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Catalytic Regioselective Synthesis of Structurally Diverse Indene Derivatives from *N*-Benzylic Sulfonamides and Disubstituted Alkynes

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ABSTRACT

An unprecedented protocol has been developed for the regioselective synthesis of structurally diverse indene derivatives from readily accessible *N*-benzylic sulfonamides and disubstituted alkynes through $FeCl_3$-catalyzed cleavage of sp^3 carbon−nitrogen bonds to generate benzyl cation intermediates. In the presence of 10 mol % of $FeCl_3$, a broad range of *N*-benzylic sulfonamides smoothly react with internal alkynes, alkynylcarbonyl compounds, alkynyl chalcogenides, or alkynyl halides to afford various functionalized indene derivatives with extremely high regioselectivity.

The traditional cleavage of carbon−halogen bonds under acidic conditions has been widely applied to the formation of carbon−carbon bonds in chemical synthesis (e.g., the Friedel−Crafts reaction). Nevertheless, strongly acidic hydrogen halides are inevitably generated as byproducts in the reaction and are able to promote undesired side reactions such as elimination and overalkylation.[1] In this regard, the acid-catalyzed cleavage of carbon−nitrogen bonds offers opportunities to avoid such problems and consequently to enhance reaction selectivity and efficiency. The employment of *N*-sulfonyl groups in combination with either Brønsted[2] or Lewis acids[3] has recently emerged as a useful strategy to cleave the carbon−nitrogen bonds of benzylic primary amines to generate benzyl cations together with primary sulfonamides as byproducts.

In the course of exploring the synthetic applications of carbon−nitrogen bond cleavage,[2d,3c,d,4] we utilized this approach to generate benzyl cation intermediates in the presence of carbon−carbon triple bonds to construct carbocycles. To our great delight, the reaction of *N*-benzylic sulfonamides with alkynes under acidic conditions afforded structurally diverse indene derivatives with extremely high

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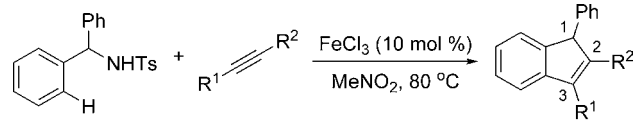
regioselectivity. While recent years have witnessed a number of reports on the construction of the indene ring system[5,6] that is present in many biologically relevant molecules,[7] chemical catalysts,[8] and materials,[9] these methods require expensive reagents/catalysts and/or lengthy synthetic sequences and introduce very limited functional groups into the indene ring system in a direct fashion. Herein, we wish to report an unprecedented protocol for the regioselective synthesis of various functionalized indene derivatives from readily accessible *N*-benzylic sulfonamides and disubstituted alkynes in the presence of an inexpensive and environmentally benign iron Lewis acid catalyst.[10]

A number of Brønsted and Lewis acids (10 mol %) were evaluated in the model reaction of *N*-(*p*-toluenesulfonyl)-benzhydrylamine (**1a**) with diphenylacetylene (**2a**) in nitromethane at room temperature for 24 h. While almost no desired reaction took place in the presence of TsOH, H_2SO_4, HCl, $ZnCl_2$, $CuCl_2$, $Pd(OAc)_2$, $AlCl_3$, or $Bi_2(SO_4)_3$, the use of $FeCl_3$ resulted in the formation of 1,2,3-triphenyl-1*H*-indene (**3a**) in 20% yield. The efforts to enhance yield proved fruitless by replacing nitromethane with acetonitrile, dichloromethane, acetone, ethyl acetate, or 1,2-dichloroethane. Gratifyingly, the yield was increased to 66% when the reaction temperature was elevated to 80 °C despite the fact that product **3a** was partially consumed through its alkylation with sulfonamide **1a** (Table 1, entry 1).[11,12] In addition, a

Table 1. $FeCl_3$−Catalyzed Regioselective Synthesis of Indene Derivatives from Sulfonamide **1a** and Disubstituted Alkynes[a]



1a **2** **3a-n**

entry	**2**	R^1	R^2	product	time/h	yield[b]/%
1	**2a**	Ph	Ph	**3a**	12	66
2	**2b**	4-$MeOC_6H_4$	Ph	**3b**	5	75
3	**2c**	Ph	4-$O_2NC_6H_4$	**3c**	24	53
4	**2d**	Ph	*n*-Pr	**3d**	10	60
5	**2e**	Ph	COOEt	**3e**	24	74
6	**2f**	Ph	COOH	**3f**	24	83
7	**2g**	Ph	COPh	**3g**	24	66
8	**2h**	Ph	COMe	**3h**	24	69
9	**2i**	SPh	Ph	**3i**	3	43
10	**2j**	SePh	Ph	**3j**	6	58
11	**2k**	Br	Ph	**3k**	4	72
12	**2l**	Br	*n*-Bu	**3l**	24	61
13	**2m**	Cl	Ph	**3m**	12	66
14	**2n**	I	Ph	**3n**	6	72

[a] Reaction conditions: sulfonamide **1a** (0.20 mmol), alkyne **2** (0.24 mmol), $FeCl_3$ (10 mol %), nitromethane (2.0 mL), 80 °C. [b] Isolated yield.

gram-scale synthesis of indene derivative **3a** (2.34 g, 68% yield) was successfully performed according to this protocol.

In the presence of 10 mol % of $FeCl_3$, the reaction of sulfonamide **1a** with a diphenylacetylene bearing either an electron-donating or an electron-withdrawing group proceeded smoothly to afford the corresponding indene derivative with greater than 99:1 regioselectivity (Table 1, entries 2 and 3).[13] Subsequently, an alkyl, an alkoxycarbonyl, a carboxyl, and an acyl group were introduced exclusively into the C-2 positions of indene derivatives by employing the corresponding functionalized disubstituted alkynes (Table 1, entries 4−8). Moreover, a range of alkynyl chalcogenides and alkynyl halides served as suitable substrates to react with sulfonamide **1a** and consequently, provided a convenient access to the indene derivatives bearing heretoatoms such as sulfur, selenium, bromine, chlorine, and iodine at the C-3

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(10) For a review on the iron Lewis acid catalysis, see: Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217.

(11) The corresponding monoalkylation product was obtained in 19% yield on the basis of sulfonamide **1a**. It is noteworthy that no other byproduct was detected by ^1H NMR analysis of the crude product.

(12) The yield was not further improved at 80 °C when $FeCl_3$ was replaced with the previously examined catalysts and a few other iron salts. Catalyst (yield): TsOH (62%), $ZnCl_2$ (40%), $CuCl_2$ (28%), $Pd(OAc)_2$ (4%), $AlCl_3$ (3%), $Bi_2(SO_4)_3$ (57%), $BiCl_3$ (20%), $SnCl_4{\cdot}5H_2O$ (9%), $FeCl_3{\cdot}6H_2O$ (4%), $Fe_2(SO_4)_3{\cdot}5H_2O$ (7%), $Fe(NO_3)_3{\cdot}9H_2O$ (8%), $FeCl_2{\cdot}4H_2O$ (0%), and $FeSO_4{\cdot}7H_2O$ (0%).

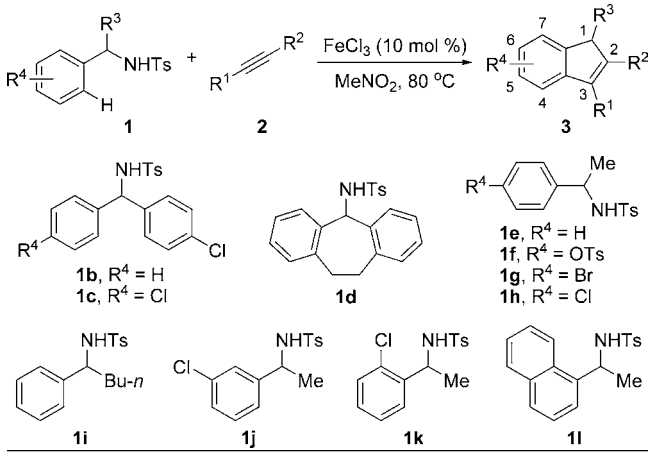
(13) No regioisomer was detected by ^1H and ^{13}C NMR analysis of the CH group at the C-1 position of an indene derivative. The product regiochemistry was assigned by 2D NOSEY analysis and/or by analogy. For details, see the Supporting Information.

positions (Table 1, entries 9−14).[14] It is noteworthy that no rearrangement was observed with the carbon−carbon double bonds under the reaction conditions, and the regioselective introduction of such diverse functional groups greatly facilitates the synthetic elaboration of indene derivatives.

A broad range of *N*-benzylic sulfonamides were found to react with disubstituted alkynes in the presence of 10 mol % of $FeCl_3$ to yield structurally diverse indene derivatives (Table 2). Notably, the phenyl group rather than the 4-chlorophenyl group in unsymmetric *N*-bisbenzylic sulfonamide **1b** was found to form a new carbon−carbon bond with a disubstituted alkyne in the reaction despite the fact that a similar carbon−carbon bond-forming reaction occurred with one of the two 4-chlorophenyl groups in symmetric *N*-bisbenzylic sulfonamide **1c** (Table 2, entries 1−3). This protocol proved useful for the construction of indene-containing polycarbocycles such as **3r**−**t** (Table 2, entries 4−6). Moreover, the $FeCl_3$-catalyzed indene synthesis proceeded smoothly with a wide variety of *N*-monobenzylic sulfonamides and significantly, heteroatoms such as chlorine, bromine, and oxygen were successfully introduced into the C-5, C-6, and C-7 positions of indene derivatives (Table 2, entries 7−16).

The reaction of optically active sulfonamide (*R*)-**1e** (95% ee) with alkyne **2a** in the presence of 10 mol % of $FeCl_3$ afforded indene derivative **3u** in nearly racemic form (1% ee). This result suggests that benzyl cation **4** is generated from *N*-benzylic sulfonamide **1** through $FeCl_3$-catalyzed sp^3 carbon−nitrogen bond cleavage (Scheme 1).[2d,3d] The regioselective attack of disubstituted alkyne **2** to benzyl cation **4** results in the formation of vinyl cation **5**,[15] which undergoes cyclization and subsequent aromatization to afford indene derivative **3**.[16] The formation of vinyl cation **5** was substantially supported by the extremely high regioselectivity exhibited in the reaction of *N*-benzylic sulfonamide **1** with disubstituted alkyne **2**, in which the R^1 group is more capable of stabilizing a positive charge relative to the R^2 group. Moreover, this mechanism accounts for the formation of alkyne **7**, rather than indene derivative **3ae**, in the $FeCl_3$-catalyzed reaction of sulfonamide **1a** with silylated alkyne **2o**, during which vinyl cation intermediate **5a** is additionally stabilized by the β-trimethylsilyl group that prefers to be eliminated to form a carbon−carbon triple bond (Scheme 2).

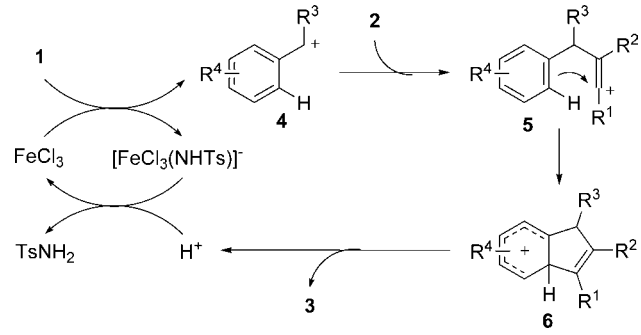
Table 2. $FeCl_3$-Catalyzed Regioselective Synthesis of Indene Derivatives from *N*-Benzylic Sulfonamides and Disubstituted Alkynes[a]



entry	1	2	product	time /h	yield /%[b]
1	**1b**	**2a**	**3o**, R^2 = Ph, R^4 = H	13	61
2	**1b**	**2d**	**3p**, R^2 = *n*-Pr, R^4 = H	18	65
3	**1c**	**2a**	**3q**, R^2 = Ph, R^4 = Cl	24	66
4	**1d**	**2a**	**3r**, R^1 = R^2 = Ph	6	61
5	**1d**	**2d**	**3s**, R^1 = Ph, R^2 = *n*-Pr	24	71
6	**1d**	**2k**	**3t**, R^1 = Br, R^2 = Ph	16	61
7	**1e**	**2a**	**3u**, R^4 = H	12	56
8	**1f**	**2a**	**3v**, R^4 = OTs	24	70
9	**1g**	**2a**	**3w**, R^4 = Br	24	80
10	**1h**	**2a**	**3x**, R^1 = R^2 = Ph	24	63
11	**1h**	**2d**	**3y**, R^1 = Ph, R^2 = *n*-Pr	24	61
12	**1h**	**2j**	**3z**, R^1 = SePh, R^2 = Ph	24	81
13	**1i**	**2a**	**3aa**, R^3 = *n*-Bu, R^4 = 5-Cl	24	56
14[c]	**1j**	**2a**	**3ab**, R^3 = Me, R^4 = 6-Cl	24	61
15	**1k**	**2a**	**3ac**, R^3 = Me, R^4 = 7-Cl	24	65
16	**1l**	**2h**	**3ad**	24	61

[a] Reaction conditions: sulfonamide **1** (0.20 mmol), alkyne **2** (0.24 mmol), $FeCl_3$ (10 mol %), nitromethane (2.0 mL), 80 °C. [b] Isolated yield. [c] 4-Chloro-1-methyl-2,3-diphenyl-1*H*-indene (**3ab′**) was obtained in 26% yield as a minor regioisomer.

Scheme 1. Proposed Reaction Pathway



(14) No indene derivative was obtained from terminal alkynes and *N*-benzylic sulfonamides under similar reaction conditions.

(15) For reviews on vinyl carbocations, see: (a) Stang, P. J.; Rappopoat, Z.; Hanack, M.; Subramanian, L. R. *Vinyl Cations*; Academic Press: New York, 1979. (b) *Dicoordinated Carbocations*; Rappoport, Z., Stang, P. J., Eds; Wiley and Sons: Chichester, 1997.

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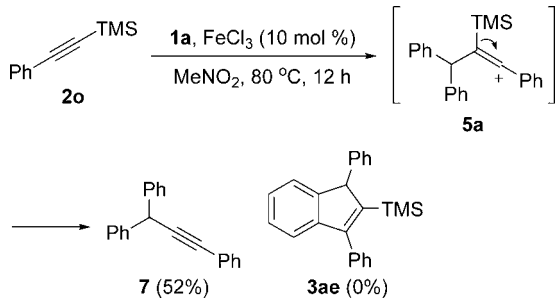
Scheme 2. Reaction of Sulfonamide **1a** with Silylated Alkyne **2o**



In summary, we have developed an unprecedented protocol for the regioselective synthesis of structurally diverse indene derivatives from readily accessible *N*-benzylic sulfonamides and disubstituted alkynes through $FeCl_3$-catalyzed cleavage of sp^3 carbon−nitrogen bonds to generate benzyl cation intermediates. In the presence of 10 mol % of $FeCl_3$, a broad range of *N*-benzylic sulfonamides smoothly react with internal alkynes, alkynylcarbonyl compounds, alkynyl chalcogenides, or alkynyl halides to afford various functionalized indene derivatives with extremely high regioselectivity. The regioselective introduction of diverse functional groups greatly facilitates the synthetic elaboration of indene derivatives for the discovery of new pharmaceutical agents and chemical catalysts. Current efforts are directed toward further methodological refinement and synthetic applications.

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Supporting Information Available: Experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR spectra for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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