DOI: 10.1002/adsc.202((will be filled in by the editorial staff))

Electrochemical Dual Trifluoromethylation/Cyclization of 2-Aryl-*N*-acryloyl Indoles Enabling Assembly of Indole-Fused Isoquinolinones

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Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract An interesting electrochemical cascade radical cyclization of 2-aryl-*N*-acryloyl indoles with sodium trifluoromethanesulfinate as a coupling partner has been explored, affording unexpected bis-trifluoromethylated indole-fused isoquinolinones as products. Experimental results and DFT calculations disclose that this reaction involves trifluoromethylation-triggered cyclization and the second trifluoromethylation as the key steps. This strategy does not need any transition-metal catalysts or oxidants, and uses readily available trifluoromethylating reagent enabling the facile synthesis of bis-trifluoromethylated indole-fused tricycles.

Keywords: electrolysis; 2-aryl-*N*-acryloyl indoles; sodium trifluoromethanesulfinate; indolo[2,1-*a*]isoquinoline; trifluoromethylation

Indolo[2,1-*a*]isoquinolines belong to an important type of indole-fused tetracyclic alkaloids, which are widely present in pharmaceutical compounds and natural products (Figure 1).[1,2] Also, indolo[2,1-*a*]isoquinoline derivatives have been demonstrated to possess a broad spectrum of biological activities, such as inhibition of estrogen receptor,[3] inhibition of tubulin polymerization,[4] and so on. Due to the unique structure and broad biological activities, this heterocyclic skeleton has garnered significant attention in medicinal and organic chemistry over the past decades.

Development of efficient methods for the construction of indolo[2,1-*a*]isoquinoline skeleton is a hot research topic in synthetic chemistry, and several elegant works have been reported in recent years.[5] In particular, cascade radical cyclization reaction with the use of 2-aryl-*N*-acryloyl indoles as radical acceptors represents an efficient method for the rapid construction of indolo[2,1-*a*]isoquinoline. Actually, various radicals have been developed for this radical cyclization, including sulfonyl radicals,[6] alkyl radicals[7], acyl radicals,[8] selenyl/sulfenyl radicals,[9] silyl radicals,[10] CO_2 radical anion,[11] and others.[12] In particular, photocatalytic trifluoromethylation triggered cyclization of radical 2-aryl-*N*-acryloyl indoles under continuous flow conditions also has been developed with diphenyl(trifluoromethyl)sulfonium trifluoromethanesulfonate as a radical source, which afforded a new strategy for constructing derivatives of trifluoromethylated indole[2,1-*a*]isoquinoline (scheme 1a).[13] However, these transformations usually need chemical oxidants, transition-metal catalyst, or harsh conditions. Thus, development of

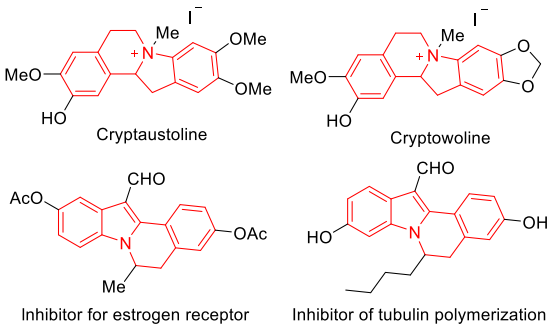
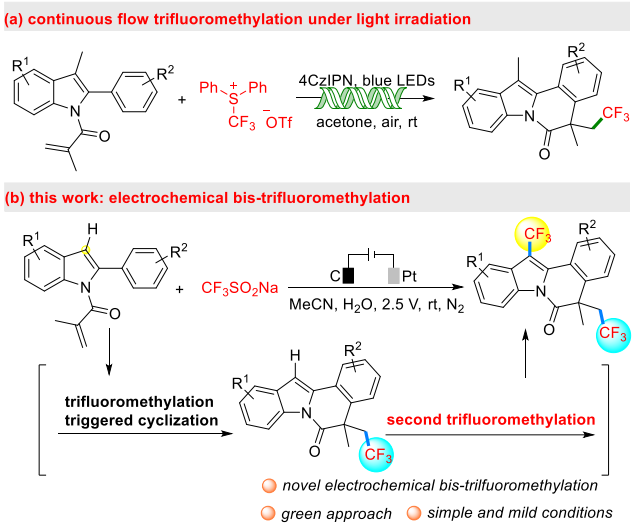


Figure 1. Examples of indolo[2,1-*a*]isoquinoline-containing natural products and bioactive compounds.

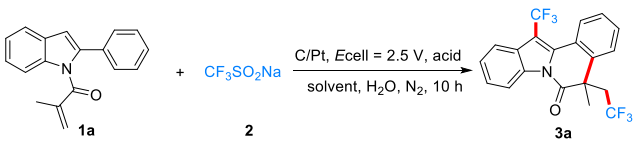
green and efficient method for the synthesis of multi-substituted indolo[2,1-*a*]isoquinolines, in particular, using electrochemical strategy,[14] still remains great challenge. On our continuous interest in the electrochemical cyclization reactions of indole derivatives[15] and synthesis of fluorinated heterocyclic compounds,[16] we embark on the development of the electrolysis of indole[2,1-*a*]isoquinoline utilizing trifluoromethanesulfinate sodium (CF_3SO_2Na)[17] as a coupling agent (Scheme 1b). Herein, we report an cascade radical reaction of 2-arylindoles with CF_3SO_2Na under electrochemical conditions, which affords the unexpected bis-trifluoromethylated indole[2,1-*a*]isoquinolines as products. The mechanism studies disclose that the reaction proceeds via trifluoromethylation-triggered cyclization and second trifluoromethylation, efficiently incorporating bis-trifluoromethyl groups (Scheme 1b). This strategy underscores the immense potential of electrochemistry in the synthesis of polycyclic compounds, offering a green and efficient pathway to the bioactive compounds bearing bis-trifluoromethyl moieties.[18]



Scheme 1. Cyclization and trifluoromethylation.

Initially, optimization of reaction conditions was carried out by using 2-methyl-1-(2-phenyl-1*H*-indol-1-yl)prop-2-en-1-one (**1a**) and sodium trifluoromethionate (**2a**) as model substrates. The reaction did happen when it was conducted with C/Pt as electrodes and $LiClO_4$ as an electrolyte using MeCN as a solvent in the presence of AcOH and H_2O under 2.5 V constant pressure at room temperature. The desired bis-trifluoromethylated indole[2,1-*a*]isoquinoline product **3a** was successfully isolated in 39% yield under a nitrogen atmosphere after 10 h (entry 1, Table 1). Inert atmosphere protection is essential for this reaction, and the reaction conducted under air led to an obviously decreased yield (17%, entry 2). In terms of voltage, 2.5 V was identified as the optimal reaction voltage, and variation of voltage did not afford any improvement on the reaction outcome (entries 3 and 4). Subsequently, the effect of the solvent on the reaction was investigated, and several regular solvents were tried for this electrochemical reaction. Unfortunately, switching acetonitrile to other examined solvents was not successful, and almost no desired product **3a** was obtained in these reaction medium (entries 5-8). Also, increasing the reaction temperature to 60 ºC did not show a positive effect on the yield (entries 9). When the electrolyte $LiClO_4$ was replaced by nBu$_4$NBF$_4$, nBu$_4$NBr, and nBu$_4$ONAc, no increase in yield was observed (entries 10-12). Further optimization were focused to the amount of HOAc additive. When the equivalent of AcOH was reduced from 2.5 to 1.5 equiv, an obviously increased yield was obtained (58% yield, entry 13). Further decreasing the amount of AcOH resulted in a dramatically decreased yield, which suggests that acetic acid is essential to facilitate the reaction (entries 13-15). The attemption to adjust the ratio of water also failed to provide any improvement in yield (entries 16 and 17). Also, the addition of hexafluoroisopropanol (HFIP) as a co-solvent did not show a positive effect on the reaction outcome (entry 18). Finally, two other acids, such as formic acid and benzoic acid, were tried as additives for this reaction, but also failed to provide any improvement of the yield (entries 19 and 20).

Table 1. Reaction condition optimization.[a]

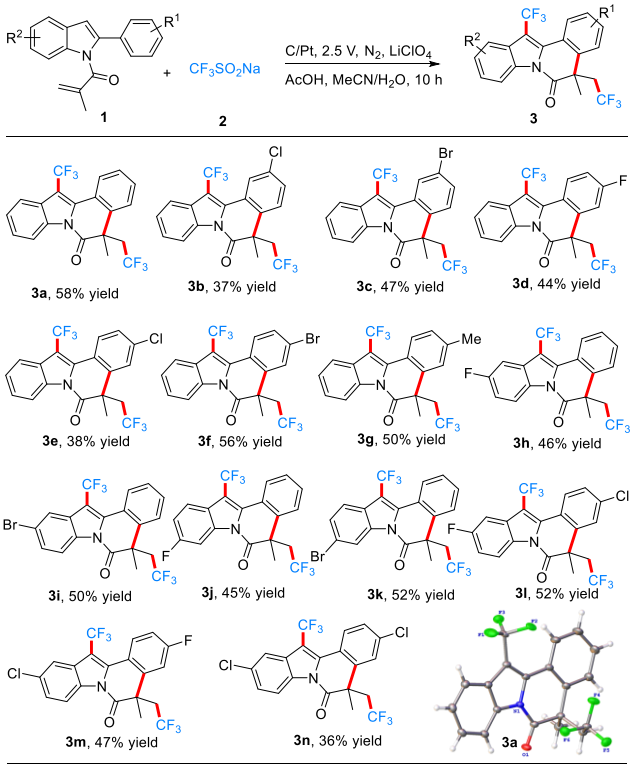


Entry	Electrolyte	Voltage (V)	Solvent	AcOH (equiv)	Yield (%)[b]
1	$LiClO_4$	2.5	MeCN	2.5	42
2	$LiClO_4$	2.5	MeCN	2.5	17[c]
3	$LiClO_4$	2.0	MeCN	2.5	39
4	$LiClO_4$	3.0	MeCN	2.5	18
5	$LiClO_4$	2.5	MeOH	2.5	trace
6	$LiClO_4$	2.5	THF	2.5	trace
7	$LiClO_4$	2.5	DMF	2.5	trace
8	$LiClO_4$	2.5	DMSO	2.5	trace
9	$LiClO_4$	2.5	MeCN	2.5	35[d]
10	nBu$_4$NBF$_4$	2.5	MeCN	2.5	39
11	nBu$_4$NBr	2.5	MeCN	2.5	41
12	nBu$_4$ONAc	2.5	MeCN	2.5	11
13	$LiClO_4$	2.5	MeCN	1.5	58
14	$LiClO_4$	2.5	MeCN	0.5	39
15	$LiClO_4$	2.5	MeCN	0	trace
16	$LiClO_4$	2.5	MeCN	1.5	32[e]
17	$LiClO_4$	2.5	MeCN	1.5	54[f]
18	$LiClO_4$	2.5	MeCN	1.5	36[g]
19	$LiClO_4$	2.5	MeCN	1.5	35[h]
20	$LiClO_4$	2.5	MeCN	1.5	35[i]

[a] Reaction conditions: 2-aryl-*N*-acryloyl indoles **1a** (0.2 mmol), CF_3SO_2Na **2a** (0.6 mmol), $LiClO_4$ (0.4 mmol), AcOH (0.3 mmol), MeCN (10 mL), H_2O (2 mL), 2.5 V under nitrogen atmosphere. [b] Yield of isolated products. [c] Under air. [d] At 60 °C. [e] H_2O (1 mL). [f] H_2O (0.5 mL). [g] Add 1 mL HFIP. [h] HCO_2H was used. [i] $PhCO_2H$ was used.

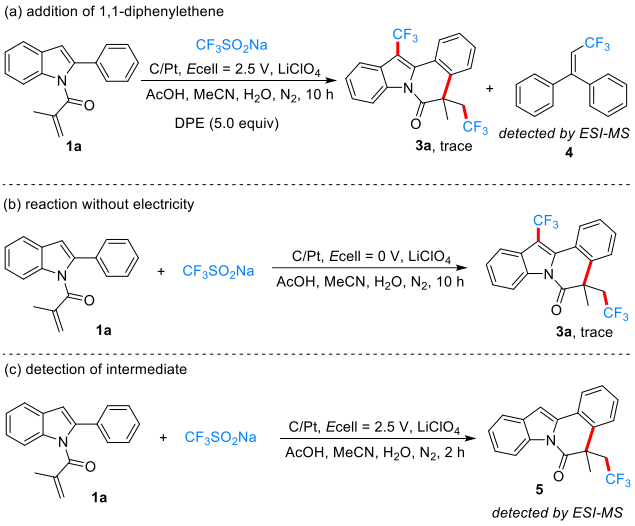
After obtaining the optimal reaction conditions, the substrate range and structural generality of this

electrochemical cyclization reaction was evaluated by using a series of 2-aryl-*N*-acryloyl indoles **1** (Scheme 2). Generally, all the examined *N*-acryloyl indoles **1** bearing different substituents on indolyl and phenyl moieties can be well compatible with this reaction system, affording the corresponding indole[2,1-*a*]isoquinolinone product **3** with moderate to good chemical yields. The electronegativity of substituted group on the 2-phenyl moiety shows an obvious effect on the reaction outcome. It was found that the substrates with an electron-withdrawing group, (chloro, fluoro, **1b**, **1d**, **1e**) could work under the standard conditions resulting in the corresponding product **3b**, **3d**, **3e** in moderate yields. While the substrate substituted by an electron-donating group, such as methyl, an increased yield of product was obtained (50% yield, **3g**). On the other hand, variations of substituents on the aromatic ring of the indole moiety were investigated. The results disclose that these substrates were also well tolerated in this reaction with moderate yields (46-52%, **3h**-**3k**). Finally, the substrates with two substituted groups were also compatible with the reaction resulted in corresponding products with acceptable yields (**3l**-**3n**). The structure of the product **3** was confirmed by the single crystal x-ray analysis of **3a**.[19]



Scheme 2. Substrate scope study of 2-aryl-*N*-acryloyl indoles **1** (Reaction conditions: 2-aryl-*N*-acryloyl indoles **1** (0.2 mmol), CF_3SO_2Na **2a** (0.6 mmol), $LiClO_4$ (0.4 mmol), AcOH (0.3 mmol), MeCN (10 mL), H_2O (2 mL), 2.5 V under N_2).

Next, a series of experiments were conducted to gain insights into the reaction mechanism. Under standard reaction conditions, when an additional 5.0 equivalent 1,1-diphenylethylene (DPE) was added as a radical trapping reagent (Scheme 3a), the reaction was completely suppressed and almost no expected indole[2,1-*a*]isoquinolinone product **3a** was obtained. This observation suggests that the reaction undergoes through a radical process. Fortunately, the DPE-trapped adduct **4** was detected by ESI-MS (for spectrum, see the SI file), although the main product **3a** was not produced. This finding further confirms the involvement of free radical processes and indicates that the sulfonyl radical is a radical intermediate in this reaction. Then, a reaction without passing electricity was carried out under the standard conditions. The reaction did not occur with almost all of the starting materials remaining in the reaction mixture, confirming the indispensable role of electric current (Scheme 3b). Attemption to obtain the information of reaction intermediate was also performed (Scheme 3c). When the reaction was stopped at 2 h, the desired product **3a** and the reaction intermediate **5** featuring one CF_3 group were detected in the reaction mixture by ESI-MS.



Scheme 3. Control experiments.

Subsequently, to gain the information of the oxidation potentials of substrates and reagents in this electrochemical process, cyclic voltammetry experiments (CV) were carried out and the results were shown in Figure 2. Cyclic voltammetry experiments revealed that there is an oxidation peak at 1.80 V vs Ag/AgCl in the CV of CF_3SO_2Na **2a**, while CV of 2-phenyl-*N*-acryloyl indole (**1a**) shows a higher oxidation potential at 1.97 V vs Ag/AgCl. Thus, CF_3SO_2Na might be preferentially oxidized at the anode over substrate **1a**.

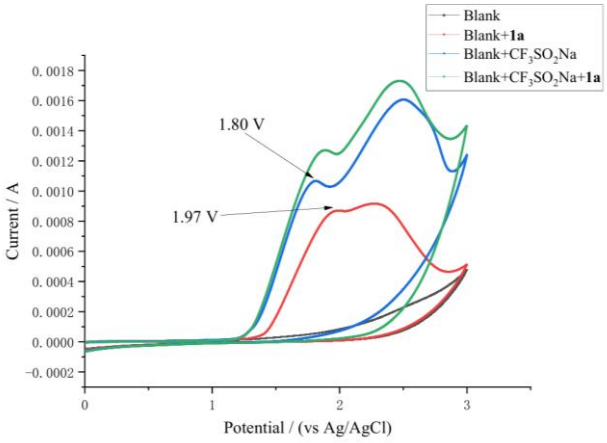
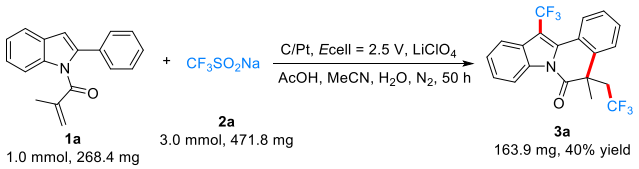


Figure 2. CV experiments.

Furthermore, to demonstrate the synthetic applicability of the electrochemical dual trifluoromethylation/cyclization reaction we conducted a scale-up (1.0 mmol) reaction based on **1a** under standard conditions (Scheme 4), but extending the reaction time to 50 h. Under these reaction conditions, we could obtain the desired bis-trifluoromethylated indole[2,1-*a*]isoquinoline **3a** with 40% yield.



Scheme 4. Scale-up synthesis.

Based on the above experimental results and density functional theory (DFT) calculations, a plausible mechanism for this electrochemical reaction is shown in Figure 3. DFT calculations were performed using Gaussian 16[20] at the wB97XD/def2TZVPP level of theory with the conductor-like polarizable continuum model (CPCM)[21] which accounts for the solvent acetonitrile. Initially, sodium triflinate undergoes decomposition via anodic oxidation and to give the reactive·CF_3• radical. Then, radical addition between CF_3• and **1a** generates radical intermediate **A**, via **TS1** with an exergonicity of 35.5 kcal/mol. The computed Gibbs activation barrier for **TS1** was 10.5 kcal/mol with a C···C bond forming distance of 2.53 Å. Next, radical intermediate **A** undergoes intramolecular radical cyclization to afford radical intermediate **B**, via **TS2** with a Gibbs activation barrier of 19.1 kcal/mol. The formation of radical intermediate **B** occurs with an exergonicity of 38.7 kcal/mol. Anodic oxidation of radical intermediate **B** gives cationic intermediate **C** with suffers a proton abstraction leading to intermediate **5**. A subsequent radical addition between ·CF_3 and intermediate **5** generates radical intermediate **D**, via **TS3** with an exergonicity of 22.4 kcal/mol. The computed Gibbs activation barrier for **TS3** was 9.1 kcal/mol. In this final TS structure, the C···C bond forming distance was found to be 2.33 Å. Another anodic oxidation gives cationic intermediate **E** from radical intermediate **D**. A final deprotonation of cationic intermediate **E** leads to product **3a**. The intramolecular radical cyclization (**TS2**) is the rate determining step in the mechanism. The optimized structures for transition states involved in the reaction mechanism are shown in Figure 3.

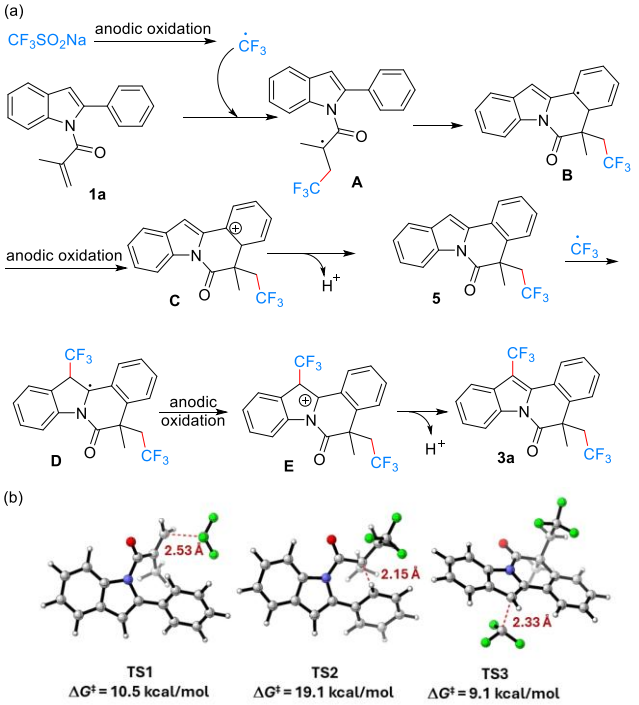


Figure 3. (a) Proposed mechanism. (b) Optimized structures of transition states. Bond forming distances are indicated in angstroms (Å).

We also analyzed the spin-center shift during the reaction mechanism. As indicated in Figure 4, the spin density is mainly located on the trifluoromethyl carbon atom (0.57) before the CF_3 addition (**RC1**). In the transition state (**TS1**), the spin density gradually flows to the adjacent β-carbon atom (0.16), and finally, most of the spin density is distributed on β-carbon (0.60) after the radical addition at radical intermediate **A**. In the **TS2**, the spin density gradually flows to the adjacent aromatic ring, and to finally distributed on β-carbon (0.60) and the aromatic ring after the radical cyclization at radical intermediate **B**. For the final CF_3 addition, the spin density is mainly located on the trifluoromethyl carbon atom (0.57) before the CF_3 addition (**RC2**). In the transition state (**TS3**), the spin density gradually flows to the adjacent β-carbon atom (0.16) and finally, most of the spin density is distributed on β-carbon (0.49) and delocalized on the phenyl ring (0.45) after the radical addition at radical intermediate **D**.

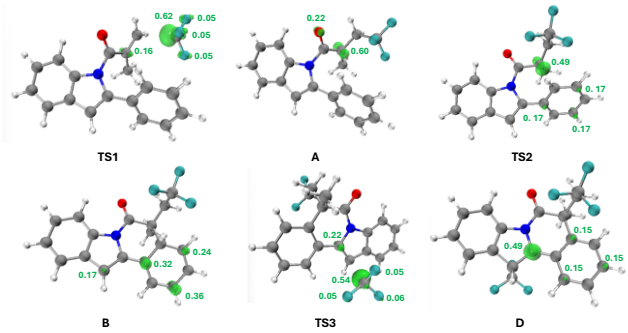


Figure 4. Spin density/distributions analysis. Hirshfeld spin distributions were computed with Multiwfn 3.8.

In summary, we have successfully developed an electrochemical dual trifluoromethylation/ cycloaddition reaction of 2-aryl-*N*-acryloyl indoles, affording various indole[2,1-*a*]isoquinolinone product with good yields. The robustness of the present transformation is well investigated using a wide variety of 2-aryl-*N*-acryloyl indoles. Mechanistic studies disclose that the reaction proceeds through the sequence of anodic oxidation to generating trifluoromethyl radical, trifluoromethylation-triggered cyclization, and second trifluoromethylation. The method features mild reaction conditions and does not need any transition-metal catalyst, which provides a green approach for the construction of bis-trifluoromethylated indole-fused heterocycles that would serve in the drug discovery of the potent fluorinated compounds.

Experimental Section

General procedure for the electrochemical reaction: In a 10 mL electrolytic cell equipped with a platinum electrodes (1.0 cm × 1.0 cm × 0.2 mm) and a graphite flakes (1.0 cm × 1.0 cm × 3 mm), 2-aryl-*N*-acrylyl indole (0.2 mmol), $LiClO_4$ (2 equiv, 0.4 mmol), CF_3SO_2Na (3 equiv, 0.6 mmol) and AcOH (1.5 equiv, 0.3 mmol) were dissolved in a mixed solvent of MeCN (5 mL) and H_2O (1 mL). The reaction mixture was stirred at room temperature under a nitrogen atmosphere, with constant voltage (2.5 V) for 10 h. Then, the reaction was diluted with H_2O (25 mL) and extracted with DCM (3 × 20 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo. The product **3** was purified by TLC plate of 20 cm × 20 cm using petroleum ether/ethyl acetate (4:1, v/v) as eluent.

Acknowledgements

We gratefully acknowledge the financial support from the National Natural Science Foundation of China (No. 21761132021). Qin Lan project from Jiangsu Province for JLH is also acknowledged. The computational resources from the Servei d'Informàtica de la Universidad de Valencia (SIUV) are gratefully acknowledged for providing access to supercomputing resources. The financial support from the National Research Development and Innovation Office of Hungary (NKFIH/OTKA K 142266) is acknowledged.

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