Annulation Reactions

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Efficient Generation of *ortho*-Naphthoquinone Methides from 1,4-Epoxy-1,4-dihydronaphthalenes and Their Annulation with Allyl Silanes**

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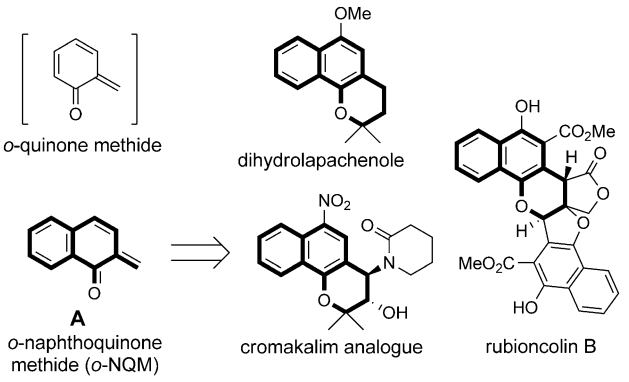
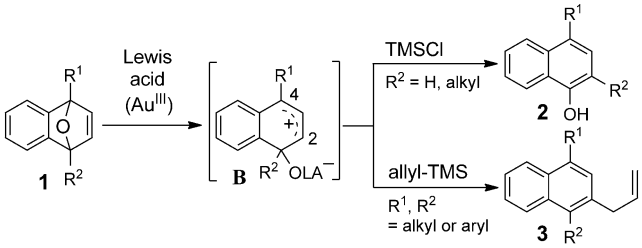
ortho-Quinone methides have a 1,3-cyclohexadiene core substituted with a carbonyl and an exomethylene group and are traditionally generated from phenol derivatives with an activated benzylic carbon atom *ortho* to the hydroxy group. They are useful and reactive intermediates for the synthesis of benzene-fused heterocycles, such as biologically active chromanes, by [4+2] cycloaddition with various electron-rich dienophiles.[1,2] The related *ortho*-naphthoquinone methides (*o*-NQMs; e.g., **A** in Scheme 1), which exist as several subtypes with respect to the positions of the carbonyl and exomethylene groups,[3–6] have also been prepared from *ortho*-substituted naphthols, although few examples of this synthetic approach have been described. 1-Naphthoquinone-2-methide derivatives, with the core structure **A**,[3] are regarded as useful precursors for the construction of 3,4-dihydro-2*H*-naphtho[1,2-*b*]pyrans (benzo[*h*]chromans) as biologically important substructures of such compounds as dihydrolapachenole,[7] which shows effective photoaffinity for cytochrome P450 3A4, rubioncolin B,[7e,8] which shows potent cytotoxic and antitumor activity, and cromakalim analogues[9] with vasorelaxant activity (Scheme 1). We now demonstrate a novel method for the generation of 1-naphthoquinone-2-methides from 1-siloxymethyl-1,4-epoxy-1,4-dihydronaphthalene derivatives and the efficient annulation of the products with allyl silanes[10] to afford a variety of dihydronaphthopyran derivatives.



Scheme 1. Construction of 3,4-dihydro-2*H*-naphtho[1,2-*b*]pyran skeletons through the use of *o*-naphthoquinone methide as a key synthon.

1,4-Epoxy-1,4-dihydronaphthalenes **1**, readily prepared by a Diels–Alder reaction between a benzyne and a furan, can be transformed into 1-naphthols **2** through a hydride shift ($R^2 = H$) or migration of the R^2 group (R^2 = alkyl) in the zwitterionic intermediate **B** resulting from the Lewis or Brønsted acid induced cleavage of a C–O bond of **1** (Scheme 2).[11] We recently discovered that the synergetic use of a Lewis acid ($HAuCl_4 \cdot 3H_2O$) and TMSCl facilitated the transformation of **1** into **2** even at a low temperature.[12] Furthermore, the unprecedented C–C bond formation associated with the epoxide-ring opening of **1** with allyltrimethylsilane (allyl-TMS) was found to give the 2-allylnaphthalenes **3** when 1,4-disubstituted 1,4-epoxy-1,4-dihydronaphthalenes **1** with alkyl and/or aryl substituents at both bridgehead positions (R^1 and R^2) were used to stabilize the intermediate **B**.[12,13]



Scheme 2. Gold-catalyzed ring opening of 1,4-epoxy-1,4-dihydronaphthalenes (**1**).[12]

We next investigated the regioselective ring-opening functionalization of unsymmetrical substrates bearing two different alkyl substituents at the bridgehead carbon atoms. Intriguingly, the reaction of 1-(*tert*-butyldimethylsiloxymethyl)-4-methyl-1,4-epoxy-1,4-dihydronaphthalene (**1a**)

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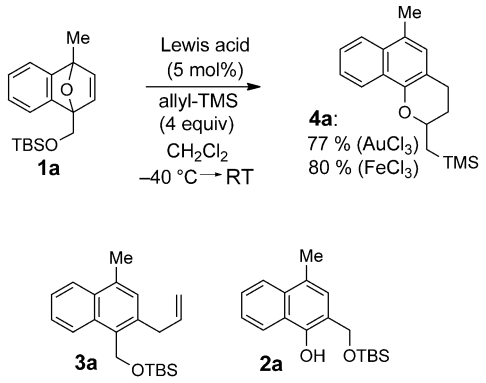
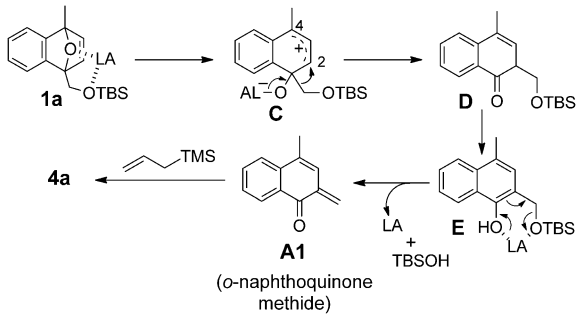


Scheme 3. Direct and selective transformation of the 1-siloxymethyl-1,4-epoxy-1,4-dihydronaphthalene **1a** into the 3,4-dihydro-2*H*-naphtho-[1,2-*b*]pyran **4a**.

with allyl-TMS in the presence of a catalytic amount of a Lewis acid in CH_2Cl_2 (−40 °C→RT) gave the dihydronaphthopyran derivative **4a** as the sole product in high yield ($AuCl_3$: 77 %, $FeCl_3$: 80 %; Scheme 3). The corresponding 1-naphthol derivative **2a**, which would result from the migration of the siloxymethyl group, and the allylated product **3a** (see Scheme 2) were not observed.

The annulation of **1a** to give **4a** can proceed via an *o*-NQM intermediate (Scheme 4). The site-selective cleavage of one C–O bond of **1a** is promoted by the coordination of the

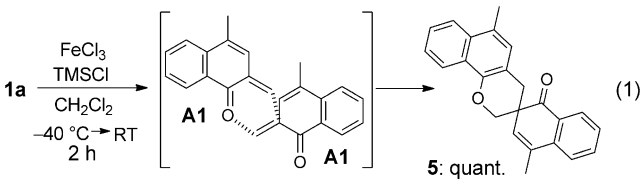


Scheme 4. Proposed annulation mechanism.

two oxygen atoms of **1a** to the Lewis acid to give a five-membered ring, which is then cleaved to give the zwitterionic intermediate **C**. Subsequent migration of the siloxymethyl group (-CH_2OTBS) and aromatization provides the 2-siloxymethyl-1-naphthol **E**. Further Lewis acid induced elimination of the silanol (TBSOH) leads to an *o*-NQM, **A1**, which undergoes annulation with allyl-TMS through a hetero-Diels–Alder reaction to give **4a** with perfect regioselectivity.[10]

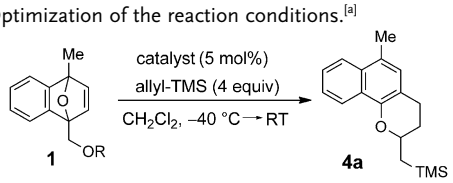
The generation of an *o*-NQM intermediate was confirmed by the self-dimerization of **A1** in the absence of allyl-TMS [Eq. (1)]. Thus, **1a** was transformed quantitatively into the spiro product **5** in the presence of $FeCl_3$ and TMSCl through [4+2] cycloaddition of the α,β-unsaturated carbonyl substructure of **A1** with the exomethylene functionality of another *o*-NQM molecule **A1**.[14]

We next optimized the reaction conditions (Table 1). The *tert*-butyldimethylsilyl (TBS) ether **1a** efficiently underwent



annulation with allyl-TMS under the catalysis of $AuCl_3$ or $FeCl_3$ in CH_2Cl_2 to provide the corresponding dihydronaphthopyran **4a** in high yield (Table 1, entries 1 and 2).[15]

Table 1: Optimization of the reaction conditions.[a]

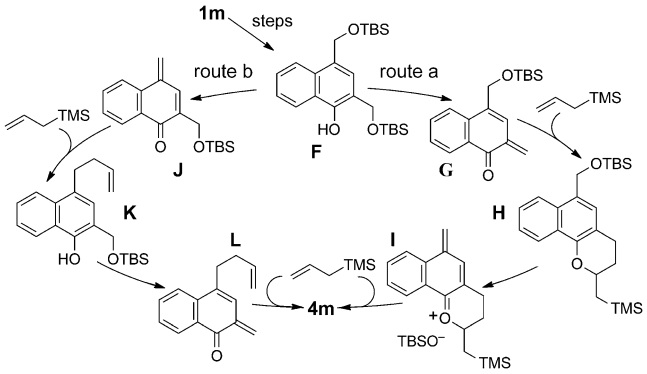


Entry	R	Catalyst	*t* [h]	Yield [%]
1	TBS (**1a**)	$AuCl_3$	2	77
2	TBS (**1a**)	$FeCl_3$	1	80
3	TBS (**1a**)	$FeBr_3$	3	73
4	H (**1b**)	$FeCl_3$	16	26
5	Bn (**1c**)	$FeCl_3$	15	77
6	Ac (**1d**)	$FeCl_3$	8	40
7	TMS (**1e**)	$FeCl_3$	3.5	32
8	TIPS (**1f**)	$FeCl_3$	5	74
9	TBDPS (**1g**)	$FeCl_3$	3.5	77
10	TBDPS (**1g**)	$AuCl_3$	16	89

[a] The reagents were combined at −40 °C, and the reaction mixture was allowed to warm slowly to room temperature until the reaction was complete.

Whereas $FeBr_3$ was also an effective catalyst (Table 1, entry 3), the use of other traditional Lewis acids, such as $FeCl_2{\cdot}H_2O$, AgOTf, $Sc(OTf)_3$, $ZnCl_2$, and $BF_3{\cdot}Et_2O$, or the Brønsted acid such as trifluoroacetic acid resulted in lower yields or no reaction even after a longer reaction time (see the Supporting Information; Tf = trifluoromethanesulfonyl). The R substituent on the oxygen atom of the side chain strongly influenced the reaction efficiency. Whereas the $FeCl_3$-catalyzed annulations of the free or acetyl-protected alcohols **1b** (R = H) and **1d** (R = Ac) led to unsatisfactory results, the benzyl ether **1c** (R = Bn) was converted efficiently into **4a** (Table 1, entries 4–6). The reaction of the corresponding trimethylsilyl (TMS) ether **1e** gave **4a** in low yield owing to the partial removal of the TMS protecting group before the migration step (**C**→**D** in Scheme 4) as a result of the Lewis acidity of $FeCl_3$. The *tert*-butyldimethylsilyl, triisopropylsilyl (TIPS), and *tert*-butyldiphenylsilyl (TBDPS) ethers, which are comparatively stable under acidic conditions, were found to be suitable for the present annulation despite the lower potential of the siloxy functionalities as leaving groups (**E**→**A1** in Scheme 4; Table 1, entries 1, 2, and 8–10). Although the TBDPS ether underwent annulation in higher yield with the catalyst $AuCl_3$ (Table 1, entry 10), substrate generality was investigated with the common and cheaper catalyst $FeCl_3$ (Tables 2 and 3).

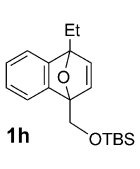
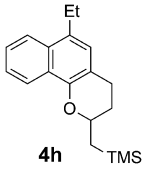
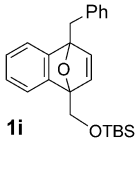
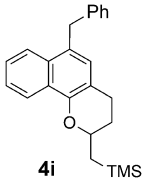
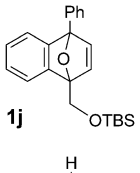
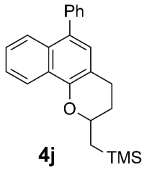
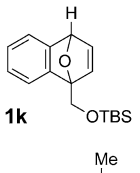
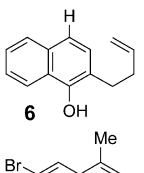
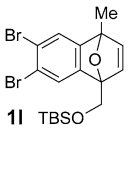
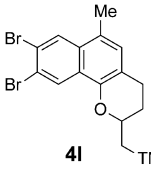
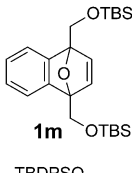
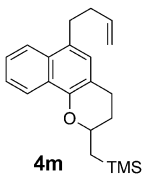
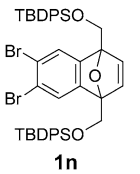
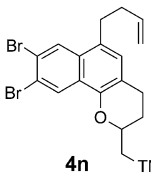
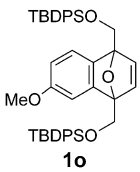
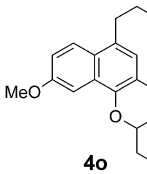
The 1-siloxymethyl-1,4-epoxy-1,4-dihydronaphthalene derivatives **1h–j** with an ethyl, benzyl, or phenyl substituent at the 4-position effectively underwent $FeCl_3$-catalyzed annulation with allyl-TMS to afford the corresponding dihydronaphthopyran derivatives **4h–j** (Table 2, entries 1–3). TMSCl as an additive was found to efficiently accelerate the annulation (Table 2, entries 1 and 2). On the other hand, the reaction of **1k**, with only a hydrogen atom at the 4-position, did not give the cyclic product; instead, 2-homoallyl-1-naphthol (**6**) was obtained in low yield (Table 2, entry 4). Substrate **1l** with two bromo substituents on the aromatic ring also underwent the annulation to afford the highly functionalized dihydronaphthopyran **4l** in high yield (Table 2, entry 5). Intriguingly, the symmetrical 1,4-bis(siloxymethyl) substrate **1m** underwent double functionalization upon treatment with excess allyl-TMS (4 equiv) to afford the 4-homoallyl-substituted dihydronaphthopyran **4m** in high yield (Table 2, entry 6). Two possible reaction mechanisms for the formation of **4m** are suggested in Scheme 5. In route a,



Scheme 5. Proposed mechanism for the formation of **4m**.

intermediate **F** resulting from ring opening and the subsequent migration of the siloxymethyl group to the adjacent carbon atom is converted into the dihydronaphthopyran **H** via *o*-NQM **G**, in analogy with the mechanism shown in Scheme 4. The subsequent elimination of the remaining TBSO moiety leads to the *para*-naphthoquinone methide (*p*-NQM) **I**, which reacts with nucleophilic allyl-TMS to give **4m**. In an alternative possible reaction pathway via *p*-NQM **J** formed by the elimination of the TBSO group at the benzylic position adjacent to C4 in **F**, a subsequent allylation to give **K** is followed by elimination of the TBSO moiety to give *o*-NQM **L** (route b). Finally, the key annulation of **L** with allyl-TMS affords **4m**. The use of only 1 equivalent of allyl-TMS led to **4m** in 50% yield, although the formation **H** or **K** was never detected. These results indicate that the rates of the steps to generate *o*-NQM (**F**→**G**, **K**→**L**) and *p*-NQM intermediates (**H**→**I**, **F**→**J**) are equally and substantially fast, and that the rate-determining step must be the ring opening of the 1,4-epoxy moiety of **1m**. The substrates **1n** and **1o** with bromo and methoxy substituents on the aromatic ring were also transformed efficiently into the corresponding homoallylated dihydronaphthopyran derivatives, **4n** and **4o**, in high yields (Table 2, entries 7 and 8).[15]

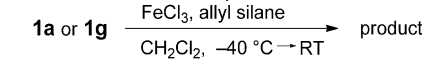
Table 2: Scope and limitations of the annulation reaction.[a]

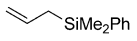
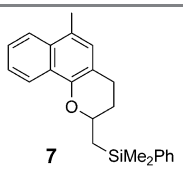
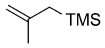
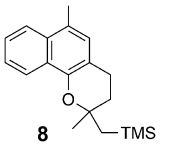
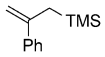
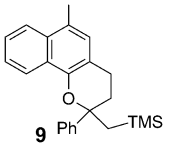
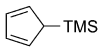
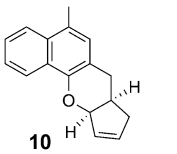
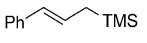
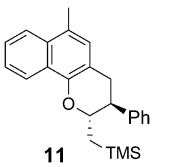
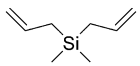
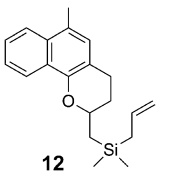
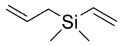
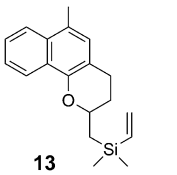
Entry	Substrate	Product	*t* [h]	Yield [%]
1	 **1h**	 **4h**	4 (0.5)	70 (82)[b]
2	 **1i**	 **4i**	12 (0.5)	89 (77)[b]
3	 **1j**	 **4j**	4.5	85
4	 **1k**	 **6**	5.5	11
5[c]	 **1l**	 **4l**	5.5	85
6	 **1m**	 **4m**	6 (2)	82 (50)[d]
7[b]	 **1n**	 **4n**	7	76
8	 **1o**	 **4o**	3.5	>99

[a] Reactions were carried out with $FeCl_3$ (5 mol%) and allyl-TMS (4 equiv) in CH_2Cl_2 at −40°C→RT unless otherwise noted. [b] TMSCl (1 equiv) was added. [c] The reaction was carried out with 1 equivalent of $FeCl_3$. [d] The reaction was carried out with 1 equivalent of allyl-TMS.

Various allyl silanes were suitable for the $FeCl_3$-catalyzed annulation when the TBS ether **1a** or the TBDPS ether **1g** were used as the substrates (Table 3).[15] With allyl(dimethyl)phenylsilane, the desired dimethyl(phenyl)silane-containing product **7** was formed efficiently, and annulations with 2-methyl- and 2-phenyl-substituted allyltrimethylsilane afforded the corresponding 2,2-disubstituted dihydronaph-

Table 3: Annulation with various allyl silanes.



Entry	Allyl silane	Product	*t* [h]	Yield [%]
1[b]		 **7**	5	84
2[b]		 **8**	9	77
3[a]		 **9**	3	72
4[b,c]		 **10**	6.5	54
5[b,c]		 **11**	1.5	86
6[b,c]		 **12**	1.5	66
7[a]		 **13**	2	76

[a] Compound **1a** was used as the substrate. [b] Compound **1g** was used as the substrate. [c] TMSCl (1 equiv) was added.

thopyrans **8** and **9**, respectively. Furthermore, the tetracyclic product **10** was obtained in 54% yield by the use of 5-trimethylsilylcyclopentadiene.[16] The annulation of **1g** with (*E*)-3-phenylallylsilane proceeded stereoselectively to afford the *trans* adduct **11**.[17] When a bis(allyl)silane was used, only monoannulation occurred to give the allylsilane-containing dihydronaphthopyran **12**. Furthermore, an allyl(vinyl)silane with two different olefin moieties reacted chemoselectively at only the allyl functionality to afford **13**.

In conclusion, we have established a $FeCl_3$-catalyzed method for the synthesis of 1-naphthoquinone-2-methides from 1-siloxymethyl-1,4-epoxy-1,4-dihydronaphthalenes and the further transformation of the products in an annulation reaction with various allyl silanes to afford biologically useful dihydronaphthopyran derivatives. Various products were obtained directly and effectively through the continuous sequence of reactions, including an exceptional hetero-Diels–Alder reaction of α,β-unsaturated carbonyl compounds and allyl silanes. This methodology can be expected to contribute to the synthesis of natural products and novel bioactive agents.

Experimental Section

General procedure: Allyl-TMS (0.8 mmol) and $FeCl_3$ (0.01 mmol) were added to a solution of the substrate **1** (0.2 mmol) in CH_2Cl_2 (2 mL) at −40 °C under argon. The reaction mixture was stirred and allowed to warm naturally to room temperature. Water was then added, and the mixture was extracted twice with CH_2Cl_2. The organic extracts were combined and dried over Na_2SO_4, then concentrated in vacuo. Purification of the residue by column chromatography on silica-gel with hexane–AcOEt (20:1) as the eluent gave the pure dihydronaphthopyran.

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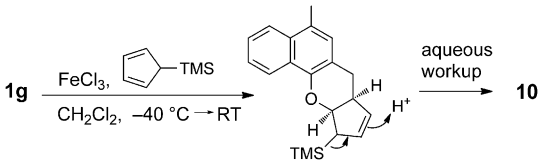
[14] The independent use of $FeCl_3$ as a Lewis acid led to a complex mixture, which included a small amount of the migration product **E**. The annulation might be accelerated by the formation of a combined Lewis acid between $FeCl_3$ and TMSCl. The formation of a combined Lewis acid derived from TMSCl and $InCl_3$ has been suggested previously: Y. Onishi, Y. Nishimoto, M. Yasuda, A. Baba, *Org. Lett.* **2011**, *13*, 2762 – 2765.

[15] Solvent effects uncovered during the optimization of the reaction conditions (for Table 1) and details regarding the scope and limitations of the reaction (Tables 2 and 3) are presented in the Supporting Information.

[16] The initial adduct bearing the allyl silane moiety may be transformed into **10** during the aqueous workup process.



[17] The annulation of **1a** (0.1 mmol) with 3-phenylallylsilane as 7:93 mixture of *E*/*Z* isomers (0.4 mmol, theoretically containing 0.028 mmol of the *E* isomer and 0.372 mmol of the *Z* isomer) gave the *trans* adduct **11** in 25% yield and the *cis* adduct **14** in 42% yield. This result and that in entry 5 of Table 3 may indicate that the final annulation step (**A1**→product in Scheme 3) proceeds preferentially by a hetero-Diels–Alder reaction rather than by nucleophilic 1,4-addition and a subsequent intramolecular cyclization of the resulting β-silyl cation **M**, since the latter reaction pathway via an sp^2-hybridized carbocation should give the same ratio of products **11** and **14** regardless of whether (*E*)- or (*Z*)-3-phenylallylsilane is used.