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Polystyrene-supported aminobenzenesulfonic acids as bifunctional heterogeneous catalysts for the synthesis of isoxazoline skeletons

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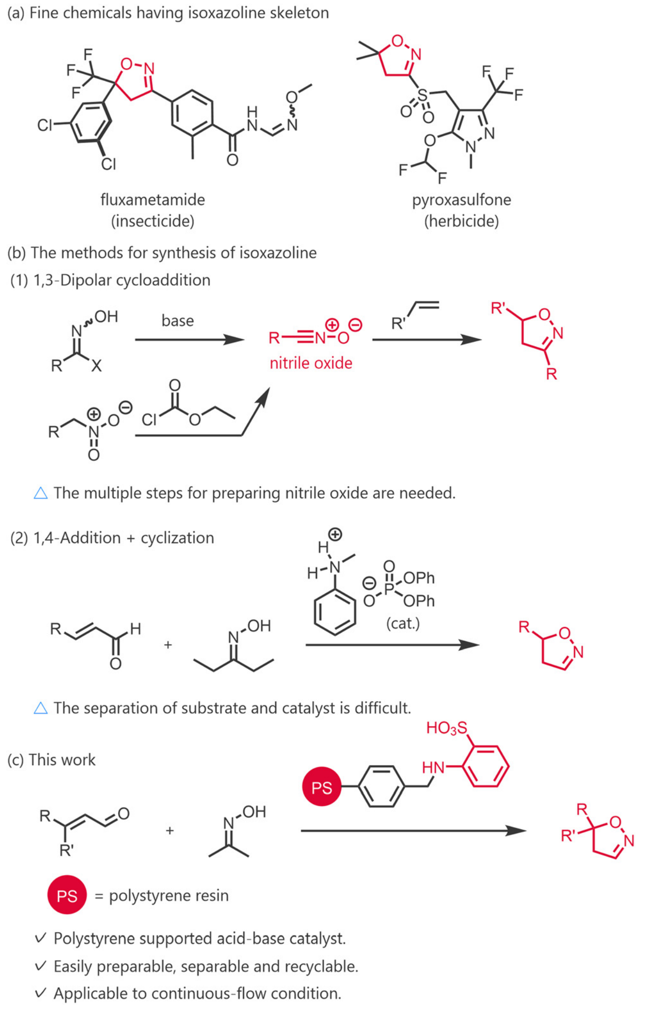
The isoxazoline skeleton is a pivotal structural motif in pharmaceuticals and agrochemicals, necessitating the development of efficient synthetic methodologies. Conventional synthesis *via* 1,3-dipolar cycloaddition often requires multiple steps to prepare nitrile oxide precursors. While acid–base catalysis offers a more direct route from α,β-unsaturated aldehydes and ketoximes, catalyst recovery remains a significant challenge. In this study, we developed robust heterogeneous acid–base catalysts by immobilizing aminobenzenesulfonic acids—inexpensive dye precursors—onto polystyrene. These catalysts effectively promote the synthesis of isoxazolines from α,β-unsaturated aldehydes and acetoximes. Notably, the catalyst system is highly compatible with continuous flow reactions, maintaining yields above 70% for over 50 hours of operation. Mechanistic investigations, supported by DFT calculations, reveal two distinct, isomer-dependent pathways: (i) an iminium-mediated 1,4-addition for the 2-aminobenzenesulfonic acid-immobilized catalyst, and (ii) a concerted acid–base activation enabling direct 1,4-addition for the 3-amino isomer.

The isoxazoline core is a versatile structural motif widely utilized in pharmaceuticals and agrochemicals.[1] Notable examples include the insecticide Fluxametamide[2] (Nissan Chemical Corporation) and the herbicide Pyroxasulfone[3] (Kumiai Chemical Industry Co., Ltd.) (Scheme 1a). Traditionally, the isoxazoline framework is synthesized *via* 1,3-dipolar cycloaddition using nitrile oxides (Scheme 1b, (1)).[4] However, this approach is often hampered by the need for multi-step synthesis of the nitrile oxide precursors. To address this challenge, Pihko and co-workers reported an alternative methodology using readily available α,β-unsaturated aldehydes and ketoximes



Scheme 1 The use and synthesis of isoxazoline skeleton.

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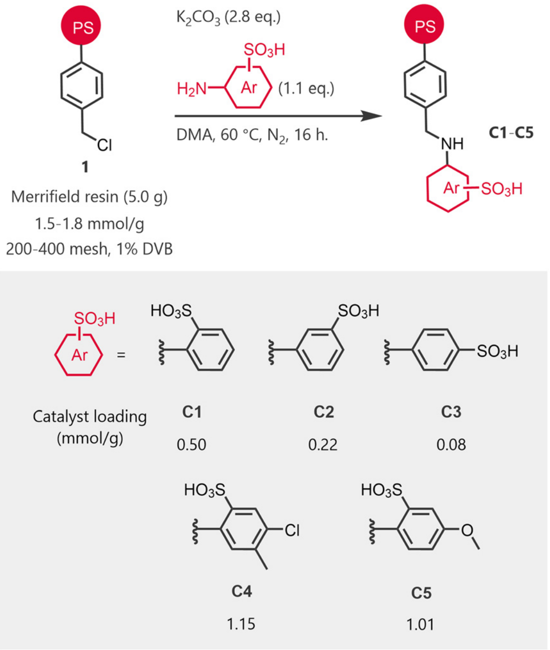


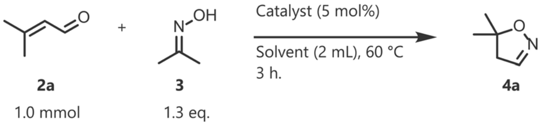
Scheme 2 The synthesis of aminobenzenesulfonic acid catalysts **C1–C5**.

(Scheme 1b, (2)).[5] Their approach employs a homogeneous catalyst system comprising *N*-methylaniline and diphenyl phosphate. The proposed mechanism involves the formation of an iminium cation, followed by 1,4-addition of the oxime and subsequent intramolecular cyclization *via* hydrolysis. Despite its utility, the separation of these homogeneous acid–base catalysts from the reaction mixture can be problematic. Consequently, catalyst immobilization presents a highly attractive alternative.[6,7] However, the co-immobilization of both acidic and basic functionalities onto a single solid support is inherently complex.[8,9] Such processes typically require multiple synthetic steps and frequently suffer from poor reproducibility. To overcome these hurdles, we focused on the aminobenzenesulfonic acid scaffold. These bifunctional molecules are highly cost-effective, as they are widely produced as precursors for azo dyes.[10] Crucially, they possess both acidic (sulfonic acid) and basic (aniline) functionalities within the same molecule.[11] We hypothesized that these bifunctional scaffolds could serve as effective catalysts for the transformation reported by Pihko's group.[5] Furthermore, we reasoned that the amino group could be readily alkylated to facilitate stable immobilization. Herein, we demonstrate that polystyrene-supported aminobenzenesulfonic acids effectively catalyze the 1,4-addition and cyclization of α,β-unsaturated aldehydes with ketoximes, providing a robust and efficient route to isoxazolines (Scheme 1c). We also successfully demonstrate the applicability of this heterogeneous catalyst in a continuous flow system.

Initially, the synthesis of polystyrene-supported aminobenzenesulfonic acid catalysts was performed (Scheme 2). Aminobenzenesulfonic acid derivatives were reacted with Merrifield resin 1 (1.8 mmol g^{-1} Cl, 200–400 mesh, 1% DVB) in the presence of potassium carbonate in *N*,*N*-dimethylacetamide (DMA) at 60 °C for 16 hours. Subsequent acidification with 1.0 M hydrochloric acid, followed by filtration and washing, afforded the immobilized catalysts **C1–C5**. The catalyst loading was confirmed *via* energy dispersive X-ray spectroscopy (EDX).

The catalytic activity was evaluated using the synthesis of isoxazoline **4a** as a model reaction (Table 1). Specifically, 3-methyl-2-butenal (**2a**) and acetoxime (3) were reacted in butyl acetate at 60 °C for 3 hours in the presence of catalysts **C1–C5**. Among the candidates, catalyst **C2** exhibited the highest reactivity (entries 1–5). Solvent screening was subsequently conducted using **C1**, as it demonstrated a smaller discrepancy between conversion and yield compared to **C2**. Nonpolar solvents such as toluene and chloroform yielded superior results. In contrast, polar solvents like acetonitrile and methanol led to significantly lower conversions and yields. Notably, when methanol was employed, the byproduct 3-methoxy-3-

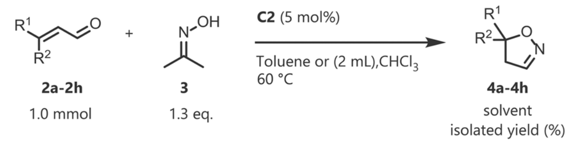
Table 1 Investigation the optimal condition for the synthesis of **4a**

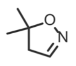
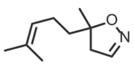
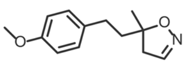
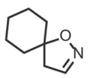
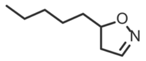
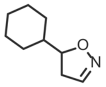
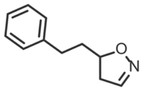
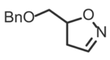


Entry	Catalyst	Solvent	Conv. (%)	**4a**[a] (%)
1	**C1**	AcO^nBu	71	47
2	**C2**	AcO^nBu	95	64
3	**C3**	AcO^nBu	70	43
4	**C4**	AcO^nBu	76	47
5	**C5**	AcO^nBu	50	23
6	**C1**	Toluene	87	76
7	**C1**	$CHCl_3$	85	74
8	**C1**	MeCN	40	26
9	**C1**	MeOH	73	18
10	***C2***	*Toluene*	*98*	*90*

[a] The conversion and yield were determined by gas chromatography analysis with biphenyl was used as an internal standard.

Table 2 Substrate scope



			
4a	**4b**	**4c**	**4d**
toluene	toluene	toluene	$CHCl_3$
90%[a]	81%	74%	81%
			
4e[b]	**4f**[b]	**4g**[b]	**4h**[b]
$CHCl_3$	$CHCl_3$	$CHCl_3$	$CHCl_3$
60%	38%	41%	29%

[a] The yield was determined by gas chromatography analysis because **4a** was highly volatile. Biphenyl was used as an internal standard. [b] 5.0 eq. of acetoxime **3** were used and the reaction was carried out at 30 °C.

methyl-1-butanal was observed, resulting from the 1,4-addition of the solvent to the aldehyde. Consequently, toluene was identified as the optimal solvent. Applying these optimized conditions to the highly active **C2** catalyst resulted in nearly complete conversion and a 90% yield of **4a** within 3 hours (entry 10).

With the optimized conditions established, the substrate scope was investigated (Table 2). Citral (**2b**), which possesses an external olefin, reacted selectively to afford the desired product **4b** in 81% yield. Aromatic rings were well-tolerated, providing the corresponding isoxazoline **4c** in high yield. Additionally, 2-cyclohexylideneacetaldehyde (**2d**) underwent the transformation efficiently. However, substrates with a single substituent at the β-position generally exhibited lower yields despite achieving full conversion (>99%). For example, the reaction of 2-octenal (**2e**) yielded only 60% of **4e** (see SI for details). This reduced yield is attributed to the high reactivity of β-monosubstituted substrates toward 1,4-addition, which facilitates substrate polymerization.[12] Other β-monosubstituted substrates similarly provided only moderate yields (**4f**–**4h**).

Finally, continuous-flow reaction conditions were investigated using **2a** as the substrate.[13] A catalyst column was prepared by charging a stainless-steel cylinder with a mixture of the catalyst and a diluent. A toluene solution of **2a** and **3** was then passed through the column to evaluate the catalytic performance. When using Celite 545 as the diluent, **C2** was more active but showed lower durability than **C1**. Based on long-term stability, **C1** was selected as the optimal catalyst for flow operations. The choice of diluent proved to be critical; the use of carboxylic acid silica gel significantly improved both durability and reactivity. Under these conditions, a turnover frequency (TOF) of 2.9 h^{-1} was achieved, and the yield of **4a** remained above 70% for over 50 hours of continuous operation. Although the precise mechanism for this improvement remains under investigation, the efficient removal of free hydroxylamine by the acidic silica gel is likely a key contributing factor to the enhanced catalytic stability (Fig. 1).

To elucidate the reaction mechanism, we first performed a control experiment using α,β-unsaturated oxime **5** with catalyst **C1** in toluene at 60 °C (Scheme 3a).[14] The reaction yielded the isoxazoline **4a** in only 12%, suggesting that the pathway involving direct cyclization of the oximated intermediate is unlikely. According to Baldwin's rules, the cyclization of **5** would require a 5-*endo-trig* pathway, which is electronically disfavored and kinetically slow.[15] We subsequently investigated the formation of an iminium intermediate. Mixing 3-methyl-2-butenal (**2a**) with aniline **6** in DMSO-d_6 at 60 °C led to the appearance of new signals in the ^{1}H-NMR spectrum (Scheme 3b). Further characterization by COSY and NOESY revealed a distinct cross-peak between the benzylic protons and the alkene protons, confirming their spatial proximity and the formation of an iminium cation.

Based on these observations, the proposed catalytic cycle for **C1** is illustrated in Scheme 4. The α,β-unsaturated aldehyde initially reacts with the aniline moiety to generate an iminium cation, which then undergoes 1,4-addition by the oxime.[16] Subsequent hydrolysis of the resulting adduct triggers an intramolecular cyclization to afford the isoxazoline. Notably, this pathway bypasses the α,β-unsaturated oxime intermediate **5**, allowing the cyclization to proceed *via* a favored 5-*exo-trig* ring closure, which accounts for the rapid reaction rate.

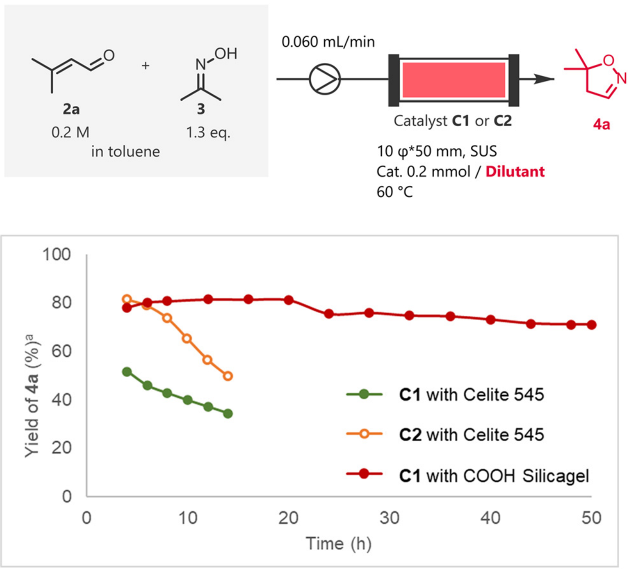
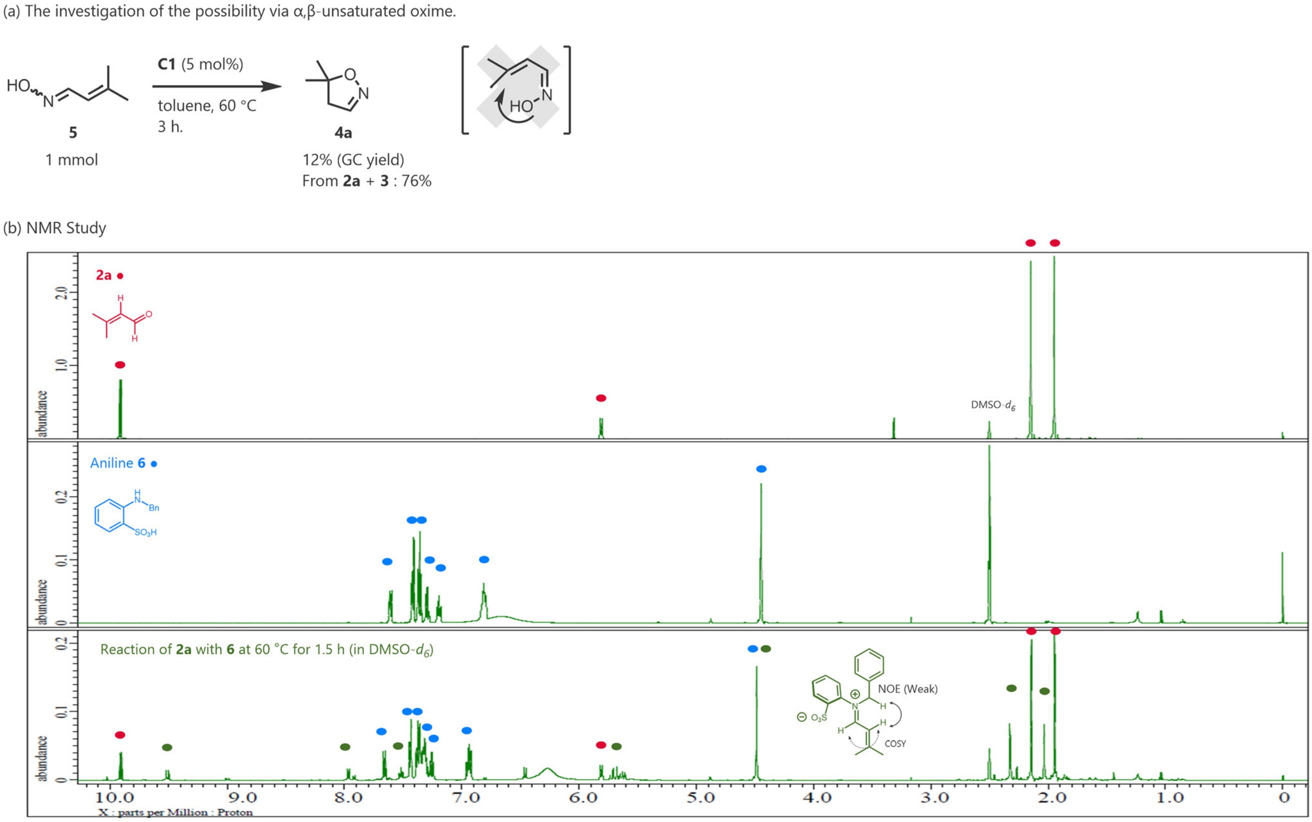
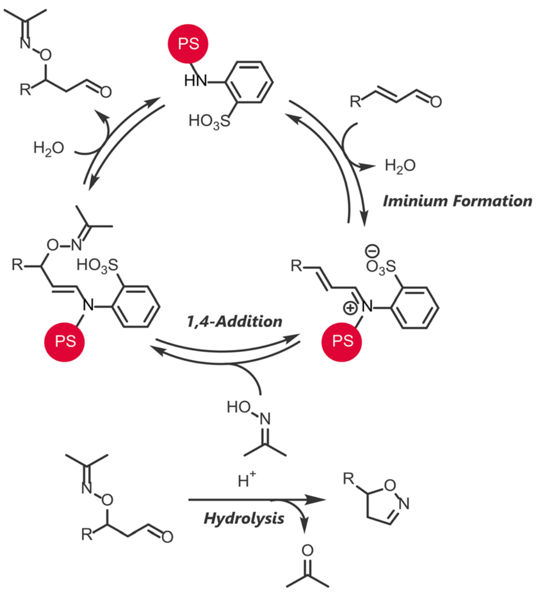


Fig. 1 The result in the continuous-flow condition. aDetermined by GC analysis.



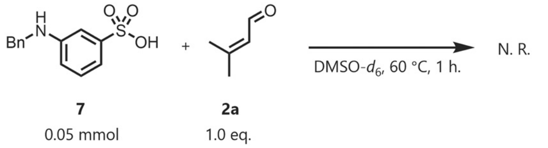
Scheme 3 The mechanistic study of 2-aminobenzenesulfonic acid catalyst **C1**.



Scheme 4 Plausible reaction mechanism using **C1**.

The mechanistic pathway for catalyst **C2** was investigated under identical conditions. Interestingly, unlike the case with **C1**, no iminium cation formation was detected by NMR when **2a** was treated with aniline derivative **7** (Schemes 3b and 5). This striking difference suggests that **C2** operates *via* a fundamentally distinct catalytic cycle that does not involve an iminium intermediate.

Despite the absence of iminium formation, the catalytic reaction using **C2** (Table 2) proceeds efficiently at 60 °C to deliver the desired isoxazolines. This observation suggests that **C2** operates *via* a mechanistic pathway distinct from that of **C1**. In catalyst **C1**, the sulfonic acid group is positioned *ortho* to the aniline nitrogen, allowing it to act as an internal Brønsted acid that protonates the α,β-unsaturated aldehyde, thereby facilitating nucleophilic attack by the nitrogen to generate an iminium ion. Conversely, in catalyst **C2**, the sulfonic acid moiety is *meta*-connected to the aniline nitrogen. This spatial arrangement precludes the promotion of iminium formation, which is consistent with the absence of iminium signals in the NMR experiments (Scheme 5). To explore alternative pathways, we performed density functional theory (DFT) calculations to map the reaction coordinate. The calculations revealed a concerted reaction pathway involving the cooperative participation of three species: the α,β-unsaturated aldehyde, the oxime, and the **C2** catalyst (Fig. 2).[17] In this bifunctional model, the sulfonic acid group of **C2** acts as a Brønsted acid to activate the aldehyde, while the aniline nitrogen serves as a Brønsted base by forming a hydrogen bond with the oxime O–H. This dual activation significantly lowers the energy barrier for the 1,4-addition of the oxime, furnishing a 1,4-adduct without prior iminium formation. The calculated activation free



Scheme 5 The mechanistic study of 3-aminobenzenesulfonic acid derivative.

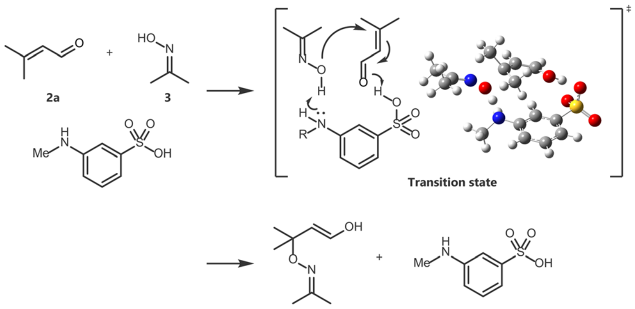


Fig. 2 1,4-Addition of an oxime to an α,β-unsaturated aldehyde *via* acid–base cooperative activation by 3-aminobenzenesulfonic acid.

energy ($\Delta G^{\ddagger}$) for the 1,4-addition transition state is 21.5 kcal mol^{-1} at 25 °C.[18] This indicates that at the experimental temperature of 60 °C, the 1,4-addition step is energetically accessible and potentially reversible. Subsequent hydrolysis of the oxime moiety and intramolecular cyclization are highly exergonic ($\Delta G \approx -10.1$ kcal mol^{-1}), driving the transformation rapidly toward the final isoxazoline product. While this scenario suggests the 1,4-adduct exists as a transient intermediate, analysis of reaction aliquots by GC and NMR failed to detect its presence. This lack of accumulation supports the conclusion that the subsequent hydrolysis and cyclization steps proceed smoothly and rapidly.

In summary, we have developed a novel class of heterogeneous catalysts by immobilizing aminobenzenesulfonic acids onto a polystyrene resin. These catalysts effectively promote the synthesis of isoxazoline skeletons from readily available α,β-unsaturated aldehydes and acetoximes. Specifically, catalysts **C1** and **C2** exhibited high catalytic activity and demonstrated compatibility with a broad range of substrates, including those bearing aromatic rings and external olefins. Furthermore, the practical utility of these catalysts was underscored by their successful application in continuous-flow reactions. By employing carboxylic acid silica gel as a diluent, the system achieved a turnover frequency (TOF) of 2.9 h^{-1} and maintained stable product yields above 70% for over 50 hours of operation. Mechanistic investigations revealed two distinct, isomer-dependent pathways: (i) the **C1**-catalyzed reaction proceeds *via* an iminium-cation-mediated 1,4-addition. (ii) DFT calculations indicated that **C2** operates through a concerted acid–base activation of both the aldehyde and the oxime, enabling a direct 1,4-addition pathway without the formation of an iminium intermediate. These findings highlight the potential of bifunctionalized solid-supported catalysts for sustainable chemical processes. Our laboratory is currently focused on the design and exploration of even more highly active acid–base catalyst systems.

Author contributions

Kai Takizawa, Shun-ya Onozawa and Shū Kobayashi conceived the idea and were in charge of overall direction and planning. Kai Takizawa and Takuma Ishihara performed the experiments. Shinki Tani and Yusuke Hamada supervised Kai Takizawa and Takuma Ishihara. Kazuhiko Sato was also in charge of planning. Tadafumi Uchimaru and Akira Yada performed the computational investigation.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI).

Supplementary information is available. See DOI: https://doi.org/10.1039/d6re00067c.

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