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Cu-Complex Catalyzed Asymmetric Aerobic Oxidative Cross Coupling of 2-Naphthols: Enantioselective Synthesis of *C*$_1$-symmetric BINOLs Bearing 3,3′-Disubstituents

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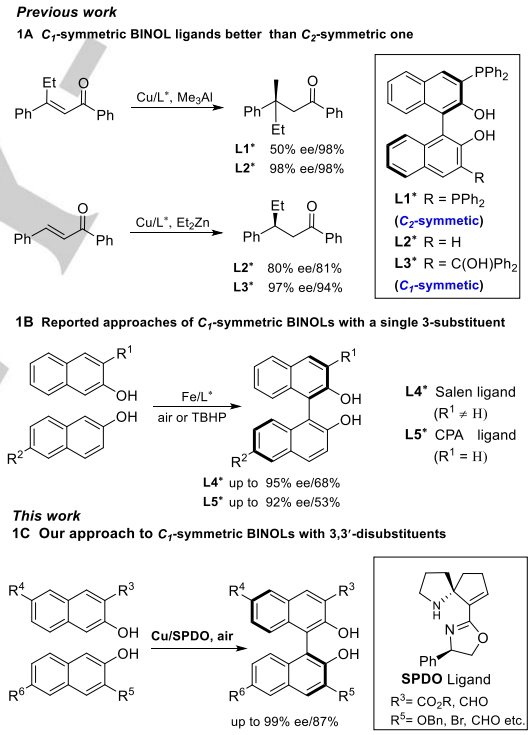
Dedication ((optional))

Abstract: A novel chiral 1,5-*N,N*-bidentate ligand based on a spirocyclic pyrrolidine oxazoline (SPDO) backbone has been designed and prepared, which *in situ* coordinates with CuBr to form an unprecedented catalyst that enables an efficient oxidative cross coupling of 2-naphthols using air as external oxidant, generating a series of *C*$_1$-symmetric chiral BINOL derivatives in high enantioselectivity (up to 99% ee) and good yield (up to 87%). This approach could be nicely tolerant of much broader substrates scope, particularly bearing bran-new various 3- and 3′-substituents. A preliminary investigation using a prepared *C*$_1$-symmetric BINOL-derived aldehyde organocatalyst exhibits better enantioselectivity than the previously reported organocatalyst toward the asymmetric α-alkylation of amino esters.

As a core structural element, the binaphthyl has been prevalently found in numerous chiral ligands, functional materials, and biologically active natural products.[1] During the past decades, the *C*2-symmetrical chiral BINOL (binaphthol) and its derivatives have exerted historical effect on asymmetric catalysis, particularly as exemplified by BINAP,[1b] BINOL derived phosphoric acid,[1h] and so on, that have been enabling a broad scope of enantioselective transformations. In recent years, however, the *C*1-symmetric BINOL-derived ligands and catalysts[2] bearing different functional groups at the 3,3′-positions (e.g. PPh3 and Bn) have been found to exhibit better enantio-induction toward some transformations than the corresponding *C*2-symmetric catalyst (e.g. Scheme **1A**) [2g] . This observation indicates the *C*1-symmetric chiral binaphthyls, that bear variable 3- and 3′-disubstituents as a "two-arms" tool to improve the stereo-controlling, would have great potential to prompt the future asymmetric catalysis.

Undoubtedly asymmetric oxidative coupling of 2-naphthol derivatives is the most straightforward approach to build up the binaphthyl chirality.[1e] And the homocoupling versions have already received a great success by use of chiral copper,[3] vanadium,[4] iron[5] and other metal catalysts.[6] In sharp contrast, the cross coupling of two different 2-naphthols have much less been described, despite Katsuki and Pappo groups have reported separately two approaches with Fe-complexes to generate a limited number of *C*1-BINOLs with a single or no 3-functional group (Scheme **1B**).[3b,7] Therefore, development of an effective catalytic system for affording a cross coupling to generate the 3,3′-disubstituted *C*1-symmetric BINOLs is of particular demand.



Scheme 1. *C*$_1$-symmetric BINOLs' Catalysis and their Construction

An ideal asymmetric catalytic system for efficient oxidative cross coupling of 2-naphthol should reach not only high enantioselectivity as well as chemoselectivity, but also a wide substrate toleration especially with the 3,3′-disubstitution. To date, however, there is still lack of sufficient knowledge documented to guide such a catalytic system design. Fortunately, a homocoupling catalyst developed by Kozlowski group, the Cu-1,5-diazadecalin affording the 3,3′-homo-disubstitution, shows the unique high efficiency toward the homo-coupling of 2-naphthol with 3-EWG (electron-withdrawing group),[3b] which gives a clue for seeking this type of catalyst. In connection with our recent effort toward this subject, two novel SPD (spirocyclic pyrrolidine) and SPA (spirocyclic amide) -type organocatalysts have successfully facilitated several asymmetric transformations,[8] suggesting that these backbones would be possibly a privileged structure for further building up new effective ligands. Herein we

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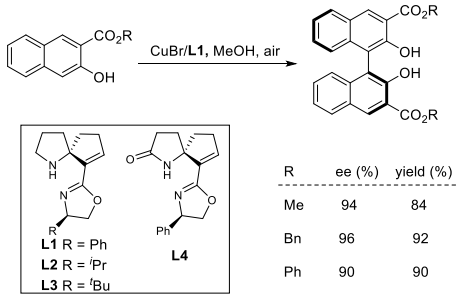
hypothesize that the 1,5-*N,N*-bidentate ligands SPDO (SPD-oxazoline) and SPAO (SPA-oxazoline) would be designed and made into Cu-SPDO or Cu-SPAO complexes, that would enable the catalytic asymmetric oxidative cross coupling as above (Scheme **1C**).

Our investigation began with the preparation of our newly designed SPDO and SPAO ligands **L1**-**L4** easily in gram-scale from SPD and SPA backbones, respectively (for details, please see supporting information). Then the asymmetric homocoupling of the 3-methyloxycarbonyl-2-naphthol using *in situ* prepared Cu-**L1**-**L4** complexes as catalyst was initially examined. To our delight, after screening of Cu(I) salts, ligands and solvents, the complex CuBr/**L1** in MeOH could catalyze the homocoupling to generate desired product in remarkably high 84% yield and 94% ee.[9] Under this conditions, other esters (with Bn and Ph) of 3-carbonyl-2-naphthols could also be readily coupled to give the satisfying results (Table 1), demonstrating the efficiency of Cu(I)-**L1** system toward the oxidative homocoupling of 2-naphthol.

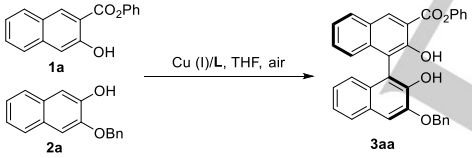
Table 1 Prelimary test of **L1-L4** toward homocoupling of 2-naphthol [a]



R	ee (%)	yield (%)
Me	94	84
Bn	96	92
Ph	90	90

[a] Reactions conditions: CuBr (0.05 equiv), **L1** (0.05 equiv), 2-naphthols (0.1 mmol) in MeOH (1 mL) at rt for 24 h.

Table 2 Optimization of asymmetric oxidative cross coupling [a]

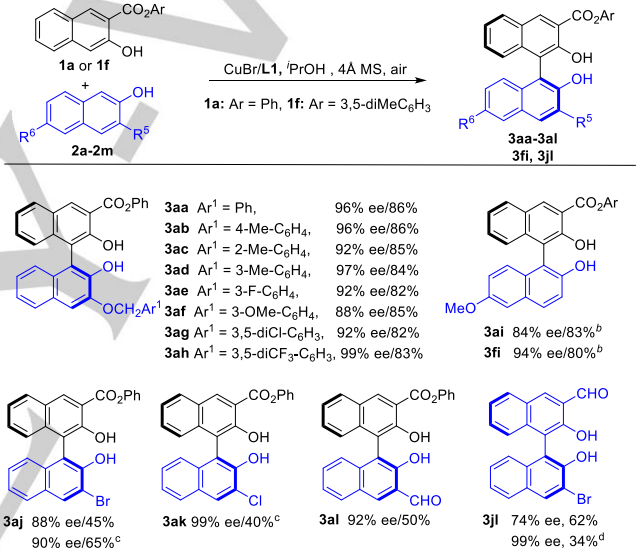


entry	Cu(I) /**L** (mol %)	solvent	t (h)	Yield (%) [b]	Ee (%) [c]
1	CuBr/**L1** (10)	THF	10	81	78
2	CuBr/**L2** (10)	THF	24	70	36
3	CuBr/**L3** (10)	THF	24	51	54
4	CuBr/**L4** (10)	THF	48	20	24
5	CuCl/**L1** (10)	THF	24	80	67
6	CuI/**L1** (10)	THF	24	72	56
7	CuBr/**L1** (10)	MeOH	10	78	20
8	CuBr/**L1** (10)	EtOH	16	75	82
9	CuBr/**L1** (10)	iPrOH	16	85	96
10	CuBr/**L1** (5)	iPrOH	36	83	85
11 [d]	CuBr/**L1** (5)	iPrOH	36	86	94
12 [d,e]	CuBr/**L1** (5)	iPrOH	30	86	96

[a] Unless otherwise noted, reactions were performed (for detail, see supporting information) using: CuBr (0.1 equiv), ligand (0.1 equiv), **1a** (0.1 mmol), and **2a** (1.5 equiv) in solvent (1 mL) at rt. [b] Isolated yield. [c] Determined by chiral HPLC. [d] 4Å molecular sieves (30 mg) was used. [e] **1a** was added in two batches over 3 h.

Subsequently, the more challenging oxidative cross coupling[10] process with two different 3-substituted-2-naphthol partners was investigated. Based on literature information, the oxidative cross coupling could preferentially occur through radical-anion coupling process only when two coupling partners have large enough redox potential difference (RPD) or ΔN values (N = theoretical global nucleophilicity).[2a,7,10] Thus the electron-deficient 3-phenyloxycarbonyl-2-naphthol (**1a**) and electron-rich 3-benzyloxy-2-naphthol (**2a**) were selected to search for the coupling conditions. Pleasingly as indicated in Table 2 (entry 1), when CuBr/**L1** (1:1, 10 mol %) in THF was used, the desired product **3aa** could be obtained with 81% yield and 78% ee.[11] Then the ligands **L2**-**L4** were further investigated, showing the alkyl-substituted **L2** and **L3** gave slightly poor results (entries 2-3 *vs* 1). And the SPAO ligand **L4** gave even the worst result (entry 4). Subsequently, Cu(I) salts (entries 5-6) and solvents (entries 7-9) were screened, indicating the system CuBr/ **L1** in iPrOH could give the remarkably high 85% yield and 96% ee (entries 5-8 *vs* 9). However, a lower loading of **L1** (5 mol %) would decrease the yield and ee (entry 10). Fortunately, this result could be further improved by adding the 4Å molecular sieves [3g] and feeding **1a** in two batches [7d] (entries 11- 12).

Table 3 Scope of electron-rich 2-naphthol patners **2** [a]

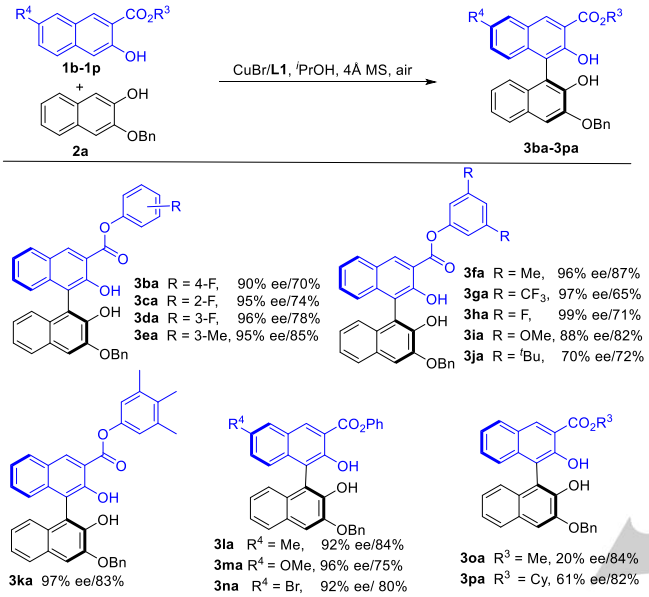


[a] Unless otherwise noted, reactions were performed (for detail, see supporting information) using **1** (0.1 mmol), CuBr (0.05 equiv) and **L1** (0.05 equiv), **2** (1.5 equiv) and 4Å molecular sieves (30 mg) in iPrOH (1 mL) at rt for 30 h. [b] CuBr (0.1 equiv) and **L1** (0.1 equiv) were used. [c] BQ (0.1 mmol) was extra used. [d] **2j** (1 mmol), **2l** (0.5 mmol) and BQ (0.5 mmol) were used, and 99% ee, 34% yield were obtained after recrystallization.

After identifying the optimal catalyst CuBr/**L1** and experimental procedures for the cross coupling (Table 2, entry 12), then a wide range of electron-rich or deficient 2-naphthols **2a**-**2m** with varying R^5 and R^6 were investigated with the electron-deficient partners **1a** and **1f**. The results (Table 3) showed that most examples could work well to generate the expected *C1*-symmetric BINOLs **3** with high enantioselectivity (up to 99% ee) and good yield (up to 86% yield). Just as we assumed in the first group of examples **2a**-**2h** with varying electron-rich 3′-benzyloxyl, the coupling with **1a** gave dominantly the *C1*-symmetric BINOLs **3aa**-**3ah** with up to 86% yield and 99% ee because the bigger difference of **1** and **2**. Notably, **2h** with 3′′,5′′-di(trifluro)methyl- 3′-benzyloxyl gave the best 99% ee of **3ah**. Secondly, substrate **2i** with 6′-OMe rather than 3′-substituent could still couple well with **1a** and **1f** to furnish **3ai** in good 84% ee and **3fi** in high 92% ee, respectively, which provided further possibility to modify the ligand/catalyst.[2] In third group of examples with both partners being the electron-deficient, however, cross coupling often led to the lower yields (40-65%) and/or ee (74%) of the products **3aj**-

3al and **3jl** due to the minor difference between two partners.[12,13] Importantly for the product **3jl**, its low enantio-purity (74% ee) could be improved to 99% ee after recrystallization, which presented good enatio-induction in an aldehyde catalysis[14] bellow (Scheme **3B**). In most examples (**3aa**-**3ai**, **3fi**) of Table 3 unless those noticed (**3aj**-**3al**, **3jl**), the homocoupling byproducts of **2** were not up to 10% yield, and no homocoupling byproduct of **1a** or **1f** was isolable.

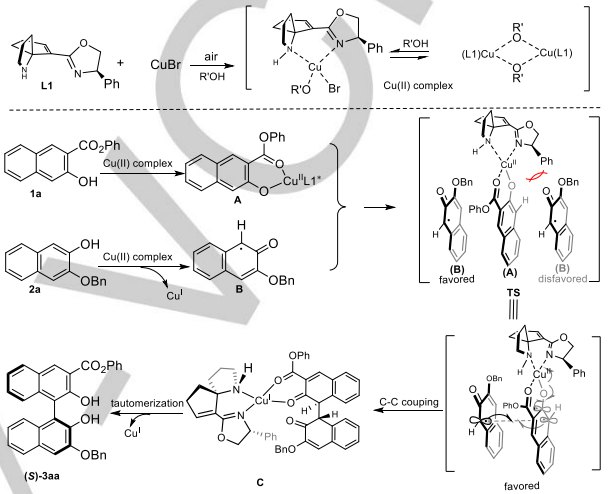
Table 4 Scope of electron-deficient 2-naphthol partners **1** [a]



[a] Unless otherwise noted, reactions were performed (for detail, see supporting information) using **1** (0.1 mmol), CuBr (0.05 equiv) and **L1** (0.05 equiv), **2** (1.5 equiv) and 4Å molecular sieves (30 mg) in ^{i}PrOH (1 mL) at rt for 30 h.

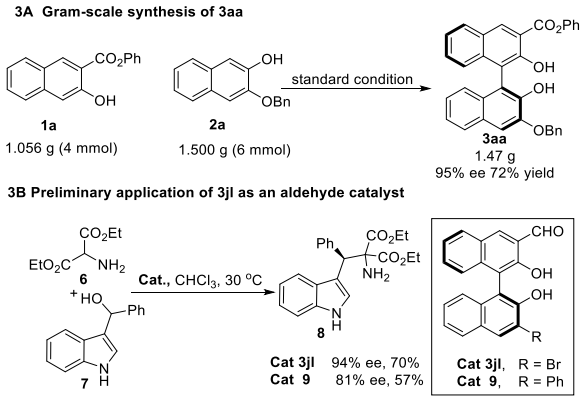
Subsequently, the cross coupling scope was further expanded by using a series of the electron-deficient partners **1b-1p** varying the 3-ester group to couple with **2a**. As summarized in Table 4, most examples could also work well to give high enantioselectivity and yield. Generally, the aromatic esters **1b-1n** gave better ee values than that of the aliphatic **1o** and **1p** (**3ba-3na** *vs* **3oa-3pa**), although the yield maintained the same level. Further detailed inspection showed that in the first group of examples **1b-1k** with mono, di and tri-substitutents at the aromatic ring, the EWG and ENG (electron-neutral group) substitutions gave better results than the EDG (**3ba-3ha** and **3ka** *vs* **3ia**), with the 3′′,5′′-difluoro-phenyl ester **1h** giving the best ee (99%) of **3ha**. An additional reason for the poor result (70 ee% and 72% yield) of **3ja** was possibly the presence of highly steric bulky *t*-butyl. The second group of examples (**1l-1n**) indicated that this method could even be tolerant of the 6-substitution of the naphthyl framework. And either electron-rich 6-MeO, or electron-deficient 6-Br substitution could afford **3la-3na** in high ee (92-96%) and yield (75-84%), which provided additional chances to modify *C1*-symmetric BINOL-derived ligand/catalyst. In the third group (**1o-1p**), however, both alkyl esters **1o-1p** gave poor enantioselectivity of **3oa-3pa** (20-61% ee), possibly due to the lack of aromatic π-π stacking between **1o-1p** and **L1**. The same as Table 3, in all cases of Table 4, no homocoupling byproduct of **1** was observed, and just less than 10% yield of the self-coupling byproduct of **2a** was isolable.

Based on the experimental results above and the literature reports on the aerobic oxidative coupling,[3b,7] a possible radical-anion coupling process was proposed (Scheme 2). Initially, the Cu(II)/**L1** complex was formed from Cu(I) and **L1** under air. Then this complex coordinated with **1a** to form species **A**, which subsequently coupled with the radical species **B** (generated from **2a** through an outer sphere electron transfer with another Cu(II) complex), to form the intermediate **C** *via* **TS** (transition states). The chiral coupling product (*S*)-**3aa** was afforded after tautomerization of **C**. Noticeable was that during this coupling process as shown in **TS**, species **B** tended to attack from Si-face of species **A** to give the (*S*)-**3aa**, which was consistent with our observed experiment results. While a Re-face attack forming (*R*)-**3aa** was disfavored because of the bigger steric hindrance effect between species **B** and **A**.



Scheme 2. The postulated TS for explaining the stereoinduction.

To support the utility of our asymmetric catalytic protocol, a gram-scale experiment was carried out in Scheme 3A, and the desired **3aa** could be obtained in 1.47 g (72% yield) with ideal 95% ee under standard conditions. In addition, the chiral *C1*-symmetric BINOL product **3jl** obtained above was also used as an aldehyde-activating catalyst toward a direct enantioselective α-alkylation of amino esters (Scheme **3B**). Compared with a reported result (81% ee) with catalyst **9**, **3jl** could yield product **8** with a much better enantioselectivity (94% ee). [14b]



Scheme 3. Synthetic applicability.

In summary, we have successfully developed a novel Cu-SPDO complex catalytic system (Cu-**L1**), using which a catalytic asymmetric aerobic oxidative cross coupling approach of 2-naphthols has been explored, generating a series of chiral *C1*-symmetric BINOLs. This convergent approach allows the rapid construction of various 3,3′-disubstitued axially chiral BINOLs, including 3-carboxylic ester, 3′-

oxylbenzyl, aldehyde, halides, and so on, featuring high enantioselectivity, good chemoselectivity (homocoupling byproducts <10% in most cases), and particularly a bran-new and broad substrate scope. We believe this methodology and the BINOL products obtained would find potential utility in asymmetric catalysis in future.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: aerobic oxidative cross coupling • SPDO • C_1-symmetric BINOL • 3,3′-disubstituents • aldehyde catalysis

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[9] The absolute stereochemistry of homocoupling products was assigned as *S* by comparison of the optical rotation with the literature 3b and 3f.

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[11] 3-methyloxycarbonyl-2-naphthol and 3-benzyloxycarbonyl-2-naphthol were also investigated, however, the ee level is very low often (< 20%). And the absolute stereochemistry of cross-coupled product was assigned as *S* by comparison of the optical rotation of **3aa** and **3oa** with the literature 7b.

[12] For the coupling of **2j** and **2l** with **1a**, benzoquinone (BQ) was needed as extra assistant oxidant to promote the ee and yield.

[13] For details, please see supporting information.

[14] a) M. J. MacDonald, D. J. Schipper, P. J. Ng, J. Moran, A. M. Beauchemin, *J. Am. Chem. Soc.* **2011**, *133*, 20100-20103; b) B. Xu, L. -L. Shi, Y. -Z. Zhang, Z. -J. Wu, L. -N. Fu, C. -L. Luo, L. -X. Zhang, Y. -G. Peng, Q. -X. Guo, *Chem. Sci.* **2014**, *5*, 1988-1991; c) W. Wen, L. Chen, M. -J. Luo, Y. Zhang, Y. -C. Chen, Q. Ouyang, Q. -X. Guo, *J. Am. Chem. Soc.* **2018**, *140*, 9974-9780; d) J. Chen, X. Gong, J. Li, Y, Li, J. Ma, C. Hou, G. Zhao, W. Yuan, B. Zhao, *Science* **2018**, *360*, 1438-1442.

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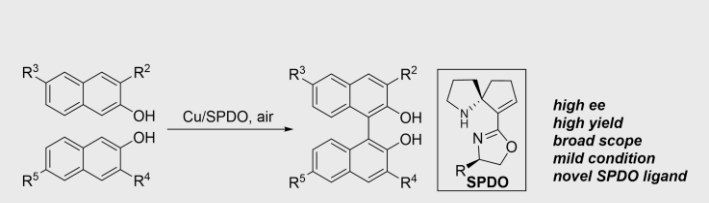

Asymmetric aerobic oxidative cross coupling of 2-naphthols enabled by a novel Cu-SPDO complex catalytic system was developed, generating a series of chiral C_1-symmetric BINOLs bearing 3,3′-disubstituents. This method features high enantioselectivity, good chemoselectivity, bran-new and broad substrate scope. A preliminary investigation using a prepared C_1-symmetric BINOL-derived aldehyde organocatalyst exhibits better enantioselectivity than the previously reported

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Cu-Complex Catalyzed Asymmetric Aerobic Oxidative Cross Coupling of 2-Naphthols: Enantioselective Synthesis of C_1-symmetric BINOLs Bearing 3,3′-Disubstituents