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Heteroaromatic Tosylates as Electrophiles in Regioselective Mizoroki–Heck-Coupling Reactions with Electron-Rich Olefins

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Abstract: Heteroaromatic 2-pyridyl tosylates were successfully applied as electrophiles in palladium(0)-catalyzed Mizoroki–Heck-coupling reactions to electron-rich olefins with complete α-regioselectivity. This protocol represents a general strategy for the application of pyridyl tosylates and mesylates in the Mizoroki–Heck coupling. The catalytic system also proved adaptable to changes in the heteroaromatic core as well as large-scale applications. Finally, the synthetic utility of the functionalized α-heteroarylvinyl amides was established providing straightforward access to highly functionalized heteroaromatic compounds including chiral benzylic amide derivatives.

Keywords: aryl tosylates · C–C coupling · Mizoroki–Heck coupling · heterocycles · palladium

Introduction

Arylation or vinylation of olefins by palladium catalysis, better known as the Mizoroki–Heck (MH)-coupling reaction, has become an indispensable tool for the construction of C–C bonds in synthetic organic chemistry.[1] The regioselective outcome of these reactions is highly dependent on the substitution pattern of the olefin, in which electron-deficient alkenes selectively provide products of β-substitution, while electron-rich alkenes favor substitution at the α-position.[2] Coupling with electron-rich alkenes is generally more demanding with respect to the catalyst compared with those with electron-poor olefins as selective α-substitution requires a cationic palladium(II) complex, which is generated in situ under the reaction conditions.[3] Traditionally, aryl triflates or halides in the presence of halide scavengers, such as silver and thallium salts, are necessary for promoting this ionic pathway.[2b,4] The literature provides examples aimed at replacing triflate electrophiles with the less costly halides without the need for additives by the use of highly polar solvents such as ionic solvents, DMF or water.[5] However, the greater abundance of commercially available aryl alcohols compared with the corresponding halides make these compounds of higher interest for coupling reactions if an alternative to the triflate derivatives could be found.

In recent years, various studies have been reported on Pd-catalyzed transformations using heterocycles as substrates. These reactions include aminations,[6] Suzuki–Miyaura,[7] Negishi[8] and Sonogashira[9] cross-coupling reactions. The MH reaction has only scarcely been applied for the functionalization of heterocycles, possibly owing to the difference and hence higher requirements of its catalytic cycle compared with the cross-coupling reactions.[10] In these few reports, vinyl ethers are the olefin of choice under cationic conditions because they easily transform into stable aryl ketone products by in situ acidic hydrolysis.[5c,d,10c,g,h] One exception was reported by Xiao et al. on MH-coupling reactions using *N*-vinyl acetamide (NVA) in combination with heteroaromatic bromides.[10f,11] The use of vinyl amides leads to products of higher synthetic value as they represent precursors of chiral heteroaromatic benzylic amide and amine derivatives.

Ideally, a two-fold enhancement of the common cationic MH methodology replacing the triflate electrophiles with the corresponding tosylates and the introduction of heteroaromatic moieties without catalyst deactivation would be of

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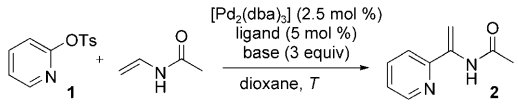
high interest.[12] Not only would this include the aryl alcohols as coupling precursors, but aryl tosylates also hold significant advantages compared with aryl triflates, such as increased stability, crystallinity and lower costs.

In this paper, we wish to report our achievements on MH-coupling reactions with enamides and vinyl ethers using 2-pyridyl tosylates as electrophiles. We show the utilization of a general catalytic protocol which proves adaptable to changes in the heteroaromatic core as well as scale up applications. Finally, the stability and synthetic usefulness of the obtained α-heteroarylvinyl amides is demonstrated as they are subject to further functionalization.

Results and Discussion

All 2-pyridyl tosylates were obtained from the corresponding commercially available 2-hydroxy pyridines by simple treatment with tosyl chloride (TsCl) in the presence of base. Two methods both using TsCl in combination with either potassium carbonate in acetone or a TEA/dichloromethane system with additional DMAP as the added organocatalyst were applied and generally afforded the desired 2-pyridyl tosylates in good to excellent yields (see Supporting Information).[13] The catalytic conditions were obtained by optimizing the coupling of 2-pyridyl tosylate **1** to NVA using a previously reported protocol as starting point (Table 1).[14,15]

Table 1. Optimization of MH coupling conditions.



Entry[a]	Ligand	Base	T [°C]	Yield [%][b] (Conversion)
1	DPPF	Cy_2NMe	85	(63)
2	DPPF	Cy_2NMe	100	87 (100)
3	DPPF	DIPEA	100	66 (100)
4	DPPP	Cy_2NMe	100	78 (100)
5	BINAP	Cy_2NMe	100	74 (100)
6	DPPF	Cy_2NMe	70	(50)[c]
7	DPPF	Cy_2NMe	100	71 (100)[d]
8	DPPF	Cy_2NMe	100	72 (100)[e]

[a] **1** (1 equiv), NVA (4 equiv). [b] Yield of the isolated product. [c] THF was used as the solvent [d] **1** (1.5 equiv), NVA (1 equiv). 2-Pyridyl mesylate (**3**) was used instead of **1**.

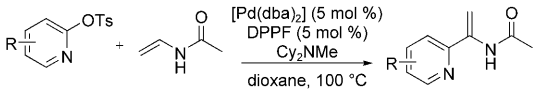
Performing the reaction at the original 85 °C did not lead to complete conversion after 24 h (entry 1), but importantly, full α-regioselectivity was obtained. Increasing the temperature to 100 °C resulted in completion of the reaction and **2** could be secured in an 87% isolated yield (entry 2). Full conversion was also obtained by using DIPEA as the organic base, but afforded only 66% yield of **2** (entry 3). In addition to 1,1′-bis(diphenylphosphino)ferrocene (DPPF), the ligands 1,3-bis(diphenylphosphino)propane (DPPP) and 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) afforded full conversion with a 78 and 74% isolated yields, respectively (entries 4 and 5). Although reactions with the ligands 1,2-bis(diphenylphosphino)ethane (DPPE), 1,2-bis(diphenylphosphino)pentane (DPPPe) and 1,1′-bis(diisopropylphosphino)ferrocene (D*i*prPF) did not go to completion, the same high α-regioselectivity was observed in all cases. *N,N*-Ligands such as 1,10-phenanthroline were the only class of ligands which provided mixtures of α- and β-substituted products (results not shown). Hence, in the following, DPPF and DPPP will be the ligands of further investigation.

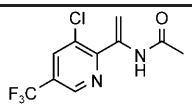
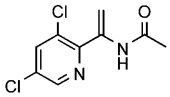
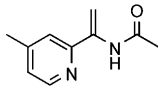
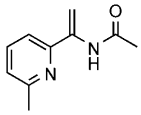
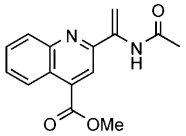
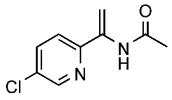
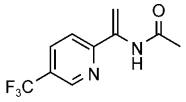
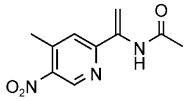
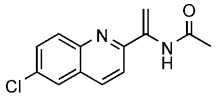
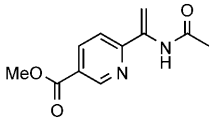
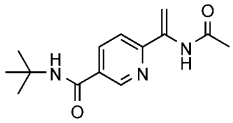
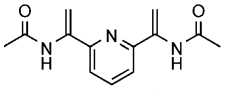
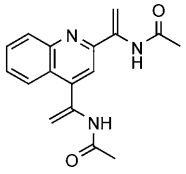
Changing the solvent to THF or altering the **1**/NVA ratio proved less effective (entries 6 and 7). The less reactive mesylate derivative **3** was also tested and did surprisingly go to completion with a 72% isolated yield (entry 8).[16] Lowering of the catalyst loading resulted in incomplete conversion of **1**. Finally, reactions performed without ligand or without palladium failed (results not shown). In the following study no products from β-substitution were obtained implying that a cationic mechanism is operating for the 2-pyridyl tosylates and mesylates.[2,14]

These optimized conditions were then tested on a variety of different 2-pyridyl tosylate derivatives, the results of which are shown in Table 2. Generally the coupling reactions went to completion within 22 h and all desired compounds could be isolated by column chromatography in good to excellent yields. Although both of the ligands proved useful for this transformation using NVA as olefin, DPPF appeared to provide a slightly more stable catalytic system compared to DPPP (entries 1, 6, 9, and 10). All 2-pyridyl tosylates except one carrying electron-withdrawing functionalities performed well under the catalytic conditions providing yields ranging from 68–79% (entries 1, 2, 5–7 and 9–11). The presence of a nitro group functionalization decreased the catalytic activity and the reaction did not go to full completion providing only a 25% isolated yield (entry 8). Double MH coupling was achieved with the ditosylated 2,6-dihydroxypyridine and despite this reaction did not go to completion a 45% isolated yield could still be secured. Surprisingly, reacting the 2,4-ditosylated hydroxyquinoline with NVA also resulted in the isolation of the product **16** in a 55% isolated yield resulting from a double MH coupling (entry 12).

Gratifyingly, butyl vinyl ether also proved to be reactive under the above-mentioned optimized catalytic conditions, the results of which are shown in Table 3. Again the reactions were generally complete within 22 h and good to excellent yields of the desired compounds could be secured upon column chromatography. DPPP and DPPF both proved to be suitable ligands for this transformation regardless of the specific 2-pyridyl tosylate substitution pattern. Upon comparison of entries 1 and 4 with 2 and 3, a small drop in reactivity was observed with substituents in the 3-position of the 2-pyridyl tosylates. Electron-withdrawing groups on the heteroaromatic system all provided acceptable to good yields (entries 7–10). Also, the pyridyl tosylate carrying the ester of Cbz-protected aminoethanol underwent successful coupling with an isolated yield of 59%, representing an example in which standard protection group chemistry is tolerat-

Table 2. MH-coupling reactions with *N*-vinyl acetamide.



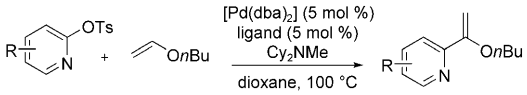
Entry[a]	Product		Yield [%][b]
1		**4**	68 (64)[c]
2		**5**	68[d]
3		**6**	74
4		**7**	81
5		**8**	74
6		**9**	88 (72)[c]
7		**10**	(81)[c]
8		**11**	(25)[c]
9		**12**	79 (74)[c]
10		**13**	73 (55)[c]
11		**14**	75
12		**15**	45
13		**16**	(55)[c]

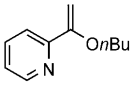
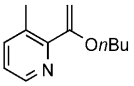
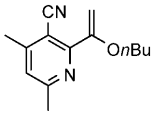
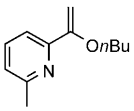
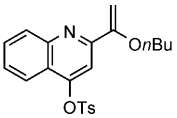
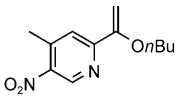
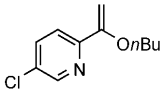
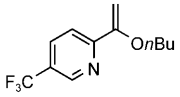
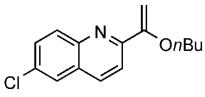
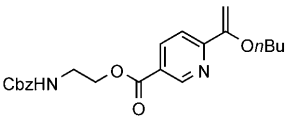
[a] 2-Pyridyl tosylate (0.3 mmol), NVA (1.2 mmol), Cy_2NMe (0.9 mmol) [b] Yield of the isolated product. [c] Yields in brackets obtained with DPPP as the ligand. [d] NVA (1 equiv) 2-pyridyl tosylate (1.5 equiv).

ed (entry 10). Interestingly, the 2,4-ditosylated hydroxyquinoline applied in the coupling depicted in entry 5 afforded only mono-substitution in a 60% isolated yield. Comparison of this result with that of Table 2, entry 13, where only the product from a double MH coupling was observed, indicates that NVA must be a more reactive olefin than butyl vinyl ether under these catalytic conditions. In addition, a MH coupling in which the two classes of olefins were allowed to compete with each other selectively afforded the product of reaction with NVA (see Supporting Information).

A few other enamides were also tested under the catalytic system at hand. Whereas reactions with an *N*-butyl-*N*-vinylurea resulted in decomposition of the enamide, the corresponding Boc-enamide did afford the desired coupling prod-

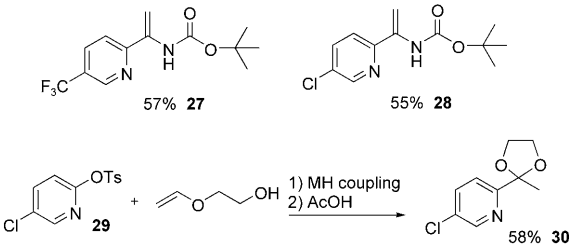
Table 3. MH-coupling reactions with butyl vinyl ether.



Entry[a]	Product		Ligand	Yield [%][b]
1		**17**	DPPF	81
2		**18**	DPPF	49
3		**19**	DPPP	69
4		**20**	DPPF	86
5		**21**	DPPP	60
6		**22**	DPPF	46
7		**23**	DPPP	81
8		**24**	DPPP	78
9		**25**	DPPP	82
10		**26**	DPPF	59

[a] 2-Pyridyl tosylate (0.3 mmol), butyl vinyl ether (1.2 mmol), Cy_2NMe (0.9 mmol) [b] Yield of the isolated product.

ucts **27** and **28** (Scheme 1). Cyclic or *N*-alkylated enamides were less reactive substrates and conversions rates below 50% were obtained in all attempts.



Scheme 1. MH-coupling reactions with functionalized olefins.

Differences in the choice of the vinyl ethers did not seem to affect the catalytic activity and even glycol vinyl ether could be applied, proving that free alcohols are tolerated. Isolation of the coupling product of the reaction with glycol vinyl ether was not attempted, but instead this product was treated with acetic acid forming the cyclic ketal **30** which was obtained in an overall 58% isolated yield.[17]

To test the further utility of the catalytic protocol, changes in the heteroaromatic core was introduced and the initial results of MH-coupling reactions with 4-pyrimidyl tosylates are depicted in Figure 1. The presence of the pyrimidyl core did not alter the catalytic activity and compounds **31** and **32** were obtained in a 61 and 69% isolated yield, respectively. Even a double MH coupling could be performed with the pyrimidines, as examplified with compound **33**.

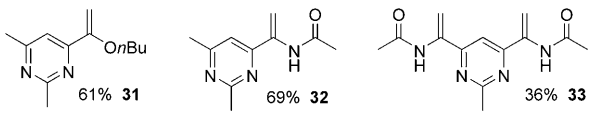
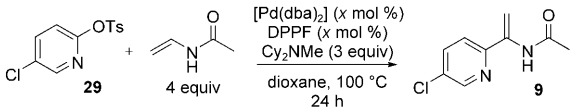


Figure 1. MH-coupling reactions with a pyrimidine heteroaromatic core.

With the above-mentioned study at hand, we decided to investigate its potential scale up application. To this end, the 5-chloropyridin-2-yl tosylate (**29**) was chosen since this particular electrophile reacted well in the preliminary studies (Table 2, entry 7 and Table 3, entry 6). Apart from the general interest in scalable systems a more detailed picture of the catalysts stability and true performance is obtained. Initial studies were conducted on 10 times the standard scale (3 mmol) and at higher concentrations by lowering the amount of solvent applied (Table 4).[18] To our satisfaction, the stability of the catalytic system proved considerably higher when operating with larger batches and catalyst loadings down to 3 and 1 mol% did not affect the yield or the time needed for completion of the reaction (entries 1 and 2, compared with Table 3, entry 6). Despite the fact that full conversion was not obtained even after 48 h using a loading of only 0.1 mol% catalyst, still a good 61% yield of **9** could be secured, resulting in a TON of 610 for the presented catalyst (entry 3). Finally, increasing the scale to 15 mmol of **29** (50× original scale) and applying 1 mol% of the catalyst for 24 h provided an excellent 88% isolated yield of **9** (2.59 g).

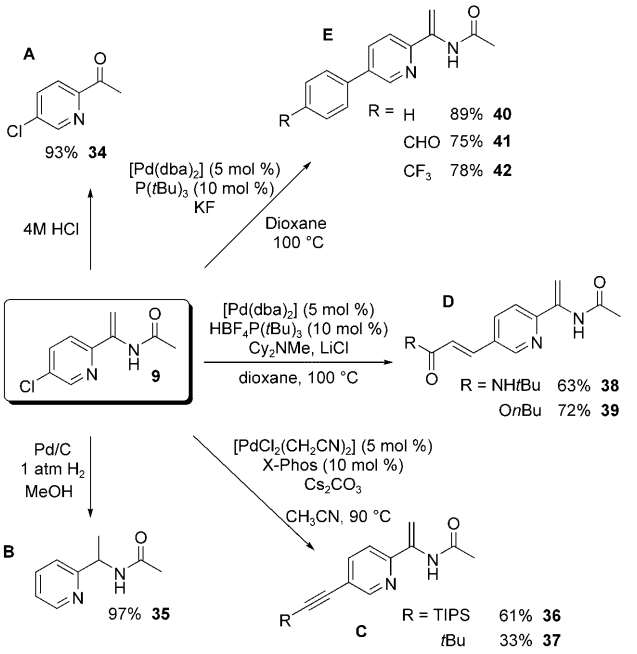
Table 4. Scale-up MH-coupling reactions using *N*-vinyl acetamide.



Entry	Scale [mmol]	Catalytic loading [%]	Yield [%][a]
1	3	3	89
2	3	1	92
3	3	0.1	61[b]
4	15	1	88

[a] Yield of the isolated product. [b] 64% conversion after 48 h.

Normally *N*-acyl α-arylvinyl amines are prone to undergo facile aqueous hydrolysis to the corresponding ketone.[15a] This instability often results in difficult purification due to decomposition during workup or on silica gel. Similar tendencies were observed when working with the 2-(1-alkoxyvinyl)pyridines shown in Table 3, however, the *N*-acyl α-(2-pyridyl)vinyl amines demonstrated a much higher degree of tolerance. This ability of the *N*-acyl α-(2-pyridyl)vinyl amines and with a batch of *N*-(1-(5-chloropyridin-2-yl)vinyl)-acetamide (**9**) in hand from the scale-up experiments encouraged us to test the ability of this substrate to undergo other transformations, the results of which are given in Scheme 2.



Scheme 2. Application of *N*-(1-(5-chloropyridin-2-yl)vinyl)acetamide.

Compound **9** could be converted to the ketone **34** under acid conditions and the reduction of **9** using palladium on charcoal afforded the dechlorinated acylated benzylic amine

35 in 93 and 97% isolated yield, respectively (routes **A** and **B**).[15c,19] Next, it was envisioned that the chloride in the 5-position on **9** could be applied as an electrophile in additional palladium-catalyzed transformations. Cu-free Sonogashira-coupling reactions by conditions developed by Buchwald et al. were attempted (**C**).[20] Despite the somewhat low yield obtained in the Sonogashira coupling with *tert*-butyl acetylene a 61% yield of **35** could be isolated upon coupling with the TIPS-protected acetylene. Both additional MH (**D**) and Suzuki–Miyaura (**E**)-coupling reactions were successful using conditions developed by Fu et al. providing coupling yields ranging from 75–89% and 63–72%, respectively, for the two reactions.[21,22] These results clearly indicate the utility of 2-pyridyl tosylates as building blocks for highly functionalized heteroaromatic compounds in few steps.

Conclusions

In conclusion, we have successfully developed catalytic conditions, which allow the use of heteroaromatic tosylates as electrophiles in electron-rich MH-coupling reactions with full regioselectivity. Both electron-rich enamides and vinyl ethers could be applied as olefins without loss of reactivity. Furthermore, changes in the heteroaromatic core of the tosylate to pyrimidines did not affect the overall catalytic activity. Increased catalytic activity was observed when this protocol was adapted in large-scale coupling reactions affording full conversion using catalyst loadings of only 1 mol%. Finally, the stability of the formed *N*-acyl α-(2-pyridyl)vinyl amines was established upon their application in a variety of different palladium-catalyzed transformations. Further work is now in progress to find suitable conditions which may increase the scope of this methodology to include other heteroaromatic systems. This work will be reported in due course.

Experimental Section

General procedure for the *N*-vinyl acetamide MH-coupling reactions: The pyridyl tosylate (1 equiv), *N*-vinyl acetamide (4.0 equiv), Cy_2NMe (3 equiv), DPPF or DPPP (0.05 equiv) and $[Pd(dba)_2]$ (0.05 equiv) were dissolved in dioxane (3 mL) and the sample vial was fitted with a Teflon sealed screwcap and removed from the glovebox. The reaction mixture was heated for the time stated below at 100°C. The crude reaction was concentrated in vacuo and purified by column chromatography.

(*N*-(1-(5-Chloro-2-pyridinyl)vinyl)acetamide (9): 5-Chloro-2-pyridinyl tosylate (85.1 mg, 0.30 mmol), *N*-vinylacetamide (102.1 mg, 1.20 mmol), Cy_2NMe (191 μL, 0.90 mmol), DPPF (8.3 mg, 0.015 mmol), $[Pd(dba)_2]$ (8.6 mg, 0.015 mmol) were dissolved in dioxane (3 mL) and reacted for 17 h at 100°C. The crude product was purified by flash chromatography on silica gel using EtOAc/pentane 3:7 to afford the title compound as colorless crystals (51.7 mg, 88%). M.p. 84–85°C; ^{1}H NMR (400 MHz, CD_3CN): δ = 8.94 (br s, 1H), 8.54 (dd, 1H, J=2.4, 1.2 Hz), 7.82–7.81 (m, 2H), 6.34 (s, 1H), 5.54 (d, J=1.2 Hz), 2.13 ppm (s, 3H); ^{13}C NMR (100 MHz, CD_3CN): δ = 169.5, 151.1, 146.9, 138.1, 137.2, 131.6, 120.8, 99.7, 24.2 ppm; HRMS (ESI): m/z: calcd for $C_9H_9ClN_2ONa$: 219.0301, found: 219.0299 [M+Na$^+$].

General procedure for the butyl vinyl ether MH-coupling reactions: The pyridyl tosylate (1 equiv), butyl vinyl ether (4.0 equiv), Cy_2NMe (3 equiv), DPPF or DPPP (0.05 equiv) and $[Pd(dba)_2]$ (0.05 equiv) were dissolved in dioxane (3 mL) and the sample vial was fitted with a Teflon sealed screwcap and removed from the glovebox. The reaction mixture was heated for the time stated below at 100°C. The crude reaction was concentrated in vacuo and purified by column chromatography.

2-(1-Butoxyvinyl)-5-(trifluoromethyl)pyridine (24): 5-(Trifluoromethyl)-2-pyridinyl tosylate (95.2 mg, 0.30 mmol), butyl vinyl ether (155.3 μL, 1.20 mmol), Cy_2NMe (191 μL, 0.90 mmol), DPPP (6.19 mg, 0.015 mmol) and $[Pd(dba)_2]$ (8.6 mg, 0.015 mmol) were dissolved in dioxane (3 mL) and reacted for 17 h at 100°C. The crude product was purified by flash chromatography on silica gel using CH_2Cl_2/pentane 2:3 to afford the title compound as a colorless oil (57.2 mg, 78%). ^{1}H NMR (400 MHz, CD_3CN): δ = 8.82 (d, 1H, J=0.8 Hz), 8.04 (dd, 1H, J=8.4, 0.8 Hz), 7.82 (d, 1H, J=8.4 Hz), 5.54 (d, 1H, J=2.0 Hz), 4.53 (d, 1H, J=2.0 Hz), 3.93 (t, 2H, J=6.4 Hz), 1.82–1.75 (m, 2H), 1.56–1.47 (m, 2H), 0.98 ppm (t, 3H, J=7.4 Hz); ^{13}C NMR (100 MHz, CD_3CN): δ = 157.8, 157.0, 146.0 (q, J=4.4 Hz), 134.5 (q, J=3.6 Hz), 125.4 (q, J=32.6 Hz), 124.3 (q, J=269.6 Hz), 118.8, 86.9, 68.2, 31.1, 19.5, 13.4 ppm; ^{19}F NMR (376 MHz, CD_3CN): δ = −63.3 ppm; HRMS (ESI): m/z: calcd for $C_{12}H_{14}NOF_3H$: 246.1106, found: 246.1107 [M+H$^+$].

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