<u>Cramic</u> LETTERS

Palladium-Catalyzed Tandem Regioselective Oxidative Coupling from Indoles and Maleimides: One-Pot Synthesis of Indolopyrrolocarbazoles and Related Indolylmaleimides

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Supporting Information

ABSTRACT: An efficient Pd(II)-catalyzed approach for the direct synthesis of indolo[3,2-a]pyrrolo[3,4-c]carbazole-6,8-diones has been developed from both free and protected (NH) indoles and maleimides via a regioselective tandem oxidative coupling reaction. The yields are moderate to excellent. In addition, 2-substituted indoles are suitable substrates in this protocol, leading to the formation of indolylmaleimides. The



present methodology provides a concise route to highly functionalized indolopyrrolocarbazole derivatives.

he indolocarbazole nucleus is incorporated in a wide range of natural products,¹ pharmaceuticals,² photorefractive materials, and organic dyes.³ Staurosporine was the first discovered indolocarbazole from Actinomyces. A variety of indolocarbazole analogues have since been isolated and confirmed.¹ Most of them have shown to be effective protein kinase inhibitors, offering tremendous promise in anticancer activity. However, staurosporine has significant specificity to kinases in the human body.⁴ Previous researchers modified the structure of staurosporine to obtain novel skeletons, such as indolylmaleimides and indolopyrrolocarbazoles.⁵ However, almost all of the indolopyrrolocarbazoles isolated from nature are indolo[2,3-a]pyrrolo[3,4-c]carbazoles; little attention has been paid to its isomers, such as indolo[3,2-*a*]pyrrolo[3,4-*c*]carbazole-6,8-dione.⁶ Fonseca et al. reported the indolo [3,2-a] pyrrolo [3,4*c*]carbazole-6,8-dione in the synthesis of arcyriaflavin-A with low yield.^{6a} Subsequently, Bergman and Janosik finished the synthesis from indole^{6b} and 2,3'-biindolyl,^{6c} respectively. The yields were still unsatisfactory (<26%). Derivatives were obtained as byproducts in the synthesis of indolylsuccinimides with 1-2% yield.^{6d,e} Thus, an efficient synthetic methodology is highly desirable for this process.

Palladium-catalyzed oxidative cross-coupling reactions have drawn much interest due to their C–C bond formations via direct C–H functionalization.^{7–16} Indeed, they have been widely utilized in the synthesis of heterocycles through oxidative crosscoupling of alkenes with arenes⁸ or heteroarenes,⁹ acrylates with vinyl carboxylates,¹⁰ 2-oxazolones with olefins,¹¹ heteroarenes with alkynes,¹² and arenes with arenes.¹³

Gaunt et al. reported indole alkenylation in a formal C–H/C– H coupling fashion in 2005, elegantly achieving C-2- or C-3selective introduction of various alkenyl groups to indoles.^{14a} In recent years, research topics on Pd-catalyzed intermolecular alkenylation of indoles or pyrrole via C–H functionalization have been reported continuously.^{15,16} Itami et al. demonstrated the formation of carbazoles from N-protected indoles via a Diels– Alder reaction using trimetallic and bimetallic systems of Pd– Cu–Ag.^{16a} Most carbazole syntheses are successful with Nprotected indoles and remain challenging with a free (NH) indole. Notably, during the preparation of this paper, a Pdcatalyzed alkenylation of indoles and subsequent conversion to the 1,3-disubstituted carbazoles appeared.^{16b} A tandem approach to functionlized carbazoles from indoles with alkenes via two successive regioselctive oxidative Heck reactions followed by thermal electrocyclization was also developed (Scheme 1).^{16c}





Nevertheless, a literature survey revealed that the synthesis of both indolopyrrolocarbazoles and indolylmaleimides via oxidative Heck reactions has not been reported. In our continued research program directed toward the synthesis of indolylsuccimides and related indolylmaleimides in this area,¹⁷ and intrigued

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Table 1. Optimization of Reaction Conditions^a



entry	catalyst ^b (mol %)	oxidant (equiv)	solvent	temp (°C)/time (h)	yield ^d (%)
1	$Pd(OAc)_2/10$	$Cu(OAc)_2/1.5$	DMSO	80/18	56
2	$Pd(OAc)_2/10$	Ag ₂ CO ₃ /1.5	DMSO	80/24	17
3	$Pd(OAc)_2/10$	AgNO ₃ /1.5	DMSO	80/24	15
4	$Pd(OAc)_2/10$	DDQ/1.5	DMSO	80/24	0
5	$Pd(OAc)_2/10$	O ₂	DMSO	80/24	0
6	$Pd(OAc)_2/10$	$Cu(OAc)_2/0.5$	DMSO	80/36	13
7	$Pd(OAc)_2/10$	$Cu(OAc)_2/1.5$	DMF	80/18	34
8	$Pd(OAc)_2/10$	$Cu(OAc)_2/1.5$	dioxane	80/24	trace
9	$Pd(OAc)_2/10$	$Cu(OAc)_2/1.5$	DMF/DMSO ^c	80/18	75
10	$Pd(OAc)_2/10$	$Cu(OAc)_2/1.5$	DMF/DMSO ^c	rt/120	27
11	$Pd(OAc)_2/10$	$Cu(OAc)_2/1.5$	DMF/DMSO ^c	120/18	58
12 ^b	$Pd(OAc)_2/10$	$Cu(OAc)_2/1.5$	DMF/DMSO ^c	80/18	16
13	$Pd(OAc)_2/10$	$Cu(OAc)_2/1.5$	AcOH/DMSO ^c	80/18	25
14	PdCl ₂ /15	$Cu(OAc)_2/1.5$	DMF/DMSO ^c	80/18	62

^{*a*}Reactions were performed using indole 1a (1.5 mmol), maleimide 2a (0.75 mmol), catalyst, and oxidant in 3 mL of solvent. ^{*b*}Indole 1a (0.75 mmol) and maleimide 2a (1.5 mmol) were used. ^{*c*}v/v = 1:5. ^{*d*}Isolated yield based on maleimide.

by the advantages of using direct Pd-catalyzed C–H functionalization for C–C bond formation, we envisioned that free or protected (NH) indoles could be linked with the C=C bond of maleimides via oxidative Heck reactions. Herein, we report the direct synthesis of indolo[3,2-a]pyrrolo[3,4-c]carbazole-6,8diones and 3-(2-substituted indol-<math>3-y])maleimides via Pdcatalyzed regioselective tandem cross-coupling reactions.

Initially, we began our study with indole 1a and maleimide 2a to screen the reaction conditions in the presence of 10 mol % of $Pd(OAc)_2$ as the catalyst and 150 mol % of $Cu(OAc)_2$ as the oxidant (Table 1). Compound indolo[3,2-a]-pyrrolo-[3,4-c]carbazole-6,8-dione 3a was obtained in 56% yield in DMSO at 80 °C (Table 1, entry 1). Product 3a was fully characterized by spectrum analysis, which was identical to the data reported in the literature.^{6a,b} Next, to improve the yield, our research plan was returned to screen various oxidants and solvents to get the optimal reaction conditions (Table 1). Unfortunately, poor results were obtained when oxidants such as Ag₂CO₃ and AgNO₃ were used (Table 1, entries 2 and 3). DDQ and O_2 barely worked as oxidant (Table 1, entries 4 and 5). Decreasing the dosage of $Cu(OAc)_2$ gave a poor yield of product 3a around 13% (Table 1, entry 6). The reaction did not work well using DMF and dioxane as solvent (Table 1, entries 7 and 8). The process afforded 3a in 75% yield using a mixture of DMF/DMSO (v/v, 1/5) as solvent (Table 1, entry 9). The reaction could work at room temperature for a long time and gave a low yield (27%, Table 1, entry 10). However, increasing the temperature to 120 °C, the reaction became complex, and the yield decreased to 58% due to the partial polymerization of maleimides (Table 1, entry 11). When the ratio of indole to maleimide was decreased to 1:2, only 3a was collected in 16% yield (Table 1, entry 12). Our results indicated 2 equiv of indoles and 1 equiv of maleimide took part in the formation of the indolo[3,2-*a*]pyrrolo[3,4-*c*]carbazole-6,8-dione annulations even if a large excess maleimide was used. Protonic acid did not work well as cosolvent (Table 1, entry 13). PdCl₂ as catalyst did not improve the results (Table 1, entry 14). The above result demonstrated that $Pd(OAc)_2/Cu(OAc)_2$ is a more effective catalyst/oxidant in this reaction. It should be noted that

without any catalyst, the reaction did not generate the desired product at all.

With the optimal reaction conditions in hand, the scope of various indoles 1 and maleimides 2 was explored to probe the general protocol (Table 2). Maleimide 1a reacted with indoles to

Table 2. Substrate Scope for the Synthesis of Indolopyrrolocarbazoles $(3)^a$

R ₂		0 mol % Pd(OAc) ₂ 50 mol % Cu(OAc) ₂ R ₂ - DMF/DMSO (1:5) air, 80°C, 18 h	
entry	1 R ₁ , R ₂	2 R ₃	3, yield ^b (%)
1	Н, Н	Н	3a , 75
2	Н, 5-ОСН ₃	Н	3b , 81
3	CH ₃ , H	Н	3c , 60
4	H, 5-Cl	Н	3d , 55
5	H, 5-OCH ₃	CH ₃	3e , 82
6	Н, Н	CH ₃	3f , 73
7	Н, Н	Ph	3g , 80
8	Н, 5-ОСН ₃	Ph	3h , 85
9	H, 5-OBn	Ph	3i , 78
10	H, 7-CH ₃	Ph	3 j, 83
11	Н, Н	Bn	3k , 63
^a Reactions maleimides	were performed 2 (0.75 mmol). b Is	using indoles 1 solated vield.	(1.5 mmol) and

form the target products 3a-3d in 55-85% yields. Both free and protected (NH) indoles could work well in this protocol (Table 2, entry 3). The substituent group in the indole moiety played an important role in reaction yield. That is, an electron-rich indole (e.g., 5-methoxylindole) had an excellent yield (Table 2, entries 2, 5, and 8), and an electron-deficient indole (e.g., 5-chloroindole) gave a moderate yield (Table 2, entry 4). The

Organic Letters

substituent from (NH) maleimides showed no obvious impact on yields (Table 2, entries 1, 6, 7, and 11). As we know, this is the first two reported indole molecules that can react with one maleimide molecule to produce the indolo[3,2-a]pyrrolo[3,4-c]carbazole-6,8-diones involving in C-3/C-2 alkenylation for indoles.

Subsequently, we turned our attention to investigating the reaction of 2-substituent indoles with maleimides. First, the maleimides were reacted with 2-substituted indoles to form 3-indolylmaleimide products 4a-4e in 77–88% yields using the protocol (Table 3). When 2-methylindole and maleimide were





^{*a*}Reactions were performed using indoles **1** (0.75 mmol) and maleimides **2** (0.75 mmol). ^{*b*}Isolated yield. ^{*c*}1.5 mmol of indole **1** was used. ^{*d*}In DMSO.

treated in ratio of 2:1 in this protocol, 4a was obtained in 85% yield and 5a was formed around 5% yield (Table 3, entry 1). Interestingly, when DMSO was used as the solvent, 4a was obtained in 43% yield, and bisindolylmaleimide 5a was isolated in 31% yield (Table 3, entry 1). It seemed that DMF could prevent the formation of bisindolylmaleimide in a cosolvent. Thus, when the ratio of indole to maleimide was decreased to 1:1, indolylmaleimides 4 were obtained in moderate to excellent yields in cosolvent conditions (Table 3, entries 2–5).

To understand the sequence of the reaction and identify the possible reaction intermediates, additional experiments were carried out. First, 2,3'-biindolyl 8 could not be obtained when indole 1a solely reacted under the optimized conditions (Scheme 2). It was not subjected to Diels—Alder reaction with maleimides





to provide indolopyrrolocarbazoles.¹⁸ 3-Indolylsuccinimide **6a** and **6b**, obtained from indole and maleimides catalyzed by ZnCl₂,^{17b} could be well oxidized in the Pd-catalyzed protocol, leading to the formation of 3-indolylmaleimides **4f** and **4g** in **81** and 86%, respectively (Scheme 2). Indeed, the reactions of indoles **1a** and **1b** with 3-indolylsuccinimide **6a** were conducted

(Scheme 3). Besides product 4f with a poor yield, both indolopyrrolocarbazoles (3a, 3l) and bisindolylmaleimides (5b,

Scheme 3. Indolylsuccinimide and Indolylmaleimide Experiments



5c) could be obtained. Similarly, indolopyrrolocarbazoles (**3g**, **3m**) were prepared from indolylmaleimides and indoles via the Pd-catalyzed protocol in 22 and 32% yields, accompanied by bisindolylmaleimides (**5d**, **5e**) with 37 and 42% yields. In addition, 2,3'-biindolylsuccinimides **9** were synthesized and subjected to oxidative dehydrogenation by SeO₂. Products **3** were obtained around 50% yield instead of compounds **10**.¹⁹ We suppose that compounds **10** could be formed and quickly undergo thermal electrocyclization to provide indolopyrrolocarbazoles **3**. Compounds **9** were also performed in Pd-catalyzed protocol to give products **3** in about 75% yield (Scheme **3**). Finally, we conducted the reactions of indolylmaleimides with maleimides in the protocol (Scheme **4**). The dipyrrolocarbazo





letetraones 7a and 7b were obtained in 68 and 84% yields, respectively. It explains the fact that Pd-catalyzed alkenylation occurs initially at the C-3-positon of indole. However, we had used 1 equiv of indole to react with 2 equiv of maleimide via the Pd-catalyzed protocol, leading to 3a in a yield of 16%. 7a was not observed (Table 1, entry 12), which may be because C–H functionalization occurs rather than the Diels–Alder reaction.

These results indicate (i) the second C–H activation starts as soon as the β -hydride elimination of the first oxidative Heck reaction; (ii) the second C–H activation occurs exclusively on the indole fraction; (iii) thermal electrocyclization occurs after the second oxidative Heck reaction.

Based on above evidence, the plausible pathway is proposed in Scheme 5. DMSO could prevent the precipitation of Pd^0 with its Pd coordination ability in the reaction.^{14a,20} The desired products **3** were synthesized directly from indoles and maleimides via regioselective double successive oxidative Heck



reactions and thermal electrocyclization. The first oxidative coupling reaction took place via regioselective C-3 palladation (I), maleimide insertion (II), and β -hydride elimination to form compouds 4 ($R_4 \neq H$). Simultaneously, the following fast intramolecular regioselective C-2 palladation of II ($R_4 = H$) was performed, and the reduced Pd(0) complex was oxidized by Cu(OAc)₂ to generate Pd(II). The intermediates 10 were formed via the second oxidative coupling reaction (III–IV). Finally, the intermediate 10 undergo thermal induced intramolecular ring closure to provide products 3. When 2-substituent indoles were used in this protocol, compounds 4 were produced and subjected to the second oxidative coupling reaction to provide compounds 5.

In summary, an efficient Pd(II)-catalyzed protocol for the direct synthesis of indolopyrrolocarbazoles from both free and protected (NH) indoles and maleimides via a regioselective oxidative cross-coupling reaction has been successfully developed. This approach is different from the usual Pd-catalyzed regioselective C-2,C-3 alkenylation of indole and will lead to further indolopyrrolocarbazole synthesis. In addition, 2-substituent indoles are suitable for this protocol, leading to the formation of indolylmaleimides.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02944.

Experimental details, characterization data of all compounds, and copies of ¹H and ¹³C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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