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β-Selective C−H Arylation of Pyrroles Leading to Concise Syntheses of Lamellarins C and I

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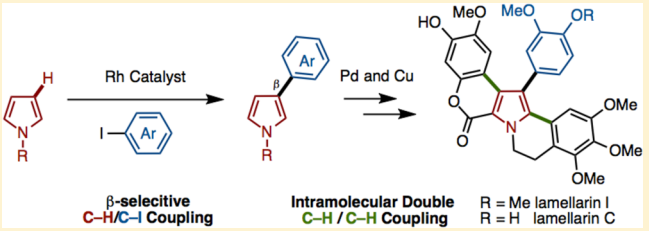
Supporting Information

ABSTRACT: The first general β-selective C−H arylation of pyrroles has been developed by using a rhodium catalyst. This C−H arylation reaction, which is retrosynthetically straightforward but results in unusual regioselectivity, could result in *de novo* syntheses of pyrrole-derived natural products and pharmaceuticals. As such, we have successfully synthesized polycyclic marine pyrrole alkaloids, lamellarins C and I, by using this β-selective arylation of pyrroles with aryl iodides (C−H/C−I coupling) and a new double C−H/C−H coupling as key steps.



INTRODUCTION

De novo construction of natural products and pharmaceutically relevant building blocks has always been a significant goal in organic synthesis. Arylpyrroles, particularly β-aryl-substituted pyrroles, form a set of structures that have been sought after by many synthetic chemists (representative compounds are showcased in Figure 1).[1] Classically, β-arylpyrroles have been synthesized by the Paal−Knorr pyrrole synthesis,[2] but the 1,4-diketone starting material (or its equivalent) is not necessarily easy to synthesize depending on the number and type of substituents (Figure 2). Furthermore, despite the development of many methods in heterocyclic chemistry and cross-coupling reactions for the synthesis of β-arylpyrroles,[3] the current state-of-the-art method involves catalytic C−H borylation of pyrroles, followed by Pd-catalyzed Suzuki−Miyaura cross-coupling.[1e]

Meanwhile, transition-metal-catalyzed C−H functionalization of organic molecules has emerged as an enabling synthetic tool for natural products and pharmaceuticals.[4,5] Particularly, the construction of C−C bonds between (hetero)arenes and arenes by C−H arylation has attracted much attention from organic chemists because it is an ideal method for the synthesis of (hetero)biaryls.[6] However, in terms of arylated pyrrole synthesis, β-selective arylation of unsubstituted pyrroles is rare compared to α-arylation[7] and a general protocol has not been reported thus far.[8,9] Herein, we report the first general β-selective C−H arylation of pyrroles by using a Rh catalyst as well as its application to the total synthesis of polycyclic pyrrole alkaloids, lamellarins C and I.

RESULTS AND DISCUSSION

β-Selective C−H Arylation of Pyrroles with Iodoarenes. It has been well documented that the C−H arylation reactions of five-membered heteroarenes, such as pyrroles, thiophenes, and furans, typically proceed preferentially at the α-positions when both α- and β-positions are available. However, we have shown in several cases in the C−H arylation of thiophenes that otherwise-difficult β-selective arylation can be achieved by catalyst control. Thus, we began by examining some of our unique catalysts with a hope to identify conditions for β-selective arylation of pyrroles (Table 1). When $PdCl_2$ (5 mol %) and an electron-deficient phosphite ligand $P[OCH(CF_3)_2]_3$ (L, 10 mol %), which were effective for the β-selective arylation of thiophenes,[10] were used, *N*-phenylpyrrole (**1A**) was coupled with iodobenzene (**2a**) using Ag_2CO_3 in *m*-xylene at 140 °C to unfortunately give arylated product **3(α)** with complete α-selectivity (entry 1).

Next, we performed the C−H arylation of pyrrole **1A** with **2a** under Ir catalysis (entries 2−4). We have also reported that Crabtree's catalyst, $[Ir(cod)(py)PCy_3]PF_6$ (cod = 1,5-cyclooctadiene, py = pyridine), is effective for the C−H arylation of thiophenes and furans with virtually complete α-selectivity.[11] When the coupling of **1A** and **2a** was performed using the reported conditions (Ag_2CO_3 in *m*-xylene), surprisingly, the β-arylated product **3(β)** was obtained, albeit in a very low yield (6%, entry 2). Encouraged by this result, we then screened several Ir catalysts,[12] and we found that $[Ir(cod)_2]BF_4$ (5 mol %) and PCy_3 (10 mol %) were effective for the C−H arylation of pyrrole, providing the β-arylated product in 39% yield (entry 3). Moreover, an increase in catalyst loading allowed for the corresponding coupling product to be formed in 64% yield (entry 4). Although we achieved a β-selective arylation of *N*-phenylpyrrole (**1A**), this iridium-based catalytic system was not

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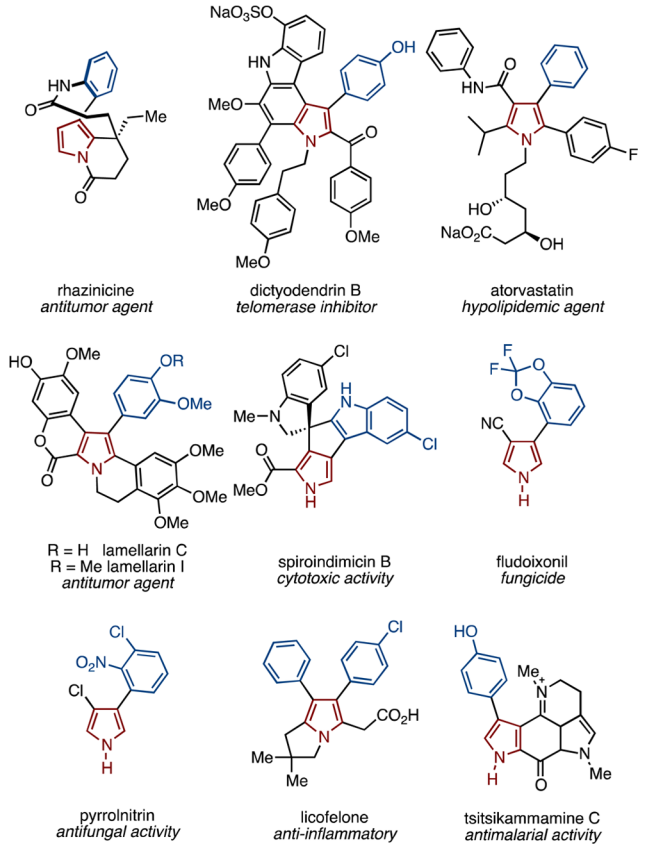

Figure 1. Arylpyrrole-derived natural products and pharmaceuticals.

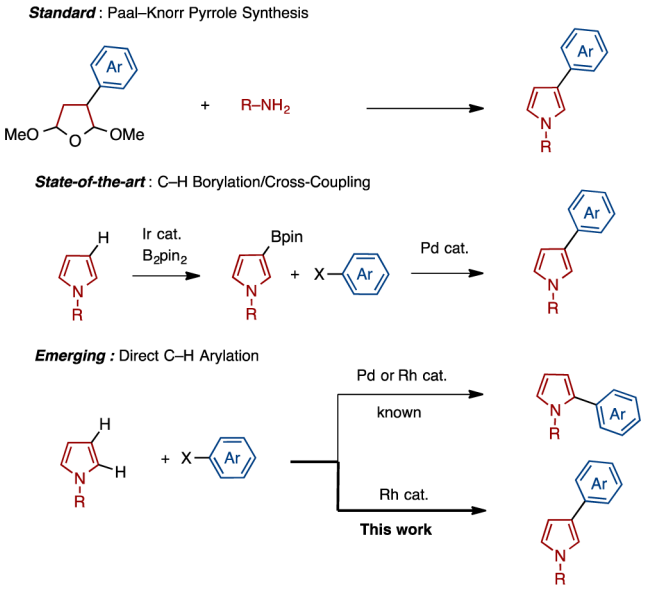

Figure 2. Synthetic methods for β-arylpyrroles.

general in terms of pyrrole substrate. For example, when *N*-methylpyrrole (**1B**) was subjected under otherwise identical conditions, the corresponding product was obtained in only 26% yield (entry 5). To gain more reactivity, we then examined other transition-metal catalysts.

Our group previously reported a direct C−H arylation of (hetero)arenes, with mainly thiophenes and furans reacting with aryl iodides in the presence of $RhCl(CO)\{P[OCH(CF_3)_2]_3\}_2$ and Ag_2CO_3 in *m*-xylene at 200 °C under microwave irradiation.[13] In these reports, only one example demonstrated the β-arylation of heteroarenes, when *N*-phenylpyrrole (**1A**) was coupled with 4-acetylaryl iodide (**2b**) in 58% yield (entry 6).[13a] When the reaction temperature was decreased to 150 °C, the yield of the corresponding coupling product increased to 84% without any change in regioselectivity, and microwave irradiation was no longer needed (entry 7). With the use of these reaction conditions, even when the pyrrole substrate was changed from **1A** to *N*-methylpyrrole (**1B**), the corresponding coupling product was obtained in 74% yield (entry 8, β/α = 93:7).

On the basis of this promising result, we further optimized the reaction conditions using *N*-methylpyrrole (**1B**) and iodobenzene (**2a**) as substrates.[12] Other Rh sources decreased the yields as well as β-selectivities (entries 9−11). When AgO was used instead of Ag_2CO_3, the decrease in yield and regioselectivity was observed (entry 12), while Ag_2O gave similar results (entry 13). The use of other bases such as K_2CO_3 completely shut down the reaction (entry 14). The use of DME (1,2-dimethoxyethane) as an additive was slightly effective for preventing double C−H arylation of pyrrole **1B** (entry 15), and 1,4-dioxane was slightly better than DME (entry 16). Finally, the amount of Ag_2CO_3 can be reduced from 1.0 to 0.5 equiv (entry 17) and the solvent system was changed to 1,4-dioxane/*m*-xylene (1:1) to allow for a greater solubility of a wider range of substrates. Under these optimized conditions, **1B** was coupled with **2a** in the presence of the same Rh catalyst to give *N*-methyl-3-pheynlpyrrole (**3Ba**) in 73% yield with 91% β-selectivity (entry 18).

On the basis of these findings, we then examined the scope of present C−H arylation by employing various pyrrole and aryl iodide substrates (Scheme 1). *N*-Methylpyrrole (**1B**) was successfully coupled with phenyl (**2a**), 3-methoxyphenyl (**2c**), 4-nitrophenyl (**2d**) and 4-trifluoromethylphenyl iodide (**2e**) to afford the corresponding coupling products **3Ba**, **3Bc**, **3Bd**, and **3Be** in moderate to good yields with high β-selectivity (β/α > 91:9). The coupling reaction of **1B** with 4-bromo-1-iodobenzene (**2f**) proceeded at the carbon−iodine bond selectively to give the resulting coupling product **3Bf** in excellent yield and excellent β-selectivity. Iodoheteroarenes such as 3-iodothiophene (**2g**) were also tolerated to give the resulting product (**3Bg**) in 72% yield. To our delight, the *N*-substituent on the pyrrole portion can be changed from methyl to ethyl (**3Ca**), benzyl (**3Dd**), phenyl (**3Ad**, **3Ab**, **3Ah**) and triisopropylsilyl (TIPS) (**3Ei**, **3Ed**). For example, when *N*-ethyl (**1C**), *N*-phenyl (**1A**), *N*-TIPS (**1E**), and *N*-alkyl (**1F**: R = $CH_2CH_2C_6H_4OMe$) pyrroles were used instead of **1B**, the coupling reaction proceeded well to give the corresponding β-arylpyrroles.

Moreover, substituted pyrroles with C2-substituents such as benzyl (**1G**), ethylpropanoate (**1H**), and ethyl acrylate (**1I**) also gave β-arylated (C4-arylated) pyrroles (**3Gd**, **3Hd**, **3Id**) in good to moderate yields. The regioselectivity was not only maintained for 2,3-disubstituted pyrrole (**1J**), but also for 3-substituted pyrrole (**1K**), thus affording the corresponding coupling products (**3Jd** and **3Kd**) in moderate yields. Even when a more sterically demanding 2,5-disubstituted pyrrole (**1L**) was reacted with iodoarene, the resulting coupling product (**3Ld**) was obtained in 51% yield. It should be noted that complete or greater than 90% regioselectivities of β-C−H arylation were achieved, and the regioisomers can be readily separated by column chromatography in all cases.

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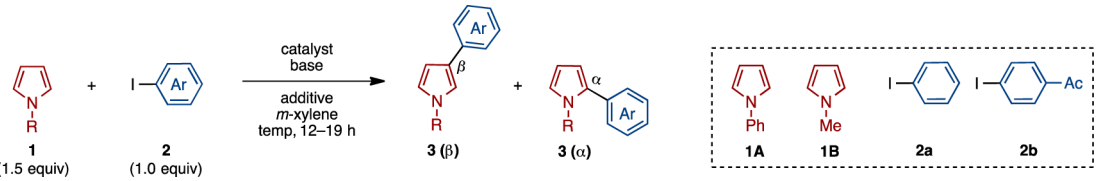
Table 1. C−H Arylation of Pyrroles with Iodoarenes Using Transition-Metal Catalysts[a]



entry	pyrrole	aryl iodide	catalyst (mol %)	base (equiv)	additive	temp (°C)	yield of **3** (%)[b]	β/α
1	**1A**	**2a**	$PdCl_2$ (5), L (10)	Ag_2CO_3 (1)	–	140	63	1:>99
2	**1A**	**2a**	**$[Ir(cod)(py)PCy_3]PF_6$ (5)**	Ag_2CO_3 (1)	–	160	6	96:4
3	**1A**	**2a**	**$[Ir(cod)_2]BF_4$ (5), PCy_3 (10)**	Ag_2CO_3 (1)	–	160	39	98:2
4	**1A**	**2a**	$[Ir(cod)_2]BF_4$ (**10**), PCy_3 (**20**)	Ag_2CO_3 (1)	–	160	64	>99:1
5	**1B**	**2a**	$[Ir(cod)_2]BF_4$ (10), PCy_3 (20)	Ag_2CO_3 (1)	–	150	26	>99:1
6	**1A**	**2b**	**$RhCl(CO)L_2$ (3)**	Ag_2CO_3 (1)	DME	200	58	>99:1
7	**1A**	**2b**	**$RhCl(CO)L_2$ (3)**	Ag_2CO_3 (1)	DME	150	**84**	>99:1
8	**1B**	**2a**	**$RhCl(CO)L_2$ (3)**	Ag_2CO_3 (1)	DME	150	**74**	**93:7**
9	**1B**	**2a**	$[Rh(nbd)_2]BF_4$ (3), L (6)	Ag_2CO_3 (1)	DME	150	29	50:50
10	**1B**	**2a**	$[Rh(nbd)_2Cl]_2$ (1.5), L (6)	Ag_2CO_3 (1)	DME	150	52	79:21
11	**1B**	**2a**	$Rh(acac)(C_2H_4)_2$ (3), L (6)	Ag_2CO_3 (1)	DME	150	24	64:36
12	**1B**	**2a**	**$RhCl(CO)L_2$ (3)**	AgO (1)	DME	150	37	85:15
13	**1B**	**2a**	**$RhCl(CO)L_2$ (3)**	Ag_2O (1)	DME	150	73	92:8
14	**1B**	**2a**	**$RhCl(CO)L_2$ (3)**	K_2CO_3 (1)	DME	150	0	–
15	**1B**	**2a**	**$RhCl(CO)L_2$ (3)**	Ag_2CO_3 (1)	–	150	66	89:11
16	**1B**	**2a**	**$RhCl(CO)L_2$ (3)**	Ag_2CO_3 (1)	**1,4-dioxane**	150	78	93:7
17	**1B**	**2a**	**$RhCl(CO)L_2$ (3)**	**Ag_2CO_3 (0.5)**	1,4-dioxane	150	77	87:13
18[c]	**1B**	**2a**	**$RhCl(CO)L_2$ (3)**	**Ag_2CO_3 (0.5)**	**1,4-dioxane**	**150**	**73**	**91:9**

[a]Reaction conditions: **1** (0.75 mmol), **2** (0.5 mmol), catalyst, base, additive (0.5 mmol), and *m*-xylene (2.5 mL), temp, 12−19 h. [b]Isolated yield. L = $P[OCH(CF_3)_2]_3$ [c]1,4-Dioxane/*m*-xylene (1:1) was used as a solvent.

Mechanistic Considerations. Through extensive investigations, we were able to identify synthetically useful conditions affecting β-selective C−H arylation of pyrroles through the agency of rhodium catalysis. Before describing our synthetic campaign toward biologically active natural products, here we provide some mechanistic considerations we have gained through these studies. One of the most interesting findings from mechanistic point of view is the observation of "seemingly" reverse regioselectivity in pyrroles (β-selective; present study) and thiophenes/furans (α-selective; our previous study)[13a,b] using the same rhodium catalyst (Figure 3a).

Previously we uncovered that $RhCl(CO)\{P[OCH(CF_3)_2]_3\}_2$ catalysis works best for electron-rich heteroarenes and benzene derivatives and the reaction sites for these substrate match nicely to those of classical electrophilic substitution reactions; α-selective for thiophenes/furans and *ortho*−*para* selective for anisole. This was achieved based on our catalyst design employing a strongly π-accepting ligand on rhodium.[13a,b] In addition to such electronic factor, however, we noticed that steric factor also contributes in determining the reaction sites of aromatic substrates. For example, in the reaction of anisole and iodoarenes, the C−H arylation took place preferentially at the *para* position over the *ortho* position (*ortho*/*para* = 29:71), indicating that the steric repulsion of an arene substituent (methoxy group in anisole) and catalyst is another controlling element in regioselectivity. We assume that the emergence of such steric factor led to the β-selective C−H arylation in pyrroles.

Shown in Figure 3b is our currently assumed mechanistic pathway for β-selective C−H arylation of pyrroles. The neutral Rh^I complex **A** first undergoes oxidative addition with an iodoarene and halide removal with Ag_2CO_3 to generate cationic aryl-Rh^{III} species **B**. The π-complexation of a pyrrole followed by C−H rhodation of thus-formed **C** leads to the key diaryl-Rh^{III} intermediates **D**. The reductive elimination from **D** releases an arylpyrrole product, with the regeneration of **A**. We assume that the steric repulsion of *N*-substituent of pyrrole substrate and bulky catalyst framework (particularly our phosphite ligand) in the key π-complexation and C−H rhodation steps facilitates the preferential generation of intermediate **D**(β), leading to the production a β-arylpyrrole. In the case of thiophenes and furans, there are no such substituents on heteroatoms. We assume that the lack of such steric factor led these substrates to follow the typical electrophilic substitution regioselectivity (α-selective).

The importance of *N*-substituents of pyrrole substrates was seen in our substrate scope study shown in Scheme 1. For example, we observed a trend that the β-selectivity increases as the *N*-substituent on the pyrrole gets larger (Me (**3Ba**) < Et (**3Ca**) < Bn (**3Dd**) = TIPS (**3Ei**)). To further check this tendency using the same arylating agent, we investigated this coupling reaction using various pyrroles and iodobenzene (**2a**) as shown in Figure 4a. As a result, the experiments clearly showed that the bigger *N*-substituent on the pyrroles increased the β-selectivity (Me, 91%; Et, 96%; Bn, >99%; and TIPS, >99%) and decreased the yield (Me, 73%; Et, 53%; Bn, 32%; and TIPS, 12%). Unfortunately, pyrroles without a *N*-substituent (N−H pyrroles) did not react at all. Additionally, when one of the β-positions is blocked as with **1K**, the selectivity was decreased (β/α = 92:8) even when using TIPS as an *N*-substituent (Scheme 1). Moreover, we found that the steric factor (*N*-substituent effect) overrides the electronic factors exerted by a *C*-substituent on pyrrole ring (Figure 4b). For example, the C2-substitution with electron-donating benzyl group, which should electronically facilitate the electrophilic

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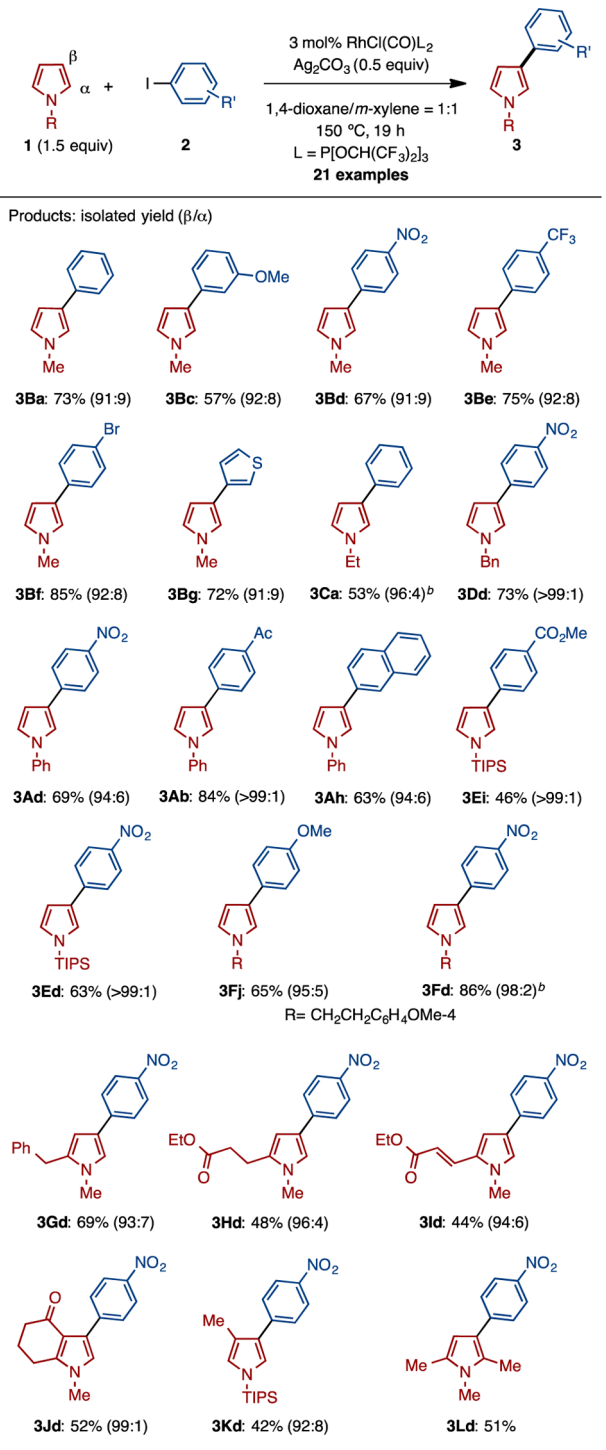
Scheme 1. Substrate Scope for the β-Selective Arylation of Pyrroles[a]



[a]Reaction conditions: **1** (0.75 mmol), **2** (0.5 mmol), RhCl(CO){P[OCH(CF$_3$)$_2$]$_3$}$_2$ (3 mol %), Ag$_2$CO$_3$ (0.25 mmol), 1,4-dioxane/*m*-xylene =1:1 (1.7 mL), 150 °C, 19 h. [b]**1** (0.75 mmol), **2** (0.5 mmol), RhCl(CO){P[OCH(CF$_3$)$_2$]$_3$}$_2$ (1.5 mol %), Ag$_2$CO$_3$ (0.25 mmol), DME (0.5 mmol), *m*-xylene (2.5 mL), 150 °C, 24 h. All product yields are isolated yields (single isomer).

substitution at the C5 position (α position), did not decrease the β-selectivity of parent system.

Application to the Concise Synthesis of Lamellarins C and I. Next, the utility of this reaction in complex molecular

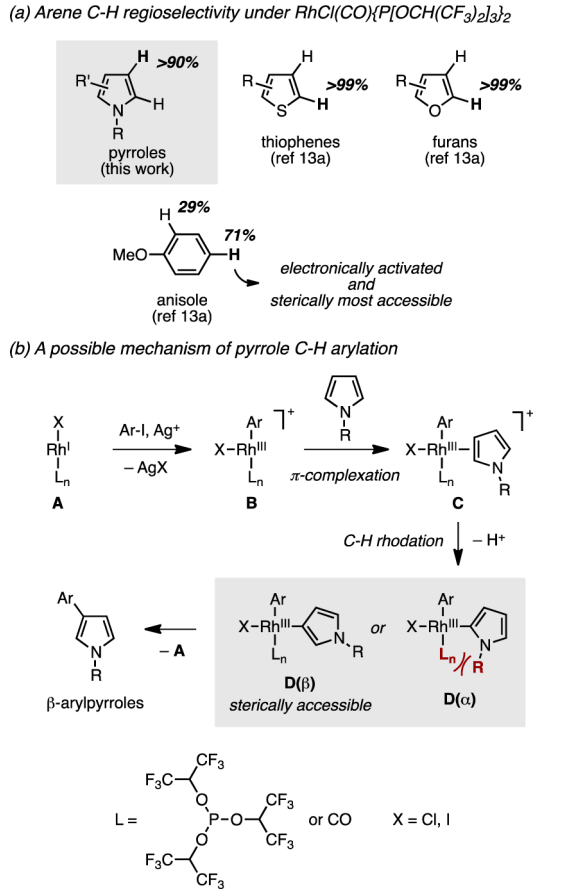


Figure 3. Arene C−H regioselectivity and a possible mechanism of pyrrole C−H arylation under RhCl(CO){P[OCH(CF$_3$)$_2$]$_3$}$_2$.

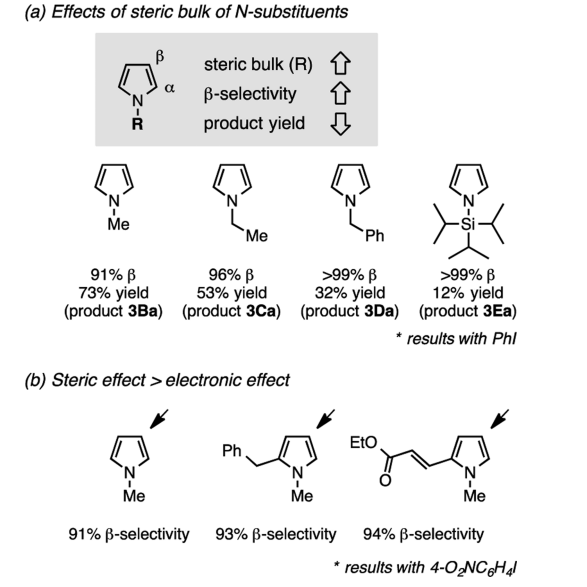


Figure 4. Importance of steric effect in pyrrole C−H arylation under RhCl(CO){P[OCH(CF$_3$)$_2$]$_3$}$_2$.

settings was demonstrated through the total synthesis of lamellarins. Lamellarins are a family of marine natural products isolated from the prosobranch mollusc *Lamellaria* sp.[14,15] This series of compounds inhibit the proliferation of cancer cells and therefore are promising candidates for anticancer drugs. In particular, in 1993, Bowden et al. reported six new lamellarin

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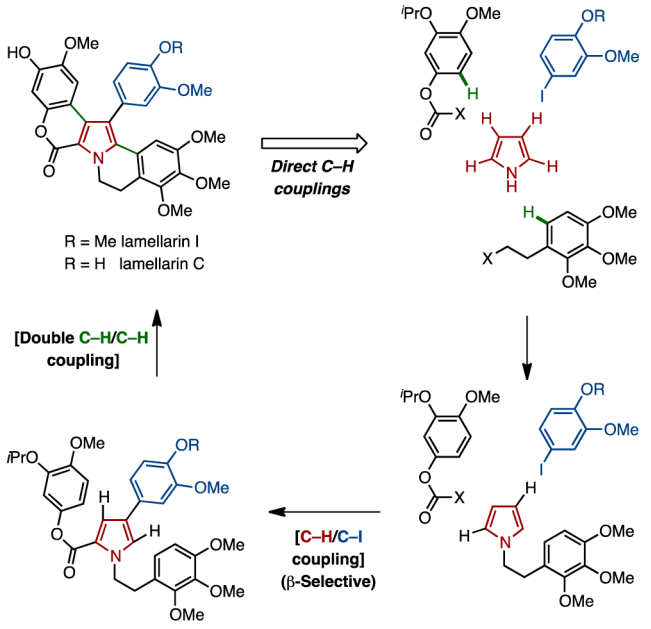
Scheme 2. Strategy for the Synthesis of Lamellarins via Direct C−H Couplings

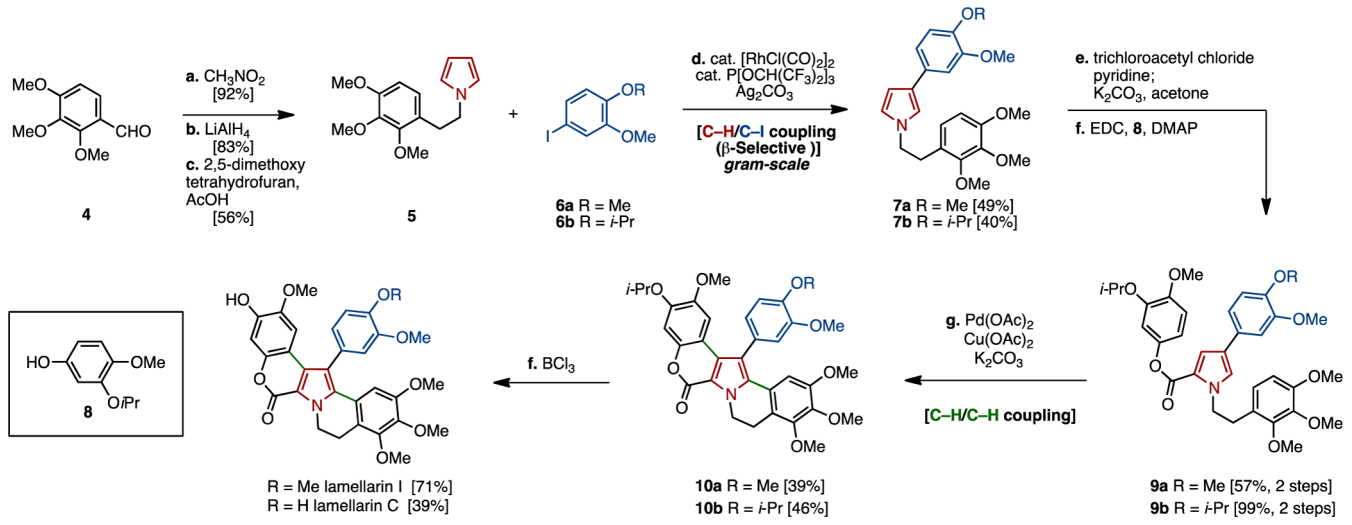


alkaloids, including lamellarin I obtained from the Australian colonial ascidian *Didemnum* sp.,[14c] which showed sensitizing effects in multidrug-resistant P388/Schabel cells to doxorubicin. Lamellarin C also demonstrates potent cytotoxicity against 10 human tumor cell lines.[14d] Although the syntheses of lamellarins were already reported by several research groups, these syntheses all required more than 10 steps (all steps, not just longest linear ones, are included in this count).[16]

Our blueprint for the synthesis of lamellarins C and I is shown in Scheme 2. Aiming to apply the β-selective arylation of pyrroles for the synthesis of lamellarins, we planned to connect its building blocks using direct C−H couplings. As the first step, the present C−H arylation method would couple an *N*-substituted pyrrole at the β-position (C3-position) with an iodoarene. Then, a carbonyl moiety would be introduced onto the pyrrole ring at the C5-position. Lastly, the connection between the C2- and C4-positions of the pyrrole with arene units would be accomplished by intramolecular double C−H/C−H couplings.

The synthesis of lamellarins C and I commenced with aldehyde **4**, a commercially available compound, which was readily converted to a pyrrole by a three-step sequence (nitroaldol reaction, reduction of the nitro group, followed by pyrrole synthesis) to afford pyrrole **5** (Scheme 3).[16,17] Under our standard conditions, **5** smoothly underwent β-selective arylation with aryl iodides **6a** and **6b** to give the corresponding coupling products **7a** and **7b** in 49% and 40% yields, respectively. The synthesis of **7a** was feasible on 1.0 g scale without showing a decrease in yield. Treatment of **7a** and **7b** with trichloroacetyl chloride (Friedel−Crafts acylation), followed by hydrolysis of the trichloroacetyl group, produced the corresponding carboxylic acids.[18,19] These carboxylic acids were then condensed with phenol derivative **8** to afford esters **9a** and **9b** in 57% and 99% yield, respectively, over 2 steps. With the core framework of the lamellarins in hand, we set out to connect two C−C bonds between the pyrrole unit and the peripheral aryl groups. Exposure of **9a** and **9b** with various oxidants such as phenyliodonium diacetate (PIDA), phenyliodonium ditrifluoroacetate (PIFA), DDQ, ceric ammonium nitrate (CAN), and $K_2S_2O_8$ did not yield the desired cyclodehydrogenation products. Finally, we discovered that an exceedingly simple construction of these C−C bonds was

Scheme 3. Synthesis of Lamellarins C and I[a]



[a]Reagents and conditions: (a) CH_3NO_2 (15 equiv), piperidine (6 mol %), 4 Å MS, toluene, 110 °C, 20 h, 92%; (b) $LiAlH_4$ (3.0 equiv), THF, 0 °C to reflux, 1.5 h, 83%; (c) 2,5-dimethoxytetrahydrofuran (1.2 equiv), AcOH/EtOH = 1:1, 90 °C, 18 h, 56%; (d) for **7a**: **5** (1.4 equiv), **6a** (1.0 equiv), $[RhCl(CO)_2]_2$ (1.4 mol %), $P[OCH(CF_3)_2]_3$ (5.8 mol %), Ag_2CO_3 (0.94 equiv), DME (1.0 equiv), *m*-xylene, 150 °C, 25 h, 49%; for **7b**: **5** (1.5 equiv), **6b** (1.0 equiv), $RhCl(CO)\{P[OCH(CF_3)_2]_3\}$ (3 mol %), Ag_2CO_3 (1.0 equiv), 1,4-dioxane/*m*-xylene = 2:3, 150 °C, 24 h, 40%; (e) trichloroacetyl chloride (1.8 equiv), pyridine (1.8 equiv), THF, 23 °C, 20 h; K_2CO_3(aq) (30 equiv), acetone, 23 °C, 13 h; (f) **8** (1.5 equiv), EDC HCl (1.5 equiv), DMAP (1.5 equiv), benzene, 23 °C, 14 h, 57% (2 steps for **9a**), 99% (2 steps for **9b**); (g) for **10a**: $Pd(OAc)_2$ (1.0 equiv), $Cu(OAc)_2$ (6.0 equiv), K_2CO_3 (2.0 equiv), DMAc, 80 °C, 27 h, 39%; for **10b**: $Pd(OAc)_2$ (2.0 equiv), $Cu(OAc)_2$ (6.0 equiv), K_2CO_3 (2.0 equiv), DMAc, 80 °C, 27 h, 46%; (h) BCl_3 (6.0 equiv), CH_2Cl_2, −78 to 23 °C, 71% (for lamellarin I), 39% (for lamellarin C).

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possible by palladium mediation. Thus, **9a** and **9b** were treated with stoichiometric $Pd(OAc)_2$, $Cu(OAc)_2$ and K_2CO_3 (for which catalytic conditions were reported by Greaney and coworkers[20]) to successfully furnish products **10a** and **10b** in 39% and 43% yields, respectively. Finally, after removal of the *i*-Pr group selectively by treatment with BCl_3, the synthesis of lamellarins C and I was accomplished (8 steps from commercially available starting materials).

CONCLUSIONS

In summary, we have developed a general method for the β-selective C−H arylation of pyrroles by using a rhodium catalyst. This β-selective C−H/C−I coupling followed by intramolecular double C−H/C−H coupling was applied to a concise synthesis of lamellarins C and I. Although tremendous advances in C−H arylation have been achieved, to continue pushing the boundaries of this field involves not only efficient ways to generate known compounds, but also a strategy to construct new motifs that are difficult to make using classical methods. In this regard, "regiodivergent" C−H arylation has garnered interest from the synthetic community since it is retrosynthetically straightforward and provides divergent regioselectivities in the given products.[21] We believe that this C−H coupling technology would allow for a re-examination of previous syntheses and a development of *de novo* syntheses of biologically active molecules.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and spectral data for all compounds, including scanned image of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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