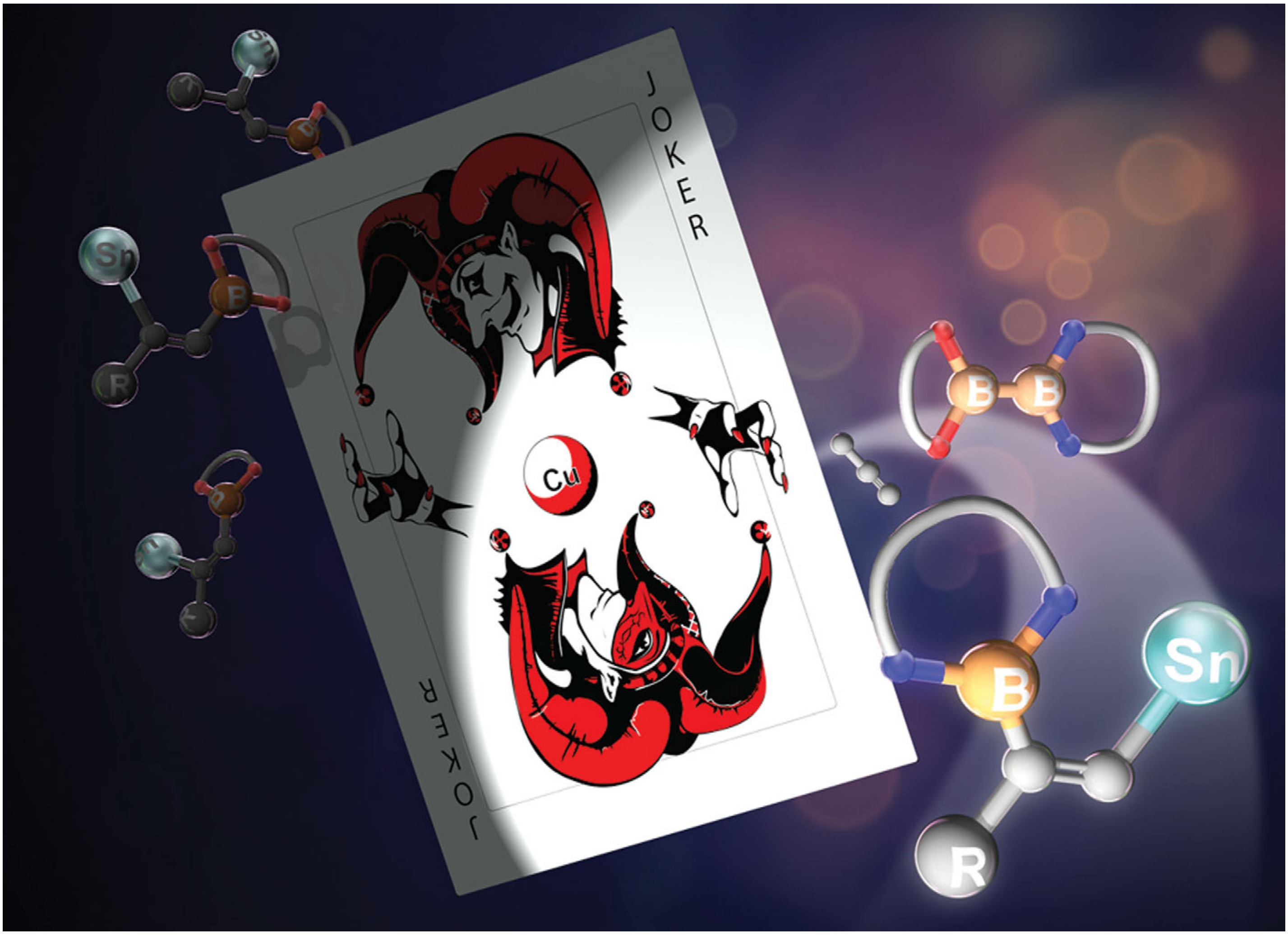


Showcasing the work from Dr Hiroto Yoshida's Group, Faculty of Engineering, Department of Applied Chemistry, Hiroshima University, Japan.

Borylstannylation of alkynes with inverse regioselectivity: copper-catalyzed three-component coupling using a masked diboron

Borylstannylation of terminal alkynes proceeds with inverse regioselectivity to those of the previous borylstannylations by utilizing a masked diboron as a boron source under copper catalysis.

As featured in:

See H. Yoshida *et al.*, *Chem. Commun.*, 2015, **51**, 6297.

ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: Chem. Commun., 2015, 51, 6297

Received 16th January 2015, Accepted 3rd February 2015

DOI: 10.1039/c5cc00439j

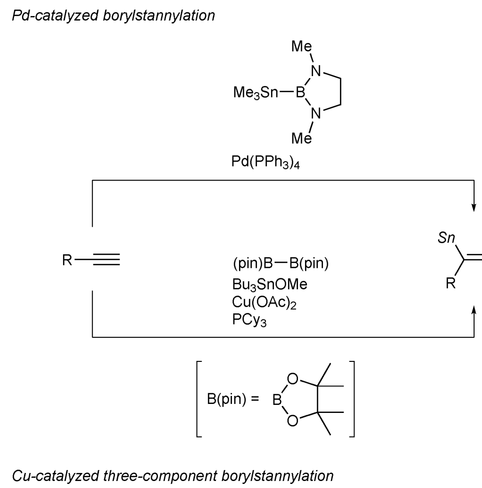
www.rsc.org/chemcomm

Borylstannylation of alkynes with inverse regioselectivity: copper-catalyzed three-component coupling using a masked diboron†

H. Yoshida,*[ab] Y. Takemoto[a] and K. Takaki[a]

A variety of terminal alkynes are facilely convertible into *cis*-boryl(stannyl)alkenes with inverse regioselectivity to those of the previous borylstannylation by the copper-catalyzed three-component reaction using a masked diboron. The synthetic utility of the resulting boryl(stannyl)alkenes has been demonstrated by chemoselective coupling reactions.

Transition metal-catalyzed dimetallation of alkynes has commanded considerable attention[1] because it provides a convenient and direct method for constructing regio- and stereo-defined dimetallated alkenes, whose carbon–metal bonds are utilizable for carbon–carbon bond-forming processes[2] to give multisubstituted alkenes, which constitute an important class of biologically and pharmaceutically active molecules. One of the most valuable dimetallation reactions would be borylstannylation, in which the resulting hetero-dimetallic moieties can undergo chemoselective cross-coupling reactions (Suzuki–Miyaura[3] and Migita–Kosugi–Stille coupling[4]) in tandem with high functional group compatibility under controlled reaction conditions. Since the pioneering work reported by Tanaka,[5a] borylstannylation has hitherto been achieved by direct insertion of alkynes into a B–Sn bond of borylstannanes under palladium catalysis.[5] On the other hand, we have recently disclosed a different mode of the borylstannylation by a copper-catalyzed three-component coupling using a diboron and a tin alkoxide.[6–8] Irrespective of the catalytic systems and the reaction modes, terminal alkynes exclusively accept the regioselective addition of the boryl group at the terminal carbon and the stannyl group at the internal carbon in a *cis* fashion to give (*Z*)-1-boryl-2-stannyl-1-alkenes (Scheme 1), and thus we have focused our attention on the reversal of regioselectivity, which increases structural diversity of *vic*-boryl(stannyl)alkenes and thereby broadens the synthetic utility of the borylstannylation. Herein we report that the use of a masked diboron[9] in the copper-catalyzed three-component borylstannylation of terminal alkynes completely inverts the regioselectivity, and that this method provides a convenient and direct access to unprecedented hetero-dimetallated alkenes having masked boryl and stannyl moieties.[10]



Scheme 1 Reported borylstannylation of terminal alkynes.

First we conducted the reaction of 1-octyne (**1a**) with a masked diboron ((pin)B–B(dan), pin: pinacolato, dan: naphthalene-1,8-diaminato[11]) and tributyltin methoxide in THF at room temperature in the presence of an *N*-heterocyclic carbene (NHC)-coordinated copper complex ((SIPr)CuCl), and found that the *cis*-borylstannylation took place with regioselectivity inverse to those of the previous borylstannylation (74% yield, **2a** : **2′a** = 96 : 4), leading to the introduction of the boryl group at the internal carbon and the stannyl group at the terminal carbon (Table 1, entry 1). It is noteworthy that the B(dan) moiety was solely installed in the product, and a borylstannylation product having the B(pin) moiety was not formed at all. The regioselectivity for the formation of **2a** was generally high with bulky ligands

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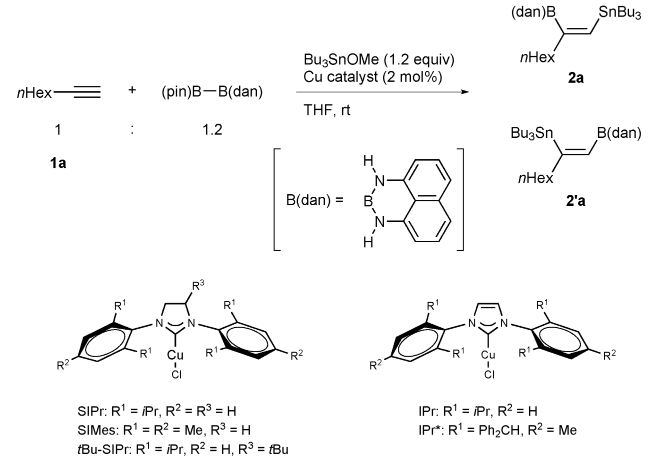
† Electronic supplementary information (ESI) available: Experimental procedures and characterization data. See DOI: 10.1039/c5cc00439j

Table 1 Ligand effect on Cu-catalyzed borylstannylation of 1-octyne[a]



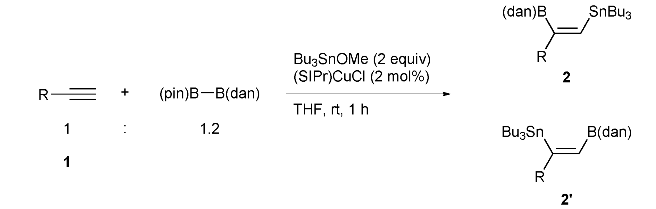
Entry	Cu catalyst	Time (h)	Yield[b] (%)	2a : 2′a[c]
1	(SIPr)CuCl	7	74	96 : 4
2	(SIMes)CuCl	2	81	90 : 10
3	(tBu-SIPr)CuCl	20	69	94 : 6
4	(IPr)CuCl	5	75	96 : 4
5	(IPr*)CuCl	11	80	96 : 4
6[d]	P(tBu)$_3$, CuCl	2	81	93 : 7
7	(PPh$_3$)$_3$CuCl	48	75	44 : 56
8[d]	PCy$_3$, CuCl	14	60	84 : 16
9[e]	(SIPr)CuCl	10	86	96 : 4

[a] General procedure: **1a** (0.30 mmol, 1 equiv.), (pin)B–B(dan) (0.36 mmol, 1.2 equiv.), Bu$_3$SnOMe (0.36 mmol, 1.2 equiv.), Cu catalyst (6.0 μmol, 2 mol%), THF (1 mL). [b] Isolated yield. [c] Determined using ^{1}H NMR. [d] Ligand = 4 mol%. [e] Bu$_3$SnOMe = 2 equiv.

(SIMes, tBu-SIPr, IPr, IPr*[12] and P(tBu)$_3$) (entries 2–6), whereas the use of triphenylphosphine ((PPh$_3$)$_3$CuCl) led to the formation of regioisomeric mixtures (**2a** : **2′a** = 44 : 56, entry 7). In addition, the reaction with PCy$_3$, used for the previous borylstannylation with bis(pinacolato)diboron,[6a] also afforded **2a** preferentially (**2a** : **2′a** = 84 : 16, entry 8), which reveals that the choice of a diboron as well as a ligand is the key to achieving the present regioselectivity.[13] Since an increase in the amount of tributyltin methoxide resulted in an increase in the yield with the highest regioselectivity (86% yield, entry 9), we selected the conditions for further studies.[14]

With the optimum conditions in hand (Table 1, entry 9), the substrate scope of alkynes was next investigated (Table 2). Such aliphatic terminal alkynes as 1-hexyne (**1b**), 4-methyl-1-pentyne (**1c**) and 4-phenyl-1-butyne (**1d**) also underwent the borylstannylation with high degrees of regioselectivity to give **2b**, **2c** and **2d** in 78, 81 and 74% yield (entries 1–3). The functional group compatibility of the reaction was sufficiently high, and thus a C–Br bond[15] in **1e** and a cyano group in **1f** remained intact throughout the reaction (entries 4 and 5). The present regioselectivity was also observed by using enyne (**1g**) and phenylacetylene (**1h**) (entries 6 and 7), and furthermore the reaction of propargyl ethers (**1i** and **1j**) or a THP-protected propargyl alcohol (**1k**) resulted in the exclusive formation of **2i**–**2k** (entries 8–10). In addition, propargyl amine (**1l**) and trimethylsilylacetylene (**1m**) accepted the addition of the B(dan) moiety at their internal carbon with perfect regioselectivity (entries 11 and 12).[16] The versatility of

Table 2 NHC–Cu-catalyzed borylstannylation of terminal alkynes[a]

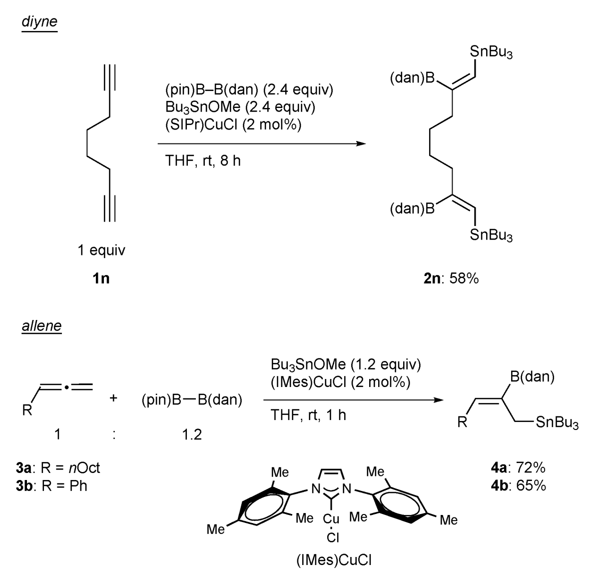


Entry	R	Yield[b] (%)	2 : 2′[c]	Products
1	nBu (**1b**)	78	94 : 6	**2b**, **2′b**
2	iBu (**1c**)	81	99 : 1	**2c**, **2′c**
3	Ph(CH$_2$)$_2$ (**1d**)	74	94 : 6	**2d**, **2′d**
4	Br(CH$_2$)$_2$ (**1e**)	87	99 : 1	**2e**, **2′e**
5	NC(CH$_2$)$_3$ (**1f**)	79	95 : 5	**2f**, **2′f**
6	1-Cyclohexenyl (**1g**)	81	99 : 1	**2g**, **2′g**
7	Ph (**1h**)	73	99 : 1	**2h**, **2′h**
8	MeOCH$_2$ (**1i**)	66	> 99 : 1	**2i**
9	BnOCH$_2$ (**1j**)	66	> 99 : 1	**2j**
10	THPOCH$_2$ (**1k**)	66	> 99 : 1	**2k**
11	Et$_2$NCH$_2$ (**1l**)	69	> 99 : 1	**2l**
12	Me$_3$Si (**1m**)	75	> 99 : 1	**2m**

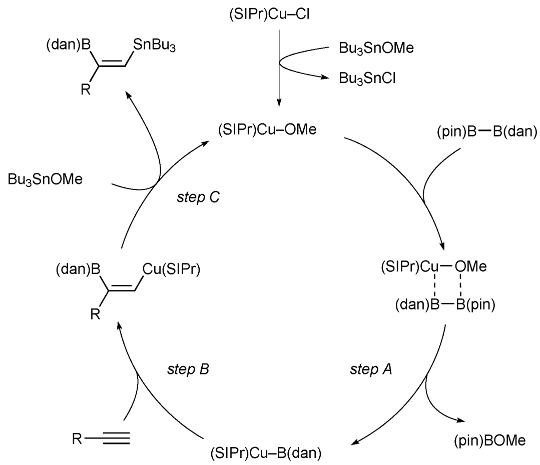
[a] General procedure: **1** (0.30 mmol, 1 equiv.), (pin)B–B(dan) (0.36 mmol, 1.2 equiv.), Bu$_3$SnOMe (0.60 mmol, 2 equiv.), (SIPr)CuCl (6.0 μmol, 2 mol%), THF (1 mL). [b] Isolated yield. [c] Determined using ^{1}H NMR.

the borylstannylation was further expanded by application to 1,7-octadiyne[17] (**1n**) and allenes[18] (**3a** and **3b**): both of the triple bonds were convertible regioselectively into the borylstannylalkenes in the former case, and the regio- and stereoselective reaction proceeded to provide (Z)-1-stannyl-2-boryl-2-alkenes (**4a** and **4b**) as the single product, although the regioselectivity is similar to that of the previous borylstannylation with bis(pinacolato)diboron[6b] in the latter case (Scheme 2).

Similarly to the previous copper-catalyzed borylstannylation with bis(pinacolato)diboron,[6] generation of a borylcopper species, Cu–B(dan), from Cu–OMe and a masked diboron commences the reaction (Scheme 3, step A). Subsequent insertion of an alkyne



Scheme 2 Borylstannylation of a diyne and allenes.

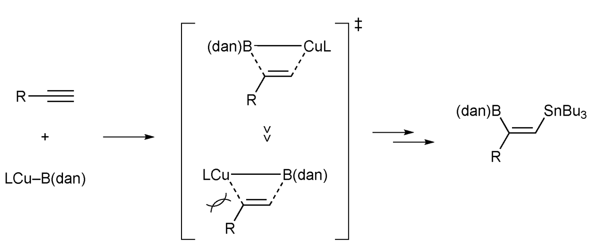


Scheme 3 A plausible catalytic cycle for borylstannylation.

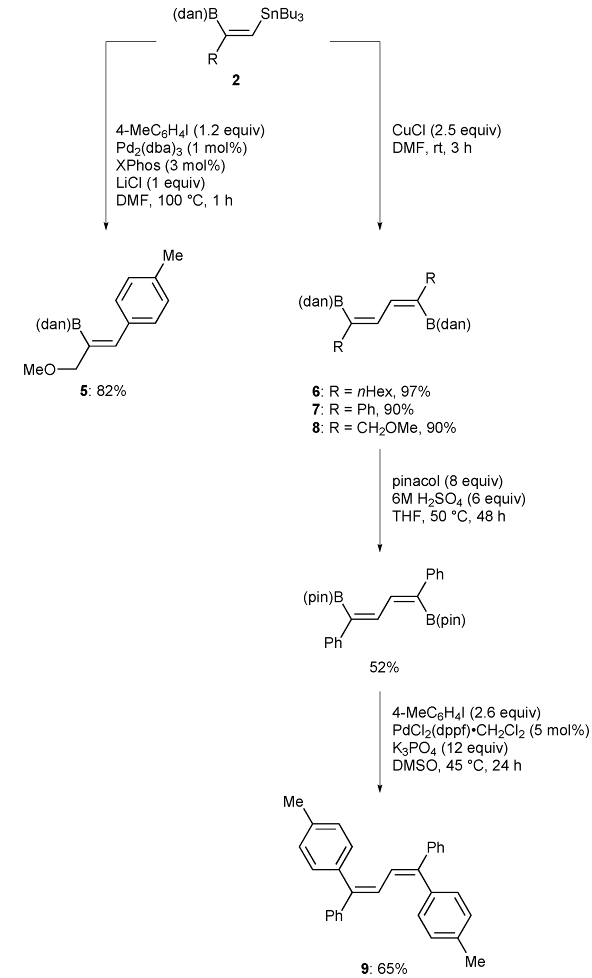
into the Cu–B(dan) bond, which produces a β-borylalkenylcopper species (borylcupration, step B),[19] followed by capturing with tin methoxide furnishes the product (step C).[20] The formation of Cu–B(dan) (*vs.* Cu–B(pin)) can be rationally explained by selective interaction between the Lewis acidic B(pin) moiety of (pin)B–B(dan) and the methoxy moiety of Cu–OMe in step A, leading to the exclusive introduction of the masked boryl moiety across the triple bond of alkynes. The orientation of a borylcopper species in the borylcupration step entirely governs the regiochemical outcome of the borylstannylation (Scheme 4), and the mode of the borylcupration with Cu–B(dan) would simply be controlled by steric repulsion between a substituent on alkynes and a bulkier copper moiety as was the case with the hydroboration.[10a] Hence, the B(dan) moiety is solely installed into the internal carbon of terminal alkynes,[21,22] which results in the inverse regioselectivity in the present borylstannylation.

Synthetic utility of the boryl(stannyl)alkenes was demonstrated by the chemoselective cross-coupling: a C–Sn bond of **2i** was solely convertible into a C–C bond by the palladium-catalyzed Migita–Kosugi–Stille reaction to provide an 82% yield of **5** with a masked boryl moiety remaining intact (Scheme 5). Furthermore, the masking enabled the copper-mediated oxidative homocoupling to take place at the C–Sn bond selectively, affording 1,4-diboryl-1,3-butadienes (**6–8**) stereoretentively in high yield. Unmasking of the resulting 1,4-diboryl-1,3-butadiene, followed by the Suzuki–Miyaura reaction with 4-iodotoluene furnished 1,1,4,4-tetraarylbutadiene **9**.

In conclusion, we have disclosed that the borylstannylation of terminal alkynes proceeds with inverse regioselectivity by the



Scheme 4 Regioselectivity in the borylcupration.



Scheme 5 Transformation of borylstannylation products.

copper-catalyzed three-component reaction using a masked diboron, which gives us a convenient and potent approach to diverse *cis*-boryl(stannyl)alkenes bearing the masked boryl moiety at the internal carbons. Moreover, the synthetic versatility of the resulting boryl(stannyl)alkenes has been shown by the chemoselective coupling reactions depending on the difference in the reactivity between the masked boryl and the stannyl moieties. Further studies on copper-catalyzed borylation reactions using a masked diboron as well as on the details of the mechanism are in progress.

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13 A boryl moiety is selectively installed into a terminal carbon of 1-octyne in the borylstannylation with bis(pinacolato)diboron under the Cu–PCy_3 catalysis, which is in marked contrast to the results described herein. See ref. 6*a*.

14 The alkyne (**1a**) had already been consumed at the time indicated in Table 1, and thus the yields would not change if the reactions are left longer.

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18 Palladium-catalyzed borylstannylation of an allene with a borylstannane is accompanied by dimerization of an allene. See: S. Onozawa, Y. Hatanaka and M. Tanaka, *Chem. Commun.*, 1999, 1863.

19 Generation of a borylcopper species (step A) and insertion of an alkyne into the Cu–B bond (step B) have been widely accepted as fundamental elementary steps in the copper-catalyzed borylation reactions of alkynes with diborons. See ref. 8.

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21 Installation of a B(pin) moiety into a terminal carbon of terminal alkynes is commonly observed in copper-catalyzed hydroboration with (pin)B–B(pin). See: (*a*) J.-E. Lee, J. Kwon and J. Yun, *Chem. Commun.*, 2008, 733; (*b*) Y. Lee, H. Jang and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2009, **131**, 18234; (*c*) H. Jang, A. R. Zhugralin, Y. Lee and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2011, **133**, 7859.

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