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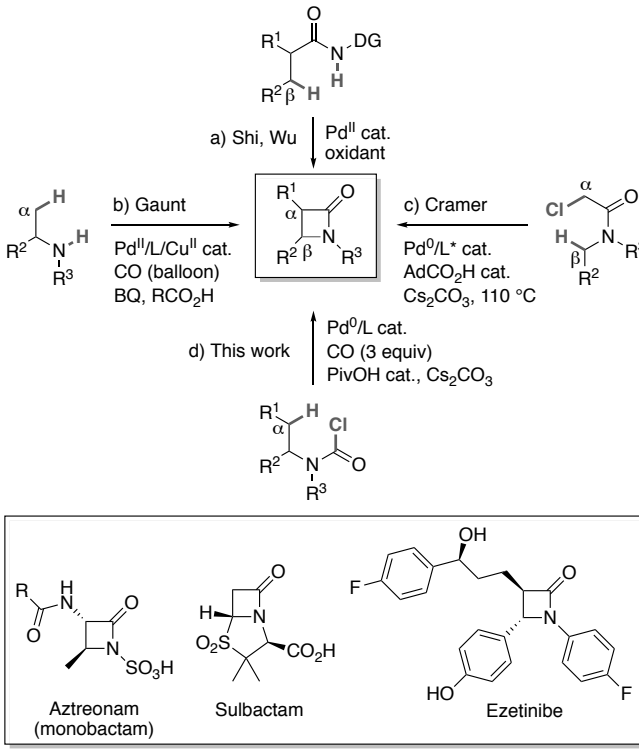
Synthesis of β-Lactams by Palladium(0)-Catalyzed C(sp^3)–H Carbamoylation**

*David Dailler, Ronan Rocaboy, and Olivier Baudoin**

***Abstract**: A general and user-friendly synthesis of β-lactams is reported via Pd^0-catalyzed carbamoylation of C(sp^3)–H bonds, operating under stoichiometric carbon monoxide in a two-chamber reactor. This reaction is compatible with a range of 1^{ary}, 2^{ary} and activated 3^{ary} C–H H bonds, in contrast to previous C(sp^3)–H activation-based methods. In addition, the feasibility of an enantioselective version using a chiral phosphonite ligand is demonstrated. Finally, this method can be employed to synthesize valuable enantiopure free β-lactams and β-aminoacids.*

β-Lactams are very important scaffolds for drug discovery, as illustrated with the structure of numerous monocyclic (e. g., Aztreonam) and bicyclic antibiotics (e. g., Sulbactam) as well as the cholesterol-lowering drug Ezetinibe (Scheme 1, bottom).[1] They are also valuable synthetic intermediates, for instance in the synthesis of β-aminoacids and their derivatives upon ring-opening.[2] In the past few years, C(sp^3)–H activation-based methods have been introduced to access this motif in a straightforward manner. On one hand, methods employing Pd^{II} catalysis and requiring a stoichiometric oxidant have been reported. The groups of Shi[3a] and Wu[3b,c] employed a pyridine or quinoline-based directing group (DG), respectively, to form the N–$C_β$ bond of the β-lactam ring (Scheme 1a). The reaction is operationally simple, but requires the installation and removal of a DG possessing a comparatively high molecular weight. In addition, only 2^{ary} C–H bonds could be functionalized, and the bidentate nature of the DG could hinder the development of an enantioselective version. In parallel, Gaunt and co-workers described a carbonylative C–H activation method to synthesize β-lactams from simple aliphatic 2^{ary} amines (Scheme 1b).[4] The reaction requiring Cu^{II} co-catalysis, benzoquinone (BQ) as the terminal oxidant and excess CO (balloon) shows impressive scope, but was only reported with 1^{ary} C–H bonds. A nitrogen ligand was found to be beneficial, which opens to a future enantioselective version. On the other hand, as initially shown by our group,[5-6] C(sp^3)–H activation reactions operating through Pd^0 catalysis allow to form a wide variety of ring systems under oxidant-free conditions, compatible with the use of a range of monodentate ligands from electron-poor



Scheme 1. Synthesis of β-lactams by Pd^{II}- and Pd^0-catalyzed C(sp^3)–H activation: state-of-the-art and current work

phosphoramidites[7] to electron-rich phosphines[8] and *N*-heterocyclic carbenes.[9] This feature allows for the modulation of reactivity and site-selectivity, and for the development of enantioselective reactions. In this context, Cramer and co-workers employed α-chloroamides as precursors to construct the $C_α$–$C_β$ bond of β-lactams (Scheme 1c).[10] Using a chiral phosphoramidite ligand, high enantioselectivities were achieved for the desymmetrization of enantiotopic 2^{ary} C–H bonds. However, the reaction occurred only on activated methylenes adjacent to a (hetero)aryl or ester group. Recently, we were able to access highly strained α-alkylidene-β-lactams from bromoalkenes, but this system, which was tailored for γ-lactams, lacked generality and efficiency.[11] Inspired by the work of Takemoto and co-workers on the carbamoylation of 1^{ary} benzylic and cyclopropyl C–H bonds,[12] we envisioned that carbamoyl chlorides could constitute more appropriate substrates to construct the C(O)-$C_α$ bond of β-lactams through Pd^0-catalyzed C(sp^3)–H activation (Scheme 1d). Carbamoyl chlorides are easily accessed from the corresponding 2^{ary} amines upon reaction with triphosgene, and can be engaged in the reaction without purification. We report therein the development of a convenient method to synthesize β-lactams by C(sp^3)–H carbamoylation, which is compatible with both 1^{ary} and 2^{ary} C–H

[*] D. Dailler, R. Rocaboy, Prof. Dr. O. Baudoin
University of Basel, Department of Chemistry, St. Johanns-Ring 19, CH-4056 Basel, Switzerland
E-mail: olivier.baudoin@unibas.ch

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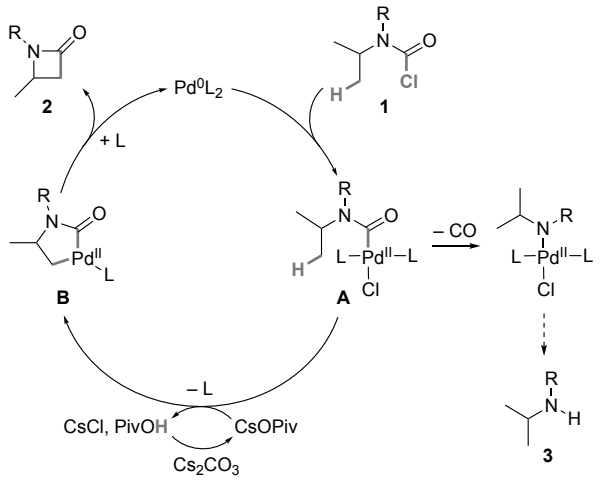
bonds and adaptable to an enantioselective version.

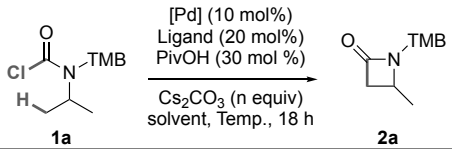
At the outset of our work, we were aware that competitive decarbonylation, occurring prior to the C–H activation step and leading to secondary amine **3**, would likely impact the reaction efficiency (Scheme 2).[12] To limit this side-reaction, we first conducted reactions under excess CO (balloon), as reported by Takemoto and co-workers (Table 1). Optimization studies were performed with TMB-protected[13] carbamoyl chloride **1a**. Initially, we employed $Pd(PPh_3)_4$ as the catalyst and cesium pivalate as the active base,[11] which gave rise to β-lactam **2a** in modest yield (entry 1), together with amine **3a**. Variations of the Pd source, ligand, solvent, acid additive, equivalents of carbonate, and temperature (entries 2-10)[14] allowed to identify $PdCl_2/PAd_2(n\text{-Bu})$ as the optimal catalyst, in combination with cat. PivOH (30 mol%)/Cs_2CO_3 (3 equiv) as the basic system in mesitylene at 120 °C (entry 6). Employing the electron-rich $PAd_2(n\text{-Bu})$ phosphine (CataCXium® A) was crucial, likely to avoid catalyst deactivation by excess CO.[15] Well-defined Pd^{II} (entry 11) and Pd^0 (entry 12) complexes containing this phosphine ligand[16] performed with comparable efficiency to the in situ-formed catalyst. This experiment with the Pd^0L_2 complex (entry 12) indicates that this reaction is indeed proceeding via the Pd^0-Pd^{II}-Pd^0 catalytic cycle depicted in Scheme 2. Further support to this mechanism was provided by a control experiment performed with amine **3a** instead of carbamoyl chloride **1a**, which failed to give any trace of β-lactam product (entry 13).



Scheme 2. Mechanistic model.

Moreover, when the isolated complex **A** (R = *i*-Pr, L = PPh_3)[4b] was heated to 120 °C with PivOH and Cs_2CO_3 in mesitylene, the corresponding β-lactam product was formed in comparable yield to the catalytic reaction performed from the carbamoyl chloride and $Pd(PPh_3)_4$,[14] thereby indicating that complex **A** is a competent intermediate. Therefore this Pd^0-Pd^{II}-Pd^0 catalytic cycle differs from

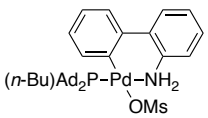
Table 1. Optimization of reaction conditions.[a]



1a **2a**

Entry	[Pd]	Ligand	n	Solvent	CO source: balloon	CO source: COgen[b] (equiv)	Temp [°C]	Yield **2a** [%][c]
1	$Pd(PPh_3)_4$	–	1.5	Xylene	✓		120	27%
2	$Pd(OAc)_2$	PPh_3	1.5	Xylene	✓		120	10%
3	$Pd(OAc)_2$	$PAd_2(n\text{-Bu})$•HI	1.5	Xylene	✓		120	45%
4	$PdCl_2$	$PAd_2(n\text{-Bu})$•HI	1.5	Xylene	✓		120	76%
5	$PdCl_2$	$PAd_2(n\text{-Bu})$•HI	3	Xylene	✓		120	82%
6	$PdCl_2$	$PAd_2(n\text{-Bu})$•HI	3	Mesitylene	✓		120	92% (85%)
7	$PdCl_2$	$PAd_2(n\text{-Bu})$•HI	3	Mesitylene	✓		110	57%
8	$PdCl_2$	$PAd_2(n\text{-Bu})$•HI	3	Mesitylene	✓		130	58%
9	$PdCl_2$	PAd_2Bn	3	Mesitylene	✓		120	18%
10	$PdCl_2$	PCy_3•HBF_4	3	Mesitylene	✓		120	28%
11	$PAd_2(n\text{-Bu})$-Pd-G3	–	3	Mesitylene	✓		120	80%
12	$Pd[PAd_2(n\text{-Bu})]_2$	–	3	Mesitylene	✓		120	88% (85%)
13[d]	$PdCl_2$	$PAd_2(n\text{-Bu})$•HI	3	Mesitylene	✓		120	0%
14	$PdCl_2$	$PAd_2(n\text{-Bu})$•HI	3	Mesitylene	–	–	120	70%
15	$PdCl_2$	$PAd_2(n\text{-Bu})$•HI	3	Mesitylene		✓ (1.5)	120	75%
16	$PdCl_2$	$PAd_2(n\text{-Bu})$•HI	3	Mesitylene		✓ (3)	120	94% (92%)
17[e]	$PdCl_2$	$PAd_2(n\text{-Bu})$•HI	3	Mesitylene		✓ (3)	120	(95%) (75%)[f]

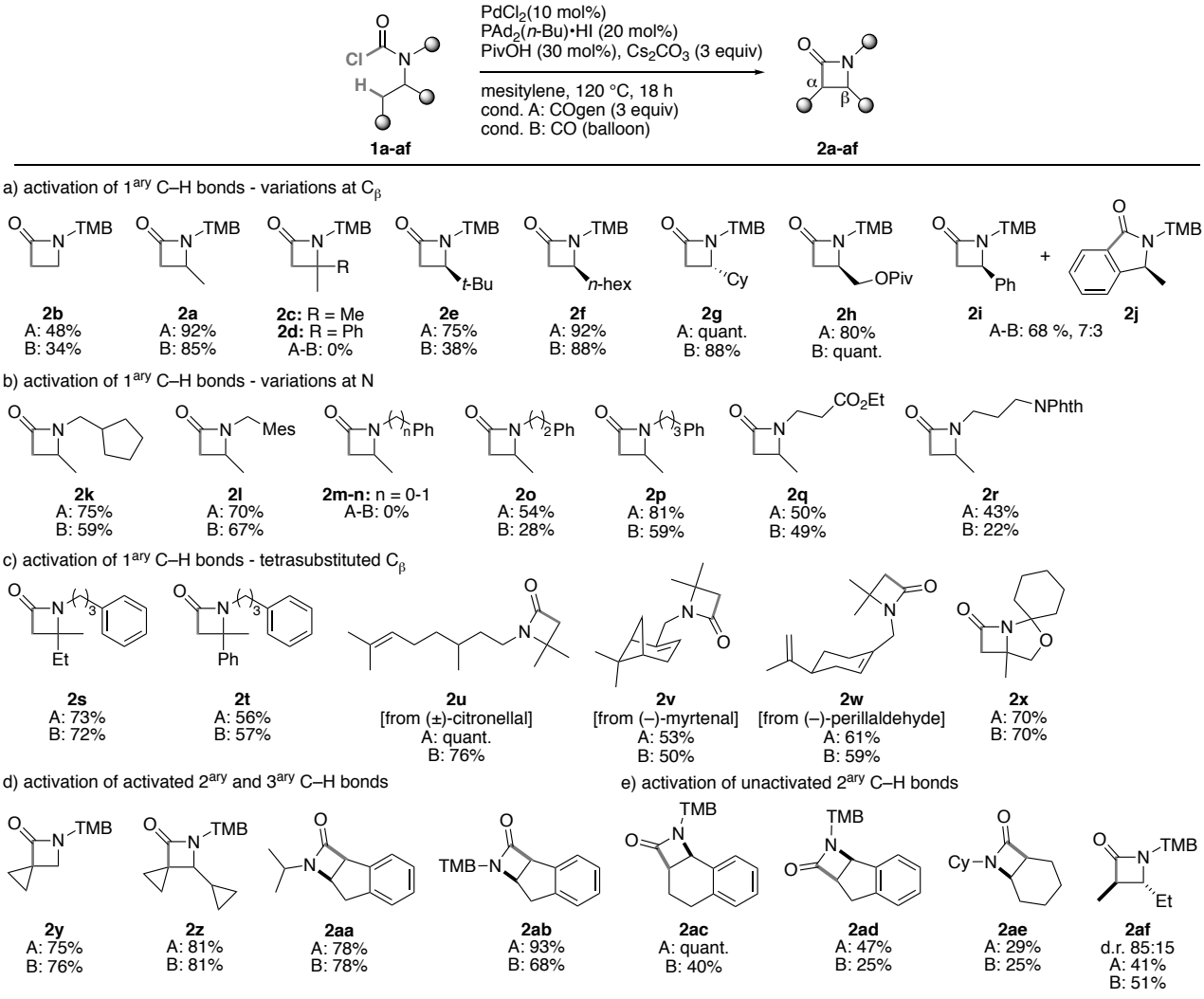
[a] Performed using 0.133 mmol of **1a** unless otherwise stated. [b] 9-Methylfluorene-9-carbonyl chloride (COgen), $Pd(OAc)_2/P(t\text{-Bu})_3$•$HBF_4$ cat., Cy_2NMe, mesitylene, two-chamber system (COware), both reaction chambers were placed at the same temperature. [c] Determined by NMR analysis using trichloroethylene as internal standard. Yield of isolated product **2a** is given within parentheses. [d] Using amine **3a** instead of **1a**. [e] Performed using 1.33 mmol (400 mg) of **1a**. [f] Performed using technical-grade mesitylene under non-inert conditions. TMB = 2,4,6-trimethoxybenzyl.

$PAd_2(n\text{-Bu})$-Pd-G3 = 

3a

the Pd^{II}-Pd^{0}-Pd^{II} mechanism operating in the case of secondary amines (Scheme 1b).[4b] In the absence of CO (entry 14), the reaction proceeded with reduced (–22%), but yet acceptable yield (70%), in contrast to observations of Takemoto and co-workers.[12a] In order to develop a more convenient protocol which can be employed without special safety equipment, we looked for an appropriate nongaseous source of stoichiometric CO. After unsuccessful tries with various in situ CO sources,[14] we turned to the use of the two-chamber (COware) system developed by Skrydstrup and co-workers.[17] Gratifyingly, using 3 equiv of COgen (entries 15-16), the yield of isolated **2a** was increased to 92%, thereby surpassing the yield obtained with excess CO (85%, entry 6). Of note, the same reaction performed with ^{13}COgen led to a very low (2.5%) incorporation of ^{13}C in the β-lactam product,[14] which suggests that the role of the added CO is mainly to saturate the reaction solution to limit the decarbonylation of intermediate **A** (Scheme 2). Finally, scaling up the reaction tenfold did not affect the yield (95%, entry 17). Moreover, the reaction was performed successfully when technical-grade solvent was employed and the experiment was set up under air (75% yield), thereby demonstrating the robust and user-friendly character of this protocol.

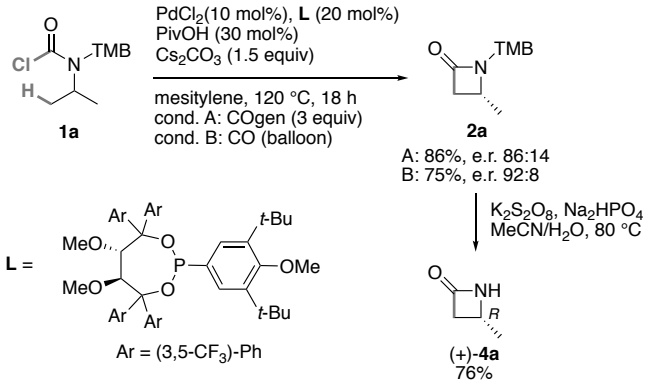
The scope of the reaction was next investigated, and for comparison both CO balloon and COgen conditions were tested for each substrate (Scheme 3). In most cases, the COgen conditions were found to be superior or equal to the CO-balloon ones. Moreover, in several instances like **2e**, **2o-p**, **2r**, **2u**, **2ab-ad**, the yield difference was greater than 20%, thereby making the COgen-mediated reaction an efficient β-lactam synthesis when the CO-balloon method was sluggish. The carbamoylation of 1^{ary} C–H bonds was first investigated from TMB-protected substrates **1a-i** (Scheme 3a). Excellent yields were obtained with reactants bearing a trisubstituted β position, including enantiopure ones (**2e-h**). In the case of substrate **1i** bearing Me and Ph substituents on $C_β$, a competition between C(sp^3)–H and C(sp^2)–H was observed, albeit in favor of the former (**2i**/**2j** 7:3), which is somewhat unusual given the higher reactivity of the latter,[18] but likely reflects the preferential formation of the kinetically favorable 5-membered palladacycle intermediate in the C–H activation step. The reaction also occurred when the β position was disubstituted (**2b**), albeit with markedly reduced efficiency. Nevertheless, this is a rare case of C(sp^3)–H functionalization of such an unfunctionalized substrate, which does not benefit from favorable conformational effects. Surprisingly, β-tetrasubstituted substrates **1c-d** failed to undergo C–H carbamoylation, likely due to excessive repulsion with the adjacent TMB group. Fortunately, less hindered N-substituents restored reactivity for this interesting class of substrates (Scheme 3c). Indeed the nature of the N-substituent had a marked effect on the reaction efficiency (Scheme 3b). For instance a phenyl substituent was



Scheme 3. Scope and limitations of the β-lactam synthesis. Compounds **2e-j** and **2v-w** were obtained from enantiopure amines.

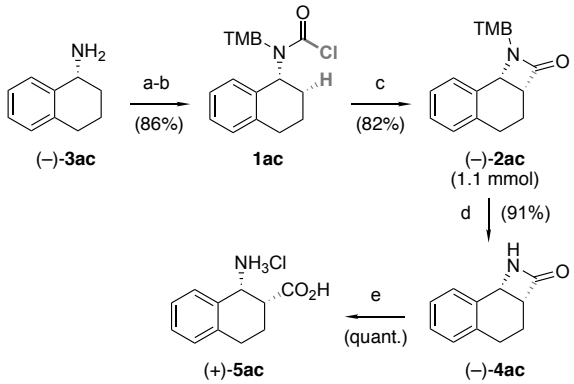
tolerated, but only when it was separated from the N atom by a sufficiently long carbon chain (**2o-p**), presumably because competitive C(sp^2)–H activation occurs when the chain is too short (**2m-n**). Other functional groups such as an ester (**2q**) and a protected amine (**2r**) could be employed, although the reaction occurred with moderate yield. A range of carbamoyl chlorides bearing a tetrasubstituted C_β also reacted successfully (Scheme 3c), including those derived from more elaborate acyclic and cyclic monoterpene precursors (**1u-x**). The reaction selectivity is especially noteworthy for **2v** and **2w**, wherein the alkene group did not undergo competitive carbopalladation or C(sp^2)–H activation. The example of fused β-lactam **2x**, reminiscent of bicyclic antibiotics, is also worth highlighting. In addition to 1^{ary} C–H bonds, activated 3^{ary} cyclopropyl C–H bonds (**2y-z**) and benzylic 2^{ary} C–H bonds (**2aa-ab**) were found to be reactive, thus affording original spirocyclic and fused β-lactams in high yields (Scheme 3d). Moreover, we were pleased to find out that less activated methylenes of both cyclic (**2ac-ae**) and acyclic (**2af**) substrates also underwent carbamoylation (Scheme 3e), albeit with variable efficiency. The latter was maximal for product **2ac**, which was obtained in quantitative yield using the two-chamber system, whereas the CO-balloon conditions were much less efficient (40%).

Another attractive feature of Pd^0-catalyzed C(sp^3)–H activation is the possibility to induce enantioselectivity by using either a chiral ancillary ligand[19] or a chiral base.[20] We pursued this direction by examining the effect of various chiral catalysts in the enantioselective desymmetrization of carbamoyl chloride **1a** (Scheme 4). Extensive screening, followed by optimization of the best ligand lead structure, converged towards the new TADDOL-derived phosphonite **L**, which allowed formation of β-lactam **2a** in 76% yield and good e.r. (92:8) under excess CO.[14] Using the COgen conditions impacted positively the yield (86%), but the enantioselectivity slightly decreased (e.r. 86:14). Although levels of enantioselectivity higher than 92:8 could not be reached, this result constitutes a proof-of-concept enantioselective synthesis of β-lactams by desymmetrization of unactivated methyl groups, which is to date unprecedented.[10] The cleavage of the TMB group was best performed employing potassium persulfate[21] to give the known free lactam (*R*)-**4a**, which was previously synthesized through the separation of diastereoisomeric precursors.[22]



Scheme 4. Proof-of-concept enantioselective synthesis of β-lactams by desymmetrization of methyl groups.

Finally, this C–H carbamoylation method was applied to the synthesis of the enantiopure free β-lactam **4ac** and β-aminoacid **5ac**. The latter, which was previously obtained by enzymatic resolution, is of high interest for the synthesis of β-peptides (Scheme 5).[23] Commercially available enantiopure tetrahydronaphthylamine **3ac** was converted to carbamoyl chloride **1ac**, which underwent C–H carbamoylation under the optimal COgen conditions to give TMB-protected β-lactam **2ac** in 82% yield. Persulfate-mediated oxidative cleavage provided β-lactam **4ac**, which underwent acidic hydrolysis to give (+)-**5ac** in very good overall yield (64% for 5 steps).



Scheme 5. Synthesis of an enantiopure β-aminoacid. Reagents and conditions: a) 2,4,6-trimethoxybenzaldehyde (1 equiv), $NaBH(OAc)_3$ (2 equiv), AcOH (2 equiv), 1,2-dichloroethane, 20 °C, 100%; b) triphosgene (0.34 equiv), benzene, 60 °C, 86%; c) see Scheme 3, cond. A; d) $K_2S_2O_8$ (2 equiv), $Na_2HPO_4•7H_2O$ (2 equiv), MeCN/H_2O 2:1, 80 °C, 91%; e) 6M HCl, reflux, quant.

In conclusion, we have reported a new method to synthesize valuable β-lactams through Pd^0-catalyzed C(sp^3)–H carbamoylation from readily accessible carbamoyl chlorides. This reaction is compatible with a range of 1^{ary}, 2^{ary} and activated 3^{ary} C–H bonds, in contrast with previous C(sp^3)–H activation-based methods, and is adaptable to an enantioselective version using a chiral ligand. Finally, its applicability to the synthesis of valuable enantiopure free β-lactams and β-aminoacids was demonstrated.

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C–H Activation

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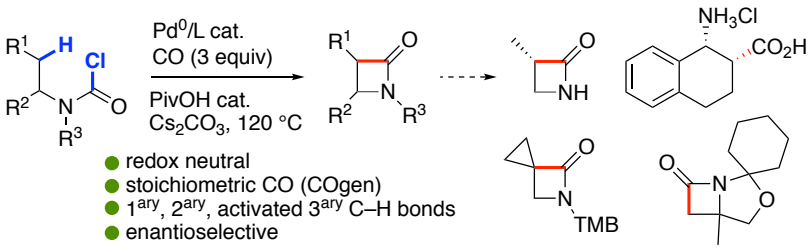
Synthesis of β-Lactams by Palladium(0)-Catalyzed C(sp^3)–H Carbamoylation



- redox neutral
- stoichiometric CO (COgen)
- 1^{ary}, 2^{ary}, activated 3^{ary} C–H bonds
- enantioselective