DOI: 10.1002/adsc.201300513

Enantioselective Oxidative Coupling of 2-Naphthol Derivatives by Copper-(*R*)-1,1′-Binaphthyl-2,2′-diamine-TEMPO Catalyst

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Received: June 11, 2013; Published online: ■■ ■■, 0000

Dedicated to Professor M. Periasamy on the occasion of his 60th birthday.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201300513.

Abstract: An efficient chiral copper catalytic system [(*R*)-(+)-1,1′-binaphthyl-2,2′-diamine-copper(I) chloride-TEMPO] for the asymmetric oxidative coupling of 2-naphthol derivatives to synthesize enantiomerically enriched BINOL derivatives has been developed with good to excellent enantiomeric excess (up to 97% *ee*). The addition of a catalytic quantity of 2,2,6,6-tetramethylpiperidin-1-yl oxyl (TEMPO) to the copper-(*R*)-(+)-1,1′-binaphthyl-2,2′-diamine complex greatly enhanced the reactivity and enantioselectivity of the enantioselective oxidative coupling of 2-naphthol derivatives and also reduced the reaction temperature from 90 °C to room temperature in dichloromethane solvent.

Keywords: asymmetric synthesis; BINOL; chiral copper catalyst; molecular oxygen; oxidative coupling

Axially chiral biaryls constitute a large class of biologically important natural products, structurally divergent chiral auxiliaries and ligands (Figure 1).[1] Particularly, axially chiral 1,1′-binaphthol (BINOL), which is stable at high temperature due to the high rotational barrier, has proved itself and its derivatives to be excellent chiral ligands in the asymmetric synthesis.[1c,d,2] Generally, enantiopure BINOL is synthesized by enzymatic or chemical resolution from the corresponding racemic BINOL.[2] Asymmetric oxidative coupling of 2-naphthols is the simplest alternative route to synthesize chiral BINOL.

The first successful asymmetric oxidative coupling was reported by Brussee[3] using a super stoichiometric quantity of Cu(II)-(*S*)-amphetamine complex. The catalytic version of the asymmetric oxidative coupling was developed by Nakajima using L-proline-derived diamine-Cu(I) complex.[4] Subsequent improvements were made by Kozlowski[5] using Cu(I)-1,5-diazadecaline or (−)-sparteine complex. Later on, Kim used Cu(I)-BINAM complex as a catalyst for the oxidative coupling of 2-naphthols.[6] Independent reports by Uang, Chen and Gong using a chiral oxovanadium complex[7] of Schiff bases represented significant progress in the oxidative coupling of 2-naphthols. In addition, the chiral ruthenium,[8] iron complexes[9] and N-heterocyclic carbene copper complexes[10] were reported by other research groups and have added strength to the field of asymmetric oxidative coupling.

Recently, we have synthesized an enantiopure model of galactose oxidase (GO) enzyme and this has been efficiently utilized for the aerobic oxidative kinetic resolution (AOKR) of racemic benzoins to synthesize highly enantiomerically enriched benzoins in the presence of molecular oxygen and 2,2,6,6-tetramethylpiperidin-1-yl oxyl (TEMPO).[11] To demonstrate the further utility of this enantiopure GO model, the (*R*)-BINAM-Cu complex has been examined as a catalyst for the asymmetric oxidative coupling to synthesize enantiopure BINOL and herein we report our preliminary results.

We started our investigation with enantioselective oxidative coupling of methyl 3-hydroxy-2-naphthoate **10** using 5 mol% of $Cu(OTf)_2$ and 5 mol% of (*R*)-BINAM in toluene at 90 °C in the presence of molecular oxygen. The reaction took 7 days to furnish 45% of dimethyl 2,2′-dihydroxy-1,1′-binaphthyl-3,3′-dicarboxylate **11** with just 4% enantiomeric excess (Table 1, entry 1). When the $Cu(OTf)_2$ was replaced by CuCl, the enantioselectivity of the oxidative coupling drastically increased to 97% *ee*, however the reaction took 8 days and afforded only 27% of the product (Table 1, entry 2). Then several copper salts were screened with chiral BINAM, but all of them

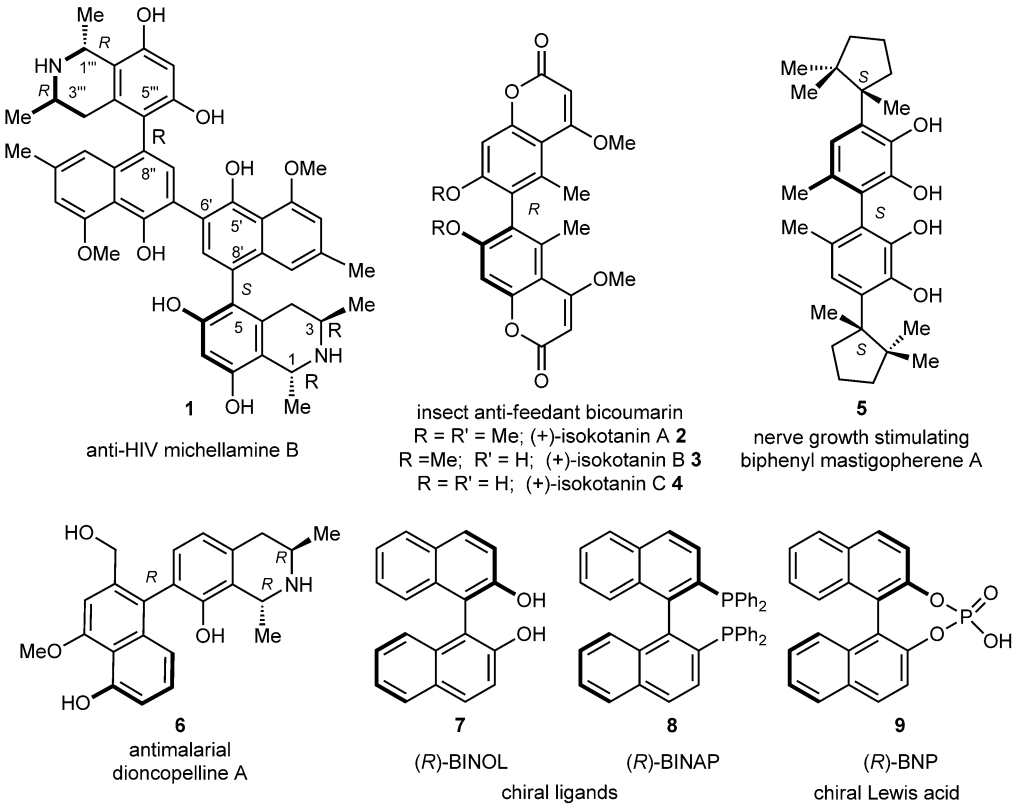
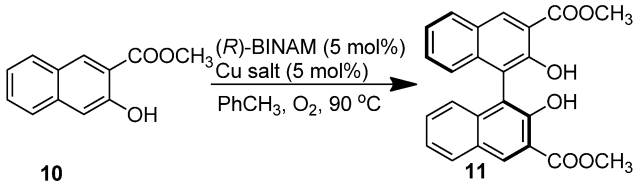


Figure 1. Axially chiral biaryl-containing biologically active natural products and chiral ligands.

Table 1. Effect of copper salts on the asymmetric oxidative coupling of 2-naphthol derivative **10**.



10 11

Entry	Cu salt	Time [d]	Yield [%][a]	*ee* [%][b]
1	$Cu(OTf)_2$	7	45	04
2	CuCl	8	27	97
3	CuI	9	09	10
4	CuBr	9	46	61
5	Cu_2O	9	65	14
6	$Cu(OAc)_2$	9	67	10
7	$CuSO_4$	9	08	25
8	CuCN	9	10	24
9	$CuCl_2$	9	18	93

[a] Isolated yields.

[b] The % *ee* was determined by HPLC using a Daicel chiralPAK AD-H column. The absolute configuration of the product BINOL derivative **11** was determined as (*S*) based on the sign of its specific rotation and comparison with the literature values.[4] See the Supporting Information for further details.

were found to be inferior to CuCl in terms of selectivity (Table 1, entries 3–9).[12]

To improve the yield of the oxidative coupling reaction, several chiral ligands such as BINOL, (−)-sparteine and Schiff base ligands were screened with CuCl in toluene at 90 °C in the presence of molecular oxygen (Figure 2). Although in some cases the yields are slightly improved, all these ligands gave less selectivity than (*R*)-BINAM-CuCl complex and the (*R*)-BINAM-CuCl complex turned out to be the best choice for the oxidative coupling of **10**.

Subsequently the reaction was studied with different solvents to increase the yield of the oxidative coupling reaction (Table 2). Among various solvents screened, toluene was found to be the best solvent in view of the enantioselectivity, but the setback of low yield remained unsolved (Table 2, entry 8). Recently, we have used Cu-BINAM complex in combination with TEMPO in the presence of molecular oxygen as an efficient catalytic system for the enantioselective oxidation of alcohols. Also, the oxidative coupling is a radical reaction and TEMPO being a radical species might promote the oxidative coupling. Based on the above-mentioned facts, we reasoned that the Cu-BINAM catalyst in combination with a catalytic quantity of TEMPO could be an efficient catalyst for oxidative coupling of 2-naphthols. As per our expectations, the addition of a catalytic quantity of TEMPO (5 mol%) increased the yield from 27% to 80%, but the enantiomeric excess was reduced to 56% (Table 2,

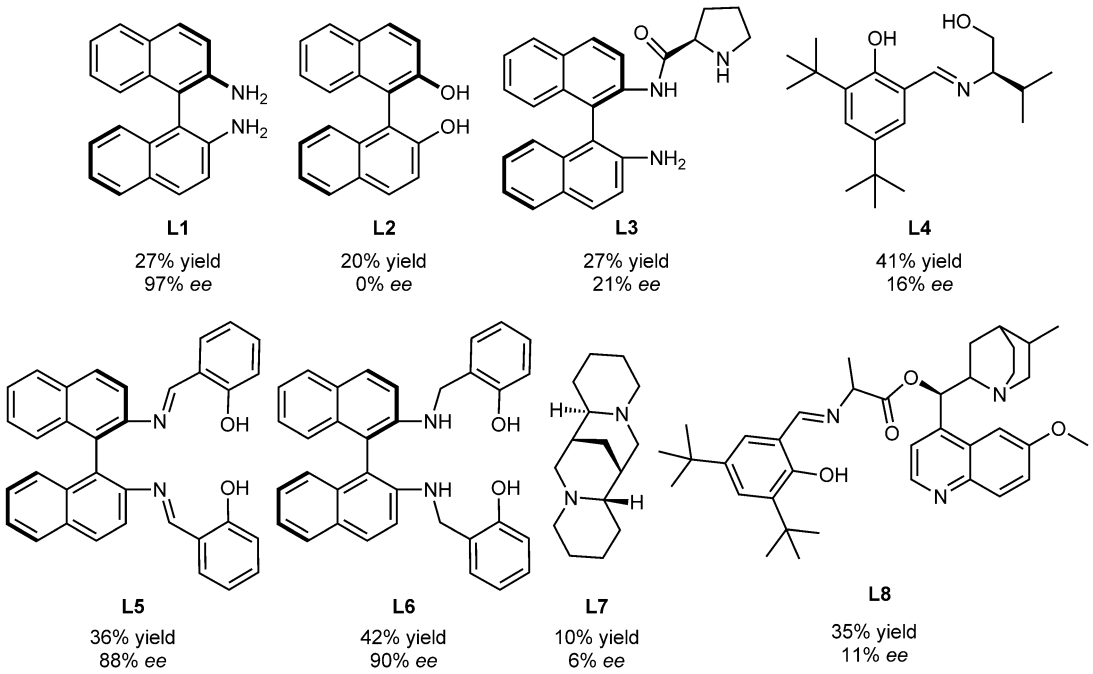
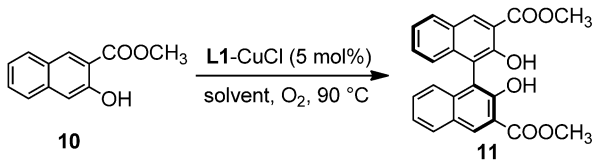


Figure 2. Effect of ligands on the asymmetric oxidative coupling of **10**.

Table 2. Effect of solvents on the oxidative coupling of **10**.



10 11

Entry	Solvent	Time [d]	Yield [%]	*ee* [%]
1	CH_3CN[a]	9	7	11
2	benzene[a]	4	74	63
3	xylene	6	46	46
4	DMSO	2	74	0
5	THF[a]	8	34	31
6	$CHCl_3$[a]	9	22	04
7	EtOAc[a]	7	40	86
8	PhMe	8	27	97
9	CCl_4[a]	9	-	-
10	MeOH[a]	18	97	08
11	DCE[a]	7	08	26
12	DCM[a]	7	40	94
13	PhMe[b]	9	80	56
14	DCM[c]	3	95	94

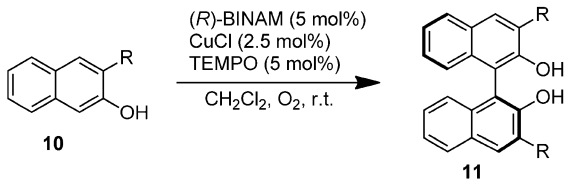
[a] Reaction was carried out in a pressure tube filled with O_2.
[b] Reaction was carried out with 5 mol% TEMPO.
[c] Reaction was carried out with 5 mol% TEMPO at room temperature.

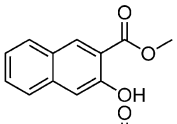
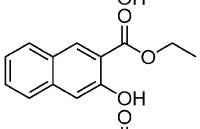
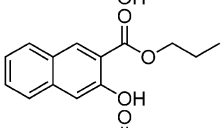
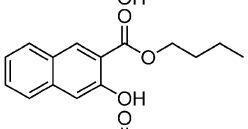
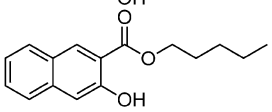
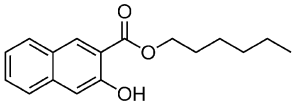
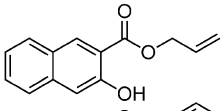
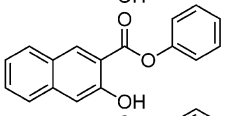
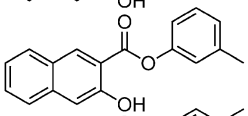
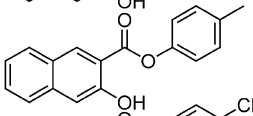
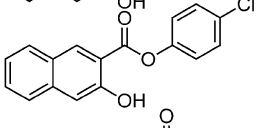
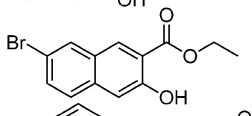
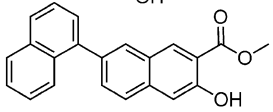
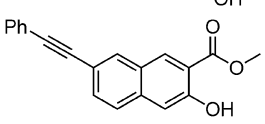
entry 13) at 90 °C. To solve the problems of longer reaction time, high reaction temperature and poor enantioselectivity, the reaction was studied with different solvents at room temperature. Surprisingly, dichloromethane was found to be the best choice, giving 94% *ee* and 95% yield in 3 days at room temperature (Table 2, entry 14).

Next, we examined the effect of the ratio of ligand **L1** and CuCl in the asymmetric oxidative coupling of **10**. Among the several combinations of Cu salt and ligand, a 1:2 ratio of copper chloride and ligand **L1** provided better selectivity. with a 1:2 ratio of catalysts, 2.5 mol% of CuCl and 5 mol% of ligand **L1** gave a maximum of 97% *ee* and 90% yield in 48 h at room temperature.

To prove the scope of the (*R*)-BINAM-CuCl-TEMPO catalytic system, several BINOL derivatives were synthesized using the optimized reaction conditions and the results are summarized in Table 3. Different ester groups were tolerated at the C-3 position of naphthol **10**. Interestingly, short-chain aliphatic alcohols such as methanol, ethanol and propanol esters of 2-naphthol derivatives gave good enantioselectivity.[13] When the chain length of the alcohol of the ester was increasing, the selectivity was also gradually decreasing (Table 3, entries 1–6). Enantiomeric excess did not alter even after replacing the methyl by allyl or phenyl group (Table 3, entries 7 and 8). Phenyl rings containing both the electron-releasing groups such as methyl group[14] and electron-withdrawing group such as chloro group were well tolerated in this oxidative coupling reaction (Table 3, entries 9–11). Even substitutions on the 2-naphthol skeleton provided moderate to very good enantioselectivity for the oxidative coupling reaction (Table 3, entries 12–14). The enantiomeric excesses of the BINOLs were deter-

Table 3. Substrate scope for the (*R*)-BINAM-CuCl-TEMPO-catalyzed oxidative coupling of 2-naphthol derivatives **10**.



Entry	2-Naphthol derivative	Time [d]	Yield [%][a]	*ee* [%][b]
1		2	90	97
2		3	93	90
3		3	85	88
4		3	88	81
5		3	91	75
6		4	95	67
7		4	77	91
8		3	91	94
9		4	91	73
10		4	80	75
11		3	88	85
12		3	88	94
13		2	98	48
14		3	77	70

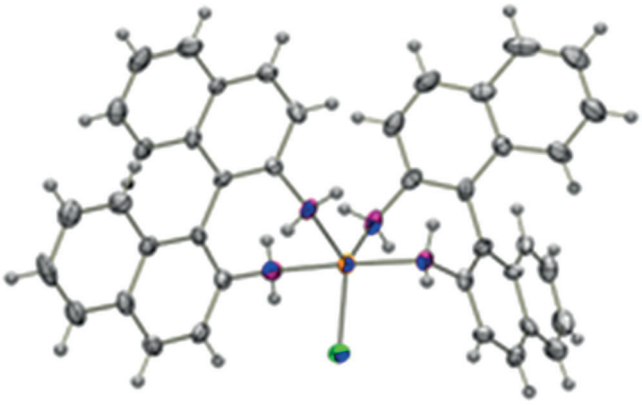


Figure 3. The single crystal XRD structure of (*R*)-BINAM-CuCl complex (30% probability).[16]

mined by HPLC using Daicel chiralPAK AD-H and OD-H columns.

The single crystal X-ray diffraction structure of the (*R*)-BINAM-CuCl complex is shown in Figure 3.[15] The X-ray structure analysis shows that the Cu complex possesses a square pyramidal geometry with four nitrogen atoms [from two (*R*)-BINAM molecules] coordinated with copper and one chloride ion occupies the axial position. The complex crystallized in monoclinic crystal system with space group C2 and unit cell dimensions $a=26.325(3)$, $b=10.7088(10)$, $c=14.3108(13)$, $\beta=100.767(4)$.; $Z=4$; cell volume$=3963.4(6)$ Å^3.[16]

In this reaction, the copper(I) complex will be oxidized to copper(II) by molecular oxygen. The resulting copper(II) complex will oxidize the β-naphthols to BINOLs through oxidative coupling and the copper(II) complex will be reduced to the copper(I) complex. The reduced copper(I) complex could be oxidized back to complete the catalytic cycle by molecular oxygen. We assume that the addition of TEMPO in this oxidative coupling reaction makes the redox reaction more facile. The TEMPO will oxidize the reduced copper(I) complex to the copper(II) complex and the TEMPO will be reduced to its hydroxy amine (TEMPOH). This TEMPOH will be easily oxidized back to TEMPO by molecular oxygen which is somewhat like the established protocol in copper complex-TEMPO-O_2-catalyzed alcohol oxidation reactions. However, a detailed study to understand the mechanism, application and scope of this catalyst is underway.

In summary, we have developed an efficient chiral copper catalytic system [(*R*)-BINAM-CuCl-TEMPO]

[a] Isolated yield.
[b] The % *ee*s of all the compounds were determined by HPLC using Daicel chiralPAK AD-H and OD-H columns.

for the asymmetric oxidative coupling of 2-naphthol derivatives to synthesize enantiomerically enriched BINOL derivatives with good to excellent enantiomeric excess (up to 97% *ee*). Addition of TEMPO to the (*R*)-BINAM-CuCl complex-catalyzed oxidative reaction drastically increases the reaction rate and the selectivity at room temperature in dichloromethane solvent.

Experimental Section

Typical Experimental Procedure for Asymmetric Oxidative Coupling

A mixture of (*R*)-BINAM (14.2 mg, 0.05 mmol) and copper(I) chloride (2.8 mg, 0.025 mmol) in 4 mL of dichloromethane was stirred at room temperature for 10 min, TEMPO (7.82 mg, 0.05 mmol) was added to the reaction mixture. After stirring for 5 min, methyl 3-hydroxy-2-naphthoate (202 mg, 1 mmol) was added and then the reaction mixture was stirred under an O_2 atmosphere (using an O_2 balloon). After completion of the reaction (as monitored by TLC), the reaction mixture was concentrated and the resulting residue was directly purified on silica gel column chromatography using hexanes-ethyl acetate mixture as eluent to obtain (*S*)-*dimethyl 2,2′-dihydroxy-1,1′-binaphthyl-3,3′-dicarboxylate*; yield: 181 mg (90%); mp 238–241 °C; R_f 0.29 (hexanes:ethyl acetate = 90:10); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.75 (s, 2H), 8.70 (s, 2H), 7.96–7.90 (m, 2H), 7.38–7.32 (m, 4H), 7.20–7.15 (m, 2H), 4.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7, 154.1, 137.3, 133.0, 129.9, 129.6, 127.3, 124.8, 124.1, 117.1, 114.3, 52.9; IR (neat): ν = 3187, 2954, 1676, 1325, 1210, 1076, 727 cm^{-1}; HR-MS: m/z = 403.1173 $[M+1]^+$, calcd. for $C_{24}H_{19}O_6$: 403.1182; $[\alpha]_D^{25}$: −155.5 (c = 1 in $CHCl_3$). [lit.[4] $[\alpha]_D^{25}$: −125.0 (c = 1 in THF)]. The enantiomeric excess (% ee) was determined to be 97% by HPLC (ChiralPAK AD-H column, 10% *i*-PrOH/hexanes, 1 mL min^{-1}): t_R (major) = 11.3 min, t_R (minor) = 20.0 min.

Acknowledgements

We thank CSIR, New Delhi (01(2378)/10/EMR-II) for the financial support. SKA thanks CSIR for a fellowship during his Ph.D. period, EP thanks DST-fast track project (SR/FT/CS-033/2008) and DGP thanks CSIR for a fellowship.

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[12] When NaCl (source for chloride counter ion; 0.05 mmol, 1 equiv. with respect to Cu salt) was added as additive to $CuSO_4$, the reaction afforded 30% *ee* and 10% isolated yield in 8 days. Similarly, when NaCl (source for chloride counter ion; 0.5 mmol, 1 equiv. with respect to Cu salt) was added to $CuSO_4$, (*R*)-(+)-1,1′-binaphthyl-2,2′-diamine and TEMPO in dichloromethane solvent at room temperature, the reaction afforded 41% *ee* and 20% isolated yield in 2 days. These experimental results show that the addition of external chloride counter ion (NaCl as additive) to Cu salt has no significant effect in the selectivity and hence the effect of the copper salt on the selectivity may be a solubility factor.

[13] A branched alcohol ester (isopropyl ester) gave 45% *ee*, 91% yield in 2 days.

[14] An *ortho*-methylphenyl substituted ester gave 63% *ee* and 72% isolated yield.
[15] For the X-ray single crystal structure of the racemate see: G. Zi, L. Xiang, Y. Zhang, Q. Wang, Z. Zhang, *Appl. Organomet. Chem.* **2007**, *21*, 177–182.
[16] CCDC 802244 contains the supplementary crystallographic data for the (*R*)-BINAM-CuCl complex in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.