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# Highly Efficient Asymmetric Morita–Baylis–Hillman Reaction Promoted by Chiral Aziridine-Phosphines

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**Abstract:** Continuing our research on the use of organophosphorus derivatives of aziridines in asymmetric synthesis and expanding the scope of their applicability, chiral aziridine-phosphines obtained earlier in our laboratory were used as chiral catalysts in the asymmetric Morita–Baylis–Hillman reaction of methyl vinyl ketone and methyl acrylate with various aromatic aldehydes. The desired chiral products were formed in moderate to high chemical yields and with enantiomeric excess reaching value of 98% *ee* in some cases. The use of catalysts being pairs of enantiomers led to the desired products with opposite absolute configurations.

**Keywords:** asymmetric organocatalysis; chiral aziridine-phosphines; enantioselective Morita–Baylis–Hillman reaction; stereoselectivity



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## 1. Introduction

Asymmetric synthesis is still one of the most dynamically developing areas of modern organic chemistry [1]. Numerous research centers in the world undertake various catalytic strategies, like e.g., aerobic oxidations, transition metal-catalyzed reactions, or dual catalytic transformations [1]. Among the many techniques used in the synthesis of chiral organic compounds, organocatalysis is the field of the most intense research [2]. Currently, more and more attention is paid to organocatalytic processes carried out in environmentally friendly conditions ("green chemistry") [3]. These include reactions under solvent-free conditions, the use of immobilized organocatalysts, the application of microwave or ultrasounds irradiation, processes in water or another "green solvents", and many others [3].

Organocatalytic asymmetric Morita–Baylis–Hillman (MBH) reaction constitutes one of the most important carbon–carbon bond constructing transformation [4]. Among the huge number of catalysts known in the literature, and used in this reaction, the following can be mentioned: brucine diol-derivatives [5], pyrrolidine-based organocatalysts [6], chiral thiourea [7], and thiourea-based bifunctional catalytic systems [8], cinchona alkaloids [9], and chiral phosphines [10]. More unusual approaches include the use of pepsin [11], cationic chiral surfactant-based micelle [12], or catalyst based on metal-organic framework and chiral ionic liquid [13].

Asymmetric Morita–Baylis–Hillman reaction is a significant transformation in modern organic synthesis because, among other things, it is one of the key steps in the synthesis of: andranginine, i.e., a pentacyclic monoterpenoid indole alkaloid [14]; (+)-[$^{13}C_4$]-anatoxin-a, for quantifying the content of anatoxin-a in water (cyanobacterial toxin produced by algae) [15]; vincadifformine (indole alkaloid displaying remarkable cytotoxicity in vitro against a total of 60 human tumor cell lines) [16]; benzoxaboroles acting as carbapenemase inhibitors [17]; entecavir (hepatitis B virus inhibitor) [18], and various useful synthons for the synthesis of heterocycles [19].

Organocatalysts containing a phosphine motif are extremely popular in the literature, nevertheless, combinations of phosphines with aziridines, which for us is most interesting because research on this subject matter has been conducted for several decades, are described rarely [20]. On the basis of our experience in the field of the use of aziridines in asymmetric synthesis [21,22], and in the application of aziridine phosphines (or phosphine oxides) as organocatalysts in Michael addition [23], Mannich reaction [24], Friedel–Crafts alkylation of indoles [25], Simmons–Smith cyclopropanation, and diethylzinc addition to aldehydes [26] and taking all the aforementioned data into account, we decided to check the catalytic activity of chiral, enantiomerically pure aziridine-phosphines in the organocatalytic asymmetric Morita–Baylis–Hillman reaction of methyl vinyl ketone (MVK) (or methyl acrylate) with aromatic aldehydes. Although there are reports in the literature describing the use of chiral phosphine catalysts in an asymmetric MBH reaction, there are no known instances of the use of phosphino-aziridines in this conversion. We also wanted to show that the chiral catalytic systems containing the aziridine ring, which have been studied for many years in our group, are universal in nature and are capable of efficiently catalyzing a wider and wider range of asymmetric reactions.

## 2. Results and Discussion

### *2.1. Synthesis of Chiral Catalysts* **1**–**8**

The enantiomerically pure aziridines **1**–**8** (Figure 1) functionalized by triphenylphosphine moiety were prepared as previously described [25] (*via* reduction of the appropriate phosphine oxides).

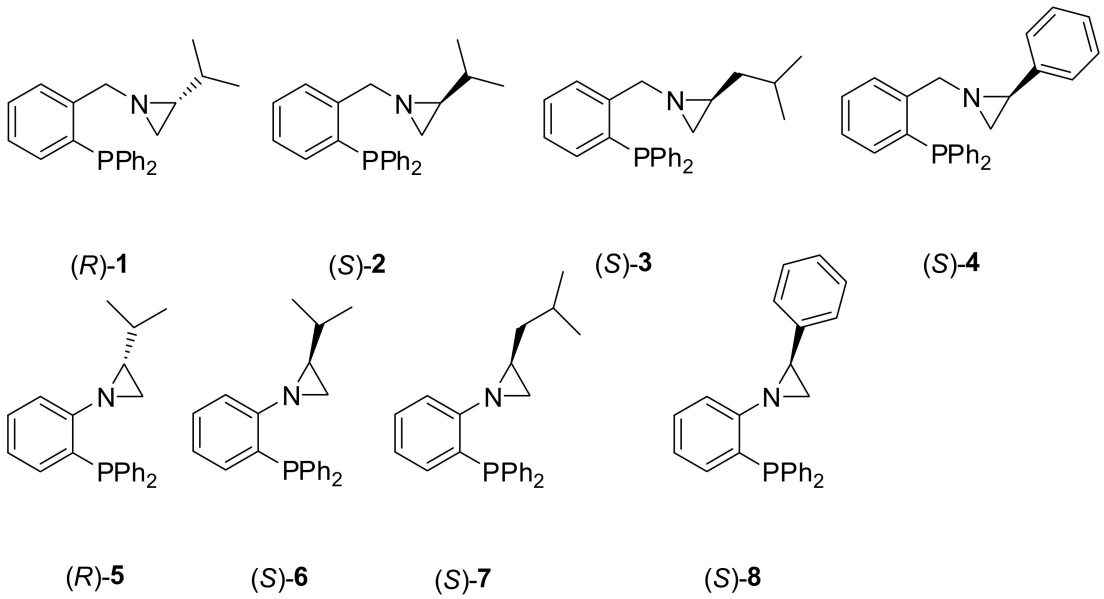
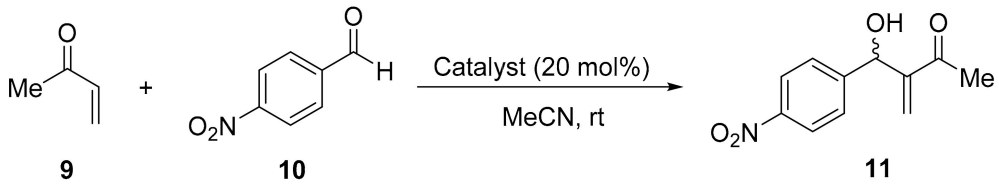



**Figure 1.** Optically pure chiral catalysts **1**–**8**.

### *2.2. Asymmetric Morita–Baylis–Hillman Reaction Promoted by Aziridine-Phosphines* **1**–**8**

In the next stage of the research, we decided to check the catalytic efficiency of chiral junctions **1**–**8** in the organocatalytic asymmetric Morita–Baylis–Hillman reaction. As a model transformation, the reaction of methyl vinyl ketone (MVK) (**9**) with p-nitrobenzaldehyde (**10**) is carried out in acetonitrile, and in the presence of 20 mol% of the catalyst at room temperature [5] (Scheme 1). All the results of the aforementioned asymmetric processes (yields, enantiomeric excess (*ee*), and absolute configuration of products of type **11**) are summarized in Table 1.




**Scheme 1.** Model MBH reaction methyl vinyl ketone with *p*-nitrobenzaldehyde promoted by catalysts **1**–**8**.

**Table 1.** Asymmetric Morita–Baylis–Hillman reaction catalyzed by aziridine-phosphines **1**–**8**.

| Entry | Catalyst | Yield [%] | *ee* [%] [a] | Abs. Conf. [b] |
|---|---|---|---|---|
| 1 | 1 | 42 | 54 | (*R*) |
| 2 | 2 | 48 | 56 | (*S*) |
| 3 | 3 | 46 | 51 | (*S*) |
| 4 | 4 | 43 | 44 | (*S*) |
| 5 | 5 | 95 | 96 | (*R*) |
| 6 | 6 | 96 | 98 | (*S*) |
| 7 | 7 | 92 | 96 | (*S*) |
| 8 | 8 | 94 | 90 | (*S*) |

[a] Determined by chiral HPLC using Chiralcel OD-H column. [b] According to literature data [5]. Conditions: 20 mol% of the catalyst, MVK (0.5 mmol), *p*-nitrobenzaldehyde (0.25 mmol), MeCN (1 mL), rt, 48 h.

A careful analysis of the data collected in Table 1 allows to draw some conclusions. First, the use of chiral aziridine-phosphines **1**–**4** containing a methylene linker connecting aziridine subunit with aromatic ring led to the Morita–Baylis–Hillman reaction product **11** in moderate chemical yields and also with moderate enantioselectivity (Table 1, entries 1–4). The chiral systems **5**–**8** in which the aziridine nitrogen is directly linked to the aromatic ring of the phosphine showed a much higher catalytic activity in the model reaction, leading to the desired product with very high yield and enantiomeric excess values (Table 1, entries 5–8); moreover, which is very important, the absolute configuration of the catalyst determined configuration of the chiral product. The application of both enantiomeric phosphine-aziridines led to the formation of enantiomers of **11** having opposite absolute configurations (Table 1, entries 1, 2, and 5, 6). Thus, we have access to both enantiomeric forms of the MBH reaction product owing to the use of enantiomeric catalysts. These observations are in line with our previous research [23–26].

As we started with 20 mol% catalysts, we decided to check whether lowering the catalyst loading will have an impact on the yield and enantioselectivity of the MBH model reaction. Thus, we performed two additional reactions between MVK and *p*-nitrobenzaldehyde using 10 and 5 mol% of catalyst **6**, respectively. All the results of the research on the amount of the catalyst used are summarized in Table 2.

**Table 2.** Asymmetric MBH reaction with various catalysts **6** loading.

| Entry | Catalyst 6 Loading [mol%] | Yield [%] | *ee* [%] [a] |
|---|---|---|---|
| 1 | 5 | 72 | 90 |
| 2 | 10 | 85 | 93 |
| 3 | 20 | 96 | 98 |

[a] Determined by chiral HPLC using Chiralcel OD-H column. Conditions: 5–20 mol% of the catalyst, MVK (0.5 mmol), *p*-nitrobenzaldehyde (0.25 mmol), MeCN (1 mL), rt, 48 h.

Inspection of Table 2 shows that lowering the catalyst loading did not significantly affect the enantioselectivity of the model reaction, but it caused quite a significant reduction in chemical yield. Moreover, all attempts to increase the reaction temperature were associated with a drastic decrease in enantioselectivity (Table 3).

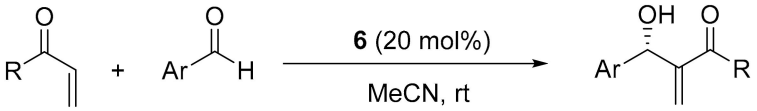
**Table 3.** Asymmetric MBH reactions at elevated temperatures.

| Entry | Temperature [°C] | Yield [%] | *ee* [%] [a] |
|---|---|---|---|
| 1 | 40 | 90 | 52 |
| 2 | 60 | 91 | 37 |

[a] Determined by chiral HPLC using Chiralcel OD-H column. Conditions: 20 mol% of the catalyst, MVK (0.5 mmol), *p*-nitrobenzaldehyde (0.25 mmol), MeCN (1 mL), 40–60 °C, 48 h.

### *2.3. Organocatalytic Asymmetric Morita–Baylis–Hillman Reaction Catalyzed by Aziridine-Phosphine 6—Scope of the Substrates*

Based on previous screening research, the most effective catalyst was selected as the system **6** containing (*S*)-aziridine subunit. Therefore, further MBH reactions utilizing variously substituted aromatic aldehydes and also methyl acrylate as the α,β-unsaturated carbonyl compound were performed in the presence of the most efficient catalyst **6** (Scheme 2). The results are collected in Table 4.




**12-17**

**Scheme 2.** Asymmetric MBH reactions promoted by aziridine-phosphine **6**.

**Table 4.** Asymmetric MBH reaction promoted by aziridine-phosphine **6**.

| Entry | R | Ar | Product | Yield [%] | *ee* [%] [a] | Abs. conf. [b] |
|---|---|---|---|---|---|---|
| 1 | Me | Ph | **12** | 90 | 97 | (*S*) |
| 2 | Me | 2-Naphthyl | **13** | 93 | 96 | (*S*) |
| 3 | Me | 4-$CF_3C_6H_4$ | **14** | 89 | 82 | (*S*) |
| 4 | Me | 4-$BrC_6H_4$ | **15** | 91 | 98 | (*S*) |
| 5 | Me | 4-$MeOC_6H_4$ | **16** | traces | nd [c] | nd [c] |
| 6 | OMe | 4-$NO_2C_6H_4$ | **17** | 85 | 74 | (*S*) |

[a] Determined by chiral HPLC using Chiralcel OD-H column. [b] According to literature data [5,27,28]. [c] not determined. Conditions: 20 mol% of **6**, aldehyde (0.5 mmol), α,β-unsaturated carbonyl derivative (0.5 mmol), MeCN (1 mL), rt, 48–96 h.

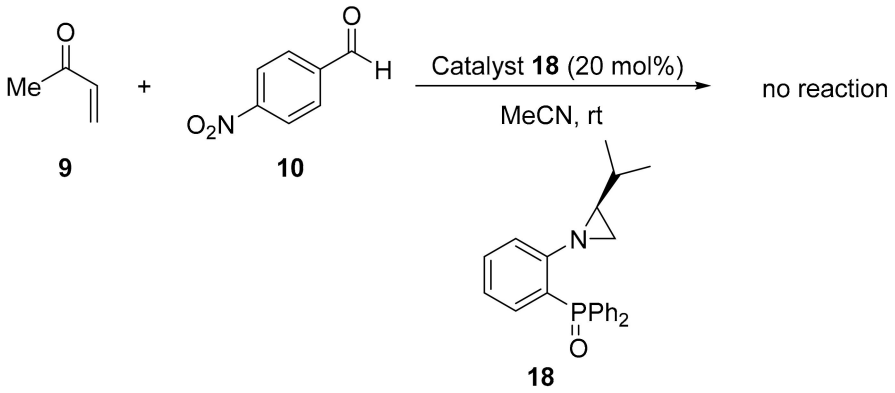
Inspection of Table 4 indicates that aziridine-phosphine **6** efficiently catalyzes the asymmetric Morita–Baylis–Hillman reaction giving the corresponding chiral products **12–15** and **17** in high yields and excellent enantioselectivity. Slightly lower catalytic activity was observed in the case of the use of methyl acrylate as α,β-unsaturated carbonyl component (Table 4, entry 6). Moreover, it should be mentioned that for the above transformation, longer reaction time (96 h) was necessary. Reaction between MVK and *p*-methoxybenzaldehyde (Table 4, entry 5) gave product **16** only in trace amounts ($^1$H NMR and TLC analysis revealed mainly the presence of unreacted starting materials). This was probably due to the fact that electron donating groups (EDGs) make carbon centers weaker for electrophiles and less reactive to nucleophiles.

At the end of the research on the asymmetric MBH reaction, we decided to check the importance of the phosphine moiety in this transformation. For this reason, a model MBH reaction of methyl vinyl ketone with *p*-nitrobenzaldehyde was performed in the presence of the corresponding phosphinoyl-aziridine **18** [23] (Scheme 3).

As anticipated, no reaction product was observed which may indicate that the phosphine group is a very important factor for the asymmetric Morita–Baylis–Hillman reaction.

Careful analysis of the stereochemical course of the reaction reveals that the use of a catalyst containing a carbon atom in the aziridine subunit of the (*S*)-configuration yields a chiral allylic alcohol also having a stereogenic carbon atom of the absolute (*S*)-configuration. As this tendency has also appeared in our previous research on organophosphorus derivatives of aziridines [23–25], it seems reasonable that the proposed transition state model for

aziridine-phosphine catalyzed asymmetric MBH reaction is similar to those described by us earlier.




**Scheme 3.** Asymmetric MBH reaction in the presence of phosphine oxide.

Thus, the proposed transition state (Figure 2) involves first complexing the catalyst with a vinyl ketone molecule. Figure 2 shows the complex with such a configuration in which steric interactions are minimized. The large aryl substituent on the aziridine nitrogen and the isopropyl group are on either side of the ring. The diphenylphosphine group and the aziridine ring are opposite and the enol complex is in between. The positive charge of the phosphorus atom interacts with the oxygen atom of the aldehyde molecule, which theoretically may approach from the side of the unsubstituted methylene group of the ring. The approach on the other side of the ring is prevented by steric hindrance of the isopropyl group. In the key stage for the product configuration, the aldehyde molecule is approached and the C-C bond is formed. This can take place in such a way that the aryl ring comes closer to the least crowded side of the ring, leading to the (*S*)-configured product. The (*R*)-enantiomer would be formed by an approach in which the aryl ring approaches the side of the phenyl group bound to the phosphorus atom, but this is sterically impossible.

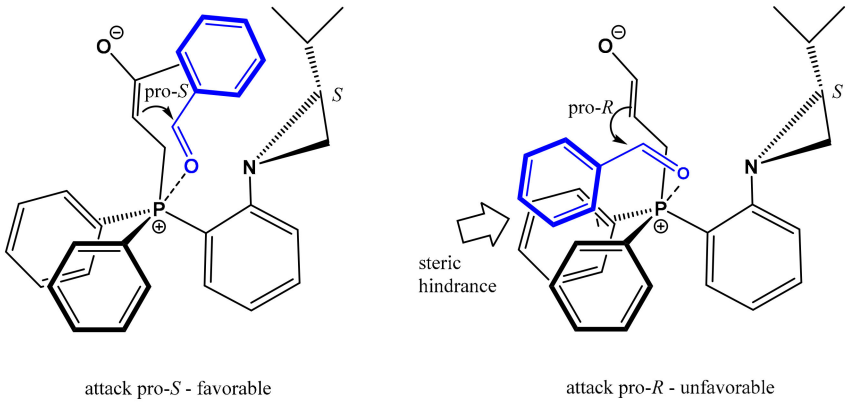



**Figure 2.** Proposed transition state model.

## 3. Materials and Methods

### *3.1. Materials*

Acetonitrile (anhydrous, 99.8%) was purchased from Sigma-Aldrich and used without additional purification. *n*-Hexane and ethyl acetate were distilled before use. The NMR spectra were recorded on a Bruker (Bruker, Billerica, MA, USA) instrument at 600, 150, and 243 MHz using $CDCl_3$ as a solvent and TMS as internal standard. Data are reported as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. s = broad singlet. Column chromatography was carried out using Merck 60 silica gel. TLC was performed on Merck 60 $F_{254}$ silica gel plates (Merck Group (Merck KgaA), Darmstadt, Germany).

The enantiomeric excess (*ee*) was measured via HPLC using column with chiral support (Chiralcel OD-H). Chiral catalysts **1**–**8** and **18** were prepared as previously described [23,25].

### *3.2. Methods*

Asymmetric Morita–Baylis–Hillman Reaction—General Procedure

The catalyst (0.05 mol, 20 mol%), an aldehyde (0.25 mmol, 1 equiv.), and methyl vinyl ketone (or methyl acrylate) (0.5 mmol, 2 equiv.) in acetonitrile (1 mL) were placed in a round-bottom flask. The resulting solution was magnetically stirred at room temperature for 48 h (96 h in the case of methyl acrylate) (monitored by TLC). Afterwards, the solvent was evaporated in vacuo and the crude product was subjected to purification via column chromatography (silica gel, hexane:ethyl acetate from 9:1 to 8:2) to provide the corresponding allylic alcohols. The NMR spectra of the products are consistent with literature data [5,27,28]. In the case of the synthesis of racemic samples, 4-(dimethylamino)pyridine (DMAP) was used as catalyst (20 mol%). Copies of $^1$H NMR spectra of MBH products and their HPLC chromatograms are collected in Supplementary Materials.

(*S*)-3-(hydroxy(4-nitrophenyl)methyl)but-3-en-2-one 11

$^1$H NMR (600 MHz, $CDCl_3$) δ = 2.39 (s, 3H), 3.33 (d, *J* = 5.8 Hz, 1H), 5.71 (d, *J* = 5.6 Hz, 1H), 6.06 (d, *J* = 1.0 Hz, 1H), 6.29 (s, 1H), 7.57–7.59 (m, 2H), 8.21–8.23 (m, 2H). The same spectrum was recorded for (*R*)-3-hydroxy(4-nitrophenyl)methyl)but-3-en-2-one;

(*S*)-3-(hydroxyphenyl)methyl)but-3-en-2-one 12

$^1$H NMR (600 MHz, $CDCl_3$) δ = 2.37 (s, 3H), 3.14 (d, *J* = 5.2 Hz, 1H), 5.65 (d, *J* = 5.0 Hz, 1H), 6.00 (d, *J* = 1.0 Hz, 1H), 6.22 (s, 1H), 7.30–7.32 (m, 1H), 7.35–7.40 (m, 4H);

(*S*)-3-(hydroxy(naphthalene-2-yl)methyl)but-3-en-2-one 13

$^1$H NMR (600 MHz, $CDCl_3$) δ = 2.39 (s, 3H), 3.26 (d, *J* = 5.1 Hz, 1H), 5.83 (d, *J* = 5.0 Hz, 1H), 6.03 (d, *J* = 1.0 Hz, 1H), 6.26 (s, 1H), 7.46–7.52 (m, 3H), 7.84–7.88 (m, 4H);

(*S*)-3-(hydroxy(4-fluorophenyl)methyl)but-3-en-2-one 14

$^1$H NMR (600 MHz, $CDCl_3$) δ = 2.29 (s, 3H), 3.17 (d, *J* = 5.6 Hz, 1H), 5.58 (d, *J* = 5.3 Hz, 1H), 5.93 (d, *J* = 1.0 Hz, 1H), 6.18 (s, 1H), 7.41–7.43 (m, 2H), 7.52–7.54 (m, 2H);

(*S*)-3-(hydroxy(4-bromophenyl)methyl)but-3-en-2-one 15

$^1$H NMR (600 MHz, $CDCl_3$) δ = 2.37 (s, 3H), 3.21 (d, *J* = 5.3 Hz, 1H), 5.58 (d, *J* = 5.0 Hz, 1H), 6.00 (d, *J* = 1.0 Hz, 1H), 7.25–7.27 (m, 2H), 7.47–7.49 (m, 2H);

Methyl (*S*)-2-(hydroxy(4-nitrophenyl)methyl) acrylate 17

$^1$H NMR (600 MHz, $CDCl_3$) δ = 3.34 (d, *J* = 6.2 Hz, 1H), 3.78 (s, 3H), 5.66 (d, *J* = 5.9 Hz, 1H), 5.89 (s, 1H), 6.43 (s, 1H), 7.59–7.61 (m, 2H), 8.22–8.24 (m, 2H).

## 4. Conclusions

Enantiomerically pure chiral phosphines containing aziridine moiety exhibited very high catalytic activity in asymmetric Morita–Baylis–Hillman reaction of methyl vinyl ketone (or methyl acrylate) with aromatic aldehydes. The corresponding allylic alcohols were prepared very efficiently (in most cases) in terms of chemical yield and enantiomeric excess. The use of enantiomeric pairs of chiral catalysts led to the formation of opposite enantiomers of MBH chiral products.

**Supplementary Materials:** The following are available online at https://www.mdpi.com/article/10.3390/catal12040394/s1: $^1$H NMR spectra of MBH products, HPLC chromatograms of Morita–Baylis–Hillman reaction products.

**Author Contributions:** Conceptualization and methodology, S.L. and M.R.; software, A.B.-S., A.Z. and M.R.; investigation, A.B.-S. and A.Z.; writing—original draft preparation, M.R.; writing—review and editing, S.L. and M.R.; supervision, M.R. and S.L. All authors have read and agreed to the published version of the manuscript.

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**Conflicts of Interest:** The authors declare no conflict of interest.

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