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Palladium catalyzed stereoselective intramolecular [3 + 2] cycloaddition reactions of (*E*) & (*Z*)-ene-vinylidenecyclopropanes†

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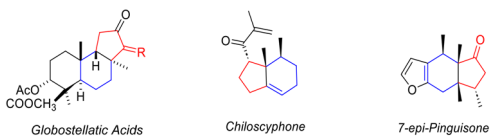
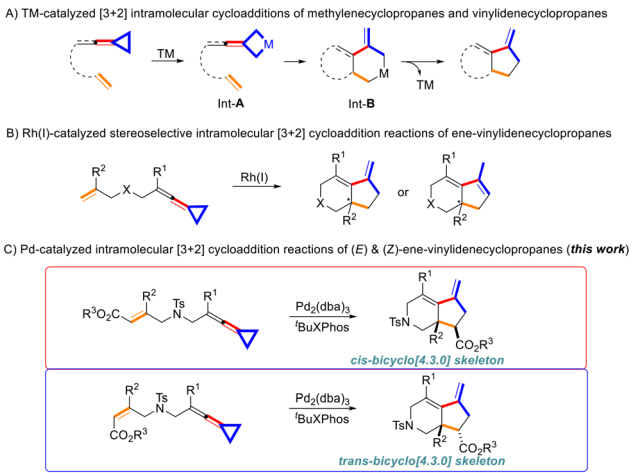
A palladium-catalyzed ring-opening cyclization of (*E*) & (*Z*)-ene-vinylidenecyclopropanes has been developed *via* an intramolecular [3 + 2] cycloaddition process in the presence of a sterically bulky biaryl phosphine ligand, stereoselectively affording fused *cis*- & *trans*-bicyclo[4.3.0] skeletal products in good yields with a broad substrate scope and good functional tolerance. A plausible reaction mechanism was proposed on the basis of previous work and the DFT calculations.

Bicyclo[4.3.0] skeletons are widely found in natural products and are important backbones commonly observed in natural compounds with important biological activities.[1] For example, globostellatic acid is extracted from the marine sponge *Rhabdastrella globostellata*.[2] This novel triterpenoidal compound can be used as selective anti-proliferative agents against human umbilical vein endothelial cells. Chiloscyphone is a natural product with the bicyclo[4.3.0] framework that is extracted from liverworts and shows multiple antimicrobial activities.[3] Moreover, 7-*epi*-pinguisone exhibits insect antifeedant activity (Scheme 1).[4]

Among the synthetic methodologies reported in the past, transition metal (TM)-catalyzed C–C bond activation and cycloaddition reactions have been characterized by good atom economy and mild reaction conditions for the rapid construction of bicyclic compounds.[5] Therefore, transition metal catalysis provides a very powerful strategy to construct bicyclic compounds. Methylenecyclopropanes (MCPs) and vinylidenecyclopropanes (VDCPs) play important roles as three-carbon partners in the construction of bicyclic compounds.[6,7] Generally, for MCP and VDCP moieties (Scheme 2A), the oxidative addition of a TM to the distal C–C bond of a cyclopropane has been shown to produce the metallocyclobutane species **Int-A**, which is accompanied by the migratory insertion of an unsaturated bond to produce the metallocyclohexane species **Int-B**. The metallocyclohexane species **Int-B** undergoes reductive elimination to produce the bicyclic products. Recently, several significant examples of [3 + 2] cycloaddition reactions of MCPs and VDCPs using Pd,[8] Rh,[9] Co,[10] and Ni[11] as catalysts have been disclosed.



Scheme 1 Bioactive compounds containing bicyclo[4.3.0] cores.



Scheme 2 Previous work and this work.

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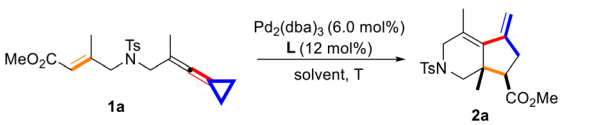
Our group has recently reported an asymmetric cycloaddition reaction of ene-VDCPs catalyzed by cationic rhodium and chiral phosphine ligands, resulting in the production of bicyclic products in high yields along with good ee values. By varying the reaction temperature, the selective construction of two different bicyclic products can be realized (Scheme 2B).[12]

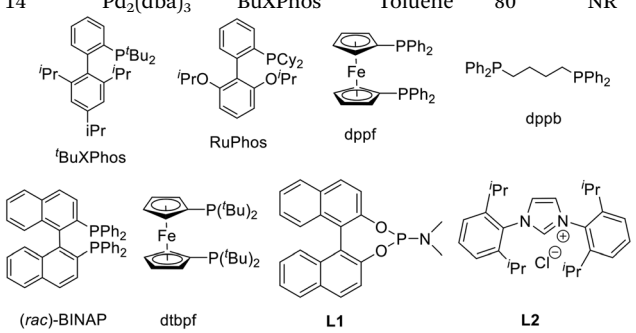
In this work, we report a novel palladium-catalyzed [3 + 2] cycloaddition of (*E*) & (*Z*)-ene-VDCPs to stereoselectively obtain fused *cis*- & *trans*-bicyclic products in good yields (Scheme 2C, this work).

At the start of our studies, (*E*)-ene-VDCP **1a** was used as the model substrate to examine the reaction outcomes. We found that the reaction successfully took place in the presence of 6.0 mol% of Pd_2dba_3 and 12 mol% of ^{t}BuXPhos in anhydrous toluene at 100 °C after 8 hours and the *cis*-bicyclic product **2a** was obtained in 96% isolated yield (Table 1, entry 1). Phosphine-RuPhos, another bulky biaryl, can also promote the reaction, affording the corresponding product **2a** in yields as low as 60% (Table 1, entry 2). Using dppf, dppb, BINAP and **L2** as ligands, the reaction did not occur (Table 1, entries 3–5, & 8). In addition, upon using dtbpf, **L1** and P^tBu_3 as ligands, this [3 + 2] cycloaddition reaction did not take place smoothly and the desired product was not obtained; the reaction system became complex and substrate **1a** decomposed and only a small amount of **1a** was recovered (Table 1, entries 6, 7, & 9). The examination of solvents showed that toluene is the best choice for this reaction (entry 3 *vs.* entries 10–13). On lowering the reaction temperature to 80 °C, no reaction occurred (Table 1, entry 14). It is worth noting that we did not find other products based on the C=C bond migration on the cyclopentane ring.

Table 1 Optimization of the reaction conditions

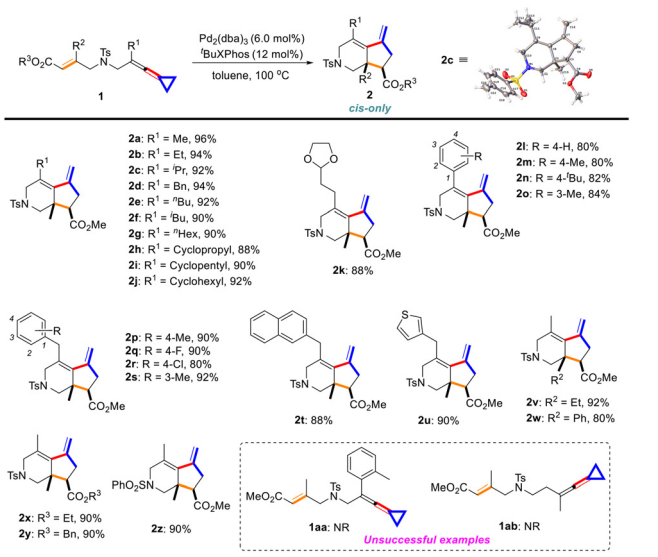


Entry[a]	Catalyst	L	Solvent	T (°C)	Yield[b]/%
1	**$Pd_2(dba)_3$**	**^{t}BuXPhos**	**Toluene**	**100**	**96**
2	$Pd_2(dba)_3$	RuPhos	Toluene	100	60
3	$Pd_2(dba)_3$	dppf	Toluene	100	NR[d]
4	$Pd_2(dba)_3$	dppb	Toluene	100	NR[d]
5	$Pd_2(dba)_3$	(*rac*)-BINAP	Toluene	100	NR[d]
6	$Pd_2(dba)_3$	dtbpf	Toluene	100	—
7	$Pd_2(dba)_3$	**L1**	Toluene	100	—
8[c]	$Pd_2(dba)_3$	**L2**	Toluene	100	NR[d]
9[c]	$Pd_2(dba)_3$	$HP^tBu_3BF_4$	Toluene	100	—
10	$Pd_2(dba)_3$	^{t}BuXPhos	Dioxane	100	80
11	$Pd_2(dba)_3$	^{t}BuXPhos	DCE	100	76
12	$Pd_2(dba)_3$	^{t}BuXPhos	PhCl	100	82
13	$Pd_2(dba)_3$	^{t}BuXPhos	MeCN	100	NR
14	$Pd_2(dba)_3$	^{t}BuXPhos	Toluene	80	NR



[a] Reaction conditions: substrate **1a** (0.10 mmol), $Pd_2(dba)_3$ (6 mol%) and **L** (12 mol%) in 0.1 mL anhydrous toluene under an argon atmosphere for 8 h. [b] Isolated yield. [c] K_2CO_3 (12 mol%) was added. [d] NR = no reaction.

Having determined the optimal reaction conditions, we next explored the substrate scope of (*E*)-ene-VDCPs **1** and the results are summarized in Scheme 3. It was found that R^1 can be an alkyl, a cycloalkyl or a benzyl group, and the desired products **2a–2j** were obtained in good yields ranging from 88% to 96%. The structure of **2c** was determined by X-ray diffraction and its ORTEP drawing is shown in Scheme 3. The (*E*)-ene-VDCP **1k** having an acetal group gave the desired product **2k** in 88% yield. We also investigated the aryl substitution in this reaction and for the electron-donating groups found at the *para*- and *meta*-positions of the benzene ring, the reaction proceeded smoothly and the target products **2l–2o** were obtained in good yields ranging from 80% to 84%. We also attempted to synthesize substrates bearing electron-withdrawing substituents such as OMe, F, Cl at the benzene ring. However, we only obtained the by-products instead of the ene-VDCPs (for details, see page S4 in the ESI†). We also investigated substrates **1p–1s** bearing electron-donating and electron-withdrawing groups at different positions of the benzyl ring, and found that the reactions took place successfully and products **2p–2s** were obtained in good yields ranging from 80% to 92%. (*E*)-ene-VDCPs **1t** and **1u** bearing a naphthalene and a thiophene ring were also compatible, providing **2t** and **2u** in 88% and 90% yields, respectively. Subsequently, we investigated the R^2 substituents located at the all-carbon quaternary center and found that R^2 could be an ethyl and a phenyl substituent,

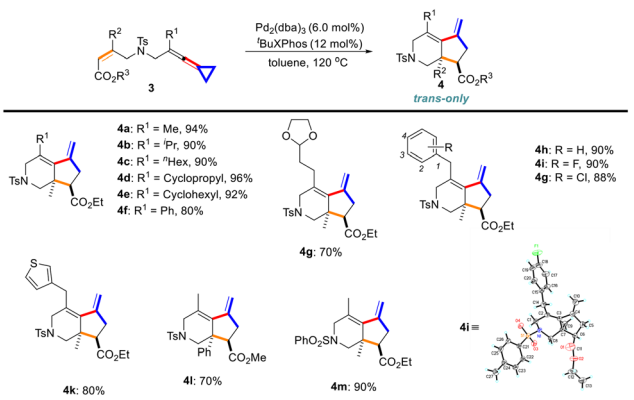


Scheme 3 Substrate scope of (*E*)-ene-VDCPs.

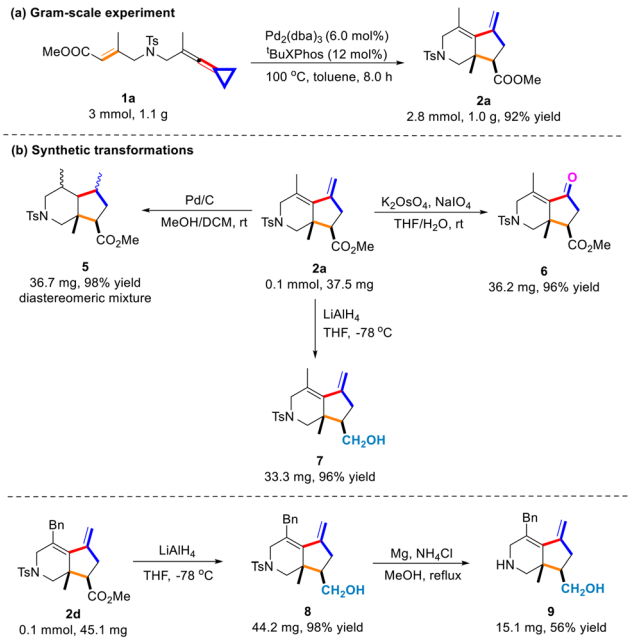
affording the desired products **2v** and **2w** in 92% and 80% yields. In addition, we examined the R^3 substituent of the ester group in this reaction as well, and both ethyl and benzyl substituents gave the corresponding products **2x** and **2y** in 90% yields. Using *N*-SO_2Ph as an *N*-protecting group (**1z**) afforded the corresponding product **2z** in 90% yield. However, substrate **1aa** with an *ortho*-substituted methyl group did not give the desired product under the standard conditions, probably due to steric hindrance. Lengthening the carbon chain as substrate **1ab** did not provide the target product as well perhaps due to the spatial issue of the *cis*-bicyclo[5.3.0] skeletons.

Next, we turned our attention to investigate the substrates (*Z*)-ene-VDCPs **3** (Scheme 4). For (*Z*)-ene-VDCPs **3**, the reaction temperature should be increased to 120 °C to promote the progress of the reaction (for details, see Table S1 in the ESI†). Using the (*Z*)-ene-VDCPs **3a–3g** as substrates, in which R^1 was a different alkyl or cycloalkyl group, a phenyl and an acetal group, provided the corresponding *trans*-bicyclic products **4a–4g** in good yields ranging from 70% to 96%. In addition, introducing a methyl, Cl and F substituents into the benzyl group delivered the target products **4h–4j** in 88% to 90% yields. The crystal structure of the *trans*-bicyclic product **4i** is shown in Scheme 4. Similarly, the thiophene moiety in (*Z*)-ene-VDCP was also tolerated, giving the corresponding product **4k** in 80% yield. Introducing a phenyl group at the quaternary carbon center gave **4l** in 70% yield and changing NTs to *N*SO_2Ph furnished the desired product **4m** in 90% yield.

To explore the synthetic applicability of the [3 + 2] cycloaddition reaction, we performed a gram-scale reaction using 3.0 mmol (1.1 g) of **1a** under the standard conditions and found that **2a** was obtained in 92% yield (Scheme 5a). Then, we conducted several transformations of **2a** (0.1 mmol scale) and the results are shown in Scheme 5b. The Pd/C catalyzed hydrogenation of **2a** produces **5** as a diastereomeric mixture in 96% yield. The olefinic moiety of product **2a** could be oxidized to yield ketone **6** in 96% yield. We also carried out the reduction of the ester group in **2a** with $LiAlH_4$ to give product **7** with an alcohol fragment at the bicyclic skeleton in 96% yield. Furthermore, we examined the synthetic utility of the bicyclic products as the *N*-tosyl group of **8** derived from **2d** was



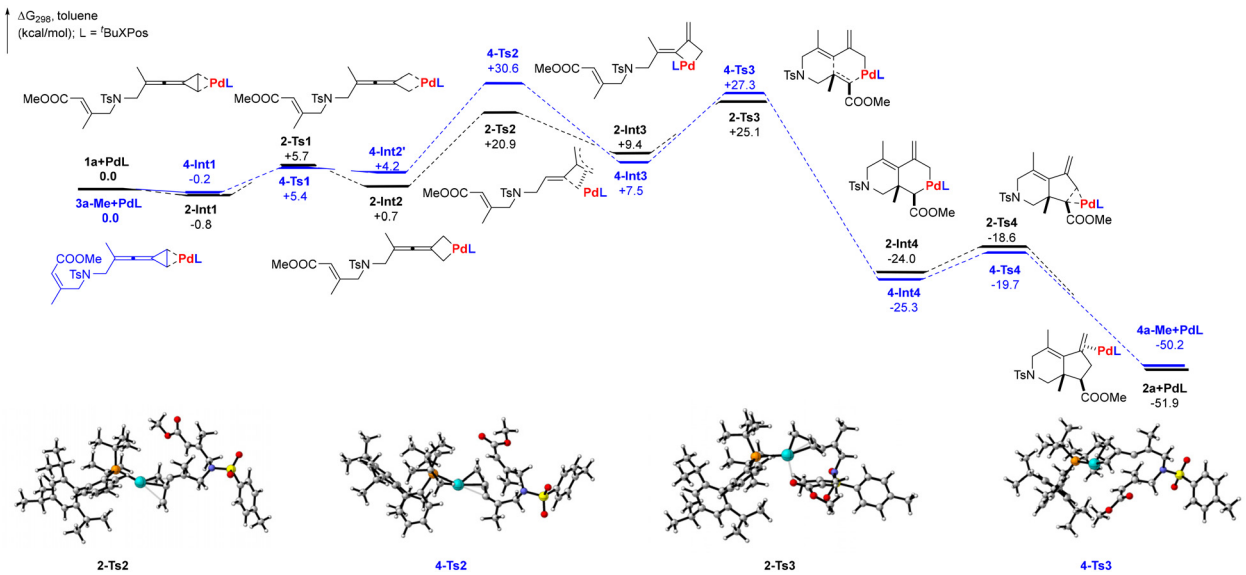
Scheme 4 Substrate scope of (*Z*)-ene-VDCPs.



Scheme 5 Gram-scale experiment and synthetic transformations.

removed upon treating with Mg and NH_4Cl in MeOH at 80 °C, affording the desired product **9** in 56% yield (Scheme 5b).

To further understand the mechanism, we attempted to clarify the influence of temperature on the reaction result and stereochemical issue. All calculations have been performed at the SMD(toluene)/M06/6-311 + G(d,p)/Lanl2dz//B3LYP/6-31G (d)/Lanl2dz level with the Gaussian 16 program. All transition states were characterized by only one imaginary frequency pertaining to the desired reaction coordinate. The intrinsic reaction coordinate (IRC) calculations were carried out at the same level of theory to further authenticate the transition states (Scheme 6). We investigated the reaction pathways using (*E*)-ene-VDCPs **1a** (black letters) and (*Z*)-ene-VDCPs **3a-Me** (blue letters) by DFT calculations, respectively (for more details, see Table S2 in the ESI†). The palladium complex coordinated with the distal C–C bond to produce **2-Int1** *via* a slightly exothermic process (ΔG = −0.8 kcal mol^{-1}). In the same manner, **4-Int1** is also generated through a slight exothermic process (ΔG = −0.2 kcal mol^{-1}). **2-Int1** undergoes an oxidative cyclometallation to give the palladacyclic intermediate **2-Int2** through **2-Ts1** with an energy barrier of 6.5 kcal mol^{-1}. Similarly, **4-Int1** undergoes an oxidative cyclometallation to give the palladacyclic intermediate **4-Int2** through **4-Ts1** with an energy barrier of 5.6 kcal mol^{-1}. In this process, the free energy between **2-Ts1** and **4-Ts1** produced by the *E* & *Z* substrates is very small (0.3 kcal mol^{-1}). The **2-Int2** then isomerizes to **2-Int3** *via* **2-Ts2** with an energy barrier of 20.2 kcal mol^{-1}. The corresponding process *via* **4-Ts2** has a higher energy barrier by 6.2 kcal mol^{-1}. Subsequently, olefinic moiety insertion occurs *via* **2-Ts3** with an activation free energy of 15.7 kcal mol^{-1} to give the palladacyclohexane intermediate **2-Int4**. The *E*- & *Z*-substrates control the stereoselectivity of the



Scheme 6 Proposed mechanism for the production of **2a** and **4a-Me**.

reaction during migratory insertion. For (*E*)-ene-VDCPs **1**, the ester group is on the same side with the methyl group and this results in the *cis* products **2** during the migration of the olefin moiety. Conversely, (*Z*)-ene-VDCPs **3** produced the *trans* products **4**. Kinetically, the reaction of (*Z*)-ene-VDCP should overcome an energy barrier that is higher than that of (*E*)-ene-VDCPs by 4.1 kcal mol^{-1}. Thus, the reaction of (*Z*)-ene-VDCPs is conducted at a higher temperature in the experiment. Then, reductive elimination converts **2-Int4** to **2a + PdL** (*via* **2-Ts4**, 5.4 kcal mol^{-1}) and **4-Int4** to **4a-Me + PdL** (*via* **4-Ts4**, 5.6 kcal mol^{-1}), respectively.

In conclusion, we have developed an efficient palladium-catalyzed intramolecular [3 + 2] cycloaddition reaction for (*E*) & (*Z*)-ene-vinylidenecyclopropanes, which stereoselectively provides the corresponding fused *cis* & *trans*-bicyclo[4.3.0] products in moderate to good yields with a broad substrate scope and good functional group tolerance. We realized the reaction on a gram scale and performed interesting transformations of the products. The rational reaction mechanisms have been proposed on the basis of DFT calculations. Further studies are underway in our laboratory to synthesize biologically active molecules using this synthetic approach.

Author contributions

C. N. contributed to the experimental work; Z. Q. Y. and Y. W. contributed to the computational work. C. N., Y. W. and M. S. contributed to ideation and writing of the paper.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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