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Asymmetric Catalysis

One-Pot Tandem Diastereoselective and Enantioselective Synthesis of Functionalized Oxindole-Fused Spiropyrazolidine Frameworks

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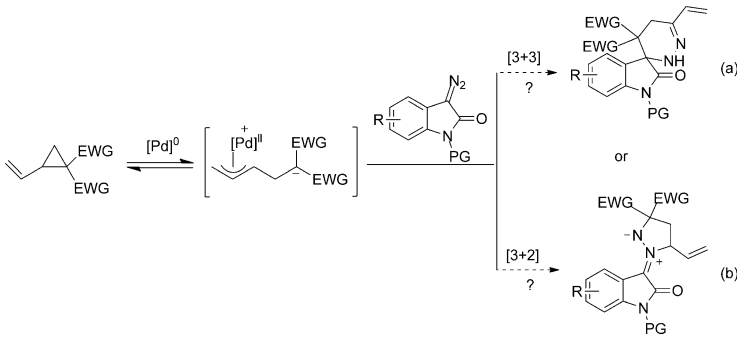
Abstract: A highly efficient palladium(0)-catalyzed asymmetric [3+2] cycloaddition using 3-diazooxindoles serving as dipolarophiles affords functionalized pyrazolidine derivatives in an atom-economical way. In addition, by trapping the pyrazolidine derivatives with maleimides, the corresponding spiropyrazolidine oxindoles containing multiple stereogenic centers have been obtained in high yields along with moderate to good levels of diastereoselectivity and enantioselectivity under mild conditions. Thus, a novel three-component one-pot tandem reaction has been developed.

The spirooxindole core is one of the most important structural motifs and exists in a number of natural products and pharmacological compounds with diverse bioactivity properties.[1] It has consequently captured great interest from synthetic and medicinal chemists, and many elegant approaches for its synthesis have been developed.[2] As a new kind of synthetic precursors for the construction of spirocyclic oxindoles, 3-diazooxindoles have recently caught much attention. By reacting with transition metals, 3-diazooxindoles can generate transient electrophilic carbenoids, which can undergo a wide range of attractive reactions such as cyclopropanations,[3] X–H insertions,[4] ylide formations,[5] and the other reactions.[6] However, among these transformations, the release of nitrogen is inevitable, which is not atom economical. To avoid this disadvantage, new types of reactions should be employed in an atom-economical way by retaining the nitrogen atoms of 3-diazooxindoles. As a matter of fact, early in 1993, Kascheres and co-workers introduced a novel synthesis of 1,2,3-triazoles through the reactions of 3-diazooxindoles with enaminones, in which 3-diazooxindoles were used as a source for generating dipoles.[7] Later, Kanemasa et al. showed the first successful examples of enantioselective [3+2] cycloadditions of trimethylsilyldiazomethane with 3-(2-alkenoyl)-2-oxazolidinones by using (*R*,*R*)-DBFOX/Ph metal perchlorate complexes as chiral Lewis acids.[8] Afterwards, several similar [3+2] annulations of other diazo substrates, such as diazoalkanes or diazoacetates, with various olefins in the presence of a base,[9] Lewis acid,[10] or in the absence of such an additive[11] have been reported. Nevertheless, among these works, all diazo compounds are restricted to acting as 1,3-dipoles that react with a dipolarophile. In addition, owing to the C–N and N–N multiple bonds, 3-diazooxindoles could also serve as potential dipolarophiles for participation in annulations with an additional 1,3-dipole; however, work related to this has not been disclosed so far. Therefore, we attempted to apply 3-diazooxindoles in the cycloaddition reactions, either by its interaction with a dipolarophile as the 1,3-dipole, or with a 1,3-dipole as the dipolarophile, thus providing an atom-economical and facile way to prepare heterocyclic compounds containing an N–N bond.



Scheme 1. Palladium-catalyzed cycloaddition of vinyl cyclopropanes with 3-diazooxindoles. EWG = electron-withdrawing group.

Recently, vinyl cyclopropanes bearing electron-withdrawing groups have emerged as useful intermediates for the synthesis of various cyclic compounds.[12] By generating the 1,3-dipolar compound in the presence of a Pd(0) catalyst and subsequent trapping with diverse dipolarophiles,[13] vinyl cyclopropanes can provide direct ways to a variety of substituted five-mem-

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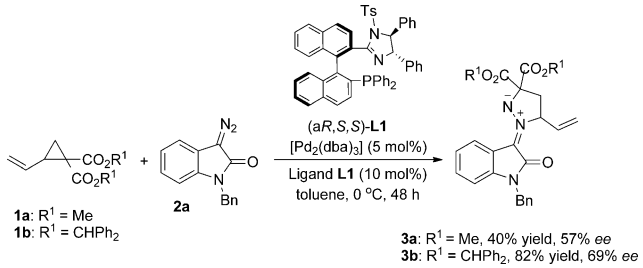
bered rings. On this aspect, we have previously reported on the Pd(0)-catalyzed [3+2] cycloaddition of vinylcyclopropane with β,γ-unsaturated α-ketoesters to afford functionalized cyclopentanes;[13f] we have also reported on the diastereo- and enantioselective construction of oxindole-fused spirotetrahydrofuran scaffolds through palladium-catalyzed [3+2] cycloaddition of vinylcyclopropane and isatins in the presence of chiral imidazoline–phosphine ligands.[13g] As part of our ongoing investigations into these cycloadditions as well as our goal to construct heterocyclic compounds containing an N–N bond, as we proposed above, we envisaged to transform 3-diazooxindoles through use of a Pd/chiral imidazoline–phosphine catalytic system (Scheme 1). On one hand, spiropyridazine oxindoles could be obtained through a [3+3] cycloaddition when 3-diazooxindoles serve as a source of 1,3-dipoles as reported (Scheme 1, reaction a); on the other hand, the pyrazolidine derivatives could be obtained if 3-diazooxindoles act as the dipolarophiles in a [3+2] annulation reaction (Scheme 1, reaction b).

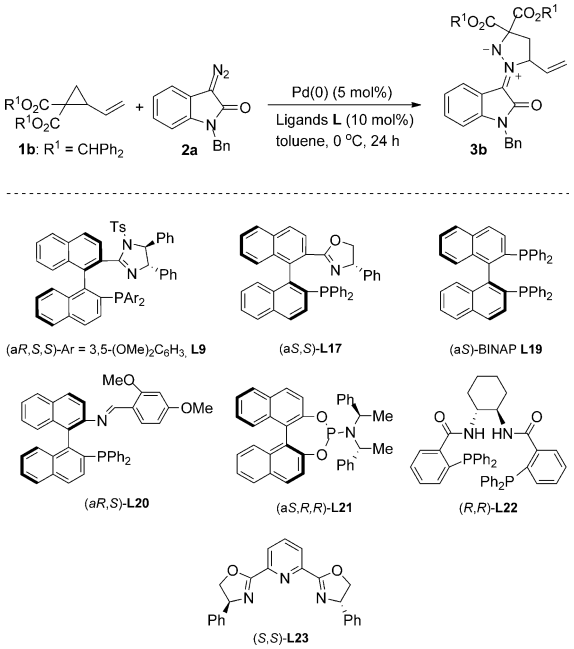
We first examined the reaction between vinyl cyclopropanes **1a** and **1b** with 1-benzyl-3-diazoindolin-2-one (**2a**) in the presence of chiral imidazoline–phosphine ligand (a*R,S,S*)-**L1** and $[Pd_2(dba)_3]$ (dba = dibenzylideneacetone) in toluene at 0 °C, as shown in Scheme 2. To our delight, the [3+2] cycloaddition proceeded smoothly to afford the pyrazolidine derivatives. Using dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (**1a**) as substrate furnished desired product **3a** in 40% yield with 57% *ee*, while the use of dibenzhydryl 2-vinylcyclopropane-1,1-dicarboxylate (**1b**) as substrate produced corresponding adduct **3b** in 82% yield with 69% *ee*. Then, screening of ligands **L1**–**L23** by using dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (**1a**) or dibenzhydryl 2-vinylcyclopropane-1,1-dicarboxylate (**1b**) and 1-benzyl-3-diazoindolin-2-one (**2a**) as model substrates in toluene resulted in chiral imidazoline–phosphine ligand (a*R,S,S*)-**L9** being identified as the best ligands for this reaction; the results of these experiments are summarized in Tables SI-1 and SI-2 in the Supporting Information. Moreover, the screening of solvents, temperature, and additives revealed that conducting the reactions in toluene at 0 °C provided the best outcomes, the results being summarized in Table SI-3 in the Supporting Information.



Scheme 2. Initial results for the Pd-catalyzed asymmetric [3+2] cycloaddition.

Based on the above preliminary results, further optimizations by screening the ligands when using dibenzhydryl 2-vinylcyclopropane-1,1-dicarboxylate (**1b**) and 1-benzyl-3-diazoindolin-2-one (**2a**) as the model substrates in the presence of $[Pd_2(dba)_3]$ in toluene at 0 °C were carried out and the results are shown in Table 1. First, the use of chiral imidazoline–phosphine ligand

Table 1. Screening of ligands and Pd catalysts for asymmetric [3+2] cycloaddition.

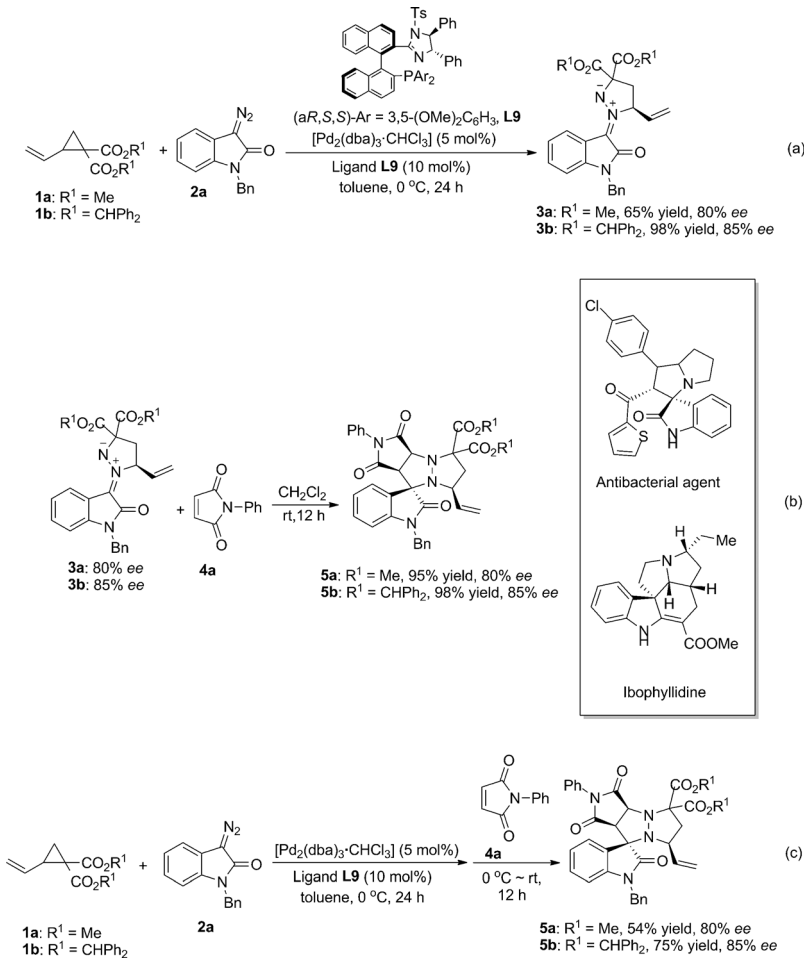


Entry[a]	Pd(0)	Ligand	Yield [%][b]	*ee* [%][c]
1	$[Pd_2(dba)_3]$	**L9**	95	81
2	$[Pd_2(dba)_3]$	**L17**	95	45[e]
3	$[Pd_2(dba)_3]$	**L19**	61	41[e]
4	$[Pd_2(dba)_3]$	**L20**	trace	n.d.
5	$[Pd_2(dba)_3]$	**L21**	trace	n.d.
6	$[Pd_2(dba)_3]$	**L22**	trace	n.d.
7	$[Pd_2(dba)_3]$	**L23**	trace	n.d.
8	$[Pd_2(dba)_3{\cdot}CHCl_3]$	**L9**	98	85
9	$[Pd_2\{3,5\text{-}(OMe)_2\text{-}dba\}_3]$	**L9**	96	81
10[d]	$[Pd_2(dba)_3{\cdot}CHCl_3]$	**L9**	95	85
11[d]	$[Pd_2(dba)_3]$	**L9**	92	81

[a] The reaction was conducted with **1b** (0.1 mmol) and **2a** (0.15 mmol) in solvent (1.0 mL). [b] Yield of isolated product. [c] The *ee* values were determined by HPLC by using a Chiralcel IB-3 column. [d] 30 mol% $CHCl_3$ was added. [e] The sense of enantioselectivity is opposite that found for **L9**.

L9 yielded desired product **3b** in 95% yield with 81% *ee*, while chiral phosphine–oxazoline ligand **L17** afforded product **3b** in 95% yield with 45% *ee* in favor of the other enantiomer (Table 1, entries 1 and 2). Next, we found that chiral BINAP ligand **L19** was also effective, though giving desired product **3b** in lower yield and *ee* value (Table 1, entry 3). However, other ligands such as **L20**–**L23** with different chiral scaffolds produced **3b** in a trace amount (Table 1, entries 4–7). On the basis of these experiments, we chose dibenzhydryl 2-vinylcyclopropane-1,1-dicarboxylate (**1b**) and 1-benzyl-3-diazoindolin-2-one (**2a**) as substrates, toluene as the solvent, and **L9** as the ligand to screen the Pd(0) source. We found that replacing $[Pd_2(dba)_3]$ with $[Pd_2(dba)_3{\cdot}CHCl_3]$ resulted in the formation of **3b** in 98% yield with 85% *ee* (Table 1, entry 8). Nevertheless, replacing $[Pd_2(dba)_3]$ with $[Pd_2\{3,5\text{-}(OMe)_2\text{-}dba\}_3]$ did not lead to better reaction outcomes (Table 1, entry 9). Considering that the trace of $CHCl_3$ in $[Pd_2(dba)_3{\cdot}CHCl_3]$ may serve as an additive in the reaction, a small amount of $CHCl_3$ (30 mol%) was added into the reaction mixtures so as to improve the reaction outcome; unfortunately, no significant improvement was observed (Table 1, entries 10 and 11). Therefore, the use of $[Pd_2(dba)_3{\cdot}CHCl_3]$ as the Pd(0) source, **L9** as the ligand, and toluene as the solvent, is the optimized conditions for this reaction (Table 1, entry 8).

Having established the optimal reaction conditions, we next turned our attention to the substrate scope and transformation of the products, the results being shown in Scheme 3. Using dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (**1a**) or dibenzhydryl 2-vinylcyclopropane-1,1-dicarboxylate (**1b**) with 1-benzyl-3-diazoindolin-2-one (**2a**) as the substrates, desired pyrazolidine derivatives **3a** and **3b** were obtained in good yields with moderate to good *ee* values (Scheme 3, equation a). Notably, products **3** could be employed as latent efficient 1,3-dipoles because they have a similar structure to that of azomethine imines.[14] Thus, we used *N*-phenylmaleimide (**4a**) as a dipolarophile to react with **3** so as to realize a later-stage [3+2] annulation. Indeed, the reaction between **3** and **4a** proceeded smoothly in CH_2Cl_2 at room temperature to deliver desired functionalized spiropyrazolidine oxindoles **5** in quantitative yields without alteration of *ee* values (Scheme 3, equation b). Moreover, because some reported antibacterial agents[11] and natural products, such as ibophyllidine,[15] have scaffolds similar to those of spiropyrazolidine oxindoles **5**, we were encouraged to further explore these two sequential cycloadditions through the construction of oxindole-fused spiropyrazolidine frameworks **5** owing to their potential interesting biological activities (Scheme 3, equation b). Therefore, we attempted to develop a one-pot tandem [3+2] cycloaddition of vinylcyclopropanes **1**, 3-diazooxindoles **2**, and maleimides **4** in the presence of $[Pd_2(dba)_3{\cdot}CHCl_3]$ and chiral imidazoline–phosphine ligand (a*R*,*S*,*S*)-**L9**. Because the product's enantioselectivity was determined in the first step of the [3+2]-cycloaddition between vinylcyclopropane **1** and 3-diazooxindole **2**, no alteration of *ee* value would be observed for the one-pot tandem process. As can be seen from Scheme 3, the spiropyrazolidine oxindoles **5a** and **5b** were successfully obtained in 54 and 75% yields, respectively, through the one-pot tandem reaction process with no alteration of *ee* values as expected compared with the stepwise process (Scheme 3, equation c). It should be emphasized here that the imidazoline–phosphine ligand plays a significant role in the formation of pyrazolidine derivatives **3** because much lower yields or *ee* values of **3** were obtained in the presence of other phosphine ligands.

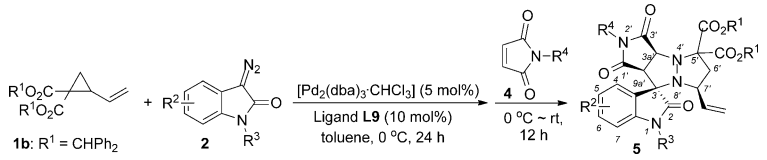


Scheme 3. Substrate scope for [3+2] cycloaddition and a trial one-pot tandem reaction.

Having determined the viability of three-component one-pot tandem reaction, different substrates **1** were examined by using 1-benzyl-3-diazoindolin-2-one (**2a**) and *N*-phenylmaleimide (**4a**) as the model substrates in the presence of [Pd_2-(dba)$_3$·$CHCl_3$] and ligand (a*R,S,S*)-**L9** and the results are summarized in Table SI–4 in the Supporting Information. No further remarkable improvement on the reaction outcomes was observed by screening a wide range of substrates **1** bearing different ester groups, such as substrates **1c**–**1k** under the standard reaction conditions. Thus, we used dibenzhydryl 2-vinylcyclopropane-1,1-dicarboxylate (**1b**), 1-benzyl-3-diazoindolin-2-one (**2a**), and *N*-phenylmaleimide (**4a**) as the substrates, toluene as the solvent, and [Pd_2(dba)$_3$·$CHCl_3$] as the catalyst in the presence of ligand (a*R,S,S*)-**L9** as the optimal reaction conditions; an array of 3-diazooxindoles **2** and maleimides **4** were evaluated and the results are shown in Table 2. At first, using dibenzhydryl 2-vinylcyclopropane-1,1-dicarboxylate (**1b**) and 1-benzyl-3-diazoindolin-2-one (**2a**) as the model substrate, we examined a variety of maleimides **4b**–**4e** bearing different N-protecting groups (Table 2, entries 2–5). All these N-protecting groups were tolerated in this reaction, affording structurally varied spiropyrazolidine oxindoles **5ab**–**5ae** in moderate yields with moderate to good levels of diastereoselectivity and 85% *ee*, while *N*-methylmaleimide (**4c**) gave the best performance. Then, different 3-diazooxindoles **2** that exhibit diverse electronic and steric effects were studied using dibenzhydryl 2-vinylcyclopropane-1,1-dicarboxylate (**1b**) and *N*-methylmaleimide (**4c**) as the model substrate (Table 2, entries 6–21). Using 3-diazooxindoles bearing different types of N-protecting groups such as **2b**, **2c**, and **2d**, the desired spirocyclic oxindoles **5bc**, **5cc** and **5dc** were obtained in 72–85% yields with 8.1:1–11.5:1 levels of diastereoselectivity and 77–80% *ee* (Table 2, entries 6–8). Subsequently, the influence of substituents at different positions of the aromatic rings of 3-diazooxindoles was explored. As can be seen from Table 2, this protocol is amenable to a diverse array of 3-diazooxindoles **2** with electronically different substituents at the C5, C6, or C7 positions, giving the corresponding spiropyrazolidine oxindoles **5fc**–**5qc** in 52–84% yields with 6.7:1–11.5:1 levels of diastereoselectivity and 61–90% *ee* (Table 2, entries 10–21). The electronic nature of the substituents impacts on the enantioselectivity and reactivity. For example, 3-diazooxindoles **2f**, **2j**, **2k**, **2o**, and **2q** with electron-donating groups on the aromatic rings produced the corresponding products **5** with 82–90% *ee* (Table 2, entries 10, 14, 15, 19, and 21), while **2g**, **2h**, **2i**, **2l**, **2m**, **2n**, and **2p** with electron-withdrawing groups on the aromatic rings delivered the corresponding products **5** with 61–80% *ee* (Table 2, entries 11–13, 16–18, and 20). However, when R^2 is at the C4 position of 3-diazooxindoles, no reaction occurred perhaps owing to a steric effect (Table 2, entry 9). To our delight, the levels of enantioselectivity of spiropyrazolidine oxindoles **5** could be largely improved by recrystallization from CH_2Cl_2/*i*PrOH/*n*-hexane (Table 2, entries 1, 15, and 17–19). Moreover, the configuration of racemate **3a** has been confirmed by X-ray diffraction, and the absolute configuration of **5oc** has also been assigned by X-ray diffraction as 3*R*, 3a′*S*, 7′*S*, 9a′*S*. Accordingly, the products **5a**–**5qc** have the same 3*R*, 3a′*S*, 7′*S*, 9a′*S* absolute configuration and the pyrazolidine derivatives **3a** and **3b** have the same *S* absolute configuration at C7′ position as that of **5oc**. The ORTEP drawing of **3a** and **5oc** and their CIF data are shown in the Supporting Information.[16]

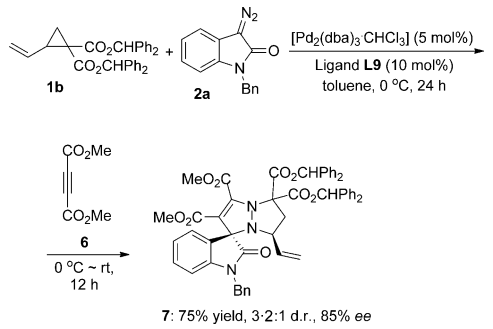
To illustrate the generality of the Pd(0)/**L9** catalytic system, dimethyl acetylenedicarboxylate **6** was used as a dipolarophile to trap the 1,3-dipole intermediate formed in situ by the reaction of **1b** and **2a**, and the reaction was examined under the standard reaction conditions (Scheme 4). Notably, desired functionalized spiropyrazolidine oxindole **7** was obtained in 75% yield, 3.2:1 d.r., and 85% *ee* in a single operation.

Table 2. Substrate scope for the Pd/**L9**-catalyzed one-pot tandem reaction.



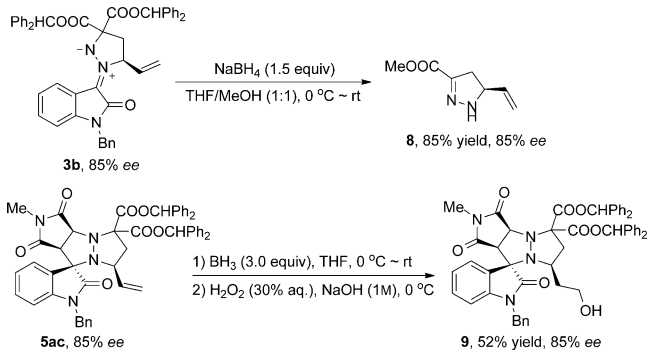
Entry[a]	R^1	R^2/R^3	R^4	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	$CHPh_2$, **1b**	H/Bn, **2a**	Ph, **4a**	**5b**, 75	6.1:1	85 (93)[f]
2	$CHPh_2$, **1b**	H/Bn, **2a**	H, **4b**	**5ab**, 72	4.0:1	85
3	$CHPh_2$, **1b**	H/Bn, **2a**	Me, **4c**	**5ac**, 80	9.0:1	85
4	$CHPh_2$, **1b**	H/Bn, **2a**	Bn, **4d**	**5ad**, 60	2.1:1	85
5	$CHPh_2$, **1b**	H/Bn, **2a**	$CHPh_2$, **4e**	**5ae**, 56	1.7:1	85
6	$CHPh_2$, **1b**	H/Me, **2b**	Me, **4c**	**5bc**, 81	8.1:1	80
7	$CHPh_2$, **1b**	H/MOM, **2c**	Me, **4c**	**5cc**, 85	11.5:1	80
8	$CHPh_2$, **1b**	H/Boc, **2d**	Me, **4c**	**5dc**, 72	10.1:1	77
9	$CHPh_2$, **1b**	4-Cl/Bn, **2e**	Me, **4c**	**5ec**, 0	n. d.[e]	–
10	$CHPh_2$, **1b**	5-Me/Bn, **2f**	Me, **4c**	**5fc**, 81	8.1:1	87
11	$CHPh_2$, **1b**	5-F/Bn, **2g**	Me, **4c**	**5gc**, 76	6.7:1	80
12	$CHPh_2$, **1b**	5-I/Bn, **2h**	Me, **4c**	**5hc**, 67	10.1:1	68
13	$CHPh_2$, **1b**	5-NO_2/Bn, **2i**	Me, **4c**	**5ic**, 70	9.0:1	64
14	$CHPh_2$, **1b**	6-Me/Bn, **2j**	Me, **4c**	**5jc**, 84	10.1:1	82
15	$CHPh_2$, **1b**	6-OMe/Bn, **2k**	Me, **4c**	**5kc**, 78	7.3:1	84 (97)[f]
16	$CHPh_2$, **1b**	6-Cl/Bn, **2l**	Me, **4c**	**5lc**, 80	7.3:1	72
17	$CHPh_2$, **1b**	7-Br/Bn, **2m**	Me, **4c**	**5mc**, 78	9.0:1	61 (90)[f]
18	$CHPh_2$, **1b**	7-CF_3/Bn, **2n**	Me, **4c**	**5nc**, 52	11.5:1	65 (86)[f]
19	$CHPh_2$, **1b**	5,7-Me_2/Bn, **2o**	Me, **4c**	**5oc**, 81	9.0:1	90 (97)[f]
20	$CHPh_2$, **1b**	5,7-Cl_2/Bn, **2p**	Me, **4c**	**5pc**, 53	9.0:1	63
21	$CHPh_2$, **1b**	5-Cl, 7-Me/Bn, **2q**	Me, **4c**	**5qc**, 73	7.3:1	84

[a] The reaction was conducted with **1** (0.1 mmol), **2** (0.15 mmol), and **4** (0.12 mmol) in toluene (1.0 mL). [b] Yield of isolated major isomer. [c] The diastereomeric ratios were determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [d] The *ee* values were determined by HPLC by using Daicel IB-3 and IF-3 columns. [e] Not detected. [f] After crystallization from CH_2Cl_2/*i*PrOH/*n*-hexane.



Scheme 4. Extension of the Pd/**L9**-catalyzed one-pot tandem reaction.

We have further explored the transformations of products **3** and **5** in order to illustrate their synthetic utility. As shown in Scheme 5, product **3b** could be easily converted into compound **8** in 85% yield with 85% *ee* by a simple treatment with $NaBH_4$ in THF/MeOH (1:1) through a cascade reaction process;

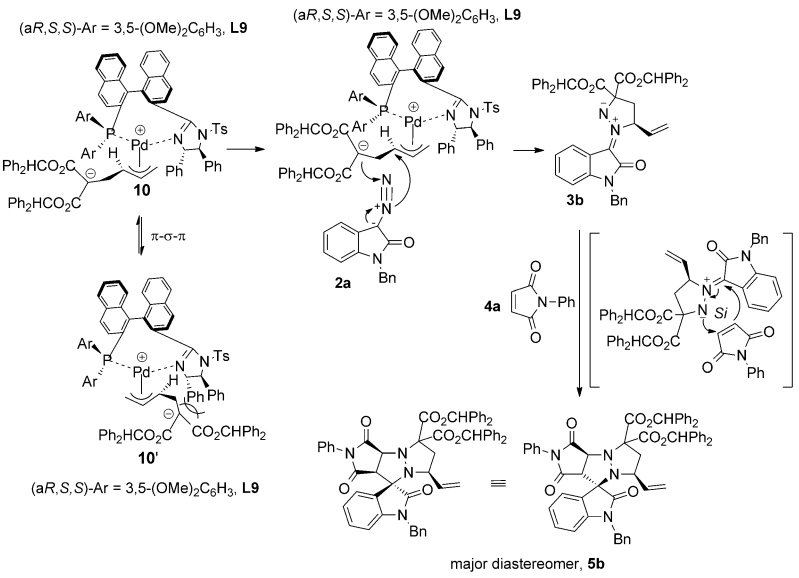


Scheme 5. Transformations of products **3b** and **5ac**.

a proposed mechanism has been shown in Scheme SI-1 in the Supporting Information. Furthermore, the corresponding alcohol **9** could be obtained from **5ac** in 52% yield with 85% *ee* through hydroboration with BH_3 in THF and subsequent treatment with 1.0 M aqueous solution of sodium hydroxide and 30% aqueous hydrogen peroxide solution. No significant change could be observed in the levels of enantioselectivity during these transformations.

To explain the stereochemical outcome of this Pd/**L9**-catalyzed tandem reaction, we tentatively proposed a plausible reaction mechanism based on our experimental results and previously reported mechanistic studies (Scheme 6).[13a,d,f,g] Firstly, the key zwitterionic (π-allyl) palladium intermediates **10** and **10′** were formed through initial nucleophilic attack of palladium at the double bond of vinylcyclopropane **1b** and interconvert through π–σ–π equilibration. Owing to the more significant steric repulsion between the phenyl group on imidazoline–phosphine ligand **L9** and the malonate moiety in vinylcyclopropane **1b**, intermediate **10** is thermodynamically more favored. Then, the nucleophilic attack of the malonate anion onto the N–N triple bond in 3-diazooxindole **2a** and the subsequent nucleophilic attack of another nitrogen atom on the in situ generated (π-allyl) palladium complex **10** gave the desired product **3b** along with the release of the Pd catalyst. Finally, observed major diastereomer **5b** was obtained through the [3+2] cycloaddition of **3b** with maleimide **4a** through the *Si* face of **4a** owing to the steric repulsion of vinyl group on **3b**.

In conclusion, we have disclosed the construction of functionalized pyrazolidine derivatives by using 3-diazooxindoles as dipolarophiles through a highly efficient palladium(0)-catalyzed asymmetric [3+2] cycloaddition in an atom-economical way. Furthermore, by trapping the pyrazolidine intermediates with maleimides, the spiropyrazolidine oxindoles containing multiple stereogenic centers have been obtained in high yields along with moderate to good levels of diastereoselectivity and enantioselectivity under mild reaction conditions. Thus, a novel one-pot tandem reaction of vinylcyclopropanes, 3-diazooxindoles and maleimides in the presence of $[Pd_2(dba)_3{\cdot}CHCl_3]$ and chiral imidazoline–phosphine ligand (a*R*,*S*,*S*)-**L9** has been developed. Imidazoline–phosphine ligand plays a crucial role to give the corresponding products in good yields and *ee* values. Further investigations on expanding the scope of this reaction towards a wide range of other 1,3-dipoles as well as the applications of this protocol to natural product synthesis are in progress.



Scheme 6. Proposed mechanism.

Acknowledgement

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