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Pd-Catalyzed Cascade Saegusa-Heck Reaction: Synthesis of β,β-Diarylacroleins from Aryl Propanals and Aryl Iodides

Li Xiao,[a] Yilin Zheng,[a] Qiong Xie*[a] and Liming Shao*[a, b]

Abstract: An efficient and convenient Pd-catalyzed cascade Saegusa-Heck protocol has been developed, and its potential use in the synthesis of symmetrical and unsymmetrical β, β-diarylacroleins with moderate to high yields has been investigated.

Introduction

As versatile synthetic building blocks, β, β-diarylacroleins were widely used in pharmaceutical industry. β,β-Diarylacroleins could be utilized to assemble diarylmethine and diarylethene fragments present in various biologically important molecules (Figure 1), such as selective serotonin reuptake inhibitor (SSRI) sertraline **1**[1], diphenylbutylpiperidines (DPBPs) D_2 receptor antagonist penfluridol **2**[2], competitive muscarinic antagonist (*R*)-tolterodine **3**[3], calcium channel blocker fendiline **4**[4] and transient receptor potential vanilloid 1 (TRPV1) antagonist **5** [5], *etc*.

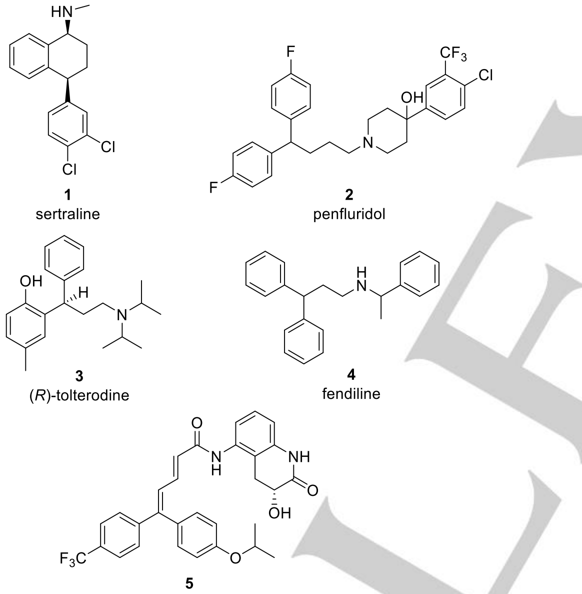
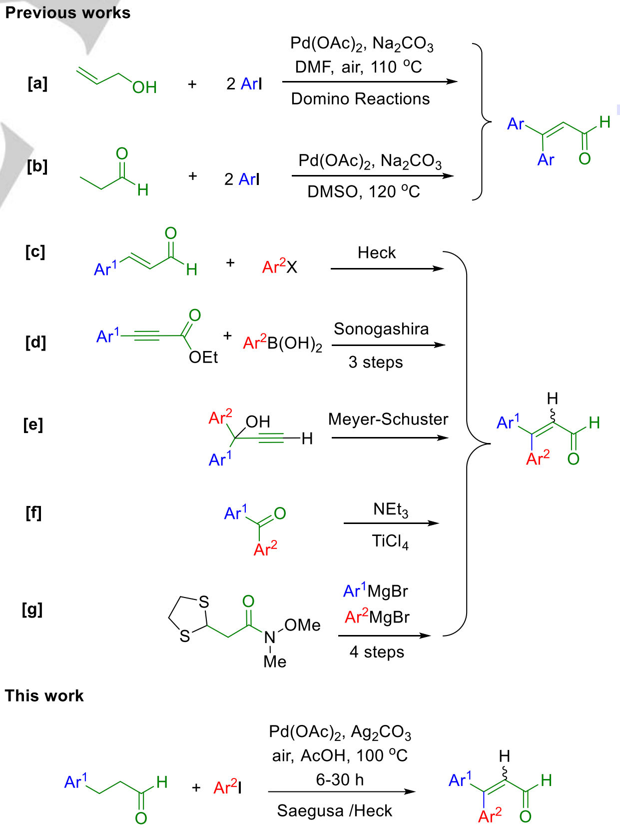


Figure 1. Biologically active molecules bearing diarylmethine and diarylethene fragments

Existing approaches for the synthesis of β,β-diarylacroleins (unsaturated aldehydes) are limited, particularly when wide variations of aryl groups at the β-position are desired. Heck reactions have been widely used in the synthesis of unsaturated carbonyl compounds (*e.g.* aldehydes, ketones, acids and esters) [6]. Simple procedures like one-pot diarylation of activated alkenes[6a] (Scheme 1, **a**) and cascade oxidative diarylation of saturated aldehydes[6b] (Scheme 1, **b**) have also been reported for the synthesis of symmetrical β,β-diarylacroleins. Zhu and co-workers[6a] published a triple transition-metal catalyzed domino reaction (Heck-isomerization /Saegusa /Heck) of allyl alcohol to give symmetrical β,β-diarylacroleins in one pot (Scheme 1, **a**). For the synthesis of unsymmetrical β,β-diarylacroleins, Heck arylation[7] (Scheme 1, **c**) of arylacroleins with aryl halides and Sonogashira-type coupling reaction[8] (Scheme 1, **d**) of aryl propiolates with aryl boronic acids are two major approaches. However, only electron-rich aryl groups were favorable under the conditions above. Some diaryl compounds could also turn into β,β-diarylacroleins, such as propargilic aryl carbinols[9] (Scheme 1, **e**) and diaryl ketones[10] (Scheme 1, **f**). In 2016, Tiwari and co-workers[11] developed a novel Weinreb amide to build β,β-diarylacroleins via sequential Grignard reactions (Scheme 1, **g**), which brings in the flexibility for expanding the reaction scope.



Scheme 1. Synthetic strategies of β,β-diarylacroleins.

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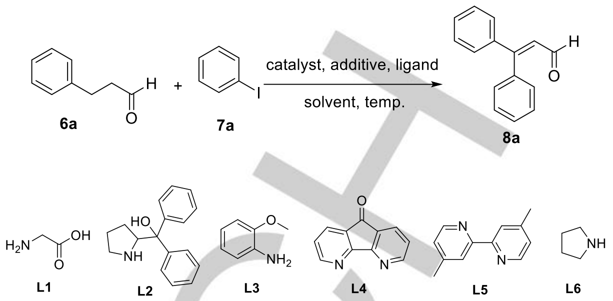
Methods for synthesizing unsymmetrical β,β-diarylacroleins are still facing problems of low synthetic efficiency, harsh reaction conditions, multi-step synthesis and extensive polymerization, *etc.* Therefore, developing more convenient method for the synthesis of β,β-diarylacroleins continues to be challenging. Saegusa oxidation is a convenient method for producing α,β-unsaturated aldehydes from saturated ones[12], which could serve as the alkene source for Heck reaction to afford the corresponding β-arylation products[6d, 7a, 7b]. Herein, we developed a novel Pd-catalyzed cascade Saegusa-Heck reaction to synthesize β,β-diarylacroleins efficiently utilizing stable and readily available aryl propanals and aryl iodides. Furthermore, this method is suitable for building various symmetrical and unsymmetrical β,β-diarylacroleins, including some electron-withdrawing aryl products.

Results and Discussion

Initially, phenylpropyl aldehyde **6a** (1.0 mmol, 1 equiv.) and iodobenzene **7a** (1.5 mmol, 1.5 equiv.) were employed as the starting materials. The reaction was performed in the presence of 10 mol% $Pd(OAc)_2$ and 1.5 equiv. of AgOAc in AcOH at 100 ℃ for 6 h (Table 1, entry 1), and the product **8a** was obtained in 26% yield. In order to increase the yield, we tried to optimize the reaction conditions. Firstly, various Ag salts (Table 1, entries 1-4) were tested where Ag_2CO_3 (Table 1, entry 4, 55%) seemed to be the most efficient. The yield increased from 26% to 50% by doubling the amount of AgOAc (entry 1, entry 6), indicating the importance of the silver ion amount. After further investigation, 1.2 equiv. was found to be the optimal amount of Ag_2CO_3 to achieve the best yield (Table 1, entry 8). Homo-coupling of **7a** was observed as a major side reaction. Therefore, the amount of **7a** was increased to 2.5 equiv., which led to a significant increase in yield to 78% (Table 1, entry 9). Subsequently, a series of Pd catalysts (Table 1, entries 9-13) were screened, and $Pd(OAc)_2$ gave the highest yield (Table 1, entry 9, 78%). In the absence of palladium catalyst (Table 1, entry 14), no reaction occurred. Various solvents (Table 1, entries 15-17) and bases (Table 1, entries 18-20) were also examined in this reaction. Acetic acid was proved the optimal solvent regarding the yield of **8a** as compared to water (Table 1, entry 17), toluene (Table 1, entry 15) and DMF (Table 1, entry 16). In basic conditions (Table 1, entries 18-20), yields of **8a** decreased significantly. To further optimize the reaction conditions, we screened a variety of ligands[12b, 13] (Table 1, entries 21-26), but did not get better results. Screening of the reaction temperatures in the range of 80 to 120 ℃ revealed that the best results were obtained at 100 ℃ (Table 1, entries 9, 27-28). Reducing the concentration of O_2 led to lower yield (44%) of the desired **8a** (Table 1, entry 29). Therefore, it could be concluded that the optimized reaction should be performed under the catalysis of 10 mol% $Pd(OAc)_2$ using 1.2 equiv. of Ag_2CO_3 in AcOH at 100 ℃ for 6 h (Table 1, entry 9, 78%).

Table 1. Optimization of reaction conditions for the synthesis of β,β-diarylacroleins.[a]

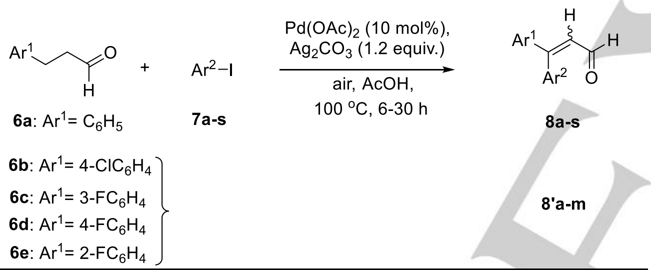


Entry	Catalyst[b]	Additive (equiv.)	Ligand	Solvent	Yield[c] [%]
1	$Pd(OAc)_2$	AgOAc (1.5)	–	AcOH	26
2	$Pd(OAc)_2$	$AgNO_3$ (1.5)	–	AcOH	8
3	$Pd(OAc)_2$	AgTFA (1.5)	–	AcOH	28
4	$Pd(OAc)_2$	Ag_2CO_3 (1.5)	–	AcOH	55
5	$Pd(OAc)_2$	–	–	AcOH	trace
6	$Pd(OAc)_2$	AgOAc (3.0)	–	AcOH	50
7	$Pd(OAc)_2$	Ag_2CO_3 (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

[a] Reaction condition: **6a** (1 mmol, 1 equiv.), **7a** (1.5 equiv. in entries 1-8, 2.5 equiv. in entries 9-29), the mixture was stirred at 100 ℃ (in entries 1-26) under air in sealed tube for 6 h. [b] 10 mol%. [c] Isolated yield based on **6a**. [d] Reaction temperature was 80 ℃. [e] Reaction temperature was 120 ℃. [f] The mixture was purge with argon.

With the reaction conditions optimized, we further explored the scope and generality of the methodology. As shown in Table 2, a variety of aryl iodides (**7a−s**) were able to react smoothly with benzenepropanal **6a** to give the desired β,β-diarylacroleins (**8a−s**) in yields of 30−83% (Table 2, entries 1-19) under standardized conditions. The results showed that electron-donating groups on the aryl iodides (Table 2, entries 2-4, entry 10, and entries 12-16) were more beneficial to this reaction than electron-withdrawing groups (Table 2, entries 5-9, entry 11, and entries 17-19). The position of substituents also influenced the reaction outcome. When *ortho*-substituted iodobenzenes (Table 2, entry 2 and entry 5) were employed, the yields decreased significantly due to steric effects. In comparison, *meta*- (Table 2, entry 3 and entry 6) or *para*-substituted iodobenzenes (Table 2, entry 4 and entry 7) still retained moderate to good yields. Furthermore, some other aryl propanals **6b-d** were successfully transformed to their corresponding products **8'a-m** (Table 2, entry 20-32). However, no desired product had been detected (Table 2, entry 33) when 3-(2-fluorophenyl)propanal (**6e**) was employed as the starting material. Thirty unsymmetrical β,β-diarylacrolein compounds were obtained as a mixture of geometrical isomers in this study, since they are difficult to be well separated. As shown in Table 2, the ratios of the stereoisomers had been calculated based on the NMR data. The *trans* or *cis* configurations of **8d**, **8h**, **8j**, **8k** and **8p** (Table 2) were identified by comparison with the spectroscopic data reported in literatures[5, 7b, 8b, 14]. The results showed that the major products were *trans* type. Additionally, when **7b** was employed as the substrate (Table 2, entry 2 and entry 20), more isomers were detected in NMR due to the steric effect of *ortho*-methyl group (see supporting information).

Table 2. Synthesis of β,β-diarylacroleins from aryl iodides and aryl propanals.[a]



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-$CF_3OC_6H_4$	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-iPrC_6H_4	14	**8m**, 38	1: 4.2
14	**6a**	**7n:** 4-tBuC_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-$NO_2C_6H_4$	12	**8r**, 39	1: 1.3
19	**6a**	**7s:** 4-$CF_3C_6H_4$	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	–

[a] Reaction condition: **6** (1 mmol), **7** (2.5 mmol), Ag_2CO_3 (1.2 mmol), $Pd(OAc)_2$ (0.1 mmol) were stirred in AcOH at 100 ℃ under air in sealed tube 6-30 h. [b] Isolated yield based on **6**. [c] Mixture of geometrical isomers. Calculated based on NMR data.

Considering all the mechanisms suggested in ear reports[6a, 15], a plausible reaction mechanism of the Pd-casca Saegusa-Heck process for the formation of β, β-diarylacroleins proposed (Figure 2).

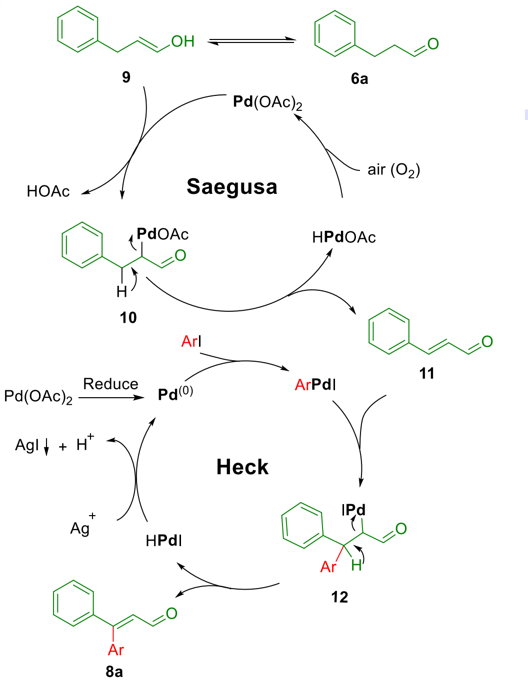


Figure 2. Proposed mechanism for Pd-catalyzed cascade Saegusa-Heck reaction.

Initially, **6** turns to **9** through tautomerism catalyzed by acid. A classic Saegusa oxidative process transforms **9** to **11** via the intermediate **10.** In this process, oxygen in air takes part in the reaction as an oxidant. Pd(0) is generated from $Pd(OAc)_2$ via reduction, and then reacts in the catalytic cycle. **11** undergoes a typical Heck reaction with aryl iodides **7** catalyzed by palladium to give the desired β,β-diarylacroleins **8**. During the reaction, silver(I) ion was precipitated to give silver iodides and the Heck reaction was promoted by this process.

Conclusions

To summarize, we developed a novel and efficient strategy for one-pot synthesis of β,β-diarylacroleins through Pd-catalyzed cascade Saegusa-Heck reaction. It is convenient and has potential extensive application. Thirty-two β,β-diarylacroleins were synthesized by using various aryl propanals and aryl iodides with moderate to good yields (30%~83%). The method tolerates a wide range of functional groups, including some electron-withdrawing groups. The polymerization of **6** and homo-coupling of **7** were detected as major side reactions.

Experimental Section

General Procedure for the Preparation of 8 and 8': In a sealed tube equipped with a magnetic stirring bar, starting materials **6** (1.0 mmol), **7** (2.5 mmol), Ag_2CO_3 (1.2 mmol) and catalyst $Pd(OAc)_2$ (22.4 mg, 0.1 mmol, 10 mol%) were added, then the tube was sealed and the mixture was stirred at 100 ℃ until the ^{1}H NMR spectrum showed complete conversion. The mixture was then filtered through a short plug of silica gel. Solvents were removed under reduced pressure. Purification by column chromatography on silica gel (*n*-hexane/ EtOAc, 20:1) afforded the corresponding product **8a–s**, **8'a-m**.

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Keywords: Synthetic methods • β, β-diarylacroleins • Saegusa-Heck reaction

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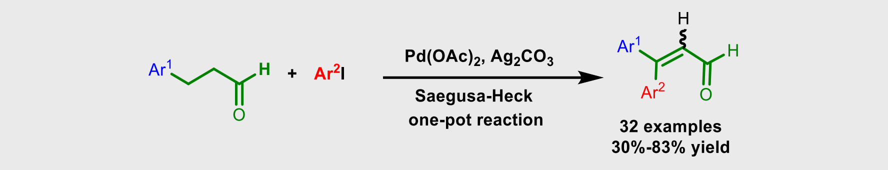

An efficient Pd-catalyzed cascade Saegusa-Heck protocol for the synthesis of synthetically useful β,β-diarylacroleins from aryl propanals and aryl iodides in moderate to high yields (30%-83%) has been developed.

Organocatalysis*

Li Xiao, Yilin Zheng, Qiong Xie and Liming Shao**

Page No. – Page No.

Title: Pd-Catalyzed Cascade Saegusa-Heck Reaction: Synthesis of β,β-Diarylacroleins from Aryl Propanals and Aryl Iodides