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Metal-free photocatalytic thiol–ene/thiol–yne reactions†

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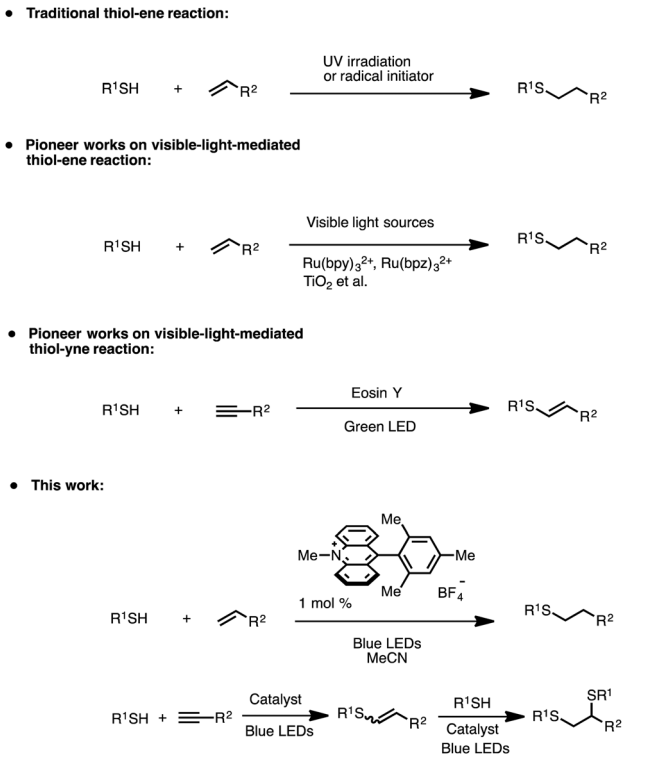
The organic photocatalyst (9-mesityl-10-methylacridinum tetrafluoroborate) in the presence of visible light is used to initiate thiol–ene and thiol–yne reactions. Thiyl radicals are generated upon quenching the photoexcited catalyst with a range of thiols. The highlighted mild nature of the reaction conditions allows a broad substrate scope of the reactants. Relying on this efficient metal-free condition, both thiol–ene and thiol–yne reactions between carbohydrates and peptides could be realized in excellent yields.

The formation of a carbon–sulfur bond (C–S) is important because organosulfur moieties are widely represented within natural products, pharmaceuticals and modern materials.[1,2] Among the various strategies of C–S bond formation, radical thiol–ene and thiol–yne reactions have been widely carried out in areas of bioconjugate chemistry, polymer science and pharmaceutical chemistry.[3,4] The atom economic process provides efficient access to sulfur containing products, fulfilling the "click" chemistry concept.[5] Traditionally, the radical thiol–ene/thiol–yne reaction is promoted by UV light or a radical initiator. However, it requires either stoichiometric reagents or a specialized UV photo-apparatus. Recently, visible-light photoredox catalysis[6] has been a leading efficient approach for forming C–S bonds.[7] In 2013, Yoon developed a transition metal based photocatalytic thiol–ene reaction, where household visible light sources were used as a convenient alternative to UV irradiation.[8] One year later, Stephenson reported a similar photocatalytic thiol–ene reaction by using the trichloromethyl radical as a radical mediator.[9] In addition to the $Ru(bpy)_3^{2+}$ catalysts, other types of catalysts, both metal-based and metal-free catalysts, were also applied for the visible-light-mediated thiol–ene reaction.[10] Moreover, Ananikov reported the first visible-light-mediated metal-free radical thiol–yne reaction using Eosin Y as the photocatalyst, furnishing a range of vinyl sulfides in good yields and selectivity.[11] The visible light photoredox catalysis provided a significantly milder approach, which makes the thiol–ene/thiol–yne reaction potentially useful in bioconjugation and polymer synthesis.[12] Continuing our interest in organic photocatalysis,[13] we report herein a visible-light-mediated thiol–ene/thiol–yne reaction initiated by the organic photocatalyst 9-mesityl-10-methylacridinium tetrafluoroborate[14] (Scheme 1). This photoredox process driven by the organic photocatalyst is synthetically complementary to both traditional (using UV irradiation or thermolysis of a radical initiator) and transition metal catalyzed approaches. In particular, the metal-free process could potentially benefit peptide and glycoprotein chemistry, since certain polypeptide sequences and proteins have been shown to interfere with transition metal mediated processes.[15]



Scheme 1 Radical thiol–ene/thiol–yne reactions.

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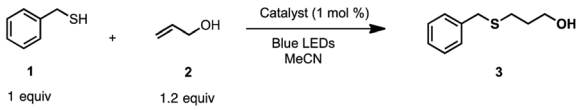
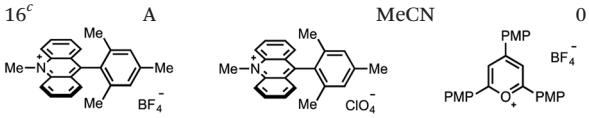
Table 1 Optimization studies for the thiol–ene reaction of benzyl mercaptan with allyl alcohol[a]



1 (1 equiv) + 2 (1.2 equiv) → 3

Entry	Catalyst	Solvent	Yield[b] (%)
1	A	CH_2Cl_2	80
2	A	THF	62
3	**A**	**MeCN**	**90**
4	A	DMF	49
5	A	1,4-Dioxane	53
6	A	PhMe	83
7	A	MeOH	55
8	B	MeCN	83
9	C	MeCN	69
10	Rhodamine 6G	MeCN	80
11	Riboflavin	MeCN	0
12	Eosin Y	MeCN	30
13	Rose Bengal	MeCN	33
14	Methylene blue	MeCN	0
15	None	MeCN	0
16[c]	A	MeCN	0

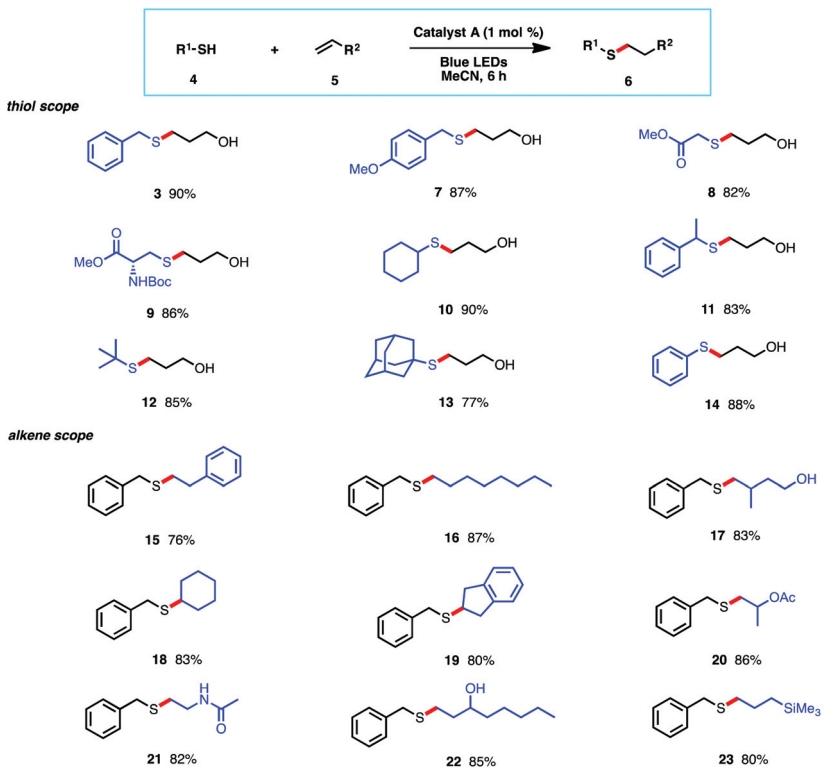


A B C

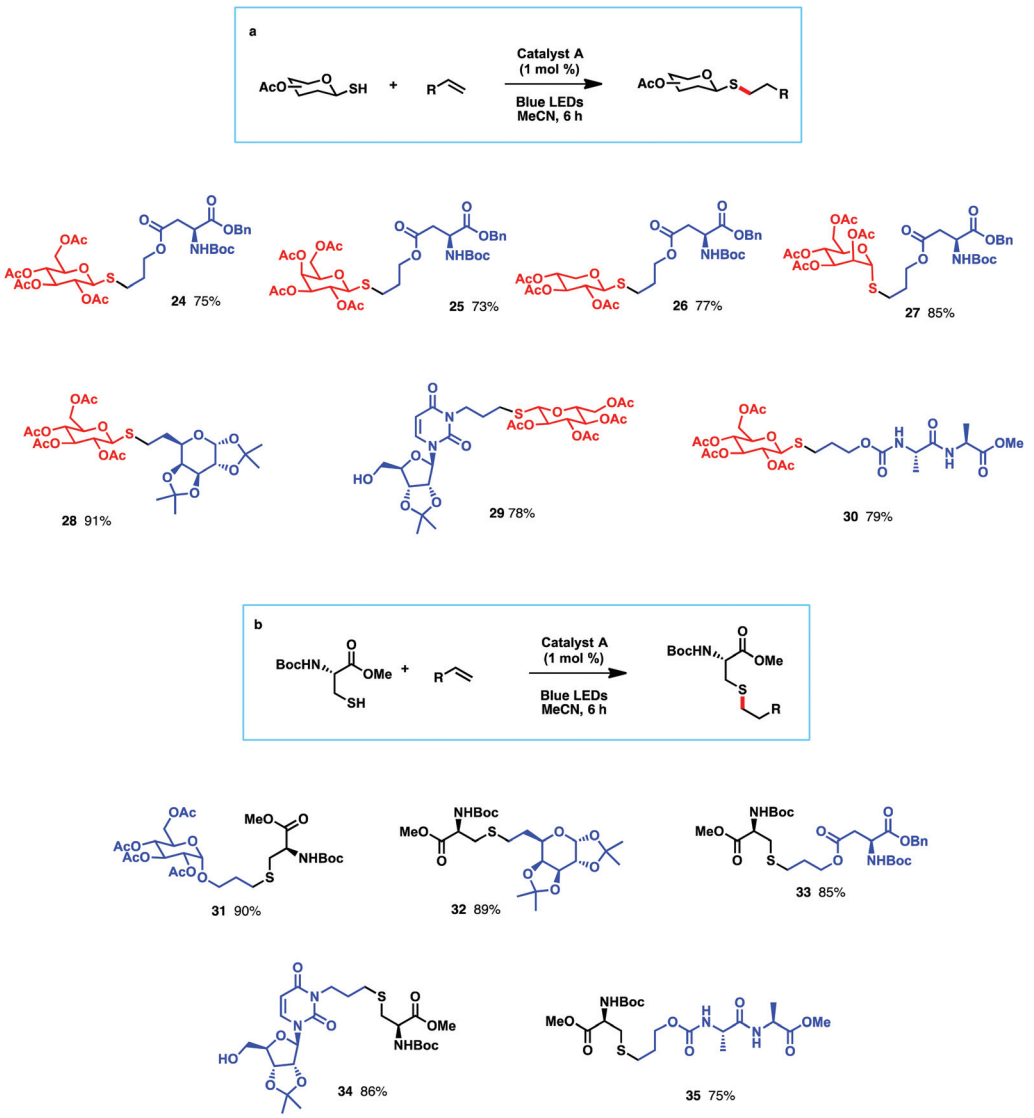
[a] Reactions conducted by irradiating **1** (0.5 mmol), **2** (0.6 mmol), and photocatalyst (1 mol%) in MeCN (1 mL) with two 12 W, 450 nm light-emitting diode (LED) flood lamps for 6 h. [b] Isolated yield. [c] Reaction conducted in the dark.

We initiated our studies by examining the thiol–ene reaction between benzyl mercaptan **1** and allyl alcohol **2**. After an investigation of organic photocatalysts and reaction solvents, we were delighted to find that several catalysts could successfully initiate the photocatalytic thiol–ene reaction under blue light-emitting diode (LED) irradiation in a variety of solvents (Table 1, entries 1–14). Among them, 9-mesityl-10-methylacridinium tetrafluoroborate (**A**) in acetonitrile has given the best outcome, providing 90% isolated yield of the thiol–ene adduct **3** (Table 1, entry 3). It is worth noting that only minimum excess (1.2 equiv.) of the alkene substrate is required for the complete conversion of thiol to the corresponding product. Control experiments (Table 1, entries 15 and 16) confirmed that both the catalyst and light irradiation are essential.

Encouraged by these results, we next evaluated the scope of the photocatalytic thiol–ene reaction. Scheme 2 summarizes experiments probing a variety of thiols (**4**) and olefins (**5**). Under the optimized reaction conditions, primary thiols (benzyl mercaptan, *para*-methoxy benzyl mercaptan, methyl thioglycolate, and cysteine derivative) reacted with allyl alcohol efficiently to generate hydrothiolated products (**3**, **7**, **8**, and **9**) in high yields (82%–90%). To our delight, more steric hindered secondary thiols and tertiary thiols also produced thiol–ene adducts (**10–13**) successfully in good yields (77%–90%). In addition, aromatic thiols could also be converted into the corresponding aryl thioether (**14**) in high yield (88%). The method was then applied to the reaction to different alkenes



Scheme 2 Scope of the thio-ene reaction.

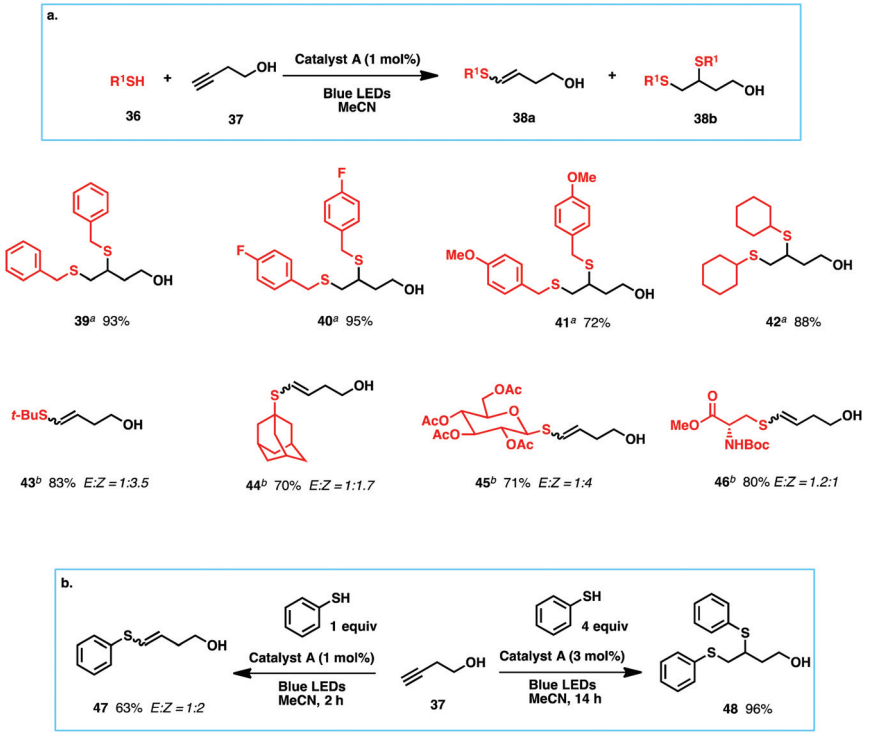


Scheme 3 Photocatalytic thiol–ene conjugations.

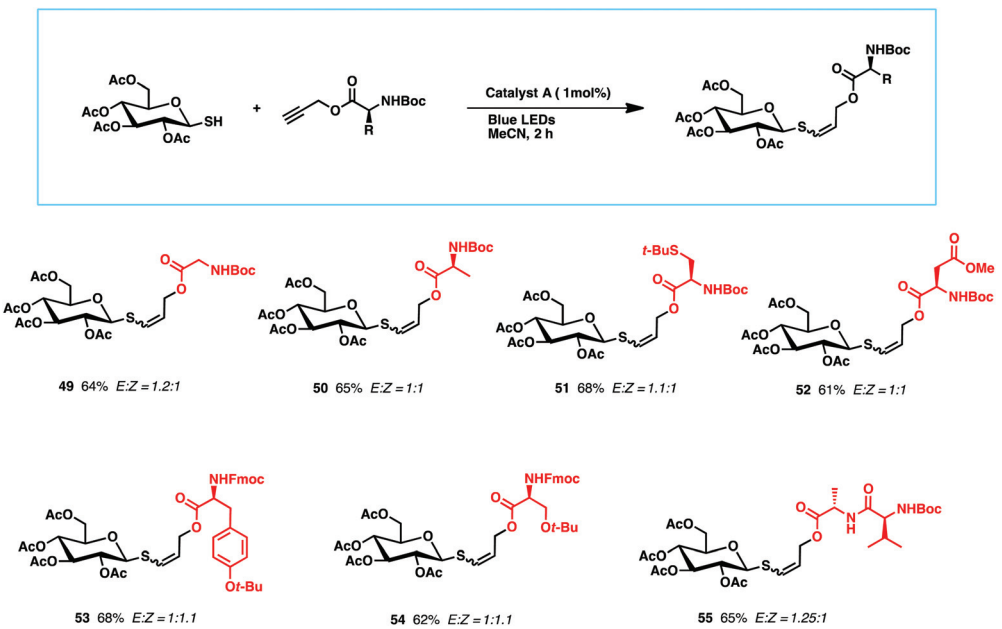
(**5**). We were delighted to find that both styrenes and aliphatic alkenes could react smoothly to afford the corresponding products (**15–19**) in good yields (76%–87%). Moreover, this radical thiol–ene process is compatible with a variety of functional groups, such as ester (**20**, 86%), formyl amide (**21**, 82%), alcohol (**22**, 85%), and silane (**23**, 80%). In all cases, high *anti*-Markovnikov regioselectivity was observed, which is consistent with the proposed radical reaction process.

Having demonstrated the high efficiency of this thiol–ene reaction, we next focused on the applicability of this chemistry to the synthesis of glycoconjugates from glycosyl thiols (Scheme 3). Glycoconjugates are important tools for the exploration of many biological processes.[16] Particularly, S-linked glycoconjugates have become useful analogs of glycopeptides and glycoproteins because of their improved chemical stability and enzymatic resistance.[17,18] To our delight, the thiol–ene reaction occurred smoothly between a variety of glycosyl thiols and an aspartic acid derivative, giving the corresponding S-linked glycoconjugates (**24–27**) in good yields (73%–85%).[19] Moreover, glucosyl thiols could also be efficiently coupled with carbohydrate derivatives, nucleoside derivatives, and N-terminus functionalized dipeptides, affording S-linked carbohydrate mimic **28**, S-linked glyconucleoside **29** and glycopeptide **30** in yields of 91%, 78% and 79%, respectively.[19] These examples further demonstrated the potential utility of this synthesis method for bioconjugation. The reverse fashion of coupling between a variety of alkenes and a cysteine derivative also provided excellent yields of the conjugated products (Scheme 3b, **31–35**, 75%–90%).

We next tested this catalytic system on a thiol–yne reaction (Scheme 4). Ideally, the first hydrothiolation between thiol (**36**) and alkyne (**37**) would provide a vinyl sulfide product **38a**, which could react with another molecule of thiol (**36**) to furnish the double hydrothiolation product **38b** (Scheme 4,

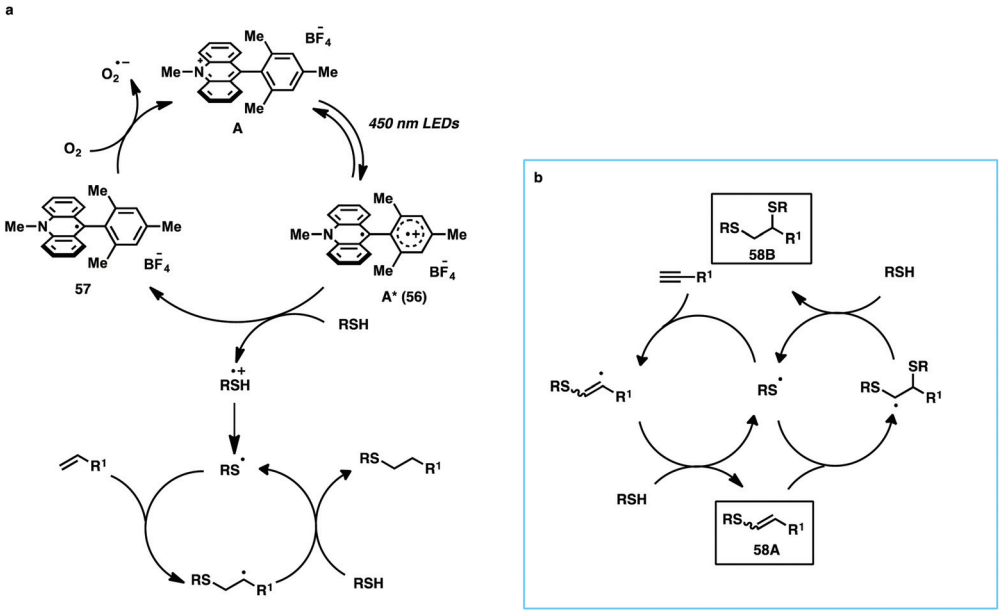


Scheme 4 Photocatalytic thiol–yne reactions. [a] Reactions irradiated with two 12 W, 450 nm light-emitting diode (LED) flood lamps for 14 h. [b] Reactions irradiated with two 12 W, 450 nm light-emitting diode (LED) flood lamps for 2 h.



Scheme 5 Photocatalytic thiol–yne conjugations.

eqn (a)). However, we found that the double hydrothiolation products were favored when less steric hindered thiols were used in the reaction, providing corresponding adducts **39–42** in good yields (72%–95%). It is difficult to make the reaction stay in the first hydrothiolation stage. Even though less than stoichiometric amounts of thiol (**36**) were used in the reaction, a mixture of **38a** and **38b** was still obtained. However, the vinyl sulfides (**38a**) could be synthesized selectively when more sterically hindered thiols were used as starting materials, affording a mixture of *E*/*Z* isomers of the resulting vinyl sulfides **43–46**



Scheme 6 Proposed mechanism.

in good yields (70%–83%). In the case of thiophenol, the reaction process could be controlled by reaction time and reagent amount. Vinyl sulfide **47** could be isolated in 63% after 2 hours of irradiation of blue LED light with stoichiometric amounts of thiophenol. Extended reaction time (14 hours) and excess thiophenol (4 equiv.) would result in a double hydrothiolation product **48** in 96% yield (Scheme 4, eqn (b)).

We then applied this efficient chemistry to the synthesis of glycoconjugates between glycosyl thiols and amino acid derivatives (Scheme 5).

To our delight, the thiol–yne reaction occurred smoothly between glucosyl thiol and a range of alkyne-containing amino acids (glycine, valine, cysteine, aspartic acid, tyrosine, and serine derived terminal alkyne), affording the corresponding S-linked glycoconjugates in good yields (**49–54**, 61%–73%).[19] The mild conditions are compatible with both Boc-protected amino groups and Fmoc-protected amino groups, which would make this method useful in the context of both Boc-SPPS and Fmoc-SPPS chemistry. Moreover, the method could be expanded to the coupling of glycosyl thiol with dipeptide, affording the corresponding glycoconjugate **55** in 65% yield.

A possible mechanism for the thiol–ene reaction is outlined in Scheme 6a. Upon photoexcitation of catalyst **A**, the strongly oxidizing state (**A***) could oxidize a thiol to generate the thiyl radical cation and one electron reduced acridinium **57**.[14,20] Deprotonation of the radical cation followed by coupling with the alkene results in the C–S bond formation with *anti*-Markovnikov selectivity. The resulting alkyl radical then abstracts a hydrogen atom from another molecule of thiol to afford the thiol–ene product and generates another equivalent of the thiyl radical. However, light irradiation is necessary for the reaction to reach completion based on our experimental results.[13a] The catalyst is likely to be regenerated by reducing a molecule of oxygen. In the thiol–yne reaction, the photocatalytic-generated thiol radical reacted with alkyne to generate a vinyl radical, which would abstract a hydrogen atom from thiol to furnish the hydrothiolation product **58A**. This vinyl sulfide could react with another thiol radical to give the double hydrothiolation product **58B** (Scheme 6b).

In summary, we have reported a visible light promoted radical thiol–ene and thiol–yne reaction using catalytic amounts of 9-mesityl-10-methylacridinium tetrafluoroborate (**A**). These highly efficient reactions have shown great scope generality. Through the successful model glycoconjugates, this radical reaction demonstrates promise for future glycoprotein studies.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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