catalysts

MDPI

Article

Synergistic Palladium-Phosphoric Acid Catalysis in (3 + 2) Cycloaddition Reactions between Vinylcyclopropanes and Imines

Vasco Corti *, Enrico Marcantonio, Martina Mamone, Alessandro Giungi, Mariafrancesca Fochi and Luca Bernardi *

Department of Industrial Chemistry "Toso Montanari" and INSTM RU Bologna, Alma Mater Studiorum—University of Bologna, V. Risorgimento 4, 40136 Bologna, Italy; enrico.marcantonio@studio.unibo.it (E.M.); martina.mamone@studio.unibo.it (M.M.); alessandro.giungi3@studio.unibo.it (A.G.); mariafrancesca.fochi@unibo.it (M.F.)

* Correspondence: vasco.corti2@unibo.it (V.C.); luca.bernardi2@unibo.it (L.B.)

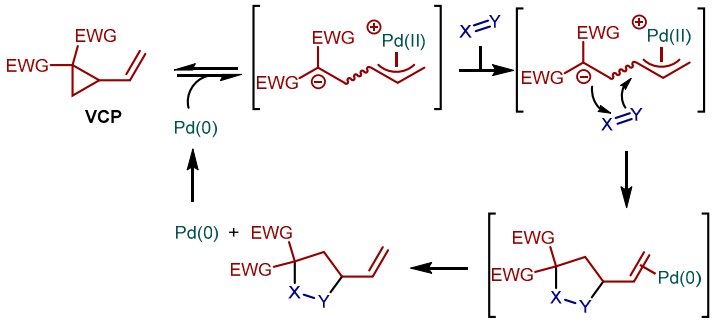
Received: 13 December 2019; Accepted: 21 January 2020; Published: 24 January 2020

Abstract: The palladium-catalyzed (3 + 2) cycloaddition reaction between vinylcyclopropanes (VCPs) bearing geminal EWG's and imines represents a straightforward and flexible entry to polysubstituted pyrrolidine derivatives. In this paper, we demonstrate that using a synergistic catalysis approach, based on the combination of phosphoric acid and palladium catalysts, it is possible to engage for the first time *N*-aryl and *N*-benzyl imines in this cycloaddition reaction. A range of polysubstituted pyrrolidines is obtained with moderate to good yields and diastereoselectivities, using a simple palladium species ($Pd(PPh_3)_4$) and an archetypical phosphoric acid as catalyst combination. A two-step scheme which exploits the same palladium catalyst for two consecutive and mechanistically distinct reactions (the cycloaddition and a Suzuki–Miyaura cross-coupling) is also presented. This synergistic catalysis approach is well posited for the development of the enantioselective version of this reaction. A screening of common BINOL-derived chiral phosphoric acids as catalyst component identified a species giving the product with moderate, yet promising, enantioselectivity (64% ee).

Keywords: (3 + 2) cycloaddition; vinylcyclopropane; palladium catalysis; H-bond catalysis; imine; stereoselective synthesis; pyrrolidine; synergistic catalysis

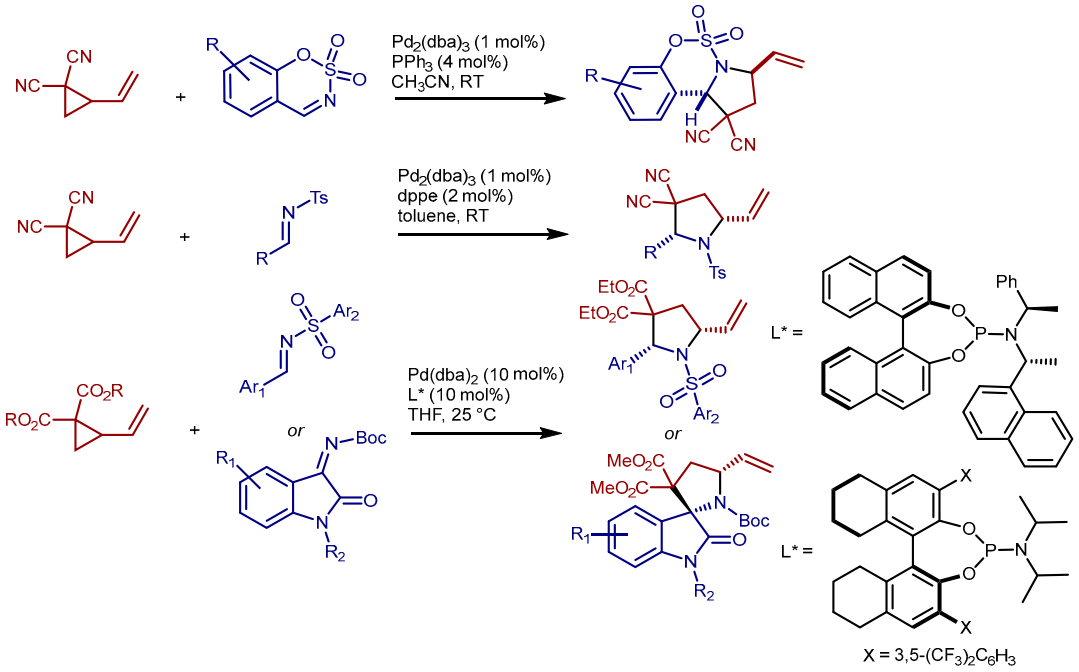
1. Introduction

Vinylcyclopropanes (VCPs) bearing two germinal electron-withdrawing groups can be activated by Pd(0) complexes, resulting in zwitterionic η^3-allyl Pd(II) species (Scheme 1). These species undergo formal (3 + 2) cycloaddition reactions with electron poor π-systems (i.e., Michael acceptors, carbonyl compounds, etc.), affording five-membered ring compounds upon Pd(0) release from their vinyl group [1–5]. The study of this VCPs reactivity, disclosed by Tsuji and co-workers in 1985 using Michael acceptors as electron poor π-partners [6], has considerably intensified in recent times, paralleling other processes based on strain-releasing formation of zwitterions by palladium chemistry (e.g., from vinylepoxides and 2-vinylaziridines). Overall, this Pd-catalyzed activation of VCPs is a versatile catalytic platform for the synthesis of five membered ring compounds. The cycloaddition has been extended to a large variety of π-acceptors, and several catalytic enantioselective transformations, mostly relying on chiral palladium complexes, have been developed.



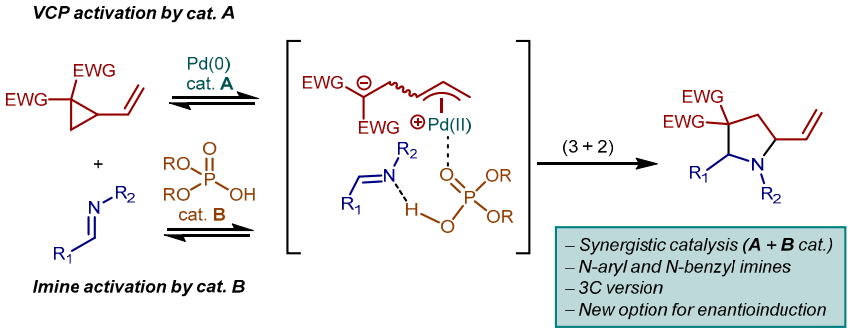
Scheme 1. Activation of VCPs by Pd(0) and formal (3 + 2) cycloaddition reaction with electron-poor π-systems X = Y.

Somewhat surprisingly, palladium catalyzed (3 + 2) cycloadditions of VCPs with imines have been reported only very recently (2018–2019), despite the unquestionable synthetic value of the resulting pyrrolidines. Four examples have been published on this reaction. A work coordinated by Xiao and Guo described the cycloaddition between (mainly) *gem*-dicyano VCPs and sulfamate-derived, cyclic, imines [7] (Scheme 2, top). Vitale and co-workers reported closely related results [8], but extended the reaction to other VCPs, and to *N*-tosyl aldimines derived from aromatic and aliphatic aldehydes (Scheme 2, middle). Sulfamate-derived cyclic imines were also employed by de Figueiredo, Campagne and co-workers in palladium catalyzed cycloadditions with more elaborated 2-alkyl-2-alkylidene cyclopropane 1,1-dicarboxylates VCPs [9]. More recently, Chu, He, Liu and co-workers published the first examples of highly enantioselective (3 + 2) cycloadditions between VCPs and imines [10] (Scheme 2, bottom). The reactions, catalyzed by chiral palladium complexes bearing phosphoramidite ligands, give very good results with both *N*-sulfonyl aldimines derived from aromatic aldehydes, and *N*-Boc isatin ketimines. Less recently, Plietker, Kurahashi, Matsubara and their co-workers demonstrated that low valent iron and nickel complexes catalyze the (3 + 2) cycloaddition reaction between VCPs and imines [11–13]. In all cases, which included a moderately enantioselective example, electron-poor *N*-sulfonyl aldimines were used as reaction partners.



Scheme 2. Palladium catalyzed (3 + 2) cycloadditions of VCPs with imines: selected literature examples. dba: dibenzylidene acetone; dppe: 1,3-di(triphenylphosphino)propane.

Herein, we present a conceptually new approach to the catalytic (3 + 2) cycloaddition between VCPs and imines, based on the synergistic combination of a palladium catalyst (**A**), for zwitterion formation from the VCP, and a phosphoric acid catalyst (**B**), for imine activation, along the lines of the simplified working model sketched in Scheme 3. Weaker acids (e.g., AcOH) have been used as sub-stoichiometric additives in palladium catalyzed cycloadditions [14]. However, the role of these acids is to buffer anionic intermediates, ultimately resulting in improved stereoselectivities in the reactions. In contrast, in our work, the acid serves to activate the electrophilic reaction partner. In fact, with this synergistic catalysis approach [15,16], we are able to engage less electrophilic *N*-aryl and *N*-benzyl imines (vs. *N*-sulfonyl imines, see Scheme 2) in reactions with VCPs, thus augmenting the structural diversity achievable. Implementation to a three-component version by forming the imine in situ is also possible, while the acid catalyst component (**B**) introduces a new option [17] for enantioinduction in VCPs reactions, beyond the common strategy based on chiral ligands at palladium. A similar approach has been briefly explored, but then abandoned in favor of chiral ligands, by de Figueredo, Campagne and co-workers during their studies on palladium catalyzed enantioselective 2-vinylaziridines cycloadditions [9]. On the other hand, a distinct synergistic catalysis combination was used in enantioselective cycloadditions between VCPs and enals [18–22], wherein chiral secondary amine and achiral palladium catalysis were successfully merged [23].



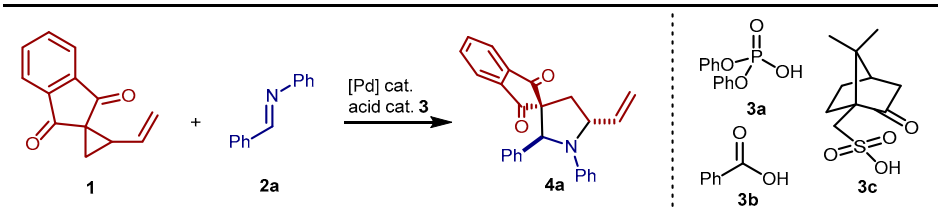
Scheme 3. This work: synergistically (palladium **A** + phosphoric acid **B** catalysts) catalyzed (3 + 2) cycloaddition between *N*-aryl and *N*-benzyl imines and VCPs: simplified working model.

2. Results and Discussion

We performed exploratory experiments with different VCPs and *N*-aryl imines, under a variety of reaction conditions. The first convincing proof of the feasibility of our plans was obtained by employing indan-1,3-dione derived VCP **1**, *N*-phenyl imine **2a**, and a combination of $Pd(PPh_3)_4$ and diphenylphosphoric acid **3a** as catalysts (10 mol% each) in toluene (Table 1, entry 1). The reaction performed with such combination resulted complete in less than one hour, affording the corresponding pyrrolidine **4a** in very good yield and moderate diastereoselectivity, in favor of the *trans*-isomer. The next two entries (2,3) of Table 1 report two crucial experiments, wherein the presence of both catalyst components ($Pd(PPh_3)_4$ and **3a**) was found to be essential to achieve an efficient transformation. While, unsurprisingly, omitting the palladium catalyst led to no reactivity, the reaction performed without **3a** gave full consumption of **1** after prolonged time. However, the poor yield of **4a** (49% yield after 24 h, vs. 92% yield after 1 h in the presence of **3a**) indicates that the dipolar intermediate was not being channeled efficiently towards product **4a** formation. Variation in the acid component **3** showed that a weaker acid catalyst, such as benzoic acid **3b** (pK_a (**3b**) = 11.1 in DMSO [24], vs. pK_a (**3a**) = 3.88 in DMSO [25]) was much less effective (entry 4), substantiating our assumption on the requirement of imine activation for reactivity. More acidic (+)-camphor-10-sulphonic acid **3c** as catalyst (pK_a of methanesulfonic acid = 1.6 in DMSO [26]) afforded results (entry 5) comparable to the phosphoric acid **3a**. With **3a**, we proceeded to evaluate the influence of the loadings of the two catalytic species. The experiments reported in entries 6–8 show that decreasing the amount of palladium improves the diastereoselectivity of the reaction, reaching up to ca. 5:1 when 2.5 mol% of $Pd(PPh_3)_4$ was applied. On the contrary, the amount of **3a** does not seem to influence strongly the

reaction outcome. $Pd(dba)_2$ as palladium component could not promote efficiently the reaction (entry 9), in line with the literature [8]. Thus, keeping a 2.5 mol% $Pd(PPh_3)_4$ and 10 mol% **3a** loadings, a short solvent screening was performed. The reaction proceeded smoothly in all solvents testes, with diastereoselectivities comparable or lower than in toluene (compare entries 10–12 with entry 6). Halide salts are often used as additives in reactions involving zwitterionic allyl palladium intermediates [9,27]. By coordinating palladium, these additives increase the rate of π-σ-π isomerization of the allyl palladium complex [28], ultimately influencing the stereochemical outcome of the reactions (vide infra). In our case, application of one equivalent of tetra-*n*-butyl ammonium bromide and iodide did improve the stereoselectivity of the reaction. However, an unacceptable rate lowering was also observed (entries 14, 15). On the contrary, the corresponding chloride salt gave a less noticeable effect (entry 13).

Table 1. Variations of catalysts and reaction conditions in the (3 + 2) cycloaddition between VCP **1** and imine **2a**: selected results.

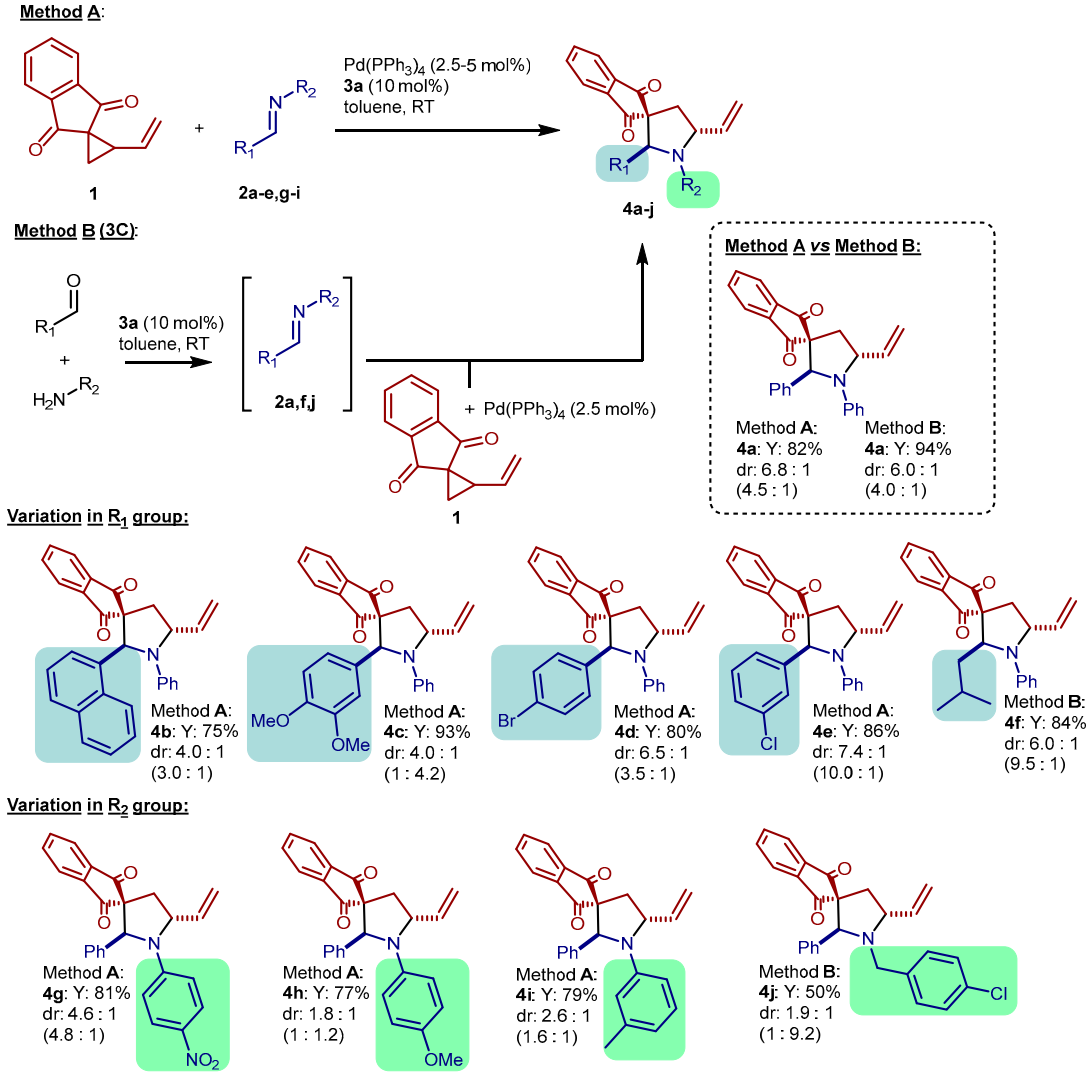


Entry [1]	[Pd] (mol%)	3 (mol%)	Solvent	Additive	*t* (h)	Y [2] (%)	d.r. [3]
1	$Pd(PPh_3)_4$ [10]	**3a** [10]	toluene	-	1	92	2.0:1
2	-	**3a** [10]	toluene	-	24	<5	-
3	$Pd(PPh_3)_4$ [10]	-	toluene	-	24	49	5.1:1
4	$Pd(PPh_3)_4$ [10]	**3b** [10]	toluene	-	3	47	1.7:1
5	$Pd(PPh_3)_4$ [10]	**3c** [10]	toluene	-	1	96	2.0:1
6	$Pd(PPh_3)_4$ [2.5]	**3a** [10]	toluene	-	1	96	5.3:1
7	$Pd(PPh_3)_4$ [2.5]	**3a** [2.5]	toluene	-	1	98	4.5:1
8	$Pd(PPh_3)_4$ [10]	**3a** [5]	toluene	-	1	>95 [4]	1.9:1
9	$Pd(dba)_2$ [5]	**3a** [10]	toluene	-	6	36 [4]	3.9:1
10	$Pd(PPh_3)_4$ [2.5]	**3a** [10]	CH_2Cl_2	-	1	88	1.5:1
11	$Pd(PPh_3)_4$ [2.5]	**3a** [10]	THF	-	1	76	4.2:1
12	$Pd(PPh_3)_4$ [2.5]	**3a** [10]	CH_3CN	-	1	97	1.2:1
13	$Pd(PPh_3)_4$ [2.5]	**3a** [10]	toluene	TBACl [5]	30	83	6.4:1
14	$Pd(PPh_3)_4$ [2.5]	**3a** [10]	toluene	TBABr [5]	30	61	11.8:1
15	$Pd(PPh_3)_4$ [2.5]	**3a** [10]	toluene	TBAI [5]	21	21	18.0:1

[1] Conditions: VCP **1** (19.8 mg, 0.10 mmol), imine **2a** (27.1 mg, 0.15 mmol), solvent (1.2 mL), $Pd(PPh_3)_4$ (x mol%), **3** (x mol%), bibenzyl internal standard, RT. [2] Determined by ^1H NMR using bibenzyl as internal standard. [3] Determined by ^1H NMR on a reaction sample. [4] Conversion, determined by ^1H NMR on a reaction sample. [5] 0.10 mmol (1 equiv.).

We then moved to study the scope of the reaction, by applying conditions related to entry 6 of Table 1 to different imines **2** (Scheme 4, Method **A**). However, first, we developed a related three-component protocol (Scheme 4, Method **B**): the imine **2** is formed in situ, taking advantage of the activity of catalyst **3a** in promoting the condensation reaction, and then VCP **1** and $Pd(PPh_3)_4$ are added. As shown in Scheme 4, product **4a** was obtained in comparable yields and diastereomeric ratios with the two methods, demonstrating the viability of the three-component protocol as well as the tolerance of the process to traces of water. Then, we applied imines **2b–f** derived from different aldehydes and aniline. The resulting pyrrolidines **4b–f** were obtained in good yields, including **4f** from an aliphatic imine. The poor stability of this imine was overcome by applying the three-component protocol (Method **B**). Diastereomeric ratios of products **4b–f**, measured on the crude mixtures, ranged from 4:1 for **4b** to 7.4:1 for **4e**. Imines **2g–j** derived by combining benzaldehyde with

different amines were also employed, affording the pyrrolidines **4g–j** in good yields and variable diastereoselectivities. The success of the reaction of benzylamine-derived **2j** shows the applicability of these protocols to a different class of imines, and its potential in delivering *N*-benzyl pyrrolidines. Finally, three VCPs bearing other *gem*-EWGs, derived from diethylmalonate, malononitrile, and Meldrum's acid, respectively, were put to test with imine **2a**. Unfortunately, none of these substrates afforded the desired pyrrolidines with good results. Even by attempting to fine-tune the reaction conditions, extensive degradation of these substrates (and of imine **2a**) occurred. However, traces (<10%) of products could be observed at least for the malononitrile and Meldrum's acid derived VCPs, leaving hope for future developments.



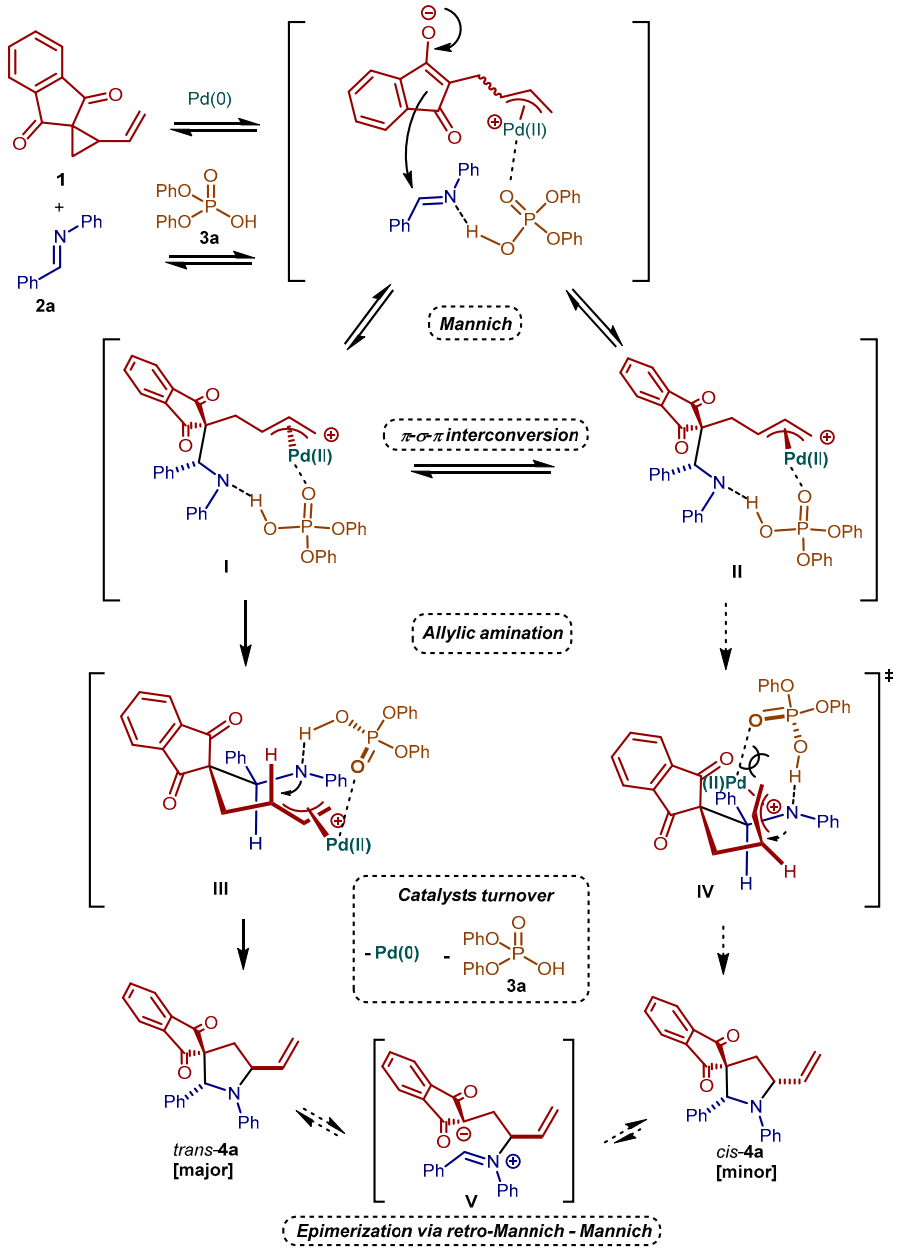
Scheme 4. Scope of the reaction. Method **A**: VCP **1** (39.6 mg, 0.20 mmol), imine **2** (0.30 mmol), **3a** (5.0 mg, 0.020 mmol, 10 mol%), $Pd(PPh_3)_4$ (5.8–11.6 mg, 0.0025–0.005 mmol, 2.5–5 mol%), toluene (2.4 mL), RT, 0.5–24 h. Method **B**: aldehyde (0.30 mmol), amine (0.30 mmol), **3a** (5.0 mg, 0.020 mmol, 10 mol%), toluene (1.2 mL), RT, 30 min; then, VCP **1** (40 mg, 0.20 mmol), $Pd(PPh_3)_4$ (5.8 mg, 0.0025 mmol, 2.5 mol%), toluene (1.2 mL), RT-40 °C, 1–42 h. Yields of compounds **4** determined after purification by chromatography on silica gel. Dr determined on the crude mixtures by ^{1}H NMR; dr in brackets refer to dr after chromatography. For further details, see Experimental Section.

In most cases, variations in the diastereomeric ratios measured before and after (dr in brackets in Scheme 4) chromatographic purification on silica gel were observed. These discrepancies were attributed to two reasons. First, the diastereosiomers of compounds **4** feature slightly different Rfs.

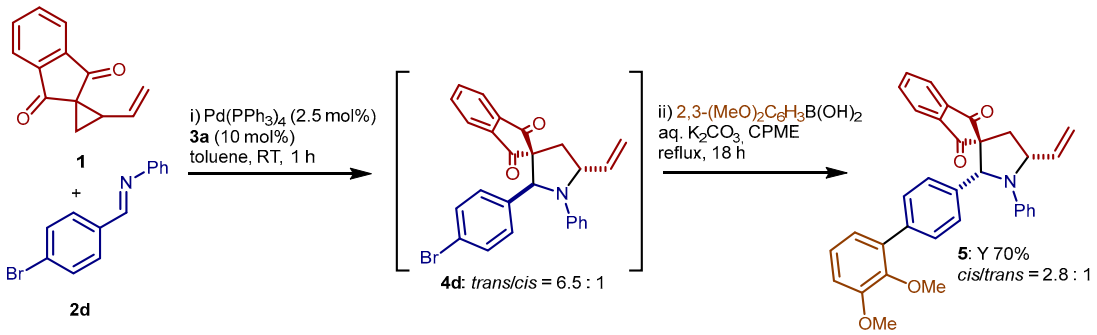
Partial losses during chromatographic purification, due to uncollected fractions, led to slightly different diastereomeric ratios between crude and purified products **4a,b,d–g,i**. Nevertheless, the different Rfs allowed to obtain the two diastereoisomers of **4a** in diastereoenriched form, and to assign the relative configuration of the major one as *trans*, and of the minor one as *cis*, by ^{1}H NOESY NMR experiments (see Supplementary Materials). Similarities between the ^{1}H NMR spectra led us to conclude that all catalytic reactions reported in Scheme 4 furnished the *trans*-diastereoisomeric products **4a–j** as the major isomers. Additionally, silica gel induced epimerization of the *trans*-isomers to their more stable [8] *cis*-counterparts is the second reason for the differences in dr before and after purification. Such process is particularly relevant in the case of the products **4c**, **4h**, and **4j**, derived from the most electron rich imines **2c**, **2h**, and **2j**. In these cases, we observed an inversion of the relative stereochemistry between the crude and the purified products **4**, which resulted enriched in the *cis*-isomers.

We can thus assume that the catalytic reactions, which lead to less stable *trans*-**4** as major isomers, are under kinetic control. A rationalization of such kinetic *trans*-diastereoselectivity can be built upon the typical Curtin–Hammett control scenario proposed in the literature for palladium catalyzed VCPs cycloaddition reactions [29,30]. The combination of such model with our working hypothesis-simplified in Scheme 3—results in the tentative mechanistic picture sketched in Scheme 5. Activation of the VCP **1** and imine **2a** by the two catalytic species triggers a Mannich-type addition, giving two diastereomeric π-allyl palladium intermediates **I** and **II**. These intermediates evolve to the two allylic amination transition states **III** and **IV**, heading to the *trans*-**4a** and the *cis*-**4a** product, respectively. Under Curtin-Hammett control, intermediates **I** and **II** are in fast equilibrium, and *trans*-selectivity is given by the lower energy of transition state **III** compared to transition state **IV**. This energy difference is due to severe 1,3-diaxial strain in the latter one. Equilibration between **I** and **II** can occur *via* σ-π-σ allyl palladium isomerization, or even retro-Mannich reaction. The results obtained by using halide additives, in which diastereoselectivities increased (Table 1, entries 13–15), reinforce the plausibility of this proposed pathway. On the other hand, the exact role of the acid component in the different steps of the catalytic cycle, as well as its potential coordination to palladium species/intermediates, are far from being fully understood. The potential reversibility of many of the steps of the catalytic cycle brings additional complexity. Nevertheless, the results obtained with a chiral acid (*vide infra*) constitute a convincing demonstration that the acid is indeed involved in the stereo-determining step(s) of the reaction. Therefore, alternative roles, such as simple activation of the palladium complex by ligand displacement, can be excluded. Last, silica gel equilibration between *trans*-**4a** and *cis*-**4a** can occur via a retro-Mannich–Mannich sequence. The intermediate **V** of this process bears a positive charge on the imine. Accordingly, as observed experimentally, compounds carrying electron-donating groups able to stabilize such positive charge (e.g., **4c**, **4h**, and **4j**) are more prone to epimerize compared to **4a**.

Inspired by a recent work [31], we decided to include our synergistically catalyzed reaction into a more complex, sequential process. We aimed to use the palladium catalyst for two sequential, mechanistically distinct, catalytic reactions: the synergistically catalyzed cycloaddition, and a Suzuki–Miyaura cross-coupling (Scheme 6). To our delight, addition of (2,3-dimethoxyphenyl)boronic acid, an inorganic base, and cyclopentyl methyl ether to the mixture of the reaction between **1** and 4-bromobenzaldehyde derived imine **2d**, once complete, followed by heating to reflux for 18 h, afforded product **5** derived from this sequential transformation in good yield. Thus, no significant deactivation of the palladium catalyst occurred during the cycloaddition, allowing its involvement in subsequent transformations. Careful inspection of the ^{1}H NMR data of compound **5**, obtained as diastereomeric mixture, suggested *cis*-**5** as the major diastereoisomer. In contrast, the cycloaddition provided *trans*-**4d** as major product. The cross-coupling conditions—heating at reflux temperature for prolonged time—are likely the cause of such epimerization of **4d** and/or of **5**.

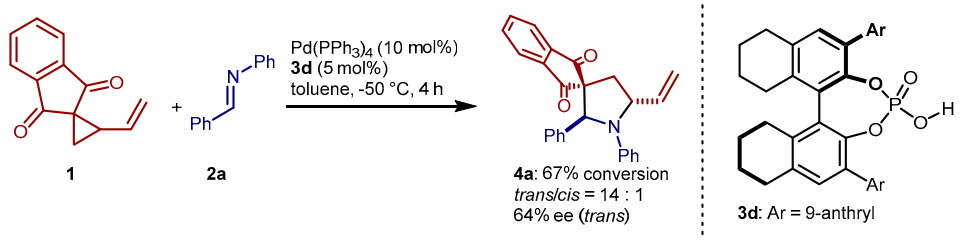


Scheme 5. Proposed reaction pathway for the synergistically catalyzed (3 + 2) formal cycloaddition reaction between VCP **1** and imine **2a**.



Scheme 6. One-pot, sequential cycloaddition—Suzuki–Miyaura reaction.

A reasonable implementation of this synergistic methodology is the utilization of chiral phosphoric acid catalysts [32], conveying an enantioselective version of this reaction. To this end, we screened several common phosphoric acids derived from BINOL and at the same explored variations in reaction conditions (solvent, temperature, stoichiometry, concentration, additives, phosphine ligands, etc.; see Supplementary Materials). After a multitude of experiments, we reached the result reported in Scheme 7. Using (*R*)-H8-BINOL derived catalyst **3d** [33], in combination with $Pd(PPh_3)_4$ and performing the reaction at low temperature, the pyrrolidine **4a** is produced with high *trans*-selectivity, and moderate enantiomeric excess. Curiously, as shown in Scheme 7, better results in terms of diastereo- and enantioselectivities were obtained by using a higher catalyst loading of the palladium component, compared to the phosphoric acid. This contrasts the reactions with achiral **3a** (Table 1). The different reaction temperature might be the main reason for such divergent behavior.



Scheme 7. Formal (3 + 2) cycloaddition catalyzed by $Pd(PPh_3)_4$ and chiral phosphoric acid **3d**.

3. Experimental Section

3.1. Materials and Methods

^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 400 spectrometer. Chemical shifts (δ) are reported in ppm relative to solvent signals for ^1H ($CHCl_3$, 7.26 ppm) and ^{13}C NMR ($CDCl_3$, 77.0 ppm) [34]. ^{13}C NMR were acquired under ^1H broadband decoupling. Mass spectra were recorded on a micromass LCT spectrometer using electronspray ionization techniques. Chromatographic purifications were performed using 70–230 mesh silica gel. The relative configuration of the major and minor diastereoisomers of pyrrolidine **4a** was assigned as 2,5-*trans* and 2,5-*cis*, respectively, by 1 D NOESY NMR experiments (see Supplementary Materials). The relative configuration of the remaining pyrrolidines **4** was assigned by analogy. Analytical grade solvents and commercially available reagents were used as received, unless otherwise stated. Imines **2** were prepared by refluxing equimolar amounts of the corresponding benzaldehydes and anilines in EtOH, and collected by filtration, or in toluene, using a Dean–Stark apparatus. VCP **1** was prepared following a literature protocol [35]. Catalyst **3d** was synthesized as previously reported [33].

*3.2. General Procedures for the Synthesis of Pyrrolidines **4***

Method A: VCP **1** (39.6 mg, 0.20 mmol), imine **2** (0.30 mmol) and diphenylphosphoric acid **3a** (5.0 mg, 0.020 mmol, 10 mol%) were sequentially added to a vial equipped with a magnetic stirring bar. Toluene (2.40 mL) was then added, followed by $Pd(PPh_3)_4$ (5.8 or 11.6 mg, 0.0025 or 0.005 mmol, 2.5 or 5.0 mol%). The resulting solution was vigorously stirred for 0.5–24 h, then passed through a short plug of silica, and the plug flushed with Et_2O. After evaporation of the solvents, the residue was analyzed by ^1H NMR to determine the diastereomeric ratios of the pyrrolidines **4** produced in the reaction. Chromatographic purification (*n*-hexane/EtOAc mixtures) afforded pure pyrrolidines **4** as diastereomeric mixtures.

Method B (three-component reaction): Aldehyde (0.30 mmol), amine (0.30 mmol) and diphenylphosphoric acid **3a** (5.0 mg, 0.020 mmol, 10 mol%) were added to a vial equipped with a magnetic stirring bar, and dissolved in toluene (1.20 mL). The resulting solution was stirred at RT for 30 min. Then, VCP **1** (39.6 mg, 0.20 mmol) was added, followed by additional toluene (1.20 mL) and $Pd(PPh_3)_4$ (5.8 mg, 0.0025 mmol, 2.5 mol%). The mixture was stirred at RT or 40 °C for 1–42 h, then passed through a short plug of silica, and the plug flushed with Et_2O. After evaporation of the

solvents, the residue was analyzed by ^{1}H NMR to determine the diastereomeric ratios of the pyrrolidines **4** produced in the reaction. Chromatographic purification (*n*-hexane/EtOAc mixtures) afforded pure pyrrolidines **4** as diastereomeric mixtures.

3.3. Experimental Results and Characterization Data of Pyrrolidines **4**

1′,2′-Diphenyl-5′-vinylspiro[indene-2,3′-pyrrolidine]-1,3-dione (**4a**). Following the general procedure, Method A (5 mol% $Pd(PPh_3)_4$, 0.5 h), the title compound was obtained as a pale yellow solid in 82% yield (*trans*/*cis* ratio: in the crude mixture, 6.8:1; after chromatographic purification, 4.5:1). Following the general procedure, Method B (2.5 mol% $Pd(PPh_3)_4$, 40 °C, 24 h), the title compound was obtained as a pale yellow solid in 94% yield (*trans*/*cis* ratio: in the crude mixture, 6.0:1; after chromatographic purification, 4.0:1). Extensive chromatography enabled the isolation of small amounts of diastereoenriched *trans* and *cis* isomers. ^{1}H NMR [*trans*-**4a**]: 7.94 (dt, *J* = 7.6, 1.1 Hz, 1 H), 7.73 (td, *J* = 7.4, 1.3 Hz, 1 H), 7.66 (td, *J* = 7.4, 1.2 Hz, 1 H), 7.58 (ddd, *J* = 7.5, 1.3, 0.8 Hz, 1 H), 7.02 (dd, *J* = 8.7, 7.3 Hz, 2 H), 6.97–6.85 (m, 5 H), 6.62 (tt, *J* = 7.3, 1.1 Hz, 1 H), 6.56–6.49 (m, 2 H), 5.80 (ddd, *J* = 17.1, 9.8, 8.7 Hz, 1 H), 5.42–5.33 (m, 2 H), 5.29–5.17 (m, 2 H), 2.54 (dd, *J* = 13.0, 7.1 Hz, 1 H), 2.36 (dd, *J* = 13.0, 7.8 Hz, 1 H); ^{1}H NMR [*cis*-**4a**]: 8.03–7.96 (m, 1 H), 7.86–7.70 (m, 3 H), 7.24–7.07 (m, 6 H), 6.78–6.65 (m, 4 H), 6.41 (ddd, *J* = 17.5, 10.3, 7.4 Hz, 1 H), 5.48 (d, *J* = 17.3 Hz, 1 H), 5.34 (d, *J* = 10.2 Hz, 1 H), 4.95 (s, 1 H), 4.82 (q, *J* = 7.5 Hz, 1 H), 2.55 (dd, *J* = 13.1, 7.8 Hz, 1 H), 2.44 (dd, *J* = 13.2, 7.3 Hz, 1 H); ^{13}C NMR [signals of both diastereoisomers]: 201.4, 200.8, 200.2, 198.1, 147.5, 144.3, 142.5, 142.3, 141.7, 141.2, 141.0, 140.7, 139.2, 136.4, 136.0, 135.8, 135.7, 135.4, 129.3, 128.6, 128.5, 128.0, 127.9, 127.5, 127.3, 126.7, 123.5, 123.3, 123.0, 122.9, 118.3, 118.2, 117.6, 117.4, 116.1, 114.6, 72.9, 70.4, 64.4, 64.2, 64.0, 63.4, 38.1, 37.4; ESI-MS: 380 m/z $[M + H]^+$.

2′-(Naphthalen-1-yl)-1′-phenyl-5′-vinylspiro[indene-2,3′-pyrrolidine]-1,3-dione (**4b**) Following the general procedure, Method A (5 mol% $Pd(PPh_3)_4$, 0.5 h), the title compound was obtained as a white solid in 75% yield (*trans*/*cis* ratio: in the crude mixture, 4.0:1; after chromatographic purification, 3.0:1). ^{1}H NMR: 8.00 (d, *J* = 7.7 Hz, 1 H_{cis}), 7.93 (d, *J* = 7.2 Hz, 1 H_{cis}), 7.88–7.72 (m, 3 H_{cis}, 2 H_{trans}), 7.70–7.62 (m, 1 H_{trans}, 1 H_{cis}), 7.57–7.50 (m, 2 H_{trans}, 2 H_{cis}), 7.51–7.41 (m, 1 H_{trans}, 1 H_{cis}), 7.40–7.20 (m, 4 H_{trans}, 3 H_{cis}), 7.12–6.94 (m, 3 H_{trans}, 1 H_{cis}), 6.76–6.70 (m, 1 H_{cis}), 6.68–6.64 (m, 2 H_{cis}), 6.65–6.56 (m, 1 H_{trans}), 6.56–6.50 (m, 2 H_{trans}), 6.39 (ddd, *J* = 17.4, 10.2, 7.3 Hz, 1 H_{cis}), 6.24 (s, 1 H_{trans}), 6.11 (ddd, *J* = 17.1, 10.1, 8.7 Hz, 1 H_{trans}), 5.76 (s, 1 H_{cis}), 5.59 (dd, *J* = 17.3, 1.2 Hz, 1 H_{cis}), 5.48–5.40 (m, 1 H_{trans}, 1 H_{cis}), 5.35–5.26 (m, 2 H_{trans}), 4.99 (q, *J* = 7.8 Hz, 1 H_{cis}), 2.79 (dd, *J* = 13.2, 7.7 Hz, 1 H_{trans}), 2.59 (dd, *J* = 13.1, 9.0 Hz, 1 H_{cis}), 2.51–2.40 (m, 1 H_{trans}, 1 H_{cis}); ^{13}C NMR [signals of both diastereoisomers]: 202.1, 201.5, 199.6, 197.4, 147.5, 144.5, 142.6, 141.9, 141.4, 141.1, 140.6, 140.4, 135.9, 135.9, 135.6, 135.6, 135.1, 134.4, 133.7, 133.5, 131.8, 130.9, 130.2, 129.4, 129.1, 128.7, 128.5, 128.1, 128.0, 127.9, 126.8, 125.8, 125.7, 125.6, 125.4, 125.3, 125.1, 123.4, 123.1, 122.9, 122.5, 122.1, 121.8, 118.2, 117.6, 117.1, 116.8, 114.5, 112.7, 68.9, 64.9, 64.2, 64.1, 62.7, 62.3, 38.5, 38.4; ESI-MS: 430 m/z $[M + H]^+$.

2′-(3,4-Dimethoxyphenyl)-1′-phenyl-5′-vinylspiro[indene-2,3′-pyrrolidine]-1,3-dione (**4c**) Following the general procedure, Method A (5 mol% $Pd(PPh_3)_4$, 2 h), the title compound was obtained as a pale yellow solid in 93% yield (*trans*/*cis* ratio: in the crude mixture, 4.0:1; after chromatographic purification, 1:4.2). ^{1}H NMR: 7.98 (d, *J* = 6.7 Hz, 1 H_{cis}), 7.93 (d, *J* = 7.5 Hz, 1 H_{trans}), 7.83–7.70 (m, 3 H_{cis}, 1 H_{trans}), 7.67 (td, *J* = 7.4, 1.2 Hz, 1 H_{trans}), 7.61 (d, *J* = 7.4 Hz, 1 H_{trans}), 7.18–7.06 (m, 2 H_{cis}), 7.02 (dd, *J* = 8.6, 7.3 Hz, 2 H_{trans}), 6.76–6.65 (m, 6 H_{cis}), 6.65–6.58 (m, 2 H_{trans}), 6.56–6.52 (m, 2 H_{trans}), 6.49–6.37 (m, 2 H_{cis}, 2 H_{trans}), 5.76 (ddd, *J* = 17.1, 10.0, 8.7 Hz, 1 H_{trans}), 5.47 (dt, *J* = 17.3, 1.2 Hz, 1 H_{cis}), 5.40–5.29 (m, 1 H_{cis}, 2 H_{trans}), 5.27–5.19 (m, 2 H_{trans}), 4.90 (s, 1 H_{cis}), 4.83–4.71 (m, 1 H_{cis}), 3.80 (s, 3 H_{cis}), 3.67 (s, 3 H_{cis}), 3.65 (s, 3 H_{trans}), 3.53 (s, 3 H_{trans}), 2.59 (dd, *J* = 13.1, 8.1 Hz, 1 H_{cis}), 2.50 (dd, *J* = 12.9, 7.0 Hz, 1 H_{trans}), 2.44–2.30 (m, 1 H_{cis}, 1 H_{trans}); ^{13}C NMR [signals of both diastereoisomers]: 201.4, 201.0, 200.4, 198.2, 148.8, 148.4, 148.3, 148.0, 147.6, 144.4, 142.7, 142.4, 141.8, 141.2, 141.2, 140.5, 136.0, 135.9, 135.6, 135.3, 131.4, 128.6, 127.9, 123.4, 123.2, 123.1, 122.8, 118.9, 118.5, 118.2, 117.8, 117.4, 115.8, 114.8, 110.9, 109.7, 73.0, 70.3, 64.5, 64.2, 64.1, 63.7, 55.8, 55.7, 55.6, 55.6, 37.9, 37.0; ESI-MS: 440 m/z $[M + H]^+$.

2′-(4-Bromophenyl)-1′-phenyl-5′-vinylspiro[indene-2,3′-pyrrolidine]-1,3-dione (**4d**) Following the general procedure, Method A (5 mol% $Pd(PPh_3)_4$, 0.5 h), the title compound was obtained as a yellow solid

in 80% yield (*trans*/*cis* ratio: in the crude mixture, 6.5:1; after chromatographic purification, 3.5:1). ^{1}H NMR: 7.99 (dd, *J* = 6.4, 1.2 Hz, 1 H_{cis}), 7.95 (dd, *J* = 7.5, 1.1 Hz, 1 H_{trans}), 7.86–7.67 (m, 2 H_{trans}, 3 H_{cis}), 7.68–7.61 (m, 1 H_{trans}), 7.39 (d, *J* = 7.5 Hz, 1 H_{cis}), 7.33 (d, *J* = 8.6 Hz, 1 H_{cis}), 7.15–7.07 (m, 2 H_{trans}, 2 H_{cis}), 7.03 (dd, *J* = 8.6, 7.3 Hz, 2 H_{trans}, 2 H_{cis}), 6.82 (d, *J* = 8.0 Hz, 2 H_{trans}), 6.75 (t, *J* = 7.3 Hz, 1 H_{cis}), 6.65 (t, *J* = 7.3 Hz, 1 H_{trans}, 2 H_{cis}), 6.50 (d, *J* = 7.6 Hz, 2 H_{trans}), 6.39 (ddd, *J* = 17.5, 10.3, 7.4 Hz, 1 H_{cis}), 5.76 (ddd, *J* = 17.1, 10.0, 8.7 Hz, 1 H_{trans}), 5.47 (d, *J* = 17.3 Hz, 1 H_{cis}), 5.42–5.16 (m, 4 H_{trans}, 1 H_{cis}), 4.92 (s, 1 H_{cis}), 4.79 (q, *J* = 7.4 Hz, 1 H_{cis}), 2.70–2.50 (m, 1 H_{trans}, 1 H_{cis}), 2.42–2.30 (m, 1 H_{trans}, 1 H_{cis}); ^{13}C NMR [signals of both diastereoisomers]: 201.1, 200.6, 199.9, 198.1, 147.3, 143.9, 142.3, 142.1, 141.6, 141.0, 140.9, 140.3, 138.4, 136.2, 136.1, 135.9, 135.73, 135.71, 131.7, 131.2, 128.7, 128.4, 128.0, 123.6, 123.4, 123.3, 123.2, 123.1, 121.8, 121.4, 118.5, 118.4, 118.0, 117.6, 116.2, 114.7, 72.1, 69.5, 64.2, 64.2, 64.0, 63.1, 38.5, 37.8; ESI-MS: 458, 460 m/z $[M + H]^+$.

2′-(3-Chlorophenyl)-1′-phenyl-5′-vinylspiro[indene-2,3′-pyrrolidine]-1,3-dione (**4e**) Following the general procedure, Method A (2.5 mol% $Pd(PPh_3)_4$, 24 h), the title compound was obtained as a pale yellow solid in 86% yield (*trans*/*cis* ratio: in the crude mixture, 7.4:1; after chromatographic purification, 10.0:1). ^{1}H NMR [signals of *trans*-**4e**]: 7.96 (dt, *J* = 7.8, 0.9 Hz, 1 H), 7.76 (td, *J* = 7.4, 1.3 Hz, 1 H), 7.69 (td, *J* = 7.6, 1.2 Hz, 1 H), 7.62 (dt, *J* = 7.5, 0.9 Hz, 1 H), 7.07–7.00 (m, 2 H), 6.95–6.87 (m, 3 H), 6.83 (br d, *J* = 7.6 Hz, 1 H), 6.64 (td, *J* = 7.4, 1.0 Hz, 1 H), 6.54–6.49 (m, 2 H), 5.78 (ddd, *J* = 18.8, 10.0, 8.8 Hz, 1 H), 5.37 (d, *J* = 17.1 Hz, 1 H), 5.32 (s, 1 H), 5.25–5.17 (m, 2 H), 2.54 (dd, *J* = 13.2, 7.2 Hz, 1 H), 2.34 (dd, *J* = 12.9, 7.4 Hz, 1 H); ^{13}C NMR [signals of *trans*-**4e**]: 200.5, 199.8, 143.9, 142.1, 141.6, 140.4, 138.9, 136.1, 135.6, 134.0, 129.4, 128.1, 127.9, 127.4, 125.7, 123.2, 123.1, 118.3, 118.0, 117.5, 69.6, 64.21, 64.16, 38.2; ESI-MS: 414, 416 m/z $[M + H]^+$.

2′-Isobutyl-1′-phenyl-5′-vinylspiro[indene-2,3′-pyrrolidine]-1,3-dione (**4f**) Following the general procedure, Method B (2.5 mol% $Pd(PPh_3)_4$, RT, 1 h), the title compound was obtained as a pale orange solid in 84% yield (*trans*/*cis* ratio: in the crude mixture, 6.0:1; after chromatographic purification, 9.5:1). ^{1}H NMR [signals of *trans*-**4f**]: 8.00–7.96 (m, 1 H), 7.94–7.91 (m, 1 H), 7.86–7.82 (m, 2 H), 7.24–7.17 (m, 2 H), 6.77–6.71 (m, 3 H), 5.94 (ddd, *J* = 17.1, 10.3, 6.8 Hz, 1 H), 5.30 (dt, *J* = 17.2, 1.2 Hz, 1 H), 5.17 (dt, *J* = 10.4, 1.2 Hz, 1 H), 4.59 (q, *J* = 8.0 Hz, 1 H), 4.01 (dd, *J* = 9.6, 4.0 Hz, 1 H), 2.47 (dd, *J* = 13.2, 8.6 Hz, 1 H), 2.37 (dd, *J* = 13.1, 7.7 Hz, 1 H), 1.94 (ddd, *J* = 14.1, 9.4, 4.2 Hz, 1 H), 1.56 (ddd, *J* = 14.3, 9.1, 4.1 Hz, 1 H), 1.23–1.13 (m, 1 H), 0.91 (d, *J* = 6.5 Hz, 3 H), 0.83 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR [signals of *trans*-**4e**]: 201.3, 199.2, 147.2, 142.2, 140.7, 140.3, 135.9, 135.8, 128.9, 123.7, 123.1, 117.3, 115.3, 113.0, 65.1, 62.3, 60.5, 41.3, 37.8, 25.8, 23.4, 22.1; ESI-MS: 360 m/z $[M + H]^+$.

1′-(4-Nitrophenyl)-2′-phenyl-5′-vinylspiro[indene-2,3′-pyrrolidine]-1,3-dione (**4g**) Following the general procedure, Method A (5 mol% $Pd(PPh_3)_4$, 18 h), the title compound was obtained as a yellow solid in 81% yield (*trans*/*cis* ratio: in the crude mixture, 4.6:1; after chromatographic purification, 4.8:1). ^{1}H NMR: 8.01 (ddd, *J* = 7.3, 1.4, 0.8 Hz, 1 H_{cis}), 8.00–7.96 (m, 2 H_{cis}), 7.95 (dt, *J* = 7.7, 1.1 Hz, 1 H_{trans}), 7.92–7.86 (m, 2 H_{trans}), 7.86–7.79 (m, 3 H_{cis}), 7.76 (td, *J* = 7.4, 1.1 Hz, 1 H_{trans}), 7.69 (td, *J* = 7.4, 1.1 Hz, 1 H_{trans}), 7.60 (dt, *J* = 7.6, 1.0 Hz, 1 H_{trans}), 7.28–7.24 (m, 3 H_{cis}), 7.10–7.03 (m, 2 H_{cis}), 7.03–6.97 (m, 3 H_{trans}), 6.87–6.81 (m, 2 H_{trans}), 6.64–6.58 (m, 2 H_{cis}), 6.54–6.44 (m, 2 H_{trans}), 6.38 (ddd, *J* = 17.6, 10.3, 7.6 Hz, 1 H_{cis}), 5.77 (ddd, *J* = 17.1, 10.1, 8.5 Hz, 1 H_{trans}), 5.56–5.45 (m, 1 H_{trans}, 2 H_{cis}), 5.43 (s, 1 H_{trans}), 5.37–5.26 (m, 2 H_{trans}), 5.03 (s, 1 H_{cis}), 4.93 (q, *J* = 7.6 Hz, 1 H_{cis}), 2.64–2.43 (m, 1 H_{trans}, 2 H_{cis}), 2.40 (dd, *J* = 13.1, 8.6 Hz, 1 H_{trans}); ^{13}C NMR [signals of both diastereoisomers]: 200.9, 199.8, 199.5, 197.2, 151.8, 149.6, 142.4, 141.9, 141.5, 140.6, 139.2, 139.0, 138.7, 138.1, 137.3, 136.4, 136.2, 136.1, 136.0, 134.8, 128.9, 128.5, 128.2, 127.2, 126.5, 126.3, 125.3, 124.6, 123.8, 123.5, 123.3, 123.2, 118.8, 117.7, 116.4, 113.2, 72.1, 70.5, 64.4, 63.9, 63.6, 62.6, 38.6, 37.4; ESI-MS: 447 m/z $[M + Na]^+$.

1′-(4-Methoxyphenyl)-2′-phenyl-5′-vinylspiro[indene-2,3′-pyrrolidine]-1,3-dione (**4h**) Following the general procedure, Method A (5 mol% $Pd(PPh_3)_4$, 0.5 h), the title compound was obtained as a dark yellow solid in 77% yield (*trans*/*cis* ratio: in the crude mixture, 1.8:1; after chromatographic purification, 1:1.2). ^{1}H NMR: 7.99–7.96 (m, 1 H_{cis}), 7.96–7.90 (m, 1 H_{trans}), 7.83–7.67 (m, 2 H_{cis}, 2 H_{trans}), 7.63 (td, *J* = 7.4, 1.1 Hz, 1 H_{cis}), 7.56 (dt, *J* = 7.5, 1.0 Hz, 1 H_{trans}), 7.21–7.10 (m, 3 H_{cis}, 3 H_{trans}), 6.93 (br s, 4 H_{cis}), 6.69 (br s, 4 H_{trans}), 6.65–6.59 (m, 2 H_{trans}), 6.54–6.47 (m, 2 H_{cis}), 6.37 (ddd, *J* = 17.6, 10.2, 7.5 Hz, 1 H_{cis}), 5.79 (ddd, *J* = 17.1, 10.0, 8.9 Hz, 1 H_{trans}), 5.43 (dt, *J* = 17.3, 1.2 Hz, 1 H_{cis}), 5.38–5.26 (m, 1 H_{cis}, 2

H_{trans}), 5.22–5.11 (m, 2 H_{trans}), 4.88 (s, 1 H_{cis}), 4.73–4.62 (m, 1 H_{cis}), 3.68 (s, 3 H_{cis}), 3.64 (s, 3 H_{trans}), 2.59–2.50 (m, 1 H_{cis}, 1 H_{trans}), 2.46–2.31 (m, 1 H_{cis}, 1 H_{trans}); ^{13}C NMR [signals of both diastereoisomers]: 201.7, 201.1, 200.4, 198.5, 152.9, 152.0, 142.5, 142.4, 141.8, 141.7, 141.4, 141.1, 140.6, 139.1, 138.4, 136.4, 135.9, 135.8, 135.6, 135.3, 128.4, 127.9, 127.8, 127.5, 127.4, 126.9, 123.4, 123.2, 122.9, 122.9, 119.8, 117.4, 117.0, 116.1, 114.2, 113.5, 73.8, 70.7, 65.1, 64.7, 63.5, 55.5, 55.3, 37.7, 37.4; ESI-MS: 410 m/z $[M + H]^+$.

2′-Phenyl-1′-(m-tolyl)-5′-vinylspiro[indene-2,3′-pyrrolidine]-1,3-dione (**4i**) Following the general procedure, Method A (5 mol% $Pd(PPh_3)_4$, 18 h), the title compound was obtained as an orange waxy solid in 79% yield (*trans*/*cis* ratio: in the crude mixture, 2.6:1; after chromatographic purification, 1.6:1). ^{1}H NMR: 8.02–7.97 (m, 1 H_{cis}), 7.95 (dd, J = 7.6, 1.1 Hz, 1 H_{trans}), 7.85–7.69 (m, 1 H_{trans}, 3 H_{cis}), 7.65 (td, J = 7.4, 1.2 Hz, 1 H_{trans}), 7.58 (dt, J = 7.6, 1.1 Hz, 1 H_{trans}), 7.24–7.19 (m, 1 H_{trans}, 1 H_{cis}), 7.01–6.87 (m, 3 H_{trans}, 5 H_{cis}), 6.60–6.35 (m, 4 H_{trans}, 4 H_{cis}), 6.30 (dd, J = 8.1, 2.4 Hz, 1 H_{trans}), 5.82 (ddd, J = 17.1, 10.0, 8.8 Hz, 1 H_{trans}), 5.50 (dt, J = 17.3, 1.2 Hz, 1 H_{cis}), 5.42–5.32 (m, 2 H_{trans}, 1 H_{cis}), 5.27–5.20 (m, 1 H_{trans}), 4.95 (s, 1 H_{trans}), 4.83 (q, J = 7.5 Hz, 1 H_{cis}), 2.59–2.51 (m, 1 H_{trans}, 1 H_{cis}), 2.43 (dd, J = 13.1, 7.3 Hz, 1 H_{cis}), 2.36 (dd, J = 13.0, 7.7 Hz, 1 H_{trans}), 2.20 (s, 3 H_{cis}), 2.15 (s, 3 H_{trans}); ^{13}C NMR [signals of both diastereoisomers]: 201.4, 200.9, 200.2, 198.1, 147.6, 144.3, 142.5, 142.3, 141.7, 141.2, 141.0, 140.8, 139.4, 138.2, 137.4, 136.1, 135.9, 135.8, 135.7, 135.3, 128.5, 128.5, 128.0, 127.9, 127.7, 127.5, 127.3, 126.7, 123.5, 123.3, 123.3, 123.0, 119.2, 119.1, 118.6, 117.2, 116.0, 115.5, 115.3, 111.9, 73.0, 70.5, 64.4, 64.2, 64.0, 63.4, 38.0, 37.3, 21.8, 21.7; ESI-MS: 394 m/z $[M + H]^+$.

1′-(4-Chlorobenzyl)-2′-phenyl-5′-vinylspiro[indene-2,3′-pyrrolidine]-1,3-dione (**4j**) Following the general procedure, Method B (2.5 mol% $Pd(PPh_3)_4$, 40 °C, 42 h), the title compound was obtained as a white solid in 50% yield (*trans*/*cis* ratio: in the crude mixture, 1.9:1; after chromatographic purification, 1:9.2). ^{1}H NMR [signals of *cis*-**4j**]: 7.85 (dt, J = 7.5, 0.9 Hz, 1 H), 7.66 (td, J = 7.3, 1.0 Hz, 1 H), 7.59 (td, J = 7.5, 1.2 Hz, 1 H), 7.49 (br d, J = 7.7 Hz, 1 H), 7.19–7.15 (m, 2 H), 7.09–7.01 (m, 5 H), 6.98–6.93 (m, 2 H), 5.97 (ddd, J = 18.6, 10.0, 8.6 Hz, 1 H), 5.27 (dd, J = 17.2, 1.3 Hz, 1 H), 5.15 (dd, J = 10.1, 1.6 Hz, 1 H), 3.97 (s, 1 H), 3.80 (d, J = 14.6 Hz, 1 H), 3.59 (d, J = 14.6 Hz, 1 H), 3.54 (q, J = 8.5 Hz, 1 H), 2.27 (dd, J = 13.3, 8.2 Hz, 1 H), 2.13 (dd, J = 13.0, 8.5 Hz, 1 H); ^{13}C NMR [signals of *cis*-**4j**]: 202.6, 200.6, 142.7, 141.5, 140.0, 135.8, 135.5, 135.0, 134.2, 132.7, 131.2, 128.5, 128.03, 127.96, 127.94, 127.8, 122.7, 117.3, 75.6, 65.9, 64.0, 52.2, 36.4; ESI-MS: 428, 430 m/z $[M + H]^+$.

3.4. One Pot Cycloaddition—Suzuki–Miyaura Reaction: Preparation of Compound ***5***

2′-(2′,3′-Dimethoxy-[1,1′-biphenyl]-4-yl)-1′-phenyl-5′-vinylspiro[indene-2,3′-pyrrolidine]-1,3-dione (**5**) VCP **1** (39.6 mg, 0.20 mmol), 4-bromobenzaldehyde derived imine **2d** (57.2 mg, 0.22 mmol), and diphenylphosphoric acid **3a** (5.0 mg, 0.020 mmol, 10 mol%) were sequentially added to a Schlenk tube equipped with a magnetic stirring bar. Toluene (2.40 mL) was then added, followed by $Pd(PPh_3)_4$ (5.8 mg, 0.0025 mmol, 2.5 mol%). After stirring the resulting solution for 1 h to complete the cycloaddition reaction, (2,3-dimethoxyphenyl)boronic acid (72 mg, 0.40 mmol), aqueous K_2CO_3 (2 M, 260 μL, 0.52 mmol) and cyclopentyl methyl ether (126 μL) were added. The mixture was degassed by three freeze-pump-thaw cycles, then heated to reflux temperature for 18 h with stirring. The mixture was passed through a short plug of silica, and the plug flushed with Et_2O. After evaporation of the solvents, the residue was analyzed by ^{1}H NMR, showing a 2.8:1 diastereomeric ratio, likely favoring the *cis*-isomer. Chromatographic purification (petroleum ether/EtOAc 5:1) afforded the title compound as a waxy orange solid in 70% yield (*cis*/*trans* = 2.8:1). ^{1}H NMR: 8.00 (dt, J = 7.5, 1.0 Hz, 1 H_{cis}), 7.96 (dt, J = 7.7, 1.0 Hz, 1 H_{trans}), 7.81 (td, J = 7.3, 1.4 Hz, 1 H_{cis}), 7.78–7.68 (m, 2 H_{cis}, 1 H_{trans}), 7.64–7.55 (m, 2 H_{trans}), 7.41–7.38 (m, 1 H_{cis}, 1 H_{trans}), 7.18–6.94 (m, 6 H_{cis}, 6 H_{trans}), 6.94–6.86 (m, 1 H_{cis}, 1 H_{trans}), 6.83 (dd, J = 8.2, 1.5 Hz, 1 H_{trans}), 6.79–6.70 (m, 3 H_{cis}, 2 H_{trans}), 6.65 (tt, J = 7.3, 1.1 Hz, 1 H_{trans}), 6.60–6.56 (m, 1 H_{cis}), 6.49 (ddd, J = 17.5, 10.3, 7.4 Hz, 1 H_{cis}), 5.80 (ddd, J = 17.1, 10.0, 8.8 Hz, 1 H_{trans}), 5.56–5.47 (m, 1 H_{cis}), 5.44–5.34 (m, 1 H_{cis}, 2 H_{trans}), 5.32–5.22 (m, 2 H_{trans}), 5.02 (s, 1 H_{cis}), 4.87–4.78 (m, 1 H_{cis}), 3.89 (s, 3 H_{cis}), 3.84 (s, 3 H_{trans}), 3.46 (s, 3 H_{cis}), 3.20 (s, 3 H_{trans}), 2.63 (dd, J = 13.1, 8.1 Hz, 1 H_{cis}), 2.55 (dd, J = 12.9, 7.0 Hz, 1 H_{trans}), 2.48–2.36 (m, 1 H_{cis}, 1 H_{trans}); ^{13}C NMR [signals of both diastereoisomers]: 201.4, 200.8, 200.3, 198.2, 153.0, 152.9, 147.6, 146.6, 146.4, 144.3, 142.6, 142.4, 141.9, 141.5, 141.2, 140.6, 137.8, 137.6, 137.3, 136.0, 135.7, 135.6, 135.4, 135.3, 135.2, 135.2, 129.4, 128.9, 128.6, 127.9, 127.0, 126.4, 124.0,

124.0, 123.5, 123.2, 123.0, 122.8, 122.5, 122.3, 118.4, 118.2, 117.7, 117.4, 116.0, 114.8, 111.4, 111.3, 73.0, 70.6, 64.6, 64.5, 64.3, 63.8, 60.4, 60.1, 55.9, 55.9, 37.8, 37.2; ESI-MS: 516 m/z $[M + H]^+$.

*3.5. Enantioselective Cycloaddition with Chiral Phosphoric Acid **3d***

1′,2′-Diphenyl-5′-vinylspiro[indene-2,3′-pyrrolidine]-1,3-dione (**4a**)

VCP **1** (9.9 mg, 0.05 mmol), imine **2a** (10.9 mg, 0.055 mmol) and chiral phosphoric acid **3d** (1.8 mg, 0.0025 mmol, 5 mol%) were sequentially added to a vial equipped with a magnetic stirring bar, and dissolved in toluene (0.60 mL). After cooling the resulting solution to −50 °C, $Pd(PPh_3)_4$ (5.8 mg, 0.005 mmol, 10 mol%) was added. The mixture was stirred at −50 °C for 6 h, then passed through a short plug of silica, and the plug flushed with Et_2O. After evaporation of the solvents, the residue was analyzed by ^1H NMR, showing a 67% conversion with a 14:1 diastereomeric ratio favoring the *trans*-isomer of pyrrolidine **4a**. Chromatographic purification (*n*-hexane/EtOAc 6:1) afforded enantioenriched pyrrolidine **4a**, which spectral data were consistent with previously obtained *rac*-**4a**. HPLC analysis on chiral stationary phase (Daicel Chiralcel OD-H column, *n*-hexane/*i*-PrOH = 95:5, flow 0.75 mL/min, UV detector operating at λ = 254 nm), showed 64% ee for the major *trans*-isomer (t_{maj} = 10.1 min, t_{min} = 10.9 min), and 40% ee for the minor *cis*-isomer (t_{maj} = 12.3 min, t_{min} = 15.1 min).

4. Conclusions

We have developed a conceptually new approach to the formal (3 + 2) cycloaddition between VCPs and imines. The synergistic combination of a palladium (for VCP activation) and acidic (for imine activation) catalyst allowed to use for the first time *N*-aryl and *N*-benzyl imines, thus extending the range of products obtainable. All previous examples, based on a single palladium catalyst species, employed in fact electron-poor *N*-sulfonyl and *N*-carbamoyl imines in this reaction. By adjusting the reaction conditions and the catalysts loading, we were able to obtain a range of *N*-aryl and *N*-benzyl polysubstitued pyrrolidines in an efficient manner, applying in some cases a three-component protocol (i.e., by forming the imine in situ). The possibility to engage the palladium species in a one-pot process, including a subsequent, and mechanistically distinct, reaction (a Suzuki–Miyaura cross coupling) was demonstrated. By using common chiral phosphoric acids as catalyst component, a moderately enantioselective version of the cycloaddition reaction was developed, affording the benchmark product with a moderate, yet promising, 64% enantiomeric excess. We cannot exclude, and we are confident in, that: (i) understanding the mechanistic subtleties of the reaction, which encompasses a complex pathway characterized by many potentially reversible steps and catalysts interactions; or: (ii) the employment of different, less conventional, chiral phosphoric acid structures; will ultimately enable the development of a highly enantioselective version of this reaction.

Supplementary Materials: The following are available online at www.mdpi.com/xxx/s1: copies of NMR spectra and assignment of the relative configuration of compound **4a** by NOESY NMR experiments, HPLC traces for the enantioselective reaction.

Author Contributions: Conceptualization: V.C., E.M. and L.B.; methodology: V.C., E.M., M.M., and A.G.; writing—original draft preparation: L.B.; writing—review and editing: all authors; supervision: V.C., M.F., and L.B.; project administration: M.F. and L.B.; funding acquisition: M.F. and L.B. All authors have read and agreed to the published version of the manuscript.

Funding: We acknowledge financial support by the University of Bologna (RFO program), MIUR (FFABR 2017), and F.I.S. (Fabbrica Italiana Sintetici).

Acknowledgments: We thank Luca Zuppiroli for performing mass spectrometry measurements.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Jiao, L.; Yu, Z.-X. Vinylcyclopropane derivatives in transition-metal-catalyzed cycloadditions for the synthesis of carbocyclic compounds. *J. Org. Chem.* **2013**, *78*, 6842–6848.

2. Venkataraman, G.; Chandrasekaran, S. Recent advances in the synthesis and reactivity of vinylcyclopropanes. *Synthesis* **2016**, 4347-4380.
3. Meazza, M.; Guo, H.; Rios, R. Synthetic applications of vinyl cyclopropane opening. *Org. Biomol. Chem.* **2017**, *15*, 2479–2490.
4. Allen, B.D.W.; Lakeland, C.P.; Harrity, J.P.A. Utilizing palladium-stabilized zwitterions for the construction of N-heterocycles. *Chem. Eur. J.* **2017**, *23*, 13830–13857.
5. Fumagalli, G.; Stanton, S.; Bower, J.F. Recent methodologies that exploit C–C single-bond cleavage of strained ring systems by transition metal complexes. *Chem. Rev.* **2017**, *117*, 9404–9432.
6. Shimizu, I.; Ohashi, Y.; Tsuji, J. Palladium-catalyzed [3+2] cycloaddition reaction of vinylcyclopropanes with α,β-unsaturated esters or ketones. *Tetrahedron Lett.* **1985**, *26*, 3825–3828.
7. Wang, Q.; Wang, C.; Shi, W.; Xiao, Y.; Guo, H. Pd-catalyzed diastereoselective [3+2] cycloaddition of vinylcyclopropanes with sulfamate-derived cyclic imines. *Org. Biomol. Chem.* **2018**, *16*, 4881–4887.
8. Ling, J.; Laugeois, M.; Ratovelomanana-Vidal, V.; Vitale, M.R. Palladium(0)-catalyzed diastereroselective (3+2) cycloadditions of vinylcyclopropanes with sulfonyl-activated imines. *Synlett* **2018**, *29*, 2288–2292.
9. Spielmann, K.; Tosi, E.; Lebrun, A.; Niel, G.; van der Lee, A.; de Figueiredo, R.M.; Campagne, J.-M. Vinylaziridines and cyclopropanes in Pd-catalyzed (3+2)-cycloaddition reactions with cyclic N-sulfonyl imines. *Tetrahedron* **2018**, *74*, 6497–6511.
10. Huang, X.-B.; Li, X.-J.; Li, T.-T.; Chen, B.; Chu, W.-D.; He, L.; Liu, Q.-Z. Palladium-catalyzed highly enantioselective cycloaddition of vinyl cyclopropanes with imines. *Org. Lett.* **2019**, *21*, 1713–1716.
11. Dieskau, A.P.; Holzwarth, M.S.; Plietker, B. Fe-Catalyzed allylic C−C-bond activation: Vinylcyclopropanes as versatile a1,a3,d5-synthons in traceless allylic substitutions and [3 + 2]-cycloadditions. *J. Am. Chem. Soc.* **2012**, *134*, 5048–5051.
12. Pursley, D.; Plietker, B. Insertion of imines into vinylcyclopropanes catalyzed by nucleophilic iron complexes: A formal [3+2]-cycloaddition strategy for the synthesis of substituted pyrrolidine derivatives. *Synlett* **2014**, *25*, 2316–2318.
13. Tombe, R.; Kurahashi, T.; Matsubara, S. Nickel-catalyzed cycloaddition of vinylcyclopropanes to imines. *Org. Lett.* **2013**, *15*, 1791–1793.
14. Trost, B.M.; Fandrick, D.R. Dynamic kinetic asymmetric cycloadditions of isocyanates to vinylaziridines. *J. Am. Chem. Soc.* **2003**, *125*, 11836–11837.
15. Allen, A.E.; MacMillan, D.W.C. Synergistic catalysis: A powerful synthetic strategy for new reaction development. *Chem. Sci.* **2012**, *3*, 633–658.
16. Chen, D.-F.; Han, Z.-Y.; Zhou, X.-L.; Gong, L.-Z. Asymmetric organocatalysis combined with metal catalysis: Concept, proof of concept, and beyond. *Acc. Chem. Res.* **2014**, *47*, 2365–2377.
17. Mukherjee, S.; List, B. Chiral counteranions in asymmetric transition-metal catalysis: Highly enantioselective Pd/Brønsted acid-catalyzed direct α-allylation of aldehydes. *J. Am. Chem. Soc.* **2007**, *129*, 11336–11337.
18. Halskov, K.S.; Næsborg, L.; Tur, F.; Jørgensen, K.A. Asymmetric [3+2] cycloaddition of vinylcyclopropanes and α,β-unsaturated aldehydes by synergistic palladium and organocatalysis. *Org. Lett.* **2016**, *18*, 2220–2223.
19. Meazza, M.; Rios, R. Synergistic catalysis: Enantioselective ring expansion of vinyl cyclopropanes combining four catalytic cycles for the synthesis of highly substituted spirocyclopentanes bearing up to four stereocenters. *Chem. Eur. J.* **2016**, *22*, 9923–9928.
20. Laugeois, M.; Ponra, S.; Ratovelomanana-Vidal, V.; Michelet, V.; Vitale, M.R. Asymmetric preparation of polysubstituted cyclopentanes by synergistic Pd(0)/amine catalyzed formal [3+2] cycloadditions of vinyl cyclopropanes with enals. *Chem. Commun.* **2016**, *52*, 5332–5335.
21. Zhang, K.; Meazza, M.; Izaga, A.; Contamine, C.; Gimeno, M.C.; Herrera, R.P.; Rios, R. Synergistic catalysis: Asymmetric synthesis of cyclopentanes bearing four stereogenic centers. *Synthesis* **2017**, *49*, 167–174.
22. Kamlar, M.; Franc, M.; Císařová, I.; Gyepes, R.; Vesely, J. Formal [3+2] cycloaddition of vinylcyclopropane azlactones to enals using synergistic catalysis. *Chem. Commun.* **2019**, *55*, 3829–3832.
23. Afewerki, S.; Córdova, A. Combinations of aminocatalysts and metal catalysts: A powerful cooperative approach in selective organic synthesis. *Chem. Rev.* **2016**, *116*, 13512–13570.
24. Olmstead, W.N.; Bordwell, F.G. Ion-pair association constants in dimethyl sulfoxide. *J. Org. Chem.* **1980**, *45*, 3299–3305.

25. Christ, P.; Lindsay, A.G.; Vormittag, S.S.; Neudörfl, J.-M.; Berkessel, A.; O'Donoghue, A.C. pK_a Values of chiral Brønsted acid catalysts: Phosphoric acids/amides,sulfonyl/sulfuryl imides, and perfluorinated TADDOLs (TEFDDOLs). *Chem. Eur. J.* **2011**, *17*, 8524–8528.
26. McCallum, C.; Pethybridge, A.D. Conductance of acids in dimethyl-sulphoxide—II. Conductance of some strong acids in DMSO at 25 °C. *Electrochim. Acta* **1975**, *20*, 815–818.
27. Spielmann, K.; van der Lee, A.; de Figueiredo, R.M.; Campagne, J.-M. Diastereoselective palladium-catalyzed (3+2)-cycloadditions from cyclic imines and vinyl aziridines. *Org. Lett.* **2008**, *20*, 1444–1447.
28. Trost, B.M.; Toste, F.D. Regio- and enantioselective allylic alkylation of an unsymmetrical substrate: a working model. *J. Am. Chem. Soc.* **1999**, *121*, 4545–4554.
29. Trost, B.M.; Morris, P.J.; Sprague, S.J. Palladium-catalyzed diastereo- and enantioselective formal [3+2]-cycloadditions of substituted vinylcyclopropanes. *J. Am. Chem. Soc.* **2012**, *134*, 17823–17831.
30. Laugeois, M.; Ling, J.; Férard, C.; Michelet, V.; Ratovelomanana-Vidal, V.; Vitale, M.R. Palladium(0)-catalyzed dearomative [3+2] cycloaddition of 3-nitroindoles with vinylcyclopropanes: An entry to stereodefined 2,3-fused cyclopentannulated indoline derivatives. *Org. Lett.* **2017**, *19*, 2266–2269.
31. Leth, L.A.; Glaus, F.; Meazza, M.; Fu, L.; Thøgersen, M.K.; Bitsch, E.A.; Jørgensen, K.A. Decarboxylative [4+2] cycloaddition by synergistic palladium and organocatalysis. *Angew. Chem. Int. Ed.* **2016**, *55*, 15272–15726.
32. Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. Complete field guide to asymmetric BINOL-phosphate derived Brønsted acid and metal catalysis: History and classification by mode of activation; Brønsted acidity, hydrogen Bonding, ion pairing, and metal phosphates. *Chem. Rev.* **2014**, *114*, 9047–9153.
33. Caruana, L.; Fochi, M.; Ranieri, S.; Mazzanti, A.; Bernardi, L. Catalytic highly enantioselective vinylogous Povarov reaction. *Chem. Commun.* **2013**, *49*, 880–882.
34. Gottlieb, H.E.; Kotlyar, V.; Nudelman, A. NMR Chemical Shifts of Common Laboratory Solvents as Trace Impurities. *J. Org. Chem.* **1997**, *62*, 7512–7515.
35. Wei, F.; Ren, C.-L.; Wang, D.; Liu, L. Highly enantioselective [3+2] cycloaddition of vinylcyclopropane with nitroalkenes catalyzed by palladium(0) with a chiral bis(*tert*-amine) ligand. *Chem. Eur. J.* **2015**, *21*, 2335–2338.