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Synthesis of Tetrasubstituted Furans through One-Pot Formal [3 + 2] Cycloaddition Utilizing [1,2]-Phospha-Brook Rearrangement

Azusa Kondoh, Kohei Aita, Sho Ishikawa, and Masahiro Terada*

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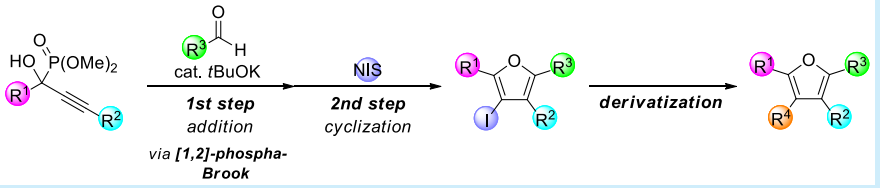

ABSTRACT: An efficient method for the synthesis of tetrasubstituted furans was developed by utilizing the [1,2]-phospha-Brook rearrangement under Brønsted base catalysis. The two-step one-pot formal [3 + 2] cycloaddition involves the nucleophilic addition of a propargyl anion, which is catalytically generated through the [1,2]-phospha-Brook rearrangement, to an aldehyde and the subsequent intramolecular cyclization mediated by *N*-iodosuccinimide to provide 2,4,5-trisubstituted-3-iodofurans. The present method with readily available substrates provides new access to a wide range of well-organized tetrasubstituted furans.

Densely functionalized furans are important five-membered heteroaromatic compounds found in numerous biologically active natural products, synthetic pharmaceuticals, and agrochemicals.[1] In addition, they can be employed as a useful building block in synthetic organic chemistry[2] as well as a potential skeleton in material science.[3] Therefore, the development of general and efficient methods for the synthesis of functionalized furans is an important subject, and massive efforts have been undertaken over the years.[4] One of the straightforward approaches for the synthesis of functionalized furans is the direct functionalization of existing furans.[5] However, challenges remain in its reaction scope and efficiency particularly for the synthesis of densely functionalized furans including tetrasubstituted furans. The intramolecular cyclization of acyclic compounds is also a well-established approach.[6] In that approach, the multistep synthesis of densely functionalized precursors is required, which hinders efficient access to diverse tetrasubstituted furans. Thus, in recent years, the construction of tetrasubstituted furan rings through the cycloaddition of multiple components has been intensively studied.[7,8] Although various types of reactions have been developed, methods that provide efficient access to a wide range of tetrasubstituted furans from readily available starting compounds are still limited.

The [3 + 2] cycloaddition is a powerful strategy for the construction of the five-membered heteroaromatic frameworks. Indeed, several efficient approaches have been established in the synthesis of multisubstituted pyrroles because various types of nitrogen-containing subunits, such as imines, enamides, and azomethyne ylides, and their reaction partners are easily available.[9] In this regard, we have recently established a method for the synthesis of polysubstituted pyrroles, which is based on the [3 + 2] cycloaddition strategy utilizing the [1,2]-phospha-Brook rearrangement under Brønsted base catalysis (Scheme 1a).[10] The formal [3 + 2] cycloaddition involves the construction of a pyrrole ring from propargyl alcohols **1** as a C3 subunit containing the requisite *umpolung* and imines as a two-atom subunit containing nitrogen, providing a diverse array of well-organized polysubstituted pyrroles.

In contrast to the efficient synthesis of multisubstituted pyrroles based on the [3 + 2] cycloaddition strategy, the reactions for the synthesis of multisubstituted furans are still underdeveloped because of the limited scope of subunits for the construction of a furan ring. We, hence, envisioned that our methodology for the formal [3 + 2] cycloaddition would be further applicable to the synthesis of tetrasubstituted furans. The use of propargyl alcohols **1** as a C3 subunit and aldehydes **2** as a two-atom subunit containing oxygen would markedly extend the usability of the [3 + 2] cycloaddition strategy and potentially lead to a significant broadening of the accessible tetrasubstituted furans. Specifically, the proposed two-step formal [3 + 2] cycloaddition of propargyl alcohols **1** to aldehydes **2** provides 2,4,5-trisubstituted-3-iodofurans **4** as shown in Scheme 1b. The first step of the formal [3 + 2] cycloaddition is the addition of propargyl alcohols **1** to aldehydes **2** under the influence of a Brønsted base catalyst. Treatment of **1** and **2** with a Brønsted base catalyst would result in the deprotonation of **1** followed by the [1,2]-phospha-

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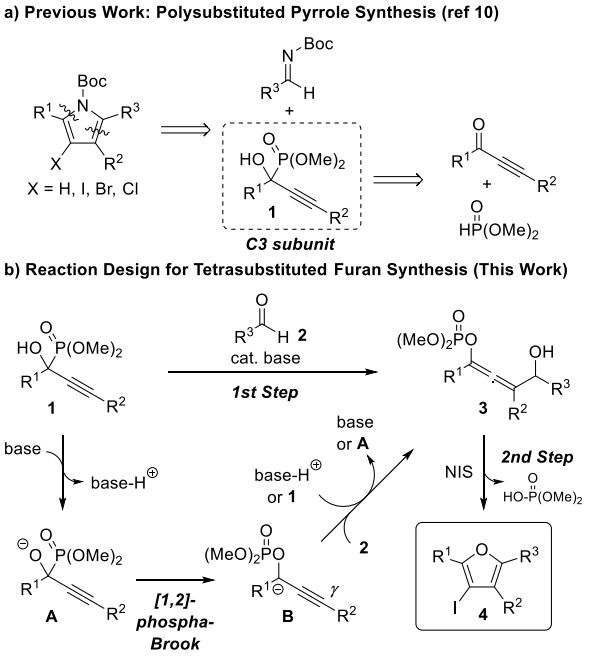
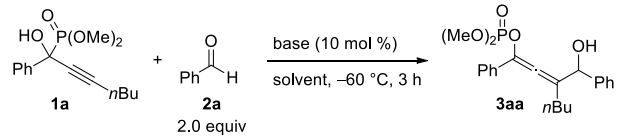
Scheme 1. Our [3 + 2] Cycloaddition Strategies for Construction of Heteroaromatic Frameworks



Brook rearrangement,[11,12] which is the migration of the dimethoxyphosphoryl moiety from carbon to oxygen, to generate α-oxygenated propargyl anion **B**. The addition of **B** to the aldehyde at the γ-position and the subsequent protonation by the conjugated acid of the Brønsted base or **1** would provide allenyl alcohol **3** along with regeneration of the Brønsted base catalyst or alkoxide **A**. The second step is the intramolecular cyclization. Based on our previous study,[10] the electrophilic activation of the allene moiety of **3** by *N*-iodosuccinimide (NIS) would cause the intramolecular addition of the alcohol to the allene moiety, and the aromatization would occur through the following elimination of dimethyl phosphate to provide 3-iodofuran **4**. Considering that propargyl alcohols **1** are easily prepared from the corresponding alkynyl ketones with a secondary phosphite by treating with an appropriate Brønsted base,[13] the method could be regarded as the construction of a furan ring from two readily available carbonyl compounds under mild reaction conditions. Particularly, a variety of aldehydes, including aromatic, aliphatic, and even densely functionalized ones, are available, which is a substantial advantage compared to conventional furan synthesis. Furthermore, the iodide moiety on the furan ring would potentially function as a handle for manipulation by various methods. Therefore, the method would provide new efficient access to a wide range of well-organized tetrasubstituted furans. Herein we report a two-step one-pot formal [3 + 2] cycloaddition that provides 2,4,5-trisubsituted-3-iodofurans. Further transformations of the iodide moiety into various carbon-based substituents are also described.

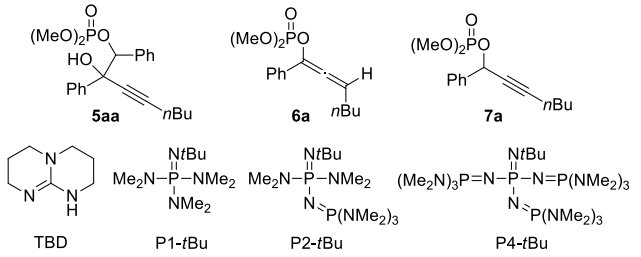
We commenced our investigation by screening the reaction conditions in the first step of the formal cycloaddition, that is, the nucleophilic addition of propargyl alcohols **1** to aldehydes **2** catalyzed by a Brønsted base. As the initial substrate, **1a** having a phenyl group at the propargylic position and a butyl group at the alkyne terminus was used. Treatment of **1a** and benzaldehyde (**2a**) with 10 mol % P1-*t*Bu in DMF at −60 °C was carried out according to the reaction conditions for our previous pyrrole synthesis (Table 1, entry 1).[10] The reaction

Table 1. Initial Screening of Reaction Conditions[a]



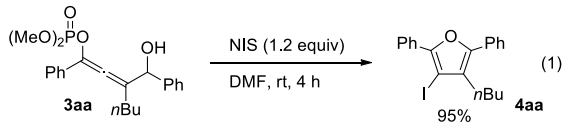
			yield (%)[b]			
entry	base	solvent	**3aa** (dr)[c]	**5aa** (dr)[c]	**6a**	**7a**
1	P1-*t*Bu	DMF	65 (60/40)	18 (58/42)	10	1
2	P2-*t*Bu	DMF	72 (60/40)	15 (63/37)	10	3
3	P4-*t*Bu	DMF	69 (61/39)	13 (54/46)	12	1
4	DBU	DMF	<1	<1	<1	<1
5	TBD	DMF	63 (63/37)	11 (63/37)	16	2
6	*t*BuOK	DMF	74 (60/40)	15 (66/34)	9	2
7	*t*BuONa	DMF	74 (62/38)	15 (59/41)	9	2
8	*t*BuOLi	DMF	68 (61/39)	19 (57/43)	6	1
9[d]	*t*BuOK	CH_3CN	27 (57/43)	26 (70/30)	26	11
10	*t*BuOK	THF	31 (66/34)	38 (55/45)	18	5
11	*t*BuOK	toluene	14 (83/17)	13 (81/19)	11	8

[a]Conditions: **1a** (0.25 mmol), **2a** (0.50 mmol), base (0.025 mmol), solvent (1.0 mL), −60 °C, 3 h. [b]NMR yields. [c]Diastereomeric ratio was determined by ^{31}P NMR analysis. [d]The reaction was conducted at −40 °C.



provided desired allenyl alcohol **3aa** as the major product in 65% NMR yield along with some byproducts including propargyl alcohol **5aa**, which was formed through the addition of the propargyl anion to **2a** at the α-position followed by the migration of the dimethoxyphosphoryl moiety, as well as allenyl phosphate **6a** and propargyl phosphate **7a**, which were formed by the direct protonation of propargyl anion at the γ- and α-positions, respectively. Screening of Brønsted bases including organobases having different basicities (entries 2−5) and alkali *tert*-butoxides (entries 6−8) was carried out, and potassium and sodium *tert*-butoxides provided **5aa** in the highest NMR yields (entries 6 and 7). Then, several solvents were tested with potassium *tert*-butoxide (*t*BuOK) as the base (entries 9−11). The effect of solvents was significant, and DMF was the solvent of choice (entry 6 vs entries 9−11).

Next, the second step of the formal [3 + 2] cycloaddition was examined. Allenyl alcohol **3aa** was treated with 1.2 equiv of NIS in DMF at room temperature to afford corresponding 3-iodofuran **4aa** in high yield (eq 1).



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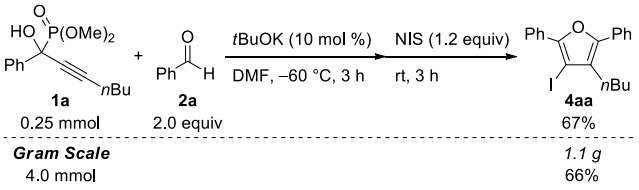
Based on this result, the one-pot synthesis of **4aa** from **1a** and **2a** was attempted (Scheme 2). **1a** and **2a** were treated

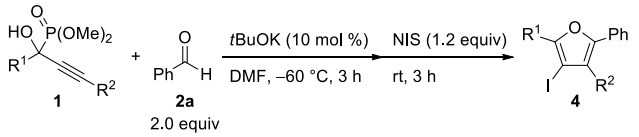
Scheme 2. One-Pot and Gram-Scale Synthesis



with 10 mol % *t*BuOK in DMF at −60 °C for 3 h. NIS was then added at that temperature, and the resulting mixture was allowed to warm to room temperature and stirred for an additional 3 h to provide **4aa** in 67% yield, which is comparable to that obtained by the two-step protocol (70% yield in two steps). In addition, this operationally simple method was sufficiently reliable to permit the synthesis of **4aa** in gram scale.

The substrate scope was investigated by using the one-pot protocol. First, the scope of propargyl alcohols **1** was examined with benzaldehyde (**2a**) as the partner (Table 2). In addition

Table 2. Scope of Propargyl Alcohols[a]



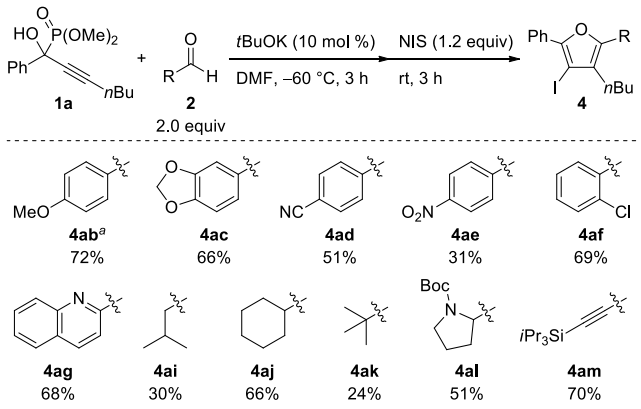
entry	R^1	R^2	4	yield (%)[b]
1	Ph	cC_6H_{11}	**4ba**	61
2	Ph	Ph	**4ca**	53
3	Ph	4-$MeOC_6H_4$	**4da**	43[c]
4	Ph	4-ClC_6H_4	**4ea**	73
5	Ph	2-MeC_6H_4	**4fa**	32
6	Ph	2-thienyl	**4ga**	80
7	4-$MeOC_6H_4$	*n*Bu	**4ha**	70
8	4-FC_6H_4	*n*Bu	**4ia**	60
9	2-MeC_6H_4	*n*Bu	**4ja**	76
10	2-thienyl	*n*Bu	**4ka**	70[c]
11	cC_6H_{11}	*n*Bu	**4la**	<1[c]
12[d]	cC_6H_{11}	Ph	**4ma**	69

[a]Conditions: **1** (0.25 mmol), **2a** (0.30 mmol), *t*BuOK (0.025 mmol), DMF (1.0 mL), − 60 °C, 3 h, then NIS (1.2 equiv), rt, 3 h. [b]Isolated yields unless otherwise noted. [c]NMR yield. [d]Reaction was conducted with DMF (2.0 mL).

to a primary alkyl group, a secondary alkyl group was applicable as substituent R^2 at the alkyne terminus (entry 1). A variety of (hetero)aryl groups were applicable as substituents R^2 at the alkyne terminus, and the corresponding 3-iodofurans were obtained in moderate to good yields (entries 2−6). Among them, **1f** having a sterically hindered *ortho*-tolyl group provided *α*-adduct **5** as the major product, and thus the yield of **4fa** was moderate (entry 5). The substituent at propargylic position R^1 was screened with substrates possessing a butyl group at the alkyne terminus (entries 7−10). The substrates having (hetero)aryl groups underwent the reaction without any problems, and the corresponding products were obtained in good yields. However, no reaction occurred when propargyl alcohol **1l** possessing alkyl groups at both the propargylic position (R^1 = cC_6H_{11}) and the alkyne terminus (R^2 = *n*Bu) was applied as the substrate (entry 11). On the other hand, in the case of the propargyl alcohol having a phenyl group at the alkyne terminus, an alkyl group, such as a cyclohexyl group, could be used as a substituent at the propargylic position (entry 12).

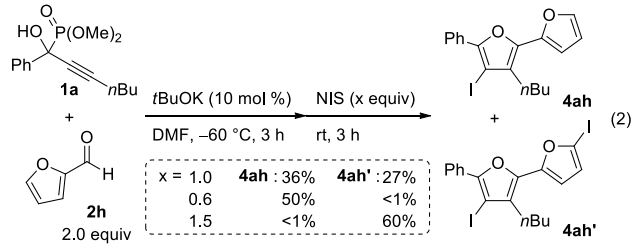
Next, the scope of aldehydes **2** was investigated (Scheme 3). Aromatic aldehydes **2b** and **2c** with an electron-donating

Scheme 3. Scope of Aldehydes



[a]Reaction was conducted with NIS (1.0 equiv).

alkoxy group at the *para* position afforded corresponding products **4ab** and **4ac** in good yields. In contrast, when **2d** and **2e** having a strong electron-withdrawing group, such as a cyano group and a nitro group, at the para position were used, significant amounts of *α*-adducts **5** were formed and the yields of **4ad** and **4ae** were moderate. The reactions of 2-chlorobenzaldehyde (**2f**) and quinolone-2-carboxaldehyde (**2g**) proceeded without any problem to provide **4af** and **4ag** in good yields. In the case of furfural (**2h**), the amount of NIS for the second step influenced the reaction outcome (eq 2).



The use of 0.6 equiv of NIS provided **4ah** selectively. In contrast, an excess of NIS caused the iodination of the furan ring derived from furfural, and **4ah′** was obtained exclusively. Aliphatic aldehydes were also examined. Secondary alkyl-substituted **2j** provided the desired product in good yield, whereas the use of primary and tertiary alkyl-substituted **2i** and **2k** resulted in low yields of **4**. Functionalized aldehydes, such as *N*-Boc prolinal (**2l**) and alkynyl aldehyde **2m**, were also applicable, and **4al** and **4am** were obtained in good yields, respectively.[14]

Two types of double cycloaddition were attempted with substrates having two reaction sites (Scheme 4). The reaction of **1a** with terephthalaldehyde (**2n**) gave two furan rings at once, providing **4an** with a teraryl core structure albeit in moderate yield (Scheme 4a). On the other hand, diol **1n**

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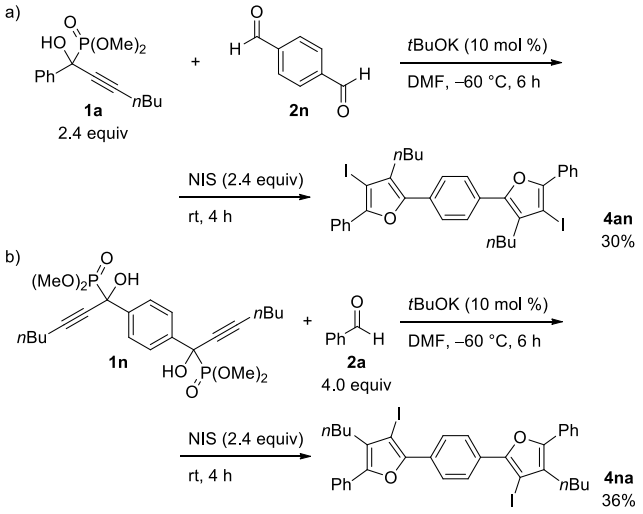
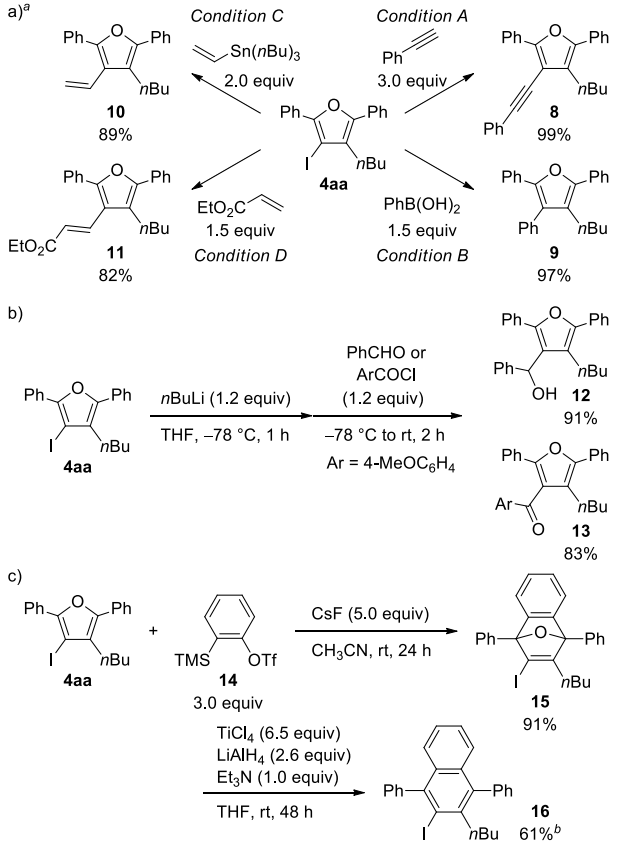
Scheme 4. Double Cycloaddition



successfully participated in the double cycloaddition to afford **4na**, the structural isomer of **4an** (Scheme 4b).

Finally, the derivatization of iodofuran **4aa** obtained by the two-step [3 + 2] cycloaddition was conducted (Scheme 5). As the transformation utilizing an iodide moiety, a variety of palladium-catalyzed reactions, such as the Sonogashira coupling reaction, the Suzuki–Miyaura coupling reaction, the Migita–Kosugi–Stille coupling reaction, and the Mizoroki–Heck reaction, could be performed and corresponding coupling products **8**–**11** were obtained in high yields (Scheme 5a). Furthermore, **4aa** was amenable to lithiation through the halogen–metal exchange followed by trapping with electrophiles, such as an aldehyde and an acid chloride, providing densely functionalized tetrasubstituted furans **12** and **13** in good yields (Scheme 5b). As a different type of derivatization of **4aa**, the transformation of the furan ring was performed. The Diels–Alder reaction with benzyne generated from **14** and the subsequent deoxygenative aromatization[15] provided 1,2,3,4-tetrasubstituted naphthalene **16** (Scheme 5c).

Scheme 5. Derivatization of 4aa



[a]Condition A: $PdCl_2(PPh_3)_2$ (10 mol %), CuI (10 mol %), Et_3N, 50 °C, 8 h. Condition B: $Pd(PPh_3)_4$ (5.0 mol %), K_3PO_4 (2.0 equiv), DMF, 100 °C, 24 h. Condition C: $Pd(PPh_3)_4$ (5.0 mol %), DMF, 120 °C, 19 h. Condition D: $Pd(OAc)_2$ (5.0 mol %), PPh_3 (15 mol %), Et_3N (2.0 equiv), DMF, 90 °C, 19 h. [b]NMR yield.

In conclusion, we have established an efficient method for the synthesis of tetrasubstituted furans on the basis of the [3 + 2] cycloaddition strategy utilizing the [1,2]-phospha-Brook rearrangement under Brønsted base catalysis. The two-step one-pot formal [3 + 2] cycloaddition involves the nucleophilic addition of an α-oxygenated propargyl anion, which is catalytically generated through the [1,2]-phospha-Brook rearrangement, to the aldehyde at the γ-position and the subsequent intramolecular cyclization mediated by NIS to furnish 2,4,5-trisubstituted-3-iodofurans possessing various substituents in a positional selective manner. The iodofurans obtained by the cycloaddition were applicable to a variety of transformations, including palladium-catalyzed cross-coupling reactions, alkylation and acylation through halogen–metal exchange, and the Diels–Alder reaction. Therefore, the present method with readily available substrates provides new access to a wide range of well-organized tetrasubstituted furans.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00619.

Experimental procedures and characterization data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Masahiro Terada – *Department of Chemistry, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan;* orcid.org/0000-0002-0554-8652; Email: mterada@tohoku.ac.jp

Authors

Azusa Kondoh – *Research and Analytical Center for Giant Molecules, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan;* orcid.org/0000-0001-7227-8579

Kohei Aita – *Department of Chemistry, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan*

Sho Ishikawa – *Department of Chemistry, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c00619

Notes

The authors declare no competing financial interest.

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