Synthesis of Vinylsulfones Via Palladium-Catalyzed Decarboxylative Coupling of Cinnamic Acids with Aromatic Sulfinic Acid Sodium Salts

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Abstract A highly efficient synthesis of vinylsulfones was achieved via decarboxylative cross-coupling reaction of cinnamic acids with aromatic sulfinic acid sodium salts catalyzed by $Pd(OAc)_2$ and dppb in the presence of Ag_2 . CO_3 . The reaction was found to furnish various vinylsulfones in good yields instead of the expected desulfitative product stilbenes. Mechanistic investigation also suggested that the decarboxylation is likely to take place after the transmetallation step.

Keywords $Pd(AcO)_2 \cdot Ag_2CO_3 \cdot Cinnamic acid \cdot Aromatic sulfinic acid sodium salts \cdot Decarboxylative coupling$

1 Introduction

The development of Pd-catalyzed decarboxylative couplings (For some reviews on decarboxylative couplings, see [1-3]) has attracted significant attention lately since these couplings utilize readily available carboxylic acids instead of the usually expensive organometallic reagents [4-44]. Moreover, these carboxylic acids, after undergoing decarboxylations, only produce CO₂, an innocuous compound, as the side-product. Though Nilsson reported the first transition metal mediated decarboxylative biaryl coupling [4], it was through the efforts of Goossen [5–11],

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R. Guo · Q. Gui · D. Wang · Z. Tan (⊠) College of Chemistry and Chemical Engineering, Hunan University, Changsha 410082, People's Republic of China e-mail: ztanze@gmail.com Myers [12–14] and others [15–44] that the field of Pdcatalyzed decarboxylative coupling has blossomed. By using different coupling partners, a number of different Pdcatalyzed decarboxylative couplings have been developed to access styrenes [12–17], biaryls [5–11, 18–32], ketones [33–38], esters [39], nitriles [40], diarylmethanes [41, 42] and phenanthrenes [43]. Among these couplings, those relying on the direct arylation of arene approach [24–26, 34, 35, 38, 43, 44, 49] are particularly noteworthy since these transformations are C-H activation based, thus making the synthesis extremely efficient in terms of step economy and overall yield. For example, Larrosa et al. and Su et al. reported the intermolecular decarboxylative couplings between indole or thiophene derivatives and arene carboxylic acids [24-26]. Greaney and our group discovered that benzothiazoles and oxazoles can undergo intermolecular decarboxylative couplings with aryl carboxylic acids [27, 28]. Although the decarboxylative coupling of arene carboxylic acids has been studied extensively, reports on the decarboxylative coupling of vinyl carboxylic acids are quite few [17]. Given the fact that a large number of cinnamic acid derivatives are commercially available or can be conveniently prepared by the classical Perkin reaction from the corresponding benzaldehydes, utilization of them in Pd-catalyzed decarboxylative couplings seems highly desirable. Along this line, Wu in 2009 reported that stilbenes can be efficiently constructed by the coupling of cinnamic acids with aryl iodides and bromides in the presence of PdCl₂ catalyst and using CyJohnphos as the ligand [Eq. (1)] [17].

Aryl sulfinic acid sodium salts which are relatively stable, easily prepared from sulfonyl chlorides, are mainly used as sulfonylation reagents for preparing organosulfonyl compounds (Recent examples [45–48]). However, recent studies revealed that aryl sulfinic acids and their salts could

also serve as the arene sources via desulfitative reactions. especially under transition metal catalysis [49-62]. Graves was the first to report a desulfitative biaryl synthesis in 1970 using aryl sulfinic acids and their salts as aryl donors [49]. In 1992, Sato and Okoshi showed that biaryls can be synthesized via Pd-catalyzed desulfitative couplings between aryl bromides with aromatic sulfinic acids in NMP [50]. Later on Li and Duan showed that arvl triflates were also viable substrates [61]. In addition to the reactions with aryl halides, Pd-catalyzed desulfitative Heck type coupling with olefins was also successfully developed by Deng to provide various stilbenes [Eq. (2)] [62]. By using different Pd-catalyst combinations, Li and Duan showed that the reaction of olefins with aromatic sulfinic acids can be stopped after the desulfitation-addition step and the saturated products instead of the alkenes (Heck coupling product) were obtained [60]. More recently this type of desulfitative couplings was successfully extended to azoles, indoles and other heterocycles by Wang, Deng and You [51, 52, 57]. Inspired by these results and as a continuation of our research on transition-metal-catalyzed decarboxylative coupling, we envision that 1,2-diaryl olefins can be synthesized via Pd-catalyzed decarboxylative/desulfitative coupling between cinnamic acids and aromatic sulfinic acid sodium salts (Eq. 3). As a result, we systematically studied the coupling of cinnamic acids with arenesulfinic acid sodium salts under Pd-catalysis and we found that cinnamic acids did undergo decarboxylation under the reaction conditions. However vinyl sulfones instead of the desulfitative product stilbenes were obtained in good to excellent yields. (For some recent syntheses of vinylsulfones from alkenes or alkynes and aryl sulfinates, please see [63, 64]).

2 Experimental

2.1 Instruments and Materials

All solvents and reagents were purchased from the suppliers and used after further dried. ¹H NMR and ¹³C NMR were recorded in CDCl₃ at room temperature on the spectrometer (400 MHz ¹H, 100 MHz ¹³C). The chemical-shifts scale is based on internal TMS. Data for ¹H NMR and ¹³C NMR are reported as follows: chemical shift (δ , ppm), multiplicity, integration, and coupling constant (Hz). All reactions were carried out under dry nitrogen atmosphere.

2.2 General Procedure for Palladium-Catalyzed Decarboxylative Cross-Coupling Reaction of Cinnamic Acids with Aromatic Sulfinic Acid Sodium Salts

To a 15-mL sealed tube were added $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), dppb (22 mg, 0.05 mmol), Ag₂CO₃ (264 mg, 1 mmol), cinnamic acid (0.5 mmol) and aromatic sulfinic acid sodium salt (1.0 mmol). The tube was capped and stirred under N₂ at 75 °C for 6 h. The reaction mixture was cooled to room temperature and diluted with EtOAc, filtered through a short pad of Celite, washed with EtOAc, and concentrated in vacuo. The resulting residue was purified by flash column chromatography using hexanes:EtOAc (4:1) as the eluent. All compounds are characterized by ¹H NMR, ¹³C NMR, LRMS and their comparison to literature values.



Table 1 Reaction condition optimization



Entry	$PdX_2 \pmod{\%}$	Additive (equiv)	Ligand	Solvent	T (°C)	Yield ^a
1	PdCl ₂	Ag ₂ CO ₃	PPh ₃	DMF	150	25 %
2	PdCl ₂	Ag ₂ CO ₃	PPh ₃	DMF	125	27 %
3	PdCl ₂	Ag ₂ CO ₃	PPh ₃	DMF	100	53 %
4	PdCl ₂	Ag ₂ CO ₃	PPh ₃	DMF	75	75 %
5	PdCl ₂	Ag_2CO_3	PPh ₃	DMF	50	27 %
6	PdCl ₂	Ag ₂ CO ₃	PPh ₃	DMF	25	trace
7 ^c	PdCl ₂	Ag ₂ CO ₃	PPh ₃	DMF	75	62 %
8	PdCl ₂	AgOAc	PPh ₃	DMF	75	44 %
9	PdCl ₂	K ₂ CO ₃	PPh ₃	DMF	75	trace
10	PdCl ₂	K_3PO_4	PPh ₃	DMF	75	trace
11	Pd(OAc) ₂	Ag ₂ CO ₃	PPh ₃	DMF	75	76 %
12	Pd(OAc) ₂	Ag ₂ CO ₃	PPh ₃	Cl(CH ₂₎₂ Cl	75	10 %
13	Pd(OAc) ₂	Ag ₂ CO ₃	PPh ₃	toluene	75	7 %
14	Pd(OAc) ₂	Ag ₂ CO ₃	PPh ₃	H_2O	75	31 %
15	Pd(OAc) ₂	Ag ₂ CO ₃	PPh ₃	DMSO	75	63 %
16 ^d	Pd(OAc) ₂	Ag ₂ CO ₃	PPh ₃	DMF	75	44 %
17	Pd(OAc) ₂	Ag ₂ CO ₃	dppf	DMF	75	74 %
18	Pd(OAc) ₂	Ag ₂ CO ₃	Xantphos	DMF	75	30 %
19	Pd(OAc) ₂	Ag ₂ CO ₃	Tri(o-tolyl)phosphine	DMF	75	73 %
20	Pd(OAc) ₂	Ag ₂ CO ₃	dppb	DMF	75	94 %
21	Pd(OAc) ₂	Ag ₂ CO ₃	dppm	DMF	75	68 %
22	Pd(OAc) ₂	Ag ₂ CO ₃	dppe	DMF	75	48 %
23	Pd(OAc) ₂	Ag_2CO_3	dppp	DMF	75	57 %
24		Ag ₂ CO ₃	dppb	DMF	75	0 %

Conditions: 1a (0.5 mmol), 2a (1.0 mmol), PdX_2 (0.05 mmol), Additive (1.0 mmol), Ligand (0.1 mmol for monodentate ligand, 0.05 mmol for bidentate ligand), 3 mL of solvent, at 75 °C for 6 h unless otherwise noted

Only 5 mol % Pd catalyst and 10 mol % ligand were used

The amount of DMF used was decreased to1.5 mL

^a Yields are based on 1**a**

3 Results and Discussion

3.1 Optimization of Reaction Conditions for Pd-Catalyzed Decarboxylative Coupling of Cinnamic Acids with Aromatic Sulfinic Acid Sodium Salts

In order to study Pd-catalyzed decarboxylative-desulfitative coupling between cinnamic acids and aromatic sulfinic acid sodium salts, we decided to use the coupling of cinnamic acid **1a** and benzenesulfinic acid sodium salt **2a** as our model reaction. When cinnamic acid **1a** was heated with 2 equiv of benzenesulfinic acid sodium salt and 2 equiv. of Ag_2CO_3 in the presence of 10 mol % of PdCl₂ and 0.2 equiv of PPh₃ in DMF (6 mL/mmol) at 150 °C for 12 h, much to our surprise, we found that the product isolated in 25 % yield was actually vinyl sulfone **3a** instead of the expected stilbene product **4a** (Table 1, entry 1). Clearly, the desulfination did not take place as expected. It is important to note that the stereochemistry of the isolated product was exclusively *trans* based on the large coupling constant of the two olefinic protons. In order to improve the reaction yield, several reaction parameters were screened and the results were summarized in Table 1. From the table, we can see that lowering the reaction temperature benefited the reaction. In fact, best yield (75 %) was reached at 75 °C while further lowering of the reaction



Table 2 Palladium-catalyzed decarboxylative cross-coupling of cinnamic acids with arenesulfinic acid sodium salts

Isolated yields based on cinnamic acid 1a

Scheme 1 Proposed mechanism for Palladiumcatalyzed decarboxylative cross-coupling of cinnamic acids with aromatic sulfinic acid sodium salts



temperature actually was detrimental to the reaction (Table 1, entries 2–6). When the reaction was run at room temperature, no desired product was observed (Table 1, entry 6). When the amount of Pd-catalyst used was reduced to 5 mol %, the yield dropped to 62 % (Table 1, entry 7). When the oxidant Ag₂CO₃ was switched to AgOAc, the vield dropped to 44 % (Table 1, entry 8). When Ag₂CO₃ was substituted with either K₂CO₃ or K₃PO₄, almost no reaction took place (Table 1, entries 9, 10). This is to be expected because Ag₂CO₃ acted not only as a base but also as an oxidant. The yield did not change much when Pd(OAc)₂ was utilized in place of PdCl₂ as the catalyst (Table 1, entry 11). Tests also showed that DMF gave the best yield (76 %) whereas other solvents such as ClCH₂₋ CH₂Cl, toluene, DMSO and H₂O were less effective (Table 1, entries 12–15). When the volume of DMF was switched to 3 mL/mmol, the yield of reaction also suffered (44 %, Table 1, entries 16). Comparable results were also encountered when the ligand was changed to dppf, or Tri(o-tolyl)phosphine while Xantphos gave inferior results (Table 1, entries 17,18 and 19). However, much to our delight, we found that the yield could be improved to 94 % when ligand dppb was used in combination with $Pd(OAc)_2$ while the use of dppm, dppe, dppp proved less efficient (Table 1, entry 20–23). Control reaction also proved that no desired reaction took place in the absence of Pd-catalyst (Table 1, entry 24).

3.2 General Procedure for Palladium-Catalyzed Decarboxylative Cross-Coupling Reaction of Cinnamic Acid with Aromatic Sulfinic Acid Sodium Salt

With the optimized protocol in hand, we next set out to explore the scope and the limitation of the reaction (Table 2). We found that the reaction worked very well for a wide variety of substituted cinnamic acids, affording the desired vinyl sulfones in yields ranging from 45 to 88 %. It is important to note that, in all the reactions, only one stereoisomer was obtained and the stereochemistry of the isolated vinylsulfones were all *E*. Both electron-donating

and electron-withdrawing groups such as methyl, chloro, bromo, fluoro, methoxy as well as nitro group are well tolerated on the phenyl ring of the cinnamic acids. They can also be placed at the ortho, meta and para positions, resulting little difference on the product yields. The results of nitro-substituted substrates are important because the nitro group can be easily transformed into other functional groups. The results of chloro and bromo-substituted substrates are also important because they offered convenient handles for future transition metal catalyzed C-C and C-X bond formation. As for the substituted aryl sulfinic acid sodium salts, we found methyl, tert-butyl, fluoro and bromo-substituted phenyl sulfinic acid sodium salts worked satisfactorily to afford the desired vinyl sulfones in 50-88 % yield (Table 2, 3am-3bc). 2-Naphthyl sulfinic acid sodium salt worked well too (Table 2, 3bd). It is worthwhile to point out that 2-methyl cinnamic acid can also participate in the cross coupling with phenyl sulfinic acid sodium salt successfully, furnishing the desired trisubstituted vinyl sulfone 3az in 45 % yield. Though the yield is rather low, it should be noted that only one stereoisomer was obtained and analysis of the product indicated that it was the E product, showing the stereochemistry of the starting cinnamic acid was retained during the coupling. However, when we tried to use alkyl sulfinic acid sodium salt such as sodium methanesulfinate as the coupling partner, the reaction became very messy (Table 2, 3be) (Scheme 1)

3.3 Investigation into the Reaction Mechanism

Based on previous reports [5-11, 51-62], we have considered two possible reaction mechanisms for this coupling. As expected, the cinnamic acid first underwent anion exchange with Pd(OAc)₂ to generate palladium cinnamate I. In catalytic cycle A, this intermediate next reacted with arene sulfinic acid sodium salt to form intermediate II. After decarboxylation, intermediate II turned into intermediate III which after reductive elimination should furnish the desired vinyl sulfone product. The Pd(0) is oxidized by the silver salt back to Pd(II), thus



(a) ¹H NMR spectrum of cinnamic acid, mesitylene and DMF in DMSO-d₆ at 25 $^{\circ}$ C

Scheme 2 ¹H NMR (400 MHz) study of the reaction between cinnamic acid and aromatic sulfinic acid sodium salt catalyzed by the combination of Pd(OAc)₂ and PPh₃ in the presence of Ag₂CO₃. **a** ¹H NMR spectrum of cinnamic acid, mesitylene and DMF in DMSO-d₆ at 25 °C. **b** reaction mixture 1 h at 75 °C. **c** ¹H NMR

spectrum after the addition of Pd(OAc)₂, PPh₃ and Ag₂CO₃ at 25 °C. **d–e** ¹H NMR spectra after 5 min at 50 °C and 1 h at 75 °C. **f** ¹H NMR spectrum after the addition of PhSO₂Na at 75 °C. **g** ¹H NMR spectrum after 1 h at 75 °C

completing the catalytic cycle. However, another possible pathway is catalytic cycle **B**. In cycle **B**, palladium cinnamate **I** will decarboxylate first before reacting with arene sulfinic acid sodium to form intermediate **IV**. This intermediate will react with the arene sulfinic acid sodium to form intermediate **III** which is also formed in cycle **A**. In order to differentiate these two pathways, several mechanistic experiments were performed. We tried to monitor the coupling reaction in situ using NMR spectroscopy using mesitylene as the internal standard (Scheme 2). For solubility reasons, we opted to add some DMSO-d₆ to the reaction mixture as the NMR solvent. From the spectra, we can see that even at 75 °C with Pd catalyst, PPh₃ and Ag₂CO₃, the signal at 6.61 ppm which we assigned to be the proton of the 2-position of cinnamic acid did not decrease. This showed that decarboxylation did not take place at the reaction temperature. However, after we added arene sulfinic acid sodium to the NMR tube, the intensity of the peak decreased drastically in just 1 h at 75 °C (Scheme 2, g), showing decarboxylation took place in the presence of arene sulfinic acid sodium. Based on the above results, we concluded that the catalytic cycle **A** is more likely though other mechanisms may operate here as well.

4 Conclusions

In conclusion, we have developed a highly effective method of synthesizing vinyl sulfones via Pd-catalyzed decarboxylative cross-coupling reaction of cinnamic acid with arene sulfinic acid sodium salts. The best result was obtained by using catalyst combination of $Pd(OAc)_2$ and dppb in DMF using Ag_2CO_3 as the base and oxidant. The reaction was found to tolerate both electron withdrawing and electron donating groups, affording various vinyl sulfones in 45–94 % yield. Currently efforts are underway to expand the reaction scope and the results will be reported in due course.

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