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Optically Active (*aR*)- and (*aS*)-Linear and Vaulted Biaryl Ligands: Deracemization versus Oxidative Dimerization

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Abstract: The copper-mediated deracemization of the *C*2-symmetric vaulted biaryl ligands VANOL and VAPOL has been investigated. In the course of the studies that have led to a more reliable procedure for this process, an unprecedented oxidative dimerization of these ligands has been uncovered. The structures of these oxidative dimerization products were elucidated by a series of NMR experiments, and these assignments were supported by other spectroscopic techniques as well as their chemical reactivity. This oxidative dimerization process was not observed for the linear biaryl ligands BANOL and BINOL, although the new deracemization procedure was effective for the generation of BINOL with high optical purity. The (*aS*)-enantiomers of BINOL, VANOL and VAPOL were accessible with a copper complex of (−)-sparteine, and the (*aR*)-enantiomeric series were accessible with a copper complex of O'Brien's diamine. Both (−)-sparteine and O'Brien's diamine give higher optical purities with VANOL and VAPOL than with BINOL, and this is consistent with the steric congestion present in the matched and mismatched copper complexes of these diamines with the biaryl ligands.

Introduction

*C*2-Symmetric biaryl compounds are among the most versatile and efficient ligands in asymmetric synthesis with BINOL **4a** as undoubtedly the most important ligand in this class.[1] Much effort has been focused on the modification of BINOL **4a** to afford a larger and more defined chiral pocket in order to improve enantioselectivity with the majority of the most successful BINOL derivatives bearing substituents in the 3- and 3′-positions (**4**, R ≠ H).[2] We have developed a new class of *C*2-symmetrical biaryl ligands in which the conjugated π-aromatic fused-ring systems of the ligand serve to define the chiral pocket. The two prototypes of this class of vaulted biaryl ligands are VANOL **2a** and VAPOL **3** (Scheme 1).[3,4] The term vaulted biaryl is used as a descriptor for VANOL and VAPOL since the aromatic ring systems curve around the nascent active site as opposed to BINOL, a linear biaryl, where the two aromatic ring systems are parallel to each other and thus linearly disposed. As a consequence of this design, the VANOL and VAPOL ligands have proven to be superior to BINOL in many important catalytic asymmetric reactions including Diels−Alder reactions,[5] aziridination reactions,[6] Mannich reactions,[7] Baeyer−Villiger reactions,[8] heteroatom Diels−Alder reactions,[9] the amidation[10] and imidation[11] of imines, the asymmetric reduction of imines,[12] desymmetrization of aziridines,[13] the Petasis reaction,[14] and the hydroarylation of alkenes.[15] We have also previously developed a method for the copper(II)-mediated deracemization of the VANOL and VAPOL ligands, which in the presence of (−)-sparteine constitutes a method for the conversion of the racemate of either VANOL or VAPOL into the corresponding (*aS*)-ligands with high mass conversion and >99% ee in each case.[16] Unfortunately, (+)-sparteine is not a naturally occurring ma-

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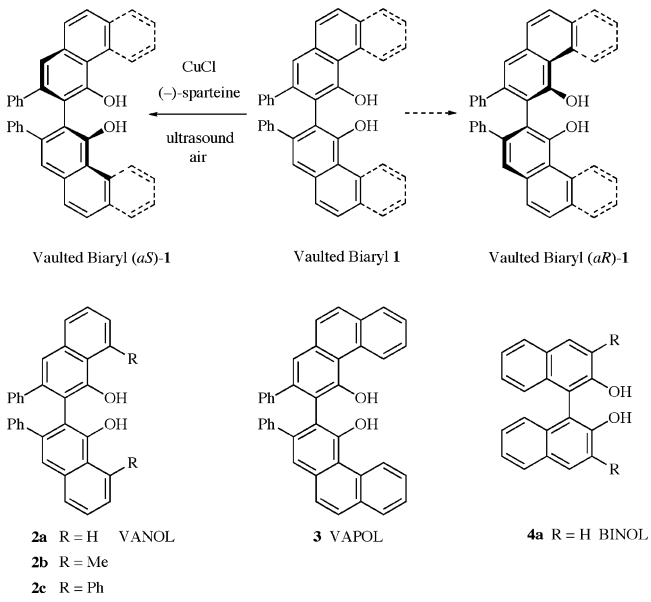
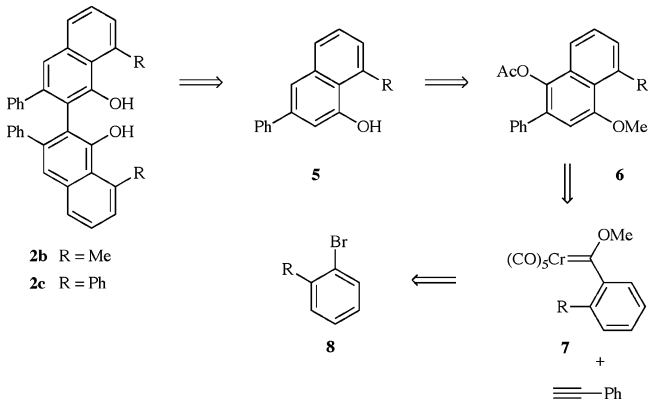
Scheme 1



Scheme 2



terial, and for access to (*aR*)-VANOL and (*aR*)-VAPOL one must rely on a classical resolution.[3] The purpose of the present work is 2-fold: (1) determine if O'Brien's surrogate for (+)-sparteine will enable access to the (*aR*)-enantiomers of VANOL and VAPOL from a copper-mediated deracemization, and (2) the synthesis and deracemization of the two new 8,8′-disubstituted VANOL derivatives **2b** and **2c**, which should have an even more defined chiral pocket than VANOL. In addition to the successful realization of these two objectives, a dramatically improved protocol has been developed for the deracemization procedure, and an unprecedented copper-mediated dimerization of the VANOL and VAPOL ligands was observed during the course of the optimization of the deracemization procedure.

Synthesis of the 8,8′-VANOL Derivatives 2b and 2c

The retrosynthetic analysis outlined in Scheme 2 for the proposed synthesis of **2b** and **2c** follows the strategy employed in our original synthesis of VANOL **2a**.[3] The syntheses begin with 2-bromotoluene and 2-bromobiphenyl, which serve as the precursors to the Fischer carbene complexes **7b** and **7c**. The naphthalene core is then to be assembled by the benzannulation reaction[17] of the chromium carbene complex **7** with phenylacetylene, which should give rise to a 4-methoxy-1-naphthol and, upon acetylation, the 4-methoxy-1-acetoxynaphthalene **6**. An aluminum chloride mediated reduction of the acetoxy group in **6** by 1-propanethiol would be expected to furnish the naphthol **5**, the penultimate intermediate in the retrosynthesis. The final step in the synthesis of the racemic ligands **2b** and **2c** is to be the phenolic coupling of the naphthol **5**, which is anticipated to be most effective with air as oxidant as it is in the synthesis of VANOL **2a**.

The benzannulations of the *o*-methylphenyl carbene complex **7b** and of the biphenylcarbene complex **7c** with phenylacetylene have not been previously reported. The reaction of **7b** with 2 equiv of phenylacetylene was carried out in THF at 60 °C for 19 h to give, after acetylation, a mixture of three structurally different products (Table 1, entry 1). The desired naphthalene **6b** was only obtained in 33% yield and was isolated in addition to 12% of the phenol **10b** and 25% of the naphthalene **11b**, both of which result from the incorporation of 2 equiv of phenylacetylene. Based on the mechanisms proposed for the formation of the byproduct **10** and **11**,[3,17] the amount of these products could be reduced by slow addition of phenylacetylene (1.2 equiv). Indeed, slow addition of phenylacetylene over 6 h resulted in an increase in the yield of **6b** to 61% and a concomitant reduction in **10b** and **11b** to less than measurable amounts (Table 1, entry 2). Similarly, the reaction of complex **7c** with phenylacetylene added all at once gave the naphthalene **6c** and the naphthalene **11c** resulting from the incorporation of two molecules of the alkyne (Table 1, entry 3). These two compounds proved to be difficult to separate; however, the need for separation was obviated by the fact that the formation of **11c** could be completely suppressed by either slow addition of alkyne (Table 1, entry 5) or by performing the reaction at low concentration (Table 1, entry 4). In the latter case, the low concentration led to incomplete acylation and the isolation of a mixture of the naphthalenes **6c** and **9c** in a total of 83% yield.

The demethylation of the methyl ether and the simultaneous reduction of the acetate group in the naphthyl derivatives **6b** and **6c** was achieved with aluminum chloride and a thiol following the protocol developed for the related transformation of **6a** (R = H) in the synthesis of VANOL **2a** (Scheme 3).[3] This is a mechanistically very intriguing reaction that apparently requires the presence of an aromatic hydrogen peri to the acetate group.[18] The oxidative phenol coupling reaction proceeded under the conditions developed for the synthesis of VANOL, which simply involve heating either of the naphthols **5b** or **5c** in a test tube at 165−190 °C and exposing the melt to air.[3] In this manner the two new vaulted biaryl ligands **2b** and **2c** were obtained in racemic form and were ready for conversion to optical pure material by the deracemization procedure that we had previously developed for VANOL and VAPOL.

Identification of Oxidative Dimerization Products in the Deracemization of Vaulted Biaryl Ligands

The deracemization of racemic VAPOL following the procedure we had previously developed[16] is shown in Scheme 4 and consistently provides (*aS*)-VAPOL with very high optical purity. Less consistent is the mass balance of the reaction. Although (*aS*)-VAPOL is generally obtained in good yields based on the total mass of the racemic material, there are some losses, and the yield of (*aS*)-VAPOL does vary as does the amount of an unknown yellow side product **12** that is formed

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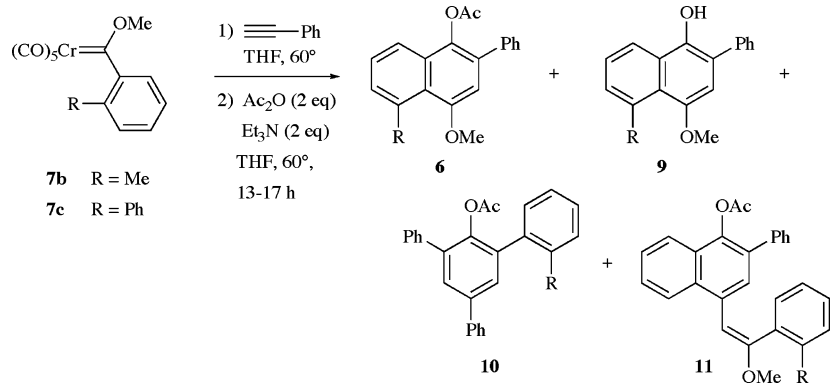
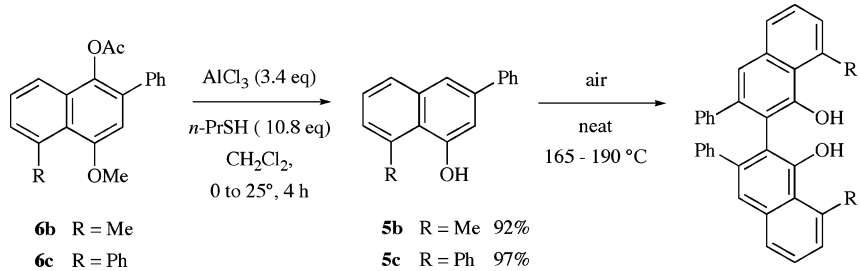
Table 1. Benzannulation of Carbene Complex **7** with Phenylacetylene[a]



entry	carbene complex	[**7**] (M)	alkyne addition[b]	yield (%)[c] **6**	**9**	**10**	**11**[d]
1	**7b**	0.5	A	33	nd	12	25
2	**7b**	0.5	B	61	nd	<1[e]	<1[e]
3	**7c**	0.5	A	41[f]	<1[e]	nd	12[f]
4	**7c**	0.005	A	29	54	nd	<1[e]
5	**7c**	0.5	B	62	<1[e]	nd	nd

[a] Unless otherwise specified, all reactions were carrried out in THF at 60 °C with 1.2−2.0 equiv of the alkyne. nd = not detected. [b] Method A: alkyne (2.0 equiv) added all at once, total reaction time for step 1 is 19 h. Method B: alkyne (1.2 equiv) added by syringe pump over a period of 6 h, total reaction time for step 1 is 7 h. [c] Unless otherwise specified, all yields are isolated yields. [d] Z-Isomer not detected. [e] Determined by ^{1}H NMR on crude reaction mixture. [f] Yield determined by the ^{1}H NMR spectrum of a purified mixture of **6c** and **11c** which are not separable by silica gel chromatography. Compound **6c** could be cleanly crystallized from the mixture in 15% yield.

Scheme 3



in the deracemization process. The structure of this yellow compound has remained elusive since it was first observed in 1996.[19] This compound is not very stable, which has hindered attempts at its characterization. The quinone **15** has been ruled out as a possible structure for this side product by comparison with an authentic sample.[16] Compound **12** slowly decomposes to VAPOL but not in a clean fashion. Although clean spectral data have not been obtained for this compound, the ^{13}C NMR spectrum suggests the presence of a carbonyl with a chemical shift of $\delta = 192.70$ ppm, which is supported by an absorption at 1635 cm^{-1} in the IR spectrum.[19] The presence of one sp^3 carbon is indicated by the 51.35 ppm resonance in the ^{13}C NMR spectrum. The ^{1}H NMR spectrum indicates the presence of one aliphatic proton at 4.09 ppm and an exchangeable hydrogen at 9.54 ppm.[19] All of these observations taken together suggested the structure **13** for this yellow side product; however, we have been hesitant to even make a tentative assignment since we have never before had any indication that VAPOL existed in any tautomeric form, although Gagné and co-workers have observed this for platinum complexes of VAPOL.[20]

The breakthrough in unraveling the structure of the side product in the deracemization reaction came with the finding that the side product **16a** in the deracemization of VANOL is much more stable and is tolerant of even the most time demanding NMR experiments. The deracemization of VANOL **2a** under our previously described conditions[16] gave (*aS*)-VANOL in 75% yield and 99.5% ee along with a 17% yield of the yellow side product **16a**. Unfortunately, the deracemization was not successful for the two new derivatives of VANOL, **2b** and **2c**. For these ligands the (*aS*)-enantiomer of **2b** and **2c** was obtained in <20% yield, and in the case of **2c** the side product **16c** was now the major product (31%). Interestingly, it was found that the side product **16a** could be converted to (*a*S)-VANOL **2a** in 82% yield and 97.5% ee by treatment with methyl lithium. This conversion is consistent with the structure **14** as the side product **16a**, but the high retention of stereoisomeric purity would not necessarily be expected for a structure of the type **14**. Instead, it might be expected that structure **14** would lead to racemization via rotation about the sp^3−sp^2 carbon−carbon bond (see Discussion section).

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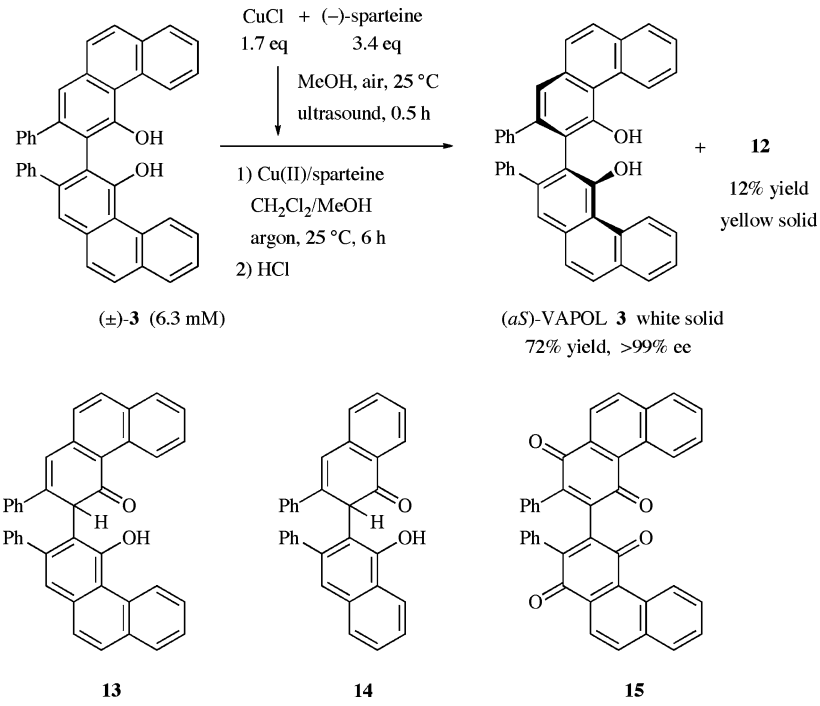
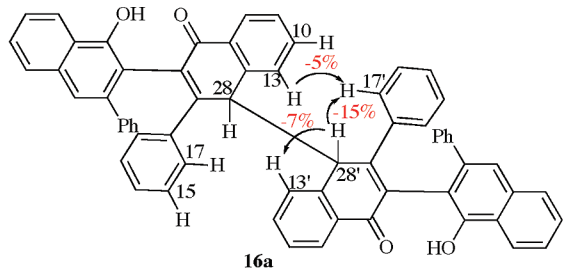
Scheme 4



The structural assignment of the byproduct **16a** (Figure 1) was made possible by a series of NMR experiments (gCOSY, gHMQC, gHMBC, DPFGSE-NOE, and ROESY). This compound results from the oxidative coupling of VANOL at a position *para* to the hydroxyl function. Key to the elucidation of this structure was the presence of a negative NOE enhancement between H13 and H17′ in the DPFGSE-NOE experiment. The magnitude and negative phase of this NOE is highly unlikely for the monomeric compound. Since all enhancements are negative, it is likely that the compound has a molecular weight above 800. This is based on the dependence of the relative phase of NOE enhancements on, among other factors, NMR field strength, sample temperature, and molecular correlation time.[21] The molecular weight for VANOL **2a** and its tautomer **14** is 438, and that for the dimer **16a** is 874. In addition, in an experiment that always gives positive NOE enhancements and never has a zero point, a 2D-ROESY experiment mapped all of the ROE enhancement peaks, which was consistent with the dimeric structure as well. Spectroscopic support for the dimeric structure was garnered from the HMBC spectrum, which shows a cross-peak between C28′ and H28. This is indicative of a two-bond coupling, which can only occur in the dimeric structure. The cross peak is not to be confused with a one-bond breakthrough peak that occurs as a result of



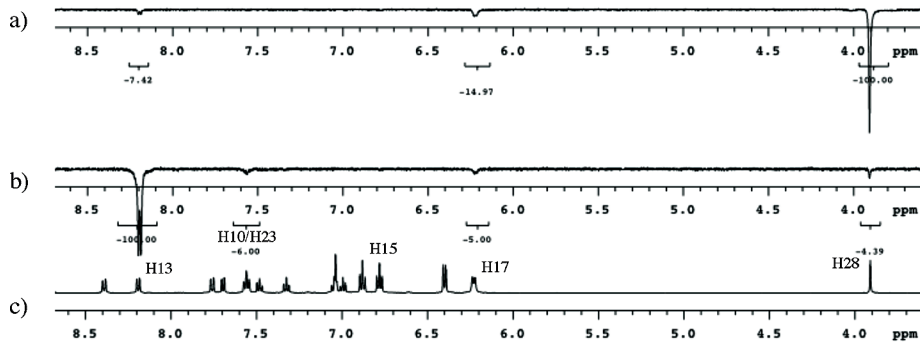
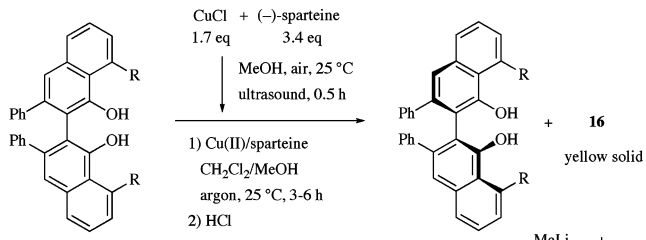


Figure 1. (a) Irradiation at H28 at 3.91 ppm gives NOE at H17 (6.22 ppm) and H13 (8.19 ppm). (b) Irradiation at H13 at 8.19 ppm gives NOE at H28 (3.91 ppm) and H17 (6.22 ppm) and H10 (7.56 ppm together with H23). (c) ^{1}H NMR spectrum of **16a** in d_6-DMSO.

Scheme 5



Biaryl	R	% Yield **2**	% ee **2**	% Yield **16**
2a	H	75	99.5	17
2b	Me	19	85	18
2c	Ph	10	96.5	31

incomplete suppression by the J-filter. The HMBC is run without decoupling and the one-bond peak is observed as a doublet with a coupling constant between 125 and 210 Hz. The cross peak we observed was a singlet. Finally, a molecular ion of the dimer could not be observed in the mass spectrum with either EI or FAB ionization techniques; however, with electrospray ionization (ESI) a parent peak for the structure **16a** was observed.

The VANOL dimer **16a** is a stereogenically enriched species since all spectral data are consistent with a single diastereomer. Unfortunately, a crystal structure could not be obtained for the dimer **16a**, which would have made the assignment of the relative stereochemistry of the four different chiral elements in the molecule relatively straightforward. However, the dimer **16a** is an optically active compound, and as indicated in Scheme 5, cleavage of **16a** with methyllithium gives (*aS*)-VANOL with an optical purity of 97.5% ee. Therefore, the two axial chirality elements in the dimer **16a** can be assigned as *aS*. With the two remaining centers of chirality at carbons 28 and 28′ (Figure 1), the actual structure of dimer **16a** must be one of the four diastereomers indicated in Figure 2. The relative energies of each of these diastereomers were determined by energy minimization with the PM3 method with the Spartan program (Wavefunction, Inc.). The isomer with the lowest energy was found to be the (*aS,S,S,*a*S*) isomer, and on this basis the stereochemistry of dimer **16a** was assigned as the (*aS*,*S*,*S*,*aS*) isomer with the assumption that the more stable isomer is preferentially formed. It is interesting to note that the calculations reveal that of the four diastereomers, the (*aS*,*S*,*S*,*aS*) isomer has the shortest contacts between H13 and H17 and between H13′ and H17′ (1.735 Å, Figures 1 and 2), and this is consistent with the NOE data shown in Figure 1. By analogy with the VANOL dimer **16a**, the structure of the unstable side product obtained from the deracemization of VAPOL is assigned as the dimer **12** shown in Scheme 6 with the (*aS,S,S,aS*) configuration. The 4,4′-biscyclohexa-2,5-dienone unit present in both **16a** and **12** has precedent in the bianthrones of the type **17**, which can be generated either by oxidizing an anthrone[22] or by partially reducing an anthraquinone.[23] The 4,4′-biscyclohexa-2,5-dienone unit can also be generated by oxidation of certain naphthols[24] and phenols,[25] although in some cases they are the kinetic products of the oxidation since the aromatic tautomeric forms are isolated after chromatography[25] or upon treatment with base.[24b] In the case of bianthrone **17** the keto form is favored in both the dimer **17** and in the monomer (anthrone). The bis-

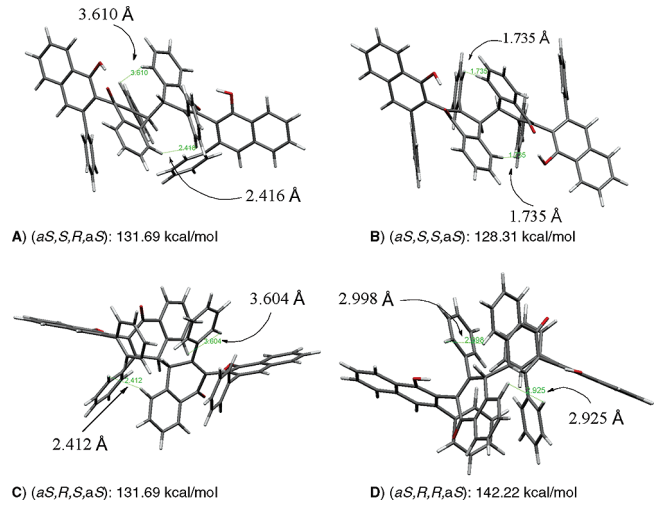
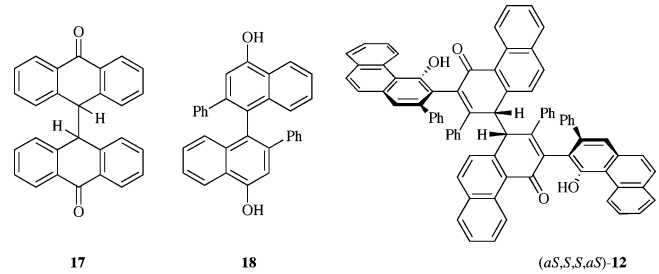


Figure 2. Computational structures of the possible diastereomers of the dimer **16a** optimized by PM3.

Scheme 6



naphthol **18** is related to structure **16a** and yet exists only in the aromatic phenol tautomeric form.[3] The fact that the coupling of VANOL and VAPOL occurs with a high fidelity in the relay of stereochemistry to give a single diastereomer of **16a** and of **12** is quite remarkable but is not understood at this time. In the rare cases where dimerization of a chiral naphthols have been reported, mixtures of diastereomers have been invariably produced.[22d,24b] Compound **18** is an isomer of VANOL **2a** and was prepared by a $FeCl_3$-mediated oxidative *para*,*para*-coupling of the naphthol **5a** (R = H), and VANOL was prepared by an air-mediated oxidative coupling of **5a** (R = H) (Scheme 3). The structure of **18** has close similarities to the dimer **16a**, and yet it exists exclusively in the enol form whereas **16a** exists exclusively in the keto form. This may be due to the increased steric congestion in **16a** and also presumably to the extra stabilization provided by intramolecular hydrogen bonding in **16a** between the phenol and the neighboring carbonyl group.

In the interest of efficiency it was decided to investigate whether the dimers of VANOL and VAPOL could be cleaved

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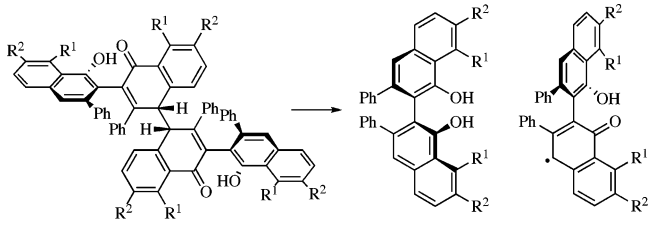
Table 2. Cleavage of Dimers of Vaulted Biaryl Ligands



(*aS*,*S*,*S*,*aS*)-**12** or (*aS*,*S*,*S*,*aS*)-**16** (*aS*)- **2** or (*aS*)- **3** **19**

entry	starting material	R^1	R^2	cleavng reagent[a]	solvent	temp (°C)	time (min)	yield (%)[b]	ee (%)[c]
1[d]	**2a**	H	H	heat	neat	195	40	95	79.5
2	**16a**	H	H	heat	neat	195	20	48	<5
3	**16a**	H	H	Triton-B	CH_2Cl_2	25	150	33	66
4	**16a**	H	H	MeLi	Et_2O	25	20	82	97.5
5	**16a**	H	H	Zn dust	HOAc	25	60	93	99.5
6[e]	**16b**	Me	H	Zn dust	HOAc	25	60	69	23
7	**16c**	Ph	H	MeLi	Et_2O	25	960	29	99
8	**16c**	Ph	H	Zn dust	HOAc	25	1960	57	95
9[f]	**12**	$-(CH)_4-$		Trition-B	CH_2Cl_2	25	15	25	<1
10	**12**	$-(CH)_4-$		Zn dust	HOAc	25	60	95	98

[a] For conditions of each experiment, see Supporting Information. [b] Isolated yield by silica gel chromatography. [c] Determined by HPLC on a Pirkle D-phenylglycine column except for **2c**, which was determined on a Chiralcel OD-H column. [d] Optical purity of **2a** was >99% ee. [e] **16b** was produced in a deracemization event that gave **2b** in 94% ee. [f] Reference 19.

to give the monomers and thus increase the mass balance in the deracemization process. All of the dimers reported in this work (**16a**, **16b**, **16c**, and **12**) are optically active and exhibit similar properties, although most are relatively unstable compared to **16a**. They are all relatively stable in the presence of HOAc, $NaHCO_3$, and Et_3N, but most decompose slowly at room temperature into their monomers but not in a clean fashion. It was anticipated that the carbon−carbon bond connecting the two monomeric units in **12** and **16** might be relatively weak. This anticipation was supported by a series of known crystal structures of bianthrones of the type **17** (Scheme 6) in which all derivatives had a very long carbon−carbon bond connecting the two anthrone units with a length of ≥1.60 Å in each case.[23] That the bond in the dimer **16a** is relatively weak is supported by the fact that heating **16a** to 195 °C for 20 min led to the complete consumption of the dimer **16a** and to the formation of VANOL **2a** in 48% yield as racemic material (Table 2, entry 2). As a control, optically pure VANOL **2a** (>99% ee) was heated at 195 °C for 40 min and was recovered in 95% yield with some loss in optical purity (79.5% ee, Table 2, entry 1). Prior to the determination of the structure of **16a**, the side product was suspected to be the keto tautomers **13** or **14** (Scheme 4), and thus it was thought that treatment with a base may lead to tautomerization to VANOL or VAPOL. This led to the experiments in which **16a** was treated with Triton B and methyllithium. In the case of methyllithium, this reaction leads to the formation of VANOL in 82% yield and 97.5% ee. In light of the structure **16a** it is likely that methyllithium is serving as a reducing agent and if this is true then a much milder reducing agent may give even better results. Indeed, when **16a** is treated with zinc dust, VANOL is obtained in 93% yield with 99.5% ee, which is the same % ee as the VANOL that is obtained from the same deracemization reaction (Scheme 5). Very similar results were obtained in the cleavage of the VAPOL dimer **12** with zinc dust (Table 2, entry 10). However, this protocol was not as useful for the VANOL derivatives **16b** or **16c** where the reactions either became quite sluggish (Table 2, entry 8) or resulted in substantially reduced optical purity of the monomeric product (Table 2, entry 6). Nonetheless, at least for VANOL and VAPOL, it is quite remarkable that the copper-mediated dimerization to produce **16a** and **12** occurs to produce a single diastereomer with four elements of chirality. Just as remarkable is the fact that the zinc(0) or methyl lithium mediated reduction of **16a** and **12** occurs with no significant epimerization of the axis of chirality to give VANOL and VAPOL. Clearly, neither the radical **19** nor the corresponding anion from subsequent reduction will undergo epimerization. Although **12** and **16** are reminiscent of the trityl dimer,[26] we have found no evidence that the radical **19** is persistent as the ^1H NMR spectrum of **16a** has all sharp resonances.[27]

Deracemization of Vaulted and Linear Biaryls

An improved protocol for the copper-mediated deracemization with (−)-sparteine was discovered during the optimization of the deracemization of the 8,8′-diphenylVANOL **2c**. Our original procedure[16] gave high asymmetric induction (≥99% ee) for both VANOL and VAPOL but nonetheless still had some drawbacks, which include the necessity for low concentration and problems with reproducibility in yield. The original procedure calls for the in situ generation of a Cu(II)−sparteine complex by the ultrasonification of a methanolic solution of 1.4 equiv of CuCl and 2.8 equiv of (−)-sparteine in the presence of air. This complex was then used to deracemize VANOL or VAPOL under an argon atmosphere, and after the appropriate time the reaction mixture was quenched with concentrated HCl. This procedure gives VANOL with 99.5% ee in 75% yield (Table 3, entry 1) and VAPOL with 99% ee in 72% yield (Table 3, entry 10). This protocol was applied to the deracemization of the diphenyl VANOL derivative **2c** with disastrous results. The optically purity of **2c** was 96.5% ee, but it was recovered in only 10% yield (Table 3, entry 6). It is notable that in this reaction the major product is the dimer **16c** (31%). Upon the chance that the loss in mass balance could be attributed to a hydrolytically resistant copper complex, the reaction was repeated but quenched with 30% aqueous ammonia rather than concentrated HCl, and much to our delight the yield of **2c** increased to 62% and the amount of dimer dropped to 3% (Table 3, entry 7). Unfortunately, when the reaction was performed on a larger scale, the asymmetric induction dropped from 98% to 88% ee (Table 3, entry 8). It was realized that excess NH_3 might replace (−)-sparteine as the copper ligand and consequently cause partial epimerization. After a few other bases were screened, it was found that a quench with saturated sodium bicarbonate gave the optically pure (99.5% ee) diphenylVANOL **2c** in 78% yield (Table 3, entry 9). This procedure brought significant improvement to the deracemization of both VANOL and VAPOL that led to a dramatic increase in the yield at the expense of the dimeric products **16a** and **12**, which were essentially eliminated (Table 3, entries 2 and 11). Unfortunately, even the improved protocol could not be used for the deracemization of 8,8′-dimethylVANOL **2b**, and the reasons for this failure are not clear at this time. Traditional resolution techniques were required to obtain optically pure enantiomers of **2b**, and these can be found in Supporting Information.

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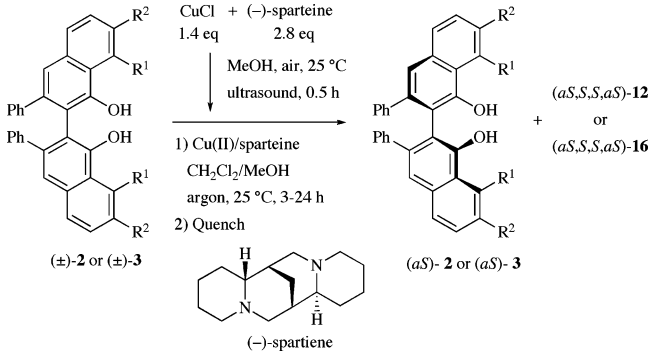
Table 3. Deracemization of Vaulted Biaryl Ligands with (−)-Sparteine[a]

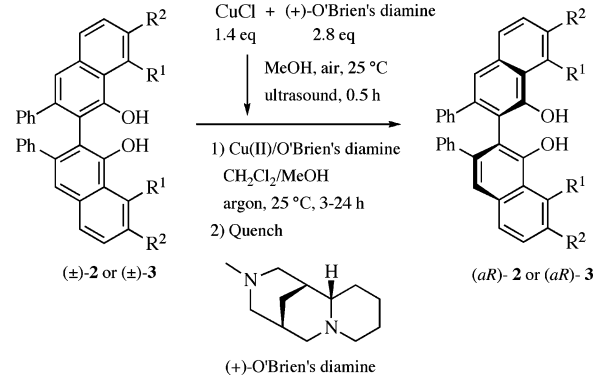


entry	Ligand	R^1	R^2	time (h)	quench[b]	yield (%) **2** or **3**[c]	ee (%) **2** or **3**[d]	yield (%) **12** or **16**[c]
1	**2a**	H	H	3	HCl	75	99.5	17
2	**2a**	H	H	3	$NaHCO_3$	92	99.5	1
3	**2b**	Me	H	4	HCl	19	85	18
4	**2b**	Me	H	4	$NaHCO_3$	4[e]	86	tr
5	**2b**	Me	H	24	$NaHCO_3$	4	95	tr
6[f]	**2c**	Ph	H	6	HCl	10	96.5	31
7[f]	**2c**	Ph	H	9	aq NH_3	62	98	3
8[f,g]	**2c**	Ph	H	9	aq NH_3	69	88	7
9[f]	**2c**	Ph	H	9	$NaHCO_3$	78	99.5	tr
10[f,h]	**3**	$-(CH)_4-$		6	HCl	72	99	12
11[f,h]	**3**	$-(CH)_4-$		6	$NaHCO_3$	92	>99	tr

[a] Unless otherwise specified, 1.4 equiv of CuCl and 2.8 equiv of (−)-sparteine were sonicated in air in methanol for 30 min at 0.05 M in CuCl. After being purged with argon for 30 min, the green Cu-diamine solution was transferred to a 0.01 M solution of the racemic ligand in deoxygenated CH_2Cl_2, and the mixture was allowed to stir at room temperature for the indicated time. The overall concentration of the ligand was 6−8 mM. [b] Quench was either with concd HCl, satd $NaHCO_3$, or 30% aq NH_3. [c] Isolated yield after silica gel chromatography. [d] Determined by HPLC on a Pirkle D-phenylglycine column except for **2c** which was determined on a Chiralcel OD-H column. [e] TLC indicated a significant component at the baseline. [f] 3.4 equiv of (−)-sparteine and 1.7 equiv of CuCl were used. [g] Entry 8 used 435 mg of **2c**, and entry 7 used 148 mg. [h] Racemic **3** was purified by crystallization from toluene and contains 0.5 equiv of toluene.

The deracemization of VANOL and VAPOL with (−)-sparteine gives the (*aS*)-enantiomers of the ligands with very high optical purity; however, it was not possible to obtain the (*aR*)-enantiomers of the ligands by the deracemization process since (+)-sparteine is not available from nature. O'Brien's diamine has been developed as a surrogate for (+)-sparteine and can be synthesized in three steps from (−)-cytisine, a natural product that is a 1.1% by weight component of the seed of *Laburnum anagyroides*.[28a] O'Brien's diamine has been demonstrated to be quite successful in some asymmetric reactions, giving selectivities in general that are comparable to those from (−)-sparteine,[28] and one of these is the deracemization of BINOL[28b] using our original procedure.[16] Some computational models indicate that this diamine should be just as efficient in chirality transfer as (−)-sparteine despite its smaller size.[29]

Table 4. Deracemization with Vaulted Biaryl Ligands with O'Brien's Diamine[a]



entry	ligand	R^1	R^2	time (h)	quench[b]	yield (%) **2** or **3**[c]	ee (%) **2** or **3**[d]	yield (%) **12** or **16**[c]
1	**2a**	H	H	2	$NaHCO_3$	97	>99.5	2
2	**2b**	Me	H	3	$NaHCO_3$	trace	nd	nd
3	**2b**	Me	H	3	HCl	33	94	9
4	**2c**	Ph	H	4	$NaHCO_3$	72	99	tr
5	**2c**	Ph	H	9	$NaHCO_3$	53	>99.5	tr
6[e]	**3**	$-(CH)_4-$		5	$NaHCO_3$	98	>99.5	tr

[a] Unless otherwise specified, these reactions were carried out as described in Table 3 [b] Quench was with either concd HCl or satd $NaHCO_3$. [c] Isolated yield after silica gel chromatography. nd = not determined. [d] Determined by HPLC on a Pirkle D-phenylglycine column except for **2c**, which was determined on a Chiralcel OD-H column. [e] Racemic **3** was purified by crystallization from toluene and contains 0.5 equiv of toluene. Reaction performed with 1.7 equiv of CuCl and 3.4 equiv of (−)-spartiene.

The data in Table 4 demonstrates that O'Brien's diamine is an effective surrogate for (+)-sparteine for the deracemization of vaulted biaryls giving comparable or even improved results in terms of both yield and enantioselectivity. VANOL and VAPOL can be obtained as the (*aR*)-enantiomers in optically pure form (>99.5% ee) in 97% and 98% yields, respectively (Table 4, entries 1 and 6). Furthermore, compared with (−)-sparteine, the deracemization time can be shortened for most of the ligands without loss of optical purity. However, O'Brien's diamine does not work well for ligand **6b**, although a higher yield and enantioselectivity were obtained than with (−)-sparteine (Table 4, entries 2 and 3).

The new deracemization protocol was extended to BINOL given the general importance of this ligand in asymmetric catalysis.[1,2] In general the deracemization of BINOL was found to be slower than the deracemization of either VANOL or VAPOL, and the asymmetric inductions were in the mid 90% range ee rather than >99% ee. With our older procedure, we had previously reported that (*S*)-BINOL could be obtained in 97% yield with 92% optical purity with a copper/(−)-sparteine complex (Table 5, entry 1).[16] The new protocol with the basic workup gives essentially the same result (Table 5, entry 2), but interestingly, a yellow side product was produced not from the reaction quenched with HCl but rather from the reaction quenched with the $NaHCO_3$. The amount of the side product is quite small to the point where the yield of (*S*)-BINOL is not significantly affected. Although yellow, the structure of the side product **20a** is quite distinct from that obtained with the vaulted biaryls. This compound is not a dimer of BINOL but rather an oxidized form of the monomer, which is assigned as compound **20a** on the basis of its spectral data. The structurally similar compound **20b** has been previously reported in 91% yield from the reaction of BINOL with $CuCl_2$ and ethanolamine in

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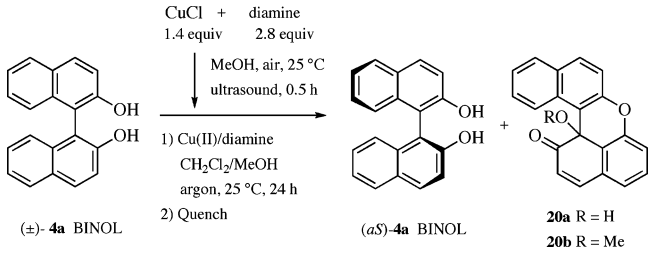
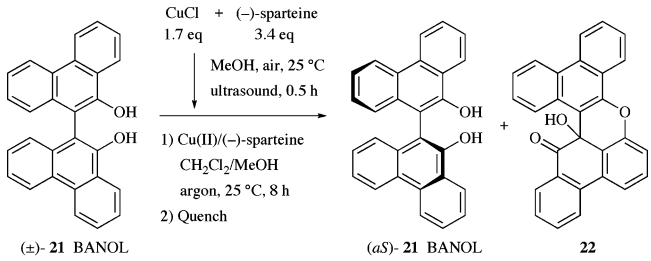
Table 5. Deracemization of (±)-BINOL with (−)-Spariene and O'Brien's Diamine[a]

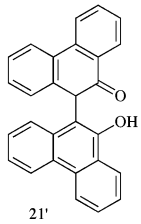


entry	diamine	quench [b]	yield (%) 4a[c]	ee (%) 4a[d]	config 4a	yield (%) 20a[c]
1[e]	(−)-sparteine	HCl	97	92	*S*	0
2	(−)-sparteine	$NaHCO_3$	95	93	*S*	3
3[f]	O'Brien's diamine	HCl	95	94 (98)	*R*	0
4	O'Brien's diamine	$NaHCO_3$	93	94.5	*R*	4
5[e]	O'Brien's diamine	$NaHCO_3$	96	93	*R*	nd

[a] Unless otherwise specified, these reactions were carried out as described in Table 3. Reaction time is 24 h. [b] Quench was with either concd HCl or satd aq $NaHCO_3$. [c] Isolated yield after silica gel chromatography. nd = not determined. Stereochemistry of **20a** was not determined. [d] Deterimined by HPLC with Chiralpak AS column. Data in parentheses was determined by Chiralpak AD column, which did not give as good separation but matches that reported in ref 28b. [e] The reaction mixture was stirred at room temperature for 8 h and then at −20 °C for 16 h and then quenched at −20 °C. [f] The reaction was carried out with the exact conditions specified in ref 28b.

Scheme 7





21'

Quench	% Yield 21 [a]	% ee 21 [b]	% Yield 22 [a]
HCl	70	55 (99)	10
$NaHCO_3$	58	34 (99)	18

[a] Isolated yield after chromatography on silica gel. The stereochemistry of **22** was not determined. [b] Determined by HPLC on a Chirpak AD column. Values in parenthesis are of material rapidly filtered through silica gel.

methanol in the presence of air.[30] The improved deracemization procedure can be used to access highly optically enriched (*aS*)-BINOL and (*aR*)-BINOL. The latter can be obtained in nearly the same yield and with a slight increase in asymmetric induction if O'Brien's diamine was used instead of (−)-sparteine.[28b]

The deracemization procedure was also examined for 10,10′-dihydroxy-9,9′-biphenanthryl **21** (BANOL), which is a biaryl ligand that has features of both the linear biaryl BINOL **4** and the vaulted biaryl VANOL **2a** (Scheme 7). BANOL has been demonstrated to be useful as a chiral ligand on several different occasions.[31] Given the highly conserved topological properties of the chiral pockets of BANOL and VANOL, it was anticipated that the deracemization of BANOL would lead to optical purities closer to those of VANOL (>99% ee) than those of BINOL (92−94% ee). Indeed, (*aS*)-BANOL of 99% ee could be obtained from the copper/(−)-sparteine-mediated deracemization of racemic **21**. Care needs to be exercised in the isolation of (*aS*)-BANOL as it apparently epimerizes during purification by column chromatography on silica gel and low optical purities are observed (34−55% ee). However, high optical purities (99% ee) can be obtained if the crude product is rapidly flashed through a small plug of silica gel.

The ease of epimerization of BANOL relative to BINOL, VANOL, and VAPOL may be related to the anticipated greater stability of the keto tautomer **21′** compared to keto tautomers for the other ligands. The deracemization of BANOL gives the side product **22** that results from oxidation of the ligand and is analogous to compound **20a** obtained in the deracemization of BINOL.

The optimized protocol for the deracemization described in the present work builds on previous studies for copper-mediated deracemization with chiral diamines. The early protocols determined the optimal stoichiometry of copper to diamine as 1:2.[16,32] Since it is thought that only 1 equiv of diamine is coordinated to the copper, the need for a second equivalent of diamine was interpreted to result from the neutralization of the HCl formed when the copper phenoxide complexes of the chiral biaryls are generated. If this is correct, then it may be possible to reduce the amount of the chiral diamines in the procedure by employing a second nonchiral base for the task of neutralization. Indeed, this is possible as indicated by the data in Table 6 where solid Na_2CO_3 was used as the second base. The procedure is essentially the same as that outlined in Table 3 and employs 1.4 equiv of CuCl, 1.4 equiv of chiral diamine, 1.4 equiv of Na_2CO_3, and a quench of the reaction with saturated aqueous $NaHCO_3$. The deracemization of BINOL with this procedure gives slightly lower yields and optical purities than with 2.8 equiv of chiral diamines (Table 5 vs Table 6), especially for O'Brien's diamine. VANOL gives essentially the same optical purities for both procedures, although the yields are a little lower with the auxiliary base protocol for both (−)-sparteine (Table 3, entry 2 vs Table 6, entry 2) and O'Brien's diamine (Table 4, entry 1 vs Table 6, entry 12). VAPOL on the other hand gives the same yield and same optical purities for both procedures with either (−)-sparteine (Table 3, entry 11 vs Table 6, entry 9) or with O'Brien's diamine (Table 4, entry 6 vs Table 6, entry 14). These results with VAPOL may be due to the fact that 1.7 equiv of the diamine is used rather than 1.4 equiv. It is also important to note that it is possible to recover (−)-sparteine and O'Brien's diamine from these reactions (see Supporting Information). Another important aspect of the use of an aqueous $NaHCO_3$ quench in these reactions is also evident in the data in Table 6; the reaction is no longer concentration-limited. The concentration of the reaction for the deracemization of VANOL can be increased by over a factor of 12, and the yields and optical purities are unchanged (Table 6, entries 2 vs 3). This same increase in concentration with our original procedure that involves an HCl quench led to a dramatic

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Table 6. Deracemization with Na_2CO_3 as Auxilliary Base[a]

entry	racemic ligand	diamine	scale (mg)	time (h)	concn (mM)[b]	yield (%) ligand [c]	ee (%) ligand [d]	config ligand	side product[b] (% yield)
1	BINOL (**4**)	(−)-sparteine	200	24	30	91	89	*aS*	**20** (4)
2	VANOL (**2a**)	(−)-sparteine	500	2	8	82	99.9	*aS*	**16a** (tr)
3[e]	VANOL (**2a**)	(−)-sparteine	1314	2	100	84	99.8	*aS*	**16a** (tr)
4[e,f]	VANOL (**2a**)	(−)-sparteine	1314	2	100	29	96.6	*aS*	**16a** (25)
5[g]	VANOL (**2a**)	(−)-sparteine	250	2	8	66	99.6	*aS*	**16a** (tr)
6[h]	VANOL (**2a**)	(−)-sparteine	500	2	8	70	99.6	*aS*	**16a** (1.5)
7[i]	Ph_2VANOL (**2c**)	(−)-sparteine	117	6	8	50	>99	*aS*	**16c** (tr)
8[i,j]	VAPOL (**3**)	(−)-sparteine	293	5	13	88	>99	*aS*	**12** (tr)
9[e,i,j,k]	VAPOL (**3**)	(−)-sparteine	1465	29	125	92	99.2	*aS*	**12** (tr)
10	BANOL (**21**)	(−)-sparteine	173	8	6	43	45 (99)	*aS*	**22** (8)
11	BINOL (**4**)	O'Brien's diamine	200	24	30	89	81	*aR*	**20** (5)
12	VANOL (**2a**)	O'Brien's diamine	500	2	15	76	>99	*aR*	**16a** (tr)
13[i]	Ph_2VANOL (**2c**)	O'Brien's diamine	117	6	8	54	>99	*aR*	**16c** (tr)
14[i,j]	VAPOL (**3**)	O'Brien's diamine	293	5	13	96	>99	*aR*	**12** (tr)

[a] Unless otherwise specified, 1.4 equiv of CuCl and 1.4 equiv of (−)-sparteine were sonicated in air in methanol for 30 min. After being purged with argon for 30 min, the green Cu-diamine solution was transferred to a suspension of the racemic ligand and 1.4 equiv of Na_2CO_3 in deoxygenated CH_2Cl_2, and the mixture was allowed to stir at room temperature for the indicated time. The reaction was then quenched with satd aq $NaHCO_3$. [b] Concentration of ligand in the CH_2Cl_2/methanol solvent system. [c] Isolated yield after chromatography on silca gel. [d] Determined by HPLC on a Pirkle D-phenylglycine column except for **2c**, which was determined on a Chiralcel OD-H column; **21**, which determined on a Chirapak AD column; and **4**, which was determined on a Chirapak AS column. Value in parentheses is on material not purified by column chromatography on silica gel. [e] Solid Na_2CO_3 and solid racemic ligand were added to the solution of the Cu-spartiene complex because it was too thick to be transferred. [f] The reaction was quenched with concd HCl. [g] The reaction was carried out with 1.05 equiv of CuCl, 1.05 equiv of (−)-sparteine, and 1.05 equiv of Na_2CO_3. [h] 2.8 equiv of $(i\text{-Pr})_2$NEt was used in place of 1.4 of equiv Na_2CO_3. [i] The reaction was performed with 1.7 equiv of diamine, 1.7 equiv of CuCl, and 1.7 equiv of Na_2CO_3. [j] Racemic VAPOL was crystallized from toluene and contained 0.5 equiv of toluene. [k] Optically purity was 88% ee after 5 h.

decrease in yield.[16] This is illustrated here by the auxiliary base protocol where the yield of VANOL with a base quench is 84% at 100 mM (Table 6, entry 3) and with an HCl quench the yield drops to 29% (Table 6, entry 4), which is accompanied by a 25% yield of the dimer **16a**. The procedures developed in the present work with base quench protocols also allows for the deracemization of VAPOL without concentration limitations (Table 6, entries 8 and 9).

Discussion

The copper-mediated deracemization of bis-phenols is an example of a dynamic thermodynamic resolution,[33] but the details of the mechanism are not known with a great deal of precision; some likely possibilities are presented in Scheme 8. The process presumably begins with the formation of the copper(II) complex **23** containing both the chiral bis-phenol ligand and the chiral diamine complex.[34] While the exact pathway by which the axial element of chirality is inverted is not known, it has been shown by crossover experiments on oligonaphthalene derivatives that the inversion does not involve rupture of the carbon−carbon bond connecting the two aryl units in a process that would be the reverse of the copper-mediated oxidative coupling of phenols.[35] Two pathways for inversion of chirality that maintain the carbon−carbon bond are shown in Scheme 8. Pathway A is proposed in light of the work of Kozlowski and co-workers on the asymmetric oxidative coupling of BINOL and its derivatives.[36] The key transformation is the rehybridization of one of the carbons comprising the 2,2′-biaryl bond via a protonation event leading to the copper complex **24**. As a consequence, one of the oxygens (carbonyl) becomes weakly bonded to the copper center and as a result the rotation barrier about the biaryl axis should be substantially reduced. This allows the terminal phenyl groups to rotate past each other (**24** to **25**), thereby converting the mismatched complex **23** to the matched complex **26**.

Pathway B is based on an unorthodox C,O binding mode which has been demonstrated in some biaryl-Pt and Pd complexes.[37] Gagné and co-workers found that both O,O binding and C,O binding can exist in platinum complexes of VANOL and VAPOL.[37c] In addition they found that in the presence of a chiral bis-phosphine ligand, the binding mode was dependent on whether the chiral bis-phenol and the chiral bis-phosphine were matched or mismatched. When the two ligands were mismatched, the C,O binding mode dominates and when they are matched, the O,O binding dominates. On the basis of these observations, we propose that pathway B for inversion of the axial element of chirality should also be considered. Gagné's results suggest that it may be the case that the mismatched O,O-bound complex **23** may prefer to exist as the C,O-bound complex **27**. Interconversion of **27** to the diastereomeric C,O-bound complex **28** can be followed by relaxation to the more stable O,O-bound matched complex **26**. One possibility for the interconversion of **27** to **28** involves the copper(I) radical species **30** that has a sp^3-hybridized radical center.[34] For all of the possible processes that invert the axial element of chirality, it is likely that sp^3-hybridization of one of the axial carbons is necessary to allow for the terminal phenyl groups to move past one another. The equilibrium between the mismatched and matched complexes **23** and **26** must be further toward the matched case for VANOL and VAPOL as compared to BINOL since the former give >99% ee and the latter gives 92−93% ee with (−)-sparteine. This would be consistent with the deeper chiral pocket for the vaulted biaryl ligands VANOL and VAPOL

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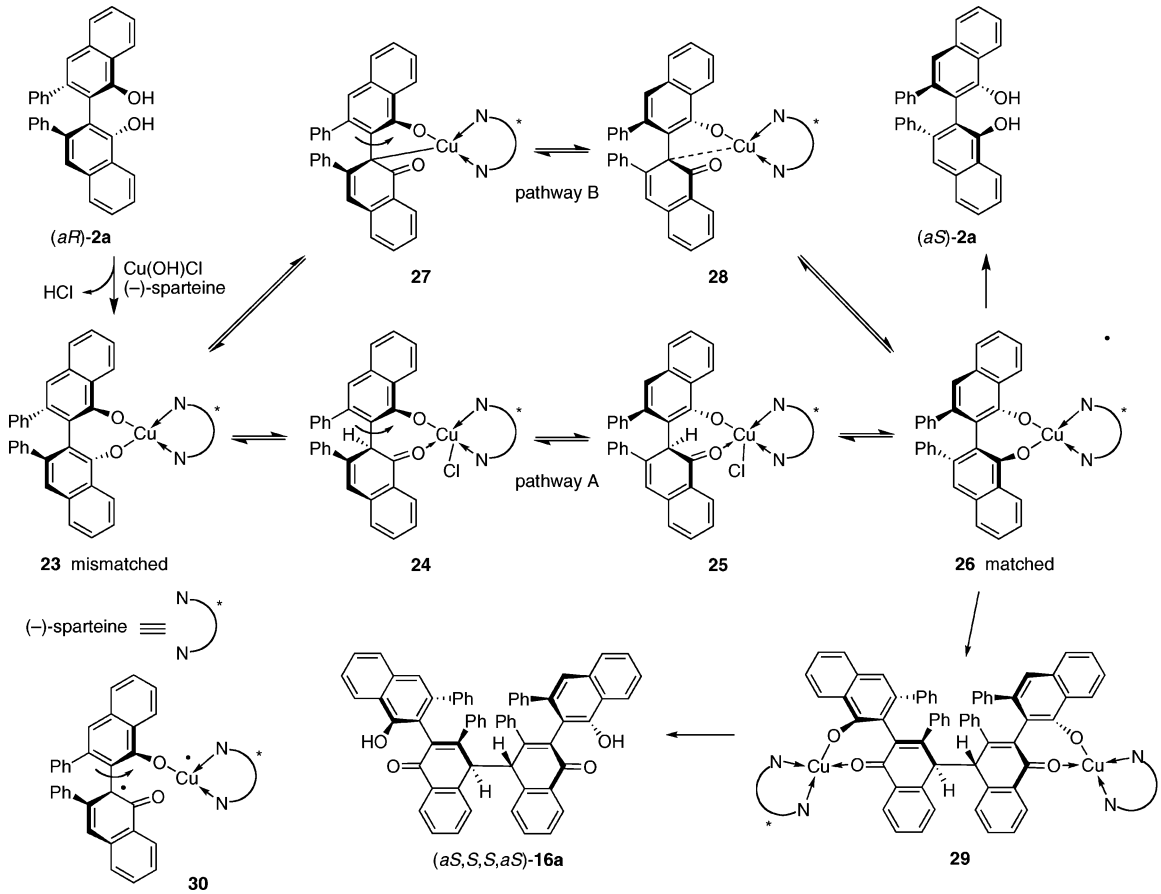
Scheme 8



compared to that of BINOL leading to a greater disparity in the energy difference between the matched complex **26** and the mismatched complex **23**. In the case of O'Brien's diamine, the matched complex would be **23** and the mismatched would be **26**. Hydrolysis of the matched complex **26** would then lead to the liberation of the (*aS*)-VANOL ligand **2a**. The dimerization product (*aS*,*S*,*S*,*aS*)-**16a** would presumably result from the hydrolysis of **29**, a dimerized form of the matched complex **26**. It is not clear at this point whether **26** and **29** are in equilibrium or whether the quench gives rise to a kinetic competition between the hydrolysis of **26** and its dimerization to **29**. Either would be consistent with the observation that more of the dimer product **16a** is obtained at higher concentrations.

Conclusion

A general method for the deracemization of chiral bis-phenols is developed that involves a copper(II) complex of (−)-sparteine. Limitations to the previous protocols were especially apparent in the deracemization of VANOL and VAPOL and included variability in yields and the necessity to perform the reactions at low concentrations (0.005 M). The development of an improved protocol began with the identification of a side product formed in the deracemization of VANOL. This product was identified as a dimer of VANOL, which results from the oxidative dimerization of VANOL at a position *para* to the phenol function. Remarkably, this compound exists exclusively in the thermodynamically more stable keto tautomer and contains four different chiral elements and yet is formed as a single diastereomer. The carbon−carbon bond connecting the two VANOL units is relative weak and can be reduced with either zinc dust or methyllithium to two molecules of VANOL in which the optical purity is retained (>99% ee). Further experimentation revealed that the formation of the dimeric side product could be suppressed by using a basic workup to quench the copper−VANOL complex. This led to increased and more reproducible yields in the deracemization of VANOL and, more importantly, to the finding that the deracemization was no longer sensitive to concentration, allowing for an increase in the scale upon which this reaction can be performed. The optimized procedure can be applied to the deracemization of VANOL and VAPOL in high yields (>90%) in optically pure form (>99% ee) and the deracemization of BINOL in high yields (97%) and excellent optical purity (93% ee). It was also shown that O'Brien's diamine could be used as a surrogate for (+)-sparteine in the deracemization of BINOL, VANOL, and VAPOL, giving the (*a*R)-enantiomers with either comparable or slightly improved yields and optical purities. Finally, it was shown that the amount of (−)-sparteine or O'Brien's diamine could be reduced from 2.8 to 1.4 equiv if a surrogate base replaced the difference.

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Supporting Information Available: Procedures for the preparation of new compounds, characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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