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SHORT COMMUNICATION

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A Mild and Selective Reduction of β-Lactams: Rh-Catalyzed Hydrosilylation towards Important Pharmacological Building Blocks

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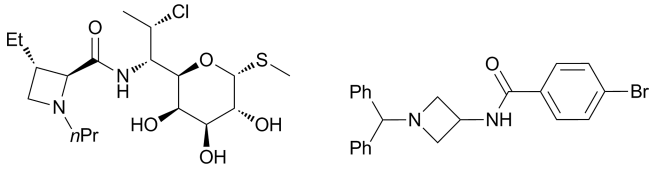
Four-membered N-heterocyclic compounds exhibit a broad range of pharmacological activities. Herein, we report a useful rhodium-catalyzed protocol for the activation of phenylsilane to reduce tertiary β-lactams. Reaction with the tertiary amides was selective over secondary amides, esters, olefins and nitriles, with no erosion of stereochemistry. A one-pot protocol from commercially available starting materials and a selective reduction of a complex penicillin derivative demonstrate the synthetic utility of this facile procedure.

Introduction

The azetidine moiety is a remarkable functional group that has received a flourish of recent interest,[1] particularly in the life science industries. The naturally occurring azitidine-2-carboxylic acid was first discovered to exhibit biological activity, and since then its incorporation into drug-like molecules has been impressive.[2] Compounds containing the four-membered heterocyclic functionality have shown activity in blood cholesterol reduction,[3] dopamine antagonists,[2d,4] antifungals[1b,5] and antibacterials[6] (Figure 1). Azetidines have also found application as organocatalysts, or chiral auxiliaries, in enantioselective transformations,[7] and in the formation of larger N-heterocycles.[8] In addition, spirocyclic azetidine systems constitute useful surrogates for heterocycles, e.g. morpholine, in medicinal chemistry, offering higher metabolic stability and bioavailability.[9]



Antibacterial drug[6] Dopamine antagonist[2d]

Figure 1. Two examples of important azetidine-derived drugs.

Azetidines are, however, the least studied representative among its four-membered heterocyclic cousins. This being primarily due to the fact that their preparation is highly cumbersome, owing to the internal strain that causes facile ring opening. One of the most applied approaches to their synthesis is by intramolecular cyclization reactions.[8,10] The scaffold can equally be constructed through a formal [2+2] cycloaddition of ketimines with allenoates,[11] iodocyclization of homoallylamines[12] or ring expansion of aziridines.[13] Unfortunately, many of these methods suffer from major drawbacks including low yields, harsh reaction conditions, toxic reagents and limited substrate scope. In general, the method of choice for the synthesis of azetidines should be the reduction of the more versatile and readily accessible β-lactam moiety. However, typical amide reductants such as $LiAlH_4$ or boranes lead to rapid ring opening. In-situ formed AlH_xCl_y can give the desired products in reasonable yields,[14] and $NaBH_4$ will reduce β-lactams containing adjacent unsaturation.[15] However, these methods employ excess reagent and are unselective towards moieties sensitive to reduction.

Recently, and during the course of this work, the reduction of β-lactams was reported by Alcaide and coworkers.[16] Employing hydrosilanes and a Zn catalyst, 3-oxygenated β-lactams were reduced in the presence of esters, nitriles and olefins. Moderate to good yields were observed employing excess hydrosilane, comparably high catalyst loading (10 mol-%) and elevated temperatures (90 °C) in sealed reaction vessels. Furthermore, Navarro et al.[17] showed the applicability of $RhH(CO)(PPh_3)_3$ in catalyzing the reduction of amino acid derived β-lactams. Again, employing excess diphenylsilane, a limited range of tertiary four-membered amides were reduced in moderate to high yields. It is worth noting that ester and urethane moieties were tolerated under the applied conditions, but the protocol was not demonstrated on sterically demanding 3,4-disubstituted β-lactams.

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Results and Discussion

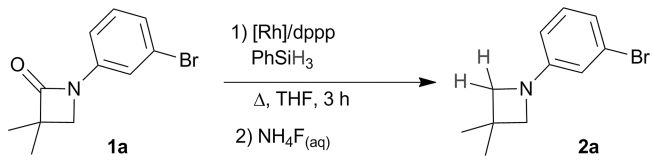
Based on our general interest in selective amide reductions, we report herein on the optimization of a mild and high yielding reduction system that exhibits impressive chemoselectivity towards tertiary β-lactams. The commercially available 1-(3-bromophenyl)-3,3-dimethylazetidin-2-one (**1a**) was employed as a model system for reaction optimization. We first tested non-noble metal based systems known for the reduction of amides[18] including $Zn(OAc)_2$,[16,18b] but unfortunately, under the criteria we set to use mild conditions, none led to any reasonable conversion (GC; Table S1, Entries 1–7). Based on our recent progress on the selective hydrosilylation of amino acid derivatives,[19] we began to investigate various rhodium precursors in the presence of 1,3-bis(diphenylphosphanyl)propane (dppp) as ligand and phenylsilane. Among the different pre-catalysts $[Rh(COD)_2]BF_4$ (2.5 mol-%) proved to be the most successful in combination with dppp (5 mol-%) (Table 1, Entry 4) at 50 °C. However, reducing the reaction temperature to ambient conditions caused the reactivity to significantly drop (Table 1, Entry 5). Switching from a coordinating (THF) to a non-coordinating (toluene) solvent, (Table S1, Entry 15) led to only a slight decrease in reactivity that was completely attenuated in methanol (Table S1, Entry 16). We turned our attention to the influence of the reductant on the reaction progress, where – interestingly – only phenylsilane gave detectable conversions (Table S1, Entries 17–19). We clarified that only one of the three possible hydrides is sufficiently activated to react, as the use of just 1.5 equiv. of the hydride source gave only 72% conversion (Table 1, Entry 8), which almost perfectly correlates with this assumption. As expected when the reductant Ph_2SiD_2 was employed, deuterium was fully incorporated into the desired azetidine, demonstrating the possibility to access selectively labeled compounds in a straightforward manner.[20]

The amenability of the optimized conditions on the substrate scope was subsequently tested. The starting materials were prepared using the Kinugasa reaction[21] or a Staudinger-type cycloaddition.[22] Since two chiral centers are formed during these cyclizations, the observed diastereomers were separated by column chromatography followed by partial crystallization. The results of the reduction are displayed in Figure 2. We began testing the reactivity of 3-oxygenated β-lactams (**1b**–**g**) under our optimized conditions {2.5 mol-% $[Rh(COD)_2]BF_4$, 5 mol-% dppp, 2 equiv. $PhSiH_3$ in THF, 50 °C, 3 h}. Compared to previously reported hydrosilylations,[16,17] in almost all cases higher isolated yields were obtained at lower temperatures, no excess hydrosilane and minimal catalyst loadings. The ester functionality of **1e** and the unsaturation in **1g** was left completely untouched. The stereochemistry of all substrates was maintained during reaction, with the only exception of compound **1g** [racemization of the OAllyl group (^{1}H NMR)]. The slight deterioration observed may be due to the presence of unsaturation in the molecule, which can facilitate stabilization of catalytic intermediates involved in an epimerization pathway. However, the single diastereomer is readily accessed by chromatography. Pleasingly, when the scale of the reaction was increased eightfold (2 mmol), product isolation is facilitated and consequently the yield was found to increase.

After establishing the reactivity of the 3-oxygenated series (**1b**–**g**), the conditions were tested on a broader range of amides. The *para*-methoxyphenyl group (PMP) was cleaved using an oxidative method,[23] and the electronic properties in the 4-position were explored, whilst a phenyl group possessed the 3-position (**1h**–**o**). Electron-donating and -withdrawing aryl substituents behaved well under the conditions, although problems were encountered with substrate **1m**, most probably caused by nitrile interaction with the active catalyst. In all cases no erosion of the stereochemical integrity was observed and, only the *cis* diastereoisomer was isolated.

Interestingly, when the secondary amide **1r** was subjected to this hydrosilylation protocol, no conversion was ob-

Table 1. Optimization of key variables in the hydrosilylation of 1-(3-bromophenyl)-3,3-dimethylazetidin-2-one (**1a**).[a,b]



Entry	[Rh] [mol-%]	$PhSiH_3$ [equiv.]	Temp. [°C]	(Conv.) yield [%][c]
1	$[Rh(COD)_2]BF_4$ 5.0	4	80	(> 99) 60
2	$[Rh(COD)_2]BF_4$ 1.5	2	80	(ca. 10) n.d.
3	$[Rh(COD)_2]BF_4$ 2.5	2	65	(> 99) 72
4	$[Rh(COD)_2]BF_4$ 2.5	2	50	(> 99) 80
5	$[Rh(COD)_2]BF_4$ 2.5	2	room temp.	(ca. 32) n.d.
6[d]	Rh(COD)acac 2.5	2	50	(ca. 65) n.d.
7	$[Rh(NBD)Cl]_2$ 2.0	2	50	(> 99) 73
8	$[Rh(COD)_2]BF_4$ 2.5	1.5	50	(ca. 72) n.d.

[a] General reaction conditions: 0.25 mmol **1a**, 0.00375–0.0125 mmol [Rh], 0–0.025 mmol dppp, 0.37–1 mmol phenylsilane, 1 mL of THF, Δ, 3 h. [b] For the complete optimization table, see the Supporting Information. [c] Conversion of starting material was determined by GC. Isolated yield not determined (n.d.) in cases of conversion < 80%. [d] No dppp added; acac = acetylacetonate.

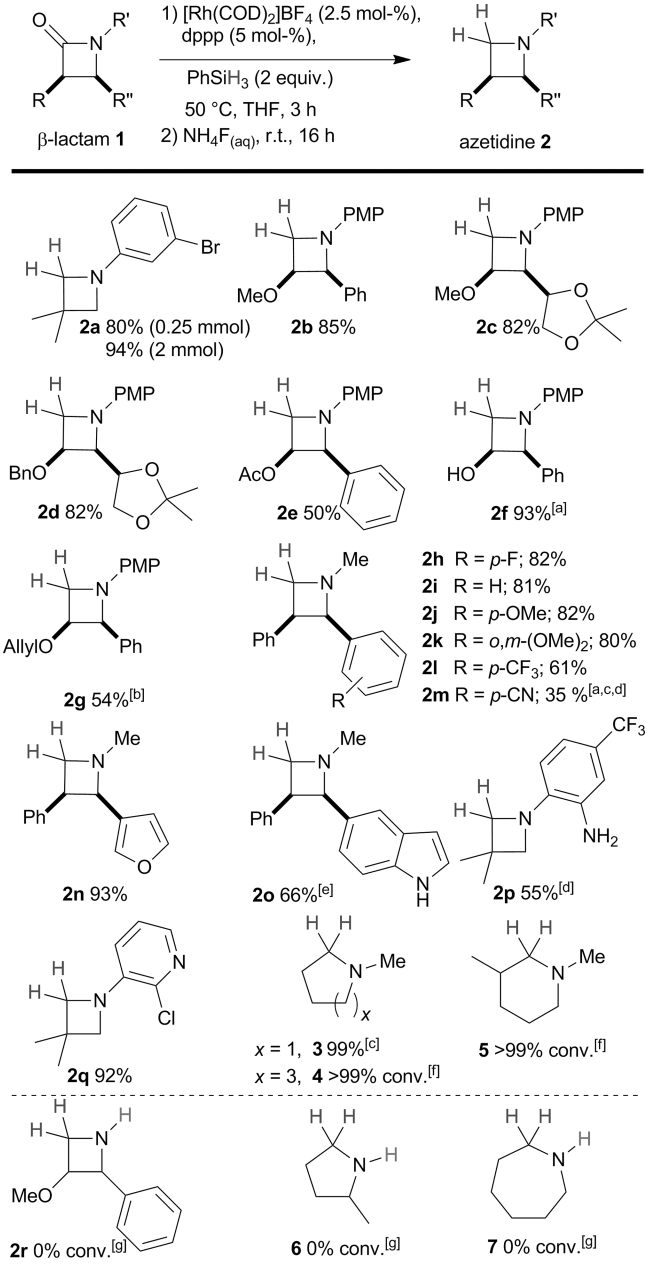
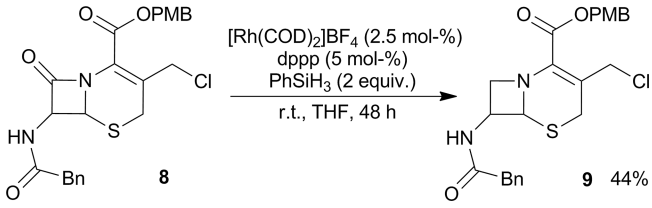


Figure 2. Substrate scope for the hydrosilylation of β-lactams. Reaction conditions: β-lactam **1** (0.25 mmol), $[Rh(COD)_2]BF_4$ (0.00625 mmol), dppp (0.0125 mmol), $PhSiH_3$ (0.5 mmol), THF (1 mL), 50 °C, 3 h; PMP = *para*-methoxyphenyl; isolated yields of pure, single diasteriomeric (*cis*) compound. [a] 18 h reaction time. [b] 3:1 diasteromeric ratio initially obtained, yield given is isolated pure *cis* isomer. [c] Calibrated GC yield. [d] Product contains low proportions of siloxane co-product after purification procedure. [e] Pure isolated product degraded over 5 d at room temp. under air. [f] Uncalibrated GC–MS only showed the volatile product peak. [g] by GC.

served, and only starting material remained, illustrating the exclusive amenability towards tertiary amide systems. This selectivity is further demonstrated by running the reaction in the presence of other functionalized compounds.[20,24] Hence, β-lactam **1a** was reduced exclusively in a mixture of thio-, ester-, alkenyl-, alcohol- and ether-containing molecules, which themselves all remained intact.[25] However, primary amines, primary amides and nitriles quenched the reduction.

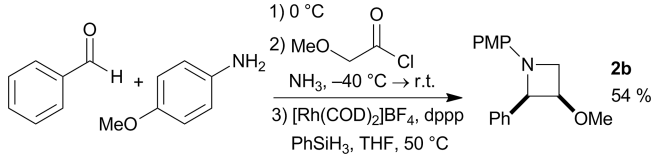
We next turned our attention towards enlarged ring systems to emphasize the adaptability of the developed methodology. Indeed, the reductions of five- (**3**), six- (**5**) and seven-membered (**4**) tertiary amides were all reliably accommodated and yielded the corresponding volatile amines in full conversion. Consistently, no conversion of secondary amides occurred when incorporated into the larger ring systems (**6** and **7**).

The impressive chemoselectivity of our protocol is illustrated by the reduction of the bioactive penicillin derivative **8**. At room temperature solely the tertiary amide carbonyl functionality, surrounded by an unsaturated thia-aza-bicyclic system, was hydrosilylated and reduced. The unsaturated ester, halide and secondary amide moieties were left intact (Scheme 1) to give a moderate yield of this complex and sensitive molecule.[26]



Scheme 1. Selective reduction of the tertiary amine in penicillin derivative **8**.

Finally, the methodology was extended by demonstrating the synthesis of azetidine **2b** in a one-pot procedure from cheap and commercially available substrates (Scheme 2).



Scheme 2. Synthesis of **2b** by sequential "one-pot" Staudinger cycloaddition and reduction.

Using the classical Staudinger-type cycloaddition[27] to generate the β-lactam in situ, it was shown that the subsequent addition of rhodium catalyst, ligand and reductant triggered the formation of the corresponding azetidine in a mixture of diasteroisomers that could be easily separated by chromatography.[26]

Conclusions

A straightforward hydrosilylation of a variety of substituted tertiary β-lactams has been developed to give good to excellent yields of the corresponding azetidene products. The combination of $[Rh(COD)_2]BF_4$ and dppp allows the

reaction to proceed rapidly under mild conditions. The chemoselectivity towards tertiary amides was demonstrated and showcased in the reduction of a highly functionalized penicillin derivative. Together with the illustration of a one-pot procedure, this protocol will form an interesting and highly useful tool for the medicinal organic chemist.

Experimental Section

Representative Procedure: A 10 mL oven-dried Schlenk tube containing a magnetic stir bar was charged with $[Rh(COD)_2]BF_4$ (2.5 mol-%, 0.05 mmol, 20.3 mg), dppp (5 mol-%, 0.1 mmol, 41.3 mg) and substrate **1a** (1 equiv., 2 mmol, 508.2 mg). Dry THF (4 mL) and phenylsilane (2 equiv., 4 mmol, 494 μL) were added after purging the Schlenk tube with argon and evacuating it three times. The resultant mixture was stirred at 50 °C for 3 h before being cooled to 0 °C; then 0.1 mL of a saturated solution of NH_4F in water was added and the mixture stirred at room temperature overnight. The organic compounds were carefully extracted with ethyl acetate (3× 10 mL), and the combined organic layers were washed with brine (2× 15 mL), dried with anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The desired product **2a** was purified, by silica gel chromatography using a mixture of pentane/ethyl acetate (25:1) as eluent, to give 451.3 mg (94%) of the pure clear liquid.

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[25] The easily reduced nitro, aldehyde and ketone functionalities were hydrosilylated under these conditions.
[26] The quenching with $NH_4F_{(aq)}$ during workup was found to be detrimental to the isolated yield; thus, this step was omitted. Clean product was still observed by ^1H and ^{13}C NMR spectroscopy. This brought doubt over the necessity of this step for the general procedure, after initially assuming it ridded the system of excess silane that jeopardises later purification.
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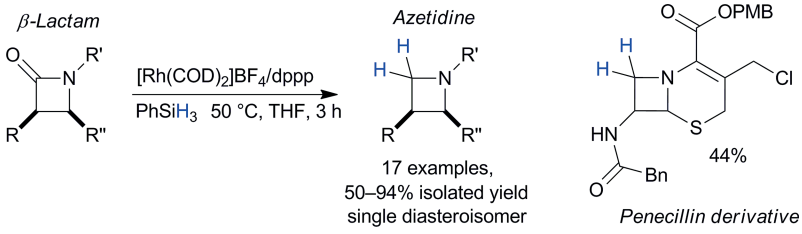

A selective Rh-catalyzed protocol to reduce β-lactams to important pharmacologically active azetidines is presented. Reaction with tertiary amides was selective over secondary amides, esters, olefins and nitriles, with no erosion of stereochemistry. A one-pot protocol from commercially available starting materials and a selective reduction of a complex penicillin derivative demonstrate the high synthetic utility of this procedure.

Keywords: Azetidines / Hydrosilylation / Lactams / Reduction / Rhodium

