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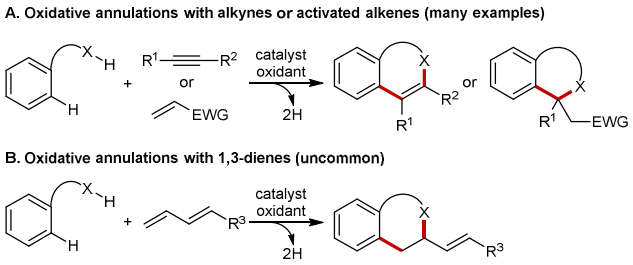
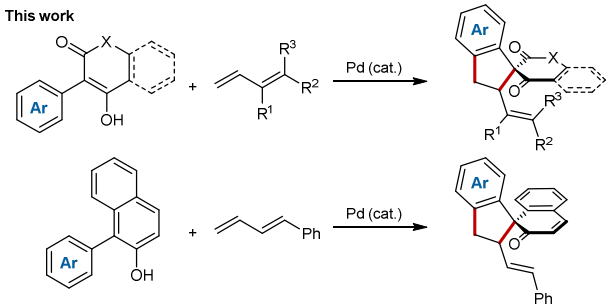
The synthesis of spiroindanes by the palladium-catalyzed oxidative annulation of non- or weakly activated 1,3-dienes with 2-aryl cyclic 1,3-dicarbonyl compounds is described. Examples of the dearomatizing oxidative annulation of 1,3-dienes with 1-aryl-2-naphthols are also presented.

The site-selective, metal-catalyzed oxidative C−H functionalization of aromatic C(sp^2)−H bonds with alkynes and activated alkenes, directed by a heteroatom-containing functional group,[1] is now well-established for the preparation of diverse heterocycles[2–5] and carbocycles (Scheme 1A).[6] Despite the impressive advances that have been made, 1,3-dienes have rarely been used as annulation partners in these types of reactions (Scheme 1B). Booker-Milburn, Lloyd-Jones, and co-workers have described the Pd-catalyzed oxidative annulation of *N*-arylureas with mostly activated 1,3-dienes (R^3 = electron-withdrawing group) to form indolines.[7] Related, *but non-oxidative*, annulations involving 1,3-dienes have been described by the Glorius group, who recently developed the redox-neutral Rh(III)-catalyzed annulation of aromatic oxime esters with 1,3-dienes to give isoquinolines.[8] Nishimura, Hayashi, and co-workers have also described non-oxidative, Ir-catalyzed annulations of cyclic ketimines with 1,3-dienes *via* C–H functionalization.[9] Although currently limited in number, these processes demonstrate the significant potential of 1,3-dienes as annulation partners in C–H functionalization reactions. The development of new types of annulations involving 1,3-dienes therefore remains an important objective to increase the range of products that can be accessed.

Herein, we describe the Pd-catalyzed oxidative annulation of 1,3- dienes with 2-aryl cyclic-1,3-dicarbonyls and 1-aryl-2-naphthols (Scheme 2). These reactions result in spiroindanes, which occur in various biologically active compounds.[10]



Scheme 1 Directed, catalytic oxidative annulations of aromatic compounds with unsaturated partners by C–H functionalization.



Scheme 2 Pd-catalyzed synthesis of spiroindanes from 1,3-dienes.

Given the utility of cyclic 1,3-dicarbonyls as directing groups in various catalytic oxidative annulations,[4f,5f,g,6d] our investigations began with the reaction of 2-phenyldimedone (**1a**) with diene **2a** (1.5 equiv) in the presence of various metal precatalysts (5 mol% metal) and $Cu(OAc)_2$ (2.1 equiv) in DMF at 90 °C (Table 1). Ruthenium[3] and rhodium[2] complexes commonly employed in C−H functionalizations were ineffective (entries 1 and 2). However, use of the palladium–*N*-heterocyclic carbene complex PEPPSI-IPr[5f,11] gave **3a** in 60% yield (entry 3). *t*-AmOH and 1,4-dioxane were inferior solvents compared with DMF (entries 4 and 5). Conducting the reaction in degassed DMF increased the yield slightly to 66% (entry 6).[12] Use of 2.5 mol% of PEPPSI-IPr gave **3a** in a more

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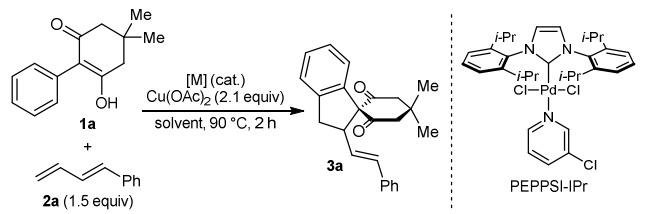
Table 1 Evaluation of conditions for the synthesis of **3a**[a]



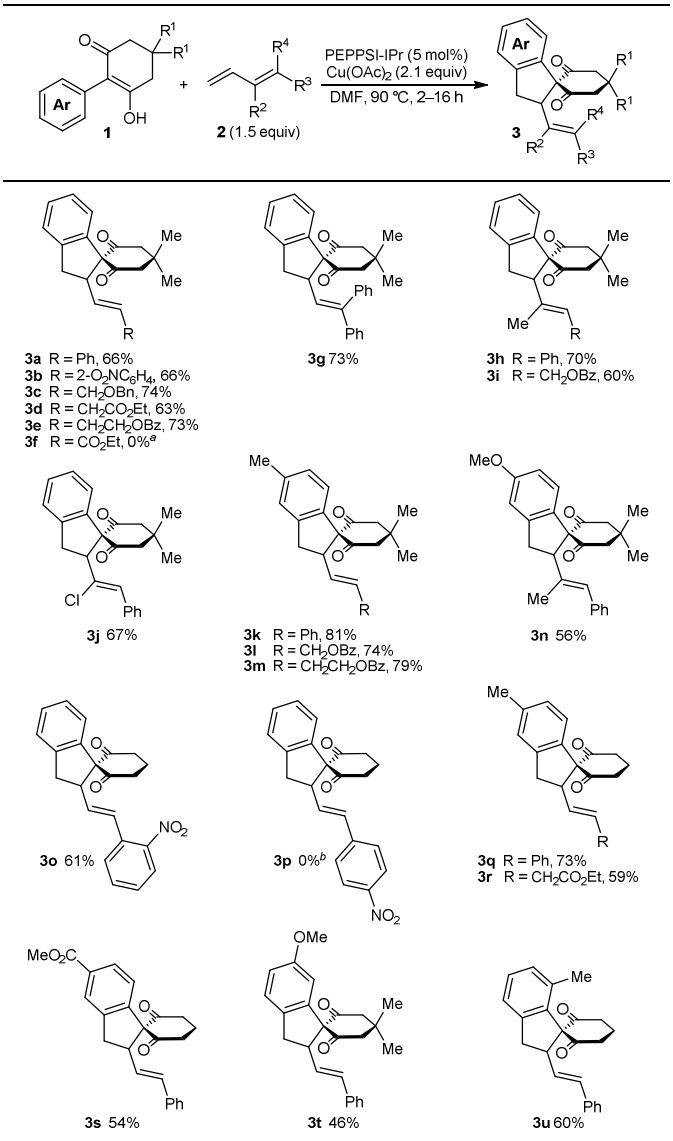
Entry	[M]	mol%	Solvent	Yield (%)[b]
1	$[RuCl_2(p\text{-cymene})]_2$	2.5	DMF	—
2	$[Cp^*RhCl_2]_2$	2.5	DMF	—
3	PEPPSI-IPr	5	DMF	60
4	PEPPSI-IPr	5	*t*-AmOH	39
5	PEPPSI-IPr	5	1,4-dioxane	46
6	PEPPSI-IPr	5	DMF	66[c]
7	PEPPSI-IPr	2.5	DMF	54[c]
8	PEPPSI-IPr	10	DMF	68[c]
9	$Pd(OAc)_2$	5	DMF	60[c]
10	PEPPSI-IPr	5	DMF	—[d]

[a] Using 0.25 mmol of **1a**. [b] Yield of isolated product. [c] Using degassed DMF. [d] Without $Cu(OAc)_2$. *t*-Am = *tert*-amyl.

modest yield of 54% (entry 7), while increasing the catalyst loading from 5 mol% to 10 mol% led only to a minimal increase in yield (entry 8, compare with entry 6). For comparison, use of $Pd(OAc)_2$ instead of PEPPSI-IPr gave **3a** in 60% yield (entry 9). Finally, $Cu(OAc)_2$ was essential for the reaction to proceed (entry 10). On the basis of these experiments, the conditions of entry 6 were selected for further investigations.

The scope of this Pd-catalyzed oxidative annulation was then explored, which gave spiroindanes **3** in 46–81% yield (Scheme 3). In addition to substrates derived from dimedone (**3a**–**3e** and **3g**–**3n**), those derived from 1,3-cyclohexanedione also reacted successfully (**3o** and **3q**–**3u**). Besides a phenyl group at the 2-position of the 1,3-diketone, aromatic moieties containing substituents at the *para*- (**3k**–**3n** and **3q**–**3s**), *meta*- (**3t**), or *ortho*-positions (**3u**) were also tolerated. The successful formation of **3u** is notable as *ortho*-substitution was not tolerated related in Ru-catalyzed oxidative annulations of 2-aryl cyclic 1,3-dicarbonyl compounds reported previously.[5f,6e] In the case of a substrate containing a *meta*-methoxyphenyl group, a complex mixture of products was obtained, from which only spiroindane **3t** could be isolated cleanly (46% yield). In **3t**, C–H functionalization occurred at the least sterically hindered position, *para*- to the substituent, which is consistent with previous observations,[5e,6d] though we cannot rule out the formation of alternative isomers.

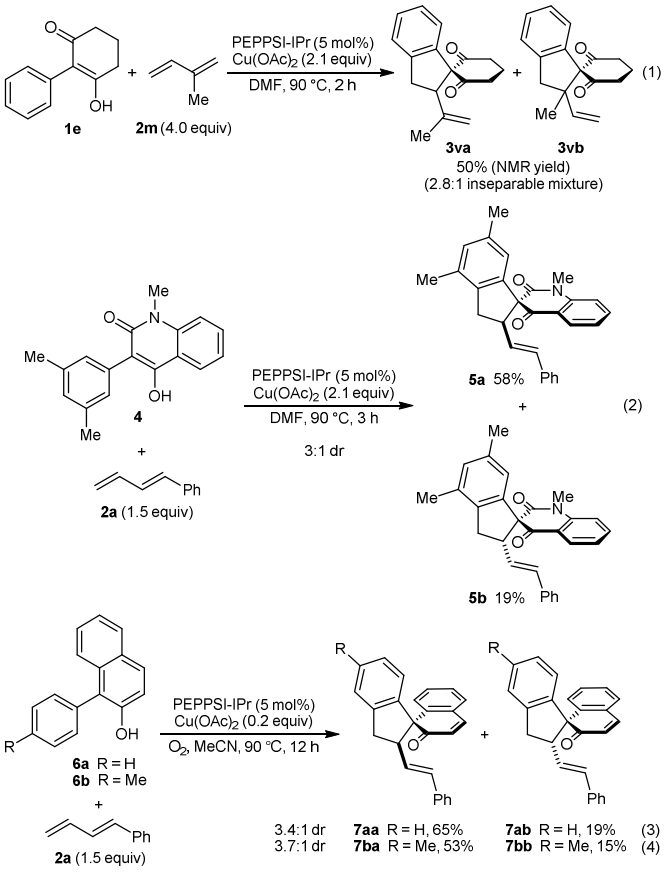
The reaction is tolerant of 1,3-dienes of varying substitution patterns. For example, 1,3-dienes **2** containing an aryl (**3a**, **3b**, **3k**, **3o**, **3q**, **3s**–**3u**) or alkyl (**3c**–**3e**, **3i**, **3l**, **3m**, **3r**) substituent at R^3 (R^2 = R^4 = H) were effective substrates. The ability to employ alkyl-substituted 1,3-dienes sets this process apart from related annulations, where highly activated 1,3-dienes containing strong electron-withdrawing groups were required for optimal results.[7,8,13,14] This point is reinforced by the fact that the use of highly activated 1,3-dienes in our reactions were unsuccessful (none of **3f** or **3p** could



Scheme 3 Oxidative annulation of various 2-aryl-1,3-dicarbonyl compounds with various 1,3-dienes. Reactions were conducted with 0.50 mmol of **1** in degassed DMF. [a] A complex mixture was obtained. [b] The 1,3-diene was returned largely unchanged while decomposition of 2-phenyl 1,3-cyclohexanedione was observed.

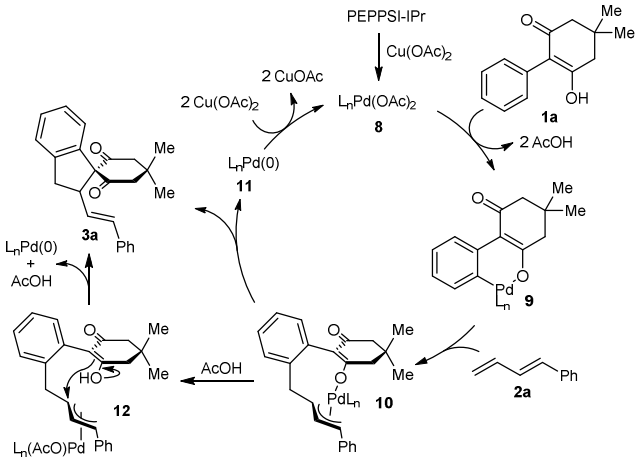
be isolated[15]). The reasons for these observations are currently not clear.[16] A 1,1-diphenyl-substituted diene smoothly underwent the reaction (**3g**), as did dienes containing methyl or chloro substituents at the internal position R^2 (**3h**–**3j** and **3n**). Where relevant, the stereochemistry of the internal alkene of the 1,3-diene was preserved in the products.[17] 1,3-Dienes that do not contain a terminal alkene, such as 1,4-disubstituted-1,3-dienes, were unreactive in this process. However, isoprene (**2m**) reacted with **1e** to provide a 2.8:1 inseparable mixture of two isomers **3va** and **3vb** (eqn (1)).[18]

The unsymmetrical 2-aryl cyclic 1,3-dicarbonyl compound **4** reacted with 1,3-diene **2a** to provide a mixture of diastereomeric spiroindanes **5a** and **5b** in 58% and 19% yield, respectively (eqn (2)). Phenol and naphthol-derived substrates have recently been found to be viable substrates for carbocycle-forming oxidative annulations with alkynes,[6i,m,n] and we were pleased to observe that



1-aryl-2-naphthol **6a** reacted smoothly with 1,3-diene **2a** to provide a diastereomeric mixture of dearomatized products **7aa** and **7ab** (eqn (3)).[17] Similar results were obtained using substrate **6b** (eqn (4)). In these cases, the highest yields were obtained using substoichiometric $Cu(OAc)_2$ and molecular oxygen (balloon) as the terminal oxidant, using MeCN as the solvent.

A possible catalytic cycle for these reactions, using substrates **1a** and **2a** for illustrative purposes, is shown in Scheme 4. First, heating PEPPSI-IPr with $Cu(OAc)_2$ is likely to form a palladium diacetate complex **8**, which can then undergo cyclometallation with **1a** to give palladacycle **9**, liberating two equivalents of acetic acid. Migratory insertion of the 1,3-diene **2a** with **9** can then occur to give a new palladacycle **10**, containing a π-allylpalladium species. An inner sphere C–C bond-forming reductive elimination[19] of **10** then provides the spiroindane **3a** and the palladium(0) species **11**, which then undergoes oxidation by $Cu(OAc)_2$ to regenerate **8**. Computational studies on the enantioselective Tsuji allylation of enolates, which proceed *via* intermediates similar to **10**, suggests that in those reactions, reductive elimination by a 3,3' pathway[20] is the lowest in energy.[19] However, in the reactions presented herein, where the palladium enolate and allylpalladium components are tethered to each other, the mechanism of reductive elimination may well be different. Alternatively, it is possible that the product could be formed by outer sphere nucleophilic attack of an enol onto a π-allylpalladium species such as in **12**,[21] which in turn could be formed by protonolysis of **10** by AcOH. Further studies will be required to shed more light on the mechanism.



Scheme 4 Possible catalytic cycle.

In summary, the synthesis of spiroindanes from the palladium-catalyzed oxidative annulation of 2-aryl cyclic 1,3-dicarbonyl compounds or 1-aryl-2-naphthols with non- or weakly activated 1,3-dienes has been reported. This work demonstrates the broad utility of palladium catalysis in oxidative annulations involving C–H functionalization, and increases the scope of carbocyclic products that can be prepared using these reactions. The development of diastereo- and enantioselective variants of these processes, along with investigations into other types of carbocycle-forming oxidative annulations, are topics for further study in our group.

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12 We currently do not have a definitive explanation for this result, though we have observed that the substrates are prone to decomposition if left exposed to atmospheric oxygen.

13 In the work of Glorius and co-workers (see ref. 8), non- or weakly-activated 1,3-dienes gave products different to those obtained from highly activated 1,3-dienes, as a result of over-oxidation.

14 Although iridium-catalyzed annulations of 1,3-dienes with cyclic ketimines (see ref. 9) occur with non-activated and highly activated 1,3-dienes, the mechanism of these reactions appears to be distinct from related processes (see ref. 7, 8, and the reactions described herein) in that the initially formed iridacycle reacts with the 1,3-diene in an oxidative cyclization rather than a migratory insertion.

15 Although a highly activated 4-nitrophenyl-substituted 1,3-diene was unsuitable in these reactions (none of **3p** could be isolated), reactions with a 2-nitrophenyl-substituted 1,3-diene, which might be expected to be electronically similar, were successful (**3b** and **3o**). Presumably, the 2-nitrophenyl group is twisted out of conjugation with the 1,3-diene to minimize unfavorable steric interactions with the 2-nitro group, thus reducing its electron-withdrawing ability.

16 Although nucleophilic addition of the 2-aryl cyclic 1,3-diketone to highly activated 1,3-dienes might be cited as a possible explanation, Michael acceptors such as acrylate esters react smoothly with 2-aryl cyclic 1,3-diketones in related oxidative annulations. See ref. 5e.

17 The structures of products **3h**, **3j**, **5a**, and **7aa** were confirmed by X-ray crystallography. See the Electronic Supplementary Information.

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