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Article

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ACS Catal., **Just Accepted Manuscript** • DOI: 10.1021/acscatal.9b00091 • Publication Date (Web): 08 Mar 2019

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Palladium Catalyzed Chemoselective Activation of sp^3 vs sp^2 C–H Bonds: Oxidative Coupling to Form Quaternary Centers

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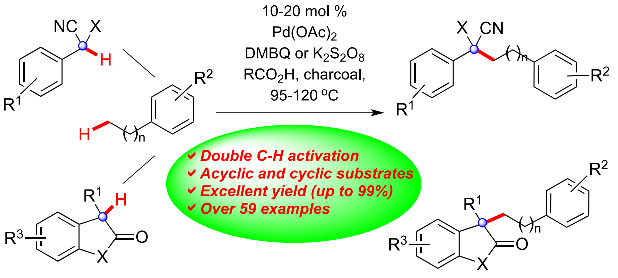
Supporting Information Placeholder

ABSTRACT: The oxidative activation of alkyl C–H bonds vs arene C–H bonds with $Pd(OAc)_2$ has been found to be generalizable to a number of nucleophilic substrates allowing the formation of a range of hindered quaternary centers. The substrates share a common mechanistic path wherein Pd(II) initiates an oxidative dimerization. The resultant dimer modifies the palladium catalyst to favor activation of alkyl C–H bonds in contrast to the trends typically observed via a concerted metalation deprotonation mechanism. Notably, insertion occurs at the terminus of the alkyl arene for hindered substrates. Two different oxidant systems were discovered that turn over the process. Parameters have been identified that predict, which substrates are productive in this reaction.



KEY WORDS: *cross dehydrogenative coupling; oxidative coupling; palladium; chemoselective activation; quaternary*

Introduction

The use of aromatic hydrocarbons as precursors to the construction of more complex structures has many intrinsic advantages. Aromatic hydrocarbons are inexpensive building blocks readily available from petroleum. Their direct functionalization to desired targets avoids the introduction of functional groups such as halides that require the use of hazardous materials or generate undesired byproducts. The aromatic hydrocarbons are also more stable than the corresponding functionalized equivalents such as benzylic halides. For example, naphthylic halide analogs are not stable and are not readily amenable to S_N2 displacement.

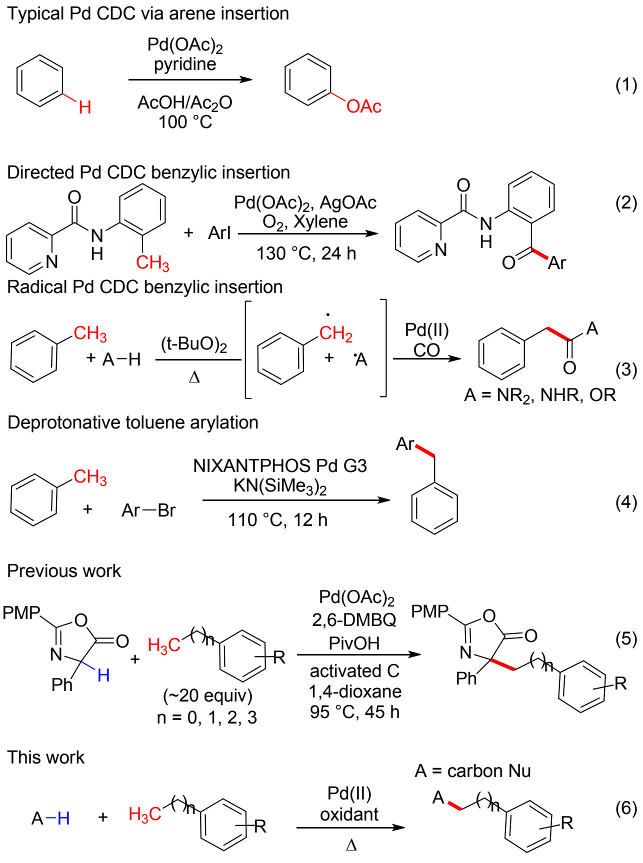
For these reasons, much research has focused on the effective use of aromatic hydrocarbons as substrates and metal catalyzed C–H activation chemistry has played a key role.[1] The use of palladium, in particular, has proven highly effective especially in the activation of sp^2 C–H bonds of arenes (e.g. Scheme 1, eq 1),[2] even allowing C–H activation of two reaction partners where the only byproduct is dihydrogen.[3] On the other hand, the activation of the sp^3 C–H bonds of aromatic hydrocarbons by palladium occurs much less readily to the point where toluene derivatives can undergo selective sp^2 C–H functionalization in the presence of one or more benzylic centers.[4] Strategies to achieve benzylic activation have relied on directing groups (Scheme 1, eq 2),[5] generation of benzylic radicals (Scheme 1, eq 3)[6], or the lower acidity of benzylic sites (Scheme 1, eq 4).[7]

Recently, we have reported an alternative strategy to activation of aromatic hydrocarbons wherein dehydrogenative coupling forms a hindered bond (Scheme 1, eq 5).[8] One unique feature of this process is the catalytic activation of benzylic C–H bonds under oxidizing conditions with palladium that typically result in sp^2 C–H activation. Another unusual feature is that coupling occurs at the terminus of the alkyl arene, presumably via a migration of the palladium center. In this article, we disclose our discovery of a range of acyclic and cyclic substrates that can participate in this process to generate hindered bonds selectively (eq 6). From the studies undertaken, guidelines are now available to predict which carbon nucleophiles will be effective.

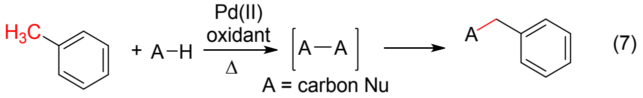
Results and Discussion

Our analysis of the reaction from eq 5 revealed the intermediacy of a dimer from the azlactone, which readily forms under a range of oxidative conditions.[9] Notably, others have found reactions that also proceed through dimers similar to those that we reported.[10] Reasoning that other substrates which form similar dimeric intermediates might be subject to a similar reaction

Scheme 1. Pd-Catalyzed Activation of Arenes and Toluenes

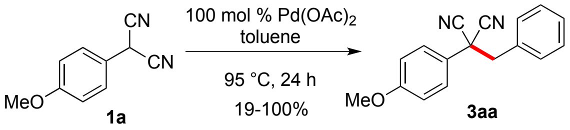


profile (eq 7), the literature was surveyed for compounds that readily undergo oxidative dimerization. A surprisingly large number of compounds with similar behavior was identified including malonates,[11] malononitrile,[12] cyanoacetate,[13] oxindoles,[14] isooxindoles,[15] benzofurans,[16] fluorenes,[17] and hydroxycoumarins.[18]



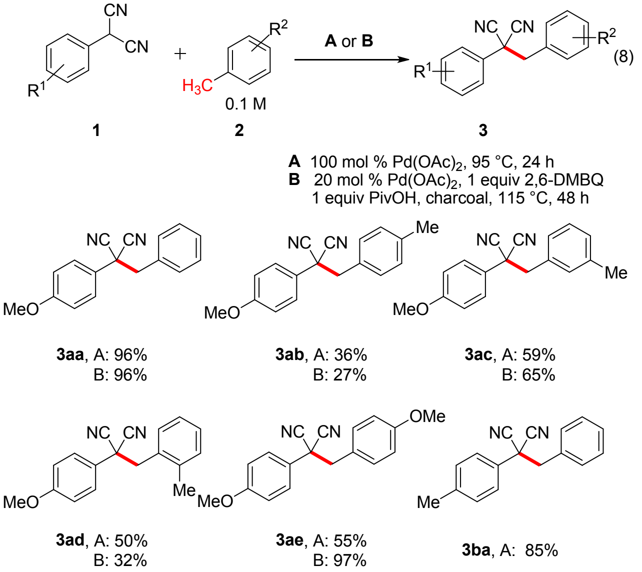
Acyclic Substrates: Malononitriles. A primary concern was whether the reaction was restricted to cyclic nucleophiles. Thus, the initial priority was to explore acyclic substrates capable of oxidative dimerization. Malononitriles are also well-known to undergo oxidative dimerization.[12] To probe the fundamental reactivity, trials were first conducted with stoichiometric $Pd(OAc)_2$ using dinitrile **1a** along with toluene (Scheme 2).

Scheme 2. Variable Yields in Dinitrile Toluene Coupling



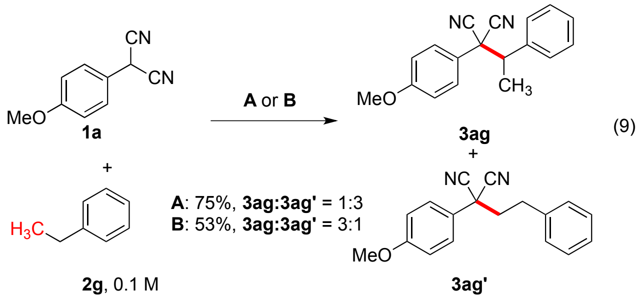
Good reactivity was observed, but the outcome was strongly affected by the batch of palladium used. Older batches of palladium were highly effective in the stoichiometric conversion of dinitrile **1a** to **3aa** with toluene (Scheme 2), while new batches were not. Different sources of $Pd(OAc)_2$ are known to give much different results due to different composition arising from the preparation, such as the red-brown $[Pd_3(OAc)_5NO_2]$. $[Pd_3(OAc)_6]$ is a dark purple solid whereas $[Pd(OAc)_2]_n$ polymer is a light grey-purple powder.[19]

Scheme 3. Catalytic Palladium Oxidative Coupling of Malononitriles with Methylarenes (eq 8)



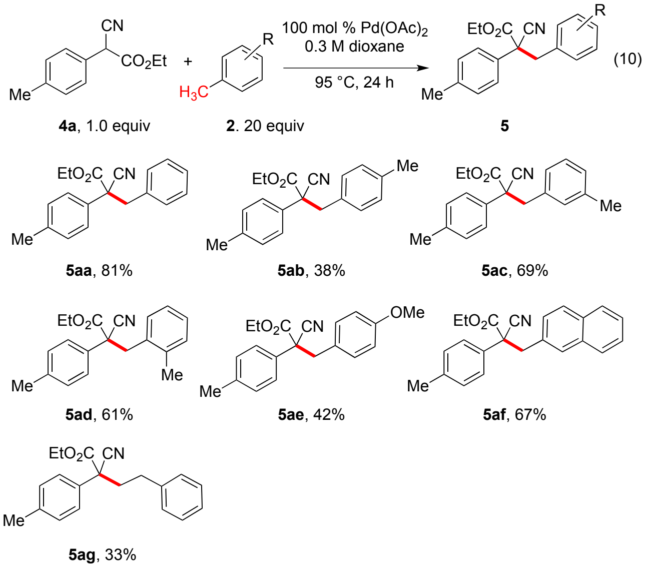
Proceeding with older batches of $Pd(OAc)_2$, the *para*-methoxyphenyl and *para*-methylphenyl malononitriles were found to be effective partners in the coupling of different toluenes (Scheme 3). Further, the same stoichiometric oxidant discovered for the azlactones, dimethylbenzoquinone (DMBQ), was found to be effective in turning over the process with catalytic amounts of $Pd(OAc)_2$. In most cases, similar yields were obtained for the catalytic vs stoichiometric palladium conditions. Amongst the xylene isomers, *para*-xylene (27-36%) was less effective than *meta*-xylene (59-65%) or *ortho*-xylene (32-50%). In all cases, reactions were conducted until all starting material was consumed and the mass balance is decomposition with no specific byproducts being isolable. Notably, higher yields were obtained under catalytic conditions for *para*-methoxytoluene. We speculate that stochiometric $Pd(OAc)_2$ can cause direct oxidation of the *para*-methoxytoluene, which was mitigated with lower amounts of $Pd(OAc)_2$ in the presence of the mild oxidant DMBQ.

For ethylbenzene, a divergence in behavior was seen relative to our prior report with azlactone (eq 5)8 where exclusive functionalization of the terminal CH$_3$ position occurred. With the malononitrile, a mixture of the terminal (methyl) vs internal (benzylic) products was observed (eq 9). The terminal product is proposed to arise from initial benzylic insertion followed by β-hydride elimination and migratory insertion.[20] We hypothesize that the driving force for rearrangement to the terminal position is largely controlled by formation of the less hindered alkyl palladium species. However, these results indicate that the nucleophile also plays a role, where sterically small nucleophiles can react at either the α- or β -positions. Under stochiometric conditions, there is a preference for the latter **3ag′**, whereas the former **3ag** predominates under catalytic conditions. Under catalytic conditions, the higher effective concentration of the nucleophile relative to the palladium species may cause greater capture of the benzylic intermediate prior to rearrangement.



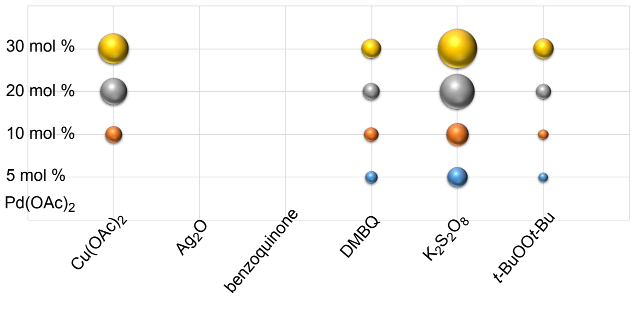
Acyclic Substrates: α-Cyanoacetates. α-Cyanoacetates are also well known to undergo such dimerizations, although somewhat more slowly.11 To probe the fundamental reactivity, trials were first conducted with stoichiometric Pd(OAc)$_2$ using cyanoacetate **4a** along with 20 equivalents of alkylarene in dioxane (eq 10, Scheme 4). At 95 °C, the reaction with toluene proceed well (81% yield). Again, *para*-xylene (38%) was less effective than *meta*-xylene (69%) or *ortho*-xylene (61%). Substrates with electron-donating groups (*para*-methoxytoluene) proceeded with moderate conversion (42%), but those with electron-withdrawing groups, such as *para*-trifluorotoluene or *para*-cyanotoluene gave no product. 2-Methylnaphthalene proceeded well (67%), whereas the more hindered 1-methylnaphthalene did not work (<10%). In contrast to the malononitriles, ethylbenzene gave the product arising exclusively from functionalization of the terminal position of the alkyl (**5ag**)

Scheme 4. Stoichiometric Palladium Oxidative Coupling of Cyanoacetates with Alkylarenes (eq 10)



Initial trials using the same DMBQ oxidant as described above for the malononitriles led to poor yields. On the whole, the α-cyanoacetates were less reactive than malononitriles. As such, high throughput screening was undertaken to identify an oxidant that would permit turnover of the process. With varying amounts of Pd(OAc)$_2$, several oxidants were examined (Scheme 5a) and K$_2$S$_2$O$_8$ was found to be superior. Having observed that carboxylic additives improved the yields with the azlactone substrate,8 presumably by ligating the palladium to prevent precipitation during the reduction, both acetic acid and pivalic acid additives were examined. Further, several solvents (DMF, NMP, 1,4-dioxane, 2-butanol, diglyme, *i*-PrOAc) were screened to minimize the amount of alkylarene employed (see SI). Overall acetic acid in dioxane performed best. Further examination of temperature (95, 110, 120 °C) revealed that higher temperatures (120 °C) were well tolerated causing little decomposition and higher yields (see SI).

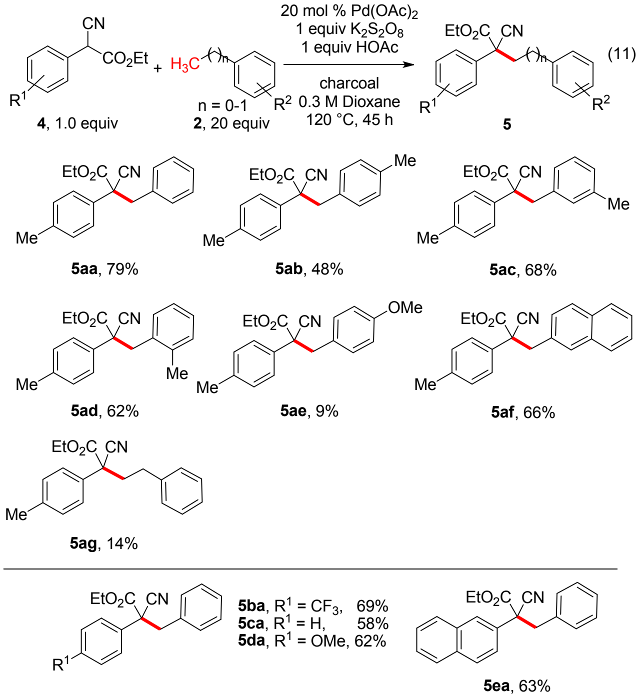
Scheme 5. Optimization of Oxidant for Cyanoacetates with Alkylarenes.[a,b]



[a]Substrate 4a, Pd(OAc)2, 0.1 M toluene, 95 °C, 15 h. [b]Sphere size correlates with conversion vs an internal standard (see SI for quantitative values).

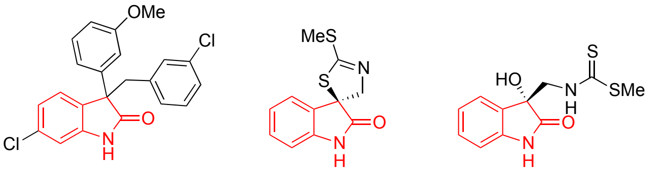
Applying the optimized conditions (eq 11) to a range of toluene substrates (top of Scheme 6) provided results as good as for the stoichiometric transformation with the exception of *para*-methoxytoluene, which likely undergoes an oxidation side reaction with the $K_2S_2O_8$. Yet again, *para*-xylene (48%) was less effective than *meta*-xylene (68%) or *ortho*-xylene (62%). Further, the catalytic conditions performed well for several different cyanoacetates (bottom of Scheme 6) including those bearing electron-withdrawing groups (**5ba**) or electron-donating groups (**5da**).

Scheme 6. Catalytic Palladium Oxidative Coupling of Cyanoacetates with Alkylarenes (eq 11)



Cyclic Substrates: Oxindoles. Moving away from acyclic substrates, oxindoles are another class of compounds that readily dimerize.14 In addition, oxindoles bearing two substituents at the 3-position are found in natural products and pharmaceutical targets (Scheme 7).[21] Notably, 3-aryl-3-benzyl motif that maps onto this method has been utilized by Hoffmann-LaRoche.21[c] Functionalization of oxindoles has been the focus of much work, including oxidative methods.[22]

Scheme 7. Bioactive Oxindole Structures



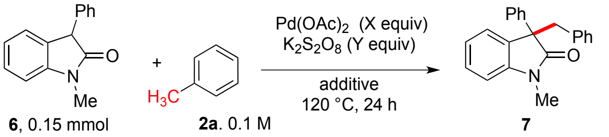
anti-cancer agent
(Hoffmann-LaRoche)

spirobrassinin

dioxibrassinin

Very good initial results were obtained in the coupling of 3-phenyloxindole (**6a**) with toluene (eq 13) with stoichiometric $Pd(OAc)_2$ (see SI). A survey of oxidants revealed $K_2S_2O_8$ as highly effective while minimizing byproduct formation (see SI). In this case, using dioxane as a solvent was not as effective (see SI), so reactions were conducted in 0.1 M alkylarene. Further optimization (Table 1) revealed that the palladium catalyst loading could be lower when a pivalic acid additive and activated charcoal were employed (entry 6).

Table 1. Optimization of 3-Phenyloxindole Toluene Coupling (eq 12)



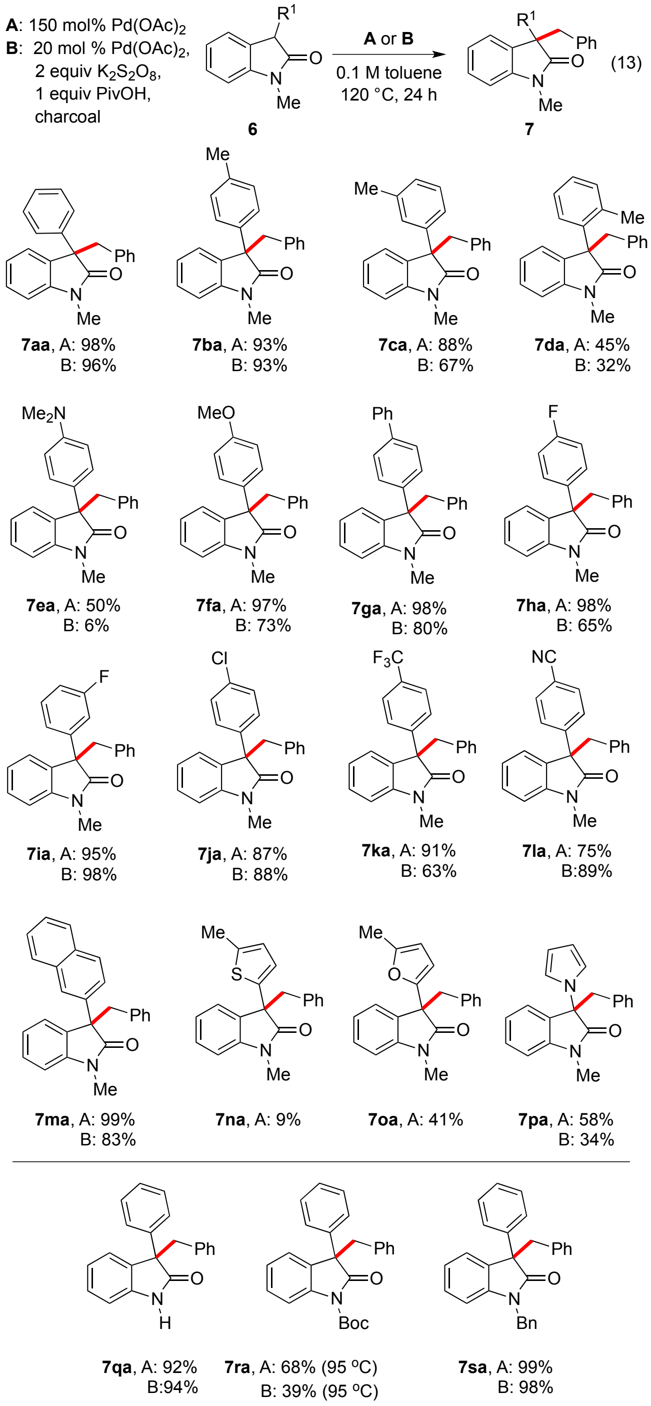
(12)

entry	X	Y	additive (equiv)	yield (%)[b]
1	0.3	2		98 (97)[c]
2	0.3	1		76
3	0.2	2		64
4	0.2	2	PivOH (1)	72
5	0.3	2	AcOH (1)	80
6	0.2	2	PivOH (1)	96[d]
7	0.3	2	AcOH (1)	77[d]
8	0.2	2	K_2CO_3 (1)	51
9	0.2	2	NaOAc (1)	44

[a] Reaction conditions: **6a** (0.15 mmol), **2a** (0.1 M), $Pd(OAc)_2$ (X mol %), $K_2S_2O_8$ (Y equiv) at 120 °C for 24 h under argon. [b] Isolated yield. [c] Run twice [d] Activated charcoal (10x weight of Pd) was added.

Additional 3-substituted oxindoles were synthesized following literature protocols[23] and were examined in the coupling with toluene (eq 13, Scheme 8). Different 3-aryl groups with both

Scheme 8. Palladium Oxidative Coupling of Oxindoles with Toluene (eq 13)

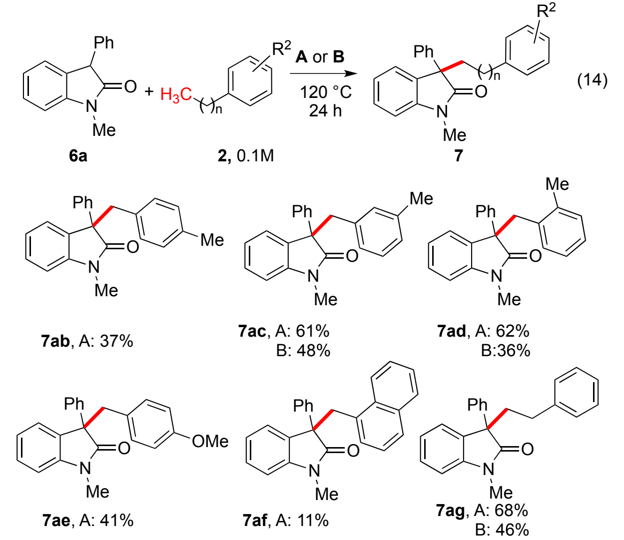


electron-donating and electron-withdrawing substituents were well tolerated leading to high yields under both stoichiometric and catalytic conditions (**7aa-7ma**). For example, generation of the oxindole cation initiates a Friedel-Crafts reaction with arenes; such a pathway cannot incorporate toluene at the benzylic carbon. Notably, this approach to **7ba**, **7fa** and similar structures is orthogonal to the oxidative coupling method reported by Li and workers[24] wherein selective coupling of the oxindole occurs via a Friedel-Crafts reaction results in functionalization of the arene C–H of toluene rather than the benzylic C–H. The 2-naphthyl substrate formed product (**7ma**) in high yield whereas the hindered 1-naphthyl substrate reacted poorly.

Heterocyclic groups could also be employed at the 3-position including a case with a nitrogen substituent (**7na-7pa**). The oxindole could also be employed directly without protection of the nitrogen (**7qa**) or with other protecting groups (**7ra, 7sa**); however, the Boc group was somewhat unstable at the high reaction temperatures.

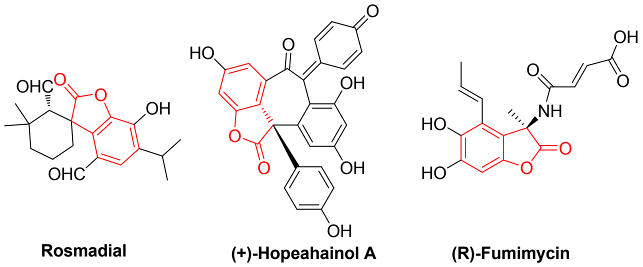
Similar trends were observed again with different arylalkanes with improved outcomes for ethylbenzene (eq 14, Scheme 9). Varying toluene, poor reactivity was again observed for substrates with electron-withdrawing groups such as *para*-methylbenzonitrile and *para*-chlorotoluene. The reaction was also unsuccessful for 2-methylfuran. To probe the β-hydride elimination and rearrangement, isobutylbenzene was examined. As expected, the addition of steric hindrance abrogated reactivity.

Scheme 9. Palladium Oxidative Coupling of Parent Oxindole with Alkylarenes (eq 14)



Cyclic Substrates: Benzofuranones. Benzofuranones are isoelectronic with oxindoles and also exhibit oxidative dimerization behavior.16 They are found in a number of natural products and pharmaceutical targets (Scheme 10).[25]

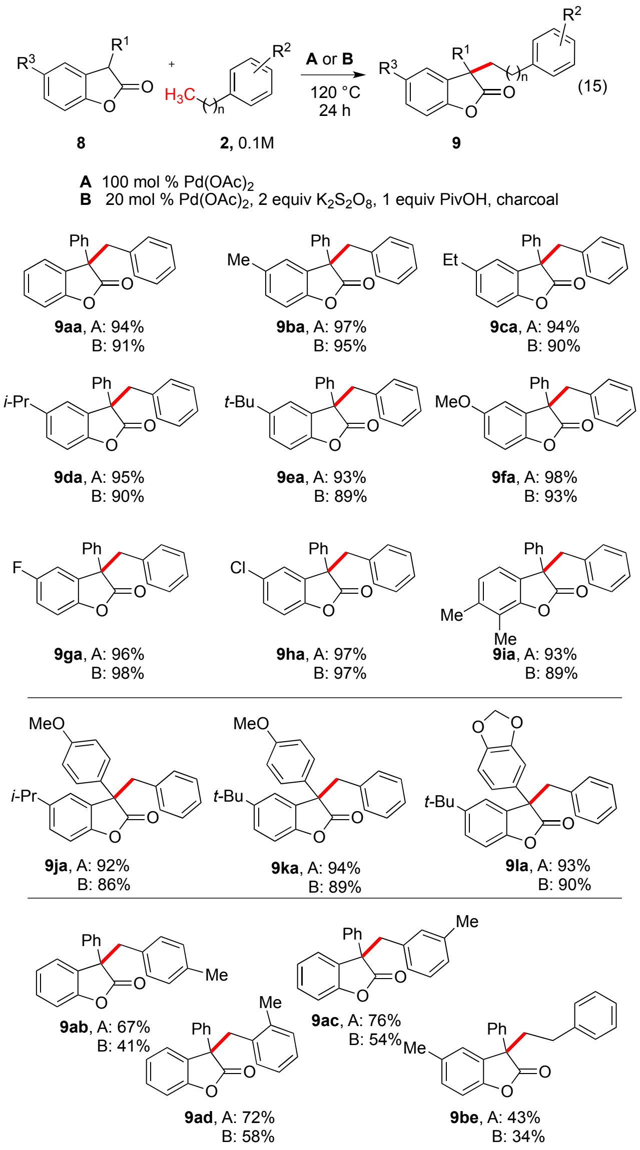
Scheme 10. Bioactive Benzofuranone Structures



Using the same conditions developed for the oxindoles, toluene coupled very well with the parent 3-phenylbenzofuranone to generate **9aa** under stoichiometric or catalytic conditions in 94% and 91% yield, respectively. Substrates varying the core ring system substituents (top Scheme 11) or the 3-aryl group (middle Scheme 11) were generated[26] and were found to couple with toluene very well. Electron-donating (**9fa, 9ja-9la**) and electron-withdrawing groups (**9ga, 9ha**) could be employed. Notably, chloro groups could be employed providing an opportunity for further derivatization (**9ha**). Lower catalyst loadings could also be employed, but required longer reaction or resulted in lower yields (for 9ba with 5 mol % $Pd(OAc)_2$, 59% and 75% product were obtained at reaction times of 24 h and 48 h, respectively).

A similar scope was seen with different alkylarenes as had been observed in the cases above (bottom, Scheme 11).

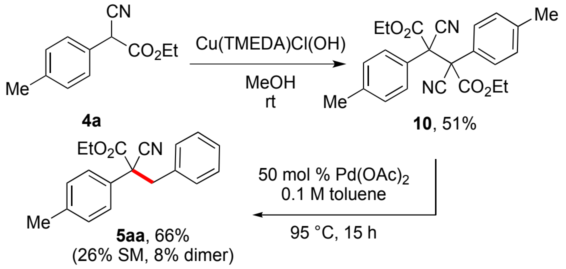
Scheme 11. Palladium Oxdiative Coupling of Benzofuranones with Alkylarenes (eq 15)[a]



[a]For **9ba**, using conditions B with 5 mol % $Pd(OAc)_2$, 59% and 75% product were obtained at reaction times of 24 h and 48 h, respectively.

Substrate Properties Correlated with Reactivity. In our prior report, the dimer of the azlactone (eq 5) was found to form under reaction conditions. When isolated and resubjected to the reaction conditions, this dimer also converted to product. The corresponding dimers were observed in the conversion of substrates **1**, **4**, **6**, and **8** although very little of the dimer built up during the conversion of oxindoles **6** or benzofuranones **8**. The dimer (**10**) of α-cyanoacetate **4a** was readily formed with oxidants and was independently synthesized (Scheme 12) with Cu(TMEDA)ClOH. Resubjection of dimer **10** to the reaction conditions with $Pd(OAc)_2$ and toluene again afforded the product **5aa** (Scheme 12).

Scheme 12. Dimer Intermediate from Cyanoacetate Substrate

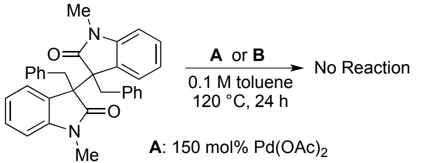


Heating the dimer with toluene alone did not form the product. Similarly, subjection of substrate under the catalytic conditions without $Pd(OAc)_2$ did not form the product. For example, when oxindole **6a** was treated with 2 equiv $K_2S_2O_8$, 1 equiv PivOH, charcoal, in 0.1 M toluene for 24 h at 120 °C, the outcome was 73% unreacted **6a**, 25% dimer, and 0% product. Thus, it appears that $Pd(OAc)_2$ plays a role in the C–H activation event of the toluene as well as in dimerization of the nucleophilic substrate.

Calculations of the bond dissociation energy (BDE) values for a range of potential nucleophilic substrates was undertaken (Table 2). If the ability to undergo dimerization via nonionic processes is the most important factor in determining reactivity, then the substrate C–H bond dissociation energy should correlate with reactivity in the overall process. A survey of all the substrates in Table 2, revealed that only entries 3-11, possessing C–H bond dissociation energies in the range of 61.0-71.6 kcal/mol, were effective in the transformation. Substrates with similarly weak C–H bonds (entries 1-2, and to a lesser extent, entries 12, 14), were found to be unreactive. All of these compounds have weaker bond dissociation energies than toluene (90 kcal/mol),[27] which accounts for why dimer alone (see above) is unable to activate toluene.

To further probe the importance of the initial oxidation to the dimer, the dimer of **6u** was independently synthesized[28] and resubjected to the reaction conditions in a similar manner as outlined in Scheme 8. Similar to monomer **6u**, the dimer of **6u** did not convert to the product in the presence of $Pd(OAc)_2$ (Scheme 13) indicating that dimerization is necessary, but not sufficient in order for the process to occur.

Scheme 13. 3-Benzyloxindole Dimer with $Pd(OAc)_2$



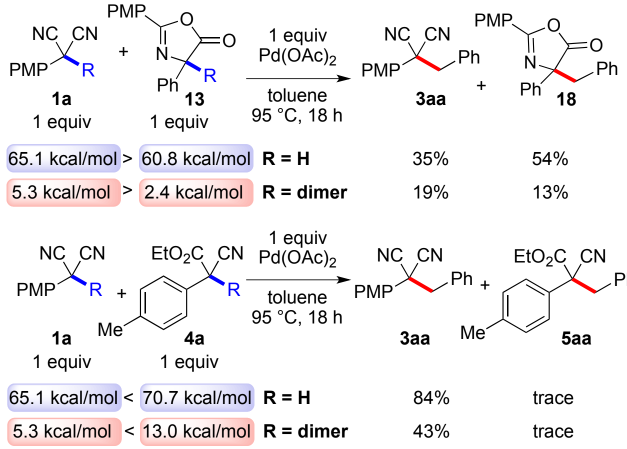
6u-dimer

A: 150 mol% $Pd(OAc)_2$
B: 20 mol % $Pd(OAc)_2$, 2 equiv $K_2S_2O_8$, 1 equiv PivOH, charcoal

The dimer BDE values were also computed and correlated more strongly with reactivity (Table 2). Substrates with dimers BDE values either below 2 kcal/mol or above 15 kcal/mol did not form product. That compounds with stronger dimer BDE values did not generate product, even when the dimer was preformed (see Scheme 13) indicates that the oxidizing power of the dimer is not the most important factor. Furthermore, the relative reactivity of the substrates in entries 3-11 followed the order of the dimer BDE values as judged by TLC monitoring.

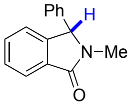
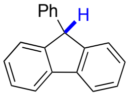
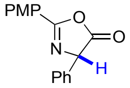
Competition experiments between substrates were performed to probe the role of BDE values (Scheme 14). Reaction from the monomer and dimer gave different outcomes, consistent with two separate steps contributing to the overall rate: dimerization by palladium and reaction of the dimer with a palladium alkyl. For all pairs, the substrates with the stronger BDE values were less reactive.

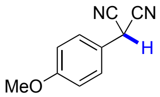
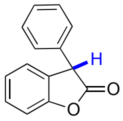
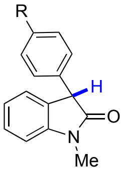
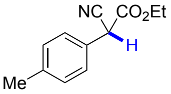
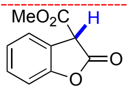
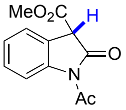
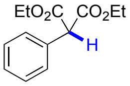
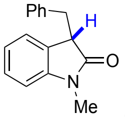
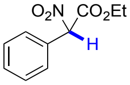
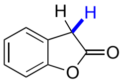
Scheme 14. Competition Experiments



[a]Yields from ^1H NMR using 4,4'-di-*t*-Bubiphenyl as an internal standard.

Table 2. Bond Dissociation Energies of A-H and A-A

Entry	A–H	monomer BDE[a] (kcal/mol)	dimer BDE[a,b] (kcal/mol)
1	 **11**	71.9	0.8
2	 **12**	71.0	1.4
3	 **13**	60.8	2.4

4		**1a**	65.1	5.3
5		**8a**	67.9	7.4
6		**6f**, R = OMe	68.1	8.7
7		**6b**, R = Me	69.0	10.0
8		**6a**, R = H	69.5	10.5
9		**6l**, R = CN	69.6	10.8
10		**6k**, R = CF_3	69.8	11.4
11		**4a**	70.7	13.0
12		**14**	71.7	22.6
13		**15**	72.1	22.7
14		**16**	79.1	24.1
15		**6u**	74.7	26.3
16		**17**	81.9	27.9
17		**8m**	78.2	38.6

^{a}Computed at uB3LYP/6-31G*. ^{b}Meso diastereomer.

All told, it appears that the dimer must be able to fragment readily, hence the poor results with compounds with higher dimer BDE (Table 2, entries 12-17). The poor results with dimers that cleave very readily (entries 1-2) are consistent with two scenarios. The dimer may play a partial role in assisting the palladium activation of toluene, in which case a modest oxidizing power is needed which the dimers of **11** and **12** lack. Alternately, the captodative radical from homolysis of the dimer must engage the palladium alkyl intermediate and cannot do so if it is too stable, as manifested in very low dimer BDE values.

Conclusions

The discovery of a range of nucleophilic substrates that can engage in the oxidative activation of alkyl C-H bonds vs arene C–H bonds with $Pd(OAc)_2$ has been described. This process uses inexpensive alkylarene precursors derived from petroleum and allows the formation of a range of hindered quaternary centers. All of the substrates react by an initial oxidative dimerization initiated by the $Pd(OAc)_2$ and/or the terminal oxidant. A number of terminal oxidants are compatible with the process with DMBQ or $K_2S_2O_8$ being the most effective to date. The resultant dimer modifies the palladium catalyst to favor activation of alkyl C-H bonds in contrast to the trends typically observed via a concerted metalation deprotonation mechanism. Notably, insertion occurs at the terminus of the alkyl arene for hindered substrates via β-hydride elimination/migratory insertion, a pathway that is not typically seen in oxidative palladium chemistry. The bond dissociation energies of the dimeric intermediates have been identified that predict which substrates are productive in this reaction. These guidelines allow rationale selection of substrates to employ in this method and further mechanistic studies are underway to understand the discrete steps of this unusual and complex mechanism.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures for all experiments and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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ACKNOWLEDGMENT

We are grateful to the NSF (CHE1464778, CHE1764298) and the NIH (GM-08765) for financial support of this research. Partial instrumentation support was provided by the NIH and NSF (1S10RR023444, 1S10RR022442, CHE-0840438, CHE-0848460, 1S10OD011980) and computational support by was provided by XSEDE (TG-CHE120052). G.H., P.N., U.N.K., and A.V. thank the Chinese Scholarship Council, the University of Guanajuato and CONACyT, Dr. Reddy's Laboratories (Dr. Rakeshwar Bandichhor), and the S. N. Bose Scholarship Program of India, respectively, for financial support. Drs. Rakesh Kohli and Charles W. Ross III are acknowledged for obtaining accurate mass data.

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