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C−H Alkenylation of Pyrroles by Electronically Matching Ligand Control

Hyun Tae Kim, Woohyeong Lee, Eunmin Kim, and Jung Min Joo*

Abstract: Directing group and substrate control strategies have frequently been employed for the regioselective C−H alkenylation of acid- and oxidant-sensitive pyrrole heterocycles. We developed an undirected, aerobic strategy for the C−H alkenylation of *N*-alkylpyrroles by ligand control. For C2-alkenylation of electron-rich *N*-alkylpyrroles, an electrophilic palladium catalyst derived from $Pd(OAc)_2$ and 4,5-diazafluoren-9-one (DAF) was used. Alternatively, a combination of $Pd(OAc)_2$ and a mono-protected amino acid ligand, Ac-Val-OH, was useful for C5-alkenylation of *N*-alkylpyrroles possessing electron-withdrawing groups at the C2 position. This approach based on the electronic effects of heterocycles and catalysts can rapidly provide a wide range of alkenyl pyrroles from readily available *N*-alkylpyrroles and alkenes.

Transition-metal-catalyzed C−H functionalization reactions of heteroarenes have emerged among the most atom- and step-economical approaches for the preparation of electronically and sterically varied heteroarenes for materials science and drug discovery. [1], [2] Pyrroles are important targets for C−H functionalization because of their prevalence in polymers, dyes, and drugs, including atorvastatin, ketorolac, and tolmetin.[3] The instability of most halopyrroles and high cost when available make the direct functionalization of pyrroles much more attractive than traditional cross-coupling reactions of the pre-functionalized congeners. [4] However, C−H functionalization of the parent pyrroles presents challenges in achieving regioselectivity and preventing polymerization of the pyrroles under acidic and oxidative conditions. [5,6] These issues have been tackled via dehydrogenative C−H alkenylation with alkenes, also known as the Fujiwara-Moritani reaction.[7] For C2-alkenylation, the use of directing groups on the nitrogen atom has been effective for increasing the regioselectivity and stability of pyrroles (Figure 1A).[8] Alternatively, a strategy based on substrate control was elegantly demonstrated, where the presence of a sterically bulky triisopropylsilyl group switched the selectivity towards the C3 position (Figure 1B).[9] However, these approaches have relied on nitrogen-protecting groups that have to be removed after the desired C−C bond forming reactions in most cases. In fact, many alkenyl pyrroles found in drug candidates and chromophores bear alkyl groups at the nitrogen atom.[10] For their preparation, the Horner–Wadsworth–Emmons reaction of the corresponding *N*-alkyl formyl pyrroles was used, and the *N*-protecting-group-dependent C−H alkenylation has not provided any decisive advantage in terms of atom- and step-economy. Hence, the direct C−H alkenylation of *N*-alkylpyrroles would be more desirable, but only a few isolated examples have been reported.[11]

Complementary to directing group and substrate control strategies, we envisioned that ligand control could lead to high selectivity and efficiency in pyrrole alkenylation. Although different catalytic systems have been developed for the regiodivergent alkenylation of given heterocycles, general ligand-controlled strategies that encompass electronically varying heterocycles are underexplored. [12] Furthermore, a single catalytic system optimized for a given heterocycle often gives a different outcome when a substituent on the heterocyclic core significantly impacts the electronic and steric properties.[11d,11e,13] To address these problems, we have developed electronically tailored catalytic systems for the regioselective C−H alkenylation of *N*-alkylpyrroles and derivatives having electron-withdrawing groups (Figure 1C).[14]

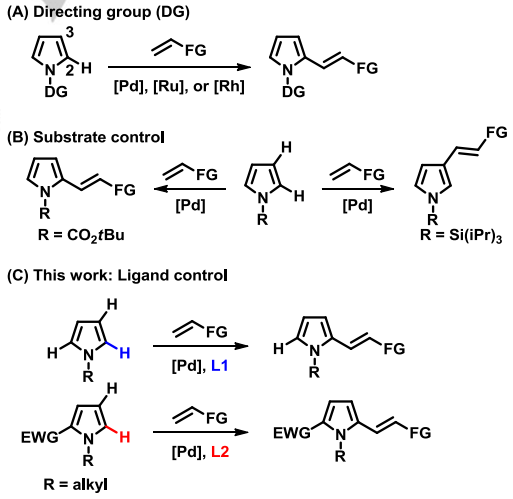

Figure 1. Strategies for regioselective C−H alkenylation of pyrroles with alkenes. FG = functional group; EWG = electron-withdrawing group.

Specifically, it was envisioned that electrophilic catalysts would be suitable for the alkenylation of electron-rich *N*-alkylpyrroles, whereas catalytic systems having efficient bases as ligands would be useful for functionalizing the relatively acidic C−H bond of pyrroles having electron-withdrawing groups. Based on our experience with the regiodivergent alkenylation of pyrazoles at the nucleophilic C4 position and acidic (C5)−H bond, we investigated palladium systems using various ligands for the pyrrole alkenylation (Table 1, see the Supporting Information for details). [15] For alkenylation of *N*-methylpyrrole **1a**, 4,5-

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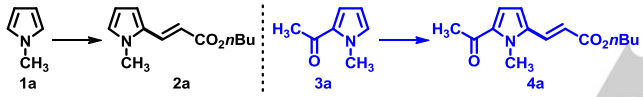
diazafluoren-9-one (DAF) showed distinctive reactivity compared to other nitrogen-based ligands (entries 1−4). [16] High regioselectivity for the C2 position and high selectivity for mono-alkenylation were achieved in the formation of **2a** (entry 4, C2:C3>15:1). The reaction with DAF in DMF gave a comparable result (entry 5). However, the use of 2-acetyl-1-methylpyrrole **3a** was not successful, giving low yields of the corresponding alkenylation product **4a**. In contrast, the addition of mono-*N*-protected amino acid (MPAA) ligands greatly facilitated C−H alkenylation of acetyl pyrrole **3a** in the presence of a stoichiometric amount of potassium acetate and DMF as a solvent (entries 6−8).[17] The regioselectivity for the C5 position of **3a** was also very high (entry 8, C5:C4>20:1). Among the MPAA ligands, Ac−Val−OH was the most efficient (entries 9 and 10). However, the MPAA system was ineffective for *N*-methylpyrrole **1a**, illustrating the importance of electronic matching between the heterocycles and catalytic systems.[18] In addition, the use of DAF instead of Ac-Val-OH resulted in low mono-selectivity for **1a** and low conversion for **3a** when potassium acetate was present (entry 11). Therefore, both the ligand and base were critical for alkenylation of the acetyl pyrrole. It is notable that regeneration of the Pd(II) species in both systems was enabled by oxygen without requiring metal oxidants.[19]

Table 1. Alkenylation of *N*-alkylpyrroles[a]



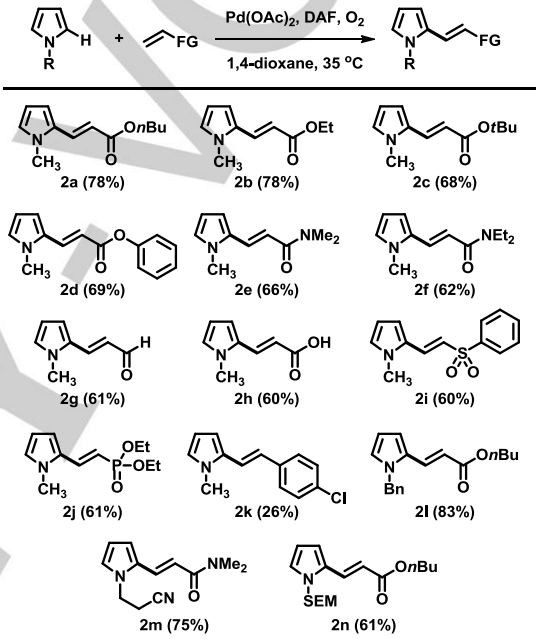
Conditions: $Pd(OAc)_2$, O_2, CO_2nBu

Entry	Ligand (equiv)	Additive	Solvent	Temp. (°C)	Yield (%)[b] 2a	4a
1	–	–	1,4-dioxane	35 °C	38	0
2	Phen. (0.10)	–	1,4-dioxane	35 °C	0	0
3	Pyridine (0.20)	–	1,4-dioxane	35 °C	22	0
4	DAF (0.10)	–	1,4-dioxane	35 °C	80	19
5	DAF (0.10)	–	DMF	35 °C	75	12
6[c]	Ac-Val-OH (0.20)	–	DMF	35 °C	33	18
7[c]	Ac-Val-OH (0.20)	KOAc	DMF	35 °C	8	30
8[c]	Ac-Val-OH (0.20)	KOAc	DMF	60 °C	14	85
9[c]	Ac-Leu-OH (0.20)	KOAc	DMF	60 °C	9	71
10[c]	Ac-Ile-OH (0.20)	KOAc	DMF	60 °C	12	75
11[c]	DAF (0.10)	KOAc	DMF	60 °C	45	9

[a] Reaction conditions: pyrrole (1.0 mmol), *n*-butyl acrylate (0.50 mmol), $Pd(OAc)_2$ (0.050 mmol), ligand (as indicated), O_2 (1.0 atm), solvent (0.50 M), 24 h (for reactions of both **1a** and **3a**). [b] ^{1}H NMR yield. [c] Reaction conditions: pyrrole (0.50 mmol), *n*-butyl acrylate (1.0 mmol), $Pd(OAc)_2$ (0.050 mmol), ligand (as indicated), additive (0.50 mmol), O_2 (1.0 atm), solvent (0.50 M), 24 h. Phen. = 1,10-phenanthroline; DAF = 4,5-diazafluoren-9-one.

Having optimized the reaction conditions, the DAF system was first applied to the C2-alkenylation of *N*-alkylpyrroles with a variety of olefins (Table 2). The reaction worked well with activated alkenes, including acrylates (**2a−2d**), acrylamides (**2e** and **2f**), acrolein (**2g**), acrylic acid (**2h**), vinyl sulfone (**2i**), and vinyl phosphonate (**2j**). However, coupling with styrene derivatives was not efficient, generating regioisomeric mixtures. For example, **2k** was obtained in 26% yield from the reaction with 4-chlorostyrene. Different *N*-alkyl groups were well tolerated, indicative of the generality of this method for *N*-allkylpyrroles (**2l**, **2m**, and **2n**).

Table 2. Substrate scope for alkenylation of *N*-alkylpyrroles[a]



[a] Reaction conditions: pyrrole (1.0 mmol), alkene (0.50 mmol), $Pd(OAc)_2$ (0.050 mmol), DAF (0.050 mmol), O_2 (1.0 atm), 1,4-dioxane (0.50 M), 35 °C, 24 h.

The alkenylation of 2-acetyl-1-methylpyrrole **3a** was then performed with $Pd(OAc)_2$, Ac-Val-OH, and KOAc (Table 3). The MPAA system did not discriminate olefins, affording generally good yields of the corresponding alkenylation products with a wide range of olefins. Acrylates and acrylamides as well as styrene derivatives were all good coupling partners.

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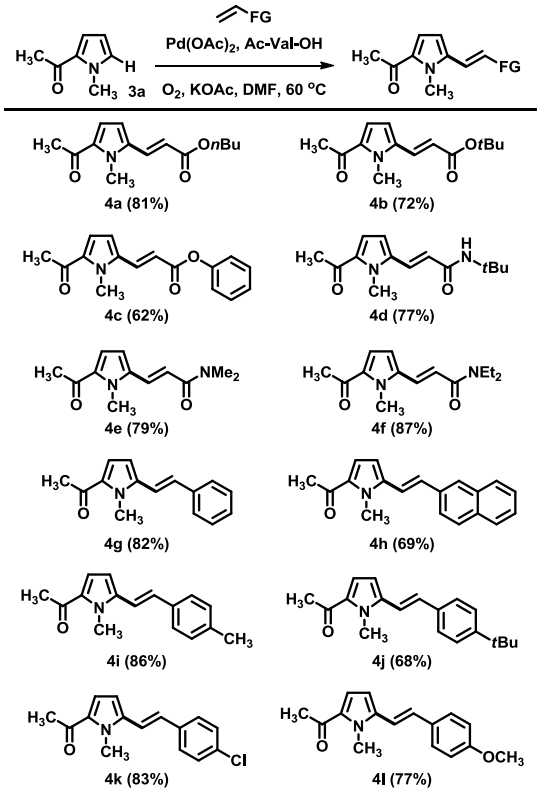
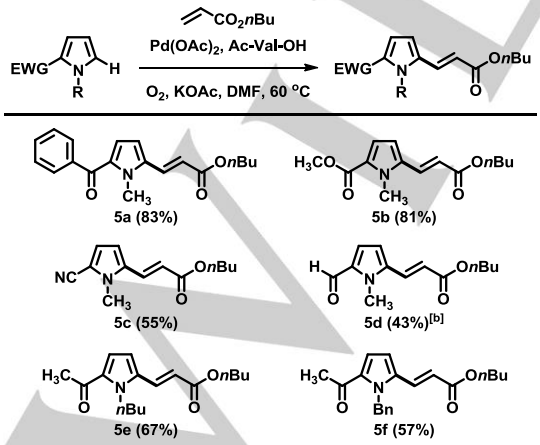
Table 3. Substrate scope for alkenylation of 2-acetyl-1-methylpyrrole[a]



[a] Reaction conditions: pyrrole (0.50 mmol), alkene (1.0 mmol), $Pd(OAc)_2$ (0.050 mmol), Ac-Val-OH (0.10 mmol), KOAc (0.50 mmol), O_2 (1.0 atm), 60 °C, DMF (0.50 M), 24 h.

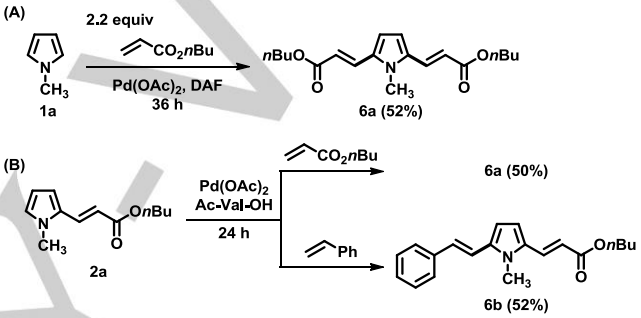
The scope of electron-withdrawing and *N*-alkyl groups of pyrroles was also evaluated. Pyrroles possessing benzoyl, methyl ester, cyano, and formyl groups at the C2 position underwent direct alkenylation (**5a**, **5b**, **5c**, and **5d**, respectively). When the *N*-alkyl group was changed to *n*-butyl and benzyl groups, the corresponding alkenylation products **5e** and **5f** were smoothly formed.

Table 4. Substrate scope for alkenylation of pyrroles having electron-withdrawing groups[a]



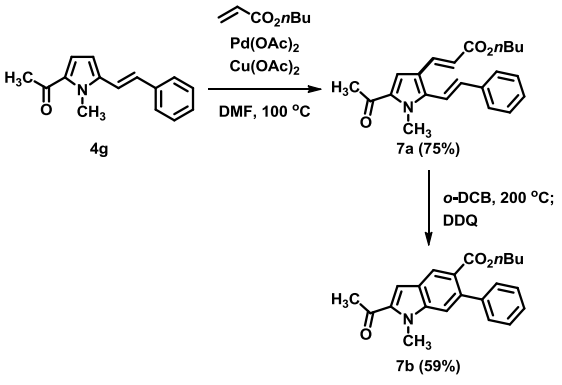
[a] Reaction conditions: pyrrole (0.50 mmol), alkene (1.0 mmol), $Pd(OAc)_2$ (0.050 mmol), Ac-Val-OH (0.10 mmol), KOAc (0.50 mmol), O_2 (1.0 atm), DMF (0.50 M), 60 °C, 24 h. [b] The corresponding 4,5-dialkenylation product was also formed in 33% yield.

Finally, the synthetic utility for the alkenylation of readily available *N*-alkylpyrroles and alkenes was demonstrated in the formation of dialkenyl pyrroles (Scheme 1). When the amount of alkenes and the reaction time were increased, dialkenylation of *N*-methylpyrrole **1a** occurred, affording **6a** in 52% yield (Scheme 1A). Alternatively, sequential alkenylation could be carried out. Because the newly installed acrylate group is weakly electron-withdrawing, the mono-alkenylation product **2a** was subjected to the MPAA conditions, yielding **6a** and **6b** (Scheme 1B). A control experiment using the DAF system for the alkenylation of **2a** afforded **6a** in 40% yield (not shown), supporting that the MPAA system was slightly more efficient than the DAF-dependent one for **2a**.



Scheme 1. Synthesis of dialkenyl pyrroles.

Furthermore, sequential alkenylation could be applied to pyrroles having electron-withdrawing groups. For example, C3-alkenylation of **4g** with $Pd(OAc)_2$ and $Cu(OAc)_2$ afforded 4,5-dialkenyl pyrrole **7a** having different alkenyl groups (Scheme 2).[11e,20] Subsequent thermal 6π-electrocyclization and oxidation facilitated ring closure, producing the multi-substituted indole **7b**.[21,22]



Scheme 2. Synthesis of indole by sequential alkenylation, 6π-electrocyclization, and oxidation.

In conclusion, an approach for the regioselective C−H alkenylation of pyrroles was developed by using two complementary palladium catalyst systems. The palladium

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complex derived from $Pd(OAc)_2$ and DAF was used for the C2-alkenylation of electron-rich *N*-alkylpyrroles. In contrast, the use of the mono-protected amino acid ligand Ac-Val-OH and potassium acetate enabled palladium-catalyzed C5-alkenylation of pyrroles having electron-withdrawing groups at the C2 position. In addition, the sequential alkenylation of pyrroles was demonstrated to illustrate the versatility of this approach. This concept based on electronic matching between heterocycles and catalytic systems should be useful for promoting the efficient C−H functionalization of heterocycles with varying electronic properties.

Experimental Section

General procedure for alkenylation of N-alkylpyrroles. An 8 mL glass vial was evacuated and filled with oxygen three times. *N*-alkylpyrrole (1.0 mmol), alkene (0.50 mmol), $Pd(OAc)_2$ (0.050 mmol, 11 mg), 4,5-diazafluorene-9-one (DAF) (0.050 mmol, 9.0 mg), and 1,4-dioxane (1.0 mL, 0.50 M) were added under oxygen atmosphere. The vial was again evacuated and filled with oxygen. After stirring for 24 h at 35 °C under 1 atm of oxygen (balloon), the reaction mixture was cooled to 25 °C and then purified by flash column chromatography to afford the desired product.

General procedure for alkenylation of N-alkylpyrroles having electron-withdrawing groups. An 8 mL glass vial was evacuated and filled with oxygen thrice. Pyrrole (0.50 mmol), alkene (1.0 mmol), KOAc (1.0 mmol, 49 mg), $Pd(OAc)_2$ (0.050 mmol, 11 mg), Ac-Val-OH (0.10 mmol, 16 mg), and DMF (1.0 mL, 0.50 M) were added under oxygen atmosphere. The vial was again evacuated and filled with oxygen. After stirring for 24 h at 60 °C under 1 atm of oxygen (balloon), the reaction mixture was cooled to 25 °C. The reaction mixture was treated with EtOAc (25 mL) and water (25 mL) and transferred to a 125 mL separatory funnel. The organic layer was collected and the aqueous layer was extracted with EtOAc (15 mL × 2). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated and purified by flash column chromatography to provide the desired product.

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Keywords: C−H activation • pyrroles • alkenes • palladium • alkenylation

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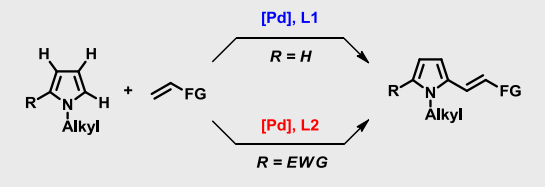

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C−H Alkenylation of Pyrroles by Electronically Matching Ligand Control

Depending on the electronic character of pyrroles, matching palladium catalytic systems were developed for regioselective C−H alkenylation. Complementary to directing group and substrate control strategies, this approach based on electronic matching between heterocycles and catalytic systems should be useful for providing a variety of alkenyl pyrroles from readily available *N*-alkylpyrroles and alkenes.

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