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

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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 annihilation 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. One important class of these reactions is the oxidative annihilation 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.

The development of corresponding processes for the synthesis of carbocyclic products would be highly valuable, and in this context, we recently reported the ruthenium-catalyzed oxidative annihilation of alkynes with 2-aryl cyclic-1,3-dicarbonyls or their enol tautomers (eq 1). These reactions proceed via sequential C(sp²)-H and C(sp³)-H functionalization to give spiroindenes in generally good yields. 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.

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

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(sp³)-H cleavage are now available; at the 3-aryl ring, and at the benzene ring of the quinolin-2-one. C–H cleavage at the former site (H¹) 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 (H¹) 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 catalysis and by the Ackermann group using ruthenium catalysis.
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 annihilation 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. 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. A greater understanding of the factors that influence switchable, site-selective C–H functionalizations, 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-dicarboxyl 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)] was found to favor the formation of benzopyran 4a in all cases (entries 1–4). Conditions employed in our previous study of spiroindene synthesis, using 2.5 mol % of [RuCl₂(p-cymene)] 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)] 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] was also a competent precatalyst, and like [RuCl₂(p-cymene)] favored the formation of benzopyran 4a (entries 5 and 6). The best result was obtained using 2.5 mol % of [RhCp*Cl₂] in DMF at 90 °C (entry 6). However, on the basis of the lower cost of [RuCl₂(p-cymene)] compared with [RhCp*Cl₂], 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, and these reactions provided spiroindene 3a as the sole product 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 palladium 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). 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 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.

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

<table>
<thead>
<tr>
<th>entry</th>
<th>[M]</th>
<th>mol %</th>
<th>solvent</th>
<th>temp (°C)</th>
<th>time (h)</th>
<th>yields (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[RuCl₂(p-cymene)]</td>
<td>2.5</td>
<td>dioxane</td>
<td>90</td>
<td>5</td>
<td>51</td>
</tr>
<tr>
<td>2</td>
<td>[RuCl₂(p-cymene)]</td>
<td>5</td>
<td>dioxane</td>
<td>90</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>3</td>
<td>[RuCl₂(p-cymene)]</td>
<td>5</td>
<td>DMF</td>
<td>90</td>
<td>5</td>
<td>87</td>
</tr>
<tr>
<td>4</td>
<td>[RuCl₂(p-cymene)]</td>
<td>2.5</td>
<td>DMF</td>
<td>120</td>
<td>5</td>
<td>86</td>
</tr>
<tr>
<td>5</td>
<td>[RhCp*Cl₂]</td>
<td>2.5</td>
<td>dioxane</td>
<td>120</td>
<td>5</td>
<td>30</td>
</tr>
<tr>
<td>6</td>
<td>[RhCp*Cl₂]</td>
<td>2.5</td>
<td>DMF</td>
<td>120</td>
<td>5</td>
<td>79</td>
</tr>
<tr>
<td>7</td>
<td>Pd(OAc)₂</td>
<td>2.5</td>
<td>DMF</td>
<td>120</td>
<td>1</td>
<td>76</td>
</tr>
<tr>
<td>8</td>
<td>PEPPSI-IPr</td>
<td>2.5</td>
<td>DMF</td>
<td>120</td>
<td>1</td>
<td>86</td>
</tr>
<tr>
<td>9</td>
<td>PEPPSI-IPr</td>
<td>2.5</td>
<td>DMF</td>
<td>120</td>
<td>2</td>
<td>87</td>
</tr>
<tr>
<td>10</td>
<td>PEPPSI-IPr</td>
<td>2.5</td>
<td>DMF</td>
<td>90</td>
<td>3</td>
<td>75</td>
</tr>
</tbody>
</table>

* Reactions were conducted using 0.25 mmol of 1a. 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 annihilation of spiroindene from the reaction of various unsymmetrical 2-aryl cyclic 1,3-dicarboxyls 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 3e), 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. Sporoindene 3b was formed as the sole regioisomer, whereas 3c was formed as a 93:7 mixture of regioisomers that were inseparable by column chromatography. Substitution at the phenyl group of the 1,3-dicarboxyl 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

- Reactions were conducted using 0.50 mmol of 1. Unless otherwise stated, cited yields are of pure, isolated material. Using 5.0 mol % of PEPPSI-IPr and 2.0 equiv of the alkyne, the regiosomeric ratio was determined by 1H NMR analysis of the unpurified reaction mixture. Product was isolated as a 93:7 inseparable mixture of regioisomers. 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 3j was obtained in 21% yield, though spiroindene 3ja was still produced as the major regioisomer (69% yield). 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 3e). The reasons for this observation are not clear at the present time.

Since the PEPPSI-IPr complex provides 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)], in place of PEPPSI-IPr provided benzopyran 6 in good yield (eq 4).

The oxidative annulation of various unsymmetrical 2-aryl cyclic 1,3-dicarboxyls 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). 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

Table 2. Ruthenium-Catalyzed Oxidative Annulations with Alkynes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Benzopyran</th>
<th>Spiroindene</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a R = Ph, 88%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4b R = Me, 80%, 94.6:8 r/r</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4c R = n-Bu, 81%, 93.7:8 r/r</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4d R = OMe, 86%</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>4e R = CO₂Me, 76%</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>4f 88%</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>4g 72%</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>4h X = NH, 9%</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>4i X = O, 80%</td>
<td></td>
</tr>
</tbody>
</table>

Reactions were conducted using 0.50 mmol of 1. Cited yields are of pure, isolated material. r/r = Regioisomeric ratio as determined by ¹H NMR analysis of the unpurified reaction mixtures. 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).

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(μ-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 [D₉]-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

A. Under palladium catalysis

B. Under ruthenium catalysis

In contrast, an analogous experiment performed with [RuCl₂(μ-cymene)]₂ at 90 °C for 15 min provided recovered [D₉]-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
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. 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 D$_2$O (Scheme 3). A reaction of 1b with diphenylacetylene using the PEPPSI-IPr precatalyst in 6.5/1 DMF/D$_2$O 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 [RuCl$_2$(p-cymene)]$_2$ for 5 min gave recovered 1b in 19% yield, benzozypran 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 precatalysts are maintained in other classes of oxidative C–H functionalizations, the annulation of 1a with various alkenes was studied.\textsuperscript{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).\textsuperscript{12,30} 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).

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*®

![Reaction Scheme]

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

mixtures. In the case of acrylonitrile, which provided benzo[4]furan 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-cyclohexene, 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. 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 hydrocarbon five bond 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 hydrocarbon atom four bonds away from the oxygen of the directing group, which produces benzopyrans 4 or benzo[4]furans 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.

REFERENCES

AUTHOR INFORMATION

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(25) Further confirmation of the beneficial effect of an N-heterocyclic carbene ligand was obtained from a comparison of the following experiments conducted using stoichiometric palladium in the absence of Cu(OAc)₂:

![Diagram of a reaction mechanism]

(26) Recrystallization of this 93:7 mixture of regioisomers gave a pure sample of 3e, the structure of which was confirmed by X-ray crystallography. See the Supporting Information for details.


(28) Attempts to isolate palladacycles or ruthenacycles from the cyclometallation of substrate 1a have been unsuccessful thus far.

