Domino Reactions

DOI: 10.1002/anie.200604544

Catalyzed Tandem Reaction of 3-Silyloxy-1,5-enynes Consisting of Cyclization and Pinacol Rearrangement**

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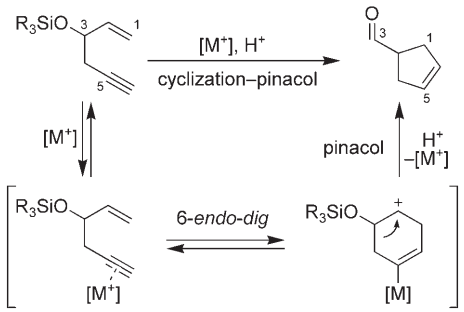
The efficient construction of natural products and increasingly complex pharmaceutical agents requires the ongoing development of new methods for their stereocontrolled synthesis. Within this context, cationic cyclization reactions terminated by a pinacol rearrangement have been shown to be of exceptional value.[1–3] For example, Overman and coworkers used a tandem reaction consisting of a Prins cyclization and a pinacol reaction for the synthesis of oxacyclic and carbocyclic natural products such as (−)-citreoviral[4] and (+)-shahamin K.[5] While various initiating groups have already been investigated in considerable detail,[6] the activation of π systems in this context is not well understood.[7] Herein we report the first tandem cyclization–pinacol reaction that is initiated by gold(I)-catalyzed alkyne activation.

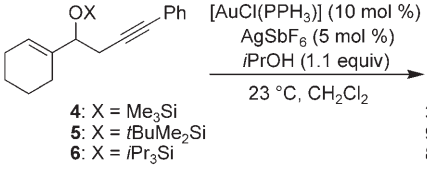
As part of our ongoing studies in this field,[8] we identified 3-silyloxy-1,5-enynes as a potentially useful class of substrates (Scheme 1). It was envisaged that coordination of a soft cation to the alkynyl functionality might initiate a 6-*endo-dig* carbocyclization.[9–11] In our projected sequence the cationic intermediate[12] is expected to undergo an irreversible pinacol rearrangement, and subsequent protonation of the carbon–transition-metal bond at C5 should generate a product containing a cyclopentene unit and regenerate the catalyst.



Scheme 1. Projected tandem cyclization–pinacol reaction.

To probe the feasibility of the proposed transformation, we initially investigated the conversion of 3-triethylsilyloxy-1,5-enyne **1a** into aldehyde **2a** (Table 1). Owing to their exceptional affinity to alkynes, noble-metal cations such as Pt^{II}, Au^{I}, and Au^{III} were expected to show appreciable activity in this reaction.[13,14] To prevent competitive heterocyclization through a free hydroxy group,[9,12] 3-silyloxy-1,5-enynes were employed. Thus, an external proton source is required for the protonolysis to regenerate the catalyst.[15] We were pleased to find that treatment of enyne **1a** with a catalytic amount of $PtCl_2$ in toluene at 100 °C for 24 h provided the *cis*-fused carbocycle **2a** in 37% yield. In this reaction, 1.1 equiv of isopropyl alcohol was used as the proton source. Interestingly, biaryl compound **3a** was formed in 30% yield presumably resulting from competing aromatization of the proposed six-membered cationic intermediate. Gratifyingly, the use of the cationic triphenylphosphinegold(I) complex derived from activation of 10 mol% of [AuCl(PPh$_3$)] with 5 mol% of $AgSbF_6$ rapidly and cleanly converted 3-silyloxy-1,5-enyne **1a** into aldehyde **2a** at room temperature in CH_2Cl_2. The reaction can be run at low catalyst loadings (2 mol% [AuCl(PPh$_3$)]/1 mol% $AgSbF_6$), although a longer period of time is required for the reaction to reach completion. Since traces of $AgSbF_6$ led to the complete decomposition of both starting material and product, catalysts generated in situ by dechlorination of [AuCl(PPh$_3$)] with $AgSbF_6$ gave low yields. Therefore, [AuCl(PPh$_3$)] was activated prior to use by reaction with 0.5 equiv of $AgSbF_6$ in CH_2Cl_2 at room temperature. Changing the counteranion by activating [AuCl(PPh$_3$)] with $AgBF_4$ was also examined; however, product formation was not observed under these conditions. Without anion exchange, [AuCl(PPh$_3$)] was unreactive. Sterically demanding alcohols such as isopropyl alcohol proved to be effective additives for cyclization–pinacol reactions.[16] The use of water as the proton source led to the desired product in diminished yields.

Other trialkylsilyl ethers were found to give cyclopentene products as well [Eq. (1)]. The low yield observed in the reaction of silyl ether **4** (X = Me_3Si) most likely resulted from



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[**] This project was supported by the Deutsche Forschungsgemeinschaft (DFG) and the Fonds der Chemischen Industrie (FCI). We thank Olaf Ackermann for assistance with HPLC. We thank Prof. Thorsten Bach and his group for helpful discussions and generous support.

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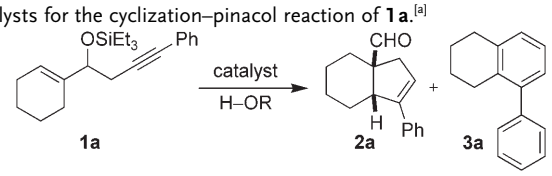
Table 1: Efficiency of transition-metal catalysts for the cyclization–pinacol reaction of **1a**.[a]



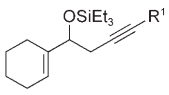
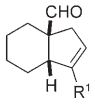
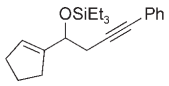
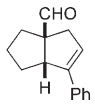
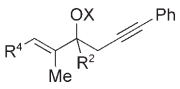
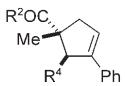
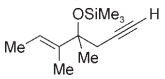
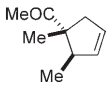
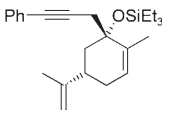
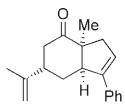
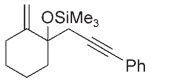
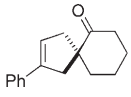
Entry	Cat. (mol%)	Conditions	Yield [%][b]		
			1a[c]	**2a**	**3a**
1	$PtCl_2$ (5)	*i*PrOH (1.1 equiv), 100°C, toluene, 24 h	0	37	30
2	CuI (10)	*i*PrOH (1.1 equiv), 80°C, DMF, 24 h	44	21	15
3[d]	$[AuCl(PPh_3)]$ (10)/$AgSbF_6$ (5)	*i*PrOH (1.1 equiv), 23°C, CH_2Cl_2, 10 min	0	93	0
4[d]	$[AuCl(PPh_3)]$ (2)/$AgSbF_6$ (1)	*i*PrOH (1.1 equiv), 23°C, CH_2Cl_2, 150 min	0	81	0
5[d]	$[AuCl(PPh_3)]$ (10)/$AgSbF_6$ (5)	CH_2Cl_2/H_2O (10:1), 23°C, 60 min	0	39	0
6	$[AuCl(PPh_3)]$ (10)/$AgBF_4$ (5)	*i*PrOH (1.1 equiv), 23°C, CH_2Cl_2, 24 h	>95	0	0
7	$[\{Au(PPh_3)\}_3O]BF_4$ (5)	*i*PrOH (1.1 equiv), 23°C, CH_2Cl_2, 24 h	>95	0	0
8	$AgSbF_6$ (5)	*i*PrOH (1.1 equiv), 23°C, CH_2Cl_2, 60 min	0	0	0

[a] Conditions: **1a** (0.1 M), catalyst, additive, solvent. [b] Yield of pure product after column chromatography. [c] Recovered starting material. [d] The precatalyst $[AuCl(PPh_3)]$ was preactivated by reaction with 0.5 equiv of $AgSbF_6$ in CH_2Cl_2.

partial loss of the $SiMe_3$ group under the reaction conditions. Nevertheless, more robust silyl ethers such as **5** (X = *t*BuMe_2Si) and **6** (X = *i*Pr_3Si) also underwent clean formation of aldehyde **2a**.

The scope of this domino reaction is summarized in Table 2. A broad variety of 3-silyloxy-1,5-enynes having aryl, heteroaryl, alkyl, and hydrogen substituents at the alkyne terminus were effectively converted into the corresponding cyclopentenes. As exemplified through the construction of all-carbon quaternary stereocenters and complex bicyclic compounds (e.g., **2**, **8**, **18**), a definitive feature of this novel route to substituted cyclopentenes is that challenging elements of structure are readily accessed.[17] Of primary importance, all reactions performed in this study resulted in the formation of a single diastereomer (d.r. > 95:5).[18]

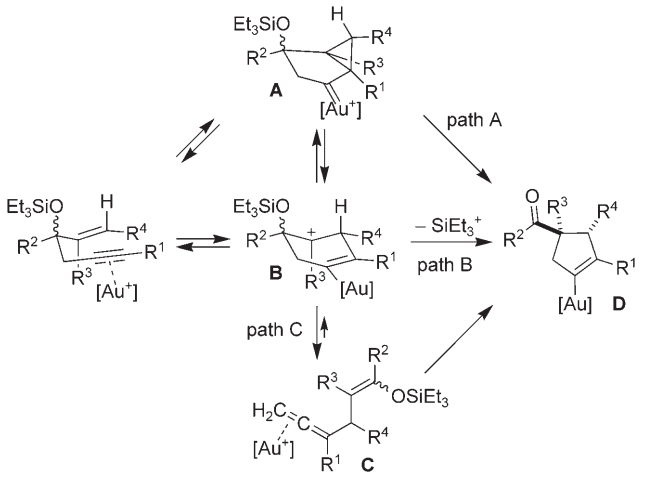
Table 2: Au^I-catalyzed tandem reactions consisting of enyne cyclization and pinacol rearrangement.[a]

Entry	Substrate		Product[b]		Yield [%][c]
1		**1b**		**2b**	83
	R^1 = *o*-MeO(C_6H_4)				
2	R^1 = 2-thienyl	**1c**		**2c**	81
3	R^1 = 1-naphthyl	**1d**		**2d**	71
4	R^1 = Me	**1e**		**2e**	54
5	R^1 = H	**1f**		**2f**	68
6		**7**		**8**	73
7[d]		**9**		**10**	72
	R^2 = H, R^4 = Me				
8[d]	R^2 = H, R^4 = H	**11**		**12**	28
9[e]	R^2 = Me, R^4 = Me	**13**		**14**	55
10		**15**		**16**	50
11		**17**		**18**	67
12		**19**		**20**	65

[a] Conditions: Substrate (0.1 M), 10 mol% $[AuCl(PPh_3)]$, 5 mol% $AgSbF_6$, 1.1 equiv *i*PrOH, 23°C, CH_2Cl_2. [b] The relative configuration was determined by ^1H NMR NOE experiments. [c] Yield of pure product after column chromatography. [d] X = *t*$BuMe_2$Si. [e] X = Et_3Si.

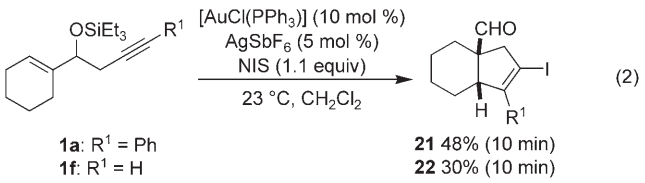
As conceptualized in our initial design, these results are consistent with a cyclization–pinacol mechanism proceeding through the cationic intermediate **B**, which is in equilibrium with cyclopropyl gold carbene **A** (Scheme 2, path B). Alternatively, the reaction might occur directly through species **A** (path A) as implicated from related transformations.[9,12c] A mechanism in which the six-membered intermediate **B** collapses to give the allenic intermediate **C** is also possible (path C). In this sequence, a Au^I-catalyzed [3,3]-sigmatropic rearrangement based on a cyclization-induced rearrangement (CIR) mechanism[19] is followed by an intramolecular 5-*endo*-*trig* cyclization.[15,20] Either way, protodemetalation of the resulting organogold intermediate **D** affords the product with simultaneous regeneration of the catalyst.

To further expand the scope of the Au^I-catalyzed process, we briefly examined the use of other electrophiles. Alkenyl iodide **21** was produced rapidly in 48% yield when the Au^I-catalyzed reaction of



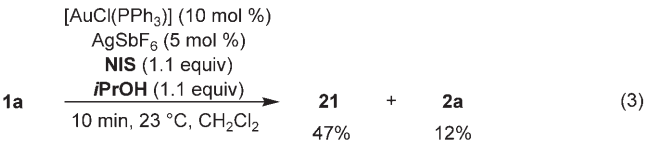
Scheme 2. Plausible mechanism.

enyne **1a** ($R^1 = Ph$) was carried out in the presence of *N*-iodosuccinimide (NIS) (10 mol% [AuCl(PPh$_3$)], 5 mol% $AgSbF_6$, 1.1 equiv NIS, 23 °C, CH_2Cl_2) [Eq. (2)]. Notably,



(2)

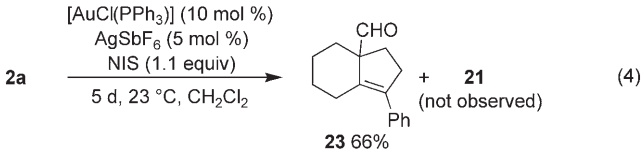
the starting enyne did not react in the absence of a Au^I catalyst.[21] Although we feel a detailed discussion of the mechanism of the Au^I-catalyzed rearrangement in the presence of NIS is premature at this point, we note that the selective introduction of the iodo substituent at C5 may be rationalized by a rapid iododemetalation of vinylgold(I) intermediate **D**.[22] An experiment with both *i*PrOH and NIS led to the formation of the iodine-containing aldehyde **21** as the major product [Eq. (3)]. A mechanism involving a rapid



(3)

reaction to cyclopentene **2a** followed by subsequent iodination of the newly formed alkene moiety can be ruled out as aldehyde **2a** failed to give iodocyclopentene **21** under the reaction conditions, providing instead the product of double-bond isomerization in a slow reaction [Eq. (4)].

In conclusion, polyfunctional cyclopentenes can be prepared stereoselectively in a convenient Au^I-catalyzed sequence from 3-silyloxy-1,5-enynes. The reaction likely proceeds by a novel mechanism involving cyclization and subsequent pinacol-type rearrangement of the gold-containing carbocationic intermediate. Although our investigations



(4)

of this chemistry are in a seminal stage, the high utility of this novel mode of carbocycle construction is already apparent. Additional applications of this concept and detailed mechanistic studies are in progress.

Experimental Section

General Procedure (Synthesis of **2a**; Table 1, entry 3): A solution of [AuCl(PPh$_3$)] (22.4 mg, 10 mol%) in CH_2Cl_2 (0.3 mL) was added to a solution of $AgSbF_6$ (7.8 mg, 5 mol%) in CH_2Cl_2 (0.3 mL), and the mixture was stirred at room temperature for 10 min. The resulting suspension was filtered through Celite and concentrated under reduced pressure. To this residue, a solution of **1a** (156 mg, 0.45 mmol) and *i*PrOH (0.04 mL, 0.50 mmol) in CH_2Cl_2 (4.5 mL) was added. The pale purple solution was stirred at room temperature for 10 min. The mixture was concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (pentanes/EtOAc 98:2) gave **2a** as a colorless oil (94.7 mg, 0.42 mmol, 93%). $R_f = 0.42$ (pentanes/EtOAc 95:5); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.20$–1.26 (m, 2H), 1.43–1.45 (m, 1H), 1.57–1.66 (m, 3H), 1.68–1.72 (m, 1H), 2.06–2.10 (m, 1H), 2.53 (d, $J = 16.7$ Hz, 1H), 2.70 (dd, $J = 16.7$, 2.7 Hz, 1H), 3.16 (t, $J = 5.8$ Hz, 1H), 6.02 (s, 1H), 7.23 (t, $J = 7.3$ Hz, 1H), 7.32 (t, $J = 7.4$ Hz, 2H), 7.41 (d, $J = 7.6$ Hz, 2H), 9.52 ppm (s, 1H); ^{13}C NMR (90.6 MHz, $CDCl_3$): $\delta = 21.9$, 22.9, 27.1, 28.5, 36.3, 44.1, 56.7, 123.5, 126.1, 127.4, 128.6, 135.4, 148.0, 205.6 ppm. MS (70 eV): *m/z* (%): 226 (58) [M^+], 197 (100), 156 (52); HRMS calcd for $C_{16}H_{18}O$: 226.1358, found: 226.1356.

Received: November 6, 2006
Published online: February 20, 2007

Keywords: cyclization · domino reactions · gold · homogeneous catalysis · rearrangement

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[16] Addition of *t*BuOH (1.1 equiv) provided **2a** in 86% yield, while the use of MeOH produced a mixture of unidentified compounds.

[17] The rearrangement of 1,5-enyne precursors was strictly limited to substrates that contain alkenes bearing an additional substituent at C2. Attempted rearrangement of 1,2-disubstituted alkenes afforded at most trace amounts of the desired cyclopentene under the reaction conditions. In these cases, the formation of the major product can be rationalized by a sequence consisting of elimination and subsequent hydration of the triple bond.

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