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Highly Enantioselective Deracemization of Linear and Vaulted Biaryl Ligands

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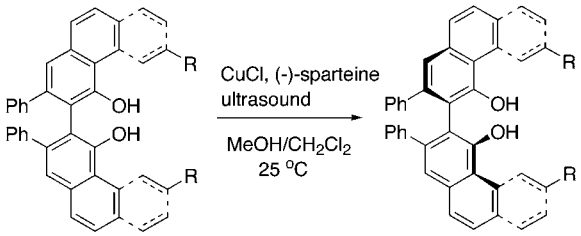
ABSTRACT



A copper-mediated deracemization of the vaulted biaryl ligands VANOL and VAPOL can be readily achieved in the presence of (–)-spartiene. The optimal procedure involves the in situ generation of copper(II) and leads to the reproducible formation of (*S*)-VANOL and (*S*)-VAPOL in greater than 99% ee from the racemates. This method is superior to existing procedures for BINOL (92% ee).

The development of highly efficient catalytic asymmetric reactions has been a major focus in modern synthetic organic chemistry and the design and synthesis of effective ligands necessarily plays an important role in this endeavor.[1] The C_2-symmetric vaulted biaryl ligands VANOL **2** and VAPOL **3** developed in our laboratories[2] have proved to be excellent ligands for several important catalytic asymmetric reactions such as Diels−Alder reactions,[3] imino aldol reactions,[4] and aziridination reactions.[5] The resolution procedures that are published for these two ligands follow a four-step procedure developed for BINOL that involves the bis-ester of phosphoric acid.[6] Salt formation of the BINOL bis-ester with (+)-cinchonine leads to diastereomers which can be separated by crystallization. Adaptation of this protocol to the resolution of VANOL and VAPOL was successful provided that (−)-brucine was used in salt formation with VANOL and (−)-cinchonidine was used with VAPOL.[2] The major drawback of this resolution protocol lies with the fact that it is a four-step sequence.

Subsequently, alternative methods for obtaining optically pure BINOL have been developed, including the optical resolution of diastereomeric salts prepared directly from BINOL,[7] asymmetric oxidative coupling of 2-naphthol,[8] and the copper-mediated deracemization of BINOL in the presence of a chiral amine or diamine.[9] As an example of the latter, the deracemization of BINOL with cupric chloride in

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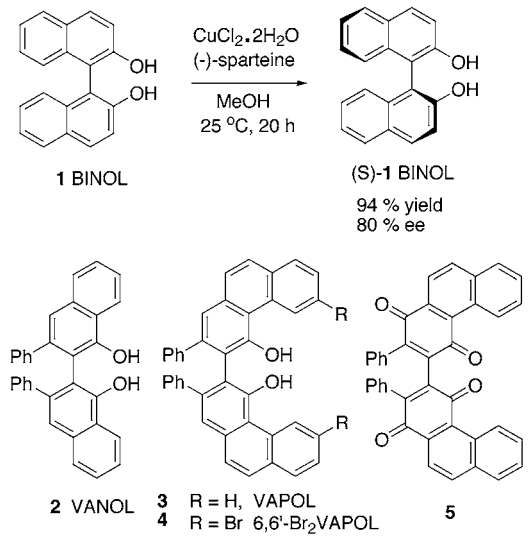
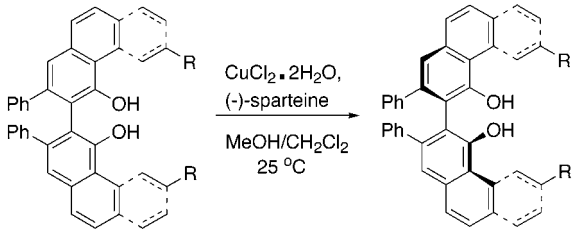
Scheme 1



the presence of (−)-sparteine has been reported to give the *S*-enantiomer of BINOL in 94% yield and in 80% ee.[9b] The subject of the present work is our studies on the adapation of this deracemization process to the VANOL and VAPOL ligands. It was found that this process works exceptionally well for both ligands with proper modifications of the experimental procedure and, furthermore, that this new procedure is also superior for the deracemization of BINOL.

The results of the direct application of the deracemization procedure reported for BINOL to the deracemization of VAPOL are shown in entry 1 of Table 1. Neither the yield nor the asymmetric induction is as high as that reported for BINOL. Given the lower solubility of racemic VAPOL in methanol, the reaction was repeated with a 1:2 mixture of methanol and methylene chloride as solvent, which provides a homogeneous solution throughout the reaction. Nonetheless, the outcome is essentially unchanged (entry 2). All other reactions in this work are also homogeneous. Decreasing the temperature of the reaction (entry 4) or decreasing the reaction time (entry 5) led to increased recovery, and the asymmetric induction in both cases dramatically decreased. In many cases the low yields are accompanied by the formation of yellow side-products that have not yet been characterized. It was shown that the quinone **5** is not produced in these reactions by oxidation with copper(II). This quinone can be obtained in 30−40% yield by the oxidation of VAPOL with cerric ammonium nitrate. Optimal results were found when the reaction was performed with 1.4 equiv of copper chloride and 2.8 equiv of (−)-sparteine, which gave a 64% yield of (*S*)-VAPOL with 99% ee (entry 7). Unfortunately, this success was not always reproducible as indicated in entry 7 when an attempt was made to scale this reaction to 1.0 g, which resulted in less than 10% recovery

Table 1. Decacemization with $CuCl_2 \cdot 2H_2O$[a]



entry	biaryl	scale (g)	solvent MeOH/CH_2Cl_2	time (h)	yield[b] (%)	ee[c] (%)
1[d]	**3**	0.1	MeOH only	24	62	71
2	**3**	0.1	1:2	20	59	75
3	**3**	0.1	1:2	2	54	49
4[e]	**3**	0.1	1:2	2	73	25
5	**3**	0.1	1:2	1	82	34
6	**3**	0.1	1:3.4	24	64	99
7	**3**	1.0	1:3.4	24	<10	
8	**4**	0.2	2:1	24	50	>98
9	**2**	0.6	2:1	20	71	90
10	**2**	0.6	2:1	46	42	98
11	**2**	0.6	2:1	50	77	99
12[f]	**2**	0.6	2:1	50	66	90
13[g]	**2**	0.6	2:1	50	55	93
14[h]	**2**	0.6	2:1	50	61	93
15	**2**	1.0	2:1	50	59	93

[a] Unless otherwise specified, the reaction was performed with 1.4 equiv of $CuCl_2 \cdot 2H_2O$ and 2.8 equiv of (−)-sparteine according to the general procedure (see Supporting Information). Entries 1−5 used 1.0 equiv of $CuCl_2 \cdot 2H_2O$ and 2.0 equiv of (−)-sparteine. The concentration was 15 mM for **3** and 7.6 mM for **2**. Entries 1−10 were deoxygenated by Argon purge, entries 11−15 were deoxygenated by the freeze−thaw method. [b] Isolated yield by chromatography. [c] Determined by HPLC on a Pirkle D-phenylglycine column. The *S*-enantiomer was obtained in all cases. [d] The VAPOL was recovered in 35% yield from a precipiate in 48% ee and in 27% yield from solution in 99% ee. [e] Reaction at 0 °C. [f] Yield is average of three runs. [g] Reaction at 40 °C. [h] Concentration of **2** was 15 mM.

of the VAPOL. This procedure could be successfully extended to the VAPOL derivative **4**.[10]

The deracemization of VANOL was performed under the conditions found optimal for VAPOL and the results are shown in Table 1, entries 9−15. After 20 h this produced a 71% recovery of VANOL that was 90% ee (entry 9). Monitoring of the time course of the reaction revealed that the deracemization is fast, giving 77% ee after the first hour (conditions as in entry 9). The optical purity could be increased to 98% ee if the reaction was allowed to continue for 46 h; however, the yield dropped to 42%. To probe the sensitivity of the reaction to traces of oxygen, these conditions were reinvestigated with reaction mixtures that were deoxygenated by the freeze−thaw method (entries 11−15).[11] We were delighted to find that the recovery was greatly improved (entries 10 vs 11) and the induction was still high (99% ee). However, the inductions were still variable as indicated by the fact that the reaction in entry 11 was repeated three times and the average of those three runs (entry 12)

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(10) The preparation of **4** will be reported separately.

(11) If the deracemization of VANOL was performed in air under the conditions in Table 1, no VANOL could be recovered.

was 90% ee. Thus, although the use of the freeze−thaw deoxygention technique generally gave better results, the procedure is time consuming, the results are variable, and it would be impractical on a larger scale.

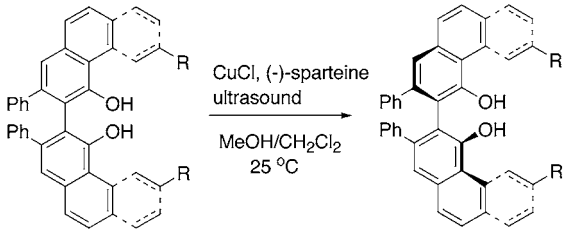
It has been suggested, but not demonstrated, that (*R*)-BINOL could be produced from a copper(I) complex with (−)-sparteine.[9c] Since (+)-sparteine is not available, this suggestion takes on great magnitude since it could provide for a direct route from racemic bis-phenols to either desired enantiotropic atropisomer. This possibility was tested on VAPOL and conducted with the aid of ultrasound due to the low solubility of cuprous chloride.[8d] The reaction was performed by deoxygenating a slurry of 1.67 equiv of CuCl, 3.3 equiv of (−)-sparteine, and 1.0 equiv of racemic VAPOL in a 1:4 mixture of methanol and methylene chloride by the freeze−thaw technique and then placing the mixture in an ultrasound bath for 10 min and allowing the homogeneous faint yellow reaction mixture to stir for 6 h in the absence of ultrasound. The VAPOL was recovered in 93% and was found still to be racemic (entry 9). The same reaction with CuCN or CuI also led to racemic VAPOL.

When the sonification of CuCl and (−)-sparteine is conducted in the presence of air, there is a rapid dissolution of CuCl along with concomitant formation of a green solution, presumably a copper(II) species (*vide infra*). If this solution is added to a solution of racemic VAPOL and allowed to react for 5 h the VAPOL is recovered in 75% yield and 95% ee. This is a much faster reaction than was seen for the deracemization with $CuCl_2$. In addition to the increased rate, this improved procedure is more reproducible and can be scaled up (entries 13 and 14).

The deracemization of VANOL with in situ generated copper(II) was found to be approximately twenty times faster than with commercial copper(II) chloride. Beginning with copper(II) chloride, the deracemization of VANOL occurs in 50 h to give a 59% recovery of material that is 93% ee (Table 1, entry 15). In contrast, beginning with copper(I) chloride, the deracemization of VANOL under the same conditions gives a 61% recovery of 99% ee material in only 2.5 h. It was also found that the deracemization of VANOL with $CuCl_2 \cdot 2H_2O$ under the aegis of ultrasound was also slow, requiring 24 h to go to completion (52% yield, 99% ee). A beneficial consequence of the shorter reaction time is that deoxygenation by the freeze−thaw method is not necessary to ensure good mass recoveries. All of the reactions in Table 2 are performed by a simple purging of the solution with argon prior to reaction. Importantly, it was found that the scale could be increased from 1 g to 5 g with no loss in recovery or asymmetric induction.

The deracemization of BINOL was also examined with the in situ generated copper(II) procedure. Employing conditions previously reported with copper(II) chloride,[9b] the in situ procedure gave a 77% recovery of BINOL with 93.5% ee. Other changes in the conditions were examined as outlined in Table 3 which lead to higher yields, but the asymmetric inductions appear to be limited to 92−93% ee. The effect of temperature on the induction was also probed with no change in the equilibrium observed for a reaction carried out at −20 °C for 16 h (entry 5). A higher recovery

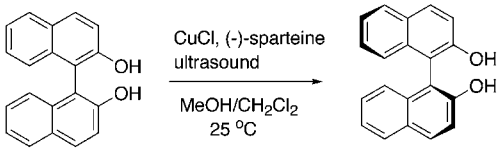
Table 2. Deracemization of Vaulted Biaryls with CuCl[a]



entry	biaryl	scale (g)	solvent MeOH/CH_2Cl_2	time (h)	yield[b] (%)	ee[c] (%)
1	**2**	0.3	1:4	1.75	79	99
2	**2**	1.0	2:1	2.5	61	99
3	**2**	1.0	1:4	2.75	72	99
4	**2**	1.0	1:9	2.5	48	98
5	**2**	1.0	CH_2Cl_2 only	48	49	84
6	**2**	2.0	1:4	2	70	99
7	**2**	5.0	1:4	2	69	99
8[d,e]	**2**	4.0	1:4	2	54	99
9[f]	**3**	1.0	1:4	6	93	0
10[e]	**3**	1.0	1:4	5	75	95
11[g]	**3**	1.0	1:4	6	72	72
12	**3**	2.0	1:4	4	74	98
13[h,i]	**3**	5.0	1:4	48	60	95
14[h,j]	**3**	5.0	1:4	6	84	99

[a] Unless otherwise specified, the reaction was performed with 1.4 equiv of CuCl and 2.8 equiv of (−)-sparteine according to the general procedure (see Supporting Information). The concentration was 6.2 mM for **3** and 7.6 mM for **2**. [b] Isolated yield by flash chromatography. [c] Determined by HPLC on a Pirkle D-phenylglycine column. [d] Concentration of **2** is 15 mM. [e] Yield is average of two runs. [f] See text for procedure. [g] Concentration of **3** is 24 mM. [h] 1.67 equiv of CuCl and 3.3 equiv of (−)-sparteine was used. [i] The product was purified by recrystallization with CH_2Cl_2/hexane. [j] The starting material used in entries 11−13 was purified by crystallization from ethyl acetate. In entry 14 the starting material was crystallized twice.

Table 3. Deracemization of BINOL with CuCl[a]



entry	concn (mM)	scale (g)	solvent MeOH/CH_2Cl_2	time (h)	yield[b] (%)	ee[c] (%)
1	33	0.286	MeOH only	20	77	93.5
2	7.6	0.2	1:4	8.5	94	92
3	7.6	0.2	1:2.5	24	83	92
4	15	0.2	1:2.5	24	93	92
5[d]	15	0.2	1:2.5	24	96	92
6[d]	30	0.2	1:2.5	24	97	92
7[d]	30	5.0	1:2.5	24	98	87

[a] Unless otherwise specified, the reaction was performed with 1.4 equiv of CuCl and 2.8 equiv of (−)-sparteine according to the general procedure (see Supporting Information). [b] Isolated yield by flash chromatography. [c] Determined by HPLC on a Chirapak AS column. [d] Reaction run at 25 °C for 8 h and then −20 °C for 16 h and then quenched at −20 °C.

is observed for those reactions that are quenched at −20 °C (entries 5−7). Nonetheless, the induction by this new procedure is significantly improved over that previously reported for BINOL (Scheme 1).

The reaction of copper(I) salts with diamines in the presence of oxygen is a well-known process that gives υ-oxo complexes that in most cases are dimers or trimers of Cu(diamine)X(OH).[12] The reaction of CuCl with 1 equiv of (−)-spartiene in methanol in the presence of air gave a 63% yield of a green solid that were assumed to be Cu(spartiene)Cl(OH).[12c] This material was not as effective in the deracemization of VAPOL as the in situ generated complex. It gave only a 47% recovery of VAPOL with 70% ee after 24 h in a 1:4 mixture of CH_2Cl_2/MeOH. This could be improved to a 57% recovery with 97% ee in the presence of 1.2 equiv of (−)-spartiene.

The preferential formation of the *S*-enantiomer is observed in the deracemization of BINOL, VANOL, and VAPOL. To probe the source of this selectivity we have performed PM3(tm) calculations with the Spartan program on the copper(II) complexes of (−)-spartiene and *R*- and *S*-VANOL (Figure 1). As has been observed experimentally for copper(II) complexes of (−)-spartiene,[12c] both complexes are seriously distorted from the normal square-planar geometry. The angle between the N−Cu−N plane and the O−Cu−O planes is 85.5° for the *R*-complex and only 40.6° for the *S*-complex, revealing that the *R*-complex is much more distorted from planarity. The *S*-complex was found to be 3.91 kcal/mol more stable than the *R*-complex, which is more than enough to account for the selectivities seen ($K_{S/R} = 730$). We imagine that the deracemization could involve keto forms of the naphthol and phenanthrol units as has been suggested previously for BINOL-type ligands.[12d]

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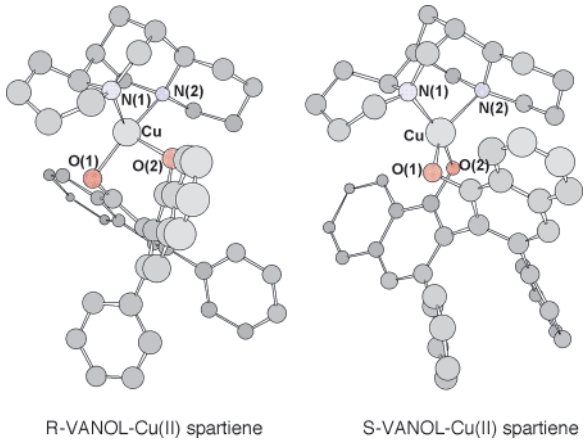

R-VANOL-Cu(II) spartiene S-VANOL-Cu(II) spartiene

Figure 1.

The deracemization procedure described above involving an in situ generated copper(II) species is superior to previous methods for the deracemization of BINOL and for the first time provides for a method for the deracemization of the VAPOL and VANOL ligands. Since (+)-spariene is not available this method is limited to preparation of the *S*-enantiomers. Recently a surrogate for (+)-spatiene has been introduced[13] and we plan to try this for the deracemization of these ligands to their *R*-enantiomers.

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

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