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Palladium-catalysed ring-opening [3 + 2]annulation of spirovinylcyclopropyl oxindole to diastereoselectively access spirooxindoles[†]

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A novel palladium-catalysed ring-opening [3 + 2]-annulation of spirovinylcyclopropyl oxindole with α,β -unsaturated nitroalkenes is reported. A series of spirooxindole derivatives were synthesized in high yields and good to excellent diastereoselectivities. This developed protocol offers a new and efficient pathway for the assembly of spirooxindoles.

Introduction

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Donor-acceptor cyclopropane (DAC) has attracted significant attention recently, due to its versatile reactivities and high efficiency in the construction of cyclic compounds.¹ In general, ring-opening [3 + n]-cycloadditions/annulations are the major work modes, which usually involve the generation of highly reactive dipoles promoted by a Lewis acid,² protic acid,³ Lewis base⁴ and palladium(0) catalyst.⁵ Among all the DACs, vinylcyclopropanes (VCPs) have attracted special attention due to their unparalleled reactivities in the context of the ringopening strategy (Scheme 1).⁶ In particular, VCPs can be used to access multicyclic or spirocyclic derivatives with the aid of a palladium(0) complex or Lewis acid.^{6a,b} Several elegant protocols have been established for the formation of spirocyclic compounds via the ring-opening [3 + 2]-annulation of VCPs with dipolarophiles.^{6c,7} Despite these encouraging advances in the synthetic utilization of VCPs, the exploitation of a new VCP-based methodology is still extremely attractive to meet the demand in the diversity and complexity of ring systems and allow for the facile construction of a wide range of cyclic scaffolds.8

Spirooxindoles are important core skeletons in biologically active alkaloids and relevant natural products (Scheme 2).⁹ Compounds bearing spirooxindole units have proven to

^aCollege of Chemistry and Materials Science, Guangxi Teachers Education University, Nanning 530001, P. R. China possess interesting biological activities such as antitumor, antibiotic and antiparasitic activities.¹⁰ For example, citrinadine B, isolated from *Penicillium citrinum* N059 by Kobayashi, displays cytotoxicity against murine leukemia L1210 cells.¹¹ Marcfortine A is a fungal metabolite of *Penicillium roqueforti* showing potent antiparasitic activity.¹² Noticing the existence of a spiro(cyclopentyl-3-oxindole) scaffold in these bioactive compounds, we envisaged that ring-opening of spirovinylcyclopropane oxindole (SVCP) might offer an efficient approach to access these spirooxindole structures. Unfortunately, this strategy has been rarely applied to construct spirooxindoles.¹³ Herein we describe a practical protocol *via* a palladium-cata-



Scheme 1 Construction of spirocyclic scaffolds via [3 + 2]-cycloaddition/annulation of vinyl cyclopropanes.



Scheme 2 Representative natural products bearing spirooxindole motifs.

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lysed ring-opening [3 + 2] annulation of SVCP for the diastereoselective synthesis of spirooxindole derivatives under mild conditions. This novel protocol would offer alternative pathways stereoselectively accessing spirocyclic systems.

Results and discussion

We initiated our studies by testing a model reaction of spirovinylcyclopropane oxindole **1a** and β -nitrostyrene **2a** catalysed by Pd(OAc)₂ and *S*-BINAP. It is noteworthy that **1a** was synthesized from *N*-benzyl-2-oxindole and **1**,4-dibromobut-2-ene in a moderate yield with >20:1 dr. Unfortunately, only 41% of diastereomer **1a**' was isolated and the desired annulation product **3a** was unable to be accessed (Scheme 3).

In order to establish a viable protocol for this strategy, a variety of Pd(II) salts and ligands were tested in this annulation process (as shown in Table 1). Interestingly, using 10 mol% of $Pd(PPh_3)_4$ as the catalyst in toluene afforded the corresponding product **3a** in 44% yield with 74 : 26 dr (Table 1, entry 1). Next, various ligands were also evaluated by using $Pd(OAc)_2$ as the catalyst. Lower yields of **3a** were obtained in the presence of 1,3-bis(diphenylphosphino)propane (DPPP) or PPh₃ (Table 1, entries 2 and 3). Pleasingly, the employment of xantphos gave the desired product **3a** in 89% yield and 86 : 14 dr within 12 h



Scheme 3 Preliminary study of the designed strategy

Table 1	Optimization	of reaction	conditions
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Entry	Cat.	Ligand	Solvent	Time (h)	$\operatorname{Yield}^{b}(\%)$	$\mathrm{dr}^{c}\left(\% ight)$
1	$Pd(PPh_3)_4$	_	Toluene	24	44	74:26
2	$Pd(OAc)_2$	DPPP	Toluene	24	31	86:14
3	$Pd(OAc)_2$	PPh ₃	Toluene	24	27	75:25
4	$Pd(OAc)_2$	Xantphos	Toluene	12	89	86:14
5	$Pd_2(dba)_3$	Xantphos	Toluene	12	81	86:14
5	$Pd(OAc)_2$	Xantphos	CH_2Cl_2	12	67	72:28
7	$Pd(OAc)_2$	Xantphos	DCE	12	90	71:29
8	$Pd(OAc)_2$	Xantphos	THF	12	80	58:42
Ð	$Pd(OAc)_2$	Xantphos	MeOH	12	16	52:48
10	$Pd(OAc)_2$	Xantphos	DMSO	12	83	75:25
11	$Pd(OAc)_2$	Xantphos	MeCN	12	77	61:39
12^d	$Pd(OAc)_2$	Xantphos	Toluene	12	88	85:15
13 ^e	$Pd(OAc)_2$	Xantphos	Toluene	12	85	82:18
14^f	$Pd(OAc)_2^2$	Xantphos	Toluene	24	77	82:18

^{*a*} Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), Pd salts (5 mol%), ligand (10 mol%), solvent (2.0 mL), rt, 12–24 h. ^{*b*} Isolated yield. ^{*c*} Determined by ¹H NMR, based on the isolated product. ^{*d*} The ratio of **1a** : **2a** = 1 : 1.5. ^{*e*} The ratio of **1a** : **2a** = 1 : 1.2. ^{*f*} The ratio of **1a** : **2a** = 1 : 1.

(Table 1, entry 4). The replacement of $Pd(OAc)_2$ with $Pd_2(dba)_3$ led to a slightly decreased yield (81%), but with unchanged dr (Table 1, entry 5). Subsequently, solvents were also extensively examined (entries 6–11) and toluene was proven to be the most suitable solvent for this transformation in terms of yield and diastereoselectivity. It is worth noting that the protonic solvent was found to have a dramatic impact on the efficiency of the annulation reaction (Table 1, entry 9). Presumably, methanol has an effect on the catalytic activity of the palladium catalyst and thus leads to the spirooxindole 3a in a poor yield and diastereoselectivity. Finally, the ratio of spirocyclo-propane 1a and nitroalkenes 2a was also modulated and the yield of 3a was slightly eroded when the amount of nitroalkenes 2a was decreased from 2.0 equiv. to 1.0 equiv. (entries 12–14).

With the optimal reaction conditions established, we next investigated the substrate scope of the title reaction by employing a series of spirovinylcyclopropyl oxindoles and α , β -unsaturated nitroalkenes. Firstly, different *N*-substituted spirocyclopropanes 1 were evaluated. As expected from our optimization efforts, N-protected spirocyclopropanes 1a-1d gave moderate to excellent yields (56%-89%) and good dr (83:17-88:12) (PG = Me, Bn, Allyl and Boc). However, the reaction of unsubstituted spirocyclopropane 1e and nitroalkenes 2a afforded 67% yield but with a significantly decreased diastereomeric ratio (51:49). Subsequently, various substituted spirocyclopropanes 1g-1l were examined. In general, high to good yields (64%-84%) and moderate to excellent drs (57:43-95:5) were achieved with the substitution at the C5, C6 or C7 position on the oxindole moiety. It is worth noting that the diastereoselectivity obviously dropped upon increasing the steric hindrance of the substituting group (1g-1i). The introduction of an electron-donating group onto the oxindole

moiety would slightly decrease the yield and increase the diastereoselectivity (1j). In contrast to C5 and C6 substituted spirocyclopropanes (1h and 1k), the substrate bearing a chloro group at the C7 position afforded a good yield (67%) and an excellent diastereoselectivity (91:9 dr). Next, various α , β -unsaturated nitroalkenes 2a-2l were also investigated. Pleasingly, para-substituted nitroalkenes 2a-2d gave good yields (80%-87%) and drs (81:11-94:6) (Table 2, 3m-3p). It was found that the introduction of a strong electron-donating group onto the phenyl group in nitroalkene 2, no matter on the para-position or the meta-position, would decrease the yield and diastereoselectivity (Table 2, 3q-3r). Interestingly, the ortho-substituted nitroalkenes gave the corresponding product 3s in good dr but the yield was remarkably decreased. Presumably, the difference in reactivity might be majorly due to the steric effect induced by the ortho-substituent. Besides, other aromatic substituted α,β -unsaturated nitroalkenes were also well tolerated (3t-3v), except for (1E)-2-phenylethenyl nitroalkene (3w). Additionally, other dipolarophiles, such as cinnamonitrile, ethyl cinnamate, 2-cyclohexen-1-one, N-tosyl-3nitroindole, 2-nitrobenzofuran and alkyne derivatives, were tested under the standard conditions, but essentially no reaction was observed. Consequently, it can be concluded that the above-mentioned dipolarophiles demonstrate relatively lower reactivity toward [3 + 2]-annulation of SVCP than nitroalkene 2. Finally, the chemical structure and relative configuration of spirooxindole 31 were unambiguously confirmed by X-ray crystal structure analysis (CCDC 1857258[†]).

At this stage, we were curious about the effect of the conversion from 1a and 1a' on the [3 + 2]-annulation process. As a result, a series of monitoring experiments were carried out in



^{*a*} Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), $Pd(OAc)_2$ (5 mol%), xantphos (10 mol%), toluene (2.0 mL), rt, 12 h. ^{*b*} **1b**' was used.

the presence of $Pd(PPh_3)_4$. Surprisingly, over half of spirocyclopropane **1a** was epimerized to its diastereomer **1a'** within 30 minutes, and an equilibrium was achieved after 6 hours with a 39:61 diastereomeric ratio (Scheme 4, eqn (1)). Interestingly, cyclopropane **1a'** was successfully employed in the title reaction and the desired spirooxindole **3a** was obtained in 78% yield with 85:15 dr, which are paralleled with the results by utilizing **1a** as the substrate (Scheme 4, eqn (2)). These unexpected results suggest that spirocyclopropane could be epimerized to the thermodynamically stable diastereomer upon the promotion by a palladium complex *via* intramolecular cyclization, which would hardly impact the annulation process.

Next, in order to better help us understand the mechanistic pathway, three independent control experiments were performed. Firstly, spirocyclopropane 4 without a terminal alkene moiety attached was tested. Unfortunately, the desired spirooxindole was unable to be obtained (Scheme 5, eqn (a)). In contrast, spirocyclopropane 5 bearing an internal alkene moiety gave spirooxindole 6 in 92% yield with good diastereoselectivity (84:16 dr, Scheme 5, eqn (b)). Finally, nonaromatic nitroalkene 7 was also examined in this annulation reaction, but a complex reaction was observed (Scheme 5, eqn (c)).



Scheme 4 Monitoring experiments and comparison experiments of SVCP.



Scheme 5 Control experiments.



Scheme 6 Plausible mechanism for the ring-opening [3 + 2]-annulation.

Presumably, the nonaromatic nitroalkene might be unstable under these conditions, leading to complex results.

On the basis of the above experimental results, a plausible mechanism is proposed in Scheme 6. First, a Pd-stabilized zwitterionic 1,3-dipole intermediate **int-1** was efficiently generated *via* a palladium-catalysed ring-opening process. Notably, intermediate **int-1** could be converted into diastereomer **1a**'. Subsequently, the intermediate **int-1** underwent a [3 + 2] annulation to give the desired product *via* the transition state **TS-1** or **TS-2** to give the annulation product. As can be seen, the steric repulsion between the phenyl moiety in **2a** and the protecting group in **1a** rendered **TS-2** unfavorable, leading to diastereomer **3a**' as the minor product. In contrast, the π - π stacking between two phenyl moieties of **1a** and **2a** facilitated the formation of **TS-1**, resulting in the generation of **3a** as the major diastereomer.

Conclusions

In summary, we have developed a diastereoselective palladium-catalysed ring-opening [3 + 2] annulation reaction for the construction of spirooxindole scaffolds in high yields and good diastereomeric ratios. The developed protocol features broad substrate scope, mild reaction conditions and high efficiency. This work broadens the application of spirovinylcyclopropane derivatives as versatile useful building blocks in the assembly of valuable spirocyclic systems. Further investigation on asymmetric catalytic annulation of spirovinylcyclopropanes is currently being pursued in our laboratory.

Conflicts of interest

There are no conflicts to declare.

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