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Assembly of indenamine derivatives through *in situ* formed *N*-sulfonyliminium ion initiated cyclization†

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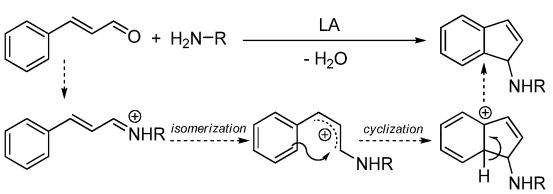
An expedient route to structurally diverse indenamine derivatives through condensation of the readily accessible substituted cinnamylaldehydes and sulfonylamines under the catalysis of $FeCl_3$ has been developed, featuring high efficiency in the generation of two bonds and one ring in a single-step and water as the only by-product.

Iminium ions are reactive intermediates in organic chemistry that play an important role in both laboratory and industry for the construction of carbon–carbon and carbon–heteroatom bonds, especially for the synthesis of nitrogen-containing heterocycles.[1] Representative examples of these transformations are *N*-acyliminium ion cyclization and Pictet–Spengler reaction which have become powerful synthetic tools for the synthesis of many alkaloids.[2,3] However, in contrast to heterocycles, very few examples exist on the use of this strategy for the construction of all-carbon ring skeletons.[4] Indenes are important core structures present in many biologically active compounds,[5] functional materials,[6] and chemical catalysts,[7] which hold a special appeal to synthetic chemists and provide an ideal target for developing and testing new synthetic strategies, particularly those that are directed toward carbocyclic ring construction.[8] We reasoned that this class of carbocycles might be accessed in one step by condensation of a cinnamaldehyde with an amine under the catalysis of Lewis acid through an *in situ* formed iminium ion initiated intramolecular cyclization (Scheme 1). To our knowledge, this approach to indene frameworks has not been reported previously. As one of our continuous interests in the synthesis of carbocyclic compounds,[9] recently we launched a study to verify this hypothesis. The preliminary results are reported herein.

Initial examination was carried out on the reaction of (*E*)-2-methyl-3-phenylacrylaldehyde (**1a**, 1.0 equiv.) with benzamide (**2a**, 1.2 equiv.) in toluene. $FeCl_3$ (15 mol%) was selected as the Lewis acid catalyst because iron is an abundant, economical, and environmentally benign metal on earth and shows increasing and promising catalytic abilities for the C–C and C–N bond formation.[10] To our disappointment, the reaction failed to produce the designed cyclization product at room temperature as well as under reflux conditions, whereas a small amount of intractable mixture was obtained along with the recovery of unreacted aldehyde **1a**. To implement our strategy, a number of other amines (*e.g.*, aniline **2b**, 4-nitroaniline **2c**, piperidine **2d**, and *p*-toluenesulfonamide **2e**) were subsequently evaluated in this model reaction. Despite **2b–d** being completely immune to this transformation under various conditions, we were pleased to find that our protocol was successfully performed upon using $TsNH_2$ (**2e**) as the amine component and gave the desired cyclization product **3a** in 89% isolated yield (Table 1, entry 1). These results indicate that this cyclization reaction is facilitated with the amines bearing a relatively strong electron-withdrawing group. Encouraged by the above results, a variety of solvents and Lewis acids were then systematically investigated in the reaction of **1a** with **2e** (Table 1, entries 2–13). These examinations revealed that treating **1a** (1.0 equiv.) with 1.2 equiv. of **2e** in toluene at 40 °C for 4 h in the presence of 20 mol% $FeCl_3$ gave the best result (98%, Table 1, entry 2). Other Lewis acids such as $FeCl_3{\cdot}6H_2O$, $BF_3{\cdot}OEt_2$, $TiCl_4$, and CuI were found to be less effective or ineffective in promoting this transformation (Table 1, entries 10–13). Among the examined Brønsted acids (*e.g.*, TfOH, TsOH, and HCl), only triflic acid showed catalytic activity towards this reaction (Table 1, entries 14–16), and a moderate yield of **3a** was obtained. Further investigation of this reaction under an argon atmosphere (Table 1, entries 17–18) reveals



Scheme 1 Design of the intramolecular cyclization reaction *via* an *in situ* formed iminium ion.

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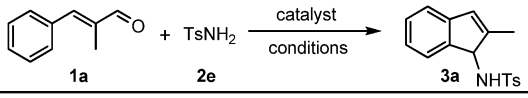
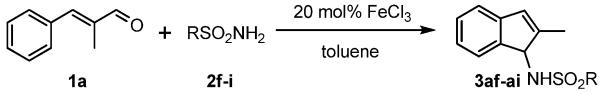
Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst (mol%)	Solvent	T (°C)/t (h)	Yield[b] (%)
1	$FeCl_3$ (15)	Toluene	40/4	89
2	$FeCl_3$ (20)	Toluene	40/4	98
3	$FeCl_3$ (20)	Benzene	80/4	78
4	$FeCl_3$ (20)	DCM	40/4	85
5	$FeCl_3$ (20)	CH_3NO_2	100/4	64
6	$FeCl_3$ (20)	THF	60/12	0
7	$FeCl_3$ (20)	MeCN	80/12	30
8	$FeCl_3$ (20)	DMF	80/4	Mess
9	$FeCl_3$ (15)	EtOH	60/12	0
10	$FeCl_3{\cdot}6H_2O$ (20)	Toluene	40/4	79
11	$TiCl_4$ (20)	Toluene	40/4	56
12	$BF_3{\cdot}OEt_2$ (20)	Toluene	40/4	82
13	CuI (20)	Toluene	40/12	0
14	TfOH (20)	Toluene	40/12	71
15	TsOH (20)	Toluene	40/12	Trace
16	HCl (20)	Toluene	40/12	0
17[c]	$FeCl_3$ (40)	Toluene	80/8	96
18[c]	$FeCl_3$ (20) + H_2O (5 μL)	Toluene	40/4	95

[a] Reaction conditions: **1a** (0.2 mmol), **2e** (0.24 mmol), solvent (3 mL). [b] Isolated yield. [c] Under argon.



2f = $CH_3SO_2NH_2$ 91 % (80 °C, 6 h)
2g = $PhSO_2NH_2$ 82 % (60 °C, 6 h)
2h = 4-Cl-$PhSO_2NH_2$ 87 % (80 °C, 12 h)
2i = 4-NO_2-$PhSO_2NH_2$ 0 % (100 °C, 12 h)

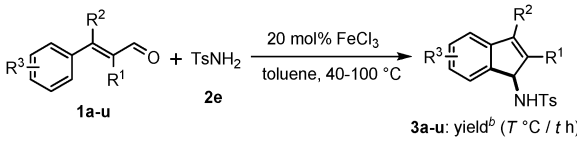
Scheme 2 Reaction of **1a** with other sulfonylamines.

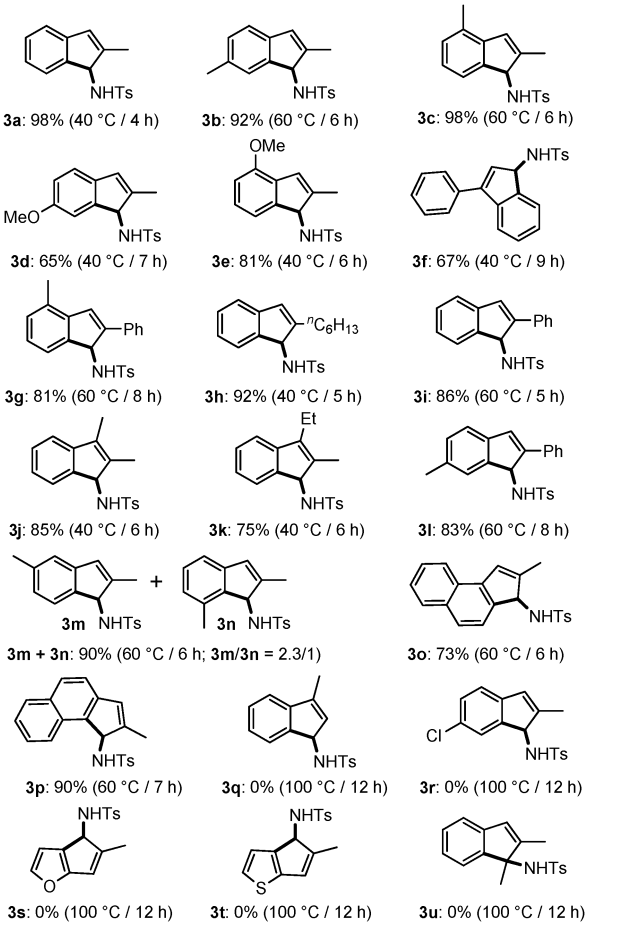
that the present reaction is catalyzed by Fe(III) species and a trace amount of water can accelerate this reaction.[11] Note that when (*Z*)-**1a** was subjected to this reaction, an almost quantitative yield of **3a** was obtained after 2.5 h at 40 °C. This suggests that the substituted cinnamaldehyde in *Z* configuration is more favorable for this transformation.[12]

Subsequently, several other sulfonylamines such as methane-sulfonamide (**2f**), benzenesulfonamide (**2g**), 4-chlorobenzenesulfonamide (**2h**), and 4-nitrobenzenesulfonamide (**2i**) were examined in this reaction (Scheme 2). Under the optimal reaction conditions, **2f–h** reacted smoothly with **1a** to afford the cyclization products **3af–ah** in 91%, 82%, and 87% yields, respectively. In contrast, **2i** was found to be an unsuitable amine source for this transformation.[13]

With the optimized reaction conditions established, the scope of the reaction between various cinnamylaldehydes (*E* isomers) and *p*-toluenesulfonamide was investigated. As shown in Table 2, most of the α-substituted cinnamylaldehydes can smoothly react with $TsNH_2$ with high efficiency to give the corresponding indenamine derivatives in good to excellent yields (Table 2, **3a–p**). However, cyclization failed to occur upon using simple (*E*)- or (*Z*)-cinnamaldehyde as the substrates. Further employment of β-substituted cinnamylaldehyde **1q** as the substrate also failed to give the desired cyclization product **3q**.[14] These results reveal that the starting

Table 2 Reaction of **2e** with various cinnamylaldehydes[a]





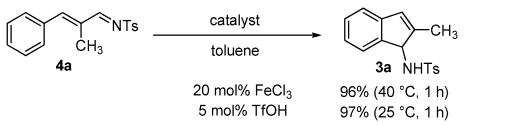
[a] Reaction conditions: **1a–u** (0.2 mmol), **2e** (0.24 mmol), toluene (3 mL), 20 mol% $FeCl_3$. [b] Isolated yield.

aldehyde has an α-substituent which is essential for this transformation. The only exception to this structural requirement is 3,3-diphenylacrylaldehyde (**1f**), which can carry out this cyclization without an additional α-substituent, presumably because of its special structure leading the carbonyl group and one of the phenyl rings in a *cis* fashion. Moreover, the electronic properties of the phenyl ring also had an obvious impact on the outcome of the reaction. The presence of electron-withdrawing groups on the phenyl ring would prevent the reaction (Table 2, **3r**).[15] With respect to the aldehydes bearing an electron-donating group on the phenyl ring, the results were more complicated. Despite the fact that either alkyl or methoxy group substituted aldehydes, *e.g.*, **1b** and **1d**, underwent this cyclization reaction smoothly, however, the alkyl substituted substrate is more favorable for this transformation (Table 2, **3b–d**). The reason for such differences in reactivity is unclear at this stage, the electronic properties and coordination abilities of these substituents should be responsible for the observed results. Upon subjecting (*E*)-2-methyl-3-*m*-tolylacryl-aldehyde (**1m**) to

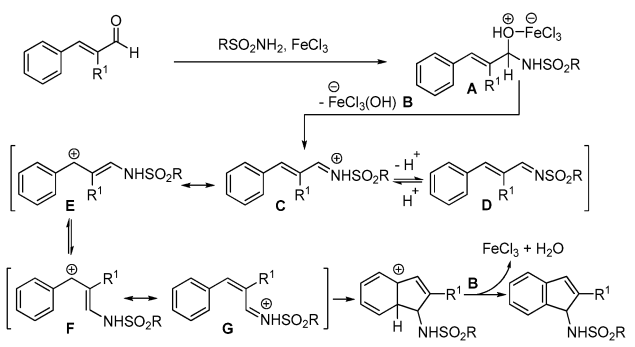
this reaction, the sterically favorable product **3m** together with its regioisomeric product **3n** was obtained in 90% yield as an unseparated mixture. Furthermore, naphthyl substituted cinnamylaldehydes **1o** and **1p** can also be applied to this reaction, providing a useful method for the construction of indene-containing polycarbocycles (Table 2, **3o–p**). Interestingly, the crystal growth of **3o** in the mixing solution of ether and petroleum ether resulted in its C–C double bond regioisomeric single crystal **3o′** exclusively.[16] The structures of compounds **3o′** and **3p** were confirmed by X-ray crystallographic analysis.[17] Notably, thiophene and furan cannot be used as the heteroaromatic nucleophiles in this reaction, continued efforts geared towards conversion of **1s** or **1t** to its cyclization product resulted in an intractable mixture. In addition, cinnamic ketone such as (*E*)-3-methyl-4-phenylbut-3-en-2-one (**1u**) was also found to be an unsuitable substrate for this reaction, which might be attributed to the difficulty in the formation of an iminium ion intermediate from the ketone.

To gain some understanding of the mechanism, the imine **4a** was tested in this reaction (Scheme 3).[18] Under the catalysis of $FeCl_3$ or TfOH, **4a** was smoothly transformed into the cyclization product **3a** in 96% and 97% yields, respectively. In the absence of the catalyst, **4a** could not be converted into **3a**. Therefore, we assumed that the iminium ion might be the reactive intermediate in this reaction.

Based on the above results, a plausible mechanism for this reaction is proposed in Scheme 4. The first step is the nucleophilic addition of a sulfonylamine to the carbonyl group of the α-substituted aldehyde with the aid of $FeCl_3$ to give the intermediate **A**, which then loses a $Fe^{-}Cl_3(OH)$ group to afford the electrophilic iminium ion **C**. The iminium ion **C**/**E** can undergo isomerization to **F**/**G**, followed by an intramolecular Friedel–Crafts alkylation reaction would give rise to the corresponding indenamine derivatives. In this ring closure reaction, we speculate that the isomerizations of intermediate **C** to its less stable resonance structure **E** and **E** to its sterically unfavorable rotamer **F** are facilitated by the substrates bearing an α-substituent; upon using aldehydes without an α-substituent, the formation of intermediate **E** or **F** is totally inhibited, which results in no cyclization product being obtained.



Scheme 3 Control experiments.



Scheme 4 Plausible mechanism.

In summary, a convenient and expeditious route to structurally diverse indenamine derivatives *via* an *in situ* formed *N*-sulfonyliminum ion initiated cyclization protocol has been developed. This methodology features using economical and readily available substituted cinnamylaldehydes and sulfonylamines as the starting materials, and generation of water as the only by-product. It displays high efficiency in the construction of two bonds and one ring in a single-step. Efforts are currently underway in our laboratory to further refine this method in organic synthesis and will be reported in due course.

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11 Under the argon atmosphere and optimized reaction conditions, only 57% yield of **3a** was obtained after 12 h along with the unreacted **1a**.
12 Isomerization of the C–C double bond in iminium ion to its *Z* configuration is essential for this transformation. Therefore, the reaction is facilitated with the cinnamylaldehydes in *Z* configuration.
13 Besides **2i**, CF_3CONH_2 and $CF_3SO_2NH_2$ were also found to be unsuitable amine sources for this reaction, which might be attributed to their lower nucleophilicity that would inhibit the formation of iminium ions. The sulfonamide **2h** can take place this reaction probably because the chlorine atom is a relatively weak electron-withdrawing group as compared to the nitryl group.
14 **1q** was partly converted into the corresponding sulfonylimine (62% yield).
15 (*E*)-2-methyl-3-(4-nitrophenyl)acrylaldehyde also failed to give the cyclization product.
16 In order to remove the *N*-tosyl group, several typical conditions were tested to **3a** (see ESI†). However, these conditions result in the isolation of its C–C double bond regioisomer exclusively. These results suggest that the C–C double bond in resulting indenamine products might be liable to rearrangement to the more substituted double bond. In the case of **3o**, the rearrangement may be promoted by itself.
17 CCDC 965332 (**3o′**) and 965333 (**3p**), see the (ESI†) for details.
18 The sulfonylimine derived from cinnamaldehyde was also tested to this reaction, it failed to give the cyclization product under various conditions.

