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Enantioselective Oxidative Biaryl Coupling Reactions Catalyzed by 1,5-Diazadecalin Metal Complexes

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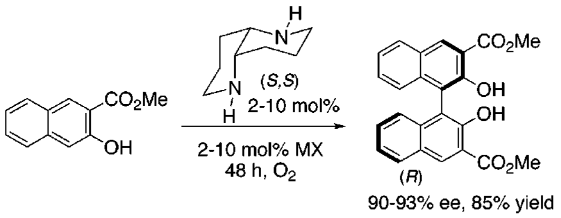
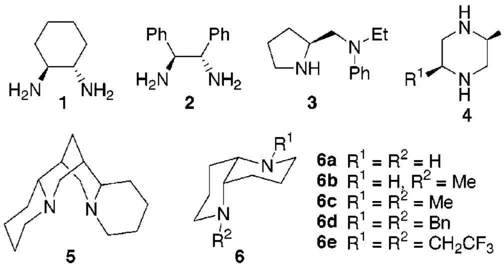
ABSTRACT



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 a 1,5-diaza-*cis*-decalin copper(I) iodide complex with oxygen as the oxidant, rapid and highly selective couplings could be achieved (90–93% ee, 85% yield).

The development of effective chiral auxiliaries and catalysts for asymmetric reactions requires appropriate chiral ligands. Chiral diamines are one class of compounds for which few significantly different structures have found general utility (Scheme 1).[1,2] Compound **6** was identified using our computer-aided procedure for the identification of novel ligands. In previous work, we have shown that diaza-*cis*-decalin **6c** was readily synthesized from commercial materials in three steps and was moderately effective in asymmetric lithiation substitutions.[3] To demonstrate further utility, reactions are being considered in which the classic diamine ligands fail to impart high levels of selectivity. In this Letter, chiral 1,5-diaza-*cis*-decalins **6** have been examined with respect to enantioselective oxidative biaryl coupling.

Scheme 1



The asymmetric synthesis of biaryl derivatives has been of intense interest because of the utility of chiral 1,1′-binaphthalene derivatives.[4] Toward this end extensive efforts have been directed to the development of catalytic asymmetric oxidative couplings of naphthol derivatives.[5−7] Al-

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(1) For reviews of 1,2-diamines, see: (a) Lucet, D.; LeGall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580−2627. (b) Bennani, Y. L.; Hanessian, S. *Chem. Rev.* **1997**, *97*, 3161−3195. (c) Mukaiyama, T.; Asami, M. *Top. Curr. Chem.* **1985**, *127*, 133−167.

(2) For reviews of sparteine, see: (a) Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2282−2316. (b) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552−560.

(3) Li, Xiaolin; Schenkel, L. B.; Kozlowski, M. C. *Org. Lett.* **2000**, *2*, 875−878.

(4) (a) Pu, L. *Chem. Rev.* **1998**, *98*, 2405−2494. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994. (c) Rosini, C.; Franzini, L.; Raffaelli, A.; Salvadori, P. *Synthesis* **1992**, 503−517. (d) Bringmann, G.; Walter, R.; Weirich, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 977−991.

(5) For a review of biaryl bond forming methods, see: Sainsbury, M. *Tetrahedron* **1980**, *36*, 3327−3359.

(6) For resolution of binaphthols, see: (a) Periasamy, M.; Venkatraman, L.; Thomas, K. R. J. *J. Org. Chem.* **1997**, *62*, 4302−4306. (b) Toda, F.; Tanaka, K. *Chem. Commun.* **1997**, 1087−1088. (c) Hu, Q.-S.; Vitharana, D.; Pu, L. *Tetrahedron: Asymmetry* **1995**, *6*, 2123-2126. (d) Cai, D.; Hughes, D. L.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1995**, 7991−7994. (e) Kawashima, M.; Hirayama, A. *Chem. Lett.* **1990**, 2299−2300.

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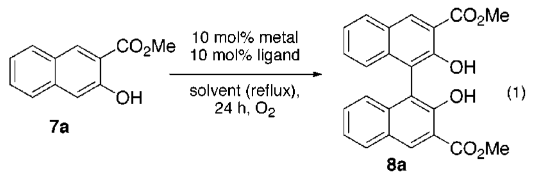
though high levels of selectivity can be achieved by employing stoichiometric amounts of chiral ligands,[8] the catalytic variants have not fared as well.[9] In the best report, Nakajima et al. employed chiral prolyldiamine ligands to obtain 78% ee in the coupling of **7a** to **8a** (eq 1).

To survey the utility of the 1,5-diaza-*cis*-decalin structure in this reaction, a number of catalysts were formed using chiral **6a** (Table 1, entries 1−3). In all cases homogeneous catalyst solutions could be obtained although MeCN was required to solubilize the Mn and Fe derivatives. Under these conditions, the reaction mixtures remained homogeneous throughout the course of the transformation.[10] Gratifyingly, the Mn,[11] Fe,[12] and Cu catalysts all provided some level of selectivity in the reaction, with the last generating **8a** in 86% ee. Only the CuCl catalyst turned over to any extent, but the reactivity was low. A 1:1 ligand:CuCl catalyst stoichiometry (entry 3) appears to be necessary for reactivity as similar conditions but with a 2:1 stoichiometry (entry 4) provide a much less active catalyst (5% vs 41% conversion). Lowering the temperature to 40 °C increased the selectivity to 91% ee (entry 5), which was found to be reproducible over a number of trials. The use of CH_3CN, which stabilizes the Cu(I) oxidation state, slightly enhanced the conversion (60%) while maintaining the high selectivity (entry 6).

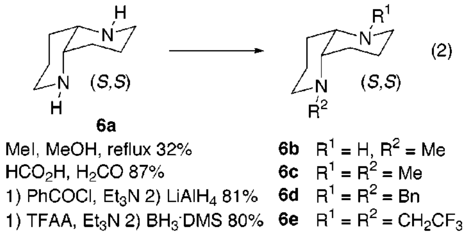
Table 1. Metal-Catalyzed Biaryl Couplings Using Ligand **6** (eq 1)



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

[a] All reactions were performed on a 0.5 mmol scale and used the (*S*,*S*)-diamines. [b] Isolated yields. [c] Enantiomeric excess determined by chiral HPLC (Chiralpak AD). Absolute configuration assigned by comparison to the literature. [d] Performed at 40 °C. [e] Reaction at rt. [f] Reference 9d.

Derivatives of ligand **6a** were prepared (eq 2) to assess the impact of structure on reactivity and selectivity. *N*,*N*′-Dialkyl derivatives were readily obtained from **6a**[3] through reductive amination (R^1 = Me, **6c**) or acylation followed by reduction (R^1 = Bn, CH_2CF_3; **6d**, **6e**). The mono *N*-alkyl derivative **6b** was obtained in 31% yield by addition of 0.5 equiv of MeI to a dilute solution of heated **6a**.



With **6b**−**6e** in hand, these derivatives were examined as ligands in the reaction in eq 1. For the purposes of comparison, these reactions were run under the conditions employed in entry 3 (Table 1, entries 7−10). All of the derivatives displayed reactivity similar to that of the parent with the exception of the *N*,*N*′-bis(trifluoroethyl) ligand **6e**. This diamine did not form a catalytically active complex, indicating that an electron-poor ligand is not effective.

In general, substitution on the nitrogen was detrimental with a decrease from 86% to 79% ee observed upon the addition of one *N*-Me group and a further decrease to 3% ee observed upon the addition of the two *N*-Me groups. Interestingly, higher selectivity was observed for *N*,*N*′-dibenzyl **6d** (22% ee) compared to dimethyl **6c** (3% ee).

Reasoning that the slow step in the catalytic cycle is reduction of Cu(II) to Cu(I), parameters that favor the latter became a focus (Table 2). In particular, the softer bromide, iodide, and triflate anions were anticipated to stabilize Cu(I) intermediates. In generating these new catalysts, their

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(7) For non-oxidative methods of chiral binaphthyl synthesis, see: (a) Hayashi, T.; Hayashizaki, K.; Kiyoi, T.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 8153−8156. (b) Shindo, M.; Koga, K.; Tomioka, K. *J. Am. Chem. Soc.* **1992**, *114*, 8732−8733. (d) Cammidge, A. N.; Crepy, K. V. L. *Chem. Commun.* **2000**, 1723−1724. (e) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12051−12052.

(8) (a) Feringa, B.; Wynberg, H. *Bioorg. Chem.* **1978**, *7*, 397−408. (b) Brussee, J.; Jansen, A. C. A. *Tetrahedron Lett.* **1983**, *24*, 3261−3262. (c) Yamamoto, K.; Fukushima, H.; Nakazaki, M. *J. Chem. Soc., Chem. Commun.* **1984**, 1490−1491. (d) Brussee, J.; Groenendijk, J. L. G.; te Koppele, J. M.; Jansen, A. C. A. *Tetrahedron* **1985**, *41*, 3313−3319. (e) Smrcina, M.; Lorenc, M.; Hanus, V.; Sedmera, P.; Kocovsky, P. *J. Org. Chem.* **1992**, *57*, 1917−1920. (f) Osa, T.; Kashiwagi, Y.; Yanagisawa, Y.; Bobbitt, J. M. *J. Chem. Soc., Chem. Commun.* **1994**, 2535−2537. (g) Saito, S.; Kano, T.; Muto, H.; Nakadai, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1999**, *121*, 8943−8944.

(9) (a) Hamada, T.; Ishida, H.; Usui, S.; Watanabe, Y.; Tsumura, K.; Ohkubo, K. *J. Chem. Soc., Chem. Commun.* **1993**, 909−911. (b) Smrcina, M.; Poláková, J.; Vyskoil,.; Kocovsky, P. *J. Org. Chem.* **1993**, *58*, 4534−4537. (c) Nakajima, M.; Kanayama, K.; Miyoshi, I.; Hashimoto, S. *Tetrahedron Lett.* **1995**, *36*, 9519−9520. (d) Nakajima, M.; Miyoshi, I.; Kanayama, K.; Hashimoto, S.-I.; Noji, M.; Koga, K. *J. Org. Chem.* **1999**, *64*, 2264−2271. (e) Ireie, R.; Masutani, K.; Katsuki, T. *Synlett* **2000**, 1453−1436. (f) Hon, S.-W.; Li, C.-H.; Kuo, J.-H.; Barhate, N. B.; Liu, Y.-H.; Wang, Y.; Chen, C.-T. *Org. Lett.* **2001**, *3*, 869−872.

(10) Homogeneous conditions were employed to preclude asymmetric induction via diastereomieric recrystallization as has been reported for some stoichiometric oxidative copper couplings. See refs 8a, 8e, and 9b.

(11) For Mn-promoted biaryl couplings, see: (a) Yamamoto, K.; Fukushima, H.; Okamoto, Y.; Hatada, K.; Nakazaki, M. *J. Chem. Soc., Chem. Commun.* **1984**, 1111−1112. (b) Dewar, M. J. S.; Nakaya, T. *J. Am. Chem. Soc.* **1968**, *90*, 7134−7135.

(12) For Fe-promoted biaryl couplings, see: (a) Ding, K.; Wang, Y.; Zhang, L.; Wu, Y.; Matsuura, T. *Tetrahedron* **1996**, *52*, 1005−1010. (b) Deussen, H.-J.; Frederiksen, P.; Bjrnholm, T.; Bechgaard, K. *Org. Prep. Proc. Int.* **1996**, *28*, 484−486. (c) Toda, F.; Tanaka, K.; Iwata, S. *J. Org. Chem.* **1989**, *54*, 3007−3009. (d) Feringa, B.; Wynberg, H. *J. Org. Chem.* **1981**, *46*, 2547−2557. (e) Pummerer, R.; Prell, E.; Rieche, A. *Chem. Ber.* **1926**, *59*, 2159−2161.

Table 2. Influence of the Metal Source on Biaryl Couplings Using **6a** (eq 1)[a]

entry	metal source	solvent	yield (%)[b]	ee (%)[c]
1	CuCl	CH_2Cl_2	56	91
2	CuBr	CH_2Cl_2	58	90
3	CuCl	CH_3CN	60	91
4	CuI	CH_3CN	85	91−93
5	Cu(OTf)	CH_3CN	81	90
6	$Cu(BF_4)_2$	CH_3CN	52	90
7	$Cu(OAc)_2$	CH_3CN	<5	62
8	$Cu(OTf)_2$	CH_3CN	<10	78
9	$Cu(NO_3)_2$	CH_3CN/H_2O	<10	44
10	CuCl	MeOH	74	80
11	$CuBr_2$	MeOH	93	60
12	$CuCl_2$	MeOH	85	76
13	$CuSO_4$	$MeOH/H_2O$	<5	76

[a] 0.5 mmol of **7a**, 10 mol % of Cu, 10 mol % of (*S*,*S*)-**6a**, 40 °C, O_2, 48 h. [b] Isolated yields. [c] Enantiomeric excess determined by chiral HPLC. Absolute configuration was (*R*).

solubility was found to vary considerably. To maintain homogeneous reaction solutions and prevent diastereomeric recrystallizations,[10] the appropriate solvent was selected for each catalyst. For comparison, the reaction employing CuCl was performed in each solvent used.

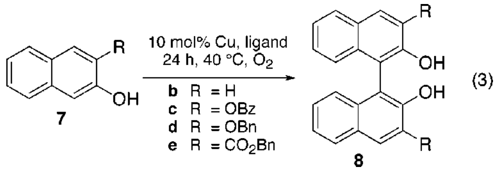
Although CuBr (entry 2) did not provide any observable improvement compared to CuCl under identical conditions, CuI (entry 4) and CuOTf (entry 5) gave significantly higher yields. With the CuI catalyst, the reaction was reliable and lower loadings (2.5 mol %) could be used. Further lowering of the catalyst loading gave unsatisfactory conversion (1 mol %, 40% conversion) due to catalyst deactivation.[13]

A survey of a number of other copper salts (Table 2) revealed two interesting trends. First, all the copper(I) sources provided the product with essentially the same level of enantioselection. As such, the counterion does not play a significant role in the stereochemistry-determining steps but is relevant to turnover. Second, with the exception of $Cu(BF_4)_2$, all the copper(II) sources led to lower selectivity (44−78% ee), indicating that a strongly coordinating second counterion is deleterious to the stereochemistry-determining step.

A number of other substrates were tested using catalysts derived from the 1,5-diaza-*cis*-decalin (Table 3, eq 3). The low level of selectivity (13% ee) in the coupling of **7b** to the BINOL parent **8b** indicates that substitution at the 3-position is critical for high induction.[9d,14] However, conversion of **8a**, which can be obtained in 91−93% ee using the method reported here, to BINOL **8b** can be accomplished.[9d]

To probe the requirement for 3-substitution further, substrates **7c**−**7e** were examined. Surprisingly, no reaction was observed with benzoyl derivative **7c**, while benzyl ether **7d** readily coupled to provide **8d** in 38% ee. Apparently an ester group at the 3-position is optimal, although various esters can be employed (entry 6).

Table 3. Other Substrates in Catalyzed Biaryl Couplings (eq 3)



entry	ligand	R	Y	Cu source	solvent	prod.	yield (%)[a]	ee (%)[b]
1	(*S*,*S*)-**6a**	H	OH	CuCl	CH_2Cl_2	**8b**	80[c,d]	13 (*R*)
2	**3**[e]	H	OH	CuCl	CH_2Cl_2	**8b**	89	17 (*S*)
3	**5**[e]	H	OH	CuCl	CH_2Cl_2	**8b**	32	18 (*S*)
4	(*S*,*S*)-**6a**	OBz	OH	CuI	$MeCN/(ClCH_2)_2$	**8c**	NR	ND
5	(*S*,*S*)-**6a**	OBn	OH	CuCl	$(ClCH_2)_2$	**8d**	77[f]	38 (*R*)
6	(*S*,*S*)-**6a**	CO_2Bn	OH	CuI	$MeCN/(ClCH_2)_2$	**8e**	79	90 (*R*)

[a] Isolated yields. [b] Enantiomeric excess determined by chiral HPLC. Absolute configuration assigned by comparison of optical rotations to the literature. [c] Using air at rt for 5 d. [d] With O_2 at rt for 48 h: 73% yield, 13% ee. [e] See ref 9d. [f] Using air at rt for 24 h.

Since the only oxidant is O_2 and the only byproduct is 1 equiv of H_2O, this coupling represents a safe, convenient, and efficient method for the formation of carbon−carbon bonds. Furthermore, the starting materials or solvent (Table 4) can be used without purification and no precautions need to be taken to remove air or atmospheric moisture. To investigate whether the water formed in the catalytic cycle inhibits the catalyst, 133 mol % of H_2O was added to the starting mixture. This addition caused a significant decrease in the rate. On the other hand, the addition of molecular sieves caused an acceleration, especially in the early stages of the reaction, indicating that the removal of water facilitates turnover.

To demonstrate the utility of this method, a 50 mmol preparative reaction was performed for **7a**. Using 2.5 mol % of catalyst derived from (*S*,*S*)-**6a** and CuI in the presence of

Table 4. Influence of Water on Biaryl Coupling Using **6a** (eq 1)[a]

entry	$ClCH_2CH_2Cl$ source	time (h)	convn (%)[b]	ee (%)[c]
1	ACS reagent[d]	3	27	89
2		16	62	89
3	dist (CaH_2)	3	23	90
4		16	58	82
5	filtered (Al_2O_3)	3	26	90
6		16	67	88
7	133 mol % of H_2O added	3	8	92
8		16	38	89
9	MS (100 mg) added	3	48	91
10		16	63	93

[a] 0.5 mmol reaction scale with 10 mol % of CuCl, 10 mol % of (*S*,*S*)-**6a** at 40 °C under O_2. [b] Conversion and enantiomeric excess determined by chiral HPLC. [c] (*R*) absolute configuration. [d] 0.01% H_2O.

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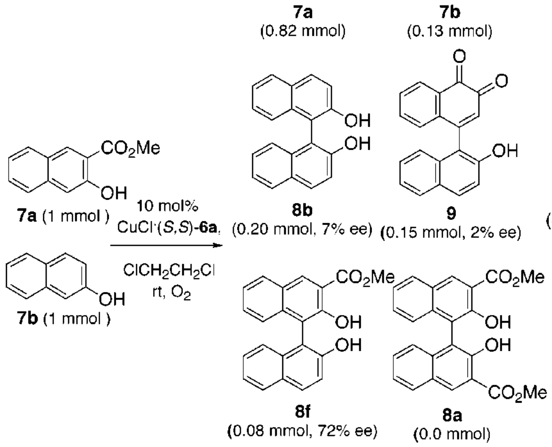
(13) Catalyst deactivation rather than reversible product inhibition is proposed on the basis of an experiment in which **7a** was treated with 5 mol % of the optimal CuI·**6a** catalyst in MeCN. Upon completion, the reaction was cooled, the solution was concentrated in vacuo, and the precipitated pure product (56%, 91% ee) was filtered away. The remaining MeCN solution was diluted to the original volume, and starting material was added to restore a 5 mol % catalyst loading. Resubjection of this solution to the reaction conditions (40 °C and O_2) resulted in no further reaction.

molecular sieves, **7a** was converted into **8a**. The crude reaction product (93% ee) was readily purified by precipitation from methanol to provide **8a** in 81% yield and 93% ee.[15]

Three mechanisms for the asymmetric induction in this biaryl coupling are possible.[8d,e,9b] Although a diastereoselective recrystallization of the product with the copper species is often observed in stoichiometric couplings, the high enantioselection observed using substoichiometric CuCl·(*S*,*S*)-**6a** or CuI·(*S*,*S*)-**6a** under homogeneous conditions (no crystallization) excludes such a pathway. The possibility of a second-order asymmetric transformation of the product was tested by treating racemic **8a** with stoichiometric CuCl·(*S*,*S*)-**6a** under the normal reaction conditions. No deracemization of **8a** was observed. Similarly, treatment of chiral (*R*)-**8a** with racemic CuCl·**6a** caused no racemization of (*R*)-**8a**. From these experiments, an asymmetric transformation of the product seems unlikely, leaving an enantioselective coupling as the most reasonable mechanism for asymmetric induction.

The enantioselective biaryl coupling could arise through a number of pathways[16] including (1) homolytic coupling of two radical species, (2) radical insertion of one partner into the other partner, (3) ionic reaction with a carbocation, or (4) intramolecular redistribution via a bridging species. Case 2 was tested by attempting the cross-coupling of **7a** with **7b** (eq 4); a radical intermediate should form from the more oxidizable substrate (**7b**)[16] and then attack the more acidic substrate (**7a**). When CuCl·**6a** was employed in such a cross-coupling experiment, compounds **8b** (39%) and **9** (29%), both of which arise from the more reactive substrate **7b**, were found to predominate. Only 8% of hetero-coupled **8f** was obtained, indicating that a significantly different mechanism predominates in these catalytic reactions compared to the variants using stoichiometric amounts of chiral copper complexes.[9b] The data from this experiment indicate that a radical−radical coupling (either intermolecularly or intramolecularly via a bridging Cu species) is competetive with a radical insertion pathway.



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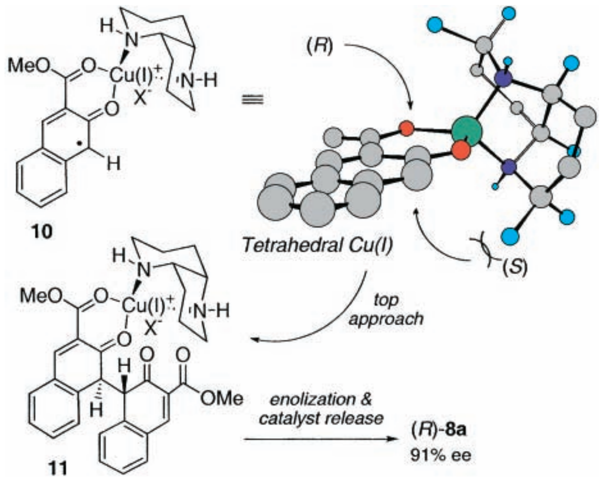

Figure 1. Tentative stereochemical model (only key hydrogens shown) for the biaryl coupling using the (*S*,*S*)-**6a** derived catalysts.

On the basis of the above studies, a tentative stereochemical model can be proposed which explains the sense of stereoselection in the biaryl coupling (Figure 1). If substrate (**7a**) undergoes ligand exchange with the catalyst to form a Cu(II)·ligand·substrate complex, then subsequent electron transfer would yield radical **10** possessing a Cu(I) tetrahedral coordination sphere. The model shown illustrates that the approach of the second substrate molecule to **10** is preferred from the top face due to steric interactions which would yield intermediate **11**. Enolization of **11** and release from catalyst would generate product with the observed stereochemistry.

In conclusion, 1,5-diaza-*cis*-decalins have been shown to be useful ligands for the copper-catalyzed oxidative coupling of 2-naphthol derivatives, providing the biaryl products in up to 93% ee. Further studies to address the scope and mechanism of these catalysts and applications of these transformations are underway.

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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.

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[14] The 3-substituent most likely chelates the metal center creating a stereochemically well-defined environment and/or ensuring that the intermediate remains associated with the metal center.

[15] To the catalyst from CuI and (*S*,*S*)-**6a** (0.44 g, 1.26 mmol) dissolved in 2:1 $ClCH_2CH_2Cl:CH_3CN$ (100 mL) were added **7a** (10.0 g, 50 mmol) and powdered 4 Å molecular sieves (5.0 g). After stirring for 3 d at 40−45 °C under O_2, the solution was decanted and the molecular sieves were rinsed with CH_2Cl_2. The resultant solution was washed with 1 N HCl, water, and brine. After drying over Na_2SO_4, the solvent was removed to provide the crude product (13.4 g) as a reddish brown solid. Treament with MeOH (100 mL) left **8a** (8.06 g, 81%, 93% ee) undissolved as a light-brown solid. Additional product (0.21 g, 2%, 98% ee) could be obtained from the MeOH portion after chromatography.

[16] Smrcina, M.; Vyskocil, S.; Maca, B.; Polasek, M.; Claxton, T. A.; Abbott, A. P.; Kocovsky, P. *J. Org. Chem.* **1994**, *59*, 2156−2163.