C–H Functionalization

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Functionalization of C_{sp^3}–H and C_{sp^2}–H Bonds: Synthesis of Spiroindenes by Enolate-Directed Ruthenium-Catalyzed Oxidative Annulation of Alkynes with 2-Aryl-1,3-dicarbonyl Compounds**

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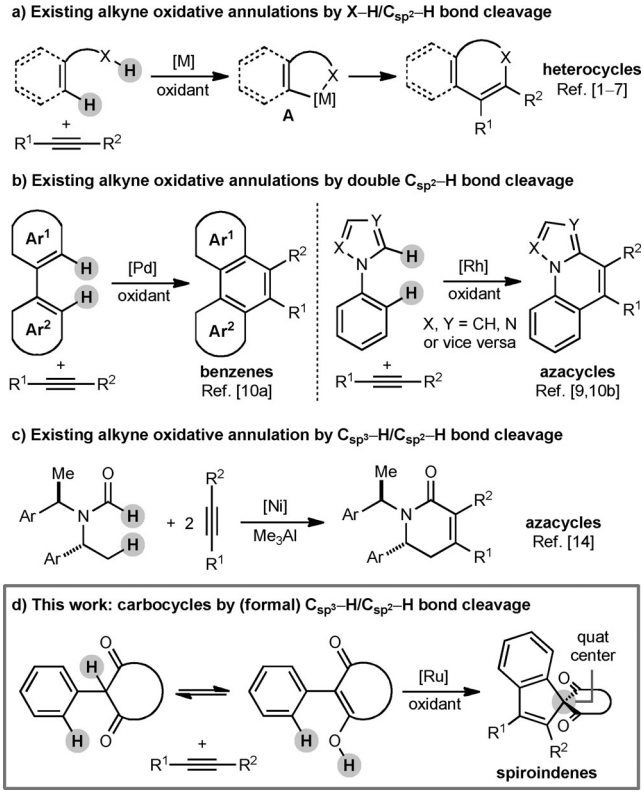
The metal-catalyzed oxidative annulation of alkynes with aryl or alkenyl substrates bearing various heteroatom-containing functional groups has proven to be a versatile, efficient, and atom-economic strategy to access a range of valuable heterocyclic products.[1–7] These processes generally rely upon coordination of the metal center to the heteroatom-containing functional group, which directs site selective C_{sp^2}–H bond cleavage[8] to form the metallacycle **A** (Scheme 1 a). Coordination and migratory insertion of the alkyne and subsequent C–X (X = heteroatom) reductive elimination then forms the heterocyclic product.

These alkyne oxidative annulations have been complemented by variants that result in the functionalization of two C_{sp^2}–H bonds, with[9] or without[10] the assistance of directing groups (Scheme 1 b).[11,12] While these reactions are effective in forming aromatic carbo- and azacycles, the scope and utility of the general process would be considerably enhanced if variants involving the functionalization of C_{sp^3}–H bonds[3j,13] could be developed, thus resulting in partially saturated cyclic products. However, progress in this area has been limited. To our knowledge, the only existing report comes from Nakao, Hiyama and co-workers, who recently described the oxidative annulation of formamides with alkynes, in which an extra equivalent of alkyne acts as the stoichiometric oxidant (Scheme 1 c).[14]

Herein, we report a new mode of catalytic alkyne oxidative annulation involving the (formal) functionalization of one C_{sp^3}–H bond and one C_{sp^2}–H bond (Scheme 1 d). This ruthenium-catalyzed process[15] results in the formation of indenes, which are important structures in various biologically active compounds[16] and functional materials.[17] A notable feature of this process is the formation of an all-carbon quaternary center, which has not been described previously in alkyne oxidative annulations.



Scheme 1. a)–d) Metal-catalyzed oxidative annulation of alkynes.

At the outset of this work, we hypothesized that α-arylcarbonyl compounds might be suitable substrates for alkyne oxidative annulations by virtue of the acidic nature of the α protons, that is, deprotonation would generate an enolate which could serve as an efficient directing group for C_{sp^2}–H bond cleavage. 2-Aryl cyclic 1,3-dicarbonyl compounds were selected for investigation on the basis of their high acidity and the permanent close proximity of the aryl and carbonyl groups. This latter feature renders these substrates conformationally predisposed for cyclometallation, thus forming a six-membered metallacycle in readiness for migratory insertion of the alkyne and spiroindene formation.

2-Aryl-1,3-diketones, which exist predominantly in the enol tautomer, were investigated first, and we began with a study of the reaction of 3-hydroxy-2-phenyl-2-cyclohexenone (**1a**) with 1-phenyl-1-propyne (**2a**; Table 1). The

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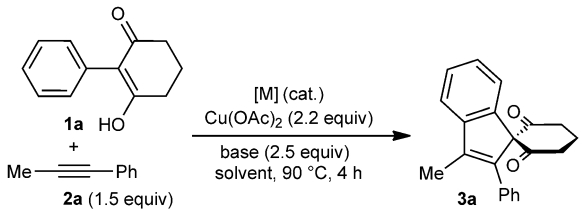
Table 1: Optimization of reaction conditions for the synthesis of **3a**.[a]



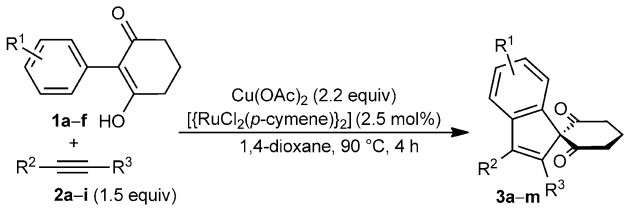
Entry	[M]	mol%	Base	Solvent	Yield [%][b]
1	$[\{RuCl_2(p\text{-cymene})\}_2]$	2.5	K_2CO_3	*t*AmOH	60
2	$[\{RuCl_2(p\text{-cymene})\}_2]$	2.5	K_2CO_3	THF	55
3	$[\{RuCl_2(p\text{-cymene})\}_2]$	2.5	K_2CO_3	1,4-dioxane	62
4	$[\{RuCl_2(p\text{-cymene})\}_2]$	2.5	–	1,4-dioxane	80
5	$[\{RuCl_2(p\text{-cymene})\}_2]$	2.5	–	DMF	15
6	$Pd(OAc)_2$	5	–	1,4-dioxane	<5
7	$Pd(OAc)_2$	5	K_2CO_3	1,4-dioxane	<5
8	$[\{RhCp^*Cl_2\}_2]$	2.5	K_2CO_3	1,4-dioxane	74
9	$[\{RhCp^*Cl_2\}_2]$	2.5	–	1,4-dioxane	88

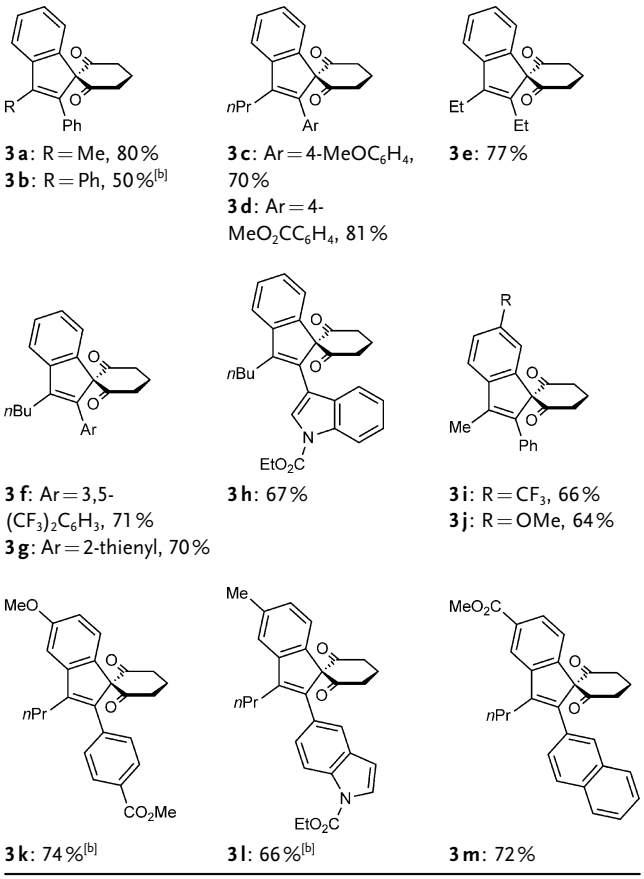
[a] Reactions were conducted using 0.25 mmol of **1a**. [b] Yield of isolated compounds. Cp* = C_5Me_5, DMF = *N*,*N*′-dimethylformamide, *t*Am = *tert*-amyl, THF = tetrahydrofuran.

reactions were conducted at 90 °C and $Cu(OAc)_2$ (2.2 equiv) was employed as the stoichiometric oxidant. Although rhodium, ruthenium, and palladium precatalysts have proven to be highly effective in a range of oxidative annulations of alkynes,[1–5,9,10] the ruthenium complex $[\{RuCl_2(p\text{-cymene})\}_2]$ (2.5 mol%) was examined first on the basis of its much lower cost compared with rhodium and palladium complexes. In the presence of K_2CO_3 (2.5 equiv), we were pleased to find that successful formation of the spiroindene **3a** occurred in a variety of solvents, (Table 1, entries 1–3). Consistent with literature precedent,[4] the reactions were highly regioselective, with initial C–C bond formation occurring exclusively at the methyl-substituted carbon atom of the alkyne.[18] Subsequently, K_2CO_3 was found to be unnecessary. In 1,4-dioxane as the solvent, the yield of **3a** increased to 80% in the absence of K_2CO_3 (Table 1, entry 4) whereas DMF provided inferior results (Table 1, entry 5). Although $Pd(OAc)_2$ proved to be totally ineffective (Table 1, entries 6 and 7), the Rh^{III} complex $[\{RhCp^*Cl_2\}_2]$ provided an 88% yield of **3a** in the absence of K_2CO_3 (Table 1, entry 9). Although $[\{RhCp^*Cl_2\}_2]$ provided the highest yield of **2a**, $[\{RuCl_2(p\text{-cymene})\}_2]$ was selected for further experimentation on the basis of its lower cost.

An assessment of the reaction scope was conducted by varying the alkyne, and the aryl group of the 3-hydroxy-2-cyclohexenone (Table 2). These experiments revealed that the process demonstrates good generality. In certain cases, the inclusion of K_2CO_3 (2.5 equivalents) provided higher yields (products **3b**, **3k**, and **3l**).[19] Oxidative annulation occurred smoothly with various alkyl/(hetero)aryl-substituted alkynes. Again, regioselectivity was high with unsymmetrical alkynes, with initial C–C bond formation occurring at the alkyne carbon atom bearing the alkyl substituent.[18] With respect to the alkyne substituents, phenyl rings containing methoxy, ester, or trifluoromethyl groups were tolerated (products **3c**, **3d**, and **3f**), as was a 2-naphthyl group (product **3m**).

Table 2: Ruthenium-catalyzed oxidative annulation of various alkynes with a range of 2-aryl-3-hydroxy-2-cyclohexenones.[a]





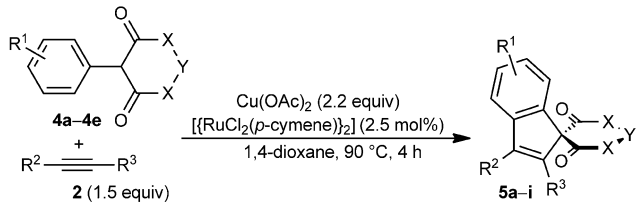
[a] Reactions were conducted using 0.50 mmol of **1a–f**. Cited yields are of the isolated material. [b] Reactions conducted with the addition of K_2CO_3 (2.5 equiv).

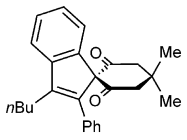
Heteroarenes on the alkyne, such as 2-thienyl (product **3g**) or indoles (products **3h** and **3l**) were also tolerated. However, terminal alkynes were unsuitable substrates, and gave complex mixtures of products.

Regarding the phenyl group of the 3-hydroxy-2-cyclohexenone, substrates containing *p*-methoxy, *p*-methyl, or *p*-carbomethoxy groups underwent efficient reaction (products **3k–m**). With *m*-substituted phenyl groups, C_{sp^2}–H functionalization occurred exclusively at the least sterically encumbered site (products **3i** and **3j**).[20] The high site selectivity observed in the formation of **3j** is notable, given that mixtures of isomers were formed when substrates containing *m*-methoxyphenyl groups were employed in related reactions.[4a,c,d] We found substrates containing *o*-substituted phenyl groups were unreactive.

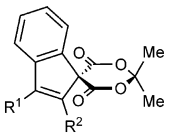
Table 3 presents the results of experiments where the 2-aryl cyclic 1,3-dicarbonyl substrate was varied. Again, a wide

Table 3: Ruthenium-catalyzed oxidative annulation of various alkynes with a range of 2-aryl cyclic 1,3-dicarbonyl compounds.[a]

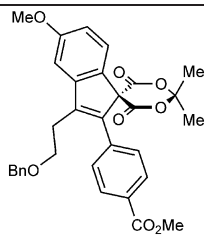




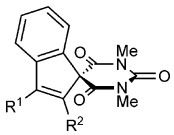
5a: 76%



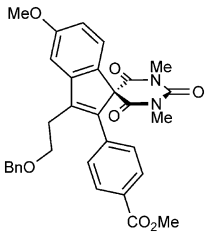
5b: R^1, R^2 = Me, Ph, 54%[b]
5c: $R^1 = R^2$ = Et, 48%[b]



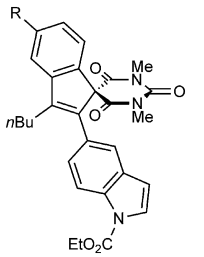
5d: 59%[b]



5e: R^1, R^2 = Me, Ph, 76%
5f: $R^1 = R^2$ = Et, 75%



5g: 84%

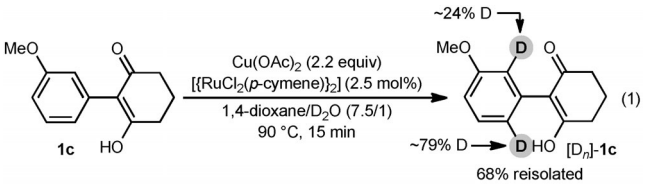


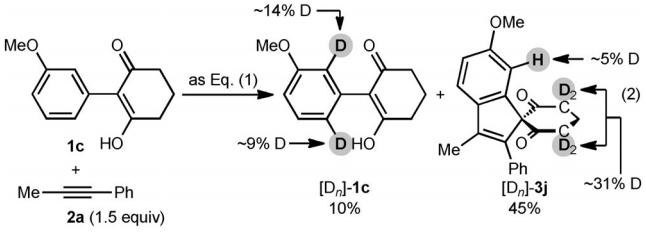
5h: R = H, 80%
5i: R = OMe, 73%

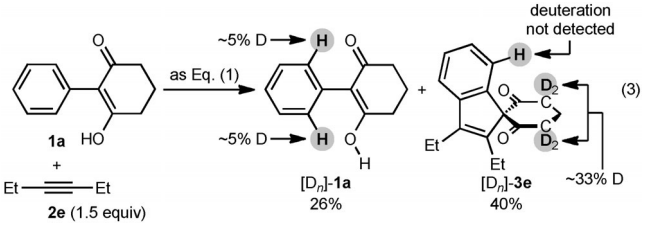
[a] Reactions were conducted using 0.50 mmol of **4a**–**e**. Cited yields are of the isolated material. [b] Reactions conducted with the addition of K_2CO_3 (2.5 equiv).

range of unsymmetrical alkynes were tolerated, and the reactions were highly regioselective. While successful formation of the product **5a** was not surprising given the results presented in Table 2, we were pleased to find that a range of Meldrum's acid derivatives containing various 2-aryl substituents (which exist predominantly in their β-dicarbonyl form rather than the enol form) also underwent annulation (products **5b**–**d**). In these cases, the presence of K_2CO_3 (2.5 equiv) was required to obtain the products in acceptable yields (48–59%).[19] Barbituric acid derivatives, which also exist in the β-dicarbonyl form, were also found to be effective in this process (products **5e**–**i** formed in 73–80% yield). Interestingly, substrates containing only one carbonyl group, such as 2-phenylcyclohexanone, do not undergo oxidative annulation under these conditions. Also, acyclic substrates such as diethyl phenylmalonate were unreactive.

To gain insight into the mechanism and regioselectivity of these reactions, deuteration experiments were carried out. First, the substrate **1c** was subjected to the standard reaction conditions with the inclusion of D_2O, but in the absence of alkyne [Eq. (1)]. After only 15 minutes, the recovered **1c** contained a significant amount of deuterium (ca. 79%) at the eventual site of spiroindene formation, as expected. Deuteration was also observed at the more sterically hindered site, albeit to a lower extent (ca. 24%). This experiment suggests that in the presence of D_2O and the absence of an alkyne, cycloruthenation is rapid, reversible, and faster at the more sterically accessible site. The recovery was relatively modest (68% yield) because of competitive substrate decomposition.



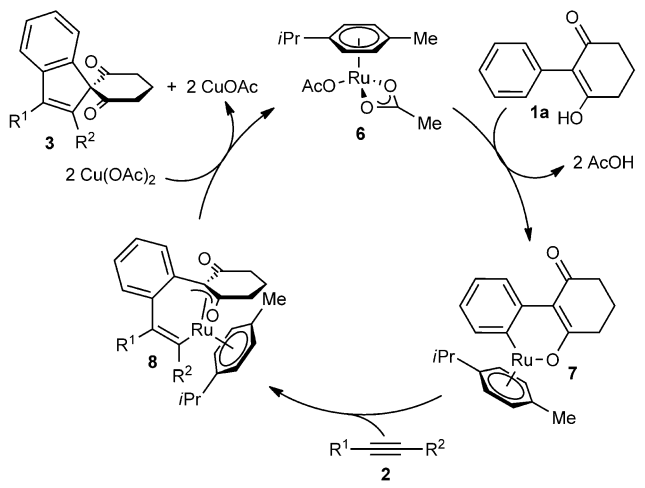




Repeating this experiment in the presence of the alkyne **2a** gave the spiroindene [D_n]-**3j** (45% yield) that contained minimal (ca. 5%) deuteration at the indene, but was partially deuterated in the cyclohexane [Eq. (2)].[21] In addition, the recovered starting material was partially deuterated. These observations are consistent with cycloruthenation being partially reversible in the presence of an alkyne. Slightly higher deuterium incorporation was observed at the more hindered site of [D_n]-**1c** obtained from the reaction in Equation (2), which is in contrast with [D_n]-**1c** obtained from the reaction in Equation (1). This outcome is consistent with migratory insertion of the alkyne being more rapid with the ruthenacycle derived from functionalization at the least hindered site of **1c**, thus depleting deuterium at this site preferentially.

Finally, cycloruthenation was found to be largely irreversible in the reaction of **1a** with **2e**, as evidenced by a reaction run to partial completion in the presence of D_2O, in which no deuteration was detected at the indene of the annulation product, and only minimal deuteration (ca. 5% at each site) was observed in recovered [D_n]-**1a** [Eq. (3)].

In line with catalytic cycles put forth for related processes,[4] a possible mechanism for these oxidative annulations is illustrated in Scheme 2.[22] Under the reaction conditions, deprotonation of the cyclic 1,3-dicarbonyl substrate generates an enolate, which is then able to direct cycloruthenation with complex **6** to form the six-membered ruthenacycle **7**. It should



Scheme 2. Possible catalytic cycle for spiroindene formation.

be noted that with one exception,[4e] all ruthenium-catalyzed alkyne oxidative annulations reported to date involve initial cyclometallation to form five-membered ruthenacycles. Coordination and migratory insertion of the alkyne **2** with **7** then occurs with preference for C–C bond formation at the alkyne carbon atom bearing the alkyl substituent to form the second ruthenacycle **8**, which although depicted as an oxa-π-allylruthenium species, could exist in the O- or C-bound forms.[23] Finally, C–C reductive elimination of **8**, with concomitant Cu^{II}-promoted oxidation of Ru^0 back to the Ru^{II} species **6**, releases the product **3**.[4k]

In conclusion, we have developed metal-catalyzed oxidative annulations of alkynes involving (formal) functionalization of C_{sp^3}–H and C_{sp^2}–H bonds, thus resulting in products containing all-carbon quaternary centers. Under the action of ruthenium catalysis, the process provides a diverse range of spiroindenes with high levels of regioselectivity. The development of further metal-catalyzed oxidative annulations, including asymmetric variants, is continuing in our group.

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Keywords: annulation · C–H functionalization · oxidation · ruthenium · synthetic methods

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c) K. Tsuchikama, M. Kasagawa, K. Endo, T. Shibata, *Synlett* **2010**, 97 – 100; d) Z.-M. Sun, S.-P. Chen, P. Zhao, *Chem. Eur. J.* **2010**, *16*, 2619 – 2627; e) F. W. Patureau, T. Besset, N. Kuhl, F. Glorius, *J. Am. Chem. Soc.* **2011**, *133*, 2154 – 2156; f) K. Muralirajan, K. Parthasarathy, C.-H. Cheng, *Angew. Chem.* **2011**, *123*, 4255 – 4258; *Angew. Chem. Int. Ed.* **2011**, *50*, 4169 – 4172; g) D. N. Tran, N. Cramer, *Angew. Chem.* **2011**, *123*, 11294 – 11298; *Angew. Chem. Int. Ed.* **2011**, *50*, 11098 – 11102; h) B.-J. Li, H.-Y. Wang, Q.-L. Zhu, Z.-J. Shi, *Angew. Chem.* **2012**, *124*, 4014 – 4018; *Angew. Chem. Int. Ed.* **2012**, *51*, 3948 – 3952.

[13] For the synthesis of pyrroles by oxidative annulation of enamines with alkynes, involving C_{sp^3}–H functionalization, see: S. Rakshit, F. W. Patureau, F. Glorius, *J. Am. Chem. Soc.* **2010**, *132*, 9585 – 9587.

[14] Y. Nakao, E. Morita, H. Idei, T. Hiyama, *J. Am. Chem. Soc.* **2011**, *133*, 3264 – 3267.

[15] For Reviews covering ruthenium-catalyzed C–H functionalization by direct arylation or alkylation, see: a) L. Ackermann, R. Vicente, *Top. Curr. Chem.* **2010**, *292*, 211 – 229; b) L. Ackermann, *Chem. Commun.* **2010**, *46*, 4866 – 4877; c) P. B. Arockiam, C. Bruneau, P. H. Dixneuf, *Chem. Rev.* **2012**, DOI: 10.1021/cr300153j.

[16] a) Y. Ishiguro, K. Okamoto, F. Ojima, Y. Sonoda, *Chem. Lett.* **1993**, 1139 – 1140; b) I. M. Karaguni, K. H. Glusenkamp, A. Langerak, C. Geisen, V. Ullrich, G. Winde, T. Möröy, O. Müller, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 709 – 713; c) O. Müller, E. Gourzoulidou, M. Carpintero, I. M. Karaguni, A. Langerak, C. Herrmann, T. Möröy, L. Klein-Hitpass, H. Waldmann, *Angew. Chem.* **2004**, *116*, 456 – 460; *Angew. Chem. Int. Ed.* **2004**, *43*, 450 – 454.

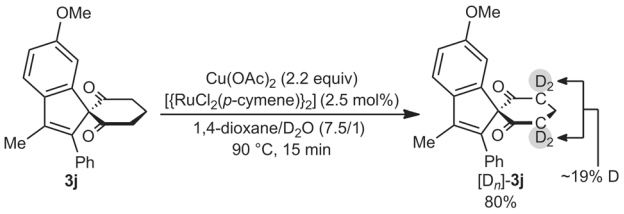
[17] a) U. Akbulut, A. Khurshid, B. Hacioglu, L. Toppare, *Polymer* **1990**, *31*, 1343 – 1346; b) J. Barberá, O. A. Rakitin, M. B. Ros, T. Torroba, *Angew. Chem.* **1998**, *110*, 308 – 312; *Angew. Chem. Int. Ed.* **1998**, *37*, 296 – 299; c) J. T. Yang, M. V. Lakshmikantham, M. P. Cava, D. Lorcy, J. R. Bethelot, *J. Org. Chem.* **2000**, *65*, 6739 – 6742.

[18] The origin of this regioselectivity is not clear at the present time.

[19] This process generates two equivalents of AcOH (see Scheme 2), and some of the 2-aryl cyclic 1,3-dicarbonyl substrates are sensitive towards acid-catalyzed decomposition under the reaction conditions. Presumably, the presence of K_2CO_3 reduces the rate of this decomposition, thus leading to, in certain cases, higher yields of the spiroindene products.

[20] The structures of the spiroindenes **3i** and **3j** were confirmed by X-ray crystallography. See the Supporting Information for details. CCDC 894550 (**3i**) and CCDC 897478 (**3j**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[21] Deuteration at the cyclohexane ring most likely occurs by reversible enolization after the formation of the spiroindene **3j**, as evidenced by the following experiment:



[22] For an alternative mechanism, see the Supporting Information.

[23] An intermediate similar to ruthenacycle **8** has been proposed previously in the palladium-catalyzed synthesis of phenanthrone derivatives by dual C–H activation: P. Gandeepan, K. Parthasarathy, C.-H. Cheng, *J. Am. Chem. Soc.* **2010**, *132*, 8569 – 8571.

