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Heterocoupling of 2-naphthols enabled by a copper–N-heterocyclic carbene complex[†]

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The reactivity of a Cu catalyst for oxidative coupling is modulated by a small molecule additive, diethyl malonate, that slows over-oxidation of 2-naphthols. Efficient heterocoupling between electron-rich and electron-poor 2-naphthols/2-naphthylamines affords C_1 -symmetric BINOLs with yields ranging from 35–98%.

A wide variety of structurally diverse, biologically active biaryls are formed in Nature via the oxidative coupling of phenols and naphthols. In an effort to mimic the efficacy of Nature, biomimetic oxidative couplings have been developed using a variety of different metal complexes derived from Cu, V, Ru, Fe and Mn.^{1,2} Copperamine complexes have attracted the most attention of the transition metals, due to their similarity to copper-containing oxidases.³ Subsequently, these copper-amine complexes have been applied to the preparation of axially chiral natural products and chiral polymers, but perhaps the most common utility is the synthesis of enantiopure binaphthyl type ligands.⁴ The axially chiral biaryl motif is considered a privileged scaffold in asymmetric catalysis.⁵ A variety of complexes have been developed for the synthesis of C2-symmetric ligand scaffolds,⁵ but much less attention has been given to the preparation of C_1 -symmetric ligand structures.² The lack of interest is surprising given the utility of the C1-symmetric structures in asymmetric catalysis, materials science and supramolecular chemistry.⁵

The oxidative coupling of electronically dissimilar 2-naphthols is typically challenging (Scheme 1).^{6,7} In general, the limitations include: (1) the formation of homocoupling products and hence the need for an excess of the electron-rich 2-naphthol coupling partner or the use of slow-addition techniques,⁸ (2) formation of overoxidation products which hamper purification. In select cases, the use of harsh oxidants such as Oxone[®] and catalysts with limited solubility are necessary.² To demonstrate the difficulty of oxidative heterocoupling, the popular CuCl–TMEDA catalyst system¹¹ was employed for the oxidative coupling of **1a** and **2a**



Scheme 1 Heterocoupling of electronically differentiated 2-naphthols.

and only a 32% yield of the desired product **3a** was obtained (Scheme 1). When more exotic heterocouplings were attempted employing 2-naphthylamines or phosphonate containing substrates, the formation of a soup of overoxidation products was observed and no trace of the desired phosphonate **4a** or the NOBIN-like amine **5a** could be isolated. Consequently, we envisioned developing a more versatile and general procedure for oxidative heterocoupling.⁹ Herein we report on the efficient oxidative heterocoupling of 2-naphthols that overcomes the aforementioned limitations.

Based upon our interest in NHC–Cu catalysts with the general structure (NHC)CuX,¹⁰ we investigated these complexes as catalysts for heterocoupling. The investigations began by studying the coupling of the methyl ester **2a** with an excess (2 eq.) of 2-naphthol **1a** (Table 1). Our investigations employed a previously reported oxidant system (Oxone[®], AgNO₃, THF).¹¹ The first two Cu-based catalysts surveyed (Cu(IPr)Br and Cu(SIMes)Br) gave good yields of the heterocoupling product **3a** (63–67%) (entries 1 and 2). However the formation of over-oxidation products was observed.¹²

In an effort to develop a milder, more environmentally friendly oxidant system, the reduction of the loading of silver additive and replacement of $Oxone^{(R)}$ by molecular oxygen was investigated. Based upon the ease of synthesis, Cu(SIMes)Br was chosen as a catalyst for further optimization of the oxidant system.¹³ When $Oxone^{(R)}$ was replaced by an atmosphere of O_2 (1 atm) and the loading of AgNO₃ was reduced, the yield increased to 77% (entry 5). Despite the increases in yield, the

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 $\label{eq:table_$

		2a + 1a — (Xeq.)	catalyst (10 mol%) AgNO ₃ (20 mol%)	
			additive (x mol%) oxidant, THF, 60°C, 15 h	- 3a
Entry	1a (# eq.)	Catalyst	Additive (mol%); oxidant ^a	$\operatorname{Yield}^{b}(\%)$
1	2	Cu(IPr)Br	None; oxone	63 ^c
2	2	Cu(SIMes)Br	None; oxone	67 ^c
3	1	Cu(SIMes)Br	None; oxone	8 ^c
4	2	Cu(SIMes)Br	None; O ₂	77 ^c
5	2	Cu(SIMes)Br	DEM (50); O ₂	98
6	1	Cu(SIMes)Br	DEM (10); O ₂	79
^{a} Oxone = 1.1 eq		$\Omega_{\rm p} = 1$ atm ^b Isolated yields after chromatography		

^{*a*} Oxone = 1.1 eq., $O_2 = 1$ atm. ^{*b*} Isolated yields after chromatography. ^{*c*} AgNO₃ = 100 mol%. DEM = diethyl malonate.

formation of highly coloured byproducts was still observed, indicating overoxidation was still occurring. Recently, Kozlowski, Stahl and co-workers reported that small molecule over-oxidation products formed in the oxidative homocoupling of ester 2a could in fact be acting as a ligand for the copper catalyst, controlling its reactivity.¹⁴ Given the structural similarity of the proposed overoxidation products with common 1,3-dicarbonyl compounds, we investigated adding diethyl malonate (DEM) to the reaction mixture to modulate the reactivity of the copper-NHC catalyst (Table 1, entries 5 and 6).15 When DEM (50 mol%) was added to the oxidative coupling of 1a and 2a, the isolated yield increased from 77% to nearly quantitative (98%). Upon further optimization it was found that by adding only 10 mol% of DEM, the heterocoupling of a 1 : 1 mixture of 1a and 2a could proceed in 79% yield without the need for any slow addition techniques.¹⁶ Other 1,3-dicarbonyl compounds were equally or less effective than DEM.¹⁷

In an effort to discern the role played by DEM, the isolated yield of the product ester **3a** was examined with respect to the quantity of DEM added (Fig. 1). The yield of the coupling product remained relatively high regardless of whether 10 or 100 mol% of DEM was used. The small amount of DEM needed implies that it may be acting as a ligand and reactivity modulator for the Cu catalyst.¹⁸ Secondly, we investigated whether the DEM could be slowing over-oxidation of the ester **3a**. Thus **3a** was resubmitted to the coupling conditions with various amounts of DEM and was re-isolated after the designated reaction time. The amount of re-isolated **3a** remained constant regardless of whether DEM is



Fig. 1 Effect of DEM on the yield and stability of **3a** under the optimized reaction conditions.

present, suggesting that DEM is needed to slow overoxidation of the 2-naphthols rather than the resulting BINOL products.

Using the optimized reaction conditions, the synthesis of C_1 -symmetric BINOLs was investigated (Table 2). Both electronrich and electron-poor 2-naphthols were studied (entries 2 and 3 respectively). The bromo-substituted BINOL derivative 3b was isolated in excellent yield (95%) when using an excess of 7-bromo-2-naphthol, and still afforded a good yield (58%) when both starting materials were used in equimolar quantities. The methoxy-BINOL 3c was formed efficiently via coupling even when both naphthol starting materials were used in a 1 : 1 ratio (75%). The oxidative coupling also proceeded smoothly when substitution was included on the 2-naphthol ester, BINOLs 3d-f were isolated in 46-98% yield depending on the ratio of coupling partners materials used. The heterocoupling using 3-phenanthrol was problematic and low yields of 3g were obtained (35-49%). Finally, the ester moiety could be substituted for other groups: (1) a nitro-containing BINOL 3h was isolated in

 Table 2
 Synthesis of C1-symmetric BINOLs via oxidative coupling



^{*a*} Isolated yields following chromatography. ^{*b*} DEM = 50 mol%. ^{*c*} Some compounds were prepared on 1 mmol scale: **3a** = 77%, **4a** = 66%.

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71% when equimolar quantities of starting materials were employed (entry 6), and (2) a bromo-substituted BINOL **3i** was isolated in 62% when a slight excess of 2-naphthol was used.

The investigation of the substrate scope continued by examining the heterocoupling of 2-naphthols containing a phosphonate at the 3-position (Table 2). BINOL products containing phosphonates in the 3 and/or 3'-positions have found use in asymmetric catalysis,¹⁹ but the synthesis of these ligands via oxidative coupling is limited to a single report involving homocoupling.^{3b} The heterocoupling of a phosphonate with an equimolar quantity of 2-naphthol afforded the desired heterocoupling product 4a in 77% yield. The heterocoupling afforded similar yields of the C_1 -symmetric products when employing more electron-poor 2-naphthols (50% of 4b) or electron-rich 2-naphthols (62% of 4c) (entries 9 and 10). The extension of the substrate scope of the oxidative protocol was expanded to include NOBIN derived ligands, which have attracted increased attention in asymmetric catalysis.²⁰ As a consequence the number of methods for NOBIN synthesis has expanded.²¹ The preliminary results involved the heterocoupling of 2-naphthylamine with ester 2a using the optimized protocol (entry 11). When using a slight excess of the 2-naphthylamine, the desired NOBIN 5a was isolated in 67% yield.

In summary, a mild, efficient, catalytic heterocoupling of 2-naphthols has been developed using the mono-NHC Cu catalyst Cu(SIMes)Br and an environmentally benign oxidant (O₂). Of note is the use of DEM as a small molecule additive that appears to slow the formation of over-oxidation by-products, eliminating the need for large excesses of one coupling partner. The protocol afforded good yields of C_1 -symmetric BINOLs and the NOBIN **5a** (35–98%) and the first reported heterocoupling of phosphonate-containing BINOLs **4a–c**.

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