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C–H bond functionalizations with palladium(II): intramolecular oxidative annulations of arenes

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Abstract

Oxidative annulations for the synthesis of carbocycles were developed using a catalytic palladium(II) system. Indoles with pendant olefin tethers were oxidatively cyclized to form annulated products. Electron-rich aromatic systems were also investigated, culminating in the synthesis of benzofurans and dihydrobenzofurans by a similar protocol. These reactions were demonstrated to proceed by an initial C–H bond functionalization event, followed by olefin insertion and β-hydride elimination.

1. Introduction

Palladium(0)-catalyzed carbon–carbon bond forming reactions have been well-established in synthetic chemistry.[1] Processes such as the Heck reaction,[2] Stille and Suzuki couplings,[3,4] and the Sonogashira reaction[5] have been widely used for the efficient construction of carbon–carbon bonds. These transformations are all initiated by the oxidative addition of an organic halide to a palladium(0) catalyst, the byproducts of these reactions being either HX (for the Heck and Sonogashira reactions) or MX (for the cross-coupling reactions).

Conversely, dehydrogenative carbon–carbon bond forming reactions catalyzed by palladium(II) have seen relatively little use in synthetic chemistry.[6] A number of oxidative transformations that can be envisioned by such a process are depicted in Figure 1. These transformations result in the functionalization of two C–H bonds and the formation of a new C–C bond. Carbons of any hybridization (sp, sp^2, or sp^3) can be viewed as potential coupling partners for these dehydrogenative bond forming reactions.

These transformations, though attractive in their simplicity, represent a significant challenge in chemical synthesis, largely due to the difficulties associated with the chemoselective functionalization of a relatively inert C–H bond. Despite this barrier, a tremendous effort has been put forth over the past 30

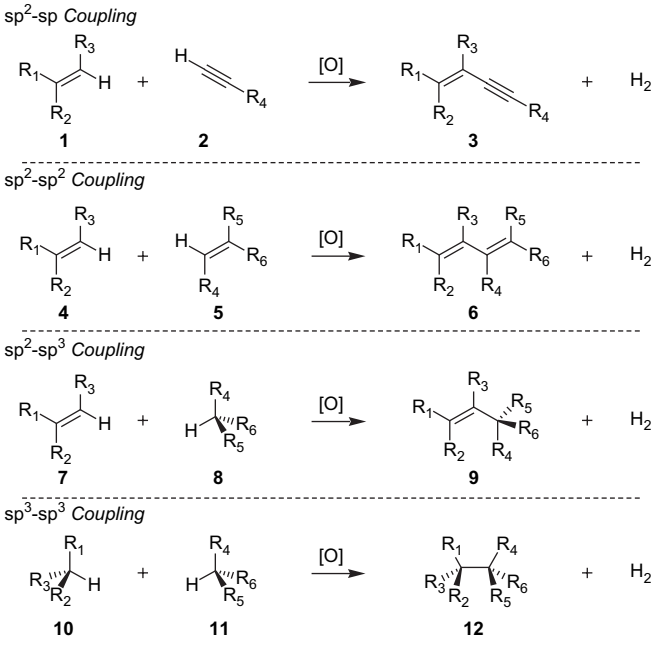

Figure 1. Oxidative carbon–carbon bond forming reactions.

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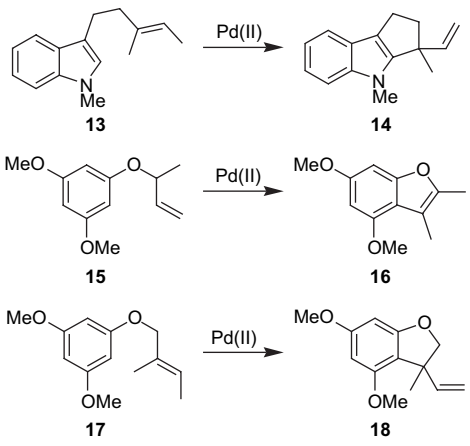
years toward the transition metal activation of C–H bonds.[7] One such reaction manifold is the oxidative coupling of an arene and an olefin by palladium(II), pioneered by Fujiwara and co-workers.[8] Although successful in several intermolecular cases, examples of intramolecular reactions are rare. We hypothesized that the palladium-catalyzed aerobic systems we had been studying in other transformations (i.e., kinetic resolution of secondary alcohols,[9] oxidative heterocyclizations[10]) could be utilized in intramolecular C–C bond forming reactions between an arene and an olefin. Described herein are our efforts toward this goal, culminating in the palladium-catalyzed oxidative annulations of indoles and the syntheses of benzofuran and dihydrobenzofuran derivatives, all involving an initial C–H bond functionalization event (Scheme 1).[11]



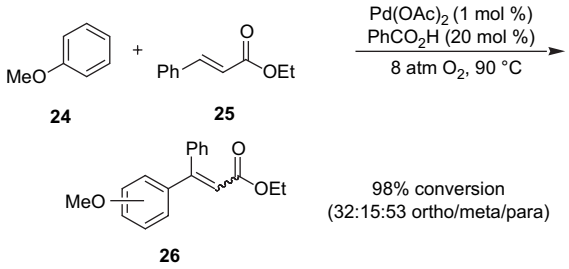
Scheme 1.

A reaction of this type is directly analogous to the intramolecular Heck reaction, wherein a halogenated arene (**19**) undergoes an oxidative addition reaction with palladium(0), followed by olefin insertion and β-hydride elimination (Scheme 2). In a dehydrogenative version, a C–H bond of an arene is directly functionalized by palladium(II), leading to a similar aryl–palladium intermediate (**23**). The reaction then proceeds in the same fashion as the Heck reaction. Oxidation of the palladium(0) species regenerates the active palladium(II) catalyst. This oxidative coupling can be considered more efficient, obviating the need to first install the halide functionality required for a Heck process.

2. Background

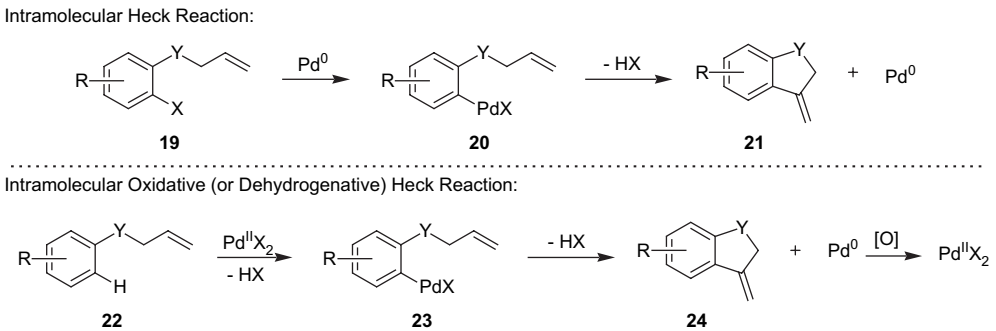
2.1. Palladium(II)-catalyzed oxidative arene–olefin couplings

Initially, reports of palladium-catalyzed couplings of arenes and olefins utilized metal salts such as copper acetate or silver acetate as the stoichiometric reoxidant. The first *aerobic* palladium-catalyzed C–C bond forming reaction was reported by Shue in 1971.[12] Benzene and styrene were coupled in the presence of $Pd(OAc)_2$ and approximately 20 atm O_2 at 100 °C to provide stilbene. Up to 11 catalytic turnovers were observed under these conditions. More recently, Jacobs and co-workers have described a similar system in the oxidative coupling of benzene derivatives and activated esters (Scheme 3).[13] In the presence of $Pd(OAc)_2$ and a cocatalytic amount of benzoic acid under approximately 8 atm O_2, benzene derivatives could be oxidatively coupled to afford styrenyl compounds. Under these conditions, the turnover number and turnover frequency of the catalyst could reach remarkably high values (762 and 73 h^{-1}, respectively).

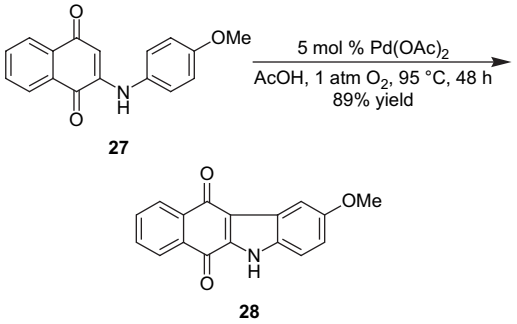


Scheme 3.

Oxidative C–C bond forming reactions using oxygen as the sole stoichiometric oxidant almost exclusively involved intermolecular examples wherein a solution of an activated olefin (e.g., acrylate esters) in neat arene was stirred under high pressures of oxygen. One notable exception was reported by Åkermark and co-workers in 1999 (Scheme 4).[14] Arylaminoquinone **27** was oxidatively cyclized under catalytic $Pd(OAc)_2$ and 1 atm O_2 in AcOH at 95 °C to afford product **28**, resembling the core structures of a number of natural products (e.g., murrayaquinone A and pyrayaquinone A).



Scheme 2.



Scheme 4.

Palladium-mediated oxidative coupling reactions involving the indole nucleus have been studied extensively by Itahara and co-workers.[15] Catalytic examples, however, were consistently plagued by low yields (Scheme 5). *N*-2,6-Dichlorobenzoylindole (**29**) was oxidatively coupled with methyl acrylate by catalytic $Pd(OAc)_2$ and a number of stoichiometric oxidants (e.g., AgOAc, $Cu(OAc)_2$, $Na_2S_2O_8$, and $NaNO_2$),[15a] but the yield never exceeded 20% in these systems. Alternatively, the oxidative coupling of *N*-tosylindole (**31**) was examined, in this case with higher catalyst loadings.[15b] Although the yields were marginally improved (up to 42%), they were still not particularly useful synthetically. Fujiwara and co-workers recently described a single example of a catalytic intermolecular oxidative coupling using the indole nucleus.[16] Under $Pd(OAc)_2$ and a benzoquinone/TBHP reoxidation system, indole (**33**) was coupled to methyl acrylate to provide **34** in 52% yield.

2.2. Synthetic importance of annulated indoles

Although some success has been achieved in oxidative couplings involving the indole nucleus, intramolecular catalytic examples had never been reported when we began our work in this area in 2003.[17] In a general reaction scheme, indole **35** would cyclize onto a tethered olefin to afford annulated indole **36** (Scheme 6). A reaction of this type would be highly useful to the synthetic community. Several biologically active natural products (e.g., paxilline,[18] penitrem A,[19] and yuehchukene[20]) containing the core annulated indole structural motif could be potentially accessed by such a reaction.

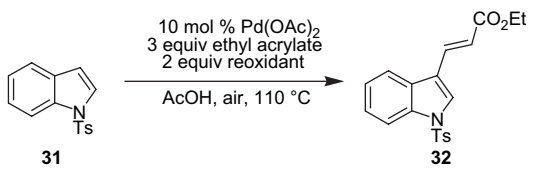
We were not the first to recognize the potential utility of an intramolecular indole annulation in natural product synthesis (Scheme 7). In 1978, Trost reported the palladium-mediated cyclization and subsequent reduction of indole **40** to produce (+)-ibogamine.[21,22] Fifteen years later, Williams and co-workers described the total synthesis of paraherquamide B using a similar palladium(II)-promoted cyclization/reduction sequence of indole **42** as the key transformation.[23] More recently, Corey has reported the oxidative cyclization of indole **45** using palladium(II) in the syntheses of members of the austamide class of natural products.[24,25] Although the cyclizations were all effective in the synthetic context, they all required stoichiometric amounts of palladium(II) salts. By comparison, the catalytic palladium/pyridine/O_2 system we had been studying had proven quite effective in a number of oxidative transformations. We therefore sought to extend this system to catalytic C–C bond forming reactions, specifically oxidative indole annulations.[26,27]

3. Results and discussion

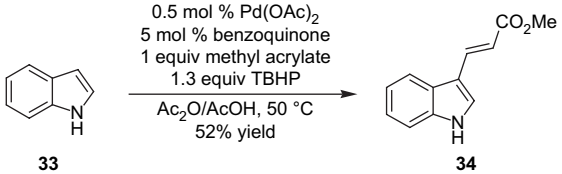
3.1. Reaction development

As an initial test of the viability of a catalytic oxidative indole annulation, indole **13** was treated with 10 mol % $Pd(OAc)_2$ and 40 mol % pyridine under 1 atm O_2 in toluene at 80 °C

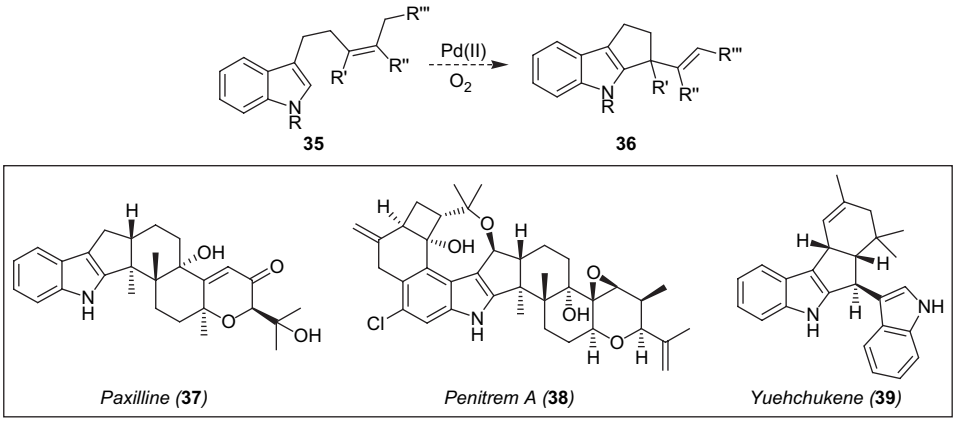
Reoxidant	TON	Yield (%)
stoich. $Pd(OAc)_2$	--	25
AgOAc	8.8	18
$Cu(OAc)_2$	5.2	10
$Na_2S_2O_8$	3.2	6
$NaNO_2$	3.4	7



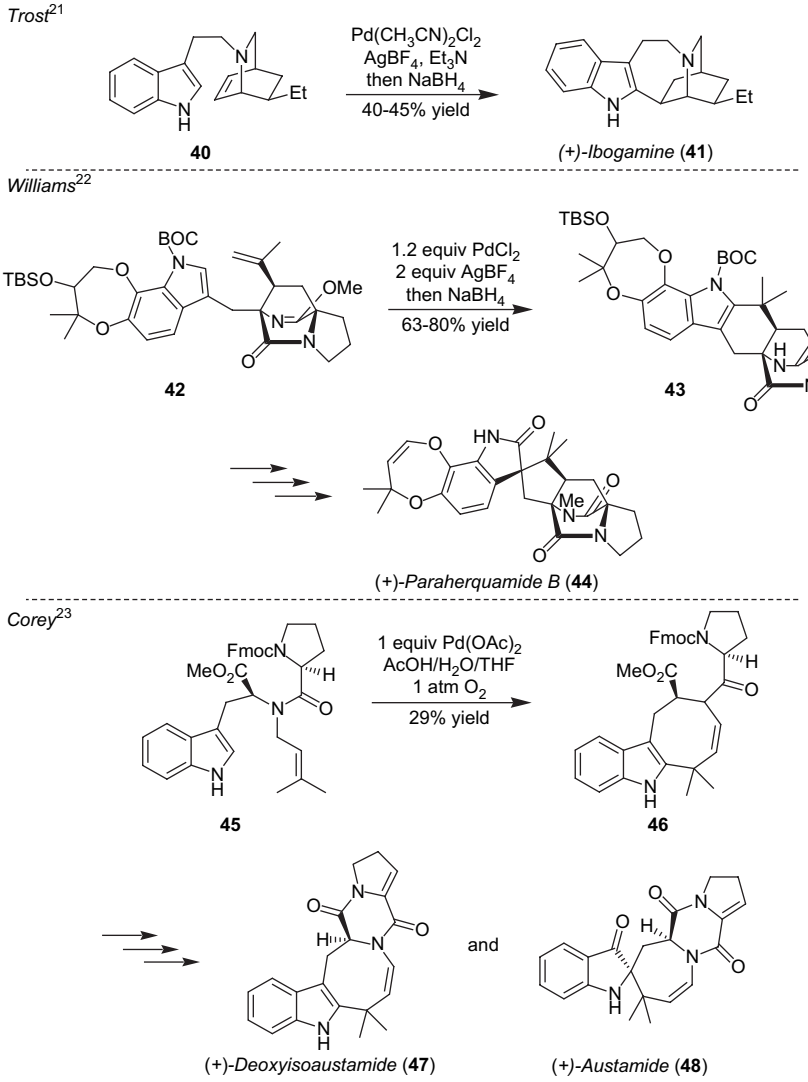
Reoxidant	TON	Yield (%)
stoich. $Pd(OAc)_2$	--	48
AgOAc	3.2	31
$Cu(OAc)_2$	4.1	41
$Na_2S_2O_8$	4.2	42
$NaNO_2$	1.6	16



Scheme 5.



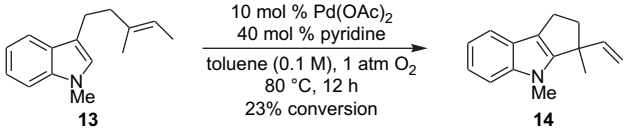
Scheme 6.



Scheme 7.

(Scheme 8).[28] Gratifyingly, oxidative cyclization to annulated indole **14** occurred; the overall reactivity, however, was noticeably sluggish (23% conversion after 12 h) relative to the other oxidative processes we had studied thus far (i.e., alcohol oxidation[9] and various heterocyclizations[10]). It was hypothesized that the catalytic center was not sufficiently electron-deficient for substrate activation. By increasing the electrophilicity of the catalyst, potentially higher reaction rates could be achieved.

To that end, we surveyed a range of electronically differentiated pyridine ligands with $Pd(OAc)_2$ (Table 1). Interestingly,

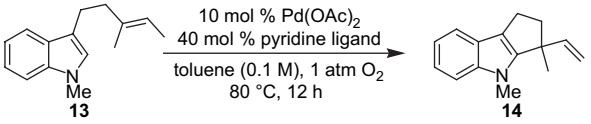


Scheme 8.

there was a noticeable correlation between the electronic nature of the ligand (estimated by the measured pK_a of their respective pyridinium ions)[29] and the overall reactivity. More electron-rich pyridine ligands shut down the reaction (entries 1 and 2), while switching to pyridines substituted with electron-withdrawing groups effected an increase in the reactivity, peaking with ethyl nicotinate (entry 5). Further increasing the electron-deficiency, however, was detrimental to the overall reaction (entries 6–9). These ligands are likely unable to sufficiently coordinate to the palladium center, hampering the catalyst's reactivity and/or palladium(0) reoxidation. Because ethyl nicotinate appeared to strike the appropriate electronic balance for overall reactivity, it was selected as the ligand for further studies.

With the optimal ligand in hand, other parameters in the oxidative cyclization of indole **13** were investigated. The choice of palladium(II) salt was found to be important; $Pd(OAc)_2$ was more effective than $Pd(TFA)_2$, in contrast to the heterocyclization chemistry.[10] $PdCl_2$ and other palladium(II) halides were completely unreactive. The most significant effects on the reaction outcome were determined by the solvent (Table 2). Moving from nonpolar aromatic solvents (entries 1–3) to more polar solvents moderately increased the reactivity and overall yield of annulated indole **14**.[30] There was still a noticeable discrepancy, however, between the conversion of **13** and the overall yield of **14**.[31] At this point, the combined yield of **13** and **14** (starting material and product) was observed to decrease in a nonlinear fashion over time. One possible rationalization of this observation is that the product decomposes over the course of the reaction.[32] Interestingly, this problem could be minimized by the addition of AcOH as a cosolvent

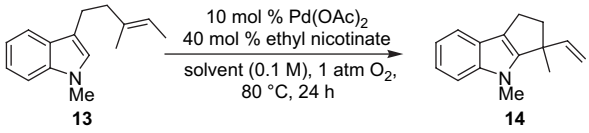
Table 1
Examination of electronic effects of the pyridyl ligand



Entry	Pyridine ligand	pK_a ($PyrH^+$)[a]	Conversion[b] (%)
1	4-MeO	6.47	3
2	4-*t*-Bu	5.99	1
3	Unsubstituted	5.25	23
4	4-CO_2Et	3.45	52
5	***3-CO_2Et***	***3.35***	***76***
6	3-$COCH_3$	3.18	58
7	3-F	2.97	64
8	3-CN	1.39	55
9	3,5-di-Cl	0.90	22

[a] Ref. 29.
[b] Conversion (%) measured by GC relative to an internal standard.

Table 2
Solvent effects in the indole annulation



Entry	Solvent	Conversion[a] (%)	Yield[a] (%)
1	Toluene	88	33
2	Xylenes	88	31
3	Chlorobenzene	85	40
4	Dioxane	87	42
5	Diglyme	99	37
6	Butyl acetate	95	49
7	*tert*-Amyl alcohol	94	53
8	Pinacolone	95	58
9	AcOH	86	25
10	Pinacolone/AcOH (4:1)	91	76
11	*tert*-Amyl alcohol/AcOH (4:1)	99	82[b]

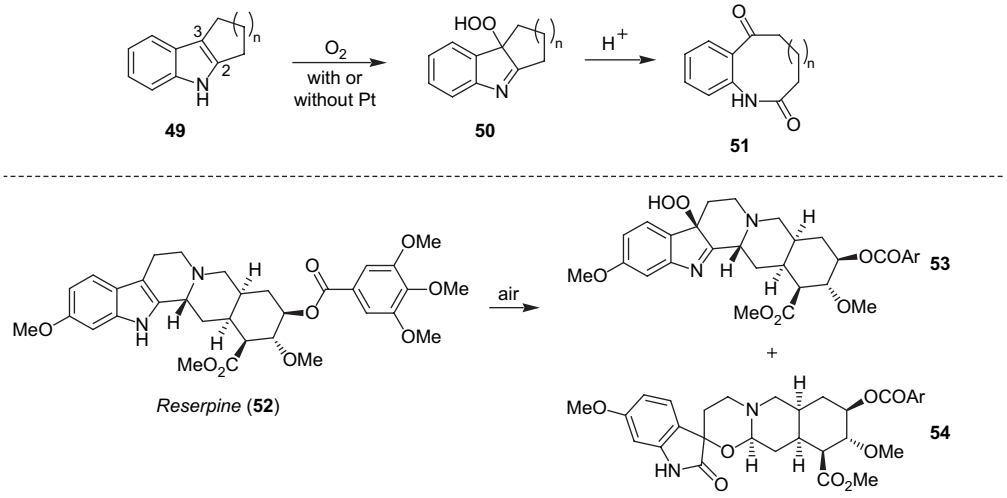
[a] Conversion (%) and yield (%) measured by GC relative to an internal standard.
[b] Isolated yield.

(entries 10 and 11). Ultimately, we found that employing a 4:1 mixture of *tert*-amyl alcohol and AcOH as the solvent resulted in an 82% isolated yield of annulated indole **14**.

3.2. Susceptibility of annulated indoles to oxygen

This difficulty with product decomposition was somewhat anticipated considering previous reports on reactions of 2,3-disubstituted indoles with oxygen.[33] In 1951, Witkop and coworkers described the autoxidation of indoles with fused rings attached to the C-2 and C-3 positions (**49**, Scheme 9).[34] Under an oxygen atmosphere with or without reduced platinum oxide, the indoles were converted to intermediate peroxides by addition at the C-3 position, which upon workup afforded keto lactams (**51**). More recently, the oxidation of reserpine (**52**), which contains an annulated indole core, under an atmosphere of oxygen was investigated by Awang and co-workers (Scheme 9).[35] Two products were observed, peroxide **53** and dioxyreserpine (**54**), that arose from reaction with oxygen at ambient temperature.

The product decomposition of our oxidative indole cyclization was probed in more detail (Fig. 2). Annulated indole **14** was subjected to the reaction conditions for 24 h, and the decomposition was monitored by GC analysis relative to an internal standard (tridecane).[36] A slight increase in product stability was observed in *tert*-amyl alcohol versus toluene, consistent with our observations of the cyclization reaction. Addition of the catalyst (10 mol % $Pd(OAc)_2$, 40 mol % ethyl nicotinate) had a remarkable impact, limiting product decomposition to approximately 30% over 24 h. The stability was improved further by the addition of AcOH as a cosolvent. The reasons behind the beneficial nature of the catalyst and AcOH toward the suppression of oxidative decomposition are currently unclear. One potential explanation is that since oxidative decomposition is initiated by nucleophilic addition



Scheme 9.

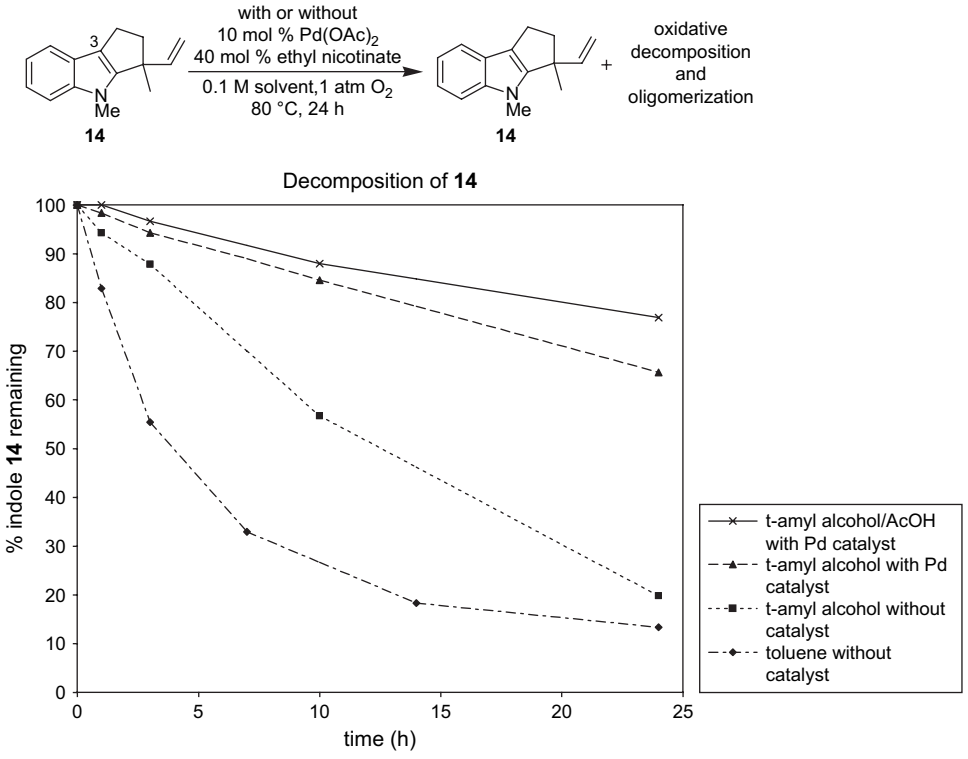


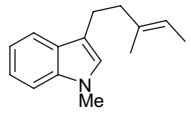
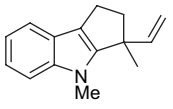
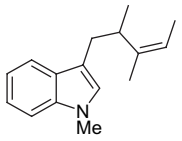
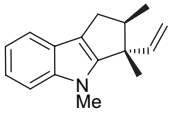
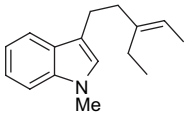
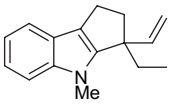
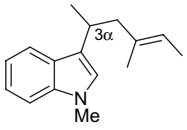
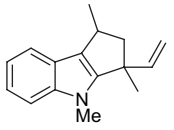
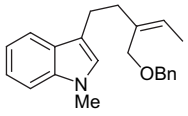
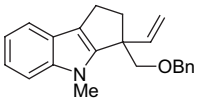
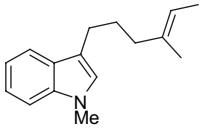
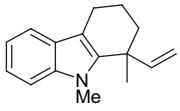
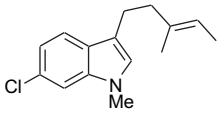
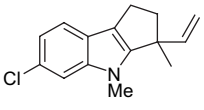
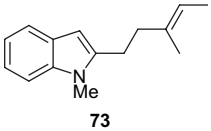
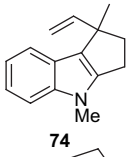
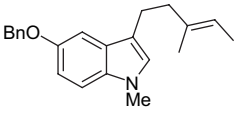
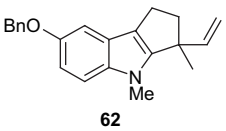
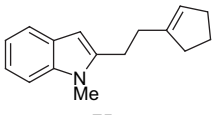
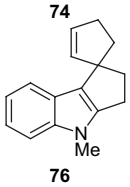
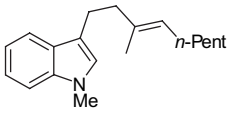
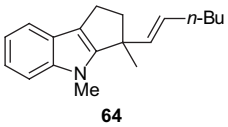
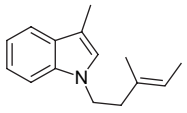
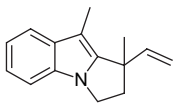
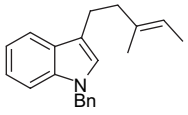
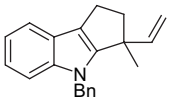
Figure 2. Oxidative decomposition studies of indole **14**.

of indole into dioxygen, the electrophilic palladium center may act as a competitive inhibitor via palladation at C-3. AcOH could act either as a second competitive inhibitor via association at C-3 or as an ionizing agent for $L_nPd(OAc)_2$, protonating off an acetate ligand to afford a more reactive cationic palladium(II) center.[37]

3.3. Substrate scope

With this optimized system now in hand, the substrate scope was investigated. As shown in Table 3, good to excellent yields can be obtained across a range of substituted indoles. Indoles substituted with electron-withdrawing or electron-donating groups on the arene cyclize efficiently (entries 4 and 5). Substitution on the tether α to the olefin resulted in a diastereoselective cyclization (entry 8), whereas substitution at the C-3α site imparted no diastereoselectivity (entry 9). Ring sizes of 5 or 6 (entry 10) can be accessed via the oxidative cyclization. The annulation is not limited to bond formation at the C-2 position. The cyclization can proceed from C-2 to C-3 positions (entries 11 and 12), as well as from N-1 to C-2 (entry 13).[38]

Table 3
The palladium-catalyzed oxidative indole annulation[a]

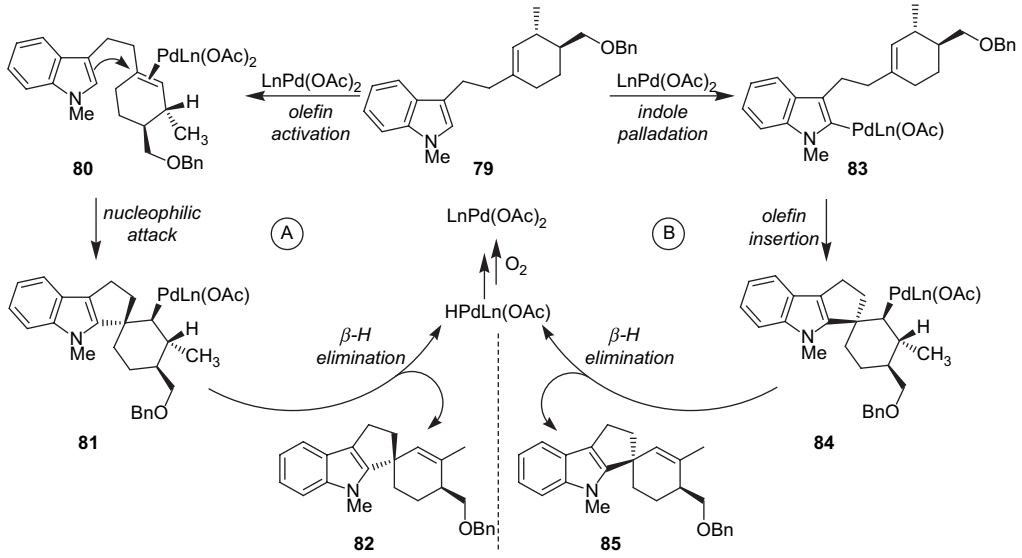
Entry	Substrate[b]	Product	Yield[c] (%), time (h)	Entry	Substrate[b]	Product	Yield[c] (%), time (h)
1	 **13**	 **14**	82, 24	8	 **67**	 **68**	76, 18 (6:1 dr)
2	 **55**	 **56**	74, 18	9	 **69**	 **70**	64, 53 (1:1 dr)
3	 **57**	 **58**	60, 24	10	 **71**	 **72**	66, 39[e]
4	 **59**	 **60**	62, 32	11	 **73**	 **74**	73, 6[f]
5	 **61**	 **62**	73, 20	12	 **75**	 **76**	68, 5[f]
6	 **63**	 **64**	79, 30[d]	13	 **77**	 **78**	74, 18
7	 **65**	 **66**	69, 48				

[a] $Pd(OAc)_2$ (10 mol %), 40 mol % ethyl nicotinate, 1 atm O_2, 80 °C, 0.1 M substrate in *tert*-amyl alcohol/AcOH (4:1).
[b] Typically used as a mixture of olefin isomers.
[c] Isolated yields.
[d] Product isolated as a 58:42 mixture of olefin isomers.
[e] 0.1 M in pinacolone.
[f] 0.1 M in *tert*-amyl alcohol.

3.4. Mechanistic insights

The relative rates of reactivity of the substrates with substitutions on the tethering carbons between the indole nucleus and the olefin (i.e., entries 8 and 9, Table 3) were particularly interesting; substrate **69** was considerably slower in the cyclization than substrate **67**. This observation pointed toward a mechanism involving initial palladation at C-2, followed by olefin insertion and β-hydride elimination. Branching at the C-3α position (as in substrate **69**) would be expected to sterically interfere with the palladation event, which would cause a decrease in the overall rate. An alternative mechanism involves palladium(II) electrophilic activation of the olefin, intramolecular nucleophilic attack by the indole, and β-hydride elimination akin to a Wacker-type mechanism, which we believed was operative in our heterocyclization studies.[39]

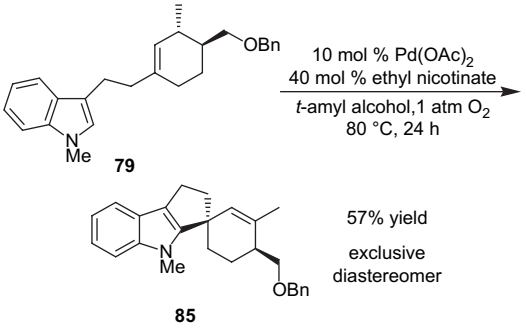
In order to differentiate between these two possible pathways, we designed a cyclization substrate that could act as a mechanistic probe (**79**, Scheme 10). In pathway A, the cyclization of diastereomerically pure indole **79** proceeds via olefin activation, *anti* nucleophilic attack, and *syn* β-hydride elimination to afford annulated indole **82**. The availability of only one



Scheme 10.

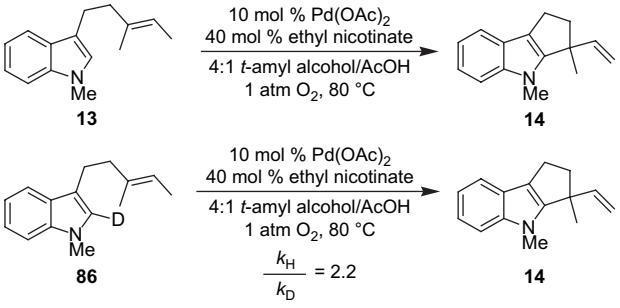
β-hydrogen and the general assumption of both an *anti* nucleophilic attack and a *syn* β-hydride elimination explain the expected stereochemistry of the product indole. Pathway B proceeds by initial palladation, followed by *syn* olefin insertion and *syn* β-hydride elimination. In this case, a *syn* insertion and elimination are assumed to be operative, as is typical for palladium-catalyzed reactions, ultimately resulting in product indole **85**, which is diastereomerically distinct from **82**.

Indole **79** was subjected to the standard indole annulation conditions (10 mol % $Pd(OAc)_2$, 40 mol % ethyl nicotinate, 1 atm O_2, 80 °C in *tert*-amyl alcohol[40]). Annulated indole **85** was thus obtained in 57% yield as a single diastereomer (Scheme 11).[41] This result strongly suggested that the reaction was proceeding through initial palladation (net C–H bond functionalization), followed by olefin insertion and β-hydride elimination (pathway B). The mechanism elucidated here is in full agreement with those previously proposed for related reactions.[15a,21] Additionally, this reaction highlights the capacity of this chemistry to set quaternary carbon centers diastereoselectively via a chirality transfer from a tertiary carbon center.



Scheme 11.

To further verify the C–H bond functionalization pathway, the rate of cyclization of indole **13** was compared to that of (C-2)-deuteroindole **86** (Scheme 12). The rates of consumption of **13** and **86** were measured by GC analysis. The kinetic isotope effect for this cyclization was measured to be 2.2, which is consistent with the kinetic isotope effects measured for other palladium(II)-catalyzed reactions involving C–H bond functionalization events.[42] This value also suggests that C–H bond functionalization is a slow step in the catalytic cycle.

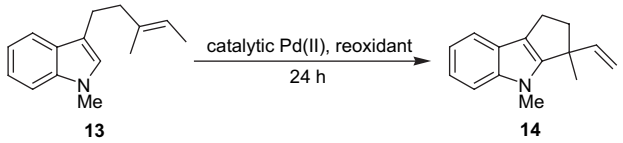


Scheme 12.

3.5. Methodology comparisons

A direct comparison of the indole annulation method we have developed to other known oxidative palladium(II)-catalyzed C–C bond forming reactions highlights the remarkable efficacy of our system (Table 4). Indole **13** was subjected to a variety of previously reported oxidative systems employing different solvent systems and oxidants.[15,16,43] Clearly, the $Pd(OAc)_2$/ethyl nicotinate/O_2/*tert*-amyl alcohol/AcOH conditions are vastly superior at catalyzing this annulation. The desired product was observed in only three other cases, with the highest yield reaching just 13%. Even the conditions that were highly successful for the indole oxidative coupling reported by Fujiwara and co-workers[16] were ineffective for this transformation (entry 8). The oxidative system described herein has strong potential for other oxidative C–C bond forming

Table 4
Comparison of methods for the oxidative annulation of **13**



13 **14**

Entry	Conditions[a]	Ref.	Yield[b] (%)
1	$Pd(OAc)_2$, AgOAc, AcOH, air, 110 °C	15a	4
2	$Pd(OAc)_2$, $Cu(OAc)_2$, AcOH, air, 110 °C	15a	0
3	$Pd(OAc)_2$, $K_2S_2O_8$, AcOH, air, 110 °C	15a	0
4	$Pd(OAc)_2$, $NaNO_2$, AcOH, air, 110 °C	15a	0
5	$Pd(OAc)_2$, $Cu(OAc)_2$, dioxane/AcOH (4:1), O_2, 100 °C	43a	13
6	$Pd(OAc)_2$, benzoquinone, $TsOH\cdot H_2O$, toluene/AcOH (2:1), O_2, 23 °C	43b	0
7	$Pd(OAc)_2$, $H_6PMo_9V_3O_{40}$, acetylacetonate, NaOAc, AcOH, O_2, 90 °C	43c	0
8	$Pd(OAc)_2$, cat. benzoquinone, TBHP, $AcOH/Ac_2O$ (4:1), 50 °C	16	5
9	$Pd(OAc)_2$, ethyl nicotinate, *tert*-amyl alcohol/AcOH (4:1), O_2, 80 °C		82

[a] For details, see Section 5.
[b] Yield (%) measured by GC relative to an internal standard.

reactions, where previously developed conditions may be too harsh or simply ineffective.

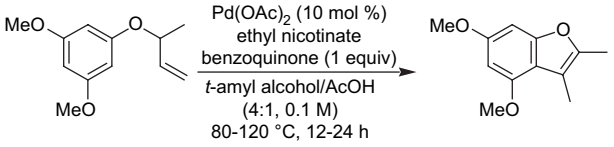
3.6. The synthesis of benzofurans and dihydrobenzofurans via oxidative carbocyclizations

Intent on further developing the oxidative C–H bond functionalization systems, we then began to investigate other aromatic systems. Aryl allyl ether **15** was subjected to the optimized conditions from the indole annulation chemistry (10 mol % $Pd(OAc)_2$, 40 mol % ethyl nicotinate, 4:1 *tert*-amyl alcohol/AcOH, 1 atm O_2, 80 °C). To our delight, benzofuran **16** was produced in 56% yield (Table 5, entry 1). This reaction presumably proceeds via an initial C–H bond functionalization, followed by 5-*exo* cyclization and β-hydride elimination to afford intermediate **87**. The intermediate then isomerizes to the more thermodynamically stable aromatic compound **16**.[44] With this promising result, a variety of oxidants were evaluated in this oxidation system. Although moderate yields of **16** were obtained with a number of oxidants, oxygen and benzoquinone provided the highest yields (entries 1 and 2). Benzoquinone led to the greatest yield of **16** and was therefore used in subsequent optimization studies.

Other parameters were then examined in the oxidative cyclization of aryl allyl ether **15** (Table 6). The ratio of ligand/palladium was found to be important for this reaction, a 2:1 system being optimal. This is likely reflective of a balance between the sufficient ligation of the palladium center for Pd(0) reoxidation and the suppression of competitive binding caused by the presence of excess ligand. Further optimization studies revealed that adding 20 mol % NaOAc and increasing the temperature to 100 °C were both beneficial to the overall transformation, providing the highest yield of benzofuran **16** (77% isolated yield, entry 7).

The generality of the palladium-catalyzed benzofuran synthesis was then explored. As shown in Table 7, this process works for a variety of allyl aryl ethers with various substitution patterns, all resulting in good yields. This reaction is currently limited to electron-rich aryl groups; the palladation event

Table 6
Optimization studies for the synthesis of benzofuran **16**

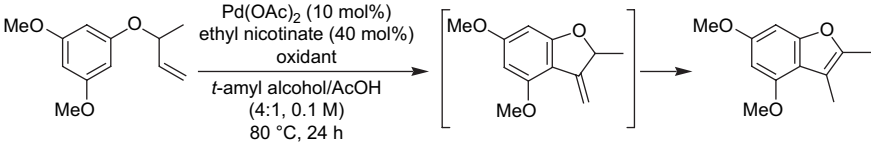


15 **16**

Entry	Ethyl nicotinate (mol %)	Additive	Temp (°C)	Time (h)	Yield[a] (%)
1	40	—	80	24	62
2	20	—	80	24	66
3	10	—	80	24	59
4	0	—	80	24	55
5	20	NaOAc (1 equiv)	80	24	70
6	20	NaOAc (20 mol %)	80	24	74
7	20	NaOAc (20 mol %)	100	12	80 (77)[b]
8	20	NaOAc (20 mol %)	120	12	67

[a] Yield (%) measured by GC relative to an internal standard.
[b] Isolated yield in parentheses.

Table 5
Oxidant screen for the synthesis of benzofuran **16**

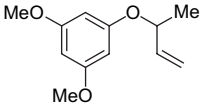
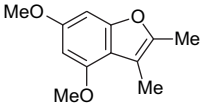
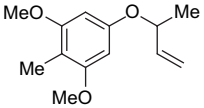
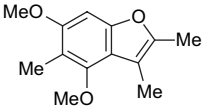
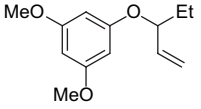
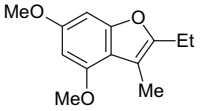
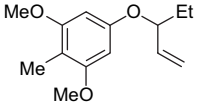
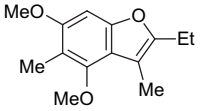
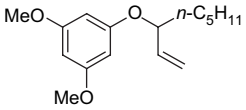
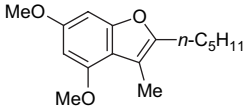
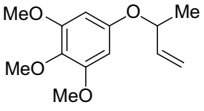
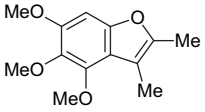
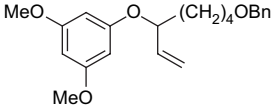
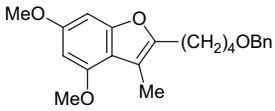
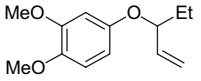
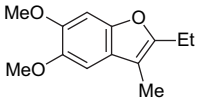
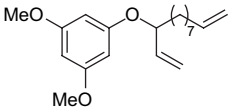
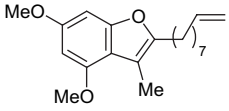
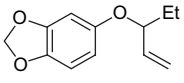
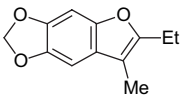
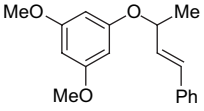
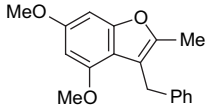


15 **87** **16**

Entry	Oxidant (1 equiv)	Yield[a] (%)	Entry	Oxidant (1 equiv)	Yield[a] (%)
1	O_2 (1 atm)	56	5	$Tl(O_2CCF_3)_3$	<10
2	Benzoquinone	62	6	$K_2S_2O_8$	30
3	$Cu(OAc)_2$	31	7	$H_2NC(S)NH_2$	<10
4	AgOAc	29	8	$PhCO_3$-*t*-Bu	42

[a] Yield (%) measured by GC relative to an internal standard.

Table 7
The palladium(II)-catalyzed oxidative benzofuran synthesis[a]

Entry	Substrate	Product	Yield[b] (%), time (h)	Entry	Substrate	Product	Yield[b] (%), time (h)
1	 **15**	 **16**	77, 12	7	 **98**	 **99**	75, 14
2	 **88**	 **89**	74, 12	8	 **100**	 **101**	79, 12
3	 **90**	 **91**	72, 13	9	 **102**	 **103**	61, 12
4	 **92**	 **93**	62, 12	10	 **104**	 **105**	56,[c] 16
5	 **94**	 **95**	54, 14	11	 **106**	 **107**	52,[c] 16
6	 **96**	 **97**	61, 12				

[a] $Pd(OAc)_2$ (10 mol %), 20 mol % ethyl nicotinate, 20 mol % NaOAc, 1 equiv benzoquinone, 0.1 M substrate in *tert*-amyl alcohol/AcOH (4:1), 100 °C.
[b] Isolated yield.
[c] Produced as a single regioisomer.

requires a sufficiently nucleophilic arene in order to occur. The aryl subunit, however, tolerates various alkyl and alkoxy substitution patterns within the electronic requirements. The allyl moiety can also accommodate several substituents (aryl, alkyl, alkoxy) at both the proximal and the distal positions.

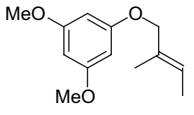
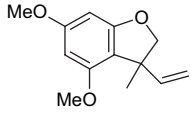
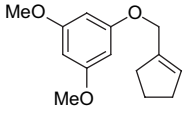
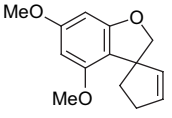
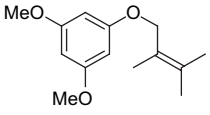
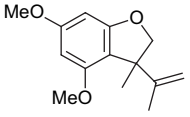
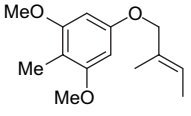
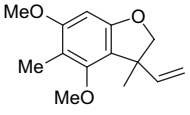
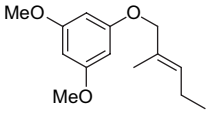
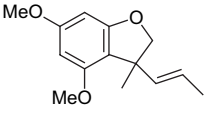
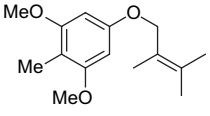
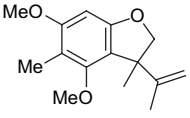
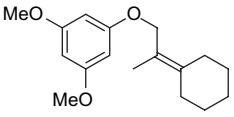
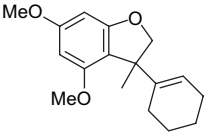
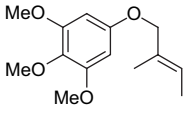
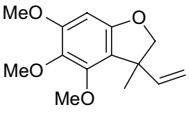
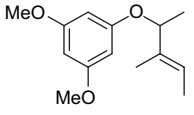
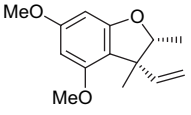
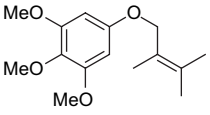
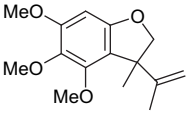
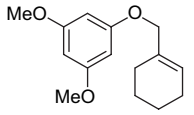
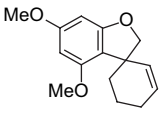
This methodology was then extended to aryl allyl ethers in which the allyl group possessed tri- and tetrasubstituted olefins. The dihydrobenzofuran products of these reactions can be obtained in good to excellent yields (Table 8). Dihydrobenzofurans are produced in these reactions because the substitution patterns lack hydrogens at the point of C–C bond formation that could eliminate to intermediates similar to **87** (vide supra, Table 7). An array of aryl and allyl substitution patterns are tolerated in this reaction.

Analogous to the indole annulation studies (vide supra), aryl allyl ether **128** was subjected to the cyclization conditions as a mechanistic probe (Scheme 13). As in the indole case, this experiment differentiates between an olefin activation/nucleophilic attack pathway (to produce **129**) and an arene palladation/olefin insertion pathway (to produce **130**). In the event, the product dihydrobenzofuran (**130**) was isolated as a single diastereomer.[45] This experiment strongly suggests that the palladation pathway (a net C–H bond functionalization) is operative, which correlates with the result from the indole study.

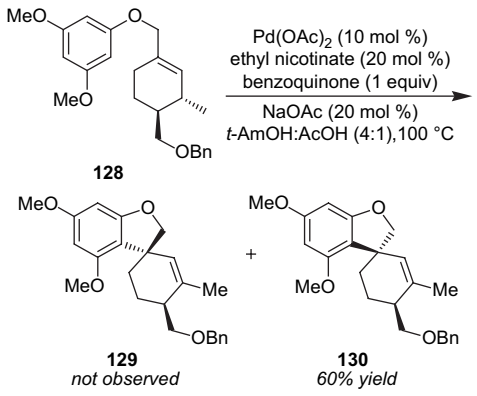
4. Conclusion

We have developed a remarkably mild oxidative system for C–C bond forming reactions that involve an initial C–H bond functionalization event. Annulated indoles, benzofurans, and dihydrobenzofurans can all be accessed through this chemistry. In the indole carbocyclizations, molecular oxygen is the sole stoichiometric oxidant, the inexpensive and abundant reagent affording only water as a byproduct. These cyclizations are also the first examples to demonstrate the use of electronically tuned pyridine ligands in the standard Pd/pyridine system. This electronic tuning has led to the discovery of unique reactivities that were previously unattainable. There are a number of future directions of research that could be envisioned with this chemistry, including intermolecular reactions,[46,47] other

Table 8
The palladium(II)-catalyzed oxidative dihydrobenzofuran synthesis[a]

Entry	Substrate	Product	Yield[b] (%), time (h)	Entry	Substrate	Product	Yield[b] (%), time (h)
1	 **17**	 **18**	74, 16	7	 **118**	 **119**	78, 18
2[c]	 **108**	 **109**	71, 12	8	 **120**	 **121**	50, 15
3	 **110**	 **111**	58,[d] 30	9	 **122**	 **123**	63, 15
4	 **112**	 **113**	55, 28	10	 **124**	 **125**	60, 15
5	 **114**	 **115**	74,[e] 15	11	 **126**	 **127**	66, 15
6	 **116**	 **117**	80, 24				

[a] $Pd(OAc)_2$ (10 mol %), 20 mol % ethyl nicotinate, 20 mol % NaOAc, 1.0 equiv benzoquinone, 0.1 M substrate in *tert*-amyl alcohol/AcOH (4:1), 100 °C.
[b] Isolated yield.
[c] Performed with 5 mol % $Pd(OAc)_2$ and 10 mol % ethyl nicotinate.
[d] An inseparable mixture of roughly 66% product (*E*/*Z*=3:1) and 10% starting material was isolated after 18 h. This mixture was subjected to another reaction with 5 mol % $Pd(OAc)_2$, 10 mol % ethyl nicotinate, 20 mol % NaOAc, and 50 mol % benzoquinone for 12 h, after which only the *E* isomer was observed. The yield presented is the overall yield of isolated product.
[e] A 2.3:1 mixture of diastereomers was isolated, with the major isomer shown.



Scheme 13.

arene systems,[17a,b] enantioselective modifications,[48] and applications in the total synthesis of natural products. In fact, our group has utilized a variant of these oxidative cyclizations as a key step in the total synthesis of the structurally complex, antiviral marine alkaloid dragmacidin F.[49]

C–H bond functionalization continues to be an active and engaging area of research. Outlined herein is an oxidative catalytic approach to C–C bond forming reactions that involve an initial C–H bond functionalization step, followed by an intramolecular cyclization onto an unactivated olefin. This is directly analogous to the corresponding intramolecular Heck reaction, but does not involve the prior halogenation necessary for the palladium(0) process. Furthermore, the oxidative carbocyclization can be considered orthogonal to the Heck reaction, as the electron-rich aromatic systems utilized in this study can be employed directly. Generally, selectively

halogenated derivatives of these types of arenes can be synthetically challenging to access; additionally, electron-rich aryl halides are typically poor reactants toward oxidative addition to palladium(0) species. Both of these complicating factors are circumvented by the oxidative cyclization chemistry. The transformations described herein provide a promising future area for the development of powerful catalytic dehydrogenative carbon–carbon bond forming reactions.

5. Experimental section

5.1. General

Unless stated otherwise, reactions were conducted in flame-dried glassware under a nitrogen atmosphere with dry solvents (either freshly distilled or passed through activated alumina columns). All commercially obtained reagents were used as-received. Reaction temperatures were controlled by an IKA-mag temperature modulator. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F_{254} pre-coated plates (0.25 mm) and visualized via UV, anisaldehyde, and potassium permanganate staining. ICN silica gel (particle size 0.032–0.063 mm) was used for flash column chromatography. Analytical GC was carried out using a DB-1701 column (30.0 m×0.25 mm) from Agilent Technologies. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 300 and 75 MHz, respectively) spectrometer. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer. High-resolution mass spectra were obtained from the California Institute of Technology Mass Spectral Facility. The syntheses and characterization data of all compounds given in Tables 3, 7 and 8 have been previously described.[11]

5.2. General procedure for the optimization of ligand and solvent (Tables 1 and 2)

A flame-dried 25 ml Schlenk flask equipped with magnetic stir bar was charged with $Pd(OAc)_2$ (4.1 mg, 0.0183 mmol) followed by solvent (1.63 ml) and ligand (0.0732 mmol, 0.40 equiv). The flask was evacuated and back-filled with O_2 (3×, balloon), heated to 80 °C, and allowed to stir under O_2 (1 atm, balloon) for 10 min. A solution of indole **13** (40.0 μl, 0.183 mmol) in toluene (200 μl) and tridecane (25.0 μl, 0.103 mmol, internal standard) were then added via syringe, and the reaction mixture was stirred under O_2 for 12 h. An aliquot (approx. 200 μl) was filtered through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by GC.

5.3. Control experiments to examine product stability

A flame-dried 25 ml Schlenk flask equipped with magnetic stir bar was charged with $Pd(OAc)_2$ (2.6 mg, 0.0118 mmol) if applicable, followed by solvent (918 μl) and ethyl nicotinate (6.4 μl, 0.0472 mmol) if applicable. The flask was evacuated and back-filled with O_2 (3×, balloon), heated to 80 °C, and allowed to stir under O_2 (1 atm, balloon) for 10 min. A solution of indole **14** (25.0 mg, 0.118 mmol) in solvent (200 μl) and tridecane (25.0 μl, 0.103 mmol, internal standard) were then added via syringe, and the reaction mixture was stirred under O_2 for 24 h. Aliquots (approx. 200 μl) were withdrawn periodically, filtered through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by GC.

5.4. General procedure for the oxidative annulation of indoles (Table 3, entry 1 is used as an example)

A flame-dried 25 ml round bottom flask equipped with magnetic stir bar was charged with $Pd(OAc)_2$ (17.2 mg, 0.0769 mmol, 0.100 equiv), *tert*-amyl alcohol (5.15 ml), acetic acid (1.54 ml), and ethyl nicotinate (42.0 μl, 0.308 mmol, 0.400 equiv), sequentially. The flask was evacuated and back-filled with O_2 (3×, balloon), heated to 80 °C, and allowed to stir under O_2 (1 atm, balloon) for 10 min. A solution of indole **13** (164 mg, 0.769 mmol) in *tert*-amyl alcohol (1.00 ml) was then added via syringe, and the reaction mixture was stirred under O_2 for the listed time. Filtration of the reaction mixture through a small pad of silica gel (1×5 cm, EtOAc eluent), concentration, and purification of the oil by flash chromatography afforded pure annulated indole.

5.5. Preparation of indole **86**

Indole **298** was prepared in four steps from 3-(3-methylpent-3-enyl)-1*H*-indole[50] by (1) N-tosylation, (2) lithiation with *n*-BuLi and quenching with D_2O,[51] (3) detosylation, and (4) N-methylation to afford indole **86** in 46% overall yield.

Indole ***86***. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J=7.8 Hz, 1H), 7.64 (d, J=7.2 Hz, 1H), 7.31 (app. t, J=8.4 Hz, 1H), 7.31 (app. t, J=8.4 Hz, 1H), 7.25 (app. d, J=8.1 Hz, 1H), 7.25 (app. d, J=8.1 Hz, 1H), 7.18–7.12 (m, 1H), 7.18–7.12 (m, 1H), 5.35 (q, J=6.6 Hz, 1H), 5.31 (q, J=6.6 Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 2.92–2.83 (comp m, 2H), 2.92–2.83 (comp m, 2H), 2.50–2.40 (comp m, 2H), 2.50–2.40 (comp m, 2H), 1.82 (s, 3H), 1.75 (s, 3H), 1.65 (d, J=6.6 Hz, 3H), 1.61 (d, J=6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.2, 136.2, 136.2, 128.1, 126.1, 125.8 (t, J=26.9 Hz), 121.6, 121.6, 119.5, 119.2, 119.2, 118.7, 118.7, 115.5, 115.4, 109.3, 109.3, 40.7, 32.7, 32.7, 24.2, 23.7, 23.6, 16.0, 13.6, 13.5; IR (film) 2915, 1469, 1373, 738 cm^{-1}; HRMS (EI^{+}) *m/z* calcd for $[C_{15}H_{18}ND]^{+}$: 214.1580, found: 214.1574.

5.6. Procedure to examine the kinetic isotope effect of the indole annulation (Scheme 12)

A flame-dried 25 ml Schlenk flask equipped with magnetic stir bar was charged with $Pd(OAc)_2$ (4.1 mg, 0.0183 mmol) followed by *tert*-amyl alcohol (1.26 ml), AcOH (366 μl), and ethyl nicotinate (10.0 μl, 0.0732 mmol). The flask was evacuated and back-filled with O_2 (3×, balloon), heated to 80 °C, and allowed to stir under O_2 (1 atm, balloon) for 10 min. A solution of indole **13** (40.0 μl, 0.183 mmol) or **86** (39.2 mg,

0.183 mmol) in *tert*-amyl alcohol (200 μl) and tridecane (25.0 μl, 0.103 mmol, internal standard) were then added via syringe, and the reaction mixture was stirred under O_2. Aliquots (approx. 100 μl) were taken hourly, filtered through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by GC.

5.7. Reaction protocol comparison (Table 4)

Entries 1–4.[15a] A flame-dried 25 ml Schlenk flask equipped with magnetic stir bar was charged with $Pd(OAc)_2$ (2.1 mg, 0.00917 mmol). The solid was dissolved in AcOH (3.67 ml), and to the solution was added oxidant (0.183 mmol), followed by indole **13** (20.0 μl, 0.0917 mmol) and tridecane (25.0 μl, 0.103 mmol, internal standard). The reaction mixture was heated to 110 °C under air and allowed to stir. Aliquots (approx. 100 μl) were taken at 5 and 24 h, partitioned between H_2O and EtOAc, and the organic phase was filtered through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by GC.

Entry 5.[43a] A flame-dried 25 ml Schlenk flask equipped with magnetic stir bar was charged with $Pd(OAc)_2$ (0.8 mg, 0.00366 mmol). The solid was dissolved in dioxane (1.83 ml) and AcOH (458 μl), and to the solution was added $Cu(OAc)_2$ (66.5 mg, 0.366 mmol), followed by indole **13** (40.0 μl, 0.183 mmol) and tridecane (25.0 μl, 0.103 mmol, internal standard). The flask was evacuated and back-filled with O_2 (3×, balloon), heated to 100 °C under O_2, and allowed to stir. Aliquots (approx. 100 μl) were taken at 5 and 24 h, partitioned between H_2O and EtOAc, and the organic phase was filtered through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by GC.

Entry 6.[43b] A flame-dried 25 ml Schlenk flask equipped with magnetic stir bar was charged with $Pd(OAc)_2$ (0.8 mg, 0.00366 mmol). The solid was dissolved in toluene (137 μl) and AcOH (275 μl), and to the solution were added benzoquinone (19.8 mg, 0.183 mmol), $TsOH \cdot H_2O$ (17.4 mg, 0.0915 mmol), indole **13** (40.0 μl, 0.183 mmol), and tridecane (25.0 μl, 0.103 mmol, internal standard), sequentially. The reaction mixture was stirred at room temperature. Complete decomposition was observed after 5 min.

Entry 7.[43c] A flame-dried 25 ml Schlenk flask equipped with magnetic stir bar was charged with $Pd(OAc)_2$ (4.1 mg, 0.0183 mmol) followed by AcOH (485 μl), NaOAc (0.8 mg, 0.00975 mmol), acetylacetonate (1.3 μl, 0.0122 mmol), and $H_6PMo_9V_3O_{40}$ (5.5 mg), sequentially. The flask was evacuated and back-filled with O_2 (3×, balloon), heated to 80 °C, and allowed to stir under O_2 (1 atm, balloon) for 10 min. A solution of indole **13** (40.0 μl, 0.183 mmol) in AcOH (125 μl) and tridecane (25.0 μl, 0.103 mmol, internal standard) were then added via syringe, and the reaction mixture was stirred under O_2. Aliquots (approx. 100 μl) were taken at 5 and 24 h, partitioned between H_2O and EtOAc, and the organic phase was filtered through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by GC.

Entry 8.[16] A flame-dried 25 ml Schlenk flask equipped with magnetic stir bar was charged with $Pd(OAc)_2$ (0.3 mg, 0.00138 mmol). The solid was dissolved in Ac_2O (91.7 μl) and AcOH (275 μl), and to the solution were added benzoquinone (1.5 mg, 0.0138 mmol), TBHP (50 μl, 70% in H_2O, 0.358 mmol), indole **13** (60.0 μl, 0.275 mmol), and tridecane (25.0 μl, 0.103 mmol, internal standard), sequentially. The flask was heated to 50 °C and allowed to stir. Aliquots (approx. 100 μl) were taken at 5 and 24 h, partitioned between H_2O and EtOAc, and the organic phase was filtered through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by GC.

5.8. Representative procedure for optimization of aryl allyl ether cyclizations (Tables 5 and 6)

A flame-dried 1-dram vial equipped with a magnetic stir bar was charged with $Pd(OAc)_2$ (2.3 mg, 0.0100 mmol), followed by ethyl nicotinate (0–40 mol %), tridecane (12.0 μl, 0.049 mmol, internal standard), **15** (20.8 mg, 0.100 mmol), NaOAc (1 equiv or 20 mol %), and a mixture of *tert*-amyl alcohol and acetic acid (1.0 ml, 4:1 v/v). The resulting mixture was stirred at 23 °C for 2 min, and then oxidant (1 equiv) was added. The reaction mixture was heated at 100 °C for 12 h. The reaction mixture was then cooled, filtered through a short plug of silica gel (Et_2O as eluent), and analyzed by GC.

5.9. Representative procedure for the Pd-catalyzed synthesis of benzofurans (Table 7, entry 1 is used as an example)

A flame-dried 2-dram vial equipped with a magnetic stir bar was charged with $Pd(OAc)_2$ (11.3 mg, 0.0500 mmol), followed by ethyl nicotinate (13.8 μl, 0.100 mmol), **15** (104.1 mg, 0.500 mmol), NaOAc (8.2 mg, 0.100 mmol), and a mixture of *tert*-amyl alcohol and acetic acid (5.00 ml, 4:1 v/v). The resulting mixture was stirred at 23 °C for 2 min, and then benzoquinone (54.1 mg, 0.500 mmol) was added. The reaction mixture was heated at 100 °C for 12 h and was then cooled, filtered through a short plug of silica gel (0.6× 5 cm, Et_2O as eluent), evaporated, and purified by flash chromatography on a silica gel column.

5.10. Representative procedure for the Pd-catalyzed synthesis of dihydrobenzofurans (Table 8, entry 1 is used as an example)

A flame-dried 2-dram vial equipped with a magnetic stir bar was charged with $Pd(OAc)_2$ (11.3 mg, 0.0500 mmol), followed by ethyl nicotinate (13.8 μl, 0.100 mmol), **17** (111 mg, 0.500 mmol), NaOAc (8.2 mg, 0.100 mmol), and a mixture of *tert*-amyl alcohol and acetic acid (5.00 ml, 4:1 v/v). The resulting mixture was stirred at 23 °C for 2 min, and then benzoquinone (54.1 mg, 0.500 mmol) was added. The reaction mixture was heated at 100 °C for 12 h and was then cooled, filtered through a short plug of silica gel (0.6×5 cm, Et_2O as eluent), evaporated, and purified by flash chromatography on a silica gel column.

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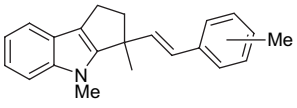
30. One complication we observed when the reactions were conducted in aromatic solvents was the oxidative coupling of the annulated product to a solvent molecule (e.g., **i**).



i

31. GC conversion was measured by consumption of indole **13** relative to an internal standard (tridecane). GC yield was measured by the amount of annulated indole **14** relative to an internal standard (tridecane).
32. Another possible scenario is that a new decomposition pathway for the starting material arises during the course of the reaction.
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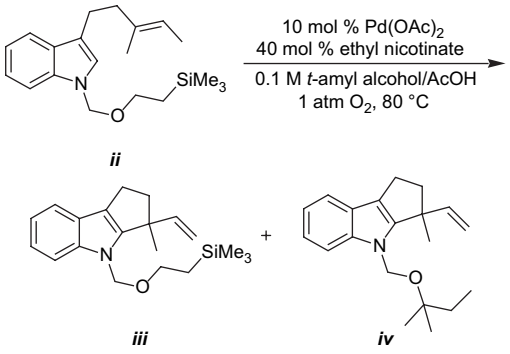
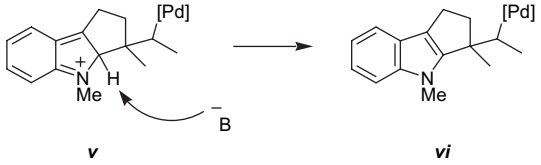
36. Because the decomposition products were oligomeric, highly polar, and numerous, none were isolated and characterized. Oligomerizations of indole compounds under oxidative conditions have been discussed.[22b]
37. AcOH has also been used frequently as a solvent in aryl palladation reactions. Therefore, other possible beneficial effects, such as favorable interactions with reaction intermediates, cannot be ruled out.

38. Other *N*-substituted indoles were not as effective. Acetyl, tosyl, or *tert*-butyldimethylsilyl groups all shut down reactivity. N–H indole was prone to heavy decomposition under the reaction conditions. SEM-protected indoles cyclized, but were complicated by an acetalization side reaction (e.g., **ii**→**iii**+**iv**).



39. Interestingly, the mechanism of the oxidative heterocyclization reactions proved to be more complicated than we initially expected. See Ref. 10b for a discussion.
40. When AcOH was used as a cosolvent, the yield of the annulated product was lower than when it was not used. Still, only one diastereomer (**85**) was produced even when AcOH was added.
41. The relative stereochemistry of **85** was confirmed by NOE analysis.
42. It should be noted that it is not clear what the deuterium isotope effect would be in the Wacker-type mechanism, and consequently this result does not necessarily rule out such a pathway. The deprotonation event (**v**→**vi**) would need to be rate determining in order for an effect to be observed.



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