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Stereochemical Control in Suzuki Cross Coupling Reactions of Acyclic (Z)-beta-haloacroleins

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By

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ABSTRACT

Beta-chloroenals are readily accessible substances and are efficient precursors for a variety of heterocyclic compounds. Suzuki type cross-coupling reactions of such compounds with arylboronic acids yield **β**,**β**-diarylacroleins with control of stereochemistry. The oxidation of these enals to the corresponding acids and subsequent oxidative lactonization leads to formation of the respective coumarins. The chemistry involved in these transformations with special attention to stereochemistry of the Suzuki coupling reaction will be discussed. A full NMR analysis involving 1H, 13C, COSY, NOESY, HSQC, and HMBC was performed to unambiguously confirm the structure and show that the reaction proceeds with retention of stereochemistry

INTRODUCTION AND BACKGROUND

Acroleins are a class of compounds that contain an alpha-beta unsaturated aldehyde. The simplest acrolein is called propenal (Figure 1).

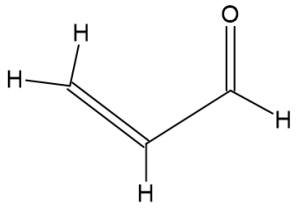


Figure 1. Propenal, the simplest acrolein.

Beta-beta substituted diaryl acroleins (Figure 2) are important precursors to a variety of drugs and biological molecules and that is the focus of a paper by Xiao[1] that was interested in the synthesis of diaryl acroleins as pharmaceutical precursors.

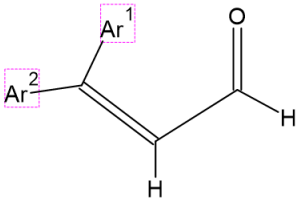


Figure 2. A general asymmetric ***β***,***β***,-Diarylacrolein. The molecule features two aryl groups substituted onto the beta position of a propenal molecule.

One application of beta-beta diaryl substituted acroleins is the synthesis of coumarins, a class of compounds that contain a benzene ring with two ortho hydrogen atoms replaced by a lactone

group (Figure 4). Two precursors relevant to the synthesis of aryl coumarins are diarylacroleins (Figure 2) and chloropropenals (Figure 3). In addition to diarylacroleins, chloropropenals with an aryl group in the beta position play a key role in Xiao's paper.

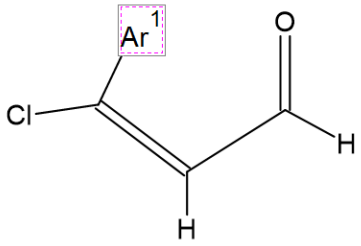


Figure 3. An aryl chloropropenal. This molecule differs from diarylacroleins in that only one aryl group is substituted onto the beta position. The other beta position is occupied by chloride.

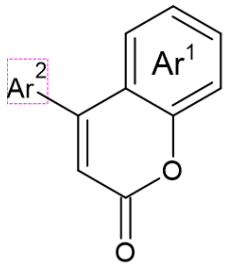


Figure 4. An aryl coumarin. A benzene ring possesses a lactone group in place of two adjacent hydrogen atoms on the benzene ring. An aryl substituent is bonded to the beta position.

Xiao's[1] work is especially relevant to the discussion of aryl coumarin synthesis because of their ability to synthesize diaryl acrolein precursors in good yield. I will therefore discuss in detail Xiao's[1] paper before explaining the NMR analysis I performed on diaryl acroleins as part of the coumarin synthesis.The primary motivation for my choice in presenting Xiao's work is therefore the connection to my research project involving the synthesis of aryl coumarins in collaboration with the Gupton lab (Figure 5).

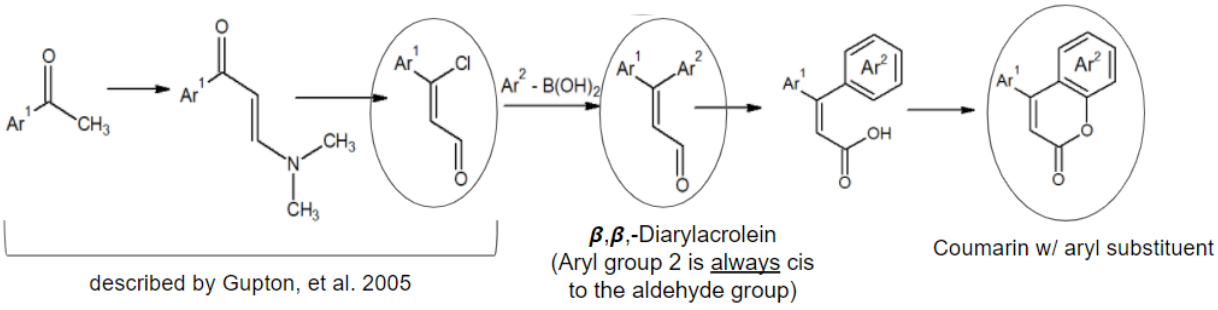


Figure 5. The proposed stepwise synthesis of aryl coumarins from aryl ketones as a part of my collaboration with the Gupton lab. The above synthesis has been implemented in high yield. It features an aryl chloropropenal, which is converted into a diarylacrolein, the molecule of focus of Xiao's work. In our work, the diarylacrolein is converted into an aryl acrylic acid, and finally into an aryl coumarin.

Our synthesis of courmarins begins with an aryl ketone that is first converted into an aryl vinylogous amide by reaction with dimethylformamide acetal followed by reaction with POCl3 to give an aryl chloropropenal[3]. The synthesis of chloropropenals is well described, and aryl chloropropenals are used commonly as important precursors to many bioactive and pharmaceutical compounds[3]. Aryl coumarins are one such class of pharmaceutical compounds. The aryl chloropropenal can be converted into a diarylacrolein by adding a second aryl group via Suzuki coupling[3] with an arylboronic acid. A profoundly important point in our work is that the synthesis of the aryl chloropropenal is stereoselective. Our chlorination step always produces the chloro substituent cis to the aldehyde group. As a result, when the second aryl group is added by

Suzuki coupling, the second aryl group is always added cis to the aldehyde of the acrolein as well. The diarylacrolein is then converted into an aryl acrylic acid, and then finally ring closed into an aryl coumarin. The second aryl group that is added in the Suzuki coupling step retains the stereochemistry and thus is the one that participates in the ring closure that yields the coumarin. Thus, the significance of our work is that the stereoselective chlorination step together with the stereoselective Suzuki coupling step allows complete stereochemical control of which aryl group is involved in the ring closing lactonization step. Therefore our easy access to aryl chloropropenals make possible the efficient stereoselective synthesis of diarylacroleins, and subsequently, of coumarins.

A broad literature search related to this project was necessary to not only gain a broader understanding of the synthesis of relevant molecules, but also to examine whether the stereoselectivity observed in this project and whether a similar method for synthesizing coumarins have been reported before.

As noted, one paper of particular interest that I found as a part of a literature search was a paper by Xiao[1] and coworkers from 2017. It involves the addition of an aryl group to an arylpropanal through the use of aryl iodides via a cascade Saegusa-Heck reaction. Xiao's work was relevant to the coumarin project due to the variety of asymmetrical diarylacroleins they synthesized, in addition to some interesting results regarding the isomers they obtain. Xiao's work will therefore be examined in depth and connected to my aryl coumarin project. However, before doing so it is instructive to review the literature on the methods of preparing ***β***,***β***,-diarylacroleins, in particular of asymmetric ones, and the motivations for their syntheses.

Motivation:

β,***β***,-Diarylacroleins are versatile synthetic building blocks used widely throughout the pharmaceutical industry. They are used to assemble diarylmethine and diarylethene fragments that are present in biologically active molecules (Figure 6).

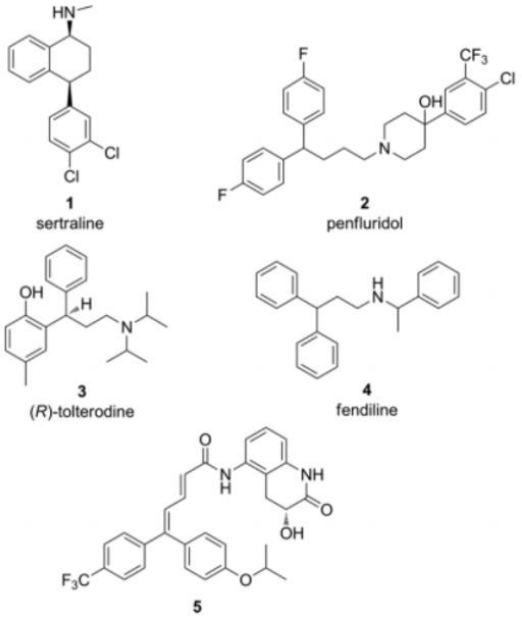
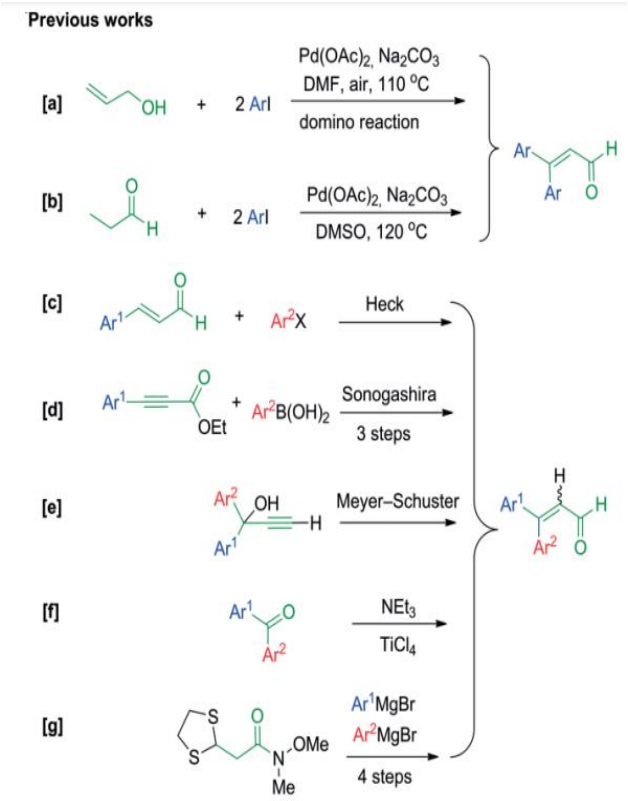


Figure 6. An array of biologically active molecules that contain diarylmethine and diarylethene fragments originating from diarylacroleins. Molecules above include sertraline (1), penfluridol (2), (R)-tolterodine (3), fendiline (4), and TRPV 1 (5)[1].

The remnants of a diarylacrolein are visible in all the above molecules in the form of two aryl groups attached to the same carbon. Sertraline (1) is a serotonin reuptake inhibitor. Penfluridol (2) acts as a D_2 receptor antagonist. (R)-tolterodine (3) is a competitive muscarinic antagonist. Fendiline (4) is a calcium channel blocker, and TRPV-1 (transient receptor potential vanilloid 1, 5) is another antagonist[1]. Thus, the use of diarylacroleins within pharmaceutical chemistry is frequent and broad in application.

Literature Review: ***β***,***β***,-Diarylacrolein Syntheses

Existing syntheses for the formation of diarylacroleins are limited[1]. An overview of these previous syntheses is important for context and to explain the decision making behind the optimization considerations taken by Xiao, et al. Although no literature reports of simple broadly applicable stereoselective syntheses of ***β***,***β***-diarylacroleins comparable to our research with Gupton were found, I did find seven references relevant to ***β***,***β***,-diarylacroleins, and in particular, relevant to understanding Xiao's[1] work. The following table summarizes a number of the prior art for the symthesis for ***β***,***β***-diarylacroleins.



A) One early report of diarylacroyl groups is that from Bergmann[5] and coworkers from 1948 (Figure 7).

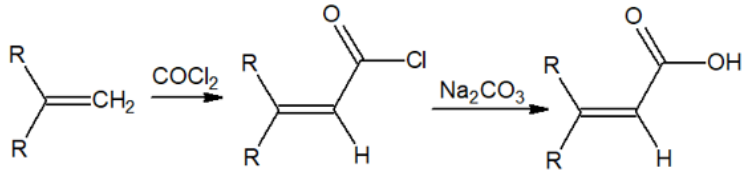


Figure 7. Part of the work undertaken by Bergmann, et al. 1948. This synthesis shows the formation of an acrylic acid as part of the synthesis of diaryl propionic acids[5].

Bergmann's[5] work was a part of a broader investigation of the properties and synthesis of diarylethylenes. As part of the synthesis of diaryl propionic acid, diaryl acrylic acids were formed. The diaryl acrylic acid was converted into a diaryl propionic acid by catalytic hydrogenation[5]. There was little discussion on further application for the acrylic acids, as they were only a precursor to the molecules of interest in the study.

B) A more recent and novel synthesis of diarylacroleins was described by Bharathi and Periasamy in 1999[6] (Figure 8).

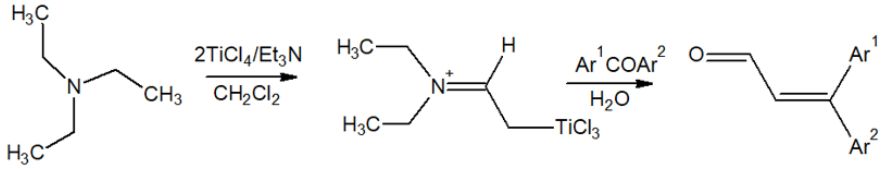


Figure 8. An abbreviated scheme for Bharathi and Periasamy's method for the formation of diarylacroleins using a titanium chloride and triethyl amine reagent system[6].

Bharathi and Periasamy's work involved the use of a Titanium chloride and triethyl amine reagent system. Imminium ions were formed en route to synthesis of diaryl acroleins[6]. The focus of this work seemed to be on the utility and efficiency of the titanium chloride and triethyl amine reagent system, therefore the paper included little discussion on the application for the diarylacroleins they formed.

C) Garcia-Alvarez[7] also investigated the formation of diarylacroleins and other similar molecules through Meyer-Schuster and Rupe rearrangements of propargylic alcohols (Figure 9).

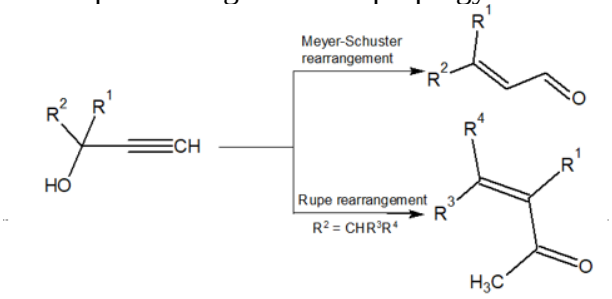


Figure 9. The synthesis of diarylacroleins and alpha-beta unsaturated ketones through Meyer-Schuster and Rupe rearrangements respectively using carbonyl Rhenium (I) catalysts[7].

Garcia-Alvarez and coworkers[7] describe the synthesis of diarlycroleins from propargylic alcohols through a Meyer-Schuster rearrangement. They are also able to form alpha-beta substituted diaryl ketones using propargylic alcohols via a Rupe rearrangement. The primary motivation for this work was the investigation of carbonyl rhenium (I) catalysts and their role in the regioselective isomerization of propargylic alcohols[7]. Again, this work focused on the analysis of the catalyst and involved little discussion about the applications for the products.

The reactions described in A, B, and C above are not particularly relevant to either Xiao's work, or the coumarin project. However, they do provide a broader insight into the synthesis of these types of molecules. The lack of discussion of applications for either diarylacroleins or diaryl acrylic acids in these references was encouraging as it is consistent with our proposed aryl coumarin synthesis being a unique one.

D) Previous methods for synthesis of diarylacroleins that involve Pd coupling with aryl boronic acids[8] are more relevant to my coumarin research collaboration, as my proposed coumarin synthesis also uses Pd coupling with aryl boronic acids (Figure 10).

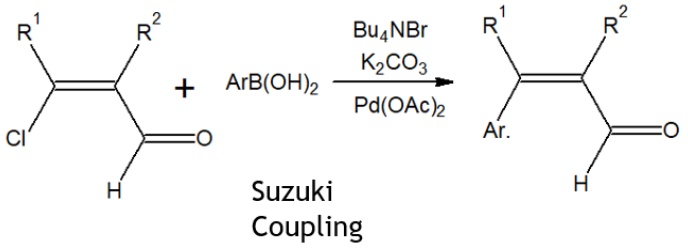


Figure 10. The synthesis of arylacroleins using aryl boronic acids and chloropropenals via Suzuki coupling[8].

Of particular relevance to this, Hesse and Kirsch[8] also use Suzuki reactions to couple substituted chloropropenal with aryl boronic acids. Suzuki coupling is often used for its easy formation of carbon-to-carbon bonds and can tolerate a large range of functional groups under mild non-anhydrous conditions. The utility of Suzuki coupling makes this reaction viable for large scale industrial practices since the inorganic byproduct is easily removed. Hesse and Kirsch[8] employed the formation of beta substituted acroleins as a part of a stepwise synthesis of tetracyclic systems[8]. This points to the use of acroleins in cyclizing reactions, which is strong precedent for our proposed synthesis of coumarins. Hesse and Kirsch also note that few other papers exist that report on similar syntheses, and that their work had potential for broad application due to the ease of access to both chloroacroleins and boronic acids.

E) A similar synthesis was reported by Yamamoto and coworkers in 2008. It involves the copper acetate catalyzed conjugate addition to alkynoates using phenyl boronic acids to yield cinnamates[9] (Figure 11).

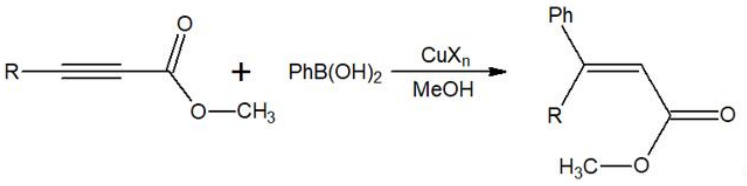


Figure 11. The synthesis for cinnamates through use of phenyl boronic acids and alkynoates[9].

Cinnamates are similar in structure to acroleins, and the use of aryl boronic acids mirrors that reported by Hesse and Kirsch[8]. The difference is that rather than using Suzukui coupling, the aryl group is added to the triple carbon bond via a conjugate addition to yield the beta substituted product[9]. This work yields further insight into the use of aryl boronic acids to form acrolein like structures, but again this work focused on an investigation of their catalyst rather than on the application of the products.

F) Finally, an examination of methods that utilized aryl halide is necessary, as the use of aryl halides relates most to how Xiao, et al. perform their synthesis of ***β***,***β***,-Diarylacroleins. Gandeepan[10] investigated the synthesis of diarylacroleins using aryl halides and a Heck type reaction in 2014 (Figure 12).

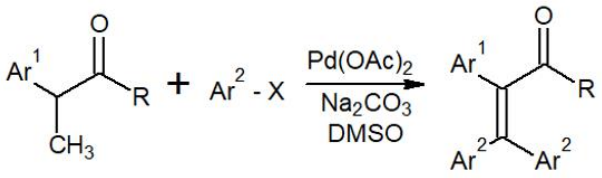


Figure 12. Gandeepan, et al.'s method for the formation of alpha-beta unsaturated diaryl ketones and acroleins using aryl halides[10].

Gandeepan[10] and coworkers also point to the importance of alpha-beta unsaturated compounds in nature and as bioactive molecules. Specifically, they identify these compounds as potential intermediates in medicinal and organic syntheses. Their work introduces the use of Heck reactions and their role in the formation of acrolein-like structures. Their synthesis was somewhat limited however, as two aryl iodides are added sequentially to the beta postion producing a symmetrical diaryl acrolein. Importantly this reaction prevents asymmetric diarylation.

G) The issue of asymmetry persists in additional papers that also report Heck-type reactions for the formation of acroleins. One such instance is the work of Zhu[2] that focused on the use of a Heck-type and Saegusa cascade reaction with aryl iodide to form disubstituted arylacroleins (Figure 13).

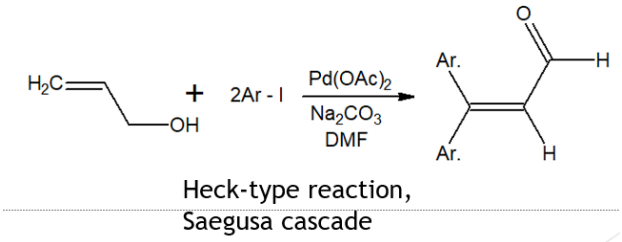


Figure 13. A Saegusa-Heck cascade reaction proposed by Zhu, et al. It involves the addition of aryl groups from aryl iodide to form a ***β***,***β***,-Diarylacrolein[2].

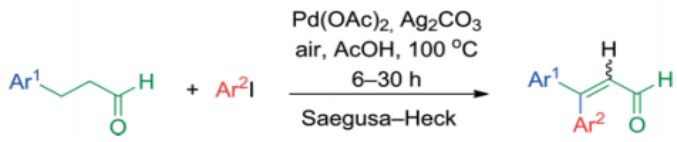
Heck reactions effect the efficient formation of carbon-carbon bonds using palladium metal catalysts[2]. Xiao's work is heavily inspired by, and often cites, Zhu's work, which is evident in Xiao's own use of aryl iodides and a Saegusa-Heck cascade reaction. Zhu's[2] work however is limited in the same way as was Gandeepan's[10] synthesis, i.e., the aryl iodide adds twice, forming

a symmetric diarylacrolein which limits the potential for broader applications of this synthesis method. Xiao and others sought, in part, to address this limitation.

Discussion of Xiao's Research: Saegusa Heck cascade synthesis of ***β***,***β***-diarylacroleins

Xiao et al reported a palladium catalyzed Saegusa Heck cascade reaction using arylpropanals and aryl iodides to form ***β***,***β***,-diarylacroleins via an efficient one-pot synthesis (Figures 15). The investigation of Xiao's work will provide valuable context for later discussion on the NMR results of my research project, and how that relates to the stereochemistry of the acroleins synthesized.

Figure 14. A scheme that details some of the previous work for the formation of diarylacroleins.



Scheme 1. Strategies for the synthesis of β,β-diarylacroleins.

Figure 15. The reaction scheme provided by Xiao[1] for the palladium catalyzed cascade Saegusa Heck synthesis of ***β***,***β***,-diarylacroleins using aryl iodides and aryl propanals.

Asymmetric Heck reactions often suffer from low synthetic efficiency, harsh reaction conditions, multistep syntheses, and polymerization[1]. Xiao and others' work builds on the work of Zhu[2] by efficiently synthesizing asymmetrical diaryl acroleins using a Saegusa-Heck cascade reaction.

Before discussing the results that Xiao and others obtain from their use of a Saegusa-Heck cascade mechanism, it is important to first describe the mechanism. The Saegusa-Heck reaction involves the simultaneous coordination of two different mechanisms, the Saegusa-Ito oxidation, and the Heck reaction.

The original Saegusa-Ito oxidation was first reported by Yoshihiko Ito and Takeo Saegusa in 1978[11]. It involves the formation of an unsaturated carbon-carbon double bond alpha, beta to ketones or aldehydes (Figure 16).

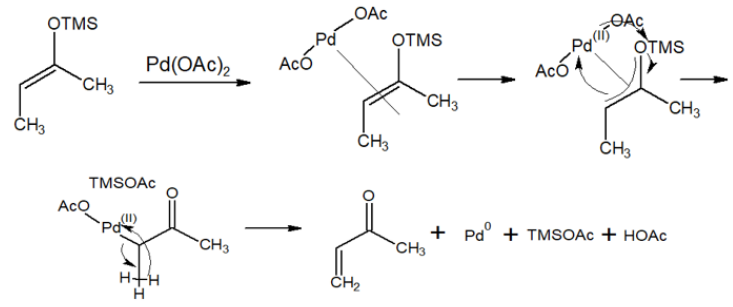


Figure 16. An abbreviated and general example of the mechanism for the Saegusa-Ito oxidation[14].

The palladium catalyst coordinates to the enol olefin across the pi bond. An oxoallyl palladium compound forms from which the silyl group is lost to give an eta-1 palladium complex. A beta-hydride elimination then occurs to form a palladium hydride enone complex that reductively eliminates to form the alpha, beta-unsaturated ketone product[14]. This mechanism is important for the formation of the initial acrolein structure during the Saegusa-Heck cascade mechanism

The other component of the cascade mechanism is a Heck reaction. This was the primary mechanism of both Zhu's[2] and Gandeepan's[10] work. The Heck reaction, described by Richard Heck in 2005, is a palladium catalyzed vinylation of organic halides[12] (Figure 17).

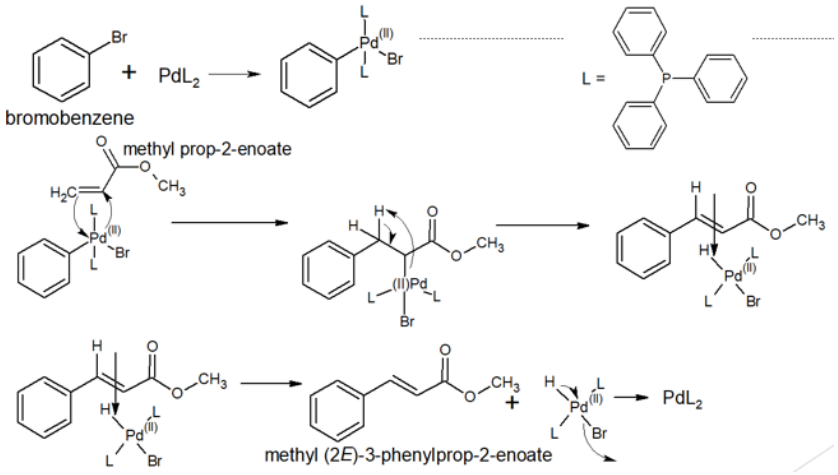


Figure 17. An abbreviated and general form of the mechanism for the Heck reaction. This one involves the vinylation of bromobenzene using methyl prop-2-enoate and palladium triphenyl phosphine catalyst[13].

The Heck reaction is a convenient method for the formation of carbon-carbon bonds in organic molecules[12]. The mechanism involves the insertion of a palladium catalyst into an aryl bromide bond through oxidation addition. In Figure 17, the palladium catalyst (shown with triphenylphosphine ligands), adds to a bromobenzene molecule. The molecule will then form a pi complex with an alkene, methyl prop-2-enoate in this case. The alkene will insert itself into the palladium-carbon bond via a syn addition. This bond then rotates to a trans configuration due to torsional strain, and then undergoes a beta-hydride elimination. This will form a new pi complex between the aryl enoate and the palladium catalyst, which is now also bonded to hydride and bromide ions in addition to the ligands. The palladium complex reforms itself through reductive elimination[13] (Figure 17).

Xiao decided to integrate both mechanisms to first form a monosubstituted aryl acrolein via a Saegusa oxidation and then a ***β***,***β***,-diarylacrolein using an aryl halide and the Heck reaction. The reaction is done in one pot with the same palladium catalyst. Below is their proposal for the cascade mechanism (Figure 18):

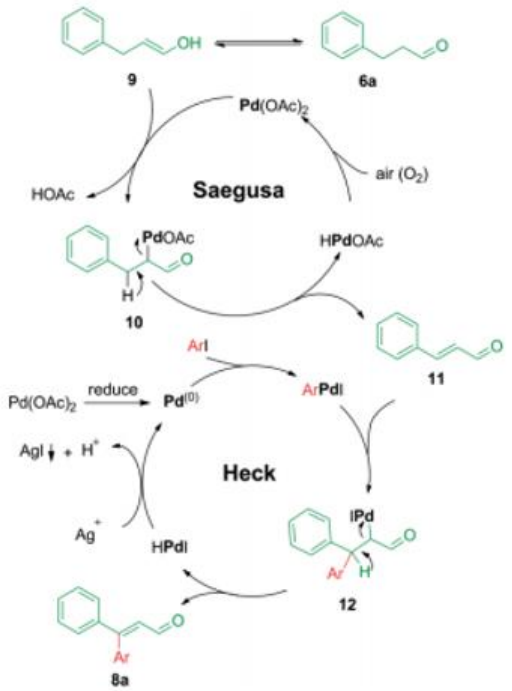


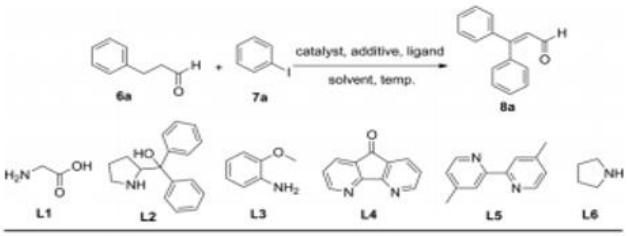
Figure 18. The proposed mechanism provided by Xiao, et al. 2017. It demonstrates the formation of an aryl acrolein, compound 11, from compound 6a and aryl propanal via Saegusa oxidation. It then demonstrates the formation of a ***β***,***β***,-diarylacrolein using an aryl halide via the Heck reaction[1].

Compound 6a is an example of one of their primary starting reagents, a phenyl propanal. Compound 6a will convert to compound 9 through an acid catalyzed tautomerization in acetic acid. Compound 9 undergoes a Saegusa oxidation to form intermediate compound 10 which features the palladium-carbon bond. Compound 10 completes the oxidation to form compound 11, a beta monosubstituted phenyl propanal[1]. The identity of this first aryl group is therefore determined by the identity of starting reagent 6a. This differs from Zhu's[2] work, where both beta substituted aryl groups' identities were dictated by the aryl halide.

Once a monosubstituted acrolein is formed, the Heck reaction can occur across compound 11's alkene bond. The palladium catalyst adds to the aryl iodide, and this molecule then forms the pi complex with compound 11 to form intermediate compound 12 with both the second aryl group and the palladium catalyst bonded to the molecule. Reductive elimination occurs to form compound 8a, a ***β***,***β***,-diarylacrolein. The identity of the second aryl is therefore controlled by the identity of the aryl halide. This allowed them to form ***β***,***β***,-diarylacroleins asymmetrically.

RESULTS & DISCUSSION

After performing various screens for different reaction components, the conditions for the Saegusa-Heck cascade reaction were optimized by Xiao[1] as seen in the data shown below (Table 1):



Entry	Catalyst[b]	Additive (equiv.)	Ligand	Solvent (equiv.)	Yield[c] [%]
1	$Pd(OAc)_2$	AgOAc (1.5)	–	AcOH	26
2	$Pd(OAc)_2$	$AgNO_3$ (1.5)	–	AcOH	8
3	$Pd(OAc)_2$	AgTFA (1.5)	–	AcOH	28
4	$Pd(OAc)_2$	Ag_2CO_3 (1.5)	–	AcOH	55
5	$Pd(OAc)_2$	–	–	AcOH	trace
6	$Pd(OAc)_2$	AgOAc (3.0)	–	AcOH	50
7	$Pd(OAc)_2$	Ag_2CO_3 (1.0)	–	AcOH	48
8	$Pd(OAc)_2$	Ag_2CO_3 (1.2)	–	AcOH	55
9	$Pd(OAc)_2$	Ag_2CO_3 (1.2)	–	AcOH	78
10	$PdCl_2$	Ag_2CO_3 (1.2)	–	AcOH	62
11	$Pd(PPh_3)_4$	Ag_2CO_3 (1.2)	–	AcOH	21
12	$Pd(tfa)_2$	Ag_2CO_3 (1.2)	–	AcOH	45
13	$Pd(dba)_2$	Ag_2CO_3 (1.2)	–	AcOH	32
14	–	Ag_2CO_3 (1.2)	–	AcOH	0
15	$Pd(OAc)_2$	Ag_2CO_3 (1.2)	–	toluene	0
16	$Pd(OAc)_2$	Ag_2CO_3 (1.2)	–	DMF	0
17	$Pd(OAc)_2$	Ag_2CO_3 (1.2)	–	H_2O	34
18	$Pd(OAc)_2$	K_2CO_3 (1.5)	–	DMF	31
19	$Pd(OAc)_2$	$NaHCO_3$ (3.0)	–	DMF	18
20	$Pd(OAc)_2$	NEt_3 (3.0)	–	DMF	0
21	$Pd(OAc)_2$	Ag_2CO_3 (1.2)	**L1** (0.2)	AcOH	29
22	$Pd(OAc)_2$	Ag_2CO_3 (1.2)	**L2** (0.2)	AcOH	67
23	$Pd(OAc)_2$	Ag_2CO_3 (1.2)	**L3** (0.2)	AcOH	38
24	$Pd(OAc)_2$	Ag_2CO_3 (1.2)	**L4** (0.2)	AcOH	53
25	$Pd(OAc)_2$	Ag_2CO_3 (1.2)	**L5** (0.2)	AcOH	57
26	$Pd(OAc)_2$	Ag_2CO_3 (1.2)	**L6** (0.2)	AcOH	19
27[d]	$Pd(OAc)_2$	Ag_2CO_3 (1.2)	–	AcOH	30
28[e]	$Pd(OAc)_2$	Ag_2CO_3 (1.2)	–	AcOH	71
29[f]	$Pd(OAc)_2$	Ag_2CO_3 (1.2)	–	AcOH	44

Table 1. The results of the attempts to optimize the reaction conditions. The table includes changes to concentrations, catalyst, base, solvent, and salt identities, and the use of different temperatures and conditions[1].

Doubling the amount of silver salt used demonstrated the importance of the silver ion in the reaction, as demonstrated by the increase in yield between entry 1 and entry 6 in Table 1 (i.e., increase from 1.5 to 3.0 equivalents). Silver carbonate was found to be the most efficient silver salt and gave the best yields at 1.2 equivalents. Homocoupling of the aryl iodides to form diphenyl was identified as a major side reaction, and so the amount of aryl iodide used was increased from 1.5 to 2.5 equivalents to compensate for this. This led to an increase in yield best demonstrated by entries 9, 27, and 28. A palladium catalyst screen (entries 9-13), confirmed palladium acetate as the best performing catalyst. Entry 14 demonstrated the essential nature of the palladium catalyst to the reaction, as the reaction did not proceed without the addition of catalyst. A solvent screen (entries 15 - 17) likewise demonstrated that acetic acid worked best. Toluene and DMF yielded no reaction, while water saw inferior product formation. A base screen (entries 18 – 20) performed in DMF confirmed carbonate ion to be the best. Potassium carbonate and sodium bicarbonate saw inferior yields, while triethyl amine yielded no reaction. A ligand screen (entries 21 – 26) was not effective at improving yield. Reduced oxygen concentrations were found to have a negative impact on yield. Finally, a temperature screen from 80 to 120 ^{o}C demonstrated that the reaction was best performed at 100 ^{o}C[1].

Therefore, Xiao[1] concluded that an optimized reaction would be performed at 100 °C with 1 equivalent of aryl propanal, 2.5 equivalents of aryl iodide, palladium acetate in 10 mol-%, silver carbonate in 1.2 equivalents in acetic acid solvent (Xiao, et al. 2017). After optimizing reaction conditions, Xiao sought to examine the scope and generality of the reaction by varying the identity of the group on both the aryl propanal and the aryl iodide. Below are the results of this examination of scope (Figure 19 and Table 2):

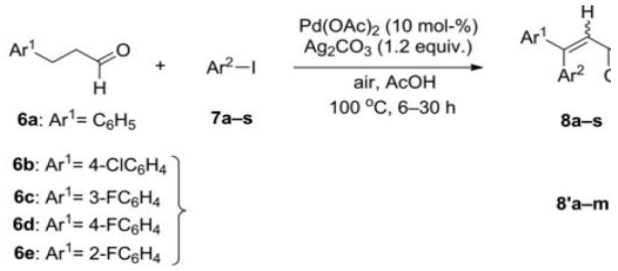


Figure 19. The optimized Saegusa-Heck cascade reaction, performed with varying identities of both compound 6 (aryl propanal) and compound 7 (aryl iodide)[1].

Entry	6	7: Ar^2	Time [h]	8/8', Yield[b,c] [%]	Isomer ratio[d]
1	6a	7a: C_6H_5	6	8a, 78	–
2	6a	7b: 2-MeC_6H_4	8	8b, 30	–
3	6a	7c: 3-MeC_6H_4	12	8c, 67	1:3
4	6a	7d: 4-MeC_6H_4	24	8d, 83	1:4.2 (*Z*/*E*)
5	6a	7e: 2-ClC_6H_4	10	8e, 34	1:4.8
6	6a	7f: 3-ClC_6H_4	14	8f, 52	1:3
7	6a	7g: 4-ClC_6H_4	30	8g, 61	1:4.2
8	6a	7h: 4-FC_6H_4	16	8h, 42	1:3 (*Z*/*E*)
9	6a	7i: 4-BrC_6H_4	12	8i, 55	1:2.8
10	6a	7j: 4-$MeOC_6H_4$	8	8j, 66	1:2.8 (*Z*/*E*)
11	6a	7k: 4-$F_3COC_6H_4$	14	8k, 58	1:3.3 (*Z*/*E*)
12	6a	7l: 4-EtC_6H_4	12	8l, 72	1:3.2
13	6a	7m: 4-*i*PrC_6H_4	14	8m, 38	1:4.2
14	6a	7n: 4-*t*BuC_6H_4	12	8n, 47	1:2.1
15	6a	7o: 3,4-$Me_2C_6H_3$	24	8o, 74	1:3.1
16	6a	7p: 3,5-$Me_2C_6H_3$	24	8p, 65	1:2.8 (*Z*/*E*)
17	6a	7q: 3,4-$Cl_2C_6H_3$	18	8q, 60	1:3.4
18	6a	7r: 4-$O_2NC_6H_4$	12	8r, 39	1:1.3
19	6a	7s: 4-$F_3CC_6H_4$	20	8s, 67	1:5
20	6b	7b: 2-MeC_6H_4	12	8'a, 32	–
21	6b	7c: 3-MeC_6H_4	12	8'b, 65	1:2.4
22	6b	7d: 4-MeC_6H_4	28	8'c, 71	1:4.2
23	6b	7e: 2-ClC_6H_4	12	8'd, 37	1:1.9
24	6b	7f: 3-ClC_6H_4	16	8'e, 54	1:4.8
25	6b	7g: 4-ClC_6H_4	20	8'f, 66	–
26	6c	7d: 4-MeC_6H_4	12	8'g, 46	1:2.5
27	6c	7g: 4-ClC_6H_4	12	8'h, 50	1:2.5
28	6c	7f: 3-ClC_6H_4	12	8'i, 48	1:2
29	6c	7a: C_6H_5	10	8'j, 64	1:2.5
30	6d	7d: 4-MeC_6H_4	10	8'k, 66	1:2
31	6d	7g: 4-ClC_6H_4	10	8'l, 58	1:1.8
32	6d	7f: 3-ClC_6H_4	10	8'm, 55	1:2.5
33	6e	7a: C_6H_5	10	8'n, 0	–

Table 2. The results of Xiao's examination of scope and generality by varying the identity of aryl groups on both compound 6 and 7[1].

Xiao[1] report that the use of electron donating groups on the aryl iodides (entries 2-4, 10, 12-16) were more beneficial to the reaction than the use of electron withdrawing groups (entries 5-9, 11, 17-19). They also identified that the position of the substituent on the aryl iodide was important. Entries 2 and 5 involve an ortho substituted aryl iodide and saw significantly lower yield than the meta substituted and para substituted aryl iodides in entries 3 and 6, and 4 and 7 respectively. This was likely due to steric effects[1].

Compounds 6b through 6e were arylpropanals with various halide substituents at different positions and were reported in entries 20 through 33. Compound 6e in entry 33 did not produced the desired product, but all the other alternative aryl propanals in entries 20 through 32 were able to successfully participate in the reaction to varying degrees of success[1].

Ultimately, Xiao[1] concluded that they could obtain 30 different ***β, β***,-diarylacroleins in mixtures of geometric isomers. The ratios of isomers seen were calculated using NMR spectroscopy. Entries with specific cis and trans designations were determined by comparison to existing literature, and the product tends to favor the trans isomer[1]. ***This reaction consistently results in the presence of stereoisomers, and this is an important limitation to take note of as it relates to the discussion of my aryl coumarin collaboration, which features complete stereoselectivity***.

My Research Results: Background on Chloropropenal Chemistry

The stereoselective synthesis of chloropropenals is particularly important with regard to our novel synthesis of aryl coumarins. Chloropropenals have often been used in the past as a precursor to the formation of various cyclic bioactive molecules[4]. An example of the stereochemistry of chloropropenals and its utility in bioactive synthesis can be seen in the paper by Gupton[4] (Figure 20):

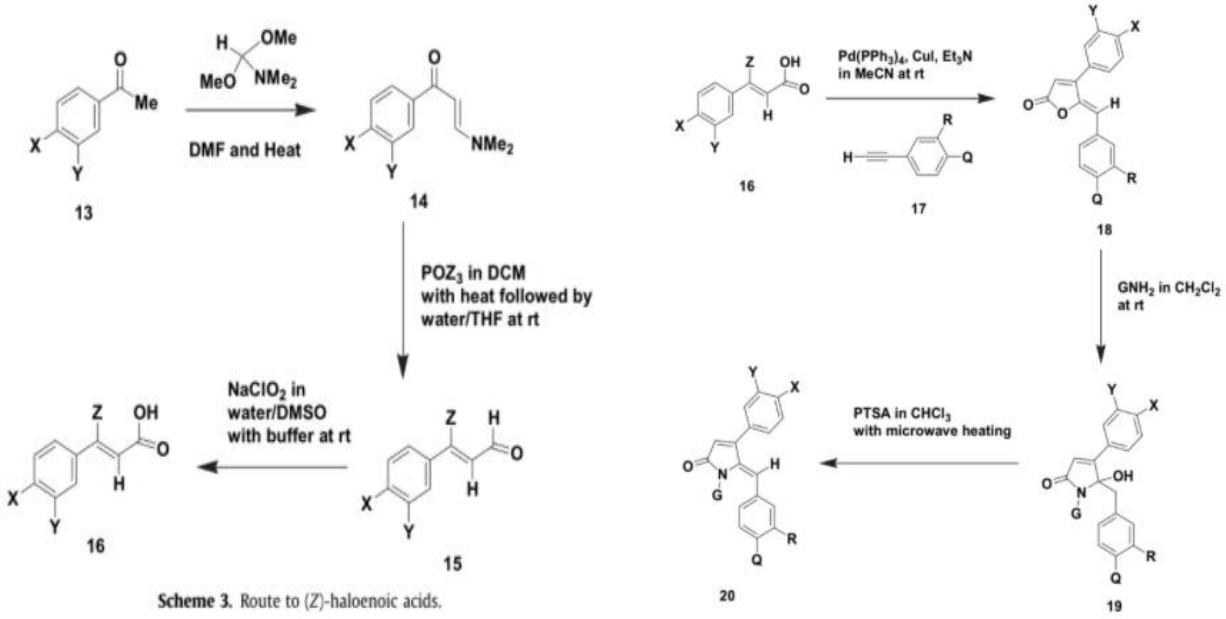


Figure 20. An example of the use of chloropropenals as an intermediate and precursor to the formation of cyclic molecules. This example from Gupton[4] involves the synthesis of aryl pyrrolones.

Vinylogous amides can be prepared in high yield from aryl ketones via the scheme in Figure 20. These vinylogous amides can be converted stepwise into (Z) chloropropenals. The cis stereochemistry of these (Z) chloropropenals has been well established and is verifiable by NMR spectroscopy[4]. The above synthesis of aryl pyrrolones is an efficient strategy for the synthesis of a bioactive molecule in good yields, and it is in part dependent upon the cis stereochemistry of (Z) chloropropenals[4]. My research project seeks to use this same stereoselectivity of chloropropenal in the stereoselective synthesis of aryl coumarins.

The ability to synthesize acroleins, acrylic acids, and coumarins is nothing new to the scientific community. However, the synthesis of coumarins from diarylacroleins via aryl chloropropenals is efficient, can produce high yields, and can be performed under mild conditions. The most unique aspect of the aryl coumarin reaction scheme is the complete conversion of the diarylacrolein to a cis isomer. Previous works dealing with the synthesis of diarylacroleins had issues with producing asymmetrical acroleins. Zhu[2] developed an efficient method for the synthesis of diarylacroleins through a novel Saegusa-Heck cascade mechanism, however they were only able to produce symmetrically substituted β, β-diarylacroleins. Xiao[1] optimized the conditions for the Saegusa-Heck cascade reaction, while proposing a method for the use of the cascade mechanism for the synthesis of asymmetrical β, β, -diarylacroleins. Xiao overcame

many previous obstacles involved in the synthesis of these molecules and identified as potentially important in bioactive synthesis with broad applications. The problem persisting in Xiao's work is the inability to effectively separate stereoisomers or synthesize a stereoisomer selectively.

Xiao's work was important as it identified a significant obstacle in the synthesis of ***β***, ***β***, -diarylacroleins that the chemistry involved in the coumarin collaboration can address. The use of (Z) chloropropenals allows for one to exercise complete control over the location and identity of aryl substituents, which can dictate which aryl participates in the ring closure to a coumarin. The ability to translate work that deals with pharmaceutical compounds into an industrial context is also important, and chloropropenals have been demonstrated as potentially beneficial to the industrial setting due to the ability to avoid separation of stereoisomers. This is in addition to the already high yields that chloropropenal precursor syntheses have demonstrated.

My research project involves looking at the stereochemistry of a Suzuki coupling used to prepare ***β***, ***β***-diarylacroleins. A complete NMR analysis and characterization of two of the ***β***, ***β***-diarylacroleins indicates that the synthesis used gave retention of chemistry and stereochemically pure products. Future work will be to convert the multistep coumarin synthesis into a continuous flow chemistry procedure, which would speak to its possible application in an industrial setting and allow the reaction to be telescoped without time consuming and yield reducing multi-pot syntheses.

Coumarins are bicyclic heterocyclic compounds (see Figure 21). Coumarins can be synthesized by various plants and are often converted into dicoumarol. Dicoumarols have been found to be useful pharmaceutical agents for affecting coagulation. This led to the development of the drug warfarin. Coumarins are also important in material science and are common as laser dyes.

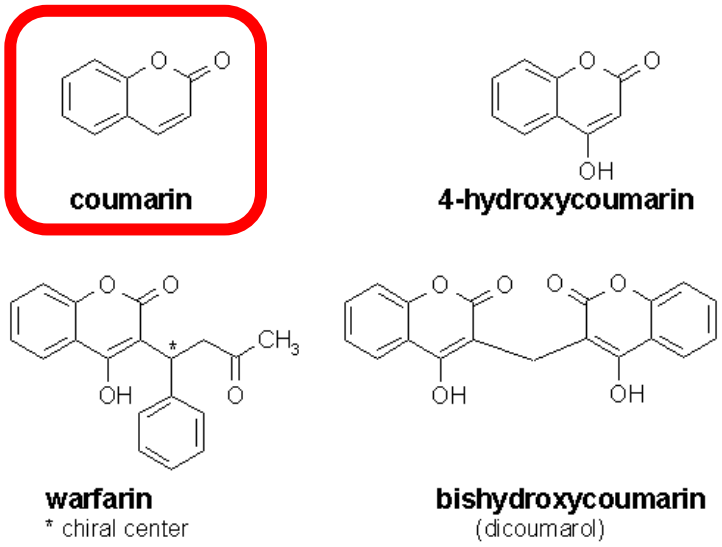


Figure 21. Examples of different coumarins and dicoumarols.

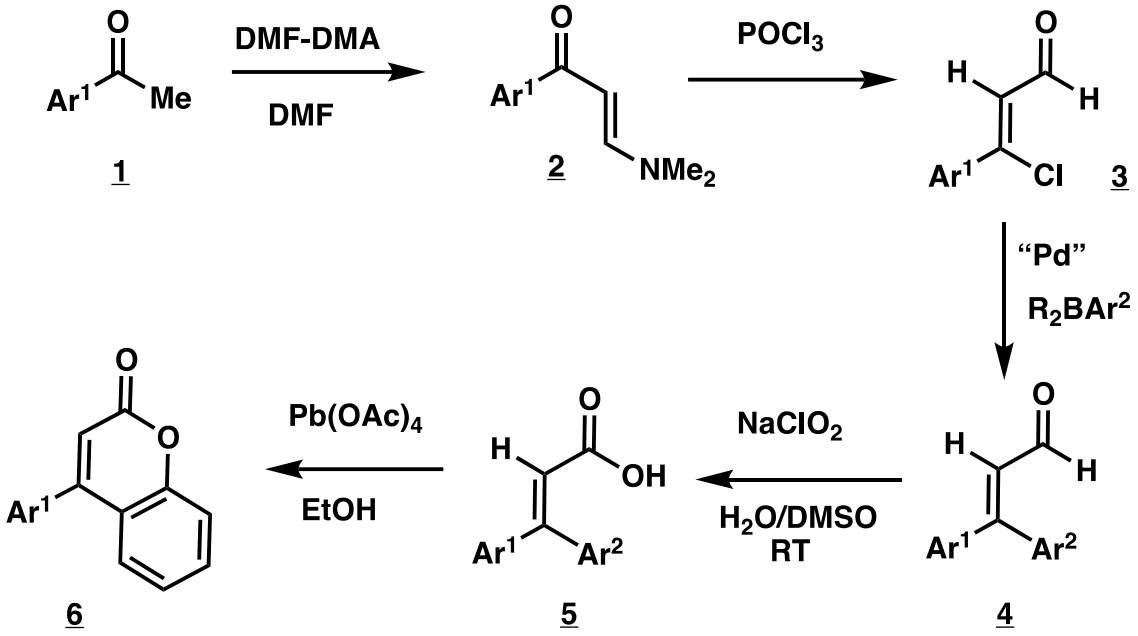


Figure 22. Synthesis of coumarin from methylketones via chloroenals.

Previous research students have developed a high yield route to preparing coumarins starting with the versatile reagent, beta-haloacroleins. These are used in our lab to make polysubstituted pyrroles among other compounds. I will discuss their use in preparing a variety of courmarins (see Figure 23).

The beta-haloacroleins are prepared by starting with an aryl methyl ketone. Using dimethylformamide acetal form compound 2, a vinylogous amide, is formed. Reaction with phosphoryl chloride or bromide gives the beta haloacrolein or haloenal. Both steps are high yield and clean reactions.

Suzuki Cross Coupling Gives High Yield ***β***, ***β***-Disubstituted Acroleins

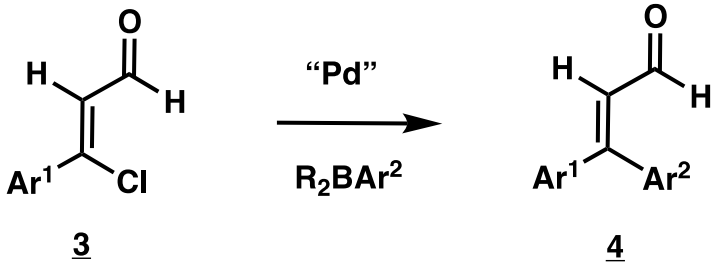


Figure 23. General scheme for the preparation of diaryl acroleins from chloropropenals.

Ar^1	Ar^2	% yield (pure)
3,4-dimethoxyphenyl	4-methylphenyl	90%
4-methoxyphenyl	4-methylphenyl	72%
4-chlorophenyl	4-methylphenyl	78%
4-methylphenyl	4-methylphenyl	71%
phenyl	4-methylphenyl	89%
4-methylphenyl	phenyl	90%
4-methylphenyl	4-methoxyphenyl	72%
4-fluorophenyl	4-methylphenyl	76%
4-methylphenyl	4-chlorophenyl	85%

Table 3. Various coumarins were synthesized via chloroenals using different aryl groups (Ar^1 and Ar^2) in good yield.

The key step in the synthetic route is the Suzuki coupling of the chloroenal with boronic acids. The discovery and subsequent application of Suzuki coupling reactions ever since they were first reported in 1979 has been a huge advance in synthetic chemistry. These reactions proceed in good yields and can be done with a variety of aryl groups. After discussing the last two steps which ultimately form the coumarins, I will come back and discuss in detail the stereochemistry of this reaction and that will be the main focus of this paper.

As I mentioned, the last two steps to forming the coumarins are oxidation of the aldehydes (4) to the corresponding carboxylic acid followed by reaction with lead tetraacetate in ethanol which leads to an electrophilic aromatic substitution on the cis aryl group to close the ring and give the coumarin product. We are still working to improve our purification methods since it appears we are losing a fair amount of product during the purification.

The ring closure occurs on the aryl group cis to the carboxylic acid. Having retention or conversion during the Suzuki coupling step is what will determine whether we obtain the Z or E isomer in compound 4. As a result, the stereochemistry of the acid precursor, 5, is key in determining which product is formed. I will now focus on the stereochemistry of the ***β***, ***β***-diarylacroleins

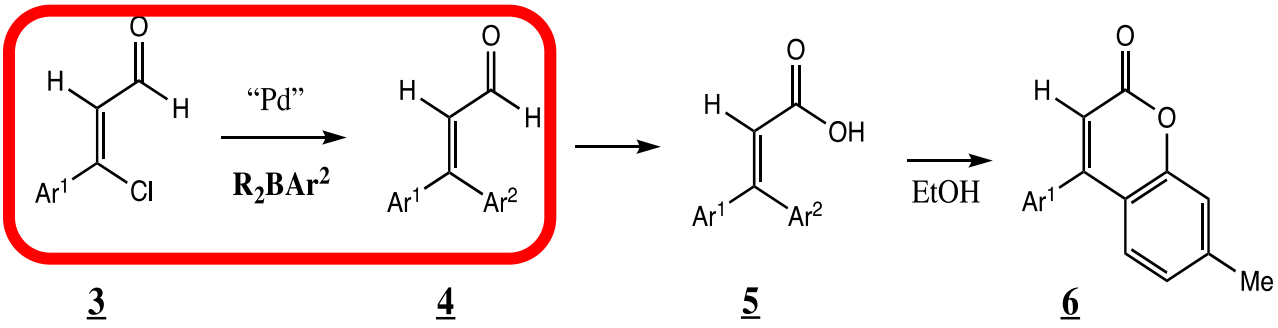
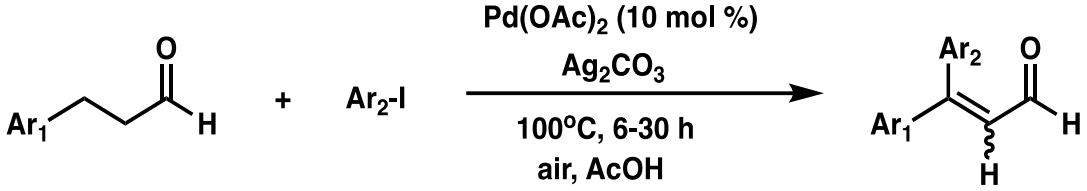


Figure 24. The scheme for the synthesis of coumarins. The step from compound 3 to 4 demonstrates the unique preservation of stereochemistry.

Previous Syntheses of **β**,**β**-diarylacroleins:

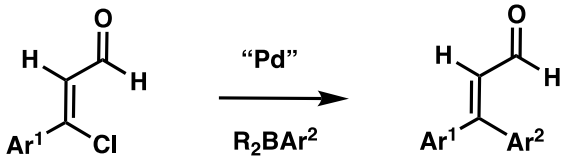


Ar_1	Ar_2	Time (h)	Yield	Isomer ratio
C_6H_5	3-MeC_6H_4	12	67	1:3
C_6H_5	4-MeC_6H_4	24	83	1:4.2 (Z/E)
C_6H_5	4-FC_6H_4	16	42	1:3 (Z/E)
4-ClC_6H_4	4-MeC_6H_4	28	71	1:4.2

Table 4. Previous syntheses of **β**,**β**-diarylacroleins by Xiao[1] with two aryl groups. Isomer ratios present are important to note.

It should be noted that these **β**,**β**-diarylacroleins are important starting materials in the pharmaceutical industry. **β**,**β**-diarylacroleins syntheses are limited, especially for asymmetrical ones which suffer from very low yields and harsh reaction conditions. As noted in the background and introduction section, in 2017, Xiao published an improved method for synthesis of **β**,**β**-Diarylacroleins based on a Pd-catalyzed Saugusa-Heck cascade protocol.

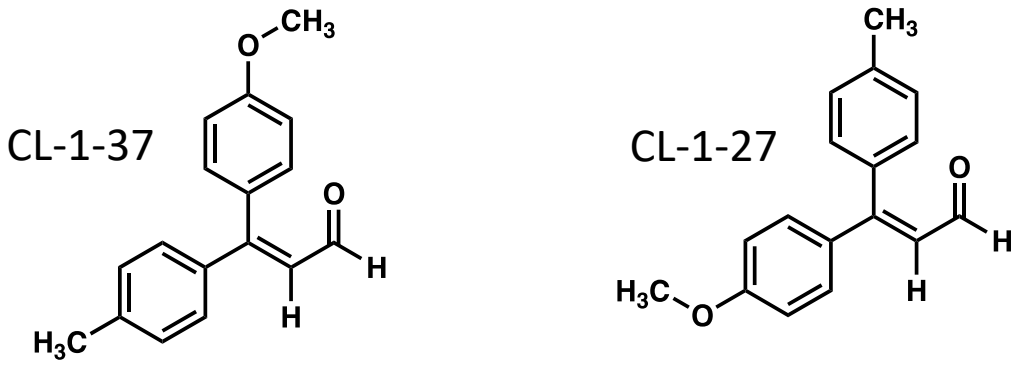
As you can see in the table (Table 4), their method gives a mixture of E and Z isomers. Our method is more stereoselective. This is a key point of this project; this is a highly Stereoselective coupling step.



3 **4**

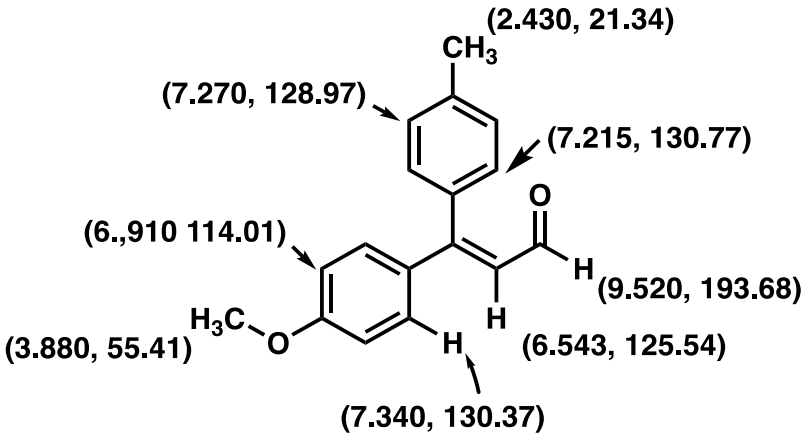
Ar1	Ar2	% yield (pure)
4-methoxyphenyl	4-methylphenyl	90% CL-1-27
4-methylphenyl	4-methoxyphenyl	72% CL-1-37

Table 3a. A focus from table 3 of two specific reaction dealing with 4-methoxyphenyl and 4-methylphenyl substituents at the different aryl positions.



Figures 25a, 25b. Products from the reactions performed above in Table 3a.

If we look at the two reactions in Table 3a, you can see that they lead to isomers of each other. By reversing which aryl group is already on the chloroenal vs which is added via the coupling reaction we can make both the E and Z isomers independently. We have done a detailed structure determination on both isomers to confirm that this coupling step proceeds exclusively with retention of configuration meaning that $Aryl^2$ will end up cis to the aldehyde group. I will describe the analysis for the E isomer named CL-1-27.



CL-1-27

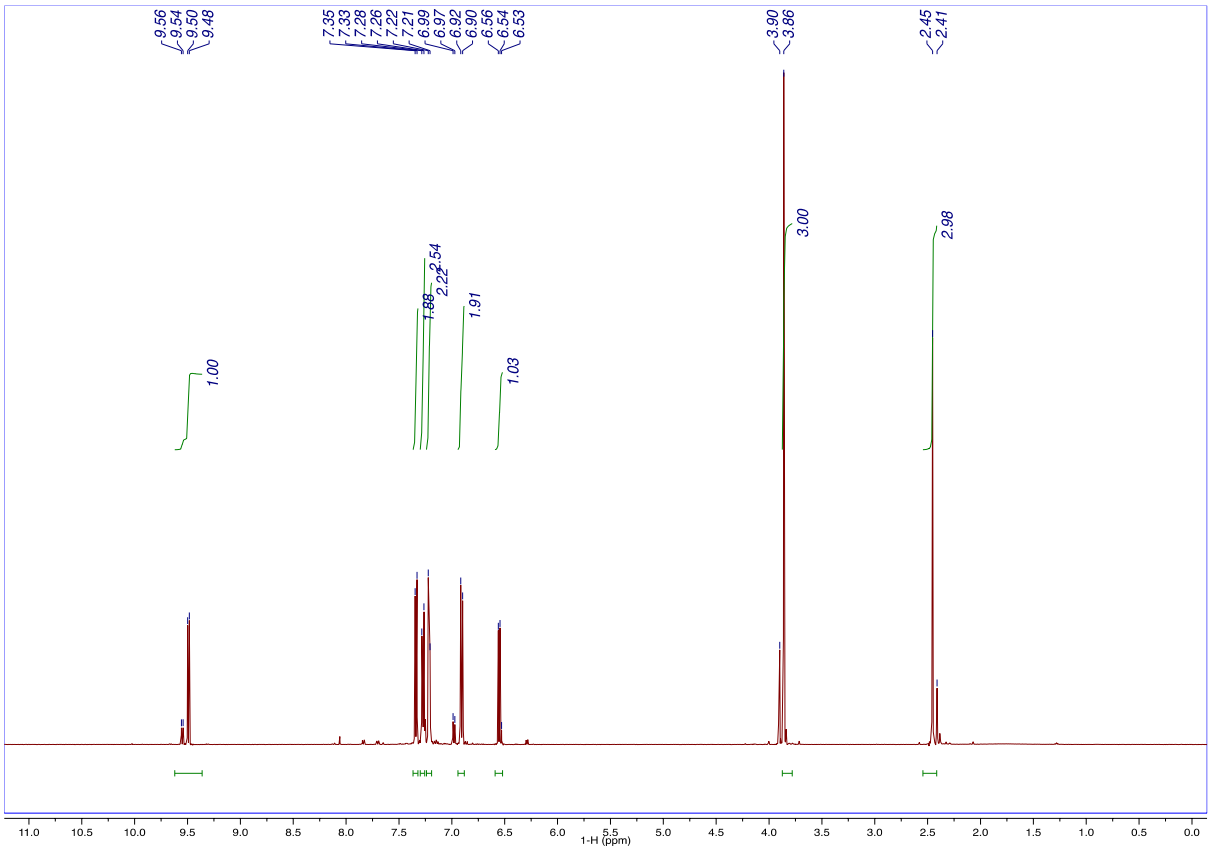


Figure 26. ^{1}H NMR of compound CL-1-27, with corresponding ^{1}H NMR and ^{13}C NMR chemical shifts assignments.

The first step is to assign each proton and each carbon with its corresponding NMR signal. From just the ^{1}H NMR, most of the protons can be assigned. COSY confirms which pair of protons couple each other on the two para-substituted phenyl rings. The only remaining question is which of the two protons in each pair is ortho vs meta to the rest of the molecule.

The proton NMR for the E isomer is shown here. The methyl, methoxy, vinyl, and aldehyde peaks can be easily identified based on chemical shift and integration. There are an additional 4 types of protons around chemical shift δ7 ppm due to the two para-substituted phenyl groups.

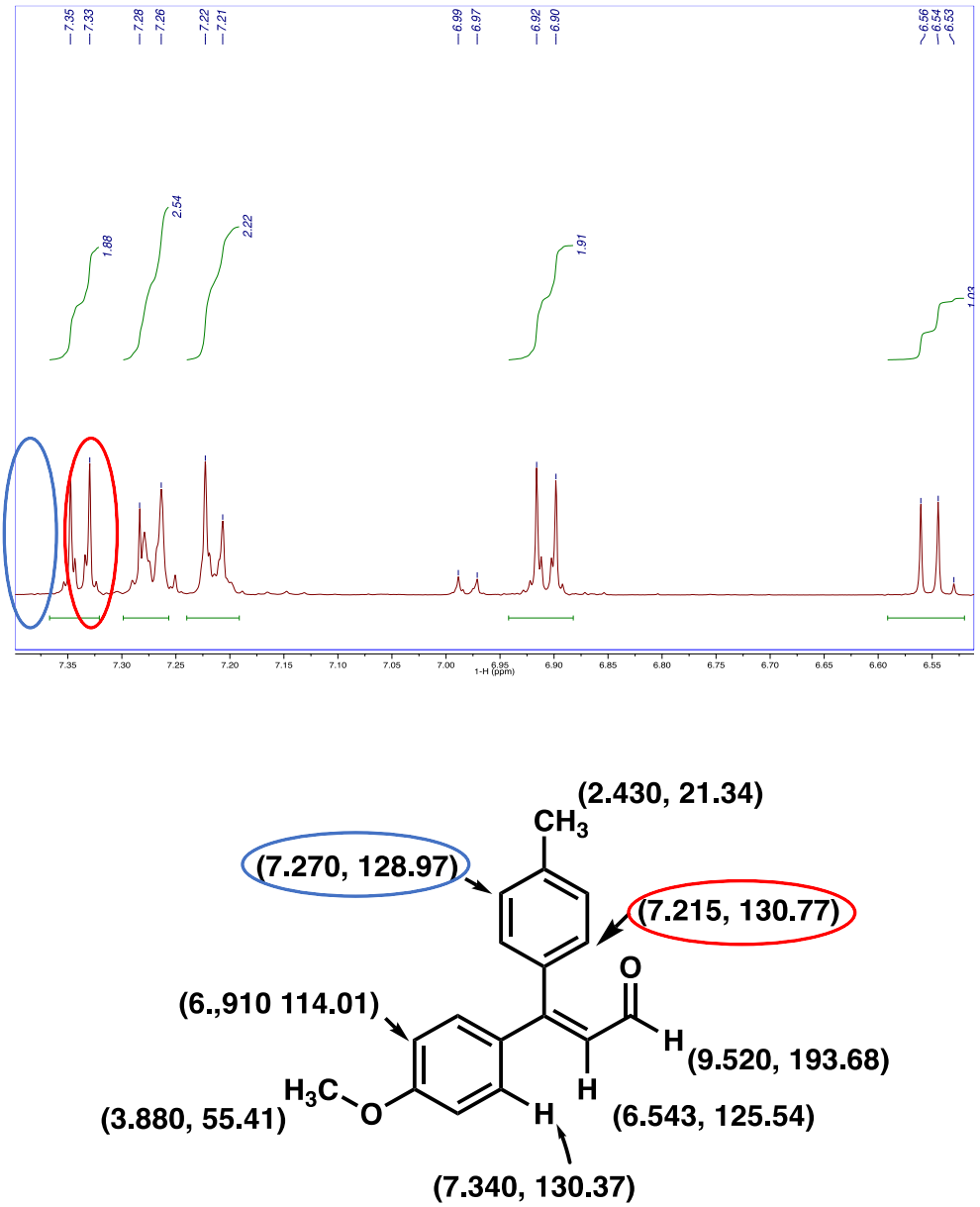


Figure 26a. A zoom in of the aryl region of compound CL-1-27's ^{1}H NMR spectra.

By zooming into this region, we clearly see the 4 types of hydrogens, all of which are doublets due to their one neighboring H. If you look closely, you can see that the signal at 7.2 is broader than the signal at 6.9 in the middle of the spectrum. This is due to long range coupling which is known to occur with a methyl attached to an aryl group (a tolyl group). This allows assignment of the 4 aryl hydrogen signals to their positions on the phenyl rings. This is also confirmed with some of the 2D NMR's. The signal at 7.267 is ortho to the tolyl methyl. The coupling constant shows that the next-door neighbor to that is at 7.125. This is confirmed with COSY and HMBC experiments. The other two doublets are on the methoxy phenyl ring, but their unambiguous assignment requires further analysis by HSQC and HMBC experiments.

HSQC spectrum plots the proton NMR on the x axis and the carbon NMR on the Y axis. This allows us to make correlations between proton signals to the carbon signal to which the proton is attached. Again, the questions remaining are the assignment for the 4 ipso carbons which do not have protons attached and which of the carbon/hydrogen signals are ortho vs meta on the methoxy substituted ring. Using HMBC allows us to make these assignments.

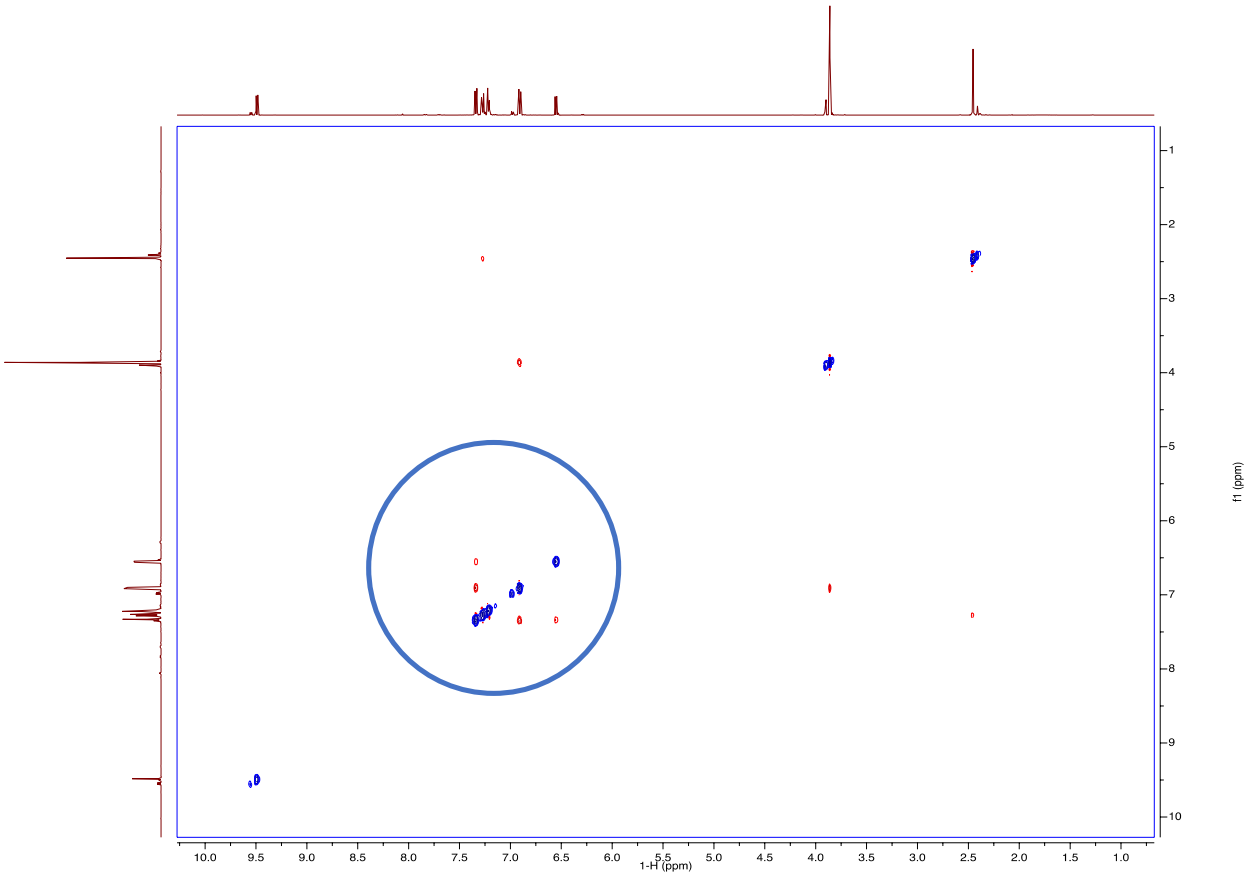


Figure 27: HSQC spectrum

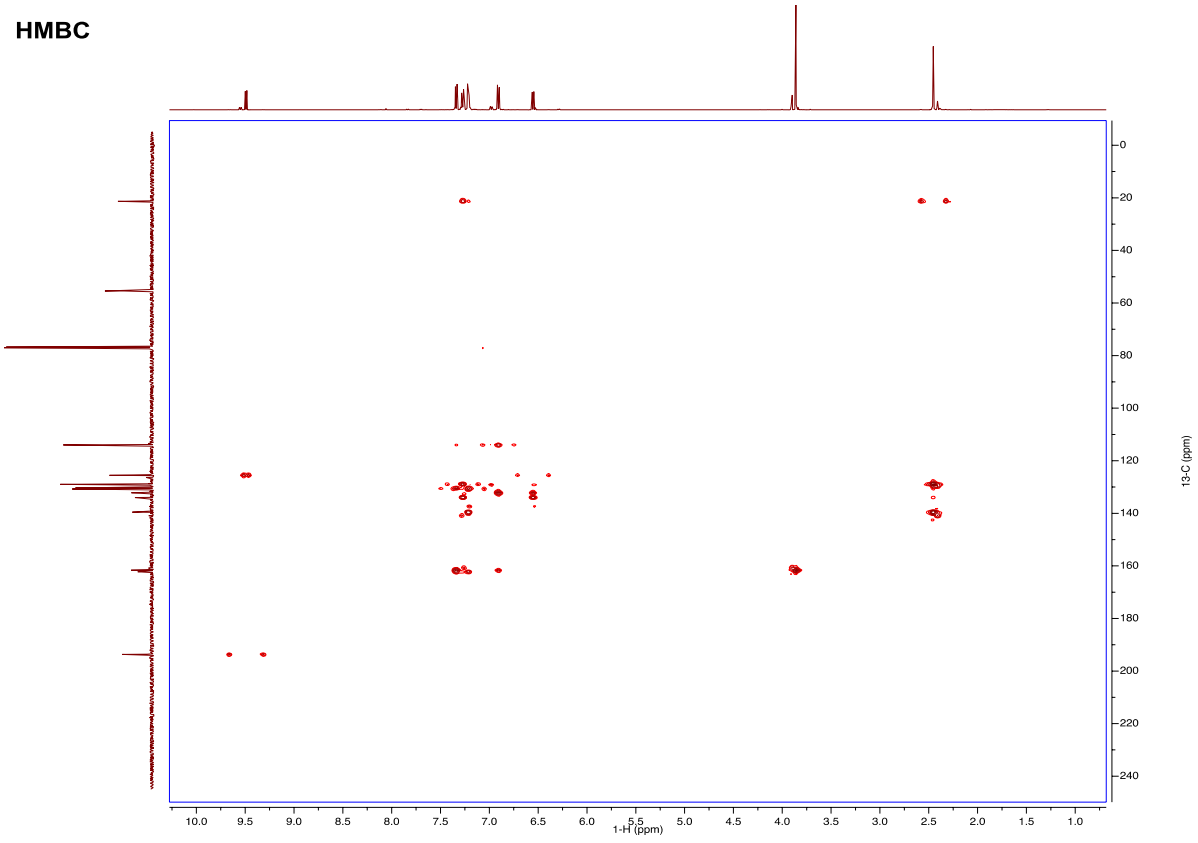


Figure 28. HMBC - Allows unambiguous assignment of all chemical shifts.

In the NOESY spectrum, we see that the vinyl proton at 6.5 has a through space connection with the ortho proton at 7.340 on the methoxy substituted phenyl ring (see green circles in Figure 28). The ortho proton on the tolyl ring at 7.215 does not show any through space correlation (see purple circles in spectrum below). In the CL-1-37 isomer, the ortho proton of the tolyl group shows that correlation. Hence, the NOESY spectrum allows confirmation of the absolute stereochemistry for the E isomer named CL-1-27.

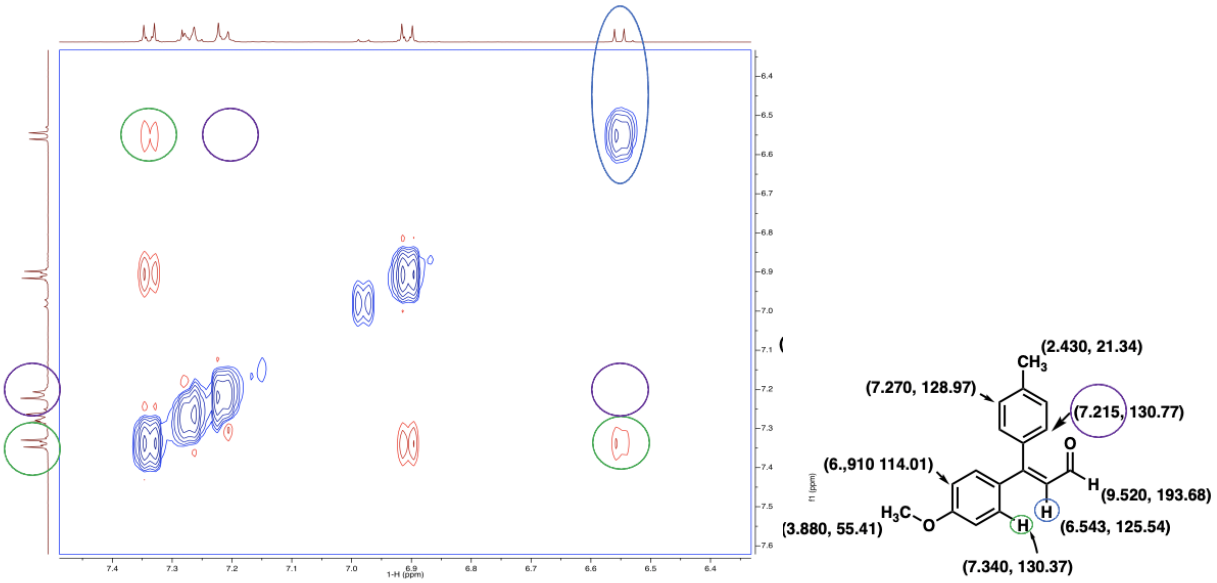


Figure 28. NOESY allows confirmation of the stereochemistry.

CONCLUSIONS

Xiao and coworkers were able to successfully synthesize a variety of ***β***, ***β***,-diarylacroleins by building on a Saegusa-Heck cascade reaction proposed by Zhu[2] and coworkers. The work of them and others provided valuable insight and context for our research project involving the stereoselective synthesis of aryl coumarins. We have developed a high yield, stereoselective synthesis for **β**,**β**-diarylacroleins for the purpose of synthesizing aryl coumarins. Suzuki coupling proceeds with retention of stereochemistry, which we unambiguously confirmed by NOESY NMR studies. These **β**,**β**-diarylacroleins are versatile reagents for synthesis of coumarins and other important pharmaceutical compounds.

EXPERIMENTAL SECTION

All chemicals were used as received from the manufacturer (Aldrich Chemicals and Fisher Scientific). All solvents were dried over 4 Å molecular sieves prior to their use. NMR spectra were obtained on either a Bruker 300MHz spectrometer, or a Bruker 500MHz spectrometer in either CDCl3, DMSO-d6 or d6-acetone solutions. IR spectra were recorded on a Nicolet Avatar 320 FT-IR spectrometer with an HATR attachment. High resolution mass spectra were obtained on a Shimadzu IT-TOF mass spectrometer at the University of Richmond. Low resolution GC-MS spectra were obtained on a Shimadzu QP 5050 instrument. Melting points and boiling points are uncorrected. Chromatographic purifications were carried out on a Biotage SP-1 instrument or a Biotage Isolera in- strument (both equipped with a silica cartridge). Gradient elution with ethyl acetate/hexane was accomplished in both instances. The reaction products were normally eluted within the range of 4-8 column volumes of eluant with a gradient mixture of 60-80% ethyl acetate in hexane. TLC analyses were conducted on silica plates with hexane/ethyl acetate as the

eluant. All purified reaction products gave TLC results, flash chromatograms, and ^{13}C NMR spectra consistent with a sample purity of >95%.

General procedure for Suzuki coupling of the chloroenal with boronic acids:

A mixture of 0.408 g (3.0 mmol) tolylboronic acid, 2.5 mmol of the chloroenal, 0.486 g (3.52 mmol) K_2CO_3, and 0.0319 g (0.027 mmol, 01%) Pd in 70mL 3:1 toluene/EtOH was refluxed for 4 hours. Cool the reaction to room temperature, add water and stir the mixture open to the air. Dilute the reaction with ethyl acetate and transfer it to a separatory funnel. Separate the two layers and re-extract the aqueous layer with ethyl acetate. Combine the organic extracts and wash them with a 5% sodium carbonate solution and brine sequentially. Transfer the organic phase to an Erlenmeyer flask equipped with a magnetic stir bar and add activated charcoal (0.50 g) and sodium sulfate (1 g). Stir this mixture for 10 min. Filter the solution through a 1 cm bed of Celite, rinsing the Celite with several portions of ethyl acetate. Concentrate the resulting pale yellow filtrate under reduced pressure to yield the crude product. Purification was carried out on a Biotage SP-1 instrument or a Biotage Isolera in- strument (both equipped with a silica cartridge).

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