JOC The Journal of Organic Chemistry

ARTICLE

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Development of Methods for the Synthesis of Libraries of Substituted Maleimides and α,β-Unsaturated-γ-butyrolactams

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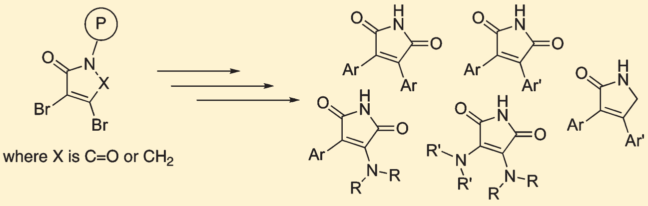
Supporting Information

ABSTRACT: Synthetic methods for the preparation of maleimide and α,β-unsaturated-γ-butyrolactam compound collections are described. These routes take advantage of Pd cross-coupling and conjugate addition/elimination reactions to permit the facile production of bisaryl-maleimides, anilinoaryl-maleimides, and bisanilino-maleimides while allowing control over the synthesis of symmetrical or nonsymmetrical derivatives. Similarly, the chemistry developed allows for the generation of bisaryl substituted α,β-unsaturated-γ-butyrolactams. The scope and limitations of the approaches are presented.



INTRODUCTION

The maleimide motif is featured in a variety of natural products including the arcyriaflavin,[1] arcyriarubin,[2] himanimide,[3] polycitrin,[4] and rebeccamycin[5] families. Biological properties of these compounds and their analogues include antibacterial and antiviral activity and angiogenesis inhibition,[6] as well as kinase inhibiton.[7] For example, groups from SmithKline Beecham,[8,9] Eli Lilly,[10] and Johnson & Johnson,[11] among others, have demonstrated that bisaryl-maleimides are potent inhibitors of glycogen synthase kinase-3 (GSK-3). In fact, compounds SB 216763 and SB 415286 (Figure 1) have been shown to inhibit the α-isoform of GSK-3 in an ATP-competitive manner with a K_i of 9 and 31 nM, respectively.[8] The syntheses of these maleimide inhibitors often involve multistep sequences that do not lend themselves readily to combinatorial approaches.

As part of a program aimed at the design and synthesis of selective kinase inhibitors, we required a route that could access chemically diverse families of substituted maleimides. We determined that Pd-catalyzed cross-coupling chemistry developed in our laboratory[12−17] is particularly well suited for this purpose, allowing for efficient derivatization at the 3,4-positions of the maleimide heterocyclic core. Furthermore, inspired by the biological activity of staurosporine,[18,19] Figure 1, we have developed a general method that allows for the synthesis of substituted α,β-unsaturated-γ-butyrolactam analogues. An ideal synthetic method should allow for the preparation of bisaryl-maleimides, anilinoaryl-maleimides, and bisanilino-maleimides; be amenable for the parallel synthesis of maleimide libraries; and allow for the control necessary to permit symmetrical or nonsymmetrical derivatives.

RESULTS AND DISCUSSION

Our initial efforts focused on the most straightforward approach to the target compounds involving two sequential Heck reactions onto a maleimide core to permit derivatization at the 3- and 4-positions. Exploratory experiments revealed that *N*-protection was necessary and *N*-(*p*-methoxybenzyl)-maleimide (**1**)[20] was chosen as a suitable substrate as a number of mild deprotection strategies have been reported.[21−24] The initial screening of reaction conditions involved the coupling of **1** with *p*-iodotoluene utilizing microwave heating and examined the effect of different ligands,[13] solvents, temperatures, palladium sources, and bases. As illustrated in Table 1, elevated temperatures (140 °C for 55 min) were required to effect coupling in good yields. When 6 equiv of the aryl halide was used, many of the conditions screened (entries 1−8) allowed for the production of monoarylated product (Table 1, **a**) predominantly. However, use of the 1,3,5,7-tetramethyl-2,4,8-trioxa-6-*o*-methoxyphenyl-6-phosphaadamantane ligand (**2**, R = OMe) and Cy_2NMe as the base allowed for a substantial increase in the diarylated product (Table 1, **b**) in dioxane (entry 9) and DMF (entry 10). Unfortunately, increasing reactions times, temperature, or the number of equivalents of *p*-iodotoluene used failed to increase the amount of diarylated maleimide generated. This was not unexpected, as the difficulty of generating tetrasubstituted alkenes using Heck coupling is well-known.[25]

Methods employing Suzuki couplings were found to be more synthetically viable, enabling access to the aryl-substituted maleimides under milder conditions. Using *N*-(*p*-methoxybenzyl)-3,4-dibromomaleimide (**3**)[26,27] as the scaffold, a series of experiments quickly determined the optimal reaction conditions (Pd source, base, and solvent) for monoarylation of the maleimide core. The results are presented in Table 2. The best yields were obtained when using the 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phenyl-6-phosphaadamantane ligand (PA-Ph: **2**, R = H) and Pd_2dba_3 at room temperature with Cs_2CO_3 in THF. However, despite

Received: December 28, 2010
Published: March 25, 2011

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dx.doi.org/10.1021/jo1025805 | J. Org. Chem. 2011, 76, 3122–3130

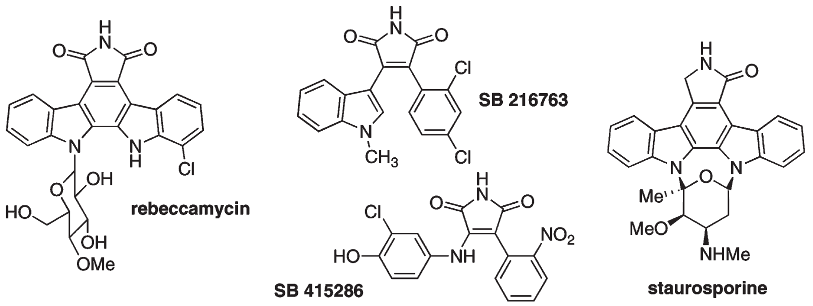
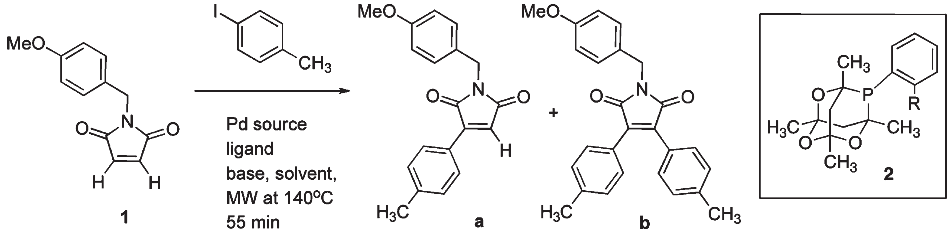


Figure 1. Systems containing maleimide and α,β-unsaturated-γ-butyrolactam substructures.

Table 1. Optimization of Reaction Parameters for the Arylation of a Maleimide Scaffold *via* a Heck Reaction



	ligand (**2**)	Pd source	base	solvent	yield (% **a**:% **b**)
1	R = H	Pd_2dba_3	Et_3N	THF	85:5
2	R = H	Pd_2dba_3	Et_3N	dioxane	82:10
3	R = H	Pd_2dba_3	Et_3N	DMF	80:16
4	R = H	$Pd(OAc)_2$	Et_3N	THF	80:5
5	R = H	$Pd(OAc)_2$	Et_3N	dioxane	83:10
6	R = H	$Pd(OAc)_2$	Et_3N	DMF	80:15
7	R = OMe	Pd_2dba_3	Et_3N	DMF	84:15
8	R = OMe	Pd_2dba_3	Cy_2NMe	THF	80:10
9	R = OMe	Pd_2dba_3	Cy_2NMe	dioxane	51:45
10	R = OMe	Pd_2dba_3	Cy_2NMe	DMF	40:55

using only 1 equiv of boronic acid, a small amount of diarylation product (Table 2, **b**) was always generated. This byproduct was easily separated from the desired monoarylated compound (Table 2, **a**) *via* column chromatography; however, for the sake of convenience, the reaction mixture could be taken forward and subjected to a second Suzuki reaction.

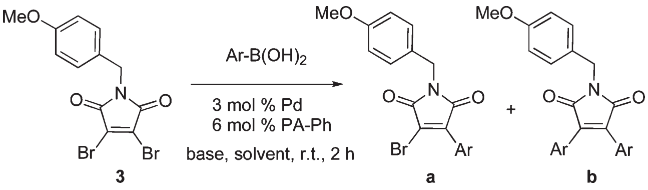
With the monoarylated-malemides in hand (Table 3, **a**), introduction of a second aryl moiety (to give Table 3, **b**) was shown to be facile and high-yielding. Deprotection with TFA in anisole (in a 1:1 (v/v) ratio) using microwave irradiation gave the desired bisarylated-maleimides (Table 3, **c**).

Symmetrical diarylation of the maleimide scaffold (Table 4) was easily achieved by using 2.2 equiv of the arylboronic acid and the Pd_2dba_3/PA-Ph catalyst system. Shorter reaction times (30−60 min) were required for the removal of the *p*-methoxybenzyl protecting group when $AlCl_3$ in anisole under microwave irradiation was employed. High yields of the desired bisarylmaleimides were obtained in all cases except for entry 5 (in Table 4), where product decomposition occurred under all deprotection conditions attempted.

A number of potent kinase inhibitors are anilinoaryl-maleimides (SB415286 in Figure 1, for example), and we next explored routes for the parallel synthesis of these systems. Exploratory experiments quickly determined that the order of introduction of the aryl and amino vectors was important and that the most facile route to the 3-amino,4-aryl-substituted maleimides involved amination before a Suzuki arylation. In this way, treatment of the *N*-(*p*-methoxybenzyl)-3,4-dibromomaleimide (**3**) with 1 equiv of an amine (primary or secondary aliphatic; anilines or *N*-monosubstituted anilines) at room temperature in THF allowed for a rapid conjugate addition/elimination reaction to provide high yields of the monosubstituted maleimide (Table 5, **a**). In fact, under these conditions and in the presence of excess amine, the monoaminated maleimide product is formed exclusively. It would appear that the installation of an amino group alters the electronic nature of the neighboring site such that a second conjugate addition does not occur at room temperature. However, utilization of the Suzuki chemistry developed above allowed for facile arylation (to give Table 5, **b**) and, after deprotection, access to 3-amino,4-aryl-substituted maleimides (Table 5, **c**) in good overall yields.

A number of complications were encountered when attempting to introduce a second amino moiety onto the monoaminated maleimide scaffold. We determined that these reactions were controlled by the subtle interplay between the electron donating ability of the first amine introduced and the nucleophilicity of the second amine. For example, treatment of 3-bromo-1-(4-methoxybenzyl)-4-(phenylamino)-maleimide (Table 5, entry 11, **a**)

Table 2. Optimization of Reaction Parameters for Monoarylated-maleimide Synthesis *via* Suzuki Chemistry



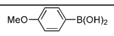
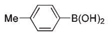
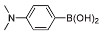
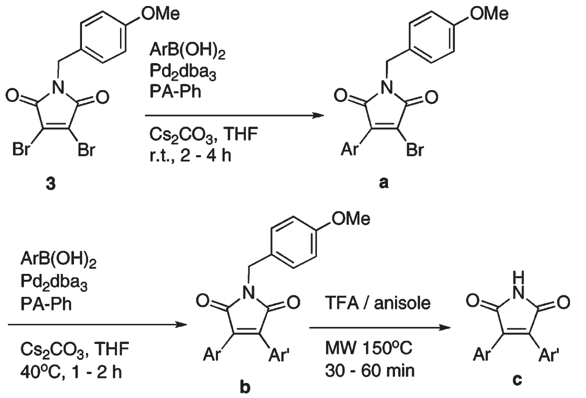
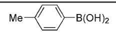
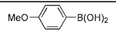
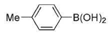
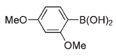
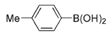
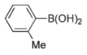
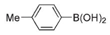
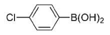
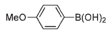
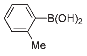
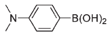
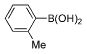
	Ar-B(OH)$_2$	Pd source	base	solvent	yield (% **a** : % **b**)
1		Pd(OAc)$_2$	CsOH	THF	15 : 10
2		Pd(OAc)$_2$	CsOH	toluene	15 : 0
3		Pd$_2$dba$_3$	CsOH	THF	15 : 10
4		Pd$_2$dba$_3$	CsOH	toluene	10 : 0
5		Pd$_2$dba$_3$	CsOH	dioxane	10 : 0
6		Pd$_2$dba$_3$	CsF	THF	50 : 35
7		Pd$_2$dba$_3$	K$_3$PO$_4$	THF	50 : 23
8		Pd$_2$dba$_3$	Cs$_2$CO$_3$	THF	55 : 23
9		Pd$_2$dba$_3$	Cs$_2$CO$_3$	THF	78 : 15
10		Pd$_2$dba$_3$	Cs$_2$CO$_3$	THF	58 : 25

Table 3. Nonsymmetrical Bisaryl Maleimides *via* Suzuki Chemistry



	Ar-B(OH)$_2$	Ar'-B(OH)$_2$	% yield **a**	% yield **b**	% yield **c**
1			78	92	84
2				95	82
3				93	86
4			55	90	81
5				91	86
6			58	94	86

with series of amines (3 equiv) and using microwave irradiation (100 °C for 30 min) resulted in diamino-maleimide products only with primary and secondary aliphatic systems such as *n*-butylamine, piperidine, and morpholine to give **4**, **5**, and **6**, respectively (Figure 2). Anilinic or *N*-substituted-anilinic amines failed to couple. It would appear that once monoaminated, the electrophilicity of the carbon bearing the Br is drastically reduced as it is now the terminus of an enamine system as well as an α,β-unsaturated amide. It is not surprising, therefore, that a second conjugate addition/elimination reaction takes place only under forcing conditions with the more nucleophilic primary or secondary aliphatic amines. In addition, both 3-bromo-1-(4-methoxybenzyl)-4-(methyl(phenyl)amino)-1*H*-pyrrole-2,5-dione (Table 5, entry 8, **a**) and 3-bromo-1-(4-methoxybenzyl)-4-morpholino-maleimide (Table 5, entry 2, **a**) were shown to couple with piperidine (to give **7** and **8**, respectively), whereas morpholine and other aromatic amines failed to react. In effect, bisamination of the maleimide scaffold **3** was only successful in cases where the addition of a less nucleophilic amine (lower pK_a, less electron-rich) is followed by reaction with a more nucleophilic amine (higher pK_a, more electron-rich). As a result, symmetrical bisaminated maleimides could not be generated using this approach. It should be noted that attempts to introduce the second amine *via* a palladium-catalyzed amination reaction were unsuccessful with only the dehalogenated product recovered.

In addition to these limitations, deprotection of the methoxybenzyl protecting group for these systems was also problematic. In systems bearing a piperidine moiety, deprotection under the conditions developed above using AlCl$_3$/anisole at room temperature resulted in trapping of the *p*-methoxybenzyl cation generated by the piperidine nitrogen to give systems **9** and **10** (from **5** and **7**, respectively, as shown in Figure 3). These results are very peculiar as trapping of the *p*-methoxybenzyl cation did not occur with analogous compounds such as entry 7 in Table 5 that underwent deprotection smoothly under microwave irradiation. Attempts at deprotection using oxidative cleavage protocols involving CAN[28] or DDQ[29] were unsuccessful.

It became clear that a different protecting group was needed, ideally one that could alter the electronics of the maleimide system and thereby help facilitate the second amination reaction. *N*-(*p*-Nitrophenyl)-3,4-dibromomaleimide (**11**), prepared by treating maleic anhydride with *p*-nitroaniline in acetic acid, was identified as an ideal substrate. Its deprotection is realized by treating with methanolic ammonia at room temperature. Once again, the order of addition of the two amino vectors is important. As presented in Table 6, addition of the first amine vector to **11** to give system **a** could be achieved in high yields (as evidence by TLC) in a few minutes. The monoaminated compound (**a**) was not isolated but used directly in the next step. Addition of a second, more nucleophilic amino moiety allowed for the requisite conjugate addition/elimination reaction (to give **b**), achieved using microwave heating a 50 °C for 30 min. Finally, treatment with methanolic ammonia at room temperature for 12 h provided the desired bisamino-maleimides (Table 6, **c**). Note that treatment of **11** with primary amines, such as *n*-

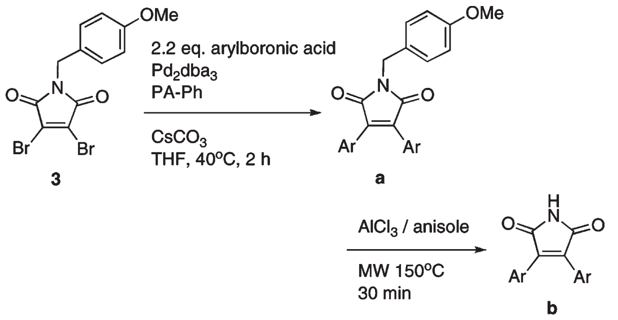
butylamine, resulted in a complex mixture of products that included those wherein the *p*-nitrophenyl moiety is substituted with the primary amine introduced.

Our attention was then turned to the application of the chemistry developed above for the syntheses of substituted α,β-unsaturated-γ-butyrolactams. These systems represent analogues of the maleimide derivatives with a deleted carbonyl and can be used to provide further information about the nature of inhibitor binding. A suitable scaffold was generated *via* the treatment of mucobromic acid with 4-methoxybenzyl amine under reductive amination conditions similar to those described by Zhang and co-workers[30] to give 3,4-dibromo-1-(4-methoxybenzyl)-1*H*-pyrrol-2(5*H*)-one (**12**) in 78% yield. Once again, optimization of the reaction parameters necessary for the introduction of a single aryl moiety *via* a Suzuki reaction was investigated (Table 7).

As expected, the first arylation takes place at the β-position of the unsaturated-γ-butyrolactam **12** (to give **a** in Table 7) thus allowing for control over the substitution pattern in the final product. The best yields were obtained when using the PA-Ph ligand and Pd_2dba_3 with KF in toluene. Furthermore, unlike the conditions used for the first arylation in the maleimide series, the initial Suzuki coupling involving **12** required elevated temperatures (60 °C). In addition, despite using only 1 equiv of the boronic acid, a small amount of diarylation product (Table 7, **b**) was generated.

Carrying the reaction mixture forward, a second aryl vector could be introduced into the butyrolactam system (to give

Table 4. Symmetrical Bisaryl Maleimides *via* Suzuki Chemistry



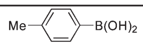
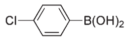
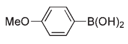
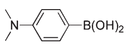
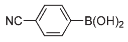
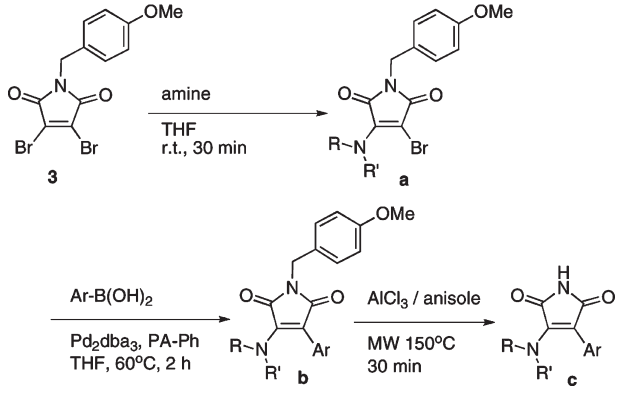
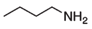
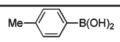
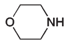
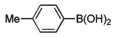
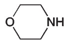
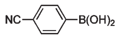
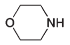
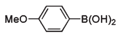
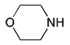
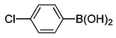
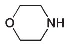
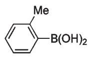
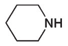
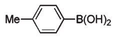
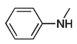
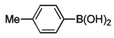
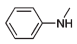
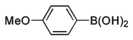
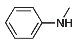
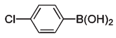
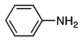
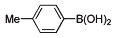
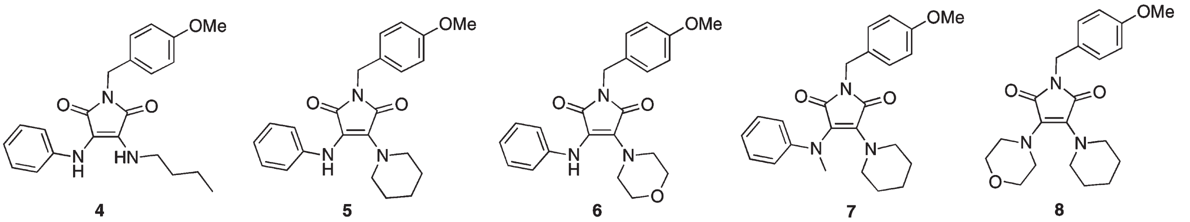
	Ar-B(OH)₂	% yield **a**	% yield **b**
1		93	91
2		91	89
3		95	88
4		96	75
5		96	0

Table 5. 3-Amino-4-aryl Substituted Maleimides



	amine	Ar-B(OH)₂	% yield **a**	% yield **b**	% yield **c**
1			92	86	84
2			98	93	84
3				72	82
4				88	85
5				85	87
6				91	88
7			94	89	91
8			95	91	84
9				87	85
10				84	81
11			92	76	73



4 5 6 7 8

Figure 2. *p*-Methoxybenzyl protected 3,4-diaminomaleimides.

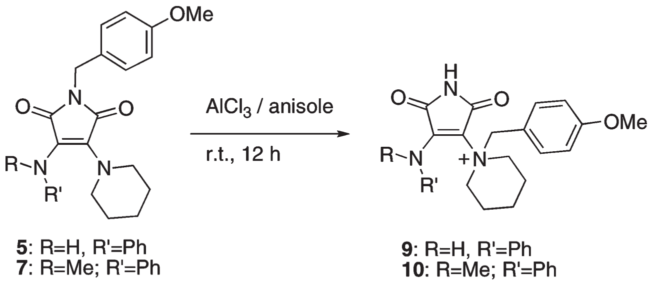
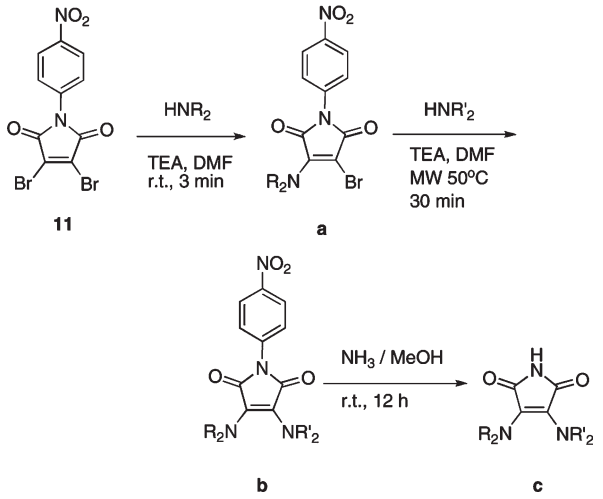


Figure 3. Trapping of the *p*-methoxybenzyl cation.

Table 6. Nonsymmetrical Bisamino Maleimides



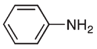
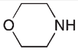
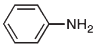
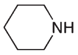
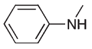
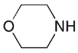
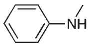
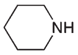
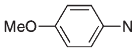
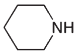
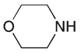
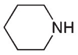
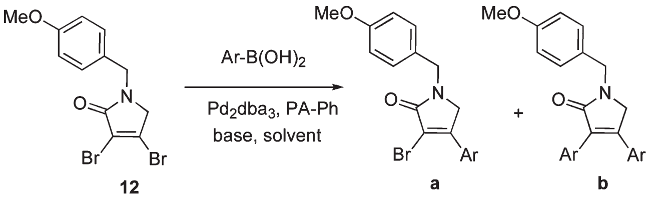
	HNR$_2$	HNR'$_2$	% yield **b**	% yield **c**
1			93	84
2			95	93
3			91	81
4			96	96
5			91	89
6			92	82

Table 8, **b**) under the similar conditions with an increase in temperature (to 80 °C) and reaction time (to 12 h). Deprotection to the desired lactam systems (Table 8, **c**) was accomplished using TFA/anisole and microwave irradiation at 150 °C for 30 min with no significant change in yield observed when the $AlCl_3$/TFA deprotection protocol was used. Finally, entries 4–6

Table 7. Optimization of Reaction Parameters for the Synthesis of Substituted α,β-Unsaturated-γ-butyrolactams



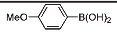
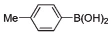
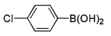
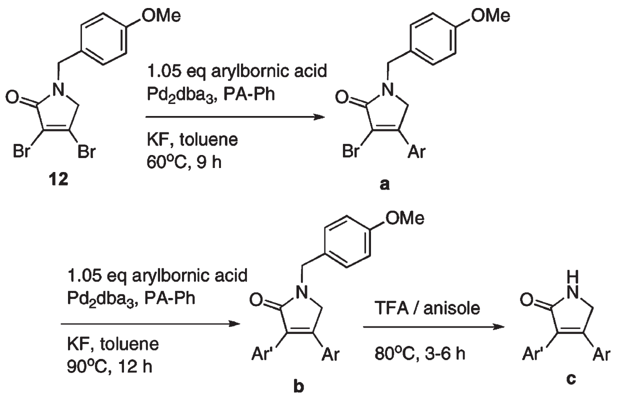
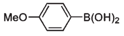
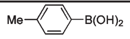
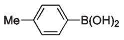
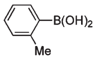
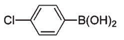
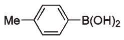
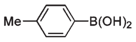
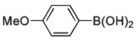
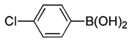
	Ar-B(OH)$_2$	base	solvent	temp	time	yield (%**a** : %**b**)
1		CsF	THF	50	2	15 : 0
2		Cs_2CO_3	THF	50	2	5 : 0
3		Cs_2CO_3	toluene	50	3	10 : 0
4		Cs_2CO_3	dioxane	50	3	10 : 0
5		CsF	toluene	50	3	15 : 0
6		KF	toluene	60	20	55 : 10
7		KF	toluene	60	20	68 : 10
8		KF	toluene	60	20	54 : 15

Table 8. 3,4-Diaryl α,β-Unsaturated-γ-butyrolactams



	Ar-B(OH)$_2$	Ar'-B(OH)$_2$	% yield **b**	% yield **c**
1			78	84
2			75	86
3			81	82
4			84	81
5			85	86
6			82	87

in Table 8 represent systems with the same aryl moiety at the α- and β-positions of the lactam and were prepared by treating **12** with 2.2 equiv of the appropriate boronic acid followed by deprotection.

Exploratory experiments aimed at the introduction of amine vectors into **12** quickly revealed that the approach developed above was inappropriate for the amination of the butyrolactam series. For example, treatment of **12** with morpholine gave a mixture of multiple products. This was not surprising as it is well-known that the methylene moiety at C5 is enolizable[31,32] and treatment with basic amines precludes the conjugate addition/elimination reaction.

CONCLUSIONS

The methods developed above allow for rapid and facile access to symmetrical and nonsymmetrical, aryl- and amino-substituted maleimides and α,β-unsaturated-γ-butyrolactams. Furthermore, the utilization of other organopalladium cross-coupling chemistries (including such reactions as the Sonogashira, Stille, ketone arylations, Negishisi, etc.) should allow for introduction of a variety of structurally diverse vectors and, thereby, an increased mapping of the chemical space probed by these compound collections.

EXPERIMENTAL SECTION

General Information. See *J. Org. Chem.* **2004**, *69* (22), 7635−7639 for the general experimental information (provided in the Supporting Information) and for the synthesis of 1,3,5,7-tetramethyl-2,4,8-trioxa-6-*o*-methoxyphenyl-6-phosphaadamantane (**2**, R = OMe). 1,3,5,7-Tetramethyl-2,4,8-trioxa-6-phenyl-6-phosphaadamantane (**2**, R = H, PA-Ph) was supplied by Cytec Canada. Microwave reactions were performed using a CEM Discover Microwave, which allowed for monitoring and control of both temperature and pressure. Unless otherwise stated, the ionization gas for the CI MS experiments was ammonia.

***N*-(*p*-Methoxybenzyl)-maleimide (1)[20].** To a solution of maleic anhydride (1.6 g, 16.3 mmol) in acetic acid (15 mL) was added *p*-methoxybenylamine (2.1 mL, 16.3 mmol). The mixture was refluxed for 5 h, cooled to room temperature, and then concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel using 20% ethylacetate in hexane as the eluent afforded **1** in 79% yield (2.8 g, 12.9 mmol): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.30 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 8.4 Hz, 2H), 6.68 (s, 2H), 4.61 (s, 2H), 3.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.6, 159.4, 134.2, 130.1, 128.6, 114.2, 55.4, 41.0; HRMS (CI) for $C_{12}H_{11}NO_3$ calculated 217.0739, found 217.0735.

Synthesis of 1-(4-Methoxybenzyl)-3-*p*-tolyl-1*H*-pyrrole-2,5-dione (Table 1, a) and 1-(4-Methoxybenzyl)-3,4-di-*p*-tolyl-1*H*-pyrrole-2,5-dione (Table 1, b) *via* a Heck Reaction. To a mixture of *N*-(*p*-methoxybenzyl)-maleimide (**1**) (100 mg, 0.46 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (23.8 mg, 0.023 mmol, 5 mol %), PA-Ph, (**2**, R = OMe, 7.7 mg. 0.023 mmol, 5 mol %), Cy_2NMe (494 μL, 2.3 mmol, 5 equiv), and 4-iodotoluene (300.9 mg, 1.38 mmol, 6 equiv) was added dried DMF (3 mL). The mixture was degassed, placed under an atmosphere of argon, and microwaved at 140 °C for 55 min. The solvent was evaporated under reduced pressure, and the reaction mixture was purified by column chromatography on silica gel using 30% ethylacetate/hexane. **1-(4-Methoxybenzyl)-3-*p*-tolyl-1*H*-pyrrole-2,5-dione** (Table 1, entry 10, compound **a**): ^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.82 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 2 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 6.66 (s, 1H), 4.67 (s, 2H), 3.78 (s, 3H), 2.39 (s, 3H); ^{13}C NMR ($CDCl_3$, 176 MHz) δ 170.7, 170.4, 159.3, 143.9, 141.9, 130.1, 129.8, 128.9, 128.7, 126.2, 122.8, 114.1, 55.39, 41.1, 21.7; HRMS (CI) for $C_{19}H_{17}NO_3$ calculated 307.1208 found 307.1208. **1-(4-Methoxybenzyl)-3,4-dip-tolyl-1*H*-pyrrole-2,5-dione** (Table 1, entry 10, compound **b**): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.41 (d, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 7.7 Hz, 4H), 7.15 (d, *J* = 7.7 Hz, 4H), 6.86 (d, *J* = 8.4 Hz, 2H), 4.74 (s, 2H), 3.79 (s, 3H), 2.36 (s, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.8, 159.3, 140.1, 135.6, 130.5, 129.9, 129.4, 129.1, 128.5, 126.1, 114.1, 55.4, 41.5, 21.6; HRMS (CI) for $C_{26}H_{23}NO_3$ calculated 397.1676 found 397.1678.

General Procedure for the Monoarylation of 1-(4-Methoxybenzyl)-3,4-dibromo-1*H*-pyrrole-2,5-dione (3) (Table 2). To a mixture of 1-(4-methoxybenyl)-3,4-dibromo-1*H*-pyrrole-2,5 dione (**3**)[27] (187 mg, 0.5 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (15.5 mg, 0.015 mmol, 3 mol %), PA-Ph, (**2**, R = H, 8.8 mg. 0.03 mmol, 6 mmol %), Cs_2CO_3 (366.0 mg, 1.125 mmol, 2.25 equiv), and the aryl boronic acid (1.1 eq, 0.55 mmol) was added dried THF (3 mL). The mixture was degassed, placed under an atmosphere of argon, and stirred at room temperature for 2−8 h. The solvent was evaporated under reduced pressure, and the reaction mixture was purified by column chromatography on silica gel. **1-(4-Methoxybenzyl)-3-bromo-4-*p*-tolyl-1*H*-pyrrole-2,5-dione** (Table 2, entry 9, compound **a**). Using 4-methylphenylboronic acid (75.0 mg, 0.55 mmol), and the general procedure described above, 1-(4-methoxybenzyl)-3-bromo-4-*p*-tolyl-1*H*-pyrrole-2,5-dione was obtained in 78% yield (150.1 mg, 0.38 mmol) after purification by column chromatography on silica gel using 10% diethyl ether in hexane as the eluent. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.82 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz), 4.72 (s, 2H), 3.79 (s, 3H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 168.8, 165.7, 159.6, 141.7, 130.5, 130.0, 129.7, 129.5, 128.6, 128.3, 125.1, 121.6, 55.5, 42.2, 21; HRMS (CI) for $C_{19}H_{16}BrNO_3$ calculated 385.0314, found 385.0312

General Procedure for Synthesis of Nonsymmetrical Bisaryl Maleimides (Table 3, compound b). To a mixture of the monoarylated maleimide (0.2 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (6.21 mg, 0.006 mmol, 3 mol %), PA-Ph, (**2**, R = H, 3.52 mg. 0.012 mmol, 6 mmol %), Cs_2CO_3 (162.9 mg, 0.45 mmol), and the arylboronic acid (1.2 eq 0.24 mmol) was added dried THF (3 mL). The mixture was degassed, placed under an atmosphere of argon, and stirred at 40 °C for 2 h. The solvent was evaporated under reduced pressure, and the reaction mixture was purified by column chromatography on silica gel. **1-(4-Methoxybenzyl)-3-(4-methoxyphenyl)-4-*p*-tolyl-1*H*-pyrrole-2,5-dione** (Table 3, entry 1, compound **b**). Using 1-(4-methoxybenzyl)-3-bromo-4-*p*-tolyl-1*H*-pyrrole-2,5-dione (77.2 mg, 0.2 mmol), 4-methoxyphenylboronic acid (37.7 mg, 0.24 mmol), and the general procedure described above, 1-(4-methoxybenzyl)-3-(4-methoxyphenyl)-4-*p*-tolyl-1*H*-pyrrole-2,5-dione was obtained in 92% yield (76.0 mg, 0.184 mmol) after purification by column chromatography on silica gel using 30% ethylacetate in hexane as the eluent: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.36−7.50 (m, 6H), 7.17 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 4H), 4.73 (s, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.9, 160.8, 159.2, 139.9, 135.1, 134.3, 131.5, 130.3, 129.7, 129.3, 128.9, 126.1, 121.2, 114.0, 55.3, 41.3, 21.5; HRMS (CI) for $C_{26}H_{23}NO_4$ calculated 413.1627 found 413.1628.

General Procedure for the Deprotection of Nonsymmetrical Bisaryl Maleimides using TFA in Anisole (Table 3, compound c). To a solution of the *p*-methoxybenzyl protected maleimide (0.1 mmol) in anisole (1 mL) was added TFA (1 mL). The reaction mixture was microwaved at 140 °C for 30−60 min. The solvent was evaporated under reduced pressure, and the reaction mixture was purified by column chromatography on silica gel. **3-(2,4-Dimethoxyphenyl)-4-*p*-tolyl-1*H*-pyrrole-2,5-dione** (Table 3, entry 2, compound **c**). Using 4-(1-(4-methoxybenzyl)-3-(2,4-dimethoxyphenyl)-4-*p*-tolyl-1*H*-pyrrole-2,5-dione (44.3 mg, 0.1 mmol) and the general procedure described above, 3-(2,4-dimethoxyphenyl)-4-*p*-tolyl-1*H*-pyrrole-2,5-dione was obtained in 82% yield (26.5 mg, 0.082 mmol) after purification by column chromatography on silica gel using 30% ethylacetate in hexane as the eluent: ^{1}H NMR (CDCl$_3$, 200 MHz) δ 7.36 (d, J = 8 Hz, 2H), 7.31 (s, 1H), 7.11 (d, J = 8 Hz, 2H), 6.56 (d, J = 6.2 Hz, 1H), 6.43 (s, 1H), 3.38 (s, 3H), 3.78 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (CDCl$_3$, 50 MHz) δ 171.0, 170.7, 162.6, 158.7, 140.0, 137.2, 134.5, 132.2, 129.0, 127.5, 110.9, 105. 2, 99.3, 55.6, 55.2, 21.6; HRMS (CI) for $C_{19}H_{17}NO_4$ calculated 323.1158 found 323.1158.

General Procedure for Synthesis of Symmetrical Bisaryl Maleimides (Table 4). To a mixture of 1-(4-methoxybenyl)-3,4-dibromo-1*H*-pyrrole-2,5-dione (**3**) (60.0 mg, 0.16 mmol), Pd$_2$(dba)$_3$·CHCl$_3$ (6.6 mg, 0.006 mmol, 4 mol %), PA-Ph, (**2**, R =H, 3.7 mg. 0.013 mmol, 8 mmol %), Cs$_2$CO$_3$ (208.0 mg, 0.64 mmol 4 equiv) and the arylboronic acid (0.35 mmol, 2.2 equiv) was added dried THF (3 mL). The mixture was degassed, placed under an atmosphere of argon and stirred at 40 °C for 2 h. The solvent was evaporated under reduced pressure and the reaction mixture was purified by column chromatography on silica gel. **1-(4-Methoxybenzyl)-3,4-bis(4-methoxyphenyl)-1*H*-pyrrole-2,5-dione** (Table 4, entry 3, compound **a**). Using 4-methoxyphenylboronic acid (53.5 mg, 0.35 mmol, 2.2 equiv) and the general procedure described above, 1-(4-methoxybenzyl)-3,4-bis(4-methoxyphenyl)-1*H*-pyrrole-2,5-dione was obtained in 95% yield (65.3 mg, 0.152 mmol) after purification by column chromatography on silica gel using 30% ethylacetate in hexane as the eluent: ^{1}H NMR (CDCl$_3$, 200 MHz) δ 7.44 (overlap, 6H), 6.86 (d, J = 8.6 Hz, 6H), 4.72 (s, 2H), 3.84 (s, 3H), 3.82 (s, 3H), 3.78 (s, 3H). ^{13}C NMR (CDCl$_3$, 50 MHz) δ 171.2, 160.8, 159.3, 134.2, 131.6, 130.5, 129.1, 114.2, 55.4, 41.4; HRMS (CI) for $C_{26}H_{24}NO_5$ (M+1) calculated 430.1654 found 430.1645.

General Procedure for Deprotection of Symmetrical Maleimides using AlCl$_3$ in Anisole (Table 4, compound b). To a solution of the *p*-methoxybenzyl protected maleimide (0.1 mmol) in 1 mL anisole was added 5 - 8 equiv of AlCl$_3$. The reaction mixture was microwaved at 140 °C for 30 - 55 min and then poured into water (5 mL). The mixture was extracted with DCM (3 × 6 mL) and the organic layer dried with Na$_2$SO$_4$. Concentration of the solvent under a reduced pressure and purification using column chromatography on silica gel with 30% ethylacetate in hexane as the eluent yielded the deprotected product. **3,4-Bis(4-methoxyphenyl)-1*H*-pyrrole-2,5-dione** (Table 4, entry 3, compound **b**).[33] Using 1-(4-methoxybenzyl)-3,4-bis(4-methoxyphenyl)-1*H*-pyrrole-2,5-dione (43 mg, 0.1 mmol), AlCl$_3$ (66.5 mg, 0.5 mmol, 5 equiv) and the general procedure described above, 3,4-bis(4-methoxyphenyl)-1*H*-pyrrole-2,5-dione was obtained in 88% (27.2 mg, 0.088 mmol) yield: ^{1}H NMR (CDCl$_3$, 200 MHz) δ 7.47 (d, J = 9.1 Hz, 4H), 6.88 (d, J = 9.1 Hz, 4H), 3.83 (s, 6H); ^{13}C NMR (CDCl$_3$, 50 MHz) δ 170.9, 161.0, 135.1, 131.6, 121.2, 114.3, 55.5; HRMS (CI) for $C_{18}H_{15}NO_4$ calculated 309.0998, found 309.1001.

General Procedure for the Synthesis of Monoamino Substituted Maleimides (Table 5, compound a). To a mixture of 1-(4-methoxybenyl)-3,4-dibromo-1*H*-pyrrole-2,5-dione (**3**) (150 mg, 0.4 mmol) and Na$_2$CO$_3$ (134 mg, 1 mmol, 2.5 equiv) in THF (6 mL) was added the amine (0.42 mmol, 1.05 equiv). The reaction mixture was stirred at room temperature for 30 min and up to 2 h depending on the amine used (monitored via TLC) at which time the solvent was evaporated under a reduced pressure. The residue was taken up in DCM (40 mL), washed with water (2 × 10 mL) and dried with Na$_2$SO$_4$. Concentration of DCM under reduced pressure yielded the mono amino substituted maleimide after purification by column chromatography on silica gel. **1-(4-Methoxybenzyl)-3-(*N*-methyl-*N*-phenylamino)-4-bromo-1*H*-pyrrole-2,5-dione** (Table 5 entry 8, compound **a**). Using *N*-methylaniline (45.5 μL, 0.42 mmol, 1.05 equiv) and the general procedure described above, the reaction mixture was warmed to 40 °C for 2 h. 1-(4-Methoxybenzyl)-3-(*N*-methyl-*N*-phenylamino)-4-bromo-1*H*-pyrrole-2,5-dione was obtained in 95% yield (160.4 mg, 0.40 mmol) after purification by column chromatography on silica gel using 10% ethylacetate in hexane as the eluent: ^{1}H NMR (CDCl$_3$, 200 MHz) δ 7.34−7.41 (m, 5H), 7.13 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H); ^{13}C NMR (CDCl$_3$, 50 MHz) δ 166.5, 165.7, 159.2, 144.3, 144.0, 130.2, 129.1, 126.7, 125.2, 114.0, 87.6, 55.3, 41.8, 41.5; HRMS (CI) for $C_{19}H_{17}BrN_2O_3$ calculated 400.0423, found 400.0420.

General Procedure for the Synthesis of 3-Amino-4-aryl Maleimides (Table 5, compound b). To a mixture of the mono aminated maleimide (0.2 mmol), Pd$_2$(dba)$_3$·CHCl$_3$ (6.21 mg, 0.006 mmol, 3 mol %), PA-Ph, (3.52 mg. 0.012 mmol, 6 mmol %), Cs$_2$CO$_3$ (162.9 mg, 0.5 mmol) and the arylboronic acid (1.2 eq, 0.24 mmol) was added dried THF (3 mL). The mixture was degassed, placed under an atmosphere of argon and stirred at 60 °C for 2 h. THF was evaporated under reduced pressure and the reaction mixture was purified by column chromatography on silica gel. **1-(4-Methoxybenzyl)-3-morphilono-4-*p*-tolyl-1*H*-pyrrole-2,5-dione** (Table 5, entry 2, compound **b**). Using 1-(4-methoxybenzyl)-3-bromo-4-morpholino-1*H*-pyrrole-2,5-dione (76.2 mg, 0.2 mmol), 4-methylphenyl boronic acid (32.6 mg, 0.24 mmol) and the general procedure described above, 1-(4-methoxybenzyl)-3-morpholino-4-*p*-tolyl-1*H*-pyrrole-2,5-dione was obtained in 93% yield (71.4 mg, 0.185 mmol) after purification using column chromatography on silica gel with 20% ethylacetate in hexane as the eluent: ^{1}H NMR (CDCl$_3$, 200 MHz) δ 7.35 (d, J = 8.6 Hz, 2H), 7.17 (s, 4H), 6.84 (d, J = 8.6 Hz, 2H), 4.61 (s, 2H), 3.78 (s, 3H), 3.67 (t, J = 4.2 Hz, 4H), 3.50 (t, J = 4.2 Hz, 4H), 2.35 (s, 3H); ^{13}C NMR (CDCl$_3$, 50 MHz) δ 170.9, 167.8, 159.2, 142.9, 137.7, 130.4, 130.1, 129.2, 128.9, 127.7, 114.0, 105.9, 66.8, 55.4, 46.1, 40.9, 21.4. HRMS (CI) for $C_{24}H_{24}N_2O_4$ calculated 392.1736, found 392.1782.

3-(4-Methoxyphenyl)-4-morpholine-1*H*-pyrrole-2,5-dione (Table 5, entry 4, compound c). Using 1-(4-methoxybenzyl)-3-(4-methoxyphenyl)-4-morphholine-1*H*-pyrrole-2,5-dione (40.8 mg, 0.1 mmol), AlCl$_3$ (66.5 mg, 0.5 mmol, 5 equiv) and the general procedure described for deprotection of symmetrical aryl maleimides, 3-(4-methoxyphenyl)-4-morphholine-1*H*-pyrrole-2,5-dione was obtained in 85% yield (24.8 mg, 0.085 mmol) after purification using column chromatography on silica gel with 30% ethylacetate in hexane as the eluent: ^{1}H NMR (CDCl$_3$, 200 MHz) δ 7.24 (d, J = 8.6 Hz, 2H), 6.92 (d, J = 8.6 Hz, 2H) 3.82 (s, 3H), 3.68 (t, J = 4.4 Hz, 4H), 3.51 (t, J = 4.4 Hz, 4H), 170.6, 168.0, 159.3, 142.7, 131.4, 128.5, 122.4, 113.7, 107.0 66.8, 55.3, 48.8; HRMS (CI) for $C_{15}H_{17}N_2O_4$ (M + 1) calculated 289.1188 found 289.1180.

General Procedure for the Synthesis of PMB-Protected Diamino Maleimides. Monoaminated, PMB-protected maleimide (0.2 mmol) in DMF (0.5 mL) was treated with the amine (0.6 mmol, 3 equiv) and TEA (84 μL, 0.6 mmol) the microwaved at 100 °C for 30 min. The reaction mixture was taken up in DCM (10 mL) and washed with water (2 × 5 mL). The organic layer was dried with Na$_2$SO$_4$ and concentrated under reduced vacuum. Purification of the residue by column chromatography on silica gel using 20% ethylacetate in hexane as the eluent yielded the diamino products. **1-(4-Methoxybenzyl)-3-(butylamino)-4-(phenylamino)-1*H*-pyrrole-2,5-dione** (**4**). Using 1-(4-methoxybenzyl)-3-bromo-4-(phenylamino)-1*H*-pyrrole-2,5-dione (77.2 mg, 0.2 mmol) and butyl amine (60 μL, 0.6 mmol) and the general procedure described above, 1-(4-methoxybenzyl)-3-(butylamino)-4-(phenylamino)-1*H*-pyrrole-2,5-dione was obtained 84% yield (63 mg, 0.167 mmol): ^{1}H NMR (CDCl$_3$, 200 MHz) δ 7.20−7.39 (m, 5H), 7.13 (d, J = 9.2 Hz, 3H), 6.84 (d, J = 7.2 Hz, 1H), 5.10 (s, 1H), 4.89 (b, 1H), 3.78 (s, 3H), 3.14 (q, J = 6.6 Hz, 2H), 1.35−1.45 (m, 2H), 1.14−1.45 (m, 2H), 0.78 (t, J = 7.0 Hz, 3H); ^{13}C NMR (CDCl$_3$, 50 MHz) δ 171.0, 168.1, 159.3, 145.9, 130.0, 129.9, 129.4, 125.7, 119.8, 118.9, 114.8, 114.1, 55.4, 43.3, 41.0, 32.8, 19.8, 13.7: HRMS (CI) for $C_{22}H_{26}N_3O_3$ (M + 1) calculated 380.1969, found 380.1960.

1-(2,5-Dioxo-4-(phenylamino)-2,5-dihydro-1*H*-pyrrol-3-yl)-1-(4-methoxybenzyl)piperidinium Chloride (9). Using 1-(4-methoxybenzyl)-3-(phenylamino)-4-(piperidin-1-yl)-1*H*-pyrrole-2,5-dione

(39.2 mg, 0.1 mmol), $AlCl_3$ (66.5 mg, 0.5 mmol, 5 equiv), anisole (2 mL) and stirring the reaction at room temperature for 12 h, yielded compound **9** in 89% yield (34.9 mg, 0.089 mmol) after purification using 30% ethylacetate in hexane as the eluent: ^1H NMR ($CDCl_3$, 200 MHz) δ 7.48 (d, J = 7.6 Hz, 1H), 7.15−7.27 (overlap, 4H), 6.64−6.88 (overlap, 4H), 4.67 (s, 1), 4.55 (s, 3H), 3.75 (s, 3H), 2.31−2.33 (m, 4H), 1.41−1.45 (m, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 176.0, 175.6, 159.3, 149.4, 131.0, 129.8, 127.7, 126.1, 124.3, 120.4, 114.1, 78.9, 56.7, 55.3, 48.5, 42.3, 25.8, 24.5; HRMS (CI) for $C_{23}H_{26}N_3O_3$ calculated 392.1969 found 392.1966.

3,4-Bromo-1-(4-nitrophenyl)-1*H*-pyyrole-2,5-dione (11). To a mixture of 3,4-dibromomaleic anhydride (1.95 g, 7.65 mmol) in acetic acid (25 mL) was added *p*-nitroaniline (1.16 g, 8.4 mmol). The reaction mixture was refluxed for 8 h. Evaporation of the solvent under reduced pressure was followed by column chromatography on silica gel using 30% ethylacetate in hexane as the eluent, 3,4-Bromo-1-(4-nitrophenyl)-1*H*-pyyrole-2,5-dione was obtained in 75% yield (2.13 g, 5.7 mmol): ^1H NMR ($CDCl_3$, 200 MHz) δ 8.35 (d, J = 9.1 Hz, 2H), 7.66 (d, J = 9.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 162.3, 146.9, 136.7, 130.6, 125.9, 124.8; HRMS (CI) for $C_{10}H_4BrN_2O_4$ calculated 373.8538 found 373.8538.

General Procedure for the Synthesis of Bisamino Substituted Maleimides (Table 6, compound b). To a mixture of 3,4-dibromo-1-(4-nitrophenyl)-1*H*-pyrrole-2,5-dione, compound (**11**) (93 mg, 0.25 mmol), TEA (88 μL, 0.63 mmol, 2.5 equiv) in DMF (0.5 mL) was added the amine (0.26 mmol, 1.05 equiv). The reaction mixture was stirred at room for 3 min at which time additional TEA (88 μL, 0.63 mmol, 2.5 equiv) and the second amine (0.38 mmol, 1.5 equiv) were added. The reaction mixture was microwaved at 50 °C for 30 min, then taken up in DCM (10 mL) and washed with water (2 × 5 mL). The organic extract was dried with Na_2SO_4 and concentrated under reduced pressure. Purification of the mixture using column chromatography on silica gel with 20% ethylacetate in hexane as the eluent yielded the diamino substituted maleimides. **3-Morpholino-1-(4-nitrophenyl)-4-(phenylamino)-1*H*-pyrrole-2,5-dione** (Table 6, entry 1, compound **b**). Using aniline (24.6 μL, 0.26 mmol) as the first amine, morpholine (33.2 μL, 0.38 mmol) as the second amine and the general procedure described, 3-morpholino-1-(4-nitrophenyl)-4-(phenylamino)-1*H*-pyrrole-2,5-dione was obtained in 93% yield (91.5 mg, 0.23 mmol): ^1H NMR ($CDCl_3$, 700 MHz) δ 8.30 (d, J = 9.1, 2H), 7.70 (d, J = 9.1, 2H), 7.34 (t, J = 7.7 Hz, 2H), 7.03 (t, J = 7.7 Hz, 1H), 6.88 (d, J = 7.7 Hz, 2H), 6.19 (s, 1H), 3.52 (t, J = 4.9 Hz, 4H), 3.90 (t, J = 4.9 Hz, 4H); ^{13}C NMR ($CDCl_3$, 176 MHz) δ 167.3, 166.5, 145.6, 140.1, 137.8, 129.3, 124.9, 124.7, 124.5, 122.5, 118.4, 115.8, 66.9. 48.4. HRMS (CI) for $C_{20}H_{18}N_4O_5$ calculated 394.1277 found 394.1275.

General Procedure for the Deprotection of Nitroaniline-Protected Diamino Maleimides by Aminolysis (Table 6, compound c). Ammonia gas was bubbled through a solution of the nitroaniline-protected maleimide (0.15 mmol) in methanol (3 mL). The reaction mixture was stirred at room temperature for 12 h. Concentration of the methanol under reduced pressure and purification using column chromatography on silica gel with 20% ethylacetate in hexane as the eluent yielded the diamino substituted maleimides. **3-Morpholino-4-(phenylamino)-1*H*-pyrrole-2,5-dione** (Table 6, entry 1, compound **c**). Using 3-morpholino-1-(4-nitrophenyl)-4-(phenylamino)-1*H*-pyrrole-2,5-dione (59.2 mg, 0.15 mmol) and the general procedure described above, 3-morpholino-4-(phenylamino)-1*H*-pyrrole-2,5-dione was obtained in 84% yield (34.7 mg, 0.127 mmol): ^1H NMR ($CDCl_3$, 700 MHz) δ 7.29 (t, J = 4.6 Hz, 2H), 7.06 (b, 1H), 6.91 (t, J = 4.2 Hz, 1H), 6.79 (d, J = 2.2 Hz, 2H), 5.94 (s, 1H), 3.51 (t, J = 2.6 Hz, 4H), 3.38 (t, J = 2.6 Hz, 4H). ^{13}C NMR ($CDCl_3$, 176 MHz) δ 168.9, 168.2, 141.2, 129.2, 126.9, 121.7, 117.6, 114.9, 66.9, 48.0; HRMS (EI): for $C_{14}H_{15}N_3O_3$ calculated 273.1113 found 273.1129.

1-(4-Methoxybenzyl)-3,4-dibromo-1*H*-pyrrol-2(5*H*)-one (12). To a mixture of mucobromic acid (1.32 g, 5.2 mmoL) in DCM (25 mL) and acetic acid (15 mL) was added *p*-methoxybenylamine (744 μL, 5.7 mmol, 1.1 equiv) and $NaBH(OAc)_3$ (3.30 g, 15.6 mmol, 3 equiv). The reaction mixture was stirred at room temperature for 24 h at which time the mixture was taken up in $CHCl_3$ (100 mL) and washed with water (2 × 50 mL). The organic layer was dried with Na_2SO_4, concentrated under a reduced pressure and purified using column chromatography on silica gel with 30% ethylacetate in hexane as the eluent. compound **12** was obtained in 76% yield (1.4 g, 4 mmol): ^1H NMR ($CDCl_3$, 200 MHz) δ ^1H NMR 7.18 (d, J = 8 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 4.59 (s, 2H), 3.90 (s, 2H), 3.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 165.0, 159.4, 133.6, 129.3, 127.8, 120.6, 114.2, 56.8, 55.6, 47.4. HRMS (CI) for $C_{12}H_{11}Br_2NO_2$ calculated 358.9157 found 358.9155.

General Procedure for Monoarylated α,β-Unsaturated-γ-butyrolactams (Table 7, compound a). To a mixture of 1-(4-methoxybenzyl)-3,4-dibromo-1*H*-pyrrol-2(5*H*)-one compound (**12**) (100 mg, 0.28 mmol), aryl boronic acid (0.31 mmol, 1.1 equiv), KF (48.7 mg, 0.84 mmol, 3eq), $Pd_2(dba)_3 \cdot CHCl_3$ (11.4 mg, 0.011 mmol, 4 mol %), PA-Ph, (6.4 mg. 0.022 mmol, 8 mmol %), in a reaction flask was added dried toluene (3 mL). The mixture was degassed, placed under an atmosphere of argon and stirred at 60 °C for 9 h. Toluene was evaporated under reduced pressure and the reaction mixture was purified by column chromatography using 30% ethylacetate in hexane as the eluent. **1-(4-Methoxybenzyl)-3-bromo-4-*p*-tolyl-1*H*-2(5*H*)-one** (Table 7, entry 7, compound **a**). Using 4-methylphenylboronic (42.5 mg, 0.31 mmol) and the general procedure described above, 1-(4-methoxybenzyl)-3-bromo-4-*p*-tolyl-1*H*-2(5*H*)-one was obtained in 68% yield (70.5 mg, 0.19 mmol): ^1H NMR ($CDCl_3$, 200 MHz) δ ^1H NMR ($CDCl_3$, 200 MHz) δ 7.68 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.0 Hz, 4H), 6.89 (d, J = 8.6 Hz, 2H), 4.67 (s, 2H), 4.15 (s, 2H), 3.80 (s, 3H), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 167.3, 159.5, 147.9, 140.8, 129.8, 129.7, 128.9, 128.8, 127.0, 114.5, 113.0, 55.5, 52.7, 46.8, 21.7; HRMS (CI) for $C_{19}H_{18}BrNO_2$ calculated 371.0521 found 371.0520.

General Procedure for the Preparation of Bisaryl Substituted α,β-Unsaturated-γ-butyrolactams (Table 8, compound b). To a mixture of the monoarylated 3-bromo-1*H*- pyrrol-2(5*H*)-one compound (0.1 mmol), aryl boronic acid (0.12 mmol, 1.2 equiv), KF (17.7 mg, 0.3 mmol, 3 equiv), $Pd_2(dba)_3 \cdot CHCl_3$ (4.1 mg, 0.004 mmol, 4 mol %), PA-Ph, (2.3 mg. 0.008 mmol, 8 mmol %) was added dried toluene (3 mL). The mixture was degassed, placed under an atmosphere of argon and stirred 80 °C for 12 h. Toluene was evaporated under reduced pressure and the reaction mixture was purified by column chromatography using with 30% ethylacetate in hexane as the eluent. **1-(4-Methoxybenzyl)-4-(4-methoxyphenyl)-3-*p*-tolyl-1*H*-2(5*H*)-one** (Table 8, entry 1, compound **b**). Using 1-(4-methoxybenzyl)-3-bromo-4-(4-methoxyphenyl)-1*H*-2(5*H*)-one (38.8 mg, 0.1 mmol) and 4-methylphenylboronic acid (16 mg, 0.12 mmol) and the general procedure described above, 1-(4-methoxybenzyl)-4-(4-methoxyphenyl)-3-*p*-tolyl-1*H*-2(5*H*)-one was obtained in 78% yield (31.2 mg, 0.078 mmol): ^1H NMR ($CDCl_3$ 200 MHz) δ 7.18−7.32 (m, 8H), 6.88 (d, J = 8.2 Hz, 2H), 6.76 (d, J = 8.2 Hz, 2H), 4.69 (s, 2H), 4.13 (s, 2H), 3.81 (s, 3H), 3.78 (s, 3H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 176 MHz) δ 170.1, 160.1, 159.1, 146.5, 137.7, 130.8, 129.7, 129.6, 129.5, 129.4, 129.2, 128.9, 125.7, 114.1, 114.0, 55.3, 51.7, 45.8, 21.4; HRMS (CI) for $C_{26}H_{25}NO_3$ calculated 399.1834 found 399.1823.

1-(4-Methoxyphenyl)-3-*p*-tolyl-1*H*-2(5*H*)-one (Table 8, entry 1, compound c). Using 1-(4-methoxybenzyl)-4-(4-methoxyphenyl)-3-*p*-tolyl-1*H*-2(5*H*)-one (28 mg, 0.07 mmol), TFA (1 mL) anisole (1 mL) and the general procedure above, 1-(4-methoxyphenyl)-3-*p*-tolyl-1*H*-2(5*H*)-one was obtained in 84% yield (14.0 mg, 0.059 mmol): ^1H NMR ($CDCl_3$, 200 MHz) δ 7.15−7.31(m, 6H), 6.80 (d, J = 8.4 Hz, 2H), 4.34 (s, 2H), 3.80 (s, 3H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ174.8, 160.5, 149.7, 138.0, 131.0, 129.6, 129.5, 129.3, 129.2, 125.9, 114.3, 55.7, 48.1, 21.7; HRMS (CI) for $C_{18}H_{17}NO_2$ calculated 279.1259 found 279.1257.

ASSOCIATED CONTENT

Ⓢ Supporting Information. MS and ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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ACKNOWLEDGMENT

The authors thank the Natural Sciences and Engineering Research Council of Canada, the Canadian Foundation for Innovation, and the Ontario Innovation Trust for their financial support.

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