Asymmetric Catalysis

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Palladium-Catalyzed Asymmetric Decarboxylative Cycloaddition of Vinylethylene Carbonates with Michael Acceptors: Construction of Vicinal Quaternary Stereocenters**

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Abstract: *An efficient method for the diastereo- and enantioselective construction of vicinal all-carbon quaternary stereocenters through palladium-catalyzed decarboxylative cycloaddition of vinylethylene carbonates with activated Michael acceptors was developed. By using a palladium complex generated in situ from $[Pd_2(dab)_3]\cdot CHCl_3$ and a phosphoramidite ligand as a catalyst under mild reaction conditions, the process provides multifunctionalized tetrahydrofurans bearing vicinal all-carbon quaternary stereocenters in high yields with a high level of absolute and relative stereocontrol.*

The development of catalytic transformations that enable rapid access to complex molecules with multiple stereogenic centers is a principal goal in asymmetric catalysis and green chemistry.[1] These processes become more useful and challenging if the target molecules contain two vicinal all-carbon quaternary stereogenic centers.[2] Although substrate-directed diastereoselective approaches for the formation of vicinal all-carbon quaternary stereocenters are available to this end,[3] catalytic asymmetric methods for the diastereo- and enantioselective construction of these challenging skeletons remain largely unexplored.[4] One of the difficulties is low reactivity due to steric repulsion that occurs in the carbon–carbon bond formation step. It is also difficult to control the absolute and relative stereochemistry because of steric congestion and the diminished steric difference between the nonhydrogen substituents. Therefore, an efficient approach to the formation of vicinal all-carbon stereocenters in a single synthetic operation and the use of readily available and stable starting materials is highly appealing.

Transition-metal-catalyzed asymmetric interceptive decarboxylative allylations of allylic partners by unsaturated electrophiles are useful methods for the formation of multiple covalent bonds.[5,6] Most recently, we disclosed an useful interceptive decarboxylative allylation process using stable vinylethylene carbonates (VECs) as allylic donors and formaldehyde as an interceptor.[7] In the presence of a chiral palladium phosphoramidite complex as a catalyst, the process afforded tertiary vinylglycol derivatives in high yields with a high level of enantioselectivity. Based on these research results, we envisioned that vicinal all-carbon quaternary stereocenters could be constructed through the decarboxylative cycloaddition of VECs with activated Michael acceptors.[8] As illustrated in Figure 1, the zwitterionic π-allylpalladium intermediate **A**, which is generated from VECs **1** through a decarboxylative process, could attack Michael acceptors **2** to afford intermediate **B** bearing a nucleophilic tertiary carbon anion and the 1,1-disubstituted allylpalladium. The subsequent carbon–carbon bond formation of two tertiary carbons could be feasible to form favored tetrahydrofurans **3** with vicinal all-carbon stereocenters. Herein, we report the palladium-catalyzed asymmetric decarboxylative cycloaddition of VECs with activated Michael acceptors to construct highly functionalized tetrahydrofurans with excellent absolute and relative stereocontrol.

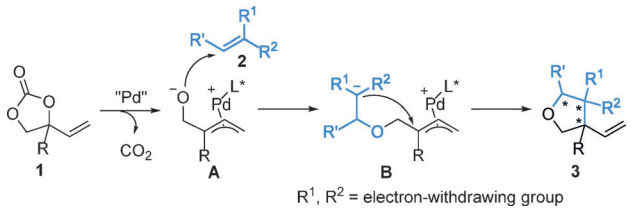

Figure 1. Strategy for palladium-catalyzed decarboxylative cycloaddition of VECs with activated Michael acceptors.

Initial studies focused on the decarboxylative cycloaddition of Ph-VEC **1a** with 2-benzylidenemalononitrile (**2a**). Based on our previous results on the cycloaddition of VECs with formaldehyde, we began our investigation by examining the cycloaddition of **1a** with **2a** in the presence of a palladium(0) catalyst bearing different phosphoramidite ligands[9] (Table 1, entries 1–7). To our delight, the reaction proceeded smoothly with phosphoramidite **L2** bearing diisopropylamino groups as a ligand in THF at 20 °C for 15 h to afford the desired cyclized product **3aa** in 98% yield with excellent

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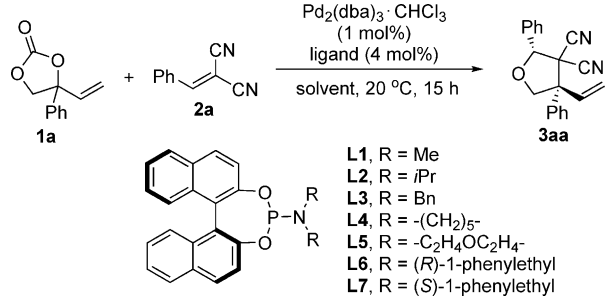
Table 1: Optimization studies on the palladium-catalyzed decarboxylative cycloaddition of Ph-VEC **1a** with 2-benzylidenemalononitrile (**2a**).[a]



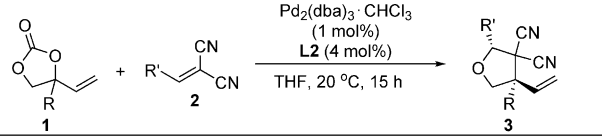
Entry	Ligand	Solvent	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**L1**	THF	85	1.6:1	75
2	**L2**	THF	98	14:1	94
3	**L3**	THF	96	1.7:1	62
4	**L4**	THF	trace	–	–
5	**L5**	THF	trace	–	–
6	**L6**	THF	48	2.3:1	38
7	**L7**	THF	20	1.9:1	35
8	**L2**	toluene	87	10:1	72
9	**L2**	CH_2Cl_2	97	4:1	62
10	**L2**	Et_2O	98	7:1	78
11	**L2**	CH_3CN	95	2.6:1	38
12	**L2**	DMF	82	2.2:1	34

[a] Reaction conditions: $[Pd_2(dba)_3]\cdot CHCl_3$ (1.0 mol%), ligand (4.0 mol%), **1a** (0.22 mmol), **2a** (0.2 mmol), solvent (1.0 mL), 20°C, 15 h. [b] Yield of isolated product included two diastereomers. [c] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [d] Determined by HPLC using a chiral stationary phase.

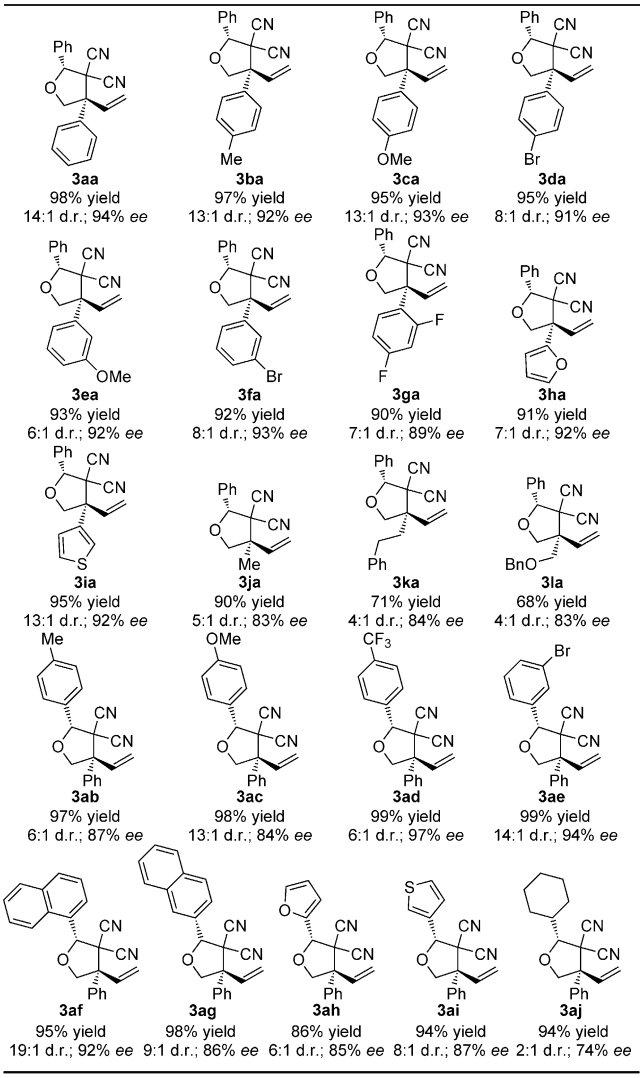
diastereo- and enantioselectivity (14:1 d.r.; 94% *ee*, entry 2). Interestingly, the reaction efficiency was clearly sensitive to the structure of ligand. When using ligands **L1** or **L3**, the reactions gave the product **3aa** with low diastereoselectivity and moderate enantioselectivity (entries 1 and 3). Ligands **L4** and **L5** were almost ineffective for the reaction (entries 4 and 5), and the diastereomeric phosphoramidite ligands **L6** and **L7** were also less effective (entries 6 and 7). The reaction also proceeded well in other solvents such as toluene, CH_2Cl_2, diethyl ether, acetonitrile, and DMF; however, relatively low diastereo- and enantioselectivities were observed (entries 8–12).

With the optimal conditions in hand, the generality of this protocol was evaluated by the combination of a variety of substituted VECs **1** and substituted methylenemalononitriles **2** (Table 2). Remarkably, various VECs **1a–1g** with substituted aryl groups bearing different electronic and steric properties were cyclized with 2-benzylidenemalononitrile (**2a**) to furnish the corresponding highly functionalized tetrahydrofurans **3aa–ga** in high yields with excellent diastereo- and enantioselectivity. In addition, the reaction of VECs with versatile furan and thiophene moieties proceeded smoothly to afford **3ha** and **3ia** in high yields with a high level of stereoselectivity. The process also worked well for alkyl-VECs **1j–1l**, however, the reaction efficiencies were slightly decreased. Next, we examined the cycloaddition of **1a** with substituted methylenemalononitriles **2** under the standard conditions. As shown in Table 2, various 2-aryl-substituted

Table 2: Pd-catalyzed decarboxylative cycloaddition of VECs **1** with 2-substituted methylenemalononitriles **2**.[a]



1a, R = Ph; **1b**, R = 4-MeC_6H_4; **1c**, R = 4-$MeOC_6H_4$; **1d**, R = 4-BrC_6H_4; **1e**, R = 3-$MeOC_6H_4$; **1f**, R = 3-BrC_6H_4; **1g**, R = 2,4-FC_6H_3; **1h**, R = 2-furanyl; **1i**, R = 3-thiophenyl; **1j**, R = Me; **1k**, R = 2-phenylethyl; **1l**, R = benzyloxymethyl; **2a**, R' = Ph; **2b**, R' = 4-MeC_6H_4; **2c**, R' = 4-$MeOC_6H_4$; **2d**, R' = 4-$CF_3C_6H_4$; **2e**, R' = 3-BrC_6H_4; **2f**, R' = 1-naphthyl; **2g**, R' = 2-naphthyl; **2h**, R' = 2-furanyl; **2i**, R' = 3-thiophenyl; **2j**, R' = cyclohexyl



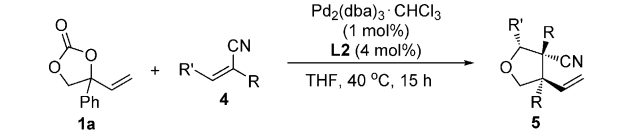
[a] Reaction conditions: $[Pd_2(dba)_3]\cdot CHCl_3$ (1.0 mol%), **L2** (4.0 mol%), **1** (0.22 mmol), **2** (0.2 mmol), THF (1.0 mL), 20°C, 15 h. Yield of isolated product included two diastereomers. The diastereomeric ratio was determined by ^{1}H NMR spectroscopy of the crude reaction mixture. The enantiomeric excess was determined by HPLC using a chiral stationary phase. The absolute configuration of **3ae** was determined by X-ray crystallography for the corresponding amide **6** (see Scheme 1). Those of the other products were assigned by analogy.

methylenemalononitriles **2b–2g** with different electronic and steric properties were tolerated under the reaction conditions, thus affording the corresponding tetrahydrofurans **3ab–ag** in high yields with excellent diastereo- and enantioselectivity.

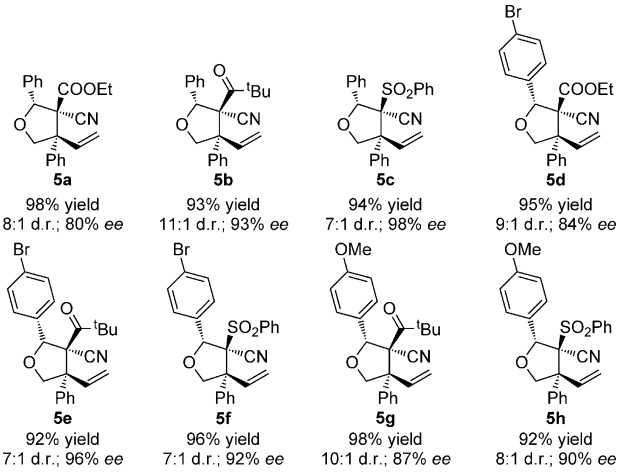
Importantly, the versatile 2-furanyl and 3-thiophenyl substituents also can be installed in the 2-position of the tetrahydrofuran ring giving high yields and good diastereo- and enantioselectivity. The reaction with 2-alkyl-substituted methylenemalononitrile **2j** still proceeded smoothly, however, lower diastereo- and enantioselectivity were observed.

After the successful realization of the cycloaddition of VECs with malononitrile derivatives, we subsequently turned our attention toward the elaboration of the cycloaddition with Michael acceptors bearing different electron-withdrawing groups. To our delight, as shown in Table 3, the process

Table 3: Pd-catalyzed decarboxylative cycloaddition of Ph-VEC **1a** with activated Michael acceptors **4**.[a]



4a, R' = Ph, R = COOEt; **4b**, R' = Ph, R = CO^{t}Bu; **4c**, R' = Ph, R = SO_2Ph; **4d**, R' = 4-BrC_6H_4, R = COOEt; **4e**, R' = 4-BrC_6H_4, R = CO^{t}Bu; **4f**, R' = 4-BrC_6H_4, R = SO_2Ph; **4g**, R' = 4-MeOC_6H_4, R = CO^{t}Bu; **4h**, R' = 4-MeOC_6H_4, R = SO_2Ph



[a] Reaction conditions: $[Pd_2(dba)_3]$·$CHCl_3$ (1.0 mol%), **L2** (4.0 mol%), **1a** (0.22 mmol), **4** (0.2 mmol), THF (1.0 mL), 40°C, 15 h. Yield of isolated product included two diastereomers. The diastereomeric ratio was determined by ^{1}H NMR spectroscopy of the crude reaction mixture. The enantiomeric excess was determined by HPLC using a chiral stationary phase. The absolute configuration of **5d** was determined by X-ray crystallography (see the Supporting Information). Those of the other products were assigned by analogy.

allowed to rapidly access multifunctionalized tetrahydrofurans with contiguous tertiary and vicinal quaternary stereocenters. All of the examples gave only two diastereomers with high diastereomeric ratios. Firstly, we conducted the cycloaddition of Ph-VEC **1a** with 2-cyano-3-phenylacrylate **4a** under the standard conditions. Gratifyingly, the reaction afforded cyclized product **5a** in high yield with only two diastereomeric isomers in an 8:1 ratio and good enantioselectivity. The process was also effective for the Michael acceptors of 3-phenyl-2-acylacrylonitrile (**4b**) and 3-phenyl-2-sulfonylacrylonitrile (**4c**), thus affording the corresponding tetrahydrofurans **5b** and **5c** in high yields with excellent diastereo- and enantioselectivities. The Michael acceptors with a bromo or methoxy group on the phenyl ring were well-tolerated under the reaction conditions, furnishing the corresponding products **5d–h** in high yields and high levels of absolute and relative stereocontrol. Thus, although a total of eight stereoisomers could potentially be generated in this transformation, a single stereoisomer predominates in each case.

According to the proposed reaction pathway as shown in Figure 1, the reaction likely undergoes reversible Michael addition and a subsequent stereochemistry-determining cycloaddition. The absolute configuration of C-4 of the cyclized products **3** and **5** is the same than that of the cycloaddition products from VECs with formaldehyde in our previous work.[7] The origin of stereochemistry of this process could be explained by our previous proposed stereochemical model. Thus, our working hypothesis is that the reaction proceeds via the conformationally favored chair-like intermediate **B′** to afford cyclized products with high levels of diastereo- and enantioselectivity (Figure 2).

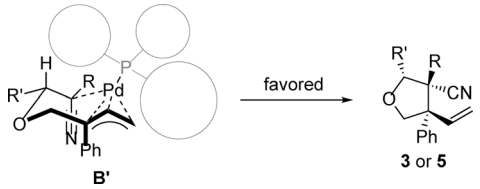
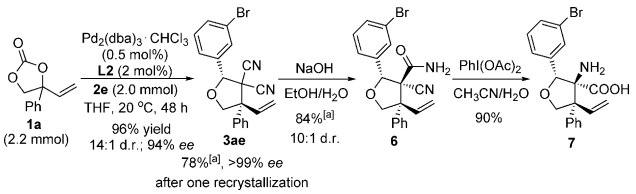


Figure 2. Proposed intermediate and plausible stereochemical outcome.

The synthetic versatility of the present protocol was demonstrated by the scale-up of the transformation and product derivatization. The cycloaddition reaction of Ph-VEC **1a** with 2-(3-bromobenzylidene)malononitrile (**2e**) on the 2.0 mmol scale proceeded well to afford the cycloadduct **3ae** in 78% yield with more than 99% *ee* after a single recrystallization (Scheme 1). Notably, the tetrahydrofuran



Scheme 1. Elaboration of the cycloaddition product **3ae**. [a] Yield for a single diastereomer.

3ae with a dinitrile group could be selectively hydrolyzed[10] to the corresponding amide **6** to create vicinal quaternary stereocenters with high diastereoselectivity (Scheme 1). The absolute configuration of **6** was unambiguously assigned by X-ray crystallography (see the Supporting Information). The compound **6** could be efficiently converted into the corresponding amino acid **7** in the presence of phenyl iodoacetate

through Hoffman rearrangement and hydrolysis in a one-pot operation.

In conclusion, we have developed an efficient method for the diastereo- and enantioselective construction of vicinal all-carbon quaternary stereocenters through palladium-catalyzed asymmetric decarboxylative cycloaddition of VECs with activated Michael acceptors. By using a palladium complex generated in situ from $[Pd_2(dab)_3]\cdot CHCl_3$ and phosphoramidite **L2** as a catalyst under mild conditions, the cycloaddition reaction afforded multifunctionalized tetrahydrofurans bearing contiguous tertiary and vicinal quaternary stereocenters in high yields and with high levels of diastereo- and enantioselectivity. The synthetic utility of the process was demonstrated by the scale-up of the transformation and product derivatization. Further studies to extend the scope of the decarboxylative cycloaddition of VECs are currently underway and will be reported in due course.

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