Directed Remote Lateral Metalation: Highly Substituted 2-Naphthols and BINOLs by *in situ* Directing Group Generation

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In Memoriam Gilbert Stork

Abstract: A general synthesis of highly substituted 2-naphthols based on a new carbanionic reaction sequence is demonstrated. The reaction exploits the dual nature of lithium bases consisting of consecutive ring opening of readily available coumarins with $LiNEt_2$ or LDA to *Z*-cinnamamides generating a directing group in situ and allowing, by conformational freedom, a lateral directed remote metalation - ring closure reaction to give the aryl 2-naphthols in good to excellent yields. These transformations can be combined to provide a more efficient one pot process. Mechanistic insight into the remote lateral metalation step demonstrating the requirement of *Z*-cinnamamide is described. Application of this methodology to the synthesis of highly substituted 3,3'-diaryl BINOL ligands is also reported.

In the course of our efforts to uncover new directed remote metalation (DreM) strategies[1,2] we required a robust methodology for the synthesis of highly substituted 2-naphthols. Naphthol structures (Figure 1A) are core components of natural products,[3] dyes and pigments[4] and essential building blocks for dimeric anisotropic BINOLs[5] which are widely used as ligands and catalysts in enantioselective synthesis[6] and molecular recognition.[7] Despite this, routes to 2-naphthols are mostly based on classical annulation and S_EAr reactions requiring multiple isolations and purifications, limiting practical access to elaborate substitution patterns.[8, 9]

We proposed to exploit the dual nucleophilic and basic nature of lithium dialkylamide bases to achieve the synthesis of 2-naphthols[10] **3** from coumarins **1** in a single reaction vessel through a ring transposition process (Figure 1B). In this transformation, the easily accessible coumarins **1** undergo nucleophilic attack generating the *Z*-cinnamamides **2**, forming a new directing group *in situ* with obligatory retention of stereochemistry. Compound **2**, conformationally liberated, undergoes bond rotation allowing spatial alignment of the amide directing group (DMG) with the remote methyl group (**2***). Subsequent chelation of the amide by the lithium dialkylamide, operative via the Complex Induced Proximity Effect (CIPE),[11] serves as a base, promoting a DreM process and generating **Li-2***. The DMG now acts as an electrophile to deliver the 2-naphthol **3**, effecting an O- to C- ring transposition in a single reaction step.

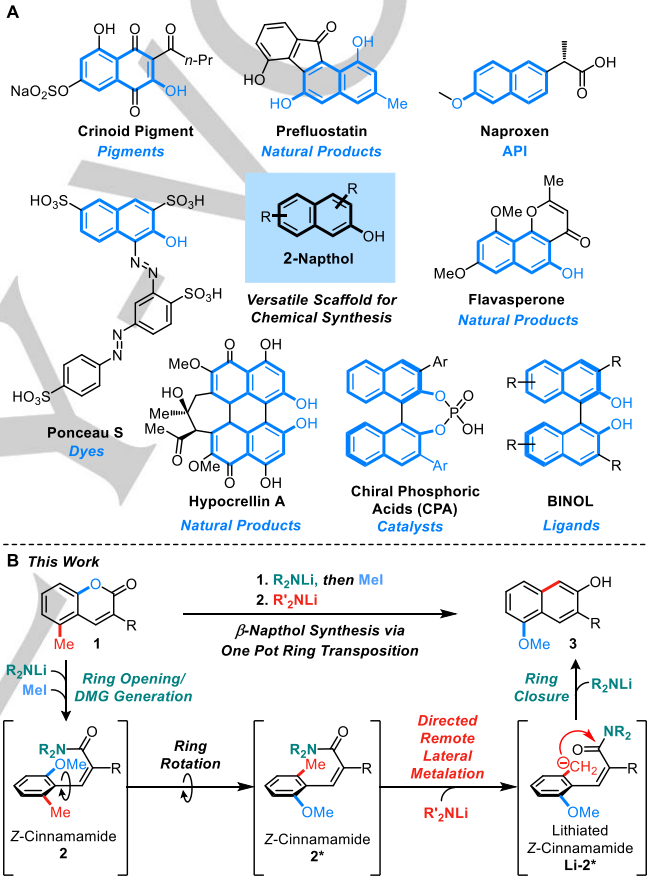

Figure 1. A) 2-Napthols in natural and bioactive molecules, drugs, and materials. B) Synthesis of 2-naphthols **3** from coumarins **1** employing a one-pot ring transposition.

To investigate the proposed transformation, we first sought to examine each individual step within the sequence separately. With gram quantities of coumarins **1** available from a modified Perkin reaction protocol (See SI),[12] optimum conditions for ring opening to the *Z*-cinnamamides **2** were established (Table 1).[13] Treatment of **1** with freshly prepared lithium diethylamide followed by sequential reaction with NaH and MeI, without isolation of the intermediate phenols, afforded single stereoisomeric *Z*-cinnamamides **2** in good yields (Table 1). The stereochemistry of *Z*-cinnamamide **2c** was confirmed by NOE experiments proving the double bond geometry had been retained (See SI). Careful choice of the lithium dialkylamide was essential. Whilst LDA

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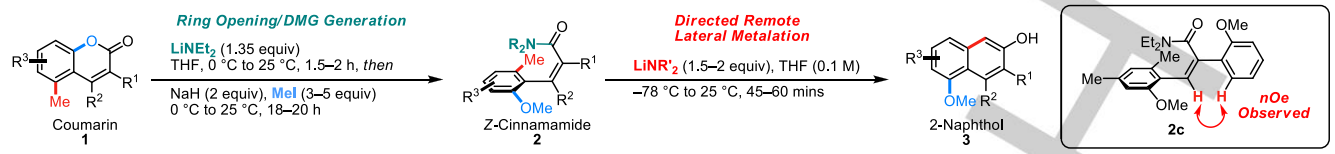
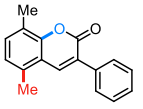
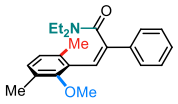
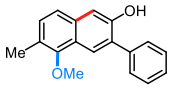
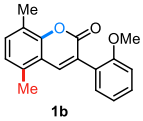
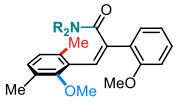
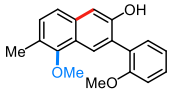
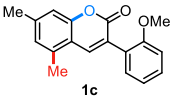
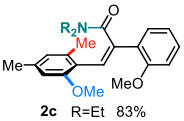
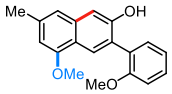
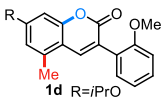
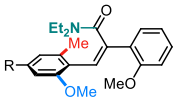
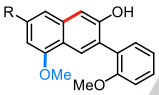
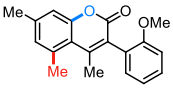
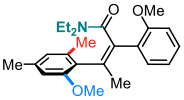
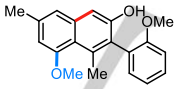
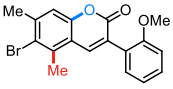
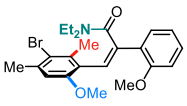
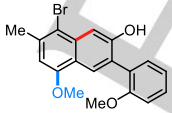
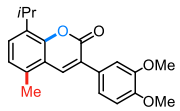
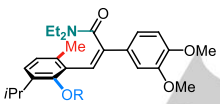
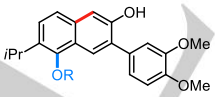
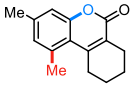
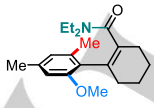
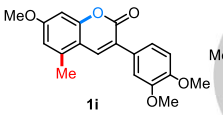
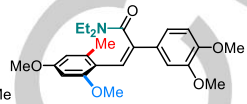
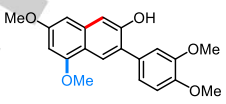
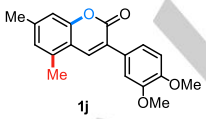
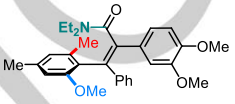
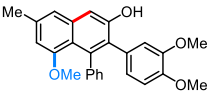
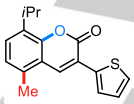
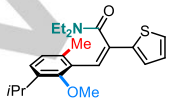
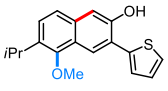
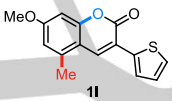
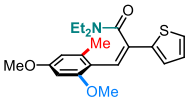
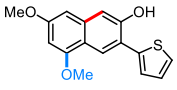
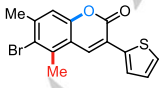
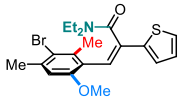
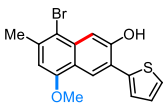
proved equally effective as $LiNEt_2$ in a number of cases (e.g. Table 1 entry 2, **2b** vs **2b'**), in some cases,



Entry	Coumarin	Z-Cinnamamide	2-Naphthol
1	 **1a**	 **2a** 85%	 **3a** 69% (from **2a**) LDA
2	 **1b**	 **2b** R=Et 72% **2b'** R=*i*Pr 86%[a]	 **3b** 76% (from **2b**) LiTMP **3b** 91% (from **2b'**) LDA
3	 **1c**	 **2c** R=Et 83% **2c'** R=*i*Pr 23%[a]	 **3c** 91% (from **2c**) LiTMP **3c** 96% (from **2c**) LDA **3c** 83% (from **2c'**) LDA
4	 **1d** R=*i*PrO **1d'** R=H	 **2d** R=*i*PrO 54% **2d'** R=H 68%[b]	 **3d** 90% (from **2d**) LDA **3d'** 0% (from **2d'**) LDA **3d'** 0% (from **2d'**) LiTMP
5	 **1e**	 **2e** 91%	 **3e** 81% LiTMP
6	 **1f**	 **2f** 77%	 **3f** 82% LiTMP
7	 **1g**	 **2g** R=Me 52% **2g'** R=Bn 92%[b]	 **3g** R = Me 90% LiTMP **3g'** R = Bn 53% LiTMP
8	 **1h**	 **2h** 81%	 **3h** 64% LiTMP

Entry	Coumarin	Z-Cinnamamide	2-Naphthol
9	 **1i**	 **2i** 52%	 **3i** 77% LiTMP
10	 **1j**	 **2j** 96%	 **3j** 74% LiTMP
11	 **1k**	 **2k** 69%	 **3k** 76% LiTMP
12	 **1l**	 **2l** 64%	 **3l** 65% LiTMP
13	 **1m**	 **2m** 61%	 **3m** 82% LiTMP
14	**1n**	**2n** 58%	**3n** 76% LiTMP
15	**1o**	**2o** 80%	**3o** 61% LDA
16	**1p**	**2p** 75%[a]	**3p** 92% LDA

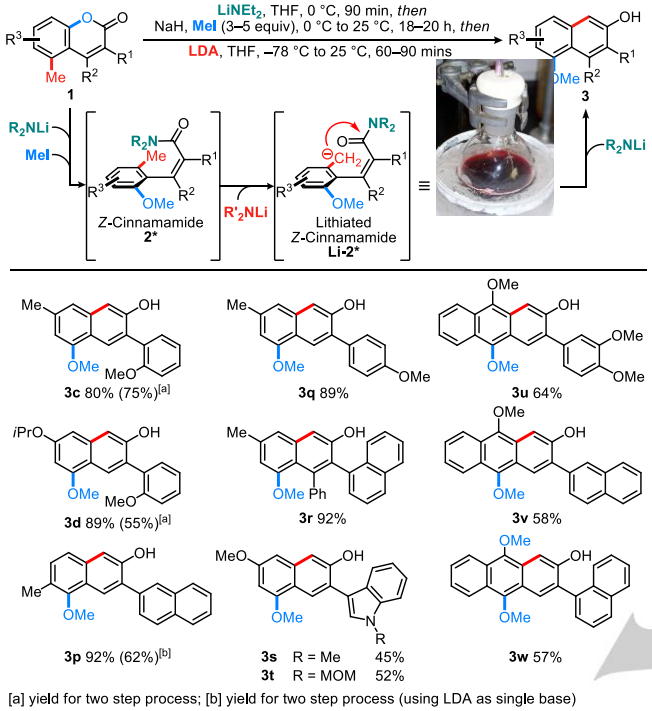
[a] LDA was used for Coumarin opening; [b] BnBr was used inplace of MeI

Table 1. Synthesis of 2-naphthols **3** from coumarins **1** via *Z*-cinnamamides **2.**

the more basic and sterically encumbered LDA failed to give useful yields of the cinnamamides (Table 1, entry 3, compare **2c** vs **2c'**) leading to $LiNEt_2$ being employed as our standard amide base throughout. A range of substituted coumarins **1** afforded the desired *Z*-cinnamamides **2** in good to excellent yields (52–96% yield).

The key lateral DreM reaction was then studied on **2** and optimized conditions using either LDA or LiTMP (1.5–2.0 equiv) were found to be equally efficient for the conversion into the 2-naphthols **3**. (In some cases, excess LDA or Li-TMP was used, see SI). Surprisingly, the only system which failed to afford 2-naphthol **3** was the unsubstituted coumarin **2d'** which decomposed under the reaction conditions. In all other examined

cases, the lateral DreM reaction proved consistently robust across a broad substrate scope, tolerating halogen, alkyl, and aryl substituents on the anisole ring as well as aryl and heteroaryl cinnamamide double bond substituted systems (**2e** and **2n**).

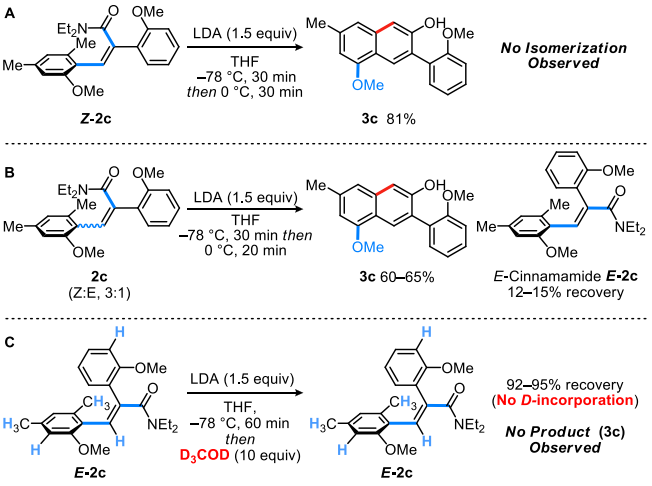


Scheme 1. One-pot synthesis of 3-aryl-2-naphthols **3** from coumarins **1**.

With each step investigated independently and optimized, attention turned to the unification of these steps into a single vessel. Thus, sequential treatment of **1** with $LiNEt_2$ and MeI, followed by a more basic lithium amide (LDA) without isolation of **2**, afforded **3** in good to excellent yields. Importantly, in all cases examined, the yields of this one-pot process were either comparable (Scheme 1. **3c**) or better (Scheme 1. **3d**, **3p**) than those of the two–step protocol. As in the two-step process, metalation proceeded with appearance of a vivid burgundy at –78 °C (Scheme 1, Photo **Li-2***) and was complete in short reaction times (typically 60–90 min) to furnish high yields of products without isolation of any intermediates.

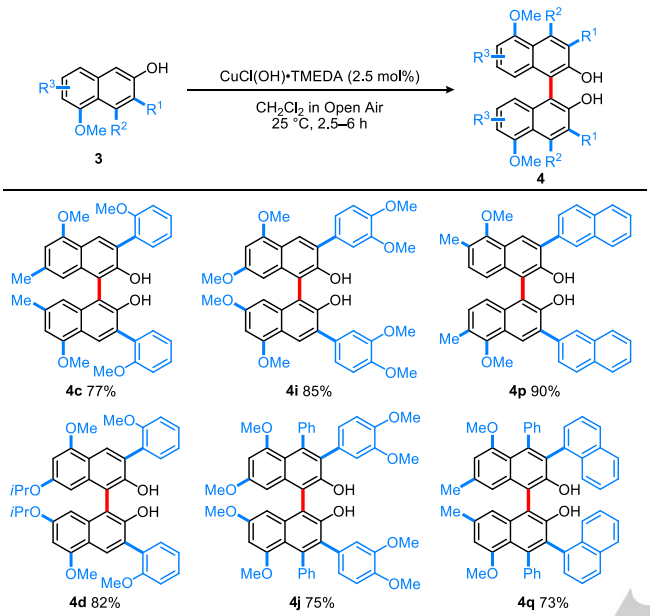
To gain insight into the mechanism of the reaction, the expected requirement (based on CIPE considerations)[11] of the *Z*-stereochemistry of cinnamamide **2** for successful remote lateral metalation-cyclization to the 2-naphthols **3** was tested (Scheme 2). First, the isolated *Z*-cinnamamide ***Z*-2c** had been shown to afford product **3c**. Examination of the crude reaction mixture showed only the generation of product, with no *E*-cinnamamide detected by ^{1}H NMR (Scheme 2A). To conclusively establish if *Z/E*-isomerization of the cinnamamide was possible, additional metalation studies were conducted. Thus, the 3:1 inseparable mixture of *Z*- and *E*-cinnamamides ***Z*-2c** and ***E*-2c**, was subjected to LDA treatment under the standard conditions and afforded the 2-naphthol **5c** and recovered ***E*-2c** in 60–65% and 12–15% respectively (Scheme 2B). Furthermore, treatment of pure *E*-cinnamamide ***E*-2c** under excess LDA conditions followed by acidic quench resulted in quantitative recovery of the starting material. Significantly, quenching the solution with MeOD or d_4-MeOH gave starting material without *d*-incorporation at any of the potential acidic hydrogen environments (NMR analysis) and in both experiments, the burgundy red color which was strikingly evident in the metalation reaction of isomer **Z-2c**, was not observed (Scheme 2C). These results are consistent with the *obligatory requirement of the directing group to facilitate metalation*, rather than functioning as purely a kinetic trap. On the basis of the consistency, within error tolerance of the isolation procedure,[14] of the ratios of starting *Z*- and *E*-cinnamamide mixture ***Z*-2c** and ***E*-2c** and those of 2-naphthol **3c** and un-cyclized *E*-cinnamamide ***E*-2c** products, it is evident that the *Z*-cinnamamide **2c** stereochemistry is necessary to effect the cyclization. Parenthetically, the conversion of ***E*-2c** to the expected thermodynamically more stable ***Z*-2c** is not observed under the excess LDA conditions, indicating the absence of a potential Michael addition-elimination reaction as may have been expected based on consideration of the mechanism of the Baylis-Hillman reaction.[15] Thus, initial LDA-amide coordination to promote the remote lateral metalation reaction of **2** to **3** following the CIPE concept[11] constitutes a significant component of the mechanism of the reaction.

The 2-naphthol **3** structure immediately evokes its relationship to the venerable BINOL motif[5,6] by way of dimerization. To verify and to stimulate further investigation, 2-naphthols **3** (Scheme 3) were subjected to one of the standard oxidative coupling conditions[16] and provided a new series of highly sterically congested BINOLs **4** in 82–95% yields. Significantly, these elaborate and densely functionalized molecules are accessible in only two reaction vessels from the coumarin precursors **3**, demonstrating the power and utility of the methodology. Further studies in this and other uses of 2-naphthols which are readily available by this route are in progress.



Scheme 2. Mechanism of the remote lateral metalation reaction of cinnamamide **2c**.

In conclusion, we have developed a general protocol for the synthesis of highly substituted 2-naphthols **3** which are unavailable by currently established routes for this class of aromatics. The disclosed reaction, a directed lateral remote metalation process assisted by CIPE,[11] may be viewed as a



Scheme 3. Highly substituted BINOL Derivatives **4** from 2-Naphthols **3**.

heterocyclic to aromatic ring transposition, **1→3** (Scheme 1) and thereby may have broader synthetic consequences. Importantly, by generating the directing group *in situ*, the one-pot process becomes more efficient than the multi-step multi-pot transformation. The availability of the 2-naphthols and BINOLs as their *O*-carbamates and triflates invites both DoM and cross coupling[17] chemistry which has already been achieved on 1- and 2-naphthols and related derivatives in our laboratories.[18] Overall, we therefore anticipate application and extension of the remote lateral metalation concept for the synthesis of new aromatic and heteroaromatic molecules.

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Keywords: directed remote metalation • lithiation • coumarin • 2-naphthol • BINOL • C-H activation

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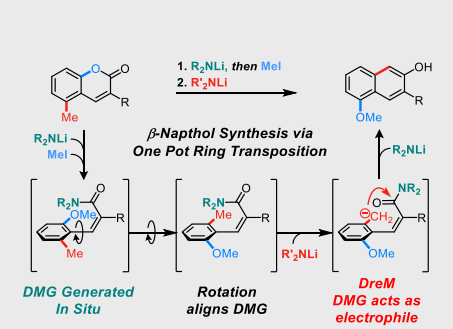

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Directed Remote Lateral Metalation: Highly Substituted 2-Naphthols and BINOLs by *in situ* Directing Group Generation

The Many Faces of Lithium Bases

A new ring transposition process converting coumarins to 2-napthols in a single flask is reported. A lithium amide first acts as a nucleophile to open coumarin rings generating a directing group in situ. This conformationally liberated system then undergoes a directed remote metalation/ring closure reaction to give 2-naphthols in excellent yields. Mechanistic insight demonstrating the requirement of Z-cinnamamide for the reaction and the synthesis of highly substituted BINOL ligands is also reported.

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