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Three-Component *cine,ipso*-Disubstitution of Nitrocoumarins

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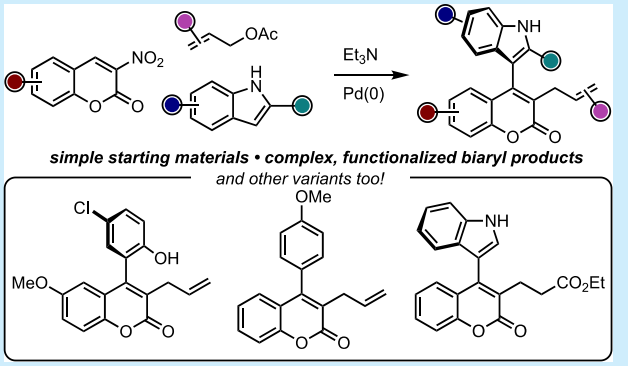
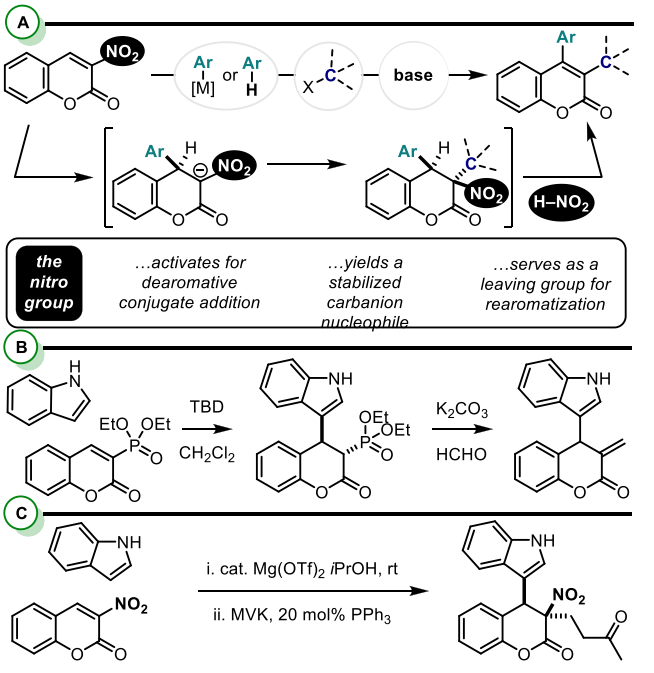
ABSTRACT: The development of a three-component *cine,ipso*-disubstitution of nitrocoumarins is reported. The reaction leverages the electrophilicity of nitrocoumarins, the nucleophilicity of nitronates, and the leaving group ability of nitrite (NO_2^-) to yield complex polyfunctionalized biaryls that often display stable axial chirality.



The three-component synthesis of complex (hetero)biaryls is controllably and rapidly critical considering the prominence of this pattern in pharmaceuticals. Examples related to this include the Catellani reaction,[1] iterative cross-coupling transformations,[2−4] and aryne chemistry.[5] We surmised that nitrocoumarins may serve as valuable starting materials for controlled, 3-component (hetero)aromatic difunctionalization. Specifically, the nitro group could be harnessed 3-fold (Scheme 1A): (1) as an activator for dearomative nucleophilic addition,[6,7] (2) as a carbanion for diastereoselective alkylation,[8−10] (3) and as a leaving group (e.g., pK_a of nitrous acid (HNO_2) = 3.4).[11] These three fundamental steps are understood, but their utility in sequence is surprisingly understudied (Scheme 1A).[12,13] For example, the most similar examples to what we aimed to realize and draw attention to are summarized in Scheme 1B,C. Deredas and co-workers[12] found that 3-diethoxyphosphorylcoumarins can react with indole under base mediated conditions. The phosphonate can then react to yield exocyclic methylene by Horner−Wadworth−Emmons (HWE) with formalin (Scheme 1B). Notably, the phosphonate serves critical roles in each individual step. Tang and co-workers[13] found that $Mg(OTf)_2$ could catalyze the addition of indoles to 3-nitrocoumarin, the addition of catalytic triphenylphosphine and methyl vinyl ketone yielded the disubstituted dihydrocoumarin (Scheme 1C). Related three-component aromatic substitution reactions by Zhou[14] and Maes[15,16] also inspires and precedes our work. Additional chemistry of note includes vicarious[17,18] and *cine*[19−21] nucleophilic aromatic substitution (including a photocatalytic variant[22]) and nitroarene cycloaddition[23−25] and cyclization[26] reactions. Herein we describe a strategy that harnesses the reactivity described in Scheme 1A and often results in axially chiral biaryls yielding products of high

Scheme 1. (A) *cine,ipso*-Disubstitution of Nitrocoumarins; (B and C) Select Related Three-Component Reactions



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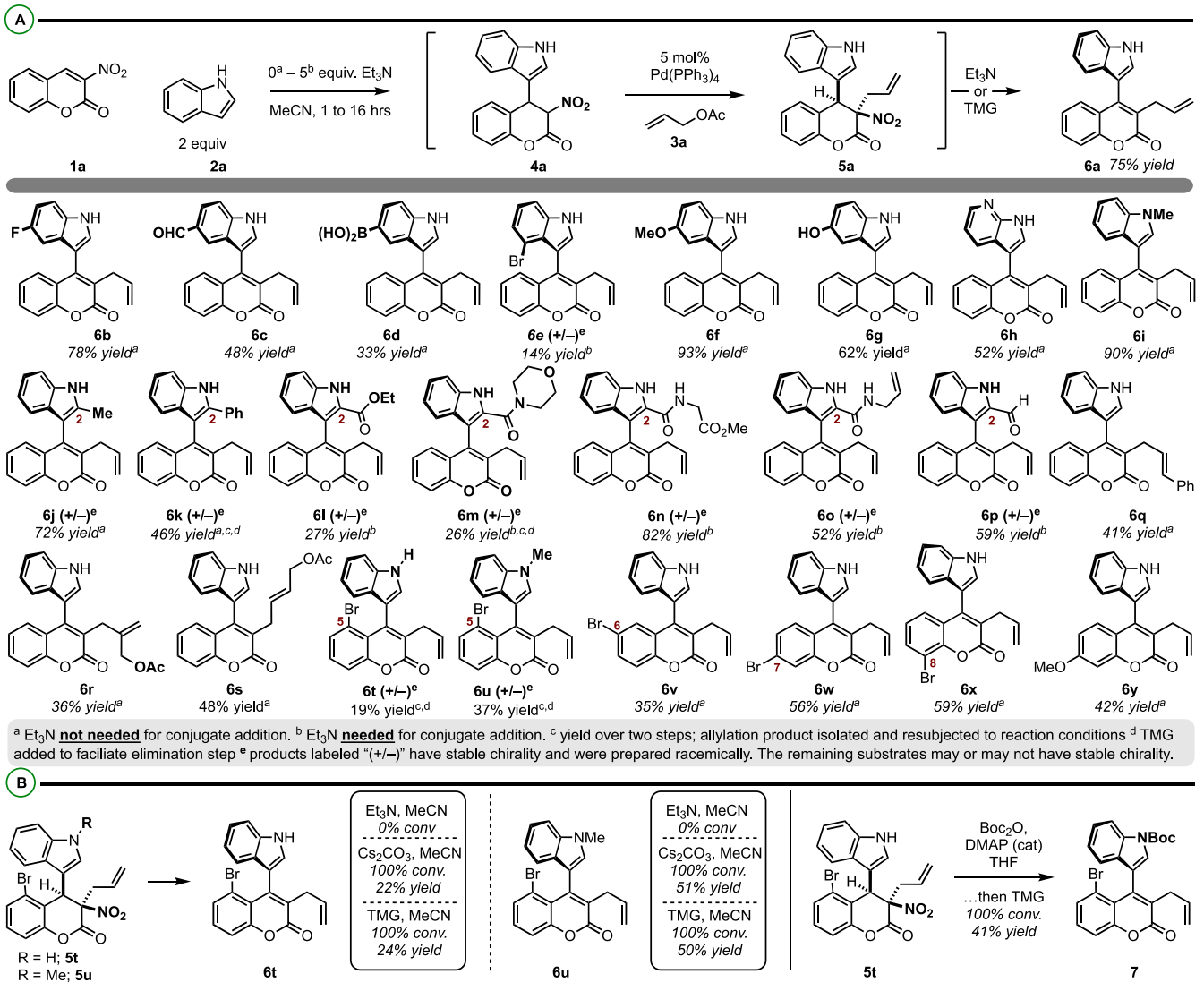
Scheme 2. (A) Scope of Three-Component Biaryl Synthesis; (B) Re-examination of the Elimination Step



functional, structural, and often chiral complexity.[27,28] Included in this study is an initial method, point-to-axial chirality transfer studies,[29] and forays beyond the initial method.

To demonstrate the value of the *cine*,*ipso*-disubstitution of nitroarenes, we explored the reaction of nitrocoumarins **1** with nucleophilic indoles **2** and allylic electrophiles **3** promoted by a base additive. The isolated products **6**, prepared via intermediates **4** and **5**, are indole−coumarin biaryls with an alkene functional handle; valuable products considering the ubiquity of indoles[30] and coumarins[31] in drug discovery. The Supporting Information contains optimization studies related to this three-component coupling. Scheme 2 describes the scope studies. First studied was indole substitution on the benzene ring (**6a**−**6h**). Electron withdrawing groups at the 5-position of indole were well tolerated (**6b**−**6d**) including often sensitive aldehydes (**6c**) and boronic acids (**6d**). Product **6e** bearing a 4-bromo group yielded the desired product but in modest yield. This was a steric problem associated with the conjugate addition step between nitrocoumarin **1a** and indole **2e**. Electron donating groups at the 5-position were also well tolerated (**6f**, **6g**). Notably, a free phenol was incorporated into the biaryl scaffold (**6g**). We were also able to prepare product **6h** bearing a basic nitrogen from 7-azaindole. *N*-Methylindole also was a competent coupling partner, yielding product **6i**. Indoles bearing various 2-functional groups were competent coupling partners, generally speaking. For example, methyl (**6j**), phenyl (**6k**), ester (**6l**), amides (morpoline (**6m**), glycinate (**6n**), and allyl (**6o**) containing) and aldehyde (**6p**) functional groups were tolerated at the 2-position, though the 2-ester indole (**2l**) was a noticeably poorer nucleophile. Also, all the 2-EWG-substituted indoles required the addition of Et_3N to promote the conjugate addition (e.g., **2l**−**2p** → **5l**−**5p**). With respect to the allyl acetate starting material, we were able to make products **6q**−**6s** derived from cinnamyl acetate, and the acetates of 2-methylenepropane-1,3-diol and *cis*-butene-1,4-diol, respectively. The last examples in Scheme 2 show that substitution on the nitrocoumarin is also tolerated at many positions. We prepared products containing a bromo-functional handle at the 5−8-positions of coumarin (**6t**−**6x**) and examined electron-rich coumarins (**6y**). Notably, the 5-substituted coumarins suffer from inefficient H−NO_2 elimination chemistry (Scheme 2A,B). For this elimination to occur, the respective intermediates **5t** and **5u** were first isolated (88% and 74% yield, respectively), and then the elimination step was

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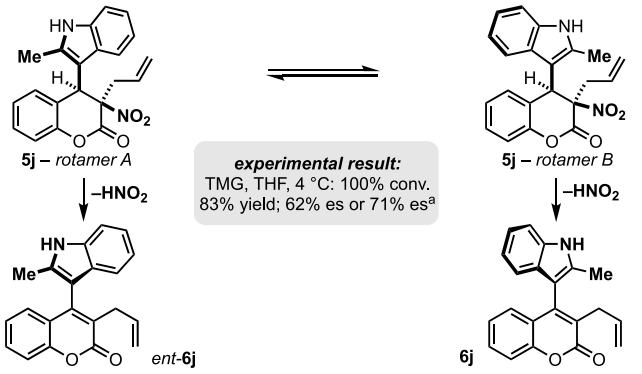
reoptimized, resulting in 1,1,3,3-tetramethylguanidine (TMG) being identified as the superior base. Considering that the *N*-Me substrate **5u** reacted more efficiently, we suspected that the free indole *N*−H was hindering the elimination step. Indeed, it was found that **5t**, upon *in situ* protection and TMG-promoted elimination, yielded the N-Boc-protected analogue **7** in improved yield compared to **6t**.

The products **6** from the three-component coupling clearly display axial chirality (enantiotopic allylic signals in ^{1}H NMR). On this line, no signal coalescence was observed for **6a** via VT-NMR up to 130 °C in DMSO-d_6 and an enantioenriched sample of **6j** was found to be conformationally stable. As such, we wished to examine the possibility of a point-to-axial chirality transfer in this type of system. Point-to-axial chirality transfer would be possible if the potential indole rotamers (**5j**-rotamers A and B, Scheme 3A) displayed significant energy differences or if the rates at which the rotamers undergo HNO_2 elimination are significantly different (or both). Interestingly, it was found that **5j** (er = >99:1; enantiomers separated via chiral supercritical fluid chromatography (SFC)) undergoes an elimination with 62−71% enantiospecificity (up to 85:15 er) (Scheme 3B). While imperfect, this result is a proof of concept for accessing unique axially chiral biaryls via *cine,ipso*-disubstitution. Understanding more deeply the impact of rotamer-biasing and the elimination step will be key.

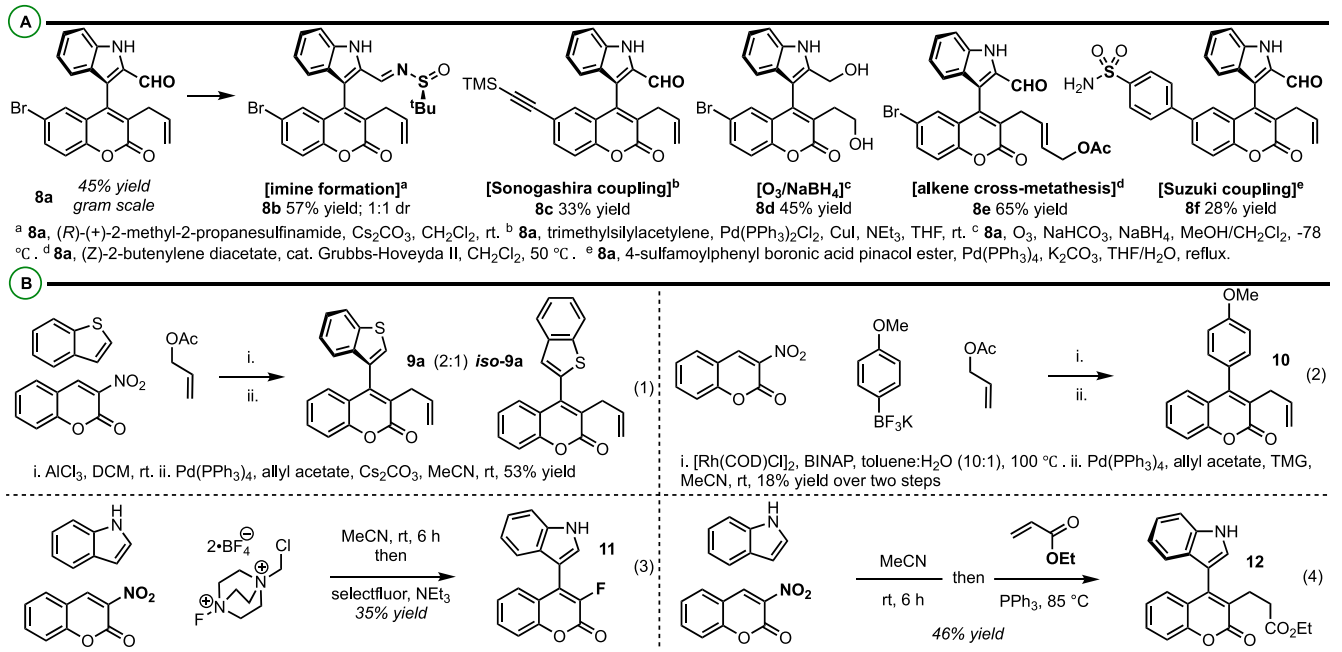
Scheme 3. Point-to-Axial Chirality Transfer Depends on the Energetics of Rotamerization and Elimination



The chemistry developed herein yields complex and functionalized indole−coumarin biaryls. Notably, indoles and coumarins are both common to drugs and drug discovery efforts, though biological/pharmaceutical studies on their biaryl conjugates are minimal.[32,33] It is possible that the bioactivity of indole−coumarins has remained understudied due to the lack of methods capable of constructing diverse and complex (structural, functional, and chiral complexity) analogues. As such, this work represents a direct and simple entry into novel and complex indole−coumarin biaryls. On this line, the indole−coumarin **8a** bearing four distinct functional groups (indole N−H, aldehyde, alkene, and Csp2−Br functional groups) was prepared on the gram-scale (Scheme 4A). In unoptimized studies, using standard conditions from the literature, **8a** was successfully derivatized via imine formation (**8b**), Sonogashira cross coupling (**8c**), ozonolysis (**8d**) (with $NaBH_4$ workup), cross metathesis (**8e**), and Suzuki cross coupling (**8f**). Thus, from commercial sources, products **8a**−**8f** are prepared in two to three steps, showcasing that diverse, axially chiral indole−coumarins are readily accessible.

In terms of the methodology, indole,allyl-*cine,ipso*-disubstitution of nitrocoumarins is a proof-of-concept study: In principle, coupling partners can be exchanged, accessing an even greater diversity of chemical space. In this regard, we examined the coupling of a nucleophilic benzothiophene (Scheme 4B, eq 1) and an arylBF_3K salt (Scheme 4B, eq 2) as well as electrophilic SelectFluor (Scheme 4B, eq 3) and ethyl acrylate (Scheme 4B, eq 4) with nitrocoumarin. Somewhat surprising was that benzothiophene did not react similarly to indole. Neutral conditions (benzothiophene + nitrocoumarin) did not promote the dearomative conjugate addition reaction. However, 1 equiv of $AlCl_3$ promoted this step as a 2:1

Scheme 4. (A) Functional Group Reactions; (B) Other Coupling Partners for *cine,ipso*-Disubstitution of Nitrocoumarins



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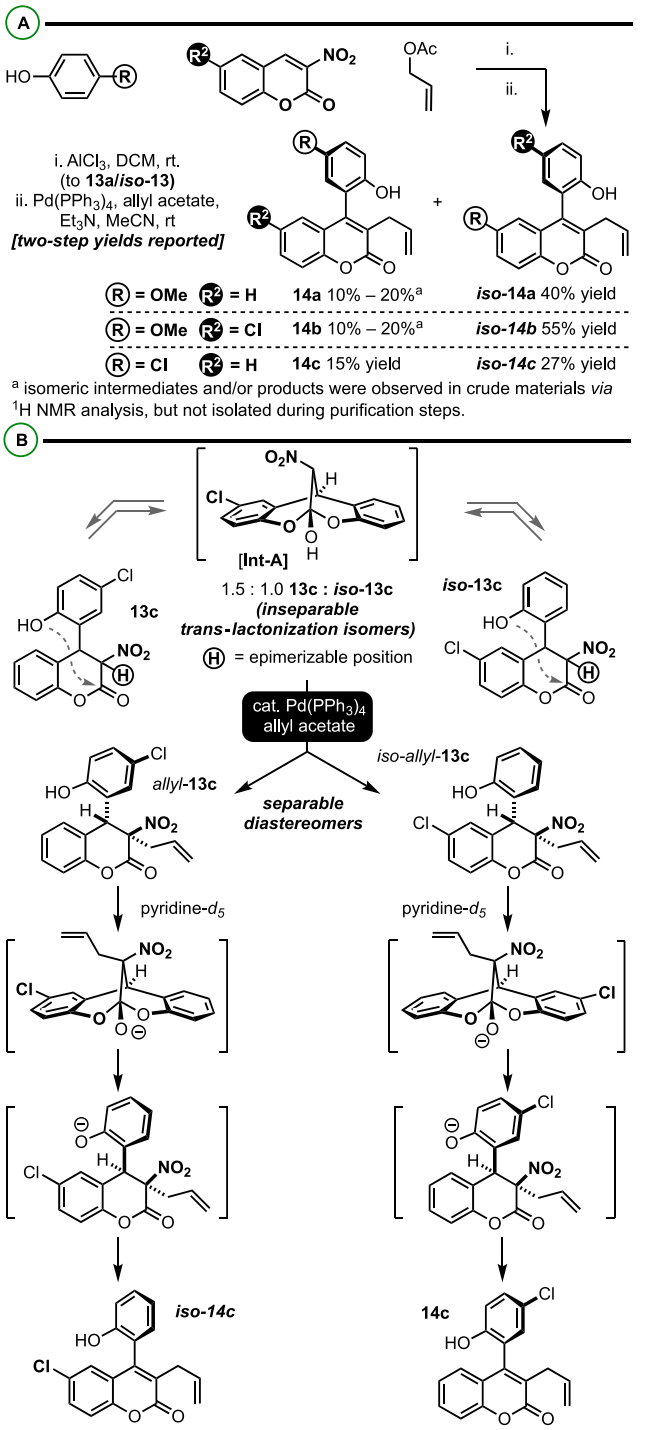
inseparable mixture of benzothiophene isomers **9a** and *iso*-**9a**. Utilizing tandem Rh(I) and Pd(0) catalysis, it was found that the aryl,allylcoumarins could be prepared. The Rh(I) catalyst first promotes the addition of dearomative conjugate addition. Then Pd(0) and TMG promotes the allylation and eliminative aromatization to **10** in modest, unoptimized 18% yield. By swapping allyl acetate/Pd(0) for SelectFluor, we were able to prepare indole,fluoro-disubstituted coumarin **11** in 35% yield.[34] We were also able to perform an indole-alkylation of nitrocoumarin using PPh_3 to promote both the Michael addition[35] and the eliminative rearomatization step. In this case, indole−coumarin biaryls **12** now contain a carboxylate functional group in place of the alkene from the standard protocol (Scheme 2). These results suggest that there are many ways to consider difunctionalizing nitrocoumarins via a *cine*,*ipso*-disubstitution approach.

One final methodological deviation that yielded interesting results was the *cine*,*ipso*-disubstitution of nitrocoumarins with phenolic nucleophiles (Scheme 5). It was observed that treating nitrocoumarins and phenols with $AlCl_3$ in CH_2Cl_2 followed by allyl acetate, $Pd(PPh_3)_4$, and Et_3N yielded unexpected isomeric products as the major products (*iso*-**14**) and the "originally anticipated" products **14** in minor amounts (Scheme 5A). The *p*-methoxylphenol nucleophile resulted in good yields of *iso*-**14a** (40% yield) and *iso*-**14b** (55% yield). The minor products, **14a** and **14b**, could not be isolated cleanly but were observed during analysis of crude materials. When *p*-chlorophenol was used as the nucleophile, a 27% yield of *iso*-**14c** was achieved along with isolable and characterizable minor product **14c**. After careful experimentation and NMR analysis (including ^1H, ^{13}C, gHMBC, and NOE analyses), it was determined that the products **14**/*iso*-**14** are arising via two distinct *trans*-lactonizations (Scheme 5B). The dearomative Michael addition yielded **13c** and *iso*-**13c**. Data supports that **13c** with *trans*-stereochemistry is stable, but the *cis*-diastereomer undergoes goes *trans*-lactonization to *iso*-**13c** via a tetrahedral intermediate [Int-A]. Pd-catalyzed allylation of **13c**/*iso*-**13c** yields separable regioisomers allyl-**13c** and *iso*-allyl-**13c** with a *cis*-relationship between the allyl and the phenolic group, likely due to a phenolic directing effect. When subjected to pyridine-d_5, the aromative elimination reaction took place to yield *iso*-**14c** and **14c**, respectively, via a *trans*-lactonization to establish the necessary stereochemistry for E2 elimination. Finally, products **14** clearly display stable axial chirality as determined by ^1H NMR and chiral HPLC analyses.

We have developed a strategy for the three-component *cine*,*ipso*-disubstitution of nitrocoumarins with various nucleophiles and electrophiles. The primary focus in this work was on three-component coupling with indoles and allylic electrophiles, though other nucleophiles and electrophiles were also examined. Further, point-to-axial chirality transfer can be accomplished, though additional design of substrates will need to be considered to improve the stereospecificity. This work will open broad possibilities: (1) What other nitroarenes can participate in *cine*,*ipso*-disubstitution? (2) What other nitrocoumarin-disubstitution reactions can be developed (3) Can point-to-axial chirality be improved and understood for enantioselective synthesis? We plan to study these questions and anticipate that we and others may find this strategy useful for streamlining complex biaryl synthesis.

Scheme 5. (A) *cine*,*ipso*-Disubstitution with Concomitant *trans*-Lactonization; (B) Proposed Mechanism



■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c03996.

Experimental procedures, characterization data, and ^1H NMR, ^{13}C NMR, HRMS spectra (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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