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Total Synthesis of Chiral Biaryl Natural Products by Asymmetric Biaryl Coupling ‡

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Abstract

This tutorial review highlights the use of catalytic asymmetric 2-naphthol couplings in total synthesis. The types of chirality, chiral biaryl natural products, prior approaches to chiral biaryl natural products, and other catalytic asymmetric biaryl couplings are outlined. The three main categories of chiral catalysts for 2-naphthol coupling (Cu, V, Fe) are described with discussion of their limitations and advantages. Applications of the copper catalyzed couplings in biomimetic syntheses are discussed including nigerone, hypocrellin, calphostin D, phleichrome, and cercosporin.

1. Introduction

1.1 Types of Chirality

Chemical compounds manifest chirality in a number of ways.¹ Most commonly, the presence of an sp^3 substituted atom with four different substituents generates a stereocenter leading to a chiral compound. Compounds of these types exhibit central chirality (Figure 1). Other types of stereogenic units are possible. For example, biaryl molecules can exhibit axial stereochemistry. In this case, the loss of rotational freedom about the stereoaxis means that it is not necessary for all four substituents to be different. It is sufficient for the pairs at each end not be symmetric (i.e. $R^1 \neq R^2$ and $R^3 \neq R^4$). With helical chiral molecules, the stereogenicity drives from the macroscopic structure, in which the compound exhibits a turn in either the clockwise direction (denoted *P*), or in the counterclockwise direction (denoted *M*).

Unlike central chirality, the enantiomers in axial and helical chiral systems are conformational isomers. These atropisomers can interconvert without breaking a bond, provided that the activation energy is sufficiently low. If the barrier is high, these molecules can be stable indefinitely. For example, the atropisomerization barrier for 1,1'-binaphthalene-2,2'-diol (BINOL) is 37.1 kcal/mol resulting in a half-life for atropisomerization of over 5 million years at room temperature.²

1.2 Biaryl-Containing Natural Products

There are a myriad of natural products that contain a biaryl bond (Figure 2).^{3,4} Not only do methodologies that are able to install the axial chirality give access to these complex molecules, but they provide an entry into an important category of chiral ligand used in asymmetric synthesis.⁵ While a number of ways have been developed to synthesize chiral biaryl compounds, catalytic enantioselective methods remain a challenge.

‡Part of the Rapid Formation of Molecular Complexity in Organic Synthesis themed issue.

1.3 Synthetic Approaches to Biaryl Natural Products

One way in which the biaryl bond has been constructed asymmetrically, is by means of a chiral auxiliary. An example is seen in the synthesis of the natural product gossypol (**4**) by Meyers and coworkers (Scheme 1).⁶ The chiral auxiliary, *tert*-butyl oxazoline, was used to direct the axial stereochemistry via an Ullman coupling of **2**, generating the biaryl in 81% yield, with an 11:1 diastereomeric ratio. With the axial stereochemistry installed, the auxiliary was removed and the biaryl was further elaborated to generate gossypol.

A different approach to asymmetric biaryl bond formation was used by Bringmann and coworkers in the first atroposelective total synthesis of knipholone (Scheme 2).⁷ A palladium-catalyzed intramolecular biaryl coupling furnished lactones **6** and **7** in 68% yield. These conformationally unstable and rapidly interconverting lactones were subjected to an atropo-enantioselective ring opening with enantiopure oxazaborolidine resulting in a dynamic kinetic resolution. Once the lactone bridge was cleaved, the resultant biaryl **8** did not atropisomerize providing the (*S*) enantiomer needed to generate the natural product.

1.4 Catalytic Asymmetric Biaryl Synthesis⁸

While great strides have been made in the synthesis of chiral biaryl natural products and in understanding the relevant stereochemical control elements, the use of catalytic asymmetric transformations to create the axial chiral biaryl bond defines the frontier of this field, providing an opportunity for superior atom economy and more streamlined syntheses. Other synthetic methods to generate chiral biaryls by desymmetrization or cyclotrimerization have also been reported but are outside the scope of this review.¹

One of the earliest such methods to generate enantiopure binaphthalenes with substoichiometric catalyst loadings is the S_NAr reaction (Scheme 3).⁹ While good selectivity (82% ee) was obtained, the functional group pattern limits substrates that can be employed and the use of an aryl lithium precludes the use of certain functional groups, which is a disadvantage for total synthesis efforts. Improved enantioselection was seen in the Kumada^{10,11} and Negishi¹² cross couplings (Scheme 3), but again the generation and use of Grignard or diaryl zinc reagents precludes many functional groups.

More recently Suzuki couplings have enjoyed greater success in the generation of axial chiral molecules.¹³ The Suzuki coupling offers advantages over the Kumada or Negishi, because the aryl boronic acids are air-stable and are much more tolerant of a variety of functional groups. However, this transformation is challenging since many other pathways are available to the activated intermediates leading to byproducts. While major advances have been made, as of yet, no general protocol is available and each coupling needs to be optimized. Lassaletta and coworker reported high yields and enantioselectivities in Suzuki couplings (Scheme 3),¹⁴ but heating was necessary to achieve reasonable reaction times which can lead to the atropisomerization of the newly generated axial chiral bond.¹³ As of yet, catalytic enantioselective S_NAr , Kumada, Negishi, or Suzuki biaryl couplings have not been employed in a total synthesis.

2. Oxidative Asymmetric Biaryl Coupling

2.1 General Considerations

Oxidative couplings of phenols and naphthols¹⁵ comprise a useful method for the synthesis of biaryl compounds and are especially suited to natural product synthesis since many of the biosynthetic routes to biaryls involve such a coupling.¹⁶ Due to a favorable one-electron phenolic oxidation, these transformations can be carried out under mild reaction conditions that tolerate many functional groups. This versatility distinguishes oxidative biaryl coupling

from other chiral biaryl synthetic methods such as the aforementioned nucleophilic aromatic substitution, Kumada coupling, Negishi coupling, and Suzuki coupling. In addition, these transformations often introduce functionality at non-functionalized centers, thereby eliminating the need for complex pre-functionalized starting materials (i.e., halides, boronic acids, etc.).

Conversely, the lack of pre-functionalization limits the regioselective control. The substrate typically dictates the available coupling products, though in some cases the regioselectivity can be controlled by the catalyst. To this end, both *ortho*- and *para*-couplings are facile, but often unwanted side products are formed if there are multiple sterically and electronically comparable positions (Table 1); *meta*-coupling is unattainable.¹⁷ Moreover, in the case of unsymmetrical natural products, such as knipholone (Figure 2), chemoselective cross-coupling of the monomers is difficult. Encouragingly, Habaue and co-workers reported high chemoselectivity in the synthesis of unsymmetrical binaphthols using copper catalysts in the presence of a Lewis acid, such as Yb(OTf)₃, but the enantioselectivities were modest.¹⁸

2.2 Copper-Mediated Naphthol Couplings

The systems first investigated in asymmetric phenolic coupling centered on chiral amine-copper salts. Seminal work by Wynberg and Feringa showed that a stoichiometric amount of a Cu(NO₃)₂ (*S*)- α -methylbenzylamine complex was highly effective in the coupling of 2-naphthol (63% yield), but the enantioselection was low (3% ee).¹⁹ Building on this work, Brussee found that a large excess of (*S*)-amphetamine combined with CuCl₂ produced (*S*)-BINOL in 98% yield and 96% ee (Scheme 4a).²⁰ Interestingly, the high enantiopurity resulted from a diastereoselective precipitation of the Cu(II)-(*S*)-amphetamine-(*S*)-BINOL with a concomitant atropisomerization of (*R*)-BINOL (*dynamic kinetic resolution*). On the other hand, Smrcina and Kocovsky discovered that the highly chemoselective cross-coupling of 2-naphthol with 2-naphthylamine (Scheme 4b) by treatment with CuCl₂ and (*R*)- α -methylbenzylamine proceeded via a *diastereoselective recrystallization* of the product-copper complex.²¹ While both of the processes established the potential of copper reagents in naphthol coupling, an *asymmetric cross-coupling* is necessary to achieve catalysis. The discovery of such a mechanism in the coupling of 2-naphthol and 3-hydroxy-2-naphthoic acid methyl ester using CuCl₂ and sparteine was thus an important achievement even though the selectivity was modest (Scheme 4c).²²

2.3 Copper Catalyzed Naphthol Couplings

The earliest breakthrough in the catalytic asymmetric oxidative coupling of 2-naphthol was reported by Nakajima and co-workers employing chiral prolyldiamine ligands to obtain the coupling product (Scheme 5).²³ However, the upper enantioselectivity limit was 78% ee with the prolyldiamines while other diamines (i.e. sparteine) provided even lower selectivity. Importantly, dioxygen was established as an effective reoxidant for this catalytic process. For these reactions most other oxidants were ineffective causing either direct substrate oxidation (peracids, peroxides), interference with substrate coordination [Mn(OAc)₃, K₃Fe(CN)₆], or insufficient reactivity (benzoquinones). While the explosive potential of dioxygen combined with organic solvents is well recognized, no adverse events have been reported in oxidative phenolic coupling and dioxygen is certainly less reactive than the corresponding peroxides. The use of metered amounts of pure dioxygen or even of air is also viable. Thus, this discovery has fueled practically all further research on asymmetric catalysts for oxidative phenol coupling.

Since few structurally different chiral diamines have found general utility in asymmetric synthesis, our group used a computer-aided procedure to remedy this deficiency and identified the 1,5-diaza-*cis*-decalin scaffold. It was postulated that the chiral 1,5-diaza-*cis*-decalin would

form a highly effective copper catalyst (**30**, Table 2) solving the selectivity limitations encountered with the classic diamine ligands.²⁴ In fact, using O₂ as the stoichiometric oxidant, catalyst **30** has been found to be remarkably effective in the enantioselective oxidative couplings of a broad range of 3-substituted-2-naphthols and the generation of a number of complex binaphthols (Table 2).²⁵

An electron-withdrawing, coordinating group at C3 has been shown to be important for selectivity. Apparently, bidentate coordination of the C3- and C2- substituents to the copper complex is crucial for enantioinduction. Even so, a wide variety of 3-substituents can be utilized resulting in the 3,3'-diester (**31a-c**), -diamide (**31d**), -diketone (**31e**), -diphosphonyl (**31g**), and -disulfonyl (**31h**) derivatives (Table 2, entries 1-9).²⁶ Notably, this system constitutes one of only two available for the highly enantioselective homo-coupling of 3-substituted-2-naphthols.

Since the oxidation proceeds via movement of an electron from the naphthol ring, the effect of substituents on the oxidation potential is expected to influence reactivity. In fact, substrates that are very electron rich (Table 2, entry 10) react extremely quickly and the products may react further, opening an avenue to atropisomerization. This can be easily controlled by modulating the ring substituents (C4-OMe to C4-OAc, Table 2, entry 11).²⁷ As mentioned above, coordination of the C3-group to the catalyst is crucial for enantioinduction and substrates where steric gearing compromises this coordination are not as effective (Table 2, entries 5,12-13).^{26,27,28} Nonetheless, it is possible to couple a large number of substrates effectively, providing functionalized 1,1'-binaphthalene-2,2'-diols in high yield and enantioselectivity as shown with a few representative examples in Table 2.^{27,29,30}

A study of the mechanism³¹ revealed a complex process explaining why these types of transformations remain challenging. Rather than a simple two-stage “ping-pong” mechanism with separate stages for coupling of the substrates and reoxidation of the catalyst, the kinetic data supported a mechanism where substrate coupling and catalyst reoxidation can occur during one step (Scheme 6). The initial burst phase constitutes stage 1 of a conventional “ping-pong” mechanism – substrate oxidation of **26** by the oxidized catalyst (*S,S*)-**30**, resulting in 0.5 equiv of product **28** and formation of the reduced catalyst **33**. Unexpectedly, reaction of **26** with catalyst **33** (Cu-complex **34**) resulted in another burst phase, corresponding to the rapid consumption of molecular oxygen and yielding the substrate oxygenation product **26^{ox}** (Cu-complex **35**). Formation of product **28** was not observed until after the oxygen-burst phase. Interestingly, this oxygenase activity was followed by the oxidase reactivity during the steady-state turnover, where **26** was converted exclusively into **28**. This evidence suggests that the oxidase reactivity arises from participation of a cofactor, **26^{ox}**, formed in a catalyst “self-processing” event. Further kinetic data supported that aerobic oxidation of Cu-complex **36** is the rate-limiting step of the reaction. Based on these results, it is now possible to design a catalyst with exclusive oxidase activity (i.e., **35**) versus a catalyst such as **33**, which possesses oxygenase activity (i.e., formation of **26^{ox}**).

Another copper catalyst derived from an octahydro BINAM has resulted in good selectivity.³² The greater reactivity of this catalyst system may arise from the lower basicity of the diamine ligand resulting in poorer stabilization of the reactive oxidation state [Cu(II)].

Other copper-catalyzed variants have been explored with aim of undertaking couplings of simple 2-naphthols. Martell and co-workers have proposed the dicopper-salen-complex (Scheme 8) as the catalyst responsible for the high yield and enantioselectivity (85%, 88% ee) in forming BINOL.³³

2.4 Other Metal Catalysts in Naphthol Couplings

More recently, a variety of vanadium-based catalysts (Figure 3) have proven viable in asymmetric oxidative biaryl couplings. These couplings proceed under mild reaction conditions, again using dioxygen as the terminal oxidant, often with air being sufficient. Early advances in the field included the development of monomeric Schiff base-derived vanadyl catalysts by Chen³⁴ and Uang³⁵ including those in entries 1-2 of Table 3. Using these principles, Iwasawa developed the first heterogeneous catalyst for the asymmetric coupling of naphthol which proved very selective (90% ee, entry 3, Table 3).³⁶

Subsequently, two groups developed elegant bimetallic catalysts based on different hypotheses. Gong proposed that the lower half of **37d** acts as a chiral controller and would provide a superior asymmetric environment thereby giving rise to higher selectivity.³⁷ This proposal is supported by the results from **37b** as well as by ingenious studies showing that the binaphthyl and amino acid stereochemistries in **37d** contribute to selectivity leading to matched (*M*-axial, *L*-amino acid) and mismatched cases (*P*-axial, *L*-amino acid). Kinetic studies, competitive coupling reactions, and HRMS spectral studies have provided evidence that the coupling reaction undergoes a radical-radical mechanism in an intramolecular manner. Further refinement of the catalyst backbone led to **37f** which provided higher selectivities.^{37,38} Elegant kinetic studies of the monomeric catalyst led Sasai to propose that a similar bimetallic catalyst (**37d**) would enable activation of the two substrates within one complex and thereby increase the rate of the second order process. As expected, higher reaction rates in the homo-couplings have been achieved compared to their monometallic counterparts.³⁸ Currently, the bimetallic vanadium catalysts represent the state of the art for coupling of 2-naphthol (entries 4-5, Table 3).

Notably, the weakly oxidizing vanadium(V) requires electron-rich substrates and longer reaction times than the copper catalysts described above. While the long reaction times have been somewhat resolved by employing dimeric catalysts, these systems cannot utilize substrates with electron-withdrawing groups, and typically, 2-naphthols with additional electron-donating substituents provided the best results (entries 6-8, Table 3). In addition, no substitution at the 3-position is tolerated. Thus, the vanadium catalysts are almost completely orthogonal to the copper catalysts for oxidative coupling.

One solution to the coupling of 2-naphthols with nonchelating 3-substituents is seen in a study by Osa utilizing an electrochemical process to power the oxidation.³⁹ A TEMPO-modified graphite electrode in conjunction with sparteine converts 2-naphthol to BINOL with an impressive 99% ee. Furthermore, very oxidatively sensitive substrates, such as 2-phenanthrol (**40**) undergo highly efficient coupling (Scheme 9). When dioxygen is used as the terminal oxidant, as is the case with the copper and vanadium catalysts, 2-phenanthrol (**40**) rapidly forms an *ortho*-quinone.

While the above solution is powerful, the use of stoichiometric sparteine is undesirable and access to the opposite product enantiomer is difficult. Another solution to the coupling of 3-substituted 2-naphthols can be found in the work of Katsuki where dioxygen from air is used as the terminal oxidant in couplings. The ruthenium salen catalyst affords good reactivity in the presence of light and can even be utilized with more electron deficient 2-naphthols, but selectivities are modest (Scheme 10).⁴⁰ On the other hand, the corresponding iron(III) catalysts proved highly effective with electron-rich 3-substituted 2-naphthols (Scheme 10), providing a class of valuable products which was hitherto inaccessible by oxidative asymmetric coupling.⁴¹

Overall, there are three effective types of catalysts for the oxidative asymmetric coupling of 2-naphthol and its derivatives. The copper catalysts are broadly useful with 2-naphthols

containing coordinating groups at the 3-position. They tolerate substitution at all other positions and are the only class of catalysts useful with electron-deficient substrates. The vanadium catalysts provide access to a wide array of BINOL-derivatives stemming from electron rich 2-naphthols so long as no substitution is present at the 3-position. Finally, iron catalysts are highly effective with electron-rich 3-substituted 2-naphthols. Thus, the major catalysts types are highly orthogonal with each having specific applications.

3. Oxidative Biaryl Coupling: Natural Product Biosynthesis

3.1 Biosynthetic Pathways

The formation of C-C bonds by oxidative reactions is a well-recognized process in biological systems, where the transformation serves as a crucial step in the biosynthesis of many natural products.¹⁶ In a laboratory setting, this type of process is highly attractive due to use of O₂ as a reagent. In addition to efficiency and low cost, dioxygen is a stable, environmentally benign oxidant. The only byproducts with dioxygen as an oxidant are water and hydrogen peroxide, which in turn is readily converted to water and dioxygen.

Specifically, the enzymatic oxidative coupling of phenols has been widely studied as a viable biosynthetic pathway to many natural products. The importance of phenol radicals during phenol oxidations was pioneered by Pummerer⁴² and has since become widely accepted as a biosynthetic intermediate.¹⁶ In exploring biologically relevant pathways for the *Erythrina* alkaloids, Barton conjectured that the phenolic coupling of the simple precursor **46** is a likely means of synthesis (Figure 4).^{16a} Similarly, radical pairing in conjunction with the structure of Pummerer's ketone suggests a biosynthetic pathway for the morphine type alkaloids involving oxidative coupling of the benzyloquinoline **47** (Figure 5).^{16a,43} The efficiencies of this retron are seen throughout nature, where a series of phenolic couplings on a simple substrate can lead to an entire family of complex natural products. Indeed, the biosynthesis of morphine has inspired many biomimetic alkaloid syntheses.

3.2 Enzymatic Naphthol Coupling

Due to the effectiveness of nature in building complexity, the ability to perform asymmetric operations utilizing enzymes has been of considerable interest. To this end, the metalloporphyrin enzyme, horseradish peroxidase has been studied for its catalytic capability in asymmetric naphthol couplings. It is thought that the peroxidases catalyze the production of free radicals that are intermediates in the coupling.¹⁶ The enzyme was found to provide suitable yields of the coupled products in modest enantioselectivities (Scheme 11).⁴⁴ A further example utilized cell cultures from *C. Sinensis* to initiate naphthol coupling (Scheme 11).⁴⁵ Such oxidations using hydrogen peroxide are of considerable interest since they represent environmentally friendly processes.

4. Applications in Total Synthesis

4.1 Naphthol Precursors

One particular advantage of the copper catalysts is the ability to couple 2-naphthols with ester groups at the 3-positions, which can not be achieved with either the vanadium or iron catalysts (see Section 2.3 and 2.4). Surprisingly, the synthesis of multisubstituted naphthol substrates is not trivial. However, 3-alkoxycarbonyl-2-naphthols are generated facilely via an intramolecular Friedel-Crafts reaction of a tricarbonyl which is in turn easily assembled from readily available phenyl acetic acids (Scheme 12). In comparison to the other methods to access naphthols, such as the Dötz annulation and Diels-Alder reactions, this method is simple and requires fewer steps. By exploiting this pathway, a host of functionalized 2-naphthols can be rapidly generated. In particular, we have synthesized the oxidative coupling substrates outlined

in Scheme 12 in this manner.^{27,28,29,46,47,48} The iodo- and bromo-derived compounds proved especially useful in that they could be used to generate further functionalized oxidative coupling substrates (Scheme 13).⁴⁸

4.2 Nigerone Total Synthesis

One such class of binaphthyl containing natural products is the bisnaphthopyrones, including nigerone (**57**) and isonigerone (**69**) (Figure 1),⁴⁹ which are mold isolates that display moderate antitumor⁵⁰ and antibacterial⁵¹ activities. Nigerone is formally, and from a biosynthetic point of view, the dimer of a tricyclic oxygen heterocycle. In a retrosynthetic analysis, however, the heterocycle can be formed last by a formal Claisen condensation with the enolate of acetone (**59**) onto **58** followed by a dehydrative cyclization to **57** (Scheme 14). When this disconnection is exercised, the binaphthyl intermediate **58** maps directly onto the type of structures (**60**) assembled with our 1,5-diaza-*cis*-decalin copper catalyst (Table 2).^{25,26,27} The necessary monomer would require substitution at both the C3,C4,C5,C7-positions, a combination that had not been examined in asymmetric oxidative coupling.

It was found that highly functionalized naphthols coupled with high selectivity when the C4,C6,C7-positions were substituted (**32b**, Figure 6). However, naphthol **32c** bearing an additional C5-methoxy group provided much lower enantioselectivity (27% ee).²⁷ While chelation of the substrate to the catalyst is readily accommodated for many substrates, the additional C5-substituent causes steric gearing which forces the methyl ester out of position for optimal coordination to the catalyst, resulting in lower selectivity. Removal of the C6 methoxy group as in **32d** would be expected to alleviate this effect, however, the selectivity only increased to 45% ee.²⁸ Use of methylidene protecting group for the C4,C5-positions should further alleviate this gearing. In line with this reasoning, **62** was produced with 66% ee.²⁸

With the findings from Figure 6, a synthesis of nigerone was designed utilizing a constrained naphthol **64**.^{28,46} This naphthol is the natural product flavasperone which we synthesized from the commercially available 3,5-dimethoxybenzoic acid (**63**). Rewardingly, the late stage asymmetric coupling of the complex intermediate **64** succeeded with the copper 1,5-diaza-*cis*-decalin catalyst furnishing the bisisonigerone **65** in 60% yield with 80% ee.

Since **65** is an isomer of the final target nigerone (**57**) and energy calculations reveal that nigerone is the most stable of the three possible isomers, an equilibration was envisioned. Using NaOH in methanol at 70 °C, the eight-step isomerization (Scheme 16) was undertaken. During the isomerization, an intermediate was observed but was consumed during the course of the reaction. We believe the intermediate was isonigerone (**69**), which was then converted to the more stable nigerone (**57**). Purification by trituration then provided nigerone (**57**) in 90% ee. With this route, both (*S*)-nigerone and (*R*)-nigerone were produced using the corresponding copper catalyst enantiomer in the oxidative coupling step.^{28,46}

The absolute configurations of bisisonigerone (**65**) and nigerone (**57**) had been assigned based upon the highly stereoregular nature of the copper catalyzed coupling reaction. However, the CD spectrum of the synthesized (*S*)-nigerone did not match the spectrum of the natural product. In the original report, the configuration was assigned by comparison to related structures, which led to nigerone being assigned erroneously the (*S*) configuration.⁴⁹ Synthesis of (*R*)-nigerone provided a material which matched the natural product CD spectrum. The configurations were further established by means of quantum chemical CD calculations using the exciton chirality method (Figure 7).²⁸ The calculated CD spectra for (*R*)-nigerone and (*R*)-bisisonigerone matched very well with the experimental CD curves whereas those of the (*S*)-enantiomers did not, allowing the absolute configuration to be assigned as (*R*).

4.3 Perylenequinone Natural Products

The perylenequinone family of natural products (**70-74**, Figure 8)^{3,52} is comprised of compounds containing a helical chiral conjugated pentacyclic core. This chromophore permits their use as photosensitizers upon exposure to light. In addition, they are potent protein kinase C (PKC) inhibitors with unique binding to the PKC regulatory domain.⁵³ The unique structural and biological aspects of these compounds have drawn the attention of many researchers.⁵⁴

From a synthetic perspective, **70-72** contain the same stereochemical elements – the chiral helical unit and stereogenic C7,C7'-2-hydroxypropyl groups. Two related perylenequinones, **73** and **74**, are characterized by additional 7-membered and 6-membered carbocyclic rings, respectively, that bridge the aromatic core. Beyond these elements, the perylenequinones are prone to atropisomerization of the helical perylene core (Figure 9). The barrier to atropisomerization of the helical configuration, entailing rotation of the C2,C2'- and C7,C7'-groups past one another, varies substantially for the compounds in this series. Whereas the calphostins and phleichrome are atropisomerically stable, the additional seven-membered ring in cercosporin lowers the barrier allowing atropisomerization at 40-60 °C, making it a particularly challenging synthetic target.⁵⁵ On the other hand, the hypocrellins atropisomerize rapidly at ambient temperature presenting two sets of sharp peaks in the NMR spectrum.⁵⁶

Prior to our investigations, total syntheses of the simplest and atropisomerically stable perylenequinones, **70** and **71** had been reported.^{57,58,59,60} In these efforts, the stereogenic C7,C7'-substitution was exploited in the atropselective formation of the biaryl axis from chiral naphthols (Scheme 17). For example, Coleman utilized a copper-promoted coupling via a higher order biaryl cyanocuprate and was rewarded with good selectivity, dr = 1:8, but unfortunately, the predominant diastereomer did not correspond to the calphostin (**70**) array as expected. But when employing *ent*-**77**, it did match that needed for **71**. Merlic employed an acid-promoted oxidative dimerization of *o*-naphthoquinone **79**. Disappointingly, a 1:2 mixture was obtained with the undesired *M*-isomer dominating. A thermal atropisomerization was utilized to provide the desired *P*-isomer as a 3:1 mixture that ultimately was transformed into **70**.

Cercosporin (**72**) and hypocrellin A (**73**) contain further complexity due to the additional seven-membered rings. Notably, a synthesis of **73**, relying on the prior methods of construction (path *b*, Scheme 18) would require oxidation of the alcohol stereocenters, which had required much effort to generate initially. With these synthetic constraints in mind, our group elected to pursue a different strategy that would mimic the likely biosynthesis. By installation of the axial chirality first, the corresponding helical stereochemistry could be established with complete stereocontrol (path *a*, Scheme 18). The helical stereochemistry can in turn be utilized to control the C7,C7'-stereochemistry. Alternately, the C7,C7'-stereochemistry can be introduced from an external source, permitting the selective synthesis of all the possible isomers of **70-73** (Figure 8). These combined approaches streamlined our syntheses of the perylenequinones to a common synthetic intermediate, chiral biaryl **87** (Scheme 19). Our use of asymmetric biaryl couplings in the total syntheses of **70-73** is detailed below.

4.4 Total Synthesis of Hypocrellin A

Our synthesis of hypocrellin A centered around a potentially biomimetic, *dynamic stereochemistry transfer (DST) reaction*.^{29,61} The biosynthesis of **73** likely involves the formation of the seven-membered ring via a transannular intramolecular aldol reaction of **94** (Scheme 20· Scheme 21). However, the stereochemistry transfer is not straightforward due to the dynamic state of the helical axis of **73**. The helical chirality of **94** is needed to direct the stereochemistry of the aldol cyclization, but following formation of the seven-membered ring,

the integrity of the helical axis is lost due to the rapid atropisomerization of **73** (4:1, *P:M*) at room temperature (Scheme 21).⁵⁶

The helical chirality for the desired aldol perylenequinone retron **86** was generated from the axial chiral common intermediate **32i** (Scheme 19, Scheme 20). Our copper 1,5-diaza-*cis*-decalin catalyst in the enantioselective oxidative coupling of **87** was used to generate the stereogenic biaryl axis (entry 18, Table 2; Scheme 20). The rapid assembly of molecular complexity further highlights the utility of this method, which provided the bisiodide enantiopure intermediate **32i** in 81% ee and good yield. The high crystallinity of **32i** yielded enantiopure material (>99% ee) with excellent mass recovery after one simple trituration. Following methylation of C2,C2',C4,C4'-phenols, a Suzuki coupling was utilized to install the C7,C7'-allyl groups to provide **89** (Scheme 20). After C5,C5'-hydroxylation using PhI(O₂CCF₃)₂, the allyl groups were further converted to the desired diketone via a Wacker oxidation. Other strategic steps to the key aldol substrate **94** included a palladium-mediated decarboxylation of **92**, oxidative cyclization where the axial stereochemistry was transferred to form the helical stereochemistry of **93**, and PdCl₂ deprotection of sensitive ketal **93**.

Prior to our synthesis of **73**, this type of 1,8-diketone aldol reaction had not been used outside of bridged or macrocyclic architectures. Molecular modeling indicated that a (*Z*)-enolate of **94** would give rise to the *syn* aldol product corresponding to hypocrellin A via a closed chair-like transition state. Analysis of the computed transition states indicated that the helical stereochemistry of **94** would preferentially expose one diastereoface of the ketone, resulting in the (*S*)-tertiary alcohol stereochemistry of **73** via transition state **A** (Scheme 21).

After screening silazide bases, which are known to give predominately (*Z*)-enolates, it was found that the aldol cyclization of **94** with LiN(SiMe₂Ph)₂ at -105 °C provided the desired 7-membered ring (Scheme 22). As expected, the two newly formed centrochiral stereocenters in the 7-membered ring were dictated by the helical (*P*)-stereochemistry and the (*Z*)-enolate geometry. A small amount of the (*E*)-enolate led to the anti aldol product leading to the diastereomeric natural product shiraichrome (**95**). Exposure to MgI₂, enabled a selective removal of the C4,C4'-methyl ethers, allowing completion of the first total synthesis of hypocrellin A (*syn:anti* = 10:1; *syn* diastereomer, 92% ee).^{29,61}

4.5 Total Syntheses Phleichrome, Calphostins, and Cercosporin

As mentioned earlier, the versatility of our perylenequinone strategy enables the synthesis of all stereoisomers of **70-73** (Scheme 19, Figure 10). With use of the 1,5-diaza-*cis*-decalin catalyst antipodes, both enantiomers of the common enantiopure intermediate (*M*-**32i** and *P*-**32i**) can be accessed. This flexibility was utilized in the total syntheses of (+)-**70**, (+)-**71** and **72**, where *M*-**32i** was employed (Figure 10).^{47,48,62,63}

Notably, **70-72** contain the same stereogenic C7,C7'-2-hydroxypropyl groups, but they differ in the stereochemistry of the alcohols. Use of an external stereochemistry source for the C7,C7'-substitution was desirable in that both **70** and **71**, which have opposite C7,C7'-stereochemistry, could be accessed without having to rely on the restrictions of relative diastereoselection. We elected to use copper-mediated epoxide-openings in an unprecedented double alkylation of the highly functionalized bisiodide to install the 2-hydroxypropyl groups.^{48,62}

Interestingly, Grignard-derived cuprates are well precedented to open epoxides, but most systems lack functional complexity. Prior to our efforts, there were no reported systems of a complex dianion effecting two ring-openings. The primary concerns were: 1) the metal-halogen exchange on an electron-rich system and in the presence of the C3,C3'-methyl esters; 2) the need for the organocopper reagent to be the limiting reagent when it is typically used in excess; 3) stability of the electron-rich biscuprate reagent. After considerable optimization of

the copper-mediated epoxide-opening reaction, the requirements of the naphthalene substitution, the protecting groups, and the copper reagents were discovered that could routinely provide the three component coupling product in $\geq 65\%$ yield (Eq 1, Eq 2).^{62,63} Furthermore, both enantiomers of propylene oxide coupled with equal efficiency allowing selective access to all the natural product stereoisomers. Apparently, the interaction between the biaryl chiral axis and the centrochiral centers of the epoxide does not lead to any kinetic resolution (matched vs mismatched cases proceed equally well).

As with hypocrellin A, reserving introduction of the stereogenic C7,C7'-substitution until after naphthalene formation and dimerization streamlined the synthesis of the naphthalene portion (see Scheme 12), which was a lengthy undertaking in prior approaches to **70** and **71**.⁵⁷⁻⁶⁰ The biaryl coupling with the (*S,S*)-diaz-*cis*-decalin catalyst provided the *M*-bisiodide **32i** in equal efficiency to that of *P*-**32i** (Scheme 23). After methylation, utilization of both enantiomers of propylene oxide allowed completely stereoselective entry to **70** and **71**, which would be difficult using a stereochemistry transfer reaction (Scheme 23). Key subsequent transformations to complete the syntheses of *ent*-calphostin D (**70**) and *ent*-phleichrome (**71**) included C5,C5'-hydroxylation via palladium catalyzed coupling of the hindered aryl chloride, C3,C3'-decarbonylation, and oxidative cyclization.

Though the stereochemical elements of cercosporin are the same as phleichrome and the calphostins, the presence of the seven-membered ring, which lowers the barrier to atropisomerization, made it a particularly challenging target. The atropisomerization barrier of phleichrome (29.4 kcal/mol) allows retention of the perylenequinone helicity up to 60 °C, but the addition of the methyldiene bridge lowers the barrier in cercosporin to 28.2 kcal/mol (27.4 kcal/mol in benzene).⁶² This facile atropisomerization requires that the combination of the perylenequinone and the methyldiene bridge be withheld as late as possible in the synthesis.

In our retrosynthetic analysis, we elected to form the methyldiene bridge before the perylenequinone since typical conditions for generating the methyldiene would atropisomerize the perylenequinone.

Utilizing the same methodology as before to install the stereochemistry (see Eq 1 and Eq 2), intermediate **101** was obtained in high yield and stereochemical integrity. Protection of the alcohol stereocenters as bisbenzyl ethers and chemoselective deprotection of the phenolic bisbenzyl ethers proceeded smoothly to provide the bisphenol (Scheme 24). After considerable screening, it was discovered that BrCH_2Cl was the best electrophile for this process, affording the seven-membered ring in good yield with no atropisomerization. Further transformations following the protocols from *entcalphostin D* (**70**, Scheme 23) yielded advanced intermediate **102**. After deprotection, the bisphenol was oxidized under mild conditions with MnO_2 to provide the perylenequinone. As previously discussed, this crucial step was held until the end of the synthesis due to the atropisomerically labile combination of the methyldiene bridge and perylenequinone. Selective removal of the C4,C4'-methyl ethers completed the first total synthesis of cercosporin (**72**, Scheme 24).

This strategy enabled a late stage diversification permitting the ready synthesis of analogs for biological study.⁶² Furthermore, the ability to stereoselectively generate all of the perylenequinones was central to the evaluation of the stereochemistry on PKC inhibition. Excitingly, the *M*-perylenequinones were shown to be up to 20 times more potent than the corresponding *P*-isomers ((+)-**70** vs (+)-**71**, (+)-**71** versus (–)-**70**, **72** vs *epi*-**72**, and *ent*-**73** vs **73**). On the other hand, changing the C7,C7'-alcohol stereochemistry resulted in only a two-fold change in binding with the (*R,R*)-array being superior.

5. Concluding Remarks

The biomimetic coupling of 2-naphthols by means of a chiral 1,5-diaza-*cis*-decalin copper catalyst has enabled biomimetic syntheses of several natural products including nigerone, hypocrellin, calphostin D, phleichrome, and cercosporin as well as numerous analogs. Even though the utility of the biaryl axis is well established in catalysis and is present in many pharmaceutical agents and natural products, asymmetric methods to synthesize such compounds remain limited. The use of biomimetic couplings relying on favorable phenolic oxidations is a powerful means to generate such compounds. The current work constitutes a step in this direction, but many challenges remain including selective cross coupling of different substrates with asymmetric control and enantioselective coupling of other types of substrates, such as 1-naphthols and phenols.

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Figure 1.
Types of Stereounits

Figure 2.
Biaryls in Nature

Scheme 1.
Synthesis of Gossypol

Scheme 2.
Synthesis of Knipholone

Scheme 3.
Asymmetric Couplings with Aryl Halides

a) *Brusee* b) *Smrcina & Kocovsky* c) *Smrcina & Kocovsky*

Scheme 4.
Asymmetric Copper Mediated Naphthol Coupling

Scheme 5.

Copper Catalyzed Asymmetric Homocoupling in the Presence of a Prolyldiamine

Scheme 6.
Sequential Mechanism for Copper Catalyzed Asymmetric Biaryl Coupling

Scheme 7.
Copper catalyzed Asymmetric Homo-coupling in the Presence of an H₈-BINAM

Scheme 8.
Asymmetric Homocoupling Catalyzed by a Copper-salen Complex

Figure 3.
Vanadium-Derived Catalysts

Scheme 9.
Asymmetric Homocoupling Under Electrochemical Conditions

Scheme 10.
Ruthenium- and Iron-catalyzed Asymmetric Couplings of 2-Naphthols

Figure 4.
Retron for the *Erythrina* Alkaloid Family

Figure 5.
Phenolic Coupling Retron for the Morphine Alkaloid Family

	Conditions	R ¹	R ²	Yield (%)	ee (%)
A: <i>Horseradish peroxidase</i> , H ₂ O ₂ , phosphate buffer (pH 6.0), MeCN	A	H	H	75	52
	A	Br	H	80	64
	A	H	CO ₂ Me	65	45
B: <i>C. Sinensis</i> cell culture, H ₂ O ₂ , B5 medium (pH 5.4)	A	H	Me	60	38
	B	H	H	47	59
	B	H	Br	28	36

Scheme 11.
Enzymatic and Cell Culture Catalyzed Asymmetric Naphthol Couplings

Scheme 12.
Construction of Functionalized 2-Naphthols

Scheme 13.
Further Functionalization of 7-Halo-2-Naphthols

Scheme 14.
Retrosynthetic Analysis of Nigerone

Figure 6.
Effect of Substitution Patterns on Enantioselectivity

Scheme 15.
Total Synthesis of Nigerone

Scheme 16.
Mechanism of Eight-Step Base Isomerization

Figure 7.
Calculated and Experimental CD Spectra

Figure 8.
Perylenequinone Natural Products

Figure 9.
Atropisomerization of the Helical Perylene Core

Broka $R^1 = \text{TBDPS}$, $R^2 = \text{MOM}$, $t\text{-BuLi}$; FeCl_3 , 47%, 3.3:1 dr

Coleman $R^1 = \text{BOM S}$, $R^2 = \text{Me}$, $n\text{-BuLi}$; CuCN ; O_2 , 68%, 1:8 dr

Hauser $R^1 = \text{Ac}$, TFA; $\text{Ti}(\text{O}_2\text{CCF}_3)_3$, 91%, 1:1 dr

Merlic $R^1 = \text{Bz}$, TFA; O_2 , 71%, 1:2 dr

Scheme 17.

Diastereomeric Biaryl Couplings Toward the Calphostins.

Scheme 18.
Retrosynthetic Considerations Toward the Perylenequinones

Scheme 19.
Common Enantiopure Intermediate **32i**

Scheme 20.
Highly Functionalized Biaryl Coupling of Iodonaphthol **87**

Scheme 21.
Dynamic Stereochemistry Transfer

Scheme 22.
Total Synthesis of Hypocrellin A

(+)-**71**, (*R,R,M*) *ent*-Phleichrome
 (+)-**70**, (*S,S,M*) *ent*-Calphostin D
72, (*R,R,M*) Cercosporin
ent-**73**, (*R,S,M*) Hypocrellin

(–)-**71**, (*S,S,P*) Phleichrome
 (–)-**70**, (*R,R,P*) Calphostin D
epi-**72**, (*R,R,P*) *epi*-Cercosporin
73, (*R,R,P*) Hypocrellin A

Figure 10.

Common Enantiopure Intermediate to Perylenequinones

Scheme 23.

Biaryl Coupling of Iodonaphthol in the Total Syntheses of *ent*-Phleichrome and *ent*-Calphostin D

Scheme 24.
Synthetic Considerations for Cercosporin

Table 1

Mixed Products in Oxidative Phenol Couplings

<p>20</p> <p><i>Phenolic Coupling</i></p> <p>21a</p> <p>21b</p> <p>21c</p>				
Oxidant	Solvent	a:b:c:d:e		
(<i>t</i> -BuO) ₂	PhCl	85:11:0:4:0		
<i>t</i> -BuOOH	H ₂ O	24:18:45:21:7:9		
Mn(acac) ₃	PhH	4:43:28:12:14		
Ag ₂ CO ₃	MeCN	1:13:24:9:53		
K ₃ Fe(CN) ₆	aq MeCN	18:23:27:22:10	<p>21d</p>	<p>21e</p>

Table 2

Copper Catalyzed Asymmetric Coupling of 2-Naphthols with a 1,5-Diaza-*cis*-decalin Ligand

Entry	Product	R ¹	Catalyst	Yield (%)	ee (%)	Entry	Product	R ²	R ³	R ⁴	R ⁵	Catalyst	Yield (%)	ee (%)
1	(<i>R</i>)-a	CO ₂ Me	(<i>S,S</i>)	85	93 (<i>R</i>)	10	a	OMe	H	OMe	OMe	(<i>S,S</i>)-CuCl	81	35 (<i>S</i>)
2	(<i>S</i>)-a	CO ₂ Me	(<i>R,R</i>)	82	92 (<i>S</i>)	11	b	OAc	H	OMe	OMe	(<i>R,R</i>)	72	90 (<i>S</i>)
3	b	CO ₂ Bn	(<i>S,S</i>)	79	90 (<i>R</i>)	12	c	OAc	OMe	OMe	OMe	(<i>S,S</i>)-CuCl	41	27 (<i>R</i>)
4	c	CO ₂ <i>n</i> -Hx	(<i>S,S</i>)	70	87 (<i>R</i>)	13	d	OAc	OMe	H	OMe	(<i>S,S</i>)	75	45 (<i>R</i>)
5	d	CON(CH ₂ CH ₂) ₂ O	(<i>S,S</i>)	61	75 (<i>R</i>)	14	e	OAc	H	OMe	H	(<i>S,S</i>)	71	86 (<i>R</i>)
6	e	COPh	(<i>S,S</i>)	88	89 (<i>R</i>)	15	f	OAc	H	OMe	<i>n</i> -propyl	(<i>S,S</i>)	85	87 (<i>R</i>)
7	f	OBn	(<i>R,R</i>)-CuBr	74	46 (<i>S</i>) ^a	16	g	OAc	H	OMe	allyl	(<i>S,S</i>)	80	85 (<i>R</i>)
8	g	P(O)(OMe) ₂	(<i>S,S</i>)	76	92 (<i>R</i>)	17	h	OAc	H	OMe	≡-TMS	(<i>S,S</i>)	85	82 (<i>R</i>)
9	h	SO ₂ C ₆ H ₄ - <i>p</i> -OMe	(<i>S,S</i>)	75	57 (<i>R</i>) (98) ^b	18	i	OAc	H	OMe	I	(<i>R,R</i>)	80	81(<i>R</i>) (99) ^b

^aAir was the oxidant. ^bAfter titration.

Table 3

Vanadium Catalysts in the Asymmetric Coupling of 2-Naphthols

Entry	Catalyst	Product	R ¹	R ²	Yield (%)	ee (%)
1	37a	39a	H	H	99	84
2	37b	39b	H	OMe	90	73
3	37c	39a	H	H	93	90
4	37d	39a	H	H	93	83
5	37e	39a	H	H	100	90
6	37d	39b	H	OMe	88	98
7	37e	39b	H	OMe	67	93
8	37f	39c	Br	On-Bu	90	97

Reaction scheme: 2-Naphthol **38a-c** (with substituents R¹ and R²) reacts with a V-catalyst (3-5 mol%) to form the biaryl product **39a-c**.