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Iterative arylation of itaconimides with diazonium salts through electrophilic Palladium catalysis: divergent β-H-elimination pathways in repetitive Matsuda-Heck reactions

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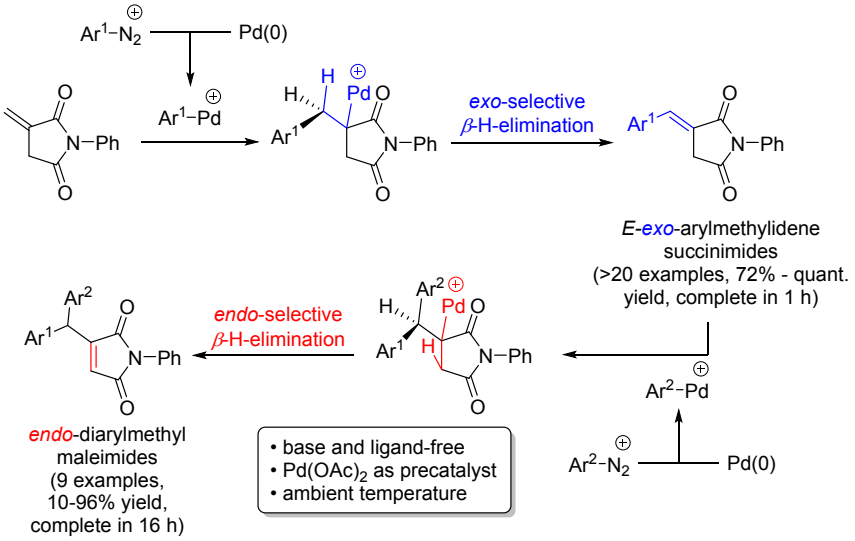


Abstract: *N*-Arylitaconimides, accessible from maleic anhydride, anilines and paraformaldehyde, react with arene diazonium salts in a Pd-catalyzed Matsuda-Heck arylation to the pharmacologically relevant *E*-configured 3-arylmethylidene pyrrolidine-2,5-diones (also known as arylmethylidene succinimides) through an *exo*-selective β-H-elimination. The coupling proceeds at ambient temperature with the simple and easy-to-handle precatalyst Pd-II-acetate under ligand- and base-free conditions. Notable features are high isolated yields as

well as regio- and stereoselectivities, and short reaction times. In a comparative investigation, aryl iodides, bromides and triflates were shown to be inferior coupling reagents in this reaction. The 3-arylmethylidene pyrrolidine-2,5-diones undergo a second Matsuda-Heck coupling, which proceeds via an *endo*-selective β-H-elimination to give diarylmethyl substituted maleimides as coupling products. These products can also be accessed in one flask by sequential addition of different arene diazonium salts to the starting itaconimide. The potential of 3-arylmethylidene succinimides as photoswitches was tested. Upon irradiation of the *E*-isomer at 300 nm partial isomerization to the *Z*-isomer (*E* : *Z* = 65 : 35 in the photostationary state) was observed. The isomerization was found to be nearly completely reversible by irradiating the mixture at 400 nm.

Introduction

3-Arylmethylidene pyrrolidine-2,5-diones of the general formula *exo*-**1** have found diverse applications (**Figure 1**). Compounds *exo*-**1bu** and *exo*-**1bv**,[1] for example, were tested as inhibitors of the type 2 5α-reductase (T2-5α-reductase), an enzyme responsible for the reduction of testosterone to the more potent androgen dihydrotestosterone.[1,2] Inhibitors of T2-5α-reductase, such as the clinically used drug finasteride, are potentially useful for the treatment of benign prostate hyperplasia.[3,4] The 3-arylmethylidene pyrrolidine-2,5-dione *exo*-**1ae** has been investigated with regard to its vasorelaxant activity, which was reported to be in the range of the standard drug doxazosin.[5] Compounds of the general formula *exo*-**1** have been used as Michael acceptors for irreversible, site-specific thiol bioconjugation,[6] as test substrates for asymmetric transformations,[7-9] and as starting materials to access other heterocyclic systems, such as pyrolo quinolines[10] or coumarins.[11] Recently, 3-arylmethylidene pyrrolidine-2,5-diones were investigated as reactants in multicomponent reactions for the synthesis of several interesting spirocyclic scaffolds.[12-15] Hydrogenation of compounds *exo*-**1** leads to 3-benzyl succinimides, which are also an important structural pattern in medicinal chemistry. For example, compound **2** was identified as an inhibitor of the leukocyte common antigen-related phosphatase, a potential target for the treatment of neurological diseases.[16] By using Ir-catalysts in combination with chiral biphenyl-oxazoline-phosphine ligands the hydrogenation of compounds *exo*-**1** to 3-benzyl succinimides can be achieved with very high levels of enantioselectivity.[7]

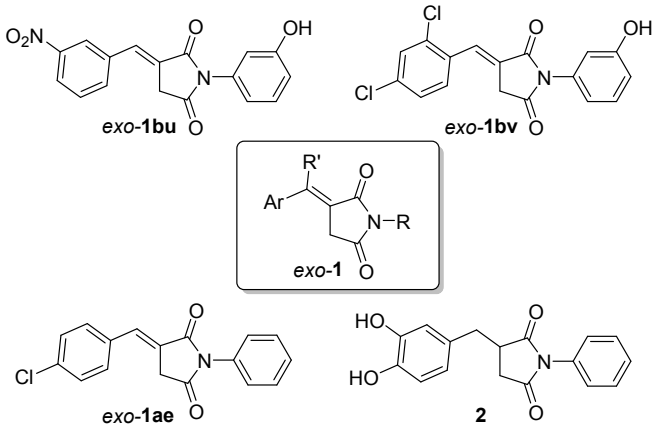
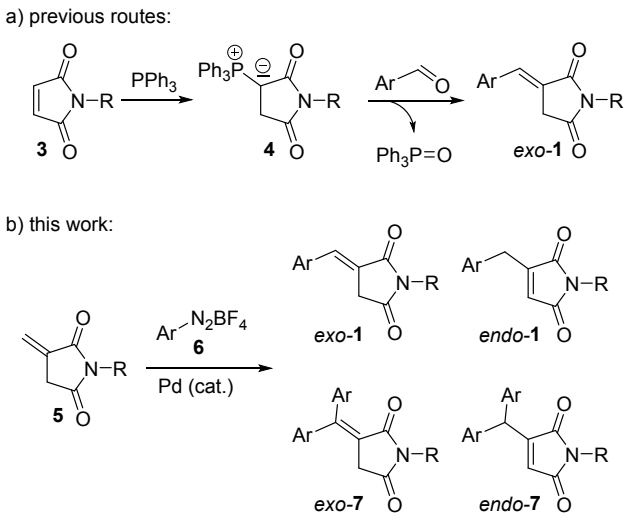


Figure 1. Structures of biologically relevant 3-arylmethylidene-pyrrolidine-2,5-diones *exo*-**1** and a 3-benzylsuccinimide **2**.

Almost all syntheses of 3-arylmethylidene pyrrolidine-2,5-diones *exo*-**1** reported in the literature use a phospha-Michael-addition / Wittig-olefination sequence. This route, originally developed by Hedaya and Theodoropulos as a two-step synthesis,[17] starts from maleimides **3** which react with phosphines in a conjugate addition / tautomerization reaction to ylides **4**. These undergo a Wittig-olefination with aromatic aldehydes in the second step (**Scheme 1a**). Although several modifications and improvements, including a catalytic variant,[18] have been published since the original report,[6,19-23] some disadvantages of this approach remain: in general, elevated temperatures and protic solvents are required to achieve useful levels of conversion, which may affect hydrolytic stability of the succinimide structure;[24] the required benzaldehydes are sometimes prone to oxidation and need to be purified beforehand; other carbonyl groups that may also undergo Wittig olefination reactions are not tolerated; the inevitable formation of stoichiometric amounts of phosphine oxides can hamper product isolation and purification if the 3-arylmethylidene pyrrolidine-2,5-diones have similar polarity.

Scheme 1. Phospha-Michael addition / Wittig-olefination (previous routes) vs. Matsuda-Heck route (this work).



In continuation of our previous investigations[25-27] into the development and application of Matsuda-Heck reactions,[28] i. e. the Pd-catalyzed Heck-type coupling of arene diazonium salts with alkenes,[29-36] we wondered whether an alternative approach to 3-arylmethylidene pyrrolidine-2,5-diones *exo*-**1** that starts from itaconimides **5** and stable and isolable arene diazonium salts **6** might be a competitive or even advantageous alternative to the phospha-Michael-addition / Wittig-olefination approach. Important questions to be answered in this context are: will the final β-H-elimination step[36] leading to the liberation of the coupling products proceed *exo*- or *endo*-selectively (i. e. to *exo*-**1** or to *endo*-**1**), or to a mixture of *exo*- and *endo*-isomers? Is it possible to identify conditions for selective single and double arylations, and will the double arylation products **7** be formed as *exo*- or *endo* isomers? (**Scheme 1b**).

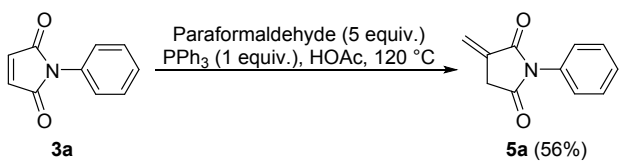
Literature precedence on Heck-arylation approaches to *exo*-arylmethylidene-pyrrolidine-2,5-diones and related lactams is scarce: we are aware of an intramolecular Heck-reaction with an aryl iodide for the synthesis of tetrahydroquinoline derivatives that were tested for their anti-hyperalgesic activity[37] and of an intermolecular Heck reaction between aryl iodides and *exo*-methylene lactams as a route to benzyl- and benzylidene pyrrolizidinones.[38] Heck reactions of

maleimides **3** with aryl iodides give the expected 3-arylmaleimides, but were found to be challenging due to increased hydrolysis of the products at elevated temperatures and prolonged reaction times.[24] These obstacles were overcome by the development of special reaction conditions for the Pd-catalyzed coupling. For a single example these conditions were applied to a 3-methylmaleimide, resulting in the formation of a 3-arylmethylidene-2,5-dione of the general formula **1** rather than the expected 3-methyl-4-arylmaleimide. The formation of the unexpected *exo*-arylmethylidene product was explained by a Pd-catalyzed isomerization of the 3-methylmaleimide to an itaconimide **5**, which subsequently undergoes a Heck-reaction.

Results and discussion

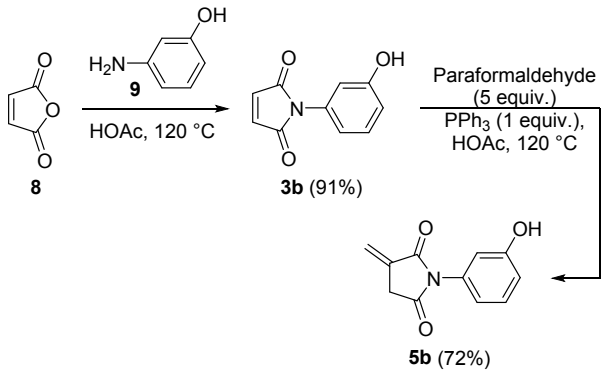
Synthesis of *N*-arylitaconimides 5. As a test substrate for the development and optimization of the envisaged Matsuda-Heck-coupling *N*-phenylitaconimide (**5a**) was chosen. This compound[39] was, like a number of other *N*-arylitaconimides such as **5b**,[40] previously synthesized from itaconic anhydride and anilines in a two-step ring-opening / cyclizative condensation sequence. Recently, this method was further developed into a one-flask synthesis by using improved conditions for the cyclizative condensation and applied to the synthesis of **5a** and several other *N*-arylitaconimides.[41] We synthesized **5a** from *N*-phenylmaleimide (**3a**) and paraformaldehyde by adaptation of the phospha-Michael-addition / Wittig-olefination sequence.[9] The yield is virtually identical to that reported for the itaconic anhydride route outlined above,[41] and the potential separation and purification problems were not observed for this particular derivative (**Scheme 2**).

Scheme 2. Synthesis of *N*-phenylitaconimide (**5a**).



With a view to the synthesis of the T2-5α-reductase inhibitors *exo*-**1bu** and *exo*-**1bv** (**Figure 1**) we also synthesized *N*-(3-hydroxyphenyl)itaconimide (**5b**)[40] by using the tandem phospha-Michael / Wittig-olefination method. To this end maleic anhydride was first reacted with 3-hydroxyaniline (**9**) to furnish the *N*-arylmaleimide **3b**,[42] which was then converted to **5b** with paraformaldehyde and triphenylphosphine in 65% yield over two steps (**Scheme 3**).

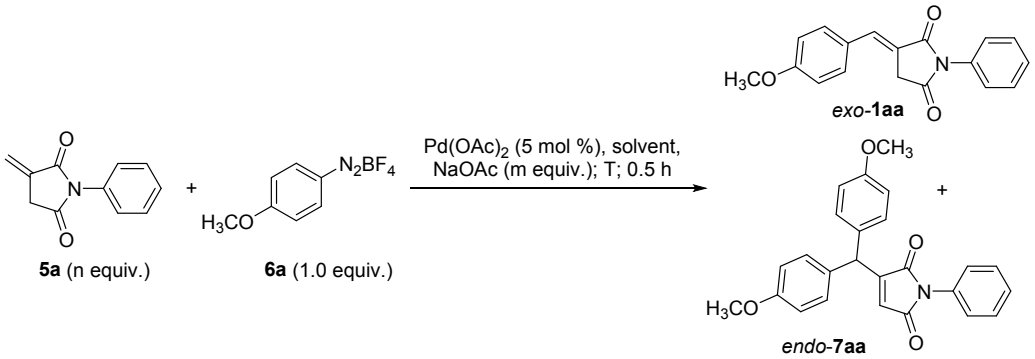
Scheme 3. Synthesis of *N*-(3-hydroxyphenyl)itaconimide (**5b**).



Optimized coupling conditions for arene diazonium salts and alternative coupling partners. The conditions for the Matsuda-Heck coupling were optimized for the reaction of *N*-phenylitaconimide (**5a**) and 4-methoxybenzenediazonium salt **6a** (**Table 1**). In the first experiments, equimolar ratios of both coupling partners were used. The most important variables in Matsuda-Heck reactions are the precatalyst, the solvent and the presence (or absence) of a base. In many cases good results can be obtained by using $Pd(OAc)_2$ as a precatalyst without additional ligands. Donor ligands often have detrimental effects on the stability of the arene diazonium salts and on the overall reactivity and should therefore be avoided.[29,43,44] Some controversy exists about the influence of bases on Matsuda-Heck reactions. Matsuda and coworkers routinely used NaOAc in their pioneering studies,[45] but later investigations revealed that addition of this base has no or even negative effects on the rate of the reaction and on the yield.[29] However, in our previous studies we found examples for both beneficial and detrimental effects of adding NaOAc, depending on the arene diazonium salt,

the olefin and the solvent used.[46] Routinely tested solvents in Matsuda-Heck reactions are acetonitrile, which is known to stabilize the catalytically active species through coordination,[47] and methanol.[30]

Table 1. Optimization of Matsuda-Heck coupling conditions.



entry	solvent[a)]	NaOAc (equiv.)	T/° C	**5a** (equiv.)	Conversion[b)]	*exo*-**1aa** (yield)[c)]	*endo*-**7aa** (yield)[c)]
1	CH_3CN	--	20	1.0	incomplete	n. d.	n. d.
2	CH_3CN	4.0	20	1.0	incomplete	n. d.	n. d.
3	methanol	--	20	1.0	quantitative	72	26
4	methanol	4.0	20	1.0	traces	n. d.	n. d.
5	methanol	--	–23	1.0	quantitative	83	10
6	methanol	--	–23	1.2	quantitative	94	n. d.
7	methanol	--	20	1.2	quantitative	95	n. d.
8[d)]	methanol	--	20	0.33	quantitative	n. d.	65

[a)]Initial concentration of diazonium salt **6a**: 0.0625 M. [b)]Qualitatively determined by TLC. [c)]Isolated yields; n. d.: not determined. [d)]Initial concentration of diazonium salt **6a**: 0.0938 M; reaction time 18 h.

In acetonitrile the formation of a Matsuda-Heck coupling product was observed both under basic and under base-free conditions, but the conversion remained incomplete (entries 1, 2). In

methanol the addition of NaOAc resulted in a nearly complete inhibition of the coupling reaction (entry 4), whereas the arene diazonium salt was rapidly and quantitatively consumed under base-free conditions (entry 3). From this reaction mixture two coupling products *exo*-**1aa** and *endo*-**7aa** could be isolated in 72% and 26% yield.

Compound *exo*-**1aa** was identified by comparison of its NMR-data with those reported in the literature[21] and additionally the assigned structure was corroborated by 2D-NOE spectroscopy. A strong NOE between the *ortho*-H of the 4-methoxyphenyl substituent and the CH_2 group supports the assigned *exo*-*E*-structure. Compound *endo*-**7aa** has not been described in the literature but could easily be distinguished from the alternative *exo*-isomer, because only one set of signals with double intensity was observed for all protons and carbons of the 4-methoxyphenyl substituent, and two singlets for the methine proton and the proton at position 4 of the heterocycle were observed.

In an attempt to suppress the formation of the double Matsuda-Heck product *endo*-**7aa** the reaction temperature was lowered to –23 °C. The selectivity towards *exo*-**1aa** was indeed notably improved, but we could still isolate 10% of *endo*-**7aa** (entry 5). In the next step, we increased the amount of itaconimide **5a** to 1.2 equivalents while keeping the reaction temperature at –23 °C. Compound *exo*-**1aa** was isolated in 94% yield, without the formation of any double arylation product (entry 6). Virtually the same result was obtained at ambient temperature under otherwise identical conditions (entry 7). In all cases the reaction was complete within 30 minutes. We noted that, in contrast to the starting materials **5a** and **6a**, the Matsuda-Heck product *exo*-**1aa** is only sparingly soluble in methanol at the chosen initial substrate concentration of 0.0625 mol•L^{-1}. This allowed us to readily isolate the product by filtration. Additional purification by chromatography is normally not required.

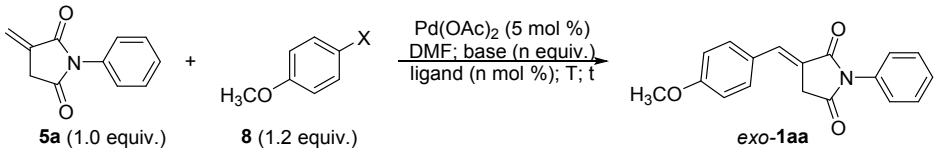
The double Matsuda-Heck product *endo*-**7aa** was selectively synthesized in 65% yield by using three equivalents of the arene diazonium salt **6a** in methanol at a higher initial concentration of

0.0938 M and a reaction time of 18 h. Under these conditions we could not detect any mono aryl product *exo*-**1aa** (entry 8).

Although arene diazonium salts are generally considered to be more reactive electrophilic coupling partners in Pd-catalyzed reactions, systematic comparative investigations to prove this superior reactivity are rare. For these reasons we investigated Mizoroki-Heck reactions of itaconimide **5a** with 4-methoxybenzenes bearing iodide (**8a**), triflate (**8b**) or bromide (**8c**) as leaving groups (**Table 2**). Optimal reaction conditions for the coupling of these reagents with electron deficient alkenes are known to differ significantly from the preferred conditions for arene diazonium salts, as can be seen from a recent comprehensive literature survey.[48] For these reasons we did not include the optimized conditions for the Matsuda-Heck coupling of **5a** and **6a** (Table 1, entry 7) in this comparative investigation, but chose previously established reaction conditions for the coupling of acyclic electron deficient alkenes[48] and *exo*-methylene γ-lactones[49] with aryl halides and triflates as general guidance. Such conditions normally involve the use of DMF as a solvent at elevated reaction temperatures, reaction times of several hours, triethylamine as a base, an excess of the electrophilic coupling partner and very often activating phosphine ligands. In a first experiment 4-methoxyiodobenzene (**8a**) was reacted with itaconimide **5a** in DMF at 90 °C, using $Pd(OAc)_2$ as a precatalyst without addition of an activating phosphine ligand (entry 1). Although **8a** was used in excess (1.2 equivalents) we did not observe the formation of any double arylation product, but isolated *exo*-**1aa** in 60% yield as the only product. Monitoring the reaction by TLC revealed that long reaction times are indeed required to achieve a synthetically useful conversion. By addition of tri-*o*-tolylphosphine as a ligand under otherwise identical conditions the yield of *exo*-**1aa** could be increased to 70%, but we still did not detect any double arylation product (entry 2). In a third experiment we could show that elevated reaction temperatures are necessary, because at ambient temperature no conversion was observed and both starting materials were recovered unchanged (entry 3). Applying the conditions of entry 2 to the triflate **8b** resulted in a very low yield of 26% (entry

4). For the bromide **8c** sodium acetate-trihydrate was tested as an alternative base (entry 5). In this case an even higher temperature of 140 °C was necessary, but the reaction was still very slow compared to the analogous diazonium salt.

Table 2. Comparative investigation of alternative coupling partners **8**.



entry	**8**	X	Ligand (mol %)	Base (equiv.)	T (° C)	t (h)	Yield of *exo*-**1aa** (%)
1	**8a**	I	--	NEt_3 (3.0)	90	18	60
2	**8a**	I	P(*o*-tolyl)$_3$ (10)	NEt_3 (3.0)	90	18	70
3	**8a**	I	P(*o*-tolyl)$_3$ (10)	NEt_3 (3.0)	20	18	--[a)]
4	**8b**	OTf	P(*o*-tolyl)$_3$ (10)	NEt_3 (3.0)	90	18	26
5	**8c**	Br	P(*o*-tolyl)$_3$ (10)	NaOAc•3H_2O (1.0)	140	1	21

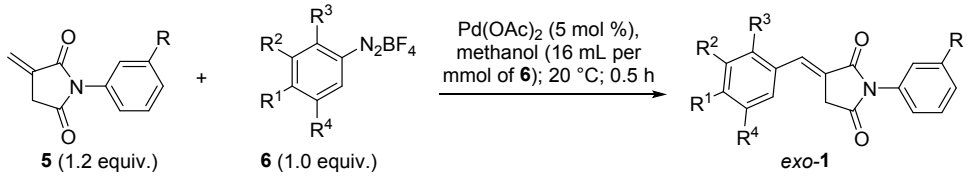
[a)]No conversion.

In summary, these experiments clearly prove that arene diazonium salts are significantly more reactive in this coupling reaction than aryl iodides, and that aryl triflates and bromides can not be used to synthesize *exo*-arylmethylidene-2,5-diones in preparatively useful yields.

Scope of Matsuda-Heck coupling reactions with itaconimides. The optimized conditions for Matsuda-Heck reactions of *N*-phenylitaconimide (**5a**) (**Table 1**, entry 7) were in the next step applied to the coupling of **5a** with various arene diazonium salts **6b-t** (**Table 3**, entries 2 – 20). From these examples only the coupling reaction with 2-nitrobenzene diazonium salt **6q** fails completely and results in the formation of a complex mixture of products (entry 17). Notably, with 2-bromobenzene diazonium salt **6p** the coupling product *exo*-**1ap** was obtained in 72%

yield in which the bromine atom is unscathed. All other arene diazonium salts **6** tested in this transformation reacted to the expected 3-arylmethylidene-2,5-pyrrolidinediones *exo*-**1** in very good to excellent yields and perfect regio- and stereoselectivities. These examples also include the vasorelaxant agent *exo*-**1ae**[5] (entry 5). For the synthesis of the T2-5α-reductase inhibitors *exo*-**1bu** and *exo*-**1bv**[1] (**Figure 1**) *N*-(3-hydroxyphenyl)itaconimide (**5b**) was coupled with diazonium salts **6u** (entry 21) and **6v** (entry 22), respectively, under the same optimized conditions.

Table 3. Scope of Matsuda-Heck reactions with itaconimides **5a**,**b**.



entry	**5**	R	**6**	R^1	R^2	R^3	R^4	*exo*-**1**	Yield (%)
1	**5a**	H	**6a**	OCH_3	H	H	H	*exo*-**1aa**	95
2	**5a**	H	**6b**	OBn	H	H	H	*exo*-**1ab**	81
3	**5a**	H	**6c**	OH	H	H	H	*exo*-**1ac**	92
4	**5a**	H	**6d**	F	H	H	H	*exo*-**1ad**	91
5	**5a**	H	**6e**	Cl	H	H	H	*exo*-**1ae**	91
6	**5a**	H	**6f**	Br	H	H	H	*exo*-**1af**	93
7	**5a**	H	**6g**	CN	H	H	H	*exo*-**1ag**	86
8	**5a**	H	**6h**	$C(O)CH_3$	H	H	H	*exo*-**1ah**	94
9	**5a**	H	**6i**	NHAc	H	H	H	*exo*-**1ai**	90
10	**5a**	H	**6j**	NO_2	H	H	H	*exo*-**1aj**	89
11	**5a**	H	**6k**	H	H	H	H	*exo*-**1ak**	88
12	**5a**	H	**6l**	H	CH_3	H	H	*exo*-**1al**	quant.
13	**5a**	H	**6m**	H	CN	H	H	*exo*-**1am**	89

14	**5a**	H	**6n**	H	H	OCH_3	H	*exo*-**1an**	87
15	**5a**	H	**6o**	H	H	F	H	*exo*-**1ao**	99
16	**5a**	H	**6p**	H	H	Br	H	*exo*-**1ap**	72
17	**5a**	H	**6q**	H	H	NO_2	H	*exo*-**1aq**	--[a)]
18	**5a**	H	**6r**	OH	Br	H	H	*exo*-**1ar**	95
19	**5a**	H	**6s**	OH	CO_2CH_3	H	H	*exo*-**1as**	93
20	**5a**	H	**6t**	OCH_3	OCH_3	H	OCH_3	*exo*-**1at**	90
21	**5b**	OH	**6u**	H	NO_2	H	H	*exo*-**1bu**	79
22	**5b**	OH	**6v**	Cl	H	Cl	H	*exo*-**1bv**	96

[a)]complex mixture of products.

Iterative Matsuda-Heck coupling. In the course of our investigation into the optimization of the Matsuda-Heck coupling (**Table 1**, entry 3) we noted that a considerable amount of the *β,β*-diarylation product *endo*-**7aa** is obtained if itaconimide **5a** and diazonium salt **6a** are used in an equimolar ratio. This product can even be synthesized selectively at ambient temperature by using three equivalents of the arene diazonium salt and prolonged reaction times (**Table 1**, entry 8). These results are remarkable, because *β,β*-diarylation reactions of electron deficient olefins are by no means facile processes. This is for instance underlined by our observation that during the analogous Mizoroki-Heck couplings (**Table 2**) no *β,β*-diarylation products were detected, although the aryl halides were used in excess and the reactions were conducted at elevated temperatures over long reaction times. A survey of pertinent literature confirms that Heck-type *β,β*-diarylation reactions of terminal alkenes or arylation reactions of *α,β*-disubstituted alkenes such as cinnamic acid derivatives indeed require much more forcing conditions (elevated temperatures, long reactions times, elaborate bases and ligands) than the monoarylation of electron deficient terminal alkenes.[50-56] Analogous Matsuda-Heck couplings have scarcely been

reported in the literature: Konno et al.[57] and Cacchi et al.[58] described successful Matsuda-Heck reactions of electron deficient acyclic olefins with aliphatic substituents in the β-position, and Taylor and Correia reported the stereoselective β-arylation of cinnamates.[59] Very recently, Lucks and Brunner found that a heterogeneous catalyst system of Pd immobilized on $AlPO_4$ is particularly reactive in the β,β-diarylation of acrylates and a few other electron deficient alkenes.[35] In all these examples modifications of the standard reaction conditions for Matsuda-Heck couplings of electron deficient olefins were required, such as elevated reaction temperatures[35,57,58] or the use of less common methanol-acetonitrile solvent mixtures in combination with a base.[59] In light of this literature precedence we thought that the facile formation of the double arylation product *endo*-**7aa** at ambient temperature deserves further attention and investigated the scope of a repetitive Matsuda-Heck coupling, starting from various 3-arylmethylidene pyrrolidine-2,5-diones *exo*-**1** and arene diazonium salts **6**. A potential obstacle for the development of a repetitive coupling reaction was observed during the optimization study of the first arylation step and the investigation into the scope of the Matsuda-Heck reaction with *N*-arylitaconimides. The products *exo*-**1** are, in contrast to the *N*-arylitaconimides **5** and the arene diazonium salts **6**, in general sparingly soluble in methanol at the concentrations routinely used for the coupling step and precipitate from the solution. While this facilitates the purification of the coupling products, as outlined above, it might impede a second arylation. For these reasons we started this part of the investigation with solubility tests, in order to identify a solvent that would allow us to conduct the second coupling under homogeneous reaction conditions. To this end, the envisaged starting material *exo*-**1aa** (15 mg, corresponding to 5.7 μmol) was mixed with 0.5 mL of various solvents at ambient temperature, which would result in a concentration of ca. 0.11 mol•L^{-1} if the starting material dissolves completely. Among the solvents tested this is only the case for hexafluoroisopropanol (HFIP) and 1,4-dioxane, whereas in methanol, ethanol, 2-propanol, 1-butanol, acetonitrile, ethyl acetate and THF substantial amounts of *exo*-**1aa** remain undissolved. Repeating the solubility tests with

1.0 mL of these solvents (corresponding to an initial starting material concentration of 0.057 mol•L^{-1}), THF also produced a homogeneous solution. The three solvents HFIP, 1,4-dioxane and THF were then tested in the Matsuda-Heck coupling of **5a** and **6a** under basic as well as base-free conditions (**Table 4**).

Table 4. Screening of alternative solvents for the Matsuda-Heck coupling of **5a** and **6a**.[a)]

entry	Solvent[b)]	NaOAc (equiv.)	Result[c)]
1	$(CF_3)_2CHOH$	--	trace amounts of *exo*-**1aa**
2	$(CF_3)_2CHOH$	4.0	trace amounts of *exo*-**1aa**
3	1,4-dioxane	--	incomplete conversion to *exo*-**1aa**
4	1,4-dioxane	4.0	incomplete conversion to *exo*-**1aa**
5	THF	--	incomplete conversion to *exo*-**1aa**
6	THF	4.0	trace amounts of *exo*-**1aa**

[a)]Itaconimide **5a** used in excess (1.2 equiv.). [b)]Initial substrate concentration 0.0625 M. [c)]Qualitative assessment; reactions monitored by TLC.

In HFIP (entries 1, 2) only trace amounts of the Matsuda-Heck product *exo*-**1aa** were detected by TLC in the presence and in the absence of NaOAc. In 1,4-dioxane (entries 3, 4) notable conversion to the product was observed under basic as well as base-free conditions, but considerable amounts of unreacted starting material **5a** were also detected. The same result was obtained with THF in the absence of NaOAc (entry 5), whereas in the presence of the base only trace amounts of the product were detected on TLC (entry 6). For these reasons we returned to methanol as a solvent for the second Matsuda-Heck reaction, but used a lower initial substrate concentration than for the Matsuda-Heck arylation of itaconimides **5**.

The reaction of *exo*-**1aa** with arene diazonium salt **6a** furnished under these standard conditions the diaryl product *endo*-**7aa** in 86% yield (**Table 5**, entry 1). Hence, the overall yield for this two-step synthesis of *endo*-**7aa** from *N*-phenyl itaconimide **5a** is 81%. This is substantially higher than the 65% yield obtained for the one-pot double arylation of **5a** with **6a** (**Table 1**,

entry 8). Compound *exo*-**1aa** was coupled in a comparable yield of 83% with the *p*-chloro substituted arene diazonium salt **6e** to the diarylated product *endo*-**7ae** (entry 2). Interestingly, the reaction of the *p*-chlorobenzylidene succinimide *exo*-**1ae** with the *p*-methoxy substituted arene diazonium salt **6a**, which would give the same product *endo*-**7ae**, fails completely (entry 3). The unsubstituted benzylidene succinimide *exo*-**1ak**, however, reacts with the same diazonium salt **6a** to the product *endo*-**7ka** in a somewhat lower, but still synthetically useful yield (entry 4). The highest yields were obtained for the trimethoxybenzylidene substituted succinimide *exo*-**1at** and diazonium salts **6a** and **6e**, which react to the products *endo*-**7ta** and *endo*-**7te**, respectively, in nearly quantitative yields (entries 5, 6). These observations suggest that more electron rich arylmethylidene units facilitate the second Matsuda-Heck arylation, a conclusion that has previously been drawn by Taylor and Correia in the course of their investigation into Matsuda-Heck couplings of cinnamates.[59] We then investigated Matsuda-Heck couplings of the trimethoxybenzylidene succinimide *exo*-**1at** with several other arene diazonium salts **6** (entries 7 – 12). The reaction fails only for the *p*-acetyl substituted arene diazonium salt **6h** (entry 8), whereas all other diazonium salts tested undergo a coupling with *exo*-**1at**, albeit in yields lower than those obtained with the diazonium salts **6a** and **6e**. With the *m*-nitro substituted arene diazonium salt **6u** conversion remains incomplete and unidentified side products are formed. Purification of the coupling product *endo*-**7tu** is difficult due to very similar polarities and could only be achieved with significant loss of yield (entry 10). An interesting exception in this series is the reaction of *exo*-**1at** and the *p*-nitro substituted arene diazonium salt **6j** (entry 9 and **Figure 2**). For this combination quantitative conversion was observed, but the reaction was rather sluggish and gave the *exo*-coupling products *E*- and *Z*-*exo*-**7tj** in a ratio of 4 : 1 as an inseparable mixture, which was contaminated with several unidentified byproducts. Assignment of the *E*-configuration to the major isomer is based on 2D-NOE-spectroscopy.

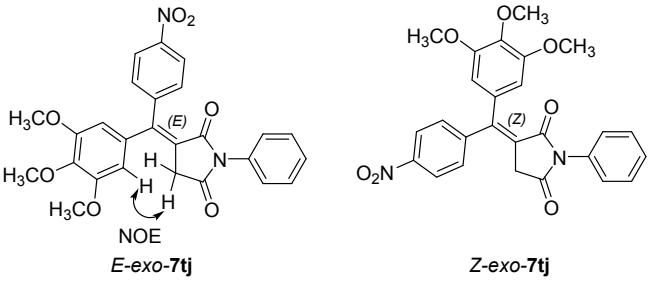
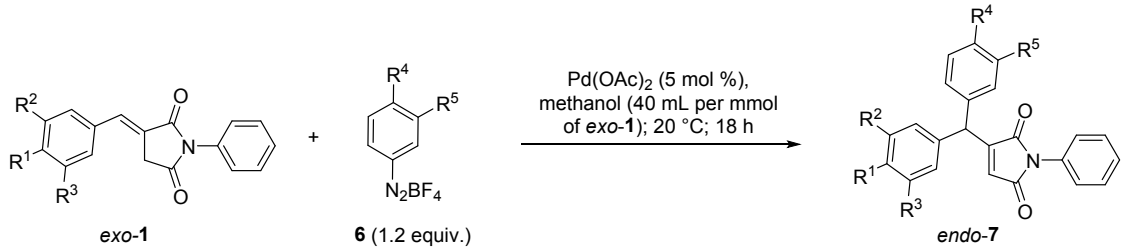


Figure 2. Structures of *E*- and *Z-exo*-**7tj** and indicative NOE-interaction.

Table 5. Scope of iterative Matsuda-Heck coupling.

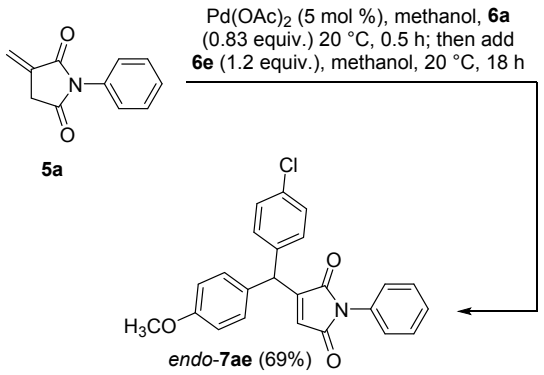


entry	*exo*-**1**	R^1	R^2	R^3	**6**	R^4	R^5	*endo*-**7**	Yield (%)
1	*exo*-**1aa**	OCH_3	H	H	**6a**	OCH_3	H	*endo*-**7aa**	86
2	*exo*-**1aa**	OCH_3	H	H	**6e**	Cl	H	*endo*-**7ae**	83
3	*exo*-**1ae**	Cl	H	H	**6a**	OCH_3	H	*endo*-**7ea**	--[a,b]
4	*exo*-**1ak**	H	H	H	**6a**	OCH_3	H	*endo*-**7ka**	74
5	*exo*-**1at**	OCH_3	OCH_3	OCH_3	**6a**	OCH_3	H	*endo*-**7ta**	96
6	*exo*-**1at**	OCH_3	OCH_3	OCH_3	**6e**	Cl	H	*endo*-**7te**	95
7	*exo*-**1at**	OCH_3	OCH_3	OCH_3	**6f**	Br	H	*endo*-**7tf**	42
8	*exo*-**1at**	OCH_3	OCH_3	OCH_3	**6h**	$C(O)CH_3$	H	*endo*-**7th**	--[a]
9	*exo*-**1at**	OCH_3	OCH_3	OCH_3	**6j**	NO_2	H	*exo*-**7tj**	96[c]
10	*exo*-**1at**	OCH_3	OCH_3	OCH_3	**6u**	H	NO_2	*endo*-**7tu**	10[d]
11	*exo*-**1at**	OCH_3	OCH_3	OCH_3	**6r**	OH	Br	*endo*-**7tr**	59
12	*exo*-**1at**	OCH_3	OCH_3	OCH_3	**6s**	OH	CO_2CH_3	*endo*-**7ts**	27

[a]No conversion. [b]*endo*-**7ea** and *endo*-**7ae** are identical. [c]Product *exo*-**7tj** was obtained as a mixture of *E*- and *Z*-isomers (*E* : *Z* = 4 : 1, determined by ^{1}H NMR spectroscopy) and minor amounts of unidentified byproducts. [d]Low yield is caused by loss of material during purification.

To conclude this part of the study we investigated the possibility of performing sequential Matsuda-Heck arylations in a one-flask reaction. To this end *N*-phenyl itaconimide (**5a**) was first reacted with diazonium salt **6a** using the optimized conditions for a monoarylation. The reaction mixture was then diluted by addition of methanol, and the second arene diazonium salt **6e** was added. Pleasingly, the double arylation product *endo*-**7ae** was isolated in 69% yield (**Scheme 4**).

Scheme 4. Repetitive one-flask Matsuda-Heck arylation of itaconimide **5a**.

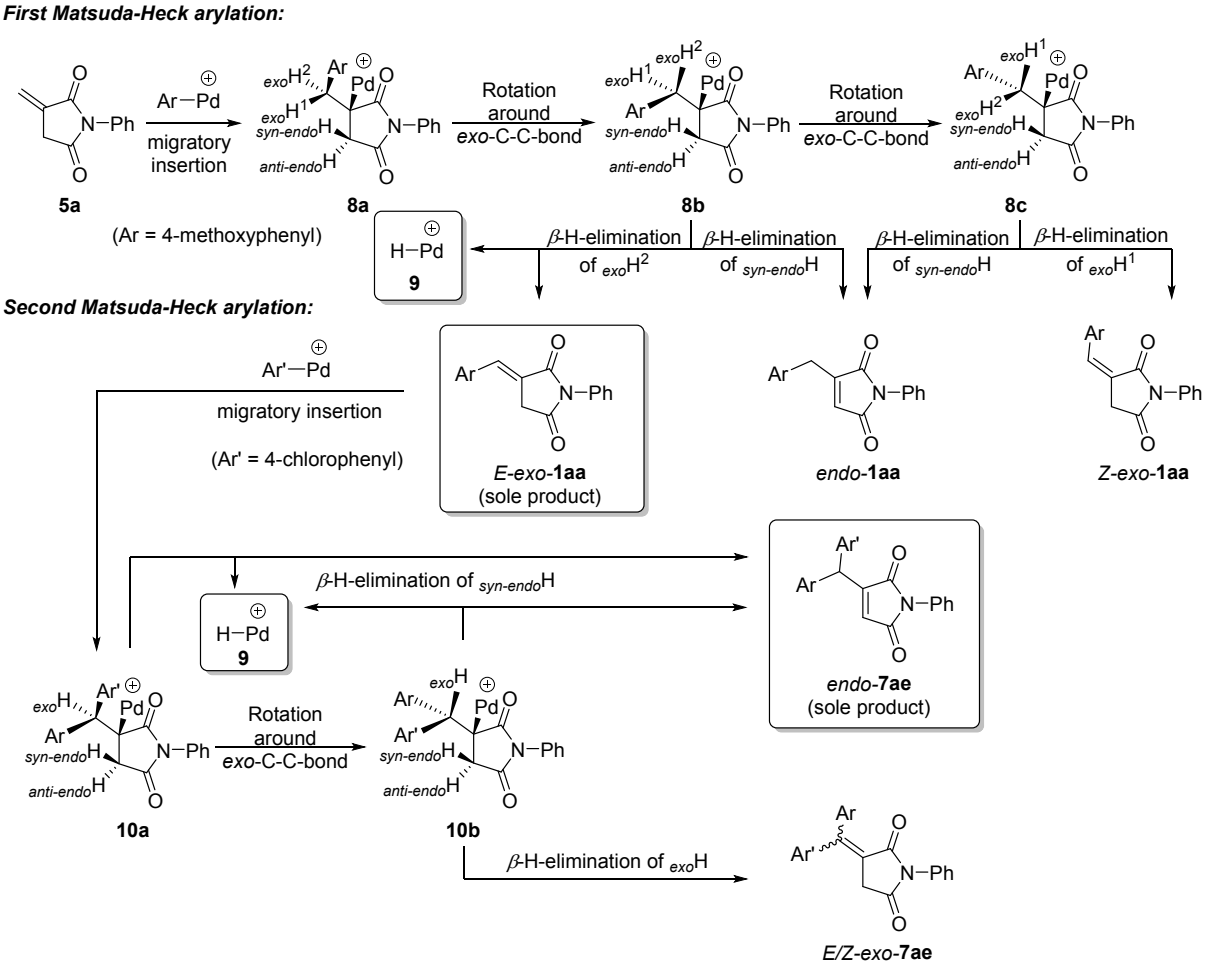


A comment on regioselectivity of the iterative Matsuda-Heck arylations. We are currently unable to provide conclusive explanations for the different regioselectivities of the iterative arylation steps. Mechanistic scenarios must take into account that the regioselectivity of Heck-type reactions may arise from kinetic or thermodynamic control. Thermodynamic control requires a sufficiently stable Pd-hydride from the β-H-elimination step, which catalyzes a subsequent double bond migration through a hydropalladation/β-H-elimination cycle ("chain walking" mechanism)[60-62] or through a 1,2-dyotropic shift followed by a β-H-elimination.[63] This scenario is sometimes referred to as "post-Mizoroki-Heck double-bond migration"[64] and it can be provoked by adding stabilizing ligands, e. g. chloride, to the reaction mixture (Jeffery-conditions).[62] In the case of Matsuda-Heck reactions cationic Pd-species are proposed as intermediates, unless strongly coordinating anionic bases or counterions are present.[47] The cationic Pd-hydrides resulting from the β-H-elimination step are destabilized by the positive

charge, and consequently virtually no subsequent double bond migration occurs, as shown by Correia and co-workers for the Matsuda-Heck reaction of 2,3-dihydrofuran.[47] Although this does exclude the possibility of post-Matsuda-Heck isomerizations completely, they are rather unlikely. Under kinetic control the regioselectivity of Heck-type reactions is determined during the β-H-elimination step[65] and can be biased by electronic effects in the substrate,[66] through catalyst control[36,67] or by conformational constraints.[26] To proceed efficiently, these eliminations normally require a H^{β}-C-C-Pd dihedral angle close to 0° (*syn*-β-hydride elimination) and a vacant coordination site at the transition metal,[68,69] because *syn*-β-hydride eliminations are initiated by an agostic interaction between the β-C-H bond and the metal.[70] For the example of the iterative Matsuda-Heck arylation of *N*-phenylitaconimide **5a** and diazonium salts **6a** in the first and **6e** in the second step the following mechanistic scenario unfolds (**Scheme 5**): the first Matsuda-Heck arylation starts with a carbopalladation (migratory insertion) of the C-C-double bond of **5a** to give initially the Pd-σ-complex **8a**, which can then undergo rotation around the *exo*-C-C-bond to access two *syn*-conformations suitable for *exo*-β-H-elimination. The experimentally observed product *E*-*exo*-**1aa** would result from conformer **8b**, whereas formation of *Z*-*exo*-**1aa** would require a β-H-elimination from conformer **8c**. If the dihedral angle between Pd and the *syn*-*endo*-H is sufficiently small, β-H-elimination could also lead to the maleimide *endo*-**1aa**. The second Matsuda-Heck reaction starts with a carbopalladation of the *exo*-double bond of *E*-*exo*-**1aa** to furnish the Pd-σ-complex **10a**. Clockwise or counterclockwise rotation around the *exo*-C-C-bond is now required to bring the *exo*-H and Pd into a *syn*-orientation (conformer **10b**), from which β-H-elimination may occur to yield *E*- and *Z*-*exo*-**7ae**. In contrast, formation of the experimentally exclusively observed product *endo*-**7ae** must proceed through β-elimination of the *syn*-*endo*-H, unless it is formed via a post-Matsuda-Heck double bond migration as outlined above.[71] In future investigations we plan a complete analysis of the catalytic cycle, with a focus on the different β-H-elimination

pathways, based on DFT-calculations. DFT-methods have previously been used to gain a deeper insight into the mechanism of Matsuda-Heck reactions, e. g. with a view towards rationalizing *E*/*Z*-selectivity,[72] understanding the role of catalyst stabilizing additives,[73] or the origin of enantiocontrol in asymmetric Matsuda-Heck reactions.[74,75]

Scheme 5. Formation of regio- and stereoisomeric Matsuda-Heck-products.



Investigation into the photochemically induced *E*/*Z*-isomerization of 3-arylmethylidene succinimides *exo*-1. The photochemically triggered *E*/*Z*-isomerization of double bonds is one of the most important functional principles of molecular switches.[76] Because biological and biochemical studies are the main area of application of these switches, a long-wave excitation (ideally in the visible range) is desirable. Besides azobenzenes[77] highly substituted olefins are potential candidates for photoswitches. In this context we were interested to find out whether

compounds *exo*-**1** could also be suitable as photoswitches. First we qualitatively investigated the photophysical and photochemical behaviour of the five derivatives *exo*-**1ac**, *exo*-**1an**, *exo*-**1ar**, *exo*-**1as** and *exo*-**1at**. All of these compounds exhibit a broad absorption band between 300 and 350 nm in the UV spectrum (**Table 6**).

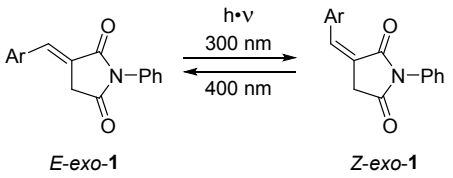
Table 6. UV-Absorption maxima of compounds **1** in acetonitrile

entry	*exo*-**1**	λ_{max} [nm][a)]	lg ε [b)]	λ_{PSS} [nm][c)]
1	*exo*-**1ac**	320	4.499	324
2	*exo*-**1an**	330	4.045	328
3	*exo*-**1ar**	315	4.396	321
4	*exo*-**1as**	307	4.496	309
5	*exo*-**1at**	319	4.366	323

[a)]Before excitation. [b)]ε in L•mol^{-1}•cm^{-1}. [c)]After excitation (PSS)

When irradiated with relatively intensive UV light (500 W Hg arc lamp, edge filter > 295 nm, acetonitrile) they underwent a non-specific decomposition. If, on the other hand, these compounds were exposed to narrow-band UV-B light (interference filter 300 nm / edge filter > 295 nm) a partial $E \rightarrow Z$-isomerisation was observed. This is indicated by a small bathochromic shift (4-6 nm) of the absorption maximum (except *exo*-**1an**) and very weakly increased absorption above 400 nm in the UV spectra. Furthermore, the occurrence of some isosbestic points in the irradiation spectra proves a selective A $\rightarrow$ B-reaction.[78] The absorption maxima in the photostationary state (λ_{PSS}) are summarized in table 6. These spectral changes are completely reversible upon irradiation with narrow-band blue light (interference filter 400 nm / edge filter > 295 nm) suggesting a reversible *E*/*Z*-isomerisation (**Scheme 6**).

Scheme 6. *E*/*Z*-Isomerization of *exo*-**1**.



To prove this assumption we examined the example *exo*-**1at** in more detail. For this purpose we investigated the irradiation by NMR spectroscopy in CD_2Cl_2 (c = 5.3 mM, λ_{IRR} = 300 nm). After several hours the photostationary state is reached with 65% of *E*- and 35% of *Z*-isomer. Irradiation of the same sample with blue light (λ_{IRR} = 400 nm) caused nearly complete reverse reaction (*E*/*Z*-ratio = 95 : 5). It should be noted that the *E*- and *Z*-isomers of *exo*-**1at** could also be separated by HPLC confirming the ratio determined by NMR (see supporting information for details). Furthermore, we found that the thermal reverse reaction is very slow at ambient temperature. In summary, compounds *exo*-**1** undergo a reversible photochemical *E*/*Z*-isomerization. However, the $E \rightarrow Z$-isomerisation is not complete. Nevertheless, these findings are promising and efficient photoswitches could be accessible by structural variation, e. g. by introducing bulky substituents on the aromatic rings.

Conclusions

In summary, we found that itaconimides undergo rapid Pd-catalyzed Heck-type arylation reactions with arene diazonium salts to furnish arylmethylidene succinimides with high *E*-selectivity. In a comparative investigation we could demonstrate that diazonium salts are indeed much more reactive than the analogous aryl iodides or triflates, and that a second arylation can be achieved only with diazonium salts. Interestingly, the two arylation reactions proceed with different regioselectivities, which we attribute to diverging *exo*- and *endo*-β-hydride elimination pathways. We could demonstrate that the C-C double bond in *exo*-arylmethylidene

succinimides *exo*-**1** is in principle photoswitchable, but that the *E*/*Z*-isomerization remains incomplete.

Experimental Section

General methods. All experiments were conducted in dry reaction vessels under an atmosphere of dry nitrogen. Solvents were purified by standard procedures. ^{1}H NMR spectra were obtained at 300 MHz, 400 MHz, 500 MHz or 600 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, 125 MHz or 150 MHz in $CDCl_3$ with $CDCl_3$ (δ = 77.1 ppm) as an internal standard. Whenever the solubility or stability of the sample or signal separation were insufficient in $CDCl_3$, it was replaced by one of the following solvents: acetone-d_6 (acetone-d_5 as internal standard for ^{1}H NMR spectroscopy, δ = 2.05 ppm, *C*D_3COCD_3 as internal standard for ^{13}C NMR spectroscopy, δ = 29.8 ppm); 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). ^{19}F NMR spectra were recorded at 376 MHz with trifluoroacetic acid (0.1 M in DMSO-d_6) as external standard. 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 (ν) are given in 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. 4-Methoxyphenyltriflate (**8b**) was synthesized following a literature procedure[79] and its analytical data match those previously described.[80] These arene diazonium salts were synthesized following previously published procedures: **6a-b**,[81] **6c**,[46] **6d**,[82] **6e**,[83] **6f**,[84] **6g**,[83] **6h**,[85] **6i**,[86] **6j**,[84] **6k-l**,[87] **6m-n**,[88] **6o**,[85] **6p-q**,[88] **6r-6s**,[46] **6t**,[89] **6u**.[88] Diazonium salt **6v** has been mentioned in the literature,[90] but no synthetic procedure and characterization data were provided.

***N*-Phenylitaconimide (5a)**. *Synthesized by analogy to a literature procedure*:[9] Maleimide **3a** (8.6 g, 50 mmol) was dissolved in glacial acetic acid (40 mL) and PPh_3 (13.1 g, 50 mmol) and paraformaldehyde (7.5 g, 250 mmol) were added. The reaction mixture was heated to reflux for one hour. After cooling to ambient temperature, water (100 mL) was added and the aqueous phase was extracted three times with ethyl acetate (100 mL each). The combined organic phases were washed with brine (100 mL) and dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica, using hexanes/ethyl acetate mixtures of increasing polarity as eluent, to furnish **5a** (5.2 g, 28 mmol, 56%): colourless solid, mp 117 - 120 °C (reported in the literature:[91] mp 118 – 120 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (dd, J = 7.4, 7.4 Hz, 2H), 7.46 - 7.40 (m, 1H), 7.34 (d, J = 7.8 Hz, 2H), 6.47 (d, J = 1.7 Hz, 1H), 5.74 (d, J = 1.5 Hz, 1H), 3.54 - 3.51 (s, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 172.9, 168.6, 133.1, 132.0, 129.3, 128.8, 126.5, 121.9, 34.1; IR (ATR) ν 1702 (s), 1662 (m), 1496 (m), 1385 (s), 1142 (s); HRMS (EI) calcd for $C_{11}H_9NO_2$ [M^+] 187.0633, found 187.0626.

***N*-(3-Hydroxyphenyl)maleimide (3b)**. *Synthesized by analogy to a literature procedure*:[92] Maleic anhydride (**8**) (392 mg, 4.0 mmol) and 3-aminophenol (**9**) (470 mg, 4.3 mmol) were dissolved in glacial acetic acid (25 mL) and stirred at reflux temperature until the reaction was completed (ca. 5 h). After cooling to ambient temperature water (50 mL) and ethyl acetate (100 mL) were added to the reaction mixture and the layers were separated. The organic phase was washed with saturated sodium bicarbonate solution (3 times 30 mL), dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica, using hexanes/ethyl acetate mixtures of increasing polarity as eluent to furnish **3b** (688 mg, 3.6 mmol, 91%): yellowish solid, mp 135 °C (reported in the literature:[42] mp 134 – 135 °C); ^{1}H NMR (300 MHz, acetone-d_6) δ 8.58 (s, 1H), 7.32 – 7.16 (m, 1H), 7.02 – 6.94 (s, 2H), 6.90 –6.74 (m, 3H); ^{13}C{^{1}H} NMR (75 MHz, acetone-d_6) δ 170.4, 158.5, 135.2,

134.0, 130.3, 118.4, 115.5, 114.5; IR (ATR) ν 3321 (w), 1693 (s), 1598 (m), 1150 (m), 825 (s); HRMS (EI) calcd for $C_{10}H_7NO_3$ [M^+] 189.0426, found 189.0422.

***N*-(3-Hydroxyphenyl)itaconimide (5b)**. Following the procedure for **5a**, maleimide **3b** (567 mg, 3.0 mmol) was converted to **5b** (438 mg, 2.2 mmol, 72%): colourless solid, mp: 168 - 169 °C (reported in the literature:[93] mp 111 – 112 °C); ^{1}H NMR (300 MHz, acetone-d_6) δ 8.57 (s, 1H), 7.28 (ddd, J = 8.9, 4.8, 1.4 Hz, 1H), 6.93 –6.78 (m, 3H), 6.26 (td, J = 2.5, 0.4 Hz, 1H), 5.73 (td, J = 2.1, 0.4 Hz, 1H), 3.52 (t, J = 2.3 Hz, 2H); ^{13}C{^{1}H} NMR (75 MHz, acetone-d_6) δ 173.5, 169.2, 158.5, 135.8, 134.9, 130.2, 120.0, 118.9, 116.0, 115.0, 34.6; IR (ATR) ν 3285 (bw), 1694 (s), 1665 (m), 1226 (s), 1139 (s); HRMS (EI) calcd for $C_{11}H_{10}NO_3$ [M+H]$^+$ 204.0661, found 204.0672.

2,4-Dichlorophenyldiazoniumtetrafluoroborate (6v). A solution of 2,4-dichloroaniline (972 mg, 6.00 mmol) in aq. HBF_4 (48 wt-%, 2.00 mL, 7.80 mmol) and water (2.00 mL) was cooled to 0 °C. A solution of $NaNO_2$ (414 mg, 6.00 mmol) in water (1.00 mL) was added dropwise and the reaction mixture was stirred for 0.5 h at 0 °C. The resulting precipitate was filtered off, dissolved in acetone (3 mL) and re-precipitated by addition of diethyl ether (150 mL). Filtration and drying in vacuo furnished **6v** (66 %, 1.030 g, 4.00 mmol): colourless solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 (d, J = 9.0 Hz, 1H), 8.54 (d, J = 1.5 Hz, 1H), 8.10 (dd, J = 8.9, 1.5 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 147.6, 136.8, 135.5, 132.4, 130.7, 115.5; IR (ATR) ν 3095 (m), 2287 (w), 1739 (s), 1367 (m), 1055 (s); HRMS (ESI) calcd for $C_6H_3{}^{35}Cl_2N_2$ [$M]^+$ 172.9668, found: 172.9669.

General procedure for the Matsuda-Heck reaction of *N*-arylitaconimides with arene diazonium salts. The appropriate *N*-arylitaconimide **5a** (56 mg, 0.30 mmol) or **5b** (61 mg, 0.30 mmol) was dissolved in methanol (4.0 mL). $Pd(OAc)_2$ (2.8 mg, 5 mol %) and the corresponding arene diazonium tetrafluoroborate **6** (0.25 mmol) were added and the mixture was stirred at ambient temperature for 0.5 h. The products precipitate from the mixture and were isolated by filtration of the reaction mixture through a short pad of celite, which was subsequently washed

with methanol (10 mL) to remove unreacted starting material **5**. The pad of celite is then flushed with ethyl acetate (10 mL) to dissolve the product. Evaporation of the ethyl acetate solution furnished the products *exo*-**1** without additional purification steps.

(*E*)-3-(4-Methoxybenzylidene)-1-phenylpyrrolidine-2,5-dione (*exo*-1aa). Following the general procedure, **6a** (56 mg, 0.25 mmol) and **5a** (56 mg, 0.30 mmol) were converted to *exo*-**1aa** (70 mg, 0.24 mmol, 95%): off-white solid, mp 149 – 151 °C (reported in the literature:[21] mp 175 – 177 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (t, J = 2.2 Hz, 1H), 7.52 – 7.45 (m, 4H), 7.43 – 7.32 (m, 3H), 6.99 (d, J = 8.8 Hz, 2H), 3.86 (s, 3H), 3.70 (d, J = 2.3 Hz, 2H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 173.3, 170.4, 161.4, 135.1, 132.3, 132.3, 129.2, 128.5, 127.0, 126.6, 120.4, 114.8, 55.6, 34.4; IR (ATR) ν 2923 (m), 1764 (m), 1699 (s), 1597 (m), 1373 (m); HRMS (EI) calcd for $C_{18}H_{15}NO_3$ [M^+] 293.1052, found 293.1048.

(*E*)-3-(4-(Benzyloxy)benzylidene)-1-phenylpyrrolidine-2,5-dione (*exo*-1ab). Following the general procedure, **6b** (75 mg, 0.25 mmol) and **5a** (56 mg, 0.30 mmol) were converted to *exo*-1ab (75 mg, 0.20 mmol, 81%): colourless solid, mp 190 - 191 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.67 (d, J = 8.9 Hz, 2H), 7.55 - 7.49 (m, 3H), 7.49 - 7.46 (m, 2H), 7.45 - 7.39 (m, 3H), 7.37 - 7.32 (m, 3H), 7.14 (dm, J = 8.9 Hz, 2H), 5.20 (s, 2H), 3.82 (d, J = 2.3 Hz, 2H); ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 173.6, 170.2, 159.7, 136.7, 132.7, 132.6, 132.3, 128.8, 128.5, 128.2, 128.0, 127.8, 127.2, 127.0, 122.4, 115.4, 69.4, 34.1; IR (ATR) ν 1772 (w), 1702 (s), 1598 (m), 1170 (s), 827 (m); HRMS (ESI) calcd for $C_{24}H_{20}NO_3$ [M+H]$^+$ 370.1443, found 370.1435.

(*E*)-3-(4-Hydroxybenzylidene)-1-phenylpyrrolidine-2,5-dione (*exo*-1ac). Following the general procedure, **6c** (52 mg, 0.25 mmol) and **5a** (56 mg, 0.30 mmol) were converted to *exo*-**1ac** (64 mg, 0.23 mmol, 92%): off-white solid, mp 270 °C (dec.); ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.13 (s, 1H), 7.55 (d, J = 8.7 Hz, 2H), 7.53 - 7.49 (m, 2H), 7.48 (t, J = 2.2 Hz, 1H), 7.42 (tt, J = 7.7, 1.3 Hz, 1H), 7.36 - 7.33 (m, 2H), 6.88 (dm, J = 8.7 Hz, 2H), 3.78 (d, J = 2.3 Hz, 2H); ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 173.6, 170.3, 159.4, 133.1, 132.8, 132.6, 128.8,

128.2, 127.2, 125.3, 121.1, 116.0, 34.1; IR (ATR) ν 3393 (w), 1769 (m), 1689 (s), 1596 (s), 1385 (s), 1158 (s); HRMS (ESI) calcd for $C_{17}H_{14}NO_3$ $[M+H]^+$ 280.0974, found 280.0971.

(*E*)-3-(4-Fluorobenzylidene)-1-phenylpyrrolidine-2,5-dione (*exo*-1ad). Following the general procedure, **6d** (52 mg, 0.25 mmol) and **5a** (56 mg, 0.30 mmol) were converted to *exo*-**1ad** (64 mg, 0.23 mmol, 91%): off-white solid, mp 194 - 197 °C (reported in the literature:[21] mp 232 – 233 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.57 - 7.48 (m, 4H), 7.45 - 7.36 (m, 3H), 7.18 (dd, J = 8.2, 8.2 Hz, 2H), 3.73 (s, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 172.9, 170.0, 163.7 (d, J = 253.2 Hz), 134.1, 132.3 (d, J = 8.6 Hz), 132.0, 130.4 (d, J = 3.3 Hz), 129.2, 128.7, 126.5, 122.7 (d, J = 2.3 Hz), 16.5 (d, J = 21.9 Hz), 34.1; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –108.3; IR (ATR) ν 1762 (w), 1702 (s), 1650 (m), 1598 (m), 1173 (s), 1160 (s); HRMS (ESI) calcd for $C_{17}H_{13}FNO_2$ $[M+H]^+$ 282.0900, found 282.0930.

(*E*)-3-(4-Chlorobenzylidene)-1-phenylpyrrolidine-2,5-dione (*exo*-1ae). Following the general procedure, **6e** (57 mg, 0.25 mmol) and **5a** (56 mg, 0.30 mmol) were converted to *exo*-**1ae** (67 mg, 0.23 mmol, 91%): colourless solid, mp 232 - 233 °C (reported in the literature:[5] mp 233 – 235 °C); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.74 (d, J = 8.6 Hz, 2H), 7.60 - 7.50 (m, 5H), 7.44 (t, J = 7.4 Hz, 1H), 7.38 - 7.33 (m, 2H), 3.86 (d, J = 2.3 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 173.4, 169.8, 134.5, 133.1, 132.6, 132.0, 131.3, 129.1, 128.9, 128.3, 127.1, 126.2, 34.1; IR (ATR) ν 1762 (w), 1701 (s), 1499 (m), 1173 (s), 825 (m); HRMS (ESI) calcd for $C_{17}H_{13}{}^{35}ClNO_2$ $[M+H]^+$ 298.0635, found 298.0645.

(*E*)-3-(4-Bromobenzylidene)-1-phenylpyrrolidine-2,5-dione (*exo*-1af). Following the general procedure, **6f** (68 mg, 0.25 mmol) and **5a** (56 mg, 0.30 mmol) were converted to *exo*-**1af** (79 mg, 0.23 mmol, 93%): off-white solid, mp 234 – 235 °C (reported in the literature:[21] mp 235 – 236 °C); ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.74 – 7.62 (m, 4H), 7.56 (t, J = 1.7 Hz, 1H), 7.52 (dd, J = 7.7, 7.7 Hz, 2H), 7.44 (t, J = 7.4 Hz, 1H), 7.36 (d, J = 7.6 Hz, 2H), 3.84 (d, J = 1.6 Hz, 2H); ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 173.4, 169.8, 133.4, 132.6, 132.2,

132.0, 131.4, 128.9, 128.3, 127.1, 126.3, 123.5, 34.1; IR (ATR) ν 1763 (m), 1702 (s), 1638 (m), 1485 (m), 1172 (s); HRMS (ESI) calcd for $C_{17}H_{13}{}^{79}BrNO_2$ $[M+H]^+$ 342.0130, found 342.0129.

(*E*)-3-(4-Cyanobenzylidene)-1-phenylpyrrolidine-2,5-dione (*exo*-1ag). Following the general procedure, **6g** (54 mg, 0.25 mmol) and **5a** (56 mg, 0.30 mmol) were converted to *exo*-**1ag** (62 mg, 0.22 mmol, 86%): off-white solid, mp 233 °C (dec.); ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.96 (dm, J = 8.5 Hz, 2H), 7.90 (dm, J = 8.4 Hz, 2H), 7.64 (t, J = 2.4 Hz, 1H), 7.55 - 7.50 (m, 2H), 7.45 (tt, J = 7.5, 1.3 Hz, 1H), 7.38 - 7.34 (m, 2H), 3.91 (d, J = 2.4 Hz, 2H); ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 173.3, 169.6, 138.7, 132.8, 132.5, 130.8, 130.6, 129.0, 128.9, 128.4, 127.1, 118.6, 111.8, 34.2; IR (ATR) ν 2232 (w), 1764 (w), 1703 (s), 1645 (w), 1172 (m), 689 (s); HRMS (ESI) calcd. for $C_{18}H_{13}N_2O_2$ $[M+H]^+$ 289.0977, found 289.0984.

(*E*)-3-(4-Acetylbenzylidene)-1-phenylpyrrolidine-2,5-dione (*exo*-1ah). Following the general procedure, **6h** (56 mg, 0.25 mmol) and **5a** (56 mg, 0.30 mmol) were converted to *exo*-**1ah** (72 mg, 0.24 mmol, 94%): off-white solid, mp 177 - 181 °C (dec.); ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.04 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 8.4 Hz, 2H), 7.64 (t, J = 2.2 Hz, 1H), 7.57 - 7.49 (m, 2H), 7.44 (dd, J = 7.3, 1.4 Hz, 1H), 7.39 - 7.31 (m, 2H), 3.91 (d, J = 2.4 Hz, 2H), 2.62 (s, 3H); ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 197.5, 173.4, 169.8, 138.4, 137.0, 132.6, 131.3, 130.5, 128.9, 128.7, 128.4, 128.0, 127.2, 34.3, 26.9; IR (ATR) ν 1765 (w), 1703 (s), 1677 (s), 1643 (m), 1348 (m), 1175 (s); HRMS (ESI) calcd for $C_{19}H_{16}NO_3$ $[M+H]^+$ 306.1130, found 306.1115.

(*E*)-*N*-(4-((2,5-Dioxo-1-phenylpyrrolidine-3-ylidene)methyl)phenyl)acetamide (*exo*-1ai). Following the general procedure, **6i** (62 mg, 0.25 mmol) and **5a** (56 mg, 0.30 mmol) were converted to *exo*-**1ai** (72 mg, 0.23 mmol, 90%): colourless solid, mp 260 - 265 °C (dec.); ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.19 (s, 1H), 7.68 (d, J = 8.7 Hz, 2H), 7.62 (d, J = 8.8 Hz, 2H), 7.48 (dd, J = 7.5, 7.5 Hz, 2H), 7.47 (t, J = 2.2 Hz, 1H), 7.40 (tt, J = 7.5, 1.3 Hz, 1H), 7.32 (dm, J = 7.5 Hz, 1H), 3.80 (d, J = 2.2 Hz, 2H), 2.05 (s, 3H); ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 173.6, 170.1, 168.8, 140.9, 132.7, 132.5, 131.4, 128.9, 128.8, 128.2, 127.2, 123.2, 119.0, 34.2,

24.1; IR (ATR): 3324 (w), 1760 (w), 1697 (s), 1649 (m), 1177 (s); HRMS (ESI) calcd for $C_{19}H_{17}N_2O_3$ $[M+H]^+$ 321.1239, found 321.1260.

(*E*)-3-(4-Nitrobenzylidene)-1-phenylpyrrolidine-2,5-dione (*exo*-1aj). Following the general procedure, **6j** (59 mg, 0.25 mmol) and **5a** (56 mg, 0.30 mmol) were converted to *exo*-**1aj** (69 mg, 0.22 mmol, 89%): yellow solid, mp 227 - 229 °C (dec.; reported in the literature for an *E*/*Z*-mixture:[22] mp 140 - 142 °C); ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.31 (dm, J = 8.8 Hz, 2H), 7.99 (dm, J = 8.9 Hz, 2H), 7.70 (t, J = 2.4 Hz, 1H), 7.53 (dd, J = 7.9, 7.5 Hz, 2H), 7.45 (tt, J = 7.6, 1.2 Hz, 1H), 7.37 (dd, J = 8.0, 1.2 Hz, 2H), 3.93 (d, J = 2.4 Hz, 2H); ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 173.2, 169.6, 147.4, 140.5, 132.5, 131.3, 130.0, 129.8, 128.9, 128.4, 127.1, 124.0, 34.2; IR (ATR) ν 1764 (w), 1701 (s), 1647 (m), 1515 (s), 1347 (s); HRMS (ESI) calcd for $C_{17}H_{12}N_2O_4$ $[M^+]$ 308.0792, found 308.0790.

(*E*)-3-Benzylidene-1-phenylpyrrolidine-2,5-dione (*exo*-1ak). Following the general procedure, **6k** (48 mg, 0.25 mmol) and **5a** (56 mg, 0.30 mmol) were converted to *exo*-**1ak** (59 mg, 0.22 mmol, 88%): colourless solid, mp 191 - 193 °C (reported in the literature:[7] mp 189 - 190 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.70 (dd, J = 8.0, 1.2 Hz, 2H), 7.58 (t, J = 2.2 Hz, 1H), 7.56 - 7.46 (m, 5H), 7.44 (tt, J = 7.5, 1.4 Hz, 1H), 7.37 (dd, J = 8.0, 1.4 Hz, 2H), 3.87 (d, J = 2.3 Hz, 2H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6) δ 173.4, 169.9, 134.1, 132.7, 132.6, 130.3, 129.9, 129.0, 128.8, 128.2, 127.1, 125.3, 34.1; IR (ATR) ν 1775 (w), 1703 (s), 1657 (m), 1388 (m), 1123 (m); HRMS (ESI) calcd for $C_{17}H_{13}NO_2$ $[M^+]$ 263.0946, found 263.0945.

(*E*)-3-(3-Methylbenzylidene)-1-phenylpyrrolidine-2,5-dione (*exo*-1al). Following the general procedure, **6l** (52 mg, 0.25 mmol) and **5a** (56 mg, 0.30 mmol) were converted to *exo*-**1al** (69 mg, 0.25 mmol, quant.): colourless solid, mp 172 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.55 - 7.48 (m, 5H), 7.44 (tt, J = 7.5, 1.3 Hz, 1H), 7.39 (dd, J = 7.6, 7.6 Hz, 1H), 7.36 (dd, J = 8.0, 1.3 Hz, 2H), 7.28 (d, J = 7.6 Hz, 1H), 3.86 (d, J = 2.3 Hz, 2H), 2.38 (s, 3H); ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 173.5, 170.0, 138.4, 134.1, 132.8, 132.6, 130.8, 130.7, 129.0,

128.8, 128.3, 127.6, 127.2, 125.1, 34.2, 21.0; IR (ATR) ν 1765 (w), 1702 (s), 1651 (m), 1160 (m), 695 (s); HRMS (ESI) calcd for $C_{18}H_{16}NO_2$ $[M+H]^+$ 278.1181, found 278.1161.

(*E*)-3-(3-Cyanobenzylidene)-1-phenylpyrrolidine-2,5-dione (*exo*-1am). Following the general procedure, **6m** (54 mg, 0.25 mmol) and **5a** (56 mg, 0.30 mmol) were converted to *exo*-**1am** (64 mg, 0.22 mmol, 89%): yellowish solid, mp 213 - 216 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.18 (s, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.91 (ddd, J = 7.9, 1.1, 1.1 Hz, 1H), 7.70 (dd, J = 7.9, 7.9 Hz, 1H), 7.61 (t, J = 2.3 Hz, 1H), 7.56 - 7.49 (m, 2H), 7.47 – 7.41 (m, 1H), 7.39 – 7.34 (m, 2H), 3.95 (d, J = 2.4 Hz, 2H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6) δ 173.3, 169.6, 135.3, 134.5, 133.5, 133.0, 132.5, 130.3, 130.2, 128.8, 128.3, 127.9, 127.1, 118.4, 112.3, 33.9; IR (ATR) ν 2230 (w), 1760 (w), 1700 (s), 1643 (m), 1380 (m), 1182 (s); HRMS (ESI) calcd for $C_{18}H_{13}N_2O_2$ $[M+H]^+$ 289.0977, found 289.0993.

(*E*)-3-(2-Methoxybenzylidene)-1-phenylpyrrolidine-2,5-dione (*exo*-1an). Following the general procedure, **6n** (56 mg, 0.25 mmol) and **5a** (56 mg, 0.30 mmol) were converted to *exo*-**1an** (64 mg, 0.22 mmol, 87%): off-white solid, mp 163 - 165 °C (reported in the literature:[94] mp 159 - 160 °C); ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.87 (t, J = 1.8 Hz, 1H), 7.63 (dd, J = 7.8, 0.9 Hz, 1H), 7.54 - 7.50 (m, 2H), 7.48 - 7.42 (m, 2H), 7.35 (d, J = 7.3 Hz, 2H), 7.14 (d, J = 8.3 Hz, 1H), 7.07 (dd, J = 7.5, 7.5 Hz, 1H), 3.89 (s, 3H), 3.80 (d, J = 2.2 Hz, 2H); ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 174.0, 170.5, 158.6, 133.1, 132.2, 129.7, 129.3, 128.7, 127.6, 127.3, 125.3, 122.9, 121.2, 112.1, 56.2, 34.4; IR (ATR) ν 1758 (w), 1703 (s), 1598 (w), 1382 (w), 696 (s); HRMS (ESI) calcd for $C_{18}H_{16}NO_3$ $[M+H]^+$ 294.1130, found 294.1123.

(*E*)-3-(2-Fluorobenzylidene)-1-phenylpyrrolidine-2,5-dione (*exo*-1ao). Following the general procedure, **6o** (52 mg, 0.25 mmol) and **5a** (56 mg, 0.30 mmol) were converted to *exo*-**1ao** (69 mg, 0.25 mmol, 99%): colourless solid, mp 159 - 161 °C (dec.); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.79 (t, J = 7.6 Hz, 1H), 7.65 (t, J = 2.0 Hz, 1H), 7.57 – 7.50 (m, 3H), 7.45 (t, J = 7.5 Hz, 1H), 7.40 – 7.27 (m, 4H), 3.85 (d, J = 2.0 Hz, 2H); ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 173.3, 169.6, 160.7 (d, J = 250.5 Hz), 132.5, 132.2 (d, J = 9.0 Hz), 129.9, 128.9, 128.3,

127.8, 127.2, 125.1 (d, J = 3.5 Hz), 123.4 (d, J = 6.3 Hz), 121.8 (d, J = 11.5 Hz), 116.0 (d, J = 21.7 Hz), 34.0; IR (ATR) ν 1774 (w), 1703 (s), 1498 (m), 1198 (m), 697 (s); HRMS (ESI) calcd for $C_{17}H_{13}FNO_2$ $[M+H]^+$ 282.0930, found 282.0902.

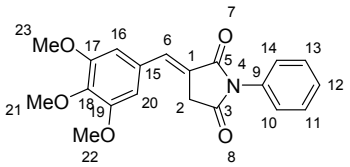
(*E*)-3-(2-Bromobenzylidene)-1-phenylpyrrolidine-2,5-dione (*exo*-1ap). Following the general procedure, **6p** (68 mg, 0.25 mmol) and **5a** (56 mg, 0.30 mmol) were converted to *exo*-**1ap** (61 mg, 0.18 mmol, 72%): colourless solid, mp 155 - 157 °C (dec.); ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.80 (dd, J = 7.8, 1.5 Hz, 1H), 7.79 (dd, J = 7.9, 1.1 Hz, 1H), 7.76 (t, J = 2.4 Hz, 1H), 7.56 – 7.50 (m, 3H), 7.45 (tt, J = 7.3, 1.3 Hz, 1H), 7.40 (ddd, J = 7.9, 7.9, 1.6 Hz, 1H), 7.38 – 7.36 (m, 2H), 3.84 (d, J = 2.4 Hz, 2H); ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 173.3, 169.6, 133.4, 133.3, 132.5, 131.5, 130.3, 130.2, 128.9, 128.4, 128.4, 128.3, 127.2, 125.4, 33.5; IR (ATR) ν 1761 (w), 1705 (s), 1500 (m), 1384 (m), 1171 (m); HRMS (ESI) calcd for $C_{17}H_{13}{}^{79}BrNO_2$ $[M+H]^+$ 342.0130, found 342.0140.

(*E*)- 3-(3-Bromo-4-hydroxybenzylidene)-1-phenylpyrrolidine-2,5-dione (*exo*-1ar). Following the general procedure, **6r** (72 mg, 0.25 mmol) and **5a** (56 mg, 0.30 mmol) were converted to *exo*-**1ar** (85 mg, 0.24 mmol, 95%): off-white solid, mp 185 °C (dec.); ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.97 (s, 1H), 7.85 (s, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.51 (dd, J = 7.7, 7.7 Hz, 2H), 7.47 (s, 1H), 7.43 (t, J = 7.4 Hz, 1H), 7.35 (d, J = 7.6 Hz, 2H), 7.06 (d, J = 8.5 Hz, 1H), 3.82 (s, 2H); ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 173.5, 170.0, 155.8, 135.4, 132.7, 131.6, 131.0, 128.8, 128.2, 127.2, 126.9, 122.8, 116.7, 110.0, 34.0; IR (ATR) ν 3405 (w), 1770 (m), 1691 (s), 1505 (m), 1169 (s); HRMS (ESI) calcd for $C_{17}H_{13}{}^{79}BrNO_3$ $[M+H]^+$ 358.0079, found 358.0108.

Methyl (*E*)-5-((2,5-dioxo-1-phenylpyrrolidin-3-ylidene)methyl)-2-hydroxybenzoate (*exo*-1as). Following the general procedure, **6s** (67 mg, 0.25 mmol) and **5a** (56 mg, 0.30 mmol) were converted to *exo*-**1as** (78 mg, 0.23 mmol, 93%): off-white solid, mp 195 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.85 (s, 1H), 8.07 (d, J = 2.3 Hz, 1H), 7.86 (dd, J = 8.8, 2.3 Hz, 1H), 7.55 (t, J = 2.3 Hz, 1H), 7.54 - 7.50 (m, 2H), 7.43 (tt, J = 7.5, 1.3 Hz, 1H), 7.37 - 7.34 (m, 2H), 7.11

(d, J = 8.7 Hz, 1H), 3.92 (s, 3H), 3.82 (d, J = 2.3 Hz, 2H); $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ 173.4, 170.0, 168.2, 160.6, 136.7, 132.9, 132.6, 131.7, 128.8, 128.2, 127.1, 125.7, 123.4, 118.4, 114.6, 52.7, 34.0; IR (ATR) ν 1703 (s), 1682 (s), 1591 (m), 1216 (m), 698 (s); HRMS (ESI) calcd for $C_{19}H_{16}NO_5$ $[M+H]^+$ 338.1028, found 338.1046.

(*E*)-1-Phenyl-3-(3,4,5-trimethoxybenzylidene)pyrrolidine-2,5-dione (*exo*-1at).



Following the general procedure, **6t** (71 mg, 0.25 mmol) and **5a** (56 mg, 0.30 mmol) were converted to *exo*-**1at** (79 mg, 0.23 mmol, 90%): colourless solid, mp 172 - 173 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.65 (t, J = 2.3 Hz, 1H, H^6), 7.50 (tm, J = 7.7 Hz, 2H, $H^{11,13}$), 7.44 – 7.35 (m, 3H, $H^{10,12,14}$), 6.75 (s, 2H, $H^{16,20}$), 3.92 (s, 3H, H^{21}), 3.90 (s, 6H, $H^{22,23}$), 3.78 (d, J = 2.3 Hz, 2H, H^2); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 173.2 (C^3), 170.1 (C^5), 153.7 ($C^{17,19}$), 140.4 (C^{18}), 135.6 (C^6), 132.1 (C^9), 129.6 (C^{15}), 129.3 ($C^{11,13}$), 128.7 (C^{12}), 126.6 ($C^{10,14}$), 122.0 (C^1), 107.8 ($C^{16,20}$), 61.1 (C^{21}), 56.4 ($C^{22,23}$), 34.4 (C^2); IR (ATR) ν 1772 (m), 1700 (s), 1652 (m), 1575 (m), 1115 (s); HRMS (ESI) calcd for $C_{20}H_{20}NO_5$ $[M+H]^+$ 354.1341, found 354.1343.

(*E*)-1-(3-Hydroxyphenyl)-3-(3-nitrobenzylidene)pyrrolidine-2,5-dione (*exo*-1bu).

Following the general procedure, **6u** (119 mg, 0.50 mmol) and **5b** (122 mg, 0.60 mmol) were converted to *exo*-**1bu** (128 mg, 0.40 mmol, 79%): yellowish solid, mp 212 °C (dec.; reported in the literature:[1] mp 198 - 199 °C); ^1H NMR (300 MHz, DMSO-d_6) δ 9.74 (s, 1H), 8.50 (t, J = 1.5 Hz, 1H), 8.27 (ddd, J = 8.2, 2.2, 0.7 Hz, 1H), 8.15 (d, J = 7.9 Hz, 1H), 7.78 (dd, J = 7.9, 7.9 Hz, 1H), 7.71 (t, J = 2.2 Hz, 1H), 7.30 (t, J = 8.3 Hz, 1H), 6.84 (ddd, J = 8.2, 2.3, 1.0 Hz, 1H), 6.80 - 6.75 (m, 2H), 3.92 (d, J = 2.3 Hz, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, DMSO-d_6) δ 173.0, 169.4, 157.6, 148.2, 135.8, 135.8, 133.3, 130.5, 130.1, 129.5, 128.3, 124.6, 124.0, 117.5, 115.3, 114.1, 33.9; IR (ATR) ν 3281 (bw), 1770 (m), 1693 (s), 1653 (s), 1526 (s); HRMS (ESI) calcd for $C_{17}H_{13}N_2O_5$ $[M+H]^+$ 325.0824, found 325.0839.

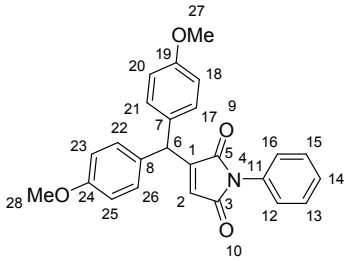
(*E*)-3-(2,4-Dichlorobenzylidene)-1-(3-hydroxyphenyl)pyrrolidine-2,5-dione (*exo*-1bv). Following the general procedure, **6v** (130 mg, 0.50 mmol) and **5b** (122 mg, 0.60 mmol) were converted to *exo*-**1bv** (167 mg, 0.48 mmol, 96%): orange solid, mp 255 °C (dec.; reported in the literature:[1] mp 269 °C); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.79 (s, 1H), 7.82 (d, J = 2.3 Hz, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.71 (t, J = 2.4 Hz, 1H), 7.56 (dd, J = 8.4, 1.9 Hz, 1H), 7.30 (dd, J = 8.3, 8.3 Hz, 1H), 6.84 (ddd, J = 8.2, 2.3, 1.0 Hz, 1H), 6.79 - 6.74 (m, 2H), 3.82 (d, J = 2.5 Hz, 2H); ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 173.2, 169.4, 157.7, 135.3, 135.0, 133.3, 131.2, 130.8, 129.6, 129.6, 129.2, 128.1, 126.3, 117.6, 115.4, 114.2, 33.7; IR (ATR) ν 3374 (bw), 1765 (m), 1697 (s), 1387 (m), 1181 (s); HRMS (ESI) calcd for $C_{17}H_{12}{}^{35}Cl_2NO_3$ $[M+H]^+$ 348.0194, found 348.0185.

Synthesis of (*E*)-3-(4-methoxybenzylidene)-1-phenylpyrrolidine-2,5-dione (*exo*-1aa) via Mizoroki-Heck reaction. *Iodo-4-Methoxybenzene (**8a**) as coupling partner (table 2, entries 1 and 2)*: To a solution of **8a** (70 mg, 0.30 mmol) and **5a** (47 mg, 0.25 mmol) in DMF (2.0 mL) were added NEt_3 (105 µL, 0.75 mmol), $Pd(OAc)_2$ (2.8 mg, 5 mol%) and tri-(*o*-tolyl)-phosphine (7.6 mg, 10 mol%). The solution was heated to 90 °C in DMF (2.0 mL) at 90 ° C for 18 h. After cooling to ambient temperature the reaction mixture was diluted with CH_2Cl_2 (30 mL), washed with water (20 mL) and brine (20 mL). The organic extracts were dried with $MgSO_4$, filtered and concentrated at reduced pressure. The crude product was purified by column chromatography using silica gel and eluent mixtures of hexanes and ethyl acetate with increasing polarity to furnish *exo*-**1aa** (51 mg, 0.18 mmol, 70%) as an off-white solid. By following this procedure without addition of the ligand tri-(*o*-tolyl)-phosphine the same coupling product *exo*-**1aa** (44 mg, 0.15 mmol, 60%) was obtained. *4-Methoxyphenyltriflate (**8b**) as coupling partner (table 2, entry 4)*: the same procedure as outlined above was used, but **8a** was replaced by **8b** (77 mg, 0.30 mmol). The identical coupling product *exo*-**1aa** (19 mg, 0.07 mmol, 26%) was obtained. *Bromo-4-methoxybenzene (**8c**) as coupling partner (table 2, entry 5)*: $Pd(OAc)_2$ (2.8 mg, 5 mol%) and tri-(*o*-tolyl)-phosphine (7.6 mg, 10 mol%) were suspended

in DMF (2.00 mL) and the mixture was stirred for 20 minutes at ambient temperature. 4-Bromoanisole (**8c**, 38 μL, 0.30 mmol) was then added, followed by **5a** (47 mg, 0.25 mmol) and NaOAc•3H_2O (34 mg, 0.25 mmol). The reaction mixture was heated to 140 ° C and stirred at this temperature for 1 h. After cooling to ambient temperature, the reaction mixture was diluted with CH_2Cl_2 (15 mL) and washed with water (30 mL). The aqueous layer was separated and extracted three times with CH_2Cl_2 (15 mL each). The combined organic extracts were dried with $MgSO_4$, filtered and evaporated. The crude product was purified by column chromatography on silica gel using hexanes / ethyl acetate mixtures of increasing polarity as eluent to furnish *exo*-**1aa** (15 mg, 0.05 mmol, 21%). All analytical data of the coupling product *exo*-**1aa** are identical to those reported above.

General procedure for the Matsuda-Heck reaction of arylmethylidene-*N*-phenylsuccinimides with arene diazonium salts. The appropriate precursor *exo*-**1** (0.25 mmol) was dissolved in methanol (10.0 mL). $Pd(OAc)_2$ (2.8 mg, 5 mol %), followed by the corresponding arene diazonium salt **6** (0.30 mmol) were added, and the mixture was stirred at ambient temperature for 18 h. After evaporation of all volatiles *in vacuo* the residue was purified by column chromatography on silica, using hexanes-ethyl acetate mixtures of increasing polarity as eluents.

3-(Bis-(4-methoxyphenyl)methyl)-1-phenyl-1*H*-pyrrol-2,5-dione (*endo*-7aa).



Following the general procedure, *exo*-**1aa** (73 mg, 0.25 mmol) and **6a** (67 mg, 0.30 mmol) were converted to *endo*-**7aa** (86 mg, 0.22 mmol, 86%). *Alternative synthesis from **5a** (table 1, entry 8)*. To a solution of **5a** (47 mg, 0.25 mmol) in methanol (8.0 mL) was added $Pd(OAc)_2$ (2.8 mg, 5 mol %) and arene diazonium tetrafluoroborate **6a** (166 mg, 0.75 mmol). The reaction mixture

was stirred at ambient temperature for 18 h, evaporated, and the residue was purified by column chromatography on silica using hexanes-ethyl acetate mixtures of increasing polarity to furnish *endo*-**7aa** (32 mg, 0.16 mmol, 65%): colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (dd, J = 7.7, 7.7 Hz, 2H, $H^{13/15}$), 7.35 (d, J = 7.5 Hz, 2H, $H^{12/16}$), 7.32 (t, J = 7.2 Hz, 1H, H^{14}), 7.13 (d, J = 8.3 Hz, 4H, $H^{17,21,22,26}$), 6.89 (d, J = 8.3 Hz, 4H, $H^{18,20,23,25}$), 6.28 (s, 1H, H^{2}), 5.33 (s, 1H, H^{6}), 3.80 (s, 6H, $H^{27,28}$); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.6 (C^{3}), 169.3 (C^{5}), 158.8 ($C^{19,24}$), 152.5 (C^{1}), 131.8 ($C^{7,8}$), 131.6 (C^{11}), 129.5 ($C^{17,21,22,26}$), 129.0 ($C^{12,16}$), 128.6 (C^{2}), 127.6 (C^{14}), 125.8 ($C^{12,16}$), 114.3 ($C^{18,20,23,25}$), 55.3 ($C^{27,28}$), 46.4 (C^{6}); IR (ATR) ν 2925 (w), 1714 (s), 1604 (w), 1510 (s), 1388 (m); HRMS (ESI) calcd for $C_{25}H_{21}NO_4$ [M^+] 399.1471, found 399.1460.

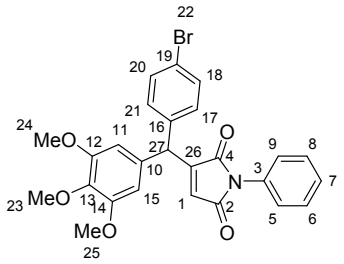
3-((4-Chlorophenyl)(4-methoxyphenyl)methyl)-1-phenyl-1*H*-pyrrole-2,5-dione (*endo*-7ae). Following the general procedure, *exo*-**1aa** (73 mg, 0.25 mmol) and **6e** (68 mg, 0.30 mmol) were converted to *endo*-**7ae** (84 mg, 0.21 mmol, 83%). *Alternative synthesis from **5a** (scheme 4)*. To a solution of **5a** (56 mg, 0.30 mmol) in methanol (4.0 mL) was added $Pd(OAc)_2$ (2.8 mg, 5 mol %) and arene diazonium tetrafluoroborate **6a** (56 mg, 0.25 mmol). The reaction mixture was stirred at ambient temperature for 0.5 h and then diluted by addition of methanol (6.0 mL). Arene diazonium salt **6e** (68 mg, 0.30 mmol) was then added and the mixture was stirred at ambient temperature for 18 h, evaporated, and the residue was purified by column chromatography on silica using hexanes-ethyl acetate mixtures of increasing polarity to furnish *endo*-**7ae** (70 mg, 0.17 mmol, 69%): colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 - 7.41 (m, 2H), 7.37 - 7.31 (m, 5H), 7.15 (dm, J = 8.5 Hz, 2H), 7.12 (dm, J = 8.7 Hz, 2H), 6.90 (dm, J = 8.7 Hz, 2H), 6.27 (d, J = 1.6 Hz, 1H), 5.34 (s (br.), 1H), 3.80 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.4, 169.1, 159.1, 151.7, 138.4, 133.4, 131.5, 130.9, 129.9, 129.7, 129.2, 129.1, 129.0, 127.8, 125.8, 114.5, 55.4, 46.7; IR (ATR) ν 1709 (s), 1598 (w), 1490 (m), 1386 (m), 1250 (m); HRMS (EI) calcd for $C_{24}H_{18}{}^{35}ClNO_3$ [M^+] 403.0970, found 403.0978.

3-((4-Methoxyphenyl)(phenyl)methyl)-1-phenyl-1*H*-pyrrole-2,5-dione (*endo*-7ka). Following the general procedure, *exo*-**1ak** (66 mg, 0.25 mmol) and **6a** (67 mg, 0.30 mmol) were converted to *endo*-**7ka** (67 mg, 0.18 mmol, 74%): yellowish solid, mp 139 – 141 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 - 7.41 (m, 2H), 7.38 – 7.34 (m, 4H), 7.33 (tt, J = 7.5, 1.3 Hz, 1H), 7.29 (tt, J = 7.3, 1.3 Hz, 1H), 7.24 – 7.20 (m, 2H), 7.15 (dm, J = 8.7 Hz, 2H), 6.90 (dm, J = 8.8 Hz, 2H), 6.29 (d, J = 1.7 Hz, 1H), 5.38 (s (br.), 1H), 3.80 (s, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 169.6, 169.3, 159.0, 152.2, 139.9, 131.6, 131.5, 129.7, 129.1, 129.0, 129.0, 128.6, 127.8, 127.5, 125.9, 114.4, 55.4, 47.3; IR (ATR) ν 1702 (s), 1513 (m), 1500 (m), 1397 (s), 693 (s); HRMS (EI) calcd for $C_{24}H_{19}NO_3$ [M^+] 369.1365, found 369.1364.

3-((4-Methoxyphenyl)(3,4,5-trimethoxyphenyl)methyl)-1-phenyl-1*H*-pyrrole-2,5-dione (*endo*-7ta). Following the general procedure, *exo*-**1at** (88 mg, 0.25 mmol) and **6a** (67 mg, 0.30 mmol) were converted to *endo*-**7ta** (110 mg, 0.24 mmol, 96%): off-white solid, mp 139 – 140 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 - 7.40 (m, 2H), 7.37 - 7.30 (m, 3H), 7.15 (dm, J = 8.6 Hz, 2H), 6.90 (dm, J = 8.8 Hz, 2H), 6.41 (s, 2H), 6.32 (d, J = 1.7 Hz, 1H), 5.30 (d, J = 1.2 Hz, 1H), 3.84 (s, 3H), 3.80 (s, 9H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.6, 169.3, 159.0, 153.6, 152.1, 137.4, 135.4, 131.6, 131.3, 129.6, 129.1, 128.8, 127.8, 125.8, 114.4, 105.8, 61.0, 56.3, 55.4, 47.5; IR (ATR) ν 1702 (s), 1615 (m), 1505 (m), 1399 (m), 1126 (s), 698 (s); HRMS (EI) calcd for $C_{27}H_{25}NO_6$ [M^+] 459.1682, found 459.1685.

3-((4-Chlorophenyl)(3,4,5-trimethoxyphenyl)methyl)-1-phenyl-1*H*-pyrrole-2,5-dione (*endo*-7te). Following the general procedure, *exo*-**1at** (88 mg, 0.25 mmol) and **6e** (68 mg, 0.30 mmol) were converted to *endo*-**7te** (110 mg, 0.24 mmol, 95%): yellowish oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 - 7.40 (m, 2H), 7.38 - 7.31 (m, 5H), 7.17 (dm, J = 8.4 Hz, 2H), 6.39 (s, 2H), 6.33 (d, J = 1.7 Hz, 1H), 5.32 (d, J = 1.0 Hz, 1H), 3.84 (s, 3H), 3.81 (s, 6H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 169.4, 169.0, 153.7, 151.2, 137.9, 137.6, 134.5, 133.6, 131.4, 129.9, 129.3, 129.2, 129.2, 127.9, 125.8, 105.8, 61.0, 56.3, 47.6; IR (ATR) ν 1710 (s), 1590 (m), 1502 (m), 1386 (m), 1125 (s); HRMS (EI) calcd for $C_{26}H_{22}{}^{35}ClNO_5$ [M^+] 463.1181, found 463.1173.

3-((4-Bromophenyl)(3,4,5-trimethoxyphenyl)methyl)-1-phenyl-1*H*-pyrrole-2,5-dione (*endo*-7tf).



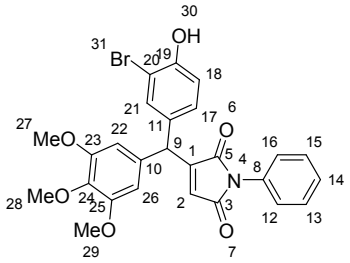
Following the general procedure, *exo*-**1at** (88 mg, 0.25 mmol) and **6f** (81 mg, 0.30 mmol) were converted to *endo*-**7tf** (53 mg, 0.11 mmol, 42%): yellowish oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49 (dm, J = 8.5 Hz, 2H, $H^{18,20}$), 7.45 - 7.42 (m, 2H, $H^{6,8}$), 7.36 - 7.32 (m, 3H, $H^{5,7,9}$), 7.11 (dm, J = 8.3 Hz, 2H, $H^{17,21}$), 6.38 (s, 2H, $H^{11,15}$), 6.33 (d, J = 1.7 Hz, 1H, H^{1}), 5.30 (d, J = 1.1 Hz, 1H, H^{27}), 3.84 (s, 3H, H^{23}), 3.81 (s, 6H, $H^{24,25}$); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 169.4 (C^{2}), 169.0 (C^{4}), 153.7 ($C^{12,14}$), 151.1 (C^{26}), 138.4 (C^{16}), 137.6 (C^{13}), 134.4 (C^{10}), 132.2 ($C^{18,20}$), 131.4 (C^{3}), 130.2 ($C^{17,21}$), 129.2 (C^{1}), 129.2 ($C^{6,8}$), 127.9 (C^{7}), 125.8 ($C^{5,9}$), 121.8 (C^{19}), 105.8 ($C^{11,15}$), 61.0 (C^{23}), 56.3 ($C^{24,25}$), 47.7 (C^{27}); IR (ATR) ν 1710 (s), 1593 (m), 1385 (m), 1123 (m), 528 (m); HRMS (EI) calcd for $C_{26}H_{22}{}^{79}BrNO_5$ [M^+] 507.0676, found 507.0680.

(*E*)-3-((4-Nitrophenyl)(3,4,5-trimethoxyphenyl)methylene)-1-phenylpyrrolidine-2,5-dione ((*E*)-*exo*-7tj) and (*Z*)-3-((4-nitrophenyl)(3,4,5-trimethoxyphenyl)methylene)-1-phenylpyrrolidine-2,5-dione ((*Z*)-*exo*-7tj). Following the general procedure, *exo*-**1at** (88 mg, 0.25 mmol) and **6j** (71 mg, 0.30 mmol) were converted to a 4 : 1 mixture of (*E*)- and (*Z*)-*exo*-**7tj**, which was contaminated with minor amounts of unidentified byproducts (107 mg, 0.24 mmol, >90%): yellowish oil. *NMR-data of the major isomer (Z)-exo-**7tj**, obtained from the mixture*: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (dm, J = 8.9 Hz, 2H, C*H*CNO_2), 7.53 – 7.27 (m, 7H, C*H*$CHCNO_2$, Ph), 6.41 (s, 2H, $C_6H_2(OCH_3)_3$), 3.89 (s, 3H, *p*-OCH_3), 3.80 (s, 6H, *m*-OCH_3), 3.73 (s, 2H, C(O)CH_2); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 172.1, 167.6, 153.7, 153.1, 150.0, 147.8, 139.5, 145.7, 134.3, 131.7, 130.0, 129.2, 128.8, 126.5, 124.6, 123.5, 122.8, 106.4, 61.1, 56.5, 36.2. *Selected ^{1}H NMR data of the minor isomer (E)-exo-**7tj**, obtained from the*

mixture: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (dm, J = 8.9 Hz, 2H, C*H*CNO_2), 6.46 (s, 2H, $C_6H_2(OCH_3)_3$).

3-((3-Nitrophenyl)(3,4,5-trimethoxyphenyl)methyl)-1-phenyl-1*H*-pyrrole-2,5-dione (*endo*-7tu). Following the general procedure, *exo*-**1at** (88 mg, 0.25 mmol) and **6u** (71 mg, 0.30 mmol) were converted to *endo*-**7tu** (12 mg, 0.03 mmol, 10%): yellowish oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.19 (ddd, J = 7.0, 2.3, 2.3 Hz, 1H), 8.13 - 8.12 (m, 1H), 7.60 - 7.55 (m, 2H), 7.47 - 7.43 (m, 2H), 7.37 - 7.33 (m, 3H), 6.40 (s, 2H), 6.38 (d, J = 1.7 Hz, 1H), 5.44 (d, J = 1.5 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 6H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 169.2, 168.7, 154.0, 150.2, 148.7, 141.7, 138.0, 134.5, 133.5, 131.3, 130.1, 129.7, 129.3, 128.1, 125.8, 123.4, 122.9, 105.9, 61.1, 56.4, 47.9; IR (ATR) ν 1711 (s), 1591 (m), 1529 (s), 1125 (m), 729 (m); HRMS (EI) calcd for $C_{26}H_{22}N_2O_7$ [M^+] 474.1422, found 474.1422.

3-((3-Bromo-4-hydroxyphenyl)(3,4,5-trimethoxyphenyl)methyl)-1-phenyl-1*H*-pyrrole-2,5-dione (*endo*-7tr).



Following the general procedure, *exo*-**1at** (88 mg, 0.25 mmol) and **6r** (86 mg, 0.30 mmol) were converted to *endo*-**7tr** (77 mg, 0.15 mmol, 59%): yellowish oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 - 7.41 (m, 2H, $H^{13,15}$), 7.36 - 7.32 (m, 3H, $H^{12,14,16}$), 7.32 (d, J = 2.1 Hz, 1H, H^{21}), 7.07 (dd, J = 8.5, 2.1 Hz, 1H, H^{17}), 7.00 (d, J = 8.4 Hz, 1H, H^{18}), 6.38 (s, 2H, $H^{22,26}$), 6.33 (d, J = 1.7 Hz, 1H, H^2), 5.75 (s, 1H, H^{30}), 5.26 (d, J = 1.2 Hz, 1H, H^9), 3.84 (s, 3H, H^{28}), 3.81 (s, 6H, $H^{27,29}$); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 169.4 (C^3), 169.1 (C^5), 153.7 ($C^{23,25}$), 151.9 (C^{19}), 151.3 (C^1), 137.6 (C^{24}), 134.6 (C^{10}), 132.9 (C^{11}), 132.0 (C^{21}), 131.4 (C^8), 129.2 (C^{17}), 129.2 ($C^{13,15}$), 129.1 (C^2), 127.9 (C^{14}), 125.8 ($C^{12,16}$), 116.6 (C^{18}), 110.8 (C^{20}), 105.8 ($C^{22,26}$), 61.0 (C^{28}), 56.4

($C^{27,29}$), 47.1 (C^{9}); IR (ATR) ν 3427 (w), 1707 (s), 1493 (m), 907 (s); HRMS (EI) calcd for $C_{26}H_{22}{}^{79}BrNO_6$ [M^+] 523.0625, found 523.0643.

Methyl 5-((2,5-dioxo-1-phenyl-2,5-dihydro-1*H*-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)-methyl)-2-hydroxybenzoate (*endo*-7ts). Following the general procedure, *exo*-**1at** (88 mg, 0.25 mmol) and **6s** (80 mg, 0.30 mmol) were converted to *endo*-**7ts** (34 mg, 0.07 mmol, 27%): yellowish oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.78 (s, 1H), 7.70 (d, J = 2.4 Hz, 1H), 7.46 - 7.42 (m, 2H), 7.37 - 7.31 (m, 4H), 7.01 (d, J = 8.6 Hz, 1H), 6.38 (s, 2H), 6.34 (d, J = 1.7 Hz, 1H), 5.29 (d, J = 1.2 Hz, 1H), 3.95 (s, 3H), 3.84 (s, 3H), 3.81 (s, 6H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 170.3, 169.5, 169.2, 161.1, 153.8, 151.5, 137.6, 135.8, 134.8, 131.5, 130.0, 129.6, 129.2, 129.0, 128.0, 125.8, 118.6, 112.7, 105.9, 61.0, 56.4, 52.7, 47.4; IR (ATR) *n* 3150 (w), 2940 (w), 1705 (s), 1401 (m), 1126 (s); HRMS (EI) calcd for $C_{28}H_{25}NO_8$ [M^+] 503.1580, found 503.1568.

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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; irradiation spectra, ^{1}H NMR spectrum and HPLC chromatogram of (*E*/*Z*)-*exo*-**1at** after irradiation (PDF).

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