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Exploring the Labile Nature of 2,4,6-Trimethoxyphenyl Moiety in Allylic Systems under Acidic Conditions

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Abstract

An investigation of the unexpected lability of the C_{sp3}-C_{sp2} bond connecting 2,4,6-trimethoxyphenyl group and an allylic moiety is carried out. We observed that the catalytic presence of either Lewis or Brønsted acid can render such 2,4,6-trimethoxyphenyl group labile. Several nucleophiles were found to substitute the labile C-C bond in mild reaction conditions resulting in very good yields of the allylated products. Even in the absence of a nucleophile, intramolecular cyclization of the parent substrate under acidic activation caused the labile C-C bond to cleave. A major motivation of this study is to understand the lability of electron-rich aryl group in acidic medium, employing 2,4,6-trimethoxyphenyl moiety as a case study. A plausible mechanism is proposed after carrying out several control reactions as well as UV-Vis and ^{1}H NMR spectroscopic studies. This work provides an insight into the activation of electron-rich arenes as a labile entity in acidic medium while also adding a conceptually novel C-C bond breaking approach to the vast literature of allylation of arenes.

Keywords

C-C bond activation, allylation of arene, 1,3,5-trimethoxybenzne, carbon-based leaving group, acidic labilization of arene.

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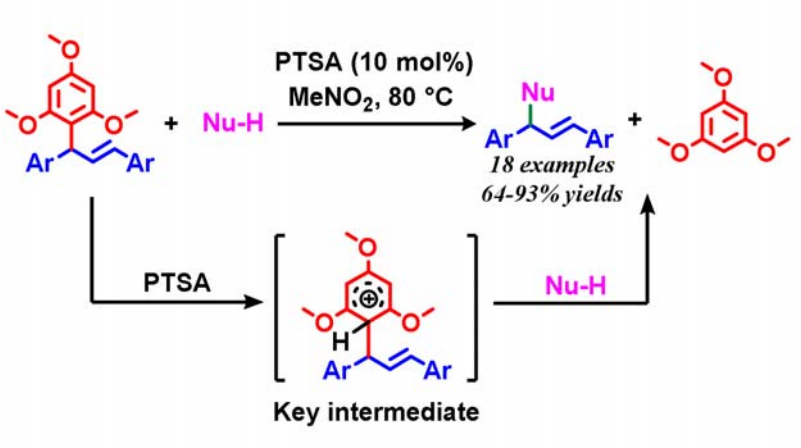
Graphical Abstract



Key Topic: C-C bond activation

Table of Contents text: A study aimed to comprehand the labile behavior of electron-rich aryl groups connected to allylic framework under acidic medium. Reveresible protonation and deprotonation at the *ipso*-carbon was found to be a driving factor in the C-C bond breaking reaction

Introduction

High thermodynamic stability of the C-C bond has not only made it ubiquitous but has also narrowed the avenue of the literature that explores the cleavage of C-C bonds. Generally, the small pool of C-C bond breaking reactions present in the literature exploits one or more of these three susceptibilities: i) release of ring strain; ii) chelation assistance; iii) cleavage of stable functional fragments such as allyl, carbonyl, cyano etc.[1] Recently a lot of interests have been focussed on the cleavage of stable carbon-based fragments for application in organic syntheses. In this regard, several 1,3-dicarbonyl species, as well as electron-rich arene such as 1,3,5-trimethoxybenzene (TMB) have been reported to act as carbon-based leaving groups (Figure 1).[2]

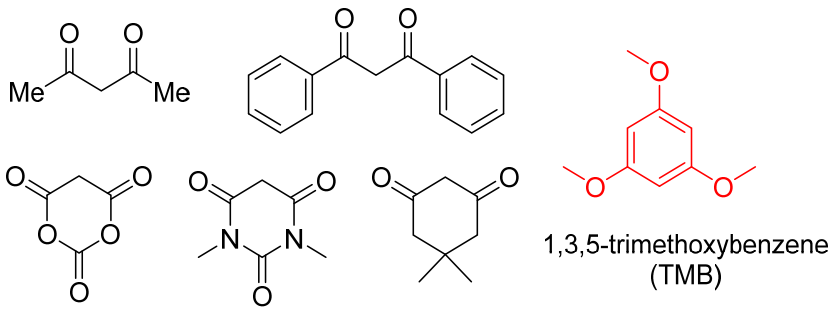
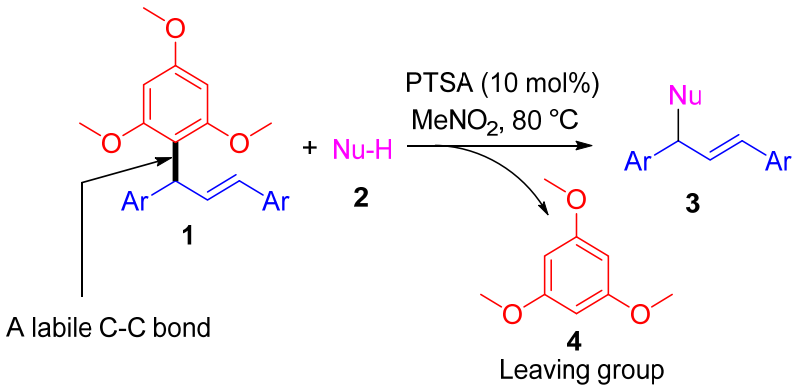


Figure 1: Molecules that cleave as stable fragments in C-C bond breaking reaction.

While different research groups have explored the chemistry of 1,3-dicarbonyl species as the cleaving fragment, we continue our role in exploring the cleavage of 1,3,5-trimethoxybenzene. In our previous works, we have revealed the leaving ability of the 2,4,6-trimethoxyphenyl moiety from benzylic systems to synthesize triarylmethanes.[2o-p] Herein, we investigate the labile nature of the 2,4,6-trimethoxyphenyl group in allylic systems using conventional and spectroscopic techniques. We have observed that the 2,4,6-trimethoxyphenyl group can readily be replaced from the allylic systems by various nucleophiles through the cleavage of the C_{sp3}-C_{sp2} bond (Scheme 1). Nucleophiles such as indoles, 2-methylfuran, 2-methylthiophene, 4-hydroxycoumarin, 4-methoxythiophenol etc. reacts smoothly to generate the corresponding derivatives in good yields while generating TMB as the by-product. We have also noted that TMB is eliminated even in the absence of a nucleophile via a C-C bond cleavage as a result of intramolecular cyclization in substrate **1** under acidic conditions. The C-C bond breaking reaction takes place in mild conditions in the presence of a Lewis or Brønsted acid. We have examined the lability of 2,4,6-trimethoxyphenyl group under various reaction conditions and in several structurally diverse substrates. Additionally, we have focussed our efforts to understand the mechanistic pathway involved in the activation of the electron-rich arene. In this regard, we have carried out

various control reactions as well as UV-Vis and ^{1}H NMR spectroscopic studies. The spectroscopic experiments suggested that the reversible protonation of the 2,4,6-trimethoxyphenyl group of **1a** in acidic medium may drive the C-C bond breaking reaction.

While exploring the lability of TMB, the results of this study also offer a viable approach of inducing lability to electron-rich aryl groups in general. As per our knowledge, there are no reports in the literature focussed at studying the labilization of such arenes in allylic systems. As a result, few reports that observed the labile nature of electron-rich arenes in acidic medium termed it unexpected.[3] We believe that the findings of this work offer an explanation to this seemingly unexpected cleavage of electron-rich arenes. The preliminary understanding revealed through this report may trigger more research directed at exploring various possible applications borne out of acidic labilization of electron-rich arene. Moreover, the C-C bond breaking reaction may be applied for the allylation of various arenes as represented in Table 2 where mild metal-free reaction conditions generate good yields of the products in short reaction times. This method of allylation of arenes via C-C bond cleavage adds a conceptually novel approach to the vast existing literature.[4]



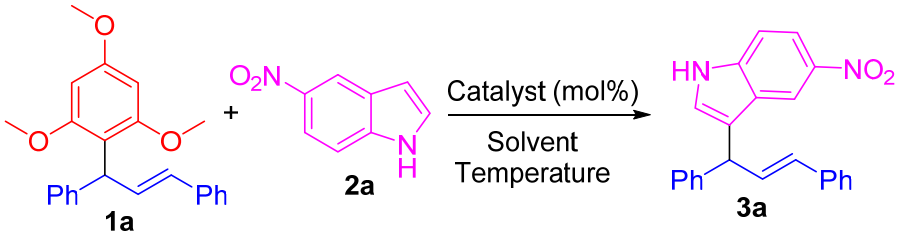
Scheme 1: Seemingly robust C-C bond turns labile in acidic medium.

Results and Discussion

With the relevant knowledge of activation of 2,4,6-trimethoxyphenyl group in acidic medium, we have reacted (*E*)-(3-(2,4,6-trimethoxyphenyl)prop-1-ene-1,3-diyl)dibenzene **1a** with model nucleophile 5-nitroindole **2a** in various conditions (Table 1). Lewis acidic metal triflates such as AgOTf, $Sn(OTf)_2$ and $Cu(OTf)_2$, activated the 2,4,6-trimethoxyphenyl group efficiently and led to the substitution product **3a** in more than 80% yields (Table 1, entries 1, 3-4). Although $Sc(OTf)_3$ was previously shown to interact strongly with 1,3,5-trimethoxybenzene,[5] it did not prove to be efficient in the C-C bond breaking reaction producing only moderate yield of the desired product (Table 1, entry 2). In benzylic systems $FeCl_3$ was demonstrated to best activate the 2,4,6-trimethoxyphenyl group but the catalyst's

supremacy does not extend to allylic systems as modest 73% yield of the substitution product **3a** is formed leaving some **1a** unreacted (Table 1, entry 6).[2o-p] But analogous to benzylic systems, $ZnCl_2$ fails to activate the 2,4,6-trimethoxyphenyl group in allylic systems as **1a** and **2a** remains unreacted in the reaction medium (Table 1, entry 7).[2p] When we tried Brønsted acids, we found that *p*-toluenesulfonic acid (PTSA) generates 91% yield of the substitution product **3a** by rendering the 2,4,6-trimethoxyphenyl group extremely labile (Table 1, entry 10). However, a stronger acid such as triflic acid (TfOH) produces a messy reaction profile (Table 1, entry 11). Other acids such as HCl and trifluoroacetic acid can also activate the electron-rich arene to moderate extent (Table 1, entries 12-13). Although both Lewis acids and Brønsted acids are comparably effective in activating the labile C_{sp3}-C_{sp2} bond, we have chosen PTSA for all the future studies. On examining the effect of various solvents employing PTSA as the catalyst, we found that both polar aprotic and non-polar aprotic solvents serve as good medium for the activation of the arene (Table 1, entries 10, 14-17). However, protic solvents such as EtOH and ^{i}PrOH stop the C-C bond breaking reaction altogether (Table 1, entries 18-19). This may be understood as extremely rapid proton-exchange between protons of the 2,4,6-trimethoxyphenyl group and the protic solvent may not allow time for a nucleophile to participate in the reaction.[5] We have also found that the reaction rate depends on temperature, as only 56% yield of **3a** is isolated after 10 h of reaction at room temperature. Gradual increase in the temperature increases the rate of the reaction as evident from Table 1 entries 10, 20-22. A 10 mol% loading of the catalyst PTSA has provided maximum amount of the substitution product, higher catalyst loading generates an unclean reaction profile while lower loading makes the reaction considerably sluggish (Table 1, entries 10, 23-24).

Table 1: Lability of 2,4,6-trimethoxyphenyl group under various reaction conditions.[a]



Entry	Catalyst	Solvent	Temp. (°C)	Yield (%)[b]
1	AgOTf	$MeNO_2$	80	81
2	$Sc(OTf)_3$	$MeNO_2$	80	55
3	$Sn(OTf)_2$	$MeNO_2$	80	86

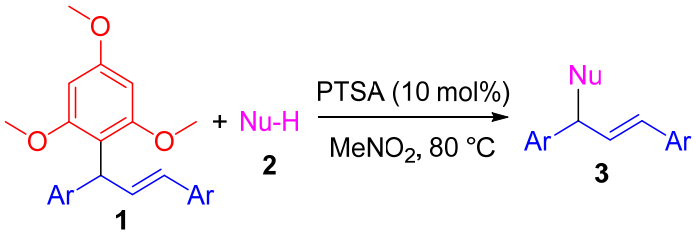
4	$Cu(OTf)_2$	$MeNO_2$	80	85
5	$Yb(OTf)_3$	$MeNO_2$	80	22
6	$FeCl_3$	$MeNO_2$	80	73
7	$ZnCl_2$	$MeNO_2$	80	-
8	$SnCl_2.H_2O$	$MeNO_2$	80	48
9	$BiCl_3$	$MeNO_2$	80	51
10	PTSA	$MeNO_2$	80	91
11	TfOH	$MeNO_2$	80	75
12	HCl	$MeNO_2$	80	32
13	CF_3COOH	$MeNO_2$	80	54
14	PTSA	MeCN	80	81
15	PTSA	Toluene	80	85
16	PTSA	DCE	80	87
17	PTSA	THF	reflux	32
18	PTSA	EtOH	reflux	-
19	PTSA	^{i}PrOH	80	-
20	PTSA	$MeNO_2$	25	15
21[c]	PTSA	$MeNO_2$	25	56
22	PTSA	$MeNO_2$	50	72
23[d]	PTSA	$MeNO_2$	80	84
24[e]	PTSA	$MeNO_2$	80	70

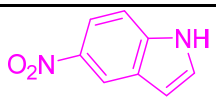
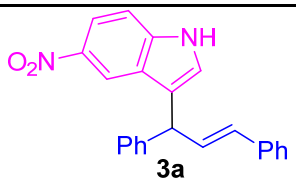
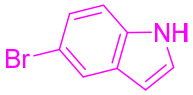
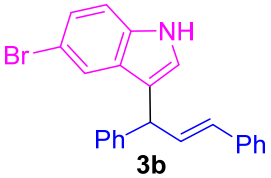
[a]Reaction conditions: **1a** (0.55 mmol), **2a** (0.5 mmol), solvent 2 mL, catalyst (10 mol%), temp. 80 °C, time 1 h; [b]Isolated yields; [c]time 10 h; [d]catalyst (5 mol%); [e]catalyst (20 mol%).

After defining the reaction conditions that best activates the 2,4,6-trimethoxyphenyl group, we set out to study the effect of various nucleophiles on the C-C bond breaking reaction. Initially, we investigated various derivatives of indoles **2a**-**e** as nucleophiles and isolated good to very good yields of the corresponding products **3a**-**e** (Table 2, entries 1-5). 5-membered heteroarenes such as 2-methylfuran **2f** and 2-methylthiophene **2g** also gave the desired reaction smoothly (Table 2, entries 6-7). Labile 2,4,6-trimethoxyphenyl group was also readily substituted by 4-hydroxycoumarin **2h** and 1,3-dimethoxybenzene **2i** yielding the desired products **3h** and **3i** in 92% and 78%, respectively (Table 2, entries 8-9). In all cases, the leaving TMB **4**, generated by the C_{sp3}-C_{sp2} bond cleavage, was also recovered during chromatographic purification of the reaction mixtures. A measure of the lability of the C-C

bond under study may be grasped from the reaction of 4-methoxythiophenol **2j** with **1a** where a new C-S bond replaces a C-C bond (Table 2, entry 10). The unlikely exchange of a usually strong C-C bond by a weaker C-S bond is made feasible under acidic activation of the electron-rich arene as suggested by the studies presented later. When we treated substrate **1a** with allyltrimethylsilane **2k**, we obtained a moderate 64% yield of the desired product **3k** while 3-phenyl-1*H*-indene **5** was formed as a side-product via intramolecular cyclization (Table 2, entry 11). The formation of indene **5** is further explained in Scheme 2B. We have also studied if the allylic backbone connected to the 2,4,6-trimethoxyphenyl group plays any crucial role in determining the lability of the C-C bond. To postpone the question of regioselectivity, initially we have chosen symmetric substituents on the allylic backbone as shown in substrate **1a-1e** (Table 2). We have noticed that the lability of the 2,4,6-trimethoxyphenyl group does not differ significantly when aromatic or heteroaromatic substituents are present symmetrically in the allylic backbone as very good yields after C-C bond cleavage were observed (Table 2, entries 12-15). It needs to be pointed out that in all the reactions presented in Table 2, the *trans*-configuration of the double bond in the allylic backbone was preserved.

Table 2: Effect of nucleophile and the allylic moiety on the C-C bond breaking reaction.[a]



Entry	Ar-, **1**	Nu-H **2**	Product **3**	Yield of **3** (%)[b]
1	Ph-, **1a**	 **2a**	 **3a**	91
2	Ph-, **1a**	 **2b**	 **3b**	84

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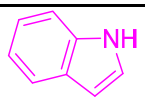
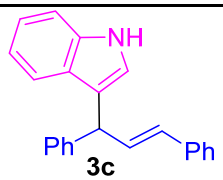
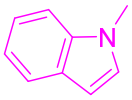
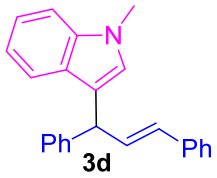
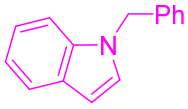
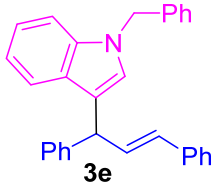
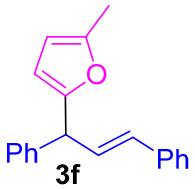
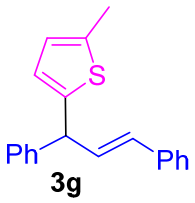
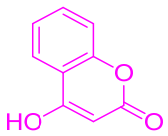
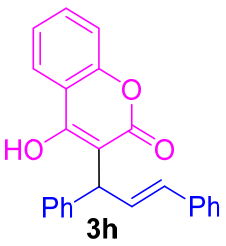
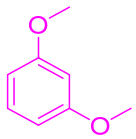
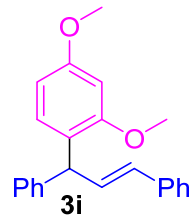
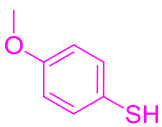
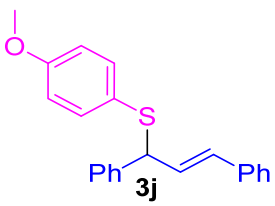
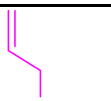
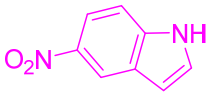
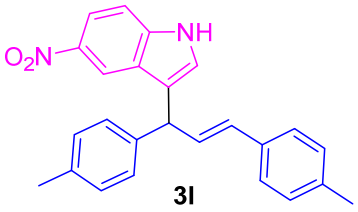
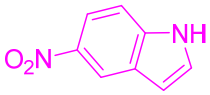
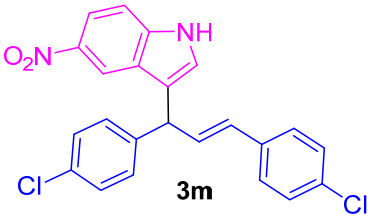
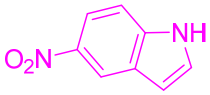
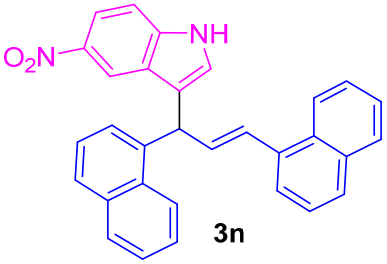
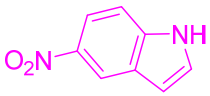
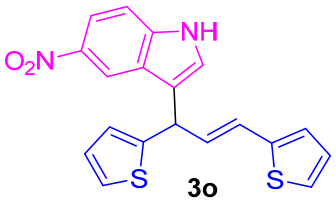
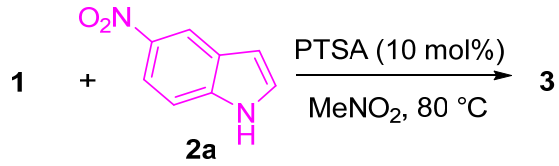
3	Ph-, **1a**	 **2c**	 **3c**	85
4	Ph-, **1a**	 **2d**	 **3d**	76
5	Ph-, **1a**	 **2e**	 **3e**	81
6	Ph-, **1a**	 **2f**	 **3f**	89
7	Ph-, **1a**	 **2g**	 **3g**	83
8	Ph-, **1a**	 **2h**	 **3h**	92
9	Ph-, **1a**	 **2i**	 **3i**	78
10	Ph-, **1a**	 **2j**	 **3j**	81

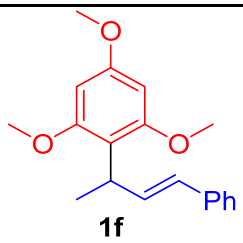
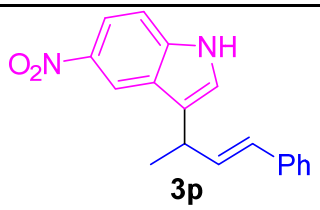
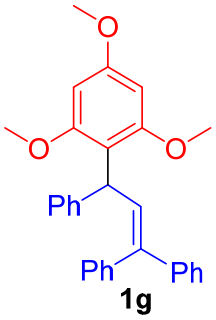
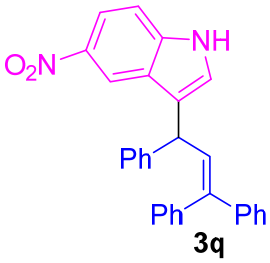
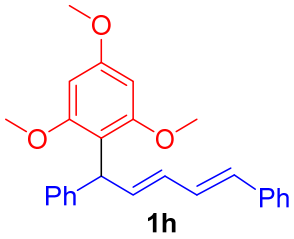
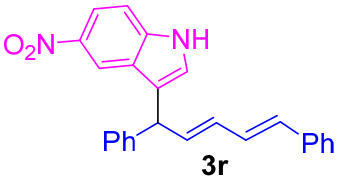
11	Ph-, **1a**	 **2k**	 **3k**	64
12	4-MeC$_6$H$_4$-, **1b**	 **2a**	 **3l**	87
13	4-ClC$_6$H$_4$-, **1c**	 **2a**	 **3m**	88
14	1-Napthyl-, **1d**	 **2a**	 **3n**	87
15	2-Thienyl-, **1e**	 **2a**	 **3o**	83

[a]Reaction conditions: **1** (0.55 mmol), **2** (0.5 mmol), PTSA (10 mol%), $MeNO_2$ 2 mL, temp. 80 °C, time 1 h. [b]Isolated yields.

When substrate **1** was unsymmetrically substituted, the reaction with nucleophile **2a** resulted in the formation of a single isomer in very high yield (Table 3). The reaction of substrate **1f** and **1g** produced **3p** and **3q** respectively, where the nucleophile attacked the less hindered terminus of the allylic moiety. Moreover, the reaction of **1h** which generated **3r** in very high yield also hints at α-selectivity of the C-C bond breaking reaction as no γ-selective product was obtained. With the reaction suggesting of being α-selective, we proceeded to investigate the mechanism of the C-C bond breaking reaction.

Table 3: Regioselectivity of the C-C bond breaking reaction.[a]

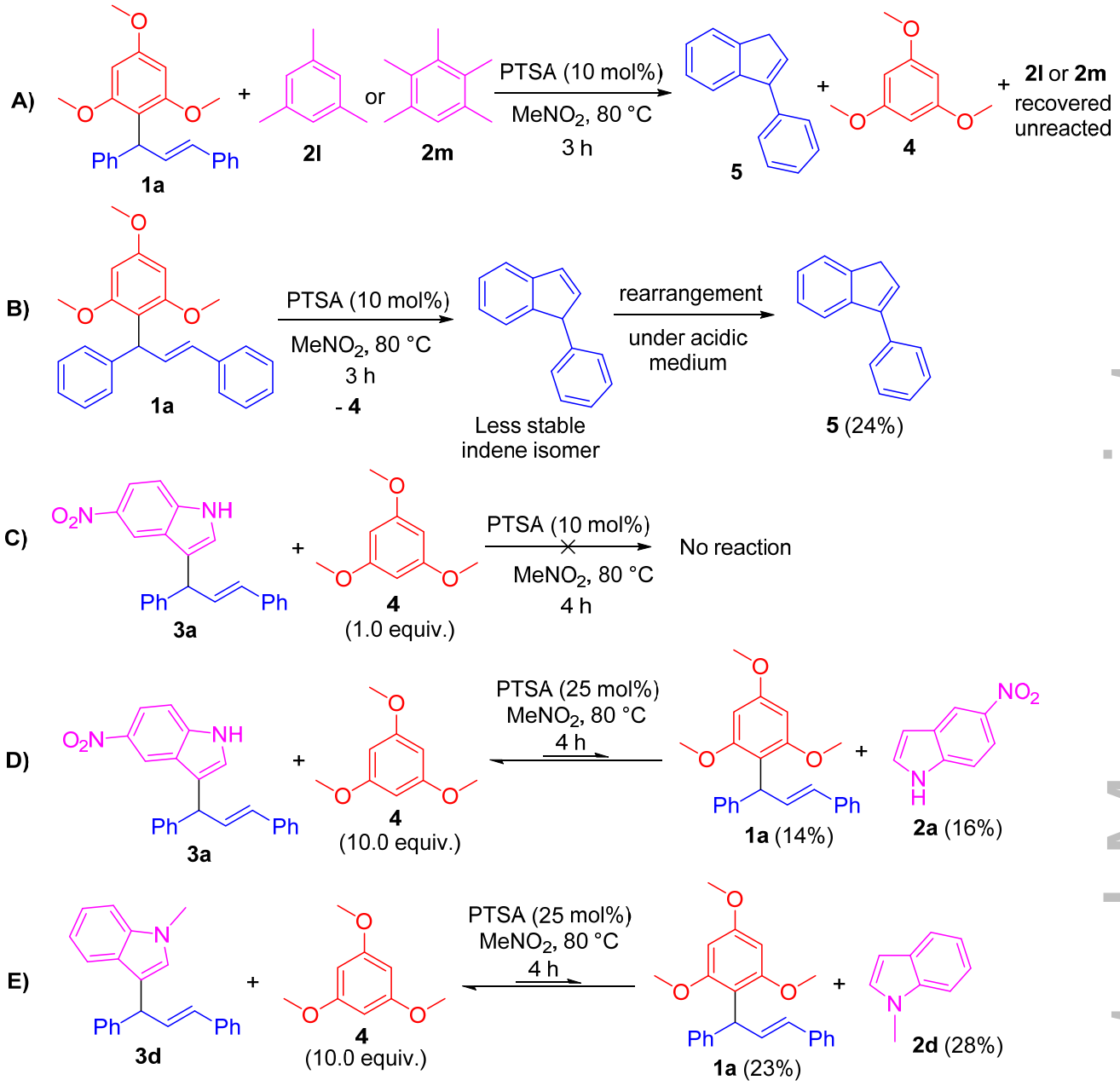


Entry	Substrate **1**	Product **3**	Yield of **3** (%)[b]
1	 **1f**	 **3p**	86
2	 **1g**	 **3q**	93
3	 **1h**	 **3r**	90

[a]Reaction conditions: **1** (0.55 mmol), **2** (0.5 mmol), PTSA (10 mol%), $MeNO_2$ 2 mL, temp. 80 °C, time 1 h. [b]Isolated yields.

Few control reactions as outlined in Scheme 2 were carried out to understand the mechanistic intricacy involved in the reaction. We noted that when weaker nucleophiles, such as mesitylene **2l** or pentamethylbenzene **2m**, were used, the expected substitution reaction did not take place (Scheme 2A). Instead, we observed that 3-phenyl-1*H*-indene **5** was formed and TMB was eliminated as a by-product while the nucleophiles **2l**/**2m** remained unreacted. We understand that when suitable nucleophile is absent, compound **5** is formed via intramolecular cyclization and subsequent rearrangement from substrate **1a** as outlined in Scheme 2B. The rearrangement of presumably formed 1-phenyl-1*H*-indene to a more stable isomer 3-phenyl-1*H*-indene **5** under acidic medium at elevated temperature is well studied.[6] In absence of any nucleophile, few unidentifiable compounds in small amounts were also

formed along with indene **5** while major portion of **1a** remained unchanged. The above observations suggest that the reaction pathway depends on the nucleophile as good nucleophiles lead to substitution reaction while weaker nucleophiles fail to compete with the intramolecular cyclization of the substrate. Nevertheless, in both reaction pathways, TMB **4** is eliminated under the acidic reaction conditions via C-C bond cleavage. In our previous work, we have demonstrated that the leaving ability of arenes depend on their electron-richness.[2o-p] From this vantage, we realize that the nucleophiles employed in the study are also electron-rich and hence the C-C bond breaking reaction may be reversible to an extent. To evaluate our hypothesis, we tried the backward reaction where we reacted **3a** with TMB **4** in the optimized reaction conditions and found that the reactants remain unreacted for 24 h (Scheme 2C, See SI for experimental details, page S3). This result supports the high product yield obtained in Table 2 and Table 3 as the reaction is not reversible in optimized reaction conditions. However, when we increased the equivalents of TMB **4** along with the catalyst loading to facilitate the backward reaction, the results indicated that a small amount of 5-nitroindole was eliminated via C-C bond cleavage (Scheme 2D). In perpetuation, we also found that 1-methylindole was eliminated when **3d** reacted with TMB **4** in the above reaction conditions (Scheme 2E). Such kind of activation of indole derivatives and their subsequent elimination under acidic medium was also observed previously.[7] To summarize, these observations suggest that electron-rich aryl groups are activated to variable extent depending on their electron-richness under the influence of an acid. Some spectroscopic experiments were then carried out to shed light on the mode of activation of electron-rich aryl groups under acidic conditions.



Scheme 2: Control experiments for insight into the mechanism.

It is conventionally known that the electron-rich arenes undergoes proton exchange in Lewis acidic conditions and Castellani et al. recently studied proton-exchange in TMB.[5,8] To understand our reaction, we investigated the protonation of TMB and the 2,4,6-trimethoxyphenyl group of **1a** in presence of PTSA. Literature suggests that protonation of TMB **4** results in the formation of species **4'** as outlined in Scheme 3A.[5] We employed UV-Vis spectroscopy to corroborate the formation of **4'** from **4** upon addition of PTSA. The UV-Vis spectrum of TMB **4** in anhydrous MeCN shows an absorption maxima at λ_{max}(TMB) = 206 nm. When 1 equiv. of PTSA is added to the solution of **4**, we noted that the absorbance at

λ_{max}(TMB) decreases. The absorbance decreases further and further on increasing the amount of PTSA as depicted in Figure 2A. We understand that as the acid concentration is increasing, more amount of TMB is getting protonated to **4'** which decreases the concentration of free TMB and hence decreases the absorbance at λ_{max}(TMB). A similar trend is observed when **1a** which shows absorption maxima at λ_{max}(**1a**) = 207 nm is treated with PTSA (Figure 2B). We interpret that the decrease in absorbance at 207 nm may be because of the formation of a species **1a'** analogous to the formation of **4'** from **4** as outlined in Scheme 3B. A proton-deuterium exchange experiment in acidic medium have established that the 2,4,6-trimethoxyphenyl group of **1a** also reciprocates the aptitude for proton-exchange as TMB (Figure 3).[5] In the ^{1}H NMR spectra recorded in CD_3OD, the peak for aromatic C-H belonging to 2,4,6-trimethoxyphenyl group of **1a** [δ (ppm) = 6.200 (s, 2H)] loses its relative intensity after PTSA is added to the solution (Figure 3A and 3B). This clearly indicates that the aromatic C-H protons of the 2,4,6-trimethoxyphenyl group of **1a** are in a dynamic equilibrium with solvent deuteriums (or protons) under acidic condition. It is understood that the proton-deuterium exchange is a result of deprotonation of the transiently formed species analogous to **1a'**. In a bid to further support our claim; we used ^{1}H NMR spectroscopy in CD_3CN to investigate possible change in the peak positions of the protons of TMB in absence and presence of PTSA (Figure 4A). No discernable shift was observed for the protons of –OCH_3 group of TMB [δ (ppm) = 3.763 (s, 9H)] upon addition of PTSA (Figure 4A). However, we observed a gradual downfield shift of the peak for aromatic C-H of TMB [δ (ppm) = 6.119 (s, 3H)] upon subsequent addition of PTSA. Kříž et al. demonstrated that in presence of acid, such a downfield shift of aromatic C-H of arene indicates protonation of the arene.[9] Similarly, when we studied **1a** in presence of increasing amount of PTSA, we noted a similar but more prominent downfield shift of the aromatic C-H of the 2,4,6-trimethoxyphenyl moiety [δ (ppm) = 6.263 (s, 2H)] (Figure 4B). Moreover, the doublet of methylene C-H [δ (ppm) = 5.407 (d, J = 8.4 Hz, 1H)] adjacent to the 2,4,6-trimethoxyphenyl moiety of **1a** also showed a prominent downfield shift upon subsequent addition of PTSA. The downfield shift of the methylene proton of **1a** further validates the idea that the adjacent 2,4,6-trimethoxyphenyl group is getting protonated. There was no shift in the –OCH_3 peaks belonging to **1a**. Conceivably, protonation of the 2,4,6-trimethoxyphenyl moiety of **1a** may lead to several possible structures and the spectra obtained is only a weighted average reflection of all the structures. We evaluated that the C-C bond breaking reaction may

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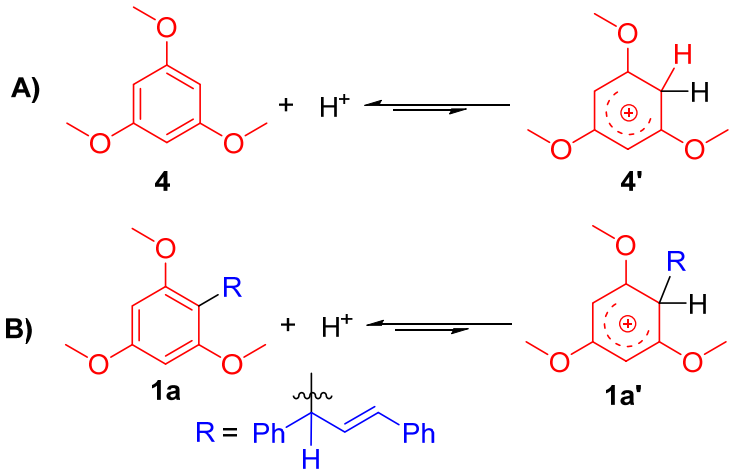
originate from species **1a'** (Scheme 3B) which is one of the possible protonated structures participating in a fast dynamic equilibrium between **1a** and H^+.



Scheme 3: Protonation of electron-rich arenes in acidic conditions.

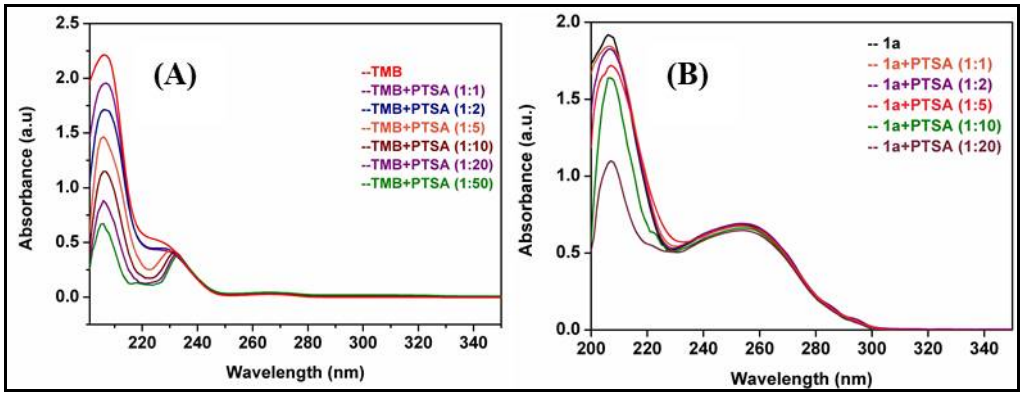


Figure 2: (A) UV-Vis spectra of TMB and solutions of TMB+PTSA at various ratios. (B) UV-Vis spectra of **1a** and solutions of **1a**+PTSA at various ratios.

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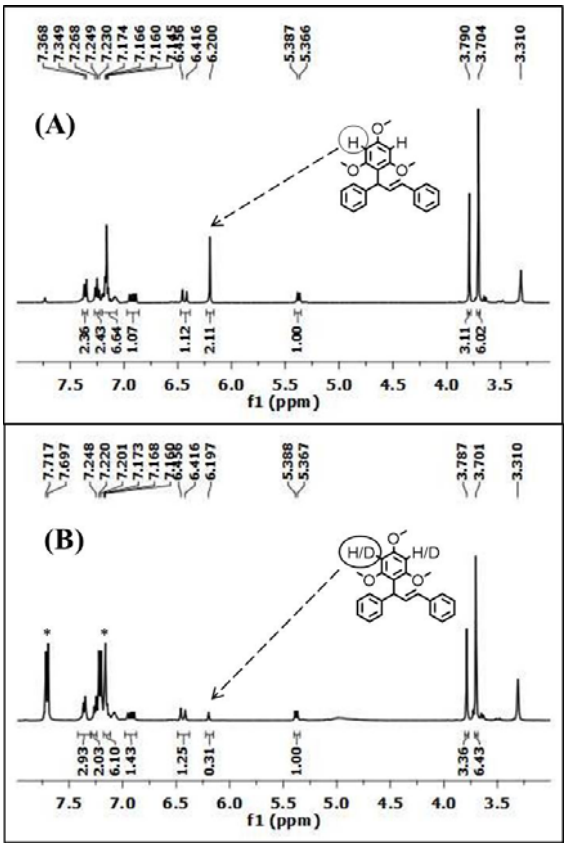

Figure 3: (A) Partial ^{1}H NMR spectra of **1a** in CD_3OD; (B) Partial ^{1}H NMR spectra of **1a** in presence of PTSA in CD_3OD; * Peaks belonging to PTSA

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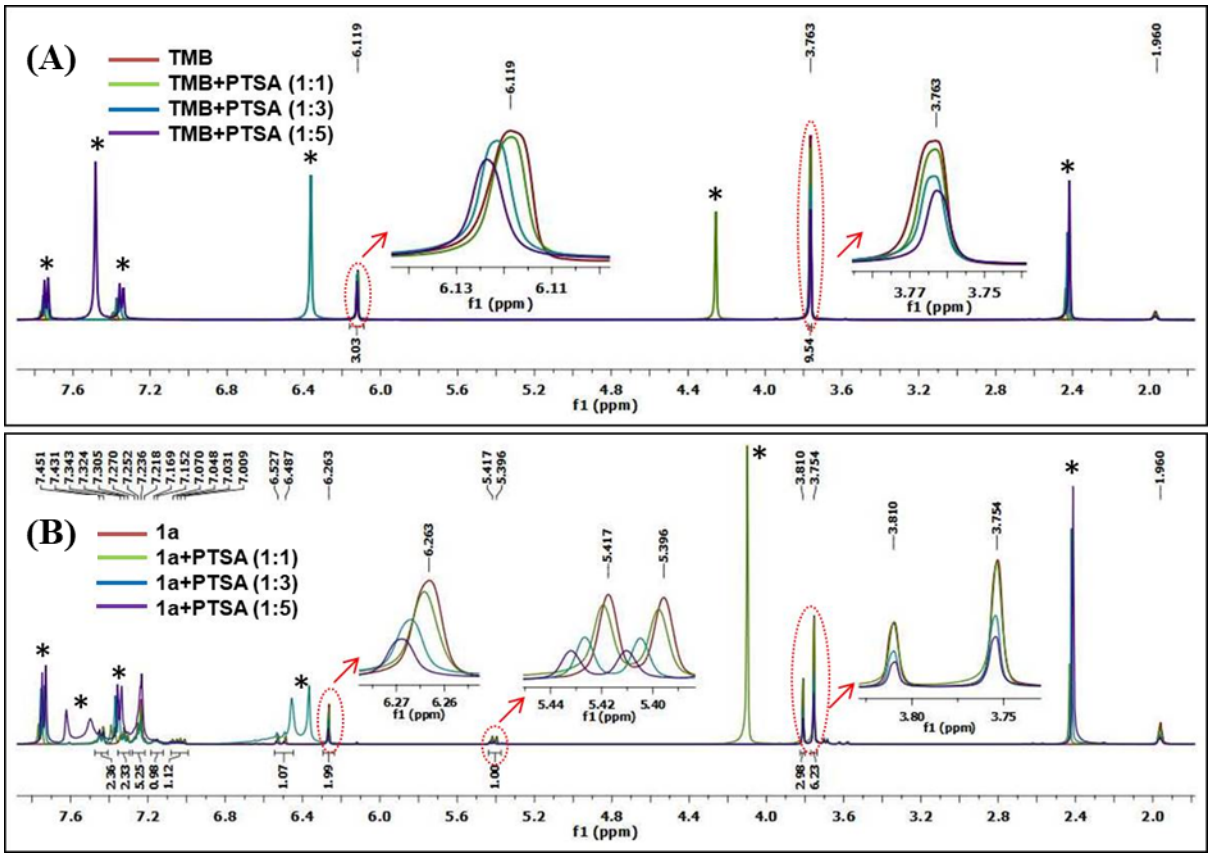

Figure 4: (A) ^{1}H NMR spectra of TMB and solutions of TMB+PTSA at various ratios (CD_3CN); (B) ^{1}H NMR spectra of **1a** and solutions of **1a**+PTSA at various ratios (CD_3CN); * Peaks belonging to PTSA.

Besides, when we recorded a ^{1}H NMR spectrum of a **1a** and PTSA (1:1) after 3 h of mixing, in $CDCl_3$, we observed a few additional peaks (Figure 5). Among the new peaks, presence of TMB **4** can readily be noted (Figure 5B), which may have eliminated from the species **1a'** (Scheme 2B). We suppose that compound **5** was also formed in the process via intramolecular cyclization (Scheme 2B), although its presence is not discernable from the spectrum.

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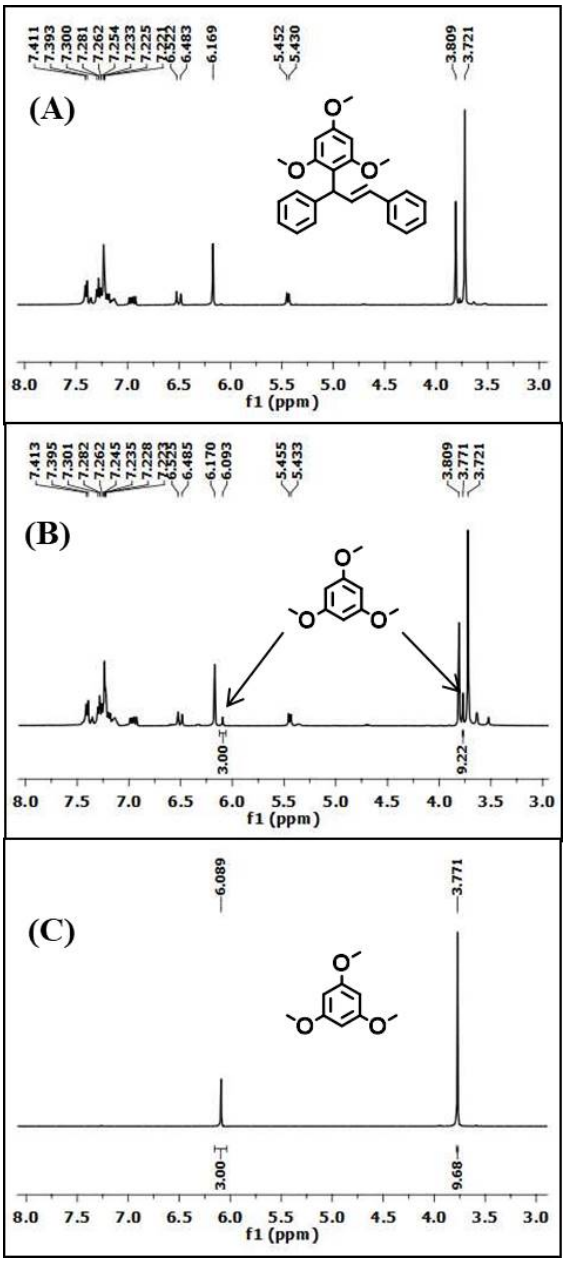
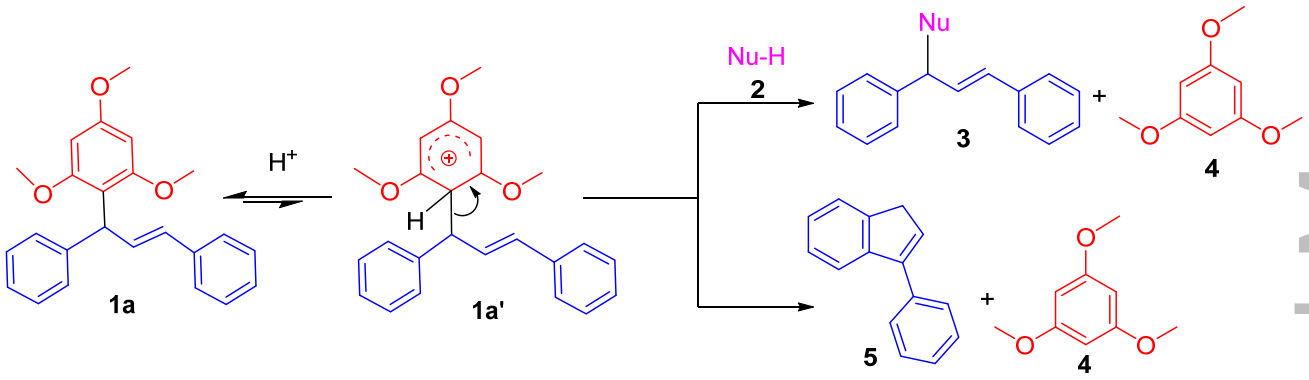


Figure 5: Partial ^{1}H NMR spectra of (A) **1a,** (B) **1a** + PTSA (1:1) (Peaks for eliminated TMB **4** indicated by arrows), (C) TMB **4**.

With the help of relevant literature and the above mentioned experiments, we propose the reaction mechanism outlined in Scheme 4. Initially, the electron-rich 2,4,6-trimethoxyphenyl moiety of **1a** gets protonated in presence of an acid which may involve several possible protonated structures under dynamic equilibrium. We propose that the structure with *ipso*-protonation of the 2,4,6-trimethoxyphenyl group **1a'** as the intermediate species which is responsible for the C-C bond breaking reaction. Such an *ipso*-protonated structure like **1a'** of arene in acidic medium leading to C-C bond cleavage was also reported by Mudududdla et al.[10] An equivalent *ipso*-substituted species may be formed in the Lewis

acid activated electron-rich arene.[2o-p,7] Species **1a'** under the influence of a good nucleophile leads to product **3** and in absence of any ideal nucleophile leads to compound **5** via intramolecular cyclization. In both events, TMB **4** is eliminated through a C_{sp3}-C_{sp2} bond cleavage. The failure of protic solvents as the reaction medium may also be explained in the light of above observations as rapid proton-exchange between **1a'** and the protic solvent does not allow for a nucleophile to participate in the reaction.[5] It may be noted that, the C_{sp3}-C_{sp2} bond between the 2,4,6-trimethoxyphenyl group and the allylic backbone in species **1a'** is adequately polarized which evidently allows nucleophilic 4-methoxythiophenol **2j** to react and form a C-S bond replacing the C-C bond. It is important to notice that the effect of the allylic moiety is largely insignificant on the activation of the electron-rich arene and such activation may also take place when a benzylic moiety is present instead of the allylic moiety. This deduction is supported by our previous results[2o-p] and also help us understand the unexpected C-C bond cleavage observed by Kim et al.[3a] and Jaratjaroonphong et al.[3b]



Scheme 4: Proposed reaction path for the C-C bond breaking reaction.

Conclusion

In summary, we have explored the unusually labile C_{sp3}-C_{sp2} bond between 2,4,6-trimethoxyphenyl group and allylic moieties in acidic conditions where we observed that the C-C bond may be rendered labile by a variety of Lewis or Brønsted acids in aprotic solvents. The 2,4,6-trimethoxyphenyl group may be readily substituted by nucleophiles such as indoles, 2-methylfuran, 2-methylthiophene, 4-hydroxycoumarin etc. A measure of the lability of the C-C bond may be grasped as a new C-S bond is able to replace the existing C-C bond. Weaker nucleophile, however, failed to compete with the intramolecular cyclization which led to the formation of an indene derivative. Mechanistic studies using UV-Vis and ^{1}H NMR spectroscopy suggested that the electron-rich arene gets reversibly protonated in presence of PTSA. Based on the studies and relevant literature, we proposed that the C-C bond breaking

reaction results when the *ipso* position of the electron-rich aryl group is protonated. The findings of this work employing 1,3,5-trimethoxybenzene as a case study, presents a general insight into the acidic labilization of electron-rich aryl groups. Further investigation about the mechanism and on adopting the reaction for other application in organic syntheses is underway in our laboratory.

Experimental Section

General procedure for the cleavage of the C_{sp2}-C_{sp3} bond

A 25 mL round-bottom flask equipped with a magnetic bar and water condenser were charged with **1** (0.55 mmol), **2** (0.5 mmol), $MeNO_2$ (2 mL) and PTSA (10 mol%) in an air atmosphere. The flask was placed in a constant temperature oil-bath at 80 °C and the progress of the reaction was monitored by TLC. After the completion of the reaction, the solvent was removed under reduced pressure and the crude product was purified by dry column vacuum chromatography (silica gel G, petroleum ether 60-80 °C/EtOAc) to obtain the desired product **3**.

Conflict of Interest

The authors declare no conflict of interests.

Supporting Information

Experimental details for reaction condition optimization, control reactions, UV-Vis studies and NMR studies are described in the supporting information. Analytical data along with ^{1}H and ^{13}C NMR spectra of compound **1**, **3**, **4** and **5** are also given in the supporting information.

Acknowledgement

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