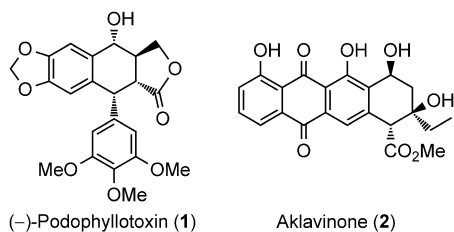


## Synthetic Methods

# An Efficient Route to Polysubstituted Tetrahydronaphthols: Silver-Catalyzed [4+2] Cyclization of 2-Alkylbenzaldehydes and Alkenes\*\*

Shifa Zhu,\* Renxiao Liang, Huanfeng Jiang, and Wanqing Wu

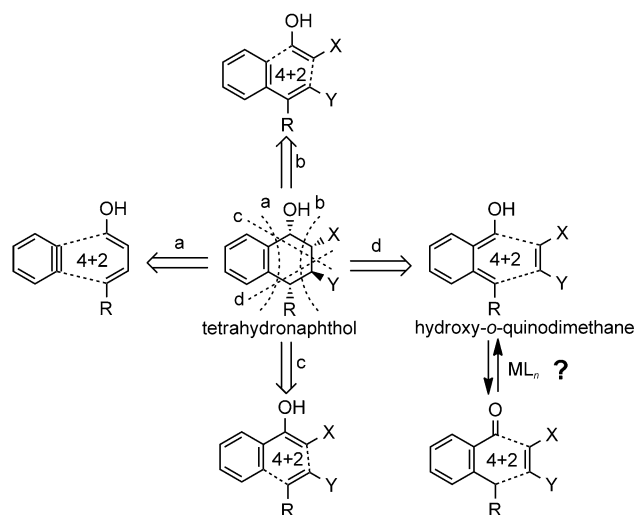
Tetrahydronaphthol is the core structure of many naturally occurring, biologically active substances<sup>[1]</sup> such as (–)-podophyllotoxin (**1**) and aklavinone (**2**; Scheme 1). Among them,



**Scheme 1.** Naturally occurring compounds containing tetrahydronaphthol.

(–)-podophyllotoxin (**1**) is an important member of the lignan class of natural products and it has shown potent cytotoxic activity against various cancer cell lines.<sup>[2,3]</sup> Aklavinone (**2**) is one of the very important precursors common to the formation of the clinically significant anthracyclines, daunomycin, doxorubicin, carminomycin, aklavin, and aclacinomycin A.<sup>[4]</sup> However, because of the easy elimination of the benzylic hydroxy group and the difficulties in controlling the stereoselectivities of substituents on the tetrahydronaphthol ring, the efficient and stereoselective synthesis of this group of compounds remains a challenge in organic synthesis.<sup>[5–7]</sup> Therefore, methods for the synthesis of tetrahydronaphthol derivatives, especially the polysubstituted ones, would be of great importance.

It is well known that [4+2] cyclization reactions are the most efficient and atom-economic way to construct a six-membered ring.<sup>[8]</sup> We therefore based our retrosynthetic analysis on a [4+2] approach. As shown in Scheme 2, there are four different [4+2] approaches, namely paths a–d. Path a requires the generation of benzyne and 1,3-butadienol, both



**Scheme 2.** Retrosynthetic analysis of tetrahydronaphthol.

of which are unstable chemical species. Paths b and c involve the disruption of the aromaticity of the benzene ring during the course of the reaction, which is energetically unfavorable. Path d involves an alkene and benzo-1,3-butadienol (also called hydroxy-*o*-quinodimethane) as synthons. Although the aromaticity of the benzene ring remains intact for path d, the hydroxy-*o*-quinodimethane, which is also an unstable chemical species, could rearrange quickly to 2-alkylbenzaldehyde. The success of this strategy would rely strongly upon the generation of the unstable hydroxy-*o*-quinodimethane species from 2-alkylbenzaldehyde. Although photoinduced enolization of 2-alkylbenzaldehyde has been reported in the literature to produce the corresponding hydroxy-*o*-quinodimethane, the photolysis reaction is highly limited because the reaction conditions are not applicable for irradiation-sensitive groups or substrates such as styrene derivatives and the halides.<sup>[7]</sup> The reported reactions typically involve very simple substrates or rather special reaction conditions.<sup>[9]</sup>

In the past decades, transition metals have shown exceptional efficiency in catalyzing a variety of chemical transformations such as cross-coupling,<sup>[10]</sup> ring-closing metathesis,<sup>[11]</sup> and Diels–Alder reactions,<sup>[12]</sup> as well as the enolization of carbonyl compounds.<sup>[13]</sup> And we were curious about the possibility of producing hydroxy-*o*-quinodimethanes by the transition-metal catalyzed enolization of 2-alkylbenzaldehyde with the ultimate aim of synthesizing polysubstituted tetrahydronaphthol (Scheme 2, path d). We anticipated this method development to lead to the development of a practical and general method for the synthesis of benzannulated systems such as those found in the lignans.

[\*] Prof. Dr. S. F. Zhu, R. X. Liang, Prof. Dr. H. F. Jiang, Dr. W. Q. Wu  
 School of Chemistry and Chemical Engineering  
 South China University of Technology  
 Guangzhou, 510640 (P. R. China)  
 E-mail: zhushf@scut.edu.cn

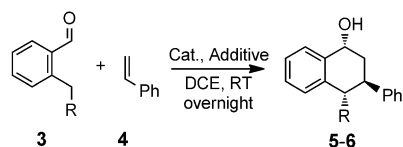
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Initial efforts were made to systematically investigate various catalytic reaction conditions for the cyclization of 2-alkylbenzaldehyde and styrene. Silver salts were chosen as the catalysts because they were typically regarded as good catalysts for the activation of carbonyl groups and C=C bonds. 2-Methylbenzaldehyde (**3a**) was initially tested for the cyclization by reacting it with 5.0 equivalents of styrene. When the reaction was conducted in DCE at room temperature with 5 mol% of AgNTf<sub>2</sub> as the catalyst, the desired product **5a** was not detected (Table 1, entry 1). It is supposed

**Table 1:** Optimization of the reaction conditions.<sup>[a]</sup>



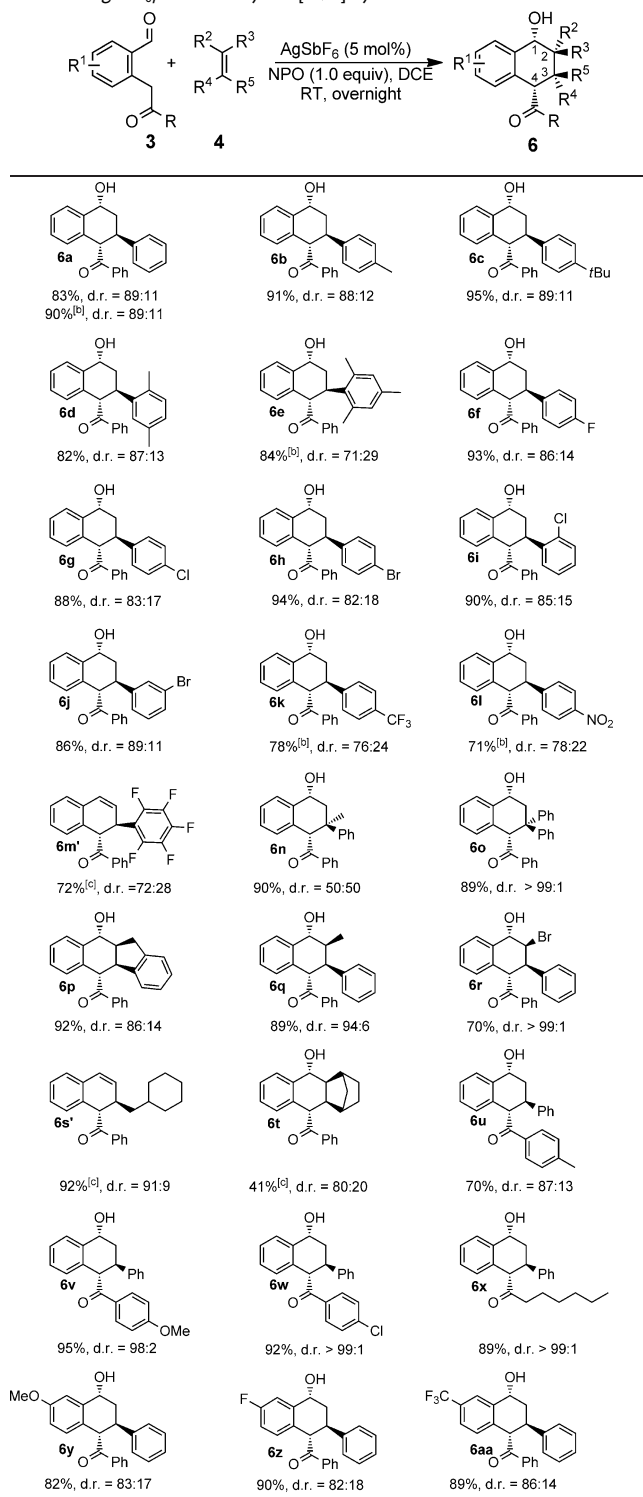
Entry	R ( <b>3</b> )	Cat.	Additive	Yield [%] <sup>[b]</sup>	d.r.
1	H ( <b>3a</b> )	AgNTf <sub>2</sub>	–	n.d. ( <b>5a</b> )	–
2	Ph ( <b>3b</b> )	AgNTf <sub>2</sub>	–	n.d. ( <b>5b</b> )	–
3	COPh ( <b>3c</b> )	AgNTf <sub>2</sub>	–	trace ( <b>6a</b> )	–
4	COPh ( <b>3c</b> )	AgOTf	–	23 ( <b>6a</b> )	–
5	COPh ( <b>3c</b> )	AgSbF <sub>6</sub>	–	34 ( <b>6a</b> )	–
6	COPh ( <b>3c</b> )	AgSbF <sub>6</sub>	DBP <sup>[c]</sup>	62 ( <b>6a</b> )	9:1
7	COPh ( <b>3c</b> )	AgSbF <sub>6</sub>	PNO	trace ( <b>6a</b> )	–
8 <sup>[d]</sup>	COPh ( <b>3c</b> )	AgSbF <sub>6</sub>	NPO	83 ( <b>6a</b> )	9:1
9 <sup>[d]</sup>	COPh ( <b>3c</b> )	AgSbF <sub>6</sub>	NPO <sup>[e]</sup>	58 ( <b>6a</b> )	9:1
10 <sup>[d]</sup>	COPh ( <b>3c</b> )	AgSbF <sub>6</sub>	NPO	90 ( <b>6a</b> ) <sup>[f]</sup>	9:1
11 <sup>[d]</sup>	COPh ( <b>3c</b> )	AgSbF <sub>6</sub>	NPO	92 ( <b>6a</b> )	8:1
12	COPh ( <b>3c</b> )	AgNTf <sub>2</sub>	NPO	12 ( <b>6a</b> )	–
13	COPh ( <b>3c</b> )	AgOTf	NPO	50 ( <b>6a</b> )	–

[a] Unless otherwise noted, the reaction was performed in DCE at RT for 12 h using 5 mol% catalyst and 1.0 equiv additive under N<sub>2</sub>. The molar ratio of **3**/**4** = 1:5. [**3**] = 0.25 M. [b] Yield determined by <sup>1</sup>H NMR spectroscopy. [c] 2,6-Dibromopyridine (DBP) [d] Yield of isolated product. [e] 0.5 equiv NPO. [f] 45 °C. [g] 80 °C, 3,4-dihydronaphthalene **6a'** obtained. DCE = 1,2-dichloroethane, Tf = trifluoromethanesulfonyl.

that the low acidity of the methyl group in **3a** makes this substrate difficult to enolize. To enhance the acidity of the substrates, a phenyl group (**3b**) and carbonyl group (**3c**) were introduced. When 2-benzylbenzaldehyde (**3b**) was used under the same reaction conditions, the desired product **5b** was not detected (entry 2). However, trace amounts of the desired product **6a** were detected when utilizing **3c** as the substrate (entry 3). Encouraged by this observation, we then conducted the systematic screening of the reaction conditions by using **3c** as the substrate. The anions of the silver salts play an essential role in the catalytic activities (entries 3–5). In contrast to the weakly coordinating NTf<sub>2</sub>, more ionic silver salts gave better yields of **6a**. For example, the yields were 23% and 34% for AgOTf and AgSbF<sub>6</sub>, respectively (entries 4 and 5). This trend could be explained by the fact that the more ionic silver salts coordinated the carbonyl oxygen atom more strongly than the less ionic silver salts, thus the former catalyzed the enolization more efficiently. Trying to increase the reaction yields by increasing the reaction temperature resulted in a complex reaction mixture. The use of an organic base such as triethylamine (TEA), pyridine, *N,N*-dimethyl-

aminopyridine (DMAP), and 2,6-dimethylpyridine, to assist the enolization process proved to be unhelpful (see entries 6–9 in Table S1 in the Supporting Information). These results could be attributed to the strong coordinating capability of the nitrogen atoms of these bases, thus poisoning the silver catalysts. However, the more weakly coordinating base, 2,6-dibromopyridine (DBP), furnished the desired product in 62% yield (entry 6). This positive result is consistent with the aforementioned hypothesis of poisoning, so we targeted those bases that are weakly coordinating. Recently, Zhang and co-workers reported that pyridine *N*-oxide derivatives served as weak bases in the gold-catalyzed cycloisomerization of (2-ethynylphenyl)alkynes.<sup>[14]</sup> Inspired by this work, we turned to pyridine *N*-oxide derivatives, but a negative effect was observed when pyridine *N*-oxide (PNO) was added as additive (entry 7). The even more weakly coordinating 4-nitropyridine *N*-oxide (NPO) was then used, and to our surprise the yield of **6a** increased to 83% (entry 8). The yield fell to 58% when the amount of NPO was lowered to 0.5 equivalents (entry 9). Higher temperature (45 °C) furnished the product in better yield (90%; entry 10), and dehydration was observed when the temperature was increased to 80 °C. The 3,4-dihydronaphthalene **6a'** was obtained in 92% yield with a d.r. of 8:1 (entry 11). When 1.0 equivalents of NPO were added to the systems using AgNTf<sub>2</sub> and AgOTf, the same trends were observed, albeit with lower yields than those obtained with AgSbF<sub>6</sub> (entries 12 and 13). All the results clearly illustrated that NPO had a remarkably positive effect on the transformations. The control reactions revealed that a silver salt is essential for the reaction (see entries 22 and 23 in Table S1). It was noted that only two diastereoisomers were obtained (d.r. 9:1). The structure of the major isomer was determined by single-crystal X-ray analysis (see Table S5 in the Supporting Information), which showed that the hydroxy and carbonyl groups are *syn* relative to each other, and the phenyl group is *anti* relative to the hydroxy and carbonyl groups.

With the optimized reaction conditions (Table 1, entries 8 and 10) in hand, the substrate scope was examined. As summarized in Table 2, the catalytic process could be successfully applied to different kinds of alkene substrates and a variety of 2-ethanone benzaldehydes **3**. For example, in addition to styrene, various styrene derivatives could be effectively reacted with 2-(2-formyl-phenyl)ethanone (**3c**; Table 2, **6b–m'**) as well. The yields were generally higher than 70%, and the d.r. values of the products derived from styrenes substituted with electron-donating groups are higher than those obtained from styrenes substituted with electron-withdrawing groups. Higher temperatures gave lower diastereoselectivities and bulky substrates gave worse diastereoselectivities. For example, the d.r. values for 4-CF<sub>3</sub>- and 4-NO<sub>2</sub>-substituted styrenes were 76:24 and 78:22, respectively (**6k** and **6l**), and 2,4,6-trimethylstyrene gave a diastereoselectivity of 71:29 for **6e**. Notably, the reaction could proceed smoothly by simply enhancing the temperature to 80 °C, even for the extremely electron-deficient pentafluorostyrene. However, in this case the elimination alkene product **6m'** was obtained instead in good yield; presumably the higher temperature promoted the elimination of the hydroxy group. The

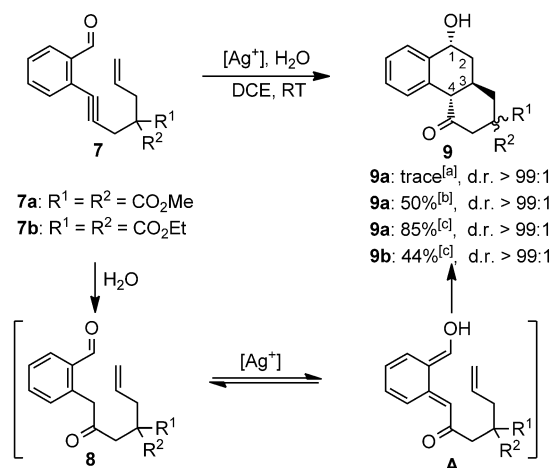
**Table 2:** AgSbF<sub>6</sub>/NPO-catalyzed [4+2] cyclization of **3** and **4**.<sup>[a]</sup>


[a] Unless otherwise noted, the reaction was performed in DCE at RT for 12 h using 5 mol % catalyst and 1.0 equiv NPO under N<sub>2</sub>. **3/4** = 1:5.

[b] = 0.25 M. The yields refer to isolated products. The d.r. values, based on the difference of C3 center, were determined by <sup>1</sup>H NMR spectroscopy. DCE = 1,2-dichloroethane, Tf = trifluoromethanesulfonyl. [c] The reaction was set at 45 °C. [c] The reaction was set at 80 °C.

d.r. value for **6m'** was 72:28. For styrenes bearing the substituents on the alkene C=C bonds, the reactions proceed smoothly (**6n–r**). For example,  $\alpha$ -methyl- and  $\alpha$ -phenylstyrene, furnished the desired products **6n** and **6o**, respectively, in excellent yields. However, the former gave almost a 1:1 diastereoselectivity, whereas the latter resulted in almost exclusively a single isomer. For the styrenes a substituent at the  $\beta$  position, both the yields and d.r. values were excellent (**6p–r**), especially for the cases **6q** and **6r**. It is worth noting that a bromine atom was introduced in the case of **6r** and can serve as a functional group for additional transformations. When using similar reaction conditions at an increased temperature (80 °C), aliphatic alkenes, which are typically challenging substrates, were also successfully converted into the desired tetrahydronaphthol or dihydronaphthalene products (**6s'** and **6t**). For terminal cyclohexylpropylene, the dihydronaphthalene **6s'** was obtained with excellent yield and diastereoselectivity. When norbornene was used under the same reaction conditions, the desired tetrahydronaphthol **6t** was obtained instead in a relatively lower yield and selectivity. Trying to expand the substrates to acrylate or vinyl ether proved unsuccessful. We also noted that in going from the parent 2-(2-formylphenyl)ethanone (**3c**) to the more substituted substrates, the reactions proceed efficiently (**6u–aa**). Both electron-donating and electron-withdrawing groups on the phenyl rings had little effect upon the product yield. In the case of **6x**, in which an octanophenone (aliphatic ketone) was used instead of aromatic ketone, both the yield and diastereoselectivity were excellent.

Having established the intermolecular reaction as a reliable and efficient process, we then proceeded to develop the intramolecular version aimed at the tricyclic tetrahydronaphthol. To realize this, the benzaldehydes **8** having a terminal C=C bond were employed (Scheme 3). The aldehydes **8** could be efficiently accessed by the hydrolysis of the enynals **7**, which can be easily synthesized from 2-



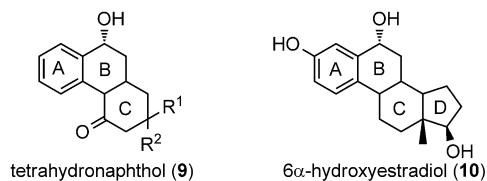
**Scheme 3.** Intramolecular annulation. The reaction was performed in DCE at RT for 12 h using 5 mol % catalyst, 2.0 equiv H<sub>2</sub>O, and N<sub>2</sub>. The yields refer to those of isolated products. The d.r. values, which are based on C3, were determined by <sup>1</sup>H NMR spectroscopy.

[a] AgSbF<sub>6</sub> + NPO. [b] AgSbF<sub>6</sub>. [c] AgNTf<sub>2</sub>.

bromobenzaldehyde and alkynes through the palladium-catalyzed Sonogashira coupling reaction.<sup>[15]</sup>

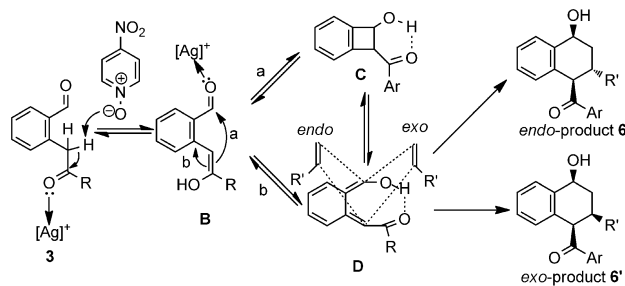
The two enynals **7a,b** were prepared for this purpose (Scheme 3). Initially, **7a** was subjected to the same reaction conditions as those used for the intermolecular reaction using NPO as an additive. However, only trace amounts of the desired product **9a** were detected by proton NMR spectroscopy. Although the starting material was consumed completely, a complex reaction mixture was observed. It is well known that pyridine *N*-oxide derivatives typically serve as oxo-transfer reagents in reactions employing alkynes.<sup>[16]</sup> So it is possible that NPO, as used herein, acted as an oxidant for the C≡C bond, rather than as a weak base for the ketone **8**. To verify this hypothesis, a control reaction without NPO was conducted.<sup>[17]</sup> In the presence of only AgSbF<sub>6</sub>, the tricyclic tetrahydronaphthol **9a** was obtained in 50% yield upon isolation, and is consistent with our speculation. The reaction may proceed via the hydroxy-*o*-quinodimethane intermediate **A**, which results from the enolization of **8a**. The yield of **9a** can be further improved to 85% by utilizing AgNTf<sub>2</sub> as the catalyst. Under the same reaction conditions, **7b** could be transformed into the desired product **9b** in 44% yield.

It is interesting to note that the tricyclic compounds **9a** and **9b** have the same ABC ring skeletons as 6 $\alpha$ -hydroxyestradiol (**10**; Scheme 4), which is one of the female sex hormones estradiol. Estradiol derivatives are the predominant form of estrogen present during a woman's reproductive years.<sup>[18]</sup>



**Scheme 4.** Tetrahydronaphthol **9a–9b** share the same ABC rings with 6 $\alpha$ -hydroxyestradiol (**10**).

With regard to the reaction mechanism, we propose the following possible pathway (Scheme 5). The reaction commences with the enolization of **3** to form the enol **B**, which then undergoes either an intramolecular aldol condensation to form the benzocyclobutanol **C** or enolization to produce the dienol **D**. As a result of the potential intramolecular



**Scheme 5.** Proposed reaction mechanism.

hydrogen-bonding interactions between the O-H and C=O groups, the intermediate **D** may form an eight-membered ring. The hydrogen-bonding interactions allow the hydroxy and carbonyl groups to remain *syn* to each other. The dienol **D** is then trapped by the intramolecular C=C bond to furnish the desired tetrahydronaphthol **6** (*endo*) or **6'** (*exo*). Based on the *endo* addition rule, which is commonly encountered in the Diels–Alder reactions, the *endo*-product **6** was the major isomer. Furthermore, the carbonyl group of the intermediate **D** and the coordination effect of the cationic Ag<sup>+</sup> may render the dienol ketone **D** electron deficient, thus making the electron-rich alkenes better  $\pi$ – $\pi$  stacking partners and thus obeying the *endo*-addition rule better.

In summary, we have developed a highly efficient and practical silver-catalyzed approach to the synthesis of poly-substituted tetrahydronaphthols through inter- or intramolecular [4+2] cyclization reactions with excellent substrate scope. Both the aromatic alkenes with different substituted groups and the challenging aliphatic alkenes were successfully converted into the corresponding tetrahydronaphthols. The addition of NPO was essential for the efficiency of the intermolecular reactions. This work represents the first highly effective and selective transition metal catalyzed synthesis of polysubstituted tetrahydronaphthols by [4+2] cyclization reactions with 2-alkylbenzaldehydes and alkenes as the starting materials. Owing to the excellent substrate scope and mild reaction conditions, this system holds considerable potential in the construction of complex molecules with tetrahydronaphthol substructures. The asymmetric version,<sup>[19]</sup> a detailed reaction mechanism, and additional applications of this reaction are underway in our laboratory.

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