JOC*Note*

One-Step Synthesis of Substituted Dihydro- and Tetrahydroisoquinolines by $FeCl_3 \cdot 6H_2O$ Catalyzed Intramolecular Friedel−Crafts Reaction of Benzylamino-Substituted Propargylic Alcohols

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A mild, versatile, and efficient method for the one-step synthesis of substituted dihydro- and tetrahydroisoquinolines has been developed by the $FeCl_3 \cdot 6H_2O$ catalyzed intramolecular allenylation/cyclization reaction of benzylamino-substituted propargylic alcohols, representing the first example of the intramolecular Friedel−Crafts reaction of propargylic alcohols.

Dihydro- and tetrahydroisoquinoline moieties are present in a wide range of natural and unnatural compounds that exhibit important biological activities and in an array of substances used as intermediates in organic synthesis.[1] Thus, a growing effort has been directed toward the efficient and selective preparation of various dihydro- and tetrahydroisoquinolines. Traditionally, the 1,2-dihydroisoquinolines can be indirectly prepared by nucleophilic addition to isoquinolinium salts, which are derived from the corresponding isoquinolines by acylation or alkylation.[2,3]

Recently, it was found that Lewis acid-catalyzed tandem intramolecular cyclization/nucleophilic addition or nucleophilic addition then cyclization of 2-alkynylarylimines can provide a concise and efficient method for the direct synthesis of 1,3- and 1,3,4-substituted 1,2-dihydroisoquinolines.[4] However, this strategy is not suitable to the selective construction of 4-substituted and 1,4-disubstituted 1,2-dihydroisoquinolines. Therefore, the search for a new strategy for the direct synthesis of 1,2-dihydro- and tetrahydroisoquinolines from readily available starting materials would be a highly valuable but challenging subject.

Catalytic substitution of the hydroxy group in alcohols with nucleophiles is an atom efficient and environmentally sound transformation that is currently receiving increased attention.[5−7] Recent works showed that propargylic alcohols can serve as novel electrophilic alkyl equivalents for the intermolecular Friedel−Crafts reactions.[5h−k,6e,7] However, the related intramolecular Friedel−Crafts reaction remains unexplored, possibly due to the difficulty of the cycloalkyne formation. Previously, we found that treatment of 1,3-dicarbonyl compounds with tertiary propargylic alcohols in the presence of Lewis acids could give the isomerized allenylation products.[8] In this case it would be expected that an intramolecular allenylation/cyclization would be operating due to avoidance of the large ring strain. As a part of our continuing research on making use of propargylic alcohols

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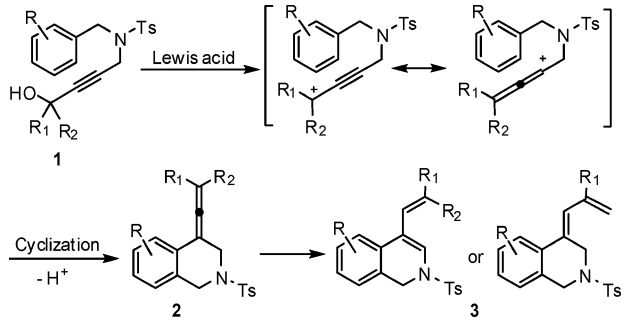
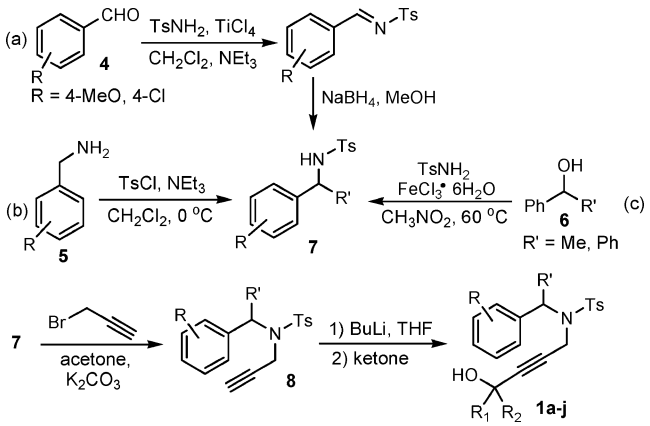
SCHEME 1. Plausible Reaction Pathway



SCHEME 2. Routes for the Synthesis of Propargylic Alcohols



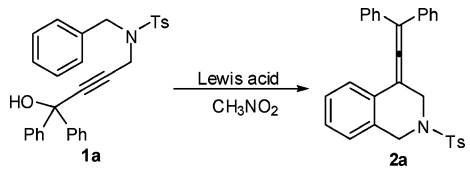
as a practical and versatile alkylation reagent, we were interested in revealing the possibility of the intramolecular Friedel−Crafts reaction of benzylamino-substituted propargylic alcohols and thus developing a concise and versatile strategy for constructing dihydro- and tetrahydroisoquinoline ring frameworks.[9] On the basis of this idea, a one-step synthetic route to tetrahydroisoquinolines and their derivatives is sketched out in Scheme 1. Herein, we report the details of the scope and limitations of this process.

After considering this possible reaction pathway, we first synthesized intermediates **7** by the following three routes:[5g,l,10] (a) reacting the corresponding aldehyde (**4**) with $TsNH_2$ and then reduction with $NaBH_4$ in MeOH; (b) direct *N*-sulfonylation of the corresponding benzylamine (**5**); and (c) the direct hydroxy substitution of the corresponding alcohols (**6**) with sulfonamide promoted by $FeCl_3 \cdot 6H_2O$. Route (a) requires two steps, but the aldehydes employed are cheap. Treatment of **7** with propargyl bromide in the presence of K_2CO_3 in acetone at reflux temperature gave *N*-tosyl, *N*-propargylic benzylamines (**8**) in good to excellent yields. Then, benzylamino-substituted propargylic alcohols **1a**−**j** were synthesized in good yields by reaction of **8** with BuLi followed by treating with ketones (Scheme 2).

Initial cyclization of **1a** was studied in the presence of various Lewis acid catalysts in nitromethane to obtain the optimum reaction conditions. Table 1 shows the major results. All Lewis acid catalysts employed exhibit good catalytic activity for the reaction (Table 1, entries 1−6). However, when the Brønsted acid such as *p*-toluenesulfonic acid monohydrate (PTS) was used as a catalyst instead of Lewis acids, the ene-ketone was isolated as a major product due to the Meyer−Schuster rearrangement (Table 1 entry 7).[11] The structure of product **2a** was confirmed by ^1H NMR, ^{13}C NMR, HRMS, and X-ray diffraction analysis. The results clearly demonstrate the isomerization of the propargyl cation to allenyl cation (Figure 1). Considering that $FeCl_3 \cdot 6H_2O$ is readily available and inexpensive, we then consistently used it to explore the scope of this reaction.

A selection of various benzylamino-substituted propargylic alcohols **1b**−**j** was investigated using $FeCl_3 \cdot 6H_2O$ as a catalyst in CH_3NO_2. Table 2 summarizes the results. With substitution of one phenyl by methyl at the propargylic position, the reaction continued to proceed smoothly to the corresponding allenylation/cyclization product **2b** in a good yield (Table 2, entry 1), despite the need to elevate the reaction temperature to 60 °C. However, when both the phenyl groups at the propargylic position were replaced by methyl groups, the desired product **2c** could be obtained only in a low yield even by increasing reaction temperature and with a higher catalyst loading (Table 2, entry 2). In addition, aryl-substituted propargylic alcohol **1d**, which

TABLE 1. Cyclization Reaction of 1a under Various Conditions[a]



entry	catalyst	*T*/°C	time/h	yield[b]/%
1	$Yb(OTf)_3$	rt	24	65
2	$Yb(OTf)_3$	60	2	85
3	$FeCl_3$	rt	1	86
4	$FeCl_3 \cdot 6H_2O$	rt	1	83
5	$InCl_3$	rt	1	88
6	$ZnCl_2$	rt	12	72
7[c]	PTS	rt	12	8
8	no	rt	12	

[a] Reaction conditions: 0.3 mmol **1a**, 5 mol % of catalyst in 2 mL of nitromethane. [b] Isolated yield. [c] The main product was $PhCH_2N(Ts)CH_2$-$COCH{=}CPh_2$.

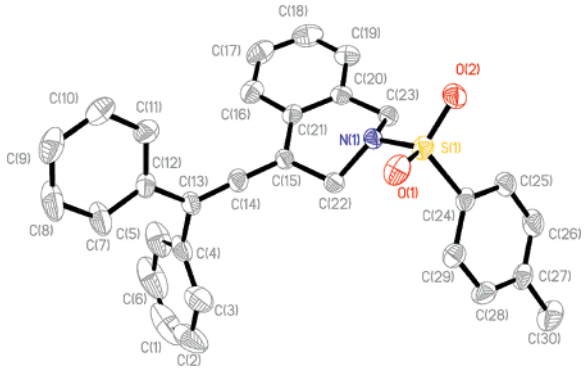


FIGURE 1. ORTEP diagram of the single-crystal X-ray Structure of **2a**.

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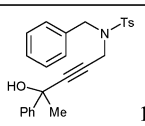
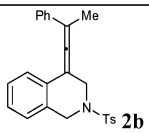
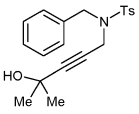
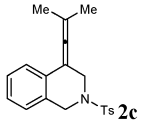
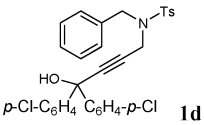
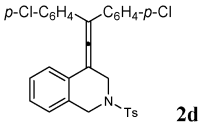
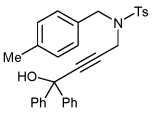
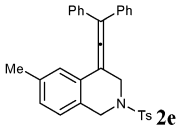
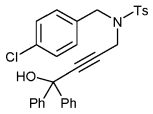
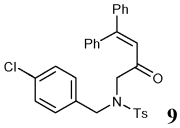
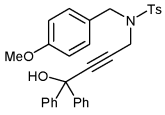
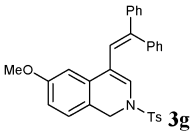
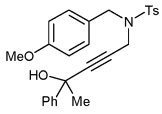
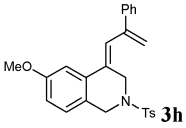
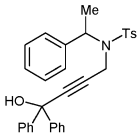
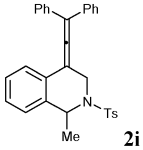
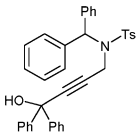
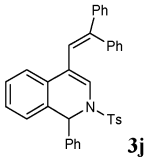
TABLE 2. Synthesis of Various Dihydro- and Tetrahydroisoquinolines[a]

Entry	Substrate	Product	Yield[b](%)
1[c]	 **1b**	 **2b**	82
2[c,d]	 **1c**	 **2c**	37
3[c,d]	 **1d**	 **2d**	75
4	 **1e**	 **2e**	65
5[c]	 **1f**	 **9**	51
6	 **1g**	 **3g**	90
7	 **1h**	 **3h**	91
8	 **1i**	 **2i**	87
9[c]	 **1j**	 **3j**	76

[a] General reaction conditions: 0.3 mmol substrate **1**, 5 mol % of $FeCl_3 \cdot 6H_2O$ in 2 mL of CH_3NO_2 at room temperature. [b] Isolated yield. [c] The reaction was carried out at 60 °C. [d] Using 30 mol % of catalyst.

has an electron-withdrawing chloride group at the para-position, was reactive enough to afford the tetrahydroisoquinoline product **2d** in 75% yield (Table 2, entry 3). All the results indicate that an aryl substituent is likely to assist the isomerization of propargyl to allenyl by the conjugative effect.

Next, we set out to study the scope and limitation of the nucleophilic coupling moiety in more detail. As shown in Table 2, various substituted benzene rings have been examined. The methyl substituent in the para-position of the benzylamine **1e** had only a slight influence on the reactivity as compared to **1a** (Table 2, entry 4), whereas **1f**, bearing an electron-withdrawing chloride group in the same position, resulted in the isolation of the Meyer−Schuster rearranged ene-ketone **9** as the main product (Table 2, entry 5). This difference might be explained

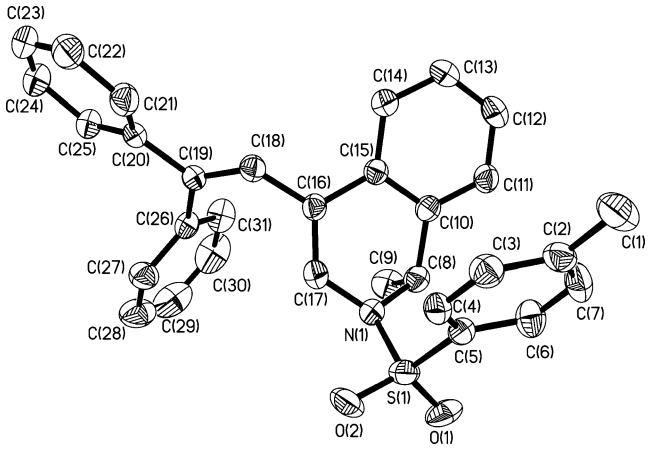


FIGURE 2. ORTEP diagram of the single-crystal X-ray structure of **3i**.

by the fact that the electron-withdrawing substituent on the benzene ring decreases the electron density of the ring, which is unfavorable to the Friedel−Crafts reaction.

Interestingly, treatment of *p*-methoxybenzylamino-substituted propargylic alcohol **1g** with $FeCl_3 \cdot 6H_2O$ under the same conditions led to the transformation of allene product to 1,3-diene one, affording dihydroisoquinoline **3g** in 90% yield (Table 2, entry 6). This indicates that the methoxy group not only activates the benzene ring but also induces isomerization of 1,2-diene to 1,3-diene. A similar isomerization has been observed previously in the synthesis of quinolines.[9b] The formation of novel isomerization product **3h** was unexpected when methoxy-activated propargylic alcohol **1h** was used as a substrate (Table 2, entry 7).[12] However, during the synthesis of **2a** no similar 1,3-diene isomer was isolated even after a prolonged reaction time or at elevated temperature.

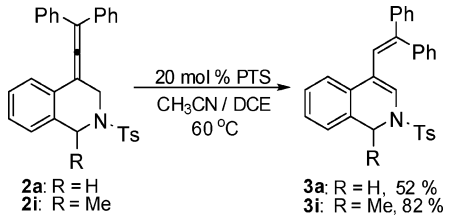
These successful results encouraged us to extend this method to the synthesis of 1,4-disubstituted dihydroisoquinolines. Treatment of propargylic alcohol **1i** with 5 mol % of $FeCl_3 \cdot 6H_2O$ afforded the corresponding 1,4-disubstituted tetrahydroisoquinoline **2i** in 87% yield (Table 2, entry 8). The structure of compound **2i** has been determined by the X-ray diffraction analysis. To our delight, for sterically hindered phenyl-substituted propargylic alcohol **1j** the 1,4-disubstituted dihydroisoquinoline product **3j** was obtained in 76% yield (Table 2, entry 9).

In addition, we found that the allene skeleton in other tetrahydroisoquinolines could also be transformed to the 1,3-diene isomers. For example, treatment of **2a** and **2i** with a catalytic amount of *p*-toluenesulfonic acid monohydrate in acetonitrile/dichloroethane at 60 °C for 6 h gave the corresponding dihydroisoquinoline derivatives **3a** and **3i**, respectively (Scheme 3). The X-ray crystal structure of **3i** (Figure 2) definitively proves that the original tetrahydroisoquinoline ring has isomerized to the dihydroisoquinoline ring.

Ishikawa and co-workers recently reported an efficient method for synthesis of quinolines and their analogues from arylamino-substituted propargylic silyl ethers.[9b] However, when the strategy was extended to the construction of tetrahydroisoquinoline rings, it required a stoichiometric amount of Lewis acid catalysts, and the substrates were limited to *N*-methoxybenzylamino-substi-

(12) For isomerization of 1-amino-3-arylallene, see: Reinhard, R.; Glaser, M.; Neumann, R.; Maas, G. *J. Org. Chem.* **1997**, *62*, 7744.

SCHEME 3. Isomerization of Tetrahydroisoquinolines to Dihydroisoquinolines



tuted propargylic silyl ethers bearing an electron-donating group in the meta-position. Thus, this new approach would complement the powerful techniques already available for the formation of dihydro- and tetrahydroisoquinoline rings. At the same time, the results presented here and in the previous paper[9b] demonstrate the synthetic potential and versatility of the intramolecular Friedel−Crafts reaction for dihydro- and tetrahydroisoquinolines.

In conclusion, we have developed an efficient method for direct synthesis of dihydro- and tetrahydroisoquinolines, which can be further functionalized, from benzylamino-substituted propargylic alcohols. Advantages of the present method are easily accessible starting materials, mild conditions, and a wide range of inexpensive catalysts, all of which allow the method to be applied on an industrial scale. Furthermore, the results represent a good example that can map out the versatility of the propargylic alcohols as alkylation precursors and demonstrate that their reactivity modes from propargylation, through allenylation, to alkenylation can be finely tuned simply by changing the substituents. Further investigations on the mechanistic details and synthetic applications of this reaction are underway in our laboratory.

Experimental Section

General Procedure. To a solution of **1** (0.3 mmol) in CH_3NO_2 (2.0 mL) was added $FeCl_3 \cdot 6H_2O$ (0.015 mmol). The reaction mixture was stirred at room temperature or the corresponding conditions noted in the text (monitored by TLC). Then, the solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography to provide the desired product. Selected example, 4-(2,2-diphenylvinylidene)-2-(*p*-toluenesulfonyl)-1,2,3,4-tetrahydroisoquinoline (**2a**): ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 2.29 (s, 3H), 4.32 (s, 2H), 4.43 (s, 2H), 7.02−7.12 (m, 5H), 7.26−7.41 (m, 11H), 7.58 (d, J = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) δ 203.5, 143.7, 136.1, 134.0, 131.0, 129.6, 128.7, 128.7, 128.6, 128.1, 127.9, 127.8, 127.5, 126.9, 126.6, 116.0, 100.1, 48.6, 47.2, 21.6. Anal. Calcd for $C_{30}H_{25}NO_2S$: C, 77.72; H, 5.44; N, 3.02. Found: C, 77.52; H, 5.47; N, 2.96; EI-MS *m*/*z* (rel intensity) 463 (M^+, 5%), 308 (M^+ − Ts, 100%); HRMS (EI) calcd for $C_{30}H_{25}NO_2S$ 463.1606, found 463.1612.

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

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