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ARTICLE

# Photo-induced glycosylation using the edible polyphenol curcumin

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Photo-induced glycosylations of trichloroacetimidate donors and alcohols using an edible polyphenol, curcumin, were examined under visible photo-irradiation (470 nm). It was found, for the first time, that these glycosylations proceed smoothly under mild reaction conditions to give the corresponding glycosides in high yield. In addition, the present glycosylation method was applicable to a wide range of trichloroacetimidate donors and alcohol acceptors, and showed high chemoselectivity over glycosyl phosphite, phosphate, (*N*-phenyl)trifluoroacetimidate, fluoride, glycal and thioglycoside.

## Introduction

Many glycosides, including glycoconjugates and oligosaccharides, are commonly found in biologically active natural products, pharmaceuticals and high-functional molecules.[1,2] Elucidating the precise biological and functional roles and structure-activity relationships of the glycosides requires homogeneous and structurally well-defined glycosides. In this context, glycosylation, a crucial synthetic reaction for binding sugars to other sugar moieties or other molecules (aglycon), is increasingly important in chemistry, biology, and materials science. Great effort has been made to develop efficient glycosylation reactions, with various efficient glycosylation methods reported to date.[3] However, most conventional glycosylation methods still use environmentally harmful catalysts such as strong acids and toxic metal reagents, making environmentally friendly glycosylation methods[4] increasingly important as environmental problems accumulate and Sustainable Development Goals (SDGs) gain importance.[5] Photo-induced glycosylation[6,7] using reusable photocatalysts[7b-7e] is an attractive approach to green and sustainable chemistry. We recently reported the photo-induced glycosylation of trichloroacetimidate donors and several alcohols using organo Brønsted photoacid (BPA) catalysts (2-naphthol (**1**), 5,8-dicyano-2-naphthol (**2**) and 1,3-bis[3,5-bis(trifluoromethyl)-phenyl]thiourea (**3**))[7b,c] or organo Lewis photoacid (LPA) catalysts (bis(2-naphthyl)disulfide (**4**) and 3,11-dimethoxydinaphthothiophen(**5**))[7d,e] under long-wavelength UV light irradiation. This approach has the interesting chemical property of increasing acidity under photo-excited states of the catalysts. Glycosylation proceeds efficiently to provide the corresponding glycoside using long-wavelength UV light irradiation (365 or 385 nm) (Fig. 1a). These glycosylations are promoted by irradiation with light as a clean energy source under mild conditions without the use of strong acids or toxic metal reagents. In addition, there is no need for a neutralization step to terminate the reaction, and the photocatalyst can be recovered and reused. Furthermore, the reaction solvent can be recovered by only evaporation and reused without further purification. However, challenges remain with these reactions: for example, photo-irradiation to activate these organo photoacid catalysts is limited to UV light wavelengths. Here, we overcame this problem by focusing on the edible polyphenol curcumin (**6**) as a new activator. Because **6** has phenolic hydroxyl group, as found in naphthol derivatives (**1**) and (**2**), they can likely be activated by visible light irradiation due to the long π-conjugated system. Furthermore, **6** is a harmless

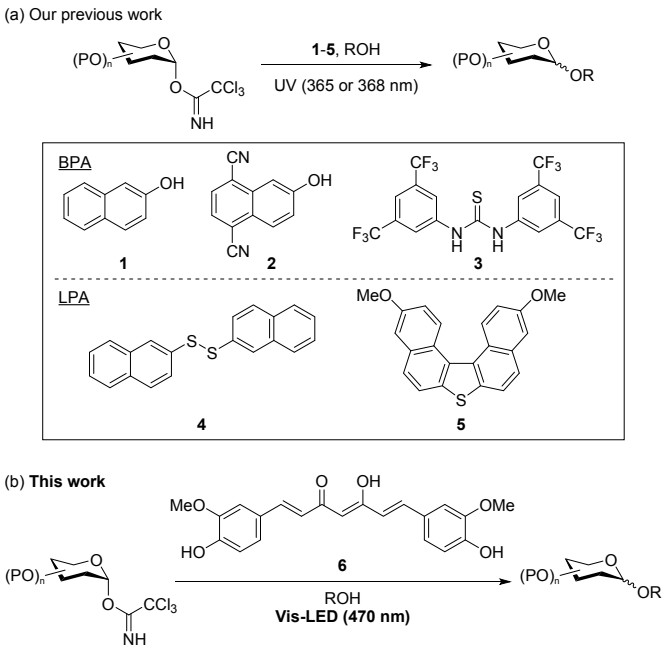


**Fig. 1** Photo-induced glycosylation using (a) organo Brønsted photoacid (BPA) catalysts **1**-**3**, organo Lewis photoacid (LPA) catalysts **4** and **5** and (b) an edible polyphenol, curcumin (**6**).

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compound found in many foods. Therefore, the use of **6** as an activator would enable more environmentally benign reactions. Herein, we report that the edible polyphenol curcumin can act as an activator to effectively promote photo-induced glycosylation under mild reaction conditions. To our knowledge, this is the first demonstrated example of a chemical glycosylation reaction using an edible chemical as an activator.

## Results and discussion

To investigate our hypothesis, we first measured the UV-Vis absorption spectra of 2-naphthol (**1**) and the edible polyphenol curcumin (**6**) (Fig. 2). Compound **6** absorbs in the visible light region, whereas **1** does not, suggesting that **6** can function as an activator under visible light irradiation. With these preliminary results in hand, we selected the glucosyl trichloroacetimidate **7a** and **6** as a glycosyl donor and activator, respectively. Initially, we examined the glycosylation of cyclohexylmethanol (**8A**) (2.0 equiv.) with **7a** using a catalytic amount of **6** (0.1 equiv.) in the presence of powdered molecular sieves (MS 5 Å) in MeCN for 4 h under irradiation with Vis-LED light (470 nm, 60 mW/cm$^2$). The strength of light irradiation of sample was measured by an actinometer and controlled by the distance between the lamp and the reaction mixture. The results are summarized in Table 1. We demonstrated for the first time that the use of a catalytic amount (0.1 equiv.) of curcumin (**6**) in the glycosylation reaction of **7a** and cyclohexylmethanol (**8A**) under photo-irradiation provided the corresponding glycoside **9aA**, although the yield was moderate (entry 1 in Table 1). Therefore, we

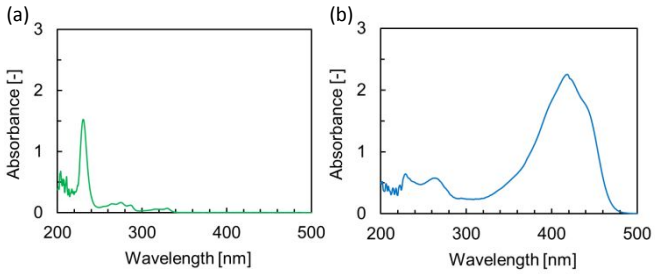
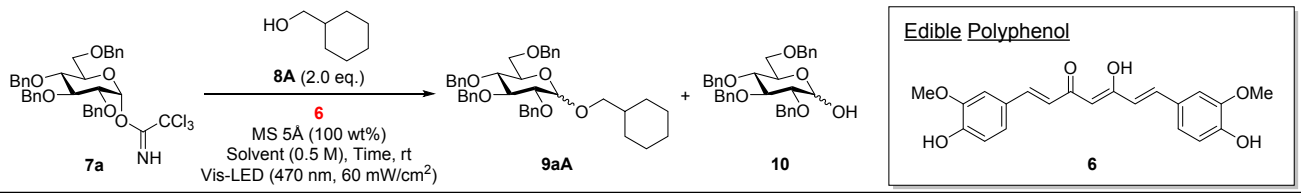



**Fig. 2** UV/Vis spectra of (a) **1** and (b) **6** (50 μM) in $CH_2Cl_2$.

**Table 1.** Glycosylations of donor **7a** and acceptor **8A** using a catalytic amount of curcumin (**6**).




| Entry | Cat. | Vis-LED | Solvent | Time (h) | Eq. of **6** | Yield (%)[a] **9aA** (α/β)[b] | **10** | **7a** |
|---|---|---|---|---|---|---|---|---|
| 1 | **6** | + | MeCN | 4 | 0.1 | 39 (19/81) | 10 | 48 |
| 2 | **6** | + | $CH_2Cl_2$ | 4 | 0.1 | 66 (32/68) | 7 | 25 |
| 3 | **6** | + | PhMe | 4 | 0.1 | 34 (19/81) | 5 | 56 |
| 4 | **6** | + | $Et_2O$ | 4 | 0.1 | 34 (32/68) | 8 | 57 |
| 5 | **6** | + | THF | 4 | 0.1 | 16 (21/79) | 9 | 70 |
| 6 | **6** | + | $CH_2Cl_2$ | 8 | 0.1 | 72 (35/65) | 8 | 20 |
| 7 | **6** | + | $CH_2Cl_2$ | 16 | 0.1 | 94 (39/61) | 3 | 0 |
| 8 | **6** | + | $CH_2Cl_2$ | 24 | 0.1 | 94 (38/62) | 2 | 0 |
| 9 | **6** | + | $CH_2Cl_2$ | 16 | 0.05 | 97 (32/68) | 0 | 0 |
| 10 | **6** | + | $CH_2Cl_2$ | 16 | 0.01 | 78 (33/67) | 8 | 10 |
| 11 | **6** | − | $CH_2Cl_2$ | 16 | 0.05 | 0 | 0 | 99 |
| 12 | — | + | $CH_2Cl_2$ | 16 | — | 13 (38/62) | 0 | 83 |

[a] Yield of the isolated product. [b] The α/β ratios were determined by $^1$H-NMR analysis. MS = Molecular sieves, THF = tetrahydrofuran.

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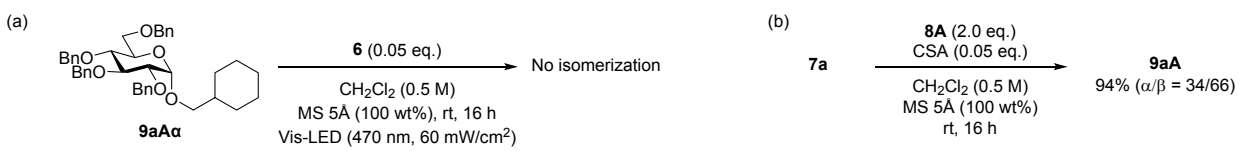
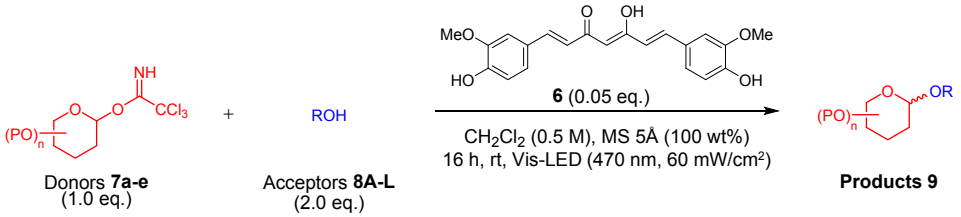
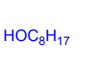
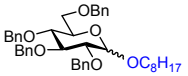
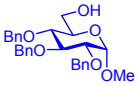
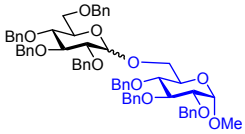
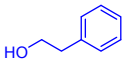
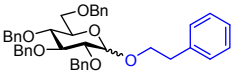
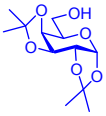
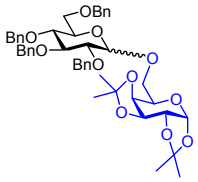
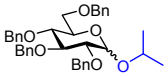
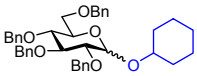
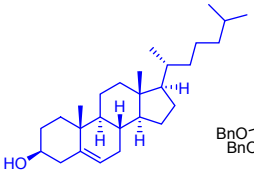
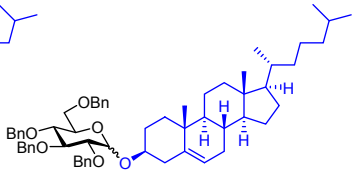
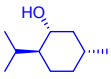
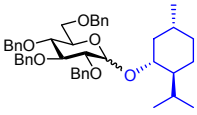
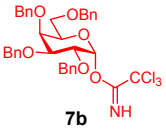
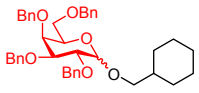
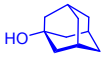
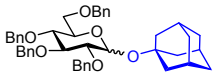
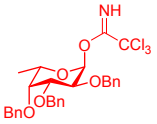
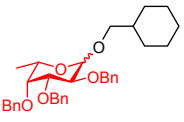
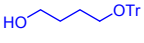
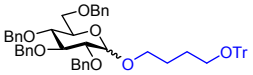
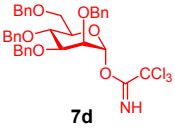
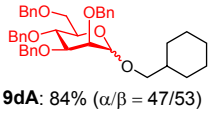
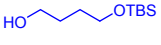
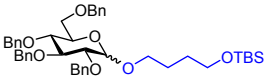
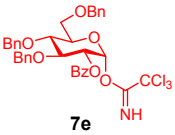
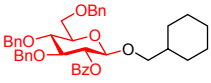



**Fig. 3** (a) Mechanistic study of the glycosylation. (b) Glycosylation of **7a** and **8A** using Brønsted acid CSA.

**Table 2.** Photo-induced glycosylations of several donors and acceptors using a catalytic amount of curcumin (**6**).




| Entry | Donor | Acceptor | Product (α/β)[a,b] | Entry | Donor | Acceptor | Product (α/β)[a,b] |
|---|---|---|---|---|---|---|---|
| 1 | **7a** |  **8B** |  **9aB**: 96% (α/β = 49/51) | 9[c] | **7a** |  **8J** |  **9aJ**: 90% (α/β = 34/66) |
| 2[c] | **7a** |  **8C** |  **9aC**: 91% (α/β = 44/56) | 10 | **7a** |  **8K** |  **9aK**: 93% (α/β = 47/53) |
| 3[c] | **7a** |  **8D** |  **9aD**: 96% (α/β = 57/43) | | | | |
| 4[c] | **7a** |  **8E** |  **9aE**: 85% (α/β = 52/48) | 11[d,e,g] | **7a** |  **8L** |  **9aL**: 73% (α/β = 62/38) |
| 5[c] | **7a** |  **8F** |  **9aF**: 90% (α/β = 41/59) | 12 |  **7b** | **8A** |  **9bA**: 81% (α/β = 14/86) |
| 6[d,e,f] | **7a** |  **8G** |  **9aG**: 90% (α/β = 49/51) | 13 |  **7c** | **8A** |  **9cA**: 87% (α/β = 12/88) |
| 7[c] | **7a** |  **8H** |  **9aH**: 91% (α/β = 41/59) | 14[d,f] |  **7d** | **8A** |  **9dA**: 84% (α/β = 47/53) |
| 8[d] | **7a** |  **8I** |  **9aI**: 95% (α/β = 44/56) | 15 |  **7e** | **8A** |  **9eA**: 72% (β only) |

[a] Yield of the isolated product. [b] The α/β ratios were determined by $^1$H-NMR analysis. [c] The reaction time was 24 h. [d] The reaction time was 48 h. [e] 0.2 M $CH_2Cl_2$ was used. [f] 0.1 eq. of **6** was used. [g] 1.0 eq. of **6** was used.

next examined solvent effects on the glycosylation of **7a** and **8A** with **6**. The results showed that **9aA** was obtained in higher yield when $CH_2Cl_2$ was used as a solvent whereas the use of PhMe, $Et_2O$ and THF gave lower yields of **9aA** (entries 2-5 in Table 1). Next, we optimized

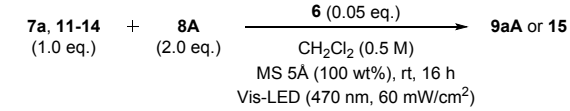
the reaction conditions: namely, reaction time and number of equiv. of **6**. To obtain the optimized reaction time, we examined the glycosylation reaction products after 4, 8, 16 and 24 h. A reaction time of 16 h was sufficient for this glycosylation reaction (entries 6-8 in Table 1). Investigation of the amount of catalyst showed that the use of 0.05 equiv. of **6** with photo-irradiation provided the same chemical yield as the use of 0.1 equiv. of **6** (entry 9 in Table 1), whereas the use of 0.01 equiv. of **6** gave a lower yield (entry 10 in Table 1). These results showed that the use of 0.05 equiv. of **6** in the glycosylation of **7a** and **8A** (2.0 equiv.) at room temperature for 16 h in $CH_2Cl_2$ under photo-irradiation (470 nm, 60 mW/cm$^2$) gave the best result, producing glycoside **9aA** in high yield (97% yield). In addition, we confirmed that glycosylation with **6** without photo-irradiation did not give **9aA** (entry 11 in Table 1), and glycosylation without **6** with photo-irradiation gave **9aA** only in 13% yield and **7a** was recovered in high yield (entry 12 in Table 1). These results clearly indicated that **6** significantly and selectively promoted the glycosylation reaction under 470 nm light irradiation. In this glycosylation reaction, β-glycoside was predominantly produced probably due to the $S_N2$ type reaction as a major pathway.

Next, we conducted mechanistic studies of this glycosylation reaction (Fig. 3) and found that when the α-glycoside **9aAα** was treated with only **6** without alcohol **8A** under the conditions used for photo-induced glycosylation, no isomerization occurred, and **9aAα** was quantitatively recovered. This indicates that α/β-stereoselectivity was determined by kinetic control (Fig. 3a). In addition, when the Brønsted acid 10-camphorsulfonic acid (CSA) (Fig. 3b) was used as a catalyst in the glycosylation of **7a** and **8A**, the resulting α/β-stereoselectivity was quite similar to that obtained using **6** under visible light irradiation (Fig. 3b). These results indicate that the relatively low α/β-stereoselectivity observed in the present photo-induced glycosylation reaction is not due to the photo-irradiation conditions, including the presence of curcumin (**6**), but rather to the nature of the glycosyl donor **7a**.

Next, the generality of the glycosylation method was examined using alcohols **8B**-**L**, including primary, secondary, tertiary, and sugar alcohols (Table 2). In all cases, glycosylations with **7a** using **6** under photo-irradiation proceeded smoothly to give the corresponding glycosides **9aB**-**L** in good to high yields. Interestingly, even the acid labile Tr (trityl) and TBS (*tert*-butyldimethylsilyl) groups were tolerated due to the mild reaction conditions (entries 7 and 8 in Table 2). Next, the effect of the type of glycosyl donor was investigated. When α-galactosyl and α-fucosyl trichloroacetimidates **7b** and **7c** were used, glycosylations of **8A** using **6** under photo-irradiation proceeded smoothly to give the corresponding glycosides **9bA** and **9cA**, respectively, in high yields with high β-stereoselectivities (entries 12 and 13 in Table 2). It is noteworthy that even the acid-labile **7c**[8] was smoothly activated to give the corresponding glycoside **9cA** in high yield. However, when α-mannosyl trichloroacetimidate **7d** was used, the corresponding glycoside **9dA** was obtained in 84% yield with almost no stereoselectivity (entry 14 in Table 2). We addressed this poor α/β-stereoselectivity by neighboring-group-assisted glycosylation using **7e**, which possesses a Bz group at the C2-position. The reaction provided the corresponding β-glucoside **9eA** in 72% yield with complete β-stereoselectivity (entry 15 in Table 2).

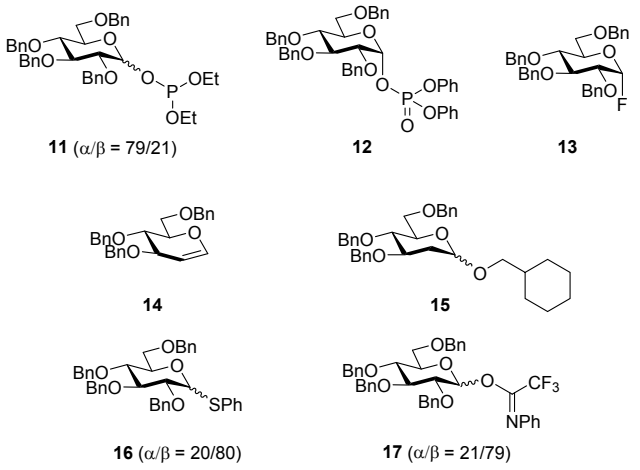
We also examined the chemoselectivity of the present glycosylation reaction against the leaving group of the donor and investigated whether the photo-induced glycosylation reaction with acceptor **8A** proceeds with several glycosyl donors which could be generally activated by a weak acid catalyst (Table 3). The use of glucosyl phosphite **11** and glucosyl phosphate **12** resulted in essentially no reaction (entries 2 and 3 in Table 3). In addition, when glucosyl fluoride **13**, glucal **14**, thiglycoside **16** and (*N*-phenyl)trifluoroacetimidate **17** were used, the donors were not activated and the corresponding glycoside **9aA** or **15** was not obtained (entries 4-7 in Table 3). Furthermore, it was confirmed that only **7a** was chemoselectively activated in the presence of both **7a** and **13**. These results indicated that the present glycosylation reaction has high chemoselectivity for the leaving group of the glycosyl donor.

**Table 3.** Glycosylations of donors **7a**, **11-14** and acceptor **8A** using a catalytic amount of curcumin (**6**).




| Entry | Donor | Product | Yield (%) (α/β)[a,b] |
|---|---|---|---|
| 1 | **7a** | **9aA** | 97 (32/68) |
| 2 | **11** | **9aA** | 11 (22/78) |
| 3 | **12** | **9aA** | 4 (57/43) |
| 4 | **13** | **9aA** | 0 |
| 5 | **14** | **15** | 0 |
| 6 | **16** | **9aA** | 0 |
| 7 | **17** | **9aA** | 0 |

[a] Yield of the isolated product. [b] The α/β ratios were determined by $^1$H-NMR analysis.



## Conclusions

In conclusion, we have developed a novel photo-induced glycosylation method using an edible polyphenol, curcumin. We found that the glycosylation of **7a** and **8A** using a catalytic amount of curcumin (**6**) (0.05 equiv.) under visible photo-irradiation (470 nm) and mild reaction conditions proceeded effectively to provide **9aA** in high yield. In addition, the present glycosylation method was applicable to a wide range of trichloroacetimidate donors **7b**-**e** and alcohol acceptors **8B**-**L**. This glycosylation reaction has high chemoselectivity for the leaving group of the glycosyl donor. This useful and environmentally benign glycosylation method should find various applications in the synthesis of not only biologically active compounds but also highly functional molecules. The development of several different types of organo photocatalysts and the use of edible polyphenols in environmentally benign organic syntheses is now under investigation in our laboratories.

## Experimental

### General information

NMR spectra were recorded on JEOL ECZ-400S (400MHz for $^1$H) spectrometer. Silica gel TLC was performed on a Merck TLC 60F-254 (0.25 mm). Column chromatography separation was performed on a Silica Gel 60N (spherical, neutral, 63-210 μm or 40-50 μm) (Kanto Chemical Co., Inc.). Curcumin (**6**) was provided by Tokyo Chemical Industry Co., Ltd. The Vis-LED lamp was purchased from OPTCODE Corporation.

### General procedure for photo-induced glycosylation

To a solution of glycosyl donor (30.0 mg, 1.0 eq.) in $CH_2Cl_2$ (0.5 M to the glycosyl donor) were added MS 5Å (30.0 mg, 100 wt% to the glycosyl donor), glycosyl acceptor (2.0 eq.) and curcumin (0.05 eq.). After stirring for 16 h under photo-irradiation using a Vis-LED lamp (470 nm, 60 mW/cm$^2$) at room temperature, the mixture was concentrated in *vacuo*. The purification of the residue by column chromatography gave the corresponding glycosides.

### Characterization of glycosides

All glycosides obtained by the present glycosylation are known compounds, and their characterization data of **9aA**-**9aE**[7b], **9aF**[7c], **9aG**[9], **9aH**[7e], **9aI**[7e], **9aJ**[7b], **9aK**[7c], **9aL**[9], **9bA**[7b], **9cA**[7d], **9dA**[7b] and **9eA**[7b] are identical with the literature data.

## Author Contributions

KT conceived and directed the project. SG and HS performed chemical syntheses. DT joined in discussions. The first draft of the manuscript was prepared by SG and KT, and the final draft was edited by all the authors.

## Conflicts of interest

There are no conflicts to declare.

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