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Synthesis of Arylidene-β-lactams via *Exo*-Selective Matsuda-Heck Arylation of Methylene-β-lactams

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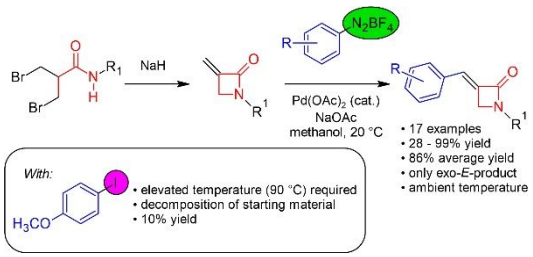


Abstract:

Exo-methylene-β-lactams were synthesized in two steps from commercially available 3-bromo-2-(bromomethyl)propionic acid and reacted with arene diazonium salts in a Heck-type arylation in the presence of catalytic amounts of $Pd(OAc)_2$ under ligand-free conditions. The products, arylidene-β-lactams, were obtained in high yields as single isomers. The β-hydride elimination step of the Pd-catalyzed coupling reaction proceeds with high *exo*-regio- and *E*-stereoselectivity. With aryl iodides, triflates, or bromides the coupling products were isolated only in low yields, due to extensive decomposition of the starting material at elevated temperatures. This underlines that arene diazonium salts can be superior arylating reagents in

Heck-type reactions and yield coupling products in synthetically useful yields and selectivities when conventional conditions fail.

Introduction

Azetidin-2-ones, also referred to as β-lactams, are the pharmacophore unit of β-lactam antibiotics, such as penicillines, cephalosporins, carbapenems and monobactams. They act by deactivating transpeptidases via an acylation of a serine residue at the catalytically active site, which hinders the final step of bacterial cell wall synthesis.[1] The main driving force for the acylation is the relief of ring strain, as the azetidin-2-one ring is opened in the process. For β-lactam antibiotics resistance mainly occurs through the expression of β-lactamases, which catalyze the hydrolytic ring opening of the antibiotics and thus deactivate them.[1] A strategy to overcome resistance toward β-lactam antibiotics relies on the co-administration of β-lactamase inhibitors, such as tazobactam, which is clinically combined with piperacillin.[2] However, some β-lactamases became in turn resistant against established, clinically used inhibitors. For instance, some variants of TEM-1 and SHV-1-β-lactamases, which are commonly produced by *Escherichia coli* and *Klebsiella pneumoniae* (bacteria responsible for infections of the urinary and respiratory tract and the bloodstream) developed a resistance against clavulanic acid.[3] As a consequence, tackling antibiotic resistance does not only involve the constant search for new antibiotics, but also the development of novel β-lactamase inhibitors[1,2] and fluorogenic probes for detecting β-lactamases.[4] Apart from diazabicyclooctanes (DBO's) and cyclic boronic acids substituted β-lactams, such as the 3-arylidene-azetidin-2-ones (**1**), have been intensively investigated as inhibitors of β-lactamases (**Figure 1**).

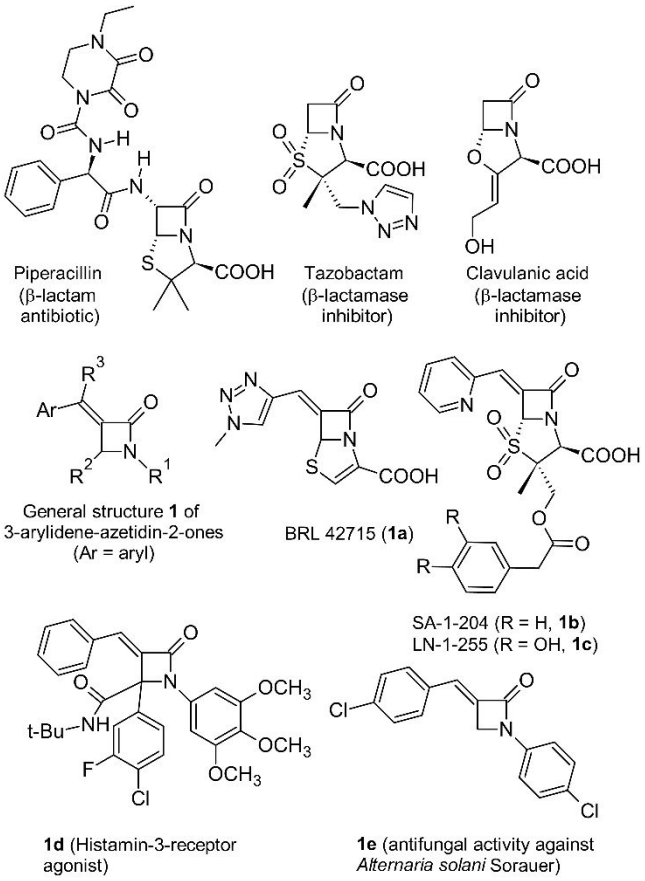


Figure 1. Structures of biologically active azetidin-2-ones.

For example, the penem BRL 42715 (**1a**) was found to inhibit certain cephalosporinases 10^4 to 10^6 times stronger than clavulanic acid.[5,6] A few years later Buynak et al. started to investigate pyridyl-alkylidene substituted penam sulfones,[7] e. g. SA-1-204 (**1b**) and LN-1-255 (**1c**), as inhibitors of β-lactamases. Compound SA-1-204 (**1b**) inhibits class A and class D β-lactamases efficiently,[8] and LN-1-255 (**1c**) combined with piperacillin was found to be more active against *Escherichia coli*-DH10B strains containing extended spectrum and inhibitor-resistant β-lactamases than the clinically used combination of piperacillin and tazobactam.[9] The mechanism of action of these β-lactamase inhibitors was elucidated by crystallographic and spectroscopic studies.[10-12] Very recently, derivatives of LN-1-255 (**1c**) that are substituted at the pyridine ring were synthesized and successfully tested against multidrug-resistant *Acinetobacter baumannii* in combination with the β-lactam antibiotic imipenem.[13] Biological

activities of arylidene-β-lactams are, however, not limited to β-lactamase inhibition: several compounds with this structural pattern (e. g. **1e**) are active against the fungal plant pathogen *Alternaria solani* Sorauer, the causal agent of early blight. This disease mainly affects potato and tomato plants and is responsible for severe economic losses.[14] Compound **1d** is an effective histamin-3-receptor-(H3R)-agonist at nanomolar concentrations. Therapeutic potential of H3R-agonists for the treatment of myocardial ischemia has been demonstrated.[15,16]

From a synthetic point of view arylidene-substituted β-lactams with the general formula **1** offer the opportunity to connect other pharmacophores to the azetidin-2-one core through a covalent bond, e. g. by conjugate addition. This concept is known as pharmacophore hybridization and has been recognized as an emerging strategy for drug discovery.[17,18] Following this concept β-lactams have been combined with purine nucleobases in search for novel antiviral agents.[19]

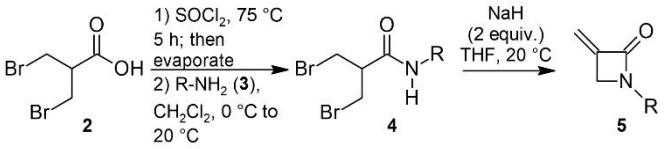
Previously reported syntheses of arylidene-β-lactams **1**, as for example the β-lactamase inhibitors SA-1-204 (**1b**) or LN-1-255 (**1c**), rely on a Wittig-olefination of 6-oxo-penicillanic acid derivatives, which were in turn synthesized from 6-aminopenicillanic acid in a multistep synthesis.[13] Alternative strategies (as e. g. used for the synthesis of **1e**) proceed via a late-stage β-lactamization of 2-aminomethyl cinnamates, which are accessible via a sequence of Baylis-Hillman reaction, dehydrative bromination and nucleophilic substitution.[14,20,21]

In continuation of previous studies from our group[22,23] on Heck-reactions of *exo*-methylene substituted heterocycles with arene diazonium salts (often named Matsuda-Heck-reactions[24-27]) we investigated the feasibility of this approach for the regio- and stereoselective synthesis of arylidene-β-lactams. The results are disclosed herein.

Results and discussion

Synthesis of α-methylene-β-lactam starting materials. Six α-methylene-β-lactams **5a-f** were synthesized by an adaptation of a previously published route that starts from commercially available 3-bromo-2-bromomethyl propionic acid (**2**).[28-30] Carboxylic acid **2** was converted to its acid chloride by heating in thionyl chloride, which was then treated with anilines **3a-f** without prior purification. Apart from the acetamide substituted derivative **4c** all amides were isolated in fair to good yields. The yield of **4c** could not be improved by using a dimethylformamide catalyzed synthesis of acid chlorides;[31] these conditions led to the formation of several unidentified byproducts. The resulting amides **4a-f** underwent a base-mediated intramolecular nucleophilic substitution/elimination to furnish the α-methylene-β-lactams **5a-f** in moderate overall yields upon treatment with NaH (**Table 1**).

Table 1. Synthesis of α-methylene-β-lactams **5**.



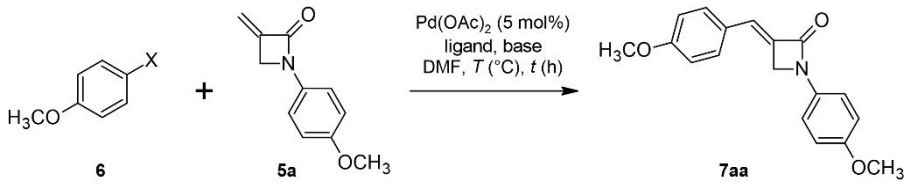
entry	**3**	R	**4**[a]	yield (%)[b]	**5**[a]	yield (%)
1	**3a**	4-$(OCH_3)C_6H_4$	**4a**[28]	50	**5a**[32,33]	92
2	**3b**	4-ClC_6H_4	**4b**	52	**5b**[32]	63
3	**3c**	4-$(NHAc)C_6H_4$	**4c**	13	**5c**	39
4	**3d**	3-BrC_6H_4	**4d**	87	**5d**	62
5	**3e**	3,4-$Cl_2C_6H_3$	**4e**[28]	74	**5e**[28]	74
6	**3f**	3-(CF_3)-4-ClC_6H_3	**4f**	62	**5f**	Quant.

[a]References reporting characterization data. [b]Yield over two steps from **2**.

Heck-reaction of α-methylene-β-lactam 5a with aryl halides and triflates. Aryl iodides, bromides and triflates are the most commonly used electrophilic coupling partners in Mizoroki-

Heck reactions.[34] Conditions that have been successfully used for the arylation of electron deficient *exo*-methylene heterocycles, e. g. α-methylene-γ-butyrolactones, involve $Pd(OAc)_2$ as a precatalyst, DMF as a solvent and heating at elevated temperatures for up to 24 hours.[35] In particular electron-rich aryl halides often react slowly in Heck-reactions and do not give the desired coupling products in acceptable yields. It has been shown that in these cases the addition of tri-*ortho*-tolyl phosphine in a precatalyst-to-ligand ratio of 1 : 2 reliably accelerates the reaction and that the coupling products can be obtained in synthetically useful yields.[36,37] We first investigated the coupling of α-methylene-β-lactam **5a** with iodo-4-methoxybenzene (**6a**) (**Table 2**).

Table 2. Mizoroki-Heck coupling of α-methylene-β-lactam **5a** with aryl halides.



entry	**6**	X	Ligand (mol %)	base (equiv.)	*T* (°C)	*t* (h)	conv. (%)	yield of **7aa** (%)[a]
1	**6a**	I	--	NEt_3 (3)	90	18	> 95	13
2	**6a**	I	P(*o*-tol)$_3$ (10)	NEt_3 (3)	20	18	< 5	n. d.
3	**6a**	I	P(*o*-tol)$_3$ (10)	NEt_3 (3)	90	18	> 95	10
4	**6b**	OTf	P(*o*-tol)$_3$ (10)	NEt_3 (3)	90	18	> 95	10
5	**6c**	Br	P(*o*-tol)$_3$ (10)	NaOAc (3)	140	1	> 95	n. d.[b]

[a]n. d. not determined. [b]No product detected.

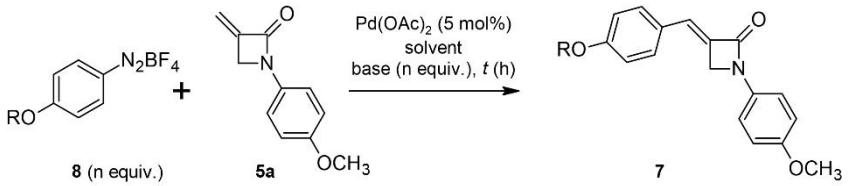
Under conditions that have previously been successfully applied to Heck-reactions of electron rich aryl iodides and α-methylene-γ-butyrolactones[35] or α-methylenesuccinimides[22] we observed full conversion of **5a**, but very low yields of coupling product **7aa** (entry 1).

Presumably, heating the reaction mixtures at high temperatures over longer periods of time causes extensive decomposition of the β-lactam starting materials due to their high ring strain. We reasoned that activating ligands would allow a lower reaction temperature to be used. Therefore, P(*o*-tol)$_3$ was added and the reaction was conducted at ambient temperature, which led to the complete recovery of unreacted **5a** (entry 2). We then tested whether the addition of P(*o*-tol)$_3$ would enhance the rate of the Heck coupling at elevated temperature to such an extent that it could compete with the decomposition reaction, but the result was virtually identical to that observed without any activating ligand (entry 3). An even lower yield was obtained with the triflate **6b**[38] (entry 4) and no coupling product at all could be detected with bromo-4-methoxybenzene (**6c**) (entry 5). In both cases complete consumption of the starting material **5a** was observed.

Optimization of coupling conditions for arene diazonium salts 8. In contrast to Heck-type reactions with aryl halides the addition of phosphine ligands has normally detrimental effects when arene diazonium salts are used. It is therefore generally advisable to avoid such ligands with these electrophilic coupling partners. However, in recent work it was demonstrated that N,N-chelating or pyridine ligands enable the control of enantioselectivity[39-41] or the use of allylic alcohols as substrates.[42] A more contentious issue is the role of the base in these reactions. Examples for beneficial as well as deleterious effects of bases in Pd-catalyzed couplings with arene diazonium salts have been reported. As Felpin et al. state, there is an apparent correlation between the solvent used and the effect of added base.[25] While in acetonitrile a base is almost always required to obtain useful conversions,[43] it should be avoided if alcohols are the preferred solvents.[22] It is sometimes difficult to predict whether acetonitrile or methanol is the solvent of choice for a Matsuda-Heck reaction. This depends on the structure of the olefin and the diazonium salt, and apart from stability issues (that take the nucleophilic nature of methanol and the sensitivity of the diazonium salt into account) the solubility of the reactants in the respective solvent plays a decisive role. For these reasons, routinely screening

Matsuda-Heck couplings with hitherto unexplored olefins in acetonitrile and methanol under both basic and base-free conditions has proved successful for identifying optimized reaction conditions. We investigated two test reactions: the coupling of **5a** with 4-methoxybenzenediazonium tetrafluoroborate (**8a**) and with 4-hydroxy-benzenediazonium tetrafluoroborate (**8b**). We know from previous investigations that these diazonium salts often require orthogonal reaction conditions; for example, the Pd-catalyzed coupling of **8a** with methyl acrylate gives higher yields in the absence of a base, while the addition of NaOAc is mandatory for phenol diazonium salt **8b**.[44] For the coupling of both diazonium salts acetonitrile turned out to be an unsuitable solvent, because neither basic nor base-free conditions led to a notable conversion of the starting material **5a** (entries 1,2, 6 and 7). The same result was observed for **8a** in methanol under base-free conditions (entry 3). Upon addition of NaOAc most of the starting material **5a** was consumed and the coupling product **7aa** was isolated in 72% yield (entry 4). Quantitative conversion and isolation of the product **7aa** in a nearly quantitative yield was accomplished by using a slight excess of the diazonium salt (1.2 equiv., entry 5).

Table 3. Optimization of conditions for the coupling of **5a** and diazonium salts **8a**,**b**.



entry	**8** (equiv.)	R	solvent	base (equiv.)	t (h)	conv.	**7**	yield (%)
1	**8a** (1.0)	CH_3	CH_3CN	--	3	< 5[a]	**7aa**	n. d.
2	**8a** (1.0)	CH_3	CH_3CN	NaOAc (4.0)	3	< 5[a]	**7aa**	n. d.
3	**8a** (1.0)	CH_3	CH_3OH	--	3	< 5[a]	**7aa**	n. d.
4	**8a** (1.0)	CH_3	CH_3OH	NaOAc (4.0)	16	n. d.[b]	**7aa**	72
5	**8a** (1.2)	CH_3	CH_3OH	NaOAc (4.0)	16	> 95[c]	**7aa**	94[f]
6	**8b** (1.0)	H	CH_3CN	--	3	< 5[a]	**7ab**	n. d.
7	**8b** (1.0)	H	CH_3CN	NaOAc (4.0)	3	< 5[a]	**7ab**	n. d.
8	**8b** (1.0)	H	CH_3OH	--	3	> 95[c,d]	**7ab**	n. d.
9	**8b** (1.0)	H	CH_3OH	NaOAc (4.0)	3	n. d.[b]	**7ab**	n. d.
10[e]	**8b** (1.0)	H	CH_3OH	--	3	> 95[c,d]	**7ab**	n. d.
11	**8b** (1.2)	H	CH_3OH	--	12	> 95[c,d]	**7ab**	n. d.
12	**8b** (1.2)	H	CH_3OH	NaOAc (4.0)	16	> 95[c]	**7ab**	quant.[f]

[a]No product observed in ^{1}H NMR spectrum of crude reaction mixture. [b]Incomplete conversion; qualitatively observed by TLC. [c]No starting material **5a** observed by TLC and ^{1}H NMR of crude reaction mixture. [d]Formation of unidentified side products. [e]Reaction mixture cooled to 0 °C. [f]Isolated yields on a 0.25 mmol scale.

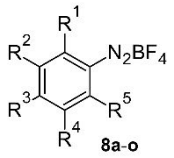
In contrast to the methoxy-substituted diazonium salt **8a** (entry 3) we observed full conversion of the starting material **5a** with phenol diazonium salt **8b** in methanol under base-free conditions (entry 8). The NMR-spectra of the crude reaction mixture show that the arylidene β-lactam **7ab** is the major product, but that at least one byproduct is formed (ca. 30%, as estimated from the integrals of the OH-protons), which could not be identified due to similar polarity and

overlapping signals in the aromatic and olefinic region of the ^{1}H NMR spectrum. Possible side products are the *Z*-stereoisomer or the *endo*-regioisomer of **7ab**, but an acid-catalyzed ring opening by trace amounts of water present in the reaction mixture is also conceivable, because one equivalent of HBF_4 is formed during the reaction, which is not neutralized in the absence of a base. Indeed, no side products were observed if the reaction was run in the presence of NaOAc, but the conversion was incomplete with equimolar amounts of reactants (entry 9). Running the reaction at lower temperature (0 °C, entry 10) or with an excess of diazonium salt (1.2 equiv., entry 11) again resulted in full conversion, but also in the formation of the same byproducts as observed under the conditions listed in entry 8. Quantitative conversion and high selectivity were observed with added NaOAc and a slight excess of diazonium salt. Under these conditions the coupling product **7ab** was obtained in quantitative isolated yield (entry 12).

The optimized conditions for the Matsuda-Heck arylation of α-methylene-β-lactams are similar to those identified earlier for itaconimides[22] or α-methylene-γ- or δ-lactones and lactams.[23] However, with these substrates base-free conditions are preferred. The reason why α-methylene-β-lactams require added base is most likely the high tendency of the strained four-membered rings to undergo hydrolytic ring opening in the presence of an acid. In contrast to Heck-type arylations with aryl iodides the coupling with the corresponding diazonium salts proceeds at ambient temperature, which is important to avoid decomposition of either the starting β-lactams or the products under the reaction conditions.

Substrate scope and limitations. We applied the optimized conditions (Table 3, entries 5 and 12) for the coupling of **5a** and diazonium salts **8a**,**b** to other diazonium salts **8c-o** (see **Table 4** for an overview of diazonium salts used in this study) and α-methylene-β-lactams **5b-e** (see **table 1**). The results are summarized in **Table 5**.

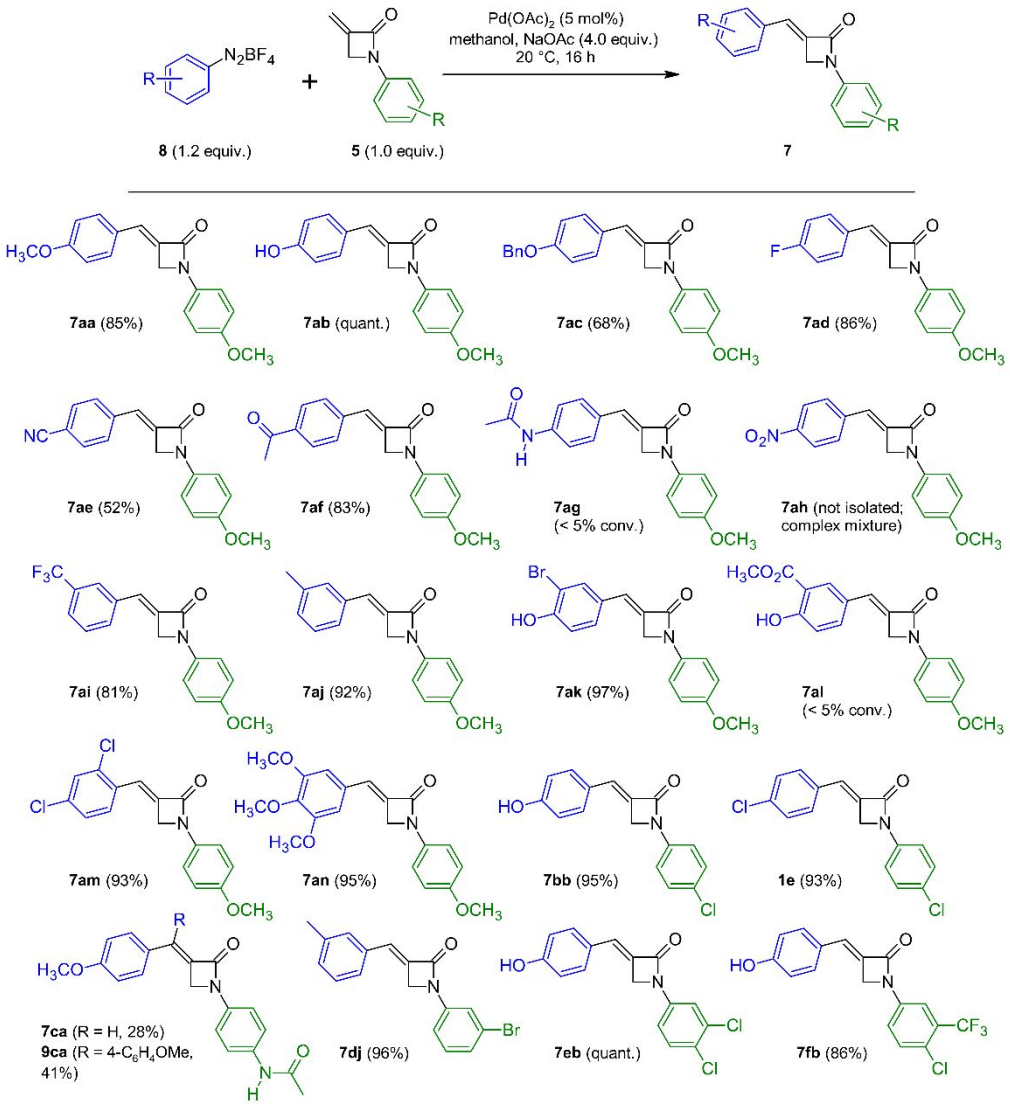
Table 4. Arene diazonium salts used in this study.



8a-o

No	R^1	R^2	R^3	R^4	R^5	Ref.
8a	H	H	OCH_3	H	H	[45]
8b	H	H	OH	H	H	[44]
8c	H	H	OBn	H	H	[45]
8d	H	H	F	H	H	[46]
8e	H	H	CN	H	H	[47]
8f	H	H	$C(O)CH_3$	H	H	[48]
8g	H	H	NHAc	H	H	[49]
8h	H	H	NO_2	H	H	[50]
8i	H	CF_3	H	H	H	[51]
8j	H	CH_3	H	H	H	[52]
8k	H	Br	OH	H	H	[44]
8l	H	CO_2CH_3	OH	H	H	[44]
8m	Cl	H	Cl	H	H	[22]
8n	H	OCH_3	OCH_3	OCH_3	H	[53]
8o	H	H	Cl	H	H	[47]

Table 5. Scope of the Matsuda-Heck arylation of α-methylene-β-lactams **5**.[a,b]



[a]The first letter of the compound number **7xy** refers to the β-lactam **5**, the second letter refers to the diazonium salt **8** used for its synthesis. [b]Coupling of **5a** and **8a** to **7aa** was performed on a 1.0 mmol scale.

In most cases the desired coupling products were obtained in good to excellent yields as single isomers, with the following exceptions: (i) Compound **7ae**, resulting from the coupling of **5a** and 4-cyanobenzene diazonium salt **8e**, was isolated in a moderate yield of 52%, which can probably be explained by partial catalyst deactivation due to coordination of the nitrile to Pd.[54] (ii) With 4-acetamido benzene diazonium salt **8g** and 3-(methylcarboxylate) phenol diazonium salt **8l** conversions to **7ag** and **7al**, respectively, remained below 5%. We have previously obtained high yields for the coupling of both diazonium salts with methyl acrylate[44,49] but only

under base-free conditions, which are not tolerated with α-methylene-β-lactams **5**. (iii) All attempts to couple **5a** with the electron deficient 4-nitrobenzene diazonium salt **8h** resulted in full conversion of the starting material, but led to the formation of a complex mixture of products. We have previously observed sluggish couplings with highly electron deficient diazonium salts, mainly due to uncontrollable addition of the solvent methanol to the C-C-double bond and hydrodediazonation of the diazonium cation.[44] (iv) In one case (the coupling of **5c** with diazonium salt **8a**) we observed the formation of a mixture of coupling products under standard conditions. The expected product **7ca** was isolated in a low yield of 28%, whereas the double arylated product **9ca** was obtained in a somewhat higher yield of 41% even though only 1.2 equiv. of diazonium salt was used. Although geminal Matsuda-Heck-diarylations have occasionally been reported as side reactions[55,56] examples for the intentional double arylation are scarce and normally require special conditions or catalysts[57,58] or at least a twofold excess of diazonium salt.[22] Currently, it remains unclear why the double arylated compound **9ca** is the major product in this case.

Compound **1e** (see **Figure 1** and introduction), obtained in 93% yield from the coupling of *p*-chlorophenyl substituted β-lactam **5b** and *p*-chlorobenzene diazonium salt **8o**, has previously been synthesized in four steps via Baylis-Hilman-reaction and intramolecular nucleophilic substitution. In an antifungal activity assay **1e** was found to be the most active out of 28 compounds tested for their activity against the plant pathogen *Alternaria solani* Sorauer.[14] All other coupling products **7** shown in **Table 5** have not been described in the literature so far.

Structure elucidation and assignment of *exo*-*E*-configuration for the coupling products 7. Several 3-arylidene-azetidin-2-ones with the general structure **1** (**Figure 1**) have previously been synthesized via one of the routes mentioned in the introduction. In almost all cases an *exo*-*E*-structure was assigned to the reaction products.[14,21,59-61] In a few reports describing the synthesis of 3-arylidene-2-azetidin-2-ones via intramolecular nucleophilic substitution the *exo*-*E*-structure was deduced from the double bond configuration of the acyclic precursors, but

evidence for their configurational assignment was not provided.[20,29] Mixtures of *E*- and *Z*-isomers of 3-arylidene-azetidin-2-ones and 3-alkylidene-azetidin-2-ones result from olefin cross metathesis reactions of α-methylene-β-lactams **5** with styrenes and 1-alkenes, respectively.[62] The stereoisomers were separated and individually characterized by 1D-NMR methods, but direct spectroscopic or other analytical evidence for the assigned stereochemistry was not given. However, in a related study on the cross metathesis of substituted α-methylene-β-lactones the observed *Z*-stereochemistry of the products was determined by NOESY-experiments, which may allow to some extent conclusions by analogy for the β-lactam cross metathesis products.[63] Examples of ring closing metathesis reactions of α-methylene-β-lactams leading to *Z*-isomers have been reported and the products have been fully characterized by single crystal X-ray structure analysis.[64] This lack of direct spectroscopic and analytical proof for the *exo*-*E*-structures assigned to 3-arylidene-azetidin-2-ones prompted us to perform a comprehensive NMR-spectroscopic investigation using 2D-methods for two 3-arylidene-azetidin-2-ones, compounds **7ab** and **7bb**, and for the double arylated product **9ca**. A combination of H,H-COSY, HSQC- and HMBC experiments allowed a full signal assignment for compounds **7ab** and **7bb**, and an assignment of the most relevant signals of **9ca**. The numbering scheme refers to the signal assignment used in the experimental section and in the discussion (**Figure 2**).

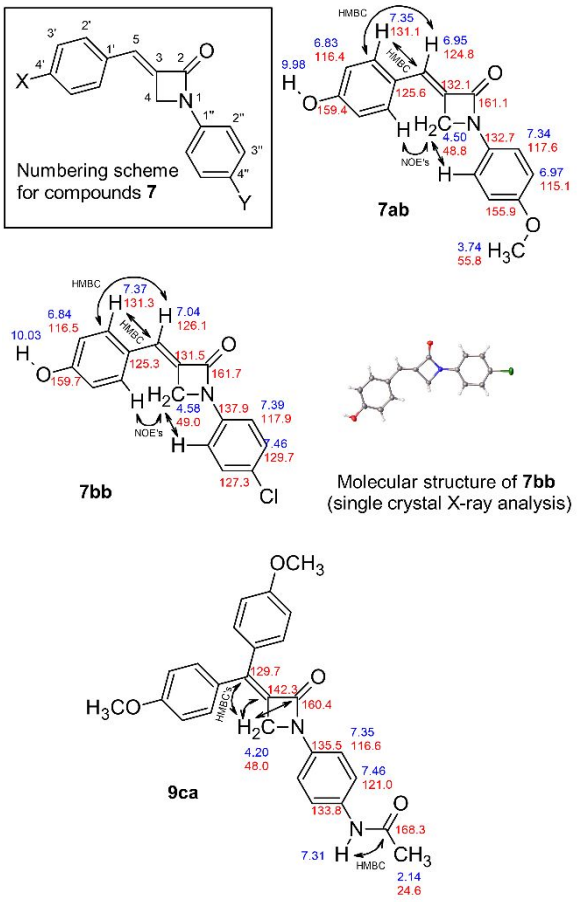


Figure 2. Numbering scheme for compounds **7**; full assignment of ^{1}H and ^{13}C NMR signals for compounds **7ab**, **7bb** and **9ca** and relevant HMBC and NOE interactions; molecular structure of **7bb** (single crystal X-ray analysis).

Proof for the *exo*-arrangement of the double bond in compounds **7** are HMBC interactions between H2' and C5 and C2' and H5, and HMBC interactions between H4 and C2, C3 and C5. In all compounds **7** the proton H5 appears as a triplet with a ^{4}J-value of 1.4 Hz at ca. 7 ppm and the methylene group H4 as a doublet with the same coupling constant at ca. 4.5 to 4.6 ppm. Howell and co-workers reported very similar values for the *E*-configured cross metathesis products of *N*-Boc-protected α-methylene-β-lactam and styrenes and notably lower (ca. 6.5 ppm for H5 and ca. 4.0 ppm for H4) values for the *Z*-isomer.[62] We observed NOE-interactions between the methylene group of the β-lactam ring (protons H4) and the *ortho*-protons of both aryl groups (protons H2' and H2''). Due to the small chemical shift differences in the aromatic region it was difficult to assign the observed NOE's unambiguously to the relevant *ortho*-

protons H2'. Gratifyingly, single crystals suitable for X-ray crystallographic analysis could be obtained from a DMSO-solution of compound **7bb**. Single crystal X-ray structure analysis revealed unambiguously the assigned *exo*-*E*-structure. One molecule of DMSO is incorporated in the unit cell; the oxygen atom of the DMSO molecule binds to the phenolic OH-group of **7bb** through a hydrogen bond (d = 183 pm).

The structure of **9ca** is supported by HMBC interactions between the protons of the β-lactam methylene group (H4) and quaternary carbons C2, C3 and C5. The signals for the carbonyl group of the β-lactam (C2) and the acetamide group can be distinguished by an HMBC interaction between the signals for the amide proton at 7.31 ppm and the acetamide carbon at 168.3.

Conclusions

In summary, we report that 3-arylidene-azetidin-2-ones, which are relevant substructures in β-lactamase inhibitors and other bioactive molecules, can be synthesized in high yield and selectivity from α-methylene-β-lactams and arene diazonium salts in a Heck-type coupling reaction, using $Pd(OAc)_2$ as precatalyst. The coupling proceeds efficiently at ambient temperature under ligand-free conditions, but requires added base to avoid acid-induced decomposition of the β-lactams. Notably, conventional Heck-coupling conditions (aryl iodides, activating ligands, elevated temperatures) fail with α-methylene-β-lactams due to decomposition of the olefinic coupling partner at the required reaction temperature. In contrast to olefin cross metathesis reactions, which give 3-arylidene-azetidin-2-ones as *E*/*Z*-mixtures from the same starting materials, the Pd-catalyzed coupling with arene diazonium salts is highly *E*-stereoselective.

Experimental Section

General methods. All experiments were conducted in dry reaction vessels under an atmosphere of dry nitrogen. Solvents were purified by standard procedures. Unless otherwise stated, reaction mixtures were heated with silicon oil baths. ^{1}H NMR spectra were obtained at 300 MHz, 400 MHz or 500 MHz in $CDCl_3$ with C*H*Cl_3 (δ = 7.26 ppm) as an internal standard. Coupling constants are given in Hz. ^{13}C NMR spectra were recorded at 75 MHz, 101 MHz or 125 MHz in $CDCl_3$ with $CDCl_3$ (δ = 77.1 ppm) as an internal standard. ^{19}F NMR spectra were recorded at 376 MHz. Whenever the solubility of the sample was insufficient in $CDCl_3$, it was replaced by DMSO-d_6 (DMSO-d_5 as internal standard for ^{1}H NMR spectroscopy, δ= 2.50 ppm, DMSO-d_6 as internal standard for ^{13}C NMR spectroscopy, δ = 39.5 ppm). In all cases where signal assignments are given for ^{1}H- and ^{13}C-NMR data, these are based on 2D-NMR-spectra such as H,H-COSY, HSQC, HMBC and NOESY. IR spectra were recorded as ATR-FTIR spectra. Wavenumbers ($\tilde{\nu}$) are rounded to 1 cm^{-1}. The peak intensities are defined as strong (s), medium (m) or weak (w). Low- and high resolution mass spectra were obtained by EI-TOF or ESI-TOF. Although arene diazonium tetrafluoroborates are generally considered to be thermally very stable and we have never experienced any cases of violent decomposition, there have been reports of explosions caused by arene diazonium tetrafluoroborates. We recommend that these compounds are therefore handled with care and that safety measures[65] are thoroughly obeyed. All arene diazonium salts used in this work were synthesized following previously published literature procedures (**Table 4**).

General procedure for the synthesis of 3-bromo-2-bromomethylpropionic acid anilides 4. 3-Bromo-2-bromomethylpropanoic acid (**2**, 1.24 g, 5.0 mmol) was heated in $SOCl_2$ (2.50 mL, 4.10 g, 34.5 mmol) at 75 °C for 5 h. The mixture was cooled to ambient temperature and all volatiles were evaporated in vacuo. The residue was dissolved in dry and degassed CH_2Cl_2 and cooled to 0 °C. A solution of the respective aniline **3** (10.0 mmol) was added dropwise at 0 °C,

the mixture was allowed to warm to ambient temperature and stirred for 12 h. It was diluted with CH_2Cl_2 (15 mL), washed with HCl (aq.) (2 M, 2•10 mL) and water (10 mL). The organic layer was dried with $MgSO_4$, filtered and evaporated until the product started to precipitate. The solution was stored at –18 °C to ensure complete crystallization for 12 h. The products were isolated as colourless crystals by removing the supernatant solution. Alternatively, the products can be purified by chromatography on silica, using hexanes-ethyl acetate mixtures of increasing polarity as eluent.

3-Bromo-2-(bromomethyl)-*N*-(4-methoxyphenyl)propanamide (4a).[28] Following the general procedure, **3a** (1.23 g, 10.0 mmol, 2.0 equiv.) was converted to **4a** (0.89 g, 2.5 mmol, 50%); purification by chromatography (hexanes-ethyl acetate mixtures 5 : 1 to 3 : 1 (v/v)): colorless solid, mp 166 – 167 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, J = 9.0 Hz, 2H), 7.36 (s (br.), 1H), 6.88 (d, J = 9.0 Hz, 2H), 3.80 (s, 3H), 3.70 (dd, J = 10.2, 8.1 Hz, 2H), 3.58 (dd, J = 10.3, 5.8 Hz, 2H), 3.09 – 3.06 (m, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 168.2, 157.3, 130.1, 122.6, 114.4, 55.7, 53.1, 31.1; IR (ATR) ν 3282 (m), 1651 (s), 1600 (m), 1542 (s), 1224 (s), 825 (s); HRMS (EI) *m/z* calcd for $C_{11}H_{13}{}^{79}Br_2NO_2$ $[M]^+$ 348.9308, found 348.9302.

3-Bromo-2-(bromomethyl)-*N*-(4-chlorophenyl)propanamide (4b). Following the general procedure, **3b** (1.28 g, 10.0 mmol, 2.0 equiv.) was converted to **4b** (0.92 g, 2.6 mmol, 52%); purification by chromatography (hexanes-ethyl acetate mixtures 5 : 1 to 3 : 1 (v/v)): colorless solid, mp 160 - 161 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.39 (s (br.), 1H), 7.64 (d, J = 8.8 Hz, 2H), 7.38 (d, J = 8.8 Hz, 2H), 3.73 – 3.63 (m, 4H), 3.32 – 3.23 (m, 1H), ; ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 168.4, 137.5, 128.7, 127.3, 120.9, 50.6, 32.0; IR (ATR) ν 3303 (m), 1656 (s), 1608 (s), 1544 (s), 1489 (s), 1398 (s), 824 (s); HRMS (ESI) *m/z* calcd for $C_{10}H_{11}{}^{79}Br_2{}^{35}ClNO$ $[M+H]^+$ 353.8896, found 353.8904.

***N*-(4-Acetamidophenyl)-3-bromo-2-(bromomethyl)propanamide (4c)**. Following the general procedure, **3c** (1.50 g, 10.0 mmol, 2.0 equiv.) was converted to **4c** (0.24 g, 0.6 mmol, 13%); purification by chromatography (hexanes-ethyl acetate mixtures 5 : 1 to 3 : 1 (v/v)):

colorless solid, mp 198 – 200 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.18 (s (br.), 1H), 9.88 (s (br.), 1H), 7.58 – 7.43 (m, 4H), 3.72 – 3.62 (m, 4H), 3.30 – 3.20 (m, 1H), 2.02 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 168.0, 167.8, 135.2, 133.8, 119.8, 119.3, 50.5, 32.2, 23.9; IR (ATR) ν 3280 (s), 1652 (s), 1549 (s), 1516 (s), 1371 (s), 1312 (m), 1127 (m), 833 (s), 715 (s); HRMS (EI) *m/z* calcd for $C_{12}H_{14}{}^{79}Br_2N_2O_2$ $[M]^+$ 375.9417, found 375.9411.

3-Bromo-2-(bromomethyl)-*N*-(3-bromophenyl)propanamide (4d). Following the general procedure, **3d** (1.72 g, 10.0 mmol, 2.0 equiv.) was converted to **4d** (1.75 g, 4.4 mmol, 87%); purification by chromatography (hexanes-ethyl acetate mixtures 5 : 1 to 3 : 1 (v/v)): colorless solid, mp 123 – 125 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.44 (s (br.), 1H), 7.99 – 7.96 (m, 1H), 7.50 (ddd, J = 7.0, 2.1, 2.1 Hz, 1H), 7.33 – 7.24 (m, 2H), 3.73 – 3.63 (m, 4H), 3.31 – 3.23 (m, 1H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 168.7, 140.1, 130.8, 126.3, 121.7, 121.6, 118.1, 50.7, 31.9; IR (ATR) ν 3280 (s), 1657 (s), 1589 (s), 1535 (s), 1476 (s), 1403 (m), 1344 (m), 1175 (m), 861 (m); HRMS (EI) *m/z* calcd for $C_{10}H_{11}{}^{79}Br_3NO$ $[M+H]^+$ 397.8391, found 397.8376.

3-Bromo-2-(bromomethyl)-*N*-(3,4-dichlorophenyl)propanamide (4e).[28] Following the general procedure, **3e** (1.62 g, 10.0 mmol, 2.0 equiv.) was converted to **4e** (1.44 g, 3.7 mmol, 74%); purification by chromatography (hexanes-ethyl acetate mixtures 5 : 1 to 3 : 1 (v/v)): colorless solid, mp 157 - 160 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.57 (s(br.), 1H), 8.00 (d, J = 2.4 Hz, 1H), 7.59 (d, J = 8.8 Hz, 1H), 7.50 (dd, J = 8.8, 2.4 Hz, 1H), 3.74 – 3.62 (m, 4H), 3.32 – 3.22 (m, 1H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 168.9, 138.6, 131.1, 130.8, 125.2, 120.5, 119.5, 50.7, 31.8; IR (ATR) ν 3107 (m), 1661 (s), 1607 (s), 1586 (s), 1531 (s), 1468 (s), 1299 (m), 820 (s); HRMS (EI) *m/z* calcd for $C_{10}H_{10}{}^{79}Br_2{}^{35}Cl_2NO$ $[M+H]^+$ 387.8506, found 387.8498.

3-Bromo-2-(bromomethyl)-*N*-[4-chloro-3-(trifluoromethyl)phenyl]propanamide (4f). Following the general procedure, **3f** (1.96 g, 10.0 mmol, 2.0 equiv.) was converted to **4f** (1.30 g, 3.1 mmol, 62%); purification by chromatography (hexanes-ethyl acetate mixtures 5 : 1 to 3

: 1 (v/v)): colorless solid, mp 96 - 99 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.73 (s (br.), 1H), 8.20 (d, J = 2.8 Hz, 1H), 7.86 (dd, J = 8.8, 2.5 Hz, 1H), 7.67 (d, J = 8.8 Hz, 2H), 3.74 – 3.65 (m, 4H), 3.34 – 3.24 (m, 1H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 169.1, 138.0, 132.3, 126.8 (q, J = 30.5 Hz), 124.4 (q, J = 1.8 Hz), 124.1, 122.6 (q, J = 272.8 Hz), 117.9 (q, J = 5.6 Hz), 50.8, 31.8; ^{19}F NMR (377 MHz, DMSO-d_6) δ –61.7 ; IR (ATR) ν 1661 (s), 1598 (m), 1543 (s), 1480 (s), 1421 (m), 1319 (s), 1175 (m), 1127 (s), 1111 (s); HRMS (EI) *m/z* calcd for $C_{11}H_{10}{}^{79}Br_2{}^{35}ClF_3NO$ $[M+H]^+$ 421.8770, found 421.8762.

General procedure for the synthesis of α-methylene-β-lactams 5. The corresponding 3-bromo-2-bromomethyl-propionamide **4** (1.00 mmol) was dissolved in dry and degassed THF (10 mL). NaH (60 wt-% dispersion in mineral oil, 80 mg, 2.00 mmol) was added in small portions at ambient temperature and the mixture was stirred for 16 h. The reactions was quenched by addition of satd. aq. NH_4Cl solution (8 mL) and ethyl acetate (30 mL) was added. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 30 mL). The combined organic layers were washed with brine (20 mL) and dried with $MgSO_4$, filtered and evaporated. The crude product was purified by column chromatography on silica, using hexanes-ethyl acetate mixtures of increasing polarity as eluent, to furnish the α-methylene-β-lactams **5**.

1-(4-Methoxyphenyl)-3-methyleneazetidin-2-one (5a).[32,33] Following the general procedure, anilide **4a** (4.50 g, 12.8 mmol) was converted to **5a** (2.23 g, 11.8 mmol, 92%); purification by chromatography (hexanes-ethyl acetate mixtures 10 : 1 to 5 : 1 (v/v)): off-white solid, mp 112 – 113 °C (reported in the literature:[33] mp 108 – 109 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 9.1 Hz, 2H), 6.89 (d, J = 9.1 Hz, 2H), 5.83 (q, J = 1.7 Hz, 1H), 5.30 (q, J = 1.3 Hz, 1H), 4.09 (t, J = 1.5 Hz, 2H), 3.79 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 159.8, 156.5, 143.8, 132.2, 117.8, 114.7, 110.6, 55.7, 48.0; IR (ATR) ν 1722 (s), 1512 (m), 1384 (m), 1239 (m), 825 (s); HRMS (ESI) *m/z* calcd for for $C_{11}H_{11}NNaO_2$ $[M+Na]^+$ 212.0682, found 212.0684.

1-(4-Chlorophenyl)-3-methyleneazetidin-2-one (5b).[32] Following the general procedure, anilide **4b** (355 mg, 1.00 mmol) was converted to **5b** (122 mg, 0.63 mmol, 63%); purification by chromatography (hexanes-ethyl acetate mixtures 10 : 1 to 5 : 1 (v/v)): off-white solid, mp 92 – 93 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 - 7.29 (m, 4H), 5.90 (q, J = 1.7 Hz, 1H), 5.37 (q, J = 1.3 Hz, 1H), 4.13 (t, J = 1.5 Hz, 2H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 160.2, 143.3, 136.9, 129.5, 129.3, 117.7, 112.0, 48.0; IR (ATR) ν 2921 (w), 1725 (s), 1491 (s), 1376 (s), 1131 (m), 826 (s); HRMS (EI) *m/z* calcd for $C_{10}H_8{}^{35}ClNO$ [M^+] 193.0289, found 193.0293.

***N*-(4-(3-Methylene-2-oxoazetidin-1-yl)phenyl)acetamide (5c)**. Following the general procedure, anilide **4c** (235 mg, 0.62 mmol) was converted to **5c** (51 mg, 0.24 mmol, 39%); purification by chromatography (hexanes-ethyl acetate mixtures 10 : 1 to 5 : 1 (v/v)): off-white solid, mp 175 - 176 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.96 (s, 1H), 7.59 (d, J = 8.9 Hz, 2H), 7.33 (d, J = 8.9 Hz, 2H), 5.76 (s, 1H), 5.45 (s, 1H), 4.19 (s, 2H), 2.02 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 168.1, 159.3, 143.7, 135.5, 133.5, 119.8, 116.6, 111.3, 47.7, 23.9; IR (ATR) ν 3321 (w), 1724 (s), 1677 (m), 1539 (m), 1512 (s), 826 (s); HRMS (ESI) *m/z* calcd for $C_{12}H_{12}N_2O_2$ [M^+] 216.0893, found 216.0887.

1-(3-Bromophenyl)-3-methyleneazetidin-2-one (5d). Following the general procedure, anilide **4d** (400 mg, 1.00 mmol) was converted to **5d** (148 mg, 0.62 mmol, 62%); purification by chromatography (hexanes-ethyl acetate mixtures 10 : 1 to 5 : 1 (v/v)): colorless solid, mp 110 - 112 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 - 7.48 (m, 1H), 7.36 (dt, J = 7.2, 1.9 Hz, 1H), 7.24 (dt, J = 7.9, 1.7 Hz, 1H), 7.22 (dd, J = 7.7, 7.4 Hz, 1H), 5.92 (q, J = 1.7 Hz, 1H), 5.39 (q, J = 1.4 Hz, 1H), 4.14 (dd, J = 1.7, 1.4 Hz, 2H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 160.3, 143.2, 139.5, 130.8, 127.2, 123.1, 119.4, 115.2, 112.3, 48.1; IR (ATR) ν 1738 (s), 1596 (m), 1482 (m), 923 (s), 769 (s); HRMS (EI) *m/z* calcd for $C_{10}H_8{}^{79}BrNO$ [M^+] 236.9784, found 236.9769.

1-(3,4-Dichlorophenyl)-3-methylideneazetidin-2-one (5e).[28] Following the general procedure, anilide **4e** (390 mg, 1.00 mmol) was converted to **5e** (169 mg, 0.74 mmol, 74%);

purification by chromatography (hexanes-ethyl acetate mixtures 10 : 1 to 5 : 1 (v/v)): colorless solid, mp 122 - 124 °C (reported in the literature: mp 128 – 129 °C)[28]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 2.4 Hz, 1H), 7.40 (d, J = 8.7 Hz, 1H), 7.27 (dd, J = 8.7, 2.4 Hz, 1H), 5.92 (q, J = 1.7 Hz, 1H), 5.40 (q, J = 1.7 Hz, 1H), 4.13 (dd, J = 1.7, 1.4 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 160.2, 143.0, 137.7, 133.4, 131.1, 127.4, 118.1, 115.9, 112.7, 48.2; IR (ATR) ν 1745 (s), 1730 (s), 1482 (s), 1394 (s), 1483 (s); HRMS (EI) *m/z* calcd for $C_{10}H_7{}^{35}Cl_2NONa$ $[M+Na]^+$ 249.9797, found 249.9790.

1-[4-Chloro-3-(trifluoromethyl)phenyl]-3-methylideneazetidin-2-one (5f). Following the general procedure, anilide **4e** (305 mg, 0.72 mmol) was converted to **5e** (188 mg, 0.72 mmol, quant.); purification by chromatography (hexanes-ethyl acetate mixtures 10 : 1 to 5 : 1 (v/v)): colorless solid, mp 100 - 102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 - 7.56 (m, 2H), 7.47 (d, J = 8.5 Hz, 1H), 5.95 (q, J = 1.8 Hz, 1H), 5.44 (q, J = 1.8 Hz, 1H), 4.18 (t, J = 1.4 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 160.3, 143.0, 137.1, 132.5, 129.3 (q, J = 31.7 Hz), 125.3 (d, J = 280.5 Hz), 121.2, 120.6, 115.2 (q, J = 5.5 Hz), 113.0, 48.2; ^{19}F NMR (377 MHz, $CDCl_3$) δ –62.9; IR (ATR) ν 1731 (s), 1486 (s), 1436 (s), 1367 (s), 1107 (s), 934 (s), 832 (s), ; HRMS (ESI) *m/z* calcd for $C_{11}H_8{}^{35}ClF_3NO$ $[M+H]^+$ 262.0241, found 262.0241.

Heck coupling of β-lactam 5a with 4-iodoanisol (6a) to 7aa. To a solution of **5a** (47 mg, 0.25 mmol) and 4-iodoanisol (**6a**, 70 mg, 0.30 mmol) in DMF (2.0 mL) were added NEt_3 (105 µL, 0.75 mmol), $Pd(OAc)_2$ (2.8 mg, 5 mol %) and optionally P(*o*-tol)$_3$ (7.6 mg, 10 mol %). The solution was heated to 90 °C for 4 h and then cooled to ambient temperature. The starting material **5a** was fully consumed, as indicated by TLC. The mixture was diluted with CH_2Cl_2 (30 mL) and washed with water (20 mL) and brine (20 mL). The organic extract was dried with $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography on silica, using hexanes-ethyl acetate mixture (10 : 1 (v/v)) as eluent, to furnish **7aa** (7 mg, 0.02 mmol, 10%). Analytical data are identical to those obtained for the product of the coupling of **5a** and diazonium salt **8a**.

General procedure for the synthesis of α-arylidene-β-lactams 7 by Matsuda-Heck coupling. To a solution of the corresponding α-methylene-β-lactam **5** (0.25 mmol) and the corresponding arene diazonium salt **8** (0.30 mmol) in methanol (4 mL) was added NaOAc (82 mg, 1.00 mmol) and $Pd(OAc)_2$ (2.8 mg, 5 mol %). The mixture was stirred at ambient temperature for 16 h, dry-loaded on silica (by mixing with silica (1 g) and evaporating all volatiles), and purified by column chromatography on silica, using hexanes-ethyl acetate mixtures of increasing polarity as eluents to furnish the coupling products **7**.

(*E*)-3-(4-Methoxybenzylidene)-1-(4-methoxyphenyl)azetidin-2-one (7aa). Following the general procedure, **5a** (189 mg, 1.00 mmol) and **8a** (266 mg, 1.20 mmol) were converted to **7aa** (251 mg, 0.85 mmol, 85%). For the optimization study (**Table 3**) compounds **5a** (47 mg, 0.25 mmol) and **8a** (67 mg, 0.30 mmol) were converted to **7aa** (69 mg, 0.23 mmol, 94%); purification by chromatography (hexanes-ethyl acetate mixture 10 : 1 (v/v)): colorless solid, mp 188 - 189 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.47 (d, J = 8.8 Hz, 2H), 7.36 (d, J = 8.8 Hz, 2H), 7.02 (t, J = 1.5 Hz, 1H), 7.01 (d, J = 8.8 Hz, 2H), 6.99 (d, J = 8.8 Hz, 2H), 4.55 (d, J = 1.5 Hz, 2H), 3.80 (s, 3H), 3.74 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6) δ 160.4, 160.3, 155.4, 132.7, 132.1, 130.5, 126.6, 124.0, 117.2, 114.6, 114.5, 55.3, 55.3, 48.3; IR (ATR) ν2926 (w), 1720 (s), 1602 (m), 1508 (s), 1241 (s); HRMS (ESI) m/z calcd for $C_{18}H_{18}NO_3$ $[M+H]^+$ 296.1287, found 296.1262.

(*E*)-3-(4-Hydroxybenzylidene)-1-(4-methoxyphenyl)azetidin-2-one (7ab). Following the general procedure, **5a** (47 mg, 0.25 mmol) and **8b** (62 mg, 0.30 mmol) were converted to **7ab** (70 mg, 0.25 mmol, quant.); purification by chromatography (hexanes-ethyl acetate mixture 10 : 1 (v/v)): yellow solid, mp 223 - 225 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.98 (s (br.), 1H, OH), 7.35 (d, J = 8.8 Hz, 2H, H2'), 7.34 (d, J = 9.1 Hz, 2H, H2''), 6.97 (d, J = 9.1 Hz, 2H, H3''), 6.95 (s (br.), 1H, H5), 6.83 (d, J = 8.6 Hz, 2H, H3'), 4.50 (s(br.), 2H, H4), 3.74 (s, 3H, OCH_3); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 160.7 (C2), 158.9 (C4'), 155.5 (C4''), 132.3 (C1''), 131.6 (C3), 130.7 (C2'), 125.2 (C1'), 124.4 (C5), 117.2 (C2''), 116.0 (C3'), 114.6

(C3''), 55.4 (OCH_3), 48.4 (C4); IR (ATR) ν 3072 (bw), 2923 (w), 1697 (s), 1604 (m), 1581 (m), 1508 (s); HRMS (ESI) *m/z* calcd for $C_{17}H_{16}NO_3$ $[M+H]^+$ 282.1130, found 282.1109.

(*E*)-3-(4-(Benzyloxy)benzylidene)-1-(4-methoxyphenyl)azetidin-2-one (7ac). Following the general procedure, **5a** (47 mg, 0.25 mmol) and **8c** (89 mg, 0.30 mmol) were converted to **7ac** (63 mg, 0.17 mmol, 68%); purification by chromatography (hexanes-ethyl acetate mixture 10 : 1 (v/v)): off-white solid, mp 209 - 211 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 - 7.30 (m, 7H), 7.32 (d, J = 8.9 Hz, 2H), 7.02 (t, J = 1.4 Hz, 1H), 6.99 (dm, J = 8.8 Hz, 2H), 6.91 (dm, J = 9.0 Hz, 2H), 5.10 (s, 2H), 4.41 (d, J = 1.4 Hz, 2H), 3.80 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 161.3, 159.9, 156.1, 136.6, 132.5, 132.4, 130.4, 128.8, 128.3, 127.6, 127.4, 124.7, 117.5, 115.6, 114.7, 70.2, 55.7, 48.7; IR (ATR) ν 1719 (s), 1602 (m), 1508 (s), 1381 (s), 1241 (s); HRMS (EI) *m/z* calcd for $C_{24}H_{21}NO_3$ $[M^+]$ 371.1521, found 371.1526.

(*E*)-3-(4-Fluorobenzylidene)-1-(4-methoxyphenyl)azetidin-2-one (7ad). Following the general procedure, **5a** (47 mg, 0.25 mmol) and **8d** (63 mg, 0.30 mmol) were converted to **7ad** (61 mg, 0.22 mmol, 86%); purification by chromatography (hexanes-ethyl acetate mixture 10 : 1 (v/v)): off-white solid, mp 147 - 148 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 - 7.33 (m, 4H), 7.10 (dd, J = 8.6, 8.6 Hz, 2H), 7.04 (t, J = 1.5 Hz, 1H), 6.92 (dm, J = 9.0 Hz, 2H), 4.43 (d, J = 1.5 Hz, 2H), 3.81 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 163.4 (d, J = 250.9 Hz), 160.8, 156.4, 134.6 (d, J = 2.5 Hz), 132.4, 130.7 (d, J = 3.4 Hz), 130.6 (d, J = 8.5 Hz), 123.9, 117.7, 116.4 (d, J = 21.9 Hz), 114.8, 55.7, 48.7; IR (ATR) ν 1727 (m), 1598 (w), 1505 (m), 1135 (m), 831 (s); HRMS (EI) *m/z* calcd for $C_{17}H_{14}FNO_2$ $[M^+]$ 283.1009, found 283.1002.

(*E*)-4-((1-(4-Methoxyphenyl)-2-oxoazetidin-3-ylidene)methyl)benzonitrile (7ae). Following the general procedure, **5a** (47 mg, 0.25 mmol) and **8e** (65 mg, 0.30 mmol) were converted to **7ae** (38 mg, 0.13 mmol, 52%); purification by chromatography (hexanes-ethyl acetate mixture 10 : 1 (v/v)): off-white solid, mp 200 °C (dec.); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (d, J = 8.0 Hz, 2H), 7.70 (d, J = 7.9 Hz, 2H), 7.38 (d, J = 8.7 Hz, 2H), 7.18 (s, 1H), 7.00 (d, J = 8.6 Hz, 2H), 4.64 (s, 2H), 3.75 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ

159.9, 156.3, 139.5, 139.2, 133.3, 132.2, 129.8, 123.0, 119.1, 118.0, 115.1, 111.8, 55.8, 49.1; IR (ATR) ν 2223 (m), 1717 (s), 1511 (m), 1242 (m), 1143 (m); HRMS (EI) *m*/*z* calcd for $C_{18}H_{14}N_2O_2$ [M^+] 290.1050, found 290.1053.

(*E*)-3-(4-Acetylbenzylidene)-1-(4-methoxyphenyl)azetidin-2-one (7af). Following the general procedure, **5a** (47 mg, 0.25 mmol) and **8f** (70 mg, 0.30 mmol) were converted to **7af** (64 mg, 0.21 mmol, 83%); purification by chromatography (hexanes-ethyl acetate mixture 10 : 1 (v/v)): yellow solid, mp 207 – 208 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (dm, J = 8.4 Hz, 2H), 7.47 (dm, J = 8.4 Hz, 2H), 7.39 (dm, J = 9.0 Hz, 2H), 7.10 (t, J = 1.5 Hz, 1H), 6.92 (dm, J = 9.0 Hz, 2H), 4.48 (d, J = 1.5 Hz, 2H), 3.81 (s, 3H), 2.62 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 197.3, 160.3, 156.6, 138.9, 137.7, 137.4, 132.2, 129.1, 128.9, 123.8, 117.8, 114.8, 55.7, 48.9, 26.8; IR (ATR) ν 1720 (s), 1675 (s), 1603 (w), 1511 (s), 1244 (s); HRMS (EI) *m*/*z* calcd for $C_{19}H_{17}NO_3$ [M^+] 307.1203, found 307.1205.

(*E*)-1-(4-Methoxyphenyl)-3-(3-(trifluoromethyl)benzylidene)azetidin-2-one (7ai). Following the general procedure, **5a** (47 mg, 0.25 mmol) and **8i** (78 mg, 0.30 mmol) were converted to **7ai** (67 mg, 0.20 mmol, 81%); purification by chromatography (hexanes-ethyl acetate mixture 10 : 1 (v/v)): yellow solid, mp 175 - 177 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 - 7.49 (m, 4H), 7.39 (dm, J = 9.0 Hz, 2H), 7.09 (t, J = 1.5 Hz, 1H), 6.92 (dm, J = 9.0 Hz, 2H), 4.47 (d, J = 1.5 Hz, 2H), 3.81 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 160.2, 156.5, 136.9, 135.2, 132.0, 131.8, 131.7 (q, J = 32.0 Hz) 129.7, 125.9 (q, J = 3.6 Hz), 125.1 (q, J = 3.8 Hz), 123.9 (q, J = 273 Hz), 123.4, 117.7, 114.7, 55.6, 48.7; IR (ATR) ν 1721 (m), 1512 (m), 1322 (m), 1123 (s), 695 (m); HRMS (EI) *m*/*z* calcd for $C_{18}H_{14}F_3NO_2$ [M^+] 333.0977, found 333.0969.

(*E*)-1-(4-Methoxyphenyl)-3-(3-methylbenzylidene)azetidin-2-one (7aj). Following the general procedure, **5a** (47 mg, 0.25 mmol) and **8j** (62 mg, 0.30 mmol) were converted to **7aj** (64 mg, 0.23 mmol, 92%); purification by chromatography (hexanes-ethyl acetate mixture 10 : 1 (v/v)): yellow solid, mp 151 - 152 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.38 (dm, J = 9.0

Hz, 2H), 7.35 - 7.30 (m, 3H), 7.22 (dm, J = 7.2 Hz, 1H), 7.02 (t, J = 1.4 Hz, 1H), 6.99 (dm, J = 9.1 Hz, 2H), 4.59 (d, J = 1.4 Hz, 2H), 3.74 (s, 3H), 2.34 (s, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ 160.2, 155.6, 138.3, 135.3, 134.1, 132.0, 130.2, 129.4, 129.0, 126.0, 124.3, 117.4, 114.6, 55.4, 48.6, 21.0; IR (ATR) ν 1726 (s), 1583 (w), 1510 (s), 1239 (s), 1142 (s); HRMS (EI) m/z calcd for $C_{18}H_{17}NO_2$ [M^+] 279.1254, found 279.1262.

(*E*)-3-(3-Bromo-4-hydroxybenzylidene)-1-(4-methoxyphenyl)azetidin-2-one (7ak). Following the general procedure, **5a** (47 mg, 0.25 mmol) and **8k** (86 mg, 0.30 mmol) were converted to **7ak** (87 mg, 0.24 mmol, 97%); purification by chromatography (hexanes-ethyl acetate mixture 10 : 1 (v/v)): yellow solid, mp 240 - 242 °C (dec.); ^1H NMR (500 MHz, DMSO-d_6) δ 10.81 (s, 1H), 7.66 (d, J = 1.8 Hz, 1H), 7.38 - 7.33 (m, 3H), 7.05 - 6.94 (m, 4H), 4.55 (s, 2H), 3.74 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 160.2, 155.5, 155.3, 133.5, 133.2, 132.1, 129.3, 126.8, 123.0, 117.2, 116.7, 114.6, 109.9, 55.3, 48.2; IR (ATR) ν 3158 (bw), 1704 (s), 1602 (m), 1510 (s), 1250 (s), 819 (s); HRMS (EI) m/z calcd for $C_{17}H_{14}{}^{79}BrNO_3$ [M^+] 359.0152, found: 359.0141.

(*E*)-3-(2,4-Dichlorobenzylidene)-1-(4-methoxyphenyl)azetidin-2-one (7am). Following the general procedure, **5a** (47 mg, 0.25 mmol) and **8m** (78 mg, 0.30 mmol) were converted to **7am** (78 mg, 0.23 mmol, 93%); purification by chromatography (hexanes-ethyl acetate mixture 10 : 1 (v/v)): off-white solid, mp 217 - 218 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, J = 2.1 Hz, 1H), 7.45 (t, J = 1.4 Hz, 1H), 7.39 (dm, J = 9.0 Hz, 2H), 7.35 (d, J = 8.4 Hz, 1H), 7.28 (dd, J = 8.4, 2.1 Hz, 1H), 6.93 (dm, J = 9.0 Hz, 2H), 4.42 (d, J = 1.5 Hz, 2H), 3.82 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 160.1, 156.5, 137.6, 135.9, 135.7, 132.1, 131.0, 130.4, 128.8, 127.6, 120.3, 117.8, 114.7, 55.7, 48.6; IR (ATR) ν 2923 (w), 1725 (s), 1709 (s), 1511 (s), 1245 (s), 808 (s); HRMS (EI) m/z calcd for $C_{17}H_{13}{}^{35}Cl_2NO_2$ [M^+] 333.0323, found: 333.0335.

(*E*)-1-(4-Methoxyphenyl)-3-(3,4,5-trimethoxybenzylidene)azetidin-2-one (7an). Following the general procedure, **5a** (47 mg, 0.25 mmol) and **8n** (85 mg, 0.30 mmol) were converted to **7an** (84 mg, 0.24 mmol, 95%); purification by chromatography (hexanes-ethyl acetate mixture

10 : 1 (v/v)): off-white solid, mp 150 - 152 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (dm, J = 9.1 Hz, 2H), 6.95 (t, J = 1.4 Hz, 1H), 6.88 (dm, J = 9.1 Hz, 2H), 6.57 (s, 2H), 4.41 (d, J = 1.4 Hz, 2H), 3.89 (s, 6H), 3.88 (s, 3H), 3.78 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 160.8, 156.3, 153.7, 139.8, 134.1, 132.3, 129.9, 125.1, 117.6, 114.7, 106.3, 61.1, 56.4, 55.6, 48.5; IR (ATR) ν 2948 (m), 1718 (s), 1583 (m), 1505 (s), 1120 (s), 726 (s); HRMS (EI) *m*/*z* calcd for $C_{20}H_{21}NO_5$ [M^+] 355.1420, found 355.1430.

(*E*)-1-(4-Chlorophenyl)-3-(4-hydroxybenzylidene)azetidin-2-one (7bb). Following the general procedure, **5b** (48 mg, 0.25 mmol) and **8b** (62 mg, 0.30 mmol) were converted to **7bb** (68 mg, 0.24 mmol, 95%); purification by chromatography (hexanes-ethyl acetate mixture 10 : 1 (v/v)): off-white solid, mp 249 - 251 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.03 (s, 1H, OH), 7.45 (d, J = 8.9 Hz, 2H, H3''), 7.39 (d, J = 8.9 Hz, 2H, H2''), 7.37 (d, J = 8.5 Hz, 2H, H2'), 7.04 (s, 1H, H5), 6.84 (d, J = 8.5 Hz, 2H, H3'), 4.58 (s, 2H, H4); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 161.7 (C2), 159.7 (C4'), 137.9 (C1''), 131.5 (C3), 131.3 (C2'), 129.7 (C3''), 127.3 (C4''), 126.1 (C5), 125.3 (C1'), 117.9 (C2''), 116.5 (C3'), 49.0 (C4); IR (ATR) ν 3116 (bw), 2924 (w), 1705 (s), 1492 (s), 824 (s); HRMS (ESI) *m*/*z* calcd for $C_{16}H_{13}{}^{35}ClNO_2$ $[M+H]^+$ 286.0635, found 286.0660.

(*E*)-3-(4-Chlorobenzylidene)-1-(4-chlorophenyl)azetidin-2-one (1e).[14] Following the general procedure, **5b** (48 mg, 0.25 mmol) and **8o** (68 mg, 0.30 mmol) were converted to **1e** (71 mg, 0.24 mmol, 93%); purification by chromatography (hexanes-ethyl acetate mixture 10 : 1 (v/v)): off-white solid, mp 140 – 141 °C (reported in the literature[14] mp 139 - 142 °C); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 (d, J = 8.5 Hz, 2H), 7.37 (d, J = 8.9 Hz, 2H), 7.33 (d, J = 8.9 Hz, 2H), 7.32 (d, J = 8.5 Hz, 2H), 7.08 (t, J = 1.4 Hz, 1H), 4.46 (d, J = 1.5 Hz, 2H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 161.0, 137.1, 135.9, 134.9, 132.6, 130.1, 129.6, 129.5, 129.2, 125.0, 117.6, 48.7; IR (ATR) ν 1735 (s), 1591 (s), 1492 (m), 1480 (s), 1373 (s), 1123 (m); HRMS (EI) m/z calcd for $C_{16}H_{11}{}^{35}Cl_2NO$ [M^+] 303.0218, found 303.0224. All analytical data match those reported in the literature.[14]

(*E*)-*N*-(4-(3-(4-Methoxybenzylidene)-2-oxoazetidin-1-yl)phenyl)acetamide (7ca) and *N*-(4-(3-(bis(4-methoxyphenyl)methylene)-2-oxoazetidin-1-yl)phenyl)acetamide (9ca). Following the general procedure, **5c** (54 mg, 0.25 mmol) and **8a** (67 mg, 0.30 mmol) were converted to a mixture of **7ca** (23 mg, 0.07 mmol, 28%) and **9ca** (44 mg, 0.10 mmol, 41%). The reaction products were separated by column chromatography on silica (hexanes-ethyl acetate mixtures 10 : 1 to 3 : 1 (v/v)). *Analytical data for **7ca***: off-white solid, mp 234 °C (dec.); ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.96 (s, 1H), 7.59 (dm, J = 9.0 Hz, 2H), 7.47 (dm, J = 8.8 Hz, 2H), 7.34 (dm, J = 8.9 Hz, 2H), 7.04 (t, J = 1.4 Hz, 1H), 7.01 (dm, J = 8.8 Hz, 2H), 4.56 (d, J = 1.4 Hz, 2H), 3.80 (s, 3H), 2.02 (s, 3H); ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 168.1, 160.6, 160.4, 135.2, 134.0, 132.6, 130.6, 126.7, 124.4, 119.9, 116.3, 114.6, 55.4, 48.3, 24.0; IR (ATR) ν 3310 (bw), 2955 (m), 2913 (m), 1725 (m), 1709 (m), 1600 (m), 1509 (s), 1248 (s), 823 (s); HRMS (EI) m/z calcd for $C_{19}H_{18}N_2O_3$ [M^+] 322.1317, found 322.1314. *Analytical data for **9ca***: off-white solid, mp 239 – 241 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50 (dm, J = 8.9 Hz, 2H, *Z* or *E*-H3'), 7.46 (dm, J = 8.9 Hz, 2H, H3''), 7.35 (dm, J = 8.9 Hz, 2H, H2''), 7.31 (s(br.), 1H, NH), 7.23 (dm, J = 8.8 Hz, 2H, *Z* or *E*-H3'), 6.92 (dm, J = 8.9 Hz, 2H, *Z* or *E*-H2'), 6.90 (dm, J = 8.9 Hz, 2H, *Z* or *E*-H2'), 4.20 (s, 2H, H4), 3.85 (s, 3H, *Z* or *E*-OCH_3), 3.83 (s, 3H, *Z* or *E*-OCH_3), 2.14 (s, 3H, C(O)CH_3); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.3 (*C*(O)CH_3), 160.4 (C2), 160.3 (*Z*- or *E*-C4'), 160.1 (*Z*- or *E*-C4'), 142.3 (C3), 135.5 (C1''), 133.8 (C4''), 131.8 (*Z*- or *E*-C3'), 131.5 (C1'), 130.8 (*Z*- or *E*-C3'), 129.7 (*Z*- or *E*-C1' or C5), 129.6 (*Z*- or *E*-C1' or C5), 121.0 (C3''), 116.6 (C2''), 114.1 (*Z*- or *E*-C3'), 113.5 (*Z*- or *E*-C3'), 55.5 (*Z*- or *E*-OCH_3), 55.4 (*Z*- or *E*-OCH_3), 48.0 (C4), 24.6 (C(O)*C*H_3); IR (ATR) ν 3307 (bw), 1712 (w), 1667 (w), 1603 (m), 1506 (s), 1246 (s), 828 (s); HRMS (EI) m/z calcd for $C_{26}H_{24}N_2O_4$ [M^+] 428.1736, found 428.1735.

(*E*)-1-(3-Bromophenyl)-3-(3-methylbenzylidene)azetidin-2-one (7dj). Following the general procedure, **5d** (60 mg, 0.25 mmol) and **8j** (62 mg, 0.30 mmol) were converted to **7dj** (79 mg, 0.24 mmol, 96%); purification by chromatography (hexanes-ethyl acetate mixture 10 :

1 (v/v)): off-white solid, mp 146 – 147 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 - 7.52 (m, 1H), 7.45 - 7.37 (m, 1H), 7.35 - 7.27 (m, 1H), 7.24 - 7.16 (m, 5H), 7.10 (t, J = 1.4 Hz, 1H), 4.47 (d, J = 1.5 Hz, 2H), 2.39 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 161.5, 139.9, 139.0, 134.0, 134.0, 130.8, 130.8, 129.8, 129.2, 126.9, 126.8, 126.1, 123.2, 119.1, 115.1, 48.9, 21.6; IR (ATR) ν 1726 (s), 1590 (s), 1568 (m), 1480 (s), 1371 (s), 773 (s); HRMS (EI) *m*/*z* calcd for $C_{17}H_{14}{}^{79}BrNO$ [M^+] 327.0259, found 327.0255.

(*E*)-1-(3,4-Dichlorophenyl)-3-(4-hydroxybenzylidene)azetidin-2-one (7eb). Following the general procedure, **5e** (57 mg, 0.25 mmol) and **8b** (62 mg, 0.30 mmol) were converted to **7eb** (79 mg, 0.25 mmol, quant.); purification by chromatography (hexanes-ethyl acetate mixture 10 : 1 (v/v)): off-white solid, mp 216 °C (dec.); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.03 (s, 1H), 7.64 (d, J = 8.7 Hz, 1H), 7.59 (s, 1H), 7.45 - 7.31 (m, 3H), 7.07 (s, 1H), 6.84 (d, J = 8.0 Hz, 2H), 4.59 (s, 2H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 161.8, 159.8, 138.9, 132.2, 131.7, 131.4, 131.2, 126.7, 125.2, 125.1, 117.7, 116.6, 116.5, 49.3; IR (ATR) ν 3356 (bw), 1743 (s), 1727 (s), 1705 (s), 1592 (m), 1479 (s), 1134 (s), 812 (s); HRMS (EI) *m*/*z* calcd for $C_{16}H_{11}{}^{35}Cl_2NO_2$ [M^+] 319.0161, found 319.0162.

(*E*)-1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-(4-hydroxybenzylidene)azetidin-2-one (7fb). Following the general procedure, **5f** (65 mg, 0.25 mmol) and **8b** (62 mg, 0.30 mmol) were converted to **7fb** (76 mg, 0.22 mmol, 86%); purification by chromatography (hexanes-ethyl acetate mixture 10 : 1 (v/v)): off-white solid, mp 207 - 208 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.04 (s, 1H), 7.76 (s, 1H), 7.74 (d, J = 8.9 Hz, 1H), 7.65 (d, J = 8.9 Hz, 1H), 7.38 (d, J = 7.9 Hz, 2H), 7.10 (s, 1H), 6.84 (d, J = 7.9 Hz, 2H), 4.65 (s, 2H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 161.5, 159.4, 137.8, 132.7, 131.0, 130.6, 127.3 (q, J = 30.9 Hz), 126.5, 124.7, 123.7 (q, J = 2.0 Hz), 122.6 (q, J = 275 Hz), 120.8, 116.0, 114.6 (q, J = 5.6 Hz), 49.3; ^{19}F NMR (376 MHz, DMSO-d_6) δ –61.6; IR (ATR) ν 3289 (bw), 1730 (m), 1722 (s), 1605 (m), 1519 (w), 1484 (s), 1108 (s); HRMS (EI) *m*/*z* calcd for $C_{17}H_{11}{}^{35}ClF_3NO_2$ [M^+] 353.0425, found: 353.0418.

Supporting Information Available statement

The Supporting Information is available free of charge on the ACS Publications website at DOI: Copies of ^{1}H and ^{13}C NMR spectra for all compounds; 2D-NMR-spectra for representative compounds.

Accession Codes

CCDC 2068052 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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References and Footnotes

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