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EFFICIENT SYNTHESIS OF INDOLES AND BENZO[*b*]FURANS VIA [3,3]-SIGMATROPIC REARRANGEMENT OF *N*-TRIFLUOROACETYL ENEHYDRAZINES AND ENEHYDROXYLAMINES

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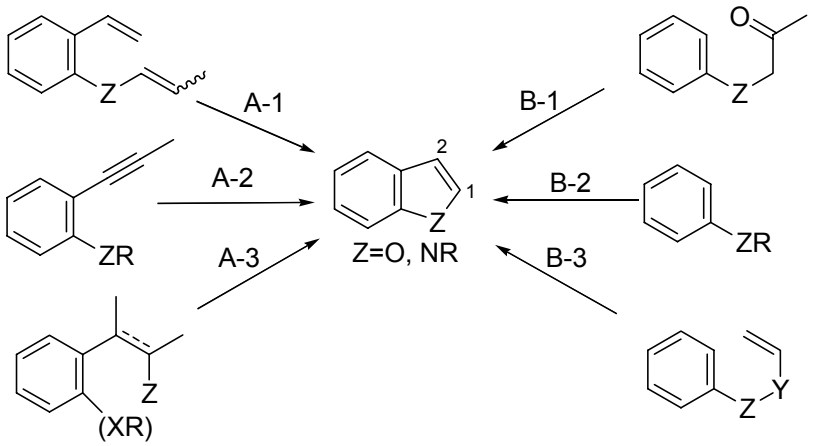
Abstract – This review summarizes an efficient synthesis of benzo[*b*]furans and indoles via [3,3]-sigmatropic rearrangements of *N*-trifluoroacetyl enehydroxylamines and enehydrazines, which were triggered by acylation of oxime ethers and hydrazines. TFAA and TFAT-DMAP have been proved to be the best reagent to induce [3,3]-sigmatropic rearrangement for the synthesis of benzo[*b*]furans and indoles. This method was successfully applied to the short synthesis of natural products.

INTRODUCTION

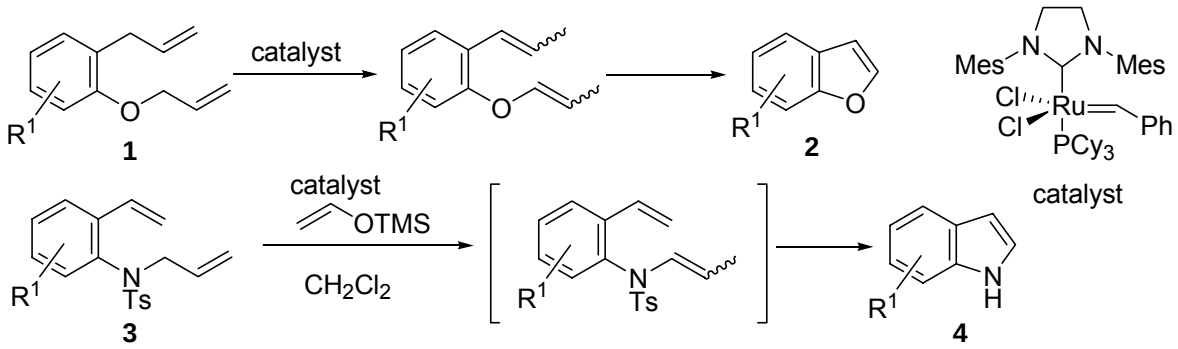
Indole and benzo[*b*]furan ring systems are the core structural elements in natural and synthetic organic compounds possessing a wide diversity of important biological activities.[1] Therefore, their synthesis has received considerable attention and a lot of synthetic methods have been developed up to today. Among known synthetic methods of indoles and benzo[*b*]furans, the main common synthetic methods based on the construction of pyrrole and furan rings from various arene derivatives can be summarized as shown in Scheme 1.[2,3] A survey of the literature shows that these methods can be basically generalized into the two categories. (A) The aniline, phenol and haloarene derivatives bearing a substituent at ortho position on the benzene ring are used as substrates (A-1, A-2, and A-3). (B) In the case of B-1, B-2, and B-3, indoles and benzo[*b*]furans are prepared from the aniline and phenol derivatives carrying the substituent not on *ortho* position of benzene ring but on Z group (Scheme 1).

(A-1) Ring closure by formation of the C_1-C_2 bond.

Substituted benzo[*b*]furans **2** have been synthesized from their corresponding substituted 1-allyl-2-allyloxybenzenes **1** using ruthenium-mediated *C*- and *O*-allyl isomerization followed by ring-closing metathesis (RCM).[4] Similarly, *N*-allylanilines **3** were derived into indoles **4** (Scheme 2).[5]



Scheme 1



Scheme 2

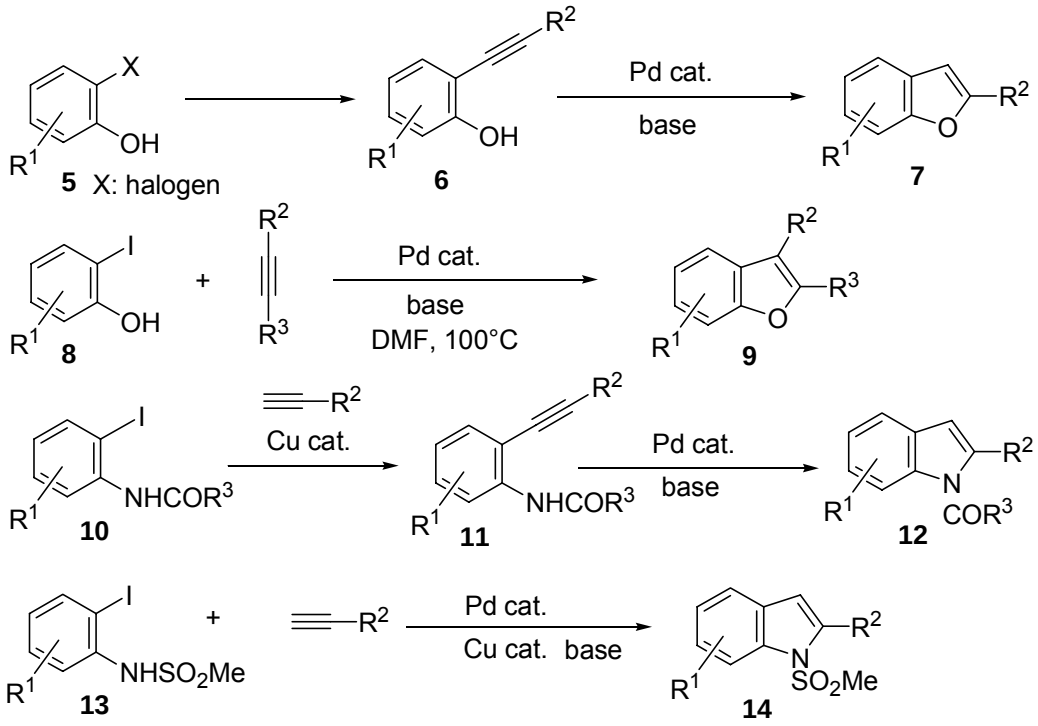
(A-2) Ring closure by formation of the Z-C_1 bond (Larock Heteroannulation)[6]

The Larock heteroannulation is an extremely attractive method for the formation of complex indoles and benzo[*b*]furans in a single operation. Heating of *o*-alkynylphenols **6**, which are available from *o*-halogenophenols **5** and alkynes, with catalysts yields benzo[*b*]furans **7**.[7] Both coupling and ring closure can be achieved in one step (**8**→**9**).[8] *o*-Amidophenylalkynes **11** are able to cyclize to indoles **12** using palladium-catalyst. The alkynes can be prepared by copper-catalyzed coupling of terminal alkynes with iodoacetanilide **10**.[9-12] The use of terminal alkynes **11** and *N*-methanesulfonyl-2-iodoanilines **13** in the presence of both copper and palladium catalysts permits a one-pot synthesis of 2-substituted indoles **14**. However, the disadvantage of this reaction is to use toxic transition metals (Scheme 3).

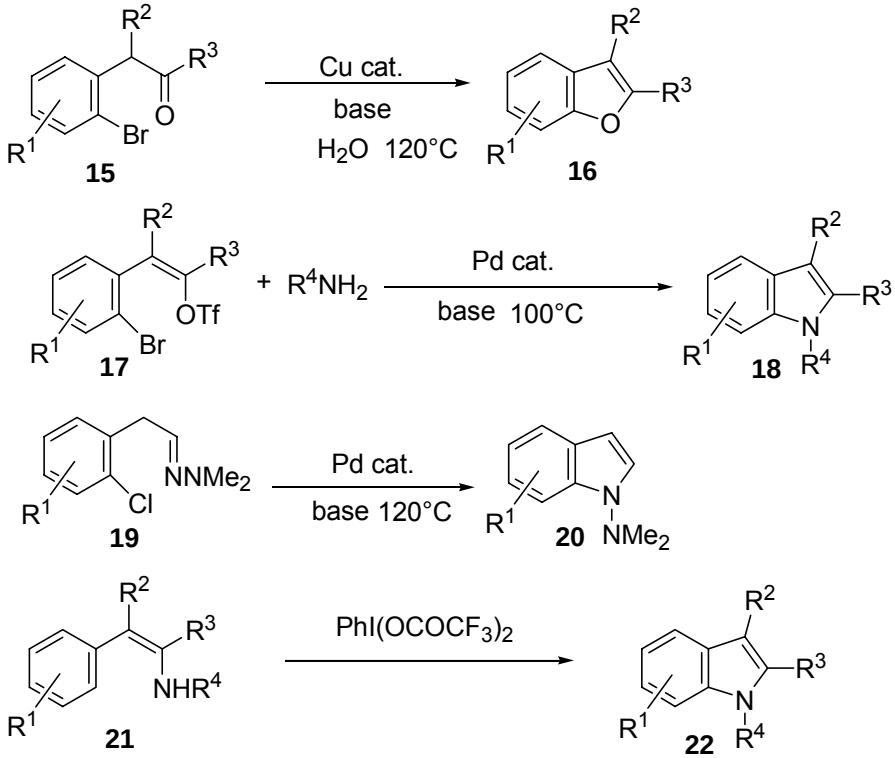
(A-3) Ring closure by formation of the Z-Ar bond

The Copper-catalyzed transformation of readily available ketone derivatives **15** into the corresponding

benzo[*b*]furan **16** were reported.[13]



Scheme 3



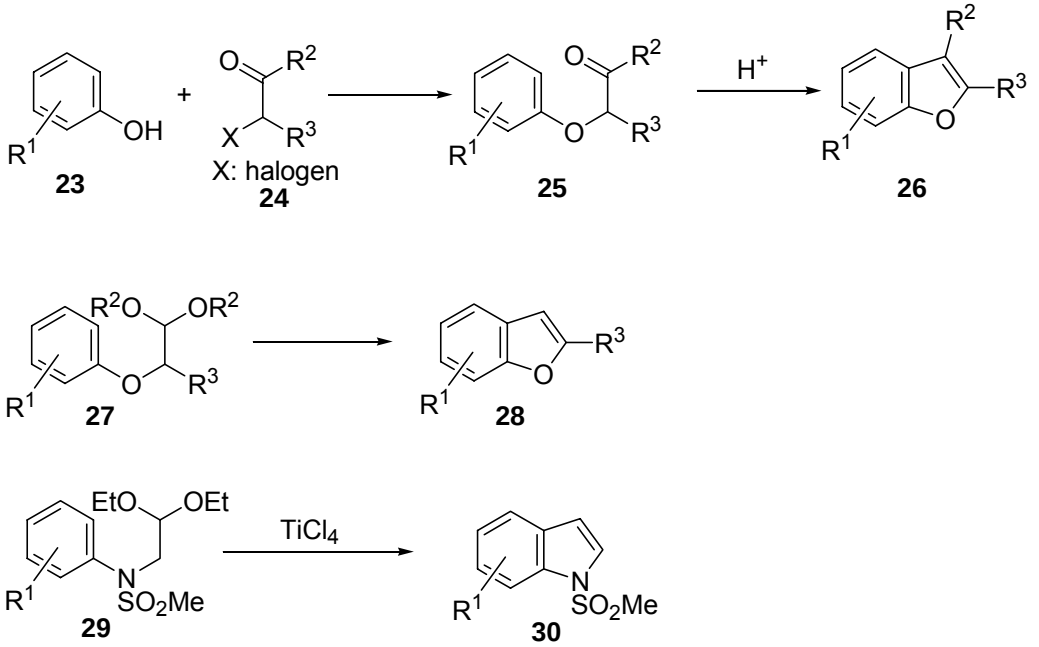
Scheme 4

The sustainable protocol uses water as the solvent without organic co-solvents. Recently, the first extensions of palladium-catalyzed *C*-*N* bond forming reaction to the direct formation of indole rings **18** by intramolecular *N*-arylation were reported.[14] The synthesis of *N*-aminoindoles **20** *via* palladium-catalyzed cyclization of *o*-chloroarylacetaldehyde *N*,*N*-dimethylhydrazones **19** were

developed.[6b,15] A variety of *N*-arylated and *N*-alkylated indoles **22** were synthesized by way of PIFA-mediated intramolecular cyclization.[16] This novel method allows for the construction of an indole skeleton by joining the *N*-atom on the side chain to the benzene ring carrying no halogen at the last synthetic step (Scheme 4).

(B-1) Ring closure by formation of Ar-C_2 bond

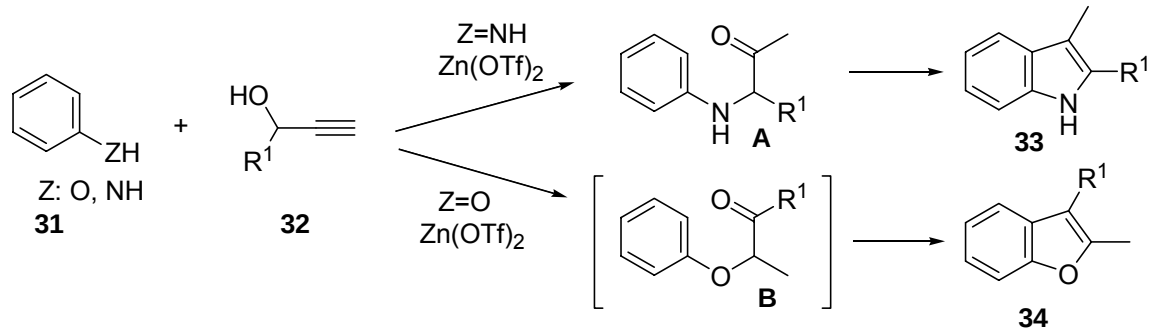
The acid-catalyzed cyclization of α-aryloxymethylcarbonyl and α-arylaminomethylcarbonyl compounds has proved to be of great value for the synthesis of a wide variety of benzo[*b*]furans and indoles.[17,18] Phenols **23** react with α-halogenoketones **24** to give aryloxy compounds **25** which are cyclized in the presence of acid to give benzo[*b*]furans **26**. Acetals **27** of α-aryloxyaldehydes which are easily available from α-halogenoacetals and phenols, are often used as the substrate of benzo[*b*]furan synthesis. Several groups have explored the use of the diethyl acetal of bromoacetaldehyde as a potential indole precursor. The cyclization of aniline derivatives **29** of aniline occurs under acidic conditions to give indoles **30** (Scheme 5).



Scheme 5

(B-2) Ring closure by two bond formations between Z-C_1 and Ar-C_2

$Zn(OTf)_2$ catalyzes reaction of propargyl alcohols **32** with PhZH (Z=O, NH) **31** in hot toluene (100 °C) to give indoles **33** and benzo[*b*]furans **34**.[18] The transformations proceeded through **A** and **B** as reaction intermediates. The 1, 2-nitrogen shift in the formation of indole **33** takes place and its mechanism has been elucidated (Scheme 6).

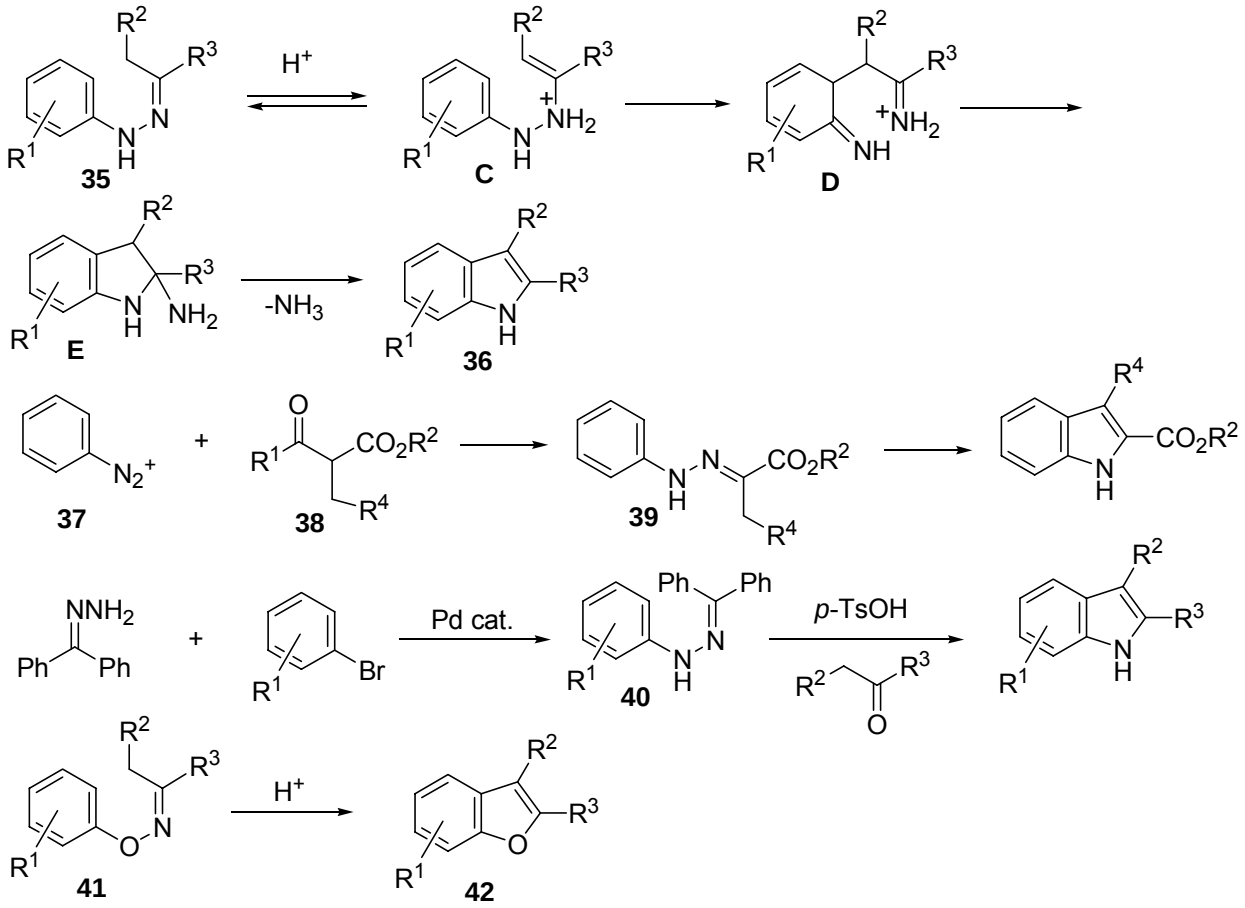


Scheme 6

(B-3) Ring closure by two bond formations between Z-C_1 and Ar-C_2

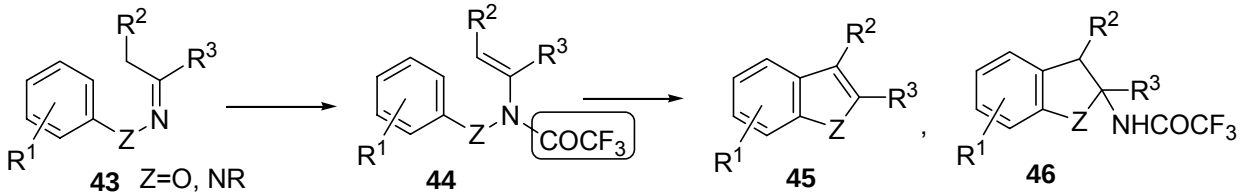
The Fischer indole synthesis[20] is probably the most versatile method for making indoles; certainly it is the most widely applied. As with the Fischer indole synthesis, an important synthetic advantage is that the initial benzene ring substrate does not need to be *ortho*-disubstituted. The reaction involves acid-catalyzed conversion of an *N*-arylhydrazone **35** to an indole **36**. The mechanism is thought to involve a [3,3]-sigmatropic rearrangement of an enehydrazine tautomer **C** to a imine **D**. Cyclization and aromatization with loss of ammonia provides the indole **36**. The *N*-arylhydrazones **35** are frequently prepared *via* condensation of an arylhydrazines with ketones. Alternatively, aryldiazonium salts **37** can be converted directly to hydrazones *via* the Japp-Klingemann reaction. This reaction involves treatment of the aryl diazonium salt **37** with an active methylene or methine compounds **38** under acidic or basic conditions to form an azo derivative which is converted to the hydrazone **39**. Highly efficient and metal-catalyzed methods to access arylhydrazone intermediates **40** useful in the Fischer cyclization have emerged over the last 5 years. Furthermore, *O*-aryloximes **41** give benzo[*b*]furans **42**. [21] This reaction resembles quite closely the Fischer indole synthesis (Scheme 7).

Despite recently developed synthetic methodologies of indoles and benzo[*b*]furans, such as metal-catalyzed transformations, the venerable Fischer indole synthesis has maintained its prominent role as a route to indoles and benzo[*b*]furans. However, the synthetic methods of benzo[*b*]furans and indoles utilizing [3,3]-sigmatropic rearrangement exhibit some disadvantages as follows: (i) acid catalysts such as H_2SO_4 and HCl, and high temperature are generally required for the successful reaction, (ii) these harsh conditions cannot be applied to acid-sensitive substrates, and (iii) in most cases, the desired benzo[*b*]furans and indoles were obtained in only moderate yields. From the background described above, we recently found that the [3,3]-sigmatropic rearrangement and subsequent cyclization of *N*-trifluoroacetyl enehydrazines[22] and *N*-trifluoroacetyl enehydroxylamines **44**[23] proceed smoothly under mild conditions to give the indoles and benzo[*b*]furans **45** and **46** (Scheme 8). Furthermore, we have also applied a newly found efficient procedure to short synthesis of natural products.



Scheme 7

Herein, we summarize our results on the synthesis of benzo[*b*]furans and indoles using [3,3]-sigmatropic rearrangement of enehydrazines and enehydroxylamines **44**.



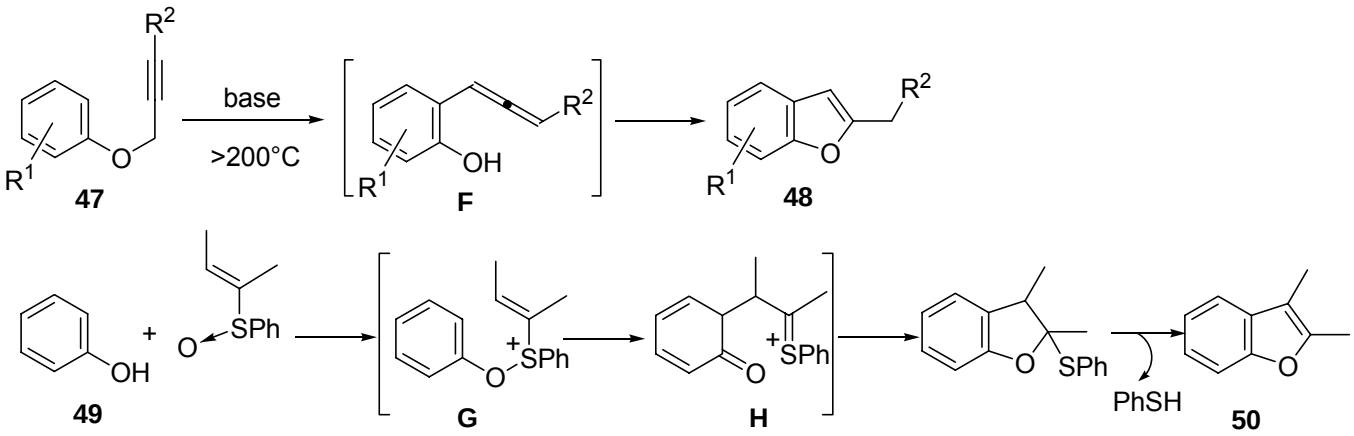
Scheme 8

BENZO[*b*]FURAN SYNTHESIS[23]

[3,3]-Sigmatropic rearrangement of *N*-trifluoroacetyl enehydroxylamines in situ generated

Sigmatropic rearrangement is eco-friendly attractive organic synthetic reaction because addition of reagent is hardly necessary. Some synthetic methods for benzo[*b*]furans using [3,3]-sigmatropic rearrangement are known besides Fischer indole synthesis. The Claisen rearrangement of propargylarylethers **47** yields allenes **F**, which in the presence of base cyclize to give benzo[*b*]furans **48**.[2,24] However, high temperature is required for such rearrangement and cyclization. Recently, J. B.

Hendrickson has reported that benzo[*b*]furans **50** were prepared from phenol and vinylsulfoxide **49** *via* [3,3]-sigmatropic rearrangement of sulfoxonium intermediate **G** transiently formed.[25] The disadvantage of this method is to prepare vinylsulfoxide **49** and eliminate thiophenol which has foul smell (Scheme 9).

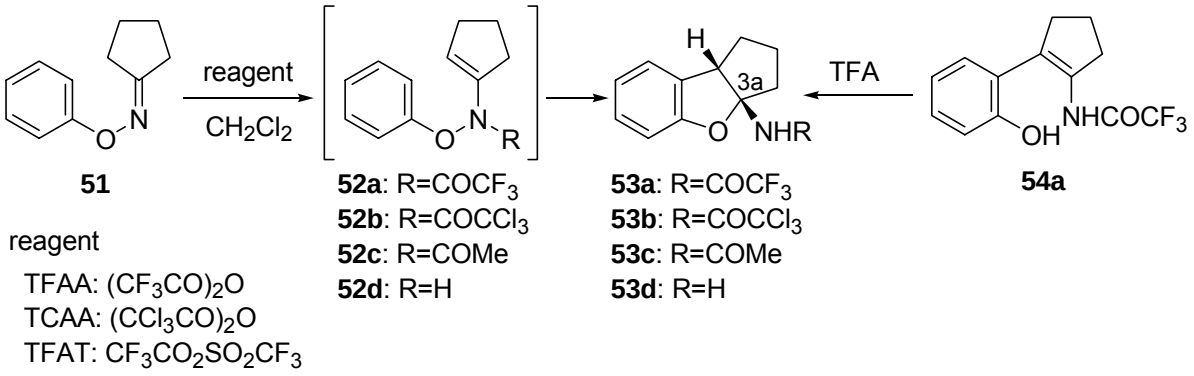


Scheme 9

In order to develop new efficient synthesis of benzo[*b*]furans using [3,3]-sigmatropic rearrangement, we first investigated acetylation of oxime ether **51** (Scheme 10, Table 1). Treatment of oxime ether **51** with trifluoroacetic anhydride (TFAA) (1 eq.) and Et_3N (1.5 eq.) in CH_2Cl_2 at 0 °C gave the rearranged product **54a** in 8% yield along with the unreacted starting material **51** (entry 1).

Upon treatment with trifluoroacetic acid (TFA), the phenol **54a** could be readily converted to dihydrobenzo[*b*]furan **53a.** This result suggests strongly that **54a** could be formed *via* acylation of oxime ether **51** with TFAA followed by [3,3]-sigmatropic rearrangement of the resulting *N*-trifluoroacetyl enehydroxylamine **52a**. Additionally, TFA was found to be essential for the cyclization reaction of rearranged product **54a** as a possible intermediate. Therefore, we expected that reaction of oxime ether **51** with TFAA in the absence of a base would proceed to afford the desired dihydrobenzo[*b*]furan **53a**. In fact, trifluoroacetylation, [3,3]-sigmatropic rearrangement, and cyclization of **51** proceeded smoothly in the presence of TFAA (1 eq.) without a base to afford the corresponding *cis*-dihydrobenzo[*b*]furan **53a** in excellent yield at even below room temperature (entry 2). In the reaction at room temperature, the desired **53a** was formed after being stirred for 1 h (entry 3). This is the first example of the formation of dihydrobenzo[*b*]furan **53a** which was formed only by acylation conditions.

In order to check the possibility that TFA itself might facilitate the [3,3]-sigmatropic rearrangement by protonation at the nitrogen atom, we examined the reaction of oxime ether **51** with only TFA and found that 3a-aminodihydrobenzo[*b*]furan **53d** was isolated in 16% yield (entry 4). Therefore, it is apparent that acylation reaction of **51** for the formation of acyl enehydroxylamine **52** is the main and crucial step for [3,3]-sigmatropic rearrangement.



Scheme 10

Table 1. Reaction of oxime ether **51** with acid anhydride.

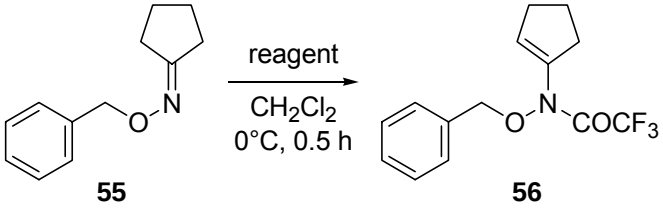
entry	reagent (eq.)	R	*T* (°C)	*t* (h)	Yield (%) **53a**
1	TFAA (1), Et_3N (1.5)	$COCF_3$	0	4	---[a]
2	TFAA (1)	$COCF_3$	0	3	99
3	TFAA (1)	$COCF_3$	rt	1	99
4	TFA (1)	H	rt	20	---[b]
5	TCAA (1)	$COCCl_3$	40	5	---[c]
6	Ac_2O (1)	COMe	40	8	---[d]
7	TFAT (1)	$COCF_3$	0	2	58
8	TFAT (2), Et_3N (1)	$COCF_3$	0	0.5	80
9	TFAT (2), DMAP(1)	$COCF_3$	0	0.5	89

a) **54a** was obtained in 8% yield and **51** was recovered.
b) **53d** was obtained in 16% yield.
c) **53b** was obtained in 94% yield.
d) **51** was recovered.

Next, we investigated systematically the acylation by changing four types of acylating reagents. When trichloroacetic anhydride (TCAA) was used as an acylating reagent, the reaction proceeded in refluxing CH_2Cl_2 to give dihydrobenzo[*b*]furan **53b** in good yield (entry 5). In contrast to TFAA and TCAA, Ac_2O did not give satisfactory results and the starting material **51** was completely recovered (entry 6). The reaction of **51** with trifluoroacetyl triflate (TFAT),[26] which is a stronger acylating reagent than TFAA, gave **53a** in lower 58% yield (entry 7). Reaction of **51** with TFAT (2 eq.) and Et_3N (1 eq.) proceeded smoothly to give the desired dihydrobenzo[*b*]furan **53a** in 80% yield (entry 8). Reaction with a combination of TFAT (2 eq.) and DMAP (1 eq.) gave the desired dihydrobenzo[*b*]furan **53a** in 89% yield (entry 9). Thus, our reaction involving acylation, [3,3]-sigmatropic rearrangement, and cyclization was found to be accelerated when oxime ether was acylated with a stronger reagent bearing an electron-withdrawing group such as the trifluoroacetyl group. We choose TFAA in the formation of dihydrobenzo[*b*]furan.

In order to establish intermediary *N*-trifluoroacetyl enehydroxylamine **52a** which would be possibly formed by acylating oxime ether **51**, we examined acylation of *O*-benzyl oxime ether **55** (Scheme 11,

Table 2). Oxime ether **55** was subjected to acylation with TFAA or TFAT in the presence of DMAP. The product was expected *N*-trifluoroacetyl enehydroxylamine **56** which was obtained in moderate to good yield (entries 1 and 2). Thus, formation of the intermediate **52a** is proposed in our reaction though the isolation was not achieved yet.



55 **56**

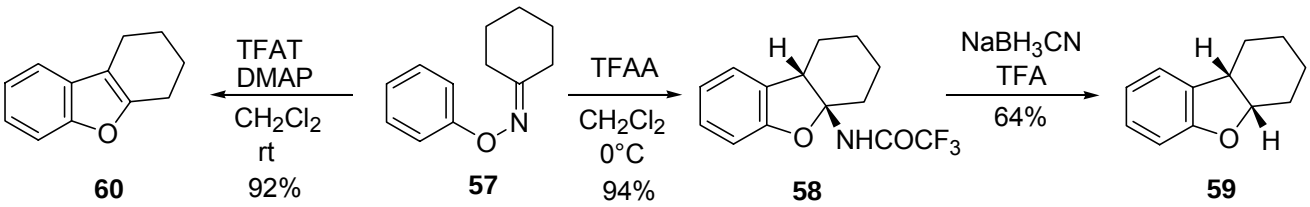
Table 2. Reaction of oxime ether **55** with TFAA or TFAT-DMAP

entry	reagent (eq.)	base (eq.)	yield (%)
1	TFAA (1)	----	81
2	TFAT (2)	DMAP (1)	63

Scheme 11

We next investigated the reaction of oxime ether **57** derived from cyclohexanone (Scheme 12). When the reaction was carried out in dichloromethane with TFAA at 0 °C, the desired dihydrobenzo[*b*]furan **58** was obtained as the sole product. On the contrary, treatment of **57** with TFAT and DMAP produced exclusively benzo[*b*]furan **60** in 92% yield. It is worthy to note that the selective synthesis of either dihydrobenzo[*b*]furan **58** or benzo[*b*]furans **60** was achieved only by changing reaction conditions such as the TFAA or TFAT-DMAP system.

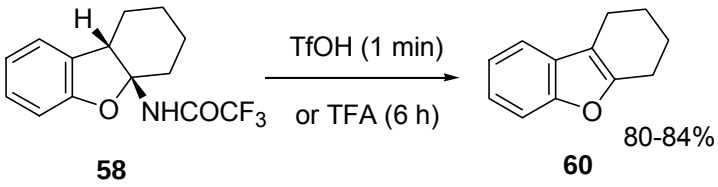
The reductive deamination of **58** with sodium cyanoborohydride in TFA proceeded to give the desired 2,3-dihydrobenzo[*b*]furan **59** in moderate yield.



60 **57** **58** **59**

Scheme 12

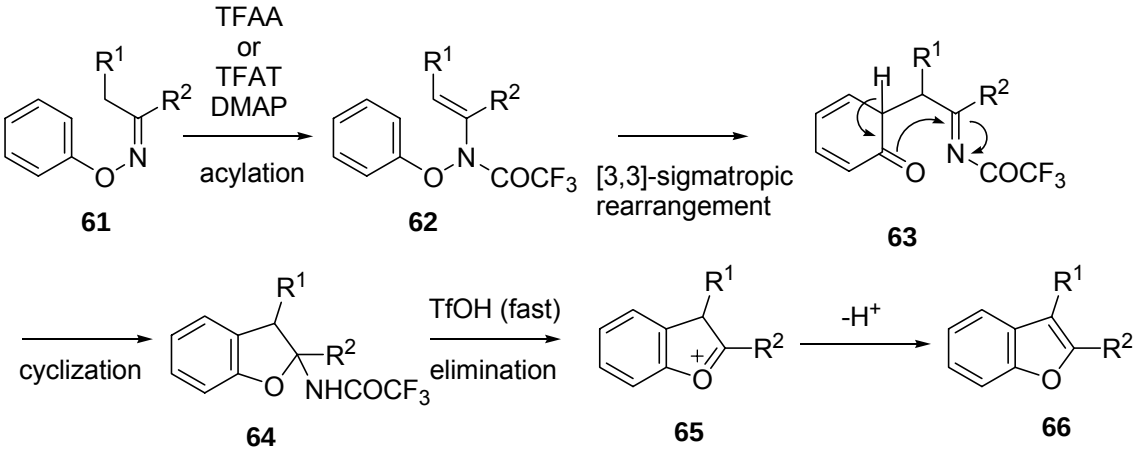
In order to propose the reaction pathway, we investigated the conversion of dihydrobenzo[*b*]furan **58** to benzo[*b*]furan **60** (Scheme 13). Treatment of dihydrobenzo[*b*]furan **58** with trifluoromethanesulfonic acid (TfOH) gave benzo[*b*]furan **60** effectively as a result of elimination of the trifluoroacetamido group while reaction with TFA required longer reaction. In the reaction with TFAT, it was clearly indicated that dihydrobenzo[*b*]furan **58** was converted to benzo[*b*]furan **60** by action of TfOH which was unavoidably generated as byproduct in the trifluoroacetylation of oxime ether **57**.



58 **60**

Scheme 13

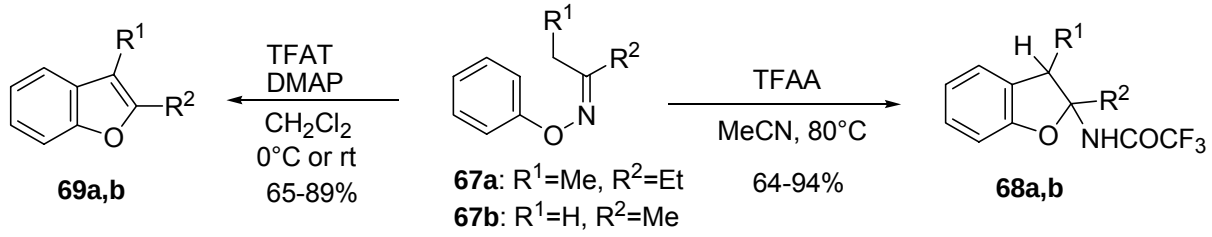
From the above results, we propose plausible reaction pathways to dihydrobenzo[*b*]furan **58** and benzo[*b*]furan **60** as follows (Scheme 14). First, acylation on the nitrogen atom of oxime ether **61** leads to the formation of *N*-trifluoroacetyl enehydroxylamine **62** and then the [3,3]-sigmatropic rearrangement smoothly follows to form acylimine **63**. Formation of dihydrobenzo[*b*]furan **64** would proceed by intramolecular cyclization of **63**. When TFAT was used as an acylating agent, benzo[*b*]furan **66** was formed through oxonium ion **65** which was generated by elimination of the trifluoroacetamido group in the presence of TfOH. Overall pathway would be very similar to that of Fischer indolization which involves analogues three step key reactions of hydrazones. However, it is generally difficult to isolate dihydrobenzo[*b*]furans under Fischer indolization conditions. To the best of our knowledge, there has been only one paper[21b] pertaining to the isolation of dihydrobenzo[*b*]furans which were synthesized from the oxime ethers bearing α,α´-disubstituted cyclopentane ring.



61 **62** **63** **64** **65** **66**

Scheme 14

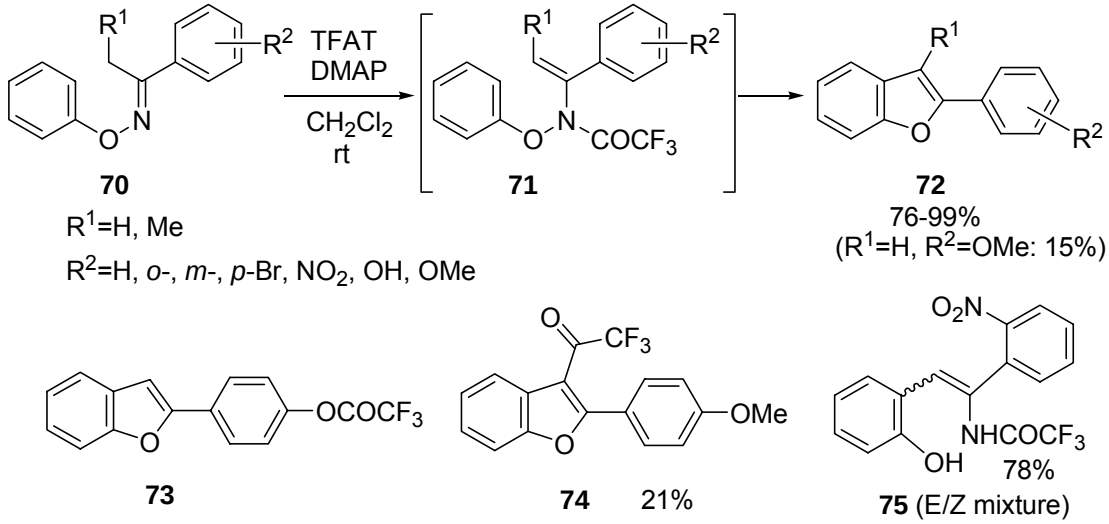
To investigate the scope and limitations of the TFAA or TFAT-DMAP system utilized for benzo[*b*]furan synthesis, we next tried to use a series of acyclic oxime ethers **67a,b** as substrate (Scheme 15). Reaction of oxime ether **67a,b** with TFAA gave dihydrobenzo[*b*]furan **68a,b** in good yield. On the contrary, reaction with a combination of TFAT and DMAP gave exclusively benzo[*b*]furan **69a,b**. These results clearly demonstrate the utility of [3,3]-sigmatropic rearrangement as a novel method for the synthesis of complex benzo[*b*]furans. The remarkable result obtained in the reaction of these oxime ethers prompted us to extend our procedure to the synthesis of various types of 2-arylbenzo[*b*]furans.



Scheme 15

The substituent effect on the benzene ring of the arylimine part; Synthesis of 2-arylbenzo[*b*]furans

Among benzo[*b*]furans, 2-arylbenzo[*b*]furans are inhibitors of cell proliferation and platelet activating factor and some of them show other interesting activities.[27] Thus, we started to investigate the substituent effect of our reaction and its application to the synthesis of 2-arylbenzo[*b*]furans (Scheme 16).



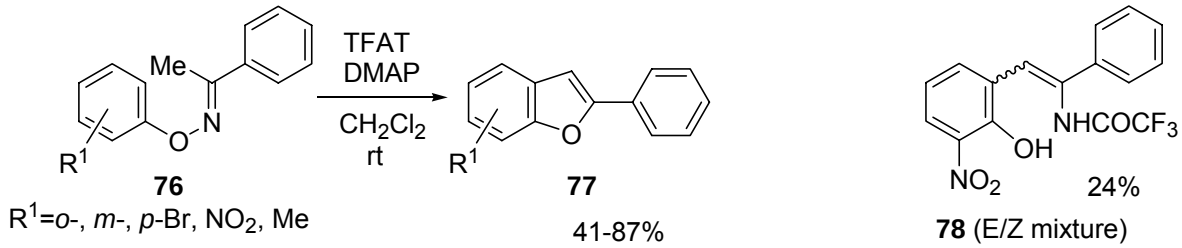
Scheme 16

Treatment of unsubstituted oxime ether **70** with TFAT and DMAP gave quantitatively the desired 2-phenylbenzo[*b*]furan **72**. Similarly, reaction of oxime ethers **70** bearing an electron-withdrawing substituent such as a bromo or nitro group at the *p*-position proceeded smoothly to give 2-arylbenzo[*b*]furan **72** in good yields. To our delight, when oxime ether **70** bearing a free hydroxy group was reacted with TFAT-DMAP, hydroxybenzo[*b*]furan **72** was directly obtained after chromatography using silica gel. We succeeded in the isolation of *p*-trifluoroacetyloxybenzo[*b*]furan **73** by only recrystallization (not chromatography) of the crude product obtained from oxime ether **70**. Unfortunately, reaction of **70** with the *p*-methoxy group afforded the desired benzo[*b*]furan **72** (15%) along with 3-trifluoroacetylbenzo[*b*]furan **74** (21%). Substituents at the *m*-position had no marked influence on the reaction giving the expected benzo[*b*]furans **72** in excellent yields.

The next substrate of choice was oxime ethers **70** with an *ortho*-substituted phenyl group. *o*-Bromo, *o*-hydroxy, and *o*-methoxy-oxime ethers **70** were employed under the same conditions to give the desired benzo[*b*]furans **72** in good yields. When *o*-nitro oxime ether **70** was treated with TFAT-DMAP, benzo[*b*]furan **72** was not obtained but rearranged product **75** was isolated.

The effects of substituents on the phenoxy ring; Synthesis of functionalized 2-phenylbenzo[*b*]furans

In order to explore wide generality of our benzo[*b*]furan synthesis, we have newly investigated the substituent effects in [3,3]-sigmatropic rearrangement of *O*-aryl enehydroxylamines which was generated *in situ* by acylation of substituted oxime ethers **76** (Scheme 17). Treatment of oxime ethers **76** carrying *p*-bromo, *p*-nitro, and *p*-methyl groups with TFAT-DMAP afforded 5-functionalized 2-phenylbenzo[*b*]furans **77** in good to excellent yields. A similar trend was observed in the reaction of oxime ethers **76** with the *o*-substituted group such as bromo, nitro, and methyl groups. *o*-Bromo and *o*-methyl oxime ethers **76** gave the corresponding 7-substituted 2-phenylbenzo[*b*]furans **77** in good yields. Reaction of oxime ether **76** carrying the *o*-nitro group proceeded to give a separable mixture of 7-substituted 2-phenylbenzo[*b*]furans **77** and rearranged product **78**. Generally, the long reaction time is required for the reaction of oxime ether carrying NO_2 group. The *m*-substituted oxime ethers gave two types of regioisomeric benzo[*b*]furans with low selectivity in all cases.



76
R^1=*o*-, *m*-, *p*-Br, NO_2, Me

77
41-87%

78 (E/Z mixture)

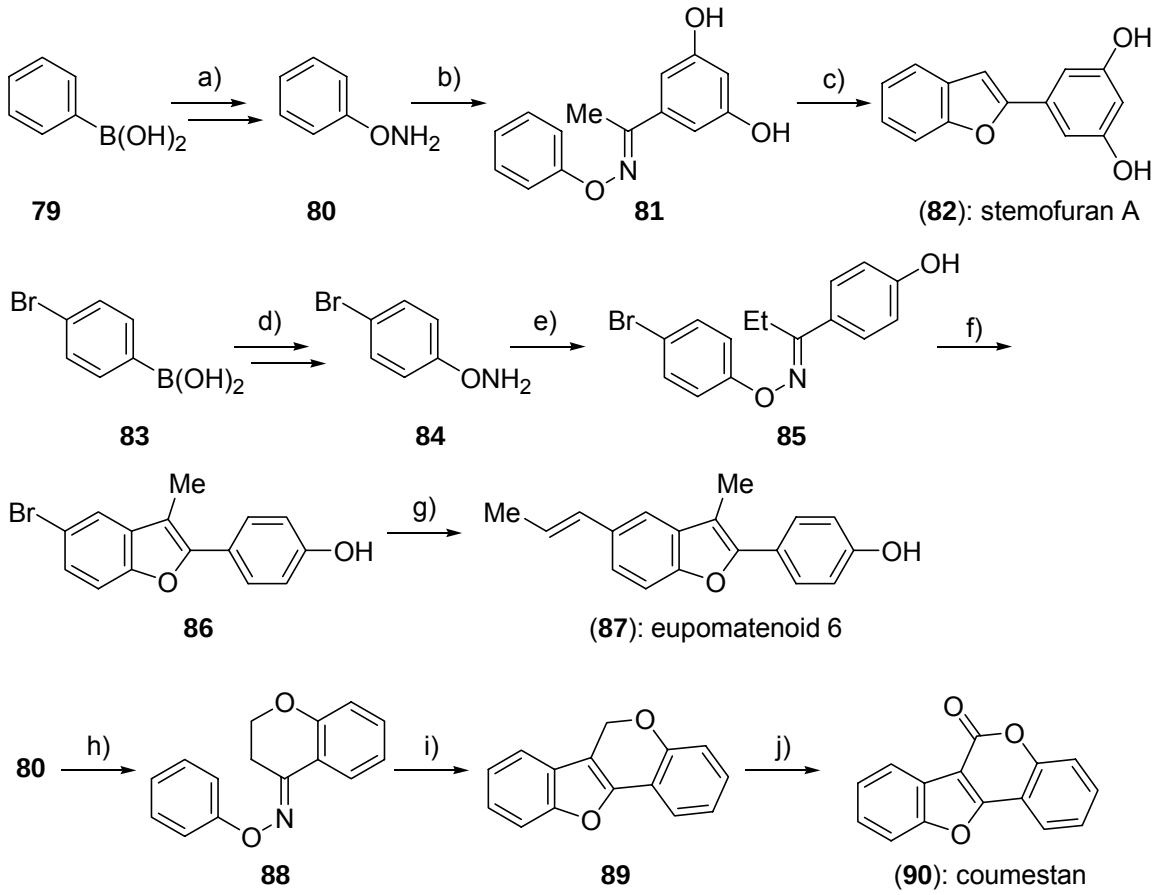
Scheme 17

Effective and short syntheses of stemofuran A, eupomatenoid 6 and coumestan

As mentioned above, our novel synthetic method for benzo[*b*]furans is efficient and practical because protection of the phenolic hydroxy groups is not required in the synthesis of hydroxylated 2-arylbenzo[*b*]furans. This finding prompts us to explore a new efficient procedure for the synthesis of biologically active natural benzo[*b*]furans. Thus, we started to synthesize natural and biologicaliy active benzo[*b*]furan products such as stemofuran A (**82**),[28] eupomatenoid 6 (**87**),[29] and coumestan (**90**),[30] the latter of which does not have a hydroxy group. Our short synthesis of these products has been accomplished without protection of the phenolic hydroxy groups (Scheme 18).

At first, we examined synthesis of stemofuran A (**82**), recently isolated from *Stemona collinsae*.[28] The known synthesis of stemofuran A reported by Pasturel *et al.*[31] involved many steps including the

protection/deprotection of the hydroxy group. *O*-Phenylhydroxylamine **80**,[23c] readily prepared from **79,** was condensed with 3,5-dihydroxyacetophenone to afford oxime ether **81** in good yield. When oxime ether **81** was treated with TFAT in the presence of DMAP at room temperature, the desired benzo[*b*]furan was isolated in excellent yield. Thus, short synthesis of stemofuran A (**82**) was accomplished in four steps with 72% overall yield.



Scheme 18. Reagents and conditions: a) 2 steps, 83%; b) 3,5-dihydroxyacetophenone, c. HCl, EtOH, rt, 3 h, 92%; c) TFAT, DMAP, CH_2Cl_2, rt, 26 h, 95%; d) 2 steps, 62%; e) 4-hydroxypropiophenone, c. HCl, EtOH, rt., 2 h, 92%; f) i) TFAT, DMAP, CH_2Cl_2, rt, 8.5 h, ii) purification by chromatography using silica gel, 95%; g) *trans*-propenylboronic acid, $Pd(PPh_3)_4$, CsF, DME, 100 °C, 7 h, 97%; h) 4-chromanone, c. HCl, EtOH, rt., 2 h, 93%; i) TFAT, DMAP, CH_2Cl_2, rt, 4 h, 78%; j) PCC, CH_2Cl_2, 40 °C, 4 h, 76%.

Secondly, we chose eupomatenoid 6 (**87**)[29] as our synthetic target which has shown antifungal, insecticidal, and antioxidant activities. Although Bach's[32] and Stevenson's[33] groups synthesized eupomatenoid 6, the syntheses include many transformations involving protection and deprotection of the hydroxy group. To introduce the (*E*)-propenyl group of eupomatenoid 6 at the last stage of our synthesis, we constructed the benzo[*b*]furan part as the first step. Condensation of *O*-phenylhydroxylamine **84**

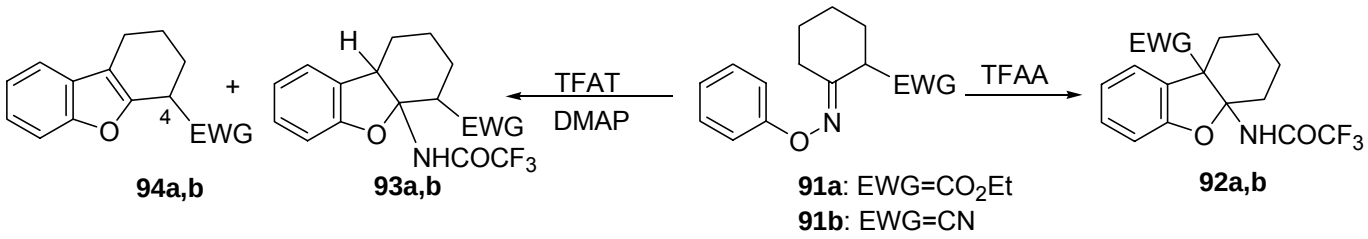
carrying the *p*-bromo group with *p*-hydroxypropiophenone gave oxime ether **85** which was subjected to our reaction conditions to afford 5-bromobenzo[*b*]furan **86** in 95% yield. Finally, benzo[*b*]furan **86** was subjected to the Suzuki coupling reaction with (*E*)-propenyl boronic acid to afford eupomatenoid 6 **87** in excellent yield. Thus, we succeeded in total synthesis of eupomatenoid 6 in 52% overall yield from **83** in five steps. Our synthesis is superior to those reported by Bach's and Stevenson's groups in both yield and number of step.

The third target of our synthesis is coumestan (**90**),[30] which is a basic pharmacophore containing coumestanes such as coumestrol[34] which shows estrogenic activity. Due to its unique structure and biological activities, coumestan (**90**) had been synthesized by many organic chemists using independent approaches.[35] Known synthetic methods involved the preparation of the benzo[*b*]furan part at the last stage while we constructed the benzo[*b*]furan part of coumestan as the first step. Condensation of a common *O*-phenylhydroxylamine **80** with 4-chromanone followed by sequential acylation and rearrangement of the resulting oxime ether **88** furnished the desired tricyclic benzo[*b*]furan **89** in 73% yield *via* two steps.

Finally, introduction of the carbonyl group was achieved by treatment of tricyclic benzo[*b*]furan **89** with PCC to give coumestan (**90**) in 76% yield. Thus, we succeeded in effective and short total synthesis of stemofuran A (**82**), eupomatenoid 6 (**87**)**,** and coumestan (**90**) without protection of the phenolic hydroxy groups in the former two cases.

Reagent-controlled regioselective [3,3]-sigmatropic rearrangement of *N*-trifluoroacetyl enehydroxylamine and its synthetic application

The tricyclic benzo[*b*]furan core with a sterically congested quaternary carbon is an important element in galanthamine-type,[36] morphine-type,[37] and lunarine-type[38] of alkaloids which exhibit remarkable and inherent biological activities. Therefore, synthetic access to such benzo[*b*]furans has long been a challenge for synthetic chemists. In constructing the universal skeleton, many synthetic methods such as biomimetic phenolic oxidative coupling, photochemical reaction, radical cyclization, intramolecular Heck reaction, semipinacol rearrangement, intermolecular alkylation, and arylation had been reported.[36-38] However, to the best of our knowledge, there have been few papers pertaining to the construction of hexahydrodibenzo[*b*]furans with a quaternary carbon in the ring juncture *via* [3,3]-sigmatropic rearrangement. Although the oxime ethers prepared from α,α'-disubstituted cyclopentanone gave dihydrobenzo[*b*]furan bearing a substituent in the ring juncture under acidic conditions,[4] unsymmetrically α-mono-substituted oxime ethers are known[21b] to give the benzo[*b*]furans as a result of rearrangement at the unsubstituted position.



Scheme 19

We have developed a new methodology for the construction of benzo[*b*]furans carrying a sterically congested quaternary carbon *via* three sequential reactions involving acylation, regioselective [3,3]-sigmatropic rearrangement, and cyclization of oxime ethers **91a,b** (Scheme 19). The treatment of oxime ethers **91a,b** carrying an electron-withdrawing group (EWG) with TFAA gave regioselectively dihydrobenzo[*b*]furans **92** carrying an EWG in the ring juncture while the reaction of **91a,b** with TFAT-DMAP afforded dihydrobenzo[*b*]furans **93a,b** and benzo[*b*]furans **94a,b** which are substituted with EWG at the 4-position.

In the absence of a base, a more acidic proton at the root of either ester or nitrile of **91a,b** was abstracted to form a more stable intermediate **95A** under the thermodynamically controlled conditions. On the other hand, in the presence of a base under the kinetically controlled conditions, the sterically less hindered methylene proton was abstracted by the base to form **95B** (Figure 1).

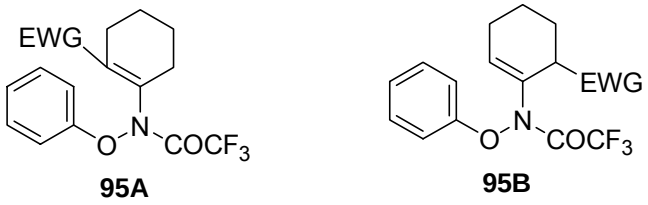
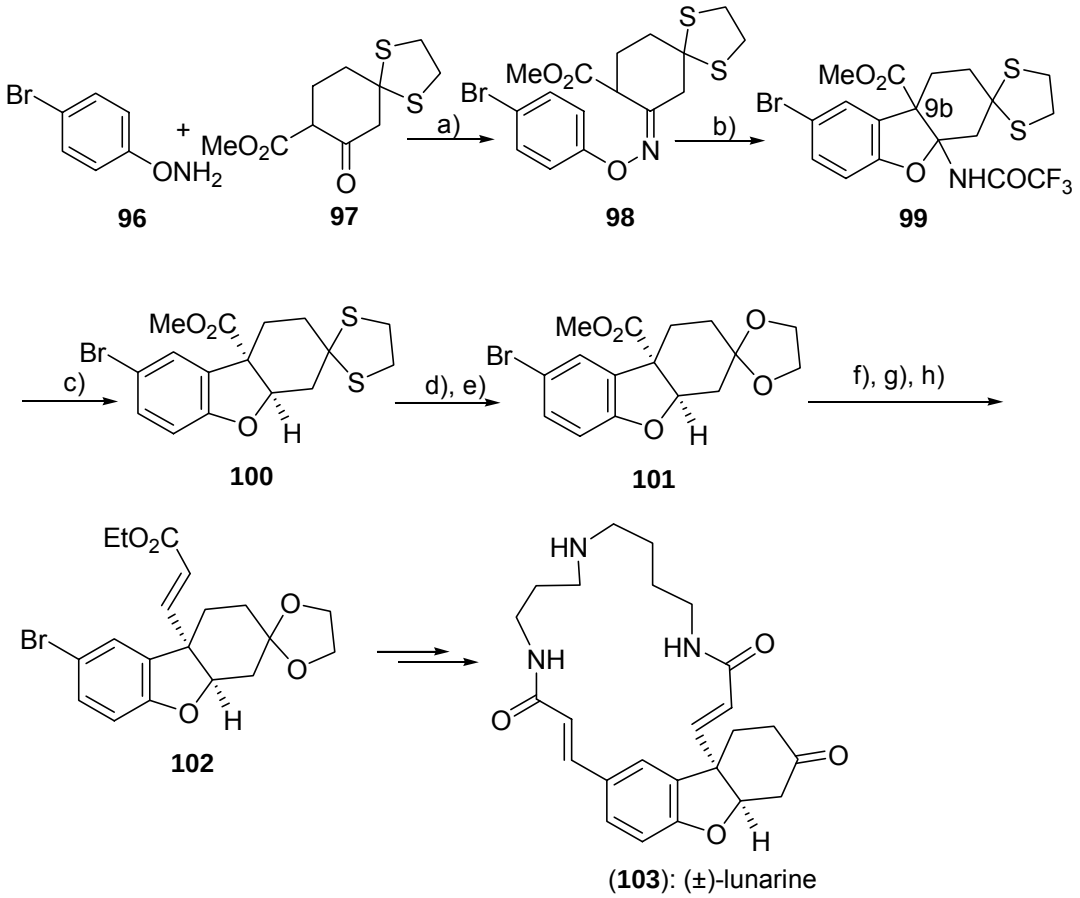


Figure 1. Two intermediates **95A** and **95B**

We then applied this reagent-controlled methodology to the efficient preparation of key intermediate **102** for synthesis of the macrocyclic spermidine alkaloid, lunarine (**103**), which was isolated from *Lunaria biennis*.[38a] This alkaloid is a competitive, promising target in drug design against tropical parasitic diseases. Lunarine and related compounds had been synthesized and evaluated against TryR in order to determine the features of lunarine that are associated with time-dependent inhibition.[38b-f] However, some of the reported syntheses involved more steps and gave low yields.[38b-f] Our attention is focused on the efficient synthesis of a key intermediate **102** which was already converted to lunarine.[38d] The appropriately substituted oxime ether **98** was prepared by the condensation of *p*-bromophenoxyamine **96** with keto-ester **97** and then treated with TFAA. The product was the desired hexahydrodibenzo[*b*]furan

99. The reductive deamidation of **99** with silylhydride followed by the transformation of the thioacetal in the resulting ester **100** into the corresponding acetal afforded dioxolane **101**. Finally, conversion of the ester **101** to aldehyde followed by the Wittig-Horner reaction afforded α,β-unsaturated ester **102** which is a key intermediate for synthesis of lunarine (**103**) (Scheme 20).



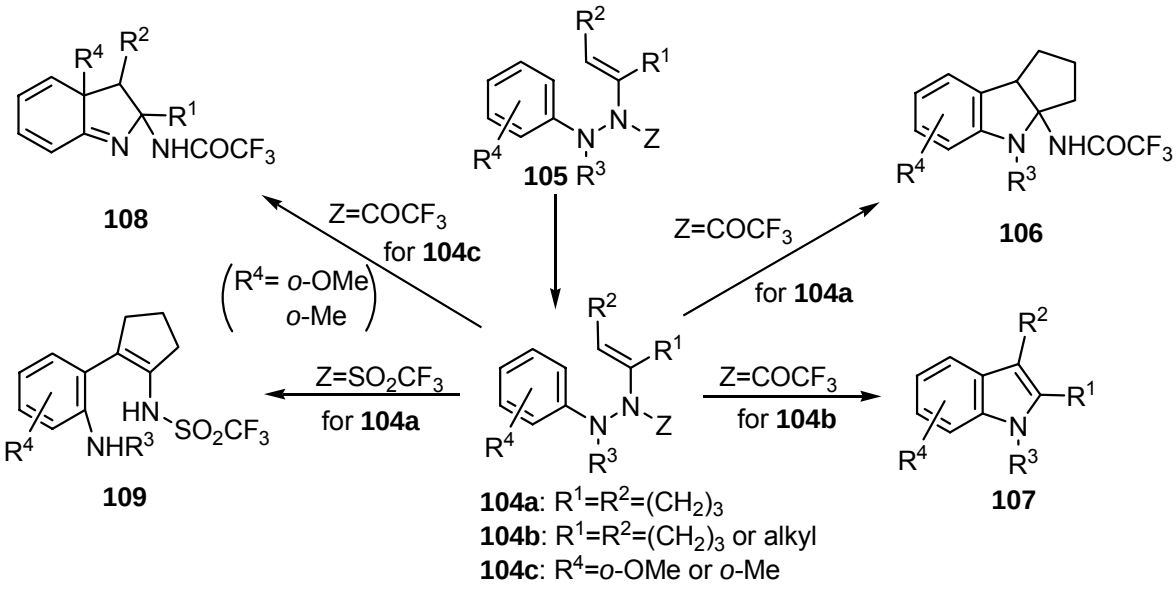
Scheme 20. Reagents and conditions: a) concd HCl, EtOH, 40 °C , 77%; b) TFAA, CH_2Cl_2, rt, 60%; c) TMSOTf, Et_3SiH, CH_2Cl_2, rt, 83%; d) MeI, MeCN-H_2O (5:1), reflux, 87%; e) Ethylene glycol, *p*-TsOH, benzene, reflux, 98%; f) $LiBH_4$, THF, rt, 99%; g) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0 °C, 88%, h) triethyl phosphonoacetate, NaH, THF, rt, 79%.

INDOLE SYNTHESIS[22]

[3,3]-Sigmatropic rearrangement of *N*-trifluoroacetyl enehydrazines

Prior to our study on benzo[*b*]furan synthesis, we have established a novel [3,3]-sigmatropic rearrangement of *N*-trifluoroacetyl enehydrazines **104** for synthesis of indolines and indoles as follows (Scheme 21). In the case of indole synthesis, *N*-trifluotoacetyl enehydrazines **104** are isolable. At below 100 °C, *N*-trifluoroacetyl enehydrazine **104** carrying a cyclopentene ring smoothly underwent

[3,3]-sigmatropic rearrangement followed by cyclization to give indolines **106** in excellent yield. On the other hand, both cyclohexenyl *N*-trifluoroacetyl enehydrazine and acyclic *N*-trifluoroacetyl enehydrazine **104** gave indoles **107** in good yield under the almost same conditions. The *N*-trifluoromethanesulfonyl enehydrazine **104** was converted into the rearranged product **109** at low temperature. The [3,3]-sigmatropic rearrangement of *N*-trifluoroacetyl enehydrazines **104** carrying either a methoxy or a methyl group at *ortho* position on the benzene ring gave dienylimines **108** which correspond to the proposed intermediates of Fischer indolization.[20] This reaction provides a new entry to the Fischer indole synthesis.



Scheme 21

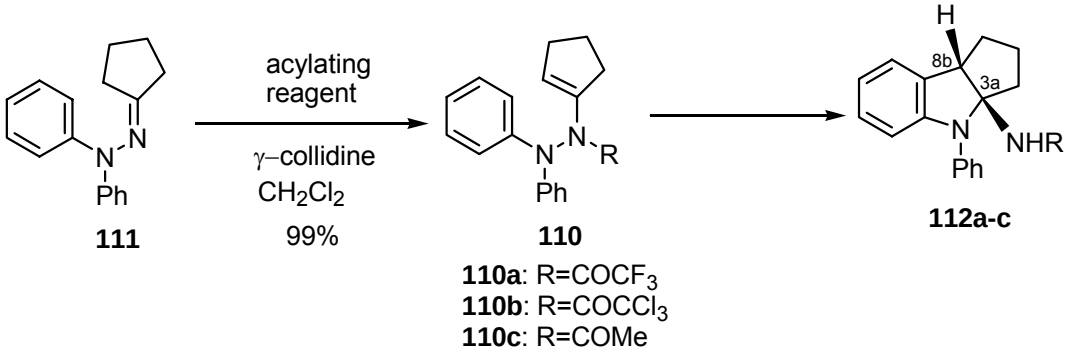
The substituent effects on the nitrogen atom in [3,3]-sigmatropic rearrangement of enehydrazines bearing a cyclopentene ring

At first, we investigated the substituent effects on the nitrogen atom. Three types of *N*-acyl enehydrazines **110a**, **110b**, and **110c** carrying a cyclopentene ring were employed as the substrate (Scheme 22). The hydrazone **111**, prepared by condensation of cyclopentanone with *N*,*N*-diphenylhydrazine was subjected to acylation with TFAA in the presence of γ-collidine to give the corresponding *N*-trifluoroacetyl enehydrazines **110a** in excellent yield. Similarly, *N*-trichloroacetyl enehydrazine **110b** and *N*-acetyl enehydrazine **110c** were prepared from **111**.

Compared with acylation reaction of oxime ether, the acylated enehydrazine **110** could be isolated under the acylating conditions.

When a solution of **110a** in THF was heated at 65 °C for 5 h, indoline **112a** was obtained in 99% yield (entry 1 in Table 3). Similarly, the reaction of *N*-trichloroacetyl enehydrazine **110b** at the same

temperature gave indoline **112b** in 56% yield (entry 2). However, in the case of **112c**, higher reaction temperature (140 °C) was required for the successful rearrangement and cyclization (entry 3). Surprisingly, the reaction of **110a** also proceeded at room temperature but required prolonged reaction time (480 h) (entry 4).

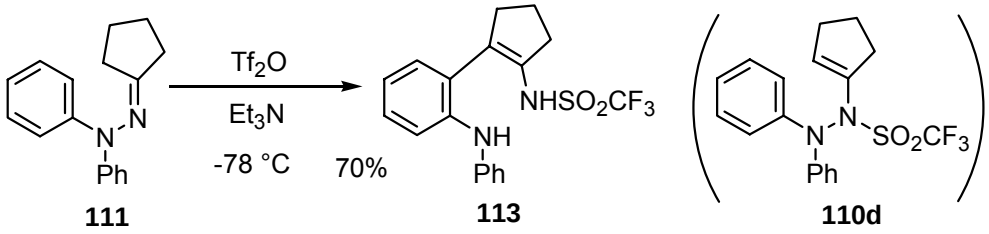


Scheme 22

Table 3. The conversion of *N*-acyl enehydrazines **110a-c** into the indolines **112a-c**

entry	substrate	R	conditions (°C)	time (h)	yield (%)
1	**110a**	$COCF_3$	THF (65)	5	99
2	**110b**	$COCCl_3$	THF (65)	5	56
3	**110c**	COMe	xylene (140)	3	65
4	**110a**	$COCF_3$	$CDCl_3$ (r.t.)	480	98

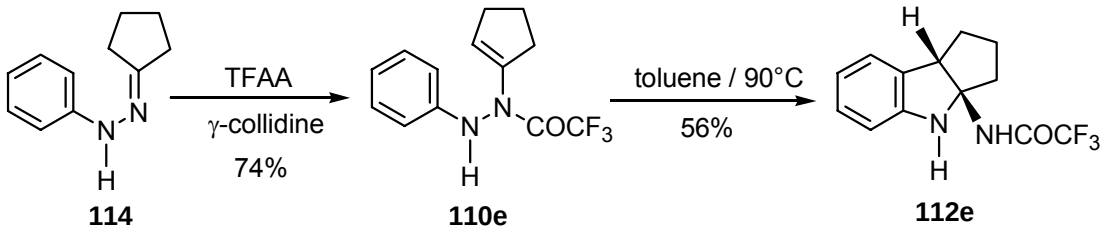
We next examined the rearrangement of the enehydrazine **110d** carrying a trifluoromethanesulfonyl group which has higher electron-withdrawing ability (Scheme 23). The sulfonylation of hydrazone **111** with trifluoromethanesulfonic anhydride (Tf_2O) was carefully carried out in the presence of γ-collidine at 0 °C. However, the reaction gave not the desired product **110d** but the rearranged product **113** in low yield, along with the decomposition of **111**.



Scheme 23

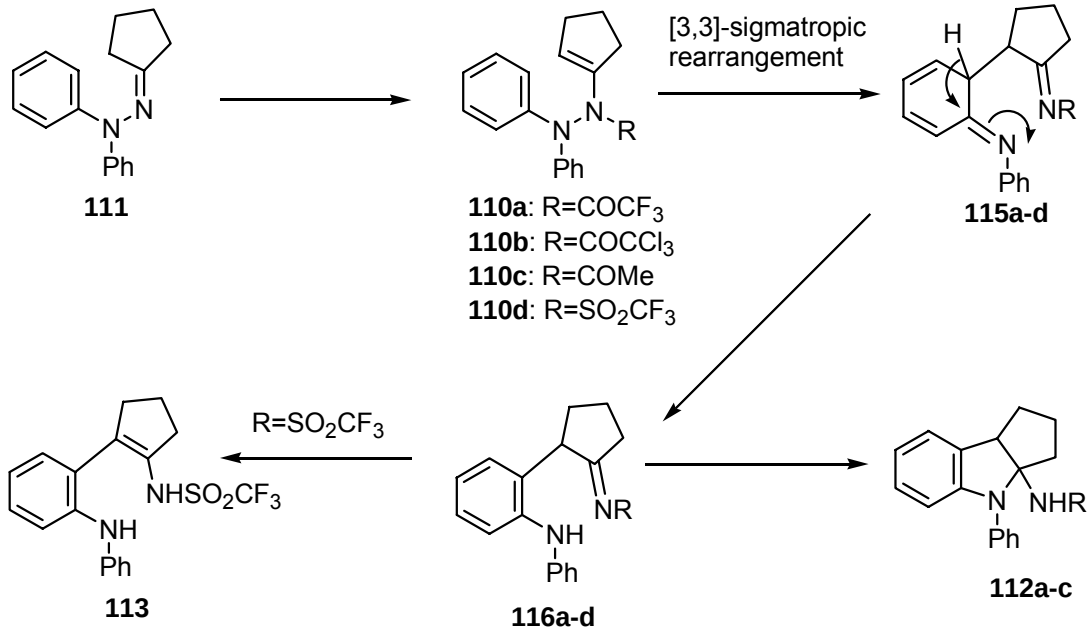
At lower reaction temperature of –78 °C, **113** was obtained in 25% yield. Replacement of γ-collidine to triethylamine as a base improved the yield to 70%. Thus, this result suggests that the enehydrazine **110a** bearing a trifluoroacetyl group is the best substrate for our indole synthesis.

Similarly, *N*-monophenylenehydrazine **110e**, prepared from **114**, worked well in toluene at 90 °C to give the indoline **112e** along with the unreacted starting material **110e** (Scheme 24).



Scheme 24

Considering our results obtained above and the related known Fischer indolization,[20] we propose a plausible reaction pathway that is shown in Scheme 25. At first, [3,3]-sigmatropic rearrangement of the *N*-acyl enehydrazines **110a-c** followed by isomerization proceeds to form *N*-acylimines **116a-c** which then cyclized intramolecularly to give the indoline **112a-c**.

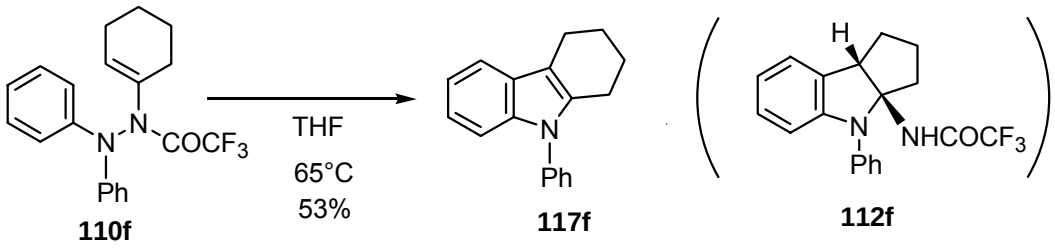


Scheme 25

In sulfonylation of hydrazone **111**, *N*-trifluoromethansulfonyl enehydrazine **110d** could not be isolated. Probably, the [3,3]-sigmatropic rearrangement of **110d** that would be transiently formed from hydrazone **111** would take place easily even at –78 °C because a trifluoromethanesulfonyl group has a very strong electron-withdrawing property. The following cyclization of rearranged intermediate **116d** was prevented due to too low temperature (–78 °C). Therefore, **113** was an isolable product in the reaction of **111** with Tf_2O.

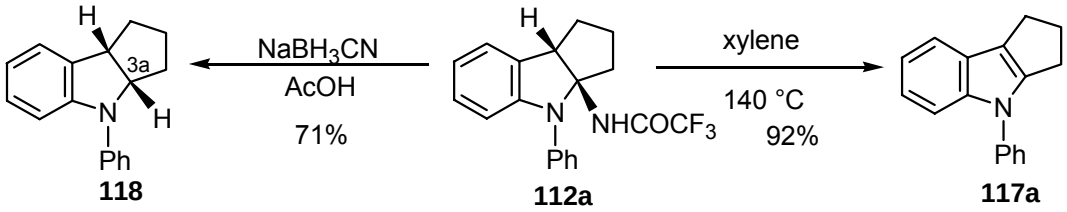
The substituent effect on the ene part in [3,3]-sigmatropic rearrangement of enehydrazines

We next investigated the substituent effects on the ene part. In the case of cyclohexenehydrazine **110f**, the indole **117f** was exclusively obtained without formation of the indoline **112f** (Scheme 26).



Scheme 26

Upon heating at 140 °C, the indoline **112a** was converted into the indole **117a** in quantitative yield as a result of the elimination of trifluoroacetamide (Scheme 27). Reductive deamination of **112a** with sodium cyanoborohydride proceeded smoothly to give the corresponding indoline **118** in 71% yield that is unsubstituted at the 3a-position (Scheme 27).



Scheme 27

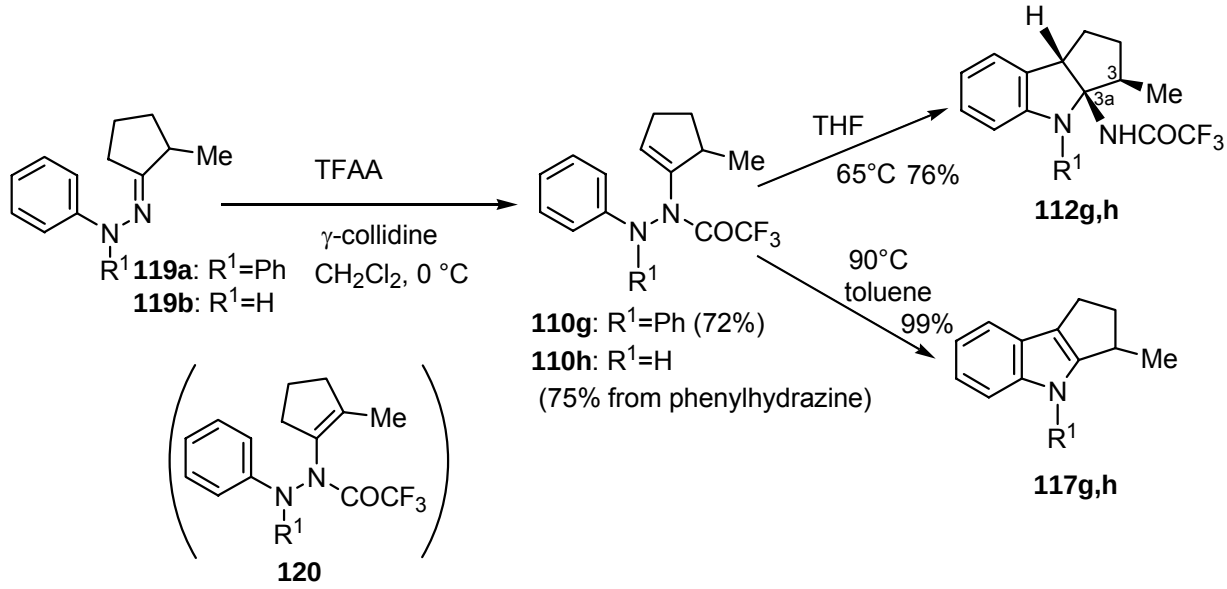
In general, it is difficult to isolate 2-aminoindolines which is proposed as an intermediate of Fischer indolization. To our knowledge, there has been only a few works[39-41] on the isolation of 2-aminoindoline derivatives.

Next, the reaction of enehydrazines **110g** and **110h** bearing a methyl group on the cyclopentene ring was examined (Scheme 28). The enehydrazines **110g** and **110h** were prepared by the treatment of hydrazones **119a** and **119b** with TFAA without formation of the regioisomer **120**. The enehydrazine **110g** was subjected to the heating at 65 °C to give the indoline **112g** in 76% yield while the indoline **112h** could not be isolated from **110h** under the same conditions probably because of its instability. On the other hand, the reaction of **110h** in toluene at 90 °C gave the indole **117h** in excellent yield.

The reactions of enehydrazines carrying ester and nitrile group are now in progress.

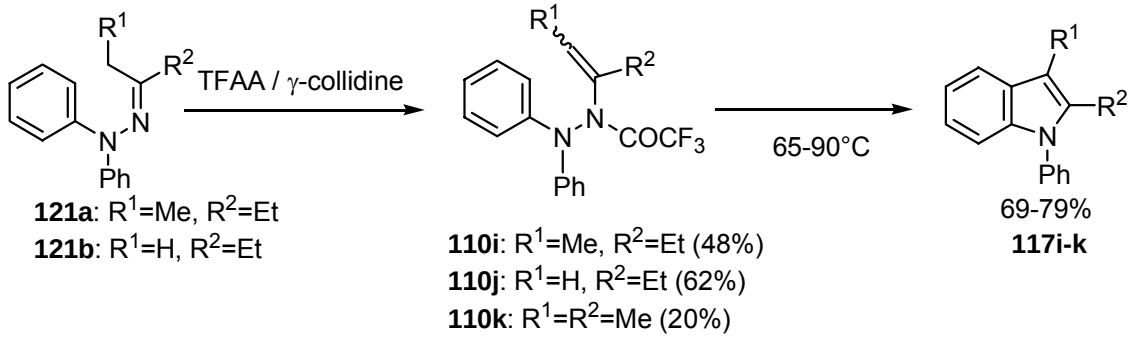
It is known[42] that the classical Fischer indolization of hydrazone prepared from unsymmetrical ketone gives a mixture of substituted indoles with no regioselectivity. Therefore, this regioselective formation of

indolines and indoles from unsymmetrical ketones **119a,b** would be useful for the synthesis of variously substituted polycyclic indole alkaloids.



Scheme 28

We then investigated the reaction of enehydrazine with an acyclic chain on the ene part (Scheme 29). The enehydrazine **110i** was prepared by the acylation of hydrazone **121a** with TFAA. The acylation of hydrazone **121b** with TFAA gave a 3 : 1 mixture of enehydrazines **110j** and **110k**. The enehydrazine **110i** was heated at 65 °C to afford the corresponding indoles **117i** as the sole product.



Scheme 29

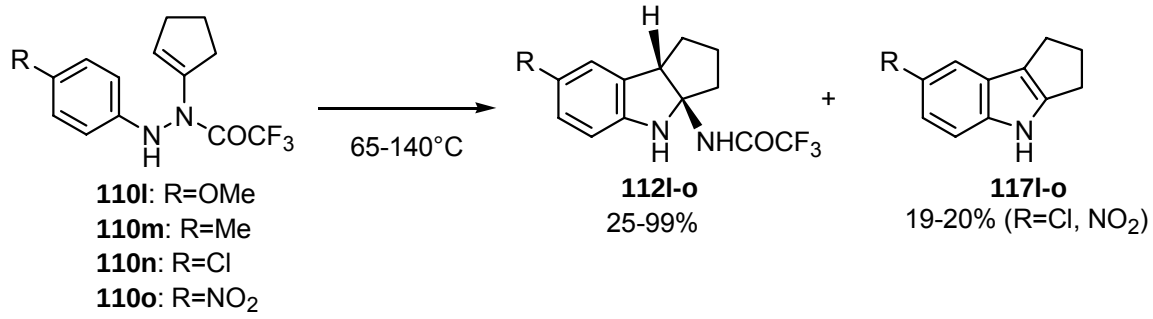
The thermal reaction of **110j** at 90 °C gave indole **117j** in 77% yield. Similarly, **117k** was obtained from **110k**. Since the rearrangement and cyclization of **110i-k** occurred with no isomerization of the olefin part under mild conditions, the substituted indoles such as 2-mono- and 2,3-disubstituted indoles would be selectively obtained as the sole product.

The substituent effects on benzene ring in [3,3]-sigmatropic rearrangement of enehydrazines bearing cycloalkene ring

To demonstrate the generality of the rearrangement and cyclization of *N*-trifluoroacetyl enehydrazines, we next investigated the substituent effects on the benzene ring. We chose methoxy, methyl, nitro, and chloro groups as a substituent. At first, the reaction of enehydrazine carrying a substituent at the *p*-position on the benzene ring was examined (Scheme 30).

The substrate **110l** carrying a methoxy group underwent cyclization at lower temperature (65 °C) than the reaction of unsubstituted enehydrazine **110e** at 90 °C (see Scheme 24). The indoline **112l** was produced in excellent yield. Similarly, the substrate **110m** with a methyl group gave the indoline **112m** (68%) at 90 °C. On the other hand, in the case of the enehydrazines **110n** and **110o** carrying an electron-withdrawing group, prolonged reaction time and high reaction temperature were required. These substituent effects are almost in agreement with those obtained in the classical Fischer indolization.[20] The existence of an electron-donating group on a benzene ring makes the thermal reaction relatively easy to occur while in the case of an electron-withdrawing group, harsh conditions were required for successful reaction.

The *m*-substituted enehydrazines gave two types of regioisomeric indoles with low selectivity in all cases.



110l: R=OMe
110m: R=Me
110n: R=Cl
110o: R=NO_2

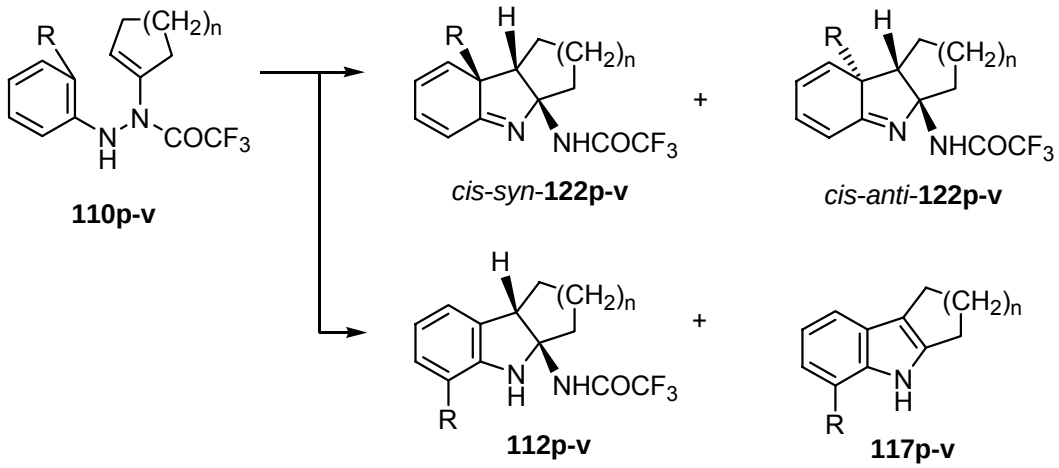
112l-o
25-99%

117l-o
19-20% (R=Cl, NO_2)

Scheme 30

We next investigated the reaction of *o*-substituted enehydrazines (Scheme 31, Table 4). At first, [3,3]-sigmatropic rearrangement of **110p** carrying an *o*-methoxy group was examined. **110p** was heated in THF at 65 °C to give a mixture of indoline **112p** and two dienylimines **122p** in 63 and 36% yields, respectively (entry 1). The dienylimines **122p** were obtained as the result of the rearrangement at the root of a methoxy group. Furthermore, **122p** was easily separated into two diastereomers, *cis-syn*-**122p** and *cis-anti*-**122p**, in a 5 : 1 ratio. Interestingly, the polarity of the organic solvent used influences both the product ratio of the indoline and dienylimine and the reaction time. In MeCN, the reaction proceeded smoothly to give a 1 : 1 mixture of **112p** and **122p** in 99% yield (entry 2). On the other hand, in a less polar solvent, such as toluene and hexane, **112p** was obtained as a major product in 69-75% yield, although prolonged reaction time was required for complete consumption of **110p** (entries 3 and 4). In

methanol, the indole **117p** and the dienylimines **122p** were obtained with no formation of indoline **112p** (entry 5).



Scheme 31

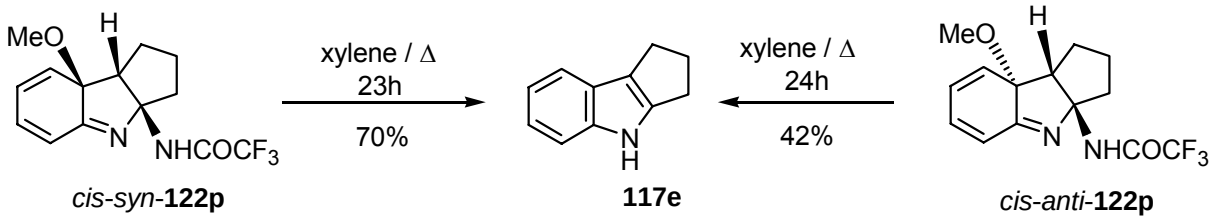
Table 4. The thermal reaction of enehydrazines **110p-v**

entry	substrate	R	n	conditions (°C)	time (h)	yield (%)		
						112	**117**	**122** (*cis-syn* : *cis-anti*)
1	**110p**	OMe	1	THF (65)	10	63	---	36 (5 : 1)
2	**110p**	OMe	1	MeCN (80)	5	51	---	48 (5 : 1)
3	**110p**	OMe	1	toluene (90)	7	69	---	29 (4 : 1)
4	**110p**	OMe	1	hexane (70)	22	75	---	24 (4 : 1)
5	**110p**	OMe	1	MeOH (80)	3	---	60	39 (7 : 1)
6	**110q**	Me	1	MeCN (80)	8	30	37	32 (7 : 1)
7	**110r**	Cl	1	toluene (90)	15	66	---	---
8	**110s**	NO_2	1	toluene (110)	29	31	---	---
9	**110t**	OMe	2	MeCN (80)	10	---	80	17 (2 : 1)
10	**110u**	OMe	3	MeCN (80)	10	---	47	35 (9 : 1)
11	**110v**	OMe	0	MeCN (80)	5.5	26	---	70 (2.5 : 1)

Next, we turned our attention to the corresponding *o*-methyl-*N*-trifluoroacetyl enehydrazine **110q**. The enehydrazine **110q** worked well in MeCN at 80 °C to give the indoline **112q**, indole **117q**,[29] *cis-syn*-**122q**, and *cis-anti*-**122q** (entry 6). When an electron-withdrawing group such as a chlorine or nitro group was present in the *o*-position, the indolization occurred regioselectively at the unsubstituted position to give 5-substituted products **112** (entries 7 and 8). The reaction of enehydrazine **110t** bearing cyclohexene ring gave indole **117t** as a major product. On the other hand, cyclobutenylenehydrazine **110v** afforded dienylimine **122v** in good yield (entries 9-11).

Furthermore, heating the dienylimines, *cis-syn*-**122p** and *cis-anti*-**122p**, in xylene at 140 °C afforded exclusively indole **117e**[31] (Scheme 32). This reaction pathway is ambiguous at the moment.

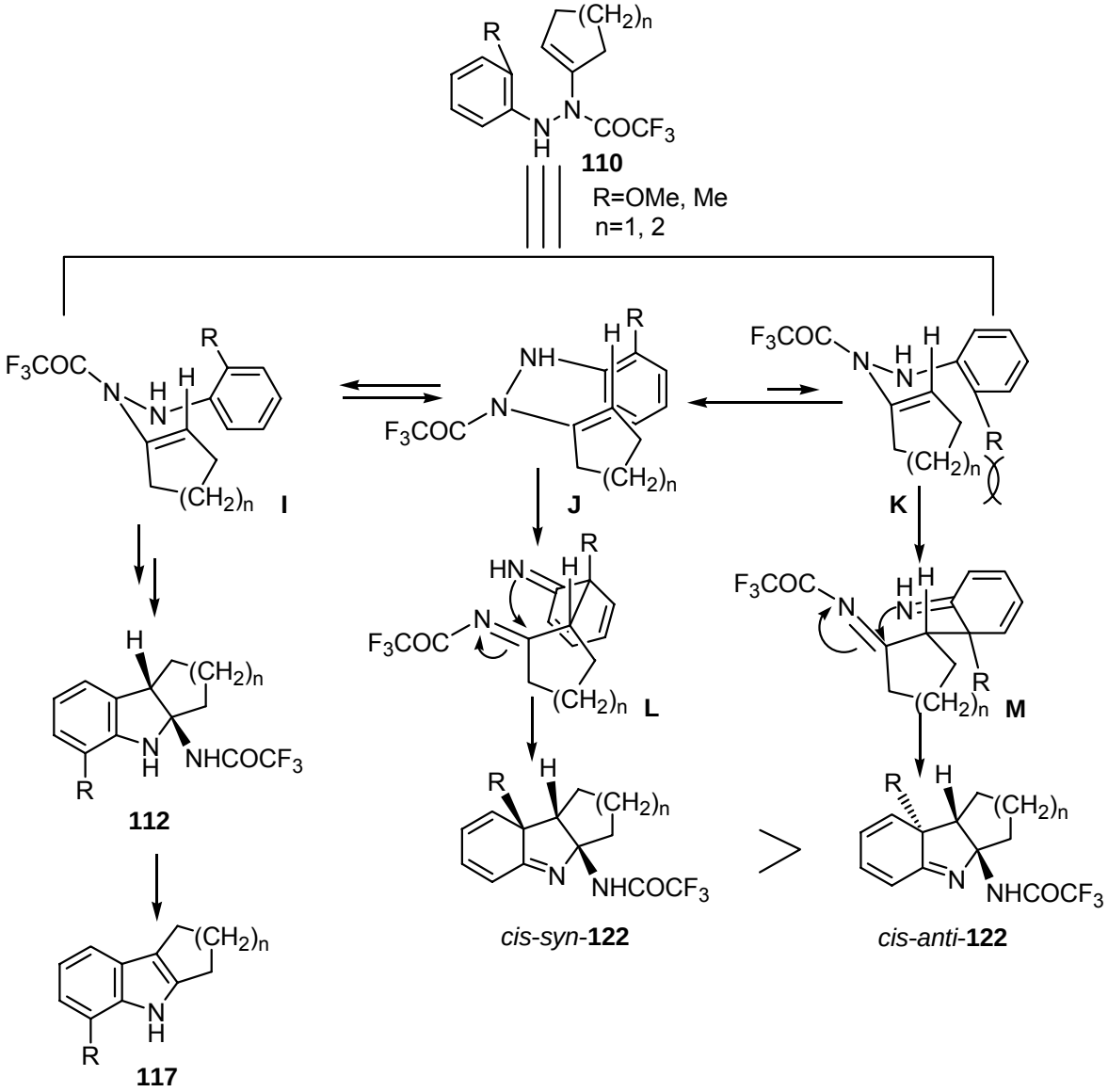
We have succeeded in the isolation and structure determination of the dienylimine intermediate in the thermal reaction of the *o*-methoxyenehydrazine. Additionally, the *cis-syn*-isomer was obtained as the major product among dienylimines.



cis-syn-**122p** **117e** *cis-anti*-**122p**

Scheme 32

It is well-known[20,43-46] that Fischer indolization of (2-methoxyphenyl)hydrazone gives 7-methoxyindole as a minor product and the abnormal 6-substituted indole as a major product without the isolation of dienylimine.



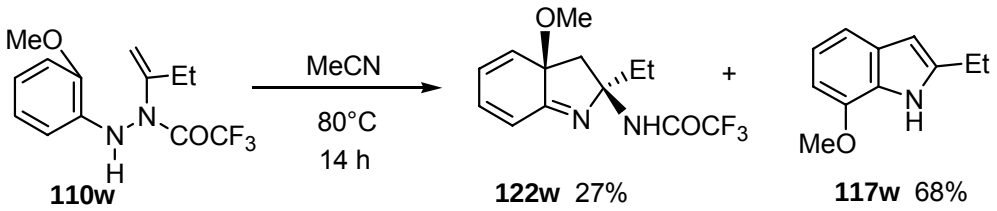
Scheme 33

The isolation and determination of the dienylimine intermediates in the Fischer indolization of *o*-methoxy and *o*-methyl enehydrazines provides good evidence for the postulated reaction mechanism, including a stereochemical rationalization, particularly for the [3,3]-sigmatropic rearrangement step.

To the best of our knowledge, there has been only one paper[47] pertaining to the isolation of a pure dienylimine carrying a methyl group at the 3a-position in which the relative configurations at the 2-, 3- and 3a-position remain to be established. Additionally, Brown[48] has reported that attemps to isolate a tricyclic dienylimine carrying a methyl group were unsuccessful. Therefore, our result is the first example of isolation and structure determination of the tricyclic dienylimine with a methyl group.

We next propose the possible reaction pathway for the formation of dienylimines **122** (Scheme 33). The enehydrazines **110** would exist in three different conformations **I**, **J**, and **K**. The indolines **112** were obtained *via* [3,3]-sigmatropic rearrangement *via* **I**. In the case of **112**, they were converted into the indoles **117** by the elimination of the trifluoroacetamido group. On the other hand, the rearrangement *via* **J** and **K** followed by the cyclization of the resulting imines **L** and **M** gave *cis*-*syn*-**122** and *cis*-*anti*-**122**, respectively. The conversion of **J** into *cis*-*syn*-**122** proceeded more readily than that into *cis*-*anti*-**122** because conformation **K** is less stable than conformation **J** due to the steric hindrance between a methoxy group and methylene on a cyclopentene or cyclohexene ring in **K**. The rearrangement of **110r,s** gave the indolines **112r,s** as the sole product. We are unable at this time to offer an explanation of the difference in regioselectivity between enehydrazine carrying an electron-donating group and enehydrazine carrying an electron-withdrawing group.

We next examined the reaction of acyclic enehydrazine **110w** carrying the *o*-methoxy group (Scheme 34). The enehydrazine **110w** was heated at 80 °C to give *cis*-dienylimines **122w** and indole **117w** in 27% and 68% yields, respectively.



110w **122w** 27% **117w** 68%

Scheme 34

CONCLUSION

We have established a highly efficient and general synthetic method for benzo[*b*]furans and indoles *via* the routes involving sequential acylation, rearrangement, and cyclization of oxime ethers under mild conditions. The [3,3]-sigmatropic rearrangement process promoted by the trifluoroacetyl group would represent a general strategy that may be of great use in the synthesis of more complex heterocycles.

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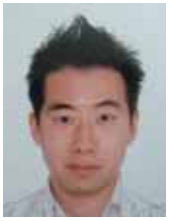

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