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Tandem (2 + 2) Annulation/Retro-4π Electrocyclization/Imino-Nazarov Cyclization Reaction of *p*-Quinone Methides with Ynamides: Expeditious Construction of Functionalized Aminoindenes

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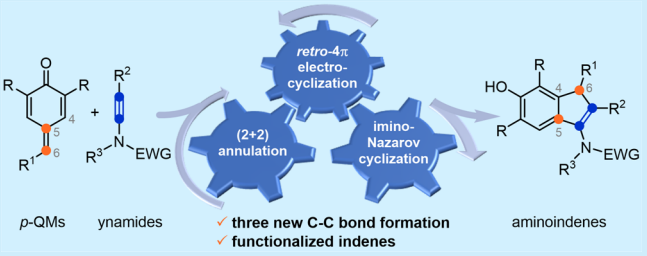
ABSTRACT: A new tandem annulation of *p*-quinone methides (*p*-QMs) with ynamides is described. This cascade reaction features a unique combination of (2 + 2) annulation, retro-4π electrocyclization, and imino-Nazarov cyclization, wherein vinyl *p*-quinone methides (*p*-VQMs) as one of the key intermediates have been identified chemically. Significantly, an unusual structural reconstruction of *p*-QMs involving the cleavage of the C5−C6 bond and the late-stage formation of the C4−C6 bond is involved, leading to a methodology development for the construction of functionalized aminoindenes.



p-Quinone methides (*p*-QMs) featuring a unique bisvinylogous enone system have been known as important structural units embedded in a lot of natural products,[1] and their transient reactive intermediates generated in situ are also involved in many biological processes.[2] Due to their intrinsic electrophilicity, partially enhanced by the aromatization driving force, *p*-QMs have received considerable attention in the design and development of methodology for organic synthesis.[3] Among the reaction modes chemically initiated by electrophilic propensity of the quinone methide unit, alkynes as C1 and C2 synthons have been recently introduced into the methodology design of *p*-QMs. For example, 1,6-conjugate additions of *p*-QMs with terminal alkynes or nucleophilic species generated in situ from alkynes have been reported for the synthesis of multisubstituted diarylmethanes (Scheme 1a).[4] The (4 + 2) annulations of *o*-aminophenyl or *o*-hydroxyphenyl-substituted *p*-QMs with ynones or electron-rich alkene intermediates derived from alkynes have been disclosed for accessing the aryl-substituted chromanes and hydroquinolines (Scheme 1b).[5] The (3 + 2) annulations of *p*-QMs with alkynes as well as a cascade 1,6-conjugate addition/cyclization of substituted *p*-QMs having a pendant alkynyl group have also been revealed to construct spiro[4.5]cyclohexadienones (Scheme 1c).[6] Despite this elegant progress, the exploration of chemical versatility of alkynes remains in high demand in the design of innovative chemical transformations of *p*-QMs. In connection with our continuing interest in the *para*-quinone methide chemistry,[7] ynamides[8] as one of the heteroatom-substituted alkyne synthons might be a class of appealing candidates for a new mode of tandem annulation of *p*-QMs (Scheme 1d), wherein chemically interesting vinyl *p*-quinone methide (*p*-VQM)[7a,9] intermediates, which would be generated in situ via (2 + 2) annulation/retro-4π electrocyclization cascade, could be unprecedentedly envisaged for imino-Nazarov cyclization[10] to yield the synthetically important aminoindenes that constitute the crucial structural unit existing in many bioactive molecules.[11,12] Noteworthy is that an uncommon structural reconstruction of *p*-QMs would be logically imposed by the C6 migration from C5 to C4 in this design. To our knowledge, the tandem chemistry involved in this methodology is yet to be presented in the synthetic community. Herein, we report our effort on this subject.

To probe the feasibility of our designed reaction, we commenced our investigation using *p*-QM **1a** and ynamide **2a** as model substrates. As shown in Table 1, commercially available and environmentally benign iron salts (e.g., $FeCl_2$, $FeCl_3$, $FeCl_3{\cdot}6H_2O$, and $Fe(OTf)_3$) as Lewis acid catalysts were chosen first (entries 1−4). Among iron(II) and iron(III) catalysts examined at room temperature in CH_2Cl_2, the use of $FeCl_3$ afforded the desired aminoindene **3aa** in 80% yield (entry 2). To improve the reaction reactivity, a series of Lewis

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Scheme 1. Modes of *p*-QMs with Alkynes and Our Design

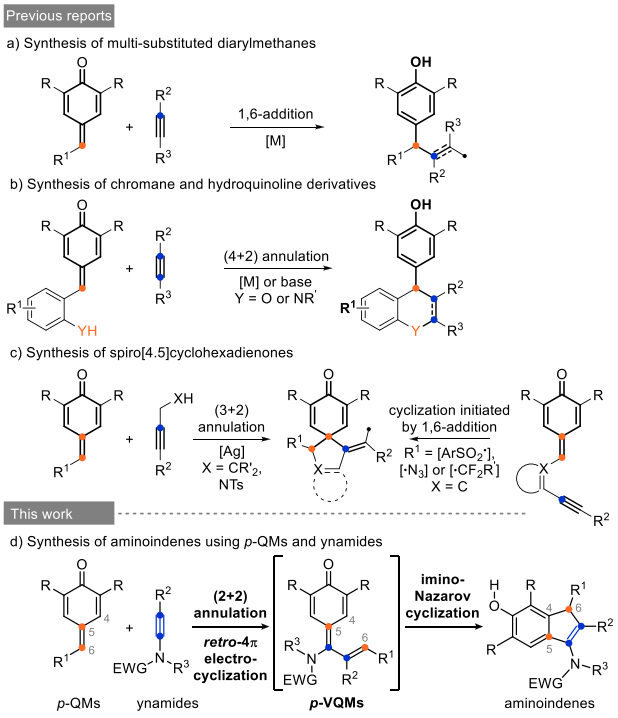
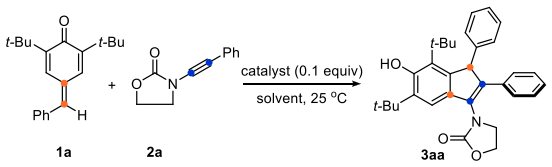


Table 1. Reaction Conditions Optimization[a]



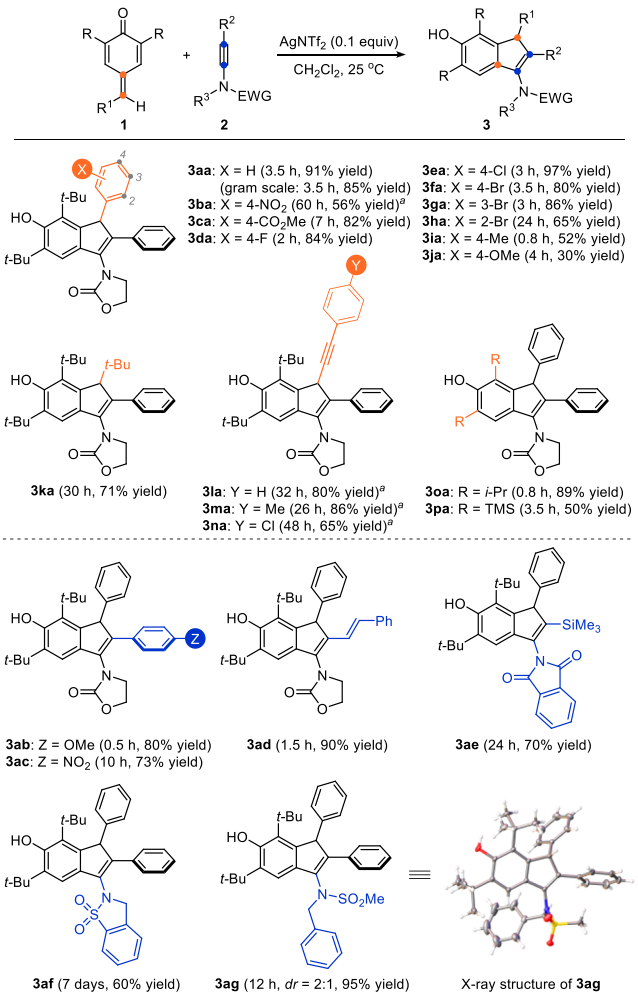
entry	catalyst	solvent	time (h)	yield[b] (%)
1	$FeCl_2$	CH_2Cl_2	16	70
2	$FeCl_3$	CH_2Cl_2	0.5	80
3	$FeCl_3·6H_2O$	CH_2Cl_2	0.5	79
4	$Fe(OTf)_3$	CH_2Cl_2	0.5	70
5	$Sc(OTf)_3$	CH_2Cl_2	2.0	67
6	$Cu(OTf)_2$	CH_2Cl_2	2.5	54
7	$Zn(OTf)_2$	CH_2Cl_2	48	40
8	$Bi(OTf)_3$	CH_2Cl_2	2.0	67
9	AgOTf	CH_2Cl_2	2.5	73
10	$AgNTf_2$	CH_2Cl_2	3.5	91
11	$AgNTf_2$	$CHCl_3$	4.0	87
12	$AgNTf_2$	EtOAc	24	85
13	$AgNTf_2$	acetone	6.5	60
14	$AgNTf_2$	PhCl	13	83

[a]Unless otherwise noted, all reactions were performed with **1a** (0.1 mmol) and **2a** (0.1 mmol) in the presence of catalyst (0.01 mmol) in the indicated solvent (1.0 mL) at 25 °C. [b]Yield of the isolated product.

acid catalysts including $Sc(OTf)_3$, $Cu(OTf)_2$, $Zn(OTf)_2$, $Bi(OTf)_3$, AgOTf, and $AgNTf_2$ were then evaluated (entries 5−10). Of them, noteworthy is that $AgNTf_2$ as catalyst could afford the desired aminoindene **3aa** in an optimal yield of 91% (entry 10). Meanwhile, the solvent effect was also surveyed using a different reaction medium (e.g., $CHCl_3$, AcOEt, acetone, and PhCl) (entries 11−14), despite no positive influence on reaction efficiency.

With the above optimized conditions in hand, as shown in Scheme 2, the scopes of *p*-QMs and ynamides were

Scheme 2. Substrate Scope for Tandem Annulation



[a]Performed at 40 °C.

investigated for this tandem annulation. Compared with the model *p*-QM **1a** (R^1 = Ph), a series of *p*-QMs (**1b−1f**, **1i**, and **1j**) with an electronically different *para*-substituted aryl R^1 group (R^1 = 4-$C_6H_4NO_2$, 4-$C_6H_4CO_2Me$, 4-C_6H_4F, 4-C_6H_4Cl, 4-C_6H_4Br, 4-C_6H_4Me, and 4-C_6H_4OMe) were investigated in the presence of ynamide **2a**. Except for the formation of **3ja** in a low yield of 30%,[13] the corresponding annulation products **3ba−3fa** and **3ia** could be isolated in moderate to good yields (52−97%). In the case using *p*-QM **1b** (R^1 = 4-$C_6H_4NO_2$), a prolonged reaction time of 60 h and an elevated reaction temperature of 40 °C were required for the formation of **3ba** in 56% yield, showing a somewhat negative influence of stronger electron-deficient property of aromatic R^1 to this tandem annulation. In addition to above examples, *meta*-substituted *p*-QM **1g** (R^1 = 3-C_6H_4Br) and *ortho*-substituted *p*-QM **1h** (R^1 = 2-C_6H_4Br) were examined subsequently. Compared with the case for readily forming the expected product **3ga** (3 h, 86% yield), the presence of unfavorable *ortho*-steric effects led to the prolonged time and decreased yield of the desired aminoindene **3ha** (24 h, 65% yield). Based on above evaluation of C(sp^2)-substituted *p*-QMs **1a−1j** (R^1 = aryl), one example using C(sp^3)-substituted *p*-QM **1k** (R^1 = *t*-Bu) was also

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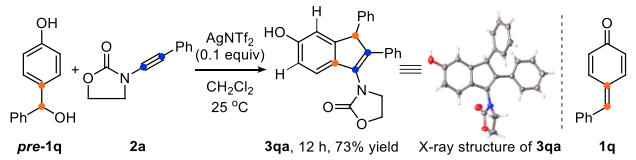
probed for this tandem reaction, and the aminoindene **3ka** could be delivered in 71% yield. The subsequent expansion of substrate scope was additionally pursued using three C(sp)-substituted *p*-QMs **1l**−**1n** having an extended π-conjugate system, and gratifyingly, the alkynyl-functionalized amino-indenes **3la**−**3na** were obtained in 65−86% yields at increased reaction temperature of 40 °C. Furthermore, two *p*-QMs (**1o** and **1p**) with different substituents at α and α' positions (R = *i*-Pr, and TMS) were subjected to standard conditions in the presence of **2a**, and the desired aminoindenes **3oa** and **3pa** could also be isolated in 89% and 50% yield, respectively. As shown in Scheme 3, chemically unstable *p*-QM **1q** generated in

Scheme 3. In Situ Protocol for Tandem Annulation

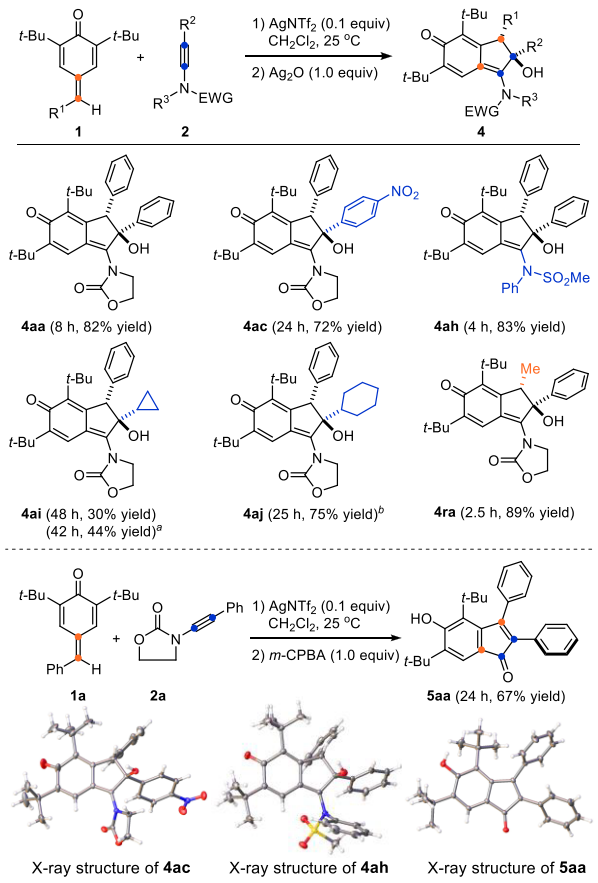


situ from *p*-hydroxybenzyl alcohol pre-**1q** was explored under standard conditions for this tandem reaction, and the anticipated aminoindene **3qa** could be readily afforded in 73% yield. The structure of **3qa** was clearly assigned by X-ray crystallographic analysis (CCDC 2088736).[14]

As another influencing factor to this reaction, the structural varieties of ynamides were further examined. As depicted in Scheme 2, several ynamides (**2b**−**2g**) bearing different substituents were probed in the presence of *p*-QM **1a**, and generally, the expected products **3ab**−**3ag** could be afforded in moderate to high yields (60−95%). For example, using ynamides **2b**−**2d** with a carbamate group and **2e** with an imide group gave the desired aminoindenes **3ab**−**3ae** in 70−90% yield, wherein styryl-substituted ynamide **2d** and silyl-substituted **2e** were suitable for the current transformation. Moreover, two ynamides with cyclic and acyclic sulfonamide moieties, **2f** (R^2 = Ph, N(R^3)EWG = dihydrosaccharin-2-yl) and **2g** (R^2 = Ph, R^3 = Bn, EWG = Ms), were introduced to the current reaction, leading to the desired products **3af** (7 days, 60% yield) and **3ag** (12 h, 95% yield) albeit at a decreased rate. Notably, the occurrence of atropisomers in **3ag** (2:1 dr) was observed in NMR spectra at room temperature, and the related atropisomerism induced by partially hindered rotation of C(sp^2)−N bond was confirmed by variable-temperature ^{1}H NMR experiments.[15] Interestingly, the recrystallization of **3ag** (2:1 dr) resulted in a crystal sample, which structure was unequivocally established by X-ray crystallographic analysis (CCDC 2076242).[14] Furthermore, a gram-scale reaction for accessing **3aa** was also performed in good yield of 85%.

Chemically inspired by the serendipitous fact that the air exposure of product **3aa** could result in the partial formation of inden-5-one **4aa**, a one-pot oxidation protocol based on this tandem annulation was then explored. As illustrated in Scheme 4, a one-pot general procedure was representatively probed using *p*-QM **1a** and ynamide **2a**, followed by addition of the oxidant Ag_2O (1.0 equiv) to the reaction mixture at the end of tandem annulation. Pleasingly, the indan-5-one product **4aa** was delivered in a good yield of 82%. Subsequently, ynamides **2c** (R^2 = 4-$C_6H_4NO_2$, N(R^3)EWG = oxazolidin-2-on-3-yl) and **2h** (R^2 = R^3 = Ph, EWG = Ms) were subjected to this protocol to provide the expected products **4ac** (72% yield) and **4ah** (83% yield). In addition, two alkyl-substituted ynamides **2i** (R^2 = cyclopropyl, N(R^3)EWG = oxazolidin-2-on-3-yl) and **2j** (R^2 = cyclohexyl, N(R^3)EWG = oxazolidin-2-on-3-yl) were investigated in a one-pot oxidation procedure modified by altering the oxidant or its equivalents, and chemically stable inden-5-ones **4ai** and **4aj** could be isolated in 44% and 75% yield, respectively. Moreover, one alkyl-substituted *p*-QM **1r** (R^1 = Me) was used in this one-pot protocol, smoothly giving the expected indan-5-one **4ra** in 89% yield.

Scheme 4. One-Pot Oxidation Based on Tandem Annulation



[a]$PhI(OAc)_2$ (2.0 equiv) instead of Ag_2O. [b]Ag_2O (2.0 equiv).

It should be noted that the corresponding in situ formed aminoindene intermediates (**3ai**, **3aj**, and **3ra**), which were involved in the generation of the above-mentioned inden-5-ones (**4ai**, **4aj**, and **4ra**), were chemically unstable during their chromatographic purification, to some extent manifesting the importance of the present one-pot oxidation protocol in expanding the scope of this tandem annulation. Based on such an investigation, the structural diversity of indenones bearing an alternative oxidative site, which could be commonly found in pharmaceutical and bioactive natural products,[12] was further examined by identifying *m*-CPBA instead of Ag_2O as oxidant, and the tandem one-pot oxidation protocol followed by dehydration and hydrolysis afforded the structurally useful inden-1-one **5aa**. The structures of **4ac**, **4ah**, and **5aa** were clearly confirmed by X-ray crystallographic analyses (CCDC 2076243, 2076244, and 2076245).[14]

To gain insight into this tandem annulation, several control experiments were run. As shown in Scheme 5, *p*-QM **1n** and ynamide **2f** were used as substrates to capture some chemically identifiable intermediates. When the title annulation was

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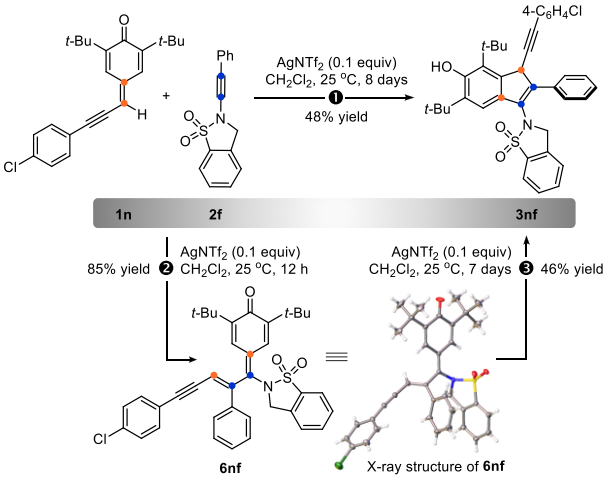
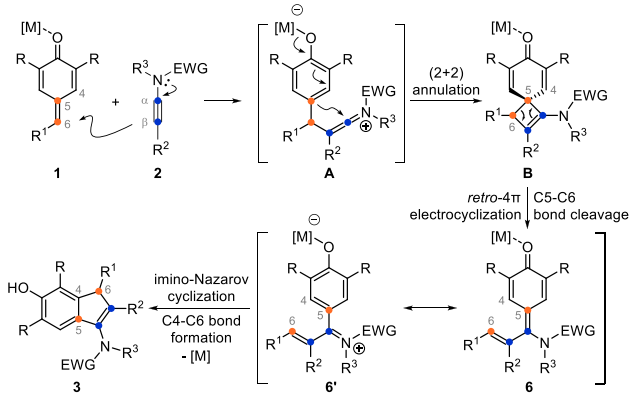
Scheme 5. Control Experiments



conducted under standard conditions, the aminoindene **3nf** could be isolated in 48% yield with a reaction time of 8 days (route ①). Importantly, the slow conversion of this reaction enables an observation of vinyl *p*-quinone methide (*p*-VQM) **6nf**, which could be isolated in 85% yield after 12 h (route ②). The structure of **6nf** was clearly assigned by X-ray crystallographic analysis (CCDC 2076246).[14] Interestingly, while *p*-VQM **6nf** was subjected to the standard conditions, the desired aminoindene **3nf** could be obtained with analogous efficiency (46% yield, 7 days) (route ③), mostly implying the possibility of *p*-VQM **6nf** as an intermediate in this tandem annulation.

Based on the above experimental results, a plausible mechanism was proposed in Scheme 6. Initially, the (2 + 2)

Scheme 6. Plausible Mechanism



annulation of *p*-QMs **1** with ynamides **2** proceeded to yield the spirocyclobutenyl *p*-dienones **B** through an intramolecular dearomatizing cyclization of keteniminium ion species **A**, resulting from 1,6-conjugate addition of ynamides **2** to *p*-QMs **1**. Driven by the release of ring strain of the cyclobutene framework, a retro-4π electrocyclization involving a C5−C6 cleavage might account for the formation of *p*-VQMs **6**, which have been chemically verified through X-ray crystallographic analysis. Then, an unusual imino-Nazarov cyclization[10] via zwitterionic **6′** as a resonance contributor of **6** took place to give the aminoindenes **3** having a partial C−C bond reconstruction.

In conclusion, an unprecedented tandem annulation reaction of *p*-QMs with ynamides has been developed, wherein the transformations including (2 + 2) annulation, retro-4π electrocyclization, and imino-Nazarov cyclization are involved. This reaction is characterized by partially structural reconstruction of *p*-QMs involving the shift of C6 from C5 to C4 through the cleavage of C5−C6 bond in retro-4π electrocyclization and subsequent formation of the C4−C6 bond in imino-Nazarov cyclization, providing an effective approach to the expeditious assembly of various highly functionalized aminoindenes. Notably, *p*-VQMs as one of the key intermediates of this tandem annulation are chemically identified via control experiments. Moreover, one-pot oxidation protocol based on this cascade annulation has also been established to yield structurally useful indenones. The present tandem annulation methodology not only furnishes a new method for assembling synthetically interesting, functionalized aminoindenes, and indenones but also enriches the chemistry of *p*-quinone methides in organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02003.

Experimental procedures and spectral data (PDF)

Accession Codes

CCDC 2076242−2076246 and 2088736 contain the supplementary crystallographic data for this paper. 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, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(14) The intensity data were collected on an Agilent SuperNova (Dual, Cu at zero, Eos) diffractometer using graphite-monochromated Cu Kα (λ = 1.54184 Å) radiation.

(15) For details, see the Supporting Information.

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