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Pd-Catalyzed Cascade to Benzoxepins by Using Vinyl-Substituted Donor-Acceptor Cyclopropanes

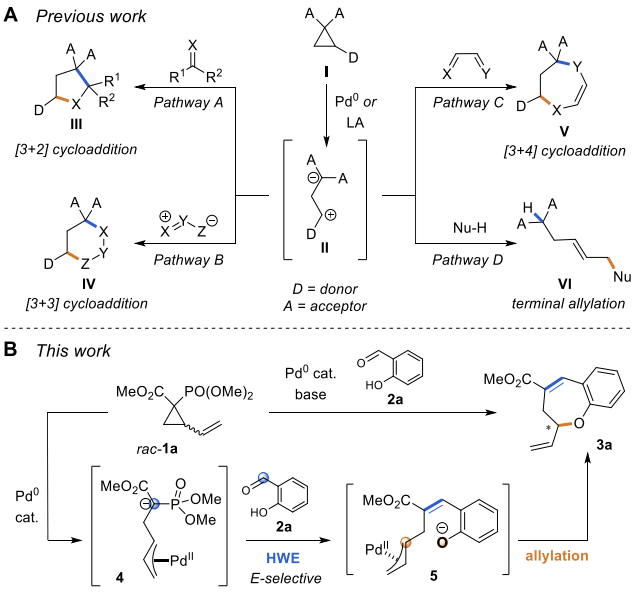
Matteo Faltracco[a], Koen N. A. van de Vrande[a], Martijn Dijkstra[a], Jordy M. Saya[b], Trevor A. Hamlin[c], Eelco Ruijter[a],*

Abstract: *A palladium-catalyzed intermolecular cascade (4+3) cyclo-condensation of salicylaldehydes and vinylcyclopropanes is reported. A key feature of the reaction is the use of a phosphonate group as an acceptor moiety on the cyclopropane, exploiting its propensity to undergo olefination with aldehydes. Subsequent O-allylation allowed the formation of a range of substituted benzoxepines. Employing a novel chiral ligand, the products could be obtained in generally very good yield and with reasonable enantioselectivity.*

Donor-acceptor cyclopropanes (DACs) are among the most useful and versatile three-carbon building blocks in organic synthesis.[1] The presence of electron-withdrawing and electron-donating groups on vicinal positions of a DAC (**I**, Scheme 1) allows facile heterolytic ring opening to give a 1,3-dipolar intermediate (**II**). Since the discovery and first applications of DACs,[2] these reagents have been widely employed, particularly in cycloaddition reactions. Among these, (3+2) cycloadditions (pathway A in Scheme 1) are by far the most common class owing to the abundance of 1,2-dipolar reaction partners, including activated olefins,[3] alkynes,[4] (ox)indoles,[5] aldehydes,[6] ketones,[7] imines[8] and ketenes[9] (also in combination with organocatalysis[10]). Compared to (3+2) cycloadditions, (3+3) [11] and (4+3) [12] cycloadditions (pathways B and C in Scheme 1) are still underdeveloped. In particular, we considered the typically challenging formation of seven-membered rings worth pursuing.[13]

The acceptor moiety of DACs often comprises two ester functionalities. However, several other electron-withdrawing groups may also activate the DAC, including nitriles, sulfones, ketones, and even arenes.[14] In formal cycloaddition reactions of DACs, electrons typically flow from this moiety bearing the negative charge to the dipolarophile and back to the donor-activated electrophilic moiety of the DAC in a likely stepwise, but mechanistically intertwined process.[15] Driven by our interest in cascade reactions and Pd-catalyzed allylic substitution,[16] we envisioned a formal cycloaddition reaction in which the two reactive sites of the DAC undergo two distinct transformations with a bifunctional reaction partner. We focused on using phosphonates as an acceptor moiety on vinylcyclopropanes (VCPs) **1** in combination with Pd-catalyzed ring opening. The resulting α-deprotonated phosphonate **4** may undergo Horner-Wadsworth-Emmons (HWE) olefination with aldehydes. Then, the electrophilic π-allylpalladium moiety of the DAC fragment may react with a pendant nucleophile on the aldehyde reaction partner. To the best of our knowledge, such a cascade reaction of DACs replacing a concerted cycloaddition by two independent transformations has not been reported to date.

The first challenge we faced was finding a suitable latent nucleophile to incorporate in the aldehyde reaction partner. Since aldehydes are also known to react with VCPs as dipolarophiles in (3+2)-cycloadditions, elimination of the dialkyl phosphate should outcompete nucleophilic substitution. To showcase our cascade approach, we selected salicylaldehyde **2a** as model substrate under palladium catalysis, which would lead to the formation of the benzoxepin **3a** (Scheme 1). After Pd-catalyzed formation of intermediate **4**, the α-deprotonated phosphonate can undergo HWE olefination with the aldehyde, leading to intermediate **5**. The π-allylpalladium moiety in **5** can then be attacked by the nucleophilic alkoxide to afford **3a**. Although there are scattered reports of DACs bearing a phosphonate EWG in the literature,[15] their active participation in an ensuing HWE olefination/allylation cascade has not been demonstrated previously.[17]



Scheme 1. **A.** Previously reported reaction types of DACs **I**. **B.** Cascade ring opening/olefination/*O*-allylation (this work). LA = Lewis acid; HWE = Horner-Wadsworth-Emmons reaction.

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As benzoxepins of both natural[18] and synthetic[19] origin display diverse biological activities, we decided to further pursue this uncommon scaffold. Preliminary investigation (for full details, see the Supporting Information (SI)) showed that the proposed reaction is indeed feasible. We then began the optimization of the reaction conditions using **1a** and **2a** as the benchmark reagents. Under the initial conditions [1.2 equiv. **1a**, 1.0 equiv. **2a**, 5 mol% Pd_2dba_3, 1.2 equiv. KO*t*Bu, THF, 50 °C], the vinylbenzoxepin product **3a** could be isolated in 43% yield (Table 1, entry 1). The yield could be marginally improved by adding trifurylphosphine (**L1**) as an ancillary ligand for Pd (entry 2). Somewhat unexpectedly, we found that two equivalents of KO*t*Bu gave the optimal result (entries 3-5).[20] Moreover, the addition of LiCl (1.2 equiv.) proved to be beneficial, significantly increasing the yield (entry 6). Finally, increasing the stoichiometry of **1a** to 2.5 equivalents was determined to be optimal, affording **3a** in 95% yield (entries 7-10).

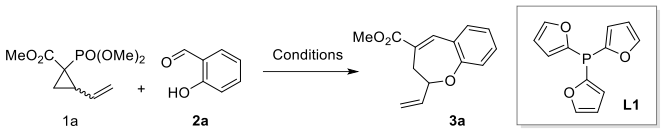
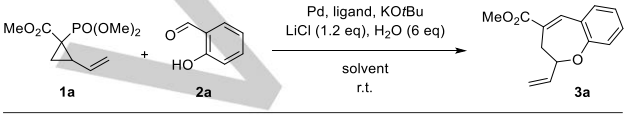


Table 1. Optimization Table.

Entry[a]	**1a** (equiv.)	Ligand (mol%)	Base (equiv.)	Additive (equiv.)	Yield[b]
1[c]	1.2	-	KO*t*Bu (1.2)	-	43
2	1.2	**L1** (20)	KO*t*Bu (1.2)	-	47
3	1.2	**L1** (20)	KO*t*Bu (1.5)	-	53
4	1.2	**L1** (20)	KO*t*Bu (2)	-	62
5	1.2	**L1** (20)	KO*t*Bu (2.5)	-	54
6	1.2	**L1** (20)	KO*t*Bu (2)	LiCl (1.2)	75
7	1.5	**L1** (20)	KO*t*Bu (2)	LiCl (1.2)	83
8	2	**L1** (20)	KO*t*Bu (2)	LiCl (1.2)	89
9	**2.5**	**L1** (20)	**KO*t*Bu (2)**	LiCl (1.2)	**95**
10	3	**L1** (20)	KO*t*Bu (2)	LiCl (1.2)	95

[a] Reaction conditions: **2a** (0.236 mmol), Pd_2dba_3 (5 mol%), **L1** (20 mol%), 1.18 mL of THF (1.18 mL), 50 °C, overnight. [b] Determined by ^{1}H NMR analysis using 2,5-dimethylfuran as an internal standard. [c] $Pd(PPh_3)_4$ was used instead of Pd_2dba_3 and **L1**.

With the optimized racemic conditions at hand, we sought to create a catalytic enantioselective process by employing a chiral ligand. This brings inherent challenges: while typically the two new bond formations in formal cycloadditions of DACs are mechanistically intertwined, our cascade transformation involves two consecutive, independent reactions, with the enantio-determining step occurring second, potentially reducing the level of stereocontrol. Moreover, while most DACs are symmetrically substituted at the acceptor moiety and hence only incorporate one stereocenter, **1a** is used as a mixture of four stereoisomers. When a chiral catalyst is used, this may lead to a number of catalyst/substrate match-mismatch cases, which may or may not readily interconvert under the reaction conditions. Consequently, it is very difficult to predict whether all diastereomers of **1** are converted with the same efficiency and/or selectivity. Nevertheless, we set out to address these challenges. Firstly, various ligand types were tested, showing that commonly used chiral phospine ligands such as (*S*)-*t*BuPHOX (**L2**) and (*S*)-BINAP (**L6**) phosphines were unable to effect the transformation (for full details, see the SI). Similarly, when Trost ligand **L8** was used, **3a** was obtained in only 15% yield and with poor enantioselectivity (entry 1). Since phosphoramidites have also been reported to be effective ligands for Pd in cycloaddition reactions of DACs,[21] we shifted our attention to this class of ligands. However, the use of **L11**, **L12** and **L15** only moderately improved the yield and/or the enantioselectivity (entries 2-4). Interestingly, we found that different diastereomers of these ligands gave dramatically different results in terms of both yield and *e.r.* (**L9** vs. **L11**, **L14** vs. **L15**; see the SI). Therefore, we designed and synthesized both diastereomers of several new phosphoramidite ligands (**L19**-**L26**, see the SI). Gratifyingly, **L24** gave **3a** in near quantitative yield and with good enantioselectivity.



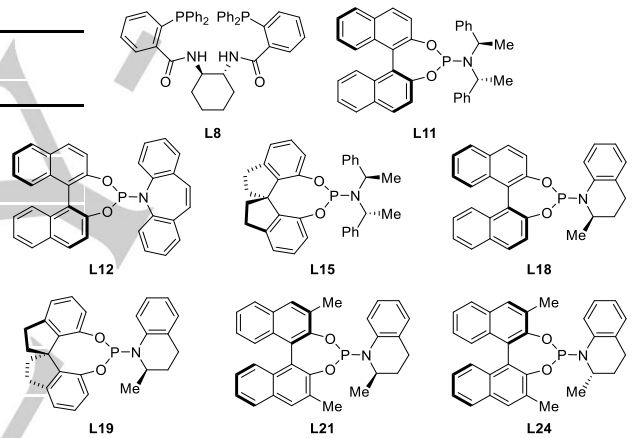


Table 2. Optimization Table.

Entry[a]	Ligand	Solvent	Yield[b]	e.r.[c]
1	**L8**	THF	15	64:36
2	**L11**	THF	30	51:49
3	**L12**	THF	31	50:50
4	**L15**	THF	40	73:27
5	**L18**	THF	79	56:44
6	**L19**	THF	20	76:24
7	**L21**	THF	15	66:34
8	**L24**	THF	98	77:23
9[d]	**L24**	THF	99	80:20
10[d,e]	**L24**	**THF**	**98**	**80:20**

[a] Reaction conditions: **2a** (0.236 mmol), Pd_2dba_3 (5 mol%), ligand (10 mol% for of bidentate 20 mol% for monodentate), **1a** (0.590 mmol), LiCl (0.283 mmol), H_2O (26 µL), KO*t*Bu (0.472 mmol) and solvent (1.18 mL), r.t, overnight. [b] Determined by ^{1}H NMR analysis using 2,5-dimethylfuran as an internal standard. [c] Determine by chiral SFC analysis. [d] 0.826 mmol of **1a**. [e] 10 mol% $PdCl_2$ instead of Pd_2dba_3, 40 mol% **L24**. n.d. = not determined.

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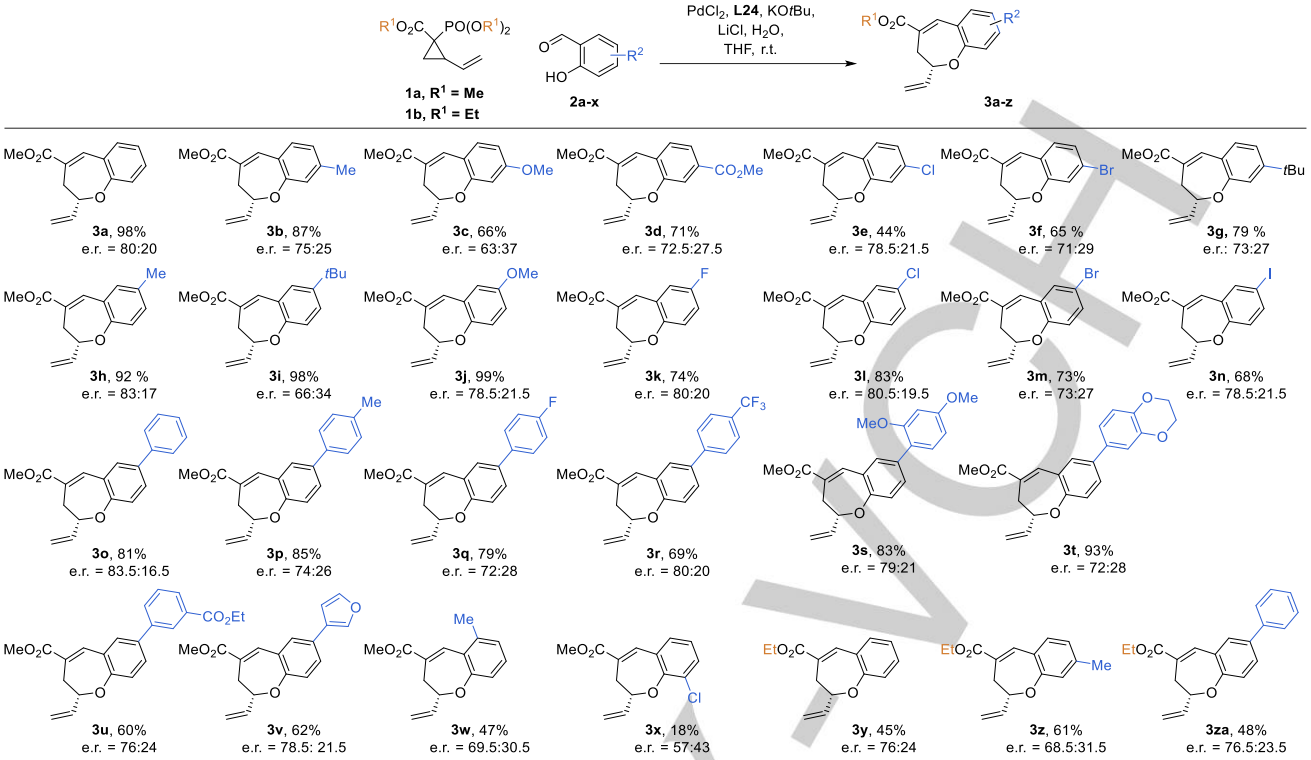

Scheme 2. Reaction conditions: **2a-x** (0.236 mmol), $PdCl_2$ (10 mol%), **L24** (40 mol%), **1a-b** (0.826 mmol), LiCl (0.283 mmol), H_2O (26 µL), KOtBu (0.472 mmol, 1.0 M in THF) and solvent (1.18 mL), r.t, overnight.

The results could only be slightly improved by increasing the stoichiometry of **1a** (entry 9), whereas varying the solvent, catalyst and ligand stoichiometry, cyclopropane substituents, or base did not improve the yield or enantioselectivity (see the SI). Upon further streamlining of the reaction conditions, we discovered that the presence of traces of water is crucial for the reaction. When solid LiCl was replaced by a 0.5 M solution of dry LiCl in THF, we found that only traces of **3a** were formed. Apparently, weighing in LiCl under non-inert conditions absorbs sufficient atmospheric moisture to promote the reaction, owing to its hygroscopic properties. Fortunately, complementing LiCl added as a THF solution with 25 µL H_2O fully restored the efficiency of the transformation, while allowing more precise and reproducible control over the reaction conditions (for details, see the SI). Finally, we found that the use of different sources and even batches of Pd_2dba_3 led to considerable fluctuations in yield. We therefore switched to $PdCl_2$ as a more reliable palladium source, although two additional equivalents of ligand were required in this case to *in situ* reduce Pd^{II} to Pd^0 (Table 2, entry 10).

With the optimal conditions in hand, we set out to investigate the scope of the reaction (Scheme 2). In general, the reaction showed high tolerance towards functional groups, affording the desired benzoxepines in good to excellent yield and consistent enantioselectivities. Alkyl groups and esters at the 4-position of the salicylaldehyde only slightly decreased yields and enantioselectivities of the resulting products (**3b**, **3g**) compared to the unsubstituted product **3a**. Similar enantioselectivities but lower yields were observed with halogen substituents, probably due to a competitive insertion of the palladium catalyst (**3e**, **3f**). Interestingly, the lowest enantioselectivity was observed for an electron-donating methoxy substituent (**3c**), although the yield was still reasonable. Electron-donating groups at the 5-position (Me, MeO) generally afforded the corresponding products in excellent yields and good enantioselectivities (**3g**, **3j**). Halogen substituents are also well tolerated (**3k-n**) with Cl and F performing best, whereas Br and I led to slightly lower yield and/or enantioselectivity. Aldehydes **2** bearing electron-deficient (halogens, ester, CF_3) or electron-rich (RO, Me) aromatic substituents were converted very efficiently, affording the corresponding products (**3o-v**) with only minor fluctuations in *e.r.* and in good to very good yield, even with a 2-furyl substituent (**3v**). In general, we observed that electron-donating substituents on the arene are beneficial for both yield and enantioselectivity. The presence of substituents on the *ortho* position with respect to both the aldehyde and phenol proved to be less favorable for both yield and enantioselectivity (**3w**, **3x**). Finally, VCP **1b** (R^1 = Et) was tested, affording products **3y**, **3z** and **3za** in similar *er* but generally lower yields (45-61%) compared to their methyl ester counterparts (**3a**, **3b** and **3o**, respectively).

We then shifted our interest to the mechanism (Scheme 3), in particular on the role of LiCl. It is well established that halide ions can improve the yield and enantioselectivity[22] of palladium-catalyzed asymmetric allylations by influencing the rates of *syn-anti* isomerization and apparent rotation processes of the π-allyl Pd complex.[23] However, in this reaction the beneficial effect was only observed with Li^+ as the counterion (see the SI for details). We postulate that the Lewis acidic Li^+ ion may stabilize the zwitterionic intermediate **4** by coordination between the oxygen atoms of the carbonyl and phosphonate moieties, leading to an overall synergic effect of LiCl. Interestingly, other lithium salts (LiBr and LiI) did not show the same effect, indicating an active role for the chloride ion. Thus far, we have been unable to rationalize the critical role of water in the reaction, although plausibly hydrogen bonding to either the aldehyde or VCP may be involved.

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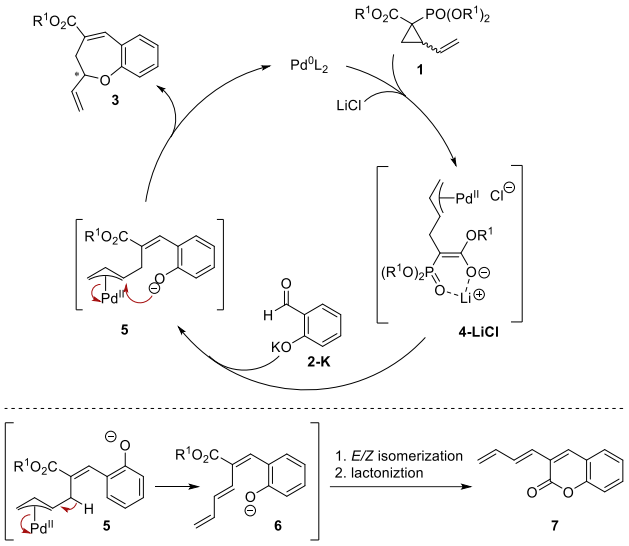
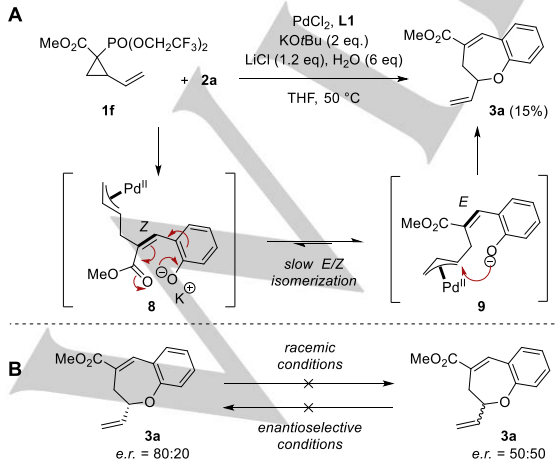


Scheme 3. Proposed mechanism.

Regarding the order of events in the mechanism, it was initially unclear whether the HWE olefination or the Pd-catalyzed *O*-allylation occurs first. However, the observation that traces of β-elimination/transesterification product **7** were formed under racemic conditions in some cases (**2e**, **2k**, **2l**) suggests that the *O*-allylation step takes place only after the initial HWE olefination. The fact that it is not observed with other, more donating substituents suggests that the nucleophilic attack is kinetically favored, hence faster, than β-elimination in the other cases, however the two rates become comparable in case of electron-withdrawing substituents. Moreover, a control experiment using vinylcyclopropane **1f** (Scheme 4A), which would generate the *Z*-configured alkene intermediate **8** by a Still-Gennari olefination,[24] still afforded **3a**, albeit in only 15% yield. This observation not only suggests that in the reaction C-C bond formation indeed precedes the *O*-allylation,[25] but also that alkene isomerization is possible (likely as a result of the reduced double bond character in the delocalized anionic intermediates **8** and **9**) and that the π-allyl-palladium complex is sufficiently stable to undergo the alkylation step at a later stage. Finally, in order to rule out reversibility of the *O*-allylation, we subjected *rac*-**3a** to the enantioselective condition and enantioenriched **3a** to the racemic conditions (Scheme 4B). No change in the enantiomeric ratio was observed in either case, suggesting that the alkylation step is irreversible**.**



Scheme 4. **A.** Still-Gennari variation. **B.** Reversibility experiments.

In order to determine the absolute configuration of the newly formed stereocenter, we attempted to grow crystals of the enantioenriched products **3** suitable for X-ray diffraction, but without success. As an alternative, we measured the circular dichroism (CD) spectrum of enantioenriched **3a**. Comparison with simulated spectra of both enantiomers led to the conclusion that the absolute configuration is *S* (see the SI for details).

In conclusion, we developed a formal (3+4)-cycloaddition of phosphonate-functionalized vinylcyclopropanes **1** and salicylaldehydes **2**, affording a range of functionalized benzoxepins **3**. The reaction proceeds via Pd-catalyzed ring opening of the vinylcyclopropane followed by HWE olefination and *O*-allylation to give the benzoxepin products in high yields (up to 99%) and with reasonable enantioselectivity (up to 83:17 *e.r.*) using a new chiral ligand.

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Keywords: benzoxepins • cascade reaction • olefination • palladium • seven-membered rings

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[25] Although all our observations suggest that C-C bond formation precedes C-O bond formation, we cannot rule out that the *O*-allylation occurs at an intermediate stage of the HWE olefination, *i.e.* the betaine or phosphaoxetane stage. As these intermediates contain an additional element of chirality and are likely formed with low stereopreference (as their formation occurs independently of the chiral catalyst), this may explain why we were not able to obtain higher enantioselectivity for the cascade reaction, despite exhaustive optimization.

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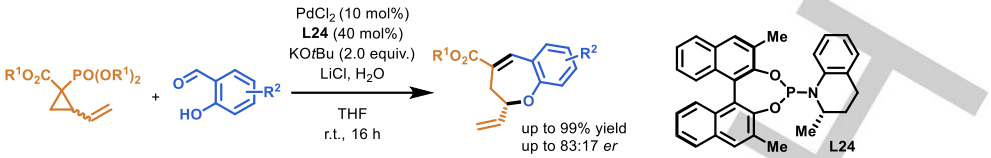

Open and close: Enantiomerically enriched benzoxepins can be synthesized from phosphonate-functionalized vinylcyclopropanes and salicylaldehydes by palladium-catalyzed ring opening followed by Horner-Wadsworth-Emmons olefination and subsequent *O*-allylation. In contrast to existing cycloaddition reactions of donor-acceptor cyclopropanes, the two bond formations each occur in a separate event, allowing greater flexibility in reaction design.

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