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Intramolecular Catalytic Friedel–Crafts Reactions with Allenyl Cations for the Synthesis of Quinolines and Their Analogues

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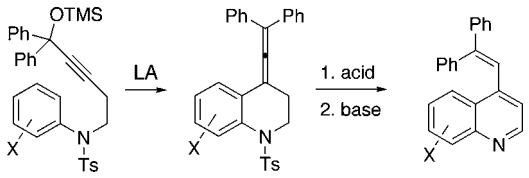
ABSTRACT

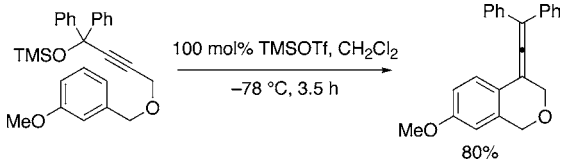


This paper describes a novel method to synthesize a quinoline backbone by incorporating allenyl cations into a catalytic intramolecular Friedel–Crafts reaction. The initial products were isomerized and aromatized upon treatment with acid and base, respectively, to give quinolines. The basic concept also proved to be promising for 1-benzazepine, 1-benzazocine, or isoquinoline synthesis.

Synthetic routes to quinolines have been studied intensively over many years due to the important role they play in industry (e.g., pharmaceutical agents, ligands, and functional materials). Since the first synthesis by Skraup over a century ago,[1] the aniline-based pathway has been the major route to generate a quinoline backbone.[2] Hence, heterocyclic rings are usually constructed using substituted aniline derivatives bearing an appropriate functional group on the nitrogen atom. Thus, the efficacy of intramolecular Friedel−Crafts (IMFC) reactions in terms of chemical yield, regioselectivity, and reaction conditions usually determines the synthetic value of such processes.[3] Various reactive intermediates such as acylium, iminium, or oxonium ions have been examined.[4] However, further studies are required, in particular with regard to the *regiochemistry* of the reactions when meta-substituted aniline derivatives are employed.

We realized that an allenyl cation can be a good electrophile in the IMFC process as shown in Scheme 1.[5] Since

Scheme 1



this reaction fulfilled the criteria mentioned above, we decided to examine its applicability to the synthesis of

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(1) Skraup, Z. H. *Ber*. **1880**, *13*, 2086−2087.

(2) Several modifications based on the Skraup method (ref 1) are well-known as Doebner-von Miller, Combes, Conrad-Limpach, and Friedländer quinoline synthesis; for these, see: Gilchrust, T. L. *Heterocyclic Chemistry*, 3rd ed.; Addison-Wesley Longman: Essex, 1997; pp 158−164.

(3) For the most recent paper concerned with Friedländer synthesis employing *o*-nitrobenzaldehydes as a starting material, see: McNaughton, B. R.; Miller, B. L. *Org. Lett*. **2003**, *5*, 4257−4259.

(4) (a) Mayr, H.; Bäuml, E. *Tetrahedron Lett*. **1983**, *24*, 357−360. (b) Mayr, H.; Bäuml, E. *Tetrahedron Lett*. **1984**, *25*, 1127−1130. (c) Nicholas, K. M. *Acc. Chem. Res*. **1987**, *20*, 207−214. (d) Müller, T. J. J.; Nets, A. *Organometallics* **1998**, *17*, 3609−3614. (e) Olah, G. A.; Krishnamurti, R.; Parakash, G. K. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I. Eds.; Pergamon: Oxford, 1991; Vol. 3, Chapter 1.8.

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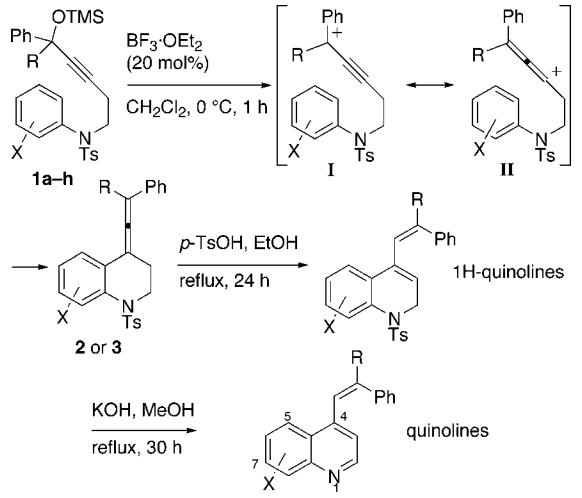
quinolines and their analogues, for which there are no previous reports. In addition, an allenyl moiety at C(4) may allow further derivatization at this position. The work described in this paper investigates IMFC reactions with the allenyl cation[6] for the synthesis of quinolines, including extension to 1-benzazepins, 1-benzazocine, and isoquinolines.

A reaction similar to that shown in Scheme 1 would be expected for propargyl silyl ethers (**1**). On the basis of this idea, a synthetic route to quinolines and their analogues is illustrated in Scheme 2. The initial product would be

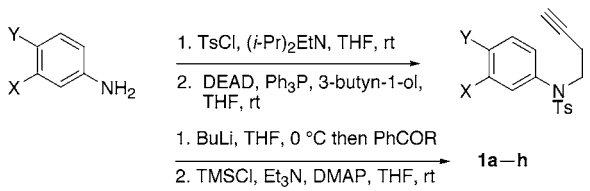
Scheme 2



regioisomeric 4-[(3,3-disubstituted)vinylidene]tetrahydroquinolines (**2** or **3**) dependent upon the canonical form (II).

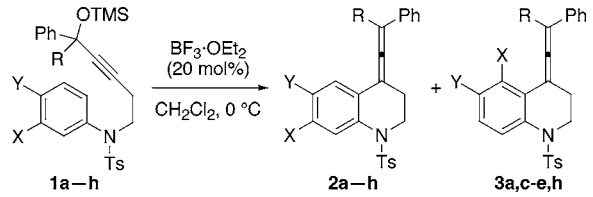
We also expected that the moiety at C(4) might play a role in converting **2** or **3** to an aromatic system, for instance by isomerization from the 1,2-dienes to 1,3-dienes[7] and desulfonylation. Propargyl trimethylsilyl ethers (**1a**−**h**) were readily prepared from aniline derivatives by a series of routine synthetic reactions. This involved N-sulfonylation and N-alkylation by the Mitsunobu reaction[8] with 3-butyn-1-ol, acetylide formation followed by coupling with ketones or aldehydes, and then finally O-trimethylsilylation (Scheme 3).[9]

Scheme 3



Ring-closing Friedel−Crafts reactions of **1a**−**h** proceeded smoothly at 0 °C in the presence of a catalytic amount of BF_3·OEt_2 (20 mol %) in marked contrast to the previous case shown in Scheme 1, which required a stoichiometric amount of a Lewis acid such as TMSOTf.[10] The results shown in Table 1 indicate that the reaction afforded an

Table 1. Synthesis of 4-(Vinylidene)tetrahydroquinolines



entry	substrate	R	X	Y	time (min)	yield of **2** + **3** (%)[a]	ratio of **2**:**3**[b]
1	**1a**	Ph	OMe	H	10	99	10:1
2	**1b**	Ph	H	OMe	10	98	
3	**1c**	Ph	Me	H	10	95	3:1
4	**1d**	*i*-Pr	Me	H	10	90	3:1
5	**1e**	Me	OMe	H	10	86	3:1
6	**1f**	H	OMe	H	10		
7	**1g**	Ph	H	H	60	68	
8	**1h**	Ph	Cl	H	60	60	3:1

[a] Yields for chromatographically pure products. [b] Determined by ^{1}H NMR analysis: isomers were inseparable.

inseparable mixture of 7-substituted tetrahydroquinolines (**2a**,**c**−**e**,**h**) and 5-substituted isomers (**3a**,**c**−**e**,**h**) (entries 1,3−5, and 8) or 6-substituted isomers (**2b**,**g**) (entries 2 and 7) in moderate to excellent yields. Entry 6 using **1f** bearing R = H resulted in the decomposition of the substrate, indicating that the tertiary nature of the propargylic center is crucial for the desired reaction to take place. Very high yields were observed for compounds bearing activating substituents on the ring (entries 1−5).

The ratio of regioisomers (**2**:**3**) for entries 1, 3, 4, and 5 listed in Table 1 suggest that the nature of the R group may play a certain role in the regiochemical outcome of the IMFC process. For instance, the ratio (10:1, entry 1) between **2** and **3** changed to 3:1 (entry 5) when the phenyl group was replaced with a methyl group. The same trend was observed when a methoxy substituent on the ring (entry 1) was displaced with a methyl group (entry 3). It would appear that the more sterically demanding the R or X moiety, the greater the yield of **2**.[11]

(5) (a) Ishikawa, T.; Okano, M.; Aikawa, T.; Saito, S. *J. Org. Chem.* **2001**, *66*, 4635−4642. (b) Ishikawa, T.; Aikawa, T.; Mori, Y.; Saito, S. *Org. Lett.* **2002**, *5*, 51−54.

(6) For ruthenium-catalyzed propargylation of aromatic compounds, see: (a) Nishibayashi, Y.; Yoshikawa, M.; Inaba, Y.; Hidai, M.; Uemura, S. *J. Am. Chem. Soc.* **2002**, *124*, 11846-11847. (b) Hishibayashi, Y.; Inaba, Y.; Hidai, M.; Uemura, S. *J. Am. Chem. Soc.* **2002**, *124*, 7900−7901.

(7) For isomerization of this class, see: Reinhard, R.; Glaser, M.; Neumann, R.; Maas, G. *J. Org. Chem.* **1997**, *62*, 7744−7751.

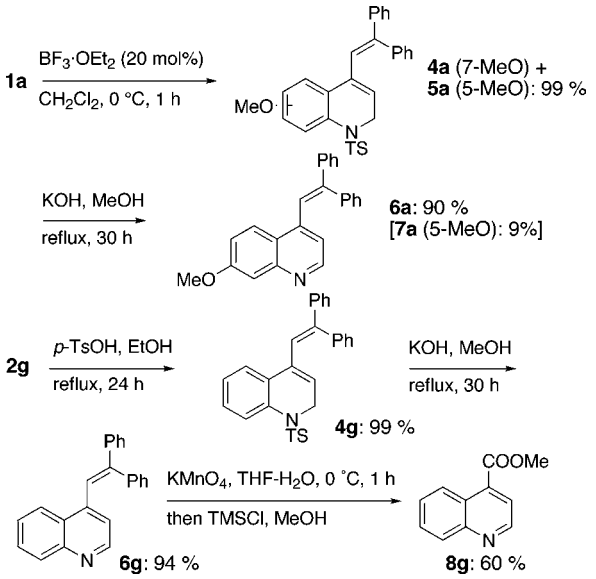
(8) Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* **1972**, *94*, 679−680.

(9) Series of reactions shown in Scheme 3 led to **1a**−**h** in 40−50% overall yields from the corresponding aniline or its derivatives. This method was unsuccessful for bromo or nitro derivatives.

(10) It should be noted that the reactions were completed by the use of only a catalytic amount of BF_3·OEt_2, whereas most of Friedel−Crafts reactions required a stoichiometric amount of Lewis acid: see ref 4e.

For the propargyl silyl ethers with an activated substituent on the ring (entries 1−5), the reaction was usually complete within 10 min under the given conditions. Interestingly, however, when the reaction time was extended (i.e., 60 min), the product composition changed. For example, prolonged reaction of **1a** resulted in an inseparable mixture of **4a** and **5a** (10:1) instead of a mixture of **2a** and **3a** (Scheme 4).

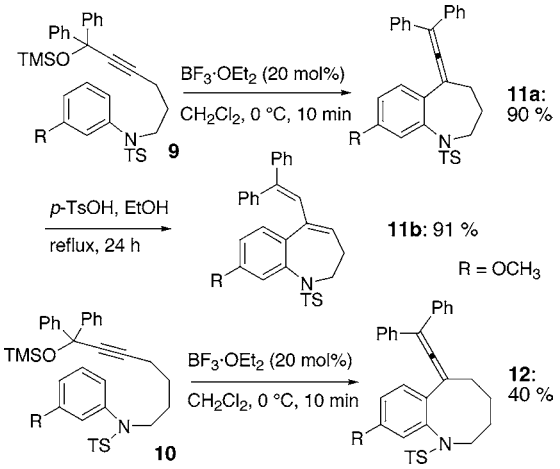
Scheme 4



Although **1g** gave only **2g** even after 60 min (see entry 7), **2g** led to **4g** on treatment with *p*-TsOH in EtOH (reflux, 24 h) (Scheme 4). Hence, the 1,2-diene function of this class can easily be isomerized to the 1,3-diene function by the action of BF_3·OEt_2 when the benzene rings were activated or by the action of acid (TsOH) when not activated. Desulfonylation of **4** (+ **5**) to **6** (+ **7**) was easily achieved by exposure to KOH in MeOH (reflux) (Scheme 4). Fortunately, the regioisomeric mixtures could be separated at this stage by column chromatography. It should be noted that the attempted desufonylation of allene derivatives **2** (or **3**) resulted in quantitative recovery of **2** (or **3**). Oxidative cleavage of the diphenylvinyl moiety of **6g** ($KMnO_4$) followed by esterification afforded **8g** that may be a useful intermediate for further synthetic studies.

These successful results prompted us to examine the applicability of the present methodology for synthesizing seven- or eight-membered ring heterocycles.[12] The results are summarized in Scheme 5. Propargyl silyl ethers **9** and **10** were prepared by a procedure similar to that described for **1**. Ring-closing IMFC reactions of **9** using BF_3·OEt_2 (20 mol %) under the reaction conditions identical to those used for **1** gave the seven-membered ring product **11** in very high yield. In this case, no regioisomeric product (6-MeO isomer) was detected at all. This is probably because one of the phenyl groups linked to the propargylic carbon becomes sterically more demanding at the transition state than is the case during the formation of **3a** (entry 1 in Table 1).

Scheme 5

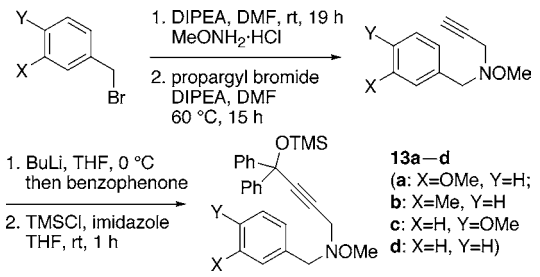


However, eight-membered ring formation using **10** afforded **12** in only 40% yield[13] probably because of the more entropically demanding nature of the reaction.

To apply this methodology to the synthesis of substituted isoquinolines, efficient synthesis of the substrates is required. For this purpose we employed *O*-methylhydroxylamine[14] as a dual nucleophile that can undergo S_N2 reactions twice with arylmethyl halides and propargyl halides. We also expected that a methoxy substituent on the nitrogen atom would trigger aromatization of the initial Friedel−Crafts products through an acid-promoted elimination process.

The outline of the preparation of substrates for isoquinoline synthesis is shown in Scheme 6. Although it was difficult

Scheme 6



to suppress *N*,*N*-diarylmethylation, the use of excessive $MeONH_2$ led to 60% yield of the desired product. The

(11) Benzophenone bearing appropriate substituents on the rings should be examined in this context, which, however, has not been done yet.

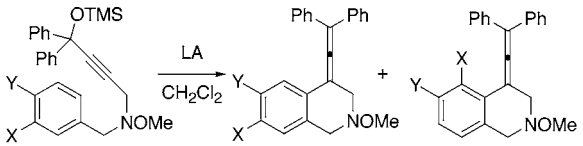
(12) Most previous reports for the synthesis of 1-benzazepine backbone from aniline derivatives featured the formation of a seven-membered heterocyclic ring relying on a functional group incorporated into an ortho substituent of the aniline derivatives: see, for example: (a) Zheng, Z. B.; Dowd, P. *Tetrahedron Lett.* **1993**, *34*, 7709−7712. (b) Anastasiou, D.; Jackson, W. R. *Austr. J. Chem.* **1992**, *45*, 21−37. (c) Sato, T.; Ito, T.; Ishibashi, H.; Ikeda, M. *Chem. Pharm. Bull.* **1990**, *38*, 3331−3334. On the other hand, to the best of our knowledge, there has been no report with respect to the formation of 1-benzazocine derivatives featuring an IMFC process for heterocyclic ring closure employing aniline derivatives as a starting material.

following N-propargylation gave the corresponding [*N*-(aryl)-methyl-*N*-propargyl]-*O*-methylhydroxylamine in high yield. A series of reactions similar to those employed for the preparation of **1** involving generation of acetylides, their addition to benzophenone, and final O-trimethylsilylation led to **13a**−**d**.[15]

The results of the isoquinoline synthesis are tabulated in Scheme 7. In these cases, a stoichiometric amount of TMSOTf in place of BF_3·OEt_2 was required for the desired Friedel−Crafts process to take place (see entries 1 and 2). In addition, the reactivity of **13** depended on the substrate structure: **13a**,**b** bearing an electron-donating group in the meta position were reactive enough to afford **14a**,**b** in high yield (entries 1 and 3), whereas **13c** or **13d**, bearing either a *p*-methoxy group or no substituent, resulted in decomposition of the substrate.[16] Under the reaction conditions described, both **14a** and **14b** were accompanied by a small amount of byproduct such as **16a** or **16b**, respectively. This was probably the result of isomerization followed by elimination (MeOH) of the initial products (**14a** or **14b**). Tetrahydroisoquinolines, a mixture of **14** and **15**, also led to 4-vinylisoquinoline (**16a** or **16b**) in high yield upon exposure to acid, resulting in isomerization followed by elimination, as shown at the bottom of Scheme 7.

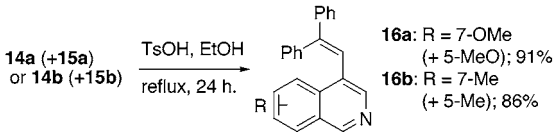
In conclusion, we have demonstrated the synthetic potential of the allenyl cations in IMFC reactions for quinoline, isoquinoline, 1-benzazepine or 1-benzazocine syntheses. In this strategy, the cations were generated by the action of a catalytic amount of BF_3·OEt_2, although the isoquinoline synthesis required a stoichiometric amount of TMSOTf as a promoter. The ease of substrate synthesis from substituted *N*-tosylanilines for **1**, **9**, or **10** and *N*-methoxybenzylamines for **13** indicates the practical aspect of this synthetic scheme.

Scheme 7



13a,**b** **14a**,**b** **15a**,**b**

entry	sub.	LA (%mol)	X	Y	temp (°C)	time (min)	yield/%[a] (**14**:**15**)
1	**13a**	TMSOTf (100)	OMe	H	−25	45	93[b] (89 : 4)[c]
2	**13a**	BF_3·OEt_2 (120)	OMe	H	0	90	5[d]
3	**13b**	TMSOTf (100)	Me	H	−15	45	89[e] (4 : 1)[c]



[a] For chromatographically pure products. [b]Accompanied by separable **16a** (5% yield). [c]Inseparable by SiO_2 column chromatography. [d]**13a**, recovered in 85% yield. [e]Accompanied by separable **16b** (9% yield).

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Supporting Information Available: Experimental procedures and spectroscopic data for the substrates (**1**, **9**−**10**, **13**) and the products (**2**−**8**, **11**, **12**, **14**−**16**) and copies of ^{1}H and ^{13}C NMR spectra for representative compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) In this case, unsaturated ketone was obtained probably through the Meyer−Schuster rearrangement due to a small amount of water inevitably present in the reaction medium. Hence, prolonged reaction did not lead to an increase in the yield of **12**.

(14) We have attempted to prepare *N*-tosyl versions of **13** by reacting *N*-tosylarylmethylamines with propargyl bromide (NaH, DMSO) or propargyl alcohol (Mitsunobu conditions), which, however, was unsuccessful. This was why we paid attention to $MeONH_2$.

(15) Series of reactions shown in Scheme 6 led to **13a**−**d** in 40−50% overall yields from the corresponding benzyl halides.

(16) No identifiable product was obtained. This probably means that the side chain was subject to decomposition due to the slow rate of the IFCR process in these cases.