Supporting Information

Immobilization of a flavin molecule onto poly(methacrylic acid)s and its application in aerobic oxidation catalysis: effect of polymer stereoregularity

Yukihiro Arakawa,* Yoshiko Sogabe, Keiji Minagawa, Miyuki Oshimura, Tomohiro Hirano,
Koichi Ute, Yasushi Imada*
Department of Applied Chemistry, Tokushima University, Minamijosanjima, Tokushima 770-8506, Japan

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I. General information

NMR spectra were recorded using JEOL JNM-ECZ-400S (^{1}H, 400 MHz) and JNM-ECA-500W spectrometers (^{1}H, 500 MHz). Chemical shifts are reported in ppm using TMS or the residual solvent peak as a reference. IR spectra were recorded on a JASCO IR-460 spectrometer with an ATR unit. Elemental analyses were carried out on a J-Science Lab JM10 micro corder. GC-FID analyses were carried out on a Shimadzu GC-2010 plus using a DB-1 glass capillary column (0.25 mm × 30 m). 10-(2-Aminoethyl)-7,8-dimethylisoalloxazine hydrochloride (**1**•HCl) was prepared from (–)-riboflavin according to the literature procedure.[1] One of syndiotactic poly(methacrylic acid)s (*st*-PMAA) was purchased from Wako chemicals (manufacturer: Polysciences, Inc., Lot number: 660158) and the other was prepared via free radical polymerization of *tert*-butyldimethylsilyl methacrylate followed by acid hydrolysis of the silyl group according to the literature procedure.[2] Isotactic poly(methacrylic acid) (*it*-PMAA) was prepared via anionic polymerization of trityl methacrylate followed by detritylation of the resulting poly(trityl methacrylate) according to the literature procedure.[3] The number-average molar mass (M_n), weight-average molar mass (M_W), and dispersity (M_w/M_n) of the commercial *st*-PMAA (M_n : 286 kg mol^{-1}), the self-made *st*-PMAA (M_n : 21.3 kg mol^{-1}), and *it*-PMAA (M_n : 33.6 kg mol^{-1}) were estimated by SEC measurements after conversion to the corresponding methyl methacrylates *st*-PMMA$_{LG}$ (M_n : 333 kg mol^{-1}, M_w/M_n : 2.4), *st*-PMMA$_{SM}$ (M_n : 24.8 kg mol^{-1}, M_w/M_n : 2.6), and *it*-PMMA (M_n : 39.0 kg mol^{-1}, M_w/M_n : 1.2), respectively, with PMMA standards. The tacticities of the commercial *st*-PMAA, the self-made *st*-PMAA, and *it*-PMAA were estimated from those of the corresponding *st*-PMMA$_{LG}$ (*mm*:*rm*:*rr* = 5:36:59, Figure S1), *st*-PMMA$_{SM}$ (*mm*:*rm*:*rr* = 3:31:66, Figure S2), and *it*-PMMA (*mm*:*rm*:*rr* = 97:1.5:1.5, Figure S3) determined by ^{1}H NMR spectroscopy as established.[4] 4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) was purchased from TCI. All other reagents were also purchased from commercial supplies and used without purification.

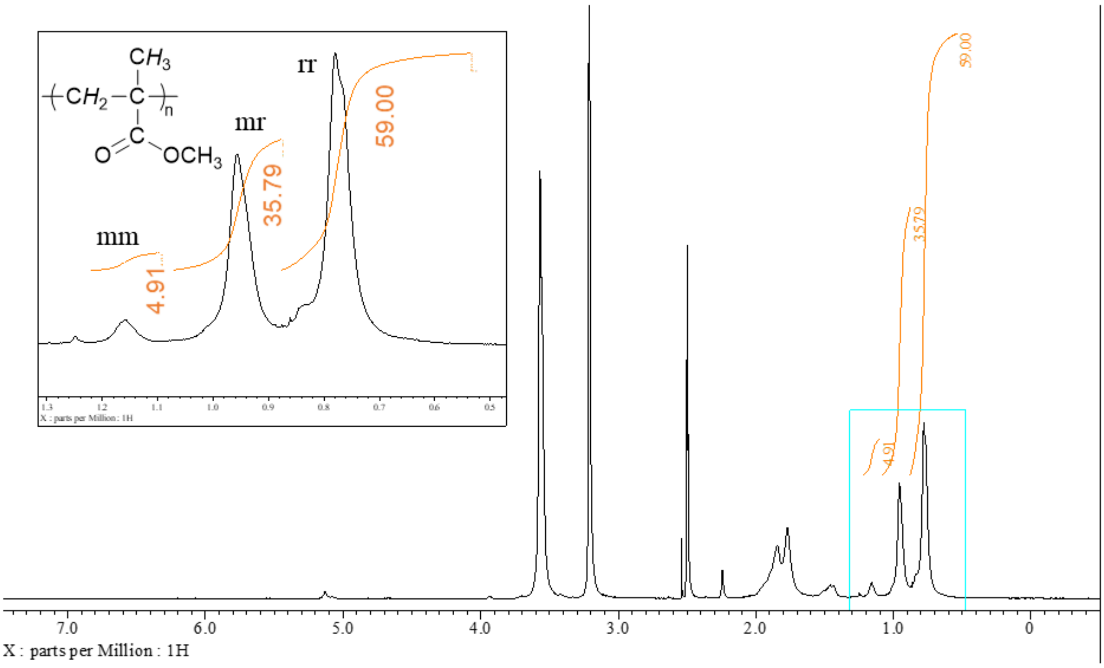


Figure S1. ^{1}H NMR spectrum of *st*-PMMA$_{LG}$ derived from the commercial *st*-PMAA (DMSO-d_6, 50 ^{o}C)

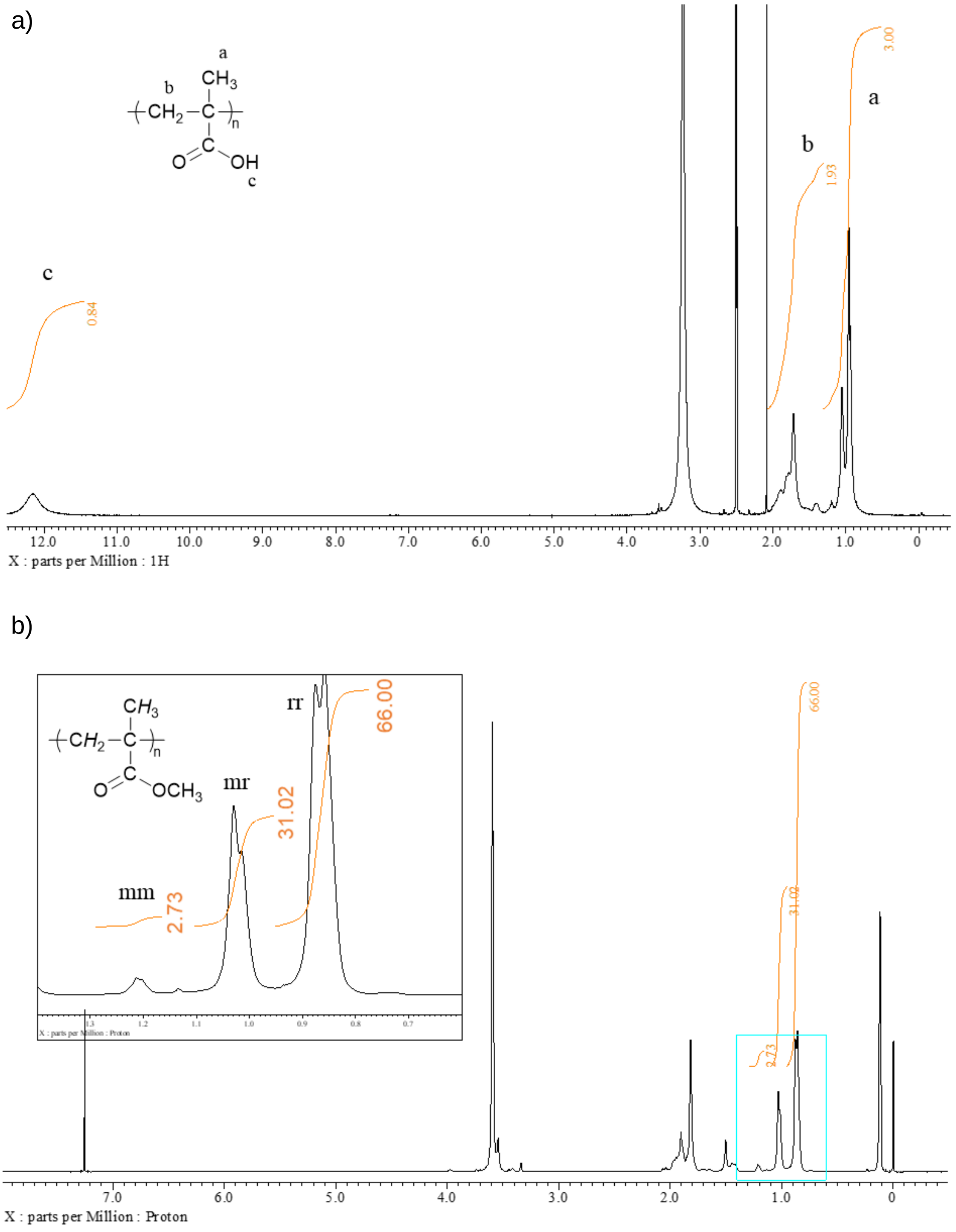


Figure S2. ^{1}H NMR spectra of the self-made *st*-PMAA (a, DMSO-d_6, 50 °C) and the corresponding *st*-PMMA$_{SM}$ (b, CDCl$_3$, 55 °C)

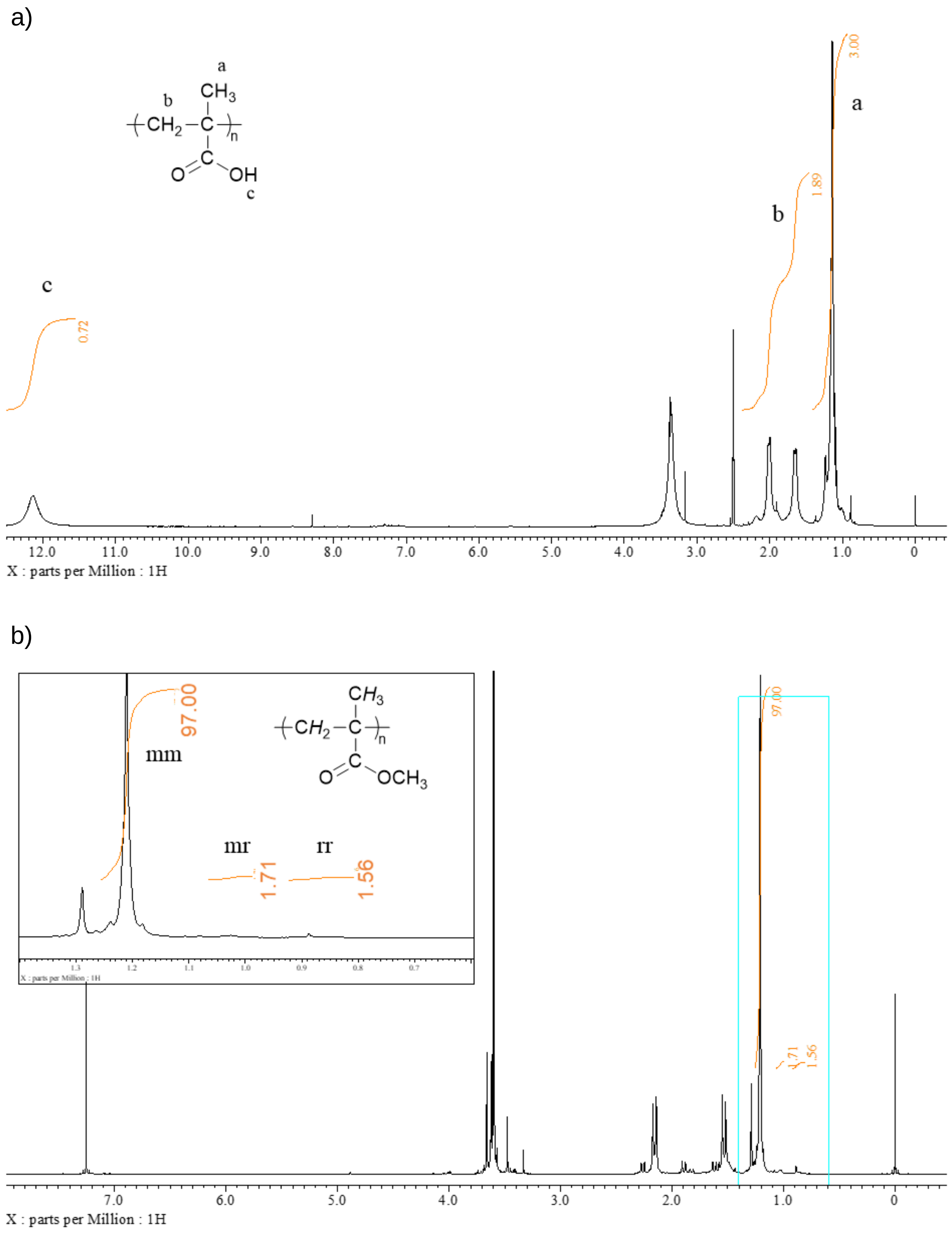
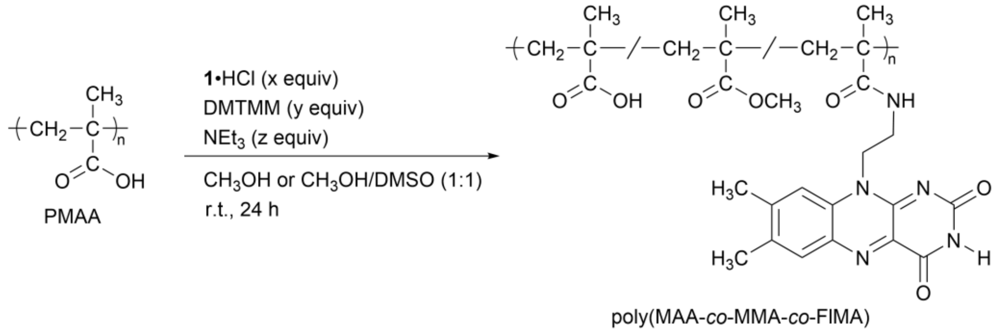


Figure S3. ^{1}H NMR spectra of *it*-PMAA (a, DMSO-d_6, 25 ^{o}C) and the corresponding *it*-PMMA (b, CDCl$_3$, 55 ^{o}C)

II. Preparation of *st*-/*it*-poly(MAA-*co*-MMA-*co*-FlMA)

Table S1. Preparation of *st*-/*it*-poly(MAA-*co*-MMA-*co*-FlMA) under different conditions



Entry	PMAA	x:y:z	solvent	*st*-/*it*-poly(MAA-*co*-MMA-*co*-FlMA)			
				DFl[a] (%)[b]	Fl loading (mmol g^{-1})[c]	MAA:MMA[b]	Yield (%)[d]
1	*st*-PMAA[e]	1.5:1:0	CH_3OH	4	0.45	≈1 : 5	83
2	*st*-PMAA[e]	1.5:1:2	CH_3OH	18	1.22	≈1 : 0.8	89
3	*st*-PMAA[e]	0.5:1:2	CH_3OH	12	0.96	≈1 : 0.8	71
4	*st*-PMAA[e]	0.5:1:2	CH_3OH/DMSO (1:1)	14	1.11	n.d.	79
5	*it*-PMAA	0.5:1:2	CH_3OH	15	0.95	≈1 : 0.8	75
6	*it*-PMAA	0.5:1:2	CH_3OH/DMSO (1:1)	16	1.13	≈1 : 0.8	55
7	*st*-PMAA[f]	0.5:1:2	CH_3OH/DMSO (1:1)	13	0.99	≈1 : 0.9	83
8	*st*-PMAA[f]	0.25:1:2	CH_3OH/DMSO (1:1)	8	0.65	n.d.	82

[a] The degree of substitution with FlMA. [b] Determined by ^{1}H NMR spectroscopy. [c] Calculated from nitrogen content determined by elemental analysis. [d] Calculated from the weight of the obtained product and the theoretical weight assuming either a 1:5 (entry 1) or 1:1 (entries 2–9) ratio of MAA and MMA in the product. [e] *mm*:*rm*:*rr* = 5:36:59, M_n : 286 kg mol^{-1}. [f] *mm*:*rm*:*rr* = 3:31:66, M_n : 21.3 kg mol^{-1}.

General procedure for reactions in CH_3OH: A 300 mL flask was charged with PMAA (20 mg, 0.23 mmol repeating units), **1**•HCl (x equiv), and methanol (150 mL), and the mixture was stirred at ambient temperature for 10 min while protected from light. To the mixture was added triethylamine (z equiv) followed by a solution of DMTMM (64 mg, 0.23 mmol, 1 equiv) in methanol (1.0 mL) dropwise, which was further stirred at ambient temperature for 24 h with the light-shielding. The pH of the mixture was adjusted to 6.7 with 2N HCl, and the mixture was evaporated in *vacuo* to concentrate the product, which was purified by dialysis with cellulose dialysis tubing (3500 MWCO) against methanol for 2 days, the mixed solvent of methanol and deionized water for 1 day, and deionized water for 2 days and then lyophilized for 7 h. The resulting yellow solid was identified to be poly(MAA-*co*-MMA-*co*-FlMA) through characterization (see below).

General procedure for reactions in CH_3OH/DMSO: In a 300 mL flask, PMAA (20 mg, 0.23 mmol repeating units) was dissolved in DMSO (75 mL) by stirring at 70 °C for 1 h while protected from light. To the solution was added **1**•HCl (x equiv), methanol (75 mL), triethylamine (z equiv), and finally a solution of DMTMM (64 mg, 0.23 mmol) in methanol (1.0 mL) dropwise, which was further stirred at ambient temperature for 24 h with the light-shielding. The pH of the mixture was adjusted to 6.7 with 2N HCl, and the mixture was evaporated in *vacuo* to concentrate the product, which was purified by dialysis with cellulose dialysis tubing (3500 MWCO) against methanol for 2 days, the mixed solvent of methanol and deionized water for 1 day, and deionized water for 2 days and then lyophilized for 7 h. The resulting yellow solid was identified to be poly(MAA-*co*-MMA-*co*-FlMA) through characterization (see below).

Spectral characterization of poly(MAA-*co*-MMA-*co*-FlMA): As a representative example, ^{1}H NMR, IR, and fluorescence spectra of *st*-poly(MAA-*co*-MMA-*co*-FlMA)$_{LG}$ are shown below.

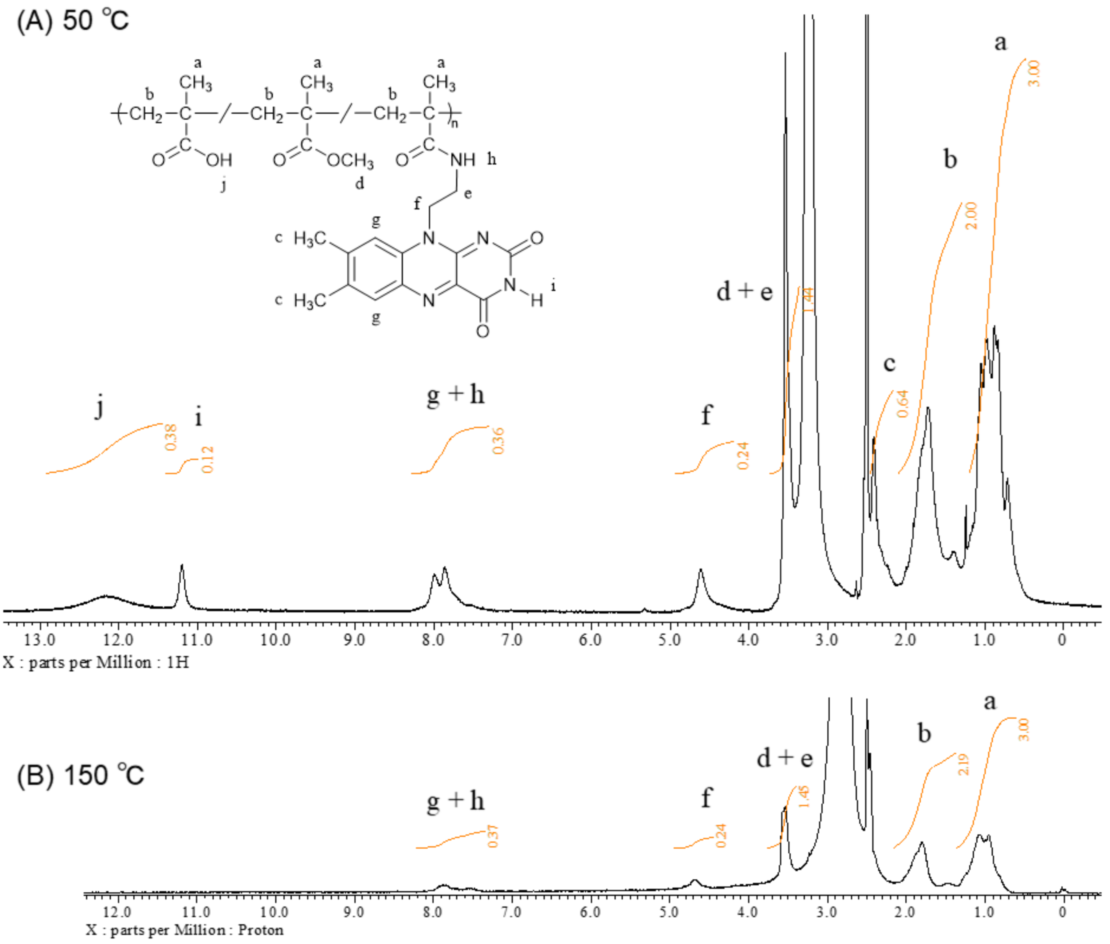


Figure S4. ^{1}H NMR spectra for *st*-poly(MAA-*co*-MMA-*co*-FlMA)$_{LG}$ with a Fl loading of 0.96 mmol g^{-1} in DMSO-d_6 (50 °C and 150 °C): The degree of substitution with FlMA (DFl) was determined using the integral ratio of *i* or (*g*+*h*)/3 or *f*/2 to *a* and *b*. The proportion of MMA was estimated from the integral ratio of [(*d*+*e*)–*f*]/3 to *a* and *b*. All components other than FlMA and MMA were considered MAA, while the integration of j was not used to avoid underestimation.

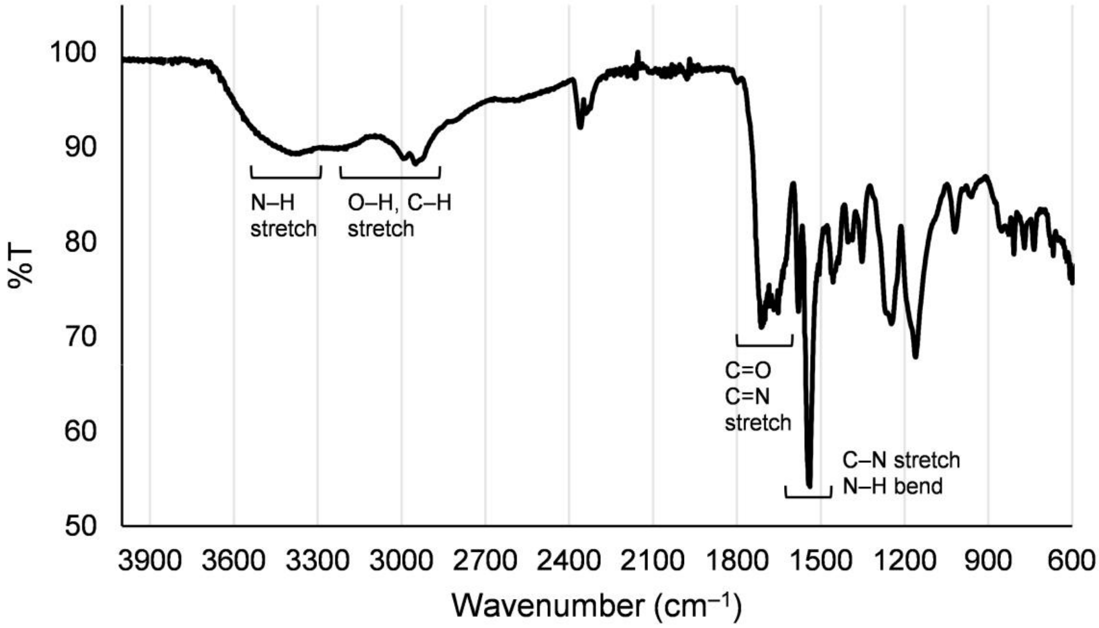


Figure S5. IR spectrum for *st*-poly(MAA-*co*-MMA-*co*-FlMA)$_{LG}$: ν = 3386 (N–H), 3210 (O–H), 2993 (C–H), 2947 (C–H), 1710 (C=O), 1660 (C=O/C=N), 1539 (C–N/N–H) cm^{-1}, which contain absorptions that suggest amide bond formation and flavin ring system.

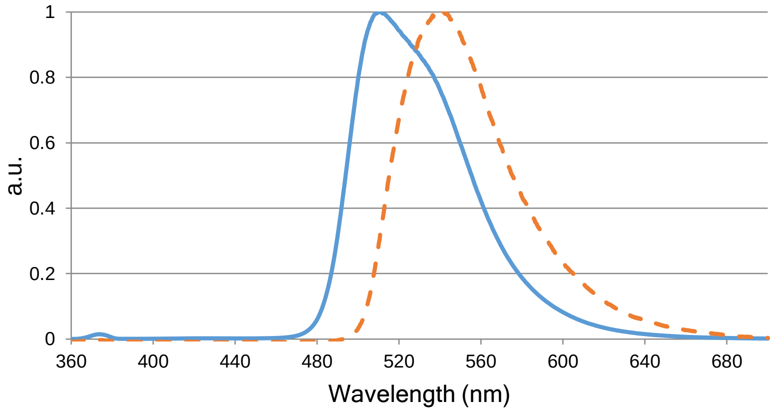


Figure S6. Fluorescence spectra for **1**•HCl (— , λ_{max} = 510 nm) and poly(MAA-*co*-MMA-*co*-FlMA) (----, λ_{max} = 540 nm) in DMSO (λ_{ex} = 370 nm)

Exploring reaction conditions (Table S1): The initial experiment was carried out using the commercial *st*-PMAA, **1**•HCl (1.5 equiv) and DMTMM (1 equiv) in the *absence* of any base in methanol (entry 1). ^{1}H NMR analysis of the resulting product suggested that most of MAA units in the substrate were converted into slightly FlMA (4%) and mostly MMA (MAA:MMA = ≈1 : 5, roughly estimated using the integration of a broad signal at 3.53 ppm assignable to methyl ester protons of MMA units and signals at 0.5–2.1 ppm assignable to main chain methylene and α-methyl protons). As expected, the addition of triethylamine (2 equiv) under otherwise identical conditions was effective for not only increasing the degree of substitution with FlMA (DFl) but also relatively suppressing the methyl esterification (entry 2). Even if the amount of **1**•HCl was reduced to one-third, the desired reaction proceeded efficiently while no significant change in the ratio of MAA and MMA units in the product (entry 3). Slightly better DFl and Fl loading were attained when DMSO was used as a cosolvent (entry 4). A similar tendency was observed by means of *it*-PMAA as a substrate (entries 5 and 6). The mixed solvent system was also applied for converting the self-made *st*-PMAA into the corresponding desired polymers with comparable flavin loadings (entries 7 and 8). It should be noted that, in any of the above cases, the MAA:MMA ratio of the product was nearly 1:1 regardless of substrate tacticity.

Solubility of poly(MAA-*co*-MMA-*co*-FlMA) in acetonitrile: A 5φ glass tube was charged with 0.5 mg of *st*-poly(MAA-*co*-MMA-*co*-FlMA) (0.96 mmol g^{-1}) and 0.4 mL of acetonitrile, and the mixture was left at room temperature. Photographs were taken immediately after mixing and after 4 days, which indicated that the polymer is hardly soluble in acetonitrile and does not even swell (Figure S7). Although the solution phase looks slightly yellow, the quantity of dissolved flavins were estimated to be less than 0.3 mol% of the loaded flavin by UV/Vis absorption spectroscopy. Similar results were obtained with *it*-poly(MAA-*co*-MMA-*co*-FlMA) (0.33 mmol g^{-1}, Figure S8), which suggested that the difference in tacticity makes no obvious differences in their solubility in acetonitrile.

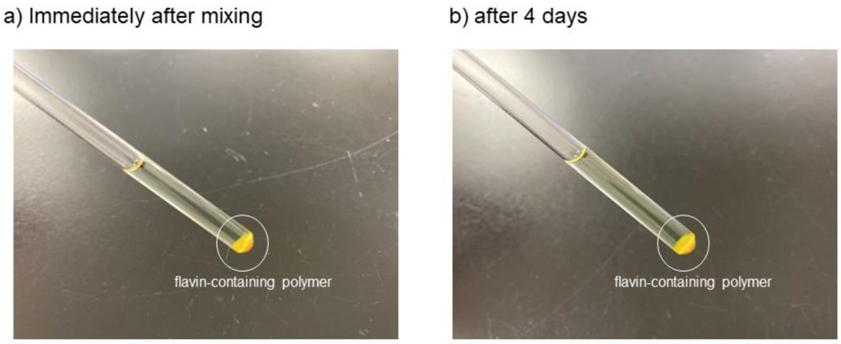


Figure S7. Photographs of *st*-poly(MAA-*co*-MMA-*co*-FlMA) in acetonitrile

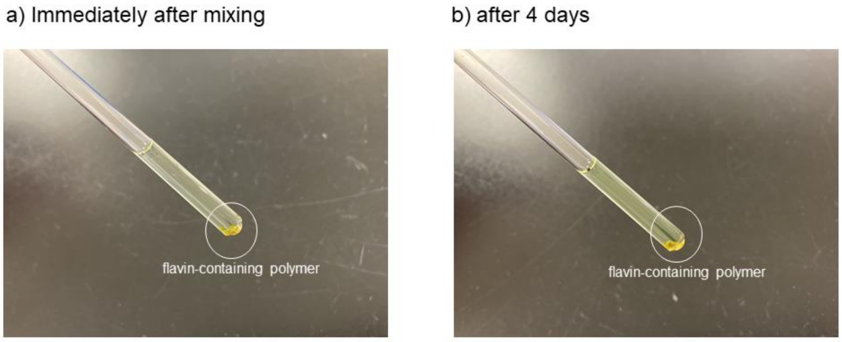


Figure S8. Photographs of *it*-poly(MAA-*co*-MMA-*co*-FlMA) in acetonitrile

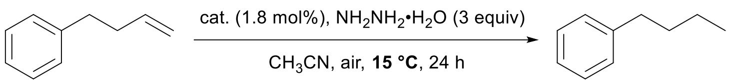
III. Typical procedures for flavin-catalyzed aerobic reactions

Flavin-catalyzed aerobic reduction of olefins: Hydrazine monohydrate (18.7 mg, 375 μmol) and acetonitrile (0.7 mL) were placed in a tubular reactor (13 mmID). After stirred for 1 min, poly(MAA-*co*-MMA-*co*-FlMA) (2.2 μmol, 1.8 mol%), an olefin (125 μmol), and acetonitrile (0.3 mL) were added in order, and the mixture was stirred at 32 °C under air for 6–24 h. The reaction was monitored by GC analysis with the corrected area normalization method. Analytical data for products were in agreement with the published data.[5,6]

Flavin-catalyzed aerobic oxidation of thioanisole: To a mixture of thioanisole (12.4 mg, 0.10 mmol) and poly(MAA-*co*-MMA-*co*-FlMA) (2.0 μmol, 2 mol%) in 2,2,2-trifluoroethanol (TFE, 0.4 mL) was added hydrazine monohydrate (20 mg, 0.40 mmol) and TFE (0.1 mL), and the resulting mixture was stirred under 1 atm of O_2 at 35 °C for 48 h. The reaction was monitored by GC analysis with the corrected area normalization method.[7,8] Analytical data for products were in agreement with the published data.[9]

IV. Some additional results of flavin-catalyzed aerobic reactions

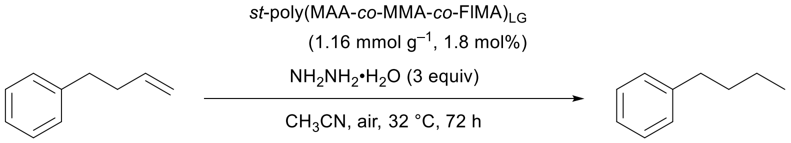
Flavin-catalyzed aerobic reduction of olefins at lower temperature: Lowering the reaction temperature to 15 °C was effective for improving the product yield, especially in the case of *it*-type catalyst (equation S1), which could support our explanation for the effect of polymer stereoregularity based on the flexibility of a polymer chain.



(S1)

cat. *st*-poly(MAA-*co*-MMA-*co*-FlMA)$_{LG}$ (0.96 mmol g^{-1}) : 87% yield
it-poly(MAA-*co*-MMA-*co*-FlMA) (0.33 mmol g^{-1}) : 82% yield

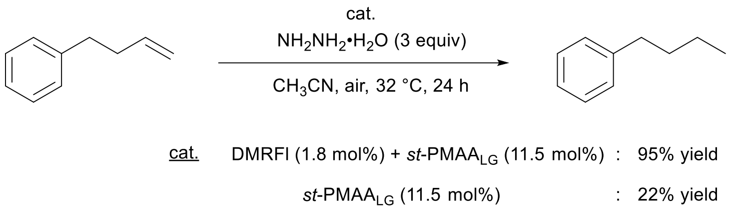
Catalyst reuse in the aerobic reduction of olefins: The reusability of *st*-poly(MAA-*co*-MMA-*co*-FlMA) (1.16 mmol g^{-1}) was evaluated in the aerobic reduction of 4-phenyl-1-butene under standard conditions. After each reaction, the catalyst was separated from the solution phase by centrifugation, washed with acetonitrile followed by diethyl ether, dried under reduced pressure, and reused for the next reaction. The experiment showed that the catalyst could be potentially reusable (equation S2).



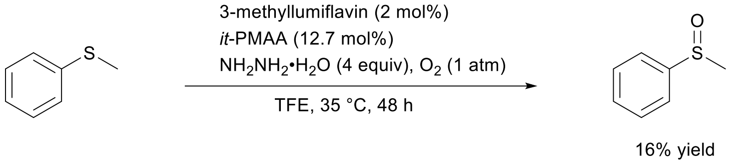
(S2)

run	yield (%)
1	97
2 (1st reuse)	97
3 (2nd reuse)	85

Low molecular weight flavin-catalyzed aerobic reactions in the presence of PMAA: The aerobic reduction of 4-phenyl-1-butene catalyzed by DMRFl was significantly accelerated in the presence of *st*-PMAA$_{LG}$, while *st*-PMAA$_{LG}$ itself did not facilitate the reaction (equation S3). Although the effect of *st*-PMAA$_{LG}$ as an additive is not clear at the moment, it may promote the dispersion of redox active flavin species in the reaction system via noncovalent interactions to suppress their self-quenching as well as the disproportionation of diimide. In contrast, the aerobic oxidation of thioanisole was not efficiently promoted with 3-methyllumiflavin in the presence of *it*-PMAA (equation S4), indicating an obvious advantage of the flavin immobilization presented in this work.



(S3)



(S4)

V. References

1) T. Matsuo, T. Hayashi, Y. Hisaeda, *J. Am. Chem. Soc.* 2002, **124**, 11234–11235.
2) M. Kamigaito, K. Ishitake, K. Satoh, Y. Okamoto, *Macromolecules* 2011, **44**, 9108–9117.
3) H. Yuki, K. Hatada, T. Niinomi, Y. Kikuchi, *Polym. J.* 1970, **1**, 36–45.
4) A. J. White, F. E. Filisko, *J. Polym. Sci., Polym. Lett. Ed.* 1982, **20**, 525–529.
5) Y. Arakawa, R. Kawachi, Y. Tezuka, K. Minagawa, Y. Imada, *J. Polym. Sci. Part A: Polym. Chem.* 2017, **55**, 1706–1713.
6) Y. Arakawa, T. Kohda, K. Minagawa, Y. Imada, *SynOpen* 2017, 1, 11–14.
7) Y. Arakawa, K. Yamanomoto, H. Kita, K. Minagawa, M. Tanaka, N. Haraguchi, S. Itsuno, Y. Imada, *Chem. Sci.* 2017, **8**, 5468–5475.
8) Y. Arakawa, F. Sato, K. Ariki, K. Minagawa, Y. Imada, *Tetrahedron Lett.* 2020, **61**, 151710.
9) Y. Imada, T. Kitagawa, T. Ohno, H. Iida, T. Naota, *Org. Lett.* 2010, **12**, 32–35.