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# Regioselective Dicouplings: Application to Differentially Substituted Pyrroles

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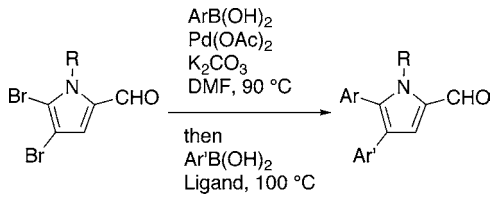
## ABSTRACT




**In an effort to develop a more concise route to differentially substituted pyrroles (such as that found in the lamellarins), a completely regioselective one-pot double Suzuki coupling has been discovered. The key feature is the use of a ligand-free palladium catalyst under optimized conditions, which results only in coupling of the C5 bromide. At this point, addition of a second boronic acid and a phosphine ligand enables coupling at the remaining C4 bromide.**

As part of our ongoing interest in the synthesis of the lamellarin family of natural products, we were interested in methods that could reduce the overall length of our first generation synthesis.[1] In examining this synthesis, it became apparent that the most promising way to reduce the number of steps was to focus on the coupling and halogenation steps. Because each one of the three aryl subunits is installed via a Suzuki coupling, this required three separate halogenations and three separate couplings. As such, just the installation of the aryl subunits accounted for over half of the total length of the synthesis (6 out of 11 steps).

In contemplating ways to reduce the number of halogenation/coupling steps, we found that one potential solution would be to explore the option of regioselective couplings on polyhalopyrroles and to conduct more than one coupling in the same pot (one-pot polycouplings). Taking this approach to its extreme, we could reduce the six steps for the installation of the aryl subunits to two steps − one triple halogenation followed by one triple coupling. As a result, our lamellarin synthesis would be reduced from 11 steps to 7 − a tremendous improvement.

The idea of regioselective couplings of polyhaloheteroaromatics has been attracting greater attention in recent years, so although it had not been studied in the context of pyrroles, it appeared promising.[2] However, the concept of conducting more than one coupling in the same reaction vessel is quite rare. Indeed, within the area of heteroaromatic systems, there are only two existing examples.[3]

To explore the potential of this regioselective polycoupling approach, we began our efforts with pyrrole aldehyde **1**. This substrate was selected for several reasons. First, for successful regioselectivity in the coupling of polyhaloheteroaromatics, there is a clear requirement for some degree of electronic difference between the different halogenated centers.[4] For the pyrrole ring system, this can be most readily achieved by substitution with an electron-withdrawing group. Further, because previous studies had indicated that the pyrrole nitrogen would need to be protected to avoid extensive reductive dehalogenation at C4 and to simplify product analysis by avoiding deprotection under the reaction condi-

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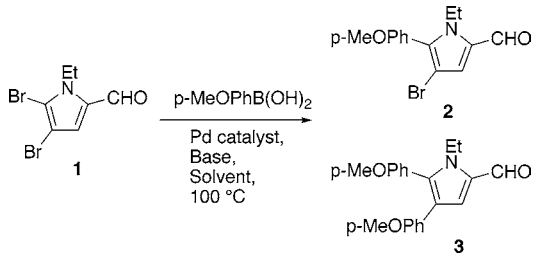
tions, an *N*-alkyl group was selected.[5] Ultimately, pyrrole aldehyde **1** was prepared via a slight modification of the literature procedure.[6]

Treatment of aldehyde **1** with *p*-methoxyphenyl boronic acid under standard Suzuki conditions did afford a separable mixture of products from which monocoupled product **2** and dicoupled product **3** could be isolated in 32 and 29% yield, respectively (Table 1, entry 1). Armed with this encouraging

**Table 1.** Regioselective Monocoupling Studies



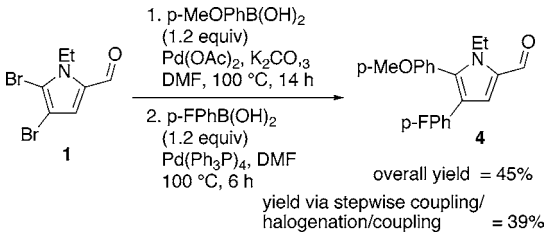

| entry | catalyst | base | solvent | % yield (**2**/**3**) |
|---|---|---|---|---|
| 1 | $Pd(Ph_3P)_4$ | $Na_2CO_3$ | DMF | 32/29 |
| 2 | $Pd(Ph_3P)_4$ | $K_2CO_3$ | DMF | 42/5 |
| 3 | $Pd(OAc)_2$ | $Na_2CO_3$ | DMF | 45/18 |
| 4 | $Pd(OAc)_2$ | $K_2CO_3$ | DMF | 56/<5 |
| 5 | $Pd(OAc)_2$ | $K_2CO_3$ | DMF | 28/7 |
| 6 | $Pd(OAc)_2$ | $Cs_2CO_3$ | DMF | 31/5 |
| 7 | $Pd(OAc)_2$ | $Ba(OH)_2$ | DMF | complex mix |
| 8 | $Pd(OAc)_2$ | $K_2CO_3$ | dioxane | 48/8 |
| 9 | $Pd(OAc)_2$ | $K_2CO_3$ | $H_2O$/acetone | complex mix |

result, several modifications with respect to the palladium catalyst, activator, and solvent were studied. Very rapidly, it was noted that a ligand-free palladium catalyst dramatically reduced the amount of dicoupled product that was observed. In conjunction with this catalyst, potassium carbonate afforded the best selectivity, although a number of other bases were effective but afforded lower conversions or simply lower isolated yields (Table 1, entries 3 and 5−7). Finally, shifting to an ethereal solvent proved to slightly increase the amount of double coupling when using potassium carbonate as the base (Table 1, entry 8), and an acetone/water mix afforded a very complex mixture of products (Table 1, entry 9).

The end result of these optimizations was a catalyst system (palladium acetate, potassium carbonate, DMF) that completely avoided any coupling at the 4-position. Indeed, coupled product **2** could be resubjected to the coupling conditions, and no trace of dicoupled product was observed even after 24 h at 100 °C. Thus, high regioselectivity could be achieved. At the same time, the question remained as to how to now accomplish the second coupling.

The first solution was to add a more active catalyst with the second boronic acid. Because tetrakis(triphenylphosphine) palladium(0) had already been shown to affect coupling at both the 4- and 5-positions, this was selected as the second catalyst. Thus, after TLC indicated complete consumption of starting material, a second boronic acid was added, along with tetrakis(triphenylphosphine) palladium(0). Much to our delight, this did lead to the formation of the desired double-coupled product **4** in 45% yield (Scheme 1).

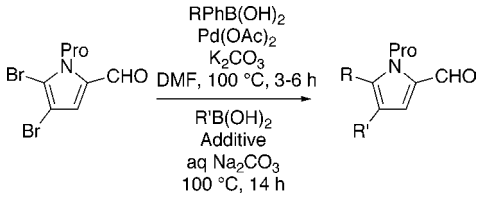
**Scheme 1.** First Regioselective Double Couplings




Although the yield may seem modest, it is an improvement over the three-step synthesis starting from 4-bromo-1-ethylpyrrole-2-carbaldehyde, which affords **4** in a 39% yield overall. Using this stepwise approach (coupling, halogenation, coupling) also enabled us to confirm the suspected regiochemical outcome of the first coupling with dibromide **1**.

The next question was whether the addition of two different catalysts was necessary. On the surface, it appeared that there might be a different approach to go from a ligand-free system to a phosphine-ligated system − simple addition of a phosphine. As a result, the first stage of the coupling was performed as before, but now, along with the second boronic acid, two equivalents of triphenylphosphine (relative to palladium acetate) were added. Gratifyingly, this resulted in an improved 48% yield of double-coupled product **4** (Table 2, entry 2). Indeed, an even better result was obtained

**Table 2.** Additional Regioselective Double Couplings




| entry | Pro | R | R′ | additive | % yield |
|---|---|---|---|---|---|
| 1 | Et | *p*-MeOPh | *p*-FPh | $Pd(Ph_3P)_4$ | 44 |
| 2 | Et | *p*-MeOPh | *p*-FPh | $Ph_3P$ | 48 |
| 3 | Et | *p*-MeOPh | *p*-FPh | $tBu_3P/HBF_4$ | 58 |
| 4 | Et | *p*-FPh | *p*-MeOPh | $tBu_3P/HBF_4$ | 51 |
| 5 | Et | *p*-MeOPh | stryenyl | $tBu_3P/HBF_4$ | 56 |
| 6 | MEM | *p*-MeOPh | *p*-FPh | $tBu_3P/HBF_4$ | 54 |

by employing the stabilized phosphonium salt form of tri-*tert*-butylphosphine popularized by Fu.[7] Now the isolated yield was 58% (Table 2, entry 3).

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These same reaction conditions were equally effective with other boronic acids, including alkenyl boronic acids (Table 2, entry 5). The alkyl group on the pyrrole nitrogen could be modified as well to other potentially more readily removable groups such as the MEM group (Table 2, entry 6).[8] This observation now opens the door for numerous synthetic applications of this one-pot, double-coupling route to substituted pyrroles such as the lamellarins, Lipitor, and the prodigiosins.[9]

In conclusion, we have reported the ability to regioselectively couple 4,5-dibromopyrrole aldehydes and to carry out two couplings in the same reaction pot by simply adding a phosphine ligand to generate a more active catalyst for the second coupling. This approach has the potential to be of great benefit in the rapid and convergent synthesis of substituted pyrroles. The extension of this method to pyrroles with other substitution patterns and even to other heteroaromatic systems is underway and will be reported in due course.

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**Supporting Information Available:** Full spectral data and experimental procedures for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Interestingly, allyl and benzyl protecting groups caused the reaction to only proceed part of the way to completion and, in the case of the allyl protecting group, completely shut down the second coupling, even under the added phosphine conditions. The origin of this change in behavior is the object of current study.

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