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Synthesis of Spiro Compounds through Tandem Oxidative Coupling and a Framework Rearrangement Reaction

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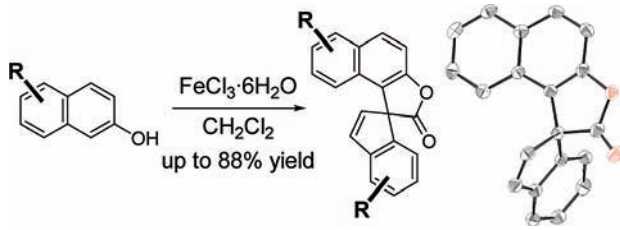
ABSTRACT



A highly efficient oxidative coupling of 2-naphthols and a rearrangement tandem reaction to afford unique spiro compounds in the presence of $FeCl_3 \cdot 6H_2O$ in up to 88% yield have been developed.

Due to the applicability and utility of binaphthyl skeletons in asymmetric synthesis and/or supramolecular chemistry, oxidative coupling reactions of 2-naphthols to 2,2′-binaphthol derivatives are one of the most well-studied reactions.[1] Although numerous coupling conditions have been reported, Fe(III) compounds, especially $FeCl_3$, are most common in this type of reaction.[2] We report an unprecedented tandem reaction, which consists of oxidative coupling of 2-naphthols and a subsequent framework rearrangement promoted by $FeCl_3 \cdot 6H_2O$, to afford extraordinary spiro compounds.[3]

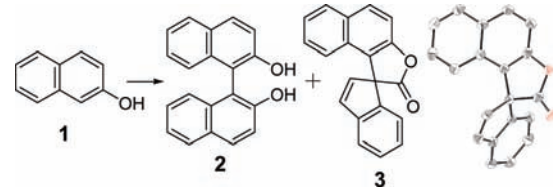


Figure 1. Unexpected formation of spiro compound (**3**) and X-ray structure of **3**.

During the coupling reaction of 2-naphthol (**1**) under longstanding $FeCl_3$ (later, we found that it absorbed moisture) in CH_2Cl_2,

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(3) Similar rearrangement products were reported as byproduct under (a) anodic oxdation: Malkowsky, I. M.; Rommel, C. E.; Wedeking, K.; Fröhlich, R.; Bergander, K.; Nieger, M.; Quaiser, C.; Griesbach, U.; Pütter, H.; Waldvogel, S. R. *Eur. J. Org. Chem.* **2006**, 241–245. (b) Cu(II) autoxidation: Ling, K.-Q.; Lee, Y.; Macikenas, D.; Protasiewicz, J. D.; Sayre, L. M. *J. Org. Chem.* **2003**, *68*, 1358–1366.

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an unknown byproduct as well as binaphthol (**2**), the major product, were generated. The byproduct had (i) a mass of 284 amu by mass spectrometry, which is two mass units less than normal product **2**, (ii) a sharp absorption at 1805 cm^{-1} in the IR spectrum, (iii) a signal at 175 ppm in ^{13}C NMR, and (iv) an unsymmetric structure in ^{1}H NMR. Despite this information, we were initially unable to determine the structure of this byproduct. Herein we report the structure of byproduct (**3**) using X-ray analysis (Figure 1). The structure contains a spiro skeleton derived from the degradation of one naphthalene ring. Due to the importance of spiro skeletons in synthetic chemistry as well as understanding of the reaction mechanism, we delved into the reaction.

Initially, we examined a variety of oxidants under reflux for 5 h using 2-naphthol (**1**) and the oxidant (5 equiv) (Table SI-1, Supporting Information). The reaction proceeded smoothly only when $FeCl_3{\cdot}6H_2O$ was used as an oxidant to afford desired compound **3** in 77% isolated yield. In contrast, other oxidants especially such as anhydrous $FeCl_3$ and $Fe(NO_3)_3{\cdot}9H_2O$, which contained water molecules, gave a messy product mixture, and **3** could not be isolated. Spiro **3** was obtained in 32% yield using a combination of anhydrous $FeCl_3$ and additional water (6 equiv).

Table 1. Solvent Effects on the Tandem Reaction of 2-Naphthol (**1**)[a]

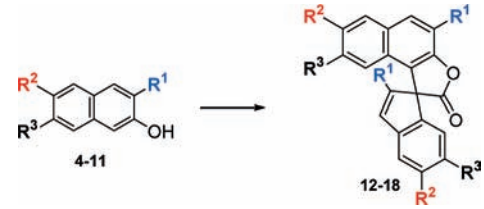
			isolated yield (%)		
entry	solvent	temp (°C)	**1**	**2**	**3**
1	DMF	60	97	–	–
2	THF	reflux	42	45	–
3	dioxane	60	65	27	–
4	DME	60	50	39	–
5	CH_3CN	60	12	63	–
6	toluene	60	–	71	15
7	$CHCl_3$	reflux	–	–	37
8	CH_2Cl_2	rt	92	8	–
9	CH_2Cl_2	reflux	–	–	77
10[b]	CH_2Cl_2	reflux	–	–	84
11[c]	CH_2Cl_2	reflux	–	–	64

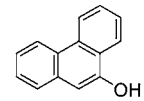
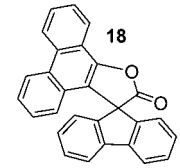
[a] Reaction conditions: **1** (40 mg), $FeCl_3{\cdot}6H_2O$ (5 equiv), in proper solvent (2 mL) for 5 h. [b] $FeCl_3{\cdot}6H_2O$ (4 equiv) was used. [c] $FeCl_3{\cdot}6H_2O$ (3 equiv) was used, and the reaction time was 12 h.

Next, we investigated the effect of solvent (Table 1). Large solvent effects were observed. Starting 2-naphthol (**1**) was recovered in DMF (entry 1), whereas the reactions were terminated at the oxidative coupling stage to give 2,2′-binaphthol (**2**) in 27−63% under ethereal solvents or acetonitrile (entries 2−5). In the case of toluene, desired spiro compound **3** was obtained as the minor product (15%) with binaphthol (71%) as the major product. In chlorinated solvents, spiro compound **3** was predominantly generated over binaphthol **2**. In particular, in dichloromethane under reflux conditions, **3** was obtained in 77% yield (entry 9), whereas at ambient temperature, the desired product was not obtained and binaphthol **2** was formed in 8% yield (entry 8). Using a reduced oxidant, a bell-shaped relationship between the yield of **3** and the equivalent of $FeCl_3{\cdot}6H_2O$ was observed (entries 9−11), and finally the optimal reaction conditions were achieved by $FeCl_3{\cdot}6H_2O$ (4 equiv) at reflux conditions in dichloromethane (entry 10).

With the optimal reaction conditions in hand, we then studied the generality of substrates for the tandem reaction using various 2-naphthols (Table 2). First, we studied a series of substituents

Table 2. Synthesis of Spiro Compounds though 2-Naphthols[a]



entry	substrate	product	yield (%)
1	**4**: R^1 = Me, R^2 = H, R^3 = H	**12**	72
2	**5**: R^1 = Ph, R^2 = H, R^3 = H	**13**	86
3	**6**: R^1 = CO_2Me, R^2 = H, R^3 = H	--	--[b]
4	**7**: R^1 = H, R^2 = Me, R^3 = H	**14**	52
5	**8**: R^1 = H, R^2 = Br, R^3 = H	**15**	70
6	**9**: R^1 = H, R^2 = OBz, R^3 = H	**16**	71
7	**10**: R^1 = H, R^2 = H, R^3 = OBz	**17**	56
8	**11** 	**18** 	88

[a] Reaction conditions: 2-naphthols **4**−**11** (0.3 mmol) and $FeCl_3{\cdot}6H_2O$ (1.2 mmol) in CH_2Cl_2 (3.0 mL) under reflux conditions for 2−24 h. (b) Binaphthol **19** was isolated in 83% yield (see Table 3, entry 2).

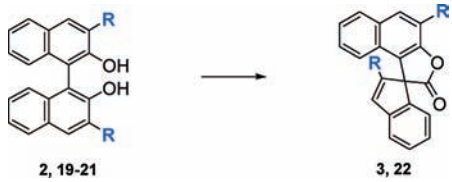
on the 3-position of 2-naphthols (entries 1−3). The electron-donating methyl group and weak electron-withdrawing phenyl group on the 3-position gave corresponding spiro compounds **12** and **13** in 72% and 86% yields, respectively (entries 1 and 2), whereas 2-naphthol possessing a strong electron-withdrawing methoxycarbonyl group was converted into corresponding binaphthol **19** in 83% yield. This data indicate that the second rearrangement step is suppressed in the presence of an electron-withdrawing group on the 3-position of 2-naphthol. In contrast, for compound **5**, the second rearrangement step proceeded faster than the first oxidative coupling step because the corresponding binaphthol could not be detected by a TLC reaction tracking. Regarding the tolerance for functional groups on the 6- or 7-position of the 2-naphthol, the corresponding tandem reactions proceeded smoothly from electron-donating groups[4] (entries 4, 6, and 7) to weak electron-withdrawing group such as bromine (entry 5). Furthermore, not only the naphthalene ring but also the phenanthrene ring is applicable for the tandem reaction in good yield (88%, entry 8).

Next we investigated the mechanistic aspects of the rearrangement step promoted by $FeCl_3{\cdot}6H_2O$ (Table 3). From entries

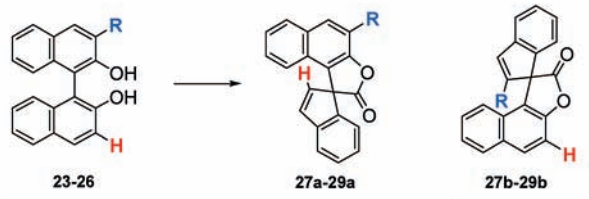
(4) Although Hammett sigma value of OAc group ($\sigma = 0.31$) indicates that OAc is an electron-withdrawing group. In this reaction, OBz group acted as an electron-donating group, probably by its large resonance effect.

1−4, we chose *C*2-symmetrical binaphthols as the starting materials. As expected (Table 2, entry 3), binaphthols with strong electron-withdrawing groups on their naphthalene rings, especially **19** and **20**, were inert under the rearrangement conditions. Compounds **2** (R = H) and **21** (R = Br) were readily transformed into corresponding spiro compounds **3** and **22** in 87% and 69% yields, respectively. From entries 5−8, a variety of binaphthols **23**−**26** with different substituents on their 3,3′-positions were examined. Binaphthol with one formyl group **23** greatly suppressed rearrangement (entry 5). In the case of compound **24**, two spiro compounds **27a** and **27b** were isolated, where **27a**, which was derived from degradation of the nonsubstituted naphthalene ring, prevailed over **27b**, which was attributed to migration of the Br-substituted naphthalene ring (**27a**/**27b** = 67/33). Binaphthols **25** and **26** were transformed into spiro compounds through rearrangement of the substituted naphthalene rings as major products (**28a**/**28b** = 24/76, **29a**/**29b** = 19/81, respectively, entries 7 and 8).

Table 3. Synthesis of Spiro Compounds though 2,2′-Binaphthols[a]



entry	substrate	product	yield (%)[b]
1	**2**: R = H	**3**	87
2	**19**: R = CO_2Me	--	NR[c]
3	**20**: R = CHO	--	NR[c]
4	**21**: R = Br	**22**	69

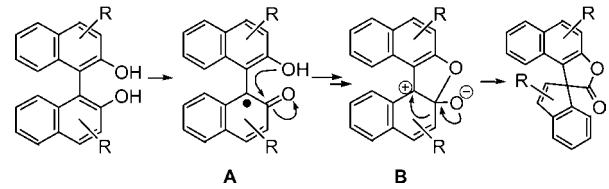


entry	substrate	product	yield (%)[b]	ratio of a/b
5	**23**: R = CHO	--/--	NR[c]	--
6	**24**: R = Br	**27a/27b**	32/19	67/33
7	**25**: R = Me	**28a/28b**	92[d]	24/76[e]
8	**26**: R = Ph	**29a/29b**	17/74	19/81

[a] Reaction conditions: 2-naphthols **2**, **19**−**21**, **23**−**26** (0.3 mmol), and $FeCl_3$·$6H_2O$ (1.5 mmol) in CH_2Cl_2 (3.0 mL) under reflux conditions for 5 h. [b] Isolated yield. [c] No reaction. [d] Because **28a** and **28b** could not be isolated by recycling HPLC, it is a combined yield of **28a** and **28b**. [e] Calculated by integrating the corresponding signals in the ^{1}H NMR.

Scheme 1 shows a plausible mechanism for the rearrangement step. Dibenzylradical intermediate **A** is generated through one-electron oxidations by $FeCl_3$·$6H_2O$. The hydroxy oxygen on the upper naphthalene reacts with the carbonyl group on the lower naphthalene of **A**. Intermediate **B** is afforded by

Scheme 1. Proposed Mechanism for the Rearrangement of 2,2′-Binaphthol Derivatives



second one-electron oxidation, and a subsequent pinacol-type rearrangement generates the corresponding spiro compounds.[3] Because electron-withdrawing groups prevent radical formation, the rate-determining step should be generation of intermediate **A**.

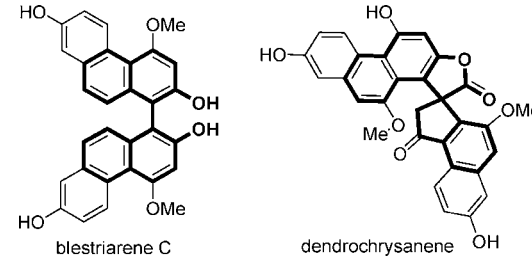


Figure 2. Biaryl and spiro compounds in natural products.

In conclusion, we have developed a highly efficient oxidative coupling of 2-naphthols and a rearrangement tandem reaction to afford unique spiro compounds in the presence of $FeCl_3$·$6H_2O$. Because the starting materials are readily available and $FeCl_3$·$6H_2O$ is inexpensive, this tandem reaction should be highly valuable in synthetic chemistry. It is especially worthwhile to note that this rearrangement reaction is associated with two types of natural products, biaryl compounds such as blestriarene C[5] and spiro compounds like dendrochrysanene,[6] which are isolated from distinct origins (Figure 2). Hence, we are currently investigating the synthesis of dendochrysanene using this rearrangement as a key step.

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Supporting Information Available: Full experimental details, characterization of all new compounds, and CIF of compound **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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