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Palladium-catalyzed intramolecular asymmetric hydrocyclopropanylation of alkynes: synthesis of cyclopropane-fused γ-lactams†

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A palladium-catalyzed intramolecular asymmetric hydrocyclopropanylation of alkynes *via* C(sp^3)–H activation has been developed for the synthesis of cyclopropane-fused γ-lactams. The presented strategy proceeds in a selective and 100% atom-economical manner. A range of cyclopropane-fused γ-lactams were prepared from readily available substrates in good yields and enantioselectivities with a chiral phosphoramidite ligand.

Introduction

Cyclopropane is the smallest carbocycle with considerable torsional and angular strains, and has constantly been of great interest to the organic community as a valuable synthetic building block.[1] In addition, this unique structure is found in a number of natural products, chemical drugs, and agrochemicals.[2] Various cyclopropane-containing natural products, spanning from terpenoids, fatty acid, pheromone, amino acid and other types of molecules, have been isolated from plants, fungus, and microorganisms. The introduction of a cyclopropane into drug molecules can increase their metabolic stability *via* spatial orientation of the substituents of the cyclopropyl subunit.

In particularly, cyclopropanes fused to pyrrolidine units are found in many important biologically active agents as key structural features (Fig. 1). For example, boceprevir is a potent oral HCV-protease inhibitor.[3] SUVN-911 is a potent neuronal nicotinic acetylcholine α4β2 receptor antagonist for the treatment of depression.[4] Saxagliptin is a selective and reversible DPP4 inhibitor with IC_{50} of 26 nM.[5]

Due to their synthetic[6] and pharmaceutical importance, substantial ongoing efforts have been devoted to develop efficient methodologies for building such an important family of cyclopropane-fused pyrrolidine scaffolds. Traditionally, these structures could be prepared *via* the Simmons–Smith reaction of N-protected dihydropyrroles[7] or the direct cyclopropanation of pyrrole derivatives employing electrophilic metallocarbenoids (Scheme 1a).[8] Other methods from non-pyrrole starting materials have also been reported.[9–11] For example, the group of Yang[11a] and then the group of Bower[11b] constructed this structure utilizing a cascade aza-Heck cyclization/cyclopropanation strategy which proceeds *via* the intramolecular aza-palladation of an alkene followed by a C–H palladation-initiated cyclopropanation (Scheme 1b). Despite advantages, these methods suffer from several drawbacks, such as harsh reaction conditions, regio- or/and stereoselectivity issues, and the use of toxic and unstable materials. Accordingly, developing direct and flexible methods for these structures that use readily available and stable starting materials in a stereoselective manner is highly desirable.

On the other hand, with the rapid development of C–H bond functionalization, transition metal catalyzed functionalization of cyclopropane has emerged as one of the promising ways to construct cyclopropane-containing compounds.[12] In 2015, Cramer reported a palladium catalyzed enantioselective C–H functionalization of chloroacetamide substrates to access cyclopropane-fused γ-lactams (Scheme 1c).[13a] Later, two cases of

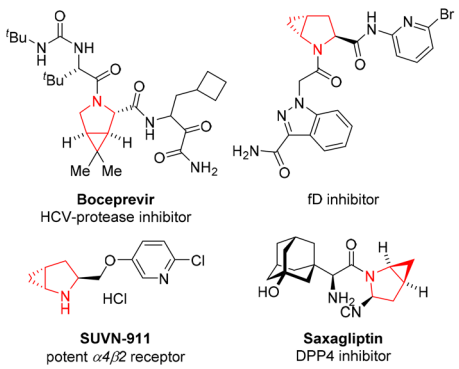

Fig. 1 Representative natural products and pharmaceuticals containing cyclopropane-fused pyrrolidines.

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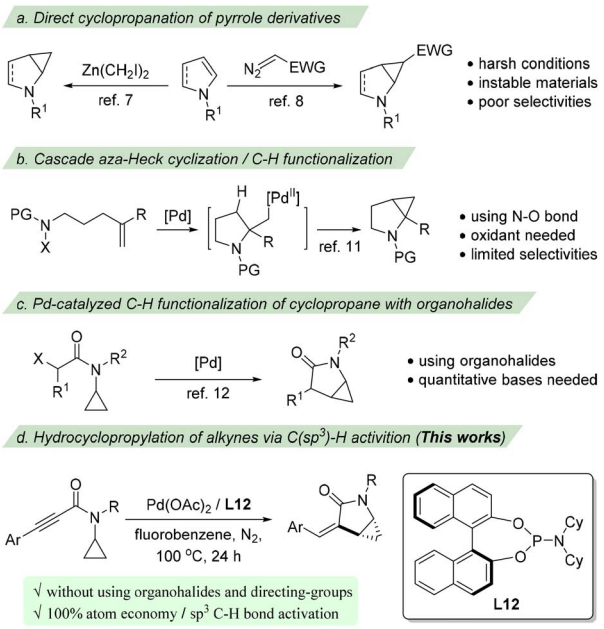


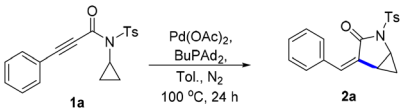
Scheme 1 Strategies for the synthesis of cyclopropane-fused pyrrolidines. (a) Direct cyclopropanation of pyrrole derivatives. (b) Cascade aza-Heck cyclization/C–H functionalization. (c) Pd-catalyzed C–H functionalization of cyclopropane with organohalides. (d) Hydrocyclopropylation of alkynes *via* C(sp^3)–H activition.

intramolecular alkenylation of cyclopropane using bromoalkenes to synthesize α-alkylidene-γ-lactams were reported by Baudoin and co-workers.[13b,c] Since organohalides were used as substrates, both procedures required quantitative amounts of bases. We assume that an intramolecular hydrocyclopropanylation of an appropriate π-system would provide an efficient and 100% atom-economic procedure to access cyclopropane-fused γ-lactams. However, despite some elegant examples of C(sp^3)–H bond alkenylation with alkynes having been disclosed *via* the directing group assisted C–H activation[14] or radical processes,[15] the direct hydroalkylation of alkynes without using halides and other functional groups[16] has been rarely reported. Herein, we report a palladium-catalyzed intramolecular hydrocyclopropanylation of alkynes *via* C(sp^3)–H activation for the synthesis of cyclopropane-fused γ-lactams (Scheme 1d). A range of cyclopropane-fused γ-lactams were prepared from readily available substrates in good yields and enantioselectivities.

Results and discussion

Initially, we commenced our study by employing *N*-cyclopropyl-3-phenylpropiolamide **1a** as the model substrate to test our assumption (Table 1). To our delight, when a toluene solution of **1a** was treated with the $Pd(OAc)_2$/DPPF catalyst system at 100 °C, the expected intramolecular hydrocyclopropanylation reaction proceeded successfully and produced cyclopropane-fused γ-lactam **2a** in 52% yield (entry 1). Other palladium catalysts such as $Pd(acac)_2$ and $Pd_2(dba)_3$ were less active and provided **2a** in 17–32% yields (entries 2 and 3). However, $Pd(PPh_3)_4$ was found to be ineffective and no desired product **2a** was obtained (entry 4). Subsequently, a series of ligands were examined and it was found that the ligand played an important role in this reaction. When the bidentate phosphine ligand with a smaller bite angle DPPP was used as a ligand, **2a** was obtained in an excellent yield of 95% (entry 5). Large bite angle ligands such as DPEphos and xantphos were less effective (entries 6 and 7). Monodentate phosphine ligands were also active and electron-rich trialkylphosphines were found to be more effective. The yield of **2a** was improved to 90% and 96% when PCy_3 and $BuPAd_2$ were used as the ligands, respectively (entries 9 and 10). The screening of the solvent revealed that toluene is the optimal. When the reaction was conducted in non-polar solvents such as THF and dioxane, the desired product **2a** was obtained in 85% and 88% yields, respectively (entries 11 and 12). However, when MeCN was used as the solvent, the reaction was totally inhibited and only a trace amount of **2a** was detected (entry 13). Strongly polar solvents like DMSO and DMF also led to decreased yields (entries 14 and 15).

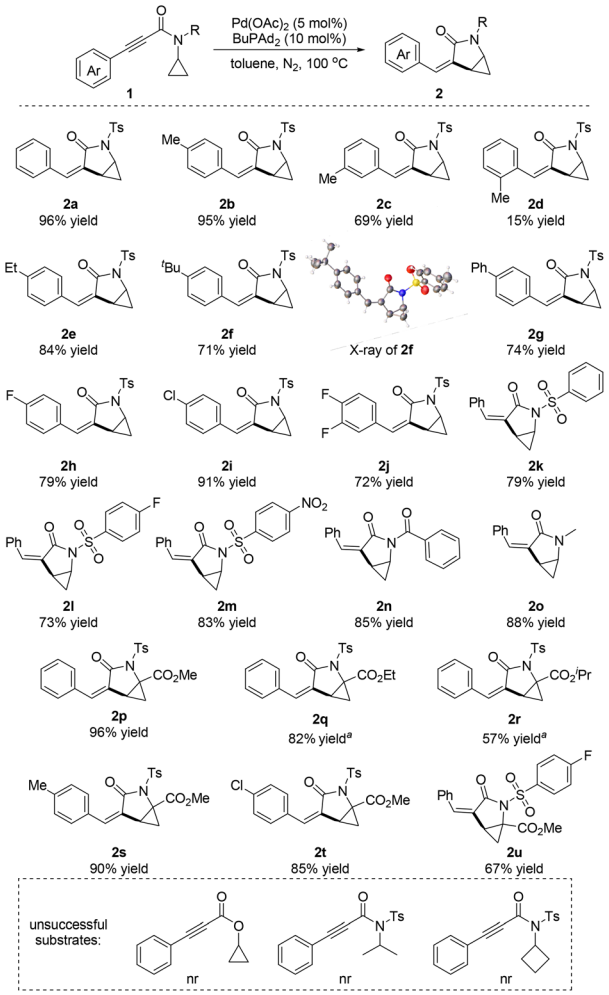
Table 1 Optimization of the reaction conditions[a]



Entry	Cat.	L.	Sol.	Yield[b] (%)
1	$Pd(OAc)_2$	DPPF	Toluene	52
2	$Pd(acac)_2$	DPPF	Toluene	17
3	$Pd_2(dba)_3$	DPPF	Toluene	23
4	$Pd(PPh_3)_4$	DPPF	Toluene	NR
5	$Pd(OAc)_2$	DPPP	Toluene	95
6	$Pd(OAc)_2$	DPEPhos	Toluene	27
7	$Pd(OAc)_2$	XantPhos	Toluene	NR
8	$Pd(OAc)_2$	PPh_3	Toluene	35
9	$Pd(OAc)_2$	PCy_3	Toluene	90
10	**$Pd(OAc)_2$**	**$BuPAd_2$**	**Toluene**	**96**
11	$Pd(OAc)_2$	$BuPAd_2$	THF	85
12	$Pd(OAc)_2$	$BuPAd_2$	Dioxane	88
13	$Pd(OAc)_2$	$BuPAd_2$	MeCN	Trace
14	$Pd(OAc)_2$	$BuPAd_2$	DMF	44
15	$Pd(OAc)_2$	$BuPAd_2$	DMSO	36

[a] Reaction conditions: **1a** (0.2 mmol), [Pd] (5 mol%), ligand (10 mol% for monodentate ligands, 5 mol% for bidentate ligands), solvent (2 mL), 100 °C, 24 h. [b] Isolated yields.

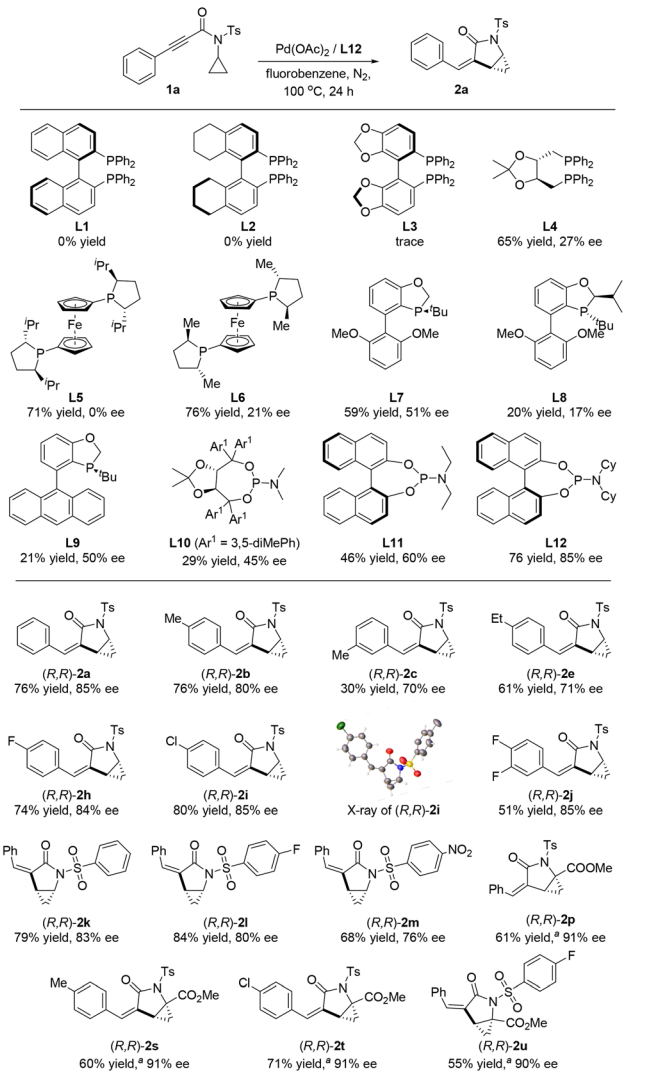
With the optimized reaction conditions in hand, we began exploration of the substrate scope by varying the substituents of *N*-cyclopropyl-3-phenylpropiolamide **1** (Scheme 2). First, the influence of the substitution on the benzene ring of *N*-cyclopropyl-3-phenylpropiolamide **1** was investigated. The electronic properties of the substituents played a minor role in this reaction. Both electron-donating (**2e–2g**) and electron-withdrawing group (**2h–2j**) substituted substrates underwent this reaction and produced the cyclopropane-fused γ-lactam products in good to excellent yields. However, the steric effect of the substituents influenced the yield significantly. When substrates with an *ortho*-substitution were used in this reaction,



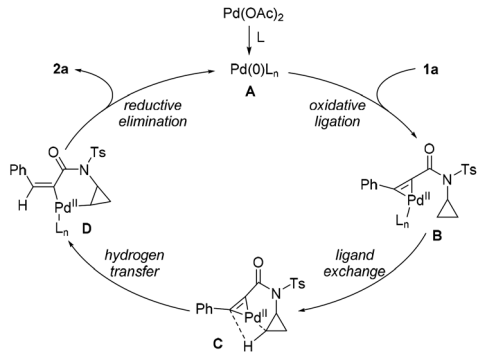
Scheme 2 Substrate scope. Reaction conditions: **1** (0.2 mmol), $Pd(OAc)_2$ (5 mol%), $BuPAd_2$ (10 mol%), toluene (2 mL), 100 °C, 24 h, isolated yields. [a]120 °C.

the yield dropped dramatically to 15% (**2d**). The configuration of product **2f** was determined by X-ray crystallography analysis.[17] Various *N*-substitutions of the *N*-cyclopropyl-3-phenylpropiolamide **1** were tolerated. When benzenesulfonamide **1k** was subjected to the standard conditions, the desired product **2k** was obtained in 79% yield. Fluoro- and nitro-substituted benzenesulfonamides aslo produced the corresponding products in 73% and 83% yields, respectively (**2l** and **2m**). In addition, *N*-benzoyl and *N*-methyl substituted substrates were tolerated as well, generating the desired products **2n** and **2o** in high yields. Notably, when a methyl ester group was attached on the cyclopropyl group, the corresponding products (**2p**, **2s–2u**) were obtained in good to excellent yields. The steric effect of the ester affected the yields significantly. When ethyl and isopropyl ester group substituted substrates were used in this reaction, a higher reaction temperature was needed and the yields dropped to 82% and 57%, respectively (**2q** and **2r**). The *N*-cyclopropyl amide was found to be critical for this reaction. The cyclopropyl 3-phenylpropiolate as well as the *N*-isopropyl and *N*-cyclobutyl amides failed in this reaction.

Since two adjacent stereogenic carbon centers are generated in the cyclopropane-fused γ-lactam product, we envisaged that an enantioselective hydrocyclopropanylation could be realized with an appropriate chiral ligand. Thus, we re-evaluated the reaction parameters with various nitrogen and phosphine chiral ligands (Scheme 3, see details in ESI†). After a thorough screening, phosphoramidite ligand **L12** was found out to be optimal. Enantio-enriched (*R*,*R*)-**2a** was obtained in good yield and enantioselectivity with the replacement of toluene with fluorobenzene. Axially chiral biphenyl ligands such as BINAP (**L1**), H_8-BINAP (**L2**) and SEGPHOS (**L3**) were ineffective, no or only trace amounts of product were detected. Bidentate phosphines with alkyl substitutions led to good yields but low levels of enantiocontrol (Scheme 3, **L4–L6**). When monophosphorus ligands such as BIDIME (**L7**), ^{i}Pr-BIDIME (**L8**) and AntPhos (**L9**) were used, lower yields and moderate selectivities were



Scheme 3 Screening of chiral ligands. Reaction conditions: **1** (0.2 mmol), $Pd(OAc)_2$ (5 mol%), **L*** (10 mol%), toluene (2 mL), 100 °C, 24 h, isolated yields. [a]**L7** instead of **L12**, 120 °C.



Scheme 4 A plausible reaction pathway.

obtained. Phosphoramidite ligands were found to be effective for this reaction (Scheme 3, **L10–L12**, see details in ESI†). The desired product **2a** was produced in 76% yield and 85% ee when phosphoramidite ligand **L12** was used. Having identified **L12** as the optimal ligand, we examined the generality of this asymmetric protocol. All the tested substrates proceeded smoothly and provided the desired products in good yields and enantioselectivities. A total of fourteen compounds were prepared with variations on the aryl group with alkyl groups and halides. The absolute configuration of the products was determined based on the X-ray crystallography analysis of (*R*,*R*)-**2i** as a representative example.[17] Notably, when methyl ester attached substrates (**1p**, **1s–1u**) were used in this asymmetric protocol, excellent enantioselectivities of ≥90% ee were obtained by using BIDIME (**L7**) as the ligand.

A plausible reaction pathway for this asymmetric hydrocyclopropanylation of alkynes is proposed based on the present results and previous literature[18] (Scheme 4). Initially, the oxidative ligation of the alkyne bond of **1** to the *in situ* generated Pd(0) generates an Pd(II)–complex **B**. Then, intramolecular ligand exchange of the C–H bond of the cyclopropyl group followed by hydrogen transfer affords the cyclopalladium complex **D** *via* the intermediacy of **C**. Finally, reductive elimination of intermediate **D** releases the desired product **2** and meanwhile regenerates Pd(0) for the next catalytic cycle.

Conclusions

In summary, we have developed a palladium-catalyzed intramolecular asymmetric hydrocyclopropanylation of alkynes *via* C(sp^3)–H activation for the synthesis of cyclopropane-fused γ-lactams. The presented strategy proceeds in a selective and 100% atom-economical manner. A range of cyclopropane-fused γ-lactams were prepared from readily available substrates in good yields and enantioselectivities with a chiral phosphoramidite ligand.

Data availability

All experimental data and detailed procedures are available in the ESI.†

Author contributions

J.-B. P. conceived and directed the project. H.-Z. L. and Z. Q. performed the experiments. Q.-M. W. and Y.-Y. J. participated in substrates synthesis and discussions. H.-Z. L. and J.-B. P. wrote the manuscript and ESI.†

Conflicts of interest

There are no conflicts to declare.

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