Enantioselective synthesis of spiro[*4H*-pyran-3,3′-oxindole] derivatives catalyzed by cinchona alkaloid thioureas: Significant water effects on the enantioselectivity

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ABSTRACT

An efficient stereoselective three-component reaction for the synthesis of functionalized spiro[4*H*-pyran-3,3′-oxindole] derivatives was realized through an organocatalyzed domino Knoevenagel/Michael/cyclization reaction using a cinchonidine-derived thiourea as the catalyst. Using water as the additive was found to improve the product ee values significantly. Under the optimized conditions, the reactions between isatins, malononitrile, and 1,3-dicarbonyl compounds yield the desired spirooxindole products in good yields (71-92%) and moderate to high ee values (up to 87% ee).

KEYWORDS

Asymmetric organocatalysis, enantioselective, spirooxindole, cinchona alkaloid, water effect.

INTRODUCTION

Multicomponent reactions (MCRs), in which three or more starting materials react to form a product in a one-pot fashion, are convergent and environmentally friendly in nature and easy to operate.[1-7] As a result, there have been tremendous developments in the MCRs in the past decades and these reactions have been extensively used in organic synthesis.[1-10] Spirooxindole, which constitutes the core structure of many natural alkaloids and drug candidates, represents one of the most important heterocyclic frameworks and has become a privileged skeleton in drug discovery.[11-14] Because of their biological relevance and the unique structural feature (containing a spiro tetrasubstituted stereogenic center), the stereoselective construction of such a spiro framework has attracted a lot of attention in recent years and numerous successes have been recorded for the stereoselective synthesis of a plethora of spirooxindole structures over past years.[15-18] Among the reported methods, the domino reaction[19-22] is one of the most important strategy for the asymmetric synthesis of spirooxindole derivatives.[15-18] Despite these advances, the stereoselective synthesis of one unique spirooxindole, spiro[4*H*-pyran-3,3′-oxindole], that incorporates a 2-amino-4*H*-pyran-3-carbonitrile ring at the C3 position of the oxindole, is still very limited (Fig. 1).[23-36] Most of the reported methods focus on the synthesis of the racemic products of

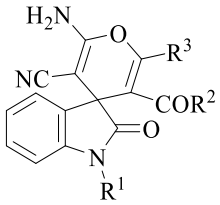


Figure 1. Structure of spiro[4*H*-pyran-3,3′-oxindole]

these spiro[4*H*-pyran-3,3'-oxindole] derivatives.[23-28] In 2010 Yuan and coworkers reported the first catalytic asymmetric synthesis of these spiro[4*H*-pyran-3,3′-oxindole] derivatives via two- or three-component reactions of *N*-protected isatins using cupreine (6'-hydroxycinchonidine) as the catalyst.[29] Soon after, Macaev briefly studied a similar three-component reaction using (*S*)-brevicolline [(*S*)-1-methyl-4-(1-methyl-2-pyrrolidinyl)-9*H*-pyrido[3,4-*b*]indole] as the catalyst.[30] In addition, these authors also realized a diastereoselective synthesis of this type of compounds in 2014.[31] Nevertheless, there is no systematic study for synthesizing these spiro[4*H*-pyran-3,3′-oxindole] derivatives directly from *N*-unsubstituted isatins in optically enriched forms.[31]

Our group is interested in developing novel asymmetric methods for the synthesis of chiral 2-amino-4*H*-pyran-3-carbonitrile[37-41] and isatin derivatives.[42-49] During the course of our research, we became interested in the synthesis of spiro[4*H*-pyran-3,3′-oxindole] derivatives using the three-component reaction of isatin, malononitrile, and ethyl acetoacetate, and in this study we found that water had a significant impact[50-56] on the asymmetric induction of the cinchona alkaloid thiourea catalysts when they were applied in the three-component reaction. It has been known that water can play a very important role in catalysis,[50-56] and many organocatalyzed reactions have been successfully conducted either in water, on water, or in the presence of water.[50-59] Herein we wish to report that water can significantly improve the enantioselectivity of the three-component reaction of isatins, malononitrile, and 1,3-dicarbonyl compounds (acetoacetate and 1,3-diketone) catalyzed by cinchona alkaloid thioureas and an efficient enantioselective synthesis of functionalized spiro[4*H*-pyran-3,3′-oxindole] derivatives can be achieved by employing a cinchonidine-derived thiourea as the catalyst and water as the additive.

RESULTS AND DISCUSSION

Some readily available cinchona alkaloid derivatives (**1**-**5**, Fig. 2)[60-64] were adopted as the catalysts and isatin (**6a**), malononitrile (**7**), and ethyl acetoacetate (**8a**) as the model substrates. The results of the catalyst screening and reaction condition optimizations are summarized in Table 1. As shown in Table 1, when quinidine thiourea (**1a**) was used as the catalyst in toluene at rt for 15 h, the desired product **9a** was obtained in a good yield of 76%, but a low ee value of 40% (entry 1). This result actually surpassed our expectations since this catalyst had been briefly evaluated by

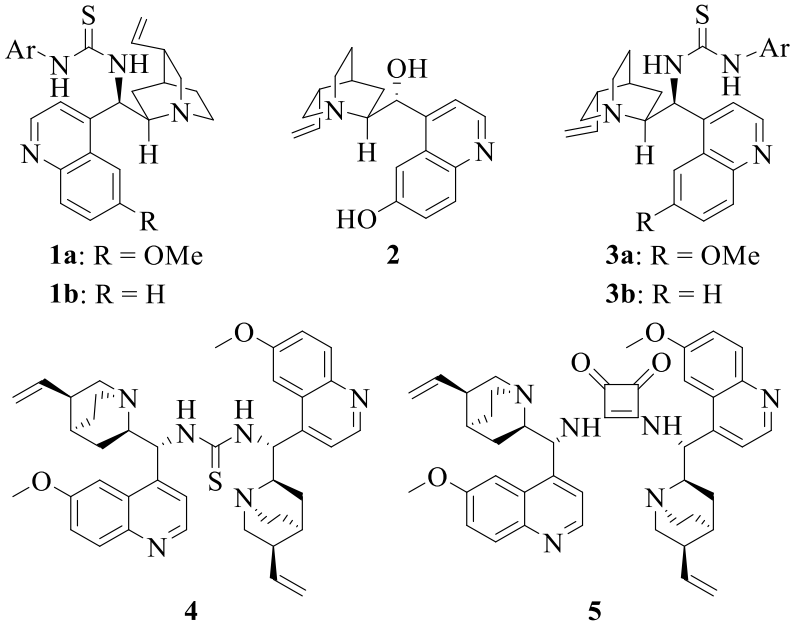


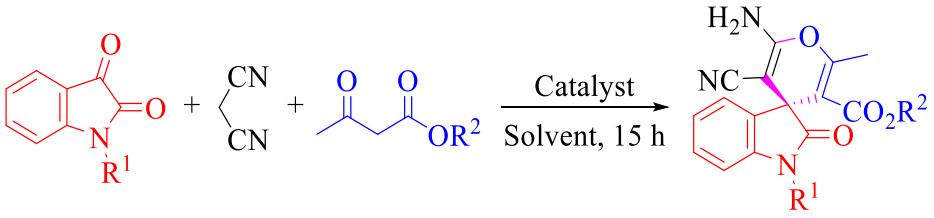
Figure 2. Catalysts screened in this study [Ar = 3,5-$(CF_3)_2C_6H_3$-]

Yuan and coworkers for *N*-MOM protected isatin and an almost racemic product was obtained.[29] In contrast, when cupreine (**2**) was used, the ee value of **9a** dropped to 32% (entry 2). This was very surprising since cupreine was reported to be a highly selective catalyst for *N*-protected isatins.[29] On the other hand, slightly better yields and ee values

were obtained when cinchonine thiourea (**1b**), quinine thiourea (**3a**), cinchonidine thiourea (**3b**) were used as the catalysts (entries 3-5), with cinchonidine thiourea (**3b**) giving the best results (82% yield, 56% ee, entry 5). Nonetheless, the more sterically demanding *N*,*N*'-bisquinidine thiourea (**4**) and *N*,*N*'-bisquinidine squaramide (**5**) both failed to improve the product yield or ee value (entries 6 and 7). It should be pointed out that opposite enantiomers were obtained as the major products from the quinidine-derived catalysts (i.e., **1a**, **1b**, **4**, and **5**) and the quinine-derived ones (i.e., **3a** and **3b**), except for cupreine (**2**), which yields the same major enantiomer as that of the quinidine-derived catalysts. Since water is formed as a side product in this reaction, in order to rule out the effect of water on the stereoselectivity of this reaction, molecular sieves were added as an additive to the reaction mixture with **3b** as the catalyst (entry 8). Surprisingly, we found that a much lower ee value of **9a** (40% ee) was obtained.[65] Since it appeared that water might actually have some beneficial effects on the product ee value, it was intentionally added to the reaction as an additive (entry 9), and, to our pleasure, the ee value of **9a** increased to 62% when 0.025 mL of water was added. The ee value of **9a** could be further increased to 66% without affecting the product yield by increasing the volume of water to 0.050 mL (entry 10) or 0.100 mL (entry 11). However, further increase of the water amount resulted in a lower product ee value (data not shown). Using **3b** as the catalyst and 0.050 mL of water as the additive, we then screened some common organic solvents. Except for xylene (entry 12), in which slightly lower yield and ee value were obtained, poor product yields and ee values were obtained in methanol (entry 13), DMSO (entry 14), CH_2Cl_2 (entry 15), and THF (entry 16). When the reaction was carried out in toluene at 0 °C with water (0.050 mL), the ee value of **9a** was further increased to 72% (entry 17). Further dropping (to -5 °C) or

increasing (to 40 °C) the temperature resulted in worse product ee values (entries 18-19). Next, the effects of the *N*-substituent on isatin (**6**) was evaluated under the optimized conditions (entries 20-21), and, it was found that the best results were obtained with *N*-unsubstituted isatin (**6a**, entry 17), whereas the *N*-methyl substituted **6b** (entry 20) and *N*-benzyl substituted **6c** (entry 21) gave much and slightly worse results, respectively. Moreover, the opposite enantiomers (i.e., the *R*-enantiomers) were obtained as the major products in these cases. The ester alkyl group of the acetoacetate was also found to have significant effects on the product ee value. While the methyl (**8b**) and benzyl (**8c**) esters both yielded worse ee values of the products (entries 22-23) than that of the ethyl ester (entry 17), the more sterically demanding isopropyl (**8d**) and *tert*-butyl (**8e**) esters led to higher product ee values (entries 24-25), with the highest ee value (87%) obtained with the isopropyl acetoacetate (**8d**, entry 24).

Table 1. Optimization of the reaction conditions of the three-component reaction[a]



6 **7** **8** **9**

6a: R^1 = H
6b: R^1 = Me
6c: R^1 = Bn

8a: R^2 = Et
8b: R^2 = Me
8c: R^2 = Bn
8d: R^2 = *i*-Pr
8e: R^2 = *t*-Bu

9a: R^1 = H; R^2 = Et
9b: R^1 = Me; R^2 = Et
9c: R^1 = Bn; R^2 = Et
9d: R^1 = H; R^2 = Me
9e: R^1 = H; R^2 = Bn
9f: R^1 = H; R^2 = *i*-Pr
9g: R^1 = H; R^2 = *t*-Bu

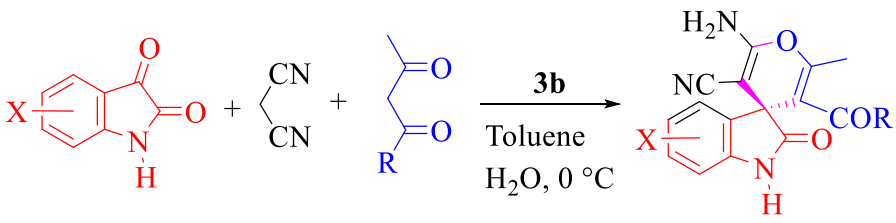
Entry	6	8	Additive	Catalyst	9	Yield (%)[b]	ee (%)[c]
1	**6a**	**8a**	None	**1a**	**9a**	76	40[d]
2	**6a**	**8a**	None	**2**	**9a**	73	32[d]
3	**6a**	**8a**	None	**1b**	**9a**	82	50[d]
4	**6a**	**8a**	None	**3a**	**9a**	78	50
5	**6a**	**8a**	None	**3b**	**9a**	82	56
6	**6a**	**8a**	None	**4**	**9a**	80	40[d]
7	**6a**	**8a**	None	**5**	**9a**	78	40[d]
8	**6a**	**8a**	MS 4Å[e]	**3b**	**9a**	78	40
9	**6a**	**8a**	H_2O[f]	**3b**	**9a**	83	62
10	**6a**	**8a**	H_2O[g]	**3b**	**9a**	84	66
11	**6a**	**8a**	H_2O[h]	**3b**	**9a**	84	66
12[i]	**6a**	**8a**	H_2O[g]	**3b**	**9a**	78	62
13[j]	**6a**	**8a**	H_2O[g]	**3b**	**9a**	52	18
14[k]	**6a**	**8a**	H_2O[g]	**3b**	**9a**	32	12
15[l]	**6a**	**8a**	H_2O[g]	**3b**	**9a**	70	19
16[m]	**6a**	**8a**	H_2O[g]	**3b**	**9a**	72	6
17[n]	**6a**	**8a**	H_2O[g]	**3b**	**9a**	84	72
18[o]	**6a**	**8a**	H_2O[g]	**3b**	**9a**	82	70
19[p]	**6a**	**8a**	H_2O[g]	**3b**	**9a**	78	46
20[n]	**6b**	**8a**	H_2O[g]	**3b**	**9b**	74	28[d,q]
21[n]	**6c**	**8a**	H_2O[g]	**3b**	**9c**	80	71[d,r]
22[n]	**6a**	**8b**	H_2O[g]	**3b**	**9d**	78	64
23[n]	**6a**	**8c**	H_2O[g]	**3b**	**9e**	80	53
24[n]	**6a**	**8d**	H_2O[g]	**3b**	**9f**	82	87
25[n]	**6a**	**8e**	H_2O[g]	**3b**	**9g**	76	82

[a] Unless otherwise specified, all reactions were carried out with **6** (0.10 mmol), **7** (0.10 mmol), **8** (0.10 mmol) and the catalyst (0.010 mmol, 10 mol%) in toluene (1.0 mL) at room temperature. [b] Yield of the isolated product after flash column chromatography [c] Determined by HPLC analysis on a ChiralPak IB, IC, or AD-H column. The absolute configuration of the reaction products was determined by the X-ray crystallographic analysis of compound **9m** (vide infra). [d] The opposite enantiomer was obtained as the major product. [e] Molecular sieves (30.0 mg) were used. [f] 0.025 mL of water was used. [g] 0.050 mL of water was used. [h] 0.100 mL of water was used. [i] The solvent was xylene. [j] The solvent was MeOH. [k] The solvent was DMSO. [l] The solvent was CH_2Cl_2. [m] The solvent was THF. [n] Reaction was carried out at 0 °C. [o] Reaction was

carried out at -5 °C. [p] Reaction was carried out at 40 °C. [q] The stereochemistry of this compound was assigned based on analogy with compound **9c**. [r] The absolute configuration of product **9c** was determined by comparing the measured optical rotation with that reported in the literature (Ref. 29).

Once the reaction conditions were optimized, the substrate scope of this three-component domino Knoevenagel/Michael/cyclization reaction was then established. The results in Table 2 are a collection of the best results of the reaction under the optimized conditions. It was found that, with different isatin derivatives, the isopropyl acetoacetate would produce the corresponding the spiro[4*H*-pyran-3,3′-oxindole] derivatives in slightly higher ee values than or practically identical ee values as the ethyl acetoacetate. As the results in Table 2 show, while the electronic nature and the position of the substituent on the isatin ring have minimal effects on the product yield, they do have some influence on the enantioselectivity of this reaction. For 5-substituted isatins (entries 3-9, and 13-15), electron-withdrawing groups usually give slightly lower ee values of the desired products than the electron-donating groups, except for 5-nitroisatin (entry 13). Also 4-chloroisatin (entry 10) leads to a much lower ee value than 5-chloro- (entry 5), 6-chloro- (entry 11), or 7-chloroisatin (entry 12). Finally, when the acetoacetate is replaced with a 1,3-ketone (2,4-petanedione), the desired product **9u** was obtained in a similar yield of 71%, but the product ee value was only 38% (entry 16).

Table 2 Substrate scope of the three-component reaction[a]



6 **7** **8** **9**

Entry	X	R	Time (h)	**9**/Yield (%)[b]	ee (%)[c]
1	5-H	OEt	15	**9a**/84	72
2	5-H	O*i*-Pr	15	**9f**/82	87
3	5-F	OEt	15	**9h**/86	60
4	5-F	O*i*-Pr	15	**9i**/81	71
5	5-Cl	OEt	24	**9j**/82	59
6	5-Cl	O*i*-Pr	24	**9k**/78	74
7	5-Br	OEt	15	**9l**/80	59
8	5-Br	O*i*-Pr	15	**9m**/83	58
9	5-I	OEt	15	**9n**/92	65
10	4-Cl	OEt	24	**9o**/78	44
11	6-Cl	O*i*-Pr	15	**9p**/80	62
12	7-Cl	O*i*-Pr	15	**9q**/78	83
13	5-NO_2	O*i*-Pr	15	**9r**/80	67
14	5-CH_3	OEt	20	**9s**/80	71
15	5-OMe	OEt	15	**9t**/78	60
16	H	Me	22	**9u**/71	38

[a] Unless otherwise specified, all reactions were carried out with **6** (0.10 mmol), **7** (0.10 mmol), **8** (0.10 mmol) and **3b** (0.010 mmol, 10 mol%) in toluene (1.0 mL) and water (0.050 mL) at 0 °C. [b] Yield of the isolated product after flash column chromatography. [c] Determined by HPLC analysis on a ChiralPak IB, IC, or AD-H column.

The absolute configuration of the stereogenic center in the reaction product was assigned as *S* according to the X-ray crystallographic analysis of compound **9m** (Fig. 3).[66]

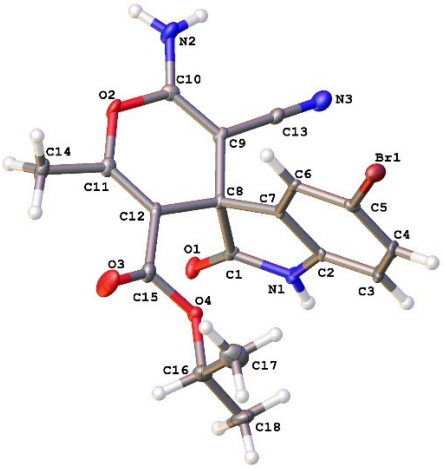
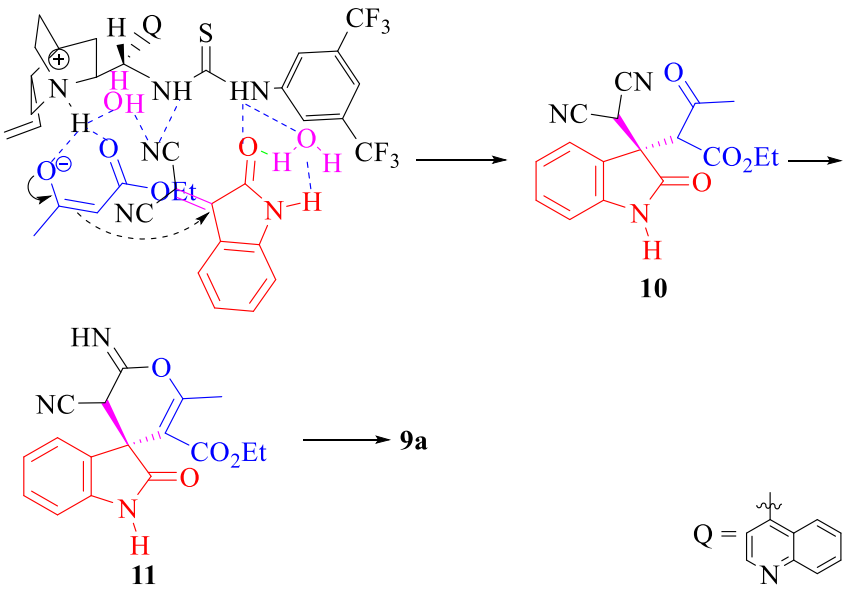


Figure 3. ORTEP drawing of compound **9m**

On the basis of the absolute stereochemistry of **9a**, a plausible transition state model is proposed (Scheme 1). As shown in Scheme 1, isatin (**6a**) first reacts with malononitrile (**7**) to yield the isatylidenemalononitrile intermediate, which hydrogen-bonded to the thiourea moiety of the catalyst. Meanwhile, the enolate form of ethyl acetoacetate (**8a**) is hydrogen-bonded to the ammonium moiety of the catalyst. In the favored transition state, the enolate is attacking the *Re* face of isatylidenemalononitrile from the back, which yields intermediate **10**. Further intramolecular cyclization of **10** gives **11**, which tautomerizes to give the expected product **9a**. Water probably helps improve the enantioselectivity of this reaction through the formation of additional hydrogen bonds between isatylidenemalononitrile and the catalyst (Scheme 1), which results in a more compact transition state and a better control of the isatylidenemalononitrile orientation in the transition state. However, such an orientation of isatylidenemalononitrile will not be favorable if the *N*-atom of the isatylidenemalononitrile is substituted with a large group, such as a benzyl group, due to the steric interactions between that substituent and the thiourea moiety of the catalyst, and that might be the reason why the opposite enantiomers were obtained with the *N*-substituted isatins.



Scheme 1. Proposal for the favored transition state for the formation of **9a**

CONCLUSION

In summary, we have developed an enantioselective method for the synthesis of spiro[4*H*-pyran-3,3'-oxindole] derivatives from the three-component reaction of isatins, malononitrile, and 1,3-dicarbonyl compounds (acetoacetates and one 1,3-diketone). Using a cinchonidine-derived thiourea catalyst (**3b**, 10 mol% loading) and water as the additive in toluene at 0 °C, the corresponding spirooxindole derivatives of *N*-unsubstituted isatins may be obtained in good yields (71-92%) and moderate to high ee values (38-87% ee). A significant improvement of the product ee values was observed in the presence of the water additive.

EXPERIMENTAL

General information. Unless otherwise mentioned, all reactions were carried out in a closed vial. ^{1}H NMR spectra were recorded on a 500 MHz spectrometer (126 MHz for ^{13}C). The following abbreviations were used to designate chemical shift mutiplicities: s = singlet, d = doublet, t = triplet, q = quartet, h = heptet, and m = multiplet. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplets (m). TLC was performed with silica gel GF254 precoated on aluminum plates and spots were visualized with UV. Flash column chromatography was performed using silica gel. HPLC analysis was performed on an HPLC instrument equipped with a UV-Vis detector. Solvents were freshly distilled under a nitrogen atmosphere before use, using the standard protocols. All the reagents were purchased from commercial sources and used as received.

General procedure for the domino Knoevenagel/Michael/cyclization reaction. To a vial were added sequentially the catalyst cinchonidine thiourea (**3b**, 5.6 mg, 0.010 mmol, 10 mol%), isatin (**6a**, 14.7 mg, 0.10 mmol), malononitrile (**7**, 6.6 mg, 0.10 mmol), toluene (1.0 mL) and water (0.050 mL). The mixture was stirred at 0 °C for 10 min before the addition of isopropyl acetoacetate (**8d**, 14.4 mg, 0.10 mmol). The reaction mixture was further stirred at 0 °C for 15 h. Upon the completion (monitored by TLC), the reaction mixture was dried over anhydrous sodium sulfate, filtered, and the solvent was evaporated. The crude reaction mixture was purified by flash column chromatography with a 40:60 hexane/EtOAc mixture as the eluent to yield to product **9f** (27.8 mg, 82%) as a white solid. The enantiomeric ratio was determined by HPLC analysis on a chiral ChiralPak IB column.

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[65] For a similar observation in thiourea catalysis, see Ref. 58.

[66] A pure enantiomer of **9m** was obtained through repeated recrystallization of the initial reaction product. CCDC 1883860 contains the supplementary crystallographic data for compound **9m**. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk

GRAPHICAL ABSTRACT

Enantioselective synthesis of spiro[4*H*-pyran-3,3′-oxindole] derivatives catalyzed by cinchona alkaloid thioureas: Significant water effects on the enantioselectivity

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