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Phosphine-Catalyzed Enantioselective (3+2) Annulation of Vinylcyclopropanes with Imines: Construction of Chiral Pyrrolidines

Fuhao Zhang,[a],[b] Xuan Dai,[a] Lei Dai,[a] Wenrui Zheng,[a] Wai-Lun Chan,[a] Xiaodong Tang,[a] Xumu Zhang, [b] and Yixin Lu*[a]

[a] F. Zhang, X. Dai, L. Dai, W. Zheng, Dr. W-L. Chan, Dr. X. Tang, Prof. Dr. Y. Lu
Department of Chemistry
National University of Singapore
3 Science Drive 3, 117543 (Singapore)
E-mail: chmlyx@nus.edu.sg

[b] F. Zhang, Prof. Dr. X. Zhang
Department of Chemistry
Southern University of Science and Technology
Shenzhen, Xueyuan Road, 518055 (China)

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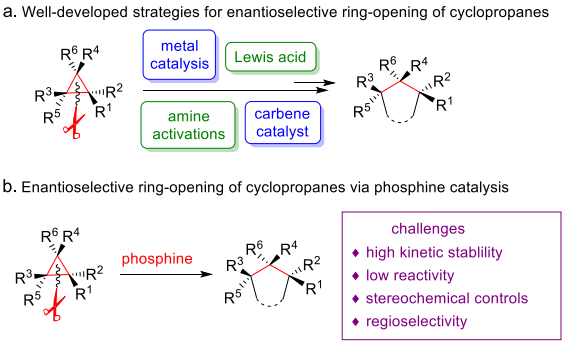
Abstract: A phosphine-catalyzed highly enantioselective and diastereoselective (up to 98% ee and >20:1 dr) (3+2) annulation between vinylcyclopropanes and *N*-tosylaldimines has been developed, which allows for facile access to a range of highly functionalized chiral pyrrolidines. Notably, this method makes use of vinylcyclopropanes as a synthon for phosphine-mediated asymmetric annulation reaction, which will offer new opportunities for potential applications of cyclopropanes substrates in phosphine-catalyzed organic transformations.

Cyclopropane, the smallest carbocycle, is a unique and important structure in organic chemistry, which has a high ring strain, about 115 kJ/mol for the total angle strain.[1] Cyclopropanes are important structural motifs that are widely present in natural products,[2] bioactive molecules[3] and pharmaceutical agents.[4] Cyclopropanes and related compounds can also serve as versatile three-membered synthetic building blocks, generally through a ring-opening process. Although the inherent ring strain is the driving force for the ring-opening of cyclopropanes, catalysts are often required to trigger such a process due to the kinetic stability of these three-membered structural motifs. Numerous creative strategies and catalytic systems have been devised to cleave the C–C bond of cyclopropanes, thus making them highly useful building blocks in organic synthesis.[5] There still is ample room to further advance enantioselective opening of cyclopropanes and their subsequent applications in asymmetric synthesis, especially through new modes of activations of such valuable building blocks.

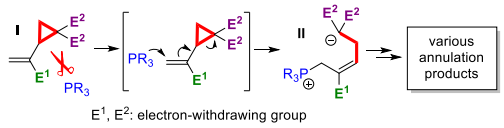
The past few decades have seen rapid development of asymmetric phosphine catalysis, which has now been well established as a powerful synthetic strategy.[6] Our group has been actively investigating this research area, and developed a family of amino acid-based bifunctional phosphine catalysts.[7] As part of our ongoing research, we were interested in devising an enantioselective synthetic strategy that makes use of phosphine-catalyzed ring-opening of cyclopropanes (Scheme 1). In the existing phosphine-triggered annulation methods, the common substrates are activated alkenes, alkynes, allenes, and the Morita–Baylis–Hillman (MBH) adducts, among others. To further advance the state-of-the-art of phosphine catalysis, it is certainly desirable to include other reaction partners, especially those cheap and readily available chemical entities. To date, there are only a few achiral synthetic reports in which cyclopropane substrates were activated by the phosphine catalysts. In their pioneering studies, Ma et al. reported a phosphine-catalyzed ring-opening of cyclopropenyl dicarboxylates.[8] Recently, Xu, Li, and their co-workers disclosed the utilization of vinylcyclopropylketones and alkylidenecyclopropanes in organic synthesis, via phosphine-catalyzed rearrangement reactions.[9] Notably, elevated temperatures were required for the cleavage of cyclopropanes in the above examples. To the best of our knowledge, an asymmetric ring-opening of cyclopropanes via phosphine catalysis is yet to be developed.



Scheme 1. The Ring-opening of Cyclopropanes.

Vinylcyclopropanes[10] (VCPs) are one type of cyclopropanes that have been widely used in organic synthesis, either through transition metal-triggered ring openings or via the addition of

appropriate radicals onto the vinyl substituent.[11] We felt VCPs will be specifically valuable in phosphine catalysis, and thus decided to design a new type of VCP, which should be readily accessible, and also amenable for the creation of different synthetic targets. We envisioned a VCP of type **I** with an activated adjacent double bond may serve our purpose; the initial nucleophilic attack of phosphine on the electron-poor double bond would generate stabilized anion, which subsequently will open up the cyclopropane ring and form zwitterionic intermediate **II**. By employing different reaction partners, a range of annulation reactions are anticipated (Scheme 2). Herein, we document a phosphine-catalyzed (3+2) annulation between a vinylcyclopropane and imines, for the enantioselective construction of highly functionalized pyrrolidines, which are important substructures often found in natural products and molecules of biological significance.[12-14]

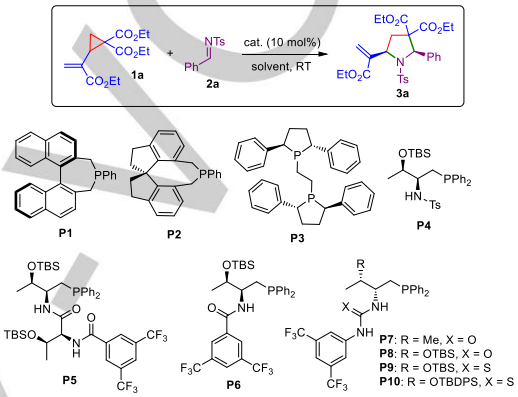


Scheme 2. The Design of Novel VCP, Our Hypothesis.

We chose vinylcyclopropane **1a**, readily prepared in high yield from commercially available starting materials (see the SI for details), to start our investigation (Table 1). To our delight, phosphine-catalyzed (3+2) annulation between **1a** and *N*-tosylaldimine **2a** proceeded smoothly, forming anticipated (3+2) annulation products. Monofunctional chiral phosphine catalysts were ineffective in asymmetric induction (entries 1–3). We then turned our attention to amino acid-based bifunctional catalysts. While L-Thr-derived sulfonamide-bearing **P4** catalyzed led to moderate enantioselectivity (entry 4), L-Thr-based dipeptide phosphine **P5** and phosphine amide **P6** were found to be poor catalysts (entries 5 and 6). Gratifyingly, phosphines (**P7**–**P10**) bearing a urea or a thiourea functionality were remarkable in chiral induction, forming the desired products in excellent diastereo- and enantioselectivities, but only with moderate yields (entries 7–10). With the best catalyst, *O*-TBDPS-D-Thr-derived **P10**, we then performed solvent screening (see Table S1 in the SI for more details). Chlorobenzene was identified as the solvent of choice; 94% ee and >20:1 dr were attainable, the yield, however, was still at 52% (entry 11).

We next focused on improving chemical yield of the reaction, which turned out to be quite interesting. We first ran the reactions with extended reaction time. Much to our surprise, the improvement of yield was accompanied by the erosion of enantioselectivity (see Table S2 in the SI for more details). We suspect the above phenomenon may be due to the unexpected addition of the same phosphine catalyst to the annulation product, thus triggering a sequence of steps, and eventually lead to the erosion of stereoselectivity. Indeed, when **3a** with 85% ee was treated with phosphine **P10**, the ee value dropped to 73% (Fig. 1a). In a plausible mechanistic pathway, nucleophilic attack of chiral phosphine on cyclopropane triggers its opening, yielding zwitterionic intermediate **Int-a**, and the subsequent well-anticipated (3+2) annulation with imine **2a** forms (*R*,*R*)-**3a** in high ee value (Fig. 1b). We suspect the same phosphine catalyst **P10** may react with the enantiomerically enriched annulation product **3a**, forming achiral zwitterionic species **Int-a**, and the re-annulation of which with imine then forms the product in an overall eroded enantiomeric excess. The fact that the enantiomeric erosion of **3a** with the progression of the reaction suggests that the cyclcopropane substrate **1a** is more reactive than annulation product **3a** towards the phosphine catalyst. We reasoned the increase of the molar equivalence of cyclopropane **1a** may circumvent the undesired competing pathway, thus increase yield without erosion of enantioselectivity. Indeed, the annulation reaction using 1.5 equivalent vinylcyclopropane **1a** with respect to *N*-tosylaldimine **2a** formed **3a** in 72% yield with 95% ee (entry 13). The inclusion of an additive prevented the decomposition of imine substrate, further improving chemical yield (entry 14).

Table 1. Optimizing Reaction Conditions.[a]



entry	cat.	solvent	additive	*t* (h)	yield (%)[b]	dr[c]	ee (%)[d]
1	**P1**	CH_2Cl_2	--	18	78	>20:1	-3[e]
2	**P2**	CH_2Cl_2	--	18	62	13:1	15
3	**P3**	CH_2Cl_2	--	18	53	>20:1	13
4	**P4**	CH_2Cl_2	--	18	69	8:1	45
5	**P5**	CH_2Cl_2	--	18	74	>20:1	-3[e]
6	**P6**	CH_2Cl_2	--	18	82	9:1	17
7	**P7**	CH_2Cl_2	--	2	58 (51[f])	>20:1	82
8	**P8**	CH_2Cl_2	--	2	56	>20:1	84
9	**P9**	CH_2Cl_2	--	2	48	>20:1	91
10	**P10**	CH_2Cl_2	--	2	52	>20:1	92
11	**P10**	PhCl	--	2	52	> 20:1	94
12	**P10**	PhCl	--	4	60	> 20:1	89
13[g]	**P10**	PhCl	--	4	71	> 20:1	95
14[g]	**P10**	PhCl	Mg_2SO_4[h]	4	89[f]	> 20:1	95

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), and the catalyst (0.01 mmol) in the solvent specified (2.0 mL) at room temperature. [b] HPLC yields. [c] Determined by crude NMR analysis. [d] Determined by HPLC analysis on a chiral-stationary-phase. [e] Denoted for products with opposite configuration. [f] Isolated Yield. [g] Reaction conditions: **1a** (0.3 mmol), **2a** (0.2 mmol), **P10** (0.02 mmol) in PhCl (2.0 mL) at room temperature. [h] Additive (100 mg per 0.1 mmol **2a**). Ts = 4-toluenesulfonyl, TBS = *tert*-butyldimethylsilyl, TBDPS = *tert*-butyldiphenylsilyl.

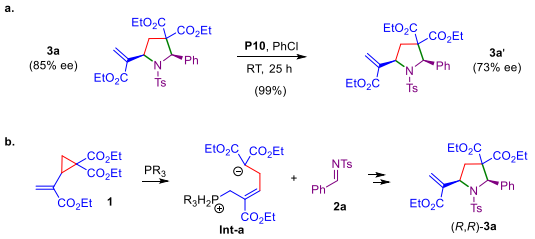
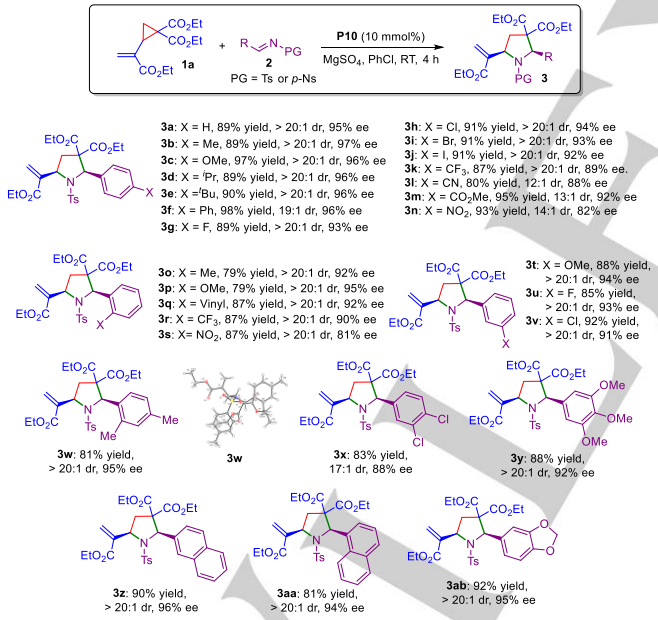


Figure 1. Erosion of Enantioselectivity.

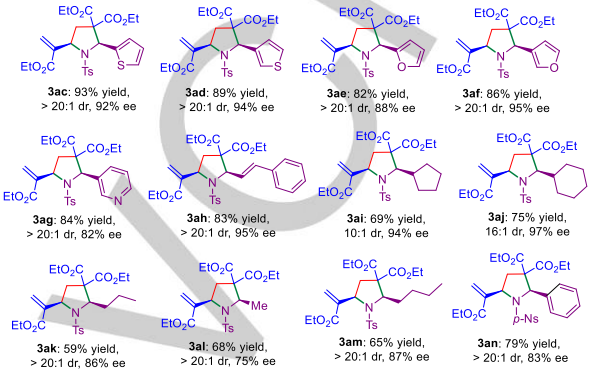
With the optimal reaction conditions in hand, we first evaluated the substrate scope by employing various aryl-derived *N*-tosylaldimines (Scheme 3). The reaction was applicable to *N*-tosylaldimines bearing different mono-substituted phenyl groups regardless of the electronic and steric nature of these substituents (**3a**–**3n**). High chemical yields, excellent enantioselectivities and diastereoselectivities were generally attainable. The presence of a strong electron withdrawing group on the phenyl ring, e.g. NO_2, CN, tended to furnish products with slightly decreased ee values (**3k**, **3l**, **3n**, and **3s**). Next, *N*-tosylaldimines bearing multi-substituted or fused aryl rings were investigated. In all the examples examined, the (3+2) annulation products were obtained in good yields with high enantiomeric excesses and excellent diastereoselectivities (**3w**–**3ab**). The absolute configurations of the annulation products were assigned by analogy, on the basis of X-ray crystallographic analysis of product **3w** (CCDC NO. 2098831).



[a] Conditions:**1** (0.3 mmol), **2** (0.2 mmol), **P10** (0.02 mmol), anhydrous $MgSO_4$ (200 mg) in PhCl (2 mL) at room temperature for 4 h; Isolated yields; The dr ratios were determined by cured NMR analysis; The ee values were determined by HPLC analysis on a chiral-stationary-phase.

Scheme 3. Substrate Scope.[a]

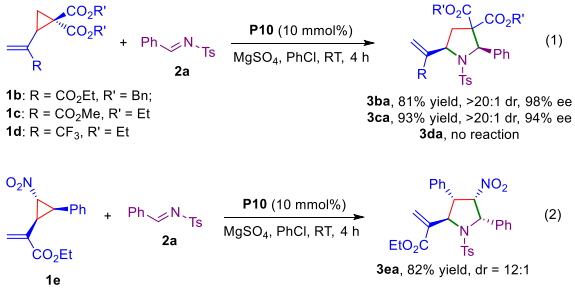
We further evaluated the suitability of *N*-tosylaldimine substrates more extensively, and the results are summarized in Scheme 4. Whereas imines bearing furan and thiophene moieties were well-tolerated (**3ac**–**3af**), pyridine-containing substrate turned out to be less ideal (**3ag**). Moreover, the annulation product bearing a vinylic substituent was also obtained in a good yield with excellent ee and dr values (**3ah**). Interestingly, *N*-tosylaldimines derived from aliphatic aldehydes were all shown to be excellent substrates, although the yields were generally lower due to the instability of these substrates. The pyrrolidine products bearing a 2-alkyl substituent, whether branched or linear alkyl groups, could be obtained, although the products with the less steric alkyl substituents were formed less enantioselectively (**3ai**-**3am**). Lastly, the employment of *N*-nosylaldimine was found to be less favorable (**3an**).



[a] Conditions: **1** (0.3 mmol), **2** (0.2 mmol), **P10** (0.02 mmol), anhydrous $MgSO_4$ (200 mg) in PhCl (2 mL) at room temperature for 4 h; Isolated yields; The dr ratios were determined by cured NMR; The ee values were determined by HPLC analysis on a chiral-stationary-phase.

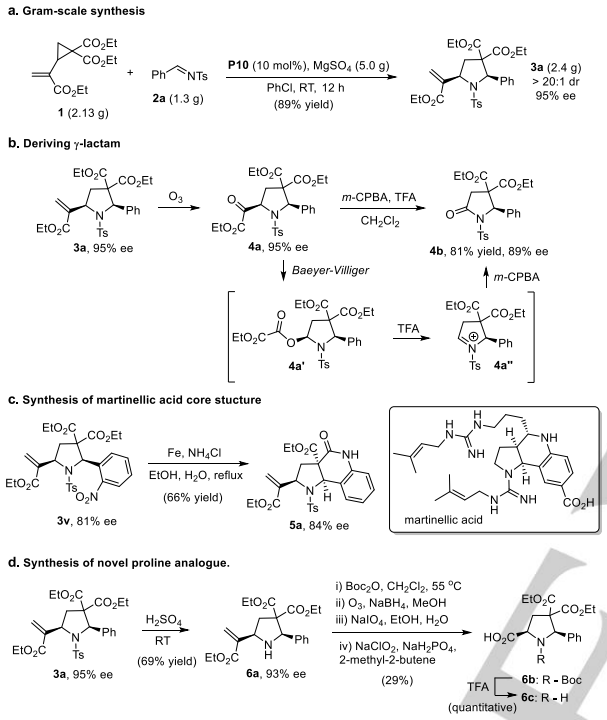
Scheme 4. Further Investigating *N*-Tosylaldimine Substrates Scope[a]

Phosphine-mediated ring opening of cyclopropanes is not only limited substrate **1a**, other vinylcyclopropanes may also be utilized. In our preliminary investigation, we prepared vinylcyclopropanes containing different ester moieties (**1b**, **1c**) and subjected them to the standard conditions; the annulation reactions proceeded efficiently to furnish products with excellent stereoselectivities (eq. 1). Apparently, the presence of different esters in the pyrrolidine products allows more room for further structural elaborations. Moreover, vinylcyclopropane **1e** bearing a nitro group was also a suitable substrate, and the desired (3+2) annulation took place smoothly to yield an interesting pyrrolidine **3ea** (eq. 2)



The (3+2) annulation products are ubiquitously existing pyrrolidines, which are also rich in functionalities that would allow for diverse structural elaborations. To demonstrate the practicality of our method, a convenient gram-scale (3+2) annulation was performed using our standard reaction conditions, furnishing **3a** in high yield with excellent ee and dr values (Scheme 5a). We developed a synthetic route to convert pyrrolidine **3a** to γ-lactam **4b**, a structural scaffold of biological significance.[15] Ketoester **4a**, obtained from ozonolysis of **3a**, was treated with *m*-CPBA to trigger a Baeyer–Villiger oxidation to yield intermediate **4a'**. Subsequent reaction with TFA led to fragmentation and formed

iminium **4a''**, which was further oxidized to give lactam **4b** (Scheme 5b). When a *para*-nitro-imine substrate was used, annulation product **3v** bearing a neighboring nitro group was obtained. The reduction of the nitro group triggered an *in-situ* diastereoselective cyclization, affording tricyclic compound **5a**, which is the core structure of martiinellic acid[16] (Scheme 5c). Proline is a well-known organic catalyst.[17] When the annulation product **3a** was treated with concentrated sulfuric acid, followed by a one-pot multi-step transformation, proline analogues **6c** was obtained, the use of which as an organic catalyst is currently being evaluated (Scheme 5d).



Scheme 5. Synthetic Manipulations of the Annulation Product.

In conclusion, we have developed a phosphine-catalyzed enantioselective (3+2) annulation between vinylcyclopropanes and *N*-tosylaldimines for highly diastereo- and enantioselective construction of pyrrolidines. A broad range of highly substituted and functionalized pyrrolidines were obtained in high yields with excellent diastereoselectivities and very good enantioselectivities. Interestingly, we observed the addition of phosphine catalyst to the annulation product, triggering unexpected reaction pathways. Notably, our reported reaction takes place under mild reaction conditions, and it represents the first example that cyclopropane substrates are activated and utilized in phosphine-mediated asymmetric transformation. Our findings suggest the great potential of utilizing various cyclopropanes as powerful synthons in phosphine catalysis, complementary to the existing well-studied synthons, e.g. allenes; we are currently exploring this exciting direction and will disclose our discoveries in due course.

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Keywords: vinylcyclopropanes • phosphine catalysis • (3+2) annulation • enantioselective •functionalized pyrrolidines

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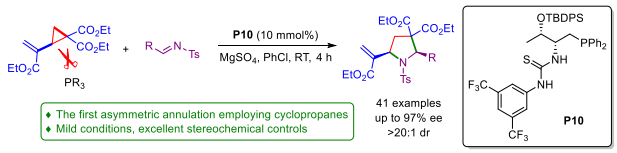

Cyclopropanes are important synthetic building blocks in organic chemistry. In this study, the first phosphine-catalyzed enantioselective (3+2) annulation between vinylcyclopropanes and *N*-tosylaldimines was achieved. Through this protocol, a broad range of highly substituted and functionalized pyrrolidines were obtained in high yields with excellent diastereoselectivities and very good enantioselectivities, which suggest the great potential of utilizing various cyclopropanes as powerful synthons in phosphine catalysis.