Denitrative hydroxylation of unactivated nitroarenes

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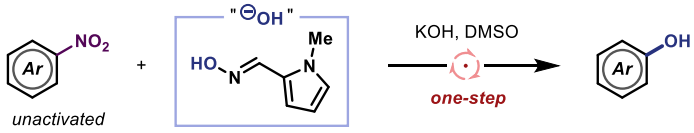
Abstract

A one-step method for the conversion of nitroarenes into phenols under operationally simple, transition-metal-free conditions is described. This denitrative functionalisation protocol provides a concise and economical alternative to conventional three-step synthetic sequences. Experimental and computational studies suggest that unactivated nitroarenes may be substituted via an electron-catalysed radical-nucleophilic substitution ($S_{RN}1$) chain mechanism.



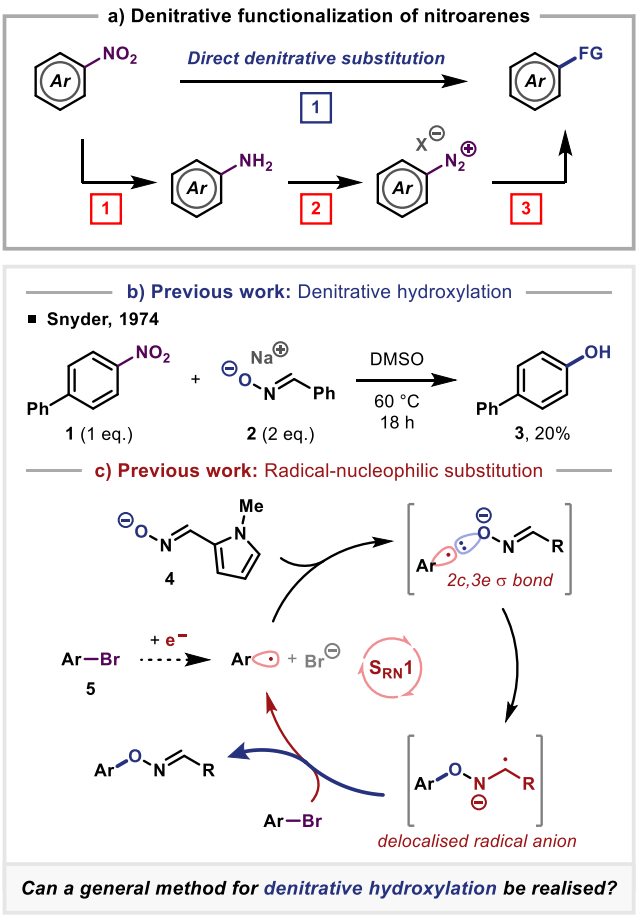
Nitroarenes are easily prepared, abundant chemical feedstocks, and privileged synthetic intermediates in organic chemistry.[1] The nitro group can be converted into a large variety of functional groups through a well-established three-step sequence consisting of (1) reduction, (2) diazotization and (3) substitution through Sandmeyer-type reactions (Scheme 1a).[2] Whilst generally reliable, this approach requires multiple synthetic steps, typically involving harsh reaction conditions and the handling of hazardous intermediates. The development of more efficient, single-step denitrative functionalization reactions is therefore an area of significant synthetic value and interest.[3,4]

In this regard, direct nucleophilic substitution is an attractive synthetic approach due to its low cost and operational simplicity.[5] However, these methods are typically narrow in scope and limited to electron-deficient (activated) nitroarenes bearing strong electron-withdrawing groups in the *ortho* or *para* positions. Methods which can overcome this limitation are known, but are rare and of limited scope.[6] For example, Snyder and co-workers reported that unactivated nitroarene **1** could be substituted with oxime anion **2** to form phenol **3** in 20% yield (Scheme 1b).[7] This denitrative hydroxylation reaction was proposed to proceed via a stepwise addition-elimination nucleophilic aromatic substitution (S_NAr) mechanism (followed by the elimination of an *O*-aryl oxime intermediate to form phenol **3**). However, the mechanism of this reaction—along with many such denitrative substitution reactions—has long been debated, with several radical-based alternatives proposed.[8]

Inspired by this work, and our recent study,[9,10] in which we postulated that oxime anion **4** can substitute aryl halides **5** through an electron-catalysed radical-nucleophilic substitution ($S_{RN}1$) chain mechanism (Scheme 1c),[11,12] we sought to determine if a general denitrative hydroxylation protocol using our designed reagent could be realised. We rationalised that a broad range nitroarenes may also be substituted by an $S_{RN}1$ mechanism if aryl radicals can be formed via the fragmentation of nitroarene radical-anions.

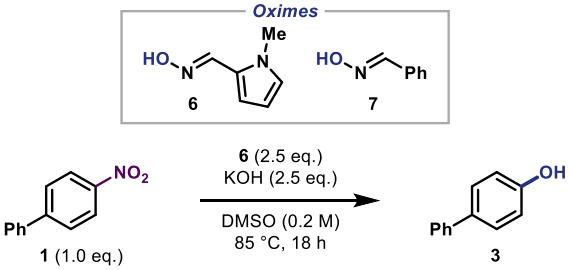
Herein, we report the selective denitrative hydroxylation of electronically diverse nitroarenes, including unactivated nitroarenes, using an easily-handled oxime nucleophile. An electron-catalysed $S_{RN}1$ chain mechanism is proposed for the substitution of unactivated nitroarenes based on experimental and DFT computational studies. This work provides rare evidence to suggest that aryl radicals can be generated via the fragmentation of a nitroarene radical-anion.

Scheme 1. Denitrative functionalization of nitroarenes.



Our studies began by investigating the reaction of nitroarene **1** with our previously described oxime reagent **6**. Pleasingly, we found that phenol **3** could be formed in 84% yield when electronically unactivated 4-nitrophenyl **1** was reacted with oxime **6** (2.5 equivalents) and KOH in anhydrous DMSO (0.2 M) at 85 °C for 18 h under nitrogen (Table 1, entry 1). No phenol **3** was observed in the absence of the oxime reagent, excluding the possibilty that KOH is the active nucleophile (entry 2). The yield of phenol **3** was also reduced when oxime **7** was used instead of **6**, highlighting the importance of our recently developed reagent. Other bases were also compatible with this reaction protocol, but all were inferior to KOH (entries 4–8). Decreasing the reaction temperature from 85 °C to 70 °C reduced the yield of phenol **3** to 26%. Changing the solvent from DMSO to other polar aprotic solvents (e.g. DMI, entry 10) was possible, but also decreased the yield of phenol **3**.

Table 1. Reaction optimization studies.



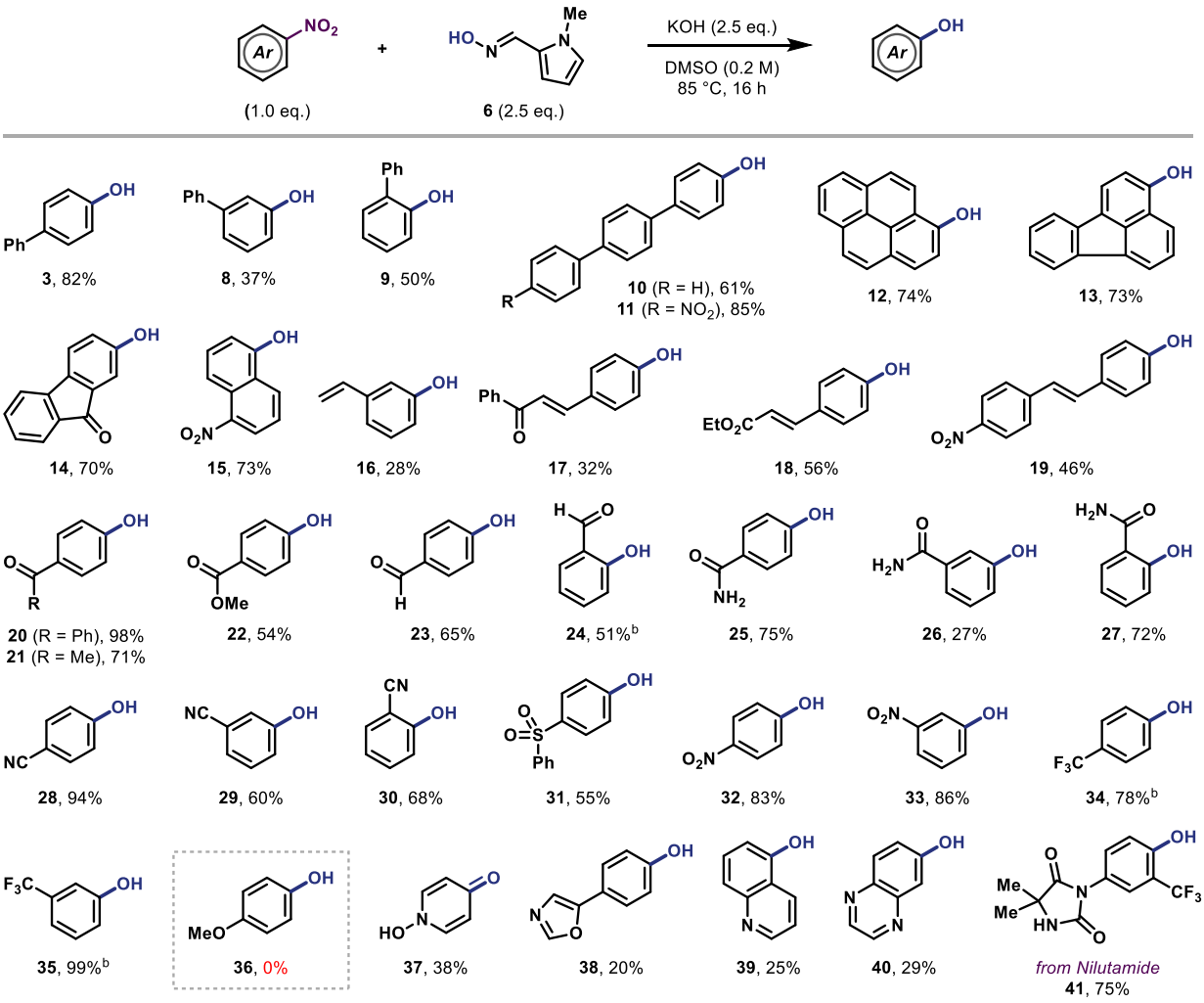
Entry[a]	Deviation from above	Yield[b] **3** / %
1	none	84
2	No oxime	0
3	Oxime **7** instead of **6**	40
4	LiOH instead of KOH	14
5	NaOH instead of KOH	54
6	RbOH instead of KOH	32
7	CsOH instead of KOH	68
8	KO*t*-Bu instead of KOH	71
9	70 °C instead of 85 °C	26
10	DMI instead of DMSO	58

[a] Unless state otherwise, all reactions were performed with 0.1 mmol of nitroarene **1** and 0.25 mmol oxime **6**/**7** with the stated base (0.2 mmol) in DMSO (0.2 M) under nitrogen. [b] Determined by ^{1}H NMR spectroscopy against an internal standard (dibromomethane).

The generality of this one-step denitrative hydroxylation reaction was then explored using the optimised reaction conditions (Scheme 2). First to elucidate the importance of any substitution pattern, the reactivity of the different *para*-, *meta*- and *ortho*- substituted nitrobiphenyl isomers was examined. Pleasingly, no limitation was found as every isomer (**3**,**8**,**9**) could be accessed through this method. Related terphenyl derivatives **10**,**11** were also formed in good to excellent yields. Polycyclic nitroarene derivatives were hydroxylated in a similar fashion to afford hydroxy-pyrene **12**, -fluoranthene **13**, -fluorenone **14** and -naphthalene **15** in generally excellent yields. In addition, no dihydroxylation was observed in the reaction to form hydroxy-naphthalene **15**, which further highlights the selectivity of this method. Interestingly, electronically unactivated 3-nitrostyrene was also successfully hydroxylated to afford phenol **16** in 28% yield. Whilst modest in yield, this transformation illustrates the potential power of this method to selectively hydroxylate nitroarenes that may be incompatible with a conventional three-step denitrative hydroxylation sequence. Other hydroxy-styrene derivatives, such as *trans*-chalcone **17**, ethyl cinnamate **18** and stilbene **19** could also be prepared with this method. Exclusive mono-hydroxylation was again observed in the reaction to form stilbene **19**. Next, *para*-substituted carbonyl and ester nitrobenzene derivatives were all selectively converted into phenols **20**–**22** in good to excellent yields. Tolerance of sensitive functional groups was also demonstrated through the synthesis of *para*- and *ortho*-substituted hydroxy-benzaldehydes **23**,**24**. Furthermore, unprotected *para*-, *meta*- and *ortho*-hydroxy-benzamides **25**–**27** could be prepared through this reaction protocol, which again demonstrates that this method is not limited to the substitution patterns typically associated with polar S_NAr reactions. Nitrile and sulfone functional groups were similarly tolerated as phenols **28**–**31** were formed in generally excellent yields. Importantly, it should be noted that the general reaction conditions were not optimised for such electron-deficient nitroarenes and that many of these transformations may occur at much lower reaction

temperatures (e.g. the formation of 4-cyanophenol **28** in quantitative yield was observed after just 30 mins at 30 °C by ^{1}H NMR spectroscopy). Strongly electron-deficient systems, such as dinitroarenes and trifluoromethyl-substituted nitroarenes also underwent selective (mono-)hydroxylation to afford phenols **32**–**35** in generally excellent yields. Conversely, a more electron-rich nitroanisole derivative could not be converted into phenol **36**. Finally, the broad synthetic utility of this method was demonstrated through the conversion of heteroaryl nitro compounds and a nitroarene drug (Nilutamide) into phenols **37**–**41**.

Scheme 2. Scope of the denitrative hydroxylation protocol.[a]

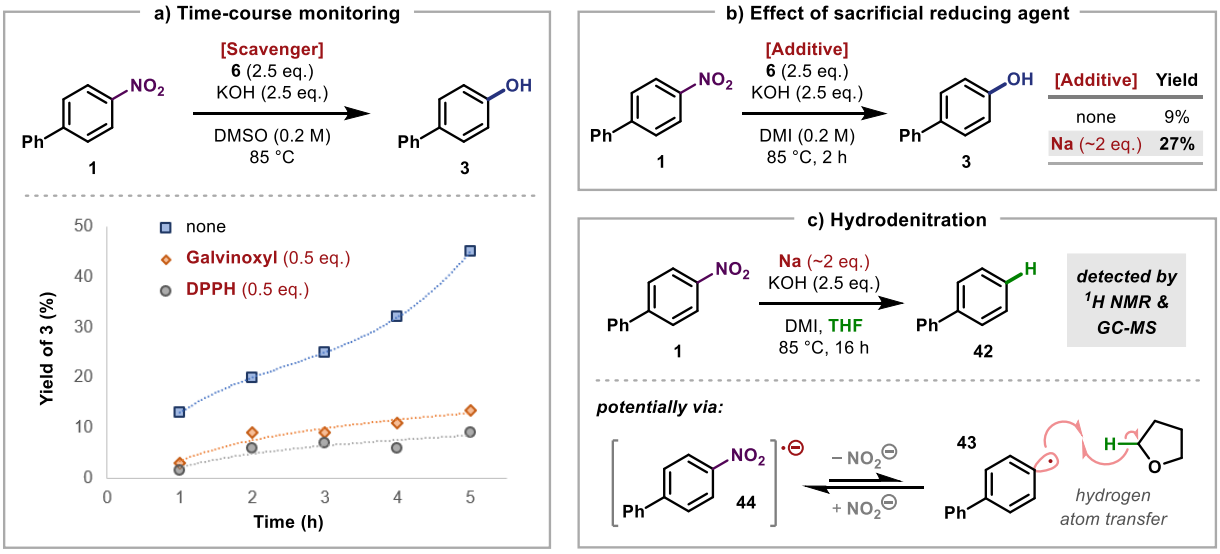


[a] Reactions performed on a 0.30 mmol scale in 1.5 mL of DMSO. [b] Yield of volatile compound determined by ^{1}H or ^{19}F NMR spectroscopy against an internal standard (dibromomethane and 1-fluoronaphthalene, respectively).

Having successfully established the broad scope of this transformation, we then sought to determine if an open-shell (e.g. $S_{RN}1$) or a polar (S_NAr) mechanism was operative. Thus, we monitored the formation of phenol **3** from the reaction of oxime **6** with our model substrate, 4-nitrobiphenyl **1**, over time in the presence of known radical/redox scavengers, Galvinoxyl and DPPH (Scheme 3a). In both cases, the formation of phenol **3** was significantly inhibited, which—as with other nitroarene substitution reactions[8c]—strongly suggested that phenol **3** is formed via a radical (chain) mechanism. Inspired by the mechanistic studies of Kornblum and co-workers and Shirakawa, Hayashi and co-workers,[12a,13] the reaction of oxime **6** with **1** was then repeated with sodium metal added to determine if this reaction could be accelerated by a sacrificial single electron donor (Scheme 3b; note: these reactions were performed in DMI as sodium metal is known to react with DMSO). After two hours the yield of phenol **3** was

increased from 9% to 27% in the presence of sodium metal, which indicated that this reaction was likely driven by one-electron reduction. More interestingly, when this reaction was repeated in the absence of oxime **6** and using THF as a co-solvent, the formation of the hydrodenitration product **42** was observed (Scheme 3c), which suggested that aryl radical **43** may be formed via the fragmentation of nitroarene radical-anion **44**. This result was consistent with the observations made by Guthrie and co-workers,[14] who noted that potassium salts of related nitroarene radical-anions undergo hydrodenitration under similar conditions. Notably, Guthrie and co-workers also proposed that hydrodenitration occurs via the formation of aryl radicals, and that the counter-cation plays a crucial role in this process (lithium salts did not undergo hydrodenitration). Finally, as nitroarene radical-anions are known to spontaneously form in basic solutions,[15] we verified that nitroarene radical-anions are also formed under the developed reaction conditions by EPR spectroscopy (see the SI). These radical-anion species are proposed to form via electron transfer from the oxime anion to the electron-deficient nitroarene.

Scheme 3. Experimental mechanistic studies.

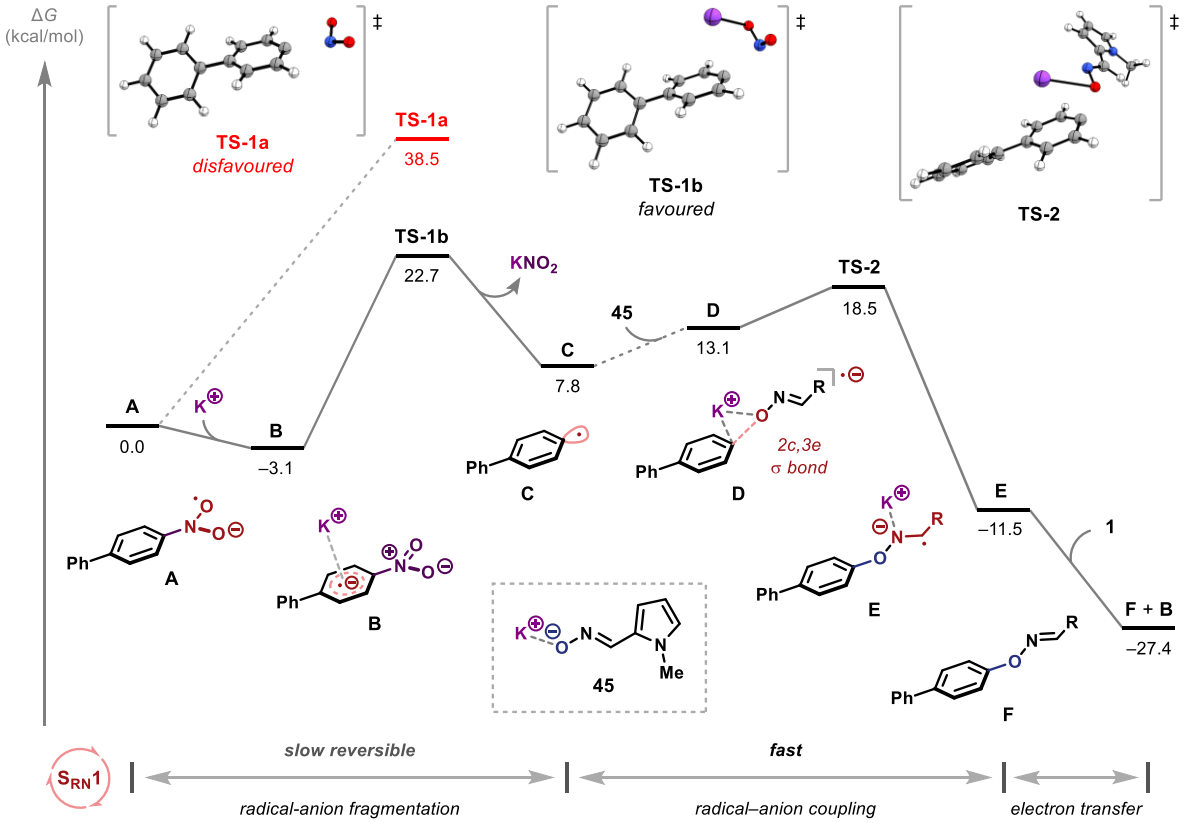


To gain further insight into the mechanism of these reactions, the substitution of unactivated nitroarene **1** was explored by DFT computational analysis (Figure 1).[16] First, a polar S_NAr pathway was examined, but the contribution of this pathway to the substitution process was considered to be low due to the significant activation barrier for the addition of the oxime anion to nitroarene **1** ($\Delta G^{\ddagger}$ = 38.7 kcal/mol, see the SI). However, this activation barrier is much smaller for more electronically activated systems, e.g. classic *ortho*- and *para*-substituted S_NAr substrates, such as 4-cyanonitrobenzene (see the SI).

Next, an open-shell $S_{RN}1$ pathway was examined. Considering that DMSO is known to strongly disrupt ion-pairing between nitroarene radical-anions and alkali metal cations,[17] the nitroarene radical-anion was modelled as a free-ion (**A**) and a weakly coordinated, solvent-separated ion-pair (represented as **B**).[18] Interestingly, the activation barrier for the direct fragmentation of free-ion **A** was determined to be substantial (**A** → **TS-1a**, $\Delta G^{\ddagger}$ = 38.5 kcal/mol). However, the activation barrier for the fragmentation of ion-pair **B** was considerably lower (**B** → **TS-1b**, $\Delta G^{\ddagger}$ = 25.9 kcal/mol), indicating that the potassium counter-cation mediates this process. Importantly, this fragmentation would be reversible as it is thermodynamically uphill (**B** → **C** + KNO_2, ΔG = 10.9 kcal/mol), but the fast, exergonic coupling of radical **C** with oxime anion **45** (**C** + **45** → **E**, ΔG = −19.3 kcal/mol) via a two-centre three-electron σ bonded species (**D** → **TS-2**, $\Delta G^{\ddagger}$ = 5.4 kcal/mol),[19] would move the position of equilibrium to compensate for this unfavourable fragmentation. Propagation of the radical chain would also be favoured as electron transfer from the coupled radical-anion **E** to the nitroarene substrate **1** is exergonic (**E** + **1** → **F** + **B**, ΔG = −15.9 kcal/mol). Whilst initially challenging, this overall free energy profile is consistent with that theorised by

Savéant for slow-cleaving radical-anion substrates in $S_{RN}1$ reactions.[20] In addition, the catalytic role of the potassium counter-cation in the proposed fragmentation process may account for the stability of nitroarene radical-anion lithium salts previously observed by Guthrie and co-workers.[14]

Figure 1. Radical-nucleophilic substitution free energy profile calculated at the ωB97X-D3(BJ)/ma-def2-QZVPP/SMD(DMSO)//ωB97X-D3(BJ)/6-311++G(d,p) level of theory. Free energies are in kcal/mol (at 85 °C, 1 M) and have been corrected to account for the excess concentration of oxime anion relative to the aryl radical.



In summary, we have reported the development of a method to directly convert nitroarenes into phenols in one-step and under operationally simple, transition-metal-free conditions. In addition, rare evidence was obtained to suggest that nitroarene radical-anions—often considered to be "stable"—can fragment to generate aryl radicals, and that this process may be mediated by alkali metal counter-cations. Our experimental and theoretical studies indicate that a wide range of electronically unactivated nitroarenes may be substituted through an electron-catalysed $S_{RN}1$ mechanism, whilst more activated nitroarenes may react via both polar and open-shell mechanisms. We hope that this work will inspire the development of many other methods for the direct denitrative functionalisation of nitroarenes and alleviate our long-standing reliance on established synthetic sequences.

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