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Enantioselective total synthesis of furofuran lignans via Pd-catalyzed asymmetric allylic cycloadditon of vinylethylene carbonates with 2-nitroacrylates

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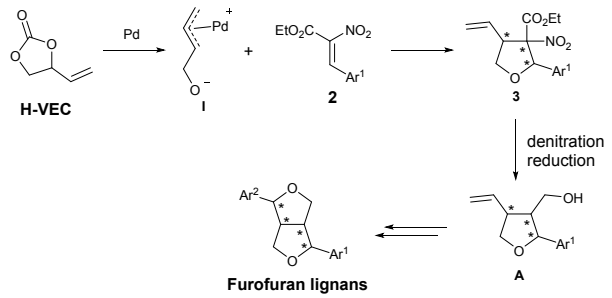
Herein, a practical and efficient approach to tetrahydrofurans with three-stereocenters has been developed through Pd-catalyzed asymmetric allylic cycloaddition of vinylethylene carbonates (VECs) with 2-nitroacrylates under mild conditions. By using this asymmetric catalytic reaction as a key step, several furofuran lignans with stereodivergency have been effectively synthesized through 5- or 6-step sequences from readily available starting materials.

Furofuran lignans, which possesses a wide variety of structures due to linkage patterns, different substituents and diverse configurations, are found in numerous plants.[1] A wide range of biological activities, including antitumor, antioxidant, antihypertensive, antidiabetic, anti-inflammatory and antiviral activities have been reported for this kind of natural product over the past decades.[2] In contrast, with more than 100 isolated furofuran lignans, enantioselective total synthesis of furofuran lignans is relatively underdeveloped.[3] In 1988, Takano and co-workers first reported asymmetric total synthesis of several furofuran lignans starting from diethyl L-tartrate in more than 15 steps.[4] Although several routes for the enantioselective synthesis of furofuran natural products have been documented,[5] most of them rely on approaches of chiral pool or chiral auxiliary induced asymmetric synthesis through longer-step transformations. Most recently, Kan and Hamashima reported the asymmetric total synthesis of several furofuran lignans by using an organocatalytic asymmetric aldol reaction as a key step through a 9-step sequence.[6] In fact, although various biological activities have been investigated to date, many furofuran lignans have never been biologically studied. In addition, the mode of action and the structure-activity relationship remains elusive. Therefore, the development of general and practical synthetic routes for enantioselective total synthesis of furofuran lignans is not only meaningful for synthetic organic chemistry, but also will play a significant role in promoting biological studies of furofuran lignans.



Scheme 1 The Plane for Enantioselective total synthesis of furofuran lignans via Pd-catalyzed asymmetric allylic cycloaddition

Pd-catalyzed allylic cycloaddition of allylic donors with unsaturated electrophiles became one of the most powerful methods for the construction of carbocycles and heterocyclic compounds.[7] Vinyl epoxides[8] and vinylethylene carbonates (VECs)[9,10] have served as efficient C,O-dipoles for Pd-catalyzed asymmetric allylic cycloaddition to furnish oxo-cyclic compounds. Most recently, we developed Pd-catalyzed asymmetric allylic cycloaddition of VECs with various unsaturated electrophiles to afford valuable oxo-heterocycles with high efficiency.[9] We found that the formal [3+2] cycloaddition of VECs with Michael acceptors can be realized to afford tetrahydrofurans with multi-stereocenters in excellent enantio- and diasteroselective control.[9d,f,j] Inspired by these results, we are interested in the enantioselective total synthesis of furofuran lignans by the Pd-catalyzed asymmetric allylic cycloaddition of VECs with Michael acceptors. As shown in Scheme 1 for our synthetic plan, we envisioned that the Pd-catalyzed allylic cycloaddition of H-VEC as a commercially available and cheap monomer for polymer synthesis with 2-nitro-3-arylacrylates **2** could afford tetrahydrofurans **3**, which can readily convert into intermediates A by denitration and ester reduction. Furofuran lignans can be synthesized from

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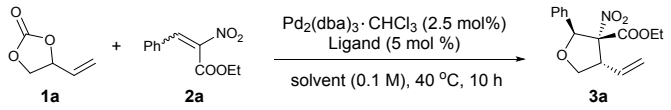
Electronic Supplementary Information (ESI) available: [Detailed experimental procedures; characterization data of all of the new compounds; copies of HPLC chromatographies, ^{1}H and ^{13}C NMR spectra of the products.]. See DOI: 10.1039/x0xx00000x

intermediates A through olefin oxidation followed by addition of Grignard reagents by a known process.[4] In our previous study, we found that stronger electrophilicMichael acceptors are required for the allylic cycloaddition reaction. Therefore, in most cases double activated Michael acceptors are needed, which is the reason why we have chosen 2-nitroacrylates as reaction partners instead of α,β-unsaturated esters. Herein, we report the palladium-catalyzed asymmetric allylic cycloaddition of VECs with 2-nitroacrylates to construct the tetrahydrofuran skeleton with three stereocenters in high yields with excellent enantio- and diastereoselective control. With this efficient asymmetric catalytic transformation as a key step, the enantioselective total synthesis of furofuran lignans with stereodivergency has been presented.

Table 1 Optimization conditions for the Pd-catalyzed allylic cycloaddition of H-VEC **1a** with ethyl 2-nitro-3-phenylacrylate (**2a**) [a]

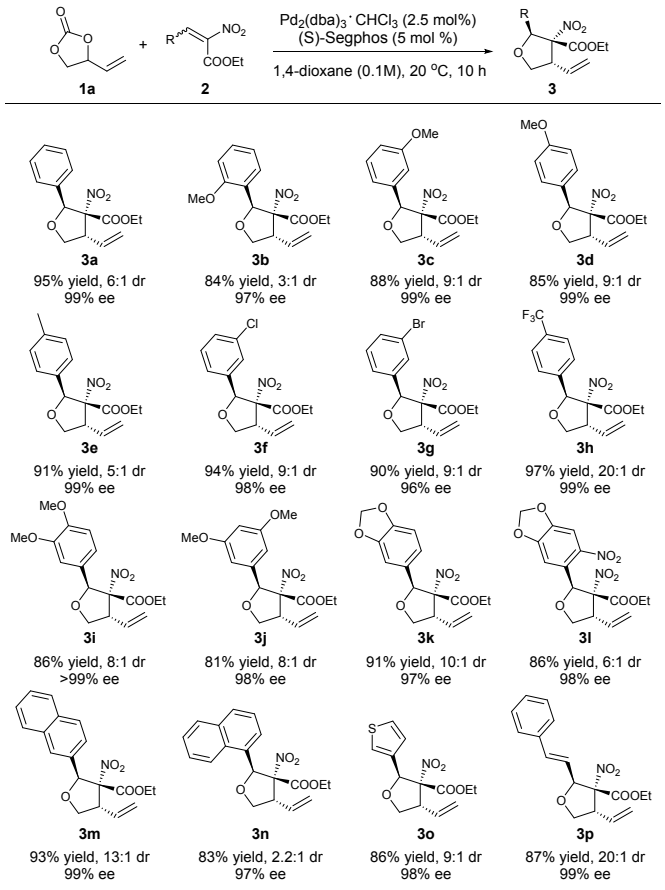


entry	ligand	solvent	T (°C)	yield (%)[b]	ee (%)[c]	dr[d]
1	phosphoramidite[e]	THF	40	NR	-	-
2	(*R*)-BINAP	THF	40	85	-93	2:1
3	(*S*)-Segphos	THF	40	95	93	2:1
4	(*S*)-Segphos	dioxane	40	94	98	5:1
5	(*S*)-Segphos	toluene	40	65	87	2:1
6	(*S*)-Segphos	CH_2Cl_2	40	NR	-	-
7	(*S*)-Segphos	PhCl	40	81	96	3:1
8	(*S*)-Segphos	dioxane	20	95	99	6:1
9	(*S*)-DM-Segphos	dioxane	20	61	98	2.8:1
10	(*S*)-DTBM-Segphos	dioxane	20	27	91	1.4:1
11	(*R*)-BINAP	dioxane	20	93	-98	4.5:1
12	(*R*)-Tol-BINAP	dioxane	20	83	-98	6:1
13	(*S*)-Xyl-BINAP	dioxane	20	85	95	5:1

[a] Reaction conditions: $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol%), ligand (5 mol%), **1a** (0.24 mmol), **2a** (0.2 mmol)， solvent (2.0 mL), 40 °C, 10 h. [b] Isolated yields of the diastereomeric mixture. [c] Determined by HPLC using a chiral stationary phase. [d] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [e] (*S*)-(3.5-dioxa-4-phosphacyclohepta[2,1-2;3,4-a′]dinaphth -alen-4yl)diisopropylamine.

Initial studies focused on the optimization conditions of Pd-catalyzed asymmetric allylic cycloaddition of H-VEC (**1a)** with ethyl 2-nitro-3-phenylacrylate (**2a**) as standard reaction partners (Table 1). Based on our previous research results, we first conducted the allylic cycloaddition of **1a** with **2a** in the presence of palladium complex generated in situ from $Pd_2(dba)_3{\cdot}CHCl_3$ with chiral phosphoramidite as a ligand. However, the reaction did not proceed at all (entry 1). To our delight, the reaction performed well with (*R*)-BINAP as a ligand in THF at 40 °C for 10 h to afford the desired cycloadduct **3a** in 85% yield with 93% ee (entry 2), albeit the diastereoselectivity was not satisfactory. The reactivity can be improved when the reaction was done with (*S*)-Segphos as a ligand (entry 3). Next, we investigated solvent effects for the reaction using (*S*)-Segphos as a ligand (entries 4-7). As a result, we found that reaction performance can be further improved when the reaction was carried out in 1,4-dioxane to afford the cycloadduct **3a** in 94% yield with 98% ee and a 5:1 diastereomeric ratio (entry 4). By reducing reaction temperature to 20 °C, excellent isolated yield and enantioselectivity were observed and the diastereoselectivity was enhanced to a 6:1 ratio (entry 8). With the conditions of 1.4-dioxane as a solvent under 20 °C, several biaryl-type bisphosphine ligands have been examined for the allylic cycloaddition (entries 9-13). The reactions with Segphos, BINAP, and their analogs all performed well. However, the reaction efficiency could not be further improved.

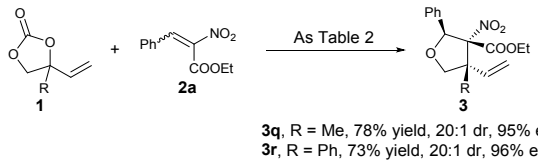
Table 2 Pd-catalyzed allylic cycloaddition of H-VEC **1a** with 2-nitroacrylates **2**[a]



[a] Reaction conditions: $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol%), (*S*)-Segphos (5 mol%), **1a** (0.24 mmol), **2** (0.2 mmol)，1,4-dioxane (2.0 mL), 20 °C, 10 h. The yields are of isolated materials of the diastereomeric mixture. The enantioselectivities were determined by HPLC using a chiral stationary phase. The absolute configuration of **3i** was confirmed by X-ray crystallography (see Supporting Information). Those of the other products were assigned by analogy.

With the optimal conditions (Table 1, entry 8) in hand, the reaction scope was investigated by the reaction of H-VEC (**1a)** with various 3-substituted 2-nitroacrylates **2** (Table 2). Firstly, we examined the allylic cycloaddition of **1a** with **2** bearing methoxy group at different position of the phenyl ring. As a result, all of the reactions proceeded well to afford corresponding cycloadducts **3b**-**3d** in high yields with excellent

enantioselectivities. However, lower diastereoselectivity was observed for the reaction with 3-ortho-methoxylphenyl-2-nitroacrylate **2b**. The reaction of H-VEC (**1a)** with 3-aryl-2-nitroacrylates **2** bearing aryl substituents with different electronic and steric properties performed quite well to furnish the corresponding tetrahydrofurans **3e**-**3l** in high yields with excellent enantioselectivities (up to >99% ee) and good to excellent diastereoselectivities (up to 20:1). A naphthyl group can be installed with high efficiency, albeit lower diastereoselectivity was observed for the reaction with 3-(1-naphthyl)-2-nitroacrylate **2n**. The versatile heteroaromatic, 3-thiophenyl group can also be introduced to afford the cycloadduct **3o** in high yield with excellent enantio- and diastereoselectivity. Significantly, the allylic cycloaddition of **1a** with 2-nitroacrylate **2p** derived from cinnamic aldehyde also proceeded well to afford the corresponding tetrahydrofuran **3p** in high yield with high level of enantio- and diastereoselectivity (99% ee, 20:1 dr). The absolute configuration was unambiguously assigned by X-ray crystallography of tetrahydrofuran **3i** (see the Supporting Information), and those of the other products were assigned by analogy.

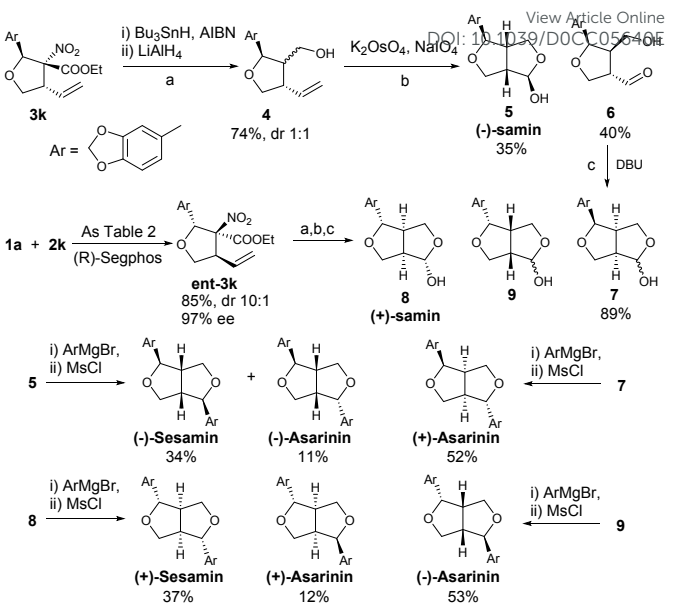


Scheme 2 Pd-catalyzed asymmetric allylic cycloaddition of Me-VEC and Ph-VEC with 2-nitro-3-phenylacrylate **2a**

Next, the Pd-catalyzed asymmetric allylic cycloaddition of substituted VECs with 2-nitro-3-phenylacrylate (**2a)** was investigated (Scheme 2). To our delight, the reactions of Me-VEC and Ph-VEC with **2a** proceeded smoothly under the reaction conditions to afford the corresponding tetrahydrofurans **3q** and **3r** with contiguous tertiary and vicinal quaternary stereocenters in acceptably high yields with excellent enantio- and diastereoselectivities.

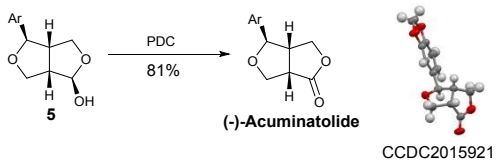
In order to demonstrate the utility of the present allylic cycloaddition reaction, the gram-scale transformation for the reaction of **1a** with 2-nitroacrylate **2k** derived from heliotropin was examined. The allylic cycloaddition on 4 mmol scale was carried out in the presence of 2 mol% of catalyst loading to afford cycloadduct **3k** in high yield (88% yield, 1.2g) with excellent stereoselective control (See Supporting Information).

After the successful realization of the allylic cycloaddition of VECs **1** with 2-nitroacrylates **2**, we next turned our attentions toward enantioselective total synthesis of furofuran lignans. As shown in Scheme 3, the substituted tetrahydrofuran **3k** can be readily converted into compound **4** in 74% yield with a 1:1 diastereomeric ratio by denitration with 2,2-azobisisobutyronitrile (AIBN) and Bu_3SnH followed by ester reduction with $LiAlH_4$. Olefin oxidation of **4** as diastereomeric mixture with K_2OsO_4 and $NaIO_4$ gave hemiacetal **5** [(-)-samin] and aldehyde **6** separated by column chromatography.



Scheme 3 Enantioselective total synthesis of furofuran lignans, Sesamin and Asarinin

Epimerization of compound **6** with DBU afforded hemiacetal **7** as a diastereomeric isomer of **5** in 89% yield. A pair of diastereomers **8** [(+)-samin] and **9** can also be synthesized by the allylic cycloaddition of **1a** with **2k** in the presence of (*R*)-Segphos and subsequent steps of a, b and c. Hemiacetal **5** was attacked by Grignard reagent derived from 4-bromo-1,2-methylenedioxybenzene and followed by cyclization to afford furofuran lignans (-)-Sesamin[11] and (-)-Asarinin[12] respectively in a 3:1 ratio after column chromatography. In the same manner, furofuran lignans (+)-Sesamin[13] and (+)-Asarinin[14] can be obtained from hemiacetal **8**. On the other hand, the transformation of hemiacetal **7** by the Grignard reagent addition and cyclization can afford (+)-Asarinin as the only product in 52% yield. In the same way, hemiacetal **9** gave (-)-Asarinin as the only product. In conclusion, two pairs of enantiomers of 3,4-methylenedioxyphenyl-substituted furofuran lignans could be obtained through the Pd-catalyzed asymmetric allylic cycloaddition of H-VEC (**1a)** with 2-nitroacrylates **2**. In order to further confirm the absolute configuration of the synthesized furofuran lignans, (-)-Acuminatolide[15] was readily synthesized from hemiacetal **5** by PDC oxidation (Scheme 4). The absolute configuration of (-)-Acuminatolide was unambiguously identified by X-ray crystallography (see Supporting Information).



Scheme 4 Enantioselective total synthesis of (-)-Acuminatolide

In conclusion, we have developed a practical and efficient method for enantio- and diastereoselective preparation of the tetrahydrofuran skeleton through Pd-catalyzed asymmetric

allylic cycloaddition of VECs with 2-nitroacrylates. By using palladium-complex generated in situ from $Pd_2(dba)_3{\cdot}CHCl_3$ and Segphos as a catalyst under mild conditions, tetrahydrofurans with three-stereocenters can be obtained from the readily accessible reaction partners in high yields with excellent enantio- and diastereoselective control. By using this practical asymmetric catalytic reaction as a key step, furofuran lignans with different stereo properties have been synthesized by 5 or 6 step transformations. We believe that this work provided the most efficient approach to enantiomerically pure furofuran lignans, which will promote biological study of this kind of natural product.

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Conflicts of interest

The authors declare no conflicts of interest.

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