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Synthesis of 4,5-fused tricyclic quinolines via an acid-promoted intramolecular Friedel–Crafts allenylation of aniline derivatives

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ABSTRACT

A novel method for synthesizing 4,5-fused tricyclic quinoline derivatives based on an acid-promoted intramolecular Friedel–Crafts allenylation of anilines. Using aryl group-substituted propargyl alcohol derivatives with a *meta*-substituted *N*-Boc aniline unit as substrates, a four-step reaction sequence involving an acid-promoted intramolecular Friedel–Crafts allenylation of anilines, an acid-promoted intramolecular C–N bond formation, deprotection of the Boc group, and air oxidation proceeded in a single pot, producing the corresponding 4,5-fused tricyclic quinoline derivatives in 31–84% yield.

Functionalized quinoline rings are ubiquitous in a wide variety of biologically active natural products and pharmaceuticals. An efficient synthetic method for quinoline derivatives is therefore in high demand in the fields of organic synthesis and medicinal chemistry.[1] The 4,5-fused tricyclic quinoline framework is present in various bioactive molecules, such as kuanoniamines (cytotoxic activity),[2a] and exatecan (topoisomerase I inhibitor),[2b] and is an attractive structural motif for scaffolds in drug design (Fig. 1). Efficient construction of a 4,5-fused tricyclic quinoline skeleton, however, remains a challenging task in organic synthesis.[3]

We recently focused on the development of a novel cascade process for synthesizing fused-polycyclic indoles[4] and hydroquinolines[5] based on an acid-promoted intramolecular Friedel–Crafts-type reaction using phenol derivatives as substrates. When aryl group-substituted propargyl alcohol derivatives with a *para*-substituted phenol unit **I** were utilized as substrates, an intramolecular *ipso*-Friedel–Crafts allenylation of phenols proceeded in the presence of an acid promoter, providing aryl group-substituted allenyl spirocyclohexadienones **II** that could be transformed into various fused heterocycles via sequential bond forming/cleaving reactions (Scheme 1(a)). The present reaction mode can be extended to the synthesis of 2,3-fused bicyclic *ortho*-allenyl anilines **IV** using *meta*-substituted aniline derivatives **III** as substrates.[6] We hypothesized that an acid-promoted six-membered ring formation would proceed sequentially from **IV** through a delocalized cationic species **V**, and subsequent deprotection and oxidation would produce the corresponding 4,5-fused tricyclic quinoline derivatives (Scheme 1(b)). Herein, we report a novel method for synthesizing 4,5-fused tricyclic quinolines based on an acid-promoted intramolecular Friedel–Crafts allenylation of anilines.

Our investigation began with the model substrate **1a** (Table 1). We first examined the reaction using 3 equiv of trifluoroacetic acid (TFA) as an acid promoter in CH_2Cl_2 (0.05 M) at room temperature. Substrate **1a** was gradually consumed, and the desired product **2a** was obtained in 12% yield, accompanied by the isolation of *N*-Boc dihydroquinoline derivative **3a** in 50% yield (entry 1). The amount of TFA remarkably affected the reactivity (entries 1–4). When the reaction was performed using 15 equiv of TFA in CH_2Cl_2 under air, the desired cascade reaction proceeded smoothly to give 4,5-

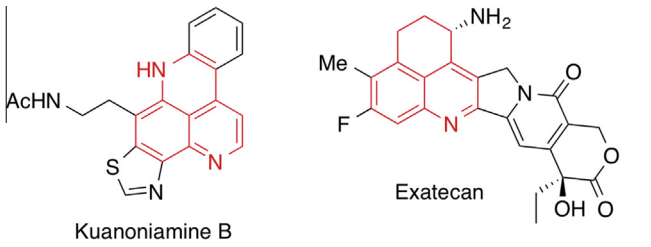

Figure 1. Examples of bioactive molecules with a 4,5-fused tricyclic quinoline skeleton.

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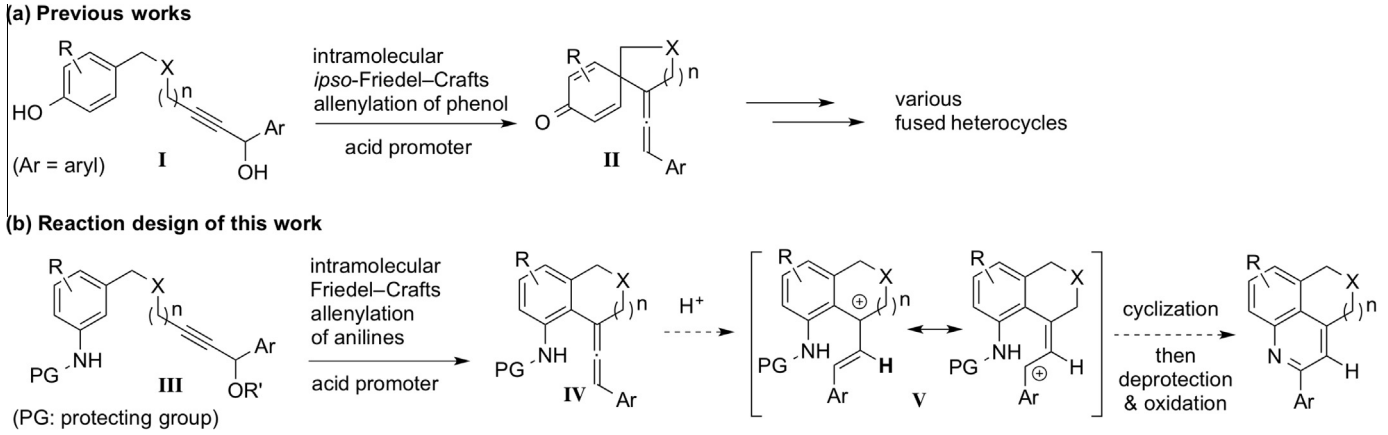
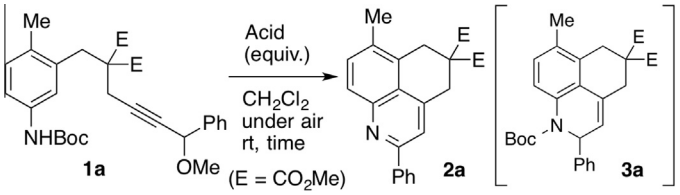


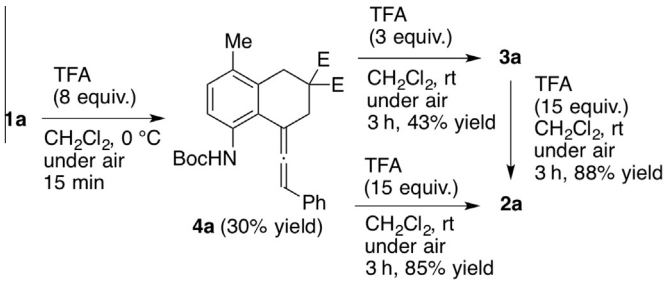
Scheme 1. Background and reaction design of this work.

Table 1
Optimization of the reaction conditions



Entry	Acid (equiv)	Concd (M)	Time (h)	Yield[a] (%)
1	TFA (3)	0.05	16	12 (50)[b]
2	TFA (8)	0.05	16	60
3	TFA (15)	0.05	3	76 (75)[c]
4	TFA (25)	0.05	3	75
5	TFA (15)	0.1	3	67
6	TFA (15)	0.025	12	74
7	TsOH·H_2O (3)	0.05	3	Messy

[a] Determined by ^{1}H NMR analysis of the crude sample. Triphenylmethane was used as an internal standard.
[b] Isolated yield of **3a**.
[c] Isolated yield of **2a**.

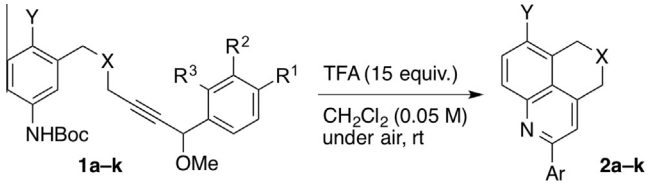


Scheme 2. Experiments for elucidating the reaction pathway.

fused tricyclic quinoline **2a** in 76% yield (75% isolated yield) (entry 4). The results were less satisfactory, however, when the reaction concentration was either increased or decreased (entries 5 and 6). The use of more acidic TsOH·H_2O resulted in a messy reaction (entry 7). Thus, we selected the conditions in entry 3 as optimum for this cascade reaction.

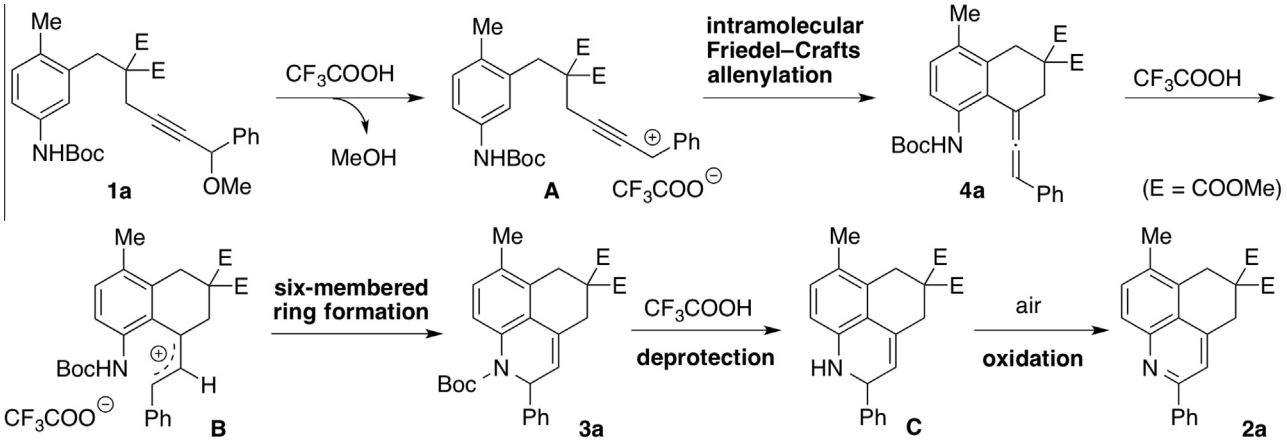
After determining the optimal reaction conditions, we investigated the scope and limitations of the developed cascade process (Table 2).[7] In addition to model substrate **1a** (entry 1), aryl

Table 2
Substrate scope



Entry	Product	X	Y	R^1	R^2	R^3	Time (h)	Yield[a] (%)
1	**2a**	$C(CO_2Me)_2$	Me	H	H	H	3	75
2	**2b**	$C(CO_2Me)_2$	Me	Me	H	H	3	53
3	**2c**	$C(CO_2Me)_2$	Me	OMe	H	H	3	62
4[b]	**2d**	$C(CO_2Me)_2$	Me	Cl	H	H	18	60
5[b]	**2e**	$C(CO_2Me)_2$	Me	Br	H	H	18	69
6	**2f**	$C(CO_2Me)_2$	Me	H	OMe	H	4	84
7	**2g**	$C(CO_2Me)_2$	Me	H	Me	H	3	79
8	**2h**	$C(CO_2Me)_2$	Me	H	H	OMe	3	82
9	**2i**	$C(CO_2Me)_2$	OMe	H	H	H	3	75
10	**2j**	$C(CO_2Me)_2$	F	H	H	H	6	53
11[b]	**2k**	NTs	Me	H	H	H	18	31

[a] Isolated yield.
[b] Reaction concentration = 0.025 M.



Scheme 3. Proposed reaction mechanism.

group-substituted propargyl alcohol derivatives with an electron-donating group or an electron-withdrawing group on the *ortho*-position (**1b**–**e**), *meta*-position (**1f** and **1g**), or *para*-position (**1h**) of the aromatic ring were applicable to this cascade process and 4,5-fused tricyclic quinoline derivatives **2b**–**h** were obtained in 53–84% yield (entries 2–9). Introduction of a methoxy group (**1i**) or fluorine group (**1j**) on the anilinic aromatic ring was also tolerant to this reaction, affording the corresponding products **2i** and **2j** in 75% yield and 53% yield, respectively. Furthermore, when *N*-Ts tethered compound **1k** was used as a substrate, the desired product **2k** was obtained in 31% yield.[8]

To gain insight into the reaction mechanism of this cascade process, we performed the following experiments (Scheme 2). When compound **1a** was reacted with 8 equiv of TFA in CH_2Cl_2 at 0 °C for 15 min, *ortho*-allenyl aniline derivative **4a** was obtained in 30% yield. Both **3a** and **4a** were transformed into **2a** under the optimal reaction conditions in 88% yield and 85% yield, respectively. Moreover, when **4a** was treated with 3 equiv of TFA in CH_2Cl_2 for 3 h at room temperature, **3a** was isolated in 43% yield. These experimental data led us to propose a reaction pathway for this cascade reaction (Scheme 3).

First, substrate **1a** reacts with TFA to give propargyl cation intermediate **A**. An intramolecular Friedel–Crafts allenylation of the *meta*-substituted aniline proceeds, providing 2,3-fused bicyclic *ortho*-allenyl aniline derivative **4a**. After the generation of delocalized cationic species **B** by protonation of the allene, the six-membered ring formation occurs sequentially to give *N*-Boc dihydroquinoline derivative **3a**. Finally, deprotection of the *N*-Boc group in the presence of TFA, followed by air oxidation of the dihydroquinoline unit,[9] affords 4,5-fused tricyclic quinoline **2a**.

In conclusion, we developed a novel synthetic method for 4,5-fused tricyclic quinoline derivatives based on an acid-promoted intramolecular Friedel–Crafts allenylation of anilines. Using aryl group-substituted propargyl alcohol derivatives with a *meta*-substituted *N*-Boc aniline unit as substrates, a four-step reaction sequence involving an acid-promoted intramolecular Friedel–Crafts allenylation of anilines, an acid-promoted intramolecular C–N bond formation, deprotection of the Boc group, and air oxidation proceeded in the presence of TFA, producing the corresponding 4,5-fused tricyclic quinoline derivatives in 31–84% yield in a single pot process. To the best of our knowledge, this is the first example of a cascade reaction for synthesizing 4,5-fused tricyclic quinoline derivatives from aryl group-substituted propargyl alcohol derivatives with a *meta*-substituted aniline unit. Further studies are in progress to examine the pharmacological activity of these quinoline derivatives.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.10.010.

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7. *General procedure* (Table 2, entry 1). To a stirred solution of **1a** (48.5 mg, 0.0952 mmol) in CH_2Cl_2 (1.90 mL) at room temperature was added trifluoroacetic acid (0.106 mL, 1.43 mmol), and the resulting solution was stirred under air at the same temperature. After 3 h, the reaction was quenched with sat. aq $NaHCO_3$ at 0 °C and the mixture was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and then concentrated in vacuo. The obtained residue was purified by flash column chromatography (SiO_2, hexane/AcOEt = 5/1) to give **2a** (26.8 mg, 75% yield) as white solid.
8. When a non-substituted propargyl ether derivative was used as a substrate, only deprotection of the Boc group occurred under the optimized reaction conditions. This result indicates that an aryl substituent is necessary for the generation of the cation intermediate.
9. When the reaction was performed under an argon atmosphere, intermediate **C** was detected in the NMR analysis of the crude sample. This intermediate was transformed into **2a** during the silica gel column purification.