C–H Activation Hot Paper

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Access to β-Lactams by Enantioselective Palladium(0)-Catalyzed C(sp^3)–H Alkylation**

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Abstract: *β-Lactams are very important structural motifs because of their broad biological activities as well as their propensity to engage in ring-opening reactions. Transition-metal-catalyzed C–H functionalizations have emerged as strategy enabling yet uncommon highly efficient disconnections. In contrast to the significant progress of Pd^0-catalyzed C–H functionalization for aryl–aryl couplings, related reactions involving the formation of saturated C(sp^3)–C(sp^3) bonds are elusive. Reported here is an asymmetric C–H functionalization approach to β-lactams using readily accessible chloroacetamide substrates. Important aspects of this transformation are challenging C(sp^3)–C(sp^3) and strain-building reductive eliminations to for the four-membered ring. In general, the β-lactams are formed in excellent yields and enantioselectivities using a bulky taddol phosphoramidite ligand in combination with adamantyl carboxylic acid as cocatalyst.*

Small four-membered heterocycles like β-lactones, β-lactams, β-sultames, and β-sultones are important structural motifs because of their rich biological activities as well as their high chemical reactivity. The most important class is β-lactams which form the backbone of antibiotic weaponry (Figure 1).[1] Moreover, sulbactam is used as a β-lactamase inhibitor.[2] Besides these bicyclic β-lactams, monocyclic congeners such as cholesterol-lowering ezetimibe[3] or the antibiotic aztreonam[4] are important. Apart from the pharmacological importance, they are also reactive starting materials used, for instance, in ring-opening reactions.[5] This significance is a great stimulus for the development of methods to access β-lactams.[6] Major synthetic strategies involve [2+2] cycloadditions like the Staudinger[7] and Kinugasa[8] reaction, and cyclizations forming either carbon–nitrogen or acyl–nitrogen bonds. Transition-metal-catalyzed C–H bond functionalizations[9] could offer complementary strategies through uncommon disconnections. For instance, asymmetric rhodium(II)-catalyzed C–H insertions with diazo amide precursors have been reported by Hashimoto and co-workers[10] and Doyle and co-workers.[11] Recently, β-lactams were obtained through N-directed palladium(II)-catalyzed C–H functionalizations and formation of the classical C–N bond.[12] Given our longstanding interest in enantioselective C–H functionalizations,[13] we envisioned expanding the scope of asymmetric palladium(0)-catalyzed C–H functionalizations for the synthesis of chiral β-lactams by formation of the complementary C(sp^3)–C(sp^3) bond. A limiting factor of palladium(0)-catalyzed[14] asymmetric intramolecular C–H functionalization is the ring size of the arising cyclic product allowing access to five-,[15] six-,[16] and seven-membered rings.[17] In all cases, the initial C(sp^2)–Pd^{II} species is obtained by oxidative addition of an aryl/vinyl halide or triflate. Corresponding C(sp^3)–Pd^{II} intermediates have been very scarcely used to induce C–H activation because of competing pathways. Hennessy and Buchwald used chloroacetanilides for the synthesis of oxindoles by achiral aromatic C(sp^2)–H functionalization.[18] The achiral construction of benzannulated four-membered rings by reductive elimination has been shown by Dyker[19] and extended to a practical level by Baudoin et al.[20] However, neither an asymmetric generation of four-membered rings, nor the reductive elimination between two sp^3 centers is known by these methods. Specifically, the reductive elimination bears a twofold challenge because of the formation of a C(sp^3)–C(sp^3) bond and the build-up of ring strain. Herein, we describe the palladium(0)-catalyzed asymmetric synthesis of β-lactam scaffolds from readily accessible chloroacetamides.

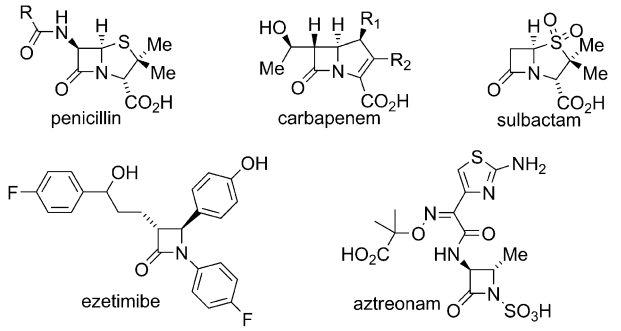

Figure 1. Examples of relevant β-lactam drugs.

α-Haloamides are relatively good electrophiles for nucleophilic substitution reactions. This characteristic complicates the envisioned C–H functionalization in two ways (Scheme 1). First, the essential carboxylate ligand engaging in the enantiodiscriminating concerted metalation–deprotonation (CMD) step[21] can serve as a nucleophile. This undesired substitution pathway not only forms the ester side product **3**, but also depletes the carboxylate stock, thus

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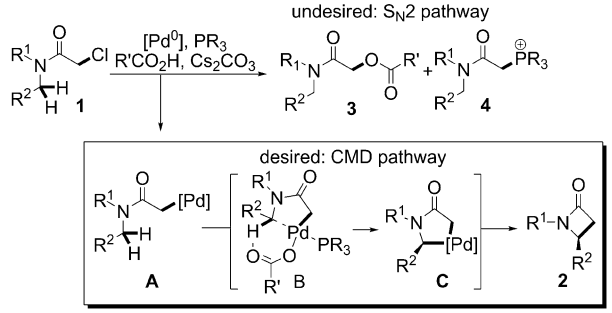
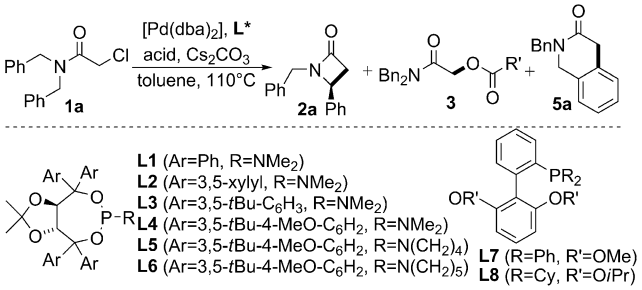


Scheme 1. β-Lactam formation by C–H functionalization and the undesired S_N2 pathway.

causing the reaction to stall once it is all consumed. Moreover, the utilized phosphine ligand should not display too high a nucleophilicity so as to avoid the formation of the phosphonium **4**.

We initially examined the reaction parameters with *N*,*N*-dibenzyl chloroacetamide (**1a**) as a model substrate (Table 1). The anticipated reactivity increase of benzylic C–H groups is traded for competing C(sp^2)–H activations, thus leading to the dihydroisoquinolone **5a**, which was only detected in small amounts. There is a highly critical balance between the substrates ability to engage in nucleophilic substitution with the employed carboxylate ligand and its propensity to undergo oxidative additions with the palladium(0) catalyst.

Table 1: Optimization of the Pd-catalyzed Cyclization.[a]



Entry	L*	Acid	Conv. [%][b]	**3** [%][b]	**5a** [%][b]	**2a** [%][c]	e.r.[d]
1[e]	**L5**	$AdCO_2H$	40 (**1a′**)	10	0	0	–
2	**L5**	–	50	0	<2	8	n. d.
3	**L5**	PivOH	100	3	18	76	98:2
4	**L5**	AcOH	84	13	5	55	92.5:7.5
5	**L1**	$AdCO_2H$	47	20	n. d.	12	n. d.
6	**L2**	$AdCO_2H$	100	20	n. d.	70	86.5:13.5
7	**L3**	$AdCO_2H$	100	14	8	63	96:4
8	**L4**	$AdCO_2H$	100	17	4	76	98:2
9	**L5**	$AdCO_2H$	100	19	0	81	98.5:1.5
10[f]	**L5**	$AdCO_2H$	100	10	7	80	97:3
11	**L6**	$AdCO_2H$	100	20	0	67	96:4
12	PPh_3	$AdCO_2H$	100	20	n. d.	58	–
13	**L7**	$AdCO_2H$	100	13	<2	83	–
14	**L8**	$AdCO_2H$	71	18	<2	30	–

[a] Reaction conditions: 0.10 mmol **1a**, 10 μmol [Pd(dba)$_2$], 20 μmol **L***, 20 μmol acid, 1.5 equiv Cs_2CO_3, 0.1 M in toluene, 110 °C, 12–16 h. [b] Determined by ^{1}H NMR spectroscopy. [c] Yield of isolated **2a**. [d] Determined by HPLC using a chiral stationary phase. [e] With bromoacetamide. [f] With 10 mol% $AdCO_2H$.

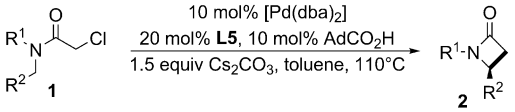
For instance dibenzyl bromoacetamide (**1a′**) is not suitable because of a more favored nucleophilic substitution pathway (entry 1). Adamantyl carboxylic acid ($AdCO_2H$) and pivalic acid proved to be superior to acetic acid in terms of enantioselectivity (entries 2–4). The evaluation of different taddol phosphoramidites revealed that increasing the bulk of the aryl groups (3,5-xylyl, 3,5-C_6H_3, 3,5-*t*Bu-4-MeO-C_6H_2) of the ligand improves both the yield and the selectivity of the process (entries 5–10). **L5**, having the DTBM-group and pyrrolidino substituent on the phosphorous atom, is the best performer (entry 9). The amount of $AdCO_2H$ could be reduced to 10 mol% (entry 10). While the enantioselective transformation could be established with **L5**, the execution of an achiral reaction required further screening. Simple PPh_3 provides **2a**, however in modest yield (entry 12). Diphenyl SPhos (**L7**) was a useful ligand (entry 13), whereas a more-electron-rich variant such as Ruphos (**L8**) was not suitable (entry 14).

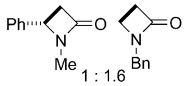
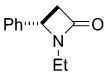
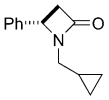
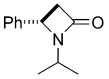
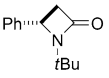
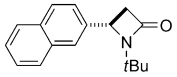
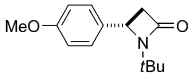
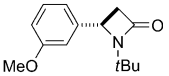
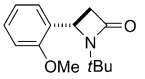
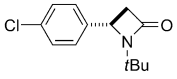
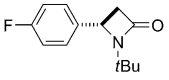
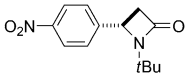
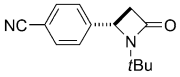
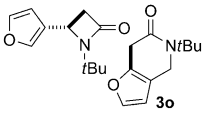
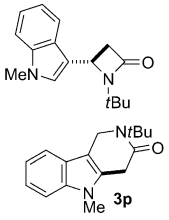
The scope for the β-lactam formation was subsequently evaluated with the aforementioned optimized reaction conditions. The reaction efficiency, but not the selectivity, proved to be dependent on the nature of the substituent R^1. While a methyl group is not suitable (Table 2, entry 1), the reaction works well with either an ethyl or cyclopropyl methyl group (entries 2 and 3). Bulkier and branched substituents are also tolerated. Specifically a *tert*-butyl group gives rise to excellent yields, presumably because of conformational preorganization which facilitates activation/cyclization (entry 5). The catalyst loading can be lowered without affecting the reaction performance on both a 0.1 mmol (2.5 mol% Pd; entry 5) and 1.0 mmol scale (5 mol% Pd; entry 6). The steric and electronic parameters of the benzyl group can be modulated over a wide range, thus maintaining the characteristics of the process (entries 6–14). Interestingly, for electron-rich five-membered heterocycles such as a furyl or indolyl group, the formation of a δ-lactam by competing C(sp^2)–H functionalization becomes dominant (entries 14 and 15). The absolute configuration of the β-lactam products was unambiguously established by X-ray crystallographic analysis of **2n** to be *S*.[22]

With substrates possessing a pre-existing stereogenic center in the form of a classical α-methyl benzylamine group [(*R*)-**1q** and (*S*)-**1q**], we investigated the degree of ligand control in the C–H activation step (Scheme 2). Indeed, for both enantiomers of **1q**, very high levels of diastereoselectivity [>95:5, 74% for (*R*)-**1q** and 94:6, 50% for (*S*)-**1q**] were observed, thus showing excellent catalyst control. However, the stereogenic center of the substrate has an influence on the reaction performance. The *S*-configured substrate **1q** is the mismatching enantiomer causing reduced yields. With the achiral ligand **L7**, we observed a low intrinsic substrate control of 55:45 and moderate yield of 44–47%.

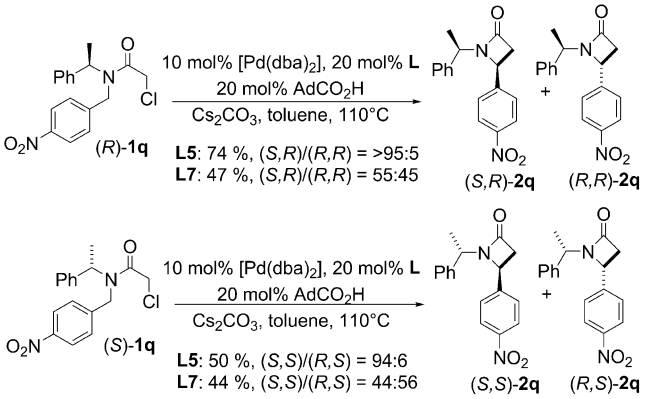
To gain further insights into the regioselectivity drivers of the reaction, the substrate **1r**, featuring an electron-rich (PMB) and an electron-poor (*p*-cyanobenzyl) benzyl group, was subjected to the asymmetric C–H functionalization (Scheme 3). The experiment showed a clear bias of 4.8:1 for the activation of the more acidic benzylic C(sp^3)–H bonds. These findings are in agreement with the CMD mechanism governed by kinetic C–H bond acidity.

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

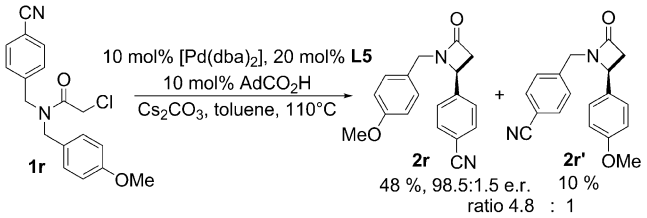


Entry	1	2		Yield [%][b]	e.r.[c]
1	**1b**	**2b**		20	n. d.
2[d]	**1c**	**2c**		74	98:2
3[d]	**1d**	**2d**		94	97.5:2.5
4	**1e**	**2e**		95	97:3
5	**1f**	**2f**		93 99[e]	98.5:1.5 98.5:1.5[e]
6	**1g**	**2g**		99 96[f]	99.5:0.5 98.5:0.5[f]
7	**1h**	**2h**		94	98:2
8	**1i**	**2i**		98	95.5:4.5
9	**1j**	**2j**		81	98:2
10	**1k**	**2k**		76	97.5:2.5
11	**1l**	**2l**		95	99:1
12	**1m**	**2m**		97	99:1
13	**1n**	**2n**		96	99.5:0.5
14	**1o**	**2o**		40 60 (**3o**)	98:2
15	**1p**	**2p**		39 59 (**3p**)	98:2

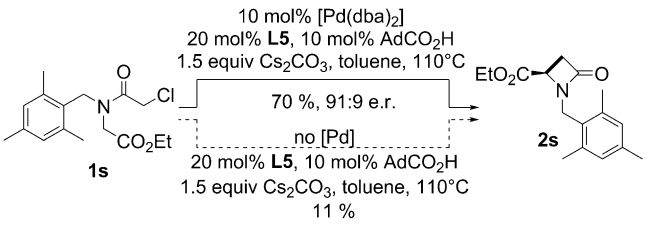
[a] Reaction conditions: 0.10 mmol **1**, 10 μmol $[Pd(dba)_2]$, 20 μmol **L4**, 10 μmol $AdCO_2H$, 1.5 equiv Cs_2CO_3, 0.1 M in toluene, 110 °C, 12 h. [b] Yield of isolated product. [c] Determined by HPLC using a chiral stationary phase. [d] An additional 10 μmol of $AdCO_2H$ added after 6 h. [e] 2.5 mol% $[Pd(dba)_2]$, 5 mol% **L4**, 5 mol% $AdCO_2H$. [f] 1.00 mmol 1, 5 mol% $[Pd(dba)_2]$ 10 mol% **L4**, 10 mol% $AdCO_2H$.



Scheme 2. Influence of a pre-existing stereogenic center on the diastereoselectivity.



Scheme 3. Electronic influence on the selectivity for the β-lactam formation.



Scheme 4. Asymmetric ring closure of a glycine ester derivative.

When exposing the glycine ester **1s** to the reaction conditions, the β-lactam **2s** was obtained in 70% yield with an enantiomeric ratio of 91:9 (Scheme 4). No benzylic activation was observed, presumably because of the hindered nature of the mesityl group. Although a small uncatalyzed background substitution reaction is observed in a palladium-free control experiment, this result suggests that the C–H activation pathway is operative and highly selective, taking the racemic background reaction into account.[23]

In summary, we reported an asymmetric C–H functionalization strategy for the synthesis of valuable β-lactams from readily accessible chloroacetamides. The palladium(0)-catalyzed process provides excellent enantioselectivities with a bulky taddol phosphoramidite ligand in combination with adamantyl carboxylic acid as a cocatalyst. Another salient feature of this reaction is a challenging $C(sp^3)$–$C(sp^3)$ and strain-building reductive elimination forming the four-membered lactam. Further work focuses on expanding the scope for the formation of higher substituted β-lactams with biological activities.

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Keywords: asymmetric catalysis · C–H activation · cross coupling · lactams · palladium

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