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Journal:	*Organic Chemistry Frontiers*
Manuscript ID	QO-RES-08-2023-001350.R1
Article Type:	Research Article
Date Submitted by the Author:	02-Oct-2023
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ARTICLE

Iodine(III)-Catalyzed Dehydrogenative Cycloisomerization-Arylation Sequence of 2-Propargyl 1,3-Dicarbonyl Compounds†

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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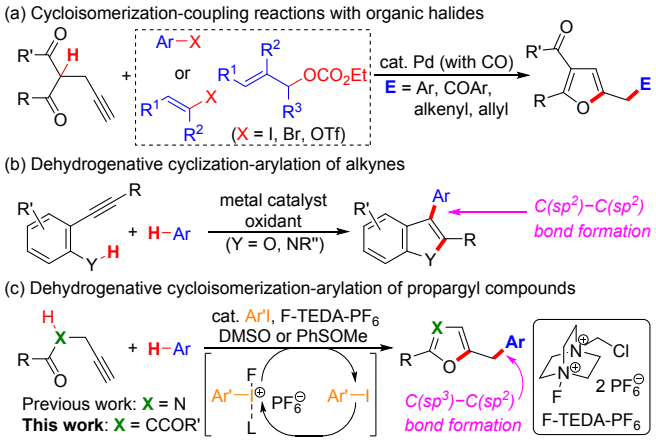
Tandem cycloisomerization-coupling reaction of a nucleophile-tethered alkyne with a coupling partner provides an efficient method that allows the construction of a cyclic skeleton concomitant with the introduction of a functional group, and its dehydrogenative version is a greener approach that does not require a prefunctionalization step of the coupling partner. Herein, we report the dehydrogenative cycloisomerization-arylation sequence of 2-propargyl 1,3-dicarbonyl compounds with unfunctionalized arenes, representing first report of the dehydrogenative cycloisomerization-functionalization reaction of alkynyl ketones.

Introduction

The furan ring is a very important heterocyclic structure that is found in many useful substances such as bioactive substances and functional materials.[1] In addition, furans are frequently used as building blocks in synthetic chemistry.[2] Therefore, many synthetic methods of furans with specific substitution patterns have been developed.[3] Among them, the cycloisomerization reaction of 2-propargyl 1,3-dicarbonyl compounds provides one of the efficient methods for the synthesis of highly substituted furans.[4] The reaction has been extended to Pd-catalyzed tandem cycloisomerization-functionalization reactions (Scheme 1a)[5] as well as the cycloisomerization reaction of substrates in situ generated from 1,3-dicarbonyl compounds and propargyl alcohols or their analogues.[6] However, although these tandem reactions have been demonstrated to afford furans having various carbon-functional groups such as aryl,[5a-c,f] alkenyl,[5c] acyl[5a,d] and allyl groups,[5e] it is necessary to use organic halides and their equivalents as coupling partners, which require tedious prefunctionalization steps and increased waste. From the viewpoint of green and sustainable chemistry, transition metal-catalyzed dehydrogenative methods[7] have been recently developed for the cycloisomerization-coupling reactions of nucleophile-tethered alkynes with unfunctionalized arenes[8a-d] or other coupling partners.[8e-g] These methods have been applied to the C(sp²)–C(sp²) bond formation via the dehydrogenative cycloisomerization-arylation sequence of various alkynes (Scheme 1b), [8a-d] but the C(sp³)–C(sp²) bond formation, such as the reaction of 2-propargyl 1,3-dicarbonyl compounds with unfunctionalized arenes, has not been achieved.



Scheme 1. Heterocyclic synthesis with introduction of functional groups.

On the other hand, as part of our research on the synthesis of heterocycles based on the hypervalent iodine(III)-catalyzed difunctionalization of alkynes,[9] we recently developed a dehydrogenative cycloisomerization-arylation sequence of *N*-propargyl carboxamides (X = N) with the C(sp³)–C(sp²) bond formation (Scheme 1c).[9a] Although hypervalent iodine(III) compounds have been shown to be effective on the dehydrogenative C-C bond formation,[10] some of which have been advanced to the iodine(III)-catalysis,[11] only a few catalytic intermolecular arylation reactions have been reported.[11a-c] Thus, iodine(III)-catalyzed intermolecular arylation reactions as well as dehydrogenative cycloisomerization-functionalization sequence with the C(sp³)–C(sp²) bond formation are still challenging research topics. Herein, we describe a metal-free

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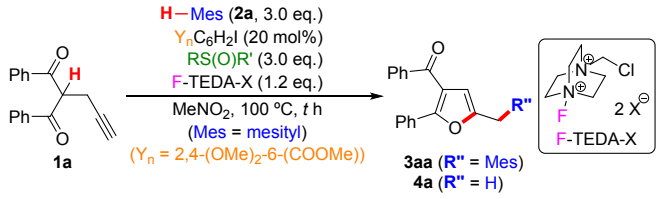
†Electronic Supplementary Information (ESI) available: experimental procedures, characterisation data for new compounds. See DOI: 10.1039/x0xx00000x

dehydrogenative cycloisomerization-arylation sequence of 2-propargyl 1,3-dicarbonyl compounds (X = CCOR') catalyzed by iodine(III) species generated from iodoarene precatalyst with sulfinyl fluoride, which are formed by the treatment of sulfoxides by F-TEDA-PF_6 (Scheme 1c).

Results and discussion

Initially, we focused on optimizing the conditions for the reaction of dicarbonyl compound **1a** with mesitylene (**2a**, 3 eq.) as show in Table 1. As with the previous method developed for the reaction of *N*-propargyl carboxamides,[9a] when substrates and iodoarene precatalyst were added after the treatment of DMSO (R = R' = Me) with F-TEDA-PF_6 at 100 ºC for 1 h in $MeNO_2$, the desired coupling product **3aa** was obtained in 64% yield at 100 ºC for 18 h (entry 1). However, the use of F-TEDA-X bearing other counter anions (X = BF_4, NTf_2, OTf) resulted in lower yields of **3aa** (22-59%, entries 2-4), and the use of *m*CPBA instead of DMSO pretreated with F-TEDA-X gave a complex mixture including **3aa** (13%, entry 5). Notably, although the use of F-TEDA-PF_6 in the absence of DMSO increased the yield of cyclized product **4a** (entry 6), there was not much difference in the yield of **3aa** in the presence of DMSO, even when the reaction time was 1 h (entry 7).

Table 1. Optimization of conditions.

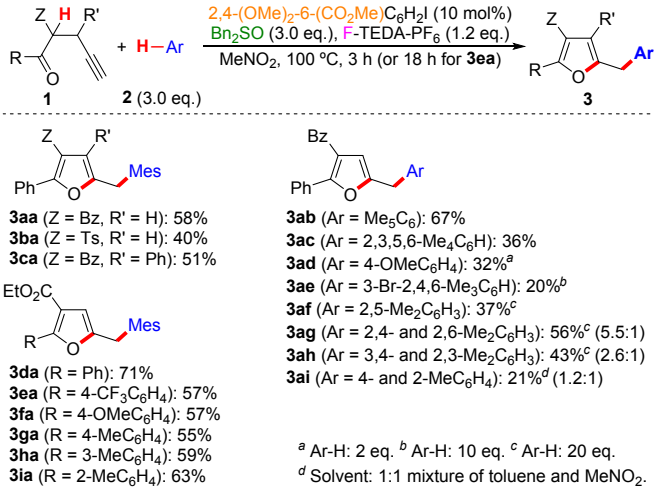


Entry	R, R'	X	*t* (h)	**3aa**[a] (%)	**4a**[a] (%)
1	Me, Me	PF_6	18	64	19
2	Me, Me	BF_4	18	59	10
3	Me, Me	NTf_2	18	50	15
4	Me, Me	OTf	18	22	19
5[b]	none	-	18	13	23
6	none	PF_6	18	38	29
7	Me, Me	PF_6	1	60	7
8	Ph, Ph	PF_6	1	63	6
9	Bn, Bn	PF_6	1	71 (58)	11
10	Ph, Bn	PF_6	1	71 (54)	7
11	Ph, Me	PF_6	1	64	4
12[c]	Ph, ^{t}Bu	PF_6	1	17	11
13[d]	Bn, Bn	PF_6	3	73 (58)	11
14[e]	Bn, Bn	PF_6	3	60	19
15[f]	Bn, Bn	PF_6	18	5	39

[a] Determined by ^{1}H NMR analysis using an internal standard. Values in parentheses were isolated yields. [b] *m*CPBA instead of F-TEDA-X. [c] Recovery of **1a**: 50%. [d] $Y_nC_6H_2I$: 10 mol%. [e] $Y_nC_6H_2I$: 5 mol%; recovery of **1a**: 7%. [f] $Y_nC_6H_2I$: 0 mol%; recovery of **1a**: 46%.

Among the attempted sulfoxides (entries 7-12, see also Table S1 in ESI), Bn_2SO and PhS(O)Bn afforded good results. Particularly, in the case of Bn_2SO, **3aa** was isolated in 58% yield (entry 9). In addition, by extending the reaction time to 3 h, the amount of catalyst could be reduced to 10 mol%, giving comparable results (entry 13). It should be mentioned that other iodoarene precatalysts (2,4-$(OMe)_2$-6-$(CONHMe)C_6H_2I$, 2,4-$(OMe)_2$-6-$(CONH^iPr)C_6H_2I$, 2,4-$(OMe)_2$-6-$(CO_2H)C_6H_2I$, 2,4,6-$(OMe)_3C_6H_2I$, *etc*) and other solvents (MeCN and DCE) gave relatively inferior results (See, Table S1 and S2 in ESI).

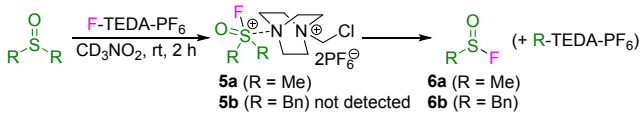
With the optimized conditions in hand, the scope of the present catalytic systems was next investigated using various carbonyl compounds **1a**-**i** and arenes **2a**-**i** (Scheme 2). Similar to dicarbonyl compound **1a**, *β*-ketosulfone **1b** and *β*-ketoesters **1d**-**i** reacted with mesitylene (**2a**) to give the corresponding arylated furans **3ba** and **3da**-**3ia** in 40–71% yields. Notably, in the case of CF_3-substituted **3ea**, the reaction time needed to be extended to 18 h probably because of the reduced nucleophilicity of **1e**. In cases of sulfonyl ketone **3ba** and ketoester **3da**-**3ia**, the reaction proceeded on the aryloyl group side, probably because the aryloyl group is easily enolized. Similar selectivity has been observed in other cycloisomerization[4b-g] and cycloisomerization-functionalization reactions.[5c,5e,5f] Also, the formation of tetrasubstituted furans **3ca** (51%) from **1ca** having Ph-substituent at the propargyl position with mesitylene (**2a**) proceeded smoothly. Furthermore, the present method could be applied to the reaction of **1a** with various arenes **2b**-**i**. Although the increased amounts of 2-bromomesitylene (**2e**, 10 eq.), xylenes **2f-h** (20 eq.) and toluene (**2i**, cosolvent) were required, the arylated furans **3ab**-**3ai** were obtained in 20–67%. Among these products, **3ag**-**3ai** were a mixture of regioisomers (**3ag**, 5.5:1; **3ah**, 2.6:1; **3ai**, 1.2:1). Note that the reduced amount of anisole (**3d**) to 2 eq. gave better result in the case of **3ad**. Unfortunately, the use of indole and furan (3 eq.) as a coupling partner afforded the complex mixture.



Scheme 2. Scope of substrates.

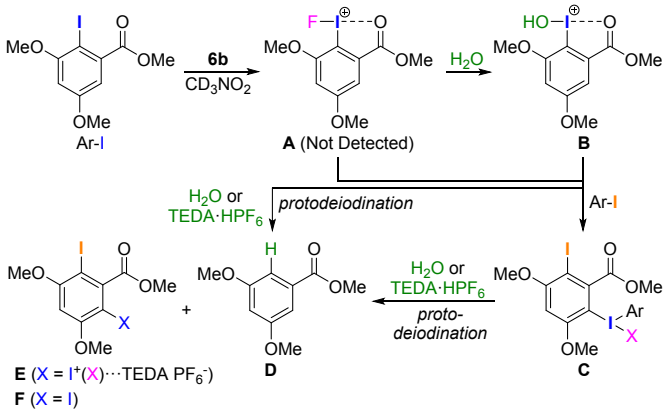
In the previous report for the cycloisomerization-arylation sequence of *N*-propargyl carboxamides,[9a] it was proposed that DMSO as a sulfoxide additive is converted to λ^6-sulfane **5a** (R =

Me) by F-TEDA-PF_6 and then sulfane **5a** works as a real oxidant that catalytically generates hypervalent iodine (Scheme 3). Therefore, in order to confirm whether similar species **5b** (R = Bn) is generated in the present method, the treatment of Bn_2SO with F-TEDA-PF_6 was attempted in CD_3NO_2 at rt for 2 h. As a result, sulfane **5b**[12a] could not be observed, but sulfinyl fluoride **6b** was detected in ^1H and ^{19}F NMR spectra (Figure S1 and S2 in SI for details). Note that a part of **5a** was decomposed into **6a** in a previous study, suggesting that **6** also works as the oxidant.



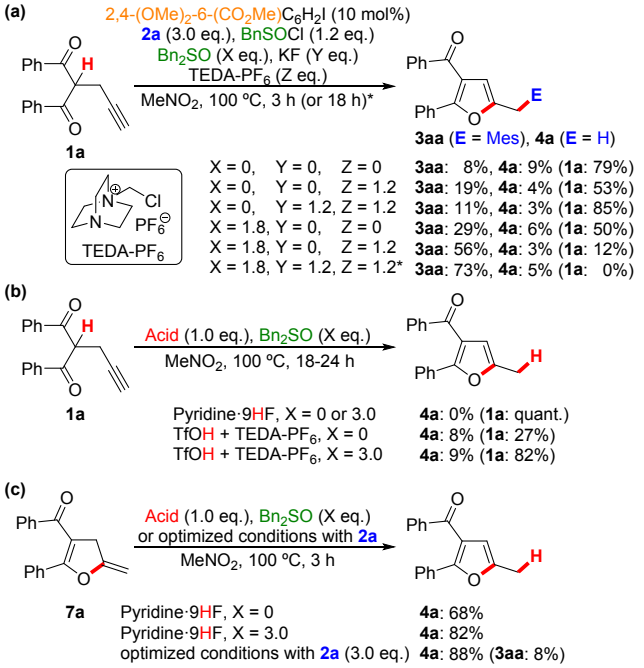
Scheme 3. Formation of fluoro-λ^6-sulfane **5** and sulfinyl fluoride **6**.

To better understand the involvement of sulfinyl fluoride as the oxidant, the time-course ^1H NMR analysis was carried out using a mixture of 2,4-$(OMe)_2$-6-$(CO_2Me)C_6H_2I$ with **6b** in situ generated from Bn_2SO and F-TEDA-PF_6 in CD_3NO_2 at room temperature (Scheme 4, see also Figure S3 in SI for details). In 24 h after the sample preparation, the peaks of λ^3-iodane **B** like hydrolysis derivative of **A** clearly appeared along with those of 3,5-dimethoxybenzoate **D** and diiodoarene **F**. In 48 h, **6b** disappeared completely, the peak intensity of 2,4-$(OMe)_2$-6-$(CO_2Me)C_6H_2I$ decreased and that of **D** increased. Considering that the compound **D** is formed by the proto-deiodination of diaryliodane **C** derived from 2,4-(OMe)2-6-$(CO_2Me)C_6H_2I$ and λ^3-iodanes **A** and/or **B**, these results suggest that sulfinyl fluoride acts as the oxidant for the formation of iodoarenes **A**. Notably, the peak intensities of **B** and **F** were hardly increased even in 48 h. The former is probably because **A** and/or **B** is very unstable and decomposes quickly in the absence of 2-propargyl 1,3-dicarbonyl compounds **1**. For the latter, it is likely because decomposition of **A** and/or **B** proceeded preferentially via the proto-deiodination of **A** and/or **B** rather than that of diaryliodane **C**, which is derived from **A** and/or **B** with 2,4-$(OMe)_2$-6-$(CO_2Me)C_6H_2I$.



Scheme 4. Proposed decomposition mechanism of **A**.

As shown in Scheme 5a, it was found out that BnSOCl in the presence of 2,4-$(OMe)_2$-6-$(CO_2Me)C_6H_2I$ (10 mol%) also promote the cycloisomerization-arylation sequence of **1a** with mesitylene (**2a**, 3 eq.). Particularly, the addition of Bn_2SO (1.8 eq.) and TEDA-PF_6 (1.2 eq.) was effective and **3aa** was obtained in 56% yield, which is similar to the result of the present catalytic systems (Table 1, entry 13). Furthermore, the addition of KF (1.2 eq.) improved the yield of **3aa** up to 73%, although it required an extension of the reaction time (18 h). However, the use of Et_3N and DABCO instead of TEDA-PF_6 did not lead to even oxidation of 2,4-$(OMe)_2$-6-$(CO_2Me)C_6H_2I$. Note that, regardless of the addition of Bn_2SO and TEDA-PF_6, no formation of sulfinyl fluoride **6b** was observed from the mixture of BnSOCl and KF.[12b] Thus, the presence of sulfinyl halides, sulfoxides, and TEDA-PF_6 is important for this reaction.

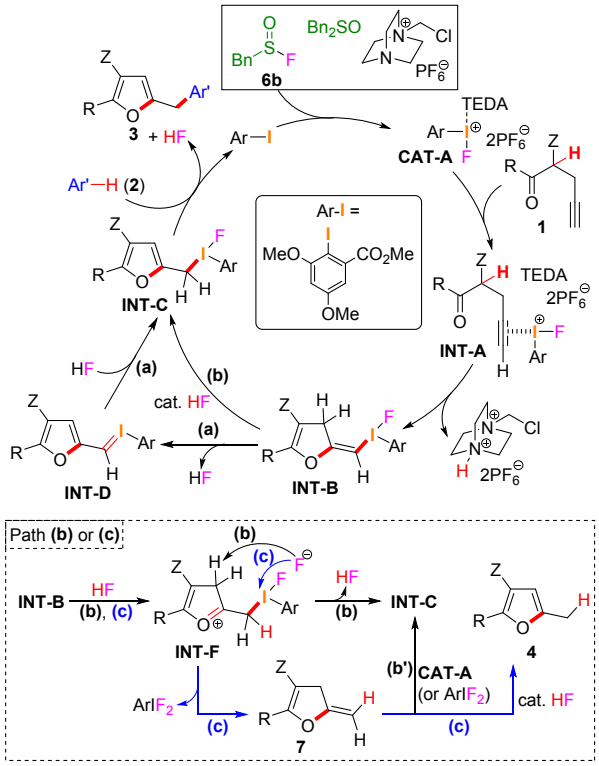


Scheme 5. Control experiments.

Since the cyclized products **4** were observed as byproducts in most of the reaction of **1** with **2**, we attempted to check the formation mechanism of **4** (Scheme 5b and 5c). Initially, considering the cycloisomerization of **1** by the generated acid in the present catalytic systems,[13] **1a** was treated with Pyridine·9HF or H-TEDA-PF_6 generated from TfOH and TEDA-PF_6 (1.0 eq.) in $MeNO_2$ at 100 ºC (Scheme 5b). However, regardless of the presence of Bn_2SO, HF did not afford **4a** at all and H-TEDA-PF_6 hardly did. Next, as an alternative possible mechanism, aromatization of methylenedihydrofuran **7** by acid[4g] was investigated (Scheme 5c). The reaction of **7a** proceeded even by Pyridine·9HF (1.0 eq.), and **4a** was obtained in 82% yield in the presence of Bn_2SO (3.0 eq.). Note that in both control experiments (Scheme 5b and 5c), the mass balance is poor in the absence of Bn_2SO, suggesting that the sulfoxide acts as a Lewis base to inhibit the acid-induced decomposition of **1** and

7. Moreover, **7a** was converted into **4a** in 88% yield even in the presence of mesitylene (**2a**, 3.0 eq.) under the optimized conditions. Thus, **7** would be mainly involved in the formation of **4**. In addition, a small amount of **3aa** (8%) was also obtained in the reaction of **7a** with mesitylene, indicating that part of **7** is involved in the formation of arylated furan **3**.

On the basis of the above observations and our previous report on the iodine(III)-mediated oxidative cycloisomerization,[9] we proposed a catalytic cycle for the synthesis of arylated furans **3** from **1** and **2** (Scheme 6). First, the ArI precatalyst is oxidized by sulfinyl fluoride **6b** derived from Bn_2SO and F-TEDA-PF_6 and/or a complex of **6b**, Bn_2O and TEDA-PF_6. The formed fluoroiodane-amine complex **CAT-A** activates the triple bond of **1** and promote the cyclization of **INT-A** to **INT-B** via the tautomerism of keto to enol form.[4e-g,5c,5e] Subsequently, **INT-B** is aromatized to **INT-C** via 1,4-elimination of HF followed by addition of HF to iodonium ylide **INT-D** (path **a**) and/or via isomerization of **INT-B** by the generated HF (path **b**). Finally, nucleophilic substitution of **INT-C** by aromatics **2** (Ar'-H) yields the arylated furans **3** with regeneration of the ArI precatalyst. As shown in Scheme 4, since **CAT-A** is a highly unstable iodine(III) species, the formation of low concentrations of **CAT-A** due to the relatively weak oxidation power of sulfinyl fluoride **6** would be effective on the catalytic reaction.



Scheme 6. Proposed formation mechanism of **3** and **4**.

It should be mentioned that the HF-catalyzed isomerization of **INT-B** into **INT-C** (path **b**) would proceed via the protonation of enol moiety of **INT-B** and the subsequent deprotonation of cyclic moiety of **INT-F** by fluoride ion (Scheme in the dotted square of Scheme 6). Hence, in the latter process, the fluoride ion induces the deiodination of **INT-F** to form **7**, which is converted into **4** by HF (path **c**). The proto-deiodination of β-iodinated enols like **INT-B** has been known.[9,14] On the other hand, **7** reacts with **CAT-A** and/or $ArIF_2$ (produced by proto-iodination of **INT-B**) prior to HF to give **INT-C** (path **b'**). This process would be partially responsible for the formation of **3**.

Conclusions

We have developed the iodine(III)-catalyzed reaction of 2-propargyl 1,3-dicarbonyl compounds and arenes for the novel and efficient synthetic method of arylated furans with the C(sp^3)–C(sp^2) bond formation. The present work is one of the few examples on C(sp^3)–C(sp^2) bond formation by the catalytic dehydrogenative cycloisomerization/arylation reaction and also represents as the first report of the dehydrogenative cycloisomerization-functionalization reaction of alkynyl ketones. Moreover, on the basis of results of control experiments, we proposed that sulfinyl fluoride would act as the terminal oxidant in this iodine(III)-catalysis. Since sulfinyl halides are unknown to be effective on the generation of hypervalent iodine compounds, this study provides useful findings in the field of λ^3-iodane catalysis as well as the powerful method of furan synthesis.

Experimental

Representative procedure for conversion of 1a with 2a into 3aa. After Bn_2SO (276 mg, 1.2 mmol) was treated with F-TEDA-PF_6 (226 mg, 0.48 mmol) in $MeNO_2$ (4.0 mL) at 100 ºC for 1 h, methyl 2-iodo-3,5-dimethoxybenzoate (12.9 mg, 0.04 mmol), **1a** (105 mg, 0.40 mmol) and **2a** (83.5 µL, 1.2 mmol) were added in turn at the ambient temperature. After being stirred at 100 ºC for 3 h, the reaction mixture was diluted with ether and filtered through a pad of silica gel. The filtrate was concentrated in vacuo to dryness and then the residue was purified by MPLC on silica gel (Hexane:AcOEt = 99:1) and by MPLC on silica gel modified with octadecylsilyl (ODS) groups (MeCN only) to give **3aa** (88.0 mg, 58%).

Author Contributions

Conceptualization, A.S.; data curation, all; formal analysis, all; funding acquisition, A.S.; investigation, Y.U. and K.W.; methodology, Y.U.; project administration, A.S.; resources, A.S.; supervision, A.S.; validation, Y.U. and K.W.; visualization, Y.U. and A.S.; writing—original draft preparation, A.S.; writing—review and editing, A.T., A.Y. and A.S.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported partly by JST CREST (No. JPMJCR19R2), Iketani Science and Technology Foundation and The Sumitomo Foundation.

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