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Ruthenium Catalyzed C−C Bond Formation via Transfer Hydrogenation: Branch-Selective Reductive Coupling of Allenes to Paraformaldehyde and Higher Aldehydes

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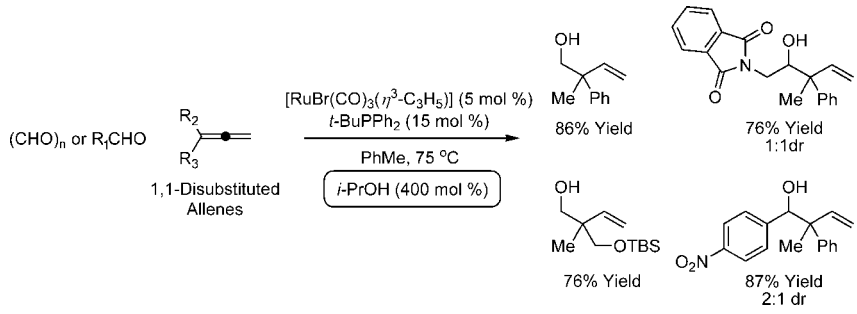
ABSTRACT



Under the conditions of ruthenium-catalyzed transfer hydrogenation employing 2-propanol as the terminal reductant, 1,1-disubstituted allenes 1a−h engage in reductive coupling to paraformaldehyde to furnish homoallylic alcohols 2a−h. Under identical transfer hydrogenation conditions, 1,1-disubstituted allenes engage in reductive coupling to aldehydes 3a−f to furnish homoallylic alcohols 4a−n. In all cases, reductive coupling occurs with branched regioselectivity to deliver homoallylic alcohols bearing all-carbon quaternary centers.

Although ruthenium-catalyzed transfer hydrogenation ranks among the foremost methods for enantioselective ketone reduction,[1] reductive C−C bond formation catalyzed by ruthenium is highly uncommon.[2−4] We have developed a family of reductive C−C bond formations employing elemental hydrogen as the terminal reductant.[5,6] More recently, we discovered that reductive C−C bond formation could be achieved under the conditions of iridium-catalyzed transfer hydrogenation, wherein allenes or cyclohexadiene are coupled to aldehydes and, remarkably, alcohols.[7] In an effort to expand the scope of such "transfer hydrogenative

(1) For selected reviews on ruthenium catalyzed transfer hydrogenation, see: (a) Zassinovich, G.; Mestroni, G.; Gladiali, S. *Chem. Rev.* **1992**, *92*, 1051. (b) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97. (c) Noyori, R.; Ohkuma, T. *Angew. Chem. Int. Ed.* **2001**, *40*, 40. (d) Noyori, R.; Yamakawa, M.; Hashiguchi, S. *J. Org. Chem.* **2001**, *66*, 7931. (e) Noyori, R. *Angew. Chem. Int. Ed.* **2002**, *41*, 2008. (f) Noyori, R. *Adv. Synth. Catal.* **2003**, *345*, 15. (g) Noyori, R. *Chem. Commun.* **2005**, 1807. (h) Gladiali, S.; Alberico, E. *Chem. Soc. Rev.* **2006**, *35*, 226. (i) Ikariya, T.; Blacker, A. J. *Acc. Chem. Res.* **2007**, *40*, 1300.

(2) Ruthenium complexes catalyze alkene hydroformylation. For a review, see: Kalck, P.; Peres, Y.; Jenck, J. *Adv. Organomet. Chem.* **1991**, *32*, 121.

(3) For ruthenium catalyzed reductive C−C bond formations beyond alkene hydroformylation, see: (a) Tsuji, Y.; Mukai, T.; Kondo, T.; Watanabe, Y. *J. Organomet. Chem.* **1989**, *369*, C51. (b) Kondo, T.; Ono, H.; Satake, N.; Mitsudo, T.; Watanabe, Y. *Organometallics* **1995**, *14*, 1945. (c) Yu, C.-M.; Lee, S.; Hong, Y.-T.; Yoon, S.-K. *Tetrahedron Lett.* **2004**, *45*, 6557.

(4) For selected reviews of ruthenium catalyzed C−C coupling, see: (a) Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067. (b) Kondo, T.; Mitsudo, T.-a. *Curr. Org. Chem.* **2002**, *6*, 1163. (c) Dérien, S.; Monnier, F.; Dixneuf, P. H. *Top. Organomet. Chem.* **2004**, *11*, 1.

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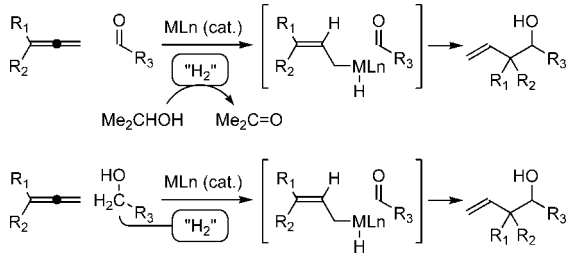
C−C bond formations", ruthenium catalysts were found to promote the coupling of acylic 1,3-dienes or 1,3-enynes to both aldehydes and alcohols to furnish products of carbonyl allylation and propargylation, respectively.[8] For these transfer-hydrogenative processes, rather than using elemental hydrogen as reductant, hydrogen embedded in 2-propanol or an alcoholic substrate is redistributed among reactants to generate nucleophile−electrophile pairs, enabling carbonyl addition from the aldehyde or alcohol oxidation level (Scheme 1).[8]

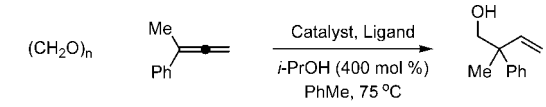
Scheme 1. Carbonyl Allylation from the Aldehyde or Alcohol Oxidation Level via Transfer Hydrogenative C−C Coupling of Allenes



As part of a continuing effort to broaden this emergent class of C−C bond formations, we investigated the coupling of 1,1-disubsituted allenes to paraformaldehyde and higher aldehydes under the conditions of ruthenium catalysis. Here we disclose that allenes **1a**−**1h** engage in branch-selective reductive coupling to paraformaldehyde and higher aldehydes under the conditions of ruthenium-catalyzed transfer hydrogenation employing 2-propanol as the terminal reductant to furnish homoallylic alcohols **2a**−**h** and **4a**−**n**, respectively, bearing all-carbon quaternary centers. Additionally, we report isotopic labeling studies that provide further insight into key mechanistic features of these processes.

In an initial set of experiments, structurally diverse ruthenium complexes were assayed for their ability to catalyze the reductive coupling of allene **1a** to paraformaldehyde using 2-propanol as the terminal reductant (Table 1, entries 1−7). It was found that the complex prepared in situ from $[RuBr(CO)_3(\eta^3\text{-}C_3H_5)]$ (5 mol %) and PPh_3 (15 mol %) in toluene (0.5 M) at 75 °C catalyzes the reductive C−C coupling of **1a** to paraformaldehyde to provide the desired adduct **2a** in 55% isolated yield along with small quantities of the corresponding formate ester, which is hydrolytically cleaved upon isolation (Table 1, entry 7).[9]

Table 1. Optimization of Ruthenium-Catalyzed Coupling of Paraformaldehyde to 1-Methyl-1-phenylallene (**1a**) via Transfer Hydrogenation[a]

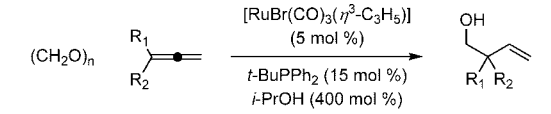


(400 mol %) **1a** (100 mol %) **2a**

entry	catalyst[b]	ligand (mol %)	concn (M)	yield (%)
1	[Cp(*p*-cymene)Ru]PF_6	PPh_3 (15)	0.5	–
2	$CpRuCl(PPh_3)_3$		0.5	–
3	$Ru_3(CO)_{12}$	PPh_3 (15)	0.5	–
4	$RuHCl(PPh_3)_3$·toluene		0.5	trace
5	$[Ru(cod)Cl_2]_n$	PPh_3 (15)	0.5	18
6	$RuHCl(CO)(PPh_3)_3$		0.5	20
7	$[RuBr(CO)_3(\eta^3\text{-}C_3H_5)]$	PPh_3 (15)	0.5	55
8	$[RuBr(CO)_3(\eta^3\text{-}C_3H_5)]$		0.5	trace
9	$[RuBr(CO)_3(\eta^3\text{-}C_3H_5)]$	BINAP (7.5)	0.5	49
10	$[RuBr(CO)_3(\eta^3\text{-}C_3H_5)]$	$MeC[CH_2PPh_2]_3$ (5)	0.5	trace
11	$[RuBr(CO)_3(\eta^3\text{-}C_3H_5)]$	CatacXium A (15)	0.5	72
12	$[RuBr(CO)_3(\eta^3\text{-}C_3H_5)]$	*t*-$BuPPh_2$ (15)	0.5	81
13	**$[RuBr(CO)_3(\eta^3\text{-}C_3H_5)]$**	*t*-$BuPPh_2$ (15)	**1.0**	**86**

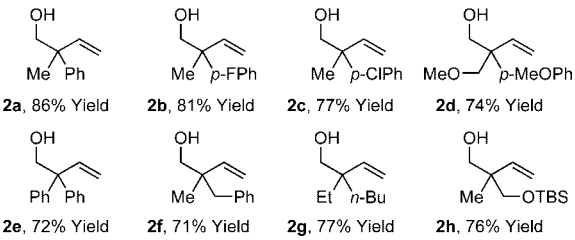
[a] Cited yields are of isolated material. [b] 5 mol % with respect to ruthenium content. See the Supporting Information for detailed experimental procedures.

Table 2. Ruthenium-catalyzed reductive coupling of paraformaldehyde to 1,1-disubstituted allenes **1a**−**h** via transfer hydrogenation[a]



1a-1h **2a-2h**

1a, R_1 = Me, R_2 = Ph
1b, R_1 = Me, R_2 = *p*-FC_6H_4
1c, R_1 = Me, R_2 = *p*-ClC_6H_4
1d, R_1 = CH_2OMe, R_2 = *p*-$MeOC_6H_4$
1e, R_1 = R_2 = Ph
1f, R_1 = Me, R_2 = CH_2Ph
1g, R_1 = Et, R_2 = *n*-Bu
1h, R_1 = Me, R_2 = CH_2OTBS



2a, 86% Yield **2b**, 81% Yield **2c**, 77% Yield **2d**, 74% Yield
2e, 72% Yield **2f**, 71% Yield **2g**, 77% Yield **2h**, 76% Yield

[a] Cited yields are of isolated material. Standard conditions employ 1 equiv of allene and 4 equiv of paraformaldehyde. See the Supporting Information for detailed experimental procedures.

(5) For reviews on hydrogenative C−C coupling, see: (a) Iida, H.; Krische, M. J. *Top. Curr. Chem.* **2007**, *279*, 77. (b) Ngai, M.-Y.; Kong, J.-R.; Krische, M. J. *J. Org. Chem.* **2007**, *72*, 1063. (c) Skucas, E.; Ngai, M.-Y.; Komanduri, V.; Krische, M. J. *Acc. Chem. Res.* **2007**, *40*, 1394.

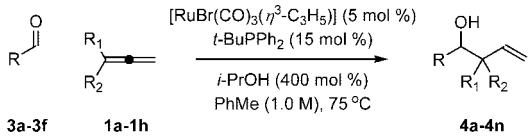
(6) For recent examples, see the following. C=X vinylation: (a) Kong, J.-R.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 718. (b) Skucas, E.; Kong, J.-R.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 7242. (c) Barchuk, A.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 8432. (d) Ngai, M.-Y.; Barchuk, A.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 12644. Aldol and Mannich addition: (e) Jung, C.-K.; Garner, S. A.; Krische, M. J. *Org. Lett.* **2006**, *8*, 519. (f) Jung, C.-K.; Krische, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 17051. (g) Garner, S. A.; Krische, M. J. *J. Org. Chem.* **2007**, *72*, 5843. (h) Bee, C.; Han, S. B.; Hassan, A.; Iida, H.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 2746. C=O allylation: (i) Skucas, E.; Bower, J. F.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 12678.

(7) (a) Bower, J. F.; Skucas, E.; Patman, R. L.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 15134. (b) Bower, J. F.; Patman, R. L.; Krische, M. J. *Org. Lett.* **2008**, *10*, 1033.

(8) (a) Shibahara, F.; Bower, J. F.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 6338. (b) Patman, R. L.; Williams, V. M.; Bower, J. F.; Krische, M. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338.

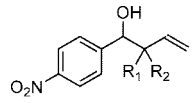
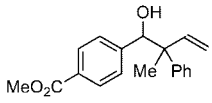
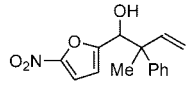
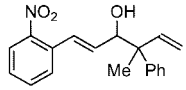
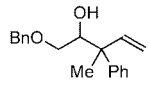
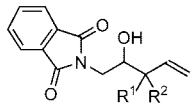
(9) See the Supporting Information for detailed experimental procedures.

Table 3. Ru-Catalyzed Reductive Coupling of Aldehydes **3a**−**f** to 1,1-Disubstituted Allenes via Transfer Hydrogenation[a]



3a-3f **1a-1h** **4a-4n**

3a, R = *p*-NO_2Ph **3c**, R = 2-(5-NO_2-Furyl) **3e**, R = CH_2OBn
3b, R = *p*-(CO_2Me)Ph **3d**, R = *o*-NO_2-Cinnamyl **3f**, R = CH_2NPhth

entry	RCHO, allene	product	yield % (dr)
1			
	3a, **1a**	**4a**, R_1 = Me, R_2 = Ph	87% (2:1 dr)
	3a, **1b**	**4b**, R_1 = Me, R_2 = *p*-FPh	86% (2:1 dr)
	3a, **1d**	**4c**, R_1 = CH_2OMe, R_2 = *p*-MeOPh	76% (1:1 dr)
	3a, **1f**	**4d**, R_1 = Me, R_2 = CH_2Ph	83% (1:1 dr)
	3a, **1g**	**4e**, R_1 = Et, R_2 = *n*-Bu	82% (1:1 dr)
2			
	3b, **1a**	**4f**	69% (2:1 dr)
3			
	3c, **1a**	**4g**	74% (1:1 dr)
4			
	3d, **1a**	**4h**	61% (2:1 dr)
5			
	3e, **1a**	**4i**, R_1 = Me, R_2 = Ph	71% (1:1 dr)
	3e, **1d**	**4j**, R_1 = CH_2OMe, R_2 = *p*-MeOPh	72% (1:1 dr)
	3e, **1g**	**4k**, R_1 = Et, R_2 = *n*-Bu	70% (1:1 dr)
6			
	3f, **1a**	**4l**, R_1 = Me, R_2 = Ph	76% (1:1 dr)
	3f, **1b**	**4m**, R_1 = Me, R_2 = *p*-FPh	77% (1:1 dr)
	3f, **1g**	**4n**, R_1 = Et, R_2 = *n*-Bu	74% (1:1 dr)

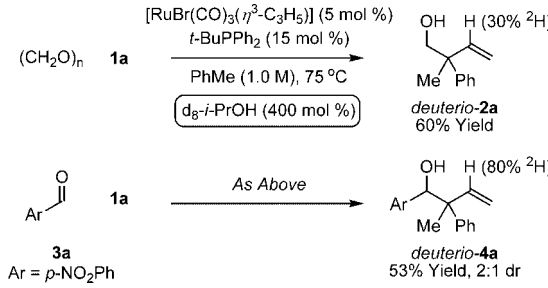
[a] Cited yields are of pure isolated material. See the Supporting Information for detailed experimental procedures.

Notably, only trace quantities of adduct are formed in the absence of PPh_3 (Table 1, entry 8), suggesting that appropriate selection of ligand is crucial. Indeed, screening the precatalyst [$RuBr(CO)_3(\eta^3\text{-}C_3H_5)$] against a series of phosphine ligands (Table 1, entries 9−13) reveals that monodentate ligands promote greater conversion than bidentate or tridentate ligands (Table 1, entries 9 and 10). Under optimal conditions employing [$RuBr(CO)_3(\eta^3\text{-}C_3H_5)$] (5 mol %) as precatalyst in combination with *t*-$BuPPh_2$ (15 mol %) as ligand in toluene (0.5 M) at 75 °C, the coupling product **2a** is obtained in 81% isolated yield (Table 1, entry 12). By increasing the concentration of the reaction mixture (1.0 M in toluene), the isolated yield was increased to 86% (Table 1, entry 13). These optimized reaction conditions proved to be quite general, as demonstrated by the coupling of paraformaldehyde to 1,1-disubstituted allenes **1a**−**h** to furnish the homoallylic alcohols **2a**−**h** (Table 2).

Under identical conditions, the coupling of allenes to higher aldehydes was explored. It was found that aromatic aldehydes (Table 3, entries 1 and 2), heteroaromatic aldehydes (Table 3, entry 3), α,β-unsaturated aldehydes (Table 3, entry 4), and aliphatic aldehydes (Table 3, entries 5 and 6) couple to a range of 1,1-disubstituted allenes in good yields but with low diastereoselectivity. Under standard conditions, electron-rich aldehydes couple less efficiently, as demonstrated by the coupling of allene **1a** to hexanal, which occurs in 38% yield to provide a 4:1 diastereomeric ratio of adducts.

To gain insight into the catalytic mechanism, the coupling of paraformaldehyde and allene **1a** was conducted employing 2-propanol-d_8 as the terminal reductant. As revealed by ^{1}H NMR analysis, deuterium is incorporated solely at the vinylic position (30% ^{2}H). Similarly, coupling of allene **1a** to *p*-nitrobenzaldehyde **3a** employing 2-propanol-d_8 as the terminal reductant also results in deuterium incorporation exclusively at the vinylic position, but to a far greater extent (80% ^{2}H). Notably, the isolated yield of coupling products in reactions employing 2-propanol-d_8 as the terminal reductant are significantly lower than the isolated yields obtained in the parent reactions (Scheme 2).[10]

Scheme 2. Ruthenium-Catalyzed Coupling of Allene **1a** to Paraformaldehyde and *p*-Nitrobenzaldehyde Employing 2-Propanol-d_8 as the Terminal Reductant[a]

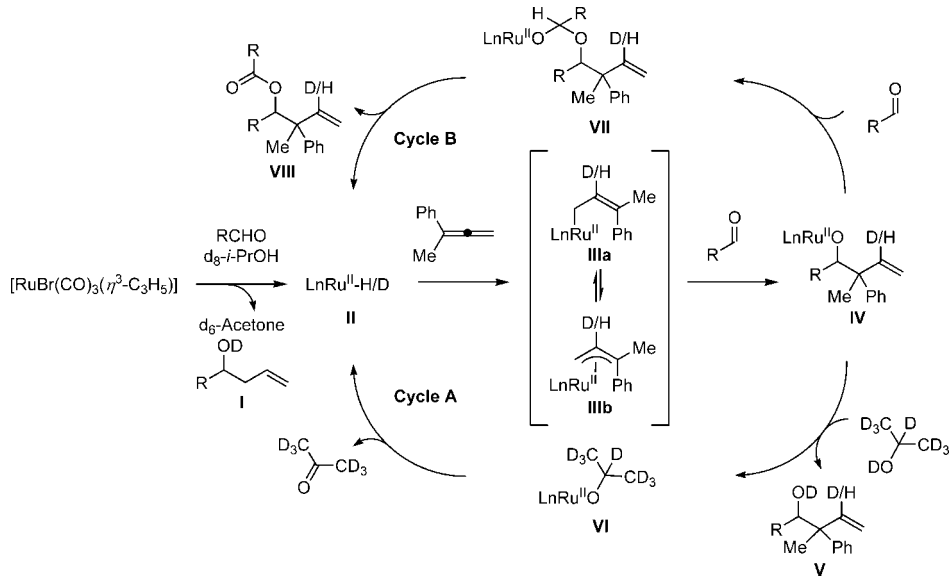


[a] Cited yields are of isolated material. See the Supporting Information for detailed experimental procedures.

A plausible catalytic cycle accounting for the relatively low levels of deuterium incorporation in the reaction of

(10) Couplings employing 2-propanol-d_8 as terminal reductant were conducted twice. The isolated yields and levels of deuterium incorporation for *deuterio*-**2a** and *deuterio*-**4a** were reproducible within experimental error.

Scheme 3. Plausible Catalytic Mechanisms As Supported by Deuterium-Labeling Studies



paraformaldehyde and allene **1a** is indicated (Scheme 3). Reaction of the precatalyst [RuBr(CO)$_3$(η^3-C$_3$H$_5$)] with aldehyde in the presence of 2-propanol generates the homoallylic alcohol **I** and active catalyst **II**,[11] which hydrometallates allene **1a** to furnish the allylruthenium complexes **IIIa** and **IIIb**.[12] Allyl transfer to the aldehyde delivers the ruthenium alkoxide **IV**. The intermediate **IV** may react with 2-propanol to provide the coupling product **V** and ruthenium isopropoxide **VI**, which upon β-hydride elimination regenerates the active catalyst **II** (cycle A). Alternatively, the intermediate **IV** may react with another molecule of aldehyde to form ruthenium complex **VII**,[13] which delivers ester **VIII** upon β-hydride elimination and regenerates the active catalyst **II** (cycle B). The latter catalytic cycle suggests that the aldehyde may serve as a hydride donor. Indeed, when the coupling of paraformaldehyde and **1a** is carried out in the absence of 2-propanol, substantial quantities of the formate ester **VIII** (R = H) are detected. Mechanisms involving ruthenium-catalyzed allene hydroacylation with subsequent 2-propanol-mediated reduction of the resulting aldehyde are inconsistent with the results of deuterium incorporation. Upon resubjecting diastereomerically enriched adduct **4a** to standard coupling conditions, a 2:1 diastereomeric ratio is reestablished, suggesting redox equilibration of the homoallylic alcohol under coupling conditions. That is, the ratio of diastereomers appears to be thermodynamically controlled.

In summary, ruthenium-catalyzed transfer hydrogenation ranks among the most powerful methods available for the reduction of polar functional groups, yet reductive C−C couplings under the conditions of ruthenium catalysis are highly uncommon. Recent studies from our laboratory are aimed at addressing this deficiency, with the ultimate goal of developing a broad new family of "*transfer hydrogenative C−C bond formations*". In prior work, ruthenium-catalyzed transfer hydrogenation was applied to the coupling of acyclic 1,3-dienes (butadiene, isoprene, and 2,3-dimethylbutadiene) and 1,3-enynes to aldehydes or alcohols. Here, we demonstrate the ruthenium-catalyzed reductive coupling of 1,1-disubstituted allenes **1a**−**h** to paraformaldehyde and higher aldehydes **3a**−**f** to furnish homoallylic alcohols **2a**−**h** and **4a**−**n**, respectively. Stereoselective variants of these transformations and the development of new transfer hydrogenative couplings, including imine additions from the amine oxidation level, are currently underway.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds (^{1}H NMR, ^{13}C NMR, IR, HRMS). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) When α-phthalimidoacetaldehyde was coupled to 1 equiv of [RuBr(CO)$_3$(η^3-C$_3$H$_5$)], the corresponding homoallylic alcohol and its isomers were detected. See also ref 3b.

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