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Controllable One-Step Synthesis of Spirocycles, Polycycles, and Di- and Tetrahydronaphthalenes from Aryl-Substituted Propargylic Alcohols

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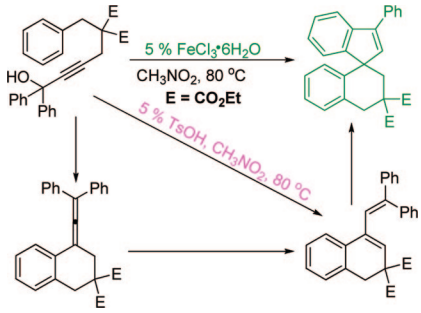
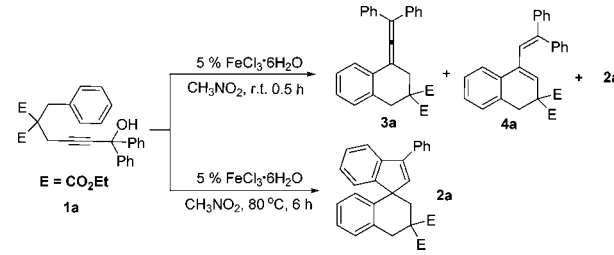


A novel, convenient, and efficient method has been developed for selective synthesis of spirocycle, polycycle, and di- and tetrahydronaphthalene systems from aryl-substituted propargylic alcohols by $FeCl_3$- or TsOH-catalyzed multiple activations of unsaturated C−C bonds and C−H bonds.

Spirocyclic hydrocarbons have attracted considerable attention as a result of their wide range of biological activities and their special optoelectronic properties, as well as increasing use in a range of important chemical and technological processes such as asymmetric synthesis.[1] Although many methodologies for constructing spirocyclic frameworks have been developed so far, there are few publications that describe the direct construction of such motifs from a linear precursor.[2] Therefore, the development of new methods and strategies for the construction of functionalized spirocyclic frameworks is highly desirable for the syntheses of delicate natural products, as well as for the fine-tuning of the biological and/or physical properties of the compounds for final application.

SCHEME 1. Intramolecular Cyclization of 1a



The direct conversion of C−H bonds to C−C bonds is a convenient, efficient, and economical strategy for organic synthesis, because C−H bonds are among the most ubiquitous and inexpensive chemical linkages in nature.[3] Particular attention has been paid to the synthetic application of the C−H based intramolecular cyclization, since new methods for useful cyclic products are anticipated. However, to our knowledge, a synthetic pathway that is based on multiple intramolecular C−H functionalization, for constructing spirocyclic frameworks, has never been reported. We have recently developed a $FeCl_3$-catalyzed intramolecular Friedel−Crafts (IFC) reaction[4] that provides direct access to biologically active di- and tetrahydroisoquinoline scaffolds from benzylamino-substituted propargylic alcohols.[5] In further investigation on the versatility of the propargylic alcohol system, we found an unprecedented intramolecular Friedel−Crafts reaction and hydroarylation sequence of aryl-substituted propargylic alcohols catalyzed by simple $FeCl_3 \cdot 6H_2O$ that allows selective one-step synthesis of functionalized spirocyclics and di- and tetrahydronaphthalenes. Herein, we report the results.

We initially studied the intramolecular cyclization of propargylic alcohol **1a**. However, treatment of **1a** in nitromethane with $FeCl_3 \cdot 6H_2O$ (5 mol %) at room temperature for 30 min gave a complex mixture. Luckily, an unexpected spirocyclic product **2a** was obtained in good yield, when the reaction temperature was increased to 80 °C (Scheme 1). The structure of **2a** was confirmed by X-ray single crystal diffraction.

Encouraged by this result, we set out to study the scope and limitation of the preparation of spirocyclic hydrocarbons directly

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(4) For recent reviews of Friedel−Crafts and related reactions, see: (a) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 550. (b) Bandini, M.; Emer, E.; Tommasi, S.; Umani-Ronchi, A. *Eur. J. Org. Chem.* **2006**, 3527. (c) Jørgensen, K. A. *Synthesis* **2003**, 1117.

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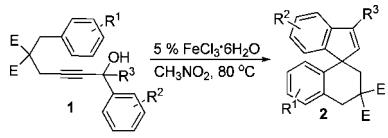
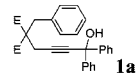
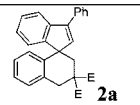
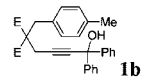
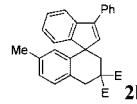
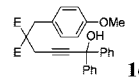
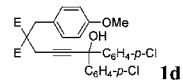
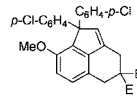
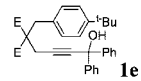
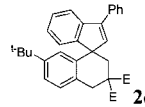
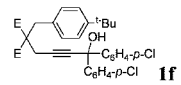
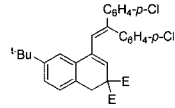
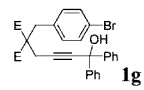
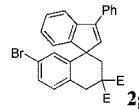
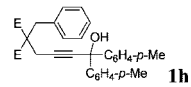
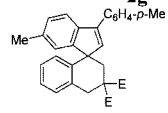
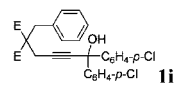
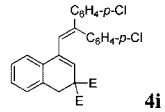
TABLE 1. One-Step Synthesis of Spirocyclic Compounds[a]

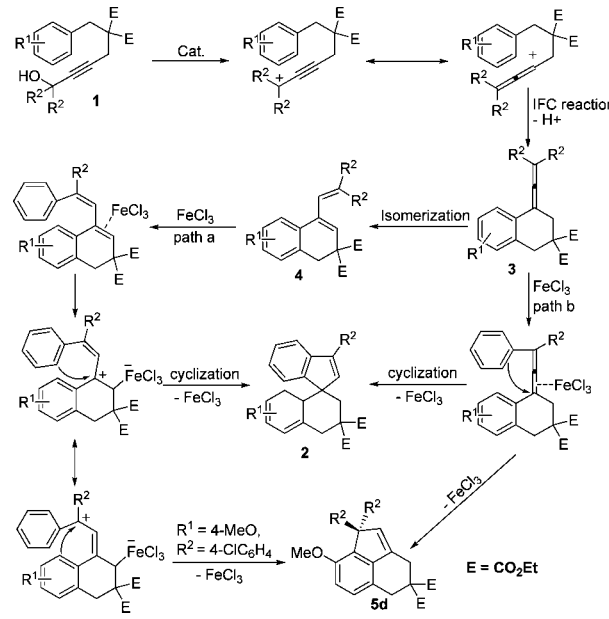


Entry	Substrate	Product	Yield (%)[b]
1[c]	 **1a**	 **2a**	90 (85[d])
2	 **1b**	 **2b**	91
3[e]	 **1c**		
4[c,f]	 **1d**	 **5d**	76
5	 **1e**	 **2e**	86
6	 **1f**	 **4f**	78
7[g]	 **1g**	 **2g**	68
8	 **1h**	 **2h**	75
9	 **1i**	 **4i**	82

[a] General reaction conditions: 0.2 mmol substrate, 5 mol % of $FeCl_3 \cdot 6H_2O$ in 2 mL of CH_3NO_2 at 80 °C for 3−9 h. [b] Isolated yield. [c] The structure of the product was further confirmed by X-ray diffraction analysis. [d] Carried out in 1 mmol scale. [e] The reaction gave an inseparable mixture of spirocycle and polycycle. [f] Along with ca. 5% unidentified compounds. [g] The reaction time was 18 h.

from propargylic alcohols in more detail. A variety of aryl-substituted propargylic alcohols have been examined, and the results are summarized in Table 1. When propargylic alcohols containing phenyl or electron-rich aryl at the propargylic position were treated with 5 mol % $FeCl_3 \cdot 6H_2O$ in CH_3NO_2 at 80 °C, the corresponding spirocyclic compounds were obtained in moderate to high yields (Table 1, entries 1, 2, and 8). Notably, sterically demanding substrate **1e** can also give the spirocyclic product **2e** in 86% yield (Table 1, entry 5). However, incorporation of an electron-withdrawing group on the aryl nucleus at the propargylic position suppressed the spirocyclization reaction, and the isolated products were dihydronaphthalenes (Table 1, entries 6 and 9). As for the substrate **1g**, bearing an electron-withdrawing bromide group on the other benzene ring, the intramolecular tandem cycloarylation reaction was sluggish and gave a mixture of 1,2-dihydronaphthalene (**4g**) and spirocycle (**2g**) under the same conditions after 6 h. Prolonged heating for 18 h made **4g** convert to **2g** completely (Table 1, entry 7).

SCHEME 2. Plausible Mechanism for $FeCl_3 \cdot 6H_2O$-Catalyzed Spirocyclic Compound Synthesis



Interestingly, the two intramolecular cycloarylation reactions of compound **1d**, in which two aromatic rings at the propargylic position bear a chloride and the other ring a 4-methoxy group, appear to occur on the same phenyl ring (the ring with the 4-methoxy substituent), leading to the exclusive formation of 1,3,4,5-tetrahydroacenaphthylene **5d** in 76% yield under the same conditions, as determined by the NMR spectrum and X-ray structural analysis (Table 1, entry 4).

On the basis of the above results, a plausible mechanism for the formation of spirocycles is proposed in Scheme 2. The C-OH activation leads to the formation of propargylic cations.[6] Isomerization of propargylic to allenylic cations[7] and subsequent IFC reaction gives tetrahydronaphthalenes **3**, while isomerization of **3** gives **4**. The formation of allyl cation intermediates occurred by the reaction of **4** with $FeCl_3$ followed by attack of the arene generates **2** or **5d** (path a).[8,9] These products are likely the result of the direct hydroarylation of allenes promoted by Lewis acid (path b).[10] The difference for the formation of **5d** might be rationalized by the hydroarylation reaction through the allyl cation intermediate. Clearly, the steric factor is favorable to the formation of spirocycles. Presumably, the driving force for the formation of **5d** most likely arises from the stronger nucleophilicity of the methoxyphenyl ring compared to the chlorophenyl ring, equalizing the steric disadvantage.

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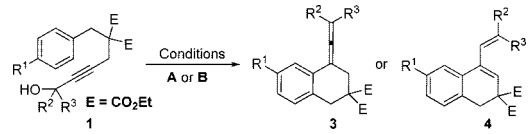
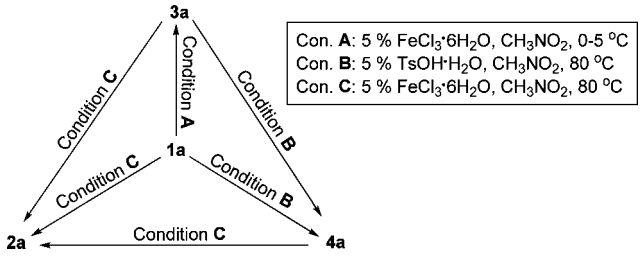
TABLE 2. Selective Synthesis of Functionalized Di- and Tetrahydronaphthalenes[a]



entry	substrate	condition A	yield (%)[b]	condition B	yield (%)[b]
1	R^1 = H, R^2 = R^3 = Ph, **1a**	**3a**	93 (89[c])	**4a**	92[d]
2	R^1 = Me, R^2 = R^3 = Ph, **1b**	**3b**	95[d]	**4b**	93
3	R^1 = MeO, R^2 = R^3 = Ph, **1c**	**3c**	90	**4c**	91
4	R^1 = MeO, R^2 = R^3 = 4-ClC_6H_4, **1d**	**3d**	85	**4d**	84
5	R^1 = ^{t}Bu, R^2 = R^3 = Ph, **1e**	**3e**	89	**4e**	90
6	R^1 = ^{t}Bu, R^2 = R^3 = 4-ClC_6H_4, **1f**	**3f**	83	**4f**	86
7	R^1 = Br, R^2 = R^3 = Ph, **1g**	**3g**	37[e]	**4g**	63
8	R^1 = H, R^2 = R^3 = 4-MeC_6H_4, **1h**	**3h**	76	**4h**	72
9	R^1 = H, R^2 = R^3 = 4-ClC_6H_4, **1i**	**3i**	87	**4i**	89
10[f]	R^1 = H, R^2 = Ph, R^3 = Me, **1j**	**3j**	80		
11[f]	R^1 = H, R^2 = 4-MeC_6H_4, R^3 = Me, **1k**	**3k**	64		

[a] General reaction conditions: 0.2 mmol substrate, 2 mL of CH_3NO_2. Condition A: 5 mol % of $FeCl_3 \cdot 6H_2O$, 0−5 °C. Condition B: 5 mol % of $TsOH \cdot H_2O$, 80 °C. [b] Isolated yield. [c] Carried out in 1 mmol scale. [d] The structure of product was further confirmed by X-ray diffraction analysis. [e] Enone was isolated as a major product. [f] Using condition **B** gave a complicated mixture.

SCHEME 3. Controllable Synthesis of Spirocycle and Dihydro- and Tetrahydronaphthalene



To confirm the reaction mechanism, a variety of experiments for isolating the intermediates **3a** and **4a** were performed. To our delight, it was found that the monocyclization allene product **3a** could be selectively obtained in 93% isolated yield when the reaction temperature was lowered to 0−5 °C (Table 2, entry 1, condition A). However, attempts to obtain the sole 1,3-diene product **4a** using this catalytic system were unsuccessful. In screening several catalysts, we found that a selective procedure for the preparation of **4a** could be developed by replacing $FeCl_3 \cdot 6H_2O$ with TsOH (*p*-toluenesulfonic acid monohydrate). In addition, it was also feasible to isolate **3a** in an excellent yield using TsOH as a catalyst if the reaction was carried out at room temperature, despite the fact that the reaction rate is slower than that in a $FeCl_3 \cdot 6H_2O$ catalytic system. Remarkably, both **3a** and **4a** were converted to **2a**, when heated to 80 °C in CH_3NO_2 and with the presence of $FeCl_3 \cdot 6H_2O$ (Scheme 3). However, no spirocyclic product was obtained in the TsOH catalytic system even after a prolonged reaction time or at elevated temperature.

The di- and tetrahydronaphthalene carbon skeletons are found in a number of naturally occurring and biologically active molecules.[11] With the strategy of controlling selective transformation of aryl-substituted propargylic alcohols in hand, we next explored the use of the reaction in synthesis of tetrahydronaphthalene derivatives. As shown in Table 2 (condition A), the results demonstrated good compatibility with various functional groups, including halide, methoxy, and ester carbonyls. For instance, the introduction of the electron-donating groups such as methyl and methoxy in the *para*-position of the nucleophilic benzene ring had only a slight influence on the reactivity as compared to **1a** (Table 2, entries 1−3, condition A). Notably, the sterically demanding *tert*-butylphenyl ring also displayed a high reactivity (Table 2, entries 5 and 6, condition A). Even the presence of an electron-withdrawing bromide group on the ring, the cyclization product was also obtained in 37% yield (Table 2, entry 7, condition A).

The present method was further applied to selective synthesis of 1,2-dihydronaphthalene derivatives under the optimized reaction conditions. Table 2 (condition B) illustrates the generality of this reaction. Treatment of a variety of aryl-substituted propargylic alcohols with TsOH in CH_3NO_2 at 80 °C afforded the corresponding 1,2-dihydronaphthalenes formed through the IFC reaction followed by successive isomerization in moderate to excellent yields, depending on the nucleophilicity of the aryl nucleus involved and the nature of substituents at the propargylic position.

The direct reaction of aromatic carbon−hydrogen bonds with unactivated unsaturated carbon−carbon functionalities represents a challenging but attractive strategy for the formation of C−C bonds.[3] Although the intramolecular cyclization of propargylic alcohols and their derivatives have been extensively studied,[12,13] to the best of our knowledge, it has not been previously reported that these substrates undergo the tandem isomerization/functionalition to generate the spirocenter. The present results

(11) Selected examples: (a) Sellars, J. D.; Steel, P. G. *Eur. J. Org. Chem.* **2007**, 3815. (b) LaLonde, R. T.; Ramdayal, F.; Sarko, A.; Yanai, K.; Zhang, M.-J. *J. Med. Chem.* **2003**, *46*, 1180. (c) Biswas, S.; Zhang, S.-H.; Fernandez, F.; Ghosh, B.; Zhen, J.; Kuzhikandathil, E.; Reith, M. E. A.; Dutta, A. K. *J. Med. Chem.* **2008**, *51*, 101.

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demonstrate the potential for increasing flexibility and reactivity of alkynes by a hydroxyl group at the propargylic position.

In conclusion, novel, controllable tandem reactions of aryl-substituted propargylic alcohols catalyzed by a simple Lewis or Brønsted acid have been established. These transformations provide facile, efficient, and versatile strategies for selective one-step construction of a variety of functionalized aromatic carbocycle skeletons. These skeletons are of interest in organic synthesis, medicinal chemistry, and materials science. Further application of this methodology to organic synthesis is currently under investigation.

Experimental Section

General Procedure. To a solution of **1** (0.2 mmol) in CH_3NO_2 (2.0 mL) was added 5 mol % $FeCl_3 \cdot 6H_2O$ or TsOH. The reaction mixture was stirred at 0−5 °C or at the temperature noted in the text (monitored by TLC or NMR). The crude product was purified by silica gel column chromatography to provide the desired product. Selected example, diethyl 4-(2,2-diphenylvinyl)naphthalene-2,2(1*H*)-dicarboxylate (**4a**): ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ 1.10 (t, J = 7.3 Hz, 6H), 3.29 (s, 2H), 3.83−3.95 (m, 2H), 4.04−4.13 (m, 2H), 5.77 (d, J = 1.4 Hz, 1H), 6.69 (d, J = 1.4 Hz, 1H), 7.08−7.20 (m, 8H), 7.27−7.38 (m, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ 169.9, 145.9, 143.0, 140.1, 137.2, 132.9, 132.8, 130.0, 128.3, 128.2, 127.9, 127.8, 127.0, 125.9, 124.8, 124.0, 61.7, 54.7, 34.2, 13.9. HRMS-ESI-TOF: calcd for $C_{30}H_{28}O_4Na$ ($[M + Na]^+$) 475.1885, found 475.1877.

The reaction can be synthesized in large scale. To a solution of **1a** (2.35 g, 5 mmol) in CH_3NO_2 (60 mL) at 80 °C was added 5 mol % TsOH, and then the reaction mixture was stirred for about 2 h. The mixture was quenched with 50 mL water, and the aqueous layer was extracted with ether (3 × 20 mL). The combined organic layer was washed with brine and dried (Na_2SO_4), and solvents were evaporated under reduced pressure to give the crude product (2.11 g, 93% yield), which was identified by NMR spectra as purity >95% (see Supporting Information for copies of spectrum).

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Supporting Information Available: Experimental details, spectroscopic characterization data, copies of ^{1}H, ^{13}C NMR of new compounds, and CIF files giving crystallographic data of **2a**, **4a**, **3b** and **5d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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