Catalysis Letters
https://doi.org/10.1007/s10562-020-03220-0

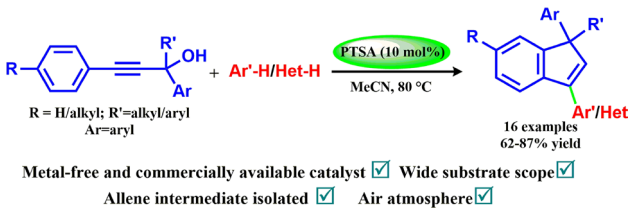
para-Toluenesulfonic Acid Catalyzed Synthesis of Indenes a Tandem Friedel–Crafts Alkylation/Hydroarylation of Tertiary Propargylic Alcohols with Electron-Rich Arenes

Gitumoni Kalita[1] · Dipankar Paul[1] · Snehadrinarayan Khatua[2] · Paresh Nath Chatterjee[1]

Received: 23 December 2019 / Accepted: 12 April 2020

Abstract
A simple protocol to synthesize indenes efficiently by PTSA catalyzed tandem Friedel–Crafts alkylation/hydroarylation of tertiary propargylic alcohol with electron-rich arenes is described. The desired indenes were obtained regioselectively in good to very good yields under mild reaction conditions. The allene intermediate was isolated to get an insight into the mechanistic pathway of the indene forming reaction.

Graphic Abstract



Keywords PTSA · Propargylic alcohol · Electron-rich arene · Indene · Allene

1 Introduction

Indene scaffolds are available in many natural products and biologically active pharmaceutical compounds [1–5]. The indene motifs constitute an integral part of several pharmaceutical compounds such as anti-tumour drug Dichroanal B [6], anti-inflammatory drug Sulindac [7, 8], estrogen receptor agonist [9, 10], etc. (Fig. 1). The indenyl-based metallocenes of group 4 and 10 metals are known for catalysing the olefin polymerization reaction [11–13]. Due to the biological relevance of indenes, the synthesis of indene derivatives has always attracted the attention of organic chemists. Considering the importance of indene moieties, various methods of indene synthesis have been reported in literature using alkynes [14–19], allenes [20–22], and propargylic alcohols [23–35] etc. as the substrates in presence of Lewis acid or Brønsted acid catalysts. Easily accessible propargylic alcohols which involve two functional groups (alkyne and hydroxyl) have often served as suitable starting substrates for the synthesis of a variety of organic motifs [36]. In 2009, Chan et al. reported the synthesis of indenols from propargylic alcohols and substituted phenols using $Yb(OTf)_3$ as the catalyst (Scheme 1) [28]. Roy et al. reported an easy access to indenes from propargylic alcohols and arenes in the presence of their in-house synthesized heterobimetallic catalyst $[Ir(COD)(SnCl_3)Cl(\mu\text{-}Cl)]_2$ (Scheme 1) [37].

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10562-020-03220-0) contains supplementary material, which is available to authorized users.

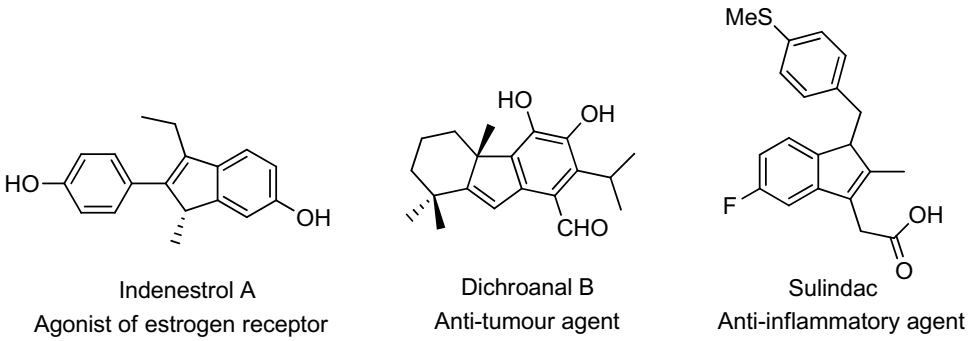
✉ Paresh Nath Chatterjee
paresh.chatterjee@nitm.ac.in

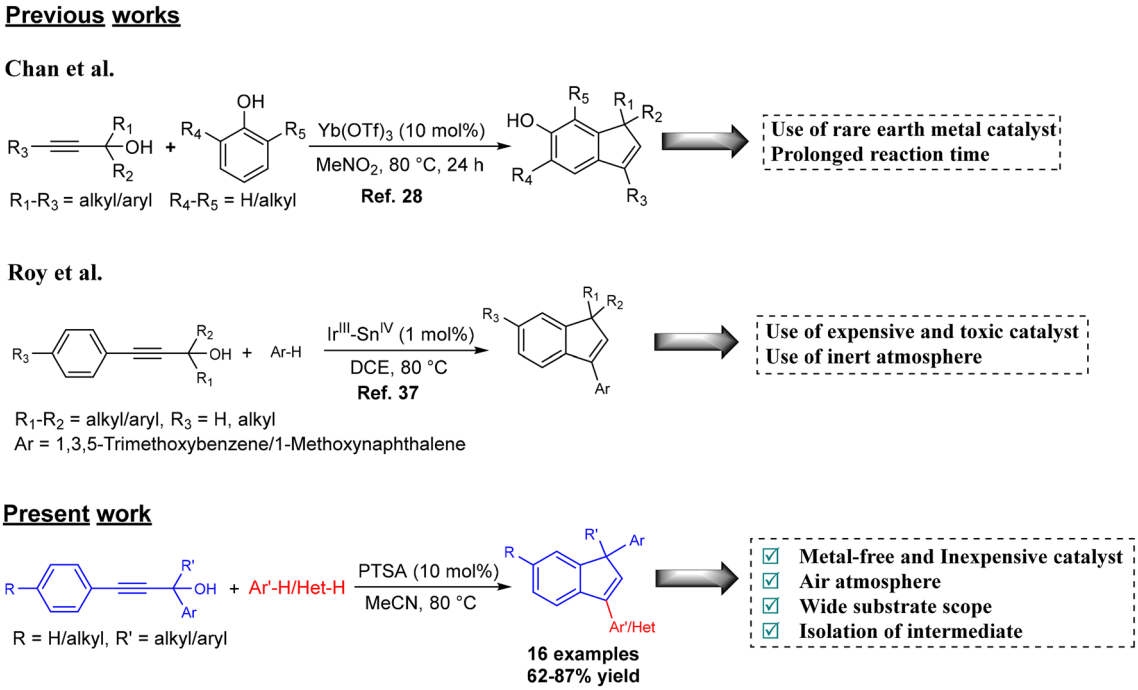
[1] Department of Chemistry, National Institute of Technology Meghalaya, Bijni Complex, Laitumkhrah, Shillong, Meghalaya 793003, India

[2] Centre for Advanced Studies, Department of Chemistry, North Eastern Hill University, Shillong, Meghalaya 793022, India

Published online: 23 April 2020

Fig. 1 Biologically important molecules bearing indene motifs





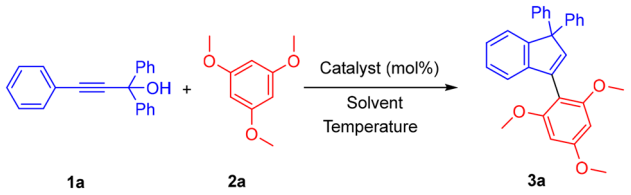
Scheme 1 Comparison of the literature with the present method

However, inert reaction conditions, difficulty in synthesizing the Roy's catalyst as well as high expense (due to iridium) makes their protocol less popular. To address these drawbacks, we planned to develop a simple protocol to construct the indene carbocycles from easily accessible starting materials using commercially available Brønsted acid catalyst. In this report, we describe a method to synthesize indene derivatives via a tandem Friedel–Crafts alkylation/hydroarylation of tertiary propargylic alcohols with sterically bulky and electron-rich arenes/heteroarenes in presence of commercially available and non-toxic *p*-toluenesulfonic acid (PTSA) catalyst under air atmosphere (Scheme 1). The reactions proceeded smoothly to give the indenes regioselectively in good yields for a wide variety of substrates under mild reaction conditions.

2 Results and Discussion

To achieve the optimized reaction conditions, initially we chose 1,1,3-triphenylprop-2-yn-1-ol **1a** and 1,3,5-trimethoxybenzene **2a** as the starting materials for the synthesis of 1,1-diphenyl-3-(2,4,6-trimethoxyphenyl)-1*H*-indene **3a** (Table 1). We screened several Brønsted and Lewis acid catalysts at 80 °C using MeCN solvent to choose an efficient catalyst for the desired reaction. Among the screened Brønsted acids (Table 1, entries 1–3), we isolated the desired indene **3a** with highest yield (85%) in presence of PTSA catalyst regioselectively. Lewis acid catalysts such as $BiCl_3$, $SnCl_2.2H_2O$, $SnCl_4$, $FeCl_3$, and $ZnCl_2$ were unable to surpass the catalytic efficiency shown by PTSA (Table 1, entries 5–9). We also used several organic

Table 1 Optimization of reaction conditions[a]



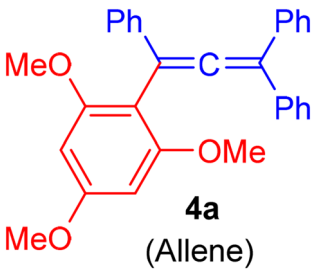
Entry	Catalyst	Solvent	Time (h)	Temp. (°C)	Yield of **3a** (%)[b]
1	PTSA	MeCN	1	80	85
2	CF_3SO_3H	MeCN	1	80	80
3	CF_3COOH	MeCN	1	80	77
4	Molecular I_2	MeCN	1	80	47
5	$BiCl_3$	MeCN	1	80	68
6	$SnCl_2{\cdot}2H_2O$	MeCN	1	80	42
7	$SnCl_4$	MeCN	1	80	59
8	$FeCl_3$	MeCN	1	80	65
9	$ZnCl_2$	MeCN	5	80	25
10	PTSA	$MeNO_2$	1	80	70
11	PTSA	DCE	1	80	34
12	PTSA	$CHCl_3$	1	60	57
13	PTSA	hexane	1	60	30
14	PTSA	EtOH	1	80	45
15	PTSA	chlorobenzene	1	80	63
16	PTSA	THF	5	60	–
17	PTSA	MeCN	5	25	–
18	PTSA	MeCN	5	55	30
19[c]	PTSA	MeCN	1	80	74
20[d]	PTSA	MeCN	1	80	83
21	No catalyst	MeCN	5	80	–

[a]Reaction conditions: **1a** (1.0 mmol), **2a** (1.1 mmol), catalyst (10 mol%), solvent (2.0 mL), Temperature 80 °C

[b]Isolated yields

[c]Catalyst (5 mol%)

[d]Catalyst (15 mol%)



4a
(Allene)

solvents such as MeCN, $MeNO_2$, DCE, $CHCl_3$, hexane, EtOH, and chlorobenzene to examine the effect of solvent in the indene forming reaction (Table 1, entries 10–15). The highest yield of **3a** was obtained in MeCN solvent within 1 h (Table 1, entry 1). In particular, THF as solvent at 60 °C did not lead to product formation (Table 1, entry

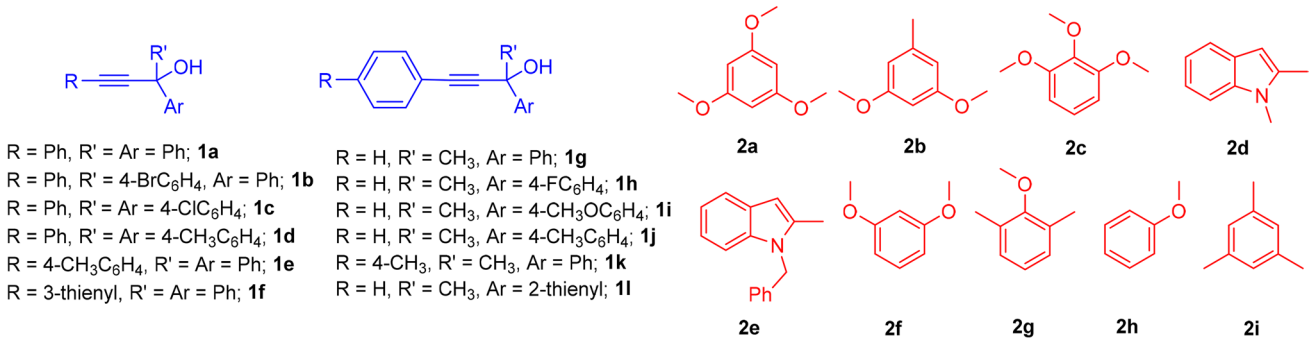


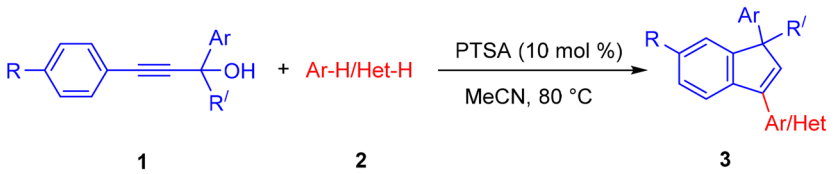
Fig. 2 List of tertiary propargylic alcohols **1** and electron-rich arenes **2** employed in the study

16). We also examined the effect of temperature which showed that the reaction did not yield the desired indene at room temperature instead allene **4a** was obtained in 82% (Table 1, entry 17). When we increased the temperature to 55 °C, the reaction gave 30% yield of **3a** along with 65% of **4a** after 5 h (Table 1, entry 18). Further studies regarding the formation of allene **4a** is discussed later. Besides, we have studied the effect of catalyst loading in the reaction and found that 10 mol% loading of PTSA catalyst was adequate for the synthesis of indene **3a** (Table 1, entries 19–20). Both the starting materials, **1a** and **2a**, remained unreacted in absence of catalyst (Table 1, entry 21).

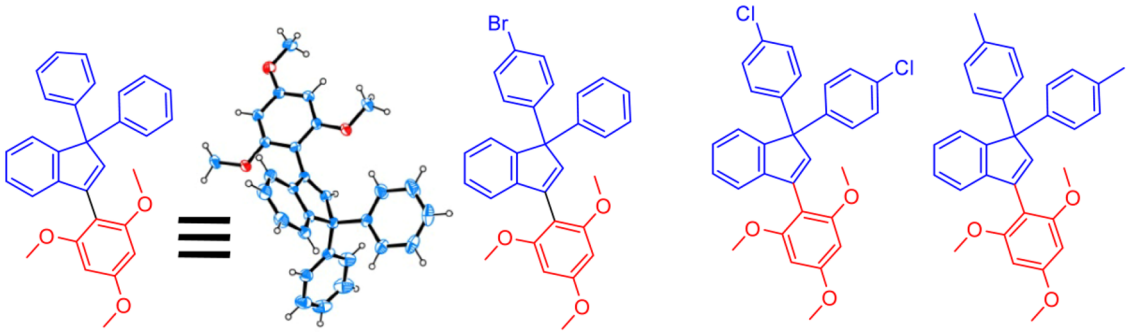
After achieving the optimized reaction conditions, we explored the generality of the present method by varying the tertiary propargylic alcohols **1** and electron-rich arenes **2** as listed in Fig. 2 for the regioselective synthesis of indene carbocycles **3** (Scheme 2). The propargylic alcohols **1** with pendant electron-donating and electron-withdrawing substituents on the carbinol or alkyne carbon reacted with **2a** to give the desired indenes **3** in good to very good yields (80–87%). We observed that the propargylic alcohols with two aryl substituents at the carbinol carbon (**1a**–**f**) gave very good yields of their corresponding indenes (**3a**–**f**) within 1 h. We observed that, propargylic alcohol **1f** containing heteroaromatic ring (3-thienyl) at the terminal position of the alkyne of the propargylic alcohol also yielded its corresponding product **3f** in good yield. The structure of indene **3a** was established by X-ray crystallographic analysis (CCDC-1960285; see supplementary file). We also tested the effect of an aliphatic substituent at the carbinol carbon (i.e. R′ = Me) of the propargylic alcohols (**1g**–**l**) and found that, lower yields (62–78%) were obtained for their corresponding indenes **3g**–**l** after prolonged reaction time. In general, we noticed that, the propargylic alcohols with electron-withdrawing substituents at the carbinol carbon gave better yields of the indenes than the propargylic alcohols with electron-donating substituents. Noteworthy is the fact that, a heteroaromatic substituent (2-thienyl) at the carbinol carbon of the propargylic alcohol **1l** can nicely be tolerated in the reaction medium producing the desired indene **3l** in 62% yield. We have also established the versatility of the reaction by taking different types of nucleophiles such as **2b–e** as the coupling partner with propargylic alcohol **1a** and in all cases, the corresponding indenes **3m–p** were isolated in good yields (62–77%). It is to be noted that, 1,3,5-trimethoxybenzene **2a** showed superior results in the indene formation reaction due to its higher steric bulkiness and electron-richness in comparison to 3,5-dimethoxy toluene **2b**. It is worth to mention that, when 1,2,3-trimethoxybenzene **2c** was employed as the electron-rich arene, we isolated an indene **3n** that was formed by the intramolecular hydroarylation of the incoming arene **2c**. Under the standard reaction conditions, the 1,2-disubstituted indoles **2d** and **2e** reacted well with the propargylic alcohol **1a** to produce the desired indenes **3o** and **3p** in good yields, respectively.

While extending the substrate scope of the present reaction, we had another interesting observation (Scheme 3). In the presence of less electron-rich arene 1,3-dimethoxybenzene **2f** the reaction with propargylic alcohol **1a** did not afford the desired indene **3q** even after prolonged reaction time and instead, it solely generated the allene product **4b** in 76% yield. Very recently, Sanz et al. have reported the PTSA catalyzed synthesis of tetra-substituted allene **4b** from tertiary propargylic alcohol **1a** at room temperature in MeCN solvent together with the regioisomer of the allene product [38]. In case of other less electron-rich arenes, such as 2,6-dimethylanisole **2g**, anisole **2h** and mesitylene **2i**, the propargylic alcohol **1a** rearranged to the α,β-conjugated ketone **5** through Meyer-Schuster rearrangement [39, 40] instead of producing the indene (**3r**–**t**) or allene (**4c**–**e**) product via the coupling reaction (Scheme 3). We have also noted that, the propargylic alcohol **1a** rearranged to the α,β-conjugated ketone **5** through Meyer-Schuster rearrangement in presence of PTSA (10 mol%) in MeCN at 80 °C.

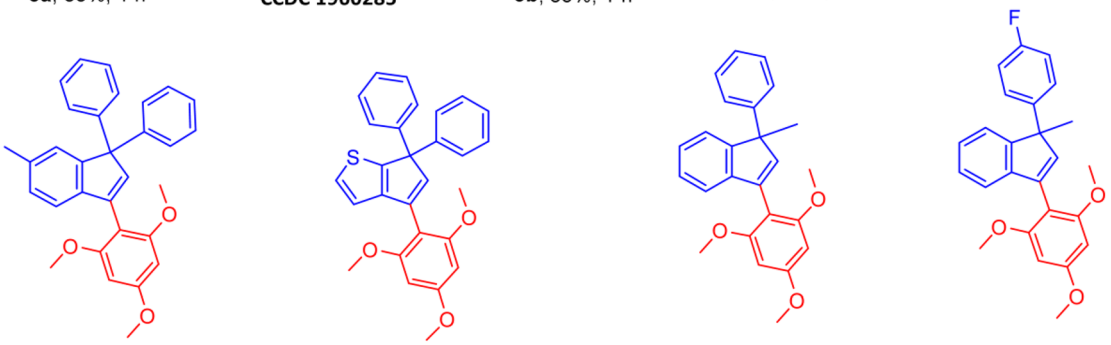
The outcome of the reaction between propargylic alcohol **1a** and less electron-rich arene **2f** in Scheme 3 gave us a hint of the probable interplay of allene intermediate in this reaction [37]. To get an insight into the plausible reaction



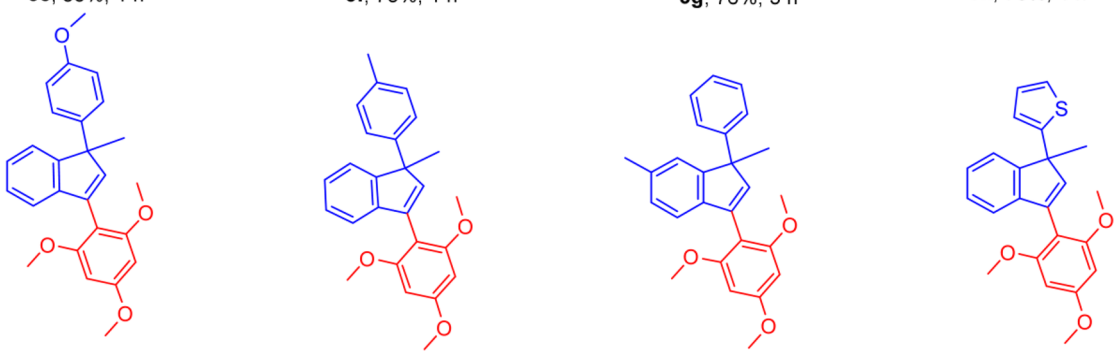
1 2 3



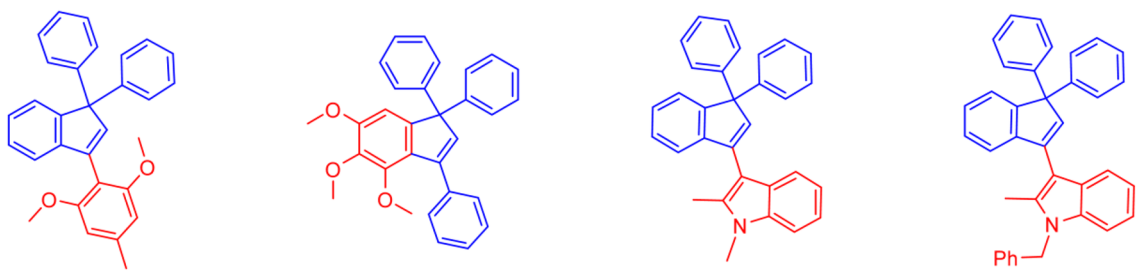
3a, 85%, 1 h — **CCDC 1960285** — **3b**, 85%, 1 h — **3c**, 87%, 1 h — **3d**, 80%, 1 h



3e, 86%, 1 h — **3f**, 73%, 1 h — **3g**, 76%, 3 h — **3h**, 78%, 1 h

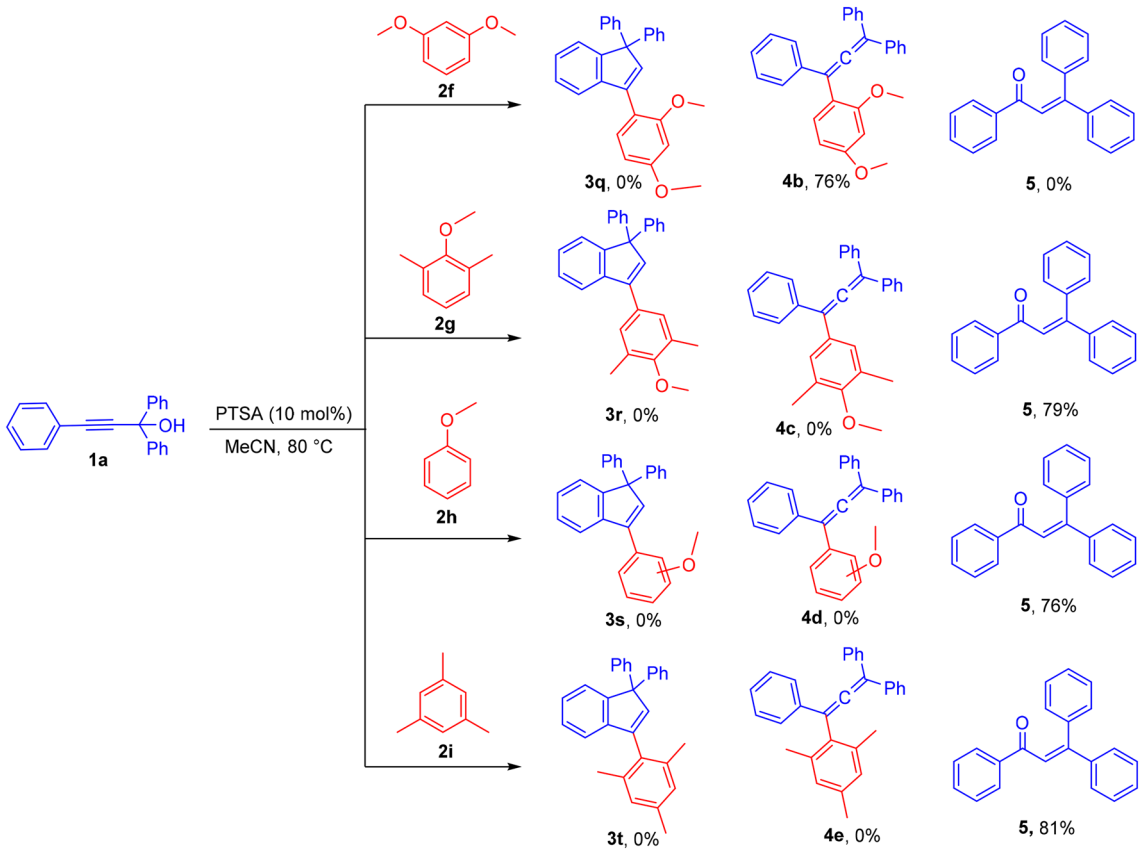


3i, 64%, 3 h — **3j**, 69%, 3 h — **3k**, 77%, 3 h — **3l**, 62%, 1.5 h

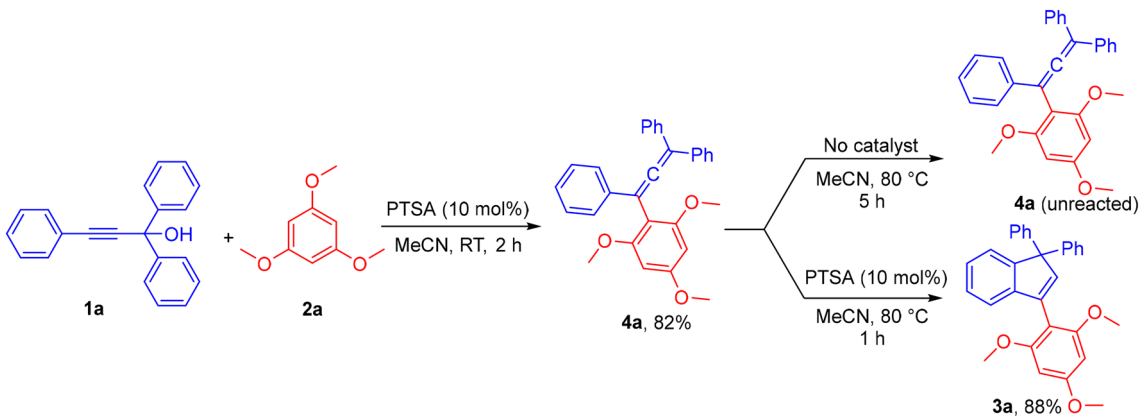


3m, 67%, 3 h — **3n**, 77%, 1 h — **3o**, 65%, 1.5 h — **3p**, 62%, 1.5 h

Scheme 2 PTSA catalysed synthesis of indenes



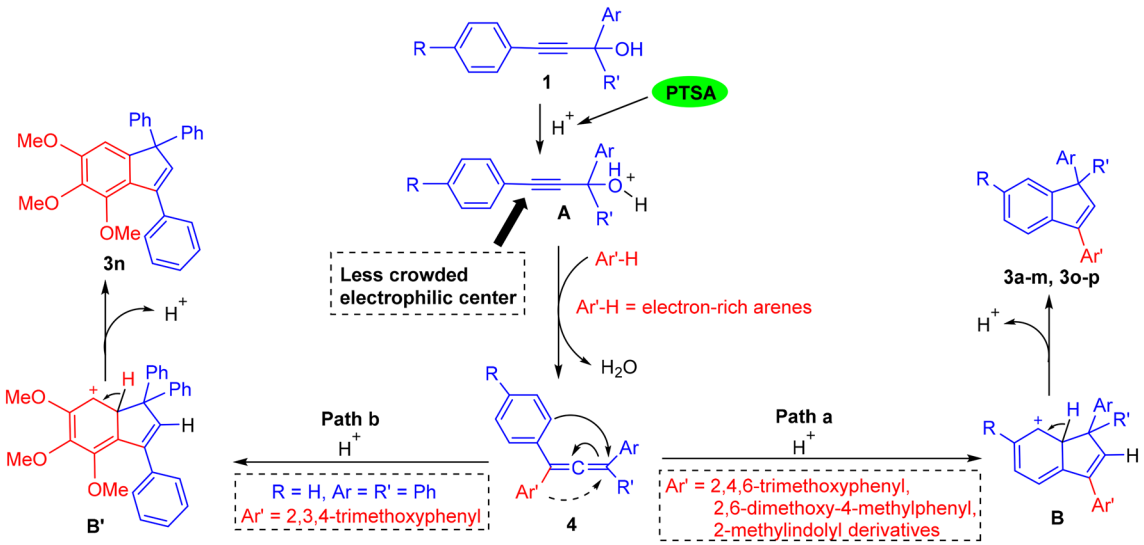
Scheme 3 Effect of less electron-rich arenes in the reaction



Scheme 4 Isolation of allene intermediate **4a** and its conversion to the indene product **3a**

mechanism we aspired to isolate the allene intermediate. In this regard, we put up a reaction of propargylic alcohol **1a** with 1,3,5-trimethoxybenzene **2a** in presence of PTSA catalyst at room temperature in MeCN solvent and successfully isolated the allene intermediate **4a** in 82% yield after 2 h (Scheme 4) [38]. On retreating the allene intermediate **4a** to the optimized reaction conditions of 10 mol% of PTSA in MeCN at 80 °C for 1 h, the expected indene **3a** was obtained in 88% yield. In absence of the PTSA catalyst, the allene intermediate remained unreacted in MeCN solvent at 80 °C after 5 h.

Based on the above findings and the knowledge of relevant literature, the probable mechanism of formation of indene **3** is proposed in Scheme 5. The reaction might be initiated by the activation of the propargylic alcohol **1** in presence of proton donor PTSA to form an ambident electrophile



Scheme 5. Plausible mechanism of indene **3** formation

A. The electron-rich and sterically bulky arenes **2** would prefer to attack the less crowded electrophilic acetylenic carbon centre of **A** via the Friedel–Crafts reaction producing an allene intermediate **4**. The allene intermediate **4** would undergo intramolecular hydroarylation followed by rearomatization in the reaction conditions to provide the desired indene derivative **3**. We observed that when the electron-rich and sterically bulky arene moiety (e.g. 2,4,6-trimethoxyphenyl, 2,6-dimethoxy-4-methylphenyl, 2-methylindolyl derivatives) in intermediate **4** has its both *ortho*-carbons substituted, the aromatic/heteroaromatic ring connected to the same allenic carbon that of the electron-rich arene (Ar′) of the allene intermediate participates in the intramolecular hydroarylation step generating product **3a–m**, **3o–p** via the rearomatization of species **B** (path a). In contrast, the hydroarylation step is completed by the electron-rich and sterically bulky arene moiety (e.g. 2,3,4-trimethoxyphenyl) in intermediate **4** when it has at least one *ortho*-carbon unsubstituted as in the case of formation of indene **3n** via the species **B′** (path b). A pivotal role of the Brønsted acid catalyst PTSA and temperature (80 °C) was noticed not only during the Friedel–Crafts alkylation reaction but also for the subsequent hydroarylation reaction as suggested by the studies presented in Scheme 4.

3 Conclusion

In summary, a simple protocol is developed for the synthesis of indene derivatives from easily accessible tertiary propargylic alcohols and electron-rich arenes using commercially available, cheap, non-toxic PTSA catalyst in our laboratory. The reaction of a wide range of propargylic alcohols containing different aliphatic and aromatic substituents with structurally different electron-rich arenes was examined to express the generality of the reported procedure. In the presence of less electron-rich arenes the formation of indene did not take place from tertiary propargylic alcohol, instead the reaction leads to the formation of allene or unsaturated ketones (via Meyer–Schuster rearrangement). The investigation of the mechanistic pathway associated with the reaction revealed the involvement of an allene intermediate which was confirmed by isolating the allene intermediate. The isolated allene intermediate was further converted to the desired indene product in the presence of PTSA catalyst at 80 °C. The methodology presented in this article could be a meaningful addition to the existing methods of indene synthesis. Further investigation of the reaction mechanism, substrate scope and application of indene products are currently under study in our laboratory.

4 Experimental Section

4.1 General Procedure for the PTSA Catalyzed Indene Synthesis from Propargylic Alcohol 1 and Electron-Rich Arene 2

A 25 mL round-bottom flask equipped with a magnetic bar and a water condenser was charged with propargylic alcohol **1** (1.0 mmol), arene **2** (1.1 mmol), MeCN (2.0 mL) and PTSA (10 mol%) in air atmosphere. The flask was placed into a constant temperature oil-bath at 80 °C and the progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure and the crude reaction mixture was purified by column chromatography.

Acknowledgements Science and Engineering Research Board (SERB) is gratefully acknowledged for financial support to P. N. C (Sanction Order No. SB/FT/CS-115/2014; dated 24/08/2015).G. K. thanks TEQIP III and D. P. thanks NIT Meghalaya for financial support. P. N. C. thanks Sharat Sarmah and Nazir Uddin for many help. We also acknowledge SAIF, NEHU, IIT Guwahati and IIT Bombay for analytical facilities.

Compliance with Ethical Standards

Conflict of interest The authors declare no conflict of interest.

References

1. Hagishita S, Yamada M, Shirahase K, Okada T, Murakami Y, Ito Y, Matsuura T, Wada M, Kato T, Ueno M (1996) J Med Chem 39:3636–3658
2. Palm J, Boegesoe KP, Liljefors T (1993) J Med Chem 36:2878–2885
3. Witiak DT, Kakodkar SV, Brunst GE, Baldwin JR, Rahwan RG (1978) J Med Chem 21:1313–1315
4. Kolanos R, Siripurapu U, Pullagurla M, Riaz M, Setola V, Roth BL, Dukat M, Glennon RA (2005) Bioorg Med Chem Lett 15:1987–1991
5. Rinaldi A, Scarpi D, Occhiato EG (2019) Eur J Org Chem 2019:7401–7419
6. Banerjee M, Mukhopadhyay R, Achari B, Banerjee AK (2003) Org Lett 5:3931–3933
7. Femia AP, Soares PV, Luceri C, Lodovici M, Giannini A, Caderni G (2015) BMC Cancer 15:611
8. Prade E, Barucker C, Sarkar R, Althoff-Ospelt G, Lopez del Amo JM, Hossain S, Zhong Y, Multhaup G, Reif B (2016) Biochemistry 55:1839–1849
9. Gao H, Katzenellenbogen JA, Garg R, Hansch C (1999) Chem Rev 99:723–744
10. Clegg NJ, Paruthiyil S, Leitman DC, Scanlan TS (2005) J Med Chem 48:5989–6003
11. Alt HG, Köppl A (2000) Chem Rev 100:1205–1222
12. Ren S, Igarashi E, Nakajima K, Kanno K, Takahashi T (2009) J Am Chem Soc 131:7492–7493
13. Leino R, Lehmus P, Lehtonen A (2004) Eur J Inor Chem 2004:3201–3222
14. Zeng X, Ilies L, Nakamura E (2011) J Am Chem Soc 133:17638–17640
15. Miyamoto M, Harada Y, Tobisu M, Chatani N (2008) Org Lett 10:2975–2978
16. Liu C-R, Yang F-L, Jin Y-Z, Ma X-T, Cheng D-J, Li N, Tian S-K (2010) Org Lett 12:3832–3835
17. Bu X, Hong J, Zhou X (2011) Adv Synth Catal 353:2111–2118
18. Chen Y, Li K, Liu X, Zhu J, Chen B (2013) Synlett 24:130–134
19. Xia J-D, Deng G-B, Zhou M-B, Liu W, Xie P, Li J-H (2012) Synlett 23:2707–2713
20. Sanz R, Miguel D, Gohain M, García-García P, Fernández-Rodríguez MA, González-Pérez A, Nieto-Faza O, de Lera AR, Rodríguez F (2010) Chem Eur J 16:9818–9828
21. Yamazaki S, Yamamoto Y, Fukushima Y, Takebayashi M, Ukai T, Mikata Y (2010) J Org Chem 75:5216–5222
22. Liu C-R, Wang T-T, Qi Q-B, Tian S-K (2012) Chem Commun 48:10913–10915
23. Meng B, Ma S (2012) Org Lett 14:2674–2677
24. Zhu Y, Yin G, Hong D, Lu P, Wang Y (2011) Org Lett 13:1024–1027
25. Rao W, Chan PWH (2010) Org Biomol Chem 8:4016–4025
26. Huang W, Zheng P, Zhang Z, Liu R, Chen Z, Zhou X (2008) J Org Chem 73:6845–6848
27. Wang S, Zhu Y, Wang Y, Lu P (2009) Org Lett 11:2615–2618
28. Zhang X, Teo WT, Chan PWH (2009) Org Lett 11:4990–4993
29. Zhang L, Zhu Y, Yin G, Lu P, Wang Y (2012) J Org Chem 77:9510–9520
30. Yao L-F, Tan D, Miao X, Huang K-W (2012) RSC Adv 2:7594–7598
31. Zhou C, Chen X, Lu P, Wang Y (2012) Tetrahedron 68:2844–2850
32. Sun L, Zhu Y, Wang J, Lu P, Wang Y (2014) Org Lett 17:242–245
33. Roh HJ, Ryu JY, Lee J, Kim JN (2017) Tetrahedron Lett 58:4094–4098
34. Zerov AV, Kazakova AN, Boyarskaya IA, Panikorovskii TL, Suslonov VV, Khoroshilova OV, Vasilyev AV (2018) Molecules 23:3079–3099
35. Nursahedova SK, Zerov AV, Boyarskaya IA, Grinenko EV, Nenajdenko VG, Vasilyev AV (2019) Org Biomol Chem 17:1215–1224
36. Zhu Y, Sun L, Lu P, Wang Y (2014) ACS Catal 4:1911–1925
37. Chatterjee PN, Roy S (2010) J Org Chem 75:4413–4423
38. Cabrera-Lobera N, Velasco N, Sanz R, Fernández-Rodríguez MA (2019) Tetrahedron 75:4071–4080
39. Swaminathan S, Narayanan K (1971) Chem Rev 71:429–438
40. Engel DA, Dudley GB (2009) Org Biomol Chem 7:4149–4158