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Enantioselective Oxidative Biaryl Coupling Reactions Catalyzed by 1,5-Diazadecalin Metal Complexes: Efficient Formation of Chiral Functionalized BINOL Derivatives

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Chiral 1,5-diaza-*cis*-decalins have been examined as ligands in the enantioselective oxidative biaryl coupling of substituted 2-naphthol derivatives. Under the optimal conditions employing 2.5−10 mol % of a 1,5-diaza-*cis*-decalin copper(II) catalyst with oxygen as the oxidant, enantioselective couplings (44−96% ee) could be achieved for a range of 3-substituted 2-naphthols including the ester, ketone, phosphonyl, and sulfonyl derivatives. The relationship between the substitution of the naphthalene starting materials and reactivity/selectivity is determined by several factors which act in concert: (1) the effect of substituents on the oxidation potential of the substrate, (2) the ability of the substrate to participate in a chelated copper complex which depends on (a) the inherent coordinating ability of the 3-substituent and (b) substituent steric interactions that affect chelation between the 2-hydroxyl and 3-substituent, (3) the effect of substituents on dissociation of the product from the copper catalyst.

Introduction

Oxidative Biaryl Coupling. Oxidative coupling of phenols and naphthols is a useful method for the synthesis of biaryl compounds.[1] Because these reactions occur via a favorable one-electron phenolic oxidation, they can generally be carried out under mild reaction conditions and tolerate many functional groups. This versatility distinguishes oxidative biaryl coupling from other methods for the synthesis of chiral biaryls such as Kumada coupling, Suzuki coupling, and nucleophilic aromatic substitution.[2,3]

Oxidative coupling of phenols also serves as a key step in the biosynthesis of many natural products.[4] Since copper ions play an important role in the phenol oxidations mediated by copper proteins, extensive efforts have been made to understand the function of copper in biological systems and the mechanism of these oxidative reactions.[5] The study of the related mechanistic and synthetic aspects of oxidative biaryl couplings catalyzed by small-molecule complexes would provide insight into these important bioorganic transformations. In addition, the potential for enantioselective oxidative C−C bond forming reactions in the synthesis of natural products and pharmaceuticals remains largely untapped.

The asymmetric synthesis of biaryl derivatives has been of intense interest due to the utility of homochiral 1,1′-binaphthalene derivatives.[6] Of particular importance is the efficient, highly enantioselective synthesis of *new* BINOL compounds.[7] While many BINOL compounds can be generated from the parent BINOL,[8,9] few can be made efficiently from achiral starting materials. In seminal work, Wynberg,[4b] Brussee,[10] Yamamoto,[11] and Kočovský[12] found that functionalized chiral BINOL derivatives could be formed from 2-naphthols with stoichiometric chiral copper(II) amine oxidants. In a later study, Nakajima et

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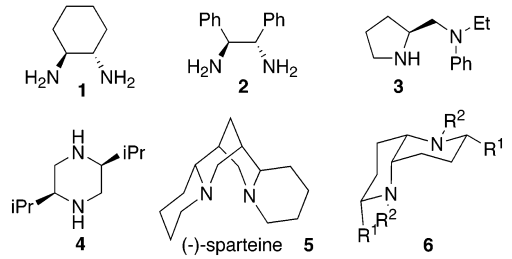
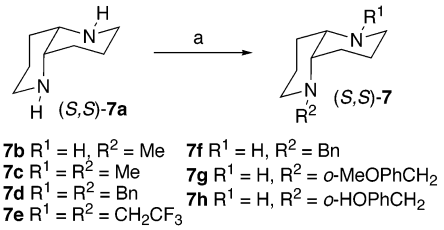
SCHEME 1



al.[9c,d] demonstrated that catalytic coupling of 3-carboalkoxy-2-naphthols with good enantioselectivity is possible using prolyldiamine (**3**) or sparteine (**5**) derived copper oxidants (Scheme 1). In a further advance, we have found that 1,5-diaza-*cis*-decalin **6** copper catalysts are highly selective in this reaction (eq 1).[13] By implementing several modifications, a variety of novel 3,3′-disubstituted BINOL derivatives can be synthesized. In this paper, we disclose the full results of these studies.

Chiral Diamines. Few significantly different chiral diamines have found general utility in asymmetric synthesis. The most widely used versions (**1**−**5**) are shown in Scheme 1.[14,15] We identified scaffold **6** as a potential lead from our efforts in the computer-aided identification of novel ligands.[16] We have demonstrated that diaza-*cis*-decalins **6**[17] are moderately effective in asymmetric lithiation−substitution[18] and highly effective in the enantioselective oxidative biaryl coupling of substituted 2-naphthol derivatives.[13a] Here, the development of the diaza-*cis*-decalin copper catalysts for the enantioselective oxidative coupling of a variety of functionalized 2-naphthols is presented.

SCHEME 2[a]



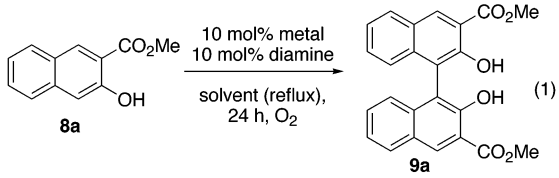
7b R^1 = H, R^2 = Me
7c R^1 = R^2 = Me
7d R^1 = R^2 = Bn
7e R^1 = R^2 = CH_2CF_3
7f R^1 = H, R^2 = Bn
7g R^1 = H, R^2 = *o*-MeOPhCH$_2$
7h R^1 = H, R^2 = *o*-HOPhCH$_2$

[a] Reagents and conditions: (a) (**7f**) BnBr, KOH, MeOH, reflux, 4 h, 50%. (**7g**) *o*-MeOPhCH$_2$Br, KOH, MeOH, reflux, 1 d, 29%. (**7g** → **7h**) BBr_3, 1 d, 29%.

Results and Discussion

Metal and Ligand Survey. Enantiomerically pure (*S*,*S*)-1,5-diaza-*cis*-decalin **7a** and its antipode (*R*,*R*)-**7a** are readily synthesized from commercial materials in three steps.[18a] The ligands **7b**−**e** (Scheme 2) were prepared from this material as described previously.[13a,18a] Ligands **7f** and **7g** were prepared by *N*-alkylation as shown in Scheme 2.

To survey the utility of the 1,5-diaza-*cis*-decalin structure, a number of oxidative metal complexes were formulated using chiral **7a** (Table 1, entries 1−3). The manganese,[19] iron,[20] and copper complexes all provided some selectivity in the oxidative biaryl coupling of 3-methoxycarbonyl-2-naphthol (**8a**) with oxygen as the terminal oxidant (eq 1). The copper catalyst gave the



(1)

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TABLE 1. Metal-Catalyzed Biaryl Couplings Using Ligand 7 (Eq 1)[a]

entry	diamine	diamine:metal	metal source	solvent	yield[b] (%)	ee[c] (%)
1	**7a**	1:1	$MnCl_2 \cdot 2H_2O$	CH_3CN	5	45 (*R*)
2	**7a**	1:1	$FeCl_3 \cdot 6H_2O$	CH_3CN	5	27 (*R*)
3	**7a**	1:1	CuCl	$ClCH_2CH_2Cl$	41	86 (*R*)
4	**7a**	2:1	CuCl	$ClCH_2CH_2Cl$	5	86 (*R*)
5	**7a**	1:1	CuCl	CH_2Cl_2	49	91 (*R*)
6	**7a**	1:1	CuCl	CH_3CN[d]	60	91 (*R*)
7	**7b**	1:1	CuCl	$ClCH_2CH_2Cl$	53	79 (*R*)
8	**7c**	1:1	CuCl	$ClCH_2CH_2Cl$	43	3 (*R*)
9	**7d**	1:1	CuCl	$ClCH_2CH_2Cl$	72	22 (*R*)
10	**7e**	1:1	CuCl	$ClCH_2CH_2Cl$	NR	
11	**7f**	1:1	CuI	$ClCH_2CH_2Cl/CH_3CN$[d]	66	70
12	**7g**	1:1	CuI	$ClCH_2CH_2Cl/CH_3CN$[d]	66	62
13	**3**[e]	1:1	CuCl	CH_2Cl_2	85	78 (*S*)
14	**5**[e]	1:1	CuCl	CH_2Cl_2	38	47 (*S*)

[a] All reactions were performed on a 0.5 mmol scale (0.1 M) and used the (*S*,*S*)-diamines. [b] Isolated yields. [c] Enantiomeric excess determined by HPLC (Chiralpak AD). Absolute configuration assigned by comparison to the literature. [d] Reaction run at 40 °C. [e] Reaction at room temperature. Results from ref 9d.

highest selectivity (86% ee in $ClCH_2CH_2Cl$ at reflux), and only the complex derived from CuCl turned over to any extent (about four turnovers). When air was used as the oxidant instead of O_2, the reaction proceeded with similar selectivity, but at a much slower rate. A 1:1 ligand−metal complex is responsible for the reactivity,[21] and excess ligand inhibits the reaction (entry 4).

Efforts were first directed at increasing the selectivity of the reaction. Lowering the reaction temperature (CH_2Cl_2 at reflux) improved the selectivity to 91% ee (entry 5). Lowering the reaction temperature further was detrimental; entry 5 at room temperature gives 33% yield and 86% ee. CH_3CN as solvent[22] enhanced conversion compared to CH_2Cl_2 or $ClCH_2CH_2Cl$ (entry 6 vs entries 5 and 3), and high selectivity (91% ee) was maintained. Since CH_3CN stabilizes the copper(I) oxidation state,[23] we were motivated to examine other variables (see below) that stabilize copper(I). For the purposes of comparison, entries 13 and 14 illustrate the best selectivities using Nakajima's prolyldiamine (78% ee) and sparteine (47% ee) derived catalysts.[9d]

To improve selectivity, derivatives of ligand **7** were examined (Table 1, entries 7−12). Although mono-*N*-methyl **7b** was slightly less selective (79% ee, entry 7) compared to parent **7a** (86% ee, entry 3), *N*,*N*′-dimethyl ligand **7c** provided no selectivity (3% ee, entry 8). A similar decrease in selectivity (entries 9 and 11) was noted upon successive substitution of **7a** with one benzyl group (**7f**; 70% ee) and two benzyl groups (**7d**; 22% ee). These results suggest that at least one secondary amine is necessary to achieve high enantioselectivity. The subtle role of the secondary amine is not clearly understood at the moment, but may involve a secondary interaction such as a hydrogen bond between the ligand N−H and the substrate carbonyl.

Interestingly, *N*-benzyl ligands **7d** and **7f** provided higher reactivity than the *N*-methyl ligands **7b** and **7c** (entry 7−9 and 11). From these data, it appears that sterically larger ligands are not deleterious to reactivity. The poorer donor properties of benzylamines ($pK_a(BnNMe_2H^+) = 9.03$ vs $pK_a(MeNMe_2H^+) = 10.12$) may explain the higher activity of the *N*-benzyl series.[24] Copper catalysts with the less basic *N*-benzyl ligands **7d** and **7f** possess a more electrophilic copper(II) which can coordinate the substrate more strongly and can undergo more facile reduction to copper(I). However, the lack of any reactivity with *N*,*N*′-bistrifluoroethyl **7e** indicates that a certain level of ligand donicity is needed.

TABLE 2. Examination of the Copper Source in the Catalyzed Biaryl Couplings (Eq 1)[a]

entry	Cu source	solvent	yield[b] (%)	ee[c] (%)
1	CuCl	CH_2Cl	56	91
2	CuBr	CH_2Cl	58	90
3	CuCl	CH_3CN	60	91
4	CuI	CH_3CN	85	91
5	CuI	CH_3CN	82	92[d]
6	CuOTf	CH_3CN	81	90
7	CuCN	CH_2Cl	5	24[d]
8	$Cu(BF_4)_2$	CH_3CN	52	90
9	$Cu(OAc)_2$	CH_3CN	<5	62
10	$Cu(OTf)_2$	CH_3CN	<10	78
11	$Cu(NO_3)_2$	CH_3CN/H_2O	<10	44
12	CuCl	MeOH	74	80
13	$CuBr_2$	MeOH	93	60
14	$CuCl_2$	MeOH	85	76
15	$CuSO_4$	$MeOH/H_2O$	<5	76

[a] 0.5 mmol of **8a** (0.1 M), 10 mol % Cu source, 10 mol % (*S*,*S*)-**7a**, 40 °C, O_2, 24−48 h. [b] Isolated yields. [c] Enantiomeric excess determined by HPLC (Chiralpak AD). The absolute configuration was *R* for all cases except entry 5. [d] (*R*,*R*)-**7a** was employed, and the (*S*)-product was obtained.

Reasoning that the slow step in the catalytic cycle is reduction of copper(II) to copper(I) under oxidizing conditions, species which stabilize the latter were examined (Table 2). In particular, the softer bromide and iodide counterions should stabilize copper(I) intermediates. In generating these new catalysts, their solubility was found to vary considerably. To allow comparison, the solvent was optimized for each catalyst to give homogeneous reaction conditions and prevent resolution via crystallization of diastereomeric complexes.[9b,10,12a]

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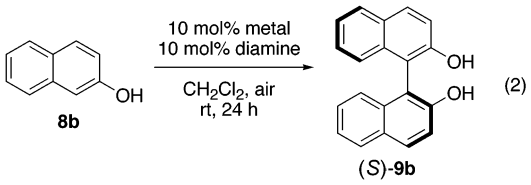
While CuBr (entry 2) did not provide any distinguishable improvement, CuI (entries 4 and 5) and CuOTf (entry 6) led to significantly higher yields. We have found that the catalyst formed from CuI, **7a**·CuI(OH)·$(H_2O)_x$, can be prepared conveniently on a large scale and stored indefinitely at room temperature.[25] As expected, the catalyst from the diamine antipode (*R*,*R*)-**7a** provided the enantiomeric product (*S*)-**9a** with the same conversion and level of selectivity as the catalyst from (*S*,*S*)-**7a**. Since both enantiomers of **7a** are readily available,[18a] both enantiomers of all the 1,1′-binaphthols described herein can be constructed using this method. CH_3CN solvent is required with CuI or CuOTf due to poor solubility in most other solvents. Solvent mixtures can be employed with no deleterious effects; for example, $ClCH_2CH_2Cl$, $CHCl_3$, and $PhCF_3$ can be added, but the addition of a coordinating solvent (acetone) lowers the yield (40%) and enantioselectivity (85% ee). The results from the copper source survey reveal three interesting trends. First, all the copper(I) sources in nonhydroxylic solvents provide essentially the same level of enantioselection with the notable exception of CuCN (entry 7). Dissociable counterions do not significantly impinge on the stereochemistry-determining step, but are relevant to turnover. The results with CuCN indicate that counterion dissociation is crucial to reactivity, perhaps by providing open coordination sites on the hindered diamine copper adduct (see below). Second, all the copper(II) sources except for Cu$(BF_4)_2$ led to lower selectivity (44−78% ee). A second coordinating counterion is deleterious in the stereochemistry-determining step. Third, the $CuCl_2$ and $CuBr_2$ catalysts in MeOH were the most reactive; however, the presumed methoxide adducts give rise to lower enantioselectivity.

For the biaryl coupling reaction of 2-naphthol (**8b**) (eq 2), overoxidation was observed when O_2 was used with



the copper catalysts, transforming **9b** (BINOL) into highly colored quinones. The biaryl coupling was sufficiently rapid that air could be used as the oxidant, which reduced byproduct formation. However, low enantioselectivities were observed (Table 3).

With the same chiral catalyst, BINOL (**9b**) was enriched in (*S*)-enantiomer in the biaryl coupling while **9a** was enriched in the (*R*)-enantiomer. Clearly, the reactions of **8a** and **8b** follow substantially different stereochemical courses. The coupling of **8a** probably proceeds via a conformationally rigid copper-bound intermediate (see Figure 2 below and the accompanying discussion). Whether **8b** reacts via a copper-bound species with low facial bias or a free radical is uncertain.

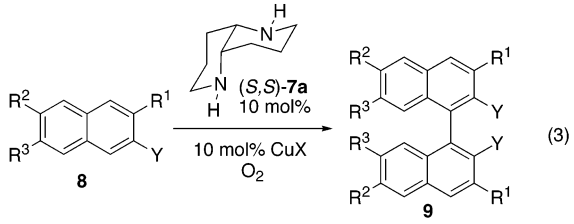
(25) Complexes (*R*,*R*)-**7a**·CuI(OH)·$(H_2O)_x$ and (*S*,*S*)-**7a**·CuI(OH)·$(H_2O)_x$ will be commercially available from Sigma-Aldrich, Inc., Milwaukee, WI, along with BINOL derivatives (*R*)-**9a** and (*S*)-**9a**.

TABLE 3. Biaryl Coupling of 2-Naphthol Using 7 (Eq 2)[a]

entry	diamine	metal source	time (d)	yield[b] (%)	ee[c] (%)
1	**7a**	CuCl	5	80	16
2	**7a**	CuCl	2	72[d]	13
3	**7a**	CuBr	2	42	14
4	**7a**	$CuBr_2$	2	52	13
5	**7a**	$Cu(BF_4)_2$	2	25	18
6	**7d**	CuCl	5	42	4
7	**7e**	CuCl	5	NR	
8	**7f**	CuCl	5	58	6
9	**7g**	CuCl	2	70	18
10	**7h**	CuCl	2	11	9
11	**3**[e]	CuCl	1	89	17
12	**5**[f]	CuCl	1	32	18

[a] All reactions were performed on a 0.5 mmol scale (0.1 M) and used the (*S*,*S*)-diamines. [b] Isolated yields. [c] Enantiomeric excess determined by HPLC (Chiralpak AS). Absolute configuration assigned by comparison to the literature. [d] Reaction run under O_2. [e] Reaction at room temperature under O_2 (from ref 9d). [f] Reaction at reflux under O_2 (from ref 9d).

Substrate Survey. A number of other substrates were then examined using the optimal **7a** copper complexes to establish the scope of the reaction (Tables 4 and 5, eq 3). Generally, O_2 was used as the oxidant, but with very



oxidizable substrates (**8d**, **8x**), air could be employed. As discussed above, substrates lacking C3 substituents, such as **8b** (entry 1 vs entry 5), underwent a much less selective coupling compared to **8a**, which possesses a C3 methyl ester. To determine if the electron-poor nature of **8a** was responsible for the elevated selectivity, 6-bromo-2-naphthol (**8c**) was examined. Even though the bromide of **8c** renders the substrate less electron rich than **8b**, similar selectivities were seen with these substrates (entries 1 and 2). The low selectivity (10−13% ee) with 9-phenanthrol (**8d**; entries 3 and 4) indicates that the presence of a simple steric group at C3 is not sufficient to ensure selectivity. Overall, these results point toward involvement of the C3 substituent in chelation[9d] with the catalyst to create a stereochemically well defined environment.

From these data, the nature of the C3 substituent appears to be important, and several additional substrates were examined to determine which chelating groups could be utilized. Ester groups are optimal, providing the products in 70−85% yield and 80−93% ee (Table 4, entries 5−8). The biaryl coupling of 6-bromo-substituted naphthol **8h** proceeded very slowly but with high selectivity (92% ee). Although the reaction was slower due to the electron-withdrawing bromide at C6, the enantioselectivity was not affected. The simple perturbation to the amides **8i**−**m**[26] (entries 11−15)

(26) The amides **8i** and **8k**−**m** were made via treatment of the acyl chloride from 3-hydroxy-3-naphthoic acid with the corresponding amines. See the Supporting Information.

TABLE 4. Scope of the Oxidative Biaryl Coupling Using 7a·CuX (Eq 3, Y = OH Unless Otherwise Noted)[a]

entry	8/9	R^1	R^2	R^3	7a	Cu source	solvent[b]	[8] (M)	t (h)	T (°C)	yield (%)	ee[c] (%)
1	**b**	H	H	H	(*S*,*S*)	CuCl	A	0.10	48	rt	81	16 (*S*)
2	**c**	H	Br	H	(*S*,*S*)	CuCl	A	0.10	24	rt	74	6 (*S*)
3	**d**	**8d** = 9-phenanthrol			(*S*,*S*)	CuCl	B	0.10	6	rt	63[d]	10 (*S*)
4	**d**	**8d** = 9-phenanthrol			(*S*,*S*)	CuCl	B	0.10	3	rt	53	11 (*S*)
5	**a**	CO_2Me	H	H	(*S*,*S*)	CuI	B or C	0.10	48	40	85	91−93 (*R*)
6	**e**	CO_2Bn	H	H	(*S*,*S*)	CuI	B	0.10	24	40	79	90 (*R*)
7	**f**	CO_2-*n*-Hx	H	H	(*S*,*S*)	CuI	B	0.10	48	40	70	87 (*R*)
8	**g**	CO_2-*t*-Bu	H	H	(*S*,*S*)	CuI	B	0.10	48	40	70	80 (*R*)
9	**h**	CO_2Me	Br	H	(*S*,*S*)	CuI	B	0.10	48	40	27	92 (*R*)
10	**h**	CO_2Me	Br	H	(*S*,*S*)	CuI	B	0.10	48	80	60	83 (*R*)
11	**i**	$CONEt_2$	H	H	(*S*,*S*)	CuI	B	0.10	48	40	48	72 (*R*)
12	**j**	$CONEt_2$	Br	H	(*S*,*S*)	CuI	B	0.10	48	40	47	53 (*R*)
13	**k**	$CON(CH_2)_4$	H	H	(*S*,*S*)	CuI	B	0.10	48	40	50	73 (*R*)
14	**l**	$CON(CH_2)_5$	H	H	(*S*,*S*)	CuI	B	0.10	48	40	48	70 (*R*)
15	**m**	$CON(CH_2CH_2)_2O$	H	H	(*S*,*S*)	CuI	D	0.10	48	40	61	75 (*R*)
16	**n**	COC_6H_4-*p*-NO_2	H	H	(*S*,*S*)	CuI	E	0.008	48	40	39	80 (*R*)[e]
17	**o**	COC_6H_4-*p*-CN	H	H	(*S*,*S*)	CuI	E	0.10	24	40	69	83 (*R*)
18	**p**	COC_6H_4-*p*-Cl	H	H	(*S*,*S*)	CuI	F	0.10	24	40	74	85 (90) (*R*)
19	**q**	COPh	H	H	(*S*,*S*)	CuI	F	0.10	24	40	88	89 (*R*)
20	**r**	COC_6H_4-*p*-OMe	H	H	(*S*,*S*)	CuI	E	0.10	24	40	93	90 (*R*)
21	**s**	COC_6H_4-*p*-Nme_2	H	H	(*S*,*S*)	CuI	E	0.10	24	40	84	94 (*R*)
22	**s**	COC_6H_4-*p*-NMe_2	H	H	(*R*,*R*)	CuI	E	0.10	24	40	82	94 (*S*)
23	**t**	COMe	H	H	(*S*,*S*)	CuI	E	0.10	24	40	7	72 (*R*)
24	**u**	CO-*t*-Bu	H	H	(*S*,*S*)	CuI	E	0.10	48	40	58	56 (*R*)
25	**v**	Y = NH_2, H	H	H	(*S*,*S*)	CuI	G	0.10	24	40	26	6 (*R*)
26	**w**	Y = NH_2, CO_2Me	H	H	(*S*,*S*)	CuI	B	0.10	72	40	<5	ND

[a] 10 mol % catalyst except entries 38, 39, and 41−44 (20 mol %). [b] A = CH_2Cl_2; B = $ClCH_2CH_2Cl$; C = CH_3CN; D = $ClCH_2CH_2Cl$, <10% THF; E = 3:2 CH_2Cl_2/MeCN; F = 2:1 CH_2Cl_2/MeCN; G = 1:1 $ClCH_2CH_2Cl$/MeCN; H = $ClCH_2CH_2Cl$, <10% DMF; I = 3:1:1 $ClCH_2CH_2Cl$/MeCN/DMF. [c] Enantioselectivity measured using HPLC (Chiralpak AD and AS). Values in parentheses are after enrichment. For entries 1−6, 11, 27, and 28 configurations assigned by comparison to the literature. For entries 13−15 and 30−32 configurations assigned by comparison to material generated from **9a**. For all others, configurations assigned by analogy. [d] Air was used as the oxidant. In all other entries O_2 was used (see eq 3). [e] Enantioselectivity measured by HPLC (Chiralpak AD) of the bismethyl ether derivative. [f] Enantioselectivity measured from the ^1H NMR spectra of the (−)-quinine complexes.

resulted in slower rates and lower selectivities; the best results were obtained with the morpholine amide **8m** (entry 15; 61% yield, 75% ee). Unlike the methyl ester example (**8a** vs **8h**), the addition of a 6-bromo substituent to the diethyl amide (**8i** vs **8j**) resulted in lower selectivity. The initial rate was slower for **8j**, but this difference was attenuated over time as **8j** and **8i** were produced with almost the same yield. Overall, a C3 amide group has a much greater effect on reactivity and selectivity compared to a C6 bromide group.

High levels of enantioselection were also observed for a variety of phenyl ketone naphthols[27] (entries 16−22). Aryl ketones with more electron withdrawing groups in the *para* position were less reactive compared to those with electron-donating substituents, but the enantioselectivities were similar (80−94% ee). The low reactivity (7% yield, 72% ee) of methyl ketone **8t** is best explained by competing enolization (entry 23). The higher reactivity (58% yield, 56% ee) afforded by the corresponding *tert*-butyl ketone **8u** (entry 24) supports this assertion.

The ester group at C3 most likely coordinates to the copper catalyst via the ester carbonyl.[9d] The lower enantioselection observed with the *tert*-butyl ester (entry 8, 80% ee) and the amides (entries 11 and 13−15, 70−75% ee) indicates that the portion of the chelating group which is pointed away from the metal can also affect the stereochemical course.[28] When this portion is large, as with **8i** (Figure 1), steric interactions destabilize the optimal planar conformation for chelation to the metal catalyst. Notably, the optimal chelating environment (coplanar naphthol C−O and C=O bonds) is found in the crystal structures of two products (**9a** and **9n**) (Figure 1) which form with high selectivity.

In analogy to 2-naphthol, the biaryl coupling of 2-naphthylamine (**8v**) to yield BINAM (**9v**) (entry 25) proceeded with low selectivity (6% ee). When the biaryl coupling of the amino analogue of **8a**, aminonaphthoate **8w**, was undertaken (entry 26), only a trace amount of the desired product **9w** was obtained. Instead, quinone imine **12** was produced in 72−80% yield (see below).

The departure from carbonyl derivatives to benzyl ether substrate **8x** (Table 5, entries 27 and 28) resulted in faster initial rates, due to the electron-rich nature of the naphthalene in **8x**, but lower selectivity (38−46% ee). In contrast to our observations with other substrates, the optimal copper source for **8x** proved to be $CuBr_2$ (entry 28) and not CuCl (entry 27) or CuI. The moderate enantioselectivity for benzyl ether **8x** suggests that a five-membered copper chelate with the two oxygens (Figure 2) allows some stereochemical induction especially compared to **8b**, which cannot form a chelate. However, this chelate is inferior to the six-membered chelate from a C3 carbonyl (Figure 2). Surprisingly, no reaction was observed with benzoyl derivative **8y**. Presumably, the disfavorable seven-membered chelate (Figure 2) prevents effective coordination of the naphthol. Coupling of benzyl

(27) The phenyl ketones were synthesized by treatment of the lithium anion of 2-methoxynaphthalene with the corresponding aryl Weinreb amides. See the Supporting Information.

(28) Nakajima et al. (ref 9d) reported a similar trend: methyl ester, 78% ee; *tert*-butyl ester, 58% ee.

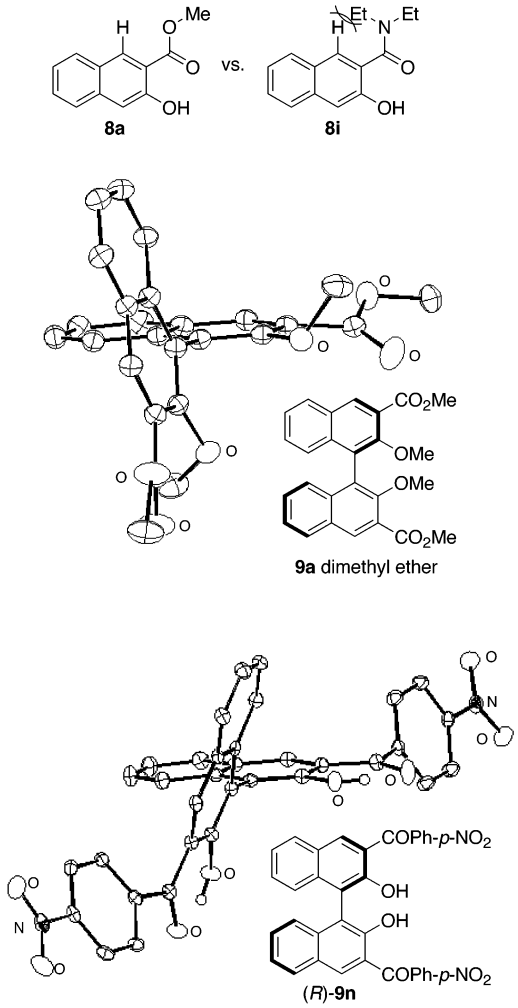


FIGURE 1. Chelating environment in the oxidative biaryl coupling. ORTEP drawings are shown with 30% probability thermal ellipsoids.

alcohol derivatives (**8z**, **8aa**) was moderately enantioselective (entries 30−32).

Diphenylphosphine oxide **8bb**[29] (entry 33) afforded especially high enantioselectivity (96% ee). Although the initial rate was high, the final yield was low (29%).[30] At higher temperature (80 °C, entry 34), a better yield could be obtained (54%) at the cost of some selectivity (82% ee). A similar reactivity profile was observed with dimethylphosphine oxide **8cc**, but the selectivity[31,32] was lower (entry 35). Reasoning that the phosphine oxide oxygen binds tightly to the copper catalyst and inhibits turnover, we screened the less coordinating methyl

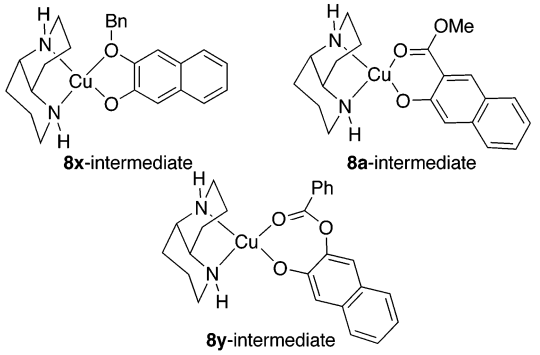


FIGURE 2. Possible intermediates for the formation of **9x**, **9a**, and **9y**.

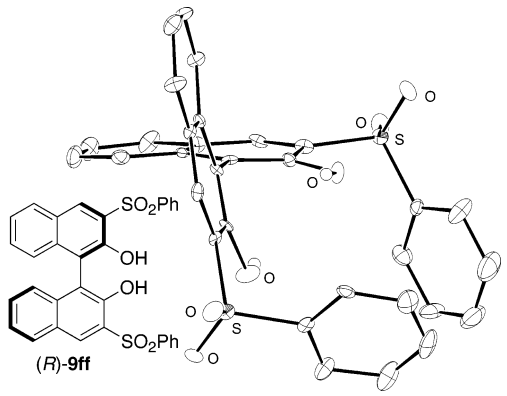


FIGURE 3. ORTEP drawing of (*R*)-**9ff** with 30% probability thermal ellipsoids. The phenyl rings are not π-stacking (closest approach 4.8 Å).

phosphonate **8dd** (entry 36). This compound displayed reactivity (76% yield) and selectivity (92% ee) analogous to those of methyl ester **8a**. The corresponding phosphonamide **8ee** (entry 37) also provides the binaphthol in high selectivity (90% ee), but the reaction rates were slow due to the sterically large dimethylamino groups in analogy to the amides described above.

Low yields were seen in initial trials with phenylsulfonyl substrates such as **8ff**[33] until the concentration was increased (0.5−1.0 M substrate). Due to the low solubility of the sulfonyls, a key finding was that ∼10% of a solubilizing species (THF or DMF) could be added without disrupting the required chelation (the same selectivity was observed for **8a** in the presence or absence of these additives). Even so, the reaction with **8ff** was less selective, providing binaphthyl **9ff** in 65% yield and 45% ee (entry 38). The crystal structure of **9ff** shows that the sulfonyl oxygens are oriented out of the naphthol plane (Figure 3). Low selectivity is observed because the optimal conformation for copper chelation is absent and **8ff** is electron poor. Since more electron rich systems typically give rise to higher selectivity (see below), the

(29) The diphenylphosphine oxide was made by treatment of the lithium anion of 2-methoxynaphthalene with the diphenylphosphonyl chloride. The remaining phosphorous naphthols were made by phosphorylation of 2-naphthol followed by anionic Fries rearrangement. See the Supporting Information.

(30) Only two other reports of BINOL-3,3′-phosphine oxides have appeared: (a) Li, J.; Li, W.; Li, Y.; Li, Y.; Yang, S. *Org. Prep. Proc. Int.* **1995**, 27, 685−690. (b) Au-Yeung, T.-L.; Chan, K. Y.; Haynes, R. K.; Williams, I. D.; Yeung, L. L. *Tetrahedron Lett.* **2001**, *57*, 457−460.

(31) The enantiomeric excess was determined from the ^{1}H NMR spectra of the diastereomeric solvates formed from (−)-quinine. For examples of analyses using chiral solvating agents, see: (a) Parker, D. *Chem. Rev.* **1991**, *91*, 1441−1457. (b) Rosini, C.; Uccello-Barretta, G.; Pini, D.; Abete, C.; Salvadori, P. *J. Org. Chem.* **1988**, *53*, 4597−4581.

(32) In the dimethylphosphine oxide case, the product modifies the active catalyst. When 10 mol % racemic **9cc** was employed with 10 mol % CuI·(*R*,*R*)-**7a** (40 °C, O_2, 48 h), **9a** was obtained in 26% yield and 84% ee (vs 85% yield and >90% ee for **9a** without **9cc**). A similar experiment with an analogue of diphenylphosphine oxides **8bb** and **9bb** (diphenylbutylphosphine oxide) demonstrated that such compounds do not modify the catalyst.

(33) The arylsulfonyls were synthesized by treatment of the lithium anion of 2-methoxynaphthalene with the corresponding sulfonyl fluoride. See the Supporting Information.

TABLE 5. Scope of the Oxidative Biaryl Coupling Using 7a·CuX (Eq 3, Y = OH)[a]

entry	8/9	R^1	R^2	R^3	7a	Cu source	solvent[b]	[8] (M)	*t* (h)	*T* (°C)	yield (%)	ee[c] (%)
27	**x**	OBn	H	H	(*S*,*S*)	CuCl	A	0.10	24	rt	77[d]	38 (*R*)
28	**x**	OBn	H	H	(*R*,*R*)	$CuBr_2$	A	0.10	24	rt	74[d]	46 (*S*)
29	**y**	OBz	H	H	(*S*,*S*)	CuI	G	0.10	24	40	NR	
30	**z**	CPh_2OH	H	H	(*S*,*S*)	CuCl	A	0.10	24	40	32	38 (*R*)
31	**z**	CPh_2OH	H	H	(*S*,*S*)	CuCl	A	0.10	24	rt	22	54 (*R*)
32	**aa**	CEt_2OH	H	H	(*S*,*S*)	CuCl	A	0.10	24	rt	25	21 (*R*)
33	**bb**	$P(O)Ph_2$	H	H	(*S*,*S*)	CuI	H	0.03	48	40	29	96 (*R*)
34	**bb**	$P(O)Ph_2$	H	H	(*S*,*S*)	CuI	H	0.03	48	80	54	82 (*R*)
35	**cc**	$P(O)Me_2$	H	H	(*R*,*R*)	CuI	B	0.10	48	40	40	46 (*S*)[f]
36	**dd**	$P(O)(OMe)_2$	H	H	(*S*,*S*)	CuI	B	0.10	48	40	76	92 (*R*)
37	**ee**	$P(O)(NMe_2)_2$	H	H	(*R*,*R*)	CuI	B	0.10	48	40	30	90 (*S*)
38	**ff**	SO_2Ph	H	H	(*S*,*S*)	CuI	I	1.00	16	80	65	45 (90) (*R*)
39	**gg**	$SO_2C_6H_4$-*p*-OMe	H	H	(*S*,*S*)	CuI	I	1.00	16	80	75	57 (98) (*R*)
40	**gg**	$SO_2C_6H_4$-*p*-OMe	H	H	(*R*,*R*)	CuI	G	0.24	16	80	45	65 (*S*)
41	**hh**	SO_2NEt_2	H	H	(*R*,*R*)	CuI	I	0.50	24	80	46	47 (*S*)
42	**ii**	SO_2Ph	H	OMe	(*R*,*R*)	CuI	I	0.50	24	80	66	68 (*S*)
43	**jj**	$SO_2C_6H_4$-*p*-OMe	H	OMe	(*S*,*S*)	CuI	I	0.50	24	40	57	75 (*R*)
44	**kk**	NO_2	H	H	(*R*,*R*)	CuI	I	1.00	40	80	38	10 (*S*)

[a] 10 mol % catalyst except entries 38, 39, and 41−44 (20 mol %). [b] A = CH_2Cl_2; B = $ClCH_2CH_2Cl$; C = CH_3CN; D = $ClCH_2CH_2Cl$, <10% THF; E = 3:2 CH_2Cl_2/MeCN; F = 2:1 CH_2Cl_2/MeCN; G = 1:1 $ClCH_2CH_2Cl$/MeCN; H = $ClCH_2CH_2Cl$, <10% DMF; I = 3:1:1 $ClCH_2CH_2Cl$/MeCN/DMF. [c] Enantioselectivity measured using HPLC (Chiralpak AD and AS). Values in parentheses are after enrichment. For entries 1−6, 11, 27, and 28 configurations assigned by comparison to the literature. For entries 13−15 and 30−32 configurations assigned by comparison to material generated from **9a**. For all others, configurations assigned by analogy. [d] Air was used as the oxidant. In all other entries O_2 was used (see eq 3). [e] Enantioselectivity measured by HPLC (Chiralpak AD) of the bismethyl ether derivative. [f] Enantioselectivity measured from the ^1H NMR spectra of the (−)-quinine complexes.

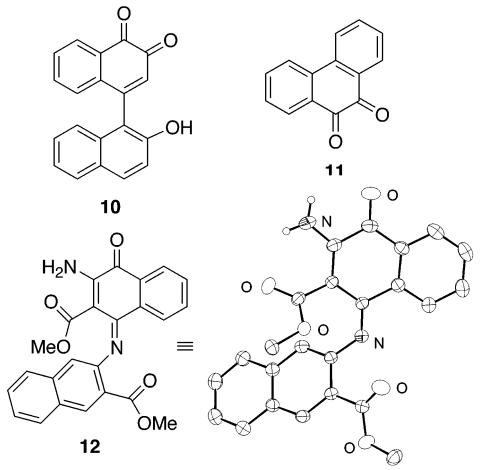
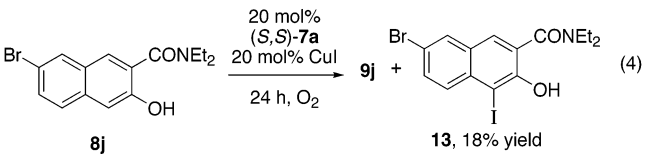


FIGURE 4. Side products in the biaryl coupling reactions. The ORTEP drawing of **12** is shown with 30% probability thermal ellipsoids.

p-methoxyphenylsulfonyl derivative **8gg** was examined (entries 39 and 40). A modest improvement was observed (57−65% ee) relative to the parent phenylsulfonyl **8ff** (45% ee). We postulated that a second electron-donating substituent on the naphthalene ring could counter the strongly electron withdrawing nature of the sulfonyl, which decreases the rate and selectivity. Oxidative biaryl coupling of the 7-methoxy derivatives **8ii** and **8jj** did provide the products in 18−23% higher enantiomeric excess relative to the derivatives lacking 7-methoxy substitution (entries 42 and 43 vs entries 38 and 39). Since the sulfonyl-substituted products were highly crystalline, simple trituration routinely provided enrichment to useful levels of enantiomeric excess (90−98% ee, entries 38 and 39). Substitution of the 3-position with a highly electron withdrawing nitro group (**8kk**),however, compromised both turnover and selectivity (entry 44).

In most cases the biaryl coupling reactions described in Tables 4 and 5 proceed cleanly, and yields after similar reaction times are correlated to reactivity (unreacted starting material accounts for the balance of the mass). With more electron rich substrates, however, side products can form. For substrates lacking any electron-withdrawing groups, such as **8b** and **8d**, *o*-quinones **10** and **11** (Figure 4), respectively, were also observed. These byproducts could arise from the same putative *o*-keto radical that leads to the biaryl products, but oxygen trapping competes with dimerization. For ester-substituted naphthylamine **8w**,[34] imine **12** was the major product (72−80% yield, Figure 4). Compound **12** could also arise from reaction of an *o*-keto radical with oxygen.

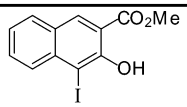
When amide **8j** was employed using 20 mol % CuI·(*S*,*S*)-**7a** catalyst, an 18% yield of *ortho*-iodinated **13** was also observed (eq 4). Upon closer examination, we identified the analogous iodinated byproducts for other substrates including **8a**, **8l**, and **8m**. Since the iodide is derived from the catalyst, the amount of this byproduct is usually small (<catalyst loading). With the CuCl and CuBr catalysts, the corresponding halogenated byproducts were not observed. We speculate that the iodinated material arises from quenching of the intermediate



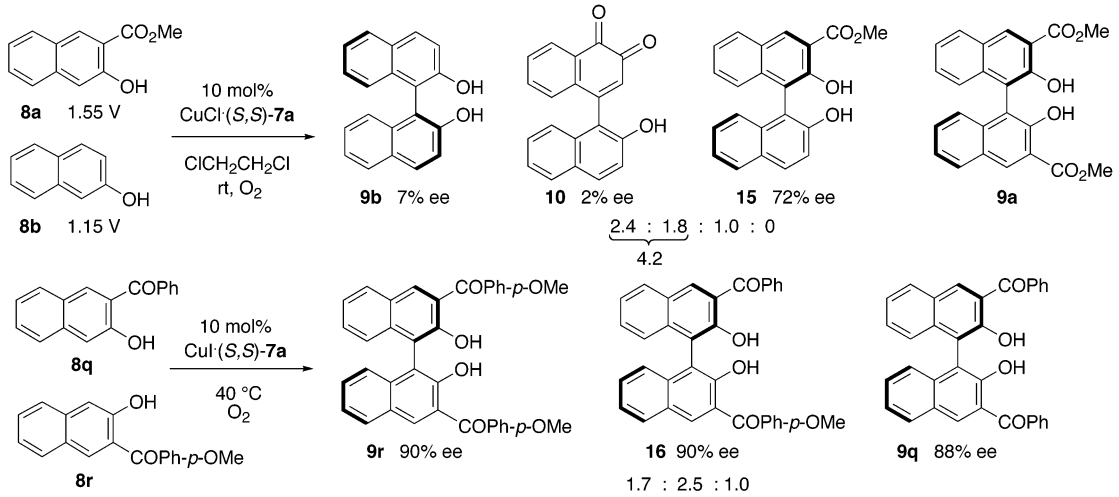
(4)

(34) Only a trace of the binaphthyl product and none of the corresponding carbazole were observed, despite prior precedent in the oxidative coupling of this naphthylamine using stoichiometric copper reagents: Vyskočil, Š.; Smrčina, M.; Lorenc, M.; Tišlerová, I.; Brooks, R. D.; Kulagowski, J. J.; Langer, V.; Farrugia, L. J.; Kočovský, P. *J. Org. Chem.* **2001**, *66*, 1359−1365.

TABLE 6. Formation of the Halogenation Side Product after 24 h (Eq 4)

entry	reagents	oxidant	T (°C)	**8a**	 *ortho*-I (**14**)	**9a**	color
1	0.1 equiv CuI·(*S,S*)-**7a**	O_2	40	10%	5%	85%	pale brown
2	1.0 equiv I_2	O_2	40	~50%	~50%	0%	purple
3	10 equiv TBAI	O_2	40	>95%	<5%	0%	pale yellow
4	10 equiv TBAI + 0.3 equiv CuCl·TMEDA	air	rt	~25%	~50%	~25%	pale brown
5	0.1 equiv CuCl·TMEDA	air	rt	<20%	0%	>80%	pale brown

SCHEME 3



radical with iodide.[9b,35] To rule out an electrophilic iodination mechanism, we investigated the role of I_2 (Table 6). In the presence of the CuI·**7a** catalyst, a small amount of the iodinated compound **14** was formed from **8a** (entry 1). When **8a** was exposed to I_2 alone, iodination did occur (entry 2). On the other hand, treatment of **8a** with tetra-*n*-butylammonium iodide (TBAI; entry 3), which simulates the iodide counterion found in the catalyzed reaction, yielded only trace **14**. The lack of color in the TBAI solution also indicates that there was no significant buildup of I_2 in the presence of O_2. In contrast, exposure of **8a** to a combination of TBAI (10 equiv) and CuCl·TMEDA (entry 4) caused formation of ~50% iodinated **14**. This iodinated material must arise from TBAI since the catalyst counterion was chloride. Furthermore, I_2 did not accumulate as judged by the absence of the characteristic color. As such, a metal-accelerated iodination utilizing iodide anion occurs. This side reaction can be effectively suppressed by employing the CuCl, CuBr, or CuOTf catalysts.

Cross-Coupling. The enantioselective biaryl couplings described above could arise through a number of pathways including (1) coupling of two radical species,[36] (2) reaction of a radical with an anion,[36] or (3) intramolecular redistribution via a bridging species. To distinguish among these possibilities, the cross-coupling of **8a** with **8b** was attempted (Scheme 3).[36] Since the oxidation potential of **8b** (1.15 V) is smaller than that of **8a** (1.55 V), a radical−radical coupling pathway should lead to a mixture reflecting the relative reactivity (i.e., homocoupled **9b** would predominate). Alternatively, a radical−anion coupling would lead to only **15** since the radical would form from the more oxidizable substrate **8b** and then attack the more stable anion from **8a**. With the CuCl·(*S,S*)-**7a** catalyst, however, we found that *both* the cross-coupled product **15** and homocoupled **9b** were formed.[13a] When **10** is taken into account (formed from the same radical that leads to **9b**), the products are produced in a statistical ratio based on the relative reaction rates (**8b** reacts ~10-fold faster than **8a**).[37]

Reasoning that these two substrates are not similar enough (i.e., **8b** cannot form a chelate) to draw a definite

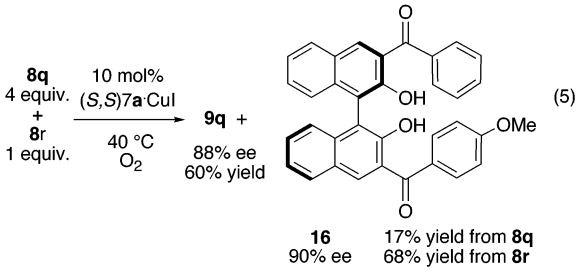
(35) Separate attempts to trap an *o*-keto radical with TEMPO, acrylonitrile, and ethyl phenylcyanoacetate have not succeeded. Another pathway to the aryl iodide is also possible via reductive elimination of an arylcopper iodide. However, the C3 coordinating group in these systems stabilizes the oxygen-bound copper form. We do not see the formation of the aryl halide with the CuCl or CuBr catalysts. While Lipshutz et al. observed a similar trend between CuI and CuCl at low temperature (ref 35a), arylcopper intermediates can give rise to Cl and Br return at the temperatures utilized in our couplings (refs 35b and 35c). (a) Lipshutz, B. H.; Kayser, F.; Siegmann, K. *Tetrahedron Lett.* **1993**, *34*, 6693−6696. (b) Kauffmann, T. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 291−305. (c) Piers, E.; McEachern, E. J.; Burns, P. A. *Tetrahedron* **2000**, *56*, 2753−2765.

(36) Smrčina, M.; Vyskočil, Š.; Maca, B.; Polasek, M.; Claxton, T. A.; Abbott, A. P.; Kočovský, P. *J. Org. Chem.* **1994**, *59*, 2156−2163.

conclusion, we then examined the cross-coupling of phenyl ketones **8q** and **8r**. Again, we found a statistical distribution of **9q**, **16**, and **9r** after taking into account the relative reaction rates of **8q** and **8r** (**8r** reacts slightly faster than **8q**). On this basis, we conclude that the behavior is most consistent with a radical−radical coupling. These results stand in contrast to cross-coupling reactions with stoichiometric amounts of chiral copper complexes for which radical−anion coupling is observed.[36]

With respect to the selectivity, the enantioselectivity of cross-coupled **15** (72% ee) is closer to that of the bis(methyl ester) derivative **9a** (90−93% ee) compared to BINOL (**9b**; 7% ee). This result indicates that an ester at the 3-position on just one of the coupling partners accounts for most of the stereoselectivity but that an ester on both coupling partners leads to the optimal stereoselectivity.

Since aryl ketones with more electron withdrawing groups in the *para* position are less reactive compared to those with electron-donating substituents, the synthesis of cross-coupled binaphthols[38] is possible. For example, eq 5 illustrates that slow addition of 1 equiv of

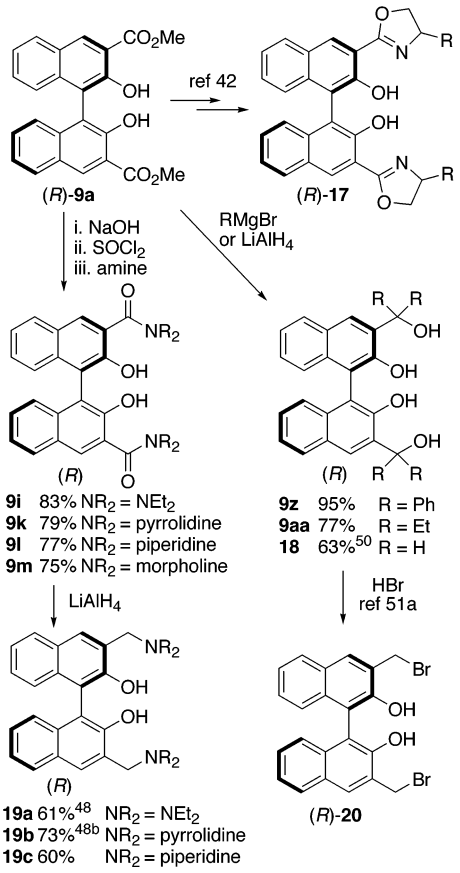


(5)

8r to 4 equiv of **8q** provided only **9q** and **16** (easily separated by chromatography), due to the greater reactivity of **8r** relative to **8q**. We anticipate that a number of cross-coupled chiral BINOL compounds for investigating the effects of electronic ligand asymmetry in asymmetric catalysis[39] can be made in this manner.

Applications of the Biaryl Coupling Products. As further evidence of utility, we have found that the chemistry described herein is very robust and reproducible. For example, **9a** can be prepared from inexpensive starting materials[40] on a preparative scale (0.25 mol of **8a**; 94 mmol, 37 g, of **9a**) without recourse to chromatography. By precipitation and trituration, **9a** is isolated in pure form with ≥99% ee.[25] Importantly, ester **9a**, in turn, is useful for the facile preparation of several related

SCHEME 4



3,3′-substituted BINOLs including those listed in Scheme 4. Previous preparations of **9** and **17**−**20** from chiral BINOL require multiple steps and are not highly efficient.[41] Ester **9a** is a precursor for the BINOLBox ligands **17** which have found utility in asymmetric 1,3-dipolar cycloadditions.[42] Binaphthol carboxamides **9i** and **9k**−**m**, which are efficiently produced from **9a**, have been employed as HIV protease inhibitors,[43] as chiral complexing agents,[44] and in the construction of chiral dendrimers.[45] They have also found utility as chiral ligands in asymmetric epoxidation,[46] cyclopropanation,[47a,b] and aldehyde alkylation.[47b−e] In addition, the carboxamides are direct precursors to BINOLAMs **19** which have been

(37) The formation of the cross-coupled product would also be anticipated if an ionic reaction between a carbocation and neutral molecule was occurring. For a discussion of cationic intermediates in copper phenolic oxidations, see: Baesjou, P. J.; Driessen, W. L.; Challa, G.; Reedijk, J. *J. Am. Chem. Soc.* **1997**, *119*, 12590−12594.

(38) For prior reports of the asymmetric synthesis of unsymmetric chiral 1,1′-binaphthols via oxidative binaphthol coupling with stoichiometric copper reagents, see refs 9b and 12a (for a discussion of the racemic cases see ref 36 and references therein). For synthesis of chiral 1,1′-binaphthols via intramolecular oxidative coupling of chiral substrates, see: (a) Lipshutz, B. H.; Shin Y.-J. *Tetrahedron Lett.* **1998**, *39*, 7017−7020 (unsymmetric 1,1′-binaphthols). (b) Lipshutz, B. H.; James, B.; Vance, S.; Carrico, I. *Tetrahedron Lett.* **1997**, *38*, 753−756 (symmetric 1,1′-binaphthols).

(39) Faller, J. W.; Grimmond, B. J.; D'Alliessi, D. G. *J. Am. Chem. Soc.* **2001**, *123*, 2525−2529 and references therein.

(40) **8a** is available from 2-hydroxy-3-naphthoic acid (∼$44/kg from Acros or Aldrich) by Fisher esterification and is easily purified by crystallization. The catalyst diamine **7a** can also be recovered and reused.

(41) For **9a**, the sequence from BINOL requires four steps: protection as the bis-MOM ether, lithiation with *n*-BuLi followed by acylation with CO_2, MOM group removal, and esterification. (a) Cox, P. J.; Wang, W.; Snieckus, V. *Tetrahedron Lett.* **1992**, *33*, 2253−2256. (b) Kitajima, H.; Ito, K.; Aoki, Y.; Katsuki, T. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 201−217.

(42) Kodama, H.; Ito, J.; Hori, K.; Ohta, T.; Furukawa, I. *J. Organomet. Chem.* **2000**, *603*, 6−12.

(43) Reetz, M. T.; Merk, C.; Mehler, G. *Chem. Commun.* **1998**, 2075−2076.

(44) (a) Baret, P.; Beaujolais, V.; Gaude, D.; Coulombeau, C.; Pierre, J.-L. *Chem.—Eur. J.* **1997**, *3*, 969−973. (b) Pinkhassik, E.; Stibor, I.; Casnati, A.; Ungaro, R. *J. Org. Chem.* **1997**, *62*, 8654−8659. (c) Hodaov, J.; Stibor, I. *Collect. Czech. Chem. Commun.* **2000**, *65*, 83−98.

(45) Lellek, V.; Stibor, I. *J. Mater. Chem.* **2000**, *10*, 1061−1073.

(46) Collman, J. P.; Wang, Z.; Straumanis, A.; Quelquejeu, M.; Rose, E. *J. Am. Chem. Soc.* **1999**, *121*, 460−461.

(47) (a) Kitajima, H.; Aoki, Y.; Ito, K.; Katsuki, T. *Chem. Lett.* **1995**, 1113−1114. (b) Kitajima, H.; Ito, K.; Aoki, Y.; Katsuki, T. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 207−217. (c) Kitajima, H.; Ito, K.; Katsuki, T. *Chem. Lett.* **1996**, 343−344. (d) Yang, X.-W.; Sheng, J.-H.; Da, C.-S.; Wang, H.-S.; Su, W.; Wang, R.; Chan, A. S. C. *J. Org. Chem.* **2000**, *65*, 295−296. (e) Yang, X.; Su, W.; Liu, D.; Wang, H.; Shen, J.; Da, C.; Wang, R.; Chan, A. S. C. *Tetrahedron* **2000**, *56*, 3511−3516.

applied to asymmetric Michael additions, *C*-alkylation of alanine Schiff bases, and cyanosilylation of aldehydes.[48]

Tetradentate alcohol ligands **9z**,[49] **9aa**, and **18**[50] are also readily generated from **9a**. Tetrol **18** can be converted further to dibromide **20**,[51a] a precursor to the chiral pseudorotaxanes and catenanes[52] and to the bifunctional phosphine oxide catalysts.[53] In addition, Cram et al. have utilized **18**−**20** in preparing many chiral crown ethers.[50,51]

Hammett Analysis, Mechanism, and Stereochemical Models. Several conclusions can be drawn based upon the substrate survey described in the preceding sections. First, there is a relationship between the electronic character of the naphthalene substrate and reaction rate/selectivity. Substrates with highly electron withdrawing groups (3-nitro, 3-sulfonyl) are relatively unreactive, whereas those with moderately electron withdrawing groups (3-carbonyl, 3-phosphonyl) are reactive, and those lacking electron-withdrawing groups (3-hydroxy, 3-benzyloxy) are very reactive. The ability of naphthol to form the corresponding naphthoxide does not have any bearing on the rate. In fact, the most acidic naphthols are the least reactive. As such, deprotonation of the substrate prior to catalyst coordination is either not necessary or is not rate-determining.[54]

Figure 5 illustrates a Hammett plot of log(er) vs the C3 substituent σ_{meta} parameter[55] for related substrates that can form six-membered chelates. There is a rough correlation between the enantioselectivity of the process and the electronic character of the substrate, with highly electron withdrawing groups giving much lower selectivity. Substrates departing from the correlation (*tert*-butyl ester **8g**, *tert*-butyl ketone **8u**, and amides **8i**−**m**) possess sterically large C3 substituents which likely impede catalyst coordination (see above).

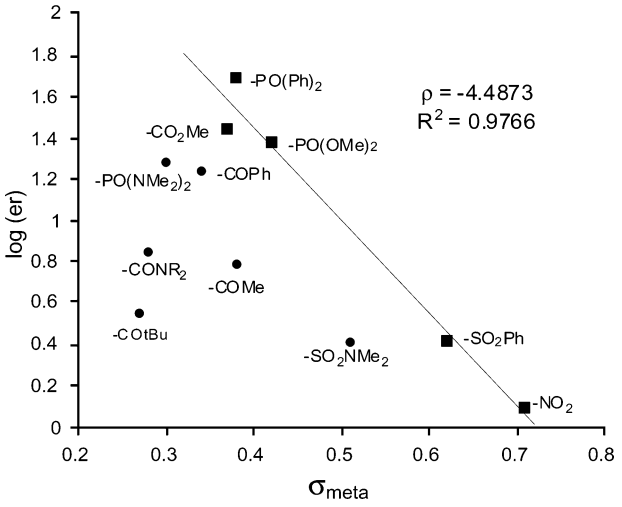
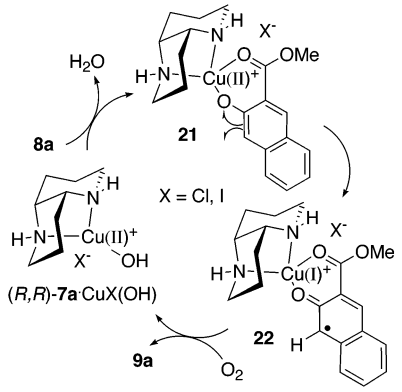


FIGURE 5. Hammett plot correlating the biaryl coupling enantiomeric excess with various R^1 groups (eq 3, Y = OH, R^2 = R^3 = H) with σ_{meta}. The ρ value and line are given for the five points indicated with solid boxes.

SCHEME 5. Overall Catalytic Cycle



The above trends are consistent with the mechanism depicted in Scheme 5. The first step is ligand exchange between (*R*,*R*)**-7a**·CuX(OH) and the substrate, which releases water and forms **21**. The fact that water inhibits the reaction[13a] supports this event. The low reactivity of diamine·CuCN species also corroborates this mechanism; with an intact copper nitrile bond such a sequence will fail due to lack of open copper coordination sites. Electron transfer in **21** then gives rise to a carbon-centered radical (**22**). This step involves reduction of the copper center from Cu(II) to Cu(I). Under the oxidizing conditions of the reaction, this redox step is likely slow. This analysis explains the relative rate trends observed: more electron withdrawing groups destabilize radical **22** (i.e., raise the oxidation potential of the naphthalene), slowing its formation. In addition, less stable versions of **22** will be more reactive and result in earlier biaryl coupling transition states. With more electron rich substrates the transition state is later and the enantioselectivity is improved, due to a greater degree of C−C bond formation which positions the chiral ligand of the catalyst closer to the second approaching substrate.

The last step in the catalytic cycle, product release, appears to be favorable in most cases. However, disfa-

(48) (a) Kitajima, H.; Ito, K.; Katsuki, T. *Tetrahedron* **1997**, *53*, 17015−17028. (b) Casas, J.; Najera, C.; Sansano, J. M.; Gonzalez, J.; Saa, J. M.; Vega, M. *Tetrahedron: Asymmetry* **2001**, *12*, 699−702. (c) Casas, J.; Najera, C.; Sansano, J. M.; Saa, J. M. *Org. Lett.* **2002**, *4*, 2589−2592.

(49) Chen et al. (see ref 9i) have reported a synthesis of **9z** via asymmetric biaryl coupling of **8z** (61% yield, 76% ee), but the method described here produces the material in the same number of steps with higher yield and selectivity (81% overall yield, >98% ee).

(50) For the synthesis of **18** from **9a**, see: Hegelson, R. C.; Koga, K.; Timko, J. M.; Cram, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 3021−3023.

(51) (a) Cram, D. J.; Helgeson, R. C.; Peacock, S. C.; Kaplan, L. J.; Domeier, L. A.; Moreau, P.; Koga, K.; Mayer, J. M.; Chao, Y.; Siegel, M. G.; Hoffman, D. H.; Sogah, G. D. Y. *J. Org. Chem.* **1978**, *43*, 1930−1946. (b) Helgeson, R. C.; Weisman, G. R.; Toner, J. L.; Tarnowski, T. L.; Chao, Y.; Mayer, J. M.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 4928−4941 and references therein.

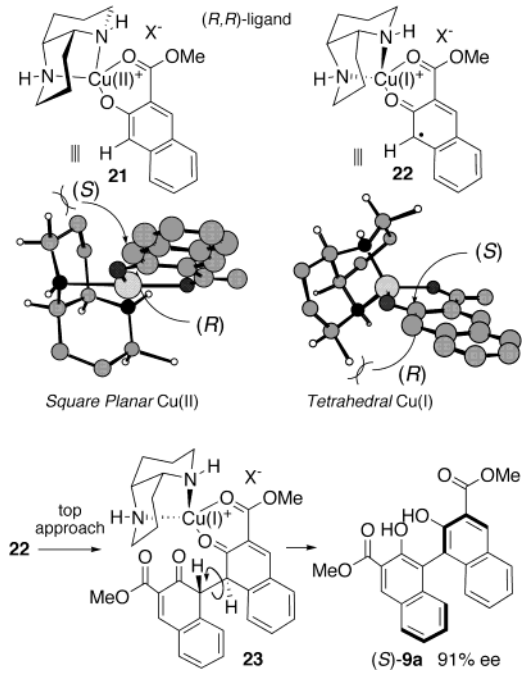
(52) (a) Asakawa, M.; Janssen, H. M.; Meijer, E. W.; Pasini, D.; Stoddart, J. F. *Eur. J. Org. Chem.* **1998**, 983−986. (b) Ashton, P. R.; Heiss, A. M.; Pasini, D.; Raymo, F. R.; Shipway, A. N.; Stoddart, J. F.; Spencer, N. *Eur. J. Org. Chem.* **1999**, 995−1004 and references therein.

(53) (a) Hamashima, Y.; Sawada, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 2641−2642. (b) Takamura, M.; Hamashima, Y.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 1650−1652. (c) Takamura, M.; Funabashi, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 6327−6328. (d) Sawada, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 10521−10532. (e) Takamura, M.; Hamashima, Y.; Usuda, H.; Kanai, M.; Shibasaki, M. *Chem. Pharm. Bull.* **2000**, *48*, 1586−1592. (f) Hamashima, Y.; Sawada, D.; Nogami, H.; Kanai, M.; Shibasaki, M. *Tetrahedron* **2001**, 57805−57814. (g) Takamura, M.; Funabashi, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 6801−6808. (h) Funabashi, K.; Ratni, H.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 10784−10785.

(54) In other phenol oxidations (which require a free anion) deprotonation is important to the rate: (a) McDonald, F. D.; Hamilton, G. A. *J. Am. Chem. Soc.* **1973**, *95*, 7752−7758. (b) Bhattacharjee, M.; Mahanti, M. K. *Bull. Soc. Chim. Fr.* **1983**, I225−I228. For a related discussion, see: (c) Russell, G. A.; Moye, A. J.; Nagpal, K. *J. Am. Chem. Soc.* **1962**, *84*, 4154−4155.

(55) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165−195.

SCHEME 6. Stereochemical Models for the Biaryl Coupling



vorable product dissociation accounts for the low yield obtained with diphenylphosphine oxide **8bb** (29%) and dimethylphosphine oxide **8cc** (40%).[56] While a steric effect may partly account for the lower reactivity of **8bb**, it is difficult to justify the difference in yield between the dimethyl phosphonate **8dd** (76%) and dimethylphosphine oxide **8cc** (40%) on these grounds. The reactivity trends are also not explained by the effect of the different phosphorus substituents on the oxidation potential of the naphthalene; the phosphine oxides of **8bb** and **8cc** are more donating, and should exhibit greater reactivity, compared to the phosphonate of **8dd**.[57] An experiment in which 10 mol % racemic **9cc** was added in the coupling of methyl ester substrate **8a** (10 mol % CuI·(*R*,*R*)-**7a**, 40 °C, O_2, 48 h) confirmed that product inhibition (26% yield with **9cc**, 85% yield without **9cc**) is the source of the lower yields for the phosphine oxide substrates.

The stereochemical induction observed in these reactions can be rationalized by the intervention of a monomeric substrate catalyst adduct (Scheme 6).[58] The stereochemistry is likely established in the C−C bond forming step, which is translated into axial chirality upon tautomerization (i.e., **23** → **9a**).[59] With the substrate bound to the copper catalyst, the metal may be either square planar (**21**, no radical character on the naphthol) or tetrahedral (**22**, significant radical character on the naphthol). Only carbon-centered radical **22** accounts for the sense of stereoselection in these reactions. Electron transfer coupled with bond formation from **21** is anticipated to lead to the other enantiomeric product due to the orientation of the ligand imposed by the square planar geometry of **21**.

Concluding Remarks

In conclusion, we have established that copper catalysts derived from the chiral diamine **7a** can be used to construct a range of symmetrical and unsymmetrical 3,3′-BINOL compounds. Substrates with functional groups (bromide, methoxy, ester, phosphonate, sulfonyl, etc.) at different positions can be utilized, which allows further functionalization of the products. The method described herein is the most general procedure to date for the highly enantioselective coupling of substituted naphthols, and complements the recently reported vanadium catalysts of Uang,[9f,k] Chen,[9g,i] and Gong[9h,j] which are useful in the coupling of electron-rich naphthols. New 3,3′-keto-, 3,3′-phosphonyl-, and 3,3′-sulfonyl-BINOL compounds were produced in >90% ee using 2.5−20 mol % copper catalyst in the presence of O_2.[60] We anticipate that these novel chiral BINOL compounds will be useful additions to the repertoire of axially chiral compounds.

On the basis of the results of our investigations and our understanding of the mechanism, the relationship between the substitution of the naphthalene starting materials and reactivity/selectivity has been defined in terms of three parameters. First, the oxidation potential of the substrate must be lower than the Cu(I) → Cu(II) potential in this system; otherwise the reaction does not proceed. The relative oxidation potential of a substrate can be qualitatively inferred from the electron-donating and electron-withdrawing properties of all the substituents. For example, substrates with a σ_{meta}(C3) parameter ≤0.50 react at good rates and produce the product with good yields (>70%), while those with σ_{meta}(C3) = 0.50−0.60 form the product with moderate yield (35−60%), and those with σ_{meta}(C3) > 0.60 react very slowly. In addition to correlating with the σ parameters, the rates of reaction also correlate well with HOMO enegy levels[36] estimated using AM1 calculations.[61] For example, the following HOMO energies (eV) were calculated: 3-nitro **8kk**, −9.133; 3-phenylsulfonyl **8ff**, −8.926; 3-phosphonyl **8dd**, −8.850; 3-methoxycarbonyl **8a**, −8.735; 3-phenyl ketone **8q**, −8.685; 3-hydro **8b**, −8.569. The reaction rates increase in this series, which correlates with the increase in energy of the respective HOMOs. These calculations provide a useful means of predicting substrate reactivity. In general, reactions proceed more rapidly with more electron rich naphthol substrates. Second, the substrate

(56) The stronger coordination of phosphine oxides vs phosphonyls accounts for this difference. The coordinating ability of phosphine oxides/phosphonyls to Ni(II) and Co(II) follows the order $Bu_3P{=}O$ > $(BuO)Bu_2P{=}O$ > $(BuO)_3P{=}O$. Vereshchagina, T. Y.; Vashman, A. A. *Zh. Neorg. Khim.* **1973**, *18*, 162−168.

(57) $\sigma_{meta}(POPh_2) = 0.38$; $\sigma_{meta}[PO(OMe)_2] = 0.42$. See ref 55.

(58) An octahedral model that is consistent with the observed stereochemical induction can also be proposed in which two molecules of the substrate **8a** and one molecule of the diamine **7a** coordinate to a single copper center. However, neither 5- or 6-coordinate geometries were observed in any (out of seven X-ray structures; see ref 21) of the 1,5-diaza-*cis*-decalin copper complexes. Furthermore, this model would require a Cu(III) to Cu(I) redox cycle, which is not supported by prior investigations of copper-promoted/catalyzed naphthol couplings nor by the low stability of Cu(III) species under the reaction temperatures employed (ambient to 80 °C).

(59) Rotation past the smaller enolizing C=O rather than the hydrogens *peri* to the biaryl bond in **23** is more likely and accounts for the observed product stereochemistry. (a) Meyers, A. I.; Lutomski, K. A. *J. Am. Chem. Soc.* **1982**, *104*, 879−881. (b) Meyers, A. I.; Wettlaufer, D. G. *J. Am. Chem. Soc.* **1984**, *106*, 1135−1136.

(60) In general, we have found that this method produces the compounds in higher yields compared to derivatization of the parent BINOL, and in some cases synthesis from BINOL fails altogether.

(61) AM1 calculations with SPARTAN v5.0 (Wavefunction, Inc., 18401 Von Karman Ave., Suite 370, Irvine, CA 92612).

must undergo bidentate coordination (via the C2 hydroxyl and the C3 substituent) with the copper catalyst. The most effective chelate size is a six-membered ring, and for a given substrate series the highest selectivities are usually seen with the most electron rich substrates. Electron-rich 2-naphthols which can effectively coordinate in a monodentate manner (via the C2 hydroxyl only) are highly reactive, but the enantioselectivity is uniformly low. In cases where steric effects imposed by other substituents can compromise chelation, reactivity and selectivity suffer. Third, product chelation must be weak enough to allow product dissociation and turnover. Thus, certain substrates which fulfill the first two criteria but possess highly coordinating C3 substituents generate the biaryl product in high selectivity but low yields. In this system, coordinating ability follows the trend $R_2P{=}O$ > $Ar_2P{=}O$ > $R_2NC{=}O$ > $(MeO)_2P{=}O$ ~ $(Me_2N)_2P{=}O$ ~ $ArS{=}O$ ~ $PhC{=}O$ > $ROC{=}O$ > RSO_2 > NO_2.[62]

In contrast to related transformations utilizing stoichiometric copper oxidants which proceed via radical−anion-type couplings,[36] a radical−radical coupling has been implicated in this process. A catalytic cycle involving a monomeric tetrahedral Cu-associated substrate radical is most consistent with all the data. The conclusions embodied in the above set of rules are in full accord with such a catalytic cycle, and further experiments examining the mechanism of this reaction will be reported separately. With these advances in understanding the reactivity/selectivity, we have been able to design suitable precursors for 1,1′-binaphthyl polymerization.[13b] The results and conclusions described for this process, such as estimating relative redox potentials of substrates, should prove useful in the development of future oxidative C−C bond forming methods.

Acknowledgment. Financial support was provided by the University of Pennsylvania Research Foundation and the National Science Foundation (Grant CHE-0094187). We thank 3D Pharmaceuticals for a graduate fellowship (C.A.M.) and the Alfred P. Sloan Foundation for a research fellowship (M.C.K.). We thank Drs. Xu Xie and Zhenrong Xu for preparation of **8f** and **8g** and Michael W. Fennie for preparation of **19c**. The invaluable assistance of Dr. Patrick Carroll in obtaining and analyzing the X-ray structures is gratefully acknowledged.

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

JO0340206

(62) The order was generated from measures of coordinating ability to Ni(II) [(a) Munakata, M.; Kitagawa, S.; Miyazima, M. *Inorg. Chem.* **1985**, *24*, 1638−1643] or alkynyl iodides [(b) Brinck, T. *J. Phys. Chem.* **1997**, *101*, 3408−3415] and proton affinites [(c) Bagno, A.; Scorrano, G. *J. Am. Chem. Soc.* **1988**, *110*, 4577−4582].