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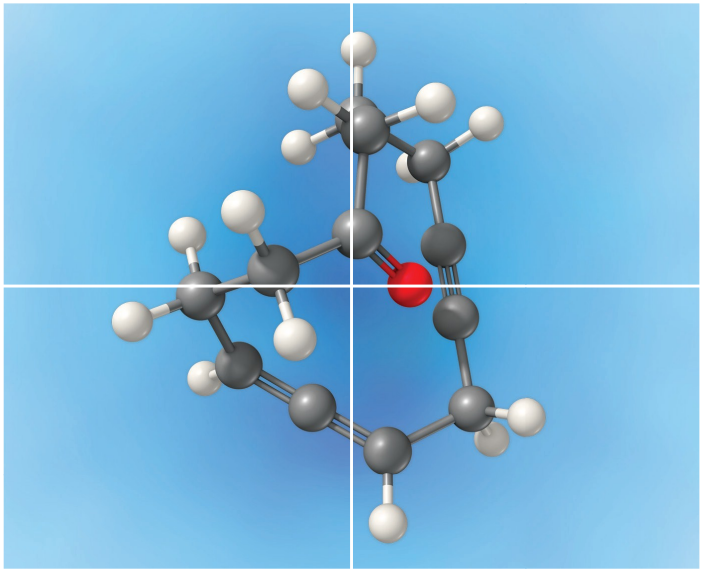

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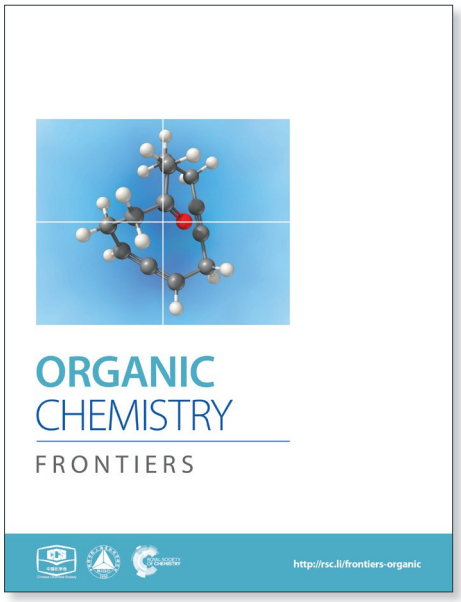

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ARTICLE TYPE

Co-catalysis between DABCO and Brønsted acid in the catalytic [4+2] annulation of isatin with but-3-yn-2-one and mechanistic investigation

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Catalytic amount of DABCO base catalyst in cooperation with a proton source (732 cation exchange resin) affords the [4+2] cycloadducts of isatins with but-3-yn-2-one in moderate to good yields. Moreover, the related plausible mechanisms have been proposed in details on the basis of control and deuterium labeling experiments.

The structures that contain spirooxindole exist in many natural and unnatural compounds that exhibit diverse biological activities.[1] Although a number of useful methods have been developed to access these interesting motifs over the past years,[2][3] the efficient synthetic strategies towards spirooxindole motifs are still in high demanding at the present stage. Tandem reactions serve as a powerful tool for the rapid and efficient assembly of complex structures from simple starting materials with minimized production of wastes. Organocatalytic tandem processes are even more appealing because of their operational simplicity and environmental friendliness.[4][5] Recently, we have reported that nitrogen-containing Brønsted base 1,4-diazabicyclo[2,2,2]octane (DABCO, 100 mol%, 1.0 eq) mediated [4+2] annulation of isatins **1** with activated ketones such as but-3-yn-2-one **2a** could proceed smoothly to give the corresponding spiro[indoline-3,2'-pyran]-2,4'(3'H)-diones or 2,3-dihydropyran-4-ones in good to excellent yields under mild conditions (Scheme 1).[6] In this paper, we wish to report the catalytic version of this transformation with DABCO (20 mol%, 0.2 eq) in the presence of 732 cation exchange resin and the mechanistic investigations based on our control and deuterium labeling experiments (Scheme 1).

According to our previous finding,[6] in the presence of catalytic amount of DABCO (20 mol%), the desired product **3a** was formed in only 17% yield along with an etherified product **5a** (see Table 2 and Figure 1) in trace and a self-condensation product **7a**[7] (see Scheme 3) of but-3-yn-2-one **2a** in 19% yield.

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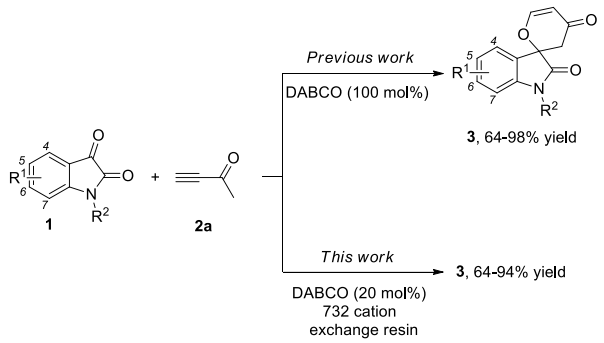
Inspired by this finding, we envisaged that if we could inhibit the self-condensation of **2a** by adding some additives such as proton source, this catalytic reaction might be able to be performed more efficiently. Moreover, the mechanistic aspect of this reaction might be also clarified along with the development of its catalytic variant.

Scheme 1. DABCO mediated [4+2] annulations of isatins with but-3-yn-2-one



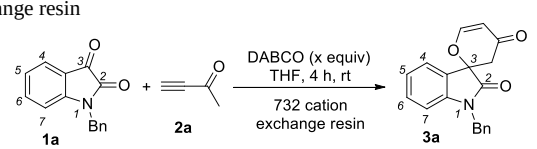
Results and Discussion

We initially utilized isatin **1a** (0.2 mmol, 1.0 equiv) and but-3-yn-2-one **2a** (0.3 mmol, 1.5 equiv) as the substrates in the presence of catalytic amounts of DABCO and 732 cation exchange resin in THF at room temperature to examine the reaction outcomes. The results are shown in Table 1. To our delight, we found that **3a** was obtained in 78% yield in the presence of 732 cation exchange resin (60 mg) using DABCO (20 mol%, 0.2 equiv) as the catalyst (Table 1, entry 1). 732 cation exchange resins can provide H^+ as proton source which are similar to the Brønsted acid. Increasing the employed amount of 732 cation exchange resin to 100 mg afforded **3a** in 85% yield (Table 1, entry 2). However, further increasing the employed amount of 732 cation exchange resin to 120 mg or decreasing the employed amount of DABCO to 0.1 equiv did not improve the yield of product **3a** (Table 1, entries 3 and 4).

On the other hand, to further improve the reaction outcomes, we also screened the other proton sources (1.0 equiv) such as PTSA, benzoic acid, phenol, benzyl alcohol, acetic acid for this reaction and the results are shown in Table 2. However, the desired product **3a** was obtained in lower yields in all cases along with some other oxa-Michael addition products **4** (proton sources to but-3-yn-2-one **2a**) or an etherified product **5a** (H_2O to but-3-

yn-2-one **2a**) in a large amount. The structure of **5a** has been also confirmed by X-ray diffraction. Its ORTEP drawing is shown in Figure 1 and the CIF data are summarized in the Supporting Information.

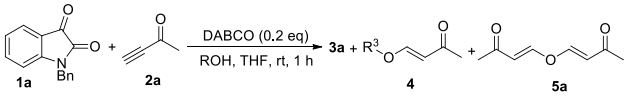
Table 1. Optimization of the conditions for the addition of 732 cation exchange resin



entry[a]	732 cation exchange resin	x equiv	yield (%)[c]
1	60 mg	0.2	78
2	100 mg	0.2	85
3	100 mg	0.1	69
4	120 mg	0.2	82

[a] The reactions were carried out on 0.2 mmol scale in solvent (2.0 mL). [b] The ratio of **1a**:**2a** was 1:1.5. [c] Isolated yields.

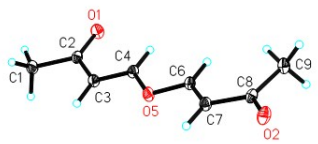
Table 2. Other Brønsted acids were used as proton sources



entry[a]	R^3OH[b]	yield (%)[c] **3a**	yield (%)[c] **4**	yield (%)[c] **5a**	recovered starting material (%)[c]
1	TsOH	ND	-	-	-
2	$PhCO_2H$	trace	**4b**, 55	13	29
3	PhOH	15	**4c**, 47	8.5	52
4	$PhCH_2OH$	19	**4d**, 52	trace	57
5	CH_3CO_2H	trace	**4e**, trace	trace	55

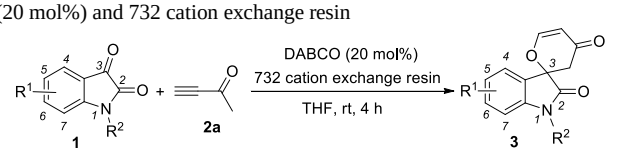
[a] The reactions were carried out on 0.2 mmol scale in solvent (2.0 mL). [b] 1.0 eq of additive was used. The ratio of **1a**:**2a** was 1:1.5. [c] Isolated yields. ND = no detected.

Figure 1. The ORTEP drawing of **5a**



Having established the optimal reaction conditions for the formation of **3a**, we next surveyed the substrate scope of the reaction by varying the structures of isatins **1** in the presence of DABCO (20 mol%) and 732 cation exchange resin (100 mg). As shown in Table 3, regardless of whether electron-donating or electron-withdrawing groups were introduced at 4-, 5-, 6- or 7-positions of isatins **1**, these reactions proceeded smoothly, giving the corresponding products **3b**-**3n** in 64-78% yields (Table 3, entries 1-15), suggesting that the electronic properties of the substituent on the benzene rings did not have a significant impact on the reaction outcome. The other N-protecting groups such as methyl, allyl or Ph were equally well-tolerated in the reaction, furnishing the desired cycloadducts **3o**-**3q** in moderate to good yields ranging from 71-94% under the standard conditions (Table 3, entries 14-16). It should be noted that the use of 4-phenylbut-3-yn-2-one in this reaction only afforded the corresponding aldol reaction product without the formation of desired annulation product.[8]

Table 3. Substrate scope of [4+2] annulation in the presence of DABCO (20 mol%) and 732 cation exchange resin

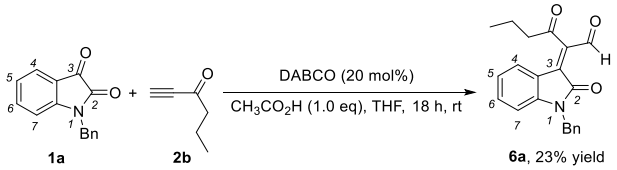


entry[a]	No.	R^1	R^2	Yield (%)[b]
1	**1b**	4-Cl	Bn	**3b**, 78
2	**1c**	4-Br	Bn	**3c**, 68
3	**1d**	5-F	Bn	**3d**, 78
4	**1e**	5-CH_3	Bn	**3e**, 75
5	**1f**	5-Cl	Bn	**3f**, 68
6	**1g**	5-Br	Bn	**3g**, 64
7	**1h**	5,7-2CH_3	Bn	**3h**, 68
8	**1i**	6-Cl	Bn	**3i**, 66
9	**1j**	6-Br	Bn	**3j**, 65
10	**1k**	6-CH_3	Bn	**3k**,69
11	**1l**	7-Cl	Bn	**3l**, 66
12	**1m**	7-Br	Bn	**3m**, 65
13	**1n**	7-F	Bn	**3n**, 65
14	**1o**	H	CH_3	**3o**, 87
15	**1p**	H	allyl	**3p**, 94
16	**1q**	H	Ph	**3q**, 71

[a] Compound **1** (0.2 mmol) and the catalyst were dissolved in solvent (2 mL) and then compound **2a** (0.3 mmol), 732 cation exchange resin (100 mg) was added to the reaction solution. The resulting reaction mixture was stirred for 4.0 h. [b] Isolated yields.

During the examination on the effect of proton source, another interesting finding is that we identified the formation of (E)-2-(1-benzyl-2-oxoindolin-3-ylidene)-3-oxohexanal **6a** in 23% yield in the presence of acetic acid (1.0 eq) at room temperature when hex-1-yn-3-one **2b** instead of but-3-yn-2-one **2a** was used as a Michael acceptor and the corresponding [4+2] annulation product was not observed. Its structure has been unambiguous determined by X-ray analysis of its single crystals. The ORTEP drawing of **6a** is shown in Figure 2 and the CIF data are presented in the Supporting Information. The similar product was identified in trace in the [4+2] annulation of isatin **1a** with but-3-yn-2-one **2a** on the basis of ^{1}H NMR spectroscopic data under the same conditions along with other trace amount of byproducts as shown in entry 5 of Table 2.

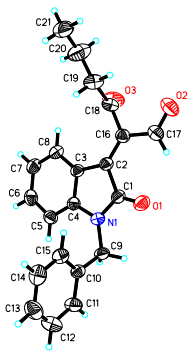
Scheme 2. The reaction of isatin with hex-1-yn-3-one **2b** in the presence of acetic acid



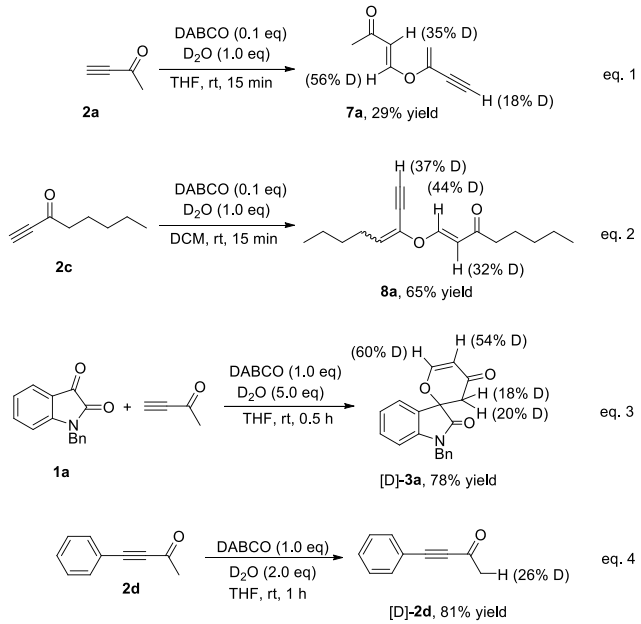
In our previous work, we proposed that the formation of **3** might undergo a stepwise aldol/intramolecular oxa-Michael addition pathway.[8] In order to gain more mechanistic insights, we performed several isotopic labeling experiments by adding D_2O (1.0 equiv) into the reaction systems. In the

first experiment, we conducted the self-condensation of but-3-yn-2-one **2a** catalyzed by DABCO (0.1 equiv) in the presence of D_2O (1.0 equiv), affording deuterium incorporated product **7a** in 29% yield as indicated by ^1H NMR spectroscopic analysis (eq. 1, Scheme 3). The self-condensation of oct-1-yn-3-one **2c** was conducted under the similar conditions, affording deuterium incorporated product **8a** in 65% yield as shown in eq. 2 of Scheme 3 (also see Supporting Information). This result clearly clarified that there is no proton exchange at the α-position of carbonyl group as well as terminal olefin in product **7a**. Next, we carried out the [4+2] annulation of isatin **1a** with but-3-yn-2-one **2a** by adding D_2O (5.0 equiv) under the standard conditions, giving the corresponding deuterium incorporated product [D]-**3a** in 78% yield (eq. 3, Scheme 3). Moreover, we also performed the reaction of 4-phenylbut-3-yn-2-one **2d** in the presence of DABCO (1.0 equiv) and D_2O (2.0 equiv) in THF at room temperature. It was found that the corresponding deuterium incorporated product [D]-**2d** was recovered in 81% yield along with 26% D content (eq. 4, Scheme 3).

Figure 2. The ORTEP drawing of **6a**



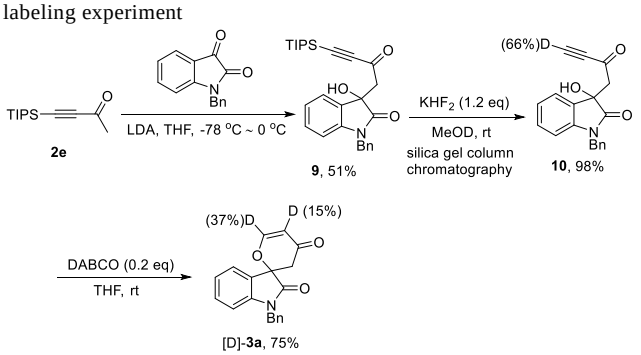
Scheme 3. Deuterium labeling experiments



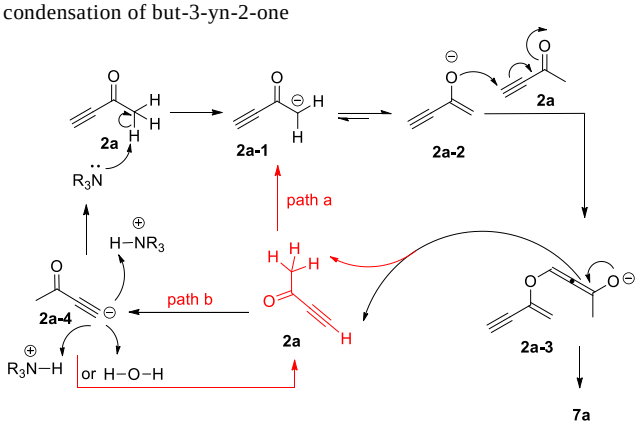
According to our previous work,[8] we also synthesized the possible terminal alkyne deuterated intermediate **10** in 98% yield along with 66% D content via desilylation with KHF_2 in MeOD after silica gel column chromatography and it should be noted that the hydroxyl group has been completely protonated (Scheme 4, also see Supporting Information). Under the standard conditions, **10** could be transformed into [D]-**3a** in 75% yield in the presence of DABCO (20 mol%) along with the acetylenic deuterium shift to the α-position of carbonyl group (Scheme 4).

Based on the deuterium labeling experiments described above, we proposed a more specific mechanism for the formation of self-condensation product **7a**, which is slightly different from the previous mechanism proposed by Ramachandran (Scheme 5).[7] The base catalyst deprotonates but-3-yn-2-one **2a** to generate an enolate intermediate **2a-1** or **2a-2**, which undergoes oxonucleophilic attack to another molecule of **2a** to produce the corresponding allenic intermediate **2a-3**. Protonation of **2a-3** by the acetylenic proton of **2a** gives self-condensation product **7a** and the corresponding acetylenic anion **2a-4**, which abstracts a proton from water or the protonated base catalyst (R_3N^+H) to regenerate the base catalyst as shown in path b. In addition, allenic intermediate **2a-3** might abstract a proton from a third molecule of alkynone, regenerating enolate intermediate **2a-1** to continue the catalytic cycle as shown in path a.

Scheme 4. Synthesis of the possible intermediate **10** and isotopic labeling experiment



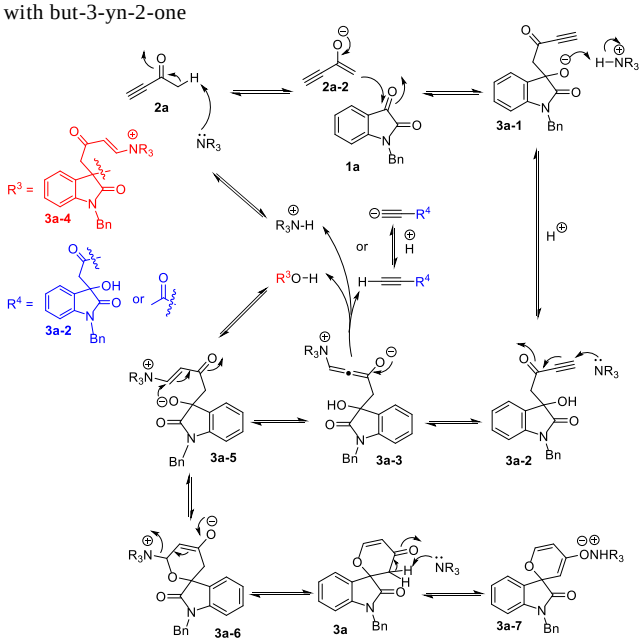
Scheme 5. Proposed mechanism for DABCO-catalyzed self-condensation of but-3-yn-2-one



Similar to the proposed mechanism for the formation of

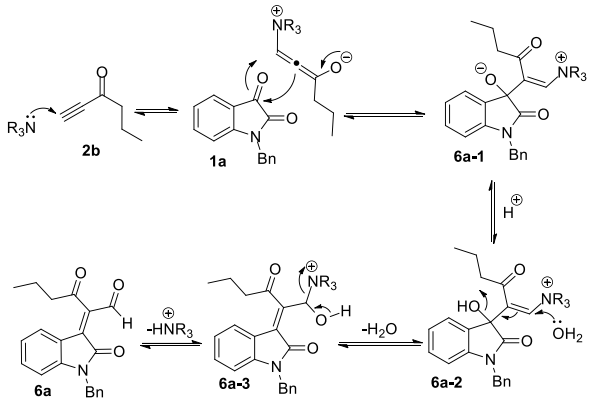
self-condensation product **7a**, a plausible stepwise mechanism for the catalytic [4+2] annulation of isatin with but-3-yn-2-one **2a** is shown in Scheme 6 in the presence of DABCO. Initially, DABCO deprotonates but-3-yn-2-one **2a** to generate enolate intermediate **2a-2**,[9] followed by a nucleophilic addition to the 3-carbonyl group of isatin **1a** to give intermediate **3a-1**, which abstracts a proton from the protonated DABCO to afford the corresponding key intermediate **3a-2** as mentioned above. Subsequently, a Michael addition of DABCO to the alkynyl group of **3a-2** gives the intermediate **3a-3**, which obtains a proton from the acetylenic proton in **3a-2**, **2a**, **3a-4** or protonated base (R_3N^+H) to give intermediate **3a-5**. This vinylogous oxonucleophile wins over the ambient carbon nucleophile. The oxoanion of intermediate **3a-5**, generated from the deprotonation of **3a-4**, undergoes Michael addition to form the six-membered cyclic intermediate **3a-6**. The release of base catalyst produces the corresponding spirooxindole **3a**. According to our previous work, product **3a** may be also deprotonated by base catalyst to form ionic pair **3a-7**, which can be dissociated by 732 cation exchange resin to generate the product **3a** and the base catalyst.

Scheme 6. Proposed mechanism for the [4+2] annulation of isatin with but-3-yn-2-one



In order to clarify the formation of **6a**, we also proposed a plausible mechanism in Scheme 7. Initially, DABCO attacks to the alkynyl moiety of **2b** to give a vinylogous intermediate, followed by a nucleophilic addition to the 3-carbonyl group of isatin **1a** to give intermediate **6a-1**. Subsequently, the ambient H_2O attacks to the alkenyl moiety in intermediate **6a-2** along with the elimination of H_2O in the presence of acetic acid to deliver intermediate **6a-3**. The release of base catalyst in **6a-3** produces the corresponding product **6a**.

Scheme 7. Proposed mechanism for the formation of **6a**



In conclusion, we have developed a novel strategy that base catalyst in cooperation with a proton source can afford the [4+2] cycloadducts of isatins **1** with but-3-yn-2-one[10] in moderate to good yields in a catalytic manner. Moreover, three plausible mechanisms have been proposed in details on the basis of previous literature and deuterium labeling experiments. The identification of new and more efficient catalytic systems to access spiro compounds beyond oxindoles with high stereoselectivity and apply this new methodology to synthesize biologically active products is the focus of current efforts in our laboratories.

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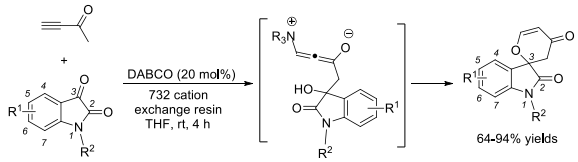
Co-catalysis between DABCO and Brønsted acid in the catalytic [4+2] annulation of isatin with but-3-yn-2-one and mechanistic investigation



Catalytic amount of DABCO base catalyst in cooperation with a proton source affords the [4+2] cycloadducts of isatins with but-3-yn-2-one in moderate to good yields. Moreover, the related plausible mechanisms have been proposed in details on the basis of control and deuterium labeling experiments.

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