Catalytic Nitrene Transfer To Alkynes: A Novel and Versatile Route for the Synthesis of Sulfinamides and *iso*-Thiazoles

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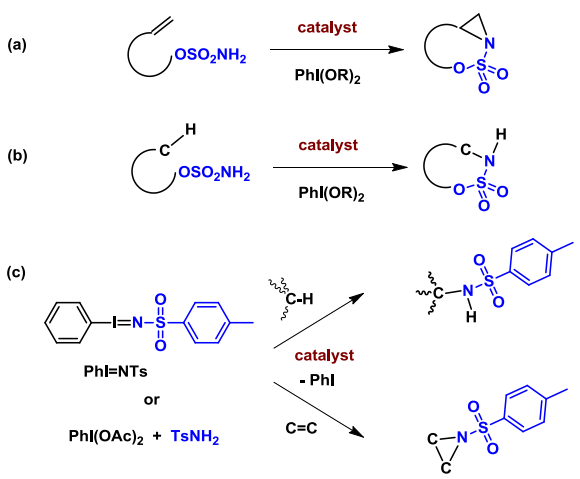
Dedication ((optional))

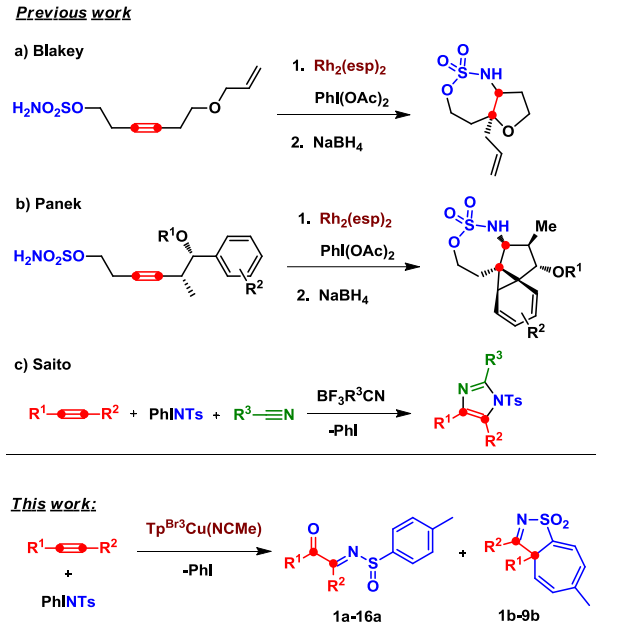
Abstract: A novel transformation is reported for the reaction of terminal or internal alkynes with the nitrene precursor PhI=NTs (Ts = *p*-toluenesulfonyl) in the presence of catalytic amounts of $Tp^{Br3}Cu(NCMe)$ (Tp^{Br3} = hydrotris(3,4,5-tribromo-pyrazolylborate). Two products containing an imine functionality have been isolated from the reaction mixtures, identified as sulfinamides and *iso*-thiazoles. The former correspond to the formal reduction of the sulfone group into sulfoxide, whereas the latter involves the insertion of an alkyne carbon atom into the aromatic ring of the N-tosyl moiety.

The metal-induced transfer of a nitrene group has emerged as an important tool in organic synthesis.[1],[2],[3] In a general manner, a hypervalent iodine reagent can be formed in situ (Scheme 1a-c) from a sulfonylamide and the corresponding oxidant [$PhI(OR)_2$], or can be isolated as the common iminoiodonane PhI=NTs (Scheme 1c). Typical transformations involve the addition of the NR unit to a C=C bond or the insertion of such moiety into a C-H bond. In some cases, these catalytic transformations have been conducted in an asymmetric manner.[3]



Scheme 1. Common metal-catalyzed nitrene transfer strategies in organic synthesis using hypervalent iodine reagents.

In spite of this progress, the use of alkynes as substrates for nitrene transfer reactions is yet under-developed. This is probably due to the fact that the addition of a nitrene NR unit to an alkyne would lead to a 2-azirine, that is unstable due to its anti-aromacity.[4] Because of this, there are very few examples (Scheme 2) of catalytic reactions involving the alkyne and nitrene groups. Blakey and Panek independently described[5,6]



Scheme 2. Previous transformation reported in the literature where a nitrene and an alkyne are involved and that described in this work.

the intramolecular nitrene attack onto a triple carbon-carbon bond (Scheme 2a-b) in the presence of a rhodium-based catalyst. The intermolecular reaction has only been described by Saito et al,[7] albeit in the presence of nitrile as a third partner, leading to imidazoles (Scheme 2c). The related reaction from triazole opening and nitriles was described by Fokin and co-worker.[8] However, the intermolecular reaction of an alkyne with a nitrene precursor such as PhI=NTs as the sole reactants remains yet undescribed. In this contribution we report such that transformation that leads to two products, the sulfinimides **1a-16a** and *iso*-thiazoles **1b-9b** shown in Scheme 2, in a general procedure that operates with a number of terminal and

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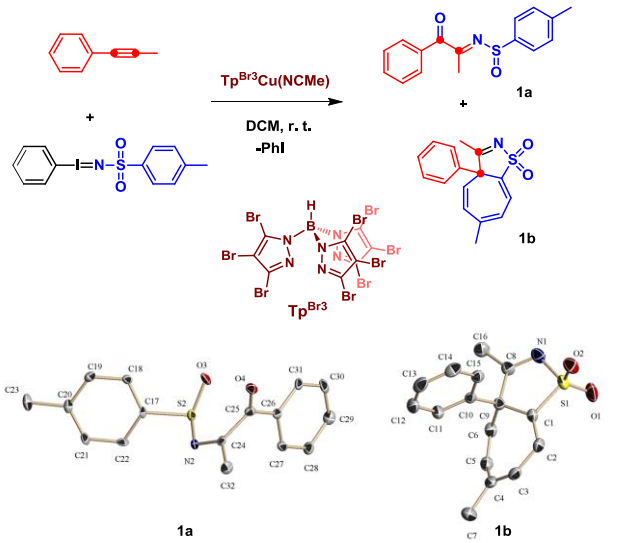
internal non-elaborated alkynes. For the former as substrates, only the sulfinimides are obtained whereas internal alkynes afford mixture of both products.

Our group has been involved in the developed of catalytic systems for the nitrene transfer reaction to saturated and unsaturated substrates.[9] The catalysts were copper or silver complexes containing trispyrazolylborate ligands, Tp^{x}, and the nitrene source either PhI=NTs or mixtures of sulfonylamides and an iodine (III) oxidizing agent.[9b] With this bulk of knowledge on



Scheme 3. The probe reaction of 1-phenyl-1-propyne with PhI=NTs in the presence of $Tp^{Br3}Cu(NCMe)$ as the catalyst. The ORTEP view of the structures of compounds **1a** y **1b** is shown with 50% thermal ellipsoids are shown. Hydrogen atoms have been omitted for clarity.

nitrene transfer reactions we faced the use of alkynes as substrates. We first employed the complex $Tp^{Br3}Cu(NCMe)$ toward the reaction of 1-phenyl-1-propyne and PhI=NTs (Scheme 3), since that complex is one of the most active for the transformations mentioned above. The reaction was carried out at room temperature in dichloromethane as solvent. Once the reaction was completed, the solvent was removed under reduced pressure and the reaction crude was analyzed by NMR spectroscopy showing the presence of two products in addition to $TsNH_2$, a typical by-product in PhI=NTs-containing reactions (Scheme 3a). Reaction workup led to single crystals[10] of the two new products that have been identified as (*E*)-4-methyl-N-(1-oxo-1-phenylpropan-2-ylidene)benzenesulfinamide (**1a**) and 3,6-dimethyl-3a-phenyl-3aH-cyclohepta[d]isothiazole 1,1-dioxide (**1b**). Formally, each compound contains one molecule of the initial alkyne and one NTs unit from PhI=NTs. Spectroscopic and analytical data of pure bulk samples of **1a** and **1b** were in agreement with such formulation (see Supporting Information).

Compounds **1a** and **1b** have an imine functionality as the result of the formation of a C=N bond between the nitrene group and the alkyne carbon atom supporting the methyl group. Interestingly, **1a** shows a reduction from S(VI) to S(IV) and the corresponding transfer of an oxygen atom to the other alkyne carbon atom. This is a rare process, since the commonly occurring reaction is that of a sulfoxide $RR'S^{(IV)}=O$ being oxidized into the sulfone $RR'S^{(VI)}O_2$. The oxygen transfer observed here has been previously described by other groups in the context of N-sulfonyl-triazoles decomposition reactions.[8,11,12] Compound **1b** displays, in addition to the imine formation, the formal insertion of the other alkyne carbon atom into a C-C bond of the aromatic ring of the tosyl group. The formation of the cycloheptatriene ring is typical of consecutive carbene addition

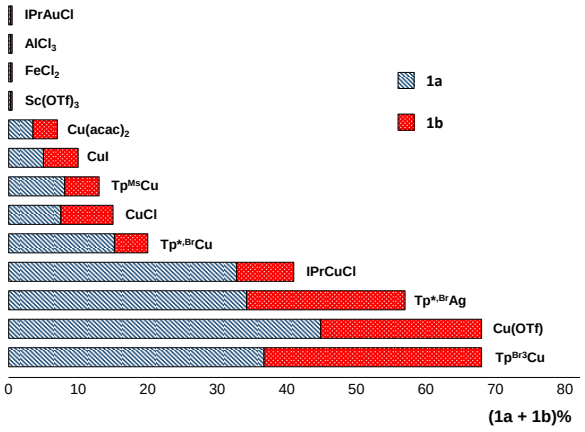


Figure 1. Catalyst screening for the nitrene transfer reaction onto 1-phenyl-1-propyne.

to an arene, norcaradiene formation and ring-opening, in the so-called Buchner reaction.[13]

In view of this unprecedented transformation, we wondered about the use of other different catalysts to promote it. We therefore screened a series of Cu-, Ag- and Au-based complexes either bearing Tp^{x} ligands as well as a NHC ligand (IPr = 1,3-bis(diisopropylphenyl)imidazole-2-ylidene). Several Lewis acids were also tested toward a possible influence of such feature in the reaction outcome, since the $Tp^{Br3}Cu$ fragment displays a significant Lewis acidity.[9a] The results are displayed in Figure 1. Lewis acids such as $AlCl_3$, $FeCl_2$ or $Sc(OTf)_3$ gave no products. The $Tp^{*,Br}Cu(NCMe)$ complex revealed low catalytic activity, achieving conversions around 20%. However, when replacing Cu with Ag as the metal center with this same ligand, the conversion increased up to 60%. The IPrAuCl complex was inert toward this transformation as catalyst. In general, Cu(I)-based catalysts were more active than those based on Cu(II), such as $Cu(acac)_2$. The most active catalysts were Cu(OTf) and $Tp^{Br3}Cu(NCMe)$, in line with previous reports of being good catalysts for olefin aziridination reactions.[14,15] Albeit both compounds displayed similar activities, we chose the complex $Tp^{Br3}Cu(NCMe)$ to develop the scope of this system, in view of its remarkable stability under air, not only in the solid state but also in dichloromethane solution.[16]

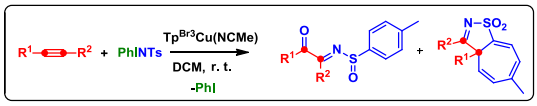
In order to optimize the reaction conditions, we carried out a set of experiments at different temperatures or reaction solvents (see Supporting Information). We found no significant changes in either the conversion or the selectivity of the reaction. Remarkably the use of acetonitrile as solvent did not infer any variation in the reaction outcome, in contrast with the results reported with Saito in their non-catalytic reaction (Scheme 2c),[7] assessing the role of the catalyst in our transformation.

The scope of the reaction has been first studied with the internal alkynes shown in Table1. The presence of an aromatic ring directly bonded to the carbon-carbon triple bond appears mandatory, since no reaction was observed using hex-3-yne, 4-methylpent-2-yne or dimethyl but-2-ynedioate as substrates. With the aryl-substituted alkynes, those bearing a donating group in the *para* position gave higher yields than those bearing H or electron-withdrawing groups, although overall the yields were above 70% in all cases (entries 1-4). The presence of

methyl groups in the *ortho* position affected the reaction outcome (entries 5-6), increasing the selectivity toward the sulfonamides with a slight decrease in yields. Also noteworthy is the effect of the methyl group in the alkyne: its substitution by Et, Ph or CH_2Cl induced a dramatic decrease in conversions (entries 6-9). Some of the new products such as **2b** or **6a** have been characterized by X-ray crystallography (see Supporting Information).

The use of terminal alkynes as reactants has brought an interesting feature of this catalytic system: the *selective* formation of the sulfinamide compounds as the unique new product of the reaction, the *iso*-thiazoles being not formed at

Table 1. Scope of the reaction of PhI=NTs and internal alkynes using $Tp^{Br3}Cu(NCMe)$ as catalyst.[a]

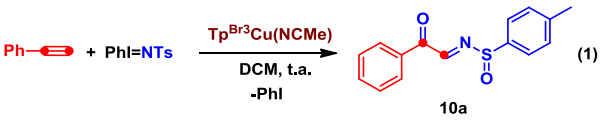


Entry	R^1	R^2	Products	Conversion[b,c] Selectivity a:b[c]
1	Ph	Me	1a / 1b	70% 54:46
2	*p*-Tol	Me	2a / 2b	79% 62:38
3	*p*-CF_3-C_6H_4	Me	3a / 3b	71% 61:39
4	*p*-CH_3O-C_6H_4	Me	4a / 4b	85% 85:15
5	*o*-Tol	Me	5a / 5b	62% 80:20
6	Mesityl	Me	6a / 6b	42% 95:5
7	Ph	Et	7a / 7b	11%[d]
8	Ph	CH_2-Cl	8a / 8b	12%[d]
9	Ph	Ph	9a / 9b	16%[d]

[a] Reactions carried out at room temperature with 0.01 mmol of catalyst, 20 equiv of PhI=NTs and 200 equiv of alkyne in 6 mL of CH_2Cl_2. Reaction time: 2 h. [b] Determined by NMR using 1,3,5-trimethoxybenzene as internal standard. $TsNH_2$ accounted for 100% initial PhI=NTs not converted in products (a+b). [c] Determined by NMR. [d] Full characterization precluded due to the low yield.

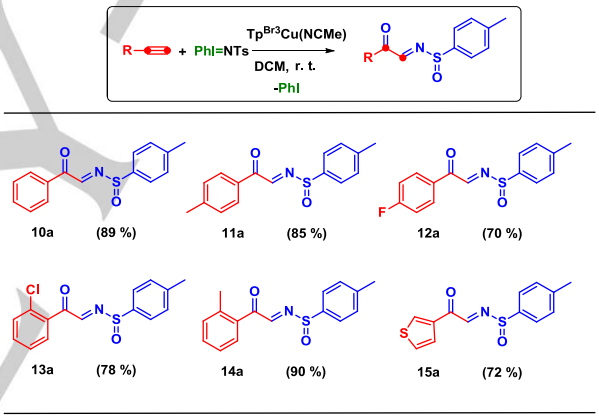
variance with the reaction with internal alkynes. Under the reaction conditions shown in Table 1, phenyl acetylene was reacted with PhI=NTs [eq. (1)], from which the sulfinamide **10a** was obtained. However, we must note that ^1H NMR monitoring of this reaction at -20 ºC showed a series of minor resonances attributable to the *iso*-thiazol **10b** at the first stages of the transformation, which disappeared with the reaction time or increasing the temperature until room temperature.

A series of terminal alkynes were reacted with PhI=NTs in the presence of $Tp^{Br3}Cu(NCMe)$, for which the sulfinamides **11a**-**15a** were obtained in yields within the range 70-90% (Scheme 4). The reactivity pattern is similar to that commented for the



internal alkynes, albeit the presence of *ortho*-substituents in the aryl group of the alkynes does not influence much in the reaction outcome. As an additional finding, the reaction proceeded with 3-ethynylthiophene with good conversions into **15a** (72%),

Scheme 4. Scope of the reaction of PhI=NTs and terminal alkynes using $Tp^{Br3}Cu(NCMe)$ as catalyst.[a-c]



[a] Reactions carried out at room temperature with 0.01 mmol of catalyst, 20 equiv of PhI=NTs and 200 equiv of alkyne in 6 mL of CH_2Cl_2. Reaction time: 2 h. [b] Determined by NMR using 1,3,5-trimethoxybenzene as internal standard. $TsNH_2$ accounted for 100% initial PhI=NTs not converted into products. [c] Determined by NMR. [

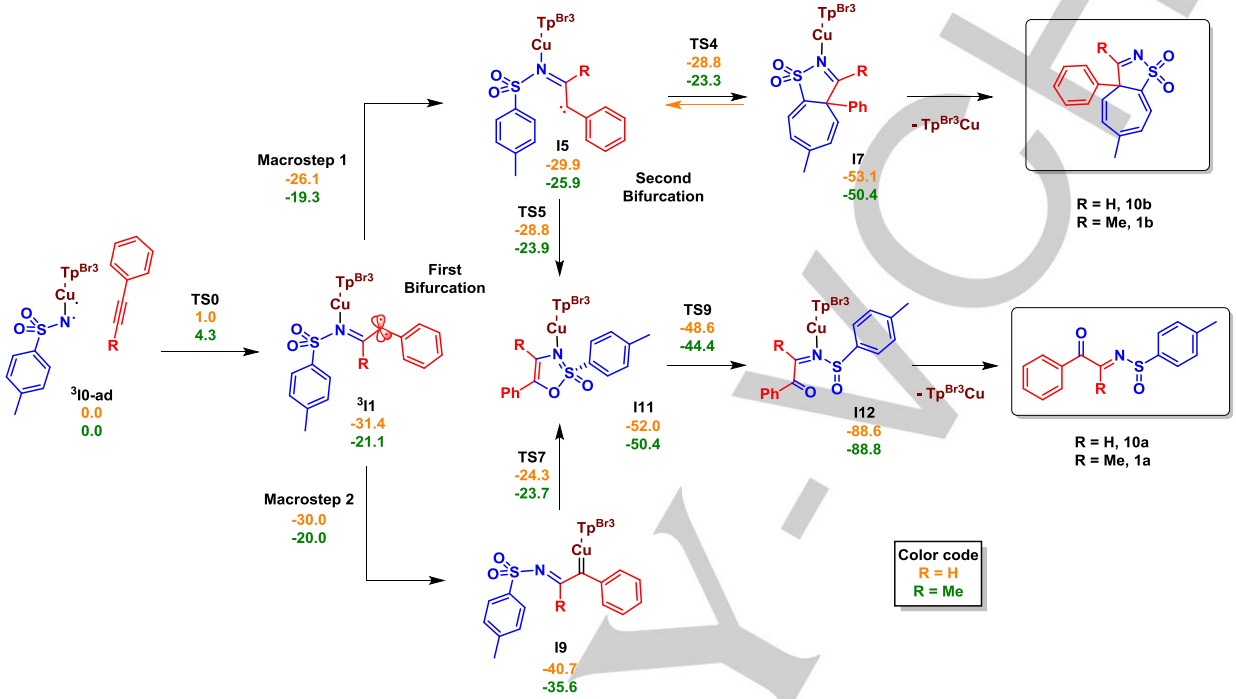
demonstrating that the reaction is not exclusive for phenyl-containing alkynes.

Albeit we have not yet performed any post-modification of the new products obtained, their synthetic utility can be exemplified by the use of N-tosylimines as synthons.[17],[18] Thus, Shimizu and co-workers described the conversion of such imines into α-amino-β-hydroxyesters. The same group also reported the reduction of N-tosylimines into the corresponding amines, in both cases titanium tetrahalides being employed as promoters of those transformations.

In view of the novelty of this transformation, we have also focused on the mechanism that governs it. To gain information about it we have performed DFT calculations[19],[20] with both the methyl substituted and the terminal alkyne. The mechanism happens to be quite complex, a simplified view is shown in Scheme 5, the detailed version is given in the Supporting Information. The origin of energies is a weak adduct between the alkyne and a metallonitrene complex, which had been previously demonstrated to be a triplet in the ground state from previous studies on the use of Tp^xM complexes (M = Cu, Ag) for

olefin aziridination reactions.[21] The results with 1-phenyl-1-propyne are discussed first (green numbers in Scheme 5). The two fragments react with a low barrier to form intermediate ^{3}**I1**, which is also in a triplet state, with both unpaired electrons in the benzylic carbon. This intermediate can evolve through multistep paths, containing both transition states (TS) and minimum

Scheme 5. Simplified view of the computed mechanism. Free energies reported in kcal/mol



energy crossing points (MECP), to either the imine intermediate **I5** or the carbene intermediate **I9**, both in the singlet state. The path from ^{3}**I1** to **I5** has been considered together in **Macrostep 1**, with a highest energy point of -19.3 kcal/mol. Remarkably, this **Macrostep1** includes an azirine intermediate (see Supporting Information) analogous to the aziridine product obtained in alkene activation, which is thus confirmed not to be stable in the alkyne activation conditions. The corresponding path from ^{3}**I1** to **I9**, **Macrostep 2**, has a highest energy point of -20.0 kcal/mol. With an energy difference of 0.7 kcal/mol both paths will be used by the system, in what it has been considered as the first bifurcation in the reaction mechanism.

The carbene route continues smoothly through intermediate **I11** towards product **I12**, which contains product **1a** coordinated to the metal center. A similar intermediate to **I11** has been proposed by several groups for this uncommon reduction of S(VI) to S(IV) through oxygen transfer.[8,11,12]

The imine path, through intermediate **I5**, has a second bifurcation, with competing highest energy points of -23.9 and -23.3 kcal/mol *en route* to **1a** or **1b**, respectively. Assuming a Boltzmann distribution between the competing paths in each bifurcation, these numbers for the methyl system predict an **1a**:**1b** ratio of 89:11. The agreement is not good with the experimental value of 54:46, but the formation of two products is correctly predicted

The mechanism for the terminal alkyne (orange numbers in Scheme 5) follows a qualitative similar path, and if we analyzed the two bifurcations with the approach described above, it would yield also a mixture of products, in disagreement with experiment. There is however a key difference*: the formation of the intermediate **I7** is reversible in this case*. The barrier for the backward step, the difference between **I7** and **TS5**, is 24.3 kcal/mol, which is an amount that may be overcome at room temperature. Thus product **10b** is also formed, but it converts with time to **10a,** which is a thermodynamic sink, more than 30 kcal/mol below **10b**, and its formation is certainly irreversible. This mechanistic hypothesis has found support in the aforementioned NMR studies of this reaction at 0 ºC (see [eq. (1)]). For comparison, the difference between the same two structures **I7** and **TS5** is 27.1 kcal/mol for the internal alkyne, yielding a barrier too high to overcome at room temperature.

Calculation thus reproduces all experimental data with these two substrates and produces a picture where the key difference between internal and terminal alkynes is that formation of the seven-member ring is reversible only for the case of terminal alkynes. The reason for this behavior is very likely related to steric effects. **TS5**, associated to rearrangement, is more congested than the product, and steric congestion will be higher with methyl than with hydrogen.

In conclusion, we have found a novel transformation for developing a substantial degree of molecular complexity from relatively simple substrates. Alkynes, terminal or internal, and the iminoiodonane PhI=NTs react in the presence of the copper catalyst Tp^{Br3}Cu(NCMe) leading to the formation of two series of imine products, that have been characterized as sulfinamides and *iso*-thiazoles, in an unprecedented reaction triggered by the formation of a copper-nitrene intermediate. The formation of the sulfonamides implies the rare reduction of the sulfone group to a sulfoxide whereas the iso-thiazole is generated in a process involving the insertion of an alkyne carbon atom into the aromatic ring of the N-Ts group. With terminal alkynes the reaction is completely selective to sulfinamides, whereas mixtures of products are obtained for internal alkynes as the substrates. A mechanistic explanation accounting for all experimental data has been proposed.

Acknowledgements

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Keywords: nitrene transfer • alkyne functionalization • copper catalysis • sulfinamides • iso-thiazoles

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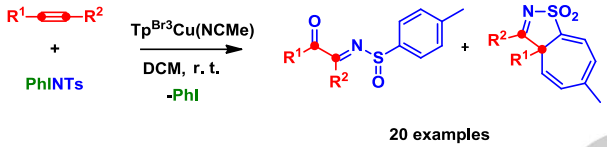
Alkyne-nitrene coupling

The reaction of alkynes and PhI=NTs in the presence of a copper catalyst affords sulfinamides and iso-thiazoles in a novel metal-mediated nitrene transfer reaction.



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