Efficient palladium-catalyzed synthesis of 3-aryl-4-indolylmaleimides

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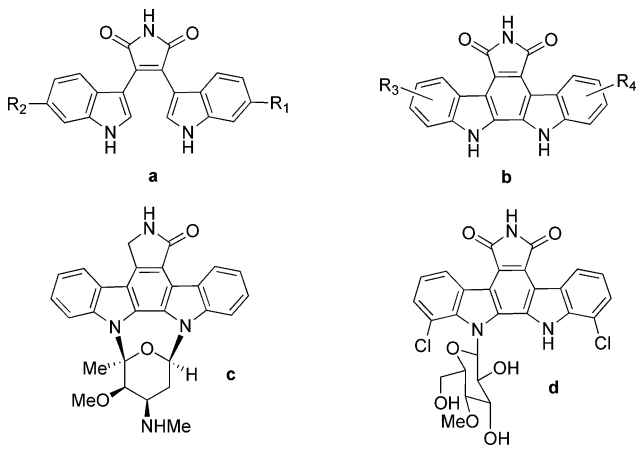
Received 12th December 2007, Accepted 28th January 2008
First published as an Advance Article on the web 14th February 2008
DOI: 10.1039/b719160j

Improved palladium catalysts for the Suzuki coupling of 3-bromo-1-methyl-4-(2-methyl-3-indolyl)maleimide have been developed. The coupling of both aryl- and heteroarylboronic acids proceeds smoothly in good to excellent yields at low catalyst loading.

A number of biologically active compounds of current interest is characterized by a 3,4-bisindolylmaleimide subunit. Among these products, arcyriarubins represent the simplest members of the naturally occurring 3,4-bisindolylmaleimides (Scheme 1; **a**).[1,2] In general, they are structurally related to the arcyriaflavines[1a,1b,1d] (**b**) and to the aglycon of the well-known staurosporine[3] (**c**), rebeccamycine[4] (**d**), and other biologically active metabolites. Notably, synthetic analogues of these and related natural products possess wide spectra of antibacterial, antiviral, antimicrobial and antigenic activities.[3g–3i, 5,6]



Scheme 1 Arcyriarubins (**a**), arcyriaflavins (**b**), staurosporine (**c**), and rebeccamycine (**d**).

Furthermore, derivatives of this class of compounds are promising agents for autoimmune diseases,[7] *e.g.* diabetes, cancer, as well as valuable inhibitors of different protein kinases,[8] especially PKC, which plays an important role in many signal transduction pathways. Interestingly, some derivatives are currently being evaluated in human clinical trials as anticancer drugs.[9]

Besides their pharmaceutical importance, 3,4-bisindolylmaleimides have also found application as components in red-light emitting diodes (LED) due to their intensive color.[10]

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Based on our interest in the development of transition metal-catalyzed syntheses of indoles,[11] and the application of novel palladium catalysts in coupling reactions of aryl and heteroaryl halides,[12] we recently became attracted to the study of palladium-catalyzed coupling reactions of 3-bromo-1-methyl-4-(2-methylindolyl)maleimide and the synthesis of novel 3-indolyl-4-aryl(heteroaryl)maleimides.

In this paper, we describe our initial investigations, which resulted in an efficient two step synthesis of potentially bioactive unsymmetrically substituted maleimides using either $Pd(OAc)_2$–triphenylphosphine or $Pd(OAc)_2$–*n*-butyl-di-1-adamantylphosphine[13] catalysts.

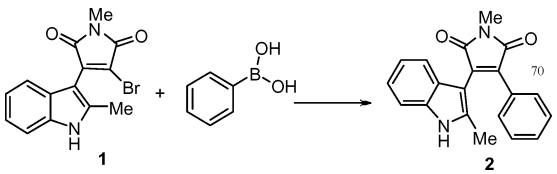
In the past, several research groups have synthesized 3-indole-substituted maleimides.[14] The most widely used synthetic protocols were developed by the groups of Steglich[15] and Faul.[16] Notably, both methods allow for the synthesis of unsymmetrically disubstituted maleimides.[17] According to the Steglich procedure, indolyl magnesium bromide is reacted with commercially available 3,4-dibromomaleimide to give mono- or disubstituted products depending on the ratio of starting materials. It should be noted that the outcome of this reaction is strongly dependent on the solvent. The procedure of Faul *et al.*[16] involves a one step condensation of substituted (aryl or indolyl) acetamides with substituted (aryl or indolyl) glyoxyl esters in the presence of strong base.

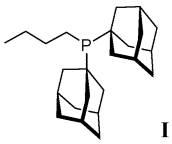
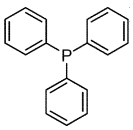
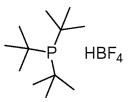
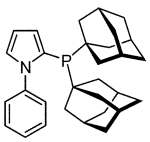
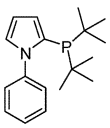
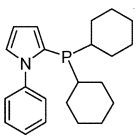
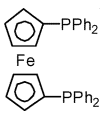
While a number of simple 3-aryl-4-(3-indolyl)maleimides is known, derivatives substituted at the 2-position of the indole are less common. Because of the easy access to such derivatives by hydroamination chemistry,[11] we chose 2-methylindole as a model substrate. Thus, we first synthesized 3-bromo-1-methyl-4-(2-methyl-3-indolyl)maleimide[6a] (**1**), starting from commercially available 3,4-dibromomaleimide and 2-methylindole. Applying the protocol of Steglich gave the desired monosubstituted product in 68% isolated yield. In addition, a minor amount of the corresponding disubstituted product (5%) was isolated. To our delight, applying lithium hexamethyldisilazane as base,[1b] compound **1** was obtained in excellent selectivity and nearly quantitative yield (98%).

Next, the Suzuki coupling reaction[18] of **1** with phenylboronic acid was performed in the presence of 0.05–4 mol% $Pd(OAc)_2$ and seven different phosphine ligands (Table 1). Notably, the first Suzuki coupling reaction of an indolylmaleimide triflate derivative to bisindolylmaleimides using $Pd_2(dba)_3$–$CHCl_3$ (4 mol%) was described by Neel *et al.*[19] So far, Suzuki coupling reactions for the synthesis of indolyl and aryl disubstituted maleimides have only been described for ligand free catalysts at high catalyst loading (10 mol% Pd).[20] To the best of our knowledge, no ligand variation has been performed for such reactions.

Low yields were observed with tri-*tert*butylphosphine **III** and 1,1′-bisdiphenylphosphinoferrocene **VII** (Table 1, entries 3

Table 1 Model coupling reaction using $Pd(OAc)_2$ and different ligands.[a]



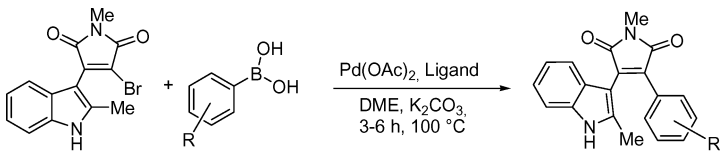
Entry	Ligand	Ligand (mol%)	$Pd(OAc)_2$ (mol%)	Reaction time/h	Yield (%)[b]
1	 **I**	1	0.5	3	99
2	 **II**	1 0.5	0.5 0.05	3 3	99 99
3	 **III**	8	4	20	10
4	 **IV**	8	4	20	58
5	 **V**	8	4	20	58
6	 **VI**	8	4	20	69
7	 **VII**	8	4	20	37

[a] *Reaction conditions:* compound **1** (1 mmol), phenylboronic acid (1.5 mmol), $Pd(OAc)_2$ (0.05–4 mol%), ligand (0.5–8 mol%), solvent: dimethoxyethane (3 ml), base: K_2CO_3 (1M solution in water, 3 ml), 100 °C. [b] Isolated yield based on **1**.

and 7). Electron rich, sterically hindered biaryl type ligands **IV–VI** gave mediocre yields (Table 1, entries 4–6). However, in the presence of *n*-butyl-di-1-adamantylphosphine **I** (cata*CX*ium A) and triphenylphosphine **II**, quantitative coupling to **2** took place. Even at comparably low catalyst loading (0.5 mol% Pd with **II** and 0.05 mol% Pd with **I**) an excellent yield of the corresponding product **2** was obtained in 3 h (Table 1, entries 1 and 2). The resulting catalyst turnover numbers up to 2000 are the highest so far reported for coupling reactions of 3-bromo-4-indolylmaleimides.

Next, coupling reactions of 4-acetyl- and 2,6-dimethylphenylboronic acid with **1** in the presence of the two best ligands **I** and **II** were performed (Table 2, entries 1–3). In case of 4-acetylphenylboronic acid, the catalyst–ligand system **I** gave a slightly higher yield compared to catalyst–ligand **II**. On the other hand, coupling of the sterically hindered 2,6-dimethylphenylboronic acid proceeded only in the presence of triphenylphosphine. Apparently, steric factors have strong influence on this coupling reaction. As shown in Table 2, the Suzuki coupling of different substituted phenylboronic acids led to the corresponding

Table 2 Pd-catalyzed coupling reactions of 3-bromo-1-methyl-4-(2-methylindolyl)maleimide **1** with arylboronic acids[a]



1 **3-13**

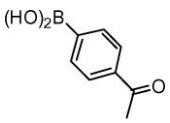
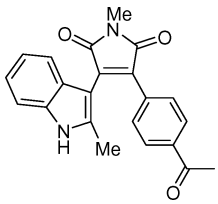
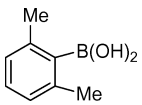
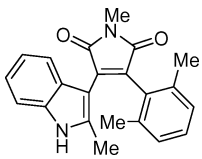
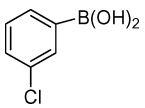
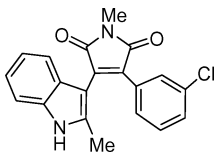
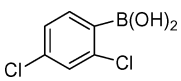
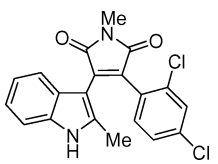
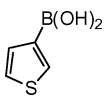
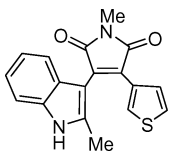
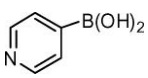
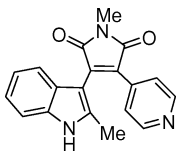
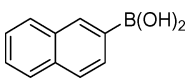
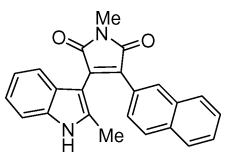
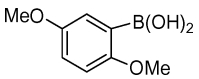
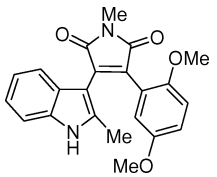
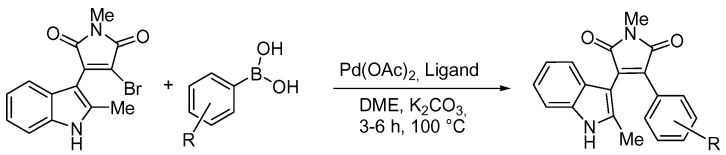
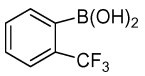
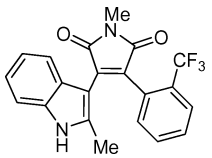
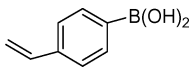
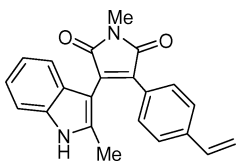
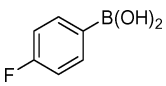
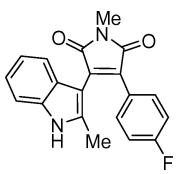
Entry	Compound	Arylboronic acid	Product	Ligand (mol%)	$Pd(OAc)_2$ (mol%)	Reaction time/h	Yield (%)[b]
1	**3**			4	2	3.5	99
2	**4**			4[c]	2	18	96
3				4[c]	2	3	87
4	**5**			1[c]	0.5	3	97
5	**6**			2	1	3	60
6	**7**			2.5	2	15	97
7	**8**			1[c]	0.5	3	95
8				3	1.5	8	60
9	**9**			1[c]	0.5	3	10
10				2.5	2	15	96
11	**10**			1[c]	0.5	3	95
12				1[c]	0.5	3	93

Table 2 (*Contd.*)



Entry	Compound	Arylboronic acid	Product	Ligand (mol%)	$Pd(OAc)_2$ (mol%)	Reaction time/h	Yield (%)[b]
13	**11**			2.5	2	15	51
14				1[c]	0.5	3	46
15	**12**[21]			2.5	2	15	93
16				1[c]	0.5	3	77
17	**13**			1[c]	0.5	3	99

[a] *Reaction conditions:* **1** (1 mmol), arylboronic acid (1.5 mmol), $Pd(OAc)_2$ (0.5–2 mol%), ligand (1–4 mol%), solvent: dimethoxyethane (3 ml), base: K_2CO_3 (1M solution in water, 3 ml), 100 °C. [b] Isolated yield based on compound **1**. [c] Ligand **II** was used.

3-aryl-4-(3-indolyl)maleimides in good to excellent yields. Except for *ortho*-substituted arylboronic acids with electron-withdrawing groups, all coupling reactions proceeded smoothly in yields >90% (often >95%) (Table 2, entries 1, 2, 4, 6, 7, 10, 11, 12, 15, and 17).

An interesting example is the coupling reaction of 4-vinylphenylboronic acid (Table 2, entries 15 and 16). Here, no competitive Heck reaction was observed and the product could be easily further functionalized. Among the used substrates, 2,4-dichlorophenylboronic acid was somewhat more problematic (60% yield; Table 2, entry 5). In this case side-reactions because of the activation of the C–Cl bond were observed. Notably, heteroarylboronic acids such as 4-pyridinyl- and 3-thiophenylboronic acids also gave the pharmaceutically interesting 3-heteroaryl-substituted maleimides in 60–97% yield (Table 2, entries 6–9). The low yield in the presence of triphenylphosphine is ascribed to competitive coordination of the pyridine.

It is worth mentioning that all coupling products are bright colored crystalline compounds.

In conclusion, the palladium-catalyzed Suzuki coupling of 3-bromo-1-methyl-4-(2-methylindolyl)maleimide with various arylboronic acids proceeded smoothly. High yields and unprecedented catalyst turnover numbers have been obtained for this class of compounds. The resulting 3-aryl-4-(2-methyl-3-indolyl)maleimides constitute new potentially biologically active compounds. Protection and deprotection of the indole nitrogen are not necessary. Biological tests of the isolated compounds are currently in progress.

Acknowledgements

This work has been supported by the State of Mecklenburg-Western Pomerania, the BMBF (Bundesministerium für Bildung und Forschung), the Deutsche Forschungsgemeinschaft (Leibniz-price; GRK 1113), and the Fonds der Chemischen Industrie (FCI). We also thank Dr W. Baumann, Dr C. Fischer, S. Schareina, S. Buchholz, A. Lehmann, K. Mevius, and K. Reincke for their excellent technical and analytical support.

Notes and references

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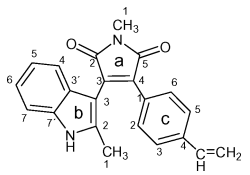
21 **General procedure:**



In an Ace-pressure tube, into a solution of 3-bromo-1-methyl-4-(2-methylindolyl)-maleimide (**1**) (1 mmol) and 4-vinylphenylboronic acid (1.5 mmol) in dimethoxyethane (3 ml) were added K_2CO_3 (1M in water, 3 ml), $Pd(OAc)_2$ (2 mol%) and ligand **I** (2.5 mol%) under argon atmosphere. The pressure tube was fitted with a Teflon cap and heated at 100 °C for 15 h (TLC control). The mixture was cooled to room temperature and diluted with ethyl acetate. The organic layer was washed with saturated aqueous ammonium chloride (2 × 30 mL) and water. After removal of the solvent *in vacuo*, the coupling product **12** was isolated by column chromatography in hexane–ethyl acetate. Isolated yield: 318 mg (93%); red-orange crystals; mp 208–210 °C (from CH_2Cl_2–heptane); R_f = 0.3 (hexane–ethyl acetate 2 : 1); ^{1}H

NMR (300 MHz, $CDCl_3$) δ 2.14 (s, 3H, H-1b), 3.17 (s, 3H, H-1a), 5.25 (dd, 1H, $J = 0.66$ Hz, $J = 10.89$ Hz, –CH=CH_2), 5.72 (dd, 1H, $J = 0.70$ Hz, $J = 17.61$ Hz, –CH=CH_2), 6.63 (dd, 1H, $J = 10.88$ Hz, $J = 17.62$ Hz, –CH=CH_2), 6.96 (m, 1H, H-6b), 7.09 (m, 2H, H-4b, H-5b), 7.23 (m, 1H, H-7b), 7.27 (m, 2H, H-3c, H-5c), 7.53 (m, 2H, H-2c, H-6c), 8.32 (br s, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.8 (C-1b), 24.3 (C-1a), 103.0 (C-3b), 110.6 (C-7b), 115.1 (–CH=CH_2), 120.4 (C-6b), 120.6 (C-4b), 122.1 (C-5b), 126.2 (2C, C-3c, C-5c), 126.6 (C-7′b), 129.6 (2C, C-2c, C-6c), 129.7 (C-1c), 132.8 (C-3a), 133.8 (C-4a), 135.8 (C-3′b), 136.3 (–CH=CH_2), 136.9 (C-2b), 138.2 (C-4c), 171.3 (C-2a), 171.6 (C-5a); MS (EI, 70 eV) m/z (rel. intensity): 342 (100) [M^+], 270 (15), 257 (16), 256 (25), 228 (5), 127 (10). HRMS (EI): Calcd for $C_{22}H_{18}N_2O_2$: 342.13628. Found: 342.13618; Anal. calcd for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30; N, 8.18. Found: C, 76.80; H, 5.31; N, 8.01%; IR (ATR, cm^{-1}): 3380, 3053, 2920, 1745, 1689, 1456, 1428, 1383, 1235, 990, 903, 847, 814, 741, 656.