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Switching the *Z*/*E* Selectivity in the Palladium(II)-Catalyzed Decarboxylative Heck Arylations of *trans*-Cinnamaldehydes by Solvent

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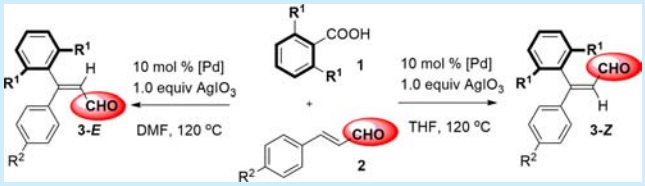
Supporting Information

ABSTRACT: The *Z*/*E* selectivity of Pd(II)-catalyzed decarboxylative Heck-type arylations of *trans*-cinnamaldehydes can be controlled readily by switching the reaction solvent. Depending on the type of solvent used, each of the two isomeric products can be obtained with good to excellent *Z*/*E* ratio. In THF, *Z*-isomers were formed preferentially, whereas DMF provided the *E*-isomers predominantly.



The different geometries (*Z*/*E*) of C=C compounds will have a great impact on their properties such as biological activities.[1] For example, (*E*)-stilbene derivatives display a higher affinity for the aryl hydrocarbon receptor (AhR) over (*Z*)-derivatives.[2] Compared with *E*-isomers, *Z*-heteroretinoids have more potent apoptosis-inducing activity in the HL-60 cell line.[3] *Trans*-fatty acids containing *trans* C=C double bond raise the risk of cardiovascular disease (CVD),[4] whereas *cis*-fatty acids have beneficial effects on CVD.[5] More importantly, numerous bioactive natural products and pharmaceuticals contain specific *Z*- or *E*-alkene functions.[6] Thus, efficiently controlling the geometry of the carbon−carbon double bond has been one of the long-standing challenges in organic synthesis. The stereoselectivities of the Wittig reaction are governed by the nature of the ylide: stabilized ylides, bearing π-acceptor groups at the α-carbon, generally react with high (*E*)-configuration selectivity, whereas nonstabilized ylides, bearing an α-alkyl group, give *Z*-alkenes.[7] On the other hand, the Julia olefination is developed primarily toward the selective formation of *trans*-alkenes, although its *E*/*Z* selectivity can be influenced by varying the sulfonyl group, solvent, and base.[8] Recently, olefin metathesis[9] and transition-metal-catalyzed cross coupling reactions[10] have been extensively used to generate stereodefined carbon−carbon double bonds. Nevertheless, it would be highly desirable that we can use a simple "switch" to control such selectivities.

The Pd-catalyzed decarboxylative Heck-type coupling reaction of arene carboxylates with olefinic substrates,[11] pioneered by Myers et al.,[11a−c] generates a substituted C=C double bond stereoselectively with a fixed geometry.[11c,f,g] Herein, *we report a simple approach to control the Z/E selectivity at will by simply "switching" the* reaction *solvent, for the palladium-catalyzed decarboxylative arylations of trans-cinnamaldehydes.*

We first selected 2,6-dimethoxybenzoic acid **1a** and *trans*-cinnamaldehyde **2a** as a coupling partner for optimizing the reaction conditions, and selected results are summarized in Table 1. Initially, some oxidizing Ag(I) salts were screened using $PdCl_2$ as catalyst and 5% DMSO−DMF as solvent. To our surprise, the reactions gave unexpected **3a-*Z*** as the major product (Table 1, entries 1−3), since the Heck-type reactions should generate the *E*-isomer preferentially.[11c,f,g] The configuration of double bond in **3a-*Z*** was determined by NOESY experiment (see the Supporting Information). Under otherwise identical conditions, we examined other solvents, which showed tetrahydrofuran (THF) being most favorable for the *Z*-isomer (Table 1, entry 8, *Z*/*E* = 25:1). In contrast, DMF can increase the yield and selectivity toward the **3a-*E*** when the reaction time is shortened (Table 1, entries 6 and 7). The configuration of **3a-*E*** was determined by X-ray crystallography (Figure 1) and NOESY experiment (see the Supporting Information). The solvent could play the switch role in the *Z*/*E* selectivities of the reactions. Other palladium catalysts were also examined: $Pd(OAc)_2$ and $Pd(TFA)_2$ gave poor results for both **3a-*Z*** and **3a-*E*** (Table 1, entries 9 and 10). Addition of ligands such as benzonitrile, triphenylphosphine, and tri(*p*-tolyl)phosphine resulted in increasing yields of **3a-*Z*** (Table 1, entries 11−16). The use of $Pd(PhCN)_2Cl_2$ as catalyst provides >35:1 *Z*/*E* stereoselectivity, albeit with a moderate yield (Table 1, entries 11 and 12). Using phosphine-based $Pd(TPTP)_2Cl_2$ and $Pd(PPh_3)_2Cl_2$ complexes as catalysts increased the product yield with a slight decrease in selectivity (Table 1, entries 13−16); **3a-*Z*** was obtained with both good yield and excellent selectivity (10:1 *Z*/*E* ratio) under THF conditions (Table 1, entry 14). On the other hand, in order to further improve the yield of **3a-*E***, palladium catalysts, reaction time, and the amount of $AgIO_3$ and acid **1a** were also optimized. Doubling the amount of acid **1a** resulted in an increased yield of **3a-*E*** (Table 1, entries 17 and 18). We reduced the reaction time to 1

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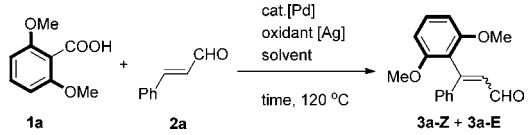
Table 1. Selected Results for the Optimal Reaction Conditions[a]



entry	[Pd] (10 mol %)	[Ag] (equiv)	amt of **1a** (equiv)	solvent	time (h)	yield[b] (%)	Z/E[c]
1	$PdCl_2$	AgOTf (0.2)	1.0	DMSO/DMF	24	4	4:1
2	$PdCl_2$	Ag_2CO_3(0.2)	1.0	DMSO/DMF	24	12	2:1
3	$PdCl_2$	$AgIO_3$ (0.2)	1.0	DMSO/DMF	24	22	13:9
4	$PdCl_2$	$AgIO_3$ (0.2)	1.0	dioxane	24	29	22:7
5	$PdCl_2$	$AgIO_3$ (0.2)	1.0	DMSO	24	36	25:11
6	$PdCl_2$	$AgIO_3$ (0.2)	1.0	DMF	24	27	16:11
7	$PdCl_2$	$AgIO_3$ (0.2)	1.0	DMF	3	48	1:6
8	$PdCl_2$	$AgIO_3$ (0.2)	1.0	THF	24	26	25:1
9	$Pd(OAc)_2$	$AgIO_3$ (0.2)	1.0	THF	24	3	<1:2
10	$Pd(TFA)_2$	$AgIO_3$ (0.2)	1.0	THF	24	4	1:1
11	$Pd(PhCN)_2Cl_2$	$AgIO_3$ (0.2)	1.0	THF	24	31	>30:1
12	$Pd(PhCN)_2Cl_2$	$AgIO_3$ (1.0)	1.0	THF	24	39	35:4
13	$Pd(TPTP)_2Cl_2$[d]	$AgIO_3$ (1.0)	1.0	THF	24	51	9.2:1
14	**$Pd(TPTP)_2Cl_2$**	**$AgIO_3$ (1.0)**	2.0	**THF**	**24**	**77**	**10:1**
15	$Pd(PPh_3)_2Cl_2$	$AgIO_3$ (1.0)	2.0	THF	24	73	8.1:1
16	$Pd(TPTP)_2Cl_2$	$AgIO_3$ (1.0)	2.0	THF	3	69	16:1
17	$PdCl_2$	$AgIO_3$ (1.0)	1.0	DMF	3	79	1:6.8
18	$PdCl_2$	$AgIO_3$ (1.0)	2.0	DMF	3	83	1:9.4
19	**$PdCl_2$**	**$AgIO_3$ (1.0)**	2.0	**DMF**	**1**	**99**	**1:5.2**
20	$PdCl_2$	$AgIO_3$ (1.0)	2.0	DMF	24	60	1:7.6
21[e]	$Pd(TPTP)_2Cl_2$	$AgIO_3$ (1.0)	2.0	THF	24	75	6:1
22[f]	$Pd(TPTP)_2Cl_2$		2.0	THF	24	0	
23[g]	$Pd(TPTP)_2Cl_2$	$AgIO_3$ (1.0)	2.0	THF	24	23	21:2
24[e]	$PdCl_2$	$AgIO_3$ (1.0)	2.0	DMF	1	92	1:6
25[f]	$PdCl_2$		2.0	DMF	1	0	
26[g]	$PdCl_2$	$AgIO_3$ (1.0)	2.0	DMF	1	67	6:61
27	$Pd(TPTP)_2Cl_2$	$AgIO_3$ (1.0)	2.0	DMF	1	36	1:3
28[h]	$PdCl_2$	$AgIO_3$ (1.0)	2.0	DMF	10 min	25	11:14

[a]Reaction conditions: 2,6-dimethoxybenzoic acid **1a**, *trans*-cinnamaldehyde **2a** (1.0 equiv), [Pd] (0.1 equiv), [Ag], solvent (2 mL), 120 °C. [b]NMR yield of isomeric mixture and mesitylene as internal standard. [c]Z/E ratios were determined by NMR of the crude reaction mixture. [d]TPTP: tri(*p*-tolyl)phosphine. [e]Conducted on gram scale. [f]O_2 as the oxidant. [g]Using 5 mol % of [Pd]. [h]Conducted under microwave irradiation (120 °C, 10 min).

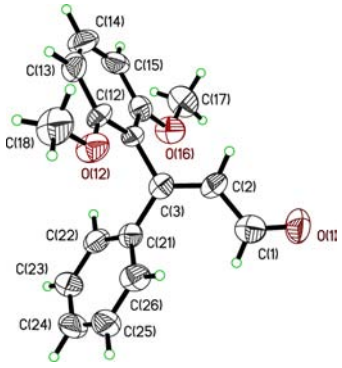


Figure 1. ORTEP view of the X-ray diffraction structure of **3a-*E*** showing one of the two independent, but conformationally identical, molecules in the unit cell.

h and obtained 99% combined yield with 1:5.2 Z/E ratio under DMF conditions (Table 1, entries 18−20). We also found that using O_2 instead of $AgIO_3$ cannot give the product in DMF or THF (Table 1, entries 22 and 25), and lowering the loading of [Pd] resulted in the decrease of the yields (Table 1, entries 23 and 26). Use of the $Pd(TPTP)_2Cl_2/AgIO_3$ system in DMF instead of THF still generated the *E*-isomer as the major product (Table 1, entry 27), which means that the ligand did not govern the Z/E selectivities. We used a microwave to heat the reaction for 10 min in DMF. The yield and the Z/E selectivity were all unsatisfactory (Table 1, entry 28). In addition, we conducted large-scale reactions, and the results revealed that this catalytic system was effective in the gram-scale reaction (Table 1, entries 21 and 24).

Under the optimized THF conditions (Table 1, entry 14) and DMF conditions (Table 1, entry 19), the scope of this reaction was investigated (Scheme 1). All examples listed in Scheme 1 have highly uniform Z/E selectivities: *Z*-isomers were preferred under the THF conditions (up to 20:1 Z/E ratio), whereas DMF gave the *E*-isomers predominantly (up to 1:19 Z/E ratio). Substituents on the benzene ring of acid **1** have a significant impact on this reaction and the yields, both under THF and DMF conditions. All di-*ortho*-substituted electron-rich carboxylic acids **1** offered the corresponding products effectively; other benzoic acids are not effective in the reactions (see the Supporting Information). On the other hand, cinnamaldehydes bearing electron-donating or electron-withdrawing substituents on the benzene ring underwent the reaction smoothly, although decreased yields were observed in some cases. An aliphatic unsaturated aldehyde, *trans*-2-pentenal,

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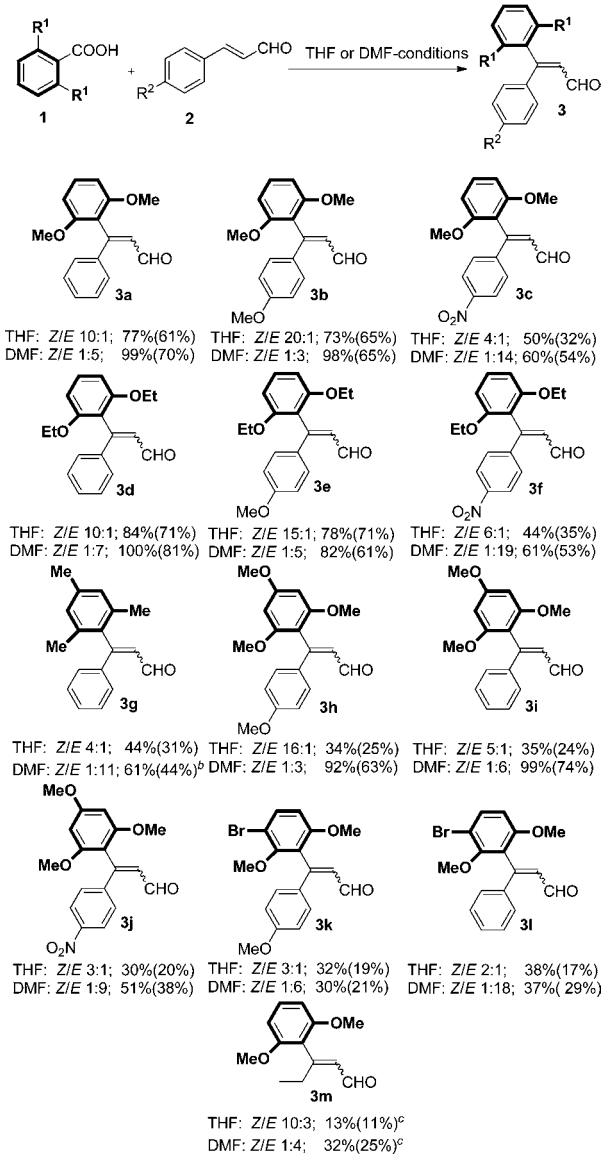
Scheme 1. Substrate Scope for Decarboxylative Heck Arylations of Cinnamaldehydes[a]

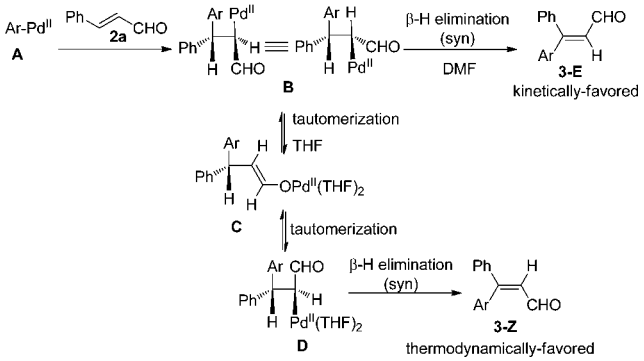


[a]THF conditions: acid **1** (2.0 equiv), *trans*-cinnamadehyde **2** (1.0 equiv), $AgIO_3$ (1.0 equiv), $Pd(TPTP)_2Cl_2$ (0.1 equiv), THF (2 mL), 3−24 h, 120 °C. DMF conditions: acid **1** (2.0 equiv), *trans*-cinnamadehyde **2** (1.0 equiv), $AgIO_3$ (1.0 equiv), $PdCl_2$ (0.1 equiv), DMF (2 mL), 0.3−4 h, 120 °C. NMR yields of isomeric mixture using mesitylene as internal standard are shown and isolated yields of the major isomer are in parentheses; *Z*/*E* ratios were determined by NMR of the crude reaction mixture. [b]Prepared using 0.2 equiv of $PdCl_2$ at 150 °C. [c]Isolated yields of isomeric mixture of **3m** are in parentheses.

could also give the Heck-type coupling product with good *Z*/*E* selectivity but in lower yields (Scheme 1, **3m**). In addition, (*E*)-4-phenyl-3-buten-2-one and *trans*-cinnamonitrile were also tested (see the Supporting Information). *trans*-Cinnamonitrile can give the same selective trend and generate *E*-isomer as the major product under DMF conditions and the *Z*-isomer under THF conditions. However, (*E*)-4-phenyl-3-buten-2-one gave the *Z*-isomer as the major product under THF and DMF conditions. This means the structures of the substrates can affect the *Z*/*E* selectivities.

In order to explain the origin of the dramatic change of geometrical *Z*/*E* selectivity caused by changing reaction solvent, we utilized both experimental and theoretical means. The reactions under THF conditions require a longer time to complete than the ones under DMF conditions. Shortening the reaction time under THF conditions (Table 1, entries 14 and 16) or prolonging the time under DMF conditions (Table 1, entries 19 and 20) had no effect on *Z*/*E* selectivity, and no interconversion between the two isomers was observed. Furthermore, the configuration of the double bond remained unchanged after heating the pure *E*-isomer under THF conditions (see Supporting Information). Preliminary density functional theory (DFT) calculations revealed that the *Z*-isomer of **3a** is more stable than the *E*-isomer. The relative Gibbs free energy of **3a-Z** is about 2.25 and 2.40 kcal/mol lower than that of **3a-E** in THF and DMF, respectively. More interestingly, DFT calculations also revealed that THF could play a beneficial role in the generation of the Pd(II) enolate (Scheme 2, **C**). According to the DFT calculations, however, palladium enolate could not be formed in DMF.

Scheme 2. Plausible Reaction Mechanism



On the basis of these experimental and theoretical results, a possible mechanism to explain the *Z*/*E* selectivity is proposed in Scheme 2. The syn insertion of arylpalladium(II) species **A** to *trans*-cinnamaldehyde **2a** generates σ-palladium(II) complex **B**, which directly undergoes syn β-hydride elimination to give the kinetically favored **3-*E*** in DMF; whereas in THF, intermediate **B** can tautomerize to form palladium(II) enolate **C**, which is also in equilibrium with intermediate **D**. The thermodynamically favored **3-Z** is then formed after syn β-hydride elimination of **D**. According to the above mechanism, *cis*-cinnamaldehyde should give *Z*-product under both conditions. However, we found that *cis*-cinnamaldehyde was very unstable and could isomerize to the *trans*-isomer quickly under the reaction conditions. Thus, *cis*-cinnamaldehyde also gave *E*-product under DMF conditions and *Z*-product under THF conditions, respectively (see the Supporting Information).

In summary, we have developed a method for controlling the *Z*/*E* selectivity of palladium-catalyzed decarboxylative Heck-type arylations of trans-cinnamaldehydes by "switching the solvent". The *Z*-isomers can be obtained in good yield and stereoselecitivity in THF, whereas the use of DMF as solvent provided kinetically favored *E*-isomers. The *Z*/*E* selectivity switch can be explained by the standard Heck-type addition−elimination process in DMF and the tautomerization of Pd(II) enolate in THF, which lead to the more stable *Z*-isomer.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental details, procedures, compound characterization data, and copies of ^{1}H and ^{13}C spectra for all compounds, selected ^{1}H spectra of the crude reaction mixture, selected NOESY spectra, X-ray crystal structures (CIF) of compound **3a-*E***, isomerization experiment of **3d-*E***, and DFT results of **3a-*Z***, **3a-*E*** and palladium(II) enolate. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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