HIGHLIGHT

Diastereo- and Enantioselective Valorization of Cyclic Organic Carbonates

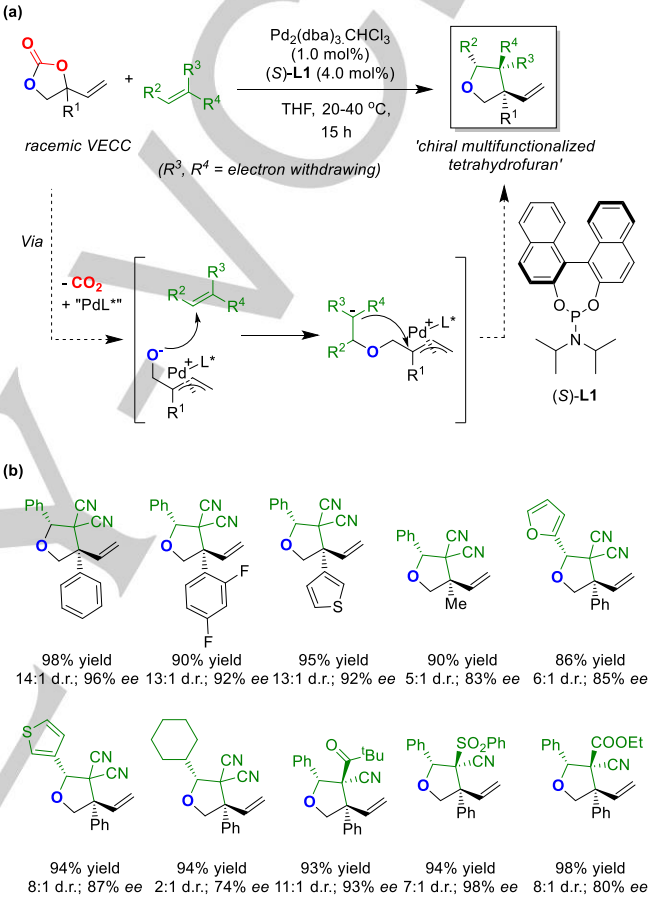
Arjan W. Kleij[a,b] and Christopher J. Whiteoak*[c]

The synthesis of 1,3-dioxolan-2-ones, more commonly referred to as cyclic organic carbonates, has been attracting significant attention. This is largely a result of their growing application potential, for example, as electrolytes in lithium ion batteries, polar aprotic solvents and fuel additives.[1] To date, a number of strategies predominantly based on carbon dioxide (CO_2) utilization have been developed for their synthesis[2] and consequently a variety of cyclic organic carbonates containing diverse functionalities are now synthetically available.[3] Despite having access to a library of high-potential synthons and efficient catalyst systems for their preparation,[3b,4] surprisingly little attention has been directed towards the application of these organic carbonates as precursors in synthetic organic chemistry.

Recently, several reports have focused on the stereo-selective formation of vicinal *cis*-diols, using cyclic organic carbonate precursors as intermediates to steer the stereoselectivity of the reaction.[5] In these examples, a *cis*-cyclic epoxide is initially transformed into the corresponding *cis*-cyclic organic carbonate intermediate with excellent retention of stereochemical information through coupling with CO_2, using non-chiral catalyst systems based on Fe or Al complexes. Treatment of the *cis*-cyclic organic carbonates with a suitable base furnishes the vicinal *cis*-diol products with high stereoselectivity, showcasing the versatile use of these organic carbonates for the synthesis of value-added compounds.

In an elegant but different approach, Trost and co-workers reported on the decarboxylative coupling of 1,2-divinylethylene carbonates (VECC; Scheme 1) with phthalimides. The reaction utilizes the pendent vinylethylene functionalities of the cyclic organic carbonate scaffolds as a directing group with the reaction proceeding through a π-allyl-palladium intermediate. This intermediate is key to the enantioselective outcome of the reaction as rapid isomerization of the π-allyl-palladium intermediates, directed by a chiral phosphine ligand results in a Dynamic Kinetic Asymmetric Transformation (DYKAT).[6] A similar approach was also described by Krische and co-workers who have reported on an Ir-catalyzed transfer hydrogenation of a VECC using aldehydes and alcohols as reaction partners realizing valuable chiral 1,3-diol motifs in high diastereo- and enantioselectivities through a formal decarboxylative carbonyl (hydroxymethyl)allylation.[7]

The preparation of complex chiral building blocks from racemic starting materials remains a key strategy for the synthesis of natural products due to the expense of chiral precursors. Whilst the two latter examples mentioned above have indicated the potential of VECC's as starting materials for the synthesis of chiral synthons using decarboxylative strategies, the scope of coupling partners still remains an open though expedient challenge.



Scheme 1. (a) Pd-catalyzed asymmetric decarboxylative coupling of Michael acceptors and racemic substituted VECC's for the formation of chiral multifunctionalized tetrahydrofurans. (b) Examples of chiral multifunctionalized tetrahydrofurans obtained.

Recently, Zhang and co-workers have reported on the Pd-catalyzed asymmetric decarboxylative coupling of racemic substituted VECC's with Michael acceptors (Scheme 1a)[8] making a significant contribution to expand on the use of VECC's as precursors in asymmetric synthesis. This reaction provides simple access to chiral, highly-functional tetrahydrofurans containing two quaternary stereo-centres, in high yields and with high levels of diastereo- and enantioselectivity (Scheme 1b). The high enantioselectivity of the products again originates from the use of a matching chiral ligand, in this case a phosphoramidite ligand, (*S*)-**L1**. Interestingly, the compounds derived from couplings with methylenemalononitriles reagents (R^3 = R^4 = CN) can be easily hydrolyzed in a one-pot procedure to furnish the corresponding chiral amino acids, exemplifying the potential of

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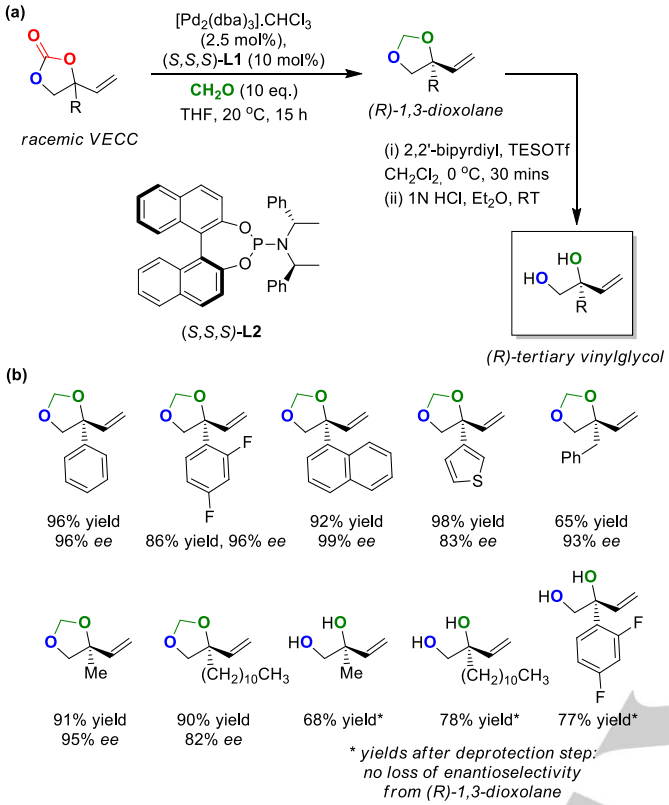
these chiral tetrahydrofurans as practical and accessible synthons for the synthesis of natural products.



Scheme 2. (a) Pd-catalyzed asymmetric decarboxylative coupling of racemic substituted VECC's with formaldehyde for the synthesis of (*R*)-1,3-dioxolanes and conversion to (*R*)-tertiary vinylglycols. (b) Examples of (*R*)-1,3-dioxolanes and (*R*)-tertiary vinylglycols that have been obtained.

The same authors have also recently applied another coupling partner, namely formaldehyde, furnishing (*R*)-1,3-dioxolanes with high enantioselectivities and yields (Scheme 2).[9] The (*R*)-1,3-dioxolane intermediates can be easily converted into the corresponding chiral vicinal diols without loss of stereochemical information in the final hydrolysis step. This procedure thus provides a facile two-step route towards a range of chiral vicinal diols with variable functionality raising the potential for application in natural product and pharmaceutical drug preparation. In particular, the authors have indicated that a (*R*)-1,3-dioxolane with a -$(CH_2)_{10}CH_3$ substituent could be successfully used as a chiral building block in the synthesis of the natural product Tanikolide. Alternatively, the (*R*)-1,3-dioxolane containing a 2,4-difluorobenzene group could be employed for the preparation of antifungal agents such as Genaconazole, Ravuconazole and Albaconazole.

When aldehydes are used as reaction partners it is also possible to effectively form cyclized products with high enantioselectivity, though with limited diastereoselectivity.[9] Thus, although other reaction partners are shown to be useful in these kind of coupling reactions with VECC's, controlling the diastereoselectivity remains so far a challenge. While the chemistry centring around the use of VECC's has grown tremendously, identification of new and useful coupling partners and the realization of high diastereo- and enantioselectivity is requisite to them becoming a common precursor in synthetic organic chemistry. The use of alternative organic carbonate synthons with directional functional groups may offer further potential for expanding on the scope of chiral molecules that can be attained from these simple precursors.

Herein, new exciting examples of the potential application of functionalized cyclic organic carbonates as valuable precursors in synthetic organic chemistry have been discussed. The recent examples using Pd-catalyzed decarboxylative coupling of racemic VECC's with formaldehyde or activated Michael acceptors as coupling partners exemplify the potential for easily constructing complex molecules in a single conversion, providing potential building blocks for natural product and pharmaceutical drug synthesis. This highlight should serve to alert other researchers to the potential of using easily prepared, functional cyclic carbonates in synthetic organic chemistry. The application of *six*-membered cyclic organic carbonates and also further amplification of the nature of the coupling partners likely provides interesting topics for further investigation.

Acknowledgements

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Keywords: Cyclic Carbonates • Decarboxylation • Asymmetric catalysis • Palladium catalysis • Synthetic methodology

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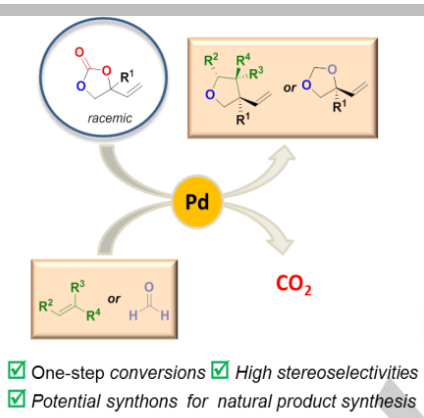
Breaking the cycle: The formation of cyclic organic carbonates is well studied, although reactions utilizing these versatile precursors are relatively limited. The conversions highlighted here showcase the use of these organic carbonates as valuable synthetic precursors, providing facile access to high-potential synthons with excellent stereochemical control.



☑ One-step *conversions* ☑ *High stereoselectivities*
☑ *Potential synthons for natural product synthesis*

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