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Synthesis of Functionalized Indenes via Cascade Reaction of Aziridines and Propargyl Alcohols

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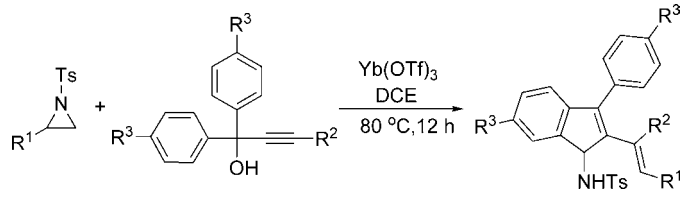
ABSTRACT



A concise synthesis of functionalized indenes via the Lewis acid catalyzed cascade reaction of aziridines and propargylic alcohols has been developed. The methodology offers great potential for the synthesis of biologically active indene derivatives and related polycyclic compounds.

Indenes are carbocyclic compounds of great interest as synthetic targets and building blocks for various biologically active molecules[1] and functional materials.[2] They can also be utilized as ligands in tailored metallocene complexes, especially for group IV metallocenes in the catalysis of olefin polymerization.[3] Consequently, much attention has been paid to the synthesis of indene derivatives. The most effective methods for the construction of indenes include Brønsted acid or Lewis acid (LA) catalyzed intramolecular Friedel−Crafts cyclization,[4] the ring expansion of substituted cyclopropenes,[5] and transition-metal-catalyzed cyclizations[6] and cycloadditions of alkynes.[7] Despite these methods, their preparative ways are fewer than those for structurally related heterocycles such as indoles and benzofurans. We recently synthesized an indene derivative **3a**, which is formed from 2-phenyl-1-tosylaziridine (**1a**) with 1,1,3-triphenylprop-2-yn-1-ol (**2a**) in the presence of a LA catalyst (Table 1). Herein, we describe the systematic optimization of this reaction and the applicability of this method to several propynols.

Exhaustive studies of the reaction conditions for the synthesis of **3a** from 2-phenyl-1-tosylaziridine (**1a**) with

(1) (a) Schneider, M. R.; Ball, H. *J. Med. Chem.* **1986**, *29*, 75. (b) Froimowitz, M.; Wu, K. M.; Moussa, A.; Haidar, R. M.; Jurayj, J.; George, C.; Gardner, E. L. *J. Med. Chem.* **2000**, *43*, 4981. (c) Yu, H.; Kim, I.-J.; Folk, J. E.; Tian, X.; Rothman, R. B.; Baumann, M. H.; Dersch, C. M.; Anderson, J. L. F.; Parrish, D.; Jacobson, A. E.; Rice, K. C. *J. Med. Chem.* **2004**, *47*, 2624. (d) Antonio, D. S.; Piera, S.; Ivana, C.; Alessandra, C.; Gianfabio, G.; Barbara, C.; Marina, M.; Antonio, L.; Claudia, M.; Giuseppe, S.; Francesco, D. P.; Elisabetta, D. M.; Francesco, P. *J. Med. Chem.* **2005**, *48*, 2646.

(2) (a) Barber, O. 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.

(3) (a) Cadierno, V.; Diez, J.; Pilar, G. M.; Gimeno, J.; Lastra, E. *Coord. Chem. Rev.* **1999**, *193*−*195*, 147. (b) Alt, H. G.; Köppl, A. *Chem. Rev.* **2000**, *100*, 1205. (c) Zargarian, D. *Coord. Chem. Rev.* **2002**, *233*−*234*, 157. (d) Leino, R.; Lehmus, P.; Lehtonen, A. *Eur. J. Inorg. Chem.* **2004**, 3201.

(4) Zhou, X. B.; Zhang, H. M.; Xie, X.; Li, Y. Z. *J. Org. Chem.* **2008**, *73*, 3958.

(5) (a) Yoshida, H.; Kato, M.; Ogata, T. *J. Org. Chem.* **1985**, *50*, 1145. (b) Zhu, Z. B.; Shi, M. *Chem.*−*Eur. J.* **2008**, *14*, 10219.

(6) For recent selected examples, see: (a) Bajracharya, G. B.; Pahadi, N. K.; Gridnev, I. D.; Yamamoto, Y. *J. Org. Chem.* **2006**, *71*, 6204. (b) Tsukamoto, H.; Ueno, T.; Kondo, Y. *Org. Lett.* **2007**, *9*, 3033. (c) Guo, L. N.; Duan, X. H.; Bi, H. P.; Liu, X. Y.; Liang, Y. M. *J. Org. Chem.* **2007**, *72*, 1538. (d) Gou, F. R.; Bi, H. P.; Guo, L. N.; Guan, Z. H.; Liu, X. Y.; Liang, Y. M. *J. Org. Chem.* **2008**, *73*, 3837. (e) Duan, X. H.; Guo, L. N.; Bi, H. P.; Liu, X. Y.; Liang, Y. M. *Org. Lett.* **2006**, *8*, 5777. (f) Miyamoto, M.; Harada, Y.; Tobisu, M.; Chatani, N. *Org. Lett.* **2008**, *10*, 2975. (g) Sanz, R.; Miguel, D.; Rodriguez, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 7354. (h) Marion, N.; Diez-Gonzalez, S.; de Fremont, P.; Noble, A. R.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3647. (i) Liu, C. C.; Korivi, R. P.; Cheng, C. H. *Chem.*−*Eur. J.* **2008**, *14*, 9503.

(7) For recent selected examples, see: (a) Chen, W. L.; Cao, J.; Huang, X. *Org. Lett.* **2008**, *10*, 5537. (b) Wu, Y. T.; Kuo, M. Y.; Chang, Y. T.; Shin, C. C.; Wu, T. C.; Tai, C. C.; Cheng, T. H.; Liu, W. S. *Angew. Chem., Int. Ed.* **2008**, *47*, 9891. (c) Kuninobu, Y.; Kawata, A.; Takai, K. *J. Am. Chem. Soc.* **2005**, *127*, 13498.

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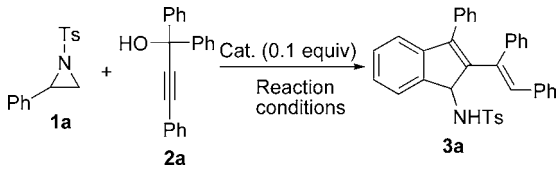
Table 1. Screening for the Reaction Conditions[a]

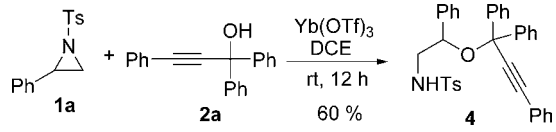


entry	catalyst	temp (°C)	time	solvent	yield (%)[b]
1	$Zn(OTf)_2$	80	12	DCE	trace
2	$Sc(OTf)_3$	80	12	DCE	35
3	$BF_3{\cdot}OEt_2$	80	5	DCE	0
4	$Cu(OTf)_2$	80	12	DCE	21
5	CF_3CO_2H	80	12	DCE	0
6	AgOTf	80	1	DCE	51
7	TfOH	80	1	DCE	41
8	$Yb(OTf)_3$	80	12	DCE	63
9	$Yb(OTf)_3$	60	12	THF	trace
10	$Yb(OTf)_3$	80	12	toluene	46
11	$Yb(OTf)_3$	20	12	DCE	0[c]
12	$Yb(OTf)_3$	80	2	DCE	30[d]

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), catalyst (0.05 mmol), solvent (5 mL). [b] Isolated yield refers to aziridine. [c] β-Alkoxyamine **4** was isolated in 60% yield. [d] Imine **5** was isolated in 20% yield.

1,1,3-triphenyl prop-2-yn-1-ol (**2a**) were conducted (Table 1). These results showed that 0.1 equiv of $Yb(OTf)_3$ was the most efficient catalyst for this transformation among others, such as $Zn(OTf)_2$, $Sc(OTf)_3$, $Cu(OTf)_2$, AgOTf, $BF_3{\cdot}Et_2O$, CF_3COOH, and TfOH (Table 1, entries 1−8), whereas dichloroethane (DCE) was the most suitable solvent (Table 1, entries 8−10). Besides these two key factors, the reaction products largely depended on the reaction temperature and reaction time. When the reaction was conducted at room temperature for 12 h, a simple nucleophilic ring-opening reaction occurred, and β-alkoxyamine **4** (Scheme 1) was isolated in 60% yield (Table 1, entry 11). It was

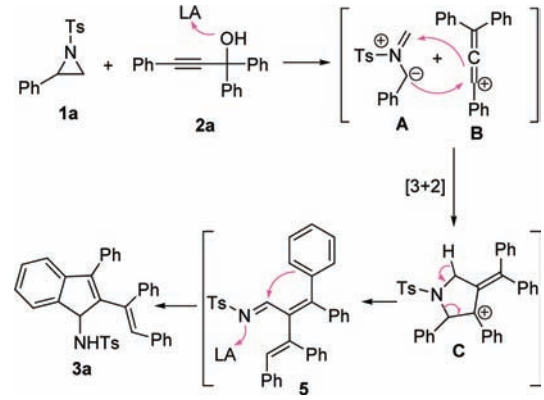
Scheme 1. Nucleophilic Ring-Opening Reaction of Aziridine **1a**



noteworthy that **4** could also be converted into **3a** at 80 °C in the presence of $Yb(OTf)_3$ which indicated that the nucleophilic ring-opening reaction is reversible. When the reaction time was shortened to 2 h at 80 °C, **3a** and intermediate imine **5** (Scheme 2) were isolated in yields of 30% and 20%, respectively (Table 1, entry 12). Thus, the most suitable reaction conditions for the formation of **3a** were established (Table 1, entry 8).

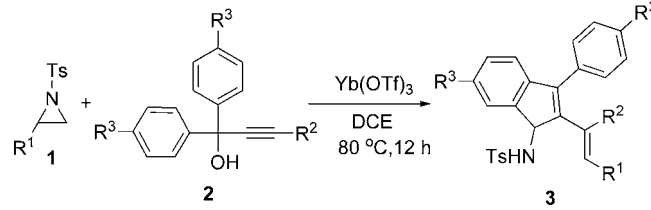
The scope of the reaction was investigated with a variety of reactants, and the results were presented in Table 2. Aziridines **1a**−**1e** and propargyl alcohols **2a**−**2h** underwent

Scheme 2. Proposed Mechanism for the Cascade Reaction



the cascade process to generate **3a**−**3s** in moderate to excellent yields (41−79%). In cases of R^2 = alkenyl or alkyl, lower yields were obtained for **3f** (45%; Table 2, entry 6), **3g** (41%; Table 2, entry 7), and **3o** (44%; Table 2, entry 15), respectively. 2-Alkyl-1-tosylaziridines were also examined for this transformation, but they did not yield the desired indene products.

Table 2. Synthesis of Indenes **3**[a]



entry	R^1	R^2/R^3	product	yield (%)[b]
1	C_6H_5 (**1a**)	C_6H_5/H (**2a**)	**3a**	63
2	**1a**	4-MeC_6H_4/H (**2b**)	**3b**	54
3	**1a**	3-MeC_6H_4/H (**2c**)	**3c**	62
4	**1a**	4-*t*-BuC_6H_4/H (**2d**)	**3d**	51
5	**1a**	4-$MeOC_6H_4$/H (**2e**)	**3e**	78
6	**1a**	1-cyclohexenyl/H (**2f**)	**3f**	45
7	**1a**	*n*-Bu/H (**2g**)	**3g**	41
8	**1a**	C_6H_5/Cl (**2 h**)	**3h**	51
9	4-MeC_6H_4 (**1b**)	**2a**	**3i**	50
10	4-*t*-BuC_6H_4 (**1c**)	**2a**	**3j**	52
11	4-ClC_6H_4 (**1d**)	**2a**	**3k**	63
12	4-BrC_6H_4 (**1e**)	**2a**	**3L**	62
13	**1d**	**2b**	**3m**	68
14	**1d**	**2e**	**3n**	62
15	**1d**	**2g**	**3o**	44
16	**1d**	**2h**	**3p**	78
17	**1e**	**2b**	**3q**	72
18	**1e**	**2h**	**3r**	79
19	**1e**	**2e**	**3s**	69

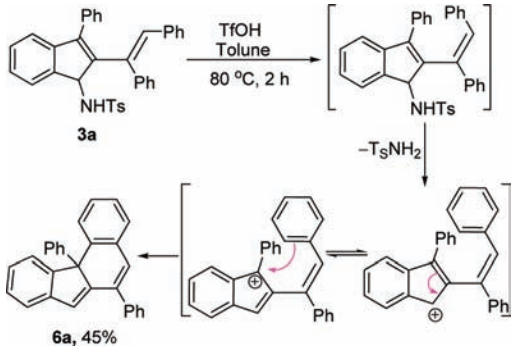
[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), $Yb(OTf)_3$ (0.05 mmol). [b] Isolated yield refers to aziridine.

A proposed mechanism for the present cascade reaction is shown in Scheme 2. In the presence of LA, the in situ ring opening of aziridine **1a** generates an azomethine ylide **A**,[8] while propynol **2a** is converted to the cationic intermedi-

ate **B** via a Meyer−Schuster rearrangement.[9] Then, **A** reacts with **B** through a [3 + 2] cycloaddition to form a five-membered ring carbocation **C**. Deprotonation along with the ring opening of **C** leads to the formation of **5**, which is sequentially transferred into the final indene product **3a** via an intramolecular Friedel−Crafts reaction promoted by LA. Furthermore, isolated **5** could also be quantitatively converted into **3a** in the presence of $Yb(OTf)_3$, which strongly supports this postulated mechanism.

We also investigated the possibility of intramolecular annulation of **3**. When indene **3a** was treated with TfOH at 80 °C for 2 h, 6,11b-diphenyl-11b*H*-benzo[c]fluorene (**6a**) was obtained in 45% yield along with a certain amount of *p*-methyl-benzenesulfonamide (Scheme 3). This cyclization

Scheme 3. Conversion of Indene **3a** to **6a**



involves an acid-catalyzed isomerization of the C═C bond and an intramolecular Friedel−Crafts reaction.

Structures of compounds **3a** (Figure 1), **4**, **5**, and **6a** were confirmed by X-ray diffraction analysis, and the results

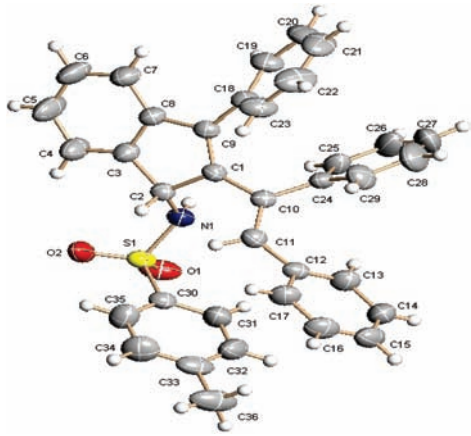
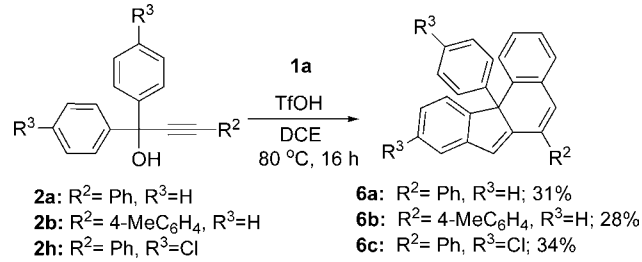


Figure 1. Crystal structure of compound **3a**.

supported the *E* configuration of the alkenyl group in the **3a** structure (see Supporting Information).

On the basis of these results, a single-step cascade synthesis of **6** from **1** and **2** was designed and achieved by using TfOH as the catalyst. Under 0.2 equiv of TfOH, **1a** reacted with **2a** at 80 °C for 16 h to afford **6a** in 31% yield (Scheme 4). Using this procedure, **6b** and **6c** were also obtained in 28% and 34% yields, respectively.

Scheme 4. Single-Step Synthesis of **6** from **1** and **2**

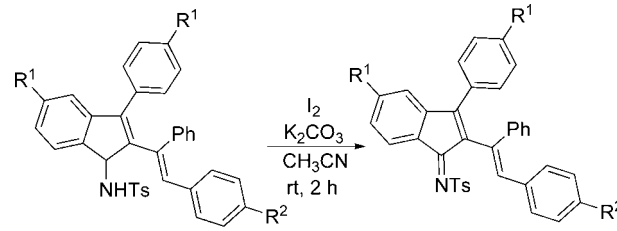


2a: R^2= Ph, R^3=H
2b: R^2= 4-MeC_6H_4, R^3=H
2h: R^2= Ph, R^3=Cl

6a: R^2= Ph, R^3=H; 31%
6b: R^2= 4-MeC_6H_4, R^3=H; 28%
6c: R^2= Ph, R^3=Cl; 34%

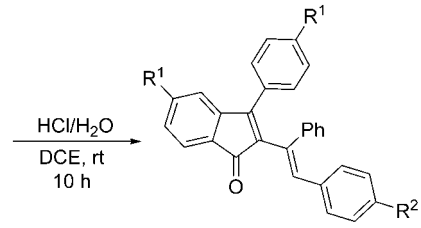
Transformation of indenes **3** to indenones **8** was also investigated further. As shown in Scheme 5, **3a**, **3h**, and **3p**

Scheme 5. Transformation of Indenes **3** to Indenimines **7** and Indenones **8**



3a: R^1 =R^2 = H
3h: R^1 = Cl, R^2 = H
3p: R^1 = Cl, R^2 = Cl

7a: R^1 =R^2 = H, 80%
7b: R^1 = Cl, R^2 = H, 82%
7c: R^1 = Cl, R^2 = Cl, 89%



8a: R^1 =R^2 = H, 93%
8b: R^1 = Cl, R^2 = H, 86%
8c: R^1 = Cl, R^2 = Cl, 95%

could be oxidized with I_2 in the presence of K_2CO_3 and resulted in indenimines **7a**[10] (80% yield), **7b** (82% yield), and **7c** (89% yield), respectively. It is also significant that hydrolysis of indenimines **7a**, **7b**, and **7c** under acid conditions yielded the corresponding indenones **8a**, **8b**, and **8c** in excellent yields (Scheme 5). Since the indenone skeleton has been discovered as a template for peroxisome

(8) (a) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765. (b) Pinho e Melo, T. M. V. D. *Eur. J. Org. Chem.* **2006**, 2873.
(9) (a) Meyer, K. H.; Schuster, K. *Chem. Ber.* **1922**, *55*, 819. (b) Swaminathan, S.; Narayanan, K. V. *Chem. Rev.* **1971**, *71*, 429.

proliferator-activated receptor γ agonists,[11] which are of interest as a treatment for diabetes, our strategy provides a new entry to this important class of compounds.[12]

In summary, we have developed a novel synthesis of functionalized indenes via a Lewis acid catalyzed cascade reaction of aziridines and propargylic alcohols. Since the substrates are readily available and the products can be converted to polycyclic indenes, indenimines and indenones, this approach may prove to be useful for the synthesis of biologically active indene derivatives and related carbocycles.

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Supporting Information Available: Detailed experimental procedures, characterization data, copies of ^{1}H and ^{13}C NMR spectra for all products, and crystallographic information files for compounds **3a**, **4**, **5**, **6a**, and **7a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) The structure of compound **7a** was unambiguously determined by X-ray diffraction analysis (see Supporting Information).

(11) Ahn, J. H.; Shin, M. S.; Jung, S. H.; Kang, S. K.; Kim, K. R.; Rhee, S. D.; Jung, W. H.; Yang, S. D.; Kim, S. J.; Woo, J. R.; Lee, J. H.; Cheon, H. G.; Kim, S. S. *J. Med. Chem.* **2006**, *49*, 4781.

(12) For papers on indenone synthesis, see: (a) Larock, R. C.; Doty, M. J.; Cacchi, S. *J. Org. Chem.* **1993**, *58*, 4579. (b) Kokubo, K.; Matsumasa, K.; Miura, M.; Nomura, M. *J. Org. Chem.* **1996**, *61*, 6941. (c) Pletnev, A. A.; Tian, Q.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 9276. (d) Harada, Y.; Nakanishi, J.; Fujihara, H.; Tobisu, M.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2007**, *129*, 5766. (e) Kerr, D. J.; Hamel, E.; Jung, M. K.; Flynn, B. L. *Bioorg. Med. Chem.* **2007**, *15*, 3290.