Regioselective Gold-Catalyzed Allylative Ring Opening of 1,4-Epoxy-1,4-dihydronaphthalenes

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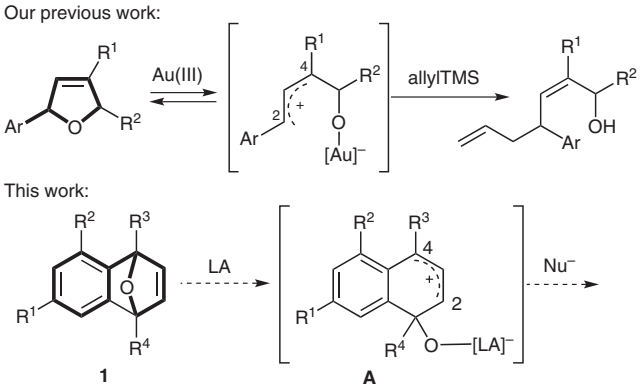
Received 17 May 2010

Abstract: In the presence of a gold catalyst, the ring opening of 1,4-epoxy-1,4-dihydronaphthalenes with allyltrimethylsilane affords allylnaphthalenes in high yield. For unsymmetrical substrates, high regioselectivity is observed in many cases. This reaction might proceed via tricyclic tetrahydrofuran intermediates which are formed stereoselectively.

Key words: allylation, ring opening, regioselectivity, naphthalene, gold catalyst

Ring-opening carbon–carbon bond formation with 1,4-epoxy-1,4-dihydronaphthalenes **1** is a valuable synthetic methodology to create highly functionalized ring systems. There appears to be no reports on the reaction of carbon nucleophiles with **1** in the presence of Lewis acids or Brønsted acids, whereas their transformations to 2-alkylated 1,2-dihydro-1-naphthols by ring-opening substitution by alkyllithium[1] and transition-metal reagents[2] (Fe,[3] Cu,[4] Pd,[5] Rh,[6] Ni[7]) has been widely developed. Normally, acid-induced ring opening of **1** affords only 1-naphthols[8] by rapid hydride shift[8d] or deprotonation of the unstable cation intermediates (cf. **A**, Scheme 1).

Recently, we have reported an unprecedented gold-catalyzed allylative ring opening of 2-aryldihydrofurans to give acyclic products[9] which might proceed via a zwitterionic intermediate comprising a benzyl cation substructure and an anionic aurate moiety (Scheme 1).[9–11]



Scheme 1 Ring openings via benzyl cation intermediates

We now suggest that the application of this method to 1,4-epoxy-1,4-dihydronaphthalenes **1** (which contain a 2-aryldihydrofuran substructure) might lead to formation of highly functionalized cyclic compounds by nucleophilic addition to cation intermediate **A** which should be formed by cleavage of the epoxy moiety of **1**.[12] Herein, we report an unprecedented direct conversion of **1** to 2-allylnaphthalenes[13] without formation of 2-alkylated-1,2-dihydro-1-naphthols. This transformation proceeds by gold-catalyzed ring opening with C–C bond formation under mild conditions in high yield and additionally with high regioselectivity for many unsymmetrical substrates.

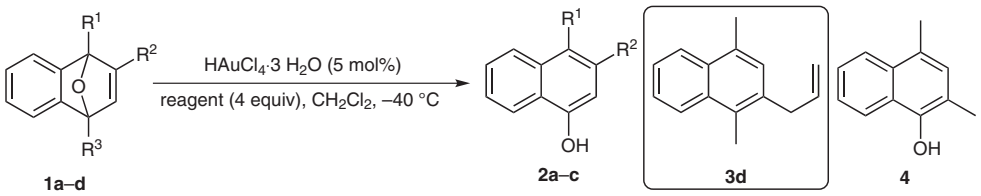
We first examined the ring opening of unsubstituted 1,4-epoxy-1,4-dihydronaphthalene **1a** in the presence of a catalytic amount of $HAuCl_4 \cdot 3H_2O$ (5 mol%) in CH_2Cl_2 at –40 °C (Table 1). Whereas the use of the gold catalyst alone gave no reaction (entry 1), the addition of either allylTMS (4 equiv, entry 2) or TMSCl (4 equiv, entry 3) afforded just 1-naphthol **2a**. Neither the desired allylated nor chlorinated products were obtained. We suppose that a rapid hydride shift[8d] in intermediate **A** to form **2a** is faster than nucleophilic addition.

Therefore, we changed the substrate to 1-methylated heterocycles **1b**,**c** with the purpose of stabilizing the cation intermediate **A** by the electron-donating methyl group. However, **1b**,**c** also did not undergo a nucleophilic addition by allylTMS but rather were converted to 1-naphthols **2b**,**c** (entries 4, 5). To prevent the hydride shift, the substrate was then modified to 1,4-dimethylated compound **1d** which is substituted at both bridgehead positions. Consequently, the reaction of **1d** with allylTMS proceeded smoothly to form the desired 2-allylnaphthalene **3d**, resulting from nucleophilic attack of the allyl group and subsequent aromatization, with 82% yield (entry 6).[14] Interestingly, chlorination with TMSCl did not proceed; rather, 2,4-dimethyl-1-naphthol (**4**) was formed with 80% yield by migration of the methyl group from C-1 to C-2 (entry 7).[15]

In order to optimize the transformation of **1d** to **3d**, various Lewis acids were tested (Table 2). With $HAuCl_4 \cdot 3H_2O$ in CH_2Cl_2, raising the reaction temperature to 0 °C resulted in a slightly lower yield (entry 1). In contrast, $NaAuCl_4 \cdot 2H_2O$ gave a mixture of **3d** and the diastereomerically pure tricyclic tetrahydrofuran **5d**[16] (Figure 1, Table 2, entry 2). An improved yield of **3d** (93%) was obtained with $AuCl_3$ (entry 3), and lower amounts of $AuCl_3$

SYNLETT 2010, No. 14, pp 2151–2155
Advanced online publication: 30.07.2010
DOI: 10.1055/s-0030-1258528; Art ID: U03810ST

Table 1 Gold-Catalyzed Various Ring Opening of 1,4-Epoxy-1,4-dihydronaphthalenes



Entry	Reagent	Starting material				Time (h)	Product	Yield (%)
		1	R^1	R^2	R^3			
1	none	**1a**	H	H	H	7	n.r.[a]	
2	allylTMS	**1a**	H	H	H	1	**2a**	53
3	TMSCl	**1a**	H	H	H	0.5	**2a**	79
4	allylTMS	**1b**	Me	H	H	1	**2b**	82
5	allylTMS	**1c**	Me	Me	H	1	**2c**	92
6	allylTMS	**1d**	Me	H	Me	2	**3d**	82
7	TMSCl	**1d**	Me	H	Me	1	**4**	80

[a] 1-Naphthol **2a** was produced above 0 °C.

(2 mol%) and allylTMS (2 equiv) gave **3d** in excellent yield of 98% (entry 4). The reaction with $AuCl_3$ was strongly influenced by the solvent. In $CHCl_3$, toluene, THF, or MeOH, no conversion was observed.

Table 2 Allylative Ring Opening of **1d** in the Presence of Various Lewis Acids[a]

Entry	Lewis acid	Temp (°C)	Time (h)	Yield (%) of **3d/4/5d**
1	$HAuCl_4·3H_2O$	0	0.5	77:0:0
2	$NaAuCl_4·2H_2O$	–40	3	34:0:22
3[b]	$AuCl_3$	–40	2	93:0:0
4[c]	$AuCl_3$	–40 to 0	4	98:0:0
5	$AuBr_3$	–40 to –5	3	60:0:0
6	$Ph_3PAuCl/AgSbF_6$	–40 to 0	3.5	77:0:0
7	$AgSbF_6$	–40 to 0	24	n.r.
8	$BF_3·OEt_2$	0	2	16:25:32
9	$Cu(OTf)_2$	r.t.	1.5	22:71:0
10	$Sc(OTf)_3$	–40 to 0	18	23:15:8
11	$In(OTf)_3$	–40 to 0	6	70:30:0
12	$Zn(OTf)_2$	–40 to 0	24	40:0:0
13	$AlBr_3$	–40 to 0	24	n.r.
14	TFA	–40 to 0	18	complex mixture

[a] Reaction conditions: Lewis acid (5 mol%) and allylTMS (4 equiv) in CH_2Cl_2.
[b] Other solvents ($CHCl_3$, toluene, THF, MeOH) gave no conversion.
[c] Conditions: 2 mol% of $AuCl_3$ and 2 equiv of allylTMS were used.

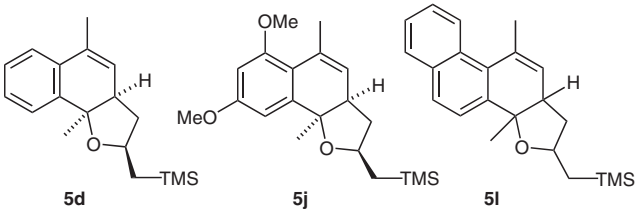
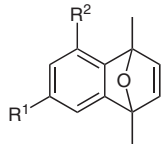
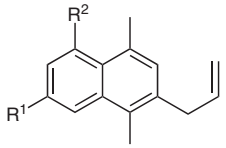
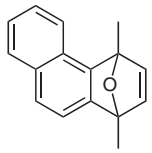
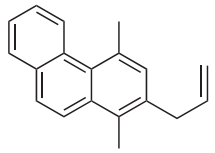
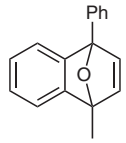
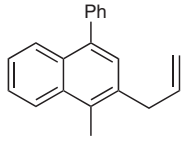


Figure 1 Tri- or tetracyclic compounds as side product

Other gold catalysts ($AuBr_3$, $Ph_3PAuCl/AgSbF_6$) were also effective to obtain **3d**, but lower reactivities were observed (entries 5, 6). With traditional Lewis acids, e.g. $BF_3·OEt_2$, $Cu(OTf)_2$, $Sc(OTf)_3$ or $In(OTf)_3$, **3d** was formed in low yield together with variable amounts of **4** and **5d** (entries 8–12). In contrast to this, $AgSbF_6$ and $AlBr_3$ gave no conversion at all (entries 7, 13), and TFA as Brønsted acid resulted in formation of a complex mixture (entry 14).

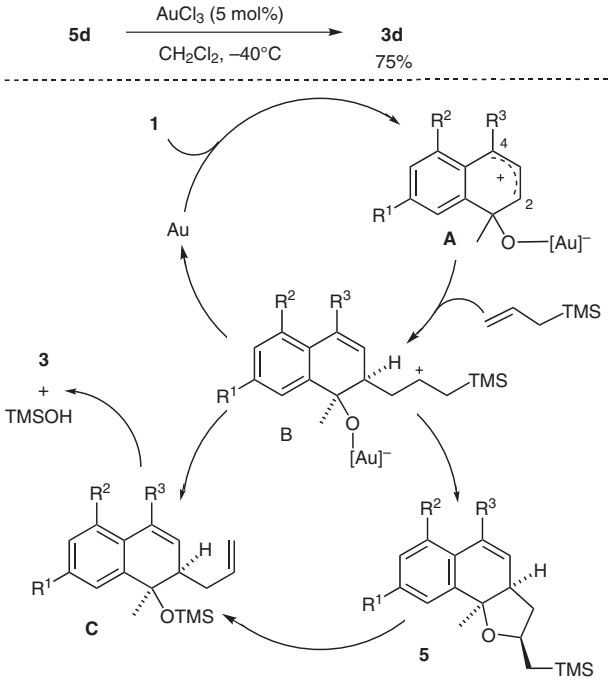
Encouraged by the high reactivity observed in the $AuCl_3$-catalyzed allylative ring opening of **1d**, we have applied the optimized conditions (Table 2, entries 3, 4) to various unsymmetrical 1,4-epoxy-1,4-dihydronaphthalenes **1e–m** which afforded the desired allylation products **3e–m** with moderate to high yield (Table 3).[14,17,18] The regioselectivity was found to be strongly substrate-dominated.[19] Compound **1e** containing a methoxy group as electron-donating substituent in the distal[20] position (R^1) of the aromatic ring underwent allylation with perfect regioselectivity and high yield (entry 1). Bromo substitution (**1f**) also favored the regioselective formation of **3f** (entry 2), whereas substrates **1g**,**h** bearing electron-withdrawing groups on the aromatic ring gave low regioselectivities even though the allylation products were obtained in high yield (entries 3, 4).

Table 3 Regioselective Allylative Ring Opening of Unsymmetrical 1,4-Epoxy-1,4-dihydronaphthalenes **1**

Entry	**1** R^1	R^2	Time (h)	Product (%, ratio **3**/**6**)
				
	1e–k			**3e–k** + regioisomer **6e–k**
1[a]	**1e** MeO	H	0.5	88 (100:0)
2[b]	**1f** Br	H	2.5	81 (88:12)
3[b]	**1g** MeO_2C	H	4	85 (31:69)
4[c]	**1h** F_3C	H	4	94 (50:50)
5[c]	**1i** H	MeO	4	93 (100:0)
6[c,d]	**1j** MeO	MeO	1	93 (100:0)
7[c]	**1k** H	Me	3	99 (91:9)
8[c]			4	
	1l			**3l** 55[e]
9[a]			0.5	
	1m			**3m** 88

[a] $AuCl_3$ (2 mol%), allylTMS (2 equiv) were used.
[b] $AuCl_3$ (5 mol%), allylTMS (4 equiv) were used.
[c] $AuCl_3$ (5 mol%), $AgSbF_6$ (15 mol%), allylTMS (4 equiv) were used.
[d] Only $AuCl_3$ (5 mol%), allylTMS (4 equiv) without $AgSbF_6$ afforded 32% of **3j** and 32% of **5j**.
[e] Tetracyclic compound **5l** was also obtained with 36% yield as single diastereomer.

In addition to these electronic effects, a large steric influence of the proximal[20] substituent R^2 on the reactivity and regioselectivity was observed. Substrates containing a substituent in this position are less reactive towards $AuCl_3$ and require the addition of $AgSbF_6$ to afford the desired allylation products in high yield (entries 5–8). The reactivity difference is particularly pronounced for the substrates **1e** and **1i** bearing a single methoxy group in the distal or proximal position (entry 5 vs. 1). Dimethoxy substitution (**1j**) also gave high yield and regioselectivity (entry 6). In the absence of $AgSbF_6$, this reaction did not go to completion, and the tricyclic compound **5j** (Figure 1) was obtained as side product with perfect regio- and stereoselectivity.[16] It is particularly noteworthy that substrate **1k** having a weak electron-donating methyl group in the proximal position underwent a high regioselective allylative ring opening in excellent yield (entry 7). As expected, the reaction of sterically hindered substrate **1l** also afforded allylated phenanthrene **3l** in perfect regioselectivity and moderate yield, accompanied by tetracycle **5l** (Figure 1).[21] In addition, 1,4-epoxy-1,4-dihydronaphthalene **1m** containing two different groups (Ph and Me) in the bridgehead positions gave only the allylated biaryl product **3m** with high yield and regioselectivity.



Scheme 2 Proposed reaction mechanism

In mechanistic terms, the electronic substituent effects on the reactivity and regioselectivity clearly point to a benzyl cation intermediate **A** formed by regioselective cleavage of the epoxy moiety in substrates **1** (Scheme 2). Intermediate **A** probably undergoes a regioselective nucleophilic attack by allylTMS at C-2 to afford β-silylcation intermediate **B**.[22] Cleavage of the carbon–silicon bond leads to the allylnaphthol derivative **C** and regenerates the gold catalyst. Finally, aromatization of **C** by elimination of TMSOH gives the allylnaphthalene product **3**. Exposure of the tricyclic tetrahydrofuran **5d** to $AuCl_3$ shows that this side product is also a precursor of allylnaphthalene **3d**. Thus, trapping of the β-silylcation **B**[23] by the oxygen atom may lead to the formation of **5** which then undergoes a ring opening, possibly catalyzed by gold, to afford **C**. Further experiments to elucidate this intriguing mechanistic proposal are in progress.

In conclusion, we have achieved an unprecedented gold-catalyzed C–C bond formation of 1,4-disubstituted-1,4-epoxy-1,4-dihydronaphthalenes **1** with allyltrimethylsilane which affords allylnaphthalenes **3** with excellent yield. This allylative ring opening requires the presence of substituents at both bridgeheads of the starting material and therefore enables the construction of highly substituted naphthalene derivatives. Moreover, the allylation takes place with high regioselectivity when unsymmetrical sub-

strates containing electron-donating groups on the aromatic ring, or an aryl group at the bridgehead are used. This regioselectivity is difficult to achieve by reported procedures.[18] The gold-catalyzed allylative ring opening of 1,4-epoxy-1,4-dihydronaphthalenes **1** also proceeds via tricyclic tetrahydrofurans **5** which are formed in a highly stereoselective manner. We continue to expand the scope of Lewis acid catalyzed nucleophilic ring-opening reactions for regio- and stereoselective construction of complex target molecules.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

This work was partially supported by Grant-in-Aid for Scientific Research (A) from the Japan Society for the Promotion of Science (JSPS) and Ritsumeikan Global Innovation Research Organization (R-GIRO) project.

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(13) For a two-step synthesis of 2-alkyl-1-naphthols by Pd-catalyzed ring opening of 1,4-epoxy-1,4-dihydronaphthalenes and subsequent oxidation, see ref. 5j.
(14) **General Procedure for the Allylative Ring Opening to Synthesize 3d–m**
Procedure A
To a solution of the substrate (0.2 mmol) in CH_2Cl_2 (2 mL) were added allylTMS (0.8 mmol) and $AuCl_3$ (0.01 mmol) at –40 °C under nitrogen. After being stirred until reaction was completed, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography using hexane–EtOAc (50:1) to give the pure allylation product.
Procedure B
To a solution of the substrate (0.2 mmol) in CH_2Cl_2 (2 mL) were added allylTMS (0.8 mmol), $AgSbF_6$ (0.03 mmol), and $AuCl_3$ (0.01 mmol) at –40 °C under nitrogen. After being stirred until reaction was completed, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography using hexane–EtOAc (50:1) to give the pure allylation product.
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(18) Regioselective synthesis of 2-alkylated-1,2-dihydro-1-naphthols from unsymmetrical substrates could be only accomplished with Rh catalysts, see ref. 6d.

(19) Regiochemistry of **3e**–**m** was determined by NOE experiments.
(20) In this paper, the same expressions as in ref. 4c are used. The position of R^1 in substrates **1e**–**k** is termed distal in relation to the dihydrofuran moiety. The position of R^2 is termed proximal.
(21) The relative configuration of **5l** could not be assigned.
(22) Reaction of **1d** with crotyltrimethylsilane afforded 1,4-dimethyl-2-(1-methylallyl)naphthalene with 38% yield, which indicates that the allyl nucleophile directly attacks at C-2 of **A**. The formation of **3** by allylation at C-4 and subsequent Cope rearrangement is disfavored by the steric hindrance at C-4, and the high activation barrier for the Cope rearrangement of 1,5-dienes which usually requires strong heating.
(23) Examples for the trapping of β-silyl cations to give cycloadducts: (a) Nishitani, K.; Harada, Y.; Nakamura, Y.; Yokoo, K.; Yamakawa, K. *Tetrahedron Lett.* **1994**, *35*, 7809. (b) Sugita, Y.; Kimura, Y.; Yokoe, I. *Tetrahedron Lett.* **1999**, *40*, 5877.