*-$MeOC_6H_4$	Me	**4m**	73
14	**3n**	1	Ph	*p*-MeC_6H_4	**4n**	84
15	**3o**	2	Ph	*p*-ClC_6H_4	**4o**	65

[a] Yield of isolated product. [b] Run for 2 h. [c] Only starting material recovered.

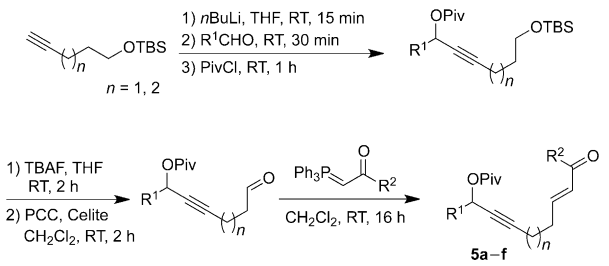
positions. Consequently, the method allowed the synthesis, in high yields, of cycloadducts that would either be regiochemically disfavored or not cleanly isolable by the traditional RC reaction. In this regard, of particular note are entries 2, 5, 10, 13, and 15 where the nature of R^1 would render the corresponding enone the least reactive towards PR_3 or NR_3, thus leading predominantly to the opposite regioisomer. Also notable are the examples shown in entries 4 and 9 where little discrimination between the two alkyl enones would be expected. Interestingly, when $R^1 = H$ (entries 6 and 11) no reaction was observed, thus corroborating previous reports that secondary propargylic aliphatic esters undergo neither 1,3 nor 1,2-migration efficiently if the alkyne is terminal.[16]

The synthesis of exocyclic enones (Scheme 5), a class of compounds hitherto not accessed by the traditional RC approach, was also examined by switching the regiochemistry of the propargyl ester motif.



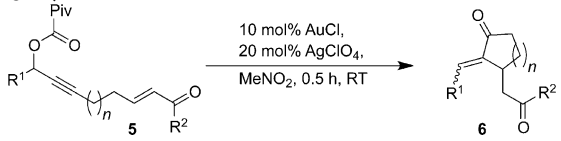
Scheme 5. Proposed mechanism for formation of exocyclic enones.

Accordingly, substrates **5a–f** were synthesized (Scheme 6) and the substrates were subsequently subjected to our standard reaction conditions (Table 3). Overall the expected exocyclic enones were obtained, almost exclusively, as the *E* isomers in high yields. Five-membered rings formed efficiently when phenyl or alkyl substituents were present at R^1 (entries 1–3). When $R^1 = i$Pr, a marked reduction in reactivity was observed (entry 4); a substoichiometric amount of the gold catalyst (25 mol%) was required for complete conversion within 3.5 hours, most likely a result of the steric hindrance from an interaction between the gold



Scheme 6. Synthesis of substrates **5a–f**.

Table 3: Cyclization reactions.



Entry	Substrate	*n*	R^1	R^2	Product	Yield [%][a]	*E*/*Z*[b]
1	**5a**	1	Ph	Me	**6a**	95	>20:1
2	**5b**	1	Ph	Ph	**6b**	87	>20:1
3	**5c**	1	$PhCH_2CH_2$	Ph	**6c**	78	9:1
4	**5d**	1	*i*Pr	Ph	**6d**	62[c]	>20:1
5	**5e**	2	Ph	Ph	**6e**	67	>20:1
6	**5f**	2	Ph	Me	**6f**	complex mixture	–

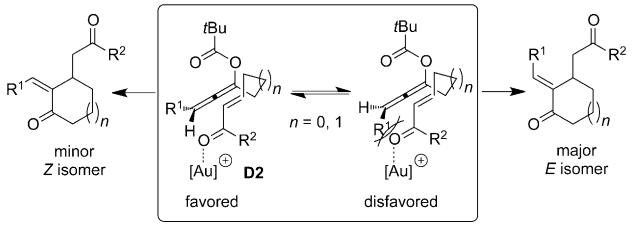
[a] Yield of isolated product. [b] Ratio determined using ^{1}H NMR spectroscopy. Stereochemistry confirmed by NOE using ^{1}H NMR spectroscopy. [c] Used 25 mol% AuCl, 50 mol% $AgClO_4$, 3.5 h.

center and the *i*Pr group in the α-vinyl gold intermediate **C2** (Scheme 5). For six-membered rings, a reasonable yield was obtained when R^1 and R^2 were phenyl substituents (entry 5), however, changing R^2 to a methyl group led to a complex mixture of products (entry 6).

No intermediates were observable by ^{1}H NMR spectroscopy or TLC for either series of substrates, thus suggesting that the initial rearrangement of the propargyl pivolate is the rate-determining step.[17] For substrates **3a–o**, it was unclear whether the key nucleophilic intermediate was the allene **D1** (Scheme 3) or the α-vinyl gold oxocarbenium ion **C1** as both gold catalysts and strong protic acids catalyzed the reaction. In the event that **D1** is the cyclization precursor, wherein an integral role for gold is suggested by its superior activity compared with protic acids, a Michael addition catalyzed by the pivalic acid by-product cannot be ruled out.

For compounds **5a–f**, the absence of the *Z* stereoisomer suggested that the allene **D2** was not the progenitor to cyclization, otherwise the enone would be expected to approach from the least hindered face, thus resulting in the formation of the *Z* product (Scheme 7). Furthermore, the predominance of the *E* stereoisomer is indicative of a *cis* relationship between R^1 and Au in **C2** (Scheme 5). This configuration is expected to be more stable than if R^1 is *cis* to the oxocarbenium group because of the reduced steric crowding as a consequence of the long Au–C(sp2) bond.[11h]

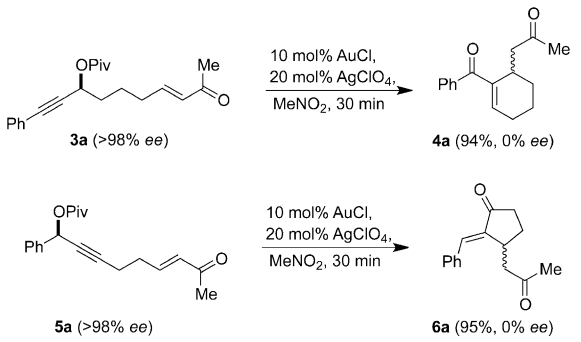
Notably, in the presence of TsOH, **5a** failed to undergo cyclization under the standard reaction conditions after 1 hour. As only **D2** (Scheme 5) can be the cyclization precursor in this case, this provides strong evidence against its involvement in the gold-catalyzed reaction. The *Z* isomer



Scheme 7. Approach of the enone.

was initially expected via a less sterically crowded transition state (Scheme 7), however, it appears that the endo nature of the nucleophilic enol makes cyclization unfavorable. In contrast the α-vinyl gold species can undergo a favored 5-*exo*-trig cyclization. Furthermore, the larger orbitals associated with Au and the longer C–Au bond length, likely reduce conformational strain in the transition state, thus aiding cyclization.

To further elucidate the reaction mechanism, particularly regarding the mechanistic ambiguity concerning substrates **3a–o**, the enantioenriched propargyl pivolates **3a** and **5a** were synthesized and subjected to the standard reaction conditions (Scheme 8). Strikingly, complete racemization was observed



Scheme 8. Reaction of enantioenriched substrates.

in both cases. Regarding **3a**, this likely rules out a reaction pathway involving the chiral allene intermediate **D1** and indicates the presence of either the achiral intermediates **A** or **C1** as significant components of the precyclization equilibrium, otherwise at least partial preservation of enantiomeric excess would be expected.[7c,18] It should be noted however that **D1** could still be the direct precursor to cyclization after racemization via **A** or **C1**. In the case of **5a**, the observed racemization adds weight to a mechanism proceeding via the achiral α-vinyl gold intermediate **C2** (Scheme 5). When considered alongside the inertness of **5a** towards TsOH, and the isolation of **6a–e** predominately as the *E* stereoisomers, this data amounts to compelling evidence for **C2** as the cyclization precursor.

In conclusion, we have demonstrated a concise strategy for the regioselective synthesis of unsaturated carbocycles, utilizing the gold-catalyzed chemoselective formation of a nucleophilic RC zwitterion equivalent. In particular this approach allows access to regioisomers which are disfavored in the traditional RC reaction. The protocol has also been extended to the synthesis of exocyclic enones. Mechanistically our results suggest the intermediacy of the α-vinyl gold oxocarbenium species **C1** and **C2**. Regarding the substrates **3a–o**, either **C1** or **D1** could be the progenitor to cyclization, and for substrates **5a–f** the case for **C2** as the precursor is persuasive. Further studies, to more accurately determine the mechanistic details and to assess the reaction scope, including an asymmetric variant, are ongoing.

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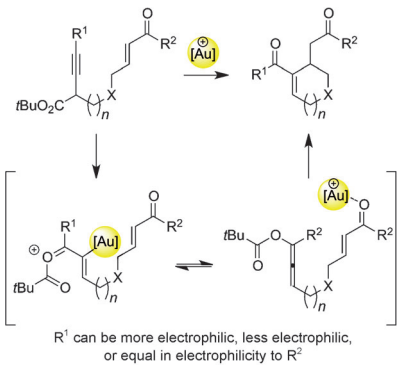
[18] a) P. Mauleón, J. L. Krinsky, F. D. Toste, *J. Am. Chem. Soc.* **2009**, *131*, 4513; b) G. Lemière, V. Gandon, K. Cariou, A. Hours, T. Fukuyama, A-L. Dhimane, L. Fensterbank, M. Malacria, *J. Am. Chem. Soc.* **2009**, *131*, 2993; c) D. Garayalde, E. Gómez-Bengoa, X. Huang, A. Goeke, C. Nevado, *J. Am. Chem. Soc.* **2010**, *132*, 4720.

Communications

Synthetic Methods

J. W. Cran,* M. E. Krafft ____ ▮▮▮▮–▮▮▮▮

Regioselective Cyclizations Utilizing a Gold-Catalyzed [3,3] Propargyl Ester Rearrangement



Switch-Au-roo: A new strategy for the regioselective synthesis of unsaturated carbocycles by chemoselective activation of a Rauhut–Currier zwitterion surrogate, formed from the Au-catalyzed [3,3] sigmatropic rearrangement of propargylic esters, has been achieved. By reversing the regiochemistry of the propargyl ester the synthesis of either the endo- or exocyclic enones is feasible.