Alloxazinium-Resins as Readily Available and Reusable Oxidation Catalysts

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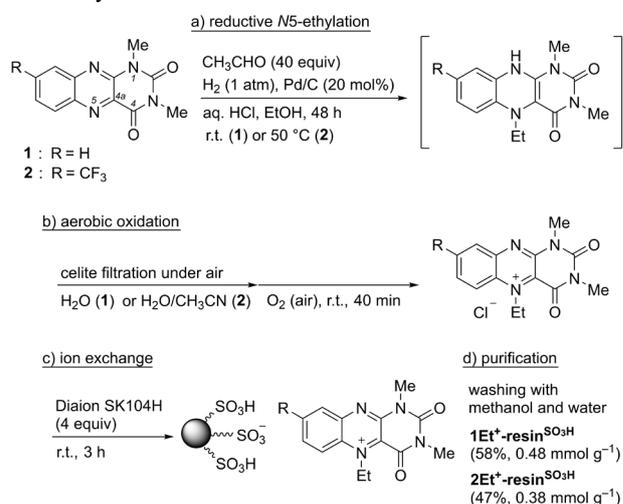E-mail: <arakawa.yukihiro@tokushima-u.ac.jp>

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Abstract

$N5$-Modified alloxazinium salts including 5-ethyl-1,3-dimethylalloxazinium and 5-ethyl-1,3-dimethyl-8-(trifluoromethyl)alloxazinium salts were readily prepared as *alloxazinium-resins* from the corresponding $N5$-unmodified ingredients via the aerobic oxidation—ion exchange protocol, previously introduced by us for the preparation of isoalloxazine analogues, and their catalysis and reusability in H_2O_2 oxidations were evaluated.

$N5$-Modified flavin molecules including isoalloxazinium salts, alloxazinium salts, and 1,10-bridged analogues have been widely investigated and found to act as an efficient metal-free catalyst for various oxidation reactions.[1,2] One of the major remaining issues in this research field is to achieve the efficient recovery and reuse of such flavinium catalysts toward their practical application. For this purpose, the concept of immobilizing catalysts on an insoluble polymer support is highly attractive.[3,4] Recently, Iida *et al.* reported, partially collaborated with us, on a heterogeneous supramolecular catalyst for hydrogen peroxide (H_2O_2)-mediated oxidation, in which the reuse of a 1,10-bridged flavinium type of catalyst was demonstrated for the first time,[5] to our knowledge, while that of isoalloxazinium catalysts or alloxazinium catalysts has so far not been studied. On the other hand, we previously introduced a safe, simple, inexpensive, and environmentally benign method for preparing isoalloxazinium salt catalysts, so called the aerobic oxidation—ion exchange protocol.[6,7] For example, 5-ethyl-3,7,8,10-tetramethylisoalloxazinium cation can be generated from its two-electron reduced intermediate, prepared via the reductive $N5$-ethylation of the corresponding isoalloxazine ring, by two-electron oxidation with molecular oxygen (O_2) in air and purified through anion exchange with a sulfonic acid cation exchange resin to isolate it as a resin-immobilized variant. Such an isoalloxazinium-resin can be used as an effective organocatalyst for aerobic oxidation reactions, although its efficient reuse is not trivial despite its insolubility due to the substantial lability of isoalloxazinium cations that may be stabilized as their 4a-hydroxy neutral species[7] in a solution phase in catalysis. By contrast, alloxazinium as well as 1,10-bridged flavinium cations are generally the most stable form in their catalysis and therefore amenable for the catalyst reuse despite the non-covalent immobilization, as previously demonstrated with the latter.[5] Herein we describe the first synthesis of $N5$-

modified alloxazines as alloxazinium-resins via the aerobic oxidation—ion exchange protocol and their catalytic activity and reusability in H_2O_2 oxidations.

Scheme 1. Synthesis of alloxazinium-resins via the aerobic oxidation—ion exchange protocol.

We started our investigations by exploring whether 1,3-dimethylalloxazine (**1**) could be adopted as a substrate for the aerobic oxidation—ion exchange protocol to give the corresponding alloxazinium-resin under conditions that had previously been optimized[6] for preparing the isoalloxazinium-resins (Scheme 1): a) **1** was treated with acetaldehyde in the presence of Pd/C and hydrogen gas under acidic aqueous-alcoholic conditions (reductive $N5$-ethylation), b) the reaction mixture was filtered through a pad of Celite under air, and the concentration of the filtrate was adjusted at 225×10^{-3} wt% with respect to **1**-related species by using deionized water to make its pH value around 0.6, which was further stirred under air at ambient temperature for 40 min (aerobic oxidation), c) the resulting solution was treated with 4 equivalents of Diaion SK104H (**resin^{SO3H}**) by gently shaking at room temperature for 3 h (ion exchange), and d) the resin was recovered by filtration and washed with methanol and water and dried in *vacuo* (purification). The formation of the corresponding alloxazinium cation was confirmed by absorption spectroscopy after the step b), and its transfer onto the resin was also confirmed by the yellow coloration of the resin in the step c) as well as elemental analysis after the step d). As a result, the desired alloxazinium-resin, **1Et⁺-resin^{SO3H}**, was successfully obtained in 58% yield with a loading of 0.48 mmol g^{-1}. Likewise, 1,3-dimethyl-8-(trifluoromethyl)alloxazine (**2**) was attempted to convert into the

corresponding alloxazinium-resin, **2Et⁺-resin^SO3H**, under identical conditions. However, the yield (11%) and loading (0.10 mmol g⁻¹) were rather disappointing even with a much longer reaction time for the step a). We noticed that the 4a-hydroxy adduct of **2Et⁺** was precipitating during the step b) probably due to its higher electrophilicity and crystallinity.[2] Thereupon, a minimum amount of acetonitrile was added to make the reaction mixture homogeneous in the step b) and, in addition, the step a) was performed at 50 °C to make the reductive *N5*-ethylation faster, which significantly improved the yield of **2Et⁺-resin^SO3H** (Scheme 1, 47%, 0.38 mmol g⁻¹).

Table 1. Catalytic oxidation of **3** with H_2O_2.[a]

$$Et_3N \xrightarrow[\text{MeOH, 25 °C, 2 h}]{\text{cat. (2 mol%), } H_2O_2 \text{ (1.5 equiv)}} Et_3N \rightarrow O$$

3 → **4**

entry	catalyst	conv. (%)[b]	yield (%)[b]
1	**1Et⁺-resin^SO3H**	91	73
2	none	18	17
3	**resin^SO3H**	34	16
4	**1Et⁺-resin^SO3Na**	63 (90)[c]	63 (87)[c]
5[d]	**1Et⁺-resin^SO3Na**	nd	27

[a]Reactions were performed with 0.2 mmol of **3** and 0.3 mmol of 30% H_2O_2 aq. in 0.6 mL of methanol in the presence of 2 mol% of catalyst. [b]Determined by ¹H NMR spectroscopy using mesitylene as an internal standard. [c]Value in 4 h. [d]The catalyst used in entry 4 was reused. nd = not determined.

The perchlorate salt of **1Et⁺** is known to be an efficient catalyst for the oxidation of tertiary amines with H_2O_2 as a terminal oxidant.[8] Indeed, the oxidation of triethylamine (**3**) with 1.5 equivalents of H_2O_2 in methanol at 25 °C was promoted in the presence of 2 mol% of **1Et⁺-resin^SO3H** to give triethylamine *N*-oxide (**4**) in 73% yield with 91% conversion of **3** in 2 h (Table 1, entry 1), while a blank reaction without any catalyst afforded **4** in 17% yield with 18% conversion of **3** under the same conditions (entry 2). When **1Et⁺-resin^SO3H** was replaced with the equal weight of **resin^SO3H**, the product yield was nearly same as the blank reaction while the conversion of **3** was 34% (entry 3). To avoid such a loss of substrates possibly caused by their acid-base interaction with sulfonic acids remaining on the resin, **1Et⁺-resin^SO3H** was converted into the corresponding neutral form **1Et⁺-resin^SO3Na** (0.33 mmol g⁻¹) by treating with saturated brine solution (see supporting information). As expected, **1Et⁺-resin^SO3Na** catalyzed the reaction without any loss of the substrate, giving **4** in 63% yield with 63% conversion of **3** under identical conditions (entry 4). Prolonging the reaction time to 4 h improved the product yield to 87% (entry 4). However, the catalyst resin significantly lost its original activity after simple filtration recovery (entry 5). This was unfortunate but still within our anticipation because the position of equilibrium between **1Et⁺** on the resin and its methanol adduct (**C**, Figure 2) could be shifted to the latter side under basic conditions.
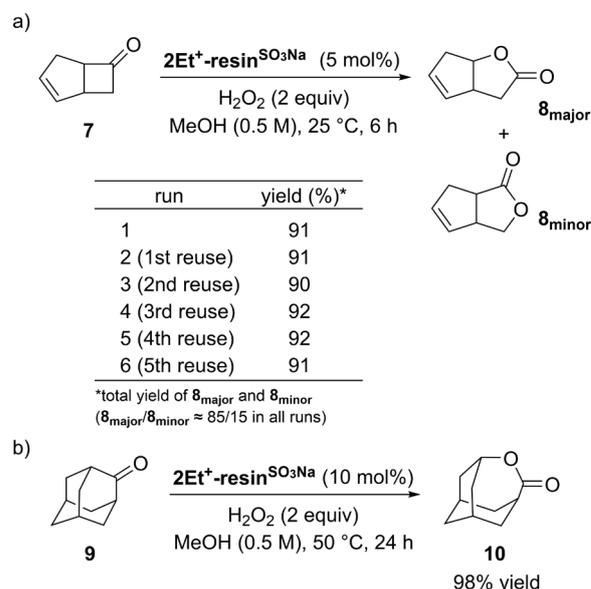
We then turned our attention to the H_2O_2-mediated oxidation of sulfides that could be carried out under neutral conditions. Cibulka *et al.* has reported that electron-deficient alloxazinium salts such as the perchlorate salt of **2Et⁺** are efficient organocatalysts for sulfoxidations with H_2O_2.[9] On one hand, such a reaction can also be catalyzed by a Brønsted acid including sulfonic acids.[10] Whereas the oxidation of *p*-tolyl methyl sulfide (**5**) was actually promoted in the presence of **resin^SO3H** (Table 2, entry 1), the corresponding sodium derivative **resin^SO3Na** was ensured to have no catalytic activity by

Table 2. Catalytic oxidation of **5** with H_2O_2.[a]

$$\text{5} \xrightarrow[\text{MeOH, 25 °C, 4 h}]{\substack{\text{cat. (2 mol%)} \\ H_2O_2 \text{ (1.5 equiv)}}} \text{6}$$

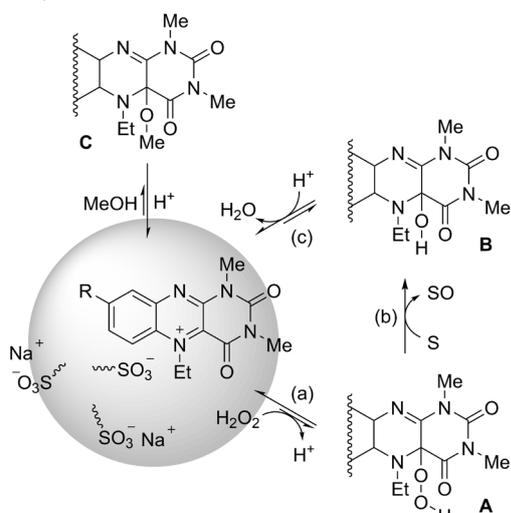| entry	catalyst	conv. (%)[b]	yield (%)[b]
1	**resin^SO3H**	97	97
2	**resin^SO3Na**	40	35
3	none	35	34
4	**2Et⁺-resin^SO3Na**	100	99
5	**1Et⁺-resin^SO3Na**	47	45
6[c]	**2Et⁺-resin^SO3Na**	nd	99
7[c]	(1st reuse)	nd	98
8[c]	(2nd reuse)	nd	98
9[c]	(3rd reuse)	nd	98
10[c]	(4th reuse)	nd	97
11[c]	(5th reuse)	nd	99

[a]Reactions were performed with 0.2 mmol of **5** and 0.3 mmol of 30% H_2O_2 aq. in 0.6 mL of methanol in the presence of 2 mol% of catalyst unless otherwise noted. [b]Determined by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [c]Reuse test under modified conditions: **5** (1 M), catalyst (5 mol%), 2 h. nd = not determined.

comparing with a blank reaction (entries 2 and 3). Therefore, **2Et⁺-resin^SO3H** was neutralized to the corresponding sodium form **2Et⁺-resin^SO3Na** (0.34 mmol g⁻¹) prior to use (see experimental). In the presence of 2 mol% of **2Et⁺-resin^SO3Na**, the oxidation of **5** smoothly proceeded with 1.5 equivalents of H_2O_2 in methanol at 25 °C to give *p*-tolyl methyl sulfoxide (**6**) in quantitative yield without overoxidation to sulfone (entry 4), while **1Et⁺-resin^SO3Na** was much less active as expected[9] (entry 5). To our delight, **2Et⁺-resin^SO3Na** showed high reusability potential, *e.g.* it was successfully reused after a simple filtration recovery for at least 5 times without a loss in activity (entries 6–11). It should be noted that the reaction nearly stopped when the catalyst was removed from the reaction system on the way while it was accelerated again when the catalyst was returned, indicating that the solid phase could be involved in the catalysis (see supporting information).

a)

run	yield (%)*
1	91
2 (1st reuse)	91
3 (2nd reuse)	90
4 (3rd reuse)	92
5 (4th reuse)	92
6 (5th reuse)	91

*total yield of **8_major** and **8_minor**
(**8_major**/**8_minor** ≈ 85/15 in all runs)

b)

Figure 1. Catalytic BV oxidations with **2Et⁺-resin^SO3Na**.

To further demonstrate the utility of alloxazinium-resins as a reusable catalyst, Baeyer-Villiger (BV) oxidation with H_2O_2 was also explored. The catalytic activities of **1Et$^+$-resin^{SO_3Na}** and **2Et$^+$-resin^{SO_3Na}** for the BV oxidation of (±)-*cis*-bicyclo[3,2,0]-hept-2-en-6-one (**7**)[5] were kinetically compared based on their initial rates, which revealed that the latter was 2.4-fold more catalytically active than the former (see supporting information). In the presence of 5 mol% of **2Et$^+$-resin^{SO_3Na}** with 2 equivalents of H_2O_2 in methanol at 25 °C, the reaction allowed for providing the corresponding *cis*-lactones **8$_{major}$** and **8$_{minor}$** in 91% total yield after 6 h and, afterwards, the catalyst was readily recovered and reused for at least 5 times without a loss in activity under identical conditions (Figure 1a). In addition, **2Et$^+$-resin^{SO_3Na}** was demonstrated to be effective also for the BV oxidation of 2-adamantanone (**9**), in which the corresponding lactone **10** was quantitatively obtained under slightly modifide conditions (Figure 1b).

Figure 2. Proposed catalysis with alloxazinium-resins.

The reusability of alloxazinium-resins can be explained as follows (Figure 2). As previously established,[11] the catalysis of the alloxazinium salt for H_2O_2-mediated oxidations in methanol can be cycled with a) the formation of the corresponding 4a-hydroperoxy species (**A**) by the nucleophilic addition of H_2O_2, b) the monooxygenation of a substrate (S) to give the oxidized product (SO) and the corresponding 4a-hydroxy species (**B**), followed by c) the dehydration to regenerate the alloxazinium salt, in which the step a) is rate-determining. It is therefore reasonable to consider that the alloxazinium cation that once separated from the solid phase will eventually return to the solid phase to be stabilized, making the catalyst reuse possible under neutral conditions. On the other hand, the presence of a base may favor the formation of **C** that can be stabilized in solution phase, thus rendering the catalyst reuse difficult (Table 1, entry 5).

In conclusion, we have introduced the preparation of alloxazinium-resins by means of the aerobic oxidation—ion exchange protocol, originally developed by us for the synthesis of isoalloxazine analogues, and demonstrated their potential utility as an efficient and reusable catalyst for H_2O_2-mediated oxidations.

Experimental

Preparation of 2Et$^+$-resin^{SO_3H} and 2Et$^+$-resin^{SO_3Na}

A mixture of 1,3-dimethyl-8-(trifluoromethyl)alloxazine (**2**, 93 mg, 0.3 mmol), Pd/C (5%; 128 mg, 0.06 mmol), and acetoaldehyde (0.75 mL, 12 mmol) in degassed ethanol (6 mL), HCl (conc.; 0.5 mL), and water (6 mL) was stirred at 50 °C for 48 h under hydrogen atmosphere. The mixture was filtered

through a pad of Celite (2.3 g) under air by using acetonitrile (15 mL) and H_2O for rinsing, and the filtrate of adjusted concentration (225×10^{-3} wt%) was vigorously stirred under air for 40 min. To the resulting bright yellow mixture was added 4 equivalents of Diaion SK104H (823 mg; MITSUBISHI CHEMICAL, ion exchange capacity ≥ 1.1 equiv L^{-1}, apparent density ≈ 750 g L^{-1}) and the heterogeneous mixture was shaken at room temperature for 3 h. The resulting yellow resin was recovered by filtration and washing successively with H_2O (15 mL), MeOH (15 mL), and H_2O (15 mL), and dried under reduced pressure to give **2Et$^+$-resin^{SO_3H}** (0.38 mmol g^{-1}, 47%). Elemental analysis, found: C 44.75; H 5.27; N 2.12.

To a saturated brine solution was added **2Et$^+$-resin^{SO_3H}** (500 mg) and the mixture was shaken at room temperature for 30 min. The resin was filtered and washed with H_2O until the filtrate became neutral and dried under reduced pressure to afford **2Et$^+$-resin^{SO_3Na}** (0.34 mmol g^{-1}). Elemental analysis, found: C 42.64; H 4.55; N 1.90.

Catalytic oxidation of 5 with 2Et$^+$-resin^{SO_3Na}

A mixture of *p*-tolyl methyl sulfide (69 mg, 0.5 mmol), 30% H_2O_2 aq. (77 μL, 0.75 mmol), **2Et$^+$-resin^{SO_3Na}** (74 mg, 0.025 mmol), and 1,3,5-trimethoxybenzene (25 mg, 0.15 mmol) as an internal standard in methanol (0.5 mL) was stirred at 25 °C for 2 h, which was evaluated by ^{1}H NMR spectroscopy. The catalyst was recovered by filtration, washed with methanol, and reused for the next run.

Catalytic BV oxidation of 9 with 2Et$^+$-resin^{SO_3Na}

A mixture of 2-adamantanone (60 mg, 0.4 mmol), 30% H_2O_2 aq. (82 μL, 0.8 mmol), **2Et$^+$-resin^{SO_3Na}** (118 mg, 0.04 mmol), and 1,3,5-trimethoxybenzene (20 mg, 0.12 mmol) as an internal standard in methanol (0.8 mL) was stirred at 50 °C for 24 h (the NMR yield was determined to be 98%). The reaction was quenched by adding saturated aqueous Na$_2$SO$_3$, which was extracted with CH$_2$Cl$_2$ (5 mL × 3). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel using a mixture of EtOAc/hexane as the eluent to give **10** as a white solid (53 mg, 88%).

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Graphical Abstract

<Title>
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<Authors' names>
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<Summary>
*N*5-Modified alloxazinium salts including 5-ethyl-1,3-dimethyl-alloxazinium and 5-ethyl-1,3-dimethyl-8-(trifluoromethyl)alloxazinium salts were successfully prepared as *alloxazinium-resins* via the aerobic oxidation—ion exchange protocol and demonstrated to be efficient and reusable organocatalysts for H_2O_2-mediated oxidations.

<Diagram>