

Catalyst-Controlled Divergent C–H Functionalization of Unsymmetrical 2-Aryl Cyclic 1,3-Dicarbonyl Compounds with Alkynes and Alkenes

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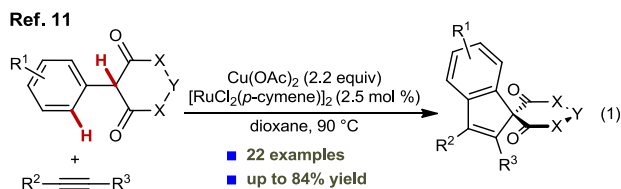
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ABSTRACT: Achieving site-selective, switchable C–H functionalizations of substrates that contain several different types of reactive C–H bonds is an attractive objective to enable the generation of different products from the same starting materials. Herein, we demonstrate the divergent C–H functionalization of unsymmetrical 2-aryl cyclic 1,3-dicarbonyl compounds that contain two distinct, non-adjacent sites for initial C–H functionalization, where product selectivity is achieved through catalyst control. Using a palladium–*N*-heterocyclic carbene complex as the precatalyst, these substrates undergo oxidative annulation with alkynes to provide spiroindenes exclusively. In contrast, a ruthenium-based catalyst system gives benzopyrans as the major products. Examples of divergent oxidative C–H alkenylations of the same substrates are also provided.

INTRODUCTION

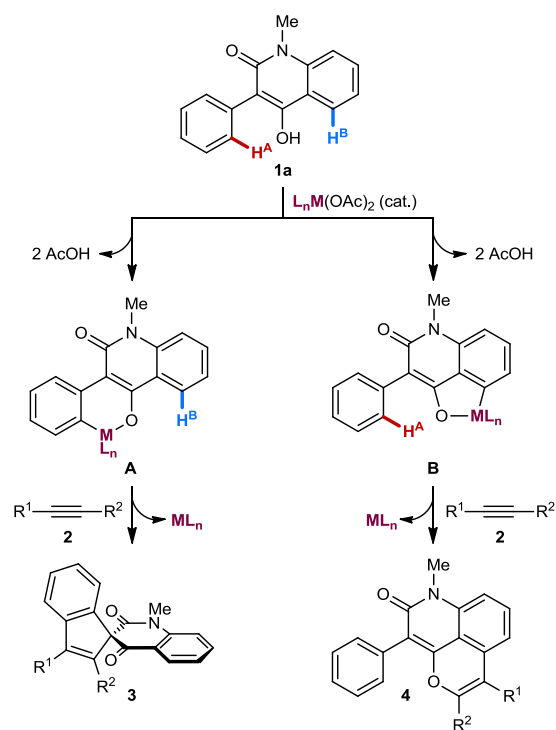
Metal-catalyzed C–H functionalization reactions are of significant interest due to their potential to streamline organic synthesis by avoiding the prior preparation of activated substrates and reducing the quantity of waste byproducts, thereby making syntheses more step- and atom-economic.¹ One important class of these reactions is the oxidative annulation of alkynes with substrates containing cleavable C–H/N–H, C–H/O–H, or C–H/N–O bonds, which enables the preparation of a diverse range of heterocycles.^{2,3,4,5,6,7,8,9}

The development of corresponding processes for the synthesis of carbocyclic products would be highly valuable,¹⁰ and in this context, we recently reported the ruthenium-catalyzed oxidative annulation of alkynes with 2-aryl cyclic-1,3-dicarbonyls or their enol tautomers (eq 1).¹¹ These reactions proceed via sequential C(sp²)–H and C(sp³)–H functionalization to give spiroindenes in generally good yields.¹² In that study, only symmetrical 2-aryl cyclic-1,3-dicarbonyl substrates were studied, which led to the formation of achiral products. Replacement of these substrates with *unsymmetrical* variants would result in chiral spiroindenes, thus providing the possibility of the development of a catalytic enantioselective process.



This prospect led us to consider 3-aryl-4-hydroxyquinolin-2-ones such as **1a** as substrates for oxidative annulation with alkynes (Scheme 1). However, these compounds present a complication in that two distinct sites for initial enol/enolate-directed C(sp²)–H cleavage are now available; at the 3-aryl ring, and at the benzene ring of the quinolin-2-one. C–H

Scheme 1. Divergent Oxidative Annulation of **1a** with an Alkyne



cleavage at the former site (H^A) with a metal acetate complex, for example, would provide a six-membered metallacycle **A**, which could then react with an alkyne **2** to give spiroindene **3**. Alternatively, C–H cleavage at the second site (H^B) would form a five-membered metallacycle **B**, which could react with the alkyne to give benzopyran **4**, a process that has been described by the group of Satoh and Murai using rhodium catalysis¹³ and by the Ackermann group using ruthenium catalysis.¹⁴

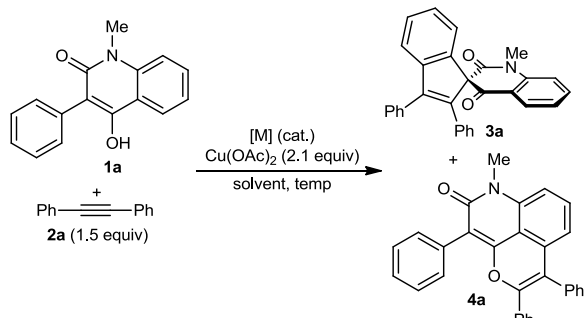
This situation highlights an inherent challenge in C–H functionalization chemistry resulting from the ubiquity of C–H bonds in organic compounds; how to control site-selectivity when more than one type of C–H bond can potentially undergo reaction. One solution to this problem is through catalyst control. The ability to form one of two possible annulation products selectively from the same reactants, simply by varying the catalyst, falls under the area of catalytic selective synthesis, which has been highlighted by Bode and co-workers in a recent review.¹⁵ Although the area of catalytic C–H functionalization has witnessed explosive growth, investigations of catalyst-controlled divergent C–H functionalizations of distinct C–H bonds are relatively uncommon.^{7c,16,17,18,19} A greater understanding of the factors that influence switchable, site-selective C–H functionalizations,²⁰ including catalyst structure, would be valuable in increasing the utility of these reactions in more complex settings. In this Article, we describe the divergent oxidative annulation of unsymmetrical 2-aryl cyclic 1,3-dicarbonyl compounds with alkynes. Site-selectivity in the initial C–H functionalization en route to spiroindene or benzopyran products may be achieved by the use of palladium- or ruthenium-based catalysts, respectively. Examples of the oxidative C–H alkenylation of the same substrates are also provided.

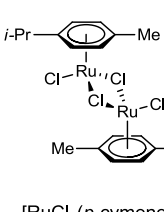
RESULTS AND DISCUSSION

Evaluation of Precatalysts in the Oxidative Annulation with Alkynes. This study began with an evaluation of precatalysts and reaction conditions for the oxidative annulation of the 4-hydroxy-3-phenylquinolin-2-one **1a** with diphenylacetylene (**2a**), using Cu(OAc)₂ (2.1 equiv) as the stoichiometric oxidant (Table 1). First, [RuCl₂(*p*-cymene)]₂ was found to favor the formation of benzopyran **4a** in all cases (entries 1–4).^{14,21} Conditions employed in our previous study of spiroindene synthesis,¹¹ using 2.5 mol % of [RuCl₂(*p*-cymene)]₂ in dioxane at 90 °C for 5 h, gave both possible products **3a** and **4a** in low yields (entry 1). An increase in the loading of [RuCl₂(*p*-cymene)]₂ to 5 mol % was beneficial, and products **3a** and **4a** were isolated in 13% and 78% yield, respectively (entry 2). Switching the solvent to DMF increased the overall yield and the selectivity for **4a** (entry 3). Although the catalyst loading could be reduced to 2.5 mol %, an increase in temperature to 120 °C was required for reasonable conversions, and the isolated yield of **4a** was only 66% (entry 4). [RhCp*Cl₂]₂ was also a competent precatalyst, and like [RuCl₂(*p*-cymene)]₂, favored the formation of benzopyran **4a** (entries 5 and 6).¹³ The best result was obtained using 2.5 mol % of [RhCp*Cl₂]₂ in DMF at 90 °C (entry 6). However, on the basis of the lower cost of [RuCl₂(*p*-cymene)]₂ compared with [RhCp*Cl₂]₂, the conditions of entry 3 were selected for further investigation of the scope of the benzopyran formation (see Table 2).

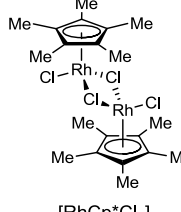
Next, palladium-based precatalysts were investigated,^{7,10} and these reactions provided spiroindene **3a** as the sole product,²¹ with none of benzopyran **4a** being detected (Table 1, entries 7–10). The use of Pd(OAc)₂ (5 mol %) in DMF gave **3a** in 76% yield after only 1 h at 120 °C (entry 7). The use of an *N*-heterocyclic carbene ligand for palladium²² provided even better results, and **3a** was obtained in 86% yield in the presence of 5 mol % of the PEPPSI-IPr complex developed by Organ and co-workers (entry 8).^{23,24,25} Reduction of the loading of PEPPSI-IPr to 2.5 mol % gave similar results after a reaction time of 2 h (entry 9). Although the temperature could be lowered to 90 °C, a slightly longer reaction time was

Table 1. Evaluation of Reaction Conditions for the Oxidative Annulation of **1a with Diphenylacetylene^a**

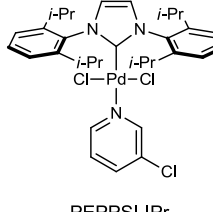




[RuCl₂(*p*-cymene)]₂



[RhCp*Cl₂]₂



PEPPSI-IPr

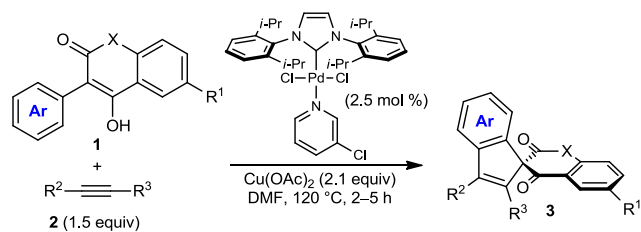
entry	[M]	mol %	solvent	temp (°C)	time (h)	yields (%) ^b
						3a 4a
1	[RuCl ₂ (<i>p</i> -cymene)] ₂	2.5	dioxane	90	5	5 15
2	[RuCl ₂ (<i>p</i> -cymene)] ₂	5	dioxane	90	5	13 78
3	[RuCl ₂ (<i>p</i> -cymene)] ₂	5	DMF	90	5	8 87
4	[RuCl ₂ (<i>p</i> -cymene)] ₂	2.5	DMF	120	5	8 66
5	[RhCp*Cl ₂] ₂	2.5	dioxane	120	5	30 61
6	[RhCp*Cl ₂] ₂	2.5	DMF	120	5	13 79
7	Pd(OAc) ₂	5	DMF	120	1	76 0
8	PEPPSI-IPr	5	DMF	120	1	86 0
9	PEPPSI-IPr	2.5	DMF	120	2	87 0
10	PEPPSI-IPr	2.5	DMF	90	3	75 0

^a Reactions were conducted using 0.25 mmol of **1a**. ^b Cited yields are of isolated material.

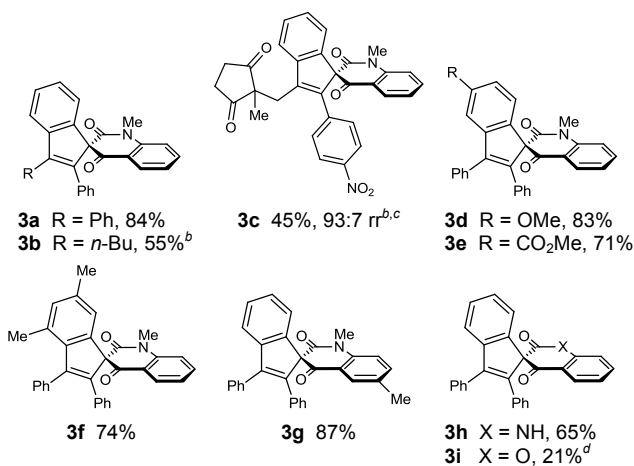
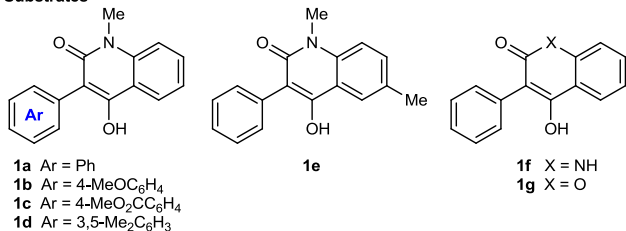
required, and **3a** was obtained in a slightly lower yield (entry 10). On the basis of these results, the conditions of entry 9 were used to investigate the scope of the spiroindene synthesis.

Palladium- and Ruthenium-Catalyzed Oxidative Annulations with Alkynes. Chart 1 presents the results of palladium-catalyzed synthesis of spiroindenes from the reaction of various unsymmetrical 2-aryl cyclic 1,3-dicarbonyls with a range of alkynes. In addition to diphenylacetylene, which provided **3a** in 84% yield, substrate **1a** underwent oxidative annulation with unsymmetrical alkyl/aryl alkynes (spiroindenes **3b** and **3c**), though 5.0 mol % of PEPPSI-IPr was required in these cases for reasonable results, and the yields were more modest due to the presence of unreacted **1a**. In these reactions, initial C–H functionalization resulted in C–C bond formation at the alkyl-substituted carbon of the alkyne. Spiroindene **3b** was formed as the sole regioisomer, whereas **3c** was formed as a 93:7 mixture of regioisomers that were inseparable by column chromatography.²⁶ Substitution at the phenyl group of the 1,3-dicarbonyl substrate with 4-methoxy or 4-carbomethoxy groups was also tolerated (spiroindenes **3d** and **3e**, respectively). The high selectivity of palladium catalysis for spiroindene formation was demonstrated by the reaction of a substrate **1d** containing a 3,5-dimethylphenyl group;

Chart 1. Palladium-Catalyzed Oxidative Annulations with Alkynes^a



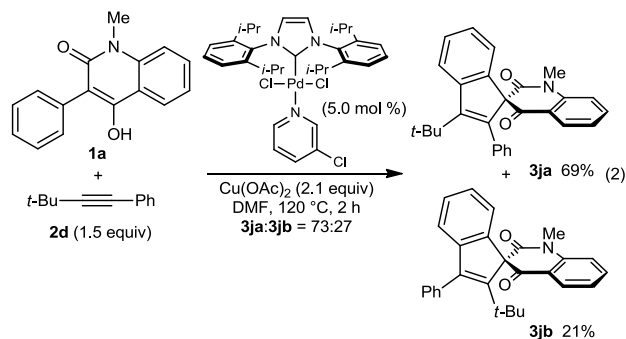
Substrates



^a Reactions were conducted using 0.50 mmol of **1**. Unless otherwise stated, cited yields are of pure, isolated material. ^b Using 5.0 mol % of PEPPSI-IPr and 2.0 equiv of the alkyne. ^c rr = Regioisomeric ratio as determined by ¹H NMR analysis of the unpurified reaction mixture. Product was isolated as a 93:7 inseparable mixture of regioisomers. ^d Product **3i** was of ca. 90% purity.

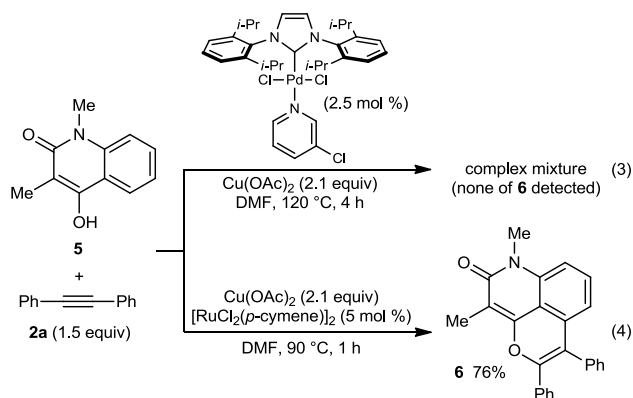
despite the increased steric hindrance of C–H functionalization resulting from the *m*-methyl substituents, this experiment provided spiroindene **3f** in 74% yield, with none of the alternative benzopyran detected in the product mixture. As expected, substitution at the benzene ring of the quinolin-2-one was tolerated (spiroindene **3g**). A methyl group on the nitrogen atom in the substrate is not necessary; substrate **1f** containing a free N–H bond also underwent oxidative annulation to give **3h** in 65% yield. However, the reaction of 4-hydroxy-3-phenylcoumarin (**1g**) with diphenylacetylene gave a complex mixture from which the only product that could be identified was spiroindene **3i**, which was isolated in only 21% yield and in ca. 90% purity. Attempted oxidative annulations of substrate **1a** with terminal alkynes such as phenylacetylene, trimethylsilylacetylene, or 1-hexyne were unsuccessful, and recovered material consisted of mainly unreacted **1a**, along with small quantities of byproducts.

A more demanding test of the preference for initial C–C bond formation at the alkyl-substituted carbon of the triple bond of alkyl/aryl alkynes was provided by the oxidative



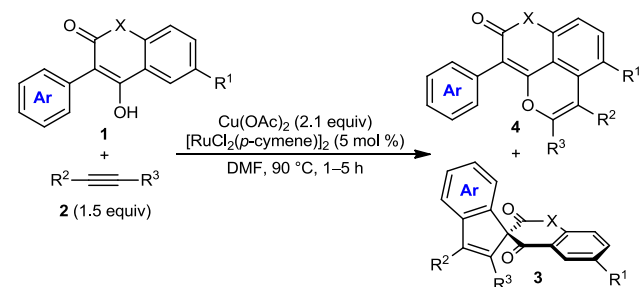
annulation of **1a** with alkyne **2d** containing a sterically demanding *t*-butyl group, which was expected to lead to a greater quantity of the alternative regioisomer (eq 2). Indeed, the alternative regioisomer **3jb** was obtained in 21% yield, though spiroindene **3ja** was still produced as the major regioisomer (69% yield).²¹ Despite the increased steric hindrance resulting from alkyne **2d**, the overall yield of this reaction (90%) was significantly higher than those obtained using other alkyl/aryl alkynes (Chart 1, spiroindenes **3b** and **3c**). The reasons for this observation are not clear at the present time.

Since the PEPPSI-IPr complex gives exclusive preference for spiroindene formation from 3-aryl-4-hydroxyquinolin-2-ones, the oxidative annulation of substrate **5**, from which spiroindene formation is not possible, was examined. In principle, **5** could result in the formation of a benzopyran. However, reaction of **5** with diphenylacetylene using the PEPPSI-IPr complex provided no evidence of benzopyran **6**, and recovered material consisted of a complex mixture of unidentified products. As expected, the same reaction conducted in the presence of [RuCl₂(*p*-cymene)]₂ in place of PEPPSI-Pr provided benzopyran **6** in good yield (eq 4).¹⁴



The oxidative annulation of various unsymmetrical 2-aryl cyclic 1,3-dicarbonyls with a range of alkynes was then conducted using the conditions of Table 1, entry 3 to examine the site-selectivity of the ruthenium-based catalyst system in greater detail (Table 2). These reactions provided benzopyrans **4** as the major products in 72–88% yield, along with small quantities of spiroindenes **3**. With unsymmetrical aryl/alkyl alkynes, the regioselectivity was high (entries 2 and 3).²¹ A 3,5-dimethylphenyl group in the substrate strongly disfavored the formation of the spiroindene **3f**, and benzopyran **4f** was isolated as the sole product in 88% yield (entry 6). A more stringent test of the selectivity for benzopyran formation was provided by the reaction of substrate **1e** containing a methyl substituent at the 6-position. As expected, the steric effect of this methyl group decreased the site-selectivity of C–H

Table 2. Ruthenium-Catalyzed Oxidative Annulations with Alkynes^a



entry	benzopyran	spiroindene
1	4a R = Ph, 88%	3a R = Ph, 8%
2	4b R = Me, 80%, 94:6 rr ^b	3k R = Me, 7%
3	4c R = <i>n</i> -Bu, 81%, 93:7 rr ^b	3b R = <i>n</i> -Bu, 2%
4	4d R = OMe, 86%	3d R = OMe, 6%
5	4e R = CO ₂ Me, 76%	3e R = CO ₂ Me, 8%
6	4f 88%	3f 0% (not detected)
7	4g 72%	3g 21%
8	4h X = NH, 0% ^c	3h X = NH, 0% ^c
9	4i X = O, 80%	3i X = O, 11%

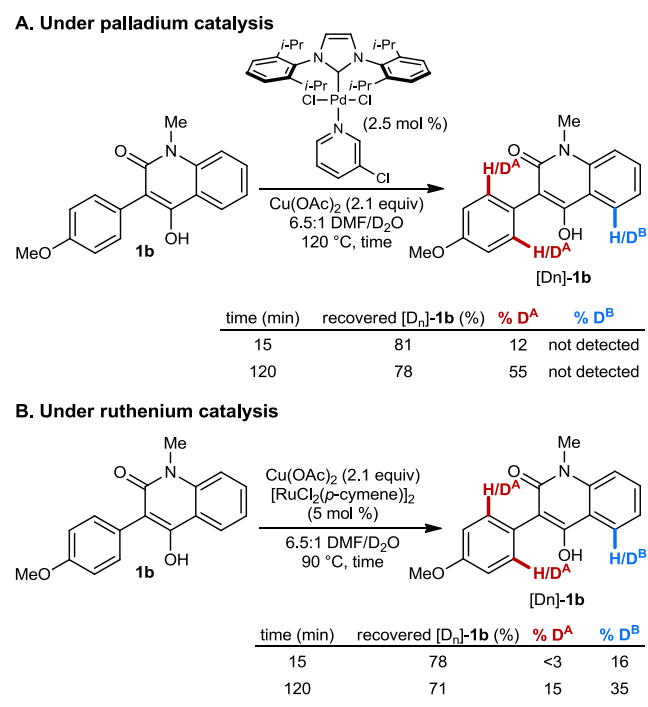
^a Reactions were conducted using 0.50 mmol of **1**. Cited yields are of pure, isolated material. ^b rr = Regioisomeric ratio as determined by ¹H NMR analysis of the unpurified reaction mixtures. ^c Reaction conducted at 120 °C for better solubility of **1f**. Recovered material was unreacted alkyne and unidentified byproducts.

functionalization, and this reaction gave benzopyran **4g** and spiroindene **3g** in 72% and 21% yield, respectively (entry 7). Although quinolin-2-one **1f** containing a free N–H bond was effective in the palladium-catalyzed formation of spiroindenes (Chart 1, product **3h**), this substrate was not competent in the

ruthenium-catalyzed oxidative annulation, and returned unreacted alkyne along with a complex mixture of unidentified products (entry 8).²⁷ In contrast, while 4-hydroxy-3-phenylcoumarin (**1g**) was poorly effective in the palladium-catalyzed synthesis of spiroindenes (Chart 1), this compound underwent smooth oxidative annulation with diphenylacetylene in the presence of [RuCl₂(*p*-cymene)]₂/Cu(OAc)₂ to give benzopyran **4i** in 80% yield and spiroindene **3i** in 11% yield (entry 9). No evidence of oxidative annulation products was observed in the reactions of substrate **1a** with terminal alkynes such as phenylacetylene, trimethylsilylacetylene, or 1-hexyne.

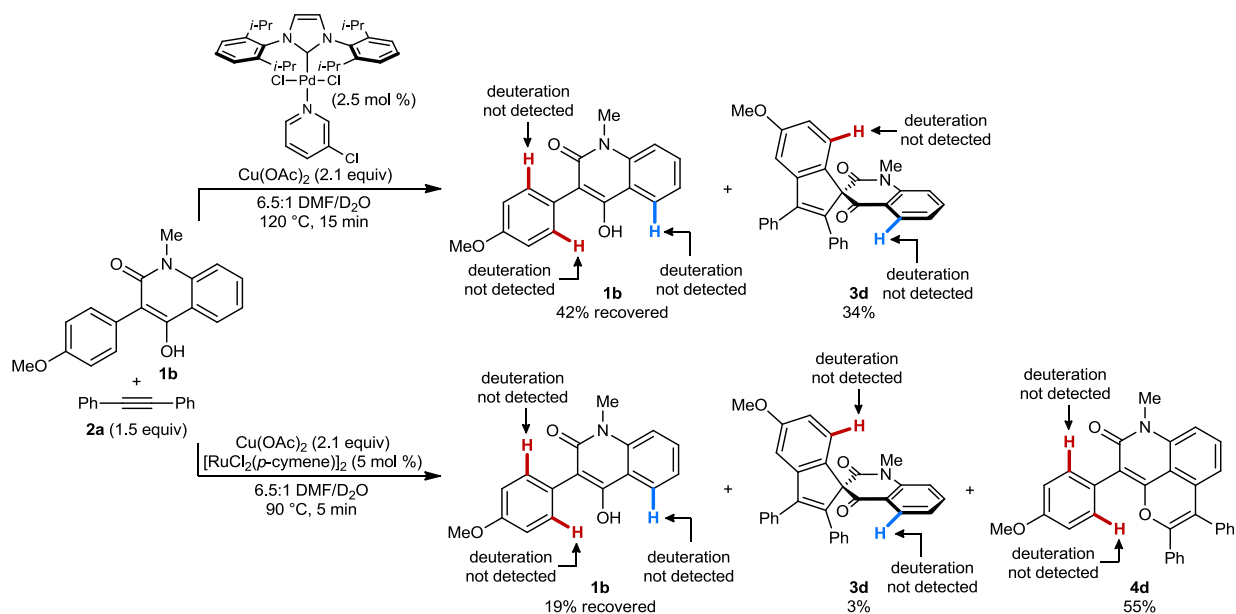
Deuteration Experiments. Deuteration experiments were then conducted to shed further light on these reactions. First, substrate **1b** was treated with PEPPSI-IPr under the conditions described in Chart 1 but with the omission of the alkyne and the inclusion of D₂O, for reaction times of 15 min and 2 h (Scheme 2A). These experiments led to recovered [D_n]-**1b** in which deuteration occurred *exclusively* at the 4-methoxyphenyl group (12% and 55% D, respectively). These results indicate that cyclopalladation is reversible in the absence of an alkyne, and the site of deuterium incorporation is consistent with the fact that the oxidative annulations presented in Chart 1 gave spiroindenes *exclusively*, with no trace of benzopyran products detected.

Scheme 2. H/D Scrambling Experiments of 1b in the Absence of an Alkyne



In contrast, an analogous experiment performed with [RuCl₂(*p*-cymene)]₂ at 90 °C for 15 min provided recovered [D_n]-**1b** in which appreciable deuteration (16% D) had occurred at the benzene ring of the quinolin-2-one, but had barely occurred at the 4-methoxyphenyl ring (Scheme 2B). Repeating this experiment for a longer duration of 2 h increased the level of deuterium incorporation at both sites (35% D at the benzene ring of the quinolin-2-one, and 15% D at the 4-methoxyphenyl ring). Again, these results are consistent with the results presented in Table 2 where benzopyrans were

Scheme 3. Oxidative Annulations of **1b** in the Presence of D₂O



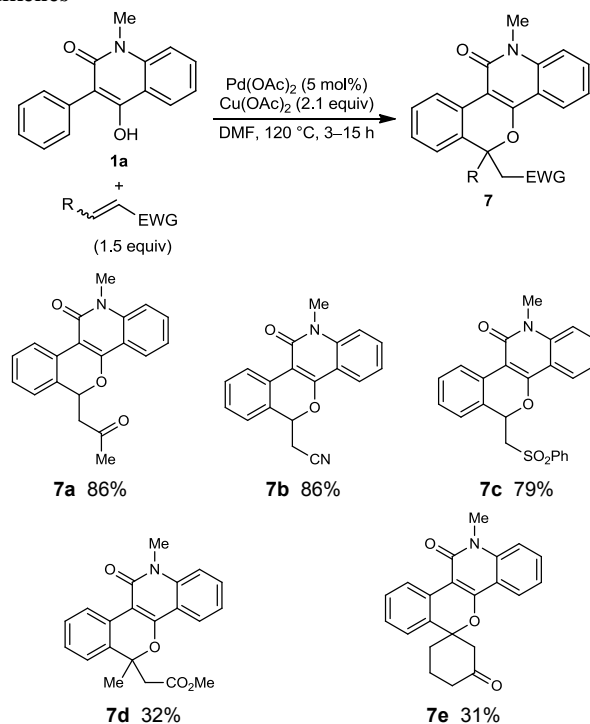
obtained as the major products, but where smaller quantities of spiroindenes were also formed.

The reasons behind the site-selectivities exhibited by the palladium- and ruthenium-based catalyst systems are not clear at the present time.²⁸ In principle, formation of the five-membered metallacycle **B** might be expected to be kinetically favored over the six-membered metallacycle **A** due to its smaller ring size (see Scheme 1), and the site-selectivity of the ruthenium catalyst system is consistent with this assumption. However, an explanation for the reluctance of palladium to form metallacycle **B** will require further investigation.

Next, oxidative annulations were conducted in the presence of D₂O (Scheme 3). A reaction of **1b** with diphenylacetylene using the PEPPSI-IPr pre-catalyst in 6.5/1 DMF/D₂O for 15 min provided recovered **1b** and spiroindene **3d** in 42% and 34% yield, respectively, in which no deuterium incorporation was detected in either compound. An analogous experiment carried out with [RuCl₂(*p*-cymene)]₂ for 5 min gave recovered **1b** in 19% yield, benzopyran **4d** in 55% yield, and spiroindene **3d** in 3% yield, in which deuterium incorporation was not detected in any of the compounds. The lack of deuterium incorporation in these experiments suggests that oxidative annulation is rapid, and that both cyclopalladation and cycloruthenation of **1b** are essentially irreversible in the presence of an alkyne.

Palladium- and Ruthenium-Catalyzed Oxidative Annulations with Alkenes. To ascertain whether the high site-selectivities obtained with palladium- and ruthenium-based pre-catalysts are maintained in other classes of oxidative C–H functionalizations, the annulation of **1a** with various alkenes was studied.^{12,29,30} Reaction of **1a** with methyl vinyl ketone, acrylonitrile, and phenyl vinyl sulfone in the presence of Pd(OAc)₂ (5 mol %) and Cu(OAc)₂ (2.1 equiv) in DMF at 120 °C provided benzopyrans **7a–7c**, respectively, in 79–86% yield with no trace of other products (Chart 2).^{12,29a} The oxidative annulations of **1a** with internal alkenes such as *trans*-methyl crotonate and 2-cyclohexenone were also successful to provide benzopyrans **7d** and **7e**, albeit in lower yields (32% and 31%, respectively).

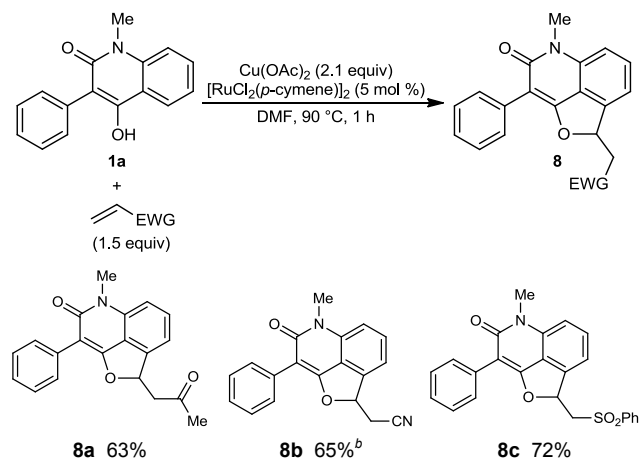
Chart 2. Palladium-Catalyzed Oxidative Annulations with Alkenes^a



^a Reactions were conducted using 0.50 mmol of **1a**. Cited yields are of isolated material.

Consistent with earlier results (Table 2), ruthenium-catalyzed oxidative annulations of **1a** with terminal alkenes led to C–H functionalization at the benzene ring of the quinolin-2-one to provide benzofurans **8a–8c** in 63–72% yield (Chart 3). These reactions were also highly site-selective, and in the reactions with methyl vinyl ketone and phenyl vinyl sulfone, only trace quantities (<5%) of the alternative benzopyran products were detected in the unpurified reaction

Chart 3. Ruthenium-Catalyzed Oxidative Annulations with Alkenes^a



^a Reactions were conducted using 0.50 mmol of **1a**. Cited yields are of isolated material. ^b This reaction also provided benzopyran **7b** in 5% isolated yield.

mixtures. In the case of acrylonitrile, which provided benzofuran **8b** in 65% yield, benzopyran **7b** was also isolated in 5% yield. In contrast with palladium catalysis (Chart 2), ruthenium catalysis was unsuccessful in the attempted oxidative annulations of **1a** with internal alkenes such as *trans*-methyl crotonate or 2-cyclohexenone, and no C–H alkenylation products were detected in these reactions.

CONCLUSION

The ability to transform common starting materials into different products in catalytic C–H functionalization reactions simply by altering the catalyst offers a broadly useful tool in the late-stage diversification of molecules and the generation of compound libraries.^{1a} In this study, the oxidative annulation of alkynes and alkenes with unsymmetrical 2-aryl cyclic 1,3-dicarbonyl compounds containing two distinct, non-adjacent sites for C–H bond functionalization has been achieved with high site-selectivity using palladium or ruthenium catalysis. Palladium catalysis enables the exclusive functionalization of a hydrogen atom five bonds away from the oxygen of the enol/enolate directing group in these substrates, leading to spiroindenes **3** or benzopyrans **7** from alkynes or electron-deficient terminal alkenes, respectively. In contrast, ruthenium catalysis mainly results in functionalization of a hydrogen atom four bonds away from the oxygen of the directing group, which produces benzopyrans **4** or benzofurans **8** from alkynes or electron-deficient terminal alkenes, respectively. Efforts to understand the origins of the differing selectivities exhibited by palladium- and ruthenium-based catalysts, along with developments in switchable, site-selective C–H functionalizations of more complex classes of substrates, are topics for future study in our laboratory.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, full spectroscopic data for all new compounds, and crystallographic data in cif format. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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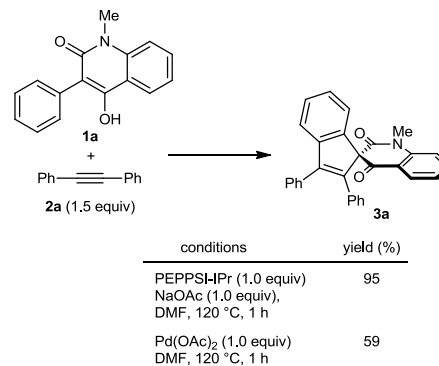
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