Gold Catalysis

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Gold-Catalyzed Cyclopenta- and Cycloheptannulation Cascades: A Stereocontrolled Approach to the Scaffold of Frondosins A and B**

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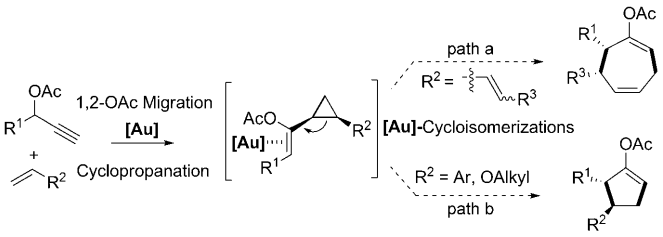
Seven-membered ring carbocycles are ubiquitous motifs in a wide variety of natural products including guanascaterpenes, colchicines, phorbols, and frondosins among many others.[1] Since direct cyclizations have proved to be inefficient to construct this particular ring size, alternative strategies have been devised and mainly focus on cycloaddition reactions.[2] Both inter- and intramolecular rhodium-mediated [5+2] cycloadditions between vinylcyclopropanes and unsaturated moieties have been successfully developed.[3] Another widespread method uses rhodium–vinyl carbenoids and dienes in formal [4+3] cycloadditions.[4] However, this methodology still presents several drawbacks: first, the metal carbenes are generated from the corresponding diazo compounds, which need to be pre-synthesized, thus adding extra steps to the overall process, and secondly, only donor–acceptor carbenoids provide high levels of selectivity. The development of versatile gold complexes in recent years has revealed gold catalysis as a powerful tool to construct molecular complexity.[5] As a representative example, the gold-catalyzed 1,2-acyloxy migration of propargyl esters generates a gold carbene, which can undergo a broad palette of transformations such as nucleophilic attack,[6] annulation,[7] subsequent acyloxy rearrangement,[8] and olefin cyclopropanation.[9] Recently, gold-catalyzed ring expansions of stabilized cyclopropyl rings were reported.[10] We envisioned that a reaction sequence involving propargyl esters and dienes could be orchestrated such that gold not only catalyzed the 1,2-acetoxy migration and subsequent cyclopropanation, but could also reactivate the in situ generated vinyl acetate, thereby triggering a formal homo-Cope rearrangement to give seven-membered rings in a straightforward manner (Scheme 1; path a).[11] Furthermore, if alkenes instead of dienes were used, highly substituted cyclopentenyl acetates could be obtained upon cyclopropyl ring opening (Scheme 1; path b). Herein, we report the realization of these concepts and an application in the formal enantioselective synthesis of marine secondary metabolites frondosins A and B.

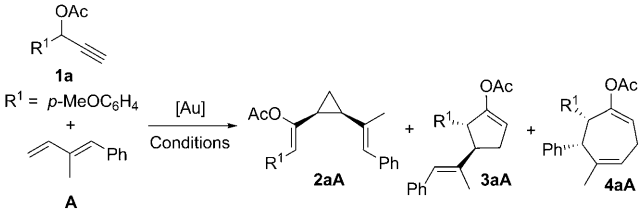
The reaction of *p*-methoxyphenylpropargyl acetate (**1a**) and (*E*)-(2-methylbuta-1,3-dienyl)benzene (**A**) in the presence of $[IPrAu]NTf_2$ cleanly delivered cyclopropane **2aA** and



Scheme 1. Design of a gold-catalyzed 1,2-acyloxy-rearrangement/cyclopropanation/cycloisomerization cascades.

cycloheptenylacetate **4aA** in a 1:2 ratio (Table 1, entry 1). In the presence of a more electrophilic phosphite ligand, five- and seven-membered rings **3aA** and **4aA** could be detected (Table 1, entry 2). The tris(2,4-di-*tert*butylphenyl)phosphite–gold complex afforded similar results upon heating to 80 °C (Table 1, entry 3; Conditions I), whereas $Ph_3PAuSbF_6$, provided a mixture of cyclopropyl **2aA** and the seven-membered ring **4aA** in a 1:2 ratio (Table 1, entry 4). A combination of 2.5 mol% $[IPrAu]NTf_2$ and 2.5 mol% $(PhO)_3PAuSbF_6$ delivered **4aA** in a 69% yield (Table 1, entry 5; Conditions II). Finally, a [(2-biphenyl)di-*tert*-butylphosphine]–gold complex selectively afforded **4aA** in a 85% yield, thereby providing

Table 1: Reaction optimization.[a]



Entry	[Au], solvent, time[a]	Cond.	**2aA/3aA/4aA**[b]
1	$[IPrAu]NTf_2$, CH_2Cl_2, 30 min	–	1:0:2
2	$(PhO)_3PAuSbF_6$, CH_2Cl_2, 30 min	–	0:1:5
3	$[(2,4\text{-di-}t\text{Bu-}C_6H_3O)_3P]AuSbF_6$, DCE, 80 °C, 30 min	I	0:1:3
4	$Ph_3PAuSbF_6$, CH_2Cl_2, 30 min	–	1:0:2
5	$[IPrAu]NTf_2$ (2.5 mol%), CH_2Cl_2, 10 min then $(PhO)_3PAuSbF_6$ (2.5 mol%), CH_2Cl_2, 30 min	II	1:1:10 (69)
6	**[{(2-biphenyl)di-*t*Bu-phosphine}Au]SbF_6, CH_2Cl_2, 30 min**	**III**	**0:0:1 (85)**

[a] Reaction conditions: **1a** (1 equiv), **A** (1.1 equiv), [Au] (5 mol%), 25 °C, 0.1 M. [b] Determined by ^1H NMR analysis of the crude reaction mixture. Numbers in brackets indicate the yields of the products isolated after column chromatography. DCE = 1,2-dichloroethane; IPr = 1,3-bis(2,6-diiso-propylphenyl)-imidazol-2-ylid.

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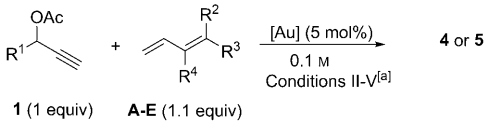
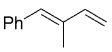
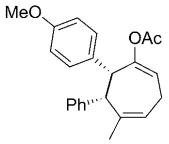
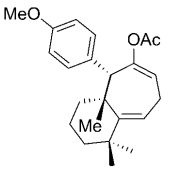
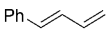
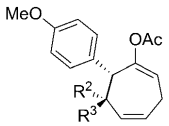
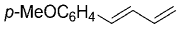
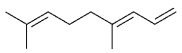
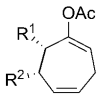
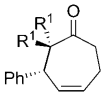
Table 2: Gold-catalyzed cycloheptannulation: Reaction scope.



1 (1 equiv) **A-E** (1.1 equiv)

Entry	**1**	Dienes	Product	Cond.[a]	Yield [%][b]
					
1	**1a** (R^1 = *p*-$MeOC_6H_4$)	**A**	**4aA**	III	85
					
2	**1a**	**B**	**4aB**	III	59
					
3	**1a**	**C**	**4aC** (R^2 = Ph, R^3 = H)	II	92
					
4	**1a**	**D**	**4aD** (R^2 = *p*-$MeOC_6H_4$, R^3 = H)	II	77
					
5	**1a**	**E**	**4aE** (R^2 = -$(CH_2)_2$-CH= $C(Me)_2$, R^3 = Me)	IV	37
					
6	**1b** (R^1 = 2-napth)	**C**	**4bC** (R^2 = Ph)	II	72
7	**1b**	**D**	**4bD** (R^2 = *p*-$OMeC_6H_4$)	II	55
8	**1c** (R^1 = Ph)	**C**	**4cC** (R^2 = Ph)	II	80
9	**1c**	**D**	**4cD** (R^2 = *p*-$MeOC_6H_4$)	II	50
10	**1d** (R^1 = 3,5-dimethoxyphenyl)	**C**	**4dC** (R_2 = Ph)	II	74
11	**1d**	**D**	**4dD** (R^2 = *p*-$MeOC_6H_4$)	II	44
					
12	**1e** (R^1 = Me, Me)	**C**	**5eC**	V	52
13	**1f** (R^1 = -$(CH_2)_5$-)	**C**	**5fC**	V	79

[a] Conditions II and III from Table 1; Conditions IV: same as Conditions III but with heating to 120 °C in DCE; Conditions V: same as Conditions IV with subsequent treatment with K_2CO_3/MeOH. [b] Yield of isolated products.

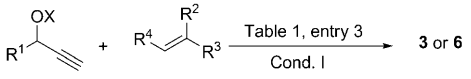
the optimal reaction conditions (Table 1, entry 6; Conditions III).

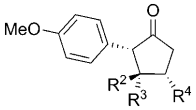
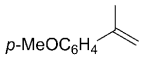
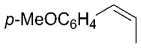
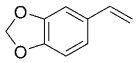
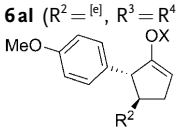
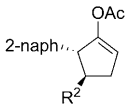
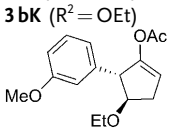
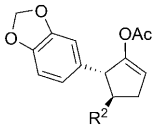
We then set out to explore the scope of this gold-catalyzed intermolecular cycloheptannulation (Table 2). Using **1a** as a benchmark substrate we evaluated the influence of the diene in the reaction. Congested alkenes reacted efficiently providing access to complex bicyclic scaffolds such as **4aB** (Table 2, entry 2), whereas more reactive monosubstituted dienes such as **C** and **D** partially polymerized under these conditions. The bi-catalytic system (see Conditions II in Table 1) proved to be highly efficient for this type of substrate, thus affording the corresponding cycloheptenylacetates **4aC,D** in high yields (Table 2, entries 3 and 4). Geranyl derivative **E** reacted with **1a** upon heating to give **4aE** in moderate yield (Table 2, entry 5). Acetates bearing 2-naphthyl-, phenyl- and 3,5-dimethoxyphenyl substituents in the propargylic position (**1b–d**) reacted smoothly under the Conditions II to give the corresponding seven-membered rings (Table 2, entries 6–11). 1,1-Dialkylsubstituted propargyl acetates **1e** and **1f** could also be transformed into the corresponding cycloheptenones **5eC** and **5fC** upon hydrolysis of the reaction mixture under basic conditions (Table 2, entries 12 and 13). This cycloheptannulation process is highly stereoselective, affording only *cis*-cycloheptenylacetates as major products.[12,13]

The chemoselectivity of the reaction is also remarkable, as neither cyclopropane intermediates (**2**)[14] nor products of a competitive intramolecular hydroarylation could be detected under these reaction conditions.[15]

We hypothesized that alkenes could also participate in this gold-catalyzed cascade (Table 3). The reaction of **1a** with 4-methoxystyrene (**F**; 1 equiv) in the presence of the tris(2,4-di-*tert*butylphenyl)phosphite–gold complex under the Conditions I proved to be extremely efficient, affording cyclopentenone **6aF** in 90% yield. **6aF** is formed upon in situ hydrolysis of the corresponding cyclopentenylacetate under the reaction conditions (Table 3, entry 1).[16] Different substitution patterns in the olefinic counterpart were then examined. 1-Methoxy-4-(prop-1-en-2-yl)benzene (**G**), (*Z*)-1-methoxy-4-(prop-1-enyl)benzene (**H**), and 5-vinylbenzo-[*d*]-

Table 3: Gold-catalyzed cyclopentannulation: Reaction scope.



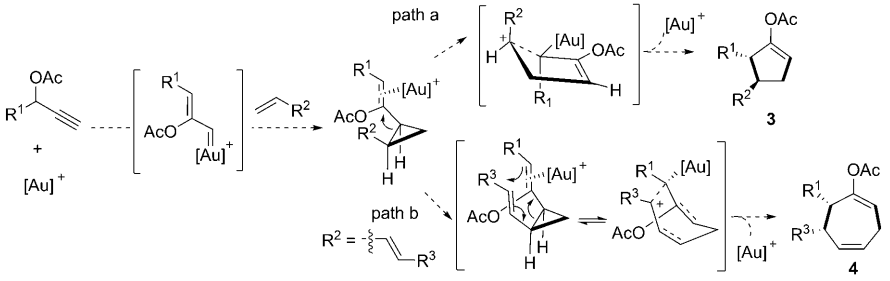
Entry		Olefin	Product	Yield [%][a]
		p-MeOC$_6$H$_4$		
1	**1a** (X = Ac, R^1 = *p*-MeOC$_6$H$_4$)	**F**	**6aF** (R^2 = *p*-OMeC$_6$H$_4$, R^3 = R^4 = H)	90
				
2	**1a**	**G**	**6aG** (R^2 = *p*-MeOC$_6$H$_4$, R^3 = Me, R^4 = H)	82[b]
				
3	**1a**	**H**	**6aH** (R^2 = *p*-MeOC$_6$H$_4$, R^3 = H, R^4 = Me)	78
				
4	**1a**	**I**	**6aI** (R^2 = [e], R^3 = R^4 = H)	63
				
5	**1a**	**J**	**3aJ** (R^2 = OBn)	83[c]
				
6	**1a**	**K**	**3aK** (R^2 = OEt)	75[c,d]
7	**1g** (X = Piv, R^1 = *p*-MeOC$_6$H$_4$)	**J**	**3gJ** (R^2 = OBn)	82[c]
				
8	**1b** (X = Ac, R^1 = 2-napth)	**J**	**3bJ** (R^2 = OBn)	79[c]
9	**1b**	**K**	**3bK** (R^2 = OEt)	73[c,d]
				
10	**1h** (X = Ac, R^1 = *m*-MeOC$_6$H$_4$)	**K**	**3hK**	60[c,d]
				
11	**1i** (X = Ac, R^1 = [e])	**J**	**3iJ** (R^2 = OBn)	87[c]
12	**1i**	**K**	**3iK** (R^2 = OEt)	87[c,d]
				
13	**1i**	**L**	**3iL** (R^2 = OBu)	59[c]
				
14	**1i**	**M**	**3iM** (R^2 = O*t*Bu)	87[c,d]

[a] Yields of compounds isolated as single diastereoisomers unless otherwise stated. [b] After hydrolysis of the crude mixture using K_2CO_3 (2 equiv), MeOH, RT, 30 min (d.r. = 7:1). RT, 1 h. [c] Reaction at room temperature. [d] Used 5 equiv olefin. [e] R^1 = 

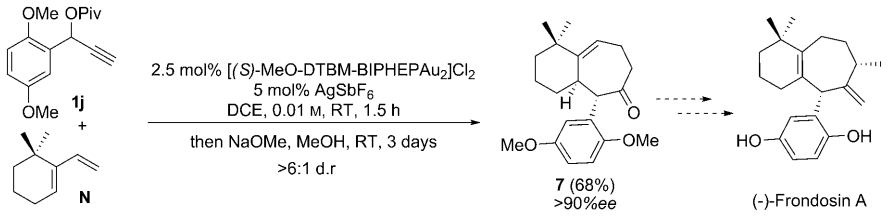
[1,3]-dioxole (**I**) reacted with **1a** affording ketones **6aG–I** in good yields (Table 3, entries 2–4). Alkoxy vinyl ethers (**J–K**) reacted smoothly with **1a** at room temperature furnishing the corresponding cyclopentenyl acetates **3aJ–K** (Table 3, entries 5 and 6). A bulkier pivaloyl ester (**1g**) was also tolerated affording **3gJ** in 82% yield (Table 3, entry 7). Comparable results were also obtained for 2-naphthyl- (**1b**), 3-methoxyphenyl- (**1h**), and benzo-[*d*]-1,3-dioxole-substituted (**1i**) propargyl acetates as shown in entries 8–14 in Table 3. The reaction is also highly diastereoselective since in most cases only *trans*-2,3-disubstituted cyclopentenyl derivatives were observed.[12]

A possible mechanism for these transformations is shown in Scheme 2. The gold-mediated isomerization of the propargyl ester leads to an Au/carbene compound, which reacts with the olefinic reactant to form a *cis*-cyclopropane intermediate.[9] Subsequent gold reactivation of the vinyl acetate moiety triggers the cyclopropyl ring-opening, provided stabilization of the in situ generated δ^+ is present, thus forming a 1,5-dipole.[10] An envelope conformation is proposed for the transition state in which substituents are disposed in a *trans*-pseudodiaxial fashion to minimize torsional/steric interactions, and yields the *trans*-2,3-disubstituted cyclopentannulation products **3** (Scheme 2; path a).[17] In contrast, when 1,4-dienes are used, the cyclopropyl system undergoes a gold-catalyzed Cope rearrangement to deliver the *cis*-2,3-disubstituted cycloheptenyl acetates **4** (Scheme 2; path b).[11] A boatlike transition state is proposed in this case to account for the observed *cis* relative stereochemistry.

To capitalize on the structural complexity developed in the formal gold-catalyzed [4+3] cycloaddition, we envisioned a synthetic application towards the core of the frondosins, marine norsesquiterpenoids with promising biological activities, with frondosin A as the most potent member of the series.[18] Several



Scheme 2. Mechanistic proposal.



Scheme 3. Formal total synthesis of frondosins A and B. (*S*)-OMe-DTBM-BIPHEP = (*S*)-(+)-2,2′-bis[di(3,5-di-t-butyl-4-methoxyphenyl)phosphino]-6,6′-dimethoxy-1,1′-biphenyl.

approaches towards the core of the frondosins have been disclosed but only one enantioselective synthesis of (+)-frondosin A has been reported thus far.[19] Treatment of pivaloate **1j** and 6,6-dimethyl-1-vinyl cyclohexene (**N**) with (*S*)-OMe-DTBM-BIPHEP–gold(I) complex afforded, quantitatively, the corresponding bicyclic cycloheptenyl pivaloate. In situ hydrolysis and subsequent equilibration with NaOMe/MeOH yielded the thermodynamically favored ketone **7** in 68% yield and more than 90% *ee* (Scheme 3).[12] Since this bicyclic enone has been recently elaborated into Frondosins A and B,[20] our approach represents a streamlined formal enantioselective synthesis of both molecules.

In summary, we report herein two highly diastereoselective, gold-catalyzed, three-step cascade processes for the synthesis of highly substituted five- and seven-membered rings from propargyl acetates and alkenes or 1,4-dienes, respectively. The reaction favors *trans*-2,3-disubstituted cyclopentenylacetates through a tightly bound carbocationic transition state whereas the gold-catalyzed Cope rearrangement delivers *cis*-2,3-disubstituted cyclopheptenylacetates. This formal [4+3] cycloaddition catalyzed by gold represents an attractive alternative to previously reported rhodium-catalyzed reactions both in terms of atom economy and functional group tolerance. In addition, the concerted nature of the process has allowed an alternative, formal enantioselective synthesis of the frondosins A and B.

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[14] The gold-free, thermal Cope rearrangement of several cyclopropyl intermediates (**2aA-C**) failed even at temperatures up to 80°C. The cyclopropane **2aB** is transformed into the corresponding cycloheptenyl acetate **4aB** upon treatment with the

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