

Highly Regio- and Diastereoselective Palladium-Catalyzed Allylic Substitution. Synthesis of 3-(2-Aminobutylidene)-4-arylazetidin-2-ones

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Abstract: The palladium-catalyzed benzylamine attack to a particular allylic moiety, the 3-alkenyl-3-bromoazetidin-2-one is herein reported. This reaction shows interesting mechanistic aspects and allows us to introduce in one step and under high regio- and stereocontrol the amino function in the C3 side chain

of non-conventional β -lactams, thus offering the opportunity for designing new potential glutamine synthetase inhibitors, such as Tabtoxin analogues.

Keywords: allylic substitution; azetidinone; diastereoselectivity; palladium; regioselectivity

Introduction

Palladium-catalyzed allylic substitution provides one of the most efficient methods for the stereoselective construction of carbon-carbon or carbon-heteroatom bond. In this context, the substitution with soft nucleophiles, such as amines, is a very efficient method for the carbon-nitrogen bond formation.^[1] One of the most interesting aspects of this type of chemistry is the possibility to control regio- and stereoselectivity on the allylic moiety.^[2] In recent years, allylic displacements on symmetrically substituted substrates leading to π -allylic intermediates have received growing interest. In this case, the step of formation of the metal complex is irrelevant for the regioselectivity of the overall reaction. For substrates bearing different groups at C1 and C3 of the allylic system, interest increases when the regioselectivity can be controlled.

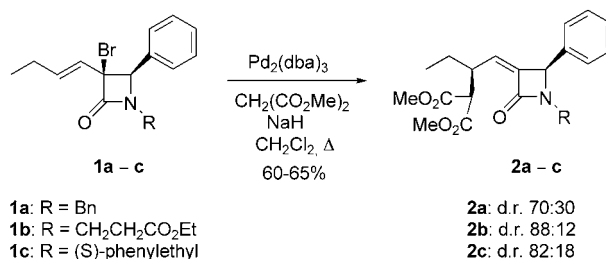
Continuing our work on metal-catalyzed reactions^[3] leading to nitrogen-containing compounds of biological interest,^[4] we now report the palladium-catalyzed benzylamine attack to a particular allylic moiety, the 3-alkenyl-3-bromoazetidin-2-one.^[5] This reaction shows interesting mechanistic aspects and allows us to introduce in one step and under high regio- and stereocontrol the amino function in the C3 side chain of the non-conventional β -lactams, thus offering the opportunity for designing new potential glutamine synthetase inhibitors, such as Tabtoxin analogues.^[6]

Results and Discussion

The starting compounds, 3-bromoazetidin-2-ones, were efficiently prepared in one step from α -bromohexenoyl chloride^[7] and TEA with a Schiff base in CH_2Cl_2 at reflux, under the conditions reported by Bose and Manhas^[8] for the preparation of α -vinyl- β -lactams. The 3-bromo-3-alkenyl- β -lactams were obtained in moderate yield, with a preferential 3,4-*cis*-configuration and exclusively with *E*-configuration of the unsaturated side chain.

First of all we tested the reactivity of our substrates in the palladium allylic alkylation with dimethyl malonate,^[9] which has become a standard nucleophile in allylic chemistry (Scheme 1).

Preliminary experiments on **1a** showed that the reaction was sluggish when $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ was used in a 5% amount at room temperature in CH_2Cl_2 for 48 hours,

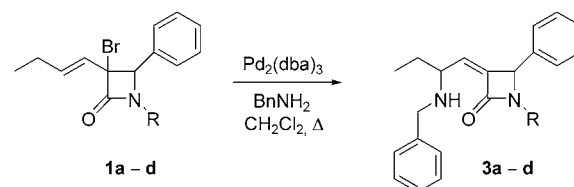


Scheme 1. Allylic alkylation of **1a–c** with dimethyl malonate.

2a being isolated only in 11% yield and a 70:30 diastereomeric ratio. The reaction performed with the same catalyst in toluene at 90 °C gave **2a** in 40% yield and a 45:55 d.r. Better results were attained when **1a** was treated with the sodium salt of dimethyl malonate, generated *in situ* from dimethyl malonate and sodium hydride, in the presence of 5 mol % of Pd₂(dba)₃ in refluxing CH₂Cl₂ for 48 hours. This simple methodology was efficiently applied to substrates **1b–c** (Scheme 1).

The yields of compounds **2a–c** were determined on isolated products after flash chromatography on silica gel, and are in the range of 60–65%. The reaction showed a complete regioselectivity to give exclusively compound **2**, in accordance with the preferential nucleophilic attack at the least hindered terminus of the π -allyl system.^[10] No trace of the 3-malonyl-substituted isomer was detected. The unsaturated β -lactams were obtained exclusively in the *Z*-configuration, unambiguously assigned on the basis of the chemical shift of the vinyl proton resonating around 5.50 ppm, in accordance with literature data.^[11] The diastereomeric ratios were established by evaluation of the integrated areas relative to this proton in the ¹H NMR spectra recorded in CDCl₃. The relative configuration of the major isomer, reported in Scheme 1, was assigned on the basis of mechanistic considerations.^[11b]

Having established optimal reaction conditions, we turned our attention to carbon-nitrogen bond formation. The palladium-catalyzed amination of allylic compounds with secondary amines has been extensively studied.^[12] For the synthesis of primary allylamine, preparation of the *N*-protected primary allylamine followed by removal of the protecting groups has been uti-



Scheme 2. Palladium-catalyzed benzylamine attack to **1a–d**.

lized. Primary amines have also been efficiently obtained *via* a palladium-catalyzed reaction with azide ion.^[13] In this work we have used benzylamine, in the presence of Pd₂(dba)₃ as catalyst, as a soft nucleophile that may be easily deprotected to the corresponding primary amine (Scheme 2).

A solution of **1a–d** in CH₂Cl₂ in the presence of 5% of Pd₂(dba)₃ was stirred at reflux temperature under an inert atmosphere for 30 minutes. Then 2 equivalents of benzylamine were added and the mixture was maintained at reflux, following the progress by TLC. Under these conditions, the reaction proceeded smoothly in good yield, although longer reaction times were required (about 72 hours). The results obtained are reported in Table 1.

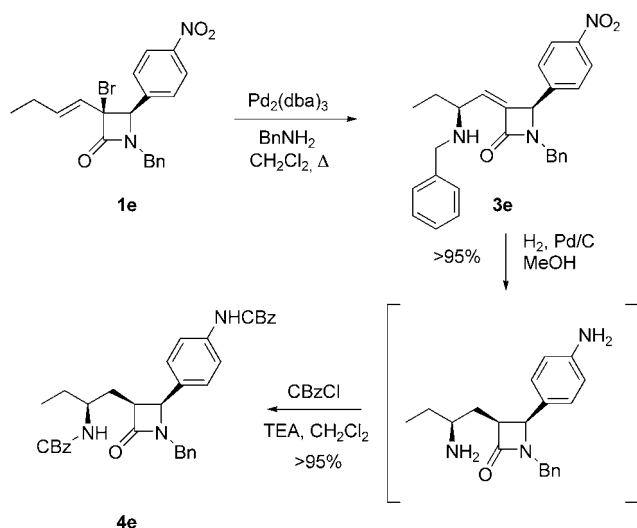
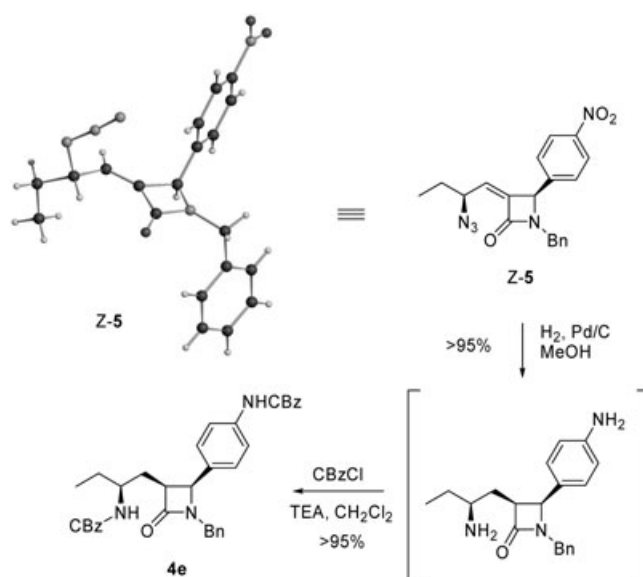
Compounds **3a–d** showed exclusively the *Z*-configuration of the double bond and good diastereomeric ratios, ranging from 81:19 to 91:9, between the isomers differing in the configuration at C2'. Diastereoselectivity was determined on the basis of ¹H NMR of the crude mixture in C₆D₆ and mechanistic considerations allowed the configuration of the major isomer to be deduced. In order to confirm the stereochemical outcome of the palladium-catalyzed allylic amination, racemic 4-(*p*-nitro-

Table 1. Palladium-catalyzed allylic alkylation with benzylamine.

Entry	1	Conversion (yield [%]) ^[a]	Major isomer	d.r. ^[b]
1		94 (85)		91:9
2		95 (90)		85:15
3		90 (80)		82:18
4		90 (80)		81:19

^[a] Conversion determined by ¹H NMR on the crude reaction mixture, yield determined for isolated compounds, after flash chromatography.

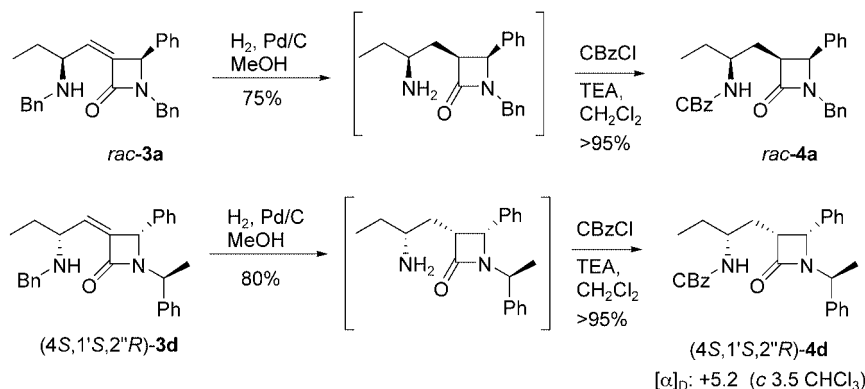
^[b] Determined by ¹H NMR on the basis on the integrated area of the vinylic proton signal.


 Scheme 3. Synthesis of 3-(2'-CBz-amino)-azetidin-2-one **4e**.

 Scheme 4. Synthesis of 3-(2'-CBz-amino)-azetidin-2-one **4e**, starting from azide **5**.

phenyl)-azetidin-2-one (**1e**) was treated under the above reported conditions and the benzylamino-derivative **3e** was obtained in 70% yield after flash chromatography as a mixture of diastereomers (80:20 d.r.). Hydrogenation of **3e** with H_2 on Pd/C for 4 h effected reduction of the double bond and the nitro group as well as deprotection of the 2'-N-benzyl group, affording the 2'-amino- β -lactam in 75% yield. Treatment of crude amine with benzyl chloroformate led to diprotected *cis*-derivative **4e** (Scheme 3). The 3,4-*cis*-stereochemistry of **4e** was assigned on the basis of the H_3, H_4 ($J = 5.2$ Hz) coupling constant. The spectroscopic properties of **4e** were compared to those of a racemic (2'*S**,4*R**)- β -lactam obtained from hydrogenation and protection of azide **5**,^[14] already available in our laboratory, whose stereochemistry was established on the basis of its X-ray analysis (Scheme 4).

The complete concordance of the analytical data of the products obtained through two different pathways allowed us to assign the (2'*S**,4*R**) configuration to the major product **3e** of the palladium-catalyzed amination. In a similar way compounds **3a** and **3d** were submitted to hydrogenation affording, after protection of the amino group, **4a** and **4d** in 75% and 80% yields, respectively (Scheme 5).

On the basis of the experimental evidence, we have found that the Pd-catalyzed benzylamine addition to **1** affords compound **3** in good yield and exclusive *Z*-configuration, with a good diastereomeric ratio. At present no explanation can be given for the preference that was found. The allylic substrate **1** reacts with the catalyst, which enters the catalytic cycle at the Pd(0) oxidation level *anti* to the bromide leaving group. Attack of the soft nucleophile benzylamine must then occur on the allyl face opposite to the palladium complex. If capture of the nucleophile is faster than palladium equilibration, the olefin face complexation becomes the stereo-determining step, therefore giving exclusively the *Z*-configuration of the final products and the (2'*S**,4*R**) relative configuration. Finally, reduction of the reaction product **3** gives access to a new class of 3-(2'-amino)-substituted


 Scheme 5. Synthesis of 3-(2'-CBz-amino)-azetidin-2-ones **4a** – **d**.

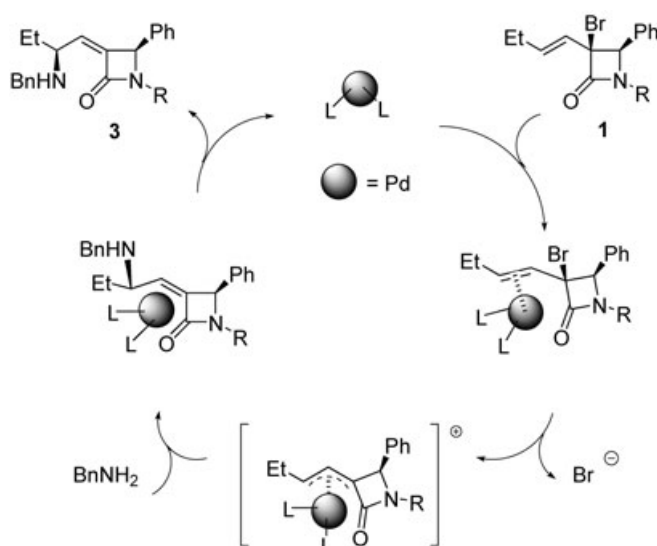


Figure 1. Mechanism suggested for the palladium-catalyzed addition of benzylamine.

β -lactams, useful precursors for the preparation of possibly biologically active compounds.^[15]

Conclusion

We have reported in this paper the palladium-catalyzed attack of benzylamine to a particular allylic moiety, the 3-allyl-3-bromo-azetidin-2-one. This reaction affords 3-(2'-benzylamino)-azetidin-2-ones exclusively in the *Z*-configuration of the double bond and good diastereomeric ratios between the isomers differing in the configuration at C2'. This methodology allows us to introduce in one step and under high regio- and stereocontrol the amino function in the C3 side chain of the non-conventional β -lactams, thus offering the opportunity for designing new potential enzyme inhibitors, such as Tabtox-in analogues.

Experimental Section

General Remarks

Unless stated otherwise, solvents and chemicals were obtained from commercial sources and used without further purification. Flash chromatography was performed on silica gel (230–400 mesh). NMR spectra were recorded with 300 or 600 MHz spectrometers. Chemical shifts were reported as δ values (ppm) relative to the solvent peak of CDCl_3 set at $\delta = 7.27$ (^1H NMR) or $\delta = 77.0$ (^{13}C NMR). Infrared spectra were recorded with an FT-IR spectrometer. Melting points are uncorrected. MS analyses were performed on a liquid chromatograph coupled with an electrospray ionization-mass spectrometer (LC-ESI-MS), using $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ as solvent at 25°C (positive scan 100–500 m/z , fragmentor 70 V). Starting azetidi-

nones **1a–e** were prepared according to a previously reported procedure^[5] and isolated by flash chromatography on silica gel and preparative HPLC (Zorbax Eclipse XDB C18 column, isocratic program, eluent $\text{CH}_3\text{CN}/\text{H}_2\text{O}$, 75/25). Complete characterizations for compounds **2a–c**, **3a–e** and **4a–e** are reported in the Supporting Information. Data for compound **Z-5** can be found in ref.^[14] (CCDC 260701).

General Procedure for the Palladium-Catalyzed Reaction of **1a–d** with Dimethyl Malonate

NaH (1.5 mmol, 36 mg) was added to a solution of dimethyl malonate (1.5 mmol, 0.17 mL) in CH_2Cl_2 (10 mL) under nitrogen atmosphere at room temperature. The mixture was stirred for 30 minutes and then added *via* cannula to a solution of **1** (1 mmol) and $\text{Pd}_2(\text{dba})_3$ (0.05 mmol, 45 mg.) in CH_2Cl_2 (10 mL) under a nitrogen atmosphere at room temperature. The solution was refluxed for 48 h and then allowed to reach room temperature. After quenching with 5 mL of water, the mixture was filtered on a celite pad and washed twice with water (10 mL). The organic layer was dried over Na_2SO_4 and solvent was removed under reduced pressure. The products were obtained after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 80/20). **2a**: yield: 65%, d.r.: 70/30; **2b**: yield: 65%, d.r.: 88/12; **2c**: yield: 65%, d.r.: 82/18.

General Procedure for the Palladium-catalyzed Reaction of **1a–d** with Benzylamine

A solution of **1** (1 mmol) and $\text{Pd}_2(\text{dba})_3$ (0.05 mmol, 45 mg.) in CH_2Cl_2 (10 mL) under a nitrogen atmosphere was stirred at refluxing temperature for 30 minutes. Benzylamine (2 mmol, 0.196 mL) was then added and the reaction was monitored by TLC and quenched after 72 h with 5 mL of water. After washing twice with water (10 mL), the organic layer was dried over Na_2SO_4 and solvent was removed under reduced pressure. The products were obtained, after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 80/20). **3a**: yield: 85%, d.r.: 91/9; **3b**: yield: 90%, d.r.: 85/15; **3c**: yield: 80%, d.r.: 82/18; **3d**: yield: 80%, d.r.: 81/19; **3e**: yield: 70%, d.r.: 80/20.

General Procedure for the Reduction and Protection of Azetidinone **3e**

To a solution of **3e** (1 mmol, 441 mg) in MeOH (10 mL), Pd/C (30 mg/1 mmol) was added in one portion. The reaction mixture was stirred vigorously at room temperature in a hydrogen atmosphere (1 atm) for 3 hours. The solution was filtered and evaporated. To a stirred solution of crude product in water/acetone (5 + 5 mL), NaHCO_3 (2 mmol, 168 mg) and CbzCl (2 mmol, 0.285 mL) were added. After 3 hours acetone was removed under reduced pressure and the residue was diluted with EtOAc (10 mL) and washed twice with 0.1 M HCl (2 $\times$ 5 mL). The organic layer was separated, dried over Na_2SO_4 and solvent was removed under reduced pressure. Compound **4e** was obtained in 75% yield after purification by flash chromatography on silica gel (cyclohexane/Et₂O, 8/2).

General Procedure for the Reduction and Protection of Azetidinones **3a** and **3d**

To a solution of **3** (1 mmol) in MeOH (10 mL), Pd/C (30 mg/1 mmol) was added in one portion. The reaction mixture was stirred vigorously at room temperature in a hydrogen atmosphere (1 atm) for 3 hours. The solution was filtered and evaporated. To a stirred solution of crude product in CH₂Cl₂, Et₃N (1.1 mmol, 1.1 equivs., 154 µL) and CbzCl (1.1 mmol, 1.1 equivs., 157 µL) were added. After 4 hours the solution was diluted with CH₂Cl₂ (10 mL), washed twice with 0.1 M HCl (2 × 5 mL), the organic layer was separated, dried over Na₂SO₄ and solvent was removed under reduced pressure. The products were purified by flash chromatography on silica gel (cyclohexane/Et₂O, 8/2).

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