TfOH/Fe(OTf)₃ cocatalyzed reaction of arylallenes with alcohols for structurally diverse indene derivatives



Congrong Liu, *, a, b Haiyun Zhang, Lianghui Ding and Juan Liu b

The indene moiety is an important unit because of its presence in many chemical catalysts, functional materials and biologically relevant molecules. Herein we report a facile reaction of arylallenes with benzylic or allylic alcohols through TfOH/Fe(OTf)₃ cocatalyzed cleavage of sp³ carbon-oxygen. In the presence of 5 mol% TfOH and 5 mol% Fe(OTf)₃, a range of arylallenes undergo carbocation initiated cyclization reaction with alkyl alcohols to give structurally diverse polysubstituted indenes in good to excellent yields. H₂O is the sole byproduct that makes this transformation high atom economy and environmentally benign.

Allenes, alcohols, cocatalyst, electrophilic cyclization, indenes

Introduction

The indene moiety is an important unit because of its presence in many natural products and drug candidates,^[1] such as enzyme inhibitors, reuptake blocking, biogenic transporters and anti-arrhythmic activity. The function of indene-related compounds has been found applications as ligands for metallocene complexes,^[2] which are widely utilized in various catalytic reactions. In addition, indene derivatives have also been found applications in material science as discotic liquid crystals, conducting polymers, coating materials for steel and so on.^[3] So developing efficient synthetic approaches to construct differently substituted indene derivatives is one of the most exciting topics in organic synthesis.^[4] Recently, Roy described a useful method for the formation of indene derivatives via heterobimetallic Ir-Sn catalyzed reaction of propargylic alcohols.^[4v]

Foregoing their past as structural oddities and molecules of only fundamental interest, allenes have proven themselves as valuable synthetic building blocks and reaction intermediates over the last decades.^[5] The higher reactivity of this type of cumulated systems compared to that of simple alkenes, offers a number of unique opportunities for the development of novel synthetic transformations.^[6] There are several reports about arylallens to be used in cyclization to form indenes.^[4k, 4m, 4x] Tian and coworkers reported an efficient method for the synthesis of indene derivatives via FeCl₃ catalyzed electrophilic cyclization of allenes with N-benzylic or N-allylic sulfonamides. [4m] However, The sulfonamides can't be available directly and the yields are not very high. Furthermore, the byproduct is TsNH₂, the relative molecular weight of which is 171 that leads to low atom economy. Ma's group reported a useful method for the formation of indene derivatives via equivalent ZnCl₂ catalyzed reaction of allenes and alcohols. But only terminal allenes and 1,3-Diarylprop-2-en-1-ols or diarylmethanols are suitable substrates and a stoichiometric amount of cycalysts is needed. So there remains room for the development of electrophilic cyclization of allenes that can expand the scope, employ plentiful and easily available substrates , use catalytic amount of catalyst and improve the atom economy. Here, we reported a TfOH/Fe(OTf)₃ cocatalyzed electrophilic cyclization of allenes with alcohols for structurally diverse indene derivatives. In sharp contrast to the reported methods, in our reaction, both 1,3-di and 1,1,3-trisubstituted arylallenes react smoothly with benzylic or allylic alcohols to afforded structurally diverse indene derivatives with good to excellent yield, and a catalytic combination of TfOH (5 mol %) and Fe(OTf) $_{3}$ (5 mol %) is employed which is powerful for the reaction (Scheme 1). $^{[7]}$ The unique by product is H2O, which makes the transformation environmentally benign and high atom economy. To our knowledge, for the first time, the highly efficient catalytic combination of TfOH and Fe(OTf)₃ is used for the synthesis of indene derivatives and electrophilic cyclization of allenes .

Scheme 1 The contrast of reported systeme and our's



Results and Discussion

To get the optimized reaction conditions, we evaluated a number of Brønsted acids and Lewis acids (5 mol %) in the model reaction of benzhydrol (**1a**) with arylallene (**2a**) in 1,2-dichloroethane at 70 °C for 12h (Table 1, Entries 1-11). The use of Fe(OTf)₃ resulted in the formation of indene **3a** in 47% yield (Table 1, Entry 6). Doubling the amount of Fe(OTf)₃ improved the yield to 60% (Table 1, Entry 12) and more excitingly, a higher yield (85%) was reached cocatalyzed by Fe(OTf)₃ (5 mol %) and TfOH (5 mol %) in 1,2-dichloroethane (Table 1, Entry 13). The reaction efficiency was significantly affected by the solvent, and a survey of common solvents revealed that the use of nitromethane improved the yield to 96% (Table 1, Entry 18). The yield of using Fe(OTf)₃ or TfOH as single catalyst in MeNO₂ was lower than that of the combination of Fe(OTf)₃ and TfOH (Table 1. Entries 19-20).

^a School of Environment Engineering, Nanjing Institute of Technology, 1 Hongjingdadao, Nanjing, Jiangsu 211167, China E-mail: congrong@mail.ustc.edu.cn

^b Department of Chemistry, University of Science and Technology of China, Hefei, Anhui 230026, China

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/cjoc.201800099

Table 1 Optimization of reaction conditions^a



 o Reaction conditions: benzhydrol **1a** (0.2 mmol), arylallene **2a** (0.24 mmol), catalyst (5 mol %), solvent (1.0 mL), 70 °C, 12 h. b Isolated yield.

The scope of this TfOH/Fe(OTf)₃ cocatalyzed reaction was expanded to a variety of alcohols (Table 2). In the presence of TfOH (5 mol %) and Fe(OTf)₃ (5 mol %), bisbenzylic, monobenzylic and allylic alcohols smoothly underwent this kind of transformation, generating structurally diverse indenes **3** in good to excellent yields (Table 2, **3a-3n**). Notably, this protocol proved useful for the construction of indene containing polycycles such as **3d-g** (Table 2, entries 4-7). This reaction was not applicable to less reactive alkyl alcohols such as cyclohexanol. Table 2 Synthesis of polysubstituted indenes from arylallene 2a and different alcoholes $\mathbf{1}^{a,b}$



^{*a*} Reaction conditions: alcohol **1** (0.20 mmol), arylallene **2a** (0.24 mmol), Fe(OTf)₃ (5 mol %), TfOH (5 mol %), nitromethane (1.0 mL), 70 °C. ^{*b*} Isolated yield. ^{*c*} dr 47:53. ^{*d*} dr 43:57. ^{*e*} dr >1:99. ^{*f*} dr 37:63. ^{*g*} dr 50:50. ^{*h*} dr 44:56.

Substrate scope is also broad with respect to the allenes. A range of 1,3-di- and 1,1,3-trisubstituted arylallenes were found to be able to react with benzhydrol **1a** in the presence of 5 mol % of TfOH/Fe(OTf)₃ (1 : 1) to afford the corresponding indenes in good to excellent yields (Table 3). The reaction is slower when the allene contains an electron-withdrawing group (Table 3, **3q-3s**, **3v-3w**). As demonstrated by the results summarized in tables 2 and 3, a variety of heteroatoms and alkyl groups were successfully introduced into the indene derivatives by employing functionalized arylallenes and benzylic /allyl alcohols.





3x, 88%, 12h

^{*a*} Reaction conditions: alcohole **1** (0.20 mmol), arylallene **2a** (0.24 mmol), Fe(OTf)₃ (5 mol %), TfOH (5 mol %), nitromethane (1.0 mL), 70 $^{\circ}$ C. ^{*b*} Isolated yield.

To gain insight into the reaction mechanism, we examined the reaction of allene **2a** with an optically active alcohol (R) - **1i**. As demonstrated by Equation 1, the reaction of alcohol (R) - **1i** (96% ee) with allene **2a** proceeded smoothly in the presence of TfOH (5 mol %) and Fe(OTf)₃ (5 mol %) to afford corresponding indene **3i** in nearly racemic form (3% ee). This result suggests that carbocation **4** is generated from alcohol **1** via a acid – promoted SP³ C-O bond cleavage (scheme 2). ^[4k, 8] Electron-rich arylallene **2** acts as an nucleophile to couple with carbocation **4** to give intermediate **5**. Friedel-Crafts cyclization of carbocation **5** followed by aromatization affords indene **3**.

Scheme 2 Proposed reaction pathway.



Conclusions

In summary, we have developed a facile raction of alcohols with arylallenes under acidic conditions. a catalytic combination of TfOH and $Fe(OTf)_3$ to afford the corresponding indene derivatives in high yield with extremely high regioselectivity. It is the first time such catalytic system has been used in the reactions of allenes. In our system, both 1,3-di and 1,1,3-trisubstituted arylallenes serve as suitable substrates to afford the corresponding indene derivatives in high to excellent yield. Furthermore, H_2O is the sole byproduct that makes this transformation high atom economy and environmentally benign. This method presents a novel example of efficient cooperative catalysis. Current efforts are directed toward further methodological refinement and synthetic applications.

Experimental

Flash chromatography was performed with Merck silica gel 60 F254 plates, and the products were visualized by UV detection. ¹H and ¹³C NMR Spectra were recorded on a Bruker AC-400 FT spectrometer (400 MHz and 100 MHz, respectively) using tetramethylsilane as internal reference. Chemical shifts (δ) and coupling constants (*J*) were expressed in ppm and Hz, respectively. IR spectra were recorded on a Perkin-Elmer 2000 FTIR spectrometer. High resolution mass spectra were recorded on a LC-TOF spectrometer (Micromass). the UV detection was monitored at 254 nm. Melting points wereuncorrected. Allenes **2a-2g** and **2h-2k** were prepared according to literature procedures.^[9] The rest of chemicals were purchased from the Sinopharm Chemical Reagent Co., Meryer, Acros, and Alfa Aesar, and used as received. Solvents were dried over MgSO₄ before use.

General Procedure for the TfOH/Fe(OTf)₃ Coatalyzed coupling reaction of Arylallenes: To a solution of alcohol **1** (0.20 mmol) in dry nitromethane (1.0 mL) were added allene **2** (0.24 mmol) and TfOH (1.5 mg, 0.010 mmol), Fe(OTf)₃ (5.0 mg, 0.010 mmol) subsequently under N₂. The resulting mixture was stirred at 70 °C until no further transformation was detected by TLC analysis. The mixture was cooled to room temperature, and purified by silica gel column chromatography, eluting with petroleum ether/ethyl acetate (100:0 to 10:1), to give indene derivative **3**.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2018xxxxx.

Acknowledgement

We are grateful for the financial support from the National Natural Science Foundation of China (No. 21202154), Natural Science Foundation of The Jiangsu Higher Education Institutes of China (15KJB150007), Nanjing Institute of Technology Scientific Research Foundation for Introducing Talents (No. YKJ201329, YKJ201326,YKJ201318, YKJ201419), Nanjing Institute of Technology.

References

 (a) Clegg, N. J.; Paruthiyil, S.; Leitman, D. C.; Scanlan, T. S. J. Med. Chem. 2005, 48, 5989; (b) Korte, A.; Legros, J.; Bolm, C. Synlett, 2004, 2397; (c) Maguire, A. R.; Papot, S.; Ford, A.; Touhey, S.; O'Connor, R.; Clynes, M. Synlett, 2001, 41; (d) Gao, H.; Katzenellenbogen, J. A.; Garg, R.; Hansch, C. Chem. Rev. 1999, 99, 723; (e) Senanayake, C. H.; Roberts, F. E.; Michele, L. M.; Ryan, K. M.; Liu, J.; Fredenburgh, L. E.; Foster, B. S.; Douglas, A. W.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. Tetrahedron Lett. 1995, 36, 3993; (f) Shanmugam, P.; Rajasingh, P. Chem. Lett. 2005, 34, 1494.

- [2] (a) Wang, B. Coord. Chem. Rev., 2006, 250, 242; (b) Alt, H. G.; Koppl,
 A. Chem. Rev., 2000, 100, 1205.
- [3] (a) Barbera, J.; Rakitin, O. A.; Ros, M. B.; Torroba, T. Angew. Chem., Int. Ed., **1998**, *37*, 296; (b) Yang, J.; Lakshmikantham, M. V.; Cava, M. P.; Lorcy, D.; Bethelot, J. R. J. Org. Chem. **2000**, *65*, 6739.
- [4] (a) Alexander, P.; Antonio, M.; Nuno, M. Chem. Eur. J. 2016, 22, 14471. (b) Yang, C.; Xu, Z. L.; Shao, H.; Mou, X. Q.; Wang, J.; Wang, S. H. Org. Lett. 2015, 17, 5288; (c) Dethe, D. H.; Murhade, G. M.; Ghosh, S. J. Org. Chem., 2015, 80, 8367; (d) Ding, W.; Shi, X. L, Chin. J. Chem. 2015, 33, 1276; (e) Dethe, D. H.; Murhade, G. Org. Lett. 2013, 15, 429; (f) Muthusamy, S.; Sivaguru, M. Org. Lett. 2014, 16, 4248; (g) Huang, X. C.; Yang, X. H.; Song, R. J.; Li, J. H. J. Org. Chem. 2014, 79, 1025; (h) Wang, Y.; Liao, W.; Huang, G. P.; Xia, Y. Z.; Yu, Z. X. J. Org. Chem. 2014, 79, 5684; (i) Huguet, N.; Lebœuf, D.; Echavarren, A. M. Chem. Eur. J. 2013, 19, 6581; (j) Hou, Q. W.; Zhang, Z. H.; Kong, F. J.; Wang, S. Z.; Wang, H. Q.; Yao, Z.-J. Chem. Commun. 2013, 49, 695; (k) Meng, B.; Ma, S. Org. Lett. 2012, 14, 2674; (I) Usanov, D. L.; Yamamoto, H. Org. Lett. 2012, 14, 414; (m) Liu, C.-R.; Wang, T.-T. Qi ,Q.-B.; Tian, S.-K. Chem. Commun., 2012, 48, 10913; (n) Qiu, G. S.; Ding, Q. P.; Gao, K.; Peng, Y. Y. J. Comb. Sci. 2011, 13, 13; (o) Patureau, F. W.; Besset, T.; Kuhl, N.; Glorius, F. J. Am. Chem. Soc., 2011, 133, 2154; (p) Zhu, Y.; Yin, G.; Hong, D.; Lu, P.; Wang, Y. Org. Lett., 2011, 13, 1024; (q) Panteleev, J.; Huang, R. Y.; Lui, E. K. J.; Lautens, M. Org. Lett., 2011, 13, 5314; (r) Zeng, X.; Ilies, L.; Nakamura, E. J. Am. Chem. Soc., 2011, 133, 17638; (s) Kurouchi, H.; Sugimoto, H.; Otani, Y.; Ohwada, T. J. Am. Chem. Soc. 2010, 132, 807; (t) Liu, C.-R.; Yang, F.-L.; Jin, Y.-Z.; Ma, X.-T.; Cheng, D.-J.; Li, N.; Tian, S.-K. Org. Lett., 2010, 12, 3832; (u) Fuchibe, K.; Atobe, K.; Fujita, Y.; Mori, K.; Akiyama, T. Chem. Lett. 2010, 867; (v) Chatterjee, P. N.; Roy, S. J. Org. Chem. 2010, 75, 4413; (w) Ye, S.; Ren, H., Wu, J. J. Comb. Chem. 2010, 12, 670; (x) Yamazaki, Y.; Yamamoto, Y.; Fukushima, M.; Takebayashi, T.; Mikata, Y. J. Org. Chem. 2010, 75, 5216.
- [5] (a) Bates, R. W.; Satcharoen, V. Chem. Soc. Rev. 2002, 31, 12; (b) Ma, S. Acc. Chem. Res. 2003, 36, 701; (c) Sydnes, L. K. Chem. Rev. 2003, 103, 1133; (d) Brandsma, L.; Nedolya, N. A. Synthesis, 2004, 735; (e) Tius, M. A. Acc. Chem. Res. 2003, 36, 284; (f) Wei, L. L.; Xiong, H.; Hsung, R. P. Acc. Chem. Res. 2003, 36, 773; (g) Ma, S. Chem. Rev.

2005, 105, 2829; (h) Ma, S. Aldrichimica Acta 2007, 40, 91; (i) Kim, H.; Williams, L. J. Curr. Opin. Drug Discovery & Development. 2008, 11, 870; (j) Brasholz, M.; Reissig, H.-U.; Zimmer, R. Acc. Chem. Res. 2009, 42, 45; (k) Ma, S. Acc. Chem. Res. 2009, 42, 1679; (q) Wang, Z. J.; Benitez, D.; Tkatchouk, E.; Goodward, W. A.; Toste, F. D. J. Am. Chem. Soc., 2010, 132, 13064; (I) Martin, T. J.; Vakhshori, V. G. Tran, Y. S.; Kwon, O. Org. Lett. 2011, 13, 2586; (m) Muneoz, M. P. Org. Biomol. Chem., 2012, 10, 3584. (n) Andrews, I. P.; Blank, B. R.; Kwon, O. Chem. Commun., 2012, 48, 5373; (o) Meng, W.; Zhao, H.-T.; Nie, J.; Zheng, Y.; Fu, A. P.; Ma, J-A. Chem. Sci. 2012, 3, 3053. (p) Fang, Y-Q.; Tadross, P. M.; Jacobsen, E. N. J. Am. Chem. Soc. 2014, 136, 17966; (q) Hurtado-Rodrigo, C.; Hoehne, S.; Munoz, M.; Chem. Commun., 2014, 50, 1494; (r) Bang, J. Y.; Kim, H.; Yu, M. O. Org. Lett. 2015, 17, 1573.; (s) Kidonakis, M.; Stratakis, M. Org. Lett. 2015, 17, 4538; (t) Liu, J.; Liu, Q.; Franke, B.; Jackstell, R.; Beller, M. J. Am. Chem. Soc. 2015, 137, 8556; (u) Lin, W. L.; Cheng, J. J.; Ma, S. Adv. Synth. Catal. 2016, 358, 1989; (v) Khrakovsky, D. A.; Tao, C. Z.; Johnson, M. W.; Thornbury, R. T.; Shevick, S. L.; Toste. F. D. Angew. Chem. Int. Ed. 2016, 55, 6079; (w) Eshon, J.; Landis, C. R.; Schomaker, J. M. J. Org. Chem. 2017, 82, 9270; (x) Martzel, T.; Lohier, J.; Gaumont, A. C; Perrio, S. Adv. Synth. Catal. 2017, 360, 231.

- [6] (a) Krause, N.; Hashmi, A. S. K. Modern Allene Chemistry, VCH, Weinheim, 2004, pp. 50-102. (b) Jana, U.; Biswas, S.; Maiti, S. Eur. J. Org. Chem. 2008, 5798.
- [7] The details of experimental procedure see supporting informant.
- [8] (a) Kuang, J-Q.; Ma, S.-M. J. Am. Chem. Soc. 2010, 132, 1786; (b)
 Xiao, Q.; Xia, Y.; Li, H.; Zhan, Y.; Wang, J.-B. Angew. Chem. Int. Ed.
 2011, 50, 1114.
- [9] (a) Kuang, J-Q.; Ma, S.-M. J. Am. Chem. Soc. 2010, 132, 1786; (b) Zhan, Y.; Wang, J.-B. Angew. Chem. Int. Ed. 2011, 50, 1114.

(The following will be filled in by the editorial staff) Manuscript received: XXXX, 2017 Revised manuscript received: XXXX, 2017 Accepted manuscript online: XXXX, 2017 Version of record online: XXXX, 2017

Entry for the Table of Contents

Page No. 4

TfOH/Fe(OTf)₃ cocatalyzed reaction of arylallenes with alcohols for structurally diverse indene derivatives



In the presence of 5 mol% TfOH and 5 mol% Fe(OTf)₃, a range of arylallenes undergo carbocation initiated cyclization reaction with alcohols to give structurally diverse polysubstituted indenes in good to excellent yields with extremely high regioselectivity.

Articl Accepted

Congrong Liu,* Haiyun Zhang, Lianghui Ding, Juan Liu