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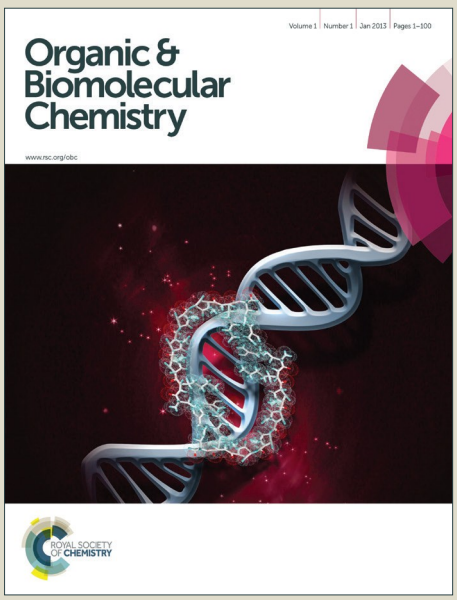

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ARTICLE TYPE

Rh(III)-Catalyzed Direct C–H/C–H Cross-Coupling of Quinones with Arenes Assisted by Directing Group: Identification of Carbazole Quinones as GSKβ Inhibitors

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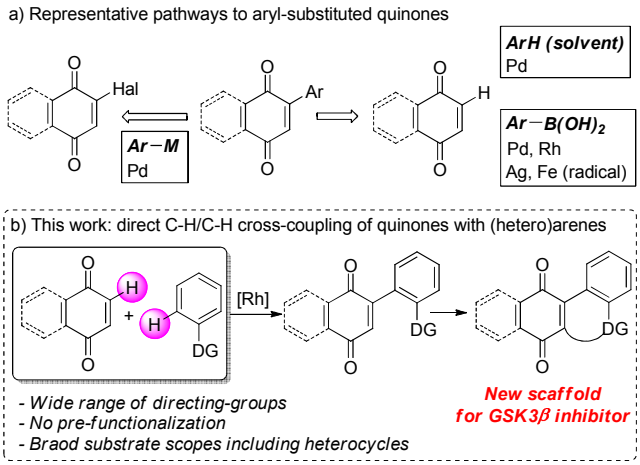
Rh-catalyzed direct C–H/C–H cross-coupling reaction of various (hetero)arenes with quinones was developed. This protocol has a broad range of both quinone and arene substrates, and a wide range of directing groups were effective for this reaction, affording structurally diverse aryl-substituted quinones with high synthetic utility. Moreover, the present synthetic route allowed for the rapid construction of carbazole quinone moiety that was identified as a new inhibitor scaffold for GSKβ.

Introduction

Quinones are ubiquitous motifs found in a plethora of natural and synthetic compounds.[1] Aryl-substituted quinones have been extensively investigated due to their broad range of biological,[2] electron-transport,[3] and colorimetric properties.[4] Despite the significant role of quinones in organic, pharmaceutical and materials chemistry, a direct transition metal-catalyzed C–H bond functionalization[5] of quinones remains a great challenge in synthetic chemistry due to the unique electronic properties of the structures.[1a] For example, the reoxidation step is often necessary to revert to a quinone oxidation state. The ability of quinones to coordinate with transition metals can also pose challenges to this type of cross-coupling reaction.[6,7] These difficulties have prompted pre-functionalization approaches, followed by either Pd-catalyzed cross-coupling[8] or through a radical pathway.[9] Another approach is based on the Pd(II)-catalyzed direct coupling of benzoquinone with an unactivated arene; however, the arene coupling partner should be used as a solvent, or very limited success has been observed only with special electron-rich substrates.[10,11]

Recently, notable advances were made in the direct C–H arylation of quinones using arylboranes as a coupling partner (Scheme 1a). In the presence of palladium or rhodium catalytic systems, various aryl-substituted quinone derivatives were successfully prepared by cross-coupling of quinones with arylboranes.[12] Baran's group reported a practical method for the cross-coupling reaction of quinones with arylboronic acids under silver catalytic systems.[13] Related reactions were achieved via iron-mediated quinone arylation with arylboranes.[14] Although these are promising approaches for preparing aryl-substituted quinones, the preparation of borylated (hetero)arenes as the pre-functionalized starting materials is often difficult due to chemo- and regio-selectivity issues. In this context, a more general method for direct and selective C–H/C–H cross-coupling reaction of quinones with arenes appears to be an attractive alternative for constructing structurally diverse aryl-substituted quinones.



Scheme 1 Overall reaction scheme for the preparation of aryl-substituted quinones

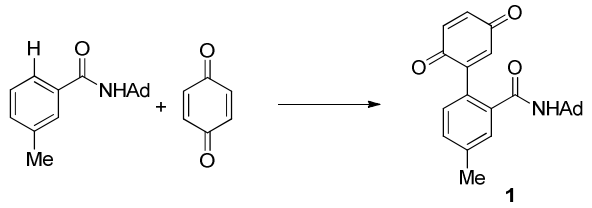
Several quinones that containing functionalized aryl groups have shown anticancer activity,[15] although the molecular anticancer mechanisms remain elusive. Our docking simulation studies indicate that quinones bearing an *ortho*-substituted aryl ring can fit into the ATP binding site of kinases. Based on the observations, we hypothesized that the anticancer activity of aryl-substituted quinones could be attributed to inhibiting the cancer-related kinases. The C–H activation approaches enable straightforward access to new chemical space, streamlining the drug-discovery process.[16] Based on our ongoing efforts to construct quinone-focused chemical libraries in order to identify novel classes of kinase inhibitors, we were particularly interested in exploring a direct C–H/C–H cross-coupling approach to avoid pre-functionalizing any of coupling partners. In this regard, we envisioned that the C–H activation of (hetero)arenes bearing a proper directing group[17] could readily be applied to the direct C–H/C–H cross-coupling of quinones with arenes. During these investigations, we established an efficient and selective Rh catalytic protocol for accessing diverse quinones that bear a

functionalized (hetero)aryl unit. Furthermore, synthesized carbazole quinones were found to be potent GSKβ (glycogen synthase kinase 3 beta) inhibitors by extensive biological evaluations, and docking models of carbazole quinones bound to GSKβ were studied to understand the structural properties of binding modes.

Results and discussion

To test the feasibility of this approach, we began by investigating the reactivity of *N*-adamantyl benzamide and benzoquinone as model substrates. Our initial attempts at benzoquinone C–H arylation were not successful with representative catalytic systems, including Pd(II), [Ru(*p*-cymene)Cl_2]$_2$ and [IrCp*Cl_2]$_2$, which are known to facilitate oxidative cross-coupling reactions.[18] To our delight, the use of a cationic rhodium catalyst, generated in situ by adding $AgSbF_6$ to [RhCp*Cl_2]$_2$ was found to initiate the cross-coupling reaction to afford the desired product **1** but only in 6% yield (Table 1, entry 1) (entry1, Table 1). Among the various oxidants screened, AgOAc was the most efficient. The solvent choice was also critical for the coupling efficiency, and acetone gave improved results with minimal by-product formation. When the reaction was carried out in the presence of $AgSbF_6$ (2 equiv) without AgOAc, no reaction occurred, indicating the crucial role of counteranion in the Rh-catalyzed cross-coupling reaction. Under the optimized reaction conditions, the cross-coupling reaction of benzamide (1 equiv) with benzoquinone (2 equiv) in the presence of [RhCp*Cl_2]$_2$ (5 mol%), $AgSbF_6$ (20 mol%) and AgOAc (2 equiv) in acetone at 60 °C, proceeded to provide the best isolated yield of 93% (entry10, Table 1).

Table 1 Optimization studies.[a]



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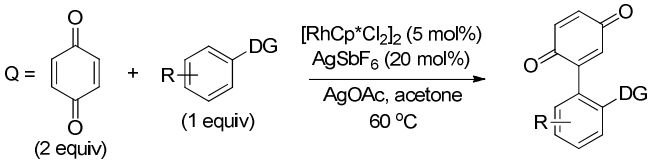
entry	catalyst (mol%)	additive (20 mol%)	oxidant (2 equiv)	solvent	yield[b] (%)
1	[RhCp*Cl_2]$_2$ (5)	$AgSbF_6$	AgOAc	1,2-DCE	6
2	[RhCp*Cl_2]$_2$ (5)	$AgSbF_6$	AgOAc	1,4-dioxane	28
3	[RhCp*Cl_2]$_2$ (5)	$AgSbF_6$	$Cu(OAc)_2$	acetone	22
4	[RhCp*Cl_2]$_2$ (5)	$AgSbF_6$	Ag_2CO_3	acetone	8
5	[RhCp*Cl_2]$_2$ (5)	$AgSbF_6$	Ag_2O	acetone	78
6	[RhCp*$(MeCN)_3$] [SbF_6] (10)	-	AgOAc	acetone	75
7	[RhCp*Cl_2]$_2$ (5)	$AgPF_6$	AgOAc	acetone	28
8	[RhCp*Cl_2]$_2$ (5)	$AgNTf_2$	AgOAc	acetone	83
9[c]	[RhCp*Cl_2]$_2$ (5)	$AgSbF_6$	AgOAc	acetone	71
10	[RhCp*Cl_2]$_2$ (5)	$AgSbF_6$	AgOAc	acetone	93

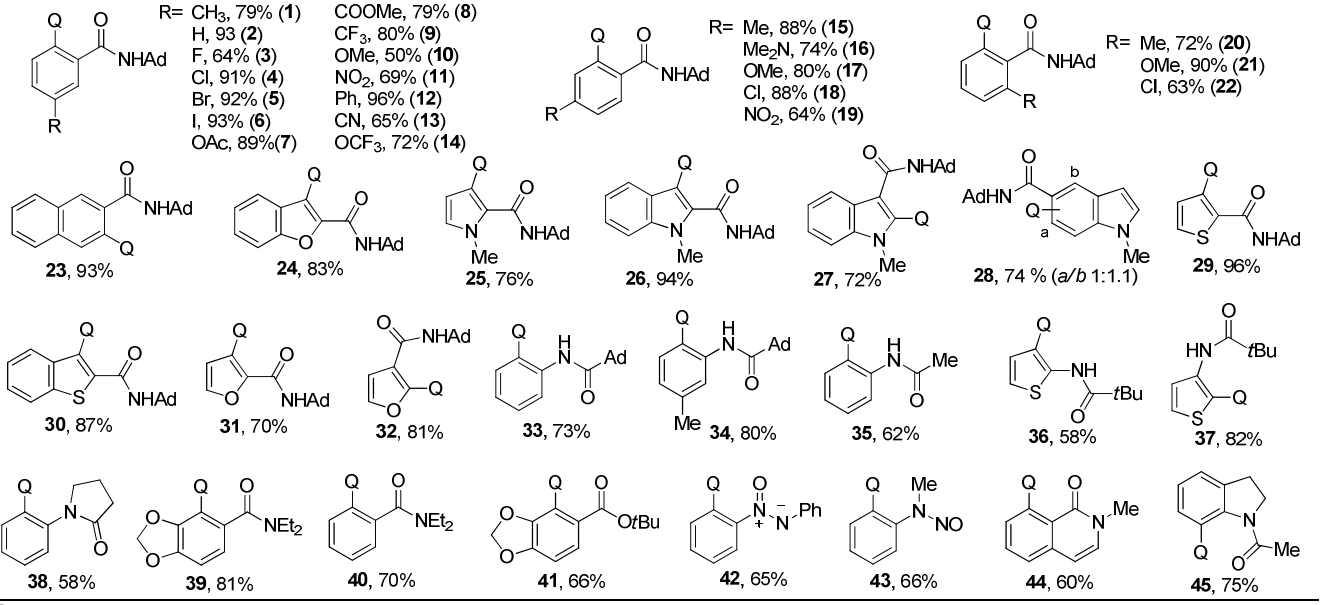
[a]Reactions were conducted with benzamide (0.1 mmol), benzoquinone (0.2 mmol), catalyst, oxidant, and solvent (0.35 mL) at 60 °C for 1 h. [b]Isolated yields. [c]Reaction was conducted at 80 °C.

Given this new method, the scope of various (hetero)arene coupling partners with benzoquinone was investigated (Table 2). In general, we observed that variation at the (hetero)arene did not significantly affect the reaction efficiency. Arenes possessing a *meta*-substituent underwent oxidative cross-coupling only at the sterically more accessible C–H bond. Notably, bromo (**5**) and iodo (**6**) groups were compatible under these reaction conditions, resulting in the isolation of synthetically versatile products for further manipulation. Additionally, various other functional groups that are commonly encountered in organic synthesis were tolerated well, such as acetoxy (**7**), ester (**8**), and phenyl groups (**12**). A broad range of electronic properties were also tolerated, from electron- donating methoxy (**10**) to electron-withdrawing trifluoromethyl (**9**), nitro (**11**), cyano (**13**), and trifluoromethoxy (**14**) groups. Both *para*- and *ortho*-substituted benzamide reactions proceeded well, and the corresponding products were obtained in good to excellent yields (**15**-**22**). The substrate 2-naphthamide was also suitable for this transformation, and benzoquinone was added to the less hindered position to give **23** in good yield. Considering the frequency of heterocyclic motifs within biologically active molecules, we turned our attention to heteroarene substrates. The utility of the present method was further broadened by cross-coupling of a wide range of heteroarenes, including benzofuran (**24**), pyrrole (**25**), indole (**26**-**28**), thiophene (**29**), benzothiophene (**30**), furan (**31**-**32**), and (Table 1). It is noteworthy that the directing group was used as a key component in guiding the desired reaction sites, regardless of the electronic nature of the heteroarenes. Subsequently, the scope of directing groups was investigated because the directing groups could be readily converted into various useful functional groups, thus providing new opportunities in pharmaceutical and materials chemistry. Significantly, (hetero)arene coupling partners with various directing groups, such as anilides (**34**-**37**), lactam (**38**), amides (**39**-**40**), ester (**41**), azoxy (**42**), and *N*-nitroso (**43**), reacted well with benzoquinone to afford the desired products in moderate to good yields under optimized conditions. Furthermore, the isoquinolinone (**44**) and indoline (**45**) moieties were also effective directing groups for facilitating the desired coupling reaction with benzoquinone.

Next, a broad range of quinone substrates were further investigated in order to extend the utility of this methodology (Table 3). Substituted benzoquinones underwent the cross-coupling reaction without difficulty to afford the desired arylated product under the optimized conditions. The regioselectivity dependence on the substituent was observable from the electronic nature of substituent and the different coordination sites. For example, a chelation event between the Rh(III) and methoxy and carbonyl groups on the benzoquinone would occur during the reaction, which resulted in a 2,5-regioisomer **46** exclusively with a 91% yield. A reversal in regioselectivity was observed for the sterically bulky *tert*-butyl-benzoquinone to afford only one 2,6-isomer **48**, which likely from the bulky group impeding complex formation with the neighboring carbonyl group. The phenyl group on the benzoquinone gave a 3:1 mixture ratio in favor of the 2,6-isomer **49**. Smaller methyl group reduced the selectivity but still favored the formation of the 2,6-isomer **47** (2:1). On the other hand, the chloro or bromo groups on the benzoquinones had less of an influence on the arylation regioselectivity, and the

Table 2 Substrate scope of various benzamides[a]

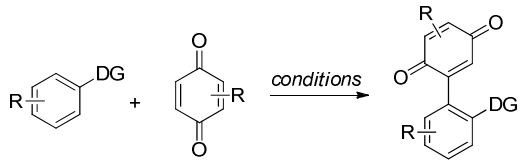


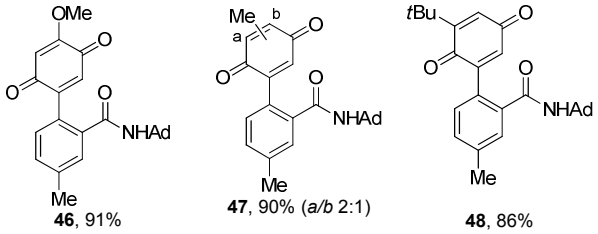


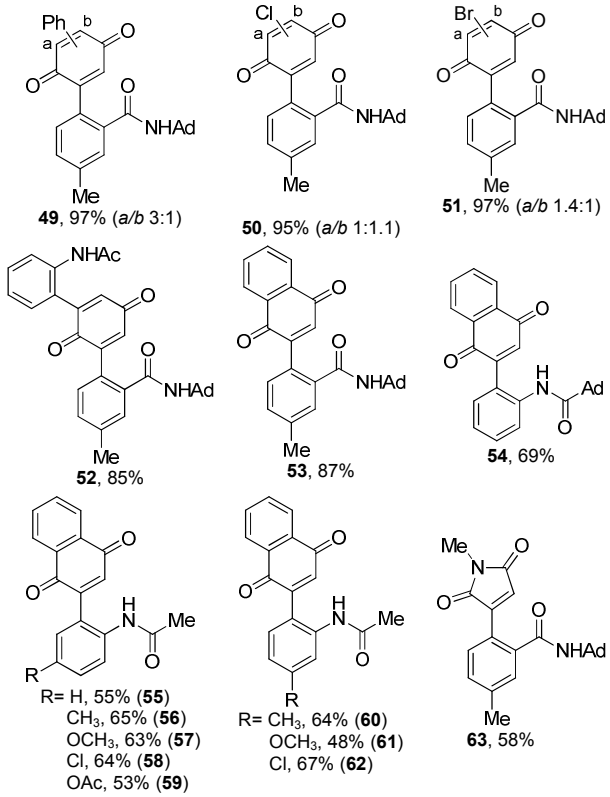
[a](Hetero)arene (1.0 equiv), benzoquinone (2.0 equiv), $[RhCp^*Cl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), AgOAc (2 equiv) in acetone at 60 °C for 0.5–12 h; isolated yields. Ad = adamantly.

coupling products were obtained with no significant selectivity (1:1.1 for **50**, 1.4:1 for **51**). The C–H heter-difunctionalization of benzoqunone was also actualized via a stepwise procudure to afford the 2,6-isomer **52**. Two other notable variations in the substrate scope included naphthoquinone and *N*-methylmaleimide. As a coupling partner, naphthoquinones reacted with similar efficiency under the optimal conditions to afford the desired product **53**. Coupling reactions of naphthoquinones with a range of anilides were also successful under the reaction conditions to produce the desired products (**54**-**62**). In a similar fashion, the reaction of *N*-methylmaleimide afforded the corresponding aryl derivative **63**.

Table 3 Rh-catalyzed direct C–H/C–H cross-coupling of various substrates.[a]





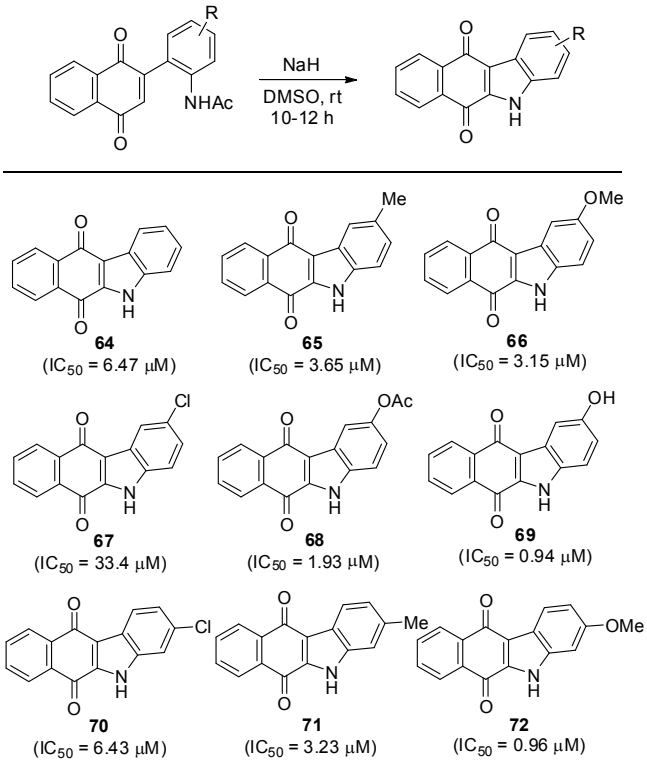


[a](Hetero)arene (1.0 equiv), benzoquinone (2.0 equiv), $[RhCp^*Cl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), AgOAc (2 equiv) in acetone at 60 °C for 1–24 h; isolated yields.

The directing groups in the products could be used as a useful synthetic handle for the further transformations. For example, the

synthetic utility of the present approach was illuminated by our finding that base-mediated cyclization (NaH in DMSO) of the obtained anilide-substituted quinones (**55-62**) allowed the rapid generation of the corresponding carbazole quinones (**64-72**).[18] The *N*-acetyl group from the carbazole quinones produced was removed spontaneously during the cyclization (Table 4). Compounds containing this skeleton are found in a number of biologically active molecules. The anticancer activity of the carbazole quinone moiety can partially be attributed to the interaction with DNA.[14d] To evaluate the bioactivities of the newly synthesized carbazole quinone derivatives, the representative derivatives were tested in a high-throughput binding assay with a panel of 96 kinases.[18,19] Among the derivatives tested, the preliminary data indicated that carbazole quinone **65** appears to inhibit GSKβ with high affinity. GSKβ, a serine kinase, has been shown to be involved in several human diseases, including diabetes, cancer and cardiovascular disease.[20] As illustrated in Table 4, full IC_{50} values were then determined,[18] and eight carbazole quinones had a micromolar inhibition range. To the best of our knowledge, a carbazole quinone scaffold has not been reported as a GSKβ inhibitor so far. Considering the low molecular weight (~280), the carbazole quinone moiety is anticipated to serve as a new inhibitor scaffold from which more potent inhibitors can be derivatized.

Table 4 Chemical structures and IC_{50} values of GSKβ inhibitors.



*staurosporine (IC_{50} = 4 nM)

To obtain structural insight into the underlying inhibitory activities, the binding mode of **69** (IC_{50} = 0.94 μM) in the GSK3β ATP-binding site (PDB code 1UV5)[21] was investigated using the Discovery Studio software. The docking studies revealed that **69** appears to be stabilized through multiple hydrogen bonds and close contacts with residues Leu188, Cys199, Val70, Ala83 and Ile62. The carbazole nitrogen atom appears to form a key hydrogen bond with the carbonyl oxygen of Val135, and the carbonyl oxygen of quinone can establish a hydrogen bond with the backbone amidic nitrogen of Tyr134. The increased potency of **69** may be rationalized by the formation of additional hydrogen bond with the Arg141 side chain.

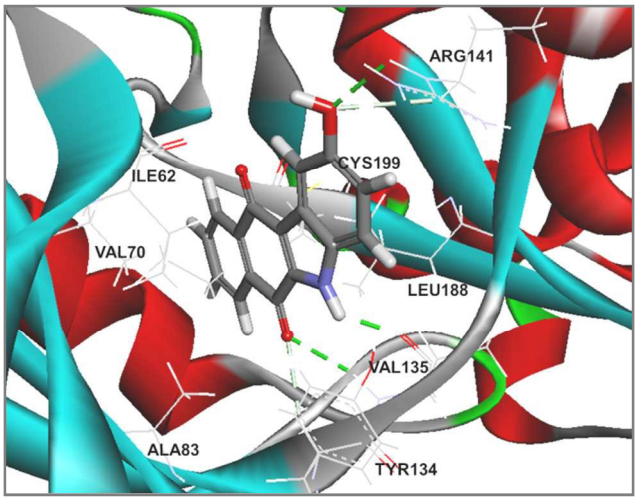


Figure 1 Compound **69** is docked into the ATP binding pocket of GSK3β (PDB code 1UV5).

Conclusions

In summary, we developed an efficient protocol to effect Rh(III)-catalyzed direct C–H/C–H cross-coupling reaction of quinones with various (hetero)arenes assisted by directing groups. This cross-coupling reaction utilizes a broad range of substrates and directing groups, providing a convenient and powerful synthetic tool for accessing structurally diverse aryl-substituted quinones with high synthetic utility. Moreover, the present synthetic strategy allows for the rapid construction of a carbazole quinone moiety that can be used in extensive biological evaluations and opens the way for analog design of more potent GSKβ inhibitors.

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Notes and references

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† Electronic Supplementary Information (ESI) available: See DOI: 10.1039/b000000x/

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