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A Succinct Synthesis of the Vaulted Biaryl Ligand Vanol via a Dienone–Phenol Rearrangement

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Dedicated to Professor Eun Lee on the occasion of his retirement and 65th birthday

Abstract: Vanol is a member of the vaulted biaryl family of ligands and it has been proven to be very effective in a number of asymmetric catalytic reactions. The previous synthesis of vanol, while effective, is limited by the cost of reagents involved. The present work evaluates three different approaches to the synthesis of 3-phenyl-1-naphthol, a key intermediate in the synthesis of vanol. The first approach has its key step as the Michael addition of a benzyl Grignard to methyl cinnamate. In the second approach the key step is the first step, a Reformatsky reaction of ethyl bromoacetate and deoxybenzoin. The final and most-efficient approach involves a dienone-phenol rearrangement of a 4-aryl-1-tetralenone generated in-situ from the reaction of 4-chloro-1-naphthol with $AlCl_3$ and benzene, and preliminary results are reported on the extension of this method to substituted vanol derivatives.

Keywords: biaryls · dienone–phenol rearrangement · Michael addition · Reformatsky reaction · vanol

Introduction

In 1993, we introduced the vaulted biaryl ligands vanol **6** and vapol **7** based on the simple premise that the nascent reaction site would be in a more defined chiral pocket than it would be in the binol ligand.[1a] The vanol and vapol ligands have been shown to be effective in chiral catalysts for a number of reactions including Diels–Alder reactions,[1] Mannich reactions,[2] Baeyer–Villiger reactions,[3] heteroatom Diels–Alder reactions,[4] the amidation[5] and imidation[6] of imines, the asymmetric reduction of imines,[7] desymmetrization of aziridines,[8] the Petasis reaction,[9] and the hydroarylation of alkenes.[10] However, perhaps the most important application of these ligands is the catalytic asymmetric aziridination of imines with diazo compounds (Scheme 1).[11,12] This reaction can give either *cis*- or *trans*-substituted aziridines with both high diastereoselectivity and high enantioselectivity. As indicated in Scheme 1, the reaction of imine **1** with ethyl diazoacetate gives *cis*-aziridine **3** in 91% *ee* with a catalyst prepared from either the vanol or vapol ligand. Although higher enantioselectivities can be obtained in toluene[11g] as well as with different types of N-protecting groups other than benzhydryl,[11h] the reaction in Scheme 1 is presented to provide a comparison of the vanol and vapol ligands[11g] with binol.[11b] Given the difference in the chiral pockets of vanol and vapol, it is quite remarkable that these ligands give the same enantioselectivity for aziridine **3**. In fact, a survey of this reaction with 12 different imines showed that the averaged difference between the two ligands over all of the substrates was 1.2% *ee*.[11g]

This similarity is not seen in any of the other reactions catalyzed by these ligands where one ligand or another usually dominates. Nonetheless, for the aziridination reaction, vanol and vapol give essentially the same outcome and this coupled with the fact that the vanol catalyst has been observed to give double the number of turnovers as the corresponding vapol catalyst[11f,13] and the fact that the molecular weight of vanol is less than that of vapol, vanol must be considered as the economically preferred ligand for the catalytic asymmetric aziridination reaction.

The original method[14] we developed for the synthesis of vanol is shown in Scheme 2, which involves the benzannulation of the phenyl carbene complex **9** with phenyl acetylene as the key step.[15] The carbene complex **9** is prepared by the addition of phenyl lithium to chromium hexacarbonyl followed by methylation with methyl triflate. The carbene complex is a crystalline red solid, and consequently can be readi-

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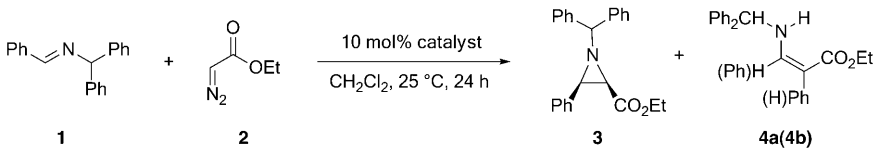
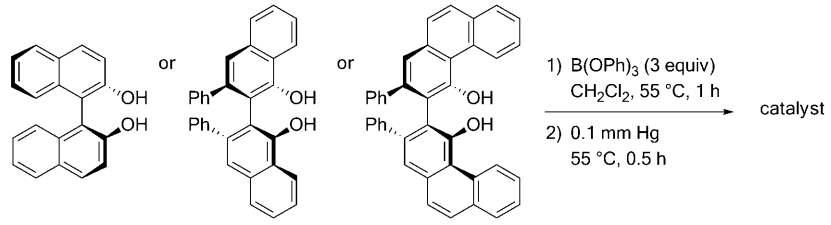


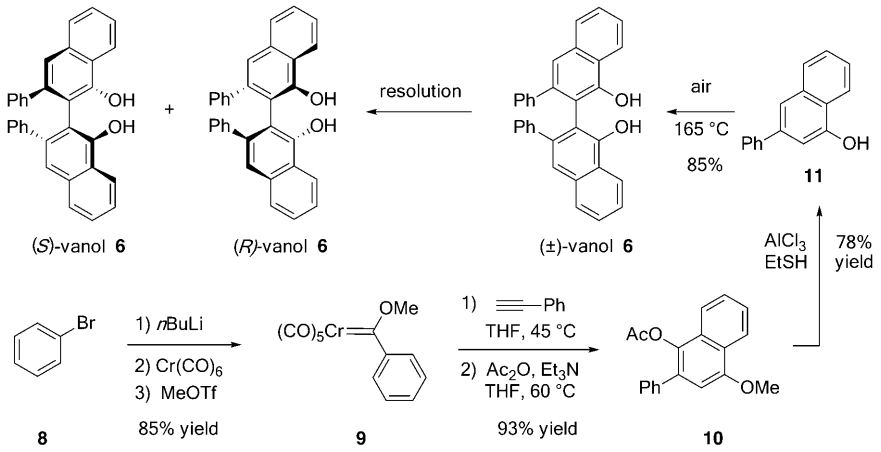
1 2 3 4a(4b)

ligand	% yield **3**	*cis*/*trans* **3**	% *ee* **3**	% yield **4**
(*S*)-binol	61	17:1	20	22
(*S*)-vanol	77	>50:1	91	5
(*S*)-vapol	67	>33:1	91	2



(*S*)-binol **5** (*S*)-vanol **6** (*S*)-vapol **7**

Scheme 1. A comparison of binol, vanol, and vapol. binol = 1,1′-binaphthalene-2,2′-diol, vanol = (*R*)-3,3′-diphenyl-2,2′-bi-1-naphthalol, vapol = (*S*)-2,2′-diphenyl-(4-biphenanthrol).



(*S*)-vanol **6** (*R*)-vanol **6** (±)-vanol **6** **11**

8 **9** **10**

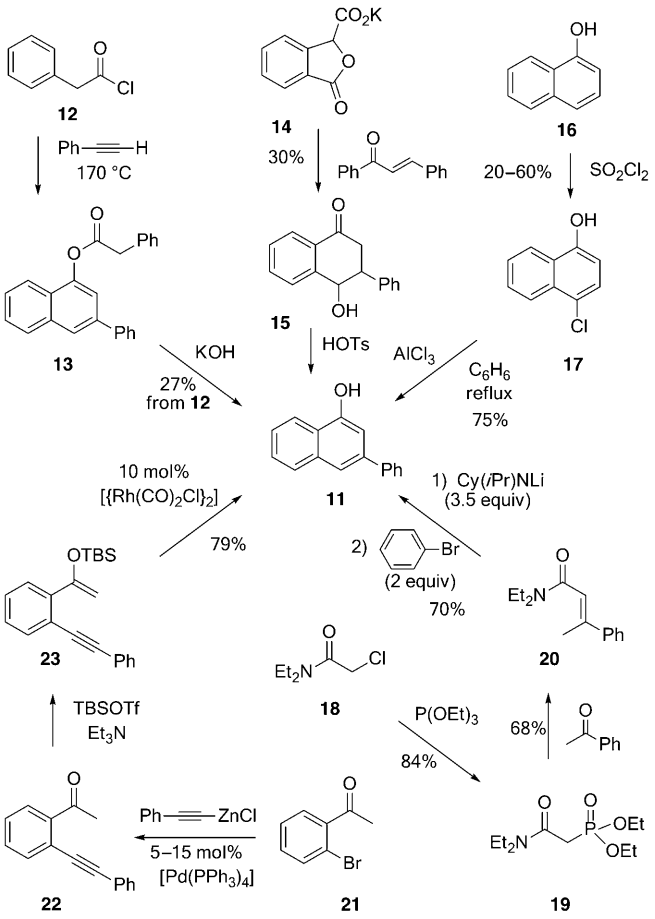
Scheme 2. The existing synthesis of vanol. Ac = acetyl, THF = tetrahydrofuran.

ly purified by crystallization and we routinely prepare this complex on 250 g scale. The resulting naphthol of the benzannulation is subsequently acetylated to give naphthalene derivative **10**, which upon exposure to a thiol in the presence of aluminum chloride, will simultaneously undergo cleavage the methyl ether and effect the reductive deacetylation to give 3-phenyl-1-naphthol **11** in high yield. This four-step process is quite efficient, giving **11** in 62% overall yield from bromobenzene and is relatively easy to scale-up to 100 g or more as chromatography is not necessary for the purification steps. However, one of the significant drawbacks of this approach is the cost of chromium hexacarbonyl, which at $6/g is not an issue on small scale, but on a 100 g scale and up it becomes prohibitive. The oxidative phenol coupling of **11** is a very cost-efficient step as air is the optimal oxidant and gives racemic vanol **6** in high yield.

Thus, in an effort to identify a more-cost-effective synthesis of vanol, the retrosynthesis was reconsidered from 3-phenyl-1-naphthol **11**.

Previous Methods for the Synthesis of 3-Phenyl-1-Naphthol 11

To date, there have been five other methods reported for the synthesis of 3-phenyl-1-naphthol **11** and these are outlined in Scheme 3. The thermolysis of phenylacetyl chloride **12** with phenylacetylene was reported by Schiefer and co-workers in 1973 to give the naphthalene derivative **13** which, after hydrolysis, led to the formation of naphthol **11** in 27% yield based on **12**.[16,17] Mechanistically, this synthesis involves a cascade of reactions beginning with ketene formation followed by a [2+2] cycloaddition with the alkyne, and then electrocyclic ring-opening of the resulting cyclobutenone and then electrocyclic ring-closure of the dienyl ketene followed by tautomerization to a naphthol, which is finally trapped by phenyl acetylchloride. Another approach reported by Janowski and Prager[18] involves the reaction of the potassium salt of phthalide-3-carboxylic acid with benzylidene acetophenone to give the tetralone **15** in 30% yield. This is a rather interesting transformation but it is not a clean reaction because **15** is accompanied by the formation of several other products. The mixture of diastereomers of **15** can be dehydrated to form 3-phenyl-1-naphthol but the yield was not reported. In addition to the fact that **15** is part of a complicated reaction mixture, this approach is not so attractive because phthalide-3-carboxylic acid is not commercially available.[19] On the other hand, the approach to 3-phenyl-1-naphthol **11** from 1-naphthol **16** via 4-chloro-1-naphthol **17** has many attractive features that would be conducive to larger scales.[20] The chlorination of 1-naphthol with sulfuryl chloride gives variable yields of 4-chloro-1-naphthol, mainly owing to the formation of 2-chloro-1-naphthol in this reaction.[20a,21,22] Undoubtedly, the conversion of 4-chloro-1-naphthol **17** into 3-phenyl-1-naphthol **11** with benzene and aluminum chloride is a mechanistically intrigu-



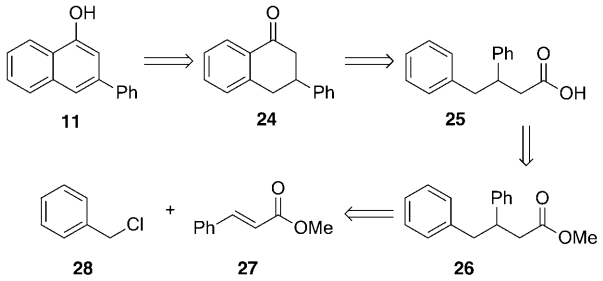
Scheme 3. Other reported syntheses of 3-phenyl-1-naphthol. Ts = *para*-toluenesulfonyl, TBS = *tert*-butyldimethylsulfonyl.

ing reaction, but it is nonetheless, quite efficient. Thus, the two-step process for the synthesis of 3-phenyl-1-naphthol **11** from 1-naphthol **16** could offer a method that is both technically simple and inexpensive, and thus will be one of the approaches that are the subject of the present work.

A rather different approach to 3-phenyl-1-naphthol **11** has been published by Watanabe et al. which involved the addition of lithiated seneciosamides to benzyne.[23] The benzyne and the lithiated amide are both generated in-situ from the same base, that is, lithium cyclohexyl(*iso*-propyl)amide. The target molecule **11** can be accessed from the α-chloroacetamide **18** in three steps in 40% overall yield. However, the anticipated costs for the reagents in this approach did not appear to be consistent with the financial profile we had envisioned for the large-scale synthesis of 3-phenyl-1-naphthol. Finally, the most recent synthesis of 3-phenyl-1-naphthol by Dankwardt involves a rhodium-catalyzed intramolecular addition of a silyl enol ether to an alkyne.[24] The necessary substrate for this reaction (**23**) is generated from a Negishi coupling of 2-bromoacetophenone **21** with metalated phenyl acetylene. The use of two different transition metals in this approach was particularly unattractive for the large scale development of this method for synthesis of 3-phenyl-1-naphthol in lieu of the other available methods.

The Michael Addition Approach to 3-Phenyl-1-Naphthol

One approach that has not been previously reported for the synthesis of 3-phenyl-1-naphthol involves the Michael addition of a benzyl organometallic species to a cinnamate ester (Scheme 4). The ready availability of the starting materials

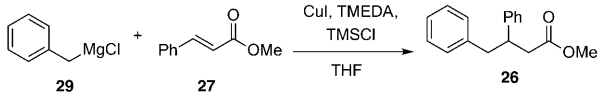


Scheme 4. 3-Phenyl-1-naphtol by Michael Addition.

for this process was tempting for a large-scale synthesis, and thus we set out to explore this approach. It has been generally observed that α,β-unsaturated esters are poor substrates for the conjugate addition of organometallic reagents owing to their relative unreactivity, especially when compared to enones and enals. This unreactivity is further exacerbated when attempts are made to coax them to react with benzyl-derived organometallics because of the propensity of the latter to undergo Wurtz coupling. The optimal procedure for the Michael addition of a benzyl group to an enoate was developed by Ferreira, van Heerden, Bezuidenhourdt, and Steenkamp[25] and this method has found use in organic synthesis.[26] The procedure involves the reaction of excess benzyl Grignard (2 equiv) promoted by copper(I) iodide (2 equiv), *N*,*N*,*N*′,*N*′-tetramethyl-ethane-1,2-diamine (TMEDA; 2 equiv), and trimethylsilyl chloride (TMSCl; 5 equiv) and an example of this procedure is given in Table 1, entry 1. Even though this method does give excellent yields of the Michael adduct, it does have several drawbacks including the use of an excess of all reagents including 2.0 equivalents of copper(I) iodide, as well as the need to maintain an intermediary temperature of −30 °C for 24 hours. The latter was included in the procedure because benzyl copper species are generally unstable above −30 °C. Herein, we describe an exploration of this reaction to see if any or all of these drawbacks are avoidable.

As a control reaction, the reaction of Grignard reagent **29** with methyl cinnamate was repeated exactly as reported in the literature on the scale of 0.8 g of methyl cinnamate **27**, which gave an 88% yield of the Michael adduct **26** which compares favorably with the 86% yield reported on a 0.13 g scale (Table 1, entry 1).[25] This reaction was reported with copper(I) iodide that had been freshly prepared[27] but we have found that this is unnecessary and that the same results can be obtained with commercial copper(I) iodide (Table 1, entry 2) and thus this change in the procedure was uniformly employed in all of the rest of the reactions in Table 1. En-

Table 1. Optimization of Michael addition of benzyl-Grignard to methyl cinnamate.[a]



29 27 26

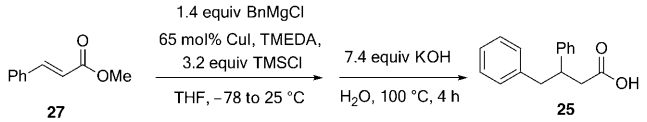
Entry	THF [ml]	**27** [g]	BnCl [equiv]	CuI [equiv][b]	TMEDA [equiv]	TMSCl [equiv]	*T* [°C]	*t* [h]	Yield **26** [%][c]
1	45	0.8	2.0	2.0[d]	2.0	5.0	−78 to −30	24	88[e]
2	45	0.8	2.0	2.0	2.0	5.0	−78 to −30	24	100
3	45	0.8	2.0	2.0	2.0	5.0	0	24	(76)
4	45	0.8	2.0	2.0	2.0	5.0	−78/6 h to	0°/15 h	89
5	40	0.8	2.0	2.0	2.0	5.0	−78 to 25	22	(33)
6	35	0.8	2.0	1.1	1.4	5.0	−78/3 h to	25°/21 h	82
7	35	0.8	2.0	0.55	0.66	5.0	−78 to 0	24	91
8	35	0.8	2.0	0.12	0.13	5.0	−78 to 25	24	(51)
9	35	0.8	2.0	0.11	0.2	5.0	−78 to 25	24	(65)
10	35	0.8	2.0	0.13	0.4	5.0	−78 to 25	24	(83)
11	35	0.8	2.0	0.20	0.4	5.0	−78 to 25	24	(64-100)[f]
12	20	0.8	2.0	0.20	0.8	5.0	−78 to 25	24	(68)
13	20	0.8	2.0	0.20	1.4	5.0	−78 to 25	7	83
14	100	4.0	2.0	0.25	1.7	5.0	−78 to 25	16	61
15	100	4.0	1.4	0.25	1.7	5.0	−78 to 25	10	69
16	100	4.0	1.4	0.25	1.7	2.5	−78 to 25	5	56
17	100	4.0	1.4	0.64	1.3	2.3	−78 to 25	9	95

[a] The Grignard reagent was prepared from benzyl chloride and magnesium turnings (2.5 equiv) at 0 to 25 °C. [b] Purchased from Aldrich and dried under vacuum (5 mmHg) at 90 °C. [c] Yield of isolated product after column chromatography on silica gel. The numbers in parentheses are from reactions that did not result in the complete consumption of enolate **27**. In these cases, the conversion of **27** is given and was determined by ^{1}H NMR spectroscopy of the crude reaction mixture by integration of the α-olefinic proton of **27** vs the γ-proton of **26**. [d] CuI was purified according to the procedure in Ref. [27]. [e] Followed the exact procedure reported in Ref. [25b] which was performed on 0.13 g and gave **27** in 86% yield. [f] A range from four different runs.

tries 3–5 in Table 1 were performed to determine if the intermediary temperature of −30 °C was necessary. Maintaining a constant temperature of 0 °C for 24 hours led to an incomplete reaction (Table 1, entry 3) while starting the reaction at −78 °C and warming to 0 °C gave complete reaction and excellent yield (Table 1, entry 4). Unfortunately, the simplest of all procedures involving starting the reaction at −78 °C and allowing the mixture to warm to ambient is not viable and leads to low conversion (Table 1, entry 5). However, quite remarkably, this procedure was effective if the amount of copper was reduced to 1.1 equivalents, with 82% yield of isolated **26** was obtained (Table 1, entry 6). Perhaps this small drop in concentration of the benzyl copper species involved was enough to disfavor the formation of bibenzyl via Wurtz coupling relative to the Michael addition. The main side-product in these reactions in Table 1 is the bibenzyl product, and its formation may account for the fact that less than 100% conversion of methyl cinnamate is observed in many cases. The use of sub-stoichiometric amounts of copper in the addition of a benzyl Grignard to an α,β-unsaturated ester or lactone has not been previously reported. Thus, we were delighted to find that we could drop the amount of copper to 0.55 equivalents and still observe complete consumption of **27** (Table 1, entry 7). Further lowering of the amount of copper to 0.12 equivalents resulted in only 51% conversion, but this could be improved to 83% conversion if the ratio of TMEDA to copper was increased by a factor of three (Table 1, entry 10). The reaction with 0.2 equivalents of copper and 0.4 equivalents of TMEDA was repeated four times and the results were variable from 64% completion to 100% completion (Table 1, entry 11). With an increase in the amount of TMEDA (1.4 equivalents), the reaction did go to completion and gave an 83% yield of isolated **26** with only 20 mol% copper(I) iodide (Table 1, entry 13). Lowering the amount of Grignard reagent to 1.4 equivalents and increasing the amount of copper to 0.25 equivalents did not give yields as high as desired (Table 1, entries 15 and 16), but increasing the amount of copper further to 0.64 equivalents gave the final optimized conditions for the reactions (Table 1, entry 17). Comparing the original procedure (Table 1, entry 1) with its finalized form (Table 1, entry 17) one can see that the net gains in the method include the reduction in the amount of benzyl halide, copper iodide, TMEDA, and TMSCl as well as the technical simplification of obviating the need for the intermediary temperature regime.

The scale-up of the reaction with the optimal procedure is shown in Table 2 and was extended from 4.0 g (Table 1, entry 17) to 20 g (Table 2, entry 1). The yield of isolated ester **26** was 95% after column chromatography on silica gel. As an alternative to the purification of the ester **26**, the crude ester was saponified with base to give the carboxylic acid **25** in 100% yield after purification by dissolution in aqueous base, extraction of the water layer with hexanes (to remove the bibenzyl pyproduct), and then acidification of the aqueous layer and extraction with diethyl ether to provide the acid **25** to be used in the next step. This procedure was also useful for the less-than-optimized reactions where the main by-product is a bibenzyl compound. With this work-up, the bibenzyl side-product can be easily removed

Table 2. Scale-up of the Michael addition of benzyl Grignard to methyl cinnamate.



27 25

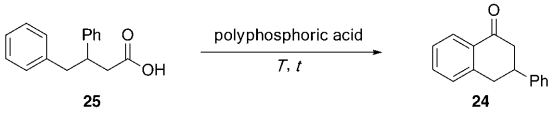
Entry	27 [g]	THF [mL]	TMEDA [equiv]	t [h]	Yield 26 [%][a]	Yield 25 [%][b]
1	20	500	1.3	9	95	–
2	20	500	1.3	10	–	100
3	100	2500	0.7	9	–	97
4	100	2500	0.7	3	–	100
5	100	2500	0.7	18	–	100

[a] Yield of isolated product after column chromatography on silica gel. [b] Purified by extraction of an aqueous KOH solution of **25** with hexanes.

without the need for column chromatography. This final procedure involving saponification was also demonstrated to be effective on a 100 g scale, which gave yields of the desired acid **25** in the range of 97–100% in three separate runs. The differences in the reaction times simply reflect differences in the size of the cooling bath and the time that it took the reaction flask to reach ambient temperature.

The intramolecular Friedel–Crafts reaction of 3,4-diphenylbutanoic acid **25** has the possibility of giving either a five- or six-membered cycloacylation product. Fortunately for our purposes, the cyclization of **25** has been reported to cleanly give the tetralone product **24** using either sulfuric acid[28] or polyphosphoric acid (PPA).[29] As the less-corrosive reagent, we choose to examine the cycloacylation of **25** with PPA and, as can be seen from Table 3, this reaction gave consistently high yields of the tetralone **24** on a scale of between 1.2–157 g. At a scale of greater than 100 g we found it necessary to carry out the reaction for at least part of the time under vacuum to remove the water formed in the reaction. The purification of the tetralone **24** by crystallization was found to be capricious, and the yields in Table 3 were determined on the crude unpurified product. Usually,

Table 3. Intramolecular Friedel–Crafts cyclization of carboxylic acid **25.**



25 24

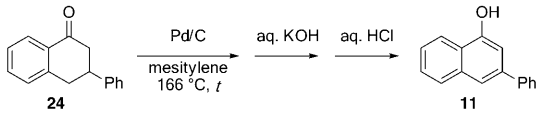
Entry	25 [g]	PPA [g]	T [°C][a]	t [h]	24 [%][b]
1	1.20	7.24	100	2.5	87.7
2	5.00	15.6	115	2	89.8
3	20.0	37.7	120	2.5	96.4
4	101	194	120	2, then vacuum 2 h[c]	98.1
5	153	301	120	4.5, then vacuum 3 h[c]	95.8
6	157	301	120	4.5,then vacuum 3 h[c]	85.4[d]

[a] Temperatures of oil bath. [b] Unless otherwise specified, the yield of the crude unpurified product. [c] Vacuum (3–5 mmHg) was applied at the indicated temperature. [d] Yield of **24** from methyl cinnamate **27**. Combined yield of **24** from crystallization and isolation from the mother liquor by chromatography column on silica gel.

attempts at crystallization lead to oiling but in one attempt, large chunks of solids were obtained (Table 3, entry 6). In this case, a single crop of **24** was taken and the remaining tetralone **24** was isolated from the mother liquor by column chromatography on silica gel to give a combined yield of 85.4% of **24** over three steps from methyl cinnamate **27**. In an attempt to eliminate one of these steps, a cycloacylation reaction was attempted directly on the ester **26**. Although Friedel–Crafts acylations on esters can be achieved in some cases,[30] in our hands, we found that the treatment of **26** with PPA resulted in a sluggish reaction and, even after 24 hours at 135 °C, the conversion was incomplete. Moreover, it was even more difficult to isolate tetralone **24** from this reaction mixture and thus this approach was not pursued further.

Numerous methods[31] have been developed for the oxidative aromatization of benzo-fused cyclohexanone derivatives and perhaps the most widely used method employs heating in a high-boiling solvent with palladium on carbon. Whilst tetralone **24** has apparently not been previously reported as a substrate for this reaction, a number of other tetralone derivatives have been aromatized in this manner in moderate to good yields.[32] Therefore, the aromatization of tetralone **24** was first investigated in refluxing *para*-cymene at 177 °C (Table 4, entry 1) and in refluxing mesitylene at 166 °C (Table 4, entry 2). On a small scale, the reaction in both solvents gave similar yields of naphthol **11** but given the propensity of *para*-cymene to form peroxides upon exposure to air, we decided to proceed with mesitylene. The reaction in (Table 4, entry 2) was nearly complete with only a trace of tetralone **24** remaining, but if the reaction time was extended to 6 hours, over-reaction occurred, with three new compounds observed by TLC. Given the cost of palladium on carbon, if the reaction in Table 4, entry 2 were to be scaled up 100-fold, the aim of inexpensive access to naphthol **11**

Table 4. Dehydrogenation of **24** in refluxing mesitylene.



24 11

Entry	24 [g][a]	Solvent [mL]	Pd/C [g][b]	t [h][c]	Yield 11 [%][d]
1	0.51	30	0.15	5	75[e]
2	1.0	30	0.27	4	77
3	5.1	50	0.30	20	38.2
4	5.1	100	0.32	20	49.5
5	18.7	200	0.98	8	21.6
6	92	1000	6.1	113	67
7	136	1500	10.8	192	54.3[f]

[a] Compound **24** was used as obtained from the Friedel–Crafts reaction without purification. [b] The ratio of Pd/C was 1:10. [c] The reaction was stopped at the indicated time. [d] Unless otherwise specified, yields are of **11** that had been purified by extraction with aqueous base and then extraction back into organic solvent after acidification. TLC indicated that none of the reaction went to completion. In entry 2, only a trace amount of the tetralone remained. [e] Reaction was carried out in *para*-cymene at 177 °C and the reported yield followed purification by column chromatography on silica gel. [f] Yield of **11** from methyl cinnamate **27**.

would not be realized. Thus, as the scale of the reaction was increased, the effect of decreasing the amount of palladium on carbon was explored. For example, increasing the amount of tetralone **24** by 19-fold but the amount of Pd/C by only 3-fold, led to a much-slower reaction with only a 22% yield of naphthol **11** (Table 4, entry 5). The majority of the mass balance was tetralone **24**. With a similar ratio of tetralone to Pd/C, the reaction on a 92 g scale only gave a 67% yield of naphthol **11** after 113 hours. No further attempts were made to optimize this reaction with increasing amounts of palladium on carbon.

The primary product before workup from the Michael addition of benzyl Grignard to methyl cinnamate is the silyl ketene acetal **30**. If this material could be oxidized into the α,β-unsaturated ester **31**, then subsequent to the Friedel–Crafts cyclization, the adduct should be in the correct oxidation state to tautomerize to the naphthol **11**. The palladium-mediated oxidation of silyl enol ethers to α,β-unsaturated enones was pioneered by Saegusa and co-workers[33] and modified by Larock and Hightower,[34] and is a very synthetically useful reaction. However, this procedure has only been sparingly applied to the conversion of ketene acetals, and even then with moderate success.[34] Nonetheless, an attempt was made to oxidize the ketene acetal **30** with Larock's procedure but this afforded only trace amounts of the α,β-unsaturated ester **31** (Scheme 5).

30 31 trace

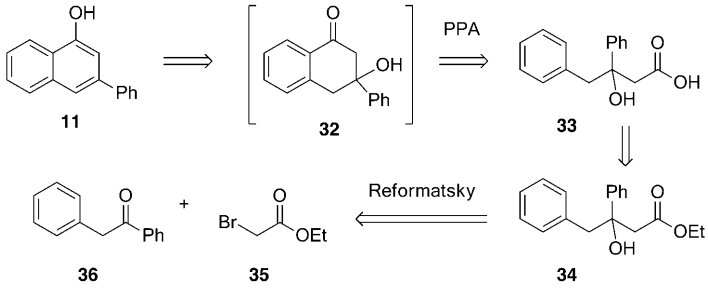
Scheme 5. Attempted oxidation of Michael adduct. DMSO = dimethyl sulfoxide.

The Michael addition route to 3-phenyl-1-naphthol **11** outlined in Scheme 4 constitutes a straightforward and efficient process from easily accessible starting materials. The overall yield of **11** is 54% (4 steps) starting from 100 g of methyl cinnamate **27**, from which 75 g of **11** can be obtained. Operationally, the whole process involves just two isolated intermediates and chromatography was not necessary to obtain pure product. Accordingly, it was possible to optimize the Michael reaction to be compatible with a large-scale synthesis in terms of reagent loading, reactions conditions, as well as workup procedures.

The process was expected to compete favorably with known methods for the preparation of vanol, but it did not meet the criteria for a practical large-scale preparation. First of all, monomer **11** was afforded in only mediocre overall yields, which was no better than the yield from the benzannulation reaction (Scheme 2). Moreover, there are a number of inherent limitations for this methodology: drastic conditions (low temperature) required by the conjugate addition reaction involving highly sensitive reagents and the difficulty in purifying tetralone **24**, which is presumably the cause of the sporadic consistency of the dehydrogenation reaction. The involvement of a costly precious metal in the dehydrogenation required unacceptably long reaction times. Thus, in light of the attendant inefficiencies, attention returned to the search for a more-suitable method for the synthesis of vanol, particularly on a large scale.

The Reformatksy Approach to 3-Phenyl-1-Naphthol

As illustrated by the dehydrogenation of tetralone **24** (Table 4), adjusting oxidation levels in the synthetic sequence resulted in an overall loss of efficiency[35] in the synthesis of 3-phenyl-1-naphthol **11**. Thus, an attractive concept was the introduction of the required oxidation level as early as possible. It was then reasoned that if the oxidation state was suitably "set" in the starting materials or in an early intermediate, such steps could be avoided. With this in mind, the idea of structure **33** came to the fore (Scheme 6), which



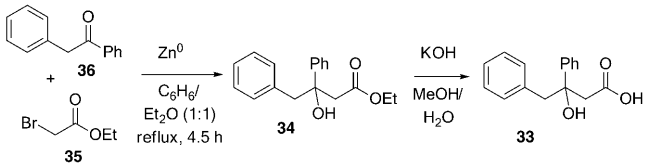
Scheme 6. Reformatsky approach to 3-phenyl-1-naphthol.

featured an oxidized β-carbon atom. Under acidic conditions, it was anticipated that the hydroxyl group could be readily eliminated during the acid-facilitated cycloacylation reaction, and therefore, the aromatic moiety could be furnished in one step. Access to the β-hydroxy acid **33** should be straightforward from the Reformatsky reaction[36] of bromo ester **35** with deoxybenzoin **36**. This approach is very appealing when compared to the Michael addition route in that it offers the replacement of the unstable organocuprate reagent requiring cryogenic conditions with a room-temperature-stable organozinc reagent.

The Reformatsky reaction of ethyl-α-bromoacetate and deoxybenzoin has been previously reported,[37] but we decided to pursue a variation of a published procedure for a closely related molecule.[38] The reaction was performed by refluxing a mixture of zinc dust, ketone **36**, and α-bromoester **35** in a mixture of benzene and diethyl ether, which gave the condensation product **34** in high yields. Hydrolysis of the ester under basic conditions gave the β-hydroxy acid **33** which could be obtained in pure form after crystallization in 82% yield over the two steps (Table 5).

The cycloacylation of the β-hydroxy acid **33** (Table 6) was first examined with the optimized conditions for acid **25** (Table 3). Heating **33** in polyphosphoric acid at 120°C for 5 hours led to complete consumption of the starting materi-

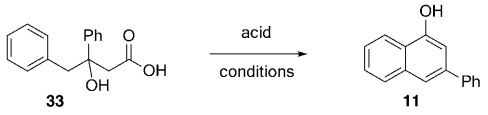
Table 5. Reformatsky reaction of deoxybenzoin.



Entry	**36** [mmol]	**35** [mmol]	Zinc(0) [mmol]	Yield **34** [%][a]	Yield **33** [%][b]
1	10	45	142	89	91
2	5	23	38	97	92
3	10	45	84	82	94
4	20	90	153	n.d.	82[c]

[a] Yield of isolated product after chromatography on silica gel. n.d. = not determined. [b] Unless otherwise specified, the yield is of material purified by base extraction. [c] Yield is over 2 steps and is the total yield of two crops crystallized from hexanes/ethyl acetate.

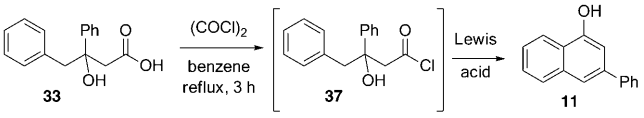
Table 6. Brønsted and Lewis acid mediated cycloacylation of acid **33**.



Entry	**33** [mmol]	Acid	Acid [mmol]	Solvent (mL)	*T* [°C][a]	*t* [h][b]	Yield **11** [%][c]
1	8.0	PPA	20 g	neat	120	5	22
2	1.35	BF_3·OEt_2	48	neat	0 to 25	24	0
					then reflux	1.5	19
3	1.28	BF_3·OEt_2	4.0	CH_2Cl_2 (20)	0 to 25	15	0
					then reflux	36	0
4	1.3	$SnCl_4$	22	neat	110	o.n.	7
5	0.51	$TiCl_4$	20	neat	reflux	13	15
6	1.31	$TiCl_4$	2.7	CH_2Cl_2 (10)	−78	5	0
					then RT	16	0

[a] The reaction in each entry went to completion at the higher temperature except for entry 4 which was already nearly complete. [b] o.n. = overnight. [c] Yield of isolated product after column chromatography on silica gel.

Table 7. Lewis Acid mediated cycloacylation of acid chloride **37**.[a]



Entry	**33** [mmol]	Lewis acid	Solvent [20 mL]	*T* [°C]	*t* [h]	Yield **11** [%][d]
1	4.70	$SnCl_4$	benzene	0	3	51.2
2	2.37	BF_3·OEt_2	CH_2Cl_2	0	3	38.8
3	2.35	$AlCl_3$	CH_2Cl_2	0	3	6.84
				RT	12	
4	2.50	$ZnCl_2$	CH_2Cl_2	0 to RT	12	6.4
				then reflux	4	
5	2.50	$FeCl_3$	CH_2Cl_2	0 to RT	12	trace
				then reflux	0.5	
6	2.50	$TiCl_4$	CH_2Cl_2	0	3	47.3
				RT	12	

[a] The acid chloride **37** was prepared by reacting **33** with 12.4 equiv of $(COCl)_2$ in 40 mL benzene. Eight equivalents of Lewis acid were used in the second step. [b] Yield is of isolated product after column chromatography on silica gel.

al; however, only a 22% yield of 3-phenyl-1-naphthol could be isolated from the crude reaction mixture. TLC analysis revealed that several other products were formed in this reaction; however, these products were not separated and identified. Likewise, the cycloacylation of acid **33** was not particularly effective with BF_3·OEt_2 as refluxing with a large excess of the neat reagent only gave a 19% yield of **11**. Other common Lewis acids that failed to give any substantial conversion into 3-phenyl-1-naphthol are indicated in Table 6. Although the product distribution from the attempts at cycloacylation of β-hydrdoxy acids of the type **33** have not been previously described in detail, it has been reported that **33** will undergo decarboxylation in refluxing formic acid[39] and that compounds closely related to **33** will form lactone products when treated with sulfuric acid[40] or PPA.[41]

Pakrashi and co-workers have reported efforts at the cycloacylation/dehydration of a β-hydroxy acid very structurally similar to **33**, but found that all attempts to induce cyclization with various reagents (including PPA) were unfruitful.[41] However, they reported that if the carboxylic acid function was first converted into an acid chloride, then the cycloacylation and dehydration to a naphthol could be effected in moderate yields (ca. 50%). This transformation was also found to be true in the present case. Conversion of the β-hydroxy acid **33** into the corresponding acid chloride and then exposure of the crude acid chloride **37** to various Lewis acids gave 3-phenyl-1-naphthol **11** in much-higher efficiencies than the direct conversion of the acid itself (Table 7). As was observed by Pakrashi and co-workers, the best that could be achieved for the two-step process was approximately 50% yield. The best yield was realized with tin tetrachloride as the Lewis acid. A number of side-products are produced in most of the reactions shown in Table 7 with the exception of entry 6. In this case, whilst titanium tetrachloride gives only a moderate yield of **11**, TLC analysis indicated that the starting material was the only other compound present in the reaction mixture. Therefore, there is the potential to further optimize this reaction for the synthesis of 3-phenyl-1-naphthol **11**. Nonetheless, because of the potential future problems in the separation and purification of **11** on a larger scale, as well as the cost concerns raised by the fact that the reaction appears likely to require the use of large excesses of Lewis acids, this approach lost its appeal and was put on hold.

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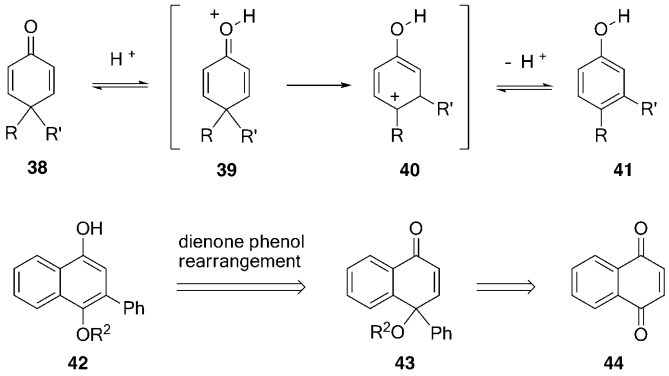
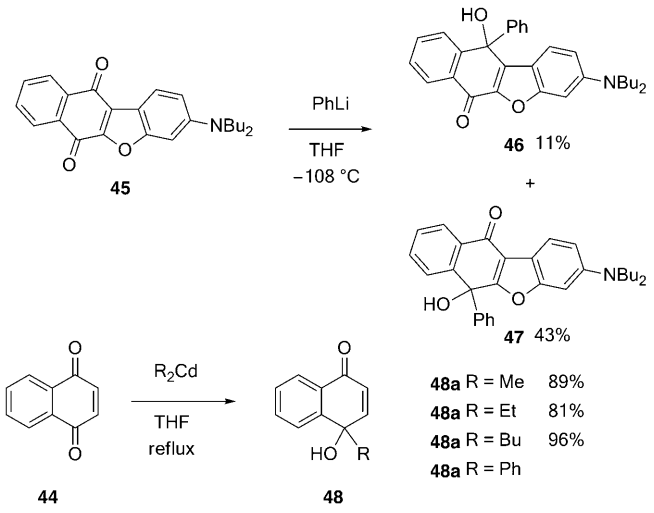
The Dienone–Phenol Approach to 3-Phenyl-1-Naphthol

As indicated in Scheme 2, our original synthesis of vanol involved the selective deoxygenation of the trisubstituted naphthalene derivative **10** to give 3-phenyl-1-naphthol **11**. It was imagined that a similar trisubstituted naphthalene derivative **42** could be obtained from a dienone–phenol rearrangement[42] of the dienone **43** which in turn could be obtained by a 1,2-alkylation of 1,4-naphthoquinone **44** (Scheme 7). The dienone–phenol rearrangement is traditionally initiated by a Brønsted acid and, in the case of the *para*-dienone **38**, the protonated species **39** undergoes a 1,2-migration of the *para*-substituent with the greatest migratory propensity and then loss of a proton provides the rearranged aromatic phenol **41** and the driving force for the reaction. This rearrangement would be expected to be particularly facile for dienones of the type **43** in which the non-migratory substituent is oxygen that would be expected to help to stabilize the intermediate carbocation.



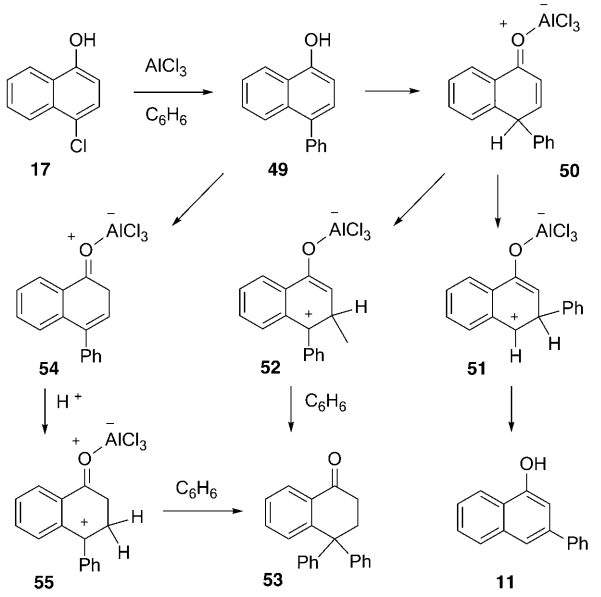
Scheme 7. Dienone phenol rearrangements of 1-naphthols.

The major anticipated problem with this approach is the 1,2-addition to the naphthoquinone **44**. It is well-known that organolithium compounds and Grignard reagents (except MeLi and MeMgBr) do not give good yields of 1,2-addition products with 1,4-quinones, but instead suffer from single-electron-transfer processes that result in the formation of the reduced quinone.[43] The only example that we have been able to find is by Yoshida and co-workers who found that phenyllithium will add to the quinone **45** to give a mixture of the regioisomers **46** and **47** in a 1:4 ratio (Scheme 8).[44] Indeed, as expected, all attempts to effect the addition of phenyl magnesium bromide, either commercial material or freshly prepared, to 1,4-naphthoquinone **44** failed. The reaction was performed at −78 °C in tetrahydrofuran and after aqueous workup a dark blue solution was formed, which quickly turned black and left a reddish-black tarry residue after removal of the solvent. Several products were detected by TLC and one was later confirmed to be the biphenyl compound. Attempts to separate and identify the other by-products failed and some seemed sensitive to air, changing to a dark-colored material that was insoluble in diethyl ether. The best direct solution to the "1,2- addition to 1,4-quinone" problem was reported by Wigal and coworkers who found that the addition of an organo-cadmium compound to 1,4-quinones gave high yields of 4-hydroxy-2,5-dienones of the type **48**.[45] They reported that a number of alkyl-cadmium reagents would give good yields in addition to 1,4-benzoquinones and 1,4-naphthoquinones but they did not examine the reaction of a diaryl cadmium with 1,4-naphthoquinone **44**. Thus, we prepared diphenyl cadmium from phenyl magnesium bromide using the standard procedure and found that upon exposure to **44**, complete consumption of the quinone was observed upon refluxing in tetrahydrofuran overnight. Workup of the reaction gave a dark green solid which contained no compounds that would elute on silica gel. Given this failure and the expense and toxicity of cadmium, the work on the approach to 3-phenyl-1-naphthol **11** outlined in Scheme 7 was abandoned.



Scheme 8. 1,2-Additions to 1,4-quinones.

The synthesis of 3-phenyl-1-naphthol **11** from 4-chloro-1-naphthol **17** shown in Scheme 3 is a mechanistically interesting reaction that involves the initial formation of 4-phenyl-1-naphthol **49** (Scheme 9).[20c] If 4-chloro-1-naphthol **17** is treated with $AlCl_3$ in benzene at room temperature, then a number of products are formed, one of which is 4-phenyl-1-naphthol **49**. It was also independently shown that the treatment of **49** with $AlCl_3$ in refluxing benzene gave **11** in 67% yield.[20b,c] The transformation of 4-phenyl-1-naphthol **49** into 3-phenyl-1-naphthol **11** is apparently a dienone–phenol rearrangement process where $AlCl_3$ triggers a tautomerization of naphthol **49** into dienone–$AlCl_3$ complex **50**.[20b] The dienone–phenol rearrangement, involving 1,2-migration of a phenyl group, would give **51** from which the loss of proton would explain the formation of 3-phenyl-1-naphthol **11**. The 4,4-diphenyl-1-tetralone **53** is often a side-product in this reaction and it can be accounted for by dienone–phenol rearrangement involving a 1,2-hydride migration in **50** to give **52** with subsequent electrophilic addition to benzene. An alternative explanation for the formation of **53** would be an

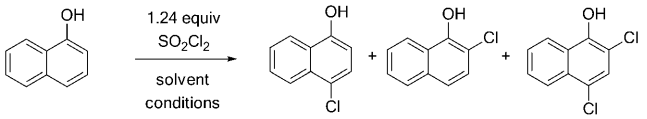


Scheme 9. Mechanism of the isomerization of **49** to **11**.

$AlCl_3$-assisted tautomerization of **49** to **54** with subsequent protonation of the alkene to give the carbocation **55** followed by electrophilic addition to benzene. The simplicity of this approach to 3-phenyl-1-naphthol **11** was deemed too-attractive not to be worthy of further investigation.

Ostensibly this is a one-step synthesis of 3-phenyl-1-naphthol **11** as 4-chloro-1-naphthol **17** is commercially available. However, 4-chloro-1-naphthol **17** is relative expensive in spite of the fact that its synthesis from 1-naphthol has been reported on a 500 kilogram (3,472 mole) scale by I. G. Farbenindustrie (Table 8, entry 1).[20a] For a synthesis of this scale, there presumably was some associated preliminary optimization and thus our study of this reaction begins with a repeat of this reported procedure but only on a 3.6 g scale (Table 8, entry 2). The formation of 2-chloro-1-naphthol **56** and 2,4-dichloro-1-naphthol **57** from this reaction have been reported,[46] but the ratio was not reported for the 500 kg scale reaction. Under the same conditions as the 500 kg scale, we found that this reaction on 3.6 g scale gave a 100:39:4 ratio of **17**/**56**/**57** and that 4-chloro-1-naphthol **17** was isolated in a slightly lower yield (35%) than that reported on 500 kg scale (40%[20a]); this difference may be because the reaction only went to 79% completion. We found that benzene was not as good a solvent as chlorobenzene, giving only a 27% yield of **17** and, in addition, it caused a switch in regiochemistry to give 2-chloro-1-naphthol as the major product. A solvent screen of tetrahydrofuran, diethyl ether, *N*,*N*-dimethylformamide, and acetonitrile revealed that all were inferior to chlorobenzene, giving more-complicated product mixtures. On the other hand, chlorinated alkanes were found to be more effective for this reaction, and thus dichloromethane, chloroform, and 1,2-dichloroethane were all screened at three different temperatures. Dichloromethane and 1,2-dichloroethane were superior to chloroform in terms of yield and the optimal conditions appeared to be at 0°C in 1,2-dichloroethane (Table 8, entry 11). The reaction under these conditions was scaled up to 100–120 g (Table 8, entries 14–16). It is fortunate that 4-chloro-1-naphthol **17** can be easily separated from **56** and **57** by crystallization or by chromatography and the yields indicated in Table 8, for most entries are of pure material that was isolated from the mixture by crystallization with hex-

Table 8. Optimization of the formation of 4-chloro-1-naphthol.



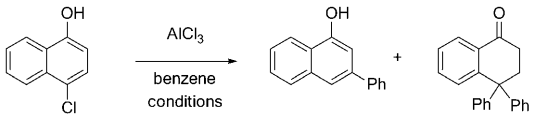
Entry	**16** [g][a]	solvent	T [°C][b]	t [h]	**17**/**56**/**57**[c]	Yield **17** [%][d]
1[e]	500000	PhCl	20	10	n.d.	40
			then 73	5		
2	3.6	PhCl	20	10	100:39:4	35[f]
			then 73	5		
3	3.6	PhH	reflux	3.5	100:128:18	27 [g]
4	3.6	CH_2Cl_2	0	3.5	100:48:13	44
5	3.6	CH_2Cl_2	25	3.5	100:76:35	47
6	18.2	CH_2Cl_2	25	3.5	100:32:8	67 [h]
7	3.6	CH_2Cl_2	reflux (40)	3.5	100:29:21	64
8	3.6	$CHCl_3$	0	3.5	100:76:12	50
9	3.6	$CHCl_3$	25	3.5	100:70:13	51
10	3.6	$CHCl_3$	reflux (61)	3.5	100:44:8	47
11	3.6	$ClCH_2CH_2Cl$	0	3.5	100:26:7	70
12	3.6	$ClCH_2CH_2Cl$	25	3.5	100:21:7	67
13	3.6	$ClCH_2CH_2Cl$	reflux (83)	3.5	100:15:5	55
14	100.4	$ClCH_2CH_2Cl$	0	6	100:20:5	76[i]
			then 25	1		
15	100.4	$ClCH_2CH_2Cl$	0	3.5	100:20:6	72[i]
			then 25	2.5		
16	120.0	$ClCH_2CH_2Cl$	0	4	n.d.	73[i]
			then 25	2.5		

[a] All reactions were carried out at 0.9–1.0 M of **16** except entry 1 which was 3.0 M. [b] The SO_2Cl_2 was added over 3 h in all cases except entry 1, which was over 10 h and used 1.0 equiv of SO_2Cl_2. Unless otherwise specified, all reactions went to 90–100% completion. [c] Determined from the relative integration of signals of compounds **17**, **56**, and **57** in the ^{1}H NMR spectrum of the crude reaction mixture. n.d. = not determined. [d] Yield of isolated product after crystallization from hexanes and CH_2Cl_2. [e] Data taken from Ref. [[20a]]. [f] Reaction went to 79% completion. [g] Reaction went to 85% completion. [h] SO_2Cl_2 was added all at once. [i] Combined yield of **17** from crystallization from hexanes/CH_2Cl_2 and then isolation of **17** from the mother liquor by column chromatography on silica gel.

anes/dichloromethane (2 crops). The yields are a little higher in the last three entries, presumably because they are on a larger scale and because in addition to taking 2 crops of **17**, the 4-chloro-1-naphthol **17** remaining in the combined mother liquors was isolated by column chromatography on silica gel.

The second step in the synthesis did not require as much optimization. The reaction of 4-chloro-1-naphthol with benzene under the influence of $AlCl_3$ has been reported to give a low yield of 3-phenyl-1-naphthol **11** at room temperature and to give a good yield (75%) in refluxing benzene.[20c] We found that at room temperature, the yield of **11** was 56% and diphenyl–tetralone **58** was formed in substantially greater amounts than had been previously reported. Interestingly, it was also found that exposure of the reaction mixture to a stream of dry HCl under the same conditions gave essentially no change in the product partition (Table 9, entry 2). This

Table 9. Phenylation of 4-chloro-1-naphthol.



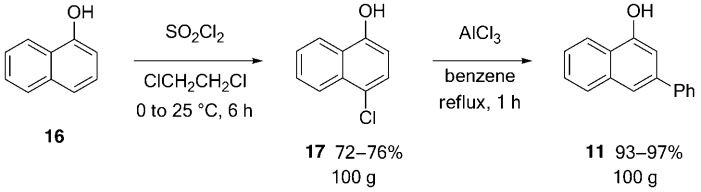
17 11 58

Entry	**17** [g][a]	$AlCl_3$ [equiv]	T [°C][b]	t [h]	**11** [%][b]	Yield **58** [%][c]
1	0.71	2.30	25	1	56	44
2[d]	0.71	2.30	25	1 (with HCl)	52	48
3	0.72	2.02	80	1	90	n.d.
4	100.3	1.60	80	1	97	n.d.
5	100.2	1.75	80	1	94	n.d.
6	100.1	1.74	80	1	93	n.d.
7	100.3	1.74	80	1	94	n.d.

[a] All reactions were carried out at 0.25–0.4 M of **17** in benzene. [b] For entries 1–3, yields of isolated products following column chromatography on silica gel. The yields for entries 4–7 are of combined yields of material isolated by crystallization from hexanes/CH_2Cl_2 and by column chromatography on silica gel of the resulting mother liquors. [c] Yield of isolated product after column chromatography on silica gel. n.d. = not detected. [d] A stream of dry HCl was slowly passed through the reaction mixture.

result suggests that the mechanism for the formation of **58** does not involve protonation of the alkene **54** as shown in Scheme 9, but more likely involves the dienone–phenol rearrangement of **50** with a 1,2-migration of hydride. This observation is in contrast to the report that the reaction of 4-phenyl-1-naphthol **49** in benzene at 25 °C with $AlCl_3$ leads to significantly increased proportions of the tetralone **58** in the presence of HCl, which was taken as evidence that the protonation of alkene **54** is taking place in this reaction.[20c] The tetralone **58** could not be detected in the reaction performed in refluxing benzene which gave the desired product **11** in 90% yield of isolated product (Table 9, entry 3). This reaction scaled up very nicely and was found to be reproducible, giving 3-phenyl-1-naphthol in 93–97% yield over four runs on a 100 g scale (Table 9, entries 5–7).

Therefore, the route of choice for the synthesis of 3-phenyl-1-naphthol **11** involves the dienone–phenol rearrangement and the final optimized procedure is shown in Scheme 10. The 3-phenyl-1-naphthol **11** is obtained in just



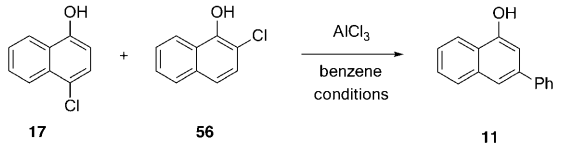
16 **17** 72–76% 100 g **11** 93–97% 100 g

Scheme 10. Optimizes synthesis of **11** from α-naphthol.

two steps in high overall yield from α-naphthol with very inexpensive reagents and requires no special equipment or low temperatures. Presumably, each step can be scaled up to any scale required as, in both cases, the product can be purified by simple crystallization. The only place that there is room for improvement is in the efficiency of the first step. Approximately one quarter of the mass balance is lost to either over-chlorination (**57**) or to chlorination in the wrong position (**56**; Table 8). The consequence of the formation of these by-products is two-fold: 1) loss of mass balance, and 2) the need to separate **17** from the by-products. Naturally, to further optimize the reaction, the question is whether either or both of these consequences are avoidable.

To tackle the question of whether **17** needs to be purified before it is converted into 3-phenyl-1-naphthol **11**, we set out to examine the possibility of converting the byproduct 2-chloro-1-naphthol **56** into 3-phenyl-1-naphthol **11**. A literature search revealed that this question had been previously taken up by Repinskaya, et al.[46] They reported that at room temperature, 2-chloro-1-naphthol **56** reacted very slowly with $AlCl_3$ in benzene, giving a mixture of products, one of which was 3-phenyl-1-naphthol **11** in 27% yield after 240 hours (Table 10, entry 1). They concluded that the conversion of **17** into 3-phenyl-1-naphthol **11** could be carried out in the presence of **56** without the formation of the by-products from **56** because it reacted about 100 times slower. Thus, we decided to see if we could improve on the synthesis in Scheme 10 by circumventing the purification of **17**. Remarkably, Repinskaya et al. did not report the phenylation of 2-chloro-1-naphthol **56** in refluxing benzene. We found that a purified sample of **56** would react with benzene under reflux in 4 hours to give 3-phenyl-1-naphthol **11** in 67% yield (Table 10, entry 2). The yield increased to 78% when the scale was increased to 100 g of **56** (Table 10, entry 3). These results clearly show that not only does 2-chloro-1-naphthol react with benzene to give 3-phenyl-1-naphthol, it does so at a rate that is only slightly slower than that of 4-chloro-1-naphthol (by about a factor of 4). We also found that we could take purified samples of **17** and **56** and create 1:1 mixtures which produce high yields of 3-phenyl-1-naphthol when refluxed in benzene for 1 hour (91% yield on 100 g scale with 100% conversion, Table 10, entry 7).

Table 10. Phenylation of 4-chloro-1-naphthol and 2-chloro-1-naphthol.

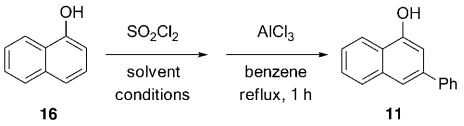


17 56 11

Entry	**17** [g]	**56** [g][a]	Benzene [mL][b]	$AlCl_3$ [equiv]	*T* [°C]	*t* [h]	Yield **11** [%][c]
1[d]	0	1.78	60	2.00	25	240	27
2	0	0.93	20	2.00	80	4	67
3	0	100	1700	1.60	80	4	78[e]
4	0.46	0.48	20	1.92	80	1	82
5	4.75	4.75	200	1.88	80	1	78
6	25.0	22.1	800	1.71	80	1	79[e]
7	50.7	50.2	2000	2.03	80	1	91[e]

[a] Purified by sublimation. [b] Reagent grade. [c] Unless otherwise specified, the yields are for isolated **11** after column chromatography on silica gel and are based on the sum of **17** and **56**. [d] Data taken from Ref. [46], and the reaction was performed for 240 h with periodic saturation with HCl. Also reported was a 16% yield of **58** and a 17% yield of 4-phenyl-1-tetralone. [e] The yields for entries 3, 6, and 7 are combined yields of material isolated by crystallization from hexanes/CH_2Cl_2 and by column chromatography on silica gel of the resulting mother liquors.

Table 11. Tandem chlorination/phenylation of 1-naphthol.[a]



16 11

Entry	Solvent	*T* [°C][a]	*t* [h]	Yield **17** [%][b]	**17**/**56**/**57**[c]	$AlCl_3$ [equiv]	Yield **11** [%][d]
1	$ClCH_2CH_2Cl$	0	3.5	n.d.	100:18:4	2.00	63
2	$ClCH_2CH_2Cl$	0	3.5	60[e]	100:20:9	2.00	55[f]
3	$CHCl_3$	25/61[h]	12/0.5[h]	n.d.	100:63:0	2.70	68
4	$ClCH_2CH_2Cl$	0	3.5	n.d.	100:18:4	2.00	63
5[g]	CH_2Cl_2	25	3.5	n.d.	100:28:4	1.60	71

[a] Unless otherwise specified, all chlorination reactions were carried out with 25 mmol of **16** and 1.2 equiv of SO_2Cl_2 in 25 mL of the indicated solvent with the indicated conditions; all phenylation reactions were carried out in 120 mL of benzene at reflux for 1 h. [b] n.d. = not determined. [c] Determined by ^1H NMR spectroscopy on the crude reaction mixture after chlorination. [d] Yield of isolated **11** after column chromatography on silica gel based on **16** (two steps). [e] Yield of isolated **17** after column chromatography on silica gel. [f] Yield of isolated product based on **16**. 91% yield based on isolated **17**. [g] This reaction was performed on 40 g of **16** (278 mmol) and employed 300 mL of CH_2Cl_2 and 800 mL of benzene. [h] This reaction was carried out at 25 °C for 12 h and then at 61 °C for 0.5 h.

Thus, clearly, both the 4-chloro- and 2-choro-isomers of α-naphthol will react to give 3-phenyl-1-naphthol in high yields. The next obvious question is whether the same high yields can be obtained on mixtures of **17**, **56**, and **57** present in the crude reaction mixture from the chlorination of α-naphthol, and the results of this exploration are shown in Table 11. The first two entries directly address this question. In the first entry, the crude chlorination mixture was directly taken up in benzene and refluxed with $AlCl_3$ to give 3-phenyl-1-naphthol **11** in higher overall yield (63%) than that for the same reaction where **17** was purified before it was reacted with benzene (55%). This increase is likely because of the conversion of the 2-chloro-1-naphthol, as compound **17** was purified by column chromatography and the 60% yield represents all the material formed in this reaction (Table 11, entry 2). This one-pot process was scaled up to 40 g of **16** and gave 3-phenyl-1-naphthol **11** in 71% yield of isolated product (Table 11, entry 5).

Given the savings in time and cost of materials for the purification of 4-chloro-1-naphthol that this one-pot procedure provides, it would be the method of choice for the synthesis of 3-phenyl-1-naphthol. However, the one-pot procedure does have some shortcomings. Foremost among them is that the quality of the crude product is lower than that from the reaction with purified **17**. Some colored impurities attend the formation of **11**, which were not possible to remove without chromatographic separation. This observation may be related to a published investigation that attempts to react 2,4-dichloro-1-naphthol with benzene and $AlCl_3$, which leads to the formation of resinous material.[46] Whilst using chromatographic separation to remove impurities may be the optimal technique on a small scale, such a technique is unsuitable for preparing **11** in large quantities owing to cost considerations and equipment availability. However, it has yet to be determined if not removing these impurities will have any detremental effect on the phenol coupling of **11** to give racemic vanol **6** (Scheme 2) or the purification of racemic vanol on large scale.

Another way to cut down on the loss of mass balance in the chlorination of α-naphthol is to increase the regioselection in favor of the desired 4-chloro-1-naphthol. Although this optimization seemingly reached its limit with SO_2Cl_2 as chlorination reagent (Table 8), bromination of α-naphthol to prepare 4-bromo-1-naphthol might be expected to give higher regioselectivity given the lower reactivities of the electrophiles involved.[47] We have briefly looked into this issue with the bromination of **16** with NBS in acetonitrile and, after 1 hour at room temperature, workup and isolation by column chromatography on silica gel gave 4-bromo-1-naphthol **59** in 88% yield with no detectable amount of the 2-bromo isomer **60**. Disappointingly, when the reaction was scaled up to 50 g, a substantial amount of the 2-bromo-1-naphthol **60** was formed and isolated (24%). The main difference in the experiments that was noted is that, on a small scale, the NBS was added all at once as a solution in acetonitrile, whereas, on a large scale, NBS was added as all at once as a solid, given the relatively low solubility of NBS in acetonitrile. Whilst this approach has not been further pursued at the present time, these results suggest that with further optimization it should be possible to increase the relative proportion of the 4-halo isomer compared to chlorination. That this could potentially be employed in the synthesis of vanol is demonstrated by the fact that 4-bromo-1-naphthol **59** will react with benzene in the presence of $AlCl_3$ to give 3-phenyl-1-naphthol **11** in 87% yield (Scheme 11).

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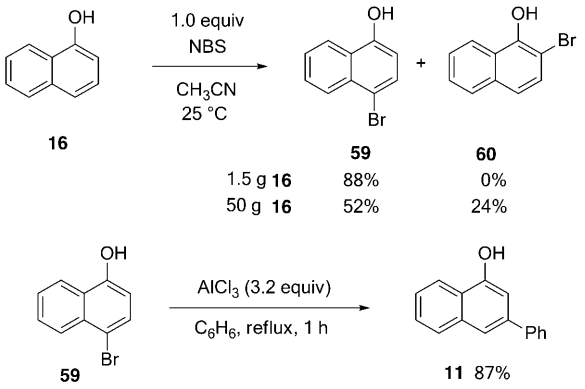
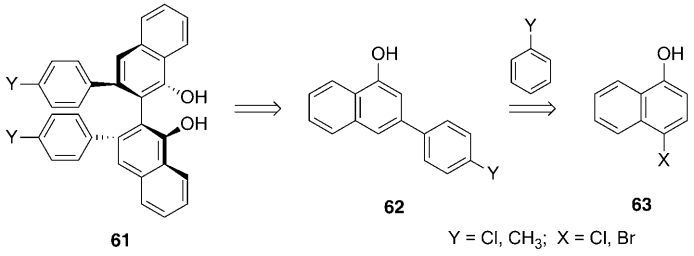


Scheme 11. Dienone phenol rearrangement of 4-bromo-1-naphthol.

Moreover, the fact that the succinimide byproduct is non-hazardous and can be easily removed by a water wash presents less safety and environmental concerns that the SO_2 and HCl produced by SO_2Cl_2.

In addition to the high efficiency that the dienone–phenol approach to vanol provides (Scheme 10), another attractive aspect is that it has the potential to allow for the synthesis of a family of vanol ligands as outlined in Scheme 12. It has been reported that the phenylation of 4-chloro-1-naphthol could be extended to substituted benzene substrates (Y = Cl, CH_3) to give 3-aryl-1-naphthol derivatives of the type **62**.[48] Phenol coupling and resolution would provide vanol derivatives of the type **61** which would be interesting to include in screens of new reactions with catalysts derived from the vanol ligand.

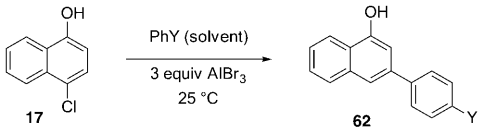


Scheme 12. Vanol derivatives by a dienone phenol rearrangement.

The reaction of 4-chloro-1-naphthol **17** with chlorobenzene in the presence of $AlBr_3$ has been reported to give an 82% yield of **62a** (Y = Cl) after crystallization from acetic acid (Table 12, entry 1).[48] In an effort to confirm this report, we repeated this reaction under the same conditions and while the 3-aryl-1-naphthol **62a** was obtained as the major product, we were not able to obtain this compound in pure form free from the side-products, even after column chromatography on silica gel and crystallization from acetic acid (Table 12, entry 2). A similar situation was encountered when the reaction was performed with bromobenzene at room temperature (Y = Br; Table 12, entry 3), and also with bromobenzene at 90 °C using $AlCl_3$ in place of $AlBr_3$ (Table 12, entry 4). Nor could pure products be obtained from 4-bromo-1-naphthol **59** carried out under the same conditions shown in Table 12 entry 3. Here again a mixture of compounds was obtained that elute together following column chromatography on silica gel and crystallize together. We had more success with repeating the reported reaction in toluene (Table 12, entry 5) where we were able to obtain naphthol **62c** in 43% yield in pure form after column chromatography on silica gel (Table 12, entry 6). No reaction was observed when the reaction was carried out with anisole and only the presence of the starting material **17** could be detected after a reaction time of 72 hours (Table 12, entry 7). This latter result is perhaps not too surprising since, as solvent in a 30 equivalent excess, anisole may deter the reaction by complexation with the $AlBr_3$. Thus, whilst it may not be possible to utilize the dienone–phenol rearrangement to introduce aryl substituents with basic oxygen and nitrogen groups into the vanol nucleus, it may be possible to introduce electronically neutral or electron-withdrawing groups provided that methods for the purification of the products can be developed.

This work is focused on the evaluation of methods for an efficient and scalable synthesis of 3-phenyl-1-naphthol, a key intermediate for the preparation of the vaulted biaryl ligand vanol. The three methods that were experimentally evaluated include: the Michael addition of a benzyl Grignard to methyl cinnamate, the Reformatsky reaction of ethyl bromoacetate to desoxybenzoin, and the dienone-phenol rearrangement of 4-aryl tetralenones. Although the Michael addition could be optimized to give very high yields

Table 12. Arylation of 4-chloro-1-naphthol **17**.[a]



Entry	**17** [g]	Y	*t* [h]	Product	Yield **62** [%]
1[b]	0.50	Cl	3.5	**62a**	87[c]
2	0.50	Cl	8	**62a**	mix[d]
3	5.19	Br	3.5	**62b**	mix[e]
4[f]	3.24	Br	1	**62b**	mix[g]
5[b]	2.10	CH_3	1.3	**62c**	20[h]
6	0.57	CH_3	1.3	**62c**	43[i]
7	0.54	OCH_3	72	**62d**	n.r.[j]

[a] Unless otherwise specified, all reactions were carried out on ca. 0.25 M of **17** in PhY as solvent, which is a 30:1 molar ratio of solvent to **17**. [b] Data taken from Ref. [48]. [c] Crystallization from acetic acid. [d] After chromatography on silica gel (hexanes/ethyl acetate = 10:1) and crystallization from acetic acid, a mixture of compounds was obtained with **62a** as the major component. [e] Column chromatography on silica gel (hexanes/ethyl acetate 10:1) and crystallization from acetic acid gave a yellow solid. Recrystallization from hexanes/CH_2Cl_2 gave a white crystal (3.18 g) which was a mixture of compounds. [f] Reaction performed with $AlCl_3$ at 90 °C for 1 h. [g] Column chromatography on silica gel (hexanes/ethyl acetate: CH_2Cl_2 = 20:1:2) and crystallization from toluene gave a mixture of compounds. [h] Crystallization from CCl_4. [i] Isolation by column chromatography on silica gel. [j] n.r. = no reaction; only **17** was present.

of the desired product, the overall synthesis in which the Michael addition was the key step only gave 3-phenyl-1-naphthol in 54% yield in four steps which is not superior to existing methods. The least-effective step in the Michael addition route was the dearomatization of 3-phenyl-1-tetralone. The Reformatsky route was also a four-step synthesis and provided the final product in 42% overall yield. The first and key step was the Reformatsky reaction which gave an excellent yield of the β-hydroxy ester, but the subsequent steps were less efficient and the Friedel–Crafts/dehydration gave moderate yields at best and required significant excesses of strong Lewis acids. Finally, the dienone–phenol rearrangement was the synthesis of choice, providing 3-phenyl-1-naphthol in 2 steps from 1-naphthol in 70% overall yield. This synthesis involved the in-situ generation of a 4-aryl tetralenone by the reaction of 4-chloro-1-naphthol with $AlCl_3$ and benzene.

Experimental Section

*Synthesis of 3,4-Diphenylbutanoic acid **25** by Michael Addition*

25.0 g magnesium turnings (1.00 mol) and 750 mL dry tetrahydrofuran were added to a 2 L round-bottom flask. The flask was flushed with N_2 and cooled to 0 °C. Benzyl chloride (100 mL, 0.870 mol) in 125 mL dry tetrahydrofuran was slowly added to this mixture. After one quarter of the solution had been added, another 28.0 g of Mg turnings (1.15 mol) was added. Addition of benzyl chloride was then resumed and completed over a period of 1 h. The ice-water bath was then removed to allow the temperature to rise to room temperature and then it was stirred for 1.5 h.

To a 5 L oven-dried 3-necked round-bottomed flask was added CuI (75 g, 0.39 mol) and a large stirrer bar. The flask was equipped with a 1 L pressure-compensating addition funnel and the other two necks were sealed with rubber septa. The top of the addition funnel was vented to a bubbler. The flask was then flushed with N_2 through one of the septa. Dry THF (1.25 L) was added followed by 65 mL TMEDA (0.43 mol). After stirring at room temperature for 15 min the solution became brown in color. The flask was cooled to −78 °C for 30 min. The $PhCH_2MgCl$ solution was transferred via a cannula. The color of the solution changed to yellow and a solid formed. The solution was stirred for 10 min before a solution of TMSCl (250 mL, 1.98 mol) and methyl cinnamate **27** (100 g, 0.625 mol) in 375 mL dry THF was added via the addition funnel over a period of 10 min. The color changed to red immediately. Stirring was maintained as the temperature was allowed to warm to 25 °C. The reaction was quenched by adding 2.5 L of saturated NH_4Cl in NH_4OH while air was bubbled into the flask for 2 h through one of the necks and all of the solid dissolved to form two layers. The top THF layer was separated and the blue aqueous layer was extracted with diethyl ether (3×500 mL). The combined organic layer was washed with water (3×400 mL) and dried over $MgSO_4$. After filtration and removal of the solvent by rotary evaporation in a 2 L round-bottomed flask, a wax-like white solid (181.6 g, mixture of **22** and bibenzyl) was afforded which was used for the next step (hydrolysis) without further purification.

To the 2 L flask containing the unpurified ester **26** was added aqueous KOH (255 g, 4.55 mol in 700 mL H_2O) and a stirrer bar. The mixture was heated at reflux for 3.5 h and, after cooling to room temperature, the aqueous solution was washed with hexanes (3×200 mL) to remove the bibenzyl product (16.4 g, 88 mmol). The water layer was acidified by adding 6 M HCl (~1.5 L) until the pH was ca. 0, and then extracted with diethyl ether (4×400 mL). The organic layer was dried over $MgSO_4$ and filtered. The filtrate was evaporated to dryness by rotary evaporation and then under a 0.5 mm Hg vacuum overnight to afford 150.0 g of 3,4-diphenylbutanoic acid **21** (0.620 mol, 100% yield) as a white solid.

Spectral data for **21**: m.p. 91.0–92.5 °C (lit[37] 95–6 °C); R_f=0.24 (1:20 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.63 (dd, 1H, J=8.3, 15.9 Hz), 2.68 (dd, 1H, J=6.9, 15.9 Hz), 2.89 (d, 2H, J=6.6 Hz), 3.38 (p, 1H J=7.8 Hz), 7.00–7.03 (d, 2H, J=9.9 Hz), 7.12–7.30 (m, 8H), 11.4 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=40.00, 43.80, 44.10, 126.24, 126.71, 127.47, 128.23, 128.40, 129.25, 139.30, 143.18, 179.90 ppm; mass spectrum, m/z (% rel. intensity) 240 M$^+$ (15), 181 (38), 180 (100), 149 (85), 108 (100), 91 (100), 77 (73), 65 (40).

*Synthesis of 3-Phenyl-1-Tetralone **24** by Intramolecular Friedel–Crafts Reaction*

Polyphosphoric acid (PPA; 300 g) was magnetically stirred and heated in a 120 °C oil bath in a 1 L round-bottomed flask. Well-ground 3,4-diphenylbutanoic acid **25** (150.0 g, 0.620 mol) was added slowly, and the temperature was maintained at 120 °C for 4.5 h. The contents of the flask were then exposed to vacuum (2 mm Hg) for 3 h at the same temperature to remove the excess water. The flask was then back-filled with argon and kept at 120 °C for another 2 h. The mixture was cooled to room temperature and H_2O (400 mL) was added to quench the reaction and the resulting mixture was stirred overnight. The reaction mixture was diluted by addition of another 400 mL H_2O and then extracted with diethyl ether (4×400 mL). The combined diethyl ether layer was washed in turn with 400 mL water, 400 mL of 10% aq. $NaHCO_3$, and 400 mL water. The organic layer was dried over $MgSO_4$ and filtered. Upon removal of the solvent under high vacuum, 3-phenyl-1-tetralone **24** was isolated as a red solid (136 g, 0.61 mol, 95.8%). This material was pure according to ^{1}H NMR and was used in the next step without further purification.

Further purification of this material on a small scale could be performed as follows: crude **24** (1.4675 g, 6.60 mmol) was dissolved in a minimum amount of CH_2Cl_2 and loaded onto a silica gel column, which was eluted by a 10:1 mixture of hexanes and EtOAc to give 1.3190 g of **20** (5.93 mmol, 89.8% yield).

Spectral data for **20**: white solid; m.p. 63.1–63.7 °C (lit[37] 65 °C); R_f=0.07 (1:9 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.62–2.88 (m, 2H), 3.00–3.19 (m, 2H), 3.24–3.38 (m, 1H), 7.24–7.39 (m, 7H), 7.50 (td, 1H, J=7.5, 1.2 Hz), 8.08 ppm (dd, 1H, J=7.5, 0.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=27.54, 37.66, 41.08, 45.93, 126.66, 126.92, 126.96, 127.18, 128.77, 128.83, 132.06, 133.78, 143.40, 197.81 ppm; mass spectrum, m/z (% rel. intensity) 222 [M]$^+$ (100), 118 (90), 104 (42), 90 (68), 89 (56), 78 (32), 63 (20), 51(27).

*Synthesis of 3-Phenyl-1-Naphthol **11** by Dehydrogenation of **24***

Tetralone **24** (92 g, 0.41 mol) was dissolved in 1 L mesitylene in a 2 L flask containing a stirrer bar, and the resulting solution was purged with argon for 30 min. Pd/C (6.1 g, 10% wt, 1.4 mmol% of Pd) was added and the flask was fitted with a condenser. The mixture was refluxed with a gentle flow of N_2 over the top of the condenser. The reaction was followed by TLC; after 113 h, the reaction was still incomplete but it was then stopped. The flask was cooled to room temperature and the Pd/C was removed by filtration through Celite. The Celite pad was washed thoroughly with mesitylene (~300 mL). The combine organic layer was extracted with 0.9 M aq KOH (3×500 mL). TLC shows that the ArOK in the water layer was accompanied by small amounts of impurities. The aqueous layer was washed with 200 mL hexanes and subsequently acidified with 6 M HCl until the pH was ca. 0. The solid that resulted was filtered and dried in vacuo to give 61.3 g of 3-phenyl-1-naphthol **11** (0.28 mol, 67%) as a grey solid. Mesitylene was recovered by vacuum distillation (56–60 °C/10 mmHg) and a red residue was produced. Attempts to isolate naphthol **11** from this material by column chromatography (hexanes/ethyl acetate=6:1) failed to produce any pure **11**. Further purification of **11** could be achieved by crystallization from hexanes/CH_2Cl_2 (−20 °C) to give 43.1 g (195.7 mmol, 70% recovery) of 3-phenyl-1-naphthol **11** as white crystals.

Spectral data for **11**: white solid; m.p. 96.0–97.5 °C (lit[14a] 96–97.5 °C); R_f=0.48 (1:3 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ=5.32 (s, 1H), 7.06 (s, 1H), 7.34 (t, 1H), 7.41–7.50 (m, 4H), 7.62–7.64 (m, 3H), 7.82 (d, 1H, J=10 Hz), 8.13 ppm (d, 1H, J=9 Hz); ^{13}C NMR ($CDCl_3$,

75 MHz): $\delta = 108.41$, 118.73, 121.39, 123.47, 125.34, 126.86, 127.20, 127.37, 127.99, 128.75, 134.85, 138.73, 140.67, 151.47 ppm; *m/z* (% rel intensity), 220 $[M]^+$ (100), 191.0 (45), 189.0 (30), 165.0 (23), 95 (23), 55 (21), 43 (25).

*Synthesis of Ethyl-3-Hydroxy-3,4-Diphenylbutanoate **34** by the Reformatsky Reaction*

Activation of Zinc: Zinc dust (10 g, 40 mesh) was stirred with 2% aq. HCl (100 mL) at 25 °C for 15 min. After filtration, the Zn was washed with 100 mL of 2% aq. HCl, followed by 100 mL water, 100 mL ethanol and then three times with 100 mL of diethyl ether. The Zn dust was dried under high vacuum (1 mmHg) overnight.

A flame-dried 50 mL 3-necked flask was charged with a stirrer bar and fitted with a condenser. To the flask was then added 2.50 g activated Zn (38.5 mmol), deoxybenzoin **36** (0.9873 g, 5.037 mmol), and 3 small I_2 crystals. Then the system was flushed with N_2 gas, followed by the addition of 10 mL of a mixture of benzene and diethyl ether (1:1) as solvent. A solution of ethyl-α-bromoacetate **35** (2.50 mL, 22.5 mmol) in 2.5 mL benzene was slowly added to the flask by syringe pump over 75 min under mild reflux. The reaction mixture was then refluxed for 4.5 h. The Zn was removed by filtration and washed with diethyl ether (3×50 mL). The organic layer was combined with 50 mL 2 M HCl and after separation, the aqueous layer was extracted with diethyl ether (3×25 mL), dried with $MgSO_4$ and filtered. The workup and purification procedure were the same as the original procedures. The diethyl ether was removed by rotary evaporation and the residue was dissolved in minimum of CH_2Cl_2 and loaded onto a silica gel column, which was eluted with a mixture of ethyl acetate and hexane (1: 10) to give 1.3810 g (4.86 mmol, 97%) of the β-hydroxy ester **34** as a white solid.

Spectral data for **34**: wax-like white solid; m.p. 58.5–60.0 °C (lit[37] 57–8 °C); $R_f = 0.36$ (1:5 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta =$ 1.05 (t, 3H, $J = 6.9$ Hz), 2.82 (d, 1H, $J = 15.9$), 2.95–3.09 (m, 3H), 3.95 (q, 2H, $J = 7.2$ Hz), 4.20 (s, br, 1H); 6.97–7.34 ppm (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 13.57$, 43.32, 49.60, 60.37, 74.94, 124.91, 126.20, 126.62, 127.44, 127.68, 130.48, 136.01, 145.09, 172.50 ppm. Anal calcd for $C_{18}H_{20}O_3$: C 76.03, H 7.09. Found: C 75.91, H 6.99.

*Synthesis of β-Hydroxy acid **33** by the Hydrolysis of **34***

The β-hydroxy ester **34** (2.52 g, 8.80 mmol) was refluxed with aqueous KOH (5.6 g, 100 mmol in 75 mL water) and MeOH (20 mL) in a 250 mL flask for 2 h. After cooling to room temperature, the reaction mixture was washed with 50 mL hexane and then acidified with 6 M HCl until the pH was ca. 0. The resulting mixture was extracted with diethyl ether (3× 50 mL). The diethyl ether layer was dried over $MgSO_4$ and the solvent was subsequently removed to give 2.06 g (8.0 mmol, 92% yield) of the β-hydroxy acid **33** as a white solid. Spectral data for **33**: wax-like white solid; m.p. 118–119.5 °C (lit[37] 120 °C); $R_f = 0.11$ (1:5 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 2.90$ (dd, 2H, $J = 16.5$, 75 Hz), 2.93–3.09 (m, 3H), 6.95 (s, 1H), 7.06–7.50 ppm (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 43.04$, 49.54, 74.88, 124.78, 126.39, 126.88, 127.56, 127.87, 130.41, 135.53, 144.53, 177.42 ppm.

*Synthesis of 3-Phenyl-1-Naphthol **11** via Cyclization of Acid Chloride **37** with $SnCl_4$*

Preparation of the acid chloride of **37**. The acid **33** 1.20 g (4.70 mmol) was refluxed for 3 h with 5 mL (58.2 mmol) oxalyl chloride in 40 mL dry benzene. Excess oxalyl chloride and benzene were removed under reduced pressure and the residue flushed three times with dry benzene, then exposed to high vacuum for 1 h. The residue was used directly without further purification. The crude acid chloride **37** was dissolved in 40 mL benzene under argon and cooled to 0 °C. Anhydrous $SnCl_4$ (2.5 mL, 21.8 mmol) was injected into the stirred solution, which turned red immediately. The reaction mixture was stirred at 0 °C for 3 h before quenching with an ice-cold solution of 5 mL of concentrated HCl in 50 mL water and the resulting solution refluxed for 30 min. After extraction of the aqueous layer with diethyl ether (3×30 mL), the combined organic layer was dried over $MgSO_4$, filtered and the solvent removed under vacuum. The residue was dissolved in a minimum amount of CH_2Cl_2 and loaded onto a silica gel column, which was eluted with hexane/ethyl acetate (6:1) to give 0.5288 g (2.40 mmol, 51%) of **11** as white flakes. The spectral data matched those presented above for **11**.

*Preparation of 4-Chloro-1-Naphthol **17** via Chlorination of 1-Naphthol **16***

A solution of freshly sublimed 1-naphthol **16** (120 g, 832.3 mmol) in 900 mL 1,2-dichloroethane (DCE) was added to a 2 L 3-necked round-bottomed flask that was warmed gently with a heat gun to dissolve the solid. The flask was equipped with a 48×18 mm oval magnetic stirrer bar, a pressure compensating addition funnel and the other two necks were sealed with glass stoppers. The top of the addition funnel was vented to a bubbler and then into a beaker filled with aqueous NaOH to trap acidic gases (HCl and SO_2). The flask and its contents were cooled to 0 °C and SO_2Cl_2 (90.0 mL, 149.9 g, 97%, 1076.9 mmol) was added over 3.5 h from the addition funnel as the reaction mixture was stirred. After addition, the mixture was stirred for an additional 0.5 h at 0 °C, and then the ice-water bath was removed and the mixture was warmed to room temperature over 2.5 h. Upon completion of the reaction, the contents of the flask were purged for 30 min with N_2 introduced through a glass tube below the surface of the solution to remove excess gasses prior to workup. The solvent was removed on a rotary evaporator and the crude product was crystallized from a minimum amount of boiling DCE (about 200 mL). After allowing the hot solution to slowly cool to room temperature, filtration gave 83.62 g (468.1 mmol, 56.2%) of 4-chloro-1-naphthol **17** as light silver–green needle-like crystals (m.p. 118–119.5 °C, lit[20a] 120–121 °C). The filtrate was poured into 500 mL of hexanes and additional product (20.00 g, m.p. 113.0–114.0 °C) could be isolated after cooling to −20 °C and filtration. This material was recrystallized from a minimum amount of boiling DCE (about 30 mL) to give 13.75 g (76.98 mmol, 9.2%, m.p. 117.1–118.1 °C) of **17** as needle-like crystals that had essentially the same coloration as the first crop. The combined yield of **17** for the first two crops is 65.4%.

Additional product can be obtained by column chromatography on silica gel. The combined filtrates from the first two crops were dried of solvent and the residue (about 50 g) was dissolved in 200 mL CH_2Cl_2 and then combined with 80 g (about 200 mL) of dry silica gel in a single-necked flask. The solvent was removed from the silica gel by purging with a nitrogen stream that was vented to a bubbler. A chromatography column (6 cm diameter) was prepared by filling the column with a 1:50 mixture of ethyl acetate and hexanes and then the addition of silica gel, such that, after settling, a depth of ca. 35 cm had been reached. The dried silica gel with the pre-adsorbed product was added to the solvent above the prepared bed and allowed to settle. The solvent level was lowered to the top of the gel and then a layer of sand was applied. The silica gel column was first eluted with a 50:1 mixture of hexanes/ethyl acetate under gravity for at least 1 h, then switched to 10:1 mixture of hexanes/ethyl acetate under nitrogen pressure. The byproducts (**56** and **57**) were first eluted, followed by **17** (11.37 g, 63.65 mmol, 7.6%, m.p. 116.8–117.8 °C). The combined yield of 4-chloro-1-naphthol **17** is 108.7 g (608.7 mmol, 73.0%).

Spectral data for **17**: needle-like gray solid; m.p. 119–120.5 °C (lit[21a] 120–1 °C); $R_f = 0.41$ (1:3 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta =$ 5.10 (br s, 1H), 6.71 (d, 1H, $J = 9.0$ Hz), 7.36 (d, 1H, $J = 9$ Hz), 7.51–7.63 (m, 2H), 8.20 ppm (d, 2H, $J = 9$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta =$ 108.04, 121.95, 123.25, 124.16, 125.30, 125.54, 125.76, 127.44, 131.28, 150.45 ppm.

*Chlorination of 1-Naphthol **16** and the Determination of the Side-Products*

A mixture of freshly sublimed 1-naphthol **16** (3.60 g, 25.0 mmol) and 20 mL 1,2-dichloroethane was gently heated in a 100 mL flask equipped with a stirrer bar under a nitrogen atmosphere until **16** was dissolved. The resulting solution was then cooled to 0 °C for 30 min. Crystals formed at this temperature. A solution of SO_2Cl_2 (2.5 mL, 29.9 mmol) in 5 mL DCE was slowly added to the solution by a syringe pump over a period of 3 h. The ice-water bath was then removed and the reaction mixture was stirred for 30 min. To the reaction mixture was added 100 mL hexanes and the solvents were removed under vacuum. The ^{1}H NMR spectrum of the residue revealed the presence of 4-chloro-1-naphthol **17**,

2-chloro-1-naphthol **56**, 2,4-dichloro-1-naphthol **57**, and 1-naphthol **16** in a ratio of 100:26:7:5. The ratio was determined by integration of the H^2 proton for **17** and **16** and the O–H proton for **56** and **57**. 4-Chloro-1-naphthol **17** and 1-naphthol **16** can be separated from the mixture by crystallization and by chromatography on silica gel. However, it was not possible to separate 2-chloro-1-naphthol **56** and 2,4-dichloro-1-naphthol **57** from each other by any method. Thus, to confirm their presence and identity in the mixture from this reaction, purified samples of each were prepared as described below. The mixture from this reaction was crystallized from boiling CH_2Cl_2 by saturation by hexanes and then cooling to −20 °C to give 3.12 g (17.5 mmol, 70.0 %) of 4-chloro-1-naphthol **17** as needle-like crystals.

*Preparation of 2-Chloro-1-Naphthol **56** by Sub-Stoichiometric Chlorination of 1-Naphthol **16***

A solution of freshly sublimed 1-naphthol **16** (7.2 g, 50 mmol) in 195 mL CH_2Cl_2 in a 500 mL 3-necked flask equipped with a stirrer bar was cooled to 0 °C under nitrogen. A solution of SO_2Cl_2 (2.5 mL, 30 mmol) in 5 mL CH_2Cl_2 was slowly added to the solution of **16** via syringe pump over 12.5 h while the temperature of the reaction flask was maintained at 0 °C. After warming to and stirring at room temperature for 30 min, the reaction mixture was poured onto 100 mL hexanes and all of the solvents were completely removed by rotary evaporation. The resulting solid (7.85 g, ^{1}H NMR ratio of **16**/**17**/**56** = 1:0.5:0.4) was dissolved in a minimum amount of CH_2Cl_2 and poured into 100 mL hexane and cooled to −20 °C. The precipitate (mainly **16** and **17**) was filtered off, and the solvents in the mother liquor were evaporated. The residue was dissolved in minimum of CH_2Cl_2, loaded onto a column, and eluted with a 10:1 mixture of hexanes/ethyl acetate under pressure to afford 1.4346 g (8.037 mmol, 16.1 %) of **56**.

Spectrum data for **56**: white solid; m.p. 64–65 °C (lit[20a] 65 °C). R_f = 0.53 (1:3 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.98 (s, 1H), 7.34 (s, 2H), 7.48–7.58 (m, 2H), 7.74–7.89 (m, 1H), 8.19–8.28 ppm (m, 1H); ^{13}C ($CDCl_3$, 75 MHz): δ = 113.20, 120.58, 121.72, 124.07, 125.53, 125.73, 126.32, 127.26, 132.89, 146.70 ppm.

*Preparation of 2,4-Dichloro-1-Naphthol **57** by Chlorination of 4-Chloro-1-Naphthol **17***

A solution of 4-chloro-1-naphthol **17** (1.887 g, 10 mmol) in 20 mL CH_2Cl_2 was added to a 100 mL flask equipped with a stirrer bar and a condenser under a N_2 atmosphere at 25 °C. A solution of SO_2Cl_2 (1 mL, 12.6 mmol) in 5 mL CH_2Cl_2 was slowly added to the solution of **17** by syringe pump over 13 h at room temperature. After the addition, the solution was stirred for an additional 30 min and then poured onto 100 mL hexanes. The solvents were completely removed by rotary evaporation. The resulting solid was dissolved in CH_2Cl_2 and then 100 mL hexane was added. All solvents were evaporated once again to make sure all the unreacted SO_2Cl_2, HCl and SO_2 had been removed. The residue was dissolved in a minimum amount of CH_2Cl_2 and loaded onto a silica gel column and eluted with a 10:1 mixture of hexanes/ethyl acetate under pressure to afford 1.44 g (6.75 mmol, 63.7 %) of **57** as white needle-like crystals.

Spectrum data for **57**: white solid m.p. 101–102 °C (lit[20a] 107–8 °C); R_f = 0.52 (1:3 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.93 (s, 1H), 7.47 (s, 1H), 7.57–7.70 (m, 2H), 8.16 ppm (dd, 2H, J = 24.9, 3.9 Hz); ^{13}C ($CDCl_3$, 75 MHz): δ = 112.35, 122.17, 123.10, 124.10, 124.63, 125.13, 126.54, 127.35, 129.94, 146.05 ppm.

*Synthesis of 3-Phenyl-1-Naphthol **11** via the Phenylation of 4-Chloro-1-Naphthol **17***

To a 5 L 3-necked round-bottomed flask equipped with a mechanical stirrer, condenser and an addition funnel was added $AlCl_3$ (130.0 g, 975.0 mmol). The flask was then flushed with N_2 for about 0.5 h. Benzene (800 mL, reagent grade) was added to the flask and the slurry was heated to reflux while the contents of the flask were stirred. A solution of 4-chloro-1-naphthol **17** (100.1 g, 560.5 mmol) was prepared by combining **17** with 1000 mL benzene (reagent grade) in a 2 L flask and then gently heating the mixture with a heat gun to dissolve the solid. The solution of **17** was transferred into the addition funnel and added to the reaction mixture over 1.5 h. Both the 2 L flask and the addition funnel were rinsed with 100 mL benzene twice and this was added to the 5 L flask as well. The benzene solution was refluxed for 1 h before it was cooled to room temperature and then 1.0 L of 6 M HCl that had been pre-chilled in an ice-bath was introduced all at once. The resulting mixture was stirred for 30 min. The benzene layer was separated and the water layer was extracted with diethyl ether (3 × 600 mL). The combined organic layer was washed with 400 mL water, 400 mL saturated aq. $NaHCO_3$, and finally with 400 mL water. The organic layer was dried over $MgSO_4$, filtered, and then all of the solvents were removed by rotary evaporation. The residue (126.7 g) was crystallized by dissolving in boiling CH_2Cl_2 (about 200 mL) and then hexane (about 500 mL) is added with heating at a rate such that constant boiling is maintained. The solution was allowed to cool to room temperature and then allowed to cool in a refrigerator overnight. The mixture was filtered to give 103.7 g (471.4 mmol, 84.1 %) of **11** as a fluffy beige amorphous solid (m.p. 96–97.5 °C; lit[14a] 96–97.5 °C).

Additional 3-phenyl-1-naphthol can be isolated from the mother liquor by extraction and column chromatography. After removal of the solvents by rotary evaporation, the residue (21.75 g) was dissolved in 200 mL toluene and the resulting solution was extracted 3 times with aq KOH (50 g in 1 L water; 400 mL+300 mL+300 mL). The combined aqueous layer was cooled in an ice bath and acidified with 6 M HCl (ca. 200 mL) to pH ~ 1. The acidified aqueous layer was extracted with diethyl ether (3 × 400 mL). The combined diethyl ether layer was washed with 400 mL water and then dried over $MgSO_4$. The diethyl ether was removed by rotary evaporation and the brownish oily residue was fairly pure 3-phenyl-1-naphthol. Further purification of this material was achieved by column chromatography. The material was dissolved in 100 mL CH_2Cl_2 and combined with 50 g (about 100 mL) of silica gel. The solvent was removed from the silica gel by purging with a nitrogen stream that was vented to a bubbler. A chromatography column (6 cm diameter) was prepared by filling the column with a 1:50 mixture of ethyl acetate/hexanes and then the addition of silica gel such that, after settling, a depth of 30 to 50 cm had been reached. The dried silica gel with the pre-adsorbed product was added to the solvent above the prepared bed and allowed to settle. The solvent level was lowered to the top of the column and then a layer of sand was applied. Elution with a 1:10 mixture of ethyl acetate/hexanes afforded 11.31 g (51.41 mmol, 9.2 %, m.p. 92.5–94.5 °C) of **11** as a light-yellow oil. This oil could be rendered to solid form by dissolving in 50 mL of CH_2Cl_2, addition of 200 mL of hexane, and then removal of the solvent by rotary evaporation to provide a fluffy light-yellow solid (total yield 115.03 g, 522.9 mmol, 93.3 %). The spectral data matched those presented above for **11**.

*Preparation of 4-Bromo-1-Naphthol **59** via Bromination of 1-Naphthol **16***

To a solution of freshly sublimed 1-naphthol **16** (1.4576 g, 10 mmol) in 40 mL of CH_3CN was added *N*-bromosuccinimide (NBS) (1.8630 g, 10.5 mmol) all at once as a solid at 25 °C while the reaction mixture was stirring. The color changed to light yellow after 1 h at which time the solvent was removed in vacuo. The residue was dissolved in 30 mL diethyl ether and washed with 10 mL water three times, and dried over $MgSO_4$. After filtration and removal of solvents, the residue was purified by column chromatography on silica gel with a 20:2:1 mixture of hexanes/CH_2Cl_2/EtOAc as eluent to afford 2.06 g of 4-bromo-1-naphthol **59** (8.92 mmol, 88.3 %) as an off-white solid.

Spectral data for **59**: m.p. 126–127 °C, decomposed (lit[20a] m.p. 129 °C); R_f = 0.40 (1:4 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.24 (br, s, 1H), 6.67 (d, 1H, J = 8.1 Hz), 7.50–7.62 (m, 3H), 8.14–8.19 ppm (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 109.43, 113.72, 122.40, 125.85, 126.29, 127.32, 128.12, 129.63, 132.97, 151.46 ppm.

This reaction was also carried out on a larger scale with 50 g of 1-naphthol **16** with the same procedure and with everything scaled appropriately. The reaction was also stopped after 1 h at which point the reaction was 96 % complete. However, this reaction gave a mixture of 4-bromo-1-naphthol **59** and 2-bromo-1-naphthol **60** in an approximately 2:1 ratio. Crystallization of the crude reaction mixture from 150 mL 1,2-dichloroethane gave 4-bromo-1-naphthol in 52 % yield. The residue from the

mother liquor was loaded onto a silica gel column and elution with a 50:1 mixture of hexanes/ethyl acetate and gave a fraction that was pure 2-bromo-1-naphthol **60** (24%) and a fraction that was a mixture of **59** and **60** (12%). Thus for large scale reactions, it will probably be necessary to added the NBS slowly over time. The limited solubility of NBS in CH_3CN suggests this will not be the optimal solvent for slow addition if NBS is to be added slowly as a solution.

*Synthesis of 3-Phenyl-1-Naphthol **11** via the Phenylation of 4-Bromo-1-Naphthol **59***

A 3-necked 100 mL round-bottomed flask equipped with a condenser was charged with a stirrer bar and $AlCl_3$ (936 mg, 7.0 mmol) under argon. Two necks of the flask were sealed with rubber septa and a slow flow of argon was maintained over the top of the condenser. To this flask was injected 6 mL of dry benzene and then the contents were heated to reflux. A solution of 4-bromo-1-naphthol **59** (490 mg, 2.2 mmol) in 10 mL benzene was added to the refluxing benzene/$AlCl_3$ mixture by syringe, and then 4 mL benzene was used to rinse the flask and the syringe. The color of the solution immediately changed to red. The reaction mixture was refluxed for 1 h before it was it was cooled and poured into 50 g ice/HCl (6 M, 50 mL). The aqueous layer was extracted with diethyl ether (3×100 mL) and the combined organic layer was dried over $MgSO_4$ and filtered. The solvents were removed by rotary evaporation and the residue was dissolved in a minimum amount of CH_2Cl_2 and was loaded onto silica gel column. Elution with a 20:1:2 mixture of hexanes/ethyl acetate/CH_2Cl_2 gave 421 mg (1.91 mmol, 87%) of 3-phenyl-1-naphthol **11** which had spectral data identical with those reported above for this compound.

*The Arylation of 4-Chloro-1-Naphthol **17** with Bromobenzene*

A 250 mL round bottomed flask containing a stirrer bar was charged with 22.63 g (84.8 mmol) of $AlBr_3$ and flushed with argon. After addition of 40 mL of bromobenzene the $AlBr_3$ dissolved to give a red solution. 4-Chloro-1-naphthol **17** (5.1934 g, 29.07 mmol) was dissolved in 60 mL of bromobenzene with slight heating and this solution was added to the flask. The reaction mixture was stirred at room temperature for 3.5 h and then poured into a mixture of 2 L of 6 M HCL and ice. The aqueous layer was extracted with diethyl ether (2×500 mL) and the combined organic layer was washed with H_2O (2×500 mL). TLC analysis indicated the presence of a single mobile fraction which, however, was found to be a mixture of compounds. The residue was loaded onto a silica gel column and eluted with a 10:1 mixture of hexanes/ethyl acetate to give a grey/greenish oil which eventually solidified. This solid was crystallized from acetic acid to afford a yellow solid which was found to be an impure mixture of products by ^{1}H NMR spectroscopy. This material was recrystallized from hexanes/CH_2Cl_2 to give 3.1824 g of material as a white solid. Again, ^{1}H NMR analysis revealed that this was not a pure compound and no further attempts to purify this product were made.

*The Arylation of 4-Chloro-1-Naphthol **17** with Toluene*

An oven-dried 50 mL 3-necked round-bottomed flask equipped with a stirrer bar was charged with $AlBr_3$ (2.16 g, 8.13 mmol), filled with argon, and the necks of the flask sealed with septa. Toluene (3 mL) was added by syringe and the mixture stirred to effect dissolution which gave a red solution. A solution of 4-chloro-1-naphthol **17** (568 mg, 3.18 mmol) in 7 mL of toluene was added to the flask by syringe over a period of 10 min. During the addition, the color changed from yellow to orange and then to dark red. The reaction mixture was stirred for 1.25 h at room temperature before it was poured into 50 mL 6 M HCl at 0 °C. The aqueous layer was extracted with diethyl ether (2×50 mL) and then the combined organic layer was washed with H_2O (2×50 mL), dried over $MgSO_4$, and filtered. All solvents from the filtrate were removed in vacuo to give 0.8632 g of residue. This material was dissolved in a minimum amount of CH_2Cl_2 and loaded onto a silica gel column and eluted with a mixture of hexanes/EtOAc (10:1) to give 3-(4-methylphenyl)-1-naphthol **62c** as an off-white solid (317 mg, 1.35 mmol, 42.5%).

Spectral data for **62c**: m.p. 135–136 °C (lit[47] 145–147 °C); $R_f=0.24$ (1:5 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=2.46$ (s, 3H), 5.33 (s, 1H), 7.12 (d, 1H, $J=1.46$ Hz), 7.31 (s, 1H), 7.33 (s, 1H), 7.48–7.58 (m, 2H), 7.61 (s, 1H), 7.64 (s, 1H), 7.68 (s, 1H), 7.89–7.91 (m, 1H), 8.18–8.22 ppm (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=31.37$, 108.60, 118.68, 121.66, 123.66, 125.42, 127.09, 127.36, 128.21, 129.80, 135.24, 137.54, 138.24, 139.08, 151.89 ppm; IR (thin film):$\tilde{\nu}=3441$br vs (vs = very strong), 1684 (m), 1653 (s), 1616 (m), 1558 (m), 1541 (w), 1506 (w), 812 cm^{-1} (m); mass spectrum, m/z (% rel intensity) 235.1 (72), 234.0 M^+ (100), 232.8 (60), 201.9 (61), 188.9 (85), 164.8 (40), 138.9 (20), 115.0 (35), 107.2 (65), 88.5 (35), 63.5 (25), 51.0 (20), 40.9 (45); HRMS calcd for $C_{17}H_{13}O$ m/z 233.0966, found 233.0968.

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