C–H Activation

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Chiral γ-Lactams by Enantioselective Palladium(0)-Catalyzed Cyclopropane Functionalizations

*Julia Pedroni and Nicolai Cramer**

Abstract: *Cyclopropanes fused to pyrrolidines are important structural features found in a number of marketed drugs and development candidates. Typically, their synthesis involves the cyclopropanation of a dihydropyrrole precursor. Reported herein is a complementary approach which employs a palladium(0)-catalyzed C–H functionalization of an achiral cyclopropane to close the pyrrolidine ring in an enantioselective manner. In contrast to aryl–aryl couplings, palladium(0)-catalyzed C–H functionalizations involving the formation of C(sp^3)–C(sp^3) bonds of saturated heterocycles are very scarce. The presented strategy yields cyclopropane-fused γ-lactams from chloroacetamide substrates. A bulky Taddol phosphonite ligand in combination with adamantane-1-carboxylic acid as a cocatalyst provides the γ-lactams in excellent yields and enantioselectivities.*

The cyclopropane ring is a frequently used design element in biologically active compounds with the aim to increase metabolic stability, as well as rigidity, by a defined three-dimensional orientation in space.[1] In particular, cyclopropanes fused to pyrrolidine units are found as key structural features in important biologically active agents such as trovafloxacin,[2] boceprevir,[3] cyproximide,[4] amitifadine,[5] and bicifadine[6] for the 3-azabicyclo[3.1.0]hexane series and saxagliptin,[7] as a 2-azabicyclo[3.1.0]hexane (Figure 1).

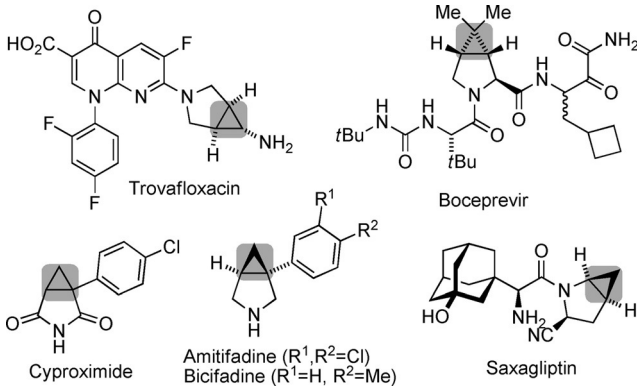

Figure 1. Examples of marketed drugs and development candidates containing a cyclopropane unit fused to a pyrrolidine.

[*] J. Pedroni, Prof. Dr. N. Cramer
Laboratory of Asymmetric Catalysis and Synthesis, EPFL SB ISIC LCSA, BCH 4305
1015 Lausanne (Switzerland)
E-mail: nicolai.cramer@epfl.ch
Homepage: http://isic.epfl.ch/lcsa

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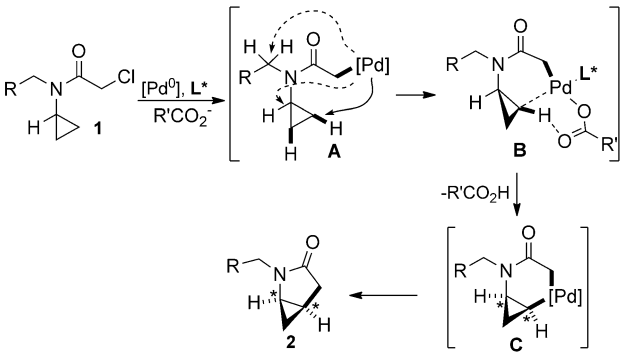
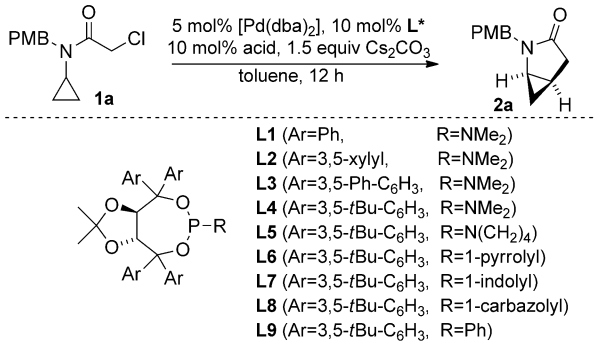
The relevance of the azabicyclo[3.1.0]hexanes makes catalytic enantioselective approaches for this scaffold synthetically very valuable. Classical synthetic approaches involve a cyclopropanation reaction of suitable unsaturated precursors.[8–10] Complementary to the construction of the cyclopropane,[11] we aimed for an enantioselective direct functionalization of an existing achiral cyclopropyl unit. Besides stoichiometric reactions using strongly basic reagents,[12] transition-metal-catalyzed C–H functionalizations of cyclopropanes have been developed.[13,14] Despite their utility, enantioselective variants remain rare.[15] In contrast to the formation of either C(sp^2)–C(sp^2) or C(sp^2)–C(sp^3) bonds,[13c,16] palladium(0)-catalyzed C–H functionalizations aimed at the construction of C(sp^3)–C(sp^3) bonds are very scarce.[13b,17,18] Herein, we report a highly enantioselective synthesis of saxagliptin-type 2-azabicyclo[3.1.0]hexane derivatives **2** by an asymmetric C–H functionalization strategy (Scheme 1). The required aminocyclopropane substrates **1** are conveniently accessed by Kulinkovich–Szymoniak[19] or Kulinkovich–de Meijere reactions.[20] The chloroacetamide group of **1** serves as the alkyl electrophile required to access the alkyl palladium intermediate **A**. So far, the use of chloroacetamides as electrophilic components for palladium-catalyzed C–H activations remain limited to reports from the group of Buchwald for the synthesis of oxindoles[21] and from our group to access β-lactams.[17a] Several selectivity challenges in the activation step have to be considered. First, the activation of the hydrogen atoms of **A**, adjacent to the nitrogen atom need to be mitigated (Scheme 1). We previously reported functionalizations of such C–H bonds for an enantioselective β-lactam synthesis.[17a] Instead, the formation of **2** would require a selective C–H activation of one of the



Scheme 1. An enantioselective palladium(0)-catalyzed C–H functionalization approach to cyclopropane-fused γ-lactams (**2**).

Table 1: Optimization of the enantioselective γ-lactam formation.[a]



Entry	L*	Acid	*T* [°C]	Yield [%][b]	e.r.[c]
1	**L1**	$AdCO_2H$	110	16	52:48
2	**L2**	$AdCO_2H$	110	76	68.5:31.5
3	**L3**	$AdCO_2H$	110	88	83.5:16.5
4	**L4**	$AdCO_2H$	110	95	84:16
5	**L5**	$AdCO_2H$	110	73	85.5:14.5
6	**L6**	$AdCO_2H$	110	93	92.5:7:5
7	**L7**	$AdCO_2H$	110	68	95:5
8	**L8**	$AdCO_2H$	110	29	95.5:4.5
9	**L9**	$AdCO_2H$	110	93	93.5:6.5
10	**L9**	AcOH	110	89	89:11
11	**L9**	Xanth-CO_2H	110	82	94:6
12	**L9**	PivOH	110	96	92.5:7.5
13	**L9**	$AdCO_2H$ (K_2CO_3)	110	96	92:8
14	**L9**	$AdCO_2H$ (Rb_2CO_3)	110	94	93:7
15[d]	**L9**	$AdCO_2H$ (5 mol%)	70	99 (89)[e]	95.5:4.5

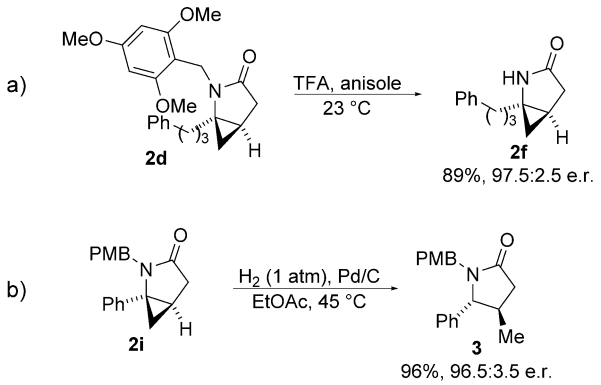
[a] Reaction conditions: 0.05 mmol **1a**, 2.5 μmol [Pd(dba)$_2$], 5.0 μmol **L***, 5.0 μmol acid, 1.5 equiv Cs_2CO_3, 0.1 M in toluene, 12 h at the indicated temperature. [b] Determined by ^{1}H NMR spectroscopy using an internal standard. [c] Determined by HPLC analysis using a chiral stationary phase. [d] 0.1 mmol scale, 24 h. [e] Yield of isolated product. dba = dibenzylideneacetone, Piv = pivaloyl.

two enantiotopic C–H bonds of the cyclopropane ring during the concerted metalation–deprotonation (CMD) step,[22] via **B**, to give the six-membered palladacycle **C**. Subsequent reductive elimination would yield the cyclopropane-fused γ-lactam **2**.

The initial reaction parameters were evaluated using chloroacetamide **1a** as a model substrate (Table 1). A brief screen of different Taddol phosphoramidite ligands showed that an increased bulk of the flanking aryl groups of the ligand (**L1**–**L4**) improved the yield as well as the selectivity of the C–H functionalization (entries 1–4), thus giving **2a** in 95% and 84:16 e.r. when using **L4**. Exchange of the dimethylamino substituent for a pyrrolidine (**L5**) had little effect (entry 5), whereas the installation of an aromatic pyrrole group (**L6**) increased the selectivity to 92.5:7.5 (entry 6). Changing the bulk of the pyrrole by replacing it with either an indole (**L7**; entry 7) or a carbazole (**L8**; entry 8) further increased the selectivity for **2a**, but drastically reduced the yield. Exchange of the 1-pyrrole substituent by a simple phenyl group (**L9**) resulted in excellent reactivity while maintaining the high selectivity (93.5:6.5) of the pyrrole-type ligands (entry 9). Among a small range of carboxylic acid additives tested (entries 9–12), adamantyl carboxylic acid provided the highest selectivities. Other carbonate bases could be used instead of cesium carbonate (entries 13 and 14). For instance, potassium carbonate gave **2a** with only slightly reduced enantioselectivity (entry 13). Remarkably, for this type of C–H activation, the reaction temperature could be lowered to 70 °C, thus further increasing the enantioselectivity to 95.5:4.5 e.r. while maintaining full conversion and high yields (entry 15).

The scope for the γ-lactam formation was subsequently evaluated with the aforementioned optimized reaction conditions (Table 1, entry 15). Several benzyl derivatives and alkyl groups are tolerated on the nitrogen atom (R^2; Table 2, entries 1–5). However, a tertiary amide is required as secondary ones do not cyclize and lead mainly to recovery of starting material (entry 6). Besides a hydrogen atom, R^1 accommodates a wide range of alkyl, benzyl, and aryl substituents. In addition, common and versatile functional groups including adjacent esters and nitriles work well (entries 7–14). The transformation furnishes, on a gram scale, the cyclized product in equally high yield and selectivity (entry 8). Concerning spirocyclic substrates, the success of the enantioselective activation is dependent on the ring size. For instance, the pyrrolidine **1n** did not provide the pyrrolizidine **2n** (entry 15). In contrast, the larger piperidine **1o** gave the indolizidine scaffold **2o** in excellent yield and enantioselectivity (entry 16). Remarkably, the reaction proceeds at reaction temperatures as low as 35 °C (entry 17). Moreover, the substrate **1q**, featuring a tetrasubstituted cyclopropane having only methine C–H bonds, is selectively functionalized to provide the tricyclic lactam **2q** (entry 19). The absolute configuration of the γ-lactams was unambiguously established to be (*R*,*R*) by X-ray crystallographic analysis of **2j**.[23]

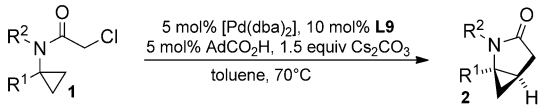
As γ-lactams with a free NH could not be directly accessed, the 2,4,6-trimethoxybenzyl group of **2d** was cleaved under acidic conditions, thus providing **2f** in good yield (Scheme 2a). Exemplarily for compound **2i**, the cyclopropane unit is shown to serve as a latent methyl group (Scheme 2b). Hydrogenation under heterogeneous conditions with Pd/C selectively yielded the *trans* γ-lactam **3** without a loss of optical purity.

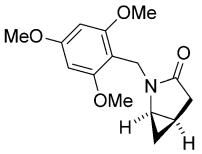
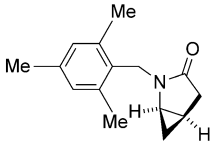
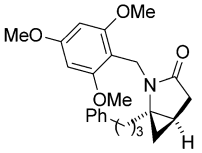
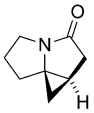
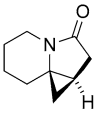
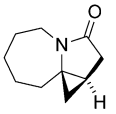
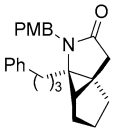


Scheme 2. Selected modifications of the γ-lactams **2**. TFA = trifluoroacetic acid.

The enantioselective γ-lactam formation is not limited to the use of cyclopropanes as source of activatable C–H bonds.

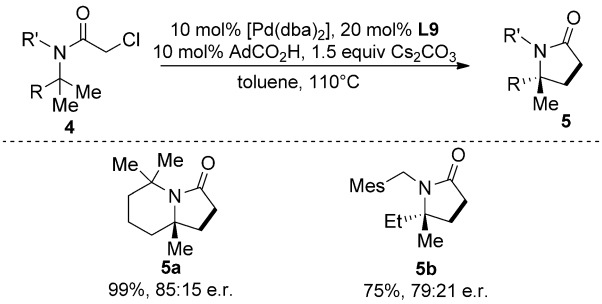
Table 2: Scope for the synthesis of the γ-lactams **2**.[a]



Entry	1	2		Yield [%][b]	e.r.[c]
1	**1a**	**2a**	R^2 = PMB, R^1 = H	89	95.5:4.5
2	**1b**	**2b**		99	96:4
3	**1c**	**2c**		99	93:7
4	**1d**	**2d**		78	98:2
5	**1e**	**2e**	R^2 = *i*Pr, R^1 = $(CH_2)_3$Ph	94	98:2
6	**1f**	**2f**	R^2 = H, R^1 = $(CH_2)_3$Ph	0	–
7	**1g**	**2g**	R^2 = PMB, R^1 = $(CH_2)_3$Ph	92	96.5:3.5
8	**1g**	**2g**	gram scale (2.69 mmol)	93	97.5:2.5
9	**1h**	**2h**	R^2 = PMB, R^1 = Bn	98	95.5:4.5
10	**1i**	**2i**	R^2 = PMB, R^1 = Ph	99	98:2
11[d]	**1j**	**2j**	R^2 = PMB, R^1 = *p*-ClC_6H_4	68	95:5
12	**1k**	**2k**	R^2 = PMB, R^1 = CN	99	92.5:7.5
13	**1l**	**2l**	R^2 = PMB, R^1 = CO_2Et	90	91.5:8.5
14	**1m**	**2m**	R^2 = PMB, R^1 = CH_2OTIPS	95	96.5:3.5
15	**1n**	**2n**		0	–
16	**1o**	**2o**		99	95:5
17[e]	**1o**	**2o**	at 35 °C	65	98:2
18	**1p**	**2p**		76	97.5:2.5
19	**1q**	**2q**		89	97.5:2.5

[a] Reaction conditions: 0.1 mmol **1**, 5.0 μmol $[Pd(dba)_2]$, 10.0 μmol **L9**, 5.0 μmol $AdCO_2H$, 1.5 equiv Cs_2CO_3, 0.1 M in toluene, 24 h at 70°. [b] Yield of isolated product. [c] Determined by HPLC analysis using a chiral stationary phase. [d] With 10.0 μmol $[Pd(dba)_2]$, 20.0 μmol **L9**, and 10.0 μmol $AdCO_2H$. [e] 75% conversion. PMB = *para*-methoxybenzyl.

Preliminary studies reveal that substrates with methyl groups can be addressed (Scheme 3). Although the obtained enantioselectivities are not yet paralleling those of the cyclopropanes, it is remarkable that the reaction allows a selection between a methyl and an ethyl group (**5b**).



Scheme 3. The γ-lactams **5** from the functionalization of enantiotopic methyl groups. Mes = 2,4,6-trimethylphenyl.

In summary, we disclosed an enantioselective C–H functionalization approach for the synthesis of valuable azabicyclo[3.1.0]hexane scaffolds using readily accessible chloroacetamides. This palladium(0)-catalyzed transformation yields cyclized products in excellent enantioselectivities by using a bulky Taddol phosphonite ligand and 1-adamantane carboxylic acid as a cocatalyst. A salient aspect of this transformation is its broad tolerance for substituents on the cyclopropane, thus enabling access to versatile molecular building blocks.

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Keywords: asymmetric catalysis · C–H activation · lactams · palladium · small-ring compounds

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[23] CCDC 1409033 (**2j**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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