Cycloisomerization of 7-En-2-yn-1-ones to Bicyclo[3.1.0]hexanes Using Electrophilic Fluorination or Chlorination Agents

Journal:	*Organic Chemistry Frontiers*
Manuscript ID	QO-RES-12-2024-002373.R1
Article Type:	Research Article
Date Submitted by the Author:	18-Feb-2025
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Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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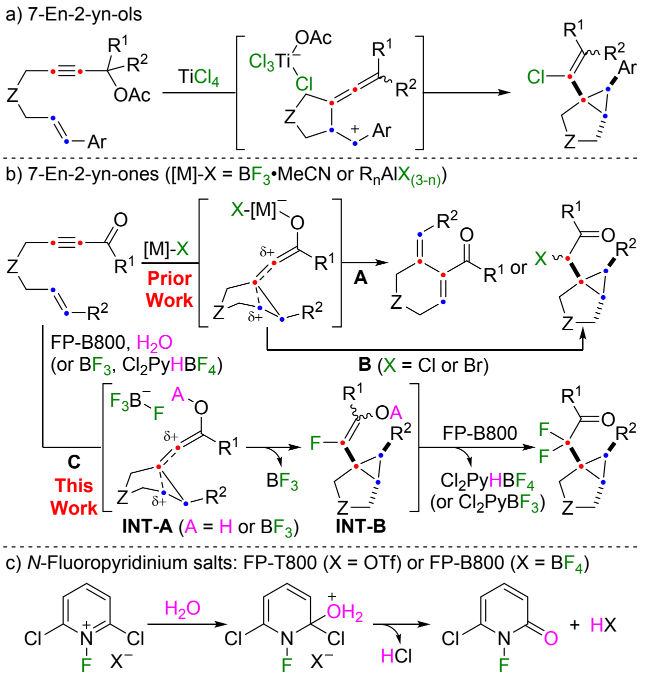
In contrast to the π-electrophilic transition metal-catalyzed cycloisomerization of enynes, systematic studies on the reaction of enynes by activation of carbonyl groups conjugated to alkynes are lacking. Herein, we report the metal-free cycloisomerization of 7-en-2-yn-1-ones to *gem*-difluorinated and *gem*-chlorofluorinated bicyclo[3.1.0]hexanes using electrophilic halogenating agents.

Introduction

Since bicyclo[3.1.0]hexanes are important cyclic compounds found in a wide variety of bioactive substances[1] and can be useful as three-dimensional mimics of cycloalkanes[1e,f] and skeletons capable of constraining conformation,[1g,h] efficient methods for this skeleton construction have been developed. Among them, cycloisomerization of enynes based on activation of alkynes by π-electrophilic Lewis acids such as Au, Pt, and other metal complexes provides one of the straightforward methods,[2] allowing the introduction of functional groups in the presence of alkenes,[3a,b] aromatics,[3c,d] diazo compounds,[3e] oxidizing agents[3f,g] or others.[3h] In addition, a few methods based on activation of oxygen functional groups such as acyloxy (Scheme 1a)[4a] and hydroxy groups[4b,c] at the propargylic position have been found, allowing the introduction of chloro and other groups with the elimination of the oxygen functional groups. Under the background, in view of the lack of systematic studies on the cycloisomerization of enynes by activation of carbonyl groups conjugated to alkynes, we have developed the BF_3-catalyzed cycloisomerization of 7-en-2-yn-1-ones to six-membered cyclic dienes (Scheme 1b, path A)[5a] as a further development of metathesis-type reactions of alkynes with heteroenes by σ-electrophilic Lewis acids.[6] Very recently, we also demonstrated the selective formation of halogenated bicyclo[3.1.0]hexanes by using aluminum halide (X = Cl and Br) instead of BF_3 catalyst (path B).[5b] However, although organofluorine compounds have been widely applied in the field of medicine and agrochemicals,[7] the synthesis of fluorine-substituted bicyclo[3.1.0]hexanes has not been achieved.



Scheme 1. Cycloisomerization of enynes.

Therefore, we focused on the fluorocyclization reaction of 2-alkynylbenzoates using *N*-fluoropyridinium salts, which were recently developed in our laboratory.[8] In the reaction, since the Brønsted acid formed by hydrolysis of *N*-fluoropyridinium by a small amount of water in the reaction system promotes the cyclization reaction (Scheme 1c), the desired reaction proceeds only with the addition of fluorinating agents. Furthermore, when BF_4^- is used as the counterion of the *N*-fluoropyridinium salt, the anion works as a nucleophilic fluorinating agent. Our method is complementary to conventional fluorocyclization methods using transition metal catalysts along with fluorine sources[9] or fluorine-containing hypervalent iodine compounds[10] because these conventional methods were not applicable to 2-alkynylbenzoates. Based on these

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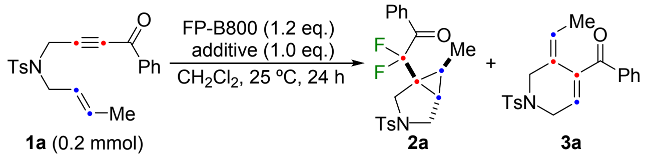
† Electronic Supplementary Information (ESI) available: experimental procedures, characterisation data for new compounds. See DOI: 10.1039/x0xx00000x

findings, we have found the metal-free cycloisomerization of 7-en-2-yn-1-ones to *gem*-difluorinated bicyclo[3.1.0]hexanes using *N*-fluoropyridinium salts (Scheme 1b, path C). We also succeeded in synthesizing *gem*-chlorofluorinated bicyclo[3.1.0]hexane in the course of this investigation, and these synthetic methods are reported herein.

Results and discussion

As our initial efforts, the evaluation of fluorinating reagents was conducted for the cycloisomerization of 7-en-2-yn-1-one **1a**. As a result, when FP-B800 was used at 25 ºC in CH_2Cl_2, the *gem*-difluorinated bicyclo[3.1.0]hexane **2a** was obtained in 13% yield (Table 1, entry 1). However, the use of other *N*-fluoropyridinium salts, *N*-fluorobenzenesulfonimide (NFSI) and Selectfluor in CH_2Cl_2 or the use of FP-B800 in other solvents such as $MeNO_2$, MeCN, and Et_2O brought about complex mixtures or significant recovery of **1a** (Table S1 in ESI†). Since the poor mass balance of the products in entry 1 (Table 1) implied that the acid formed in the reaction system had an adverse effect, the additive effects of Lewis bases were investigated (entries 2-8). Although pyridine (DN = 33.1),[11] DMF (DN = 26.6),[11] and THF (DN = 20.0)[11] with relatively high donor numbers (DN) resulted in the significant recovery of **1a** (entries 2-4), Et_2O (DN = 19.2)[11] showed the good result (**2a**: 61%, entry 5). On the other hand, MeOH (DN = 19.0)[11] and H_2O (DN = 18.0)[11] with similar donor numbers of Et_2O gave a considerable amount of byproduct other than **2a** and **3a** probably due to the nucleophilic nature of the additives (entries 6 and 7), and MeCN (DN = 14.0)[11] with lower donor numbers showed a higher formation ratio of **3a** probably due to the lower Lewis basicity (entry 8). Therefore, after examination of the FP-B800 with Et_2O system in detail (see, Table S1, entries 21-25), **2a** was isolated at 62% when 1.5 equivalents each of FP-B800 and Et_2O were used at 40ºC (entry 10). The present method gave relatively good result on the 1.0 mmol scale (entry 11).

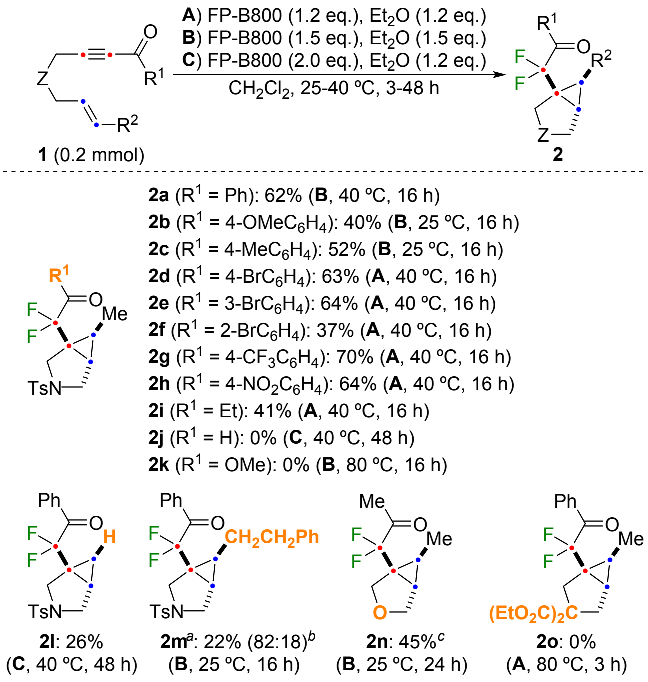
Table 1. Optimization of reaction conditions.



Entry	additive	**2a**[a] (%)	**3a**[a] (%)	**1a**[a] (%)
1	-	13	60	0
2	pyridine	0	0	98
3	DMF	0	0	92
4	THF	13	18	30
5	Et_2O	61	14	0
6	MeOH	25	7	0
7	H_2O	38	18	0
8	MeCN	24	47	0
9[b]	Et_2O	62 (60)	11	0
10[c]	Et_2O	68 (62)	trace	0
11[c,d]	Et_2O	52 (49)	24	0

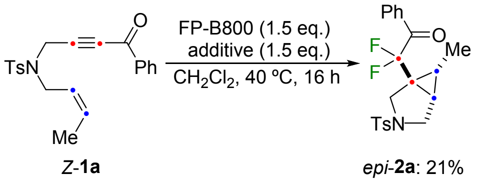
[a] Determined by ^1H NMR analysis using an internal standard. Values in parentheses show the isolated yields. [b] Et_2O: 1.2 eq. [c] FP-B800, 1.5 eq.; Et_2O, 1.5 eq.; temp., 40 °C. [d] **1a**, 1.0 mmol.

With optimization conditions in hand, the scope of substrates was next examined (Scheme 2). Similar to the unsubstituted aromatic ynone **1a**, the MeO-substituted **1b** and the Me-substituted **1c** reacted with FP-B800 (1.5 eq.) in the presence of Et_2O (1.5 eq.) (method **B**) at 25 ºC to produce the corresponding bicyclic compounds, 40% and 52%, respectively. On the other hand, in cases of **1d**-**1h** with electron-withdrawing groups, the desired product was obtained in 37-70% by using 1.2 equivalents each of FP-B800 and Et_2O (method **A**) at 40ºC. In addition, the method **A** was applicable to aliphatic ynone **1i**, although ynal **1j** gave a complex mixture and the reaction of ynoate **1k** did not proceed at all. When hydrogen (**1l**) or phenethyl groups (**1m**) were substituted instead of the methyl group as a substituent of the alkene, a similar reaction proceeded by the method **B** or **C** (FP-B800, 2.0 eq.; Et_2O, 1.2 eq.). Note that the reaction of **1m** afforded the C-6 epimer *epi*-**2m** along with **2m**, since the *E/Z* mixture of **1m** was used. Since *Z*-**1a** was also exclusively converted to *epi*-**2a** (Scheme 3), these reactions were found to proceed in a stereospecific manner. Furthermore, as for the linkage groups between the alkene and the ynone, the malonate **1o** gave a complicated mixture,[12] while the desired reaction proceeded well with ether **1n**[13] (Scheme 2).



[a] *E*:*Z* ratio of **1m** = 65:35. [b] Ratio between **2m** and its epimer (*epi*-**2m**).
[c] Yield of hydrazone **2n'** derived from **2n**.

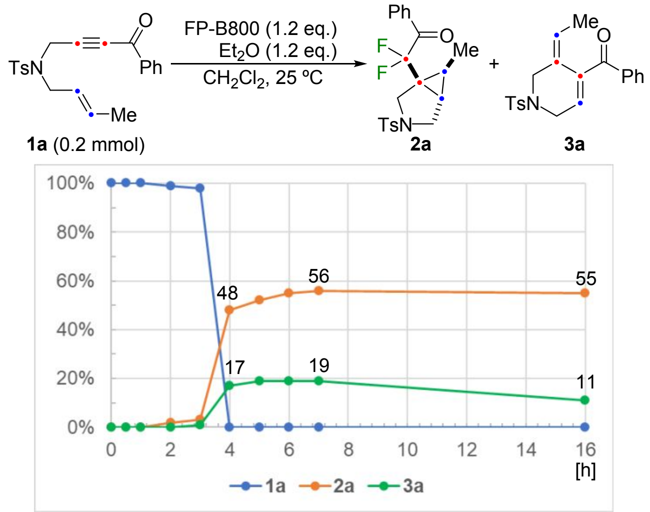
Scheme 2. Scope of synthesis of *gem*-difluorinated products.



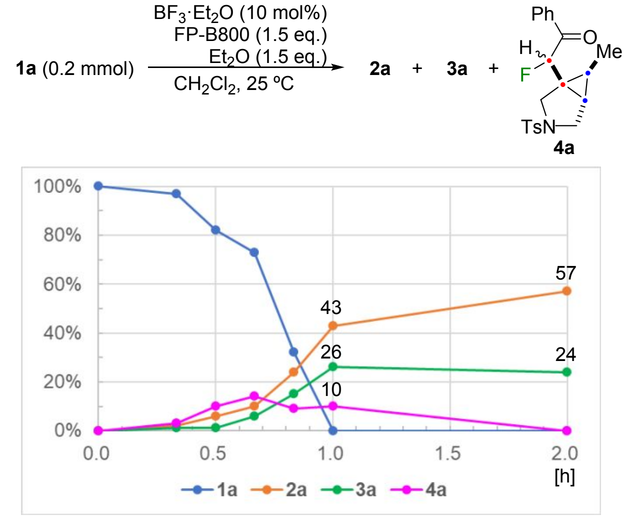
Scheme 3. Reaction of *Z*-**1a**.

To understand the reaction mechanism, the time course of the cycloisomerization of **1a** was investigated (Scheme 4a). Until 3 h after the treatment of 1a with FP-B800 (1.2 eq.) in the presence of Et_2O (1.2 eq.) in CH_2Cl_2, little formation of products (**2a** < 3%, **3a** < 1%) or consumption of **1a** (< 2%) was observed. However, in 4 h, **1a** disappears completely to afford the desired **2a** and side product **3a** in 48% and 17% yields, respectively. Furthermore, in 7 h, the yield of **2a** reached 56%, close to the yield under the optimized conditions (Table 1). Thus, since the induction phase was observed in the early stage of the reaction, it was assumed that the hydrolysis of FP-B800 occurred during this period.

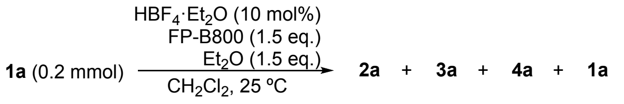
a) Time course of cycloisomerization of **1a** with FP-B800



b) Time course of cycloisomerization of **1a** with FP-B800 and BF_3



c) HBF_4-catalyzed cycloisomerization of **1a** with FP-B800



	2a	3a	4a	1a
1 h	27%	13%	11%	27%
2 h	32%	26%	0%	0%

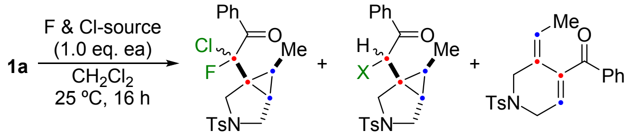
Scheme 4. Control experiments.

We then conducted the similar experiments using HBF_4 and BF_3, which would be produced after hydrolysis of FP-B800 and nucleophilic fluorination by BF_4^- (Schemes 1b and 1c), respectively (Schemes 4b and 4c). In the presence of $BF_3{\cdot}Et_2O$ (10 mol%), within 20 min after the exposure of **1a** with FP-B800 (1.5 eq.) and Et_2O (1.5 eq.) in CH_2Cl_2, not only **2a** (2%) and **3a** (1%) but also monofluorinated product **4a** was detected (Scheme 4b). In 1 h, **1a** was completely disappeared and the yields of **2a** and **3a** increase to 43% and 26%, respectively. During this period, the yields of **4a** stayed between 3-14%. In 2 h, although the yield of **3a** did not increase (24%), the yield of **2a** increased to 57%, and **4a** was completely disappeared. It should be mentioned that **4a** was not converted to **2a** by treatment with FP-B800, regardless of the addition of $BF_3{\cdot}Et_2O$. Hence, the enolate anion, which undergoes protonation to form **4a**, would be an intermediate of **2a**.

On the other hand, when $HBF_4{\cdot}Et_2O$ (10 mol%) was used instead of $BF_3{\cdot}Et_2O$, the reaction was not complete in 1 h (Scheme 4c). In addition, in 2 h, the yield of **2a** was only 32%, even though **1a** and **4a** were completely consumed. Since $BF_3{\cdot}Et_2O$ showed the results close to that under optimum conditions, it is suggested that BF_3 acts as the main acid catalyst after the induction stage, although HBF_4 would be involved in the initial stage.

Based on these results, the formation mechanism of *gem*-difluorinated bicyclo[3.1.0]hexane **2** was proposed as follows (Scheme 1b). First, HBF_4 would be generated by hydrolysis of FP-B800 with trace amounts of water in the reaction system, and then activates the carbonyl group of 7-en-2-yn-1-ones **1** to form a common intermediate **INT-A** with cyclic diene **3**. Next, nucleophilic fluorination by BF_4^- as the counterion would form an enol intermediate **INT-B** (A = H). Finally, **INT-B** would undergo electrophilic fluorination with *N*-fluoropyridinium to give the desired products **2**. Note that, after the nucleophilic fluorination would produce BF_3, BF_3 would be involved prior to HBF_4 in the activation of 7-en-2-yn-1-ones **1** and proceed the series of processes involving **INT-A** and **INT-B** (A = BF_3) together with FP-B800.

Subsequently, considering the previous method for the synthesis of monochlorinated bicyclo[3.1.0]hexanes (Scheme 1b, path B),[5b] the construction of *gem*-chlorofluorinated product **5** was attempted using alkylaluminum chloride and an electrophilic fluorinating agent (Scheme 5). It was expected that the chlorinated aluminum enolate like **INT-B** formed from 7-en-2-yn-1-one **1** and alkylaluminum chloride would react with an electrophilic fluorinating agent to give the desired **5**. However, **1a** reacted with $EtAlCl_2$ (1.0 eq.) in the



	5a	6a or 4a		3a
$EtAlCl_2$, F-source[a]	< 3%[b]	**6a** (X = Cl)	23-71%	0%
Bu_4NBF_4, NCS[c]	61%[d]	**4a** (X = F)	0%	11%
Bu_4NBF_4[e,f]	0%	**4a** (X = F)	13%[b]	0%

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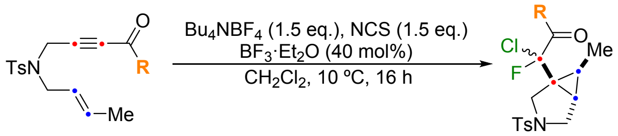
[a] F-source = FP-B800, Selectfluor, NFSI. [b] Diastereomeric ratio (DR) was not determined. [c] Additive: $BF_3{\cdot}Et_2O$ (40 mol%), temp.: 10 °C. [d] DR = 1.5:1. [e] Additive: $BF_3{\cdot}Et_2O$ (20 mol%), time: 48 h. [f] Recovery of **1a**: 62%.

Scheme 5. Extension to synthesis of *gem*-chlorofluorinated product.

presence of FP-B800 (1.0 eq.) in CH_2Cl_2 at 25 ºC for 16 h to form only monochlorinated product **6a** in 29% yield. Also, after **1a** was treated with $EtAlCl_2$ for 2 h to generate the chlorinated aluminum enolate, a fluorinating agent such as FP-B800, Selectfluor or NSFI was added, but the monochlorinated product **6a** was obtained as the main product in 23-71% regardless of the addition of Et_2O (**5a** < 3%, Table S2 in ESI† for more information).

Therefore, we investigated a method of capturing fluorinated enolates like **INT-B** (Scheme 1b, path B) generated by nucleophilic fluorination with an electrophilic chlorinating agent (Scheme 5 and Table S2 in ESI†). As a result, the reaction of **1a** with Bu_4NBF_4 (1.5 eq.) and NCS (*N*-Chlorosuccinimide, 1.5 eq.) in the presence of $BF_3{\cdot}Et_2O$ (40 mol%) in CH_2Cl_2 at 10 ºC for 16 h afforded the desired product **6a** in 61% yield (DR = 1.5:1). Note that, since monofluorinated product **4a** was obtained in the similar reaction without NCS, we believe that fluorinated enolates **INT-B** (A = BF_3) would be also involved in this reaction. This method is also applicable to a variety of 7-en-2-yn-1-ones **1** to give the corresponding *gem*-chlorofluorinated products **5** in 47-68% yields (Scheme 6). As for diastereoselectivity, **5f** showed a relatively high diastereomeric ratio (DR = 7.0:1), although the other products showed comparable results to **5a** (DR = 1.1:1 to 1.7:1). This would be likely because *ortho*-Br-substituent prevents the enolate and the 2-Br-phenyl group of **INT-B** from aligning in the coplanar plane, thereby blocking one side of the enolate in the reaction with NCS.



1 (0.2 mmol)

5

5a (R = Ph): 61% (1.5:1)^a
5b (R = 4-$OMeC_6H_4$): 68% (1.2:1)^a
5c (R = 4-MeC_6H_4): 61% (1.3:1)^a
5d (R = 4-BrC_6H_4): 47% (1.1:1)^a
5f (R = 2-BrC_6H_4): 56% (7.0:1)^a
5i (R = Et): 59% (1.7:1)^a

^{a} The ratios in parentheses represent diastereomeric ratios.

Scheme 6. Scope of synthesis of *gem*-chlorofluorinated products.

Conclusions

In summary, we have developed the metal-free synthesis of *gem*-difluorinated and *gem*-chlorofluorinated bicyclo[3.1.0]hexanes via cycloisomerization of 7-en-2-yn-1-ones using electrophilic halogenating agents. In the synthesis of *gem*-difluorinated products, we proposed that BF_3 generated after nucleophilic fluorination by BF_4^- would mainly activate the carbonyl groups to promote the cycloisomerization of 7-en-2-yn-1-ones, although HBF_4 generated by hydrolysis of FP-B800 would be involved in the initial stage. Moreover, the proposed mechanism led to an extension to the synthesis of *gem*-chlorofluorinated products. Since the systematic studies on the reaction of enynes by activation of carbonyl groups conjugated to alkynes are lacking and there is no known method that can introduce two halogen atoms at once in cycloisomerization of enynes, these findings would open new possibilities for the cycloisomerization of enynes.

Experimental

Representative procedure for synthesis of product 2. To a solution of 7-en-2-yn-1-one **1a** (73.5 mg, 0.2 mmol) and Et_2O (31.1 µL, 0.3 mmol) in CH_2Cl_2 (1 mL) was added FP-B800 (76.1 mg, 0.3 mmol) at room temperature. After being stirred at 40 ºC for 16 h, the reaction mixture was quenched with H_2O and exacted with AcOEt. The organic layer was dried over $MgSO_4$ and concentrated in vacuo to dryness. The residue was purified by medium pressure liquid chromatography (hexane:AcOEt = 80:20) to afford product **2a** (50.4 mg, 62%) as a yellow oil.

Representative procedure for synthesis of product 5. To a solution of 7-en-2-yn-1-one **1a** (73.5 mg, 0.2 mmol) and Bu_4NBF_4 (98.8 mg, 0.3 mmol) in CH_2Cl_2 (2 mL) was added NCS (40.1 mg, 0.3 mmol) and $BF_3{\cdot}Et_2O$ (10.0 µL, 20 µmol) at 0 ºC. After being stirred at 10 ºC for 16 h, the reaction mixture was quenched with sat. $NaHCO_3$ and exacted with AcOEt. The organic layer was dried over $MgSO_4$ and concentrated in vacuo to dryness. The residue was purified by MPLC (hexane:AcOEt = 90:10) to afford product **5a** (51.1 mg, 61%, diastereomeric ratio = 1.5:1) as a yellow oil.

Author Contributions

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

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported partly by JST CREST (No. JPMJCR19R2) and Shiono Wellness Foundation.

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12 Similar results were given in the case of a substrate with the Ts group of **1a** replaced by an ethoxycarbonyl group.

13 The yield of **2n** was calculated based on hydrazone **2n'** derived from **2n** due to its volatility.

Data availability

The data supporting this article have been included as part of ESI.