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New Synthesis of Vaulted Biaryl Ligands via the Snieckus Phenol Synthesis

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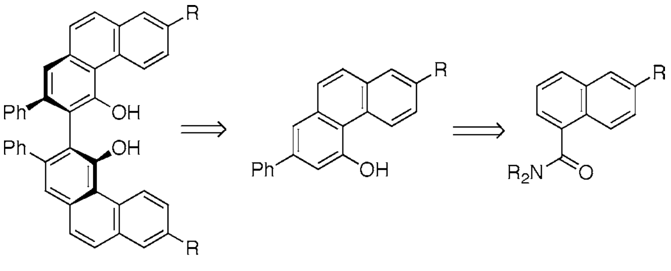
ABSTRACT



(S)-VAPOL (R = H, CH_3)

In an effort to develop a synthesis of the VAPOL ligand that avoids the use of a chromium carbene complex, a route was examined that involved the annulation of a naphthalene carboxamide via the method of Snieckus. The latter derivatives could be converted in a two-step sequence to 2-phenyl-4-phenanthrols in 60–72% overall yields. The utility of this method for the synthesis of VAPOL derivatives is demonstrated in the synthesis of (*S*)-7,7′-dimethyl-VAPOL.

The VAPOL ligand is a bis-3,3′-(4-phenanthrol) that has been developed as a member of the vaulted biaryl family of chiral ligands for applications in catalytic asymmetric synthesis.[1] Successful chiral catalysts that have been derived from VAPOL include aluminum derivatives as catalysts for Diels–Alder reactions,[2] a zirconium derivative for imino-aldol reactions,[3] and boron derivatives for catalytic asymmetric aziridination reactions.[4] The latter is particularly general over a wide range of substrates and as a result is a valuable method for the synthesis of chiral aziridines and, thus in turn, chiral amines.

The penultimate step in the current synthesis of the VAPOL ligand is the oxidative coupling of the phenanthrol **2** to give the 3,3′-bisphenanthrol carbon skeleton, and the final step is its resolution (Scheme 1).[5] The synthesis begins with 1-bromonaphthalene and provides racemic VAPOL in four steps in 40% overall yield.[1] The key step in the synthesis is the benzannulation of the 1-naphthylcarbene complex **4** with phenylacetylene, which in the presence of acetic anhydride gives the substituted phenanthrol **3**, which is reduced in high yield to the phenanthrol **2** with aluminum trichloride and ethanethiol. This reaction can be scaled-up to include a reaction of 250 g of carbene complex **4** with phenylacetylene with conveniently sized glassware (3 L). The cost of chromium carbonyl ($3/g) is not an issue on a small scale, but for large-scale synthesis of the ligand it could become prohibitive. In addition, we envisioned that there would be a need for a synthesis that would allow for access

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(1) Bao, J.; Wulff, W. D.; Dominy, J. B.; Fumo, M. J.; Grant, E. B.; Rob, A. C.; Whitcomb, M. C.; Yeung, S.-M.; Ostrander, R. L.; Rheingold, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 3392.

(2) (a) Bao, J.; Wulff, W. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **1993**, *115*, 3814. (b) Bao, J.; Wulff, W. D. *Tetrahedron Lett.* **1995**, *36*, 3321. (c) Heller, D. P.; Goldberg, D. R.; Wulff, W. D. *J. Am. Chem. Soc.* **1997**, *119*, 10551.

(3) Xue, S.; Yu, S.; Deng, Y.; Wulff, W. D. *Angew. Chem., Int. Ed.* **2001**, *40*, 2271.

(4) (a) Antilla, J. C.; Wulff, W. D. *J. Am. Chem. Soc.* **1999**, *121*, 6403. (b) Antilla, J. C.; Wulff, W. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 4518. (c) Loncaric, C.; Wulff, W. D. *Org. Lett.* **2001**, *3*, 3675.

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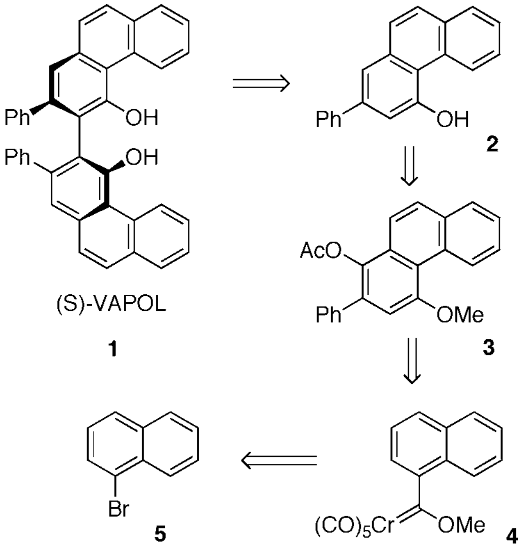
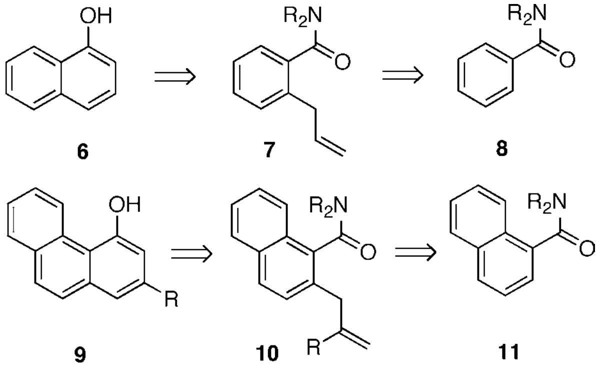
Scheme 1



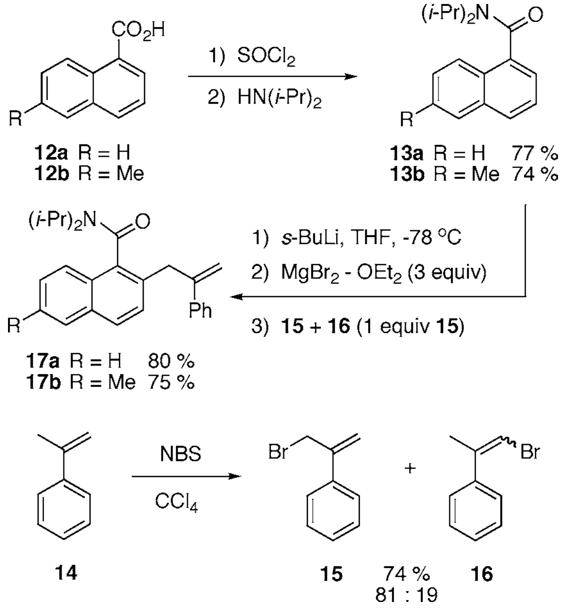
to derivatives of VAPOL that did not require starting with 1-naphthyl bromides.

Some time ago, Sibi, Dankwardt, and Snieckus reported a synthesis of naphthols from benzene carboxamides.[6] This annulation is a two-step process that involves directed metalation with an alkyllithium and then subsequent alkylation with allyl bromide to give the ortho-substituted benzamide **7** (Scheme 2). The key step in their phenol synthesis was realized with the discovery that the allyl group could be metalated with strong bases such as methyllithium and lithium diisopropylamide with subsequent intramolecular addition of the resulting carbanion to the amide function and, after ketone formation, tautomerization to a naphthol. Although other examples of this process are known,[7] this method has not yet been extended to 1-naphthyl carboxamides nor to 2-substituted allyl halides. If this were possible, then a direct approach to the synthesis of 4-phenanthrols would result as outlined in Scheme 2 (**9** from **11**).

Scheme 2



Scheme 3



Naphthalene carboxylic acids **12a** and **12b** were converted to the corresponding acid chlorides and then reacted with diisopropylamine under Schotten−Baumann conditions to give amides **13a** and **13b** in good yield (Scheme 3). As was found by Sibi, Dankwardt, and Snieckus for benzene carboxamides, [6] the ortho-lithiated amides derived from **13** could not be directly alkylated with an allylic bromide. In accord with the procedure developed by Sibi, Dankwardt, and Snieckus, if the ortho-lithiated species is trans-metalated by the addition of freshly prepared magnesium bromide etherate, the resulting organomagnesium can be alkylated with allylic halides in good yields in THF. Due to the poor solubility of the amide **13a**, an attempt to perform this reaction in ether led to no reaction. The ortho-metalation is best done at −78 °C: if it is done at 0 °C, the yield of **17a** decreases to 47%. Also, it was found that ortho-metalation of the diethylamide corresponding to **13a** gave a lower yield of **17a**.[8] In contrast to the procedure of Sibi, Dankwardt, and Snieckus,[6] we found that **13a** could be ortho-metalated without TMEDA[8] and that optimal yield could be achieved with 1 equiv of the electrophile. It was found, however, that 3 equiv of magnesium bromide etherate was required for

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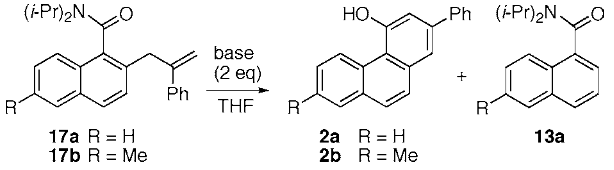
optimum yield. The requisite allylic halide, α-bromomethylstyrene **15**, is prepared by the bromination of α-methylstyrene.[9] This bromination with NBS produces an 81:19 mixture of the allylic bromide **15** and the vinyl bromide **16** that is used directly in the alkylation process since the vinyl bromide **16** is unreactive under these conditions.

The base-induced intramolecular cyclizations of the amide **17a** and **17b** were successful with methyllithium and gave high yields of the phenanthrols **2a** and **2b** as long as the reaction mixture was warmed to room temperature (Table 1). If the reaction temperature was brought from −78 to −20 °C before quench, no product was observed, and if the quench occurred at −5 °C, then only a 51% yield of **2a** was observed. The reaction could also be run in ether rather than THF. Although the amide **17a** is not completely soluble in ether and a slurry was obtained, a good yield of **2a** could nonetheless be obtained (85%). Methylmagnesium bromide could also be used as the base; however, to effect efficient closure, the solution needed to be brought to reflux. Interestingly, the use of LDA as a base led to the cleavage of the allyl group and the isolation of the amide **13a** in 60% yield (Table 1). This type of process was not observed by Sibi et al.[6] They found that LDA also gave cyclization products with benzene carboxamides that had been ortho-alkylated with simple allyl bromide.

Table 1. Ring-Closure of *O*-Allylamide **17**



17a R = H
17b R = Me

2a R = H
2b R = Me

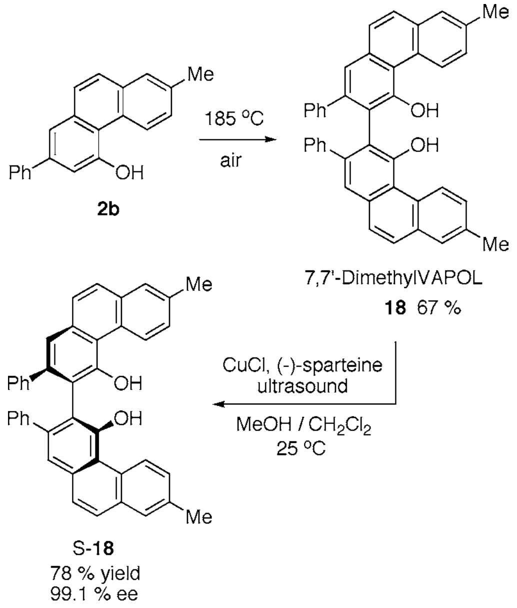
13a

substrate	base	temp	time (h)	yield of **2** (%)	yield of **13** (%)
17a	MeLi	−78 to 25 °C	15	90	
17a	LDA	−78 to 25 °C	15		60
17a	*s*-BuLi	−78 to 25 °C	20		*a*
17a	MeMgBr	25 to 68 °C	15	80	
17b	MeLi	−78 to 25 °C	15	80	

[a] A 60% yield of **13a** was isolated.

The two step conversion of the amide **13a** to the phenanthrol **2a** was also examined in a one-pot process. After the allyl bromide **15** was added to the metalated amide and warmed to room temperature, the reaction mixture was recooled to −78 °C and treated with 6 equiv of methyllithium (to compensate for the extra 2 equiv of $MgBr_2$−etherate). This led to the isolation of **2a** in a reasonable 60% yield; however, it contained a few small impuritites and was difficult to purify. While this synthesis has not been carried out on a molar scale, the alkylation of amide **13a** was performed on a 10 g scale to give **17a** in 60% yield after purification by silica gel chromatography, which is lower than that obtained on a 1 g scale (80%).

Scheme 4



2b

7,7'-DimethylVAPOL
18 67 %

S-**18**
78 % yield
99.1 % ee

This new strategy for the synthesis of vaulted biaryl ligands was applied to the preparation of 7,7′-dimethylVAPOL (Scheme 4). The oxidative dimerization of the 4-phenanthrol **2b** was accomplished by melting **2b** in an Erlenmeyer flask and then maintaining the temperature of the flask at 185 °C for 20 h in the presence of air. The product is then extracted from the dark solid mixture and purified by silica gel chromatography to give racemic 7,7′-dimethylVAPOL **18** in 67% yield. Optically pure VAPOL can be obtained either by resolution[1] or by deracemization.[5] The latter is more convenient for the preparation of small quantities of ligands for screening purposes. Thus, the deracemization of **18** was accomplished by the in situ generation of a Cu(II)−(−)-sparteine complex by the ultrasonic treatment of CuCl with (−)-sparteine in the presence of air and then the exposure of this copper complex to racemic **18** under an inert atmosphere. After 24 h, the ligand was purified by chromatography on silica gel to give 7,7′-dimethylVAPOL **18** as the (*S*)-enantiomer in 99.1% ee with a 78% recovery. The efficacy of this ligand in asymmetric catalysis will be reported independently.

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Supporting Information Available: Synthetic procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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