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Elements of Regiocontrol in Palladium-Catalyzed Oxidative Arene **Cross-Coupling**

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An increasing emphasis on waste minimization has prompted research aimed at replacing common synthetic techniques with greener alternatives. In biaryl synthesis, direct arylation^{1,2} is an emerging alternative to Suzuki and Stille couplings;3 however, a more efficient strategy would involve the direct catalytic crosscoupling of two arenes without recourse to stoichiometric activating groups (eq 1).^{4–7} This last approach presents several new challenges,



including the avoidance of unwanted arene homocoupling and the need to achieve/manipulate regioselectivity on both substrates. While much has been learned about regioselectivity in catalytic direct arene functionalizations, the ability to manipulate this character has been achieved in only a few instances.8

Herein, we demonstrate that high regiocontrol can be acheived to access both C3 and C2 arylindoles in Pd-catalyzed oxidative cross-coupling reactions. We also show that regioselectivity can occur at the benzene component, and we can validate the use of this methodology with pyrrole substrates. These findings should further encourage the development of these reactions as a tool for the synthesis of biaryl molecules, and the observations regarding regiocontrol may warrant consideration in other PdII-catalyzed processes.9

Following our success with Pd-catalyzed C3-selective indole/ benzene cross-couplings involving a stoichiometric copper(II) oxidant,6a a range of other terminal oxidants were examined (Table 1). Interestingly, AgOAc produced an inversion in selectivity compared to Cu(OAc)₂, favoring C2 arylation in a 1:4 ratio (entry 1 vs 2).¹⁰ With the goal of optimizing the reaction for C2 arylation, we determined that removal of the additives and changing from N-acetyl to N-pivalyl indole results in 100% conversion and a 1:25 C3/C2 ratio (entry 4). Under these conditions, 2 mol % Pd is sufficient to achieve 87% conversion with a 1:14 C3/C2 ratio after 15 h (entry 5). We also note the formation of some benzene homocoupling appearing once the indole conversion exceeds 90%.

These conditions are compatible with a range of indole substrates as illustrated in Table 2. Substituted benzenes may also be used (entries 7-10). Importantly, high selectivity can also be obtained for reaction at the more sterically accessible C-H bond of the benzene component. Entries 9 and 10 illustrate the potential of this approach; not only can high regioselectivity be achieved at both arenes, but it can also be controlled to give a desired indole isomer. Pyrroles can also be successfully coupled using a Pd catalyst and a silver oxidant.11 In these cases, small amounts of pyrrole dimerization is noticed (less than 10%), but synthetically useful yields of the 2-phenylpyrrole products can be achieved (Scheme 1). Currently, high yields can be achieved in reactions with indole with as few as 15 equiv of benzene, although more is commonly employed.

| RR RR | Ac; 1a Piv; 1b | + Pd Ac be P | (TFA) ₂ kidant diditive nzene iwOH 10°C 2a/b | CC N R 3a/t | { | >+ € | Ph N R 4a/b |
|-------|--------------------------|---------------------------------|--|----------------------|-------------|------------------------|---------------------------|
| entry | mol % Pd ^b | oxidant (equiv) ^b | additive (mol %) ^b | indole | time (h) | % conv ^c | 2:3:4 ^c |
| 1^d | 10 | $Cu(OAc)_2(3)$ | 3-nitropyridine (10) CsOPiv (40) | 1a | 5 | 100 | 8.9:1:0.26 |
| 2 | 10 | AgOAc (2.2) | 3-nitropyridine (10) CsOPiv (40) | 1a | 24 | 32 | 1:4:0 |
| 3 | 10 | AgOAc (2.2) | 3-nitropyridine (10) CsOPiv (40) | 1b | 24 | 78 | 1:8.7:0.3 |
| 4 | 5 | AgOAc (3) | none | 1b | 3 | 99 | 1:25:0.7 |
| 5 | 2 | AgOAc (3) | none | 1b | 15 | 87 | 1:14:0.4 |
| 6 | 20 | none | none | 1b | 3 | 18 | 1.1:1:0 |
| 7 | 50 | none | none | 1b | 3 | 45 | 1.3:1:0 |
| 8 | 100 | none | none | 1b | 3 | 61 | 3.7:1:0 |
| 9 | 300 | none | none | 1b | 3 | 100 | 99:1:0 |
| 10 | 20 | none | CsOAc (200) | 1b | 3 | 15 | 1:99:0 |

Table 1. Regioselectivity in Oxidative Arene Cross-Coupling^a

^a Conditions: Pd(TFA)₂, oxidant, 3-nitropyridine, cesium pivalate, PivOH (6 equiv), and **1a/b** were added to a screw-capped vial followed by the addition of benzene (30–60 equiv; see SI) and heating to 110 °C. ^{*b*} Relative to 1. ^{*c*} Determined by GC/MS. ^{*d*} Microwave heating.

Scheme 1. Reactions of Pyrroles^a



^a See the SI for experimental details.

The reason for the inversion in C2/C3 selectivity is a focus of continuing investigation. The possibility of in situ indole metalation by the Cu^{II} and Ag^I oxidants was ruled out by reacting the indole with stoichiometric Cu(OAc)₂ or Ag(OAc) in AcOD at 100 °C. After 14 h of reaction time, the indole is quantitatively recovered with no H/D exchange above that found in control experiments performed in the absence of metals (less than 10% at C3).

More informative is the influence of Pd concentration and acetate additives. For example, the C3 selectivity increases dramatically when the $Pd(TFA)_2$ loading is increased from 20 to 300 mol % in the absence of oxidant under otherwise identical conditions (Table

Table 2. Scope of the Pd-Catalyzed Indole/Benzene Cross-Coupling^a



^{*a*} Conditions: Pd(TFA)₂ (5 mol %), AgOAc (3 equiv), PivOH (6 equiv), and the *N*-pivalylindole were added to a screw-capped vial followed by benzene (approximately 60 equiv) and heating to 110 °C. ^{*b*} Determined by GC/MS. ^{*c*} Isolated yield. ^{*d*} Represents the ratio of C2/C3/double arylation. ^{*e*} Represents the ratio of the major (isolated) isomer to other minor isomers detected by GC/MS. ^{*f*} 10 mol % Pd used. ^{*g*} Cu(OAc)₂ used as the oxidant. See SI.

1, entries 6–9). Furthermore, the addition of 2 equiv of CsOAc to reactions performed with 20 mol % $Pd(TFA)_2$ in the absence of oxidants induces very high C2 selectivity (entry 10 vs 6).

Our rationale for the dramatic change in selectivity continues to evolve. These studies indicate that it is the acetate base, when added as a Ag^I or Cs^I salt, and not the metal counterion that imparts the increased C2 selectivity to the Pd catalyst. This may be due to carboxylate-induced cleavage of higher-order Pd clusters and the formation of monomeric Pd species (vide infra). On the other hand, when excess Cu(OAc)₂ is added to a catalytic quantity of Pd(TFA)₂, mixed Pd–Cu clusters may be formed that exhibit pronounced C3 selectivity.^{12,13} The change in C3/C2 selectivity as a function of [Pd] is indirect support for this hypothesis. At high [Pd], where the presence of trinuclear Pd carboxylate clusters should be favored, high C3 selectivity is observed. It is plausible that analogous mixed Pd–Cu complexes may behave in a similar fashion.

These results point to new opportunities for control of reactivity/ selectivity in Pd-catalyzed oxidative cross-coupling reactions and may have broader impact in Pd^{II} catalysis. They also support the potential of this approach in the synthesis of biaryl molecules.

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Supporting Information Available: Experimental procedures and spectroscopic characterization of all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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