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1,2 Wagner–Meerwein shift in aza-Nazarov cyclization: Bi(III)-catalyzed substrate-dependent divergent synthesis of highly substituted pyrroles and indenes†

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The Nazarov reaction and its variants such as aza-Nazarov and iso-Nazarov cyclizations are versatile methods for the synthesis of five-membered ring systems including pyrroles and indenes. The 1,2-Wagner Meerwein shift has been combined in a domino sequence with both Nazarov and aza-Nazarov-like reactions for the synthesis of cyclopentenone and indole derivatives, respectively. However, the same sequence has not been applied for the synthesis of pyrroles, possibly due to the high reactivity of 1-aza-pentadienyl cation intermediates. In this report, we present the first example of an aza-Nazarov/1,2-Wagner Meerwein shift domino sequence for the synthesis of highly substituted pyrroles. The use of Bi(III) as a mild main group metal catalyst was found to be crucial to control the high reactivity of the intermediate. The substrate demonstrated substituent-dependent divergence in product formation to selectively give indenes through iso-Nazarov cyclization. Detailed mechanistic investigations reveal the electrocyclization nature of the reaction involving a cationic intermediate generated under Lewis acid and/or 'hidden Brønsted acid' catalysis conditions.

Introduction

Pyrroles represent a pre-eminent heterocyclic molecular scaffold with a vast array of uses. They are ubiquitously found in natural products of both terrestrial and marine origins with a wide bioactivity profile including antibiotic, antitumor, antiviral activities *etc*.[1] Besides their natural occurrence, pyrroles are also a useful class of pharmacophores and agrochemicals (Fig. 1).[2] Atorvastatin, the cholesterol-lowering penta-substituted pyrrole drug, is one of the most successful FDA-approved drugs ever. Inspired by the rich chemistry of pyrroles in biochemical systems owing to their electron-rich nature, pyrroles have been used as synthons or advanced intermediates in organic synthesis especially within the realm of challenging natural product total synthesis.[3] The importance of pyrroles in organic materials applications has been growing steadily due to their excellent electronic properties such as a high-lying HOMO, high electrical conductivity *etc*.[4] The utility profile of indenes mirrors that of pyrroles quite well. They are naturally abundant and are also found as structural cores in FDA-approved drugs such as sulindac, dimetindene *etc.* (Fig. 1).[5] Besides these, both natural and synthetic indene analogues have been found to display a wide range of bioactivities including anti-cancer,[6a] anti-microbial,[6b] anti-allergic,[6c] and fungicidal activities.[6d] Given their importance, the synthesis of pyrroles[7] as well indenes[8] has continued to attract attention from synthetic chemists.

Nazarov cyclization,[9] a 4π-thermal conrotatory electrocyclization, and its highly useful variants such as aza-Nazarov,[10] iso-Nazarov,[11] and interrupted Nazarov cyclization[12] have been a cornerstone for the synthesis of five-membered carbocyclic as well as heterocyclic systems. While Nazarov and iso-Nazarov reactions lead to the formation of cyclopentenone derivatives, the aza-Nazarov reaction gives nitrogen-containing five-membered heterocycles such as pyrroles as products.[13] Sustained and ingenious efforts from various research groups have resulted in expanding the scope of these reactions.[14] The Frontier group merged the highly versatile 1,2-Wagner–Meerwein rearrangement as a subsequent step of the Nazarov cyclization to access carbocyclic spiro-systems.[15] Based on some early work by Moody and Rees,[16] the Driver group

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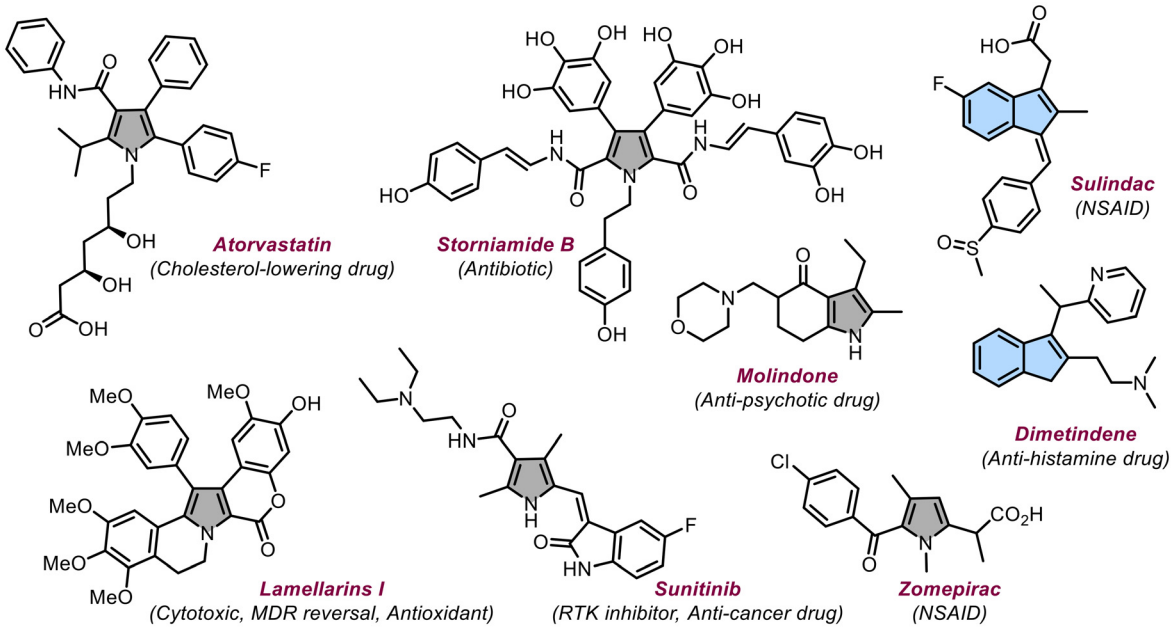


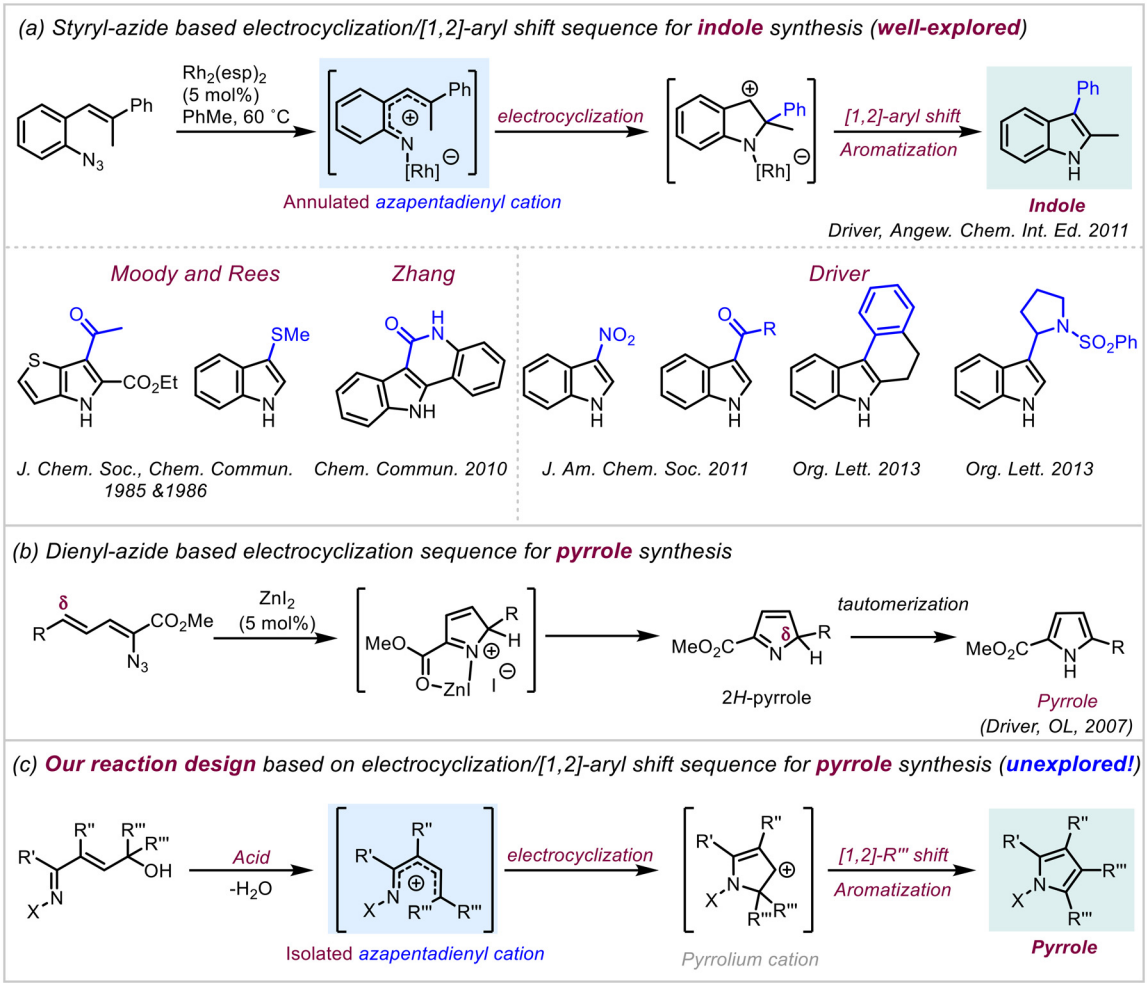
Fig. 1 Representative structures of drugs with pyrrole and indene scaffolds.

devised a strategy to merge C–N bond forming aza-Nazarov electrocyclization with the Wagner–Meerwein shift using a variety of styryl azide substrates under Rh(II) catalysis to obtain various types of indoles (Scheme 1a).[17] They proposed the involvement of a benzannulated 1-aza pentadienyl cation as the key intermediate for the electrocyclization followed by cationic rearrangement. Despite substantial mechanistic understanding, a similar domino sequence consisting of aza-Nazarov cyclization with Wagner–Meerwein rearrangement has not yet been applied for the synthesis of pyrroles. This would entail controlled generation and reactivity of the isolated 1-aza-pentadienyl cation, which is obviously challenging given the highly reactive nature of this cationic intermediate. Driver *et al.* have reported a synthesis of pyrroles from dienyl azide along the lines of indole synthesis, which involves cyclization of the aza-pentadienyl cation intermediate but it doesn't involve the 1,2-shift (Scheme 1b).[18] Their efforts to force the 1,2-shift by di-substitution on terminal carbon (δ) didn't yield any product, thus, underscoring the challenge of combining these two steps in a domino sequence with the non-annulated or isolated aza-pentadienyl cation. In our design, we hypothesized that the required non-annulated 1-azapentadienyl cation could be generated under mild acidic conditions from the 1-aza-1,3-pentadien-5-ol precursor (Scheme 1c). The cation could undergo facile electrocyclization to generate a pyrrolium cation with tetra-substituted carbon to trigger the 1,2-Wagner Meerwein rearrangement, which should eventually form a pyrrole upon aromatization.

Herein, we report the first example of a domino 4π electrocyclization/1,2-Wagner Meerwein rearrangement sequence for the synthesis of highly substituted pyrroles. The reaction was found to work optimally using $BiCl_3$, an inexpensive, mild and non-toxic main group metal catalyst, in DCE under ambient conditions.[19] Moreover, the reaction showed substrate-dependent divergent behaviour leading to highly efficient and selective synthesis of indenes through an alternative iso-Nazarov reaction pathway.

Optimization of the reaction conditions

In order to test our hypothesis, we synthesized tertiary alcohol **1a** and subjected it to various Lewis and Brønsted acidic conditions in DCE as the solvent. It was found to be highly reactive in the presence of most catalysts such as $Sc(OTf)_3$, $Cu(OTf)_2$, $InCl_3$, $SnCl_4$, $AlCl_3$, $BF_3{\cdot}OEt_2$ *etc.* leading to decomposition (Table 1, entries 1–3 and S1†). Among the catalysts attempted, $BiCl_3$ proved to be the most amenable. However, it gave penta-substituted pyrrole **3a** as the sole product in a good 55% yield instead of the expected pyrrole **2a** (Table 1, entry 4). Pyrrole **3a** seems to form from the electrophilic aromatic substitution reaction of pyrrole **2a** with the 1-azapentadienyl cation **Int-1** generated in the medium under catalytic conditions. The exclusive formation of **3a** also indicates that the rate of electrophilic aromatic substitution is at least comparable to that of the formation of pyrrole **2a**. At this point, we reasoned that increasing the amount of catalyst might ensure near simultaneous conversion of all 3° alcohol **1a** into the aza-pentadienyl cation intermediate, which will stop the reaction at pyrrole **2a** instead of **3a**. Hence, when the catalyst loading was increased to 0.2 equiv. and eventually to 1.2 equivalents, the selectivity switched in favour of the formation of pyrrole **2a** as the sole product, albeit in a modest yield of 33% (entries 5 and 6). Other Bi(III) catalysts such as $Bi(OTf)_3$ and acids such TFA and TfOH proved to be too harsh and gave much inferior



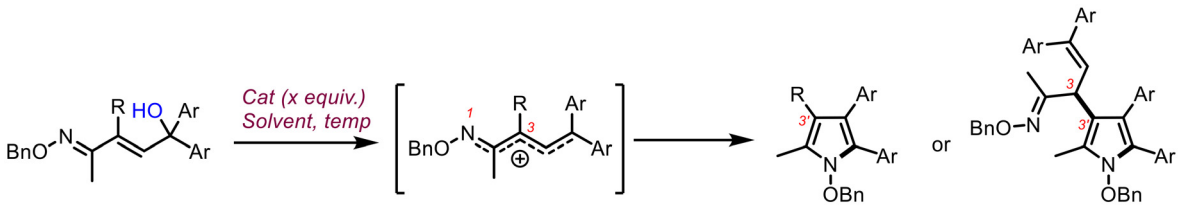
Scheme 1 (a) State of the art for the electrocyclization–Wagner Meerwein domino sequence for the synthesis of indoles; (b) synthesis of pyrroles from dienyl azide; (c) our reaction design.

results, predominantly leading to decomposition (entries 7 and 8). Except DCM, other solvents such as MeOH, THF, acetone, HFIP, DMF, DMSO *etc*. couldn't furnish any product, whereas toluene and acetonitrile showed slow reactivity and gave **3a** in a poor yield of 15% (entries 9 and 10 and S1†). Further increasing the amount of $BiCl_3$ to 2 equivalents led to lower yields (entry 11). The high reactivity of **1a** reinforced the need to block the C-3 position to protect the aza-pentadienyl cation intermediate (**Int-1**) from reacting with any potential nucleophile in the medium as well as preventing pyrrole **2a** from reacting further through electrophilic aromatic substitution. Hence, in the case of alcohol **1b** with a C-3 methyl substituent, the yield increased to 40%, which is not a significant increase. This result indicated that other factors might be responsible for the modest yields of the domino sequence (entry 12). Hence, we turned our attention to gauging the impact of the efficiency of the 1,2-Wagner–Meerwein shift, the second step of the domino sequence, on the yield of the reaction. It was presumed that an inefficient 1,2-shift might lead to decomposition of the reactive cationic intermediate. Indeed, when relatively more electron-rich *o*-tolyl was used as an aryl substituent in substrate **1c**, compared to the phenyl in **1b**, the yield of the corresponding pyrrole **2g** increased to an excellent 90% (entry 13). These two modifications *i.e.* blocking the C-3 position and using relatively electron-rich aryls allowed the reaction to be carried out successfully under catalytic conditions (20 mol% and 5 mol%) with an excellent yield of 87% (entries 14 and 15). Hence, we decided to proceed with an appropriate amount of $BiCl_3$ in DCE under ambient conditions as the optimal reaction conditions for the exploration of the scope of the aza-Nazarov/1,2-shift domino sequence.

Scope of the reaction for the synthesis of pyrroles

After optimizing various aspects of the reaction conditions for the electrocyclization–cationic rearrangement cascade, we proceeded to explore the scope of this reaction. At first, the scope with respect to the synthesis of tri-substituted pyrroles ($R^{3,4}$ =

Table 1 Optimization of reaction conditions for the synthesis of pyrroles **2** and **3**[a]



1a, R = H, Ar = Ph
1b, R = Me, Ar = Ph
1c, R = Me, Ar = *o*-tol

Int-1

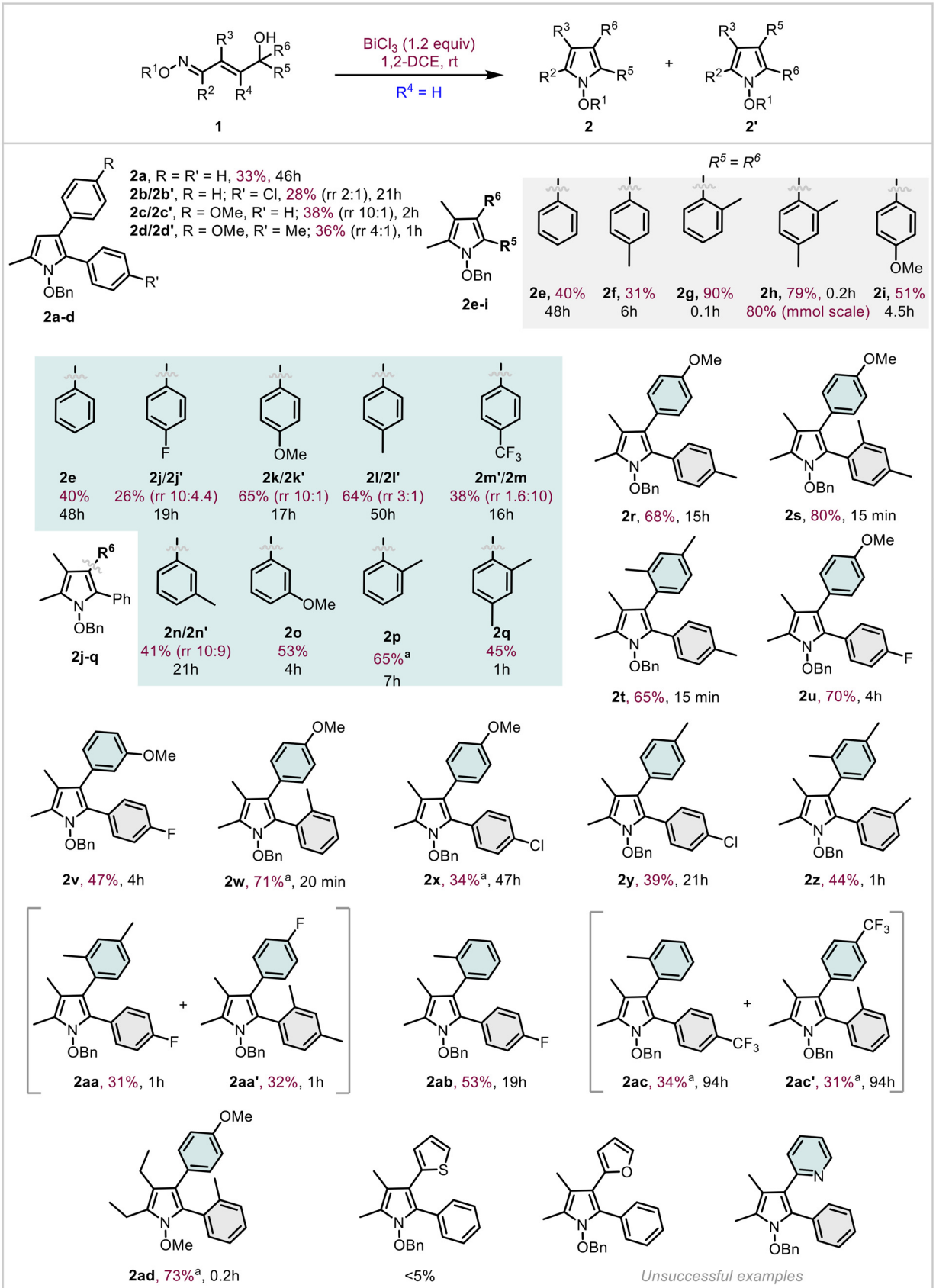
2a/2e/2g **3a**

Entry	Substrate	Catalyst	Loading (*x* equiv.)	Solvent	Yield[b] (%) 2a/2e/2g	Yield[b] (%) 3a
1	**1a**	$Sc(OTf)_3$	0.1	DCE	—	<5
2	**1a**	$Cu(OTf)_2$	0.2	DCE	—	<5
3	**1a**	$InCl_3$	0.2	DCE	—	<5
4	**1a**	$BiCl_3$	0.1	DCE	—	55
5	**1a**	$BiCl_3$	0.2	DCE	—	68
6	**1a**	$BiCl_3$	1.2	DCE	33	—
7	**1a**	$Bi(OTf)_3$	1.2	DCE	9	—
8	**1a**	TfOH/TFA	1.2	DCE	Trace	—
9	**1a**	$BiCl_3$	1.2	DCM	30	—
10	**1a**	$BiCl_3$	1.2	MeOH/THF/acetone/DMF/DMSO	Trace	—
11	**1a**	$BiCl_3$	2.0	DCE	29	
12	**1b**	$BiCl_3$	1.2	DCE	40	—
13	**1c**	$BiCl_3$	1.2	DCE	90	—
14	**1c**	$BiCl_3$	0.2	DCE	87	—
15	**1c**	$BiCl_3$	0.05	DCE	87	—

[a] Reaction conditions: **1** (0.1 mmol, 1 equiv.), $BiCl_3$ (as indicated), solvent (2 mL), rt. [b] Isolated yields after column chromatography.

H) was explored. As expected, the reactions were found to proceed with moderate efficiency and gave the expected products **2a–2d** in relatively modest yields (28–38%) (Scheme 2). Moreover, the products **2b–2d** were isolated as an inseparable mixture of two possible regioisomers emanating from migration of both the aryl groups (R^5, R^6) during the 1,2-shift. We then turned our attention to the synthesis of tetra-substituted pyrroles, beginning with identical aryl groups ($R^5 = R^6$) at the terminal carbon in **1**. The substrates with phenyl and 4-tolyl as aryl groups were found to give the corresponding pyrroles **2e** and **2f** in modest yields of 40% and 34%, respectively. Surprisingly, the substrates with 2-tolyl and 2,4-dimethylphenyl groups demonstrated much better reactivity and gave the corresponding pyrroles **2g** and **2h** in excellent 90% and 79% yields, respectively. Interestingly, these two pyrroles, owing to the presence of *ortho* methyl substituents and the resulting stereogenic axes, were obtained as a mixture of two atropisomers in ~0.7 : 1 ratio. Relatively more electron-rich 4-methoxyphenyl gave the product **2i** in a diminished 51% yield, due to its high reactivity.

We proceeded to explore the reaction with non-identical aryl groups ($R^5 \neq R^6$) at the terminal carbon, which could potentially give a mixture of regioisomeric pyrroles as the products. Towards this, a variety of alcohols with R^5 as phenyl and R^6 as variably substituted aryl groups were subjected to the reaction conditions. Expectedly, electron-donating substituents such as methoxy and methyl at the 4-position of R^6 demonstrated better reactivity and gave the corresponding products in good yields but as a mixture of regioisomers. In the case of *p*-methoxyphenyl, pyrroles **2k** and **2k′** were obtained as an inseparable mixture of regioisomers in the ratio of 10 : 1 in 65% combined yield. Similarly, *p*-tolyl gave a 3 : 1 mixture of regioisomeric pyrroles **2l**/**2l′** in 64% yield. 4-Fluorophenyl as R^6 led to pyrroles **2j** and **2j′** as a mixture of regioisomers in the ratio of 4.4 : 10 in 26% yield. The strongly electron-withdrawing CF_3 group showed diminished reactivity and gave a mixture of products **2m**/**2m′** in a 1.6 : 10 ratio in 20% yield. In contrast to *p*-substitution, electron-donating substituents at the *m*- and *o*-position displayed much better selectivity generally in 1,2-migration and gave the corresponding pyrroles **2n–2q**, predominantly as a single regioisomer in moderate to good yields (41–65%). We explored multiple other combinations of variably substituted aryls at R^5 and R^6 to obtain a range of pyrroles (**2r–2z**) in good to excellent yields. In all cases, the methoxy-substituted phenyl displayed distinct preference over other aryl groups in terms of their migrating tendency. Interestingly, combinations of *o*-tolyl with *p*-fluoro and *p*-CF_3 phenyls led to separable mixtures of regioisomeric pyrroles. Pyrroles **2aa**/**2aa′** and **2ac**/**2ac′** were obtained in an approximately 1 : 1 ratio, which could be a combined effect of the electronic and steric impact on the rate of 1,2-migration.[15] However, **2ab** was obtained predominantly as a single regioisomer in 53% yield



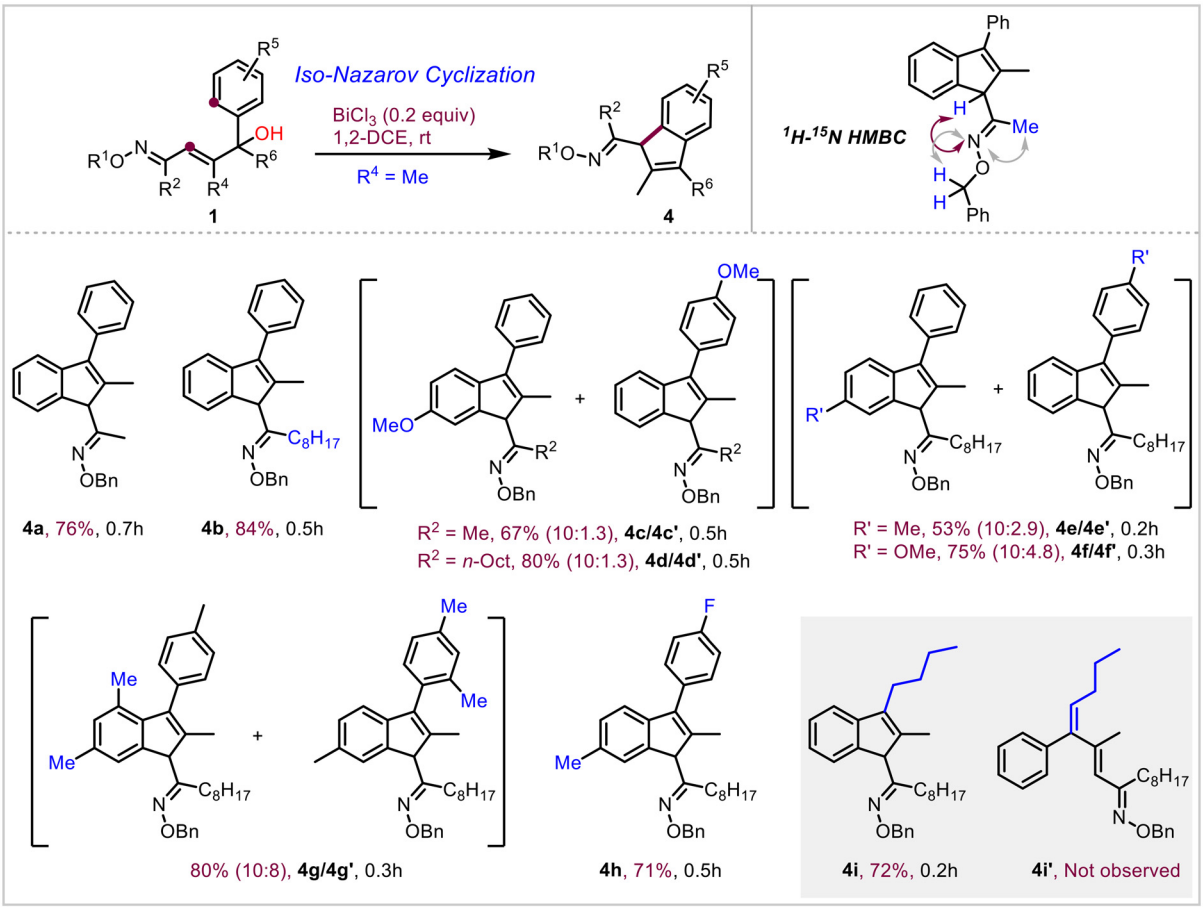
Scheme 2 Scope of the pyrrole synthesis. Reaction conditions: **1** (0.1 mmol, 1 equiv.), $BiCl_3$ (0.12 mmol, 1.2 equiv.), 1,2-DCE (2 mL), rt for the indicated time; [a] 0.2 equiv. of $BiCl_3$ were used.

with a small amount of the other isomer. The structures of the products were assigned based on NOE analysis of the regioisomers (Fig. S6–8†). The synthesis of pyrrole **2ad** in a good yield of 73% demonstrates that R^2 and R^3 are amenable for other alkyl substitutions. Heteroaryl substituents like furan and thiophene could not be tolerated in the reaction and led to complex reaction mixtures.

The scalability of a reaction is a good measure of its practicality. Pyrrole **2h** was obtained in an excellent 80% yield when the reaction was performed at 0.6 mmol scale (0.26 g), without any significant deviation from that of the small-scale reaction. Besides scalability, in general, the scope of pyrrole synthesis proved to be broad with the possibility of varying all the available positions on the pyrrole ring especially with aryl substituents.

Iso-Nazarov reaction for the synthesis of indenes 4

Interestingly, when the R^4 substituent in substrate **1** was changed to methyl instead of H, the reaction adopted a completely different path and proceeded through the iso-Nazarov pathway to give substituted indenes **4** as the sole products of the reaction under catalytic conditions and in very good yields generally (Scheme 3). The generality of this transformation was explored by varying different substituents in alcohol **1**. The oxime substituent R^2 as methyl and *n*-octyl worked very well and gave indenes **4a** and **4b** as the corresponding products in excellent yields of 76% and 84%, respectively. When two electronically different aryl groups were used as R^5 and R^6 substituents, the indenes were obtained as an inseparable mixture of regioisomeric products due to the possibility of cyclization through both the aryl groups. With R^5/R^6 as *p*-methoxyphenyl and phenyl, indenes **4c**/**4c′** were obtained in 67% yield with a 10 : 1.3 ratio, which remained the same for indenes **4d**/**4d′** with R^2 being *n*-octyl. Similarly, when one of the aryl groups was *p*-tolyl, indenes **4e**/**4e′** were obtained in 53% yield in a 10 : 2.9 ratio. A combination of 2,4-mesityl and *p*-tolyl substituents led to an almost equimolar ratio of **4g**/**4g′** in an excellent 80% combined yield. Electronically different *p*-fluoro phenyl and *p*-tolyl gave indene **4h** as a single regioisomer in 71% yield. Interestingly, when *n*-butyl was used as one of the R5/R6 substituents, the reaction still proceeded efficiently and gave indene **4i** in a very good yield of 72%. Notably, the possible highly conjugated elimination product **4i′** was not observed in

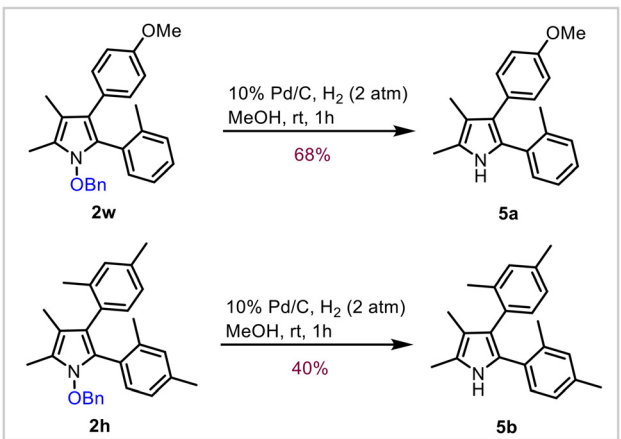


Scheme 3 Scope of the formation of indenes **4** through iso-Nazarov cyclization. Reaction conditions: **1** (0.08 mmol, 1 equiv.), $BiCl_3$ (0.016 mmol, 0.2 equiv.), 1,2-DCE (2 mL), rt.

the reaction, which indicates the selective nature of the reaction for iso-Nazarov cyclization over facile elimination. The position of the double bond in the indene ring was confirmed through $^{1}H-^{15}N$ HMBC correlation in indene **4a**, which showed strong three-bond correlation of the oxime nitrogen with the methine proton (Scheme 3, top right and Fig. S9, ESI†).

N–O bond cleavage for the synthesis of NH-pyrroles

In order to demonstrate the suitability of this methodology to obtain NH-pyrroles, we carried out N–O bond hydrogenation in pyrroles **2w** and **2h** under Pd/C conditions to obtain the corresponding NH-pyrroles **5a** and **5b** in 68% and 40% yields, respectively (Scheme 4). This further expands the scope of the reaction to obtain *N*-unsubstituted pyrroles, which are amenable for further functionalization.



Scheme 4 N–O bond hydrogenation for the synthesis of NH-pyrroles **5a** and **b**.

Crystal structures of the pyrroles

The structures of the product pyrroles were confirmed through single crystal X-ray structural analysis of compounds **2w** (left) and **2x** (right) (Fig. 2 and S1, 2†).

Mechanistic experiments

Impact of the double-bond geometry

In order to gain insights into the possible mechanism of the reaction, we conducted a range of relevant experiments. The efficiency of 4π-electrocyclization reactions is known to be impacted by the shape or conformation of the reactive intermediate and the ensuing transition states.[13a,20] In order to gauge any such potential impact of the C3–C4 double bond

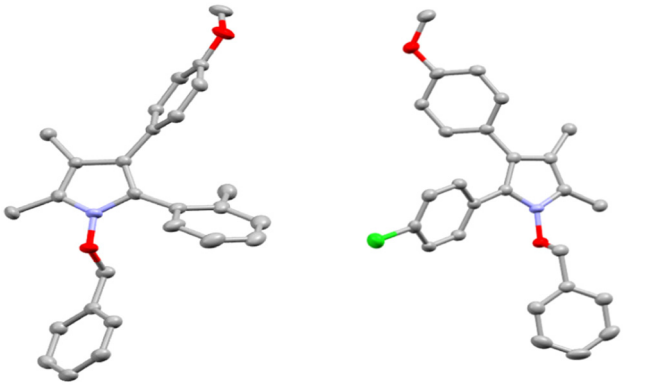
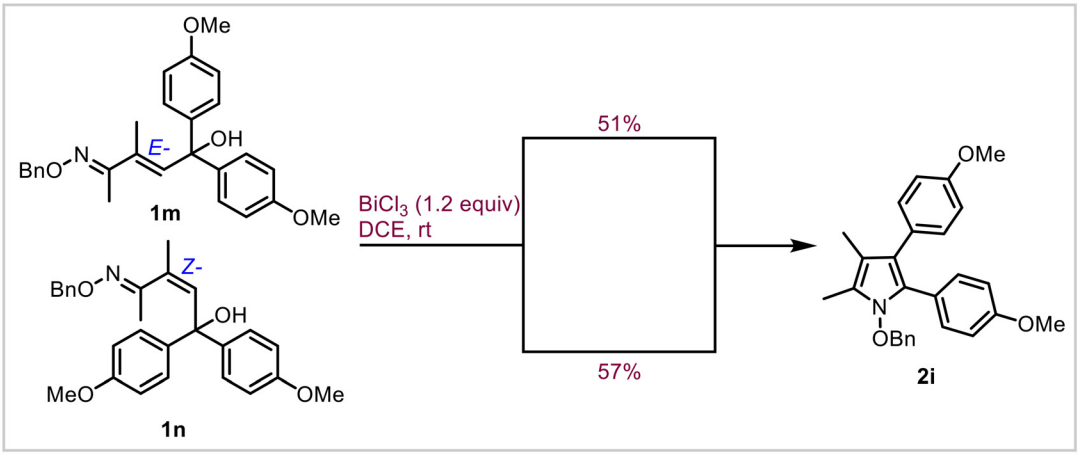


Fig. 2 Single crystal X-ray structures of pyrroles **2w** (CCDC 2413039) and **2x** (CCDC 2413038).†

geometry on the efficiency of this reaction, pure *E*- and *Z*-diastereomers were reacted separately under the reaction conditions. The *Z*-isomer **1n** reacted more efficiently than the *E*-isomer **1m** and gave pyrrole **2i** in 57% *versus* 51% yield, respectively, which hints at the electrocyclization nature of the pyrrole formation (Scheme 5 and Fig. S3–5†).

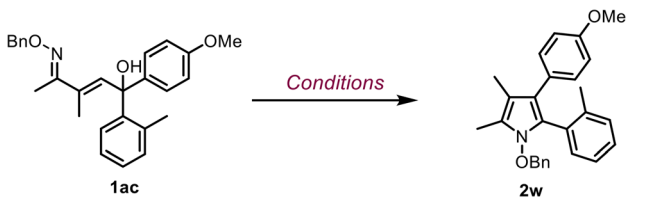
Potential role of hidden Brønsted acid catalysis

The role of the so-called 'hidden Brønsted acid catalysis' in the case of Lewis acid catalysed reactions is well documented.[21] Hence, it is important to delineate the possible mechanistic pathways as well as the catalytic species in such reactions. In the light of such literature precedence, we investigated this transformation through a series of experiments under suitable conditions with alcohol **1ac** as the substrate to obtain pyrrole **2w**. Initially, the reaction was carried out using varying amounts of $BiCl_3$ in normal DCE under ambient conditions to gauge the efficiency and the rate of the product formation. The reaction was found to be equally effective under 20 mol% and 2 mol% catalyst loading (Table 2, entries 1 and 2). However, the rate of the reaction decreased significantly from 20 min with 20 mol% to 5 h with 2 mol%. 1 mol% catalyst loading led to a highly inefficient reaction with incomplete conversion and a poor yield of 12% (entry 3). In order to study the impact of any hidden Brønsted acid, the reaction was carried out under dry conditions (dry DCE and N_2 atmosphere), which didn't result in any significant difference in the yield of the reaction (72%). However, it did prolong the reaction time to 2 h from 20 min (entry 4 *vs.* 1), possibly due to the slow generation of HCl during the cyclization under these conditions. In another experiment, water was used as a co-solvent with DCE (10% v/v) which resulted in a significantly reduced yield of only 37% after a substantially prolonged reaction time of 50 h (entry 5). This clearly indicates the inhibitory effect of excess water on the reaction. In order to further support this observation, we carried out the reaction in the presence of 1N HCl instead of $BiCl_3$, which gave the product in a comparable 42% yield, thereby, confirming the earlier observation (entry 6). Based on these experiments, it may be concluded that the reaction is



Scheme 5 Impact of the double bond geometry on the efficiency of aza-Nazarov cyclization.

Table 2 Experiments for investigating the role of a hidden Brønsted acid



S. no.	Reaction conditions	Time	Yield (%)
1	$BiCl_3$ (20 mol%), DCE	20 min	71
2	$BiCl_3$ (2 mol%), DCE	5 h	71
3	$BiCl_3$ (1 mol%), DCE	48 h	12
4	$BiCl_3$ (20 mol%), dry DCE, N_2 atm.	2 h	72
5	$BiCl_3$ (20 mol%), DCE/H_2O (9 : 1)	50 h	37
6	1 N HCl, DCE	16 h	42

catalyzed either by $BiCl_3$ alone or cooperatively with a hidden Brønsted acid resulting from the trace amount of moisture in the solvent.

Hammett relationships

Hammett equations have been traditionally employed to gain mechanistic insights into organic reactions especially with respect to the effect of substituents. Since we presumed the generation of cationic intermediates in the reaction, analysing from the perspective of Hammett relationships seemed pertinent. We used the regioisomeric ratios of the pyrroles (**2j**/**2j′**, **2k**/**2k′**, **2l**/**2l′**, **2m**/**2m′**) obtained in the case of non-identical aryl substituents (R^5, R^6) on the terminal carbon of the 1-azapentadienyl system to plot the reaction rates against substituent constants σ_{para} and σ^+ to gain insights into the nature of the 1,2-shift (Fig. 3A and B). In both cases, a linear relationship was observed with the reaction rate. The linear plot of the rate constant against σ_{para} gives a value of −2.049 for the reaction constant ρ for this reaction. ρ being a non-zero value suggests that the reaction is sensitive to the nature of substituents and it being a negative value indicates a build-up of positive charges or cationic intermediates during the course of the reaction.

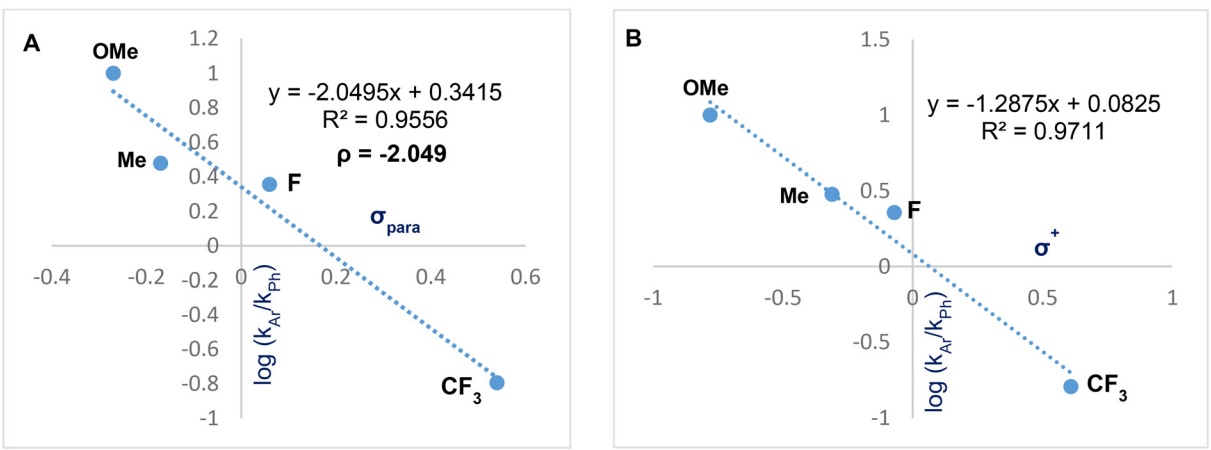
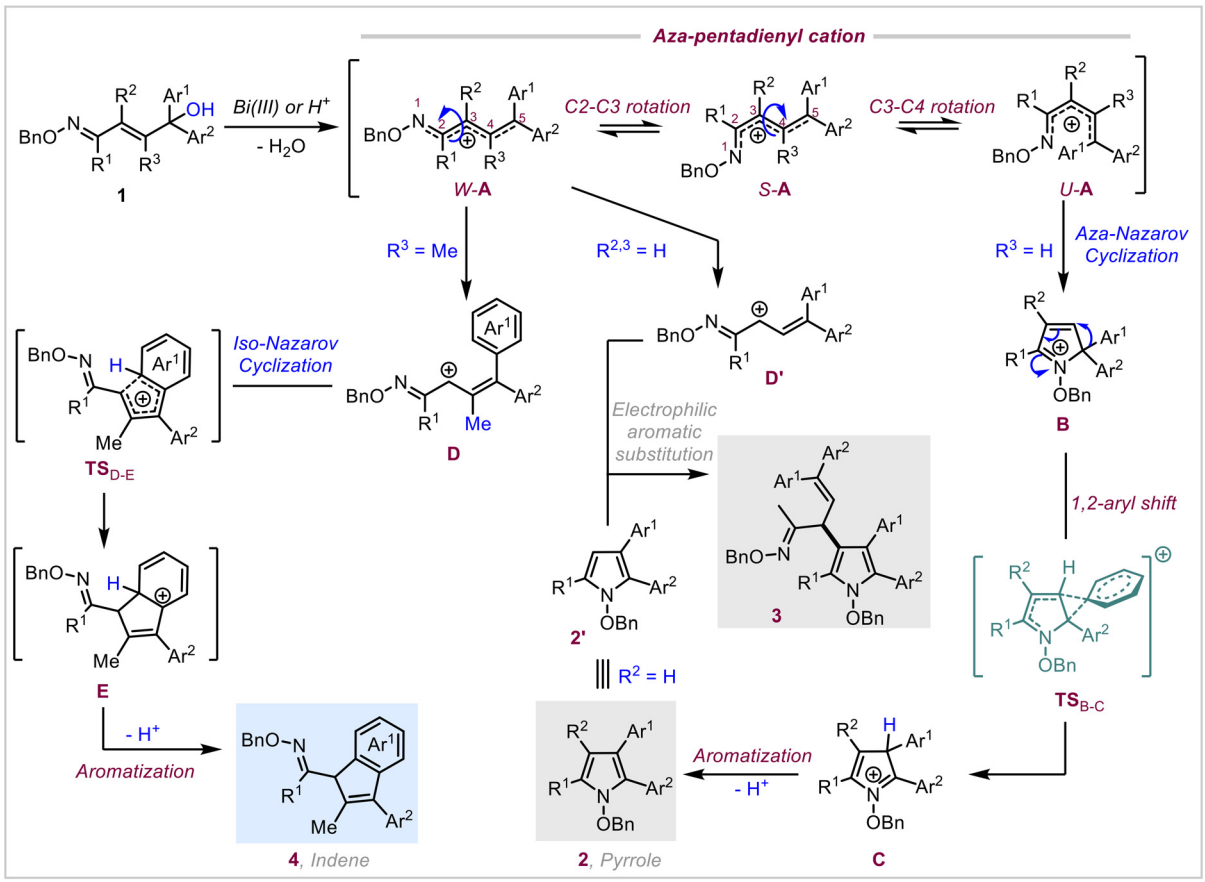


Fig. 3 Hammett plots of (A) σ_{para} *vs.* log (k_{Ar}/k_{Ph}) and (B) σ^+ *vs.* log (k_{Ar}/k_{Ph}).

Proposed mechanism

Based on the mechanistic insights gained above and literature precedence,[13,17,18] the following plausible mechanism may be proposed for the synthesis of the primary products pyrrole **2** and indene **4** as well as the secondary product pyrrole **3** (Scheme 6). The Bi(III) catalyst and/or the hidden Brønsted acid mediated dehydration to generate the aza-pentadienyl cation **A** is the common first step in the formation of all three products. The reaction shows divergence in product formation depending primarily on the nature of the R^3 substituent which gets eliminated in the last step of the domino sequence and enables aromatization in pyrrole **2**. Hence, when R^3 is a hydrogen, the cation **A** generated likely in the 'W'-conformation[13a] (W-A) has to undergo two C–C bond rotations – along C2–C3 and C3–C4 – to attain the U-conformation (U-A), which is required for electrocyclization. Based on DFT calculations,[13a] the C–C bond rotations have been shown to be energy-intensive steps in these systems which is also reflected in this reaction through the difference in the efficiency of product formation from *E*- and *Z*-isomers of the substrate (Scheme 5). Attainment of the U-conformation leads to the formation of the pyrrolium cation intermediate **B** through 4π-electrocyclization. The 1,2-aryl shift in **B** through the cationic transition state TS_{B-C} leads to the formation of the 3*H*-pyrrolium cation **C**, which undergoes aromatization through the loss of the 3H-proton to form pyrrole **2** as the final product. When both $R^{2,3}$ are hydrogens, penta-substituted pyrrole **3** is obtained as the product in the presence of a catalytic amount of the catalyst. Under catalytic conditions only a limited amount of the aza-pentadienyl cation **A** is generated at any time, which leads to a build-up of pyrrole **2′** in the presence of cation **A**. This results in a facile electrophilic aromatic substitution reaction between **2′** and **A**, thus, giving per-substituted pyrrole **3** as the final product. The simultaneous and exclusive formation of **3** under these conditions indicates a comparable or faster rate of electrophilic aromatic substitution compared to the formation of pyrrole **2**.

The substrates with a non-hydrogen R^3 substituent such as methyl, on account of their inability to undergo aromatization to form a pyrrole, undergo the competing iso-Nazarov pathway through the cationic intermediate **D**. **D** possibly undergoes cyclization through the TS_{D-E} to form **E**, which undergoes re-aromatization of the aryl ring through the loss of a proton to form indene **4** as the final product. This reaction pathway is well-precedented for the synthesis of indenes.[11] However, the reaction may also proceed through a simple electrophilic aromatic substitution to give the same product.



Scheme 6 Proposed mechanism for the formation of pyrroles **2**, **3** and indene **4**.

Conclusion

In conclusion, we have developed a mechanistically novel synthesis of highly substituted pyrroles through a domino sequence of aza-Nazarov cyclization followed by a 1,2-Wagner Meerwein shift of the aryl groups. The substrate demonstrated substituent-dependent divergence in product formation to give indenes through iso-Nazarov cyclization, besides pyrroles. The highly reactive nature of the 1-azapentadienyl cation intermediate necessitated using Bi(III) as a mild catalyst under ambient conditions for the successful synthesis of pyrroles as well as indenes. The reactions were found to generally work better with electron-rich substituents on the aryl ring. The methodology was found to possess wide scope and efficient scalability. Mechanistic investigations indicate the electrocyclization nature of the reaction involving a cationic intermediate generated cooperatively under Lewis and Hidden Brønsted acid catalysis. Hopefully, the structural as well as mechanistic determinants of the domino sequence presented in this manuscript will spur further explorations in this domain along the lines of explorations for indole synthesis.

Experimental section

General procedure for the synthesis of pyrroles 2

To a clean and dried vial containing a stir bar were added $BiCl_3$ (0.02–1.2 equiv.) and alcohol **1** (1.0 equiv.). The mixture was dissolved in 2 mL of DCE. The reaction mixture was stirred at room temperature and the progress of the reaction was monitored using TLC (EtOAc/hexane 1 : 10) under UV exposure. After completion, as demonstrated by the full consumption of alcohol **1** on TLC, the reaction mixture was quenched with saturated aq. $NaHCO_3$, and the layers were separated. The aqueous layer was washed with DCM (3 × 10 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* to obtain the crude mixture. The pure product pyrrole **2** was obtained by silica gel column chromatography using 0–2% diethyl ether in hexane as the mobile phase (eluent).

General procedure for the synthesis of indenes 4

To a clean and dried vial containing a stir bar were added $BiCl_3$ (0.02 mmol, 0.2 equiv.) and alcohol **1aj** (0.11 mmol, 1.0 equiv.). The mixture was dissolved in 2 mL of DCE. The reaction mixture was stirred at room temperature and the progress of the reaction was monitored using TLC (EtOAc/hexane 1 : 10) under UV exposure. After completion, as demonstrated by the full consumption of alcohol **1aj** on TLC, the reaction mixture was quenched with saturated aq. $NaHCO_3$, and the layers were separated. The aqueous layer was washed with DCM (3 × 10 mL) and the combined organic layer was dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* to obtain the crude mixture. The pure product **4a** was obtained by column chromatography using 0–2% diethyl ether in hexane as the mobile phase (eluent).

Data availability

The data supporting this article have been included as part of the ESI.† Crystallographic data for compounds **2w** and **2x** have been deposited at the CCDC under accession numbers 2413039 and 2413038, respectively.†

Conflicts of interest

The authors declare no conflict of interest.

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