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Tetrahedron Letters 49 (2008) 4050–4053

Tetrahedron Letters

Oxidant-controlled regioselectivity in the oxidative arylation of *N*-acetylindoles

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Received 27 March 2008; accepted 10 April 2008
Available online 15 April 2008

Abstract

N-Acetylindoles can be oxidatively coupled with arenes such as benzene or pentafluorobenzene in dioxane. The use of $Cu(OAc)_2$ as the stoichiometric oxidant produces selective arylation at the 3-position of indole while AgOAc produces selective arylation at indole's 2-position.

Keywords: Indole; Palladium; Oxidative coupling; Regioselective; Arylation; C–H functionalization

The World Drug Index contains forty-six 2-arylindoles and twenty-eight 3-arylindoles (Fig. 1).[1] These molecules are often synthesized by coupling preactivated arenes and indole substrates or by intramolecular cyclizations to construct the heterocycle. Recently, several methods have emerged that allow for the direct coupling of unfunctionalized indoles to halogenated arenes using palladium,[2] rhodium,[3] or copper catalysts.[4] Our group,[5] along with that of Fagnou,[6] has recently disclosed the seminal examples of palladium-catalyzed oxidative coupling of benzofurans and indoles with unfunctionalized arenes.[7,8] In each of these cases, the reactions were preformed at high temperatures in acidic solvents. Herein, we report that milder, non-acidic conditions can be used, and that judicious choice of oxidants can control the regioselectivity of the reactions. Moreover, we hypothesize that the formation of catalytic polymetallic clusters accounts for the unique, oxidant-controlled regioselectivity.

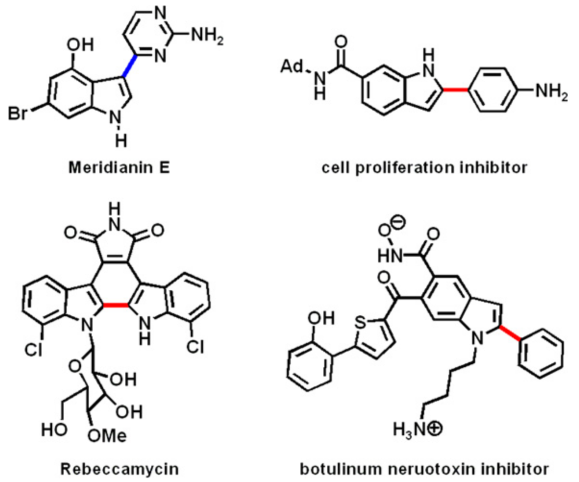

Fig. 1. Examples of biologically active compounds containing arylated indoles.

Our previous work with oxidative coupling showed that different oxidants effect the regioselectivity of the reaction (Scheme 1).[5] The use of $Cu(OAc)_2$ as a stoichiometric oxidant produced exclusive oxidative arylation of benzofuran's 2-position, while AgOAc produced nearly an even mixture of 2- and 3-arylated products. Ultimately, we discovered that aerobic conditions using catalytic amounts of $H_4PMo_{11}VO_{40}$ (HPMV) exclusively produced

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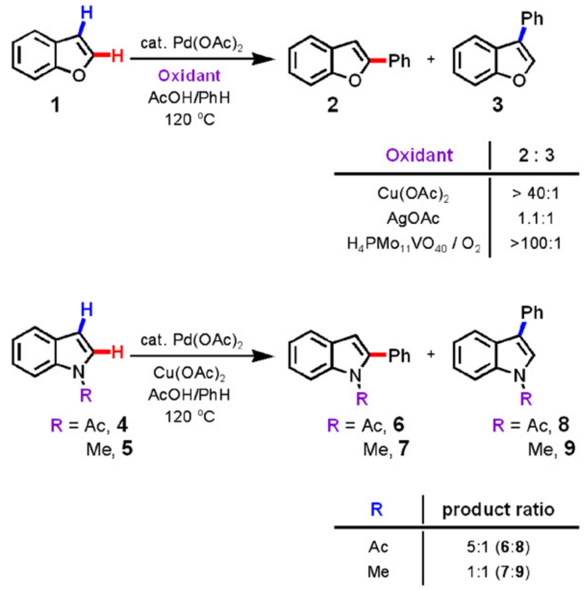
doi:10.1016/j.tetlet.2008.04.073



Oxidant	2 : 3
$Cu(OAc)_2$	> 40:1
AgOAc	1.1:1
$H_4PMo_{11}VO_{40}$ / O_2	>100:1

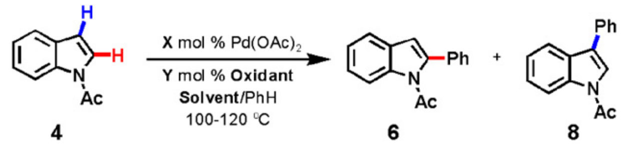
R	product ratio
Ac	5:1 (**6**:**8**)
Me	1:1 (**7**:**9**)

Scheme 1. Evidence of oxidant-controlled regioselectivity.

2-phenylbenzofuran in high yield, but these conditions were incompatible with indole substrates, due to over-oxidation. These oxidant effects seem counterintuitive when simplistic mechanisms are considered, in which the oxidant only serves to regenerate catalytically active Pd(II) from Pd(0). In fact, these observations show that the oxidant must be involved in the C–H functionalization process. When *N*-acetylindoles were subjected to the $Cu(OAc)_2$/AcOH conditions, which showed regioselectivity for benzofuran, a mixture of 2-arylated and 3-arylated regiomers was formed. This loss of regioselectivity was even more pronounced for *N*-methylindole (Scheme 1).

As shown in Table 1, switching solvents from acetic acid to dioxane allowed for regioselective control. In the presence of $Cu(OAc)_2$, *N*-acetylindole selectively underwent oxidative coupling with benzene at its 3-position. This observation contrasts with our previous studies with ben-

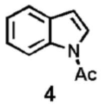
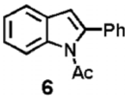
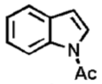
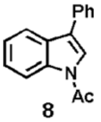
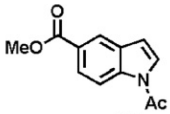
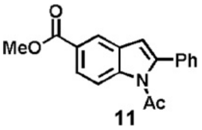
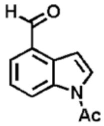
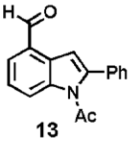
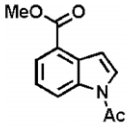
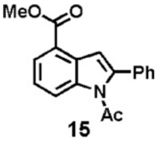
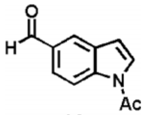
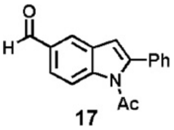
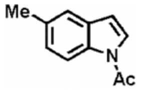
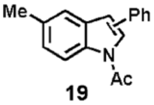
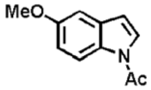
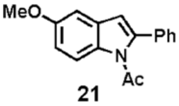
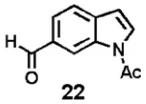
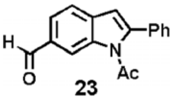
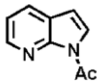
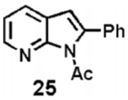
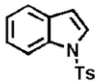
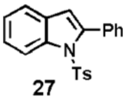
Table 1
Lead discovery and control reactions in dioxane



Entry	Solvent	Oxidant	X mol % $Pd(OAc)_2$	Y mol % Oxidant	Yield **6** (%)	Yield **8** (%)
1	AcOH	$Cu(OAc)_2$	25	400	38	8
2	Dioxane	$Cu(OAc)_2$	25	400	13	53
3	Dioxane	AgOAc	25	400	43	12
4	Dioxane	None	100	0	13	18
5	Dioxane	AgOAc	0	400	0	0
6	Dioxane	$Cu(OAc)_2$	0	400	0	0

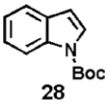
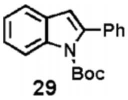
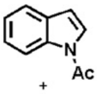
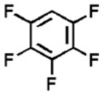
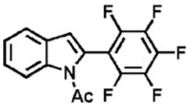
Standard reactions conditions: 0.1 mmol substrate, 25 mol % $Pd(OAc)_2$, 4 equiv oxidant, 2 mL AcOH, 3 mL PhH, 120 °C, 1 atm N_2.

Table 2
Scope of regioselective arylation reactions

Substrate	Oxidant	Temp (°C)	Product	Yield (%)
 **4**	AgOAc	120	 **6**	43
 **4**	$Cu(OAc)_2$	120	 **8**	53
 **10**	AgOAc	100	 **11**	33
 **12**	AgOAc	100	 **13**	22
 **14**	AgOAc	100	 **15**	55
 **16**	AgOAc	60	 **17**	56
 **18**	AgOAc	100	 **19**	25[a]
 **20**	AgOAc	100	 **21**	38
 **22**	AgOAc	60	 **23**	52
 **24**	AgOAc	100	 **25**	0[b]
 **26**	AgOAc	100	 **27**	30

(*continued on next page*)

Table 2 (*continued*)

Substrate	Oxidant	Temp (°C)	Product	Yield (%)
 **28**	AgOAc	100	 **29**	0[c]
 **4** +  **30**	AgOAc	100	 **31**	38

Standard reaction conditions. See Scheme 1 for details. (a) 1:1 mixture of 2- and 3-phenylated products. (b) No appreciable conversion was observed. (c) Substrate decomposition was observed.

zofuran (Scheme 1), but is congruent with the observations of both Fagnou[6] and Gaunt,[9] in which arenes and olefins couple to the 3-position of indoles in acidic media with Pd(II)/Cu(II) catalyst/oxidant systems. Contrastingly, in the presence of AgOAc, *N*-acetylindole selectively arylated at its 2-position. Reactions using stoichiometric amounts of palladium produced a 3:2 mixture of 3-phenyl- and 2-phenylindole, thus showing that the copper and silver oxidants were intimately involved in the selective arylation reactions. Furthermore, control reactions containing no palladium and stoichiometric amounts of the oxidants failed to convert the indole starting material.

The scope of the reaction was explored with respect to the indole substrate (Table 2). In light of the importance of 2-arylindoles,[1] we chose to focus primarily on the reaction using AgOAc. Aldehydes, esters, and ethers were all tolerated, and, with one exception (**19**), near exclusive regioselectivities were observed.

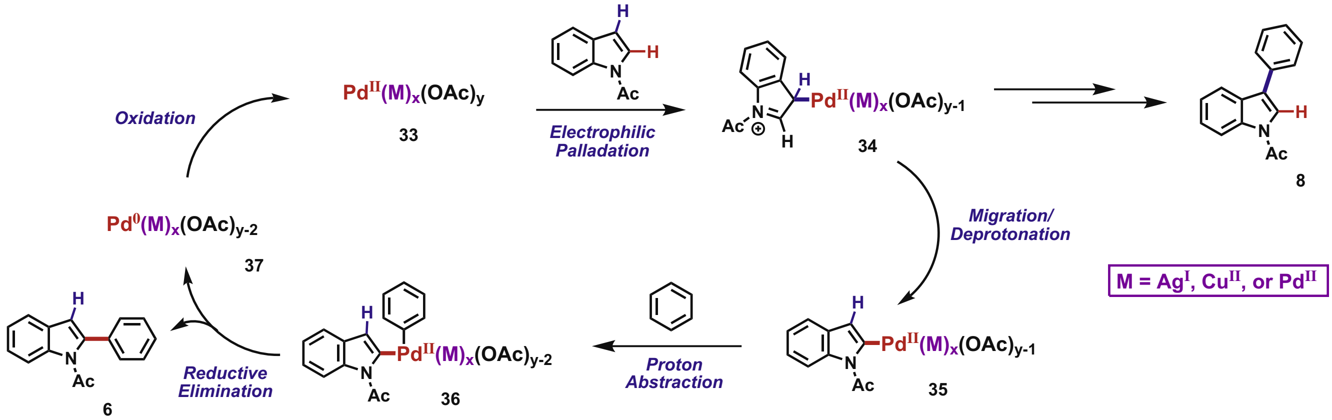
N-Tosylindole (**26**) was also a viable substrate for oxidative arylation. Thus, allowing for a synthesis of *N*-H-2-arylindoles, following tosyl deprotection.[10] Unfortunately, indoles protected with carbamate groups such as *t*-butylcarbamate (**28**) resulted in the decomposition of the substrate. The reactions are also prone to the formation of palladium black. Consequently, higher Pd(OAc)$_2$ loadings (25 mol %) were required compared to our prior work with HPMV/O$_2$ oxidants (10 mol %).[5]

With respect to the other arene substrate, electron-rich moieties such as *p*-xylene and anisole failed to react, but pentaflurorobenzene cleanly cross-coupled (**31**). This also contrasts with our previous work using the HPMV/O$_2$ oxidant system.[5]

We propose that the oxidant-controlled selectivity is a consequence of the formation of polymetallic, catalytically active clusters. The formation of [Cu$_2$Pd(OAc)$_6$] and [Cu$_2$Pd$_4$(OAc)$_{12}$] had been previously described by both Claridge and Thornton.[11] Interestingly, Claridge observed that complexes of this type do not form with alkali metal acetates, such as KOAc. This trend may extend to other mono-valent metal acetates, such as AgOAc. Alternatively, mixtures of AgOAc and Pd(OAc)$_2$ may form novel clusters. We hypothesize that the Cu(OAc)$_2$ oxidant forms a polymetallic cluster with Pd(OAc)$_2$ that selectively couples to the 3-position of *N*-acetylindole, while the AgOAc oxidant forms either a different polymetallic cluster or 'naked' Pd(OAc)$_2$ that selectively arylates the 2-position of *N*-acetylindole.

In light of the substrate scope and assumed polymetallic cluster formation, we propose the following mechanism (Scheme 2). Initially, the electron-rich indole is metallated at its nucleophilic 3-position (**33**). Deprotonation of this intermediate occurs when Cu(OAc)$_2$ is present, leading to the formation of the 3-aryl product **8**. When AgOAc is the oxidant, palladium migration from the indole's 3- to the 2-position occurs, followed by deprotonation of the indole's 2-position (**34**).[2a,9] As this migration, or lack thereof, is the regiochemistry-determining step, the oxidant must be intimately involved at this point.

Following the electrophilic palladation that forms **34**, the electron-poor arene (e.g., benzene or pentafluorobenzene) is deprotonated via an intramolecular abstraction process.[12] This hypothesis is supported by the fact that



Scheme 2. Proposed mechanism.

Table 3
Kinetic isotope effects

Substrate	Oxidant	Product	KIE
N-acetylindole **4**	AgOAc	**6** (C2, major)	2.4
		8 (C3, minor)	3.7
	$Cu(OAc)_2$	**6** (C2, minor)	3.9
		8 (C3, major)	4.0
Benzofuran **1**	AgOAc	**2** (C2, minor)	3.2
		3 (C3, major)	3.4
	$Cu(OAc)_2$	**2** (C2, major)	4.0
		3 (C3, minor)	4.2
	$HPMV/O_2$	**2** (C2, exclusive)	1.9

electron-rich arenes such as anisole failed to react, while benzene and pentafluorobenzene readily coupled with *N*-acetylindole.

Following this step, reductive elimination of the diaryl palladium intermediate **35** affords the product and a Pd(0) species **36**, and turnover is achieved by oxidation with the organometallic oxidant. Alternatively, the two key steps in the proposed mechanism, electrophilic substitution and proton abstraction, could occur in reverse order (not shown).

The rate-determining step of the process is the proposed proton abstraction. The kinetic isotope effects for both the major and minor products of reactions oxidized by both AgOAc and $Cu(OAc)_2$ were determined using GC/MS analysis of benzene/benzene-d_6 (1:1 mol/mol) competition experiments (Table 3). Interestingly, the KIE for the formation of 2-phenyl-*N*-acetylindole (**6**) for reactions employing Ag(I) and Cu(II) oxidants was significantly different. Consequently, we believe that the oxidant is not only present in the metallation of the indole substrate, but is involved in the proton abstraction step as well.

Benzofuran substrates also demonstrated significant oxidant-modulated KIEs. Interestingly, the KIEs of reactions oxidized by both AgOAc and $Cu(OAc)_2$ differed from that of our previously studied oxidant system of $HPMV/O_2$. This may imply that polymetallic clusters also form in the presence of HPMV, or that this reaction is following a different mechanism altogether.

In summary, we have demonstrated that both 3- and 2-arylindoles can be formed by the oxidative cross-coupling of unfunctionalized substrates, and that the regioselectivity of these processes is controlled by the oxidant. We propose that catalytically active polymetallic clusters are involved in all of the C–H cleaving and C–C bond forming steps of the oxidative coupling. Our future efforts in this field will include further exploration of the mechanism of these cross-couplings as well as the characterization of these unique catalysts.

Acknowledgments

The authors thank Brett Lucht for editorial assistance. This work was supported by the University of Rhode Island, the URI Foundation, the New England Green Chemistry Consortium, and the Petroleum Research Fund. J.M.H. is an awardee of the Jugend Forscht competition and a visiting international student sponsored by the URI International Engineering Program.

Supplementary data

Supplementary data (experimental procedures as well as characterization of previously unknown compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.04.073.

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