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Highly Efficient Catalytic Formation of (*Z*)-1,4-But-2-ene Diols using Water as a Nucleophile

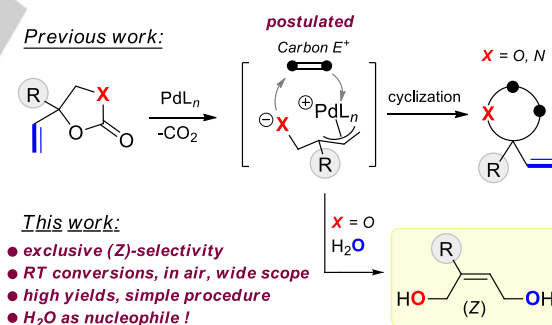
Wusheng Guo,^{[a][b]} Luis Martínez-Rodríguez,^{[a][b]} Eddy Martin,^[a] Eduardo C. Escudero-Adán^[a] and Arjan W. Kleij^{*[a][c]}

Abstract: The first general catalytic and highly stereo-selective formation of (*Z*)-1,4-but-2-ene diols is described from readily available and modular vinyl-substituted cyclic carbonate precursors using water as a nucleophilic reagent. These 1,4-diol scaffolds can be generally prepared in high yields and with ample scope in reaction partners using a simple synthetic protocol that does not require the presence of any additive or any special precaution unlike the stoichiometric approaches reported to date. Control experiments support the mechanistic view that hyper-conjugation within the catalytic intermediate after decarboxylation plays an imperative role to control the stereo-selective outcome of these reactions.

Diols are among the most ubiquitous scaffolds in chemistry being of eminent value to synthetic and polymer chemistry and typically encompassing a wide structural diversity.^[1] The stereoselective and enantio-selective preparation of 1,2-diols has undoubtedly received most of the attention of the synthetic community with the development of the hydrolytic kinetic resolution of epoxides^[2] and the asymmetric *cis*-dihydroxylation of alkenes^[3] representing important milestones in this area. As established for 1,3-diols,^[1a] diastereo-selective preparation of other diol scaffolds remains rewarding but persists to challenge synthetic chemists. In this respect, acyclic unsaturated (*Z*)-configured 1,4-diols have found important applications as transient scaffolds towards the stereo-controlled preparation of vinylcyclopropanes,^[4] vinyl glycinols^[5] and the formation of lactones.^[6] A recent contribution from Hoveyda^[7] has exposed further growth potential of these 1,4-diol synthons in catalytic and stereoselective cross-metathesis furnishing valuable acyclic (*Z*)-allylic alcohols.

Up to now, the limited amount of available strategies for (*Z*)-1,4-but-2-ene diols synthesis have in common that they require stoichiometric chemistry and/or air-sensitive reagents such as DIBAL-H (diisobutylaluminum hydride).^[4,5] Despite the increasing incentive of (*Z*)-1,4-but-2-ene diols in synthetic chemistry, the quest towards an efficient and mild catalytic protocol focusing on such (substituted) 1,4-diol scaffolds still continues.^[8] Inspired by the dearth of catalytic solutions for the stereo-controlled

construction of substituted (*Z*)-but-2-ene diols, we anticipated the use of vinyl-substituted cyclic carbonates as key reaction partners. Previous success with these latter scaffolds demonstrated that decarboxylative functionalization with suitable electrophiles such as Michael acceptors is feasible under mild reaction conditions giving access to furans,^[9a] tertiary vinylglycols^[9b] and highly functional pyrrolidines.^[9c] As an intermediate in these Pd-mediated processes a zwitter-ionic structure was postulated (see Scheme 1). Conceptually, such a charged-separated structure should possess ambivalent reactivity, with the Pd-allyl fragment being highly electrophilic and amenable to react with (very) weak nucleophiles such as water. Examples of catalytic conversions that are based on the use of water as nucleophilic reagent are, however, extremely rare.^[1f,2,10] A successful development of new catalytic methodology towards selective (*Z*)-but-2-ene diol formation by nucleophilic hydration of *in situ* formed allyl surrogates would provide a highly attractive new route towards these synthetically useful scaffolds. Here we disclose such a conceptually new and highly efficient approach for (*Z*)-but-2-ene diols that is based on a decarboxylative hydration of readily available vinyl-based cyclic carbonates under mild operating conditions (Scheme 1).



Scheme 1. A previously postulated zwitterionic Pd-allyl intermediate and current approach towards (*Z*)-1,4-but-2-ene diols using H₂O as nucleophile.

The screening phase towards appropriate reaction conditions for the synthesis of unsaturated 1,4-diol compound **1** started off with the use of vinyl carbonate **A** and using various Pd precursors and phosphine ligands (Table 1). Various Pd precursors were tested including the well-known and reactive White catalyst.^[11] We first screened various mono- and bidentate ligands (**L1–L8**) combined with this precursor using DMF as solvent.^[12] Whereas the use of mono-dentate phosphine ligands **L1–L5** (entries 1–5) did not result in any observable formation, to our delight the presence of bidentate phosphines **L6–L8** (entries 6–8) proved to be highly beneficial for the formation of the desired 1,4-but-2-ene diol **1** under ambient conditions (see also Table S1, Supporting

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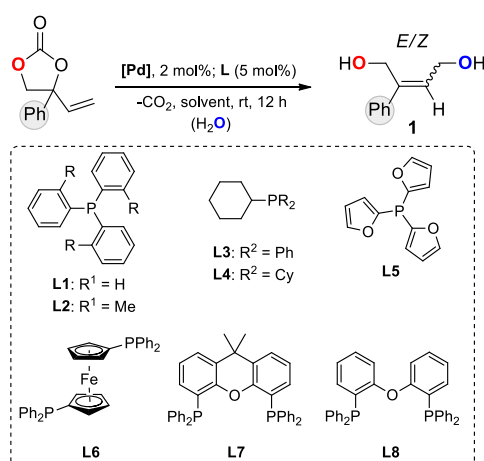
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Information). Moreover, ^1H NMR analysis supported the exclusive formation of the (*Z*)-configured product (*Z/E* >99:1). Further screening (entries 9-13) of other Pd precursors in the presence of **L8** showed $\text{Pd}(\text{dba})_2$ and $[\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3]$ (dba = dibenzylideneacetone) to be competitive precursors, but to avoid any potential problem related to the stability of these Pd precursors we decided to continue with the air-stable White precursor. Other solvents than DMF were probed (entries 14–17) but these showed inferior yields of **1** underlining the crucial importance of the polarity of the medium.

Table 1. Optimization of conditions in the synthesis of (*Z*)-but-2-ene diol **1** varying the Pd precursor, ligand **L** and solvent.^[a]



Entry	Pd precursor	L	Solvent [1M]	Yield ^{[b][c]} [%]
1	Pd/bis-sulfoxide	L1	DMF	0
2	Pd/bis-sulfoxide	L2	DMF	0
3	Pd/bis-sulfoxide	L3	DMF	0
4	Pd/bis-sulfoxide	L4	DMF	0
5	Pd/bis-sulfoxide	L5	DMF	0
6	Pd/bis-sulfoxide	L6	DMF	90
7	Pd/bis-sulfoxide	L7	DMF	95
8	Pd/bis-sulfoxide	L8	DMF	98
9	$[\text{Pd}_2(\text{dba})_3]\cdot\text{CHCl}_3$	L8	DMF	97
10	$\text{Pd}(\text{dba})_2$	L8	DMF	99
11	$\text{Pd}(\text{OAc})_2$	L8	DMF	94
12	Pd/C	L8	DMF	0
13	$\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$	L8	DMF	70
14	Pd/bis-sulfoxide	L8	CH_3CN	40
15	Pd/bis-sulfoxide	L8	MeOH	<1
16	Pd/bis-sulfoxide	L8	CH_2Cl_2	0
17	Pd/bis-sulfoxide	L8	THF	0

[a] Reaction conditions: 0.20 mmol of carbonate, 0.20 mL of solvent, rt; [b] NMR yield using toluene as internal standard, see Supporting Information for details. [c] In all cases the *Z/E* ratio was >99:1 as determined by ^1H NMR.

The optimized conditions reported in entry 8 of Table 1 were then used to investigate the product scope in detail (Figure 1). The R-groups of the vinyl carbonate reagent was systematically varied (for their preparation, see Supporting Information) and provided an entry into a series of substituted (*Z*)-but-2-ene diols **1–28**. In most cases excellent isolated yields (up to 98%) and

selectivity (>99:1) towards the (*Z*) isomer were noted. This user-friendly procedure does not require any additive and can be operated in air at ambient temperature. The introduction of various aryl groups in the olefinic unit is tolerated including *para*-, *meta*- and *ortho*-substituted (di)halo-aryls (**2**, **3**, **7**, **18**, **19**, **20**, **21**, **23** and **24**), benzoic ester (**9**) and even thioether (**12**) groups. The use of 2- and 3-furyl, thiophene- and 3-pyridyl-substituted cyclic carbonates smoothly leads to (*Z*)-1,4-diols **13–16** in high yield despite the potential of the heteroatoms to coordinate and deactivate the Pd-catalyst.

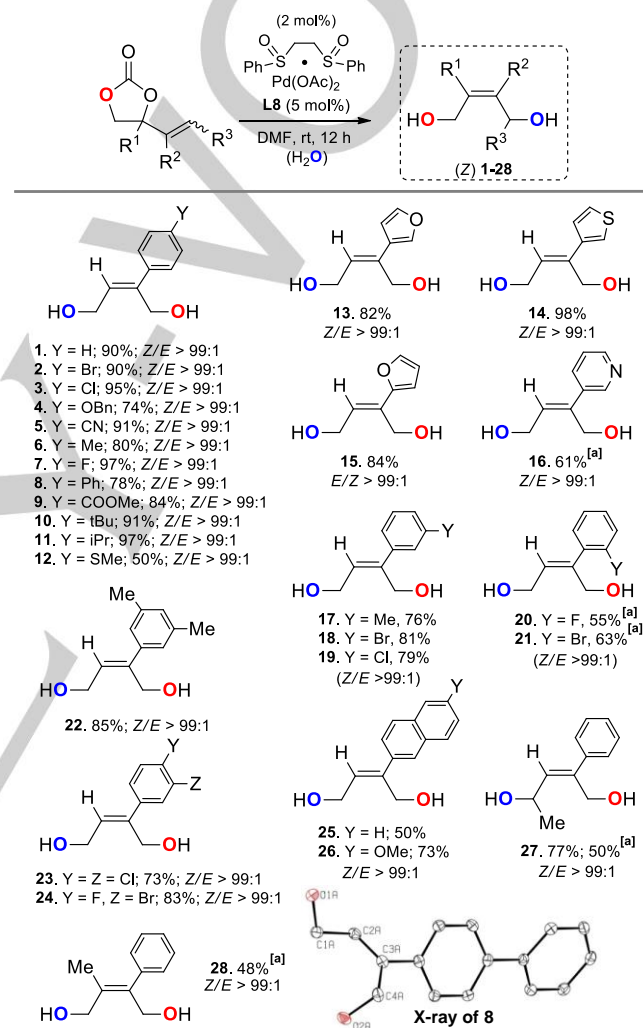
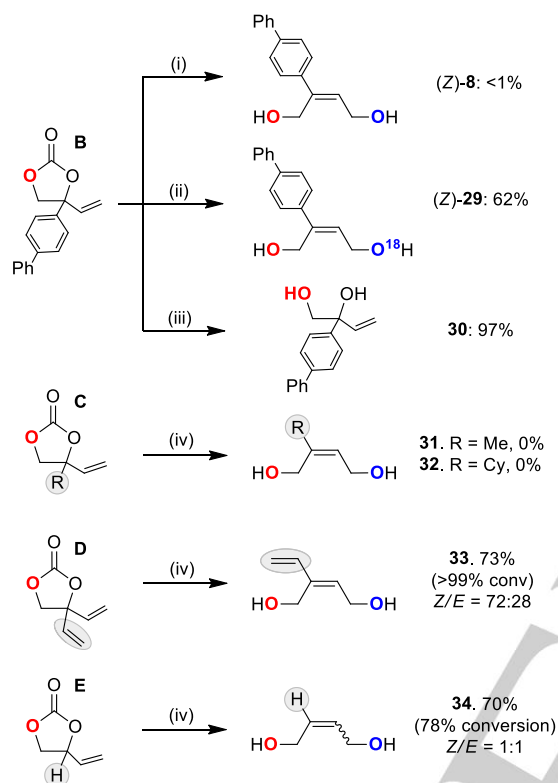


Figure 1. Product scope in the Pd-mediated formation of (*Z*)-but-2-ene diols **1–28**. Substrate amounts used: carbonate (0.20 mmol), DMF (0.20 mL). The *Z/E* ratios were determined by ^1H NMR spectroscopy (CDCl_3). Although following the same stereo-chemical formation pathway, compound **15** has formally an (*E*) configuration. [a] Using 5 mol% of Pd precursor and 10 mol% of **L8**, 60°C, 200 μL DMF, 60 μL H_2O .

Interestingly, the presence of other substitution patterns is also allowed producing an α -functionalized diol (**27**) and a tetra-substituted olefin derivative (**28**). Generally, in order to prepare these latter compounds with more elaborate substitutions and

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those incorporating *ortho*-functionalized aryl groups (cf., **20** and **21**) and 3-pyridyl based **16** a higher reaction temperature and additional water in the medium was required; for these more challenging conversions also a higher amount of Pd catalyst (5 mol%) was necessary. The (*Z*) configuration was deduced from 1D and 2D NMR analysis, whereas in the case of **8** further evidence for the preferred stereo-isomer formation was obtained from X-ray diffraction studies (Figure 1).^[13]

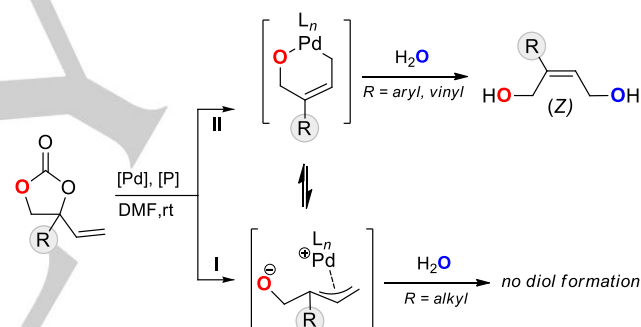


Scheme 2. Control experiments using vinyl carbonates **B–E** as substrates under different conditions: (i) anhydrous DMF (0.2 mL), White catalyst (2.0 mol%), **L8** (5.0 mol%), rt, 12 h; (ii) anhydrous DMF/H₂O¹⁸ (0.2 mL; 9:1), White catalyst (2.0 mol%), **L8** (5.0 mol%), rt, 12 h; (iii) DMF/H₂O, NaOH (5 eq), rt, 8 h. (iv) conditions as under (i) using commercial DMF.

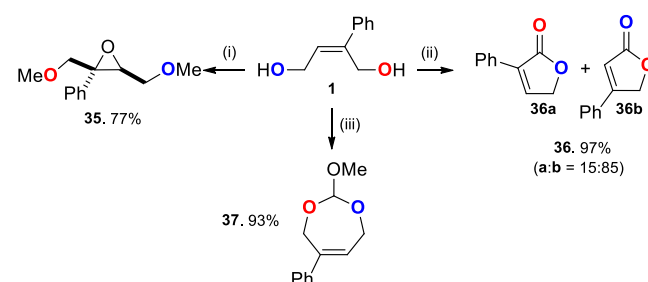
Intrigued by the highly stereo-selective nature of these conversions and in order to gain mechanistic insight, we performed a series of control experiments. Vinyl carbonate **B** (Scheme 2) was subjected to the same reaction conditions as used for **1–28** using anhydrous DMF; no conversion to diol (*Z*)-**8** could be noted. Using a combination of anhydrous DMF with ¹⁸O-labelled water (9:1 v/v) and treatment of vinyl carbonate **B** under these conditions afforded the labelled diol (*Z*)-**29** in 62% yield: these combined results support the key role of water in the stereo-selective formation of the 1,4-diols. Further to this, when carbonate **B** is treated with H₂O under basic conditions in the absence of Pd catalyst the 1,2-diol **30** is produced that results from the hydrolysis of the carbonate unit.^[3c,14] Therefore, the presence of a suitable Pd catalyst is essential to produce the 1,4-diol products. In order to examine whether other vinyl-substituted carbonates (*i.e.*, **C–E**) would equally convert to their

corresponding (*Z*)-but-2-ene diols, the synthesis of **31–34** was attempted under the optimized reaction conditions. When alkyl-substituted carbonates were probed (**C**; R = alkyl) no conversion to the targeted diols **31** and **32** could be observed up to 60°C. Interestingly, diol **33** derived from carbonate **D** that incorporates an additional vinyl substituent was obtained in 74% yield as a 72:28 mixture of both (*Z*) and (*E*) isomers. When carbonate **E** was employed the corresponding diol **34** (*Z*/*E* = 1:1) was obtained under even lower stereo-control.

From the results presented in Scheme 2 a mechanistic rationale is proposed taking the previously postulated zwitter-ionic Pd-allyl intermediate I^[9] as starting point (Scheme 3). Equilibration of η³-allyl-Pd species **I** to η¹-palladacyclic intermediate **II** is electronically biased as the presence of an aryl/vinyl substituent allows for hyper-conjugation of the double bond: this in turn controls the (*Z*) configuration of the palladacycle and thus the stereo-control towards the 1,4-diol product. In turn, the lack of reactivity towards diol formation when R is an alkyl group (*cf.*, **31** and **32**; scheme 2) is explained by a larger charge-delocalization in intermediate **I** onto which nucleophilic attack by water is disfavored for electronic reasons. Thus, clearly electron-donating groups are unable to mediate the formation of intermediate **II** and no conversion is observed as indeed noted experimentally.



Scheme 3. Proposed mechanistic manifolds related to the Pd intermediates formed after decarboxylation.



Scheme 4. Examples of post-use of (*Z*)-1,4-but-2-ene diol **1** in the synthesis of other interesting scaffolds (**35–37**). Conditions/reagents used: (i) NaH (3 eq.), Mel (4 eq.), DMF, rt; then *m*-CPBA (1.1 eq.), DCM, rt, 18 h; (ii) CuI (5 mol%), 2,2'-bipy (5 mol%), 9-azabicyclo[3.3.1]nonane *N*-oxyl (1 mol%), *N*-methyl imidazole (10 mol%), ACN, rt, 3 h; (iii) Camphorsulfonic acid (1 mol%), trimethyl orthoformate (2 eq.), DCM, rt, 5 h.

In the case of the non-substituted carbonate **E** (Scheme 2), relatively slower conversion towards diol product is observed. The low *Z/E* ratio of this latter conversion is the result of a non-stereospecific nucleophilic attack governed by steric rather than electronic considerations.

Finally, the post-modification potential of these (*Z*)-1,4-but-2-ene diols was investigated using **1** as starting material (Scheme 4). Simple oxidation of the double bond (after alcohol protection) in **1** by *meta*-chloroperoxybenzoic acid afforded **35** as a single diastereo-isomer in 77% yield. Oxidative lactonization of **1** using a radical initiator (9-azabicyclo[3.3.1]nonane *N*-oxyl) under Cu-catalysis in the presence of *N*-methyl-imidazole produced the lactone **36** in 97% yield.^[6] The cyclic *ortho*-ester **37** was prepared by combining **1** with trimethyl orthoformate^[4] under acid catalysis providing a well-known protection of this diol useful in synthetic chemistry.^[15]

In summary, we here describe a user-friendly, highly mild and stereo-selective methodology towards the formation of synthetically useful (*Z*)-1,4-but-2-ene diols in high yield and under exclusive stereo-control. This procedure utilizes readily available and modular vinyl-based cyclic carbonates and simple water as reactants, can be operated in air and does not require any additive. Such privileged conditions may greatly advance the use of these diol synthons in preparative chemistry as demonstrated herein.

Acknowledgements

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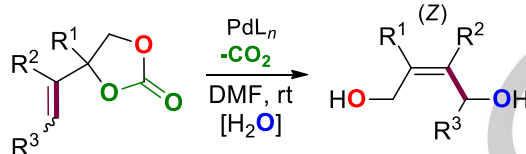
Keywords: decarboxylative functionalization • homogeneous catalysis • palladium • stereoselectivity • (*Z*)-1,4-but-2-ene diols

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A highly efficient and stereo-selective Pd-mediated synthesis of substituted (*Z*)-1,4-diols is described using allyl surrogates derived from vinyl cyclic carbonates. The methodology is characterized by its operational simplicity, high yields and stereo-control using water as a nucleophilic reagent. Control experiments support the view that hyper-conjugation plays an imperative role in these stereo-specific conversions.



- *Z/E* typically >99:1
- *rt*, open to air, good scope
- 29 examples, high yields up to 98%
- H₂O as nucleophile !

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