Tetrahedron Letters xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of highly substituted indene derivatives by Brønsted acid catalyzed Friedel–Crafts reaction of homoallylic alcohols

Xiaoxiang Zhang[a,b,*,†], Wan Teng Teo[b,†], Weidong Rao[b], Dik-Lung Ma[c], Chung-Hang Leung[d], Philip Wai Hong Chan[b,*]

[a] *College of Chemical Engineering, Jiangsu Key Lab of Biomass-based Green Fuels and Chemicals, Nanjing Forestry University, Nanjing 210037, China*
[b] *Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore*
[c] *Department of Chemistry, Hong Kong Baptist University, Kowloon Tong, Hong Kong, China*
[d] *State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences, University of Macau, Macao, China*

ARTICLE INFO

Article history:
Received 28 January 2014
Revised 27 April 2014
Accepted 8 May 2014
Available online xxxx

Keywords:
Brønsted acid
Homoallylic alcohols
Homogeneous catalysis
Friedel–Crafts reaction
Indene derivatives

ABSTRACT

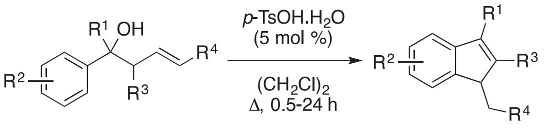
An efficient synthetic method to prepare highly substituted indenes in moderate to excellent yields that relies on Brønsted acid catalyzed Friedel–Crafts reaction of homoallylic alcohols under mild conditions is described.

© 2014 Published by Elsevier Ltd.

Indenes are important synthetic targets in organic chemistry because of the prevalence of the structural ring motif in many natural products, biologically active pharmaceutical agents, and functional materials.[1–3] They are also useful as ligands in the development of olefin polymerization reactions.[4] It is therefore not surprising to find a myriad of elegant methods for their synthesis being established over the years.[1,5–11] This has included synthetic strategies such as C—H bond activation,[5] C—C bond cleavage,[6] [3+2] cycloadditions,[7] thermal cascade,[8] and skeletal rearrangements mediated by a variety of transition metals and Lewis and Brønsted acid and base catalysts.[9–11]

Metal-free mediated methods for indene synthesis that have made use of unsaturated alcohols as electrophilic precursors have often relied upon the allylic, benzylic, or propargylic derivatives of the substrate.[11,12] To our knowledge, a synthetic approach to indene derivatives from other members of the unsaturated alcohol family of compounds such as homoallylic alcohols, by contrast, has not been explored. Added to this, the benzofused ring forming transformations typically required a stoichiometric amount of the catalyst. The cyclization of 3-iodoprop-2-en-1-ols to 3-iodoindenes mediated by $BF_3{\cdot}Et_2O$ has, thus far, remained the one and only example whereby the Lewis acid is employed in a catalytic amount.[11c] In this context and as part of an ongoing program exploring the scope of unsaturated alcohols in organic synthesis,[13] our discovery that p-TsOH·H_2O can affect the Friedel–Crafts reaction of readily accessible homoallylic alcohols of the type **1** is reported herein (Scheme 1). This provides a convenient synthetic route to a variety of substituted indene derivatives **2** in moderate to excellent yields.

We began by examining the cycloisomerization of 2-methyl-1,1-diphenylbut-3-en-1-ol **1a** by a variety of Brønsted acids to establish the reaction conditions (Table 1). This initially revealed that subjecting 0.3 mmol of **1a** in 1,2-dichloroethane to 10 mol % of p-TsOH·H_2O at reflux for 0.5 h gave 1,2-dimethyl-3-phenyl-1*H*-indene **2a** in 99% yield (entry 1). A comparable product yield was



1 **2**

Scheme 1. Synthetic strategy for the synthesis of highly substituted indenes from homoallylic alcohols.

---

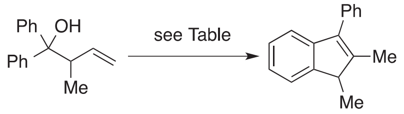
* Corresponding authors. Tel.: +86 25 85427024; fax: +86 25 85418873 (X.Z.); tel.: +65 6316 8760; fax: +65 6791 1961 (P.W.H.C.).

E-mail addresses: s070038@hotmail.com (X. Zhang), waihong@ntu.edu.sg (P.W.H. Chan).

[†] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.tetlet.2014.05.027
0040-4039/© 2014 Published by Elsevier Ltd.

Table 1
Optimization of the reaction conditions[a]



1a **2a**

Entry	Catalyst	Solvent	Time (h)	Yield[b] (%)
1	p-TsOH·H_2O	$(CH_2Cl)_2$	0.5	99
2[c]	p-TsOH·H_2O	$(CH_2Cl)_2$	0.5	99
3[d]	p-TsOH·H_2O	$(CH_2Cl)_2$	20	62
4	p-TsOH·H_2O	PhMe	15	94
5	p-TsOH·H_2O	MeCN	15	79
6	p-TsOH·H_2O	1,4-Dioxane	15	—[e]
7	p-TsOH·H_2O	$MeNO_2$	15	68
8	Tf_2NH	$(CH_2Cl)_2$	15	—[e]
9	TfOH	$(CH_2Cl)_2$	0.5	—[e]
10	TFA	$(CH_2Cl)_2$	15	—[f]
11	H_3PO_4[g]	$(CH_2Cl)_2$	15	—[f]
12	BF_3·Et_2O	$(CH_2Cl)_2$	12	75

[a] Unless stated otherwise, all reactions were performed at reflux with a catalyst/**1a** ratio of 1:10.
[b] Isolated yield.
[c] Reaction conducted with 5 mol % of p-TsOH·H_2O.
[d] Reaction conducted at room temperature.
[e] Mixture of unknown decomposition products obtained based on TLC and ^1H NMR analysis of the crude reaction mixture.
[f] No reaction based on TLC and ^1H NMR analysis of the crude reaction mixture.
[g] Used as an 80% solution in H_2O.

obtained on decreasing the catalyst loading from 10 to 5 mol % or repeating the reaction with toluene in place of 1,2-dichloroethane as the solvent (entries 2 and 4). Lower yields of 62–79% were furnished when the reaction was conducted with 10 mol % of p-TsOH·H_2O in 1,2-dichloroethane at room temperature or in acetonitrile or nitromethane instead of the chlorinated solvent at reflux (entries 3, 5, and 7). In contrast, either a mixture of unknown decomposition products or no reaction was observed in control experiments where p-TsOH·H_2O was replaced with 10 mol % of Tf_2NH, TfOH, TFA, and H_3PO_4 as the catalyst or 1,2-dichloroethane with 1,4-dioxane as the solvent (entries 6 and 8–11). On the other hand, the analogous reaction with 10 mol % of BF_3·Et_2O as the catalyst gave a product yield of 75% (entry 12). On the basis of the above results, reaction of **1a** with 5 mol % of p-TsOH·H_2O in 1,2-dichloroethane at reflux for 0.5 h was deemed to provide the optimum conditions.

With the optimized catalytic conditions in hand, we next explored their generality for a series of homoallylic alcohols **1b**–**1r** and the results are summarized in Table 2. Reactions of homoallylic alcohols **1** bearing an electron-withdrawing group at the *para* position of both phenyl rings gave the corresponding substituted indenes **2b**–**d** in good to excellent yields of 88–98% (entries 1–3). Similarly, the analogous reactions of substrates where the two phenyl rings contained a pendant electron-donating group at the *para* position (**1e** and **1f**) afforded the corresponding substituted indenes **2e** and **2f** in 90% and 82% yields, respectively (entries 4 and 5). Starting alcohols in which one of the aryl groups was replaced by a methyl substituent, as in **1g**–**1k**, were found to be well tolerated, providing the corresponding indene products **2g**–**2k** in 58–79% yield (entries 6–10). The presence of a phenyl instead of a methyl group at the α-carbon center to the alcohol functional group (**1m,n**) or a vinyl methyl ester unit (**1o**) in the substrate was found to have minimal effect on the outcome of the reaction (entries 12–14). In these reactions, the corresponding indene derivatives **2m**–**2o** were afforded in 72–76% yield. Tertiary alcohols containing *N*-methyl indole (**1l**) moiety at the carbinol carbon center or in which the identity of the α-position to the alcohol group was a methylene carbon center (**1p,q**) were also examined under the standard conditions (entries 11, 15, and 16). However, these reactions were found to give 1,4-diene **3l** and 1,3-diene **4p** in 88% and 83% yields, respectively, and for **1q**, a mixture of decomposition products.[14] In our hands, the reactivity of the secondary alcohol **1r** was additionally investigated but found to result in the recovery of the substrate in near quantitative yield (entry 17).

A tentative mechanism for the Brønsted acid catalyzed indene forming reaction is illustrated in Scheme 2. This could involve the activation of homoallylic alcohol **1** in the presence of Brønsted acid to give the cationic species **A**. As a consequence, dehydration

Table 2
p-TsOH·H_2O catalyzed reactions of **1b**–**r**[a]

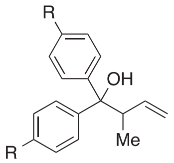
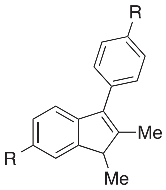
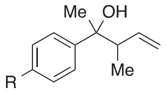
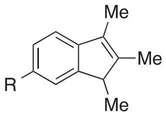
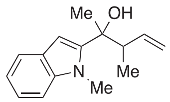
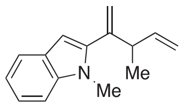
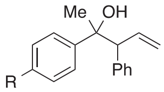
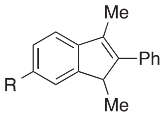
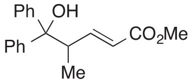
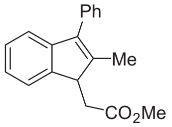
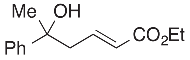
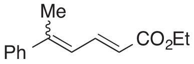
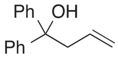
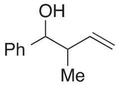
Entry	Substrate	Product		Time (h)	Yield[b] (%)
1	 **1b-1f**		**2b**, R = F	20	98
2			**2c**, R = Cl	3	88
3			**2d**, R = Br	20	88
4			**2e**, R = Me	0.5	90
5			**2f**, R = OMe	20	82
6	 **1g-1k**		**2g**, R = Cl	14	64
7			**2h**, R = Br	23	58
8			**2i**, R = H	23	60
9			**2j**, R = Me	14	79
10			**2k**, R = OMe	12	77
11	 **1l**		**3l**	0.5	83
12	 **1m,n**		**2m**, R = Br	24	73
13			**2n**, R = H	13	76

Table 2 (*continued*)

Entry	Substrate	Product		Time (h)	Yield[b] (%)
14	 **1o**		**2o**	24	72
15	 **1p**		**4p**	24	88[d]
16	 **1q**	–	–	36	–[c]
17	 **1r**	–	–	3	–[e]

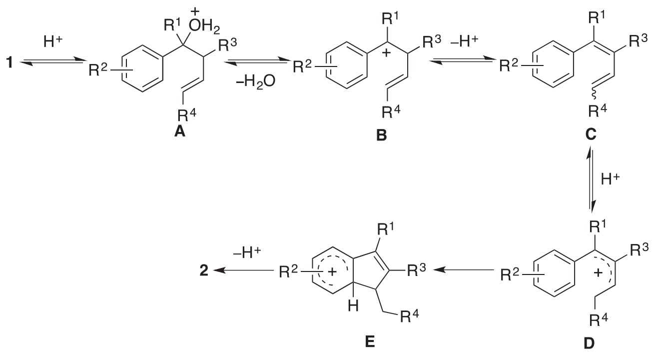
[a] All reactions were performed at reflux in $(CH_2Cl)_2$ with a *p*-TsOH·H$_2$O/**1a** ratio of 1:20.

[b] Isolated yield.

[c] Unknown side products obtained based on ^{1}H NMR analysis of the crude mixture.

[d] Obtained as a 4:1 mixture of regiosomers based on ^{1}H NMR analysis of the crude mixture.

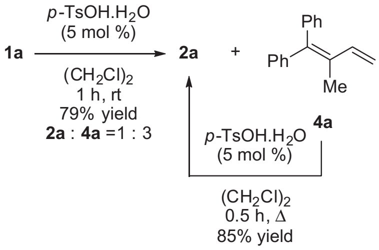
[e] Recovery of starting material based on TLC and ^{1}H NMR analysis of the crude mixture.



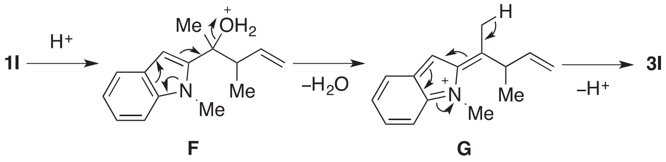
Scheme 2. Proposed mechanism.

occurs to deliver the homoallylic carbonium adduct **B**. Deprotonation of this newly formed adduct might then give 1,3-diene **C**, which on re-protonation of the distal C=C bond, would provide the internal allylic cationic intermediate **D**. This is the active species that undergoes the Friedel–Crafts reaction, which upon re-aromatization of the ensuing Wheland intermediate **E**, would produce the indene product **2**.

The proposed involvement of 1,3-diene **C** was supported by the following control experiments (Scheme 3). Treating a 1,2-dichloroethane solution containing **1a** with 5 mol % of *p*-TsOH·H$_2$O at room temperature for 1 h gave **2a** along with **4a** as a 1:3 inseparable mixture in 75% yield. On re-treating this mixture of compounds to the optimized conditions of 5 mol % of *p*-TsOH·H$_2$O in 1,2-dichloroethane at 80 °C for 0.5 h, the desired indene was afforded in 85% yield, which is comparable to that formed from **1a** described in Table 1, entry 1.



Scheme 3. Control experiment with **1a**.



Scheme 4. Proposed formation of **3l**.

As shown in Scheme 4, the preferential formation of 1,4-diene **3l** could be due to a more facile 1,3-proton transfer process on formation of the cationic species **F** from *p*-TsOH·H$_2$O mediated dehydration of **1l**.[15] Deprotonation and re-aromatization of the resulting iminium intermediate **G** might then provide the indole side-product. In the case of 1,3-diene **4p** being furnished, this could be due to resistance to carbocation formation as a result of the presence of the electron-withdrawing ester and a methylene moiety at the α-position to the alcohol group in the adduct. Likewise, while the ionization of **1q** might proceed, the absence of an α-substituent to the alcohol group in the substrate might lead to the resulting cationic species being less stable and thus more prone to a variety of decomposition pathways before Friedel–Crafts reaction can proceed. The recovery of the secondary alcohol could be due to the potential generation of a less stable secondary carbonium species being unfavorable.

In summary, we have developed an efficient approach to highly substituted indenes from *p*-TsOH·H$_2$O catalyzed Friedel–Crafts reaction of homoallylic alcohols. Achieved under mild conditions, the reaction was shown to be applicable to a variety of unsaturated alcohols. Efforts exploring the scope and synthetic applications of this approach to the benzofused carbocyclic derivative are in progress and will be reported in due course.

Acknowledgments

This work is supported by a College of Science Start-Up Grant from Nanyang Technological University and a Tier 1 Grant (MOE2013-T1-002-035) from the Ministry of Education of

Singapore (to P.W.H.C.), a Young National Natural Science Foundation of China Grant (No. 21302096), a Young Natural Science Foundation of Jiangsu Province Grant (BK20130962) and a Project Fund from the Priority Academic Program Development of Jiangsu Higher Education Institutions (to X.Z.). A Yousef Jameel Scholarship (to W.T.T.) is also gratefully acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.05.027.

References and notes

1. Gao, H.; Katzenellenbogen, J. A.; Garg, R.; Hansch, C. *Chem. Rev.* **1999**, *99*, 723.
2. For selected examples, see: (a) Clegg, N. J.; Paruthiyil, S.; Leitman, D. C.; Scanlan, T. S. *J. Med. Chem.* **2005**, *48*, 5989; (b) Hagishita, S.; Yamada, M.; Shirahase, K.; Okada, T.; Murakami, Y.; Ito, Y., et al. *J. Med. Chem.* **1996**, *39*, 3636; (c) Palm, J.; Boegesoe, K. P.; Liljefors, T. *J. Med. Chem.* **1993**, *36*, 2878; (d) Witiak, D. T.; Kakodkar, S. V.; Brunst, G. E.; Baldwin, J. R.; Rahwan, R. G. *J. Med. Chem.* **1978**, *21*, 1313.
3. (a) Yang, J.; Lakshmikantham, M. V.; Cava, M. P.; Lorcy, D.; Bethelot, J. R. *J. Org. Chem.* **2000**, *65*, 6739; (b) Barber, O. J.; Rakitin, O. A.; Ros, M. B.; Torroba, T. *Angew. Chem., Int. Ed.* **1998**, *37*, 296.
4. (a) Leino, R.; Lehmus, P.; Lehtonen, A. *Eur. J. Inorg. Chem.* **2004**, 3201; (b) Zargarian, D. *Coord. Chem. Rev.* **2002**, *233*, 157; (c) Alt, H. G.; Koeppl, A. *Chem. Rev.* **2000**, *100*, 1205.
5. (a) Bajracharya, G. B.; Pahadi, N. K.; Gridnev, I. D.; Yamamoto, Y. *J. Org. Chem.* **2006**, *71*, 6204; (b) Kuninobu, Y.; Tokunaga, Y.; Kawata, A.; Takai, K. *Org. Lett.* **2006**, *8*, 2891; (c) Kuninobu, Y.; Tokunaga, Y.; Kawata, A.; Takai, K. *J. Am. Chem. Soc.* **2006**, *128*, 202; (d) Kuninobu, Y.; Kawata, A.; Takai, K. *J. Am. Chem. Soc.* **2005**, *127*, 13498.
6. Takahashi, T.; Kuzuba, Y.; Kong, F.; Nakajima, K.; Xi, Z. *J. Am. Chem. Soc.* **2005**, *127*, 17188.
7. Park, E. J.; Kim, S. H.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 17268.
8. Krishna, B. S. M.; Yong, R. L. *Org. Lett.* **2013**, *15*, 4288.
9. For selected examples of indene synthesis catalyzed by transition metal complexes, see: (a) Shi, X.; Li, C. *Org. Lett.* **2013**, *15*, 1476; (b) Zhao, J.; Clark, D. A. *Org. Lett.* **2012**, *14*, 1668; (c) Martinez, A.; Garcia, P. G.; Rodriguez, M. A. F.; Rodriguez, F.; Sanz, R. *Angew. Chem., Int. Ed.* **2010**, *49*, 4633; (d) Chatterjee, P. N.; Roy, S. *J. Org. Chem.* **2010**, *75*, 4413; (e) Liu, C. R.; Yang, F. L.; Jin, Y. Z.; Ma, X. T.; Cheng, D. J.; Li, N., et al. *Org. Lett.* **2010**, *12*, 3832; (f) Zhang, X.; Teo, W. T.; Chan, P. W. H. *Org. Lett.* **2009**, *11*, 4990; (g) Li, C.; Zeng, Y.; Wang, J. *Tetrahedron Lett.* **2009**, *50*, 2956; (h) Ye, S.; Gao, K.; Zhou, H.; Yang, Y.; Wu, J. *Chem. Commun.* **2009**, 5406; (i) Wang, J.; Zhang, L.; Jing, Y.; Huang, W.; Zhou, X. *Tetrahedron Lett.* **2009**, *50*, 4978.
10. For selected examples of non-metal catalyzed indene synthesis, see: (a) Eom, D.; Park, S.; Park, Y.; Ryu, T.; Lee, P. H. *Org. Lett.* **2012**, *14*, 5392; (b) Kurouchi, H.; Sugimoto, H.; Otani, Y.; Ohwada, T. *J. Am. Chem. Soc.* **2010**, *132*, 807; (c) Khan, Z. A.; Wirth, T. *Org. Lett.* **2009**, *11*, 229; (d) Su, C.; Huang, X.; Liu, Q.; Huang, X. *J. Org. Chem.* **2009**, *74*, 8272; (e) Gassman, P. G.; Ray, J. A.; Wenthold, P. G.; Mickelson, J. W. *J. Org. Chem.* **1991**, *56*, 5143.
11. For selected examples of non-metal catalyzed indene synthesis from unsaturated alcohols, see: (a) Zhu, H. T.; Ji, K. G.; Yang, F.; Wang, L. J.; Zhao, S. C.; Ali, S., et al. *Org. Lett.* **2011**, *13*, 684; (b) Smith, C. D.; Rosocha, G.; Mui, L.; Batey, R. A. *J. Org. Chem.* **2010**, *75*, 4716; (c) Zhou, X.; Zhang, H.; Xie, X.; Li, Y. *J. Org. Chem.* **2008**, *73*, 3958; (d) Guo, S.; Liu, Y. *Org. Biomol. Chem.* **2008**, *6*, 2064; (e) Xi, Z.; Guo, R.; Mito, S.; Yan, H.; Kanno, K.; Nakajima, K., et al. *J. Org. Chem.* **2003**, *68*, 1252; (f) Singh, G.; Ila, H.; Junjappa, H. *Synthesis* **1986**, 744.
12. For selected reviews on alcohol proelectrophiles, see: (a) Cera, G.; Chiarucci, M.; Bandini, M. *Pure Appl. Chem.* **2012**, *84*, 1673; (b) Bandini, M.; Cera, G.; Chiarucci, M. *Synthesis* **2012**, 504; (c) Biannic, B.; Aponick, A. *Eur. J. Org. Chem.* **2011**, 6605; (d) Emer, E.; Sinisi, R.; Capdevila, M. G.; Petruzziello, D.; De Vincentiis, F.; Cozzi, P. G. *Eur. J. Org. Chem.* **2011**, 647; (e) Bandini, M.; Tragni, M. *Org. Biomol. Chem.* **2009**, *7*, 1501; (f) Muzart, J. *Tetrahedron* **2008**, *64*, 5815.
13. For selected works by us, see Ref. [9f] and: (a) Teo, W. T.; Rao, W.; Koh, M. J.; Chan, P. W. H. *J. Org. Chem.* **2013**, *78*, 7508; (b) Kothandaraman, P.; Koh, B. Q.; Limpanuparb, T.; Hirao, H.; Chan, P. W. H. *Chem. Eur. J.* **2013**, *19*, 1978; (c) Zhang, X.; Teo, W. T.; Sally; Chan, P. W. H. *J. Org. Chem.* **2010**, *75*, 6290; (d) Kothandaraman, P.; Rao, W.; Foo, S. J.; Chan, P. W. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 4619; (e) Zhang, X.; Rao, W.; Sally; Chan, P. W. H. *Org. Biomol. Chem.* **2009**, *7*, 4186; (f) Rao, W.; Zhang, X.; Sze, E. M. L.; Chan, P. W. H. *J. Org. Chem.* **2009**, *74*, 1740.
14. Xu, Y. H.; Lu, J.; Loh, T. P. *J. Am. Chem. Soc.* **2009**, *131*, 1372.
15. (a) Xiao, Y.-C.; Wang, C.; Yao, Y.; Sun, J.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2011**, *50*, 10661; (b) Patir, S.; Uludag, N. *Tetrahedron* **2009**, *65*, 115.

Please cite this article in press as: Zhang, X.; et al. *Tetrahedron Lett.* (2014), http://dx.doi.org/10.1016/j.tetlet.2014.05.027