Asymmetric Catalysis

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Palladium-Catalyzed Decarboxylative Cycloaddition of Vinylethylene Carbonates with Formaldehyde: Enantioselective Construction of Tertiary Vinylglycols**

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Abstract: *An efficient method for the enantioselective construction of tertiary vinylglycols through a palladium-catalyzed asymmetric decarboxylative cycloaddition of vinylethylene carbonates with formaldehyde was developed. By using a palladium complex generated in situ from $[Pd_2(dba)_3]\cdot CHCl_3$ and a phosphoramidite ligand as a catalyst under mild reaction conditions, the process allows conversion of racemic 4-substituted 4-vinyl-1,3-dioxolan-2-ones into the corresponding 1,3-dioxolanes, as methylene acetal protected tertiary vinylglycols, in high yields with good to excellent enantioselectivities.*

Chiral tertiary alcohols are prevalent motifs in a variety of important medicinally relevant agents and biologically active natural products. Enantioselective construction of tertiary alcohols is therefore an important objective in asymmetric catalysis.[1] The most common approach to enantioenriched tertiary alcohols includes transition-metal- or organocatalyzed asymmetric addition of carbon nucleophiles to ketones.[1a] Nevertheless, some difficulties associated with the use of ketone electrophiles for this approach have emerged, difficulties such as relatively low reactivity and challenging carbonyl enantiofacial differentiation. Asymmetric catalytic dihydroxylation[2] or epoxidation[3] of 1,1-disubstituted alkenes are useful methods for the synthesis of tertiary alcohols. However, relatively low enantioselectivities are usually obtained when the two alkene substituents are of similar steric demand. Although some other approaches are available to date,[4] the development of new efficient methods for the construction of enantioenriched tertiary alcohol derivatives is still a challenging task.

Transition-metal-catalyzed enantioselective allylic substitution with O-nucleophiles is a powerful method for the synthesis of secondary allylic alcohol derivatives.[5] However, regioselective construction of tertiary allylic ethers using this method for 1,1- or 3,3-disubstituted allylic electrophiles is difficult to achieve.[6,7] Although palladium-catalyzed asymmetric etherification of 2-substituted-2-vinyloxiranes with trialkylborane as a cocatalyst is an effective method for furnishing tertiary allylic ethers regioselectively,[8] the reaction conditions need to be carefully controlled to suppress the potential of the primary alcohol of the product acting as a nucleophile for the substrate. In addition, the process is less effective for 2-aryl-substituted vinyloxiranes.[8a] Most recently, palladium-catalyzed asymmetric interceptive decarboxylative allylations of allylic partners by unsaturated electrophiles have attracted a great deal of attention.[9] Inspired by this synthetic strategy, we envisioned that substituted vinylethylene carbonates[10] (VECs; **1**) could undergo the decarboxylative process to afford the zwitterionic π-allylpalladium intermediates **A** and **B** (Figure 1). We also reasoned that

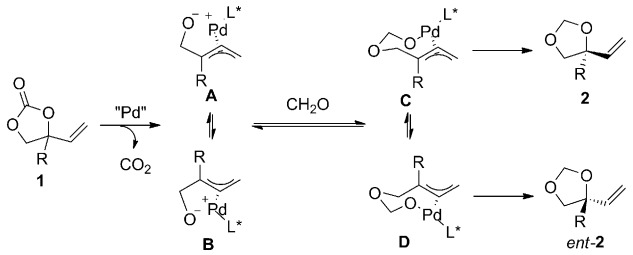

Figure 1. Strategy for palladium-catalyzed decarboxylative cycloaddition of VECs with formaldehyde.

formaldehyde, an abundant feedstock and a reactive one carbon electrophile, could intercept the intermediates to form favored five-membered 1,3-dioxolanes (**2**) regioselectively. We hypothesized that if the isomerization of the diastereomeric π-allylpalladium intermediates **A**/**B** or **C**/**D** occurs faster than subsequent nucleophilic cycloaddition, a dynamic kinetic asymmetric transformation (DYKAT) could be feasible.[11] Herein, we report the successful execution of these ideals and present a palladium-catalyzed asymmetric decarboxylative cycloaddition of the VECs **1** with formaldehyde, a first practical and efficient approach which allows conversion of the racemic 4-substituted 4-vinyl-1,3-dioxolan-2-ones **1** into the corresponding 1,3-dioxolanes **2**, as methylene acetal protected tertiary vinylglycols, in high yields with high levels of enantioselectivities.

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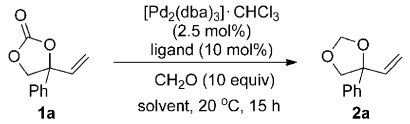
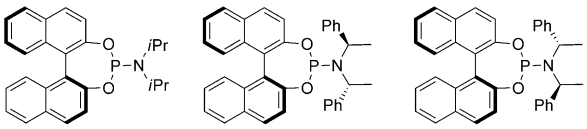
Table 1: Optimization studies.[a]



Entry	Ligand	Solvent	Yield [%][b]	*ee* [%][c]
1	(*R*)-binap	THF	23	40 (*R*)
2	(*S*)-Tol-binap	THF	43	26 (*S*)
3	(*S*)-xylyl-binap	THF	44	16 (*S*)
4	(*S*)-Cl-MeO-biphep	THF	55	19 (*S*)
5	(*S*)-Segphos	THF	22	10 (*S*)
6	(*R*,*R*)-DACH-phenyl	THF	0	–
7	**L1**	THF	82	65 (*R*)
8	(*S*,*R*,*R*)-**L2**	THF	92	84 (*R*)
9	(*S*,*S*,*S*)-**L3**	THF	96	96 (*R*)
10	(*S*,*S*,*S*)-**L3**	1,4-dioxane	82	87 (*R*)
11	(*S*,*S*,*S*)-**L3**	toluene	81	95 (*R*)
12	(*S*,*S*,*S*)-**L3**	CH_2Cl_2	93	82 (*R*)
13	(*S*,*S*,*S*)-**L3**	CyH	37	79 (*R*)
14	(*S*,*S*,*S*)-**L3**	H_2O	68	95 (*R*)
15[d]	(*S*,*S*,*S*)-**L3**	THF	87	90 (*R*)

[a] Reaction conditions: $[Pd_2(dba)_3]\cdot CHCl_3$ (2.5 mol%), ligand (5 mol% for bisphosphanes; 10 mol% for phosphoramidites), **1a** (0.2 mmol), formaldehyde (2.0 mmol, 37% aqueous solution), solvent (1.0 mL), 20°C, 15 h. [b] Yield of isolated product. [c] Determined by HPLC using a chiral stationary phase. The absolute configuration was confirmed by the deprotection of **2a** to the corresponding diol, and the comparison of the sign of optical rotation with that reported in the literature.[13] [d] The reaction was carried out with 5 equiv of paraformaldehyde. Cl-MeO-biphep = 5,5'-dichloro-6,6'-dimethoxy-2,2'-bis(diphenylphosphino)-1,1'-biphenyl, binap = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, dba = dibenzylideneacetone, DACH-phenyl = 1,2-diaminocyclohexane-*N*,*N*'-bis(2'-diphenylphosphinobenzoyl), Segphos = 5,5'-bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole, THF = tetrahydrofuran, CyH = cyclohexane.

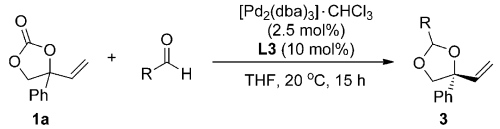


L1 (*S*,*R*,*R*)-**L2** (*S*,*S*,*S*)-**L3**

Initial investigations focused on finding effective chiral ligands for the palladium-catalyzed decarboxylative cycloaddition of the Ph-VEC **1a**, as a standard substrate, with formaldehyde (37% aqueous solution) in THF at 20°C for 15 hours (Table 1). Firstly, we tried different binap-type axially chiral bisphosphane ligands, but the reactions showed low yields and poor enantioselectivities (entries 1–5). Trost's ligand, (*R*,*R*)-DACH-phenyl, was also ineffective for the reaction (entry 6). Through replacement of the bisphosphanes with Feringa's phosphoramidite[12] ligand **L1**, the reaction efficiency was significantly improved to give the desired **2a** in acceptable yield with 65% *ee* (entry 7). To our delight, by employing the diastereomeric phosphoramidite ligands (*S*,*R*,*R*)-**L2** and (*S*,*S*,*S*)-**L3** (entries 8 and 9), we found that the reaction could be promoted dramatically using (*S*,*S*,*S*)-**L3** and it afforded **2a** in 96% yield with excellent enantioselectivity (entry 9). Although the reaction efficiency did not improve further by using other solvents (entries 10–14), it is noteworthy that the reaction could proceed reasonably in pure water to furnish **2a** in 95% *ee* (entry 14). To verify the water effect on the reaction, the reaction was performed with paraformaldehyde, instead of the aqueous solution, under otherwise identical conditions. As shown in entry 15, the reaction proceeded to give **2a** with a slightly lower *ee* value. Treatment of **1a** with $[Pd_2(dba)_3]\cdot CHCl_3$ and (*S*,*S*,*S*)-**L3** in water/THF without formaldehyde did not lead to the formation of the corresponding diol. The starting material **1a** was recovered in practically quantitative yield. These results imply that the reaction undergoes the interception of the zwitterionic π-allylpalladium intermediates by formaldehyde with subsequent cycloaddition as illustrated in Figure 1, and water has no effect on the reaction.[14]

With the optimized reaction conditions in hand, the generality of this protocol was evaluated with a variety of substituted VECs (**1**). Significantly, a wide range of aryl- and alkyl-substituted VECs were tolerated under the reaction conditions, thus affording the corresponding 1,3-dioxolanes **2** in high yields with high levels of enantioselectivities (Table 2). Various substituted aryl VECs having different electronic and steric properties were converted into the corresponding products **2b–k** in high yields (86–98%) with excellent enantioselectivities (91–99% *ee*). In addition, the reactions of VECs with naphthyl, heteroaromatic furan, and thiophene moieties also proceeded smoothly to afford the corresponding **2l**, **2m**, and **2n** in high yields with good to excellent enantioselectivities. The process also worked well for alkyl VECs, thus furnishing the 1,3-dioxolanes **2o–r** in high yields with high *ee* values (82–95% *ee*). Meaningfully, the cycloaddition reaction was also effective for more functionalized VECs, thus providing cyclized products **2s** and **2t** bearing three protected hydroxy groups and a vinyl group at one carbon stereogenic center.

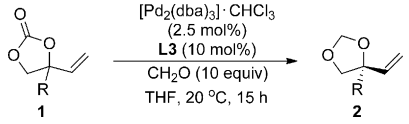
The decarboxylative cycloaddition reaction of VECs with other aldehydes was also examined. As shown in Scheme 1, the reaction conditions were also effective for other aldehydes. Thus, the reaction of **1a** with acetaldehyde (35% aqueous solution) under our standard reaction conditions gave the cyclized product **3a** in high yield with a 1:1 diastereomeric ratio and good enantioselectivity. It is noteworthy that the reactions also proceeded well with aromatic aldehydes (1.2 equiv to **1a**), thus furnishing the corresponding 1,3-dioxolanes **3b** and **3c** in high yields with excellent enantioselectivities for both of the diastereomers. The absolute configuration of quaternary carbon center of **3b** is

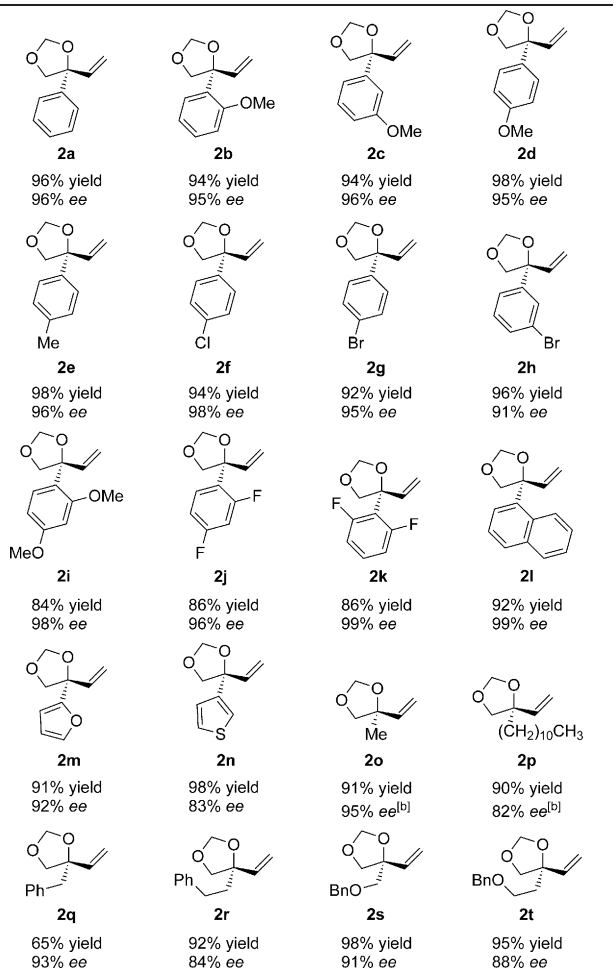


3a,[a] R = Me, 86% yield, *cis*/*trans* =1:1
75% *ee* (*cis*), 87% *ee* (*trans*)
3b,[b] R = 4-$NO_2C_6H_4$, 89% yield, *cis*/*trans* =7:3
98% *ee* (*cis*), 95% *ee* (*trans*)
3c,[b] R = 2-pyridyl, 91% yield, *cis*/*trans* =2:1
91% *ee* (*cis*), 95% *ee* (*trans*)

Scheme 1. Palladium-catalyzed asymmetric decarboxylative cycloaddition of **1a** with aldehydes. [a] Using 10 equiv of acetaldehyde (35% aqueous solution). [b] Using 1.2 equiv of aldehydes.

Table 2: Substrate scope for palladium-catalyzed decarboxylative cycloaddition of VECs with formaldehyde.[a]

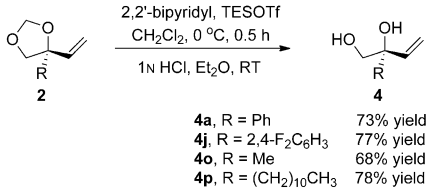




[a] Reaction conditions: $[Pd_2(dba)_3]\cdot CHCl_3$ (2.5 mol%), **L3** (10 mol%), **1** (0.2 mmol), formaldehyde (2.0 mmol, 37% aqueous solution), THF (1.0 mL), 20°C, 15 h. Yields are of isolated materials. The enantioselectivities were determined by HPLC using a chiral stationary phase. [b] The *ee* value was determined by HPLC analysis of their diol mono- or dibenzoyl esters.

same as that of **2a**.[15] Although the catalytic system is less effective for the control of the diasteroselectivity, these results further proved that the reaction undergoes the interceptive decarboxylative allylation pathway as illustrated in Figure 1.

The enantioenriched 1,3-dioxolanes **2** can be readily converted into the corresponding tertiary vinylglycols in good yields without the deterioration of enantiomeric purity (Scheme 2).[16] More significantly, the 1,3-dioxolanes **2** could be useful chiral building blocks for the synthesis of valuable compounds. For example, the enantioenriched **2p** could be a useful compound for the synthesis of the natural product tanikolide.[17] In addition, the 2,4-difluorophenyl-substituted **2j** is an important chiral building block for the preparation of



Scheme 2. Deprotection of 1,3-dioxolanes **2** to diols **4**. TES = triethylsilyl.

triazole antifungal agents[18] such as Genaconazole, Ravuconazole, and Albaconazole.

According to the proposed reaction pathway as revealed in Figure 1, the final cycloaddition step might be the stereochemistry-determining step. Although the true stereochemical outcome of this cycloaddition reaction is complicated, density functional theory (DFT) calculations using the B3LYP/def2-TZVP method (see the Supporting Information for details) were carried out for the geometry optimizations of the four plausible conformers[5c,11] of the π-allylpalladium intermediate **C** (R = Ph) to gain more information of the stereochemistry. As shown in Figure 2, the π-allylpalladium

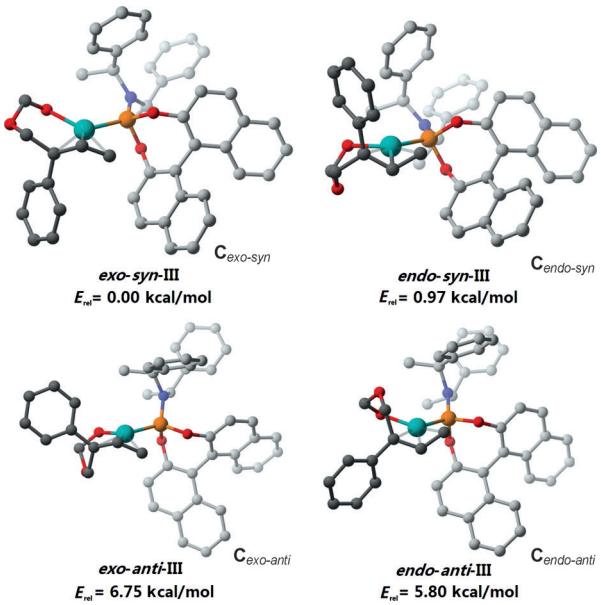


Figure 2. Calculated structures of plausible four isomers of the π-allylpalladium intermediate **C** and their relative energies.

intermediate **C**, having a *syn*-allylic unit (*syn* position between alkoxymethoxymethyl group and C2-proton of allyl group) revealed much lower energies than that with an *anti*-allylic unit. The highly organized intermediate $\mathbf{C}_{exo\text{-}syn}$ is free from steric repulsion between the phenyl ring of allylic group and phenyl group of ligand, (*S*,*S*,*S*)-**L3**, thus revealing the lowest relative energy, and delivering (*R*)-**2a** as the major enantiomer through inner-attack for the cycloaddition.[19]

In conclusion, we have developed an efficient method for the enantioselective construction of methylene acetal protected tertiary vinylglycols by palladium-catalyzed asymmetric decarboxylative cycloaddition of VECs and formaldehyde.

The reactions proceeded smoothly in the presence of $[Pd_2(dba)_3]\cdot CHCl_3$ and the phosphoramidite (*S*,*S*,*S*)-**L3** under mild reaction conditions, thus providing the 4-substituted 4-vinyl-1,3-dioxolanes **2** in high yields (up to 98%) with good to excellent enantioselectivities (82–99% *ee*). The protected tertiary vinylglycols **2** could be useful chiral building blocks for the synthesis of biologically active compounds and natural products. Moreover, the stereochemical outcome of the reaction has been explained by DFT calculations on the geometry optimization of plausible reaction intermediates. 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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