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A Four-Component Cascade C−H Functionalization/Cyclization/Nucleophilic Substitution Reaction To Construct α-Functionalized Tetrahydroquinolines by the Strategy of *in Situ* Directing Group Formation

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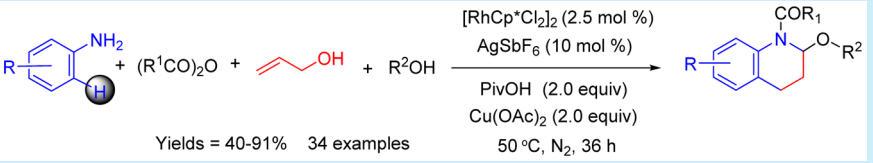
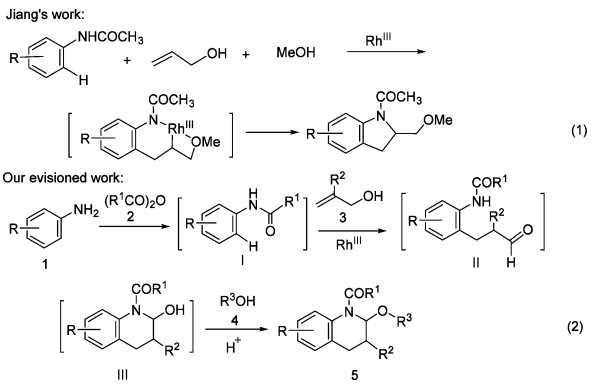
Supporting Information



ABSTRACT: A four-component cascade C−H functionalization/cyclization/nucleophilic substitution reactions of anilines, carboxylic anhydrides, propenol, and alkohols have been developed by a strategy of *in situ* directing group formation, affording an efficient and convenient synthesis of α-alkoxyl tetrahydroquinolines from basic starting materials. A plausible mechanism involving rhodium(III) catalytic C−H functionalization and double nucleophilic attacks is proposed. The nucleophilicity order of some alcohols is also obtained for the cascade reaction.

Most transition-metal-catalyzed C−H functionalizations are assisted by directing groups, which have emerged as powerful methods for the formation of C−C and C−heteroatom bonds.[1] Recently, much attention has been paid to the strategy of convertible directing groups for C−H functionalizations.[2−6] This strategy can be classified into four modes: (1) *In situ* connection of a directing group onto a substrate followed by C−H functionalization and then *in situ* disconnection of the directing group, which is fulfilled by one cascade reaction.[2,3] (2) *In situ* connection of a directing group onto a substrate followed by C−H functionalization, and then the disconnection of the directing group, which is fulfilled by two reactions.[2,4] (3) The connection of a directing group onto a substrate, C−H functionalization, and then *in situ* disconnection of the directing group, which is fulfilled by two reactions as well.[2,5] (4) The connection of a directing group onto a substrate, C−H functionalization, and then disconnection of the directing group, which is fulfilled by three reactions.[2,6] Among these modes, the second mode avoids the formation reaction of directing groups and is also more atom economic and environmentally friendly. In 2014, Huang et al. disclosed that anilines reacted with acetic anhydride to introduce the acetyl group as a directing group *in situ* to form *N*-phenyl acetamides followed by oxidative C−H activation/annulation with alkynes to give *N*-acetyl indoles. Then, disconnection of the acetyl group by the hydrolysis of aqueous sodium hydroxide produced indoles.[4b] However, C(sp^2)−H functionalization of anilines with allylic alcohols by the strategy of *in situ* directing group formation, such as via *N*-phenyl acetamide intermediates, remains unknown. In 2013, Jiang and co-workers reported that *N*-phenyl acetamides reacted with allylic alcohols to give indolines via C−H functionalization under rhodium catalysis (Scheme 1, eq 1).[7] Glorious et al. revealed one example of the reaction of *N*-phenyl acetamide with propenol via C−H activation by rhodium catalysis and using $Cu(OAc)_2$ as an oxidant, affording a dihydroquinolinone in a low yield.[8] We envisioned that *N*-phenyl amides **I** formed *in situ* from anilnes **1** and carboxylic anhydrides **2** could perform C(sp^2)−H functionalization with allylic alcohols **3**

Scheme 1. Reactions Involving *N*-Phenyl Acetamide and Propenol



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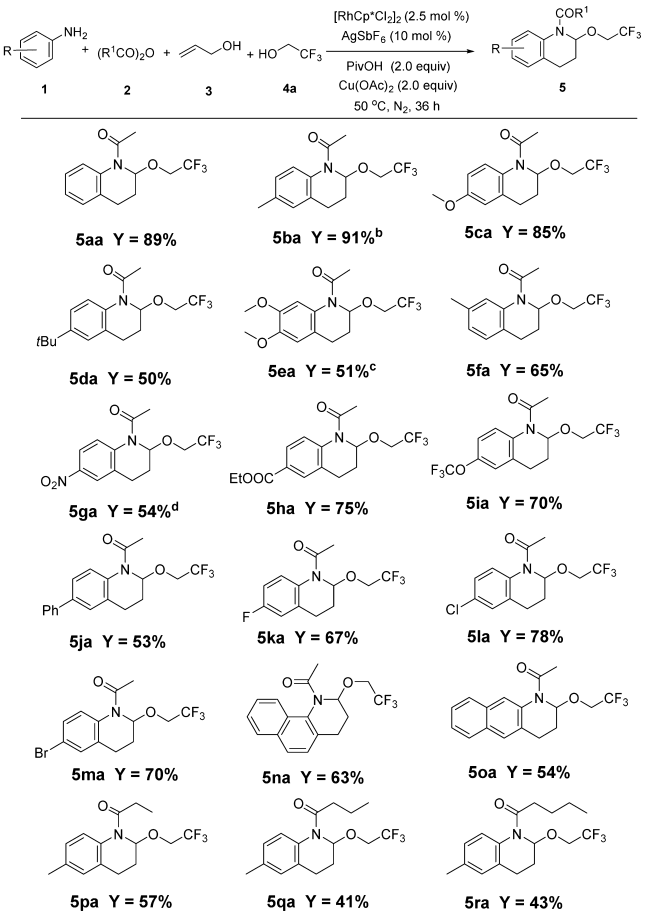
through insertion by the direction and assistance of acyl groups, generating propanalated *N*-phenyl amides **II** (Scheme 1, eq 2). Then nitrogen in the amido group could perform nucleophilic addition onto the carbonyl group in the propanal moiety to form α-hydroxyl tetrahydroquinoline **III**, which should be reactive.

As we know, multicomponent reactions have become a powerful tool to construct organic molecules from three or more compounds in a single operation.[9] A cascade reaction combines two or more bond-forming reactions into one process, without requiring isolation of intermediates. Both the multicomponent reaction and the cascade reaction are atom economic and step efficient. They reduce resource consumption and environmental impact and have been widely applied in the synthesis of natural products, pharmaceuticals, and other bioactive molecules. Thus, we further envisioned that if there is alcohol **4** as an additional component in the reaction system, the reactive α-hydroxyl tetrahydroquinoline **III** may continue to perform a nucleophilic substitution reaction with **4** in the presence of a Brønsted acid, producing a more stable α-alkoxyl tetrahydroquinoline **5** (Scheme 1, eq 2). Tetrahydroquinoline derivatives especially α-functionalized tetrahydroquinolines are present in many biologically active natural products and pharmacologically relevant therapeutic agents.[10] Thus, we embarked on the four-component cascade C−H functionalization/cyclization/nucleophilic substitution reaction between anilines, carboxylic anhydrides, allylic alcohols, and alcohols by the strategy of *in situ* directing group formation for the efficient construction of α-alkoxyl tetrahydroquinolines.

Initially, aniline **1a**, acetic anhydride **2a**, propenol **3**, and trifluoroethanol **4a** were chosen as model substrates to explore and optimize the four-component cascade C−H functionalization/cyclization/nucleophilic substitution reaction. After various transition-metal catalysts, oxidants, Brønsted acids, solvents, etc. were screened, it was concluded that the optimized reaction should be performed by the catalysis of $[RhCp^*Cl_2]_2$ (2.5 mol %) and $AgSbF_6$ (10 mol %) using $Cu(OAc)_2$ (2.0 equiv) and trimethylacetic acid (PivOH; 2.0 equiv) as an oxidant and a Brønsted acid respectively at 50 °C under neat conditions and a nitrogen atmosphere (see Supporting Information (SI)). It was found that, under the optimized conditions, various anilines bearing no group **1a**, electron-donating groups **1b−f**, or electron-withdrawing groups **1g−m** on benzene rings were able to undergo the four-component reaction smoothly with acetic anhydride **2a**, propenol **3**, and trifluoroethanol **4a** to give the desired α-trifluoroethoxyl tetrahydroquinolines **5aa−ma** in 50−91% yields (Scheme 2). The structure of **5la** was further confirmed by X-ray crystallography (see SI). The trifluoroethoxyl group has important biological activities, such as high metabolic stability and lipophilicity, and many trifluoroethoxyl group substituted compounds have been developed into drugs, such as Silodosin, Flecainide, Lansoprazole, and Fluoroxene.[12] The cascade reaction is compatible to many functional groups such as nitro, ethoxycarbonyl, fluoro, chloro, bromo, trifluoromethoxyl, methoxyl, and tertiary butyl groups. When naphthalene amines **1n−o** were employed, the four-component reaction was also conducted expediently to afford the corresponding α-trifluoroethoxyl tetrahydrobenzoquinolines **5na−oa** in satisfactory yields. The positions of the amino group on the α or β position of naphthalene rings in naphthalene amines **1n−o** determines if the reaction leads to anthracene-like tetrahydrobenzoquinoline **5na** or phenanthrene-like tetrahydrobenzoquinoline **5oa**. Allylic alcohols bearing substituents on carbon−carbon double bonds, such as 2-methylpropenol and (*E*)-but-2-enol, did not undergo the cascade reaction. The experiment also demonstrated that using propionic anhydride, butyric anhydride, or valeric anhydride for *in situ* directing group formation also assisted the reaction to give α-trifluoroethoxyl tetrahydrobenzoquinolines **5pa−ra**.

Scheme 2. Scopes of Anilines 1 and Anhydrides 2 in the Cascade Reaction[a]



[a]Reaction conditions: **1** (0.10 mmol), **2** (0.20 mmol), **3** (0.30 mmol), **4** (1.5 mL), $[RhCp^*Cl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), PivOH (2.0 equiv), $Cu(OAc)_2$ (2.0 equiv), 50 °C, for 36 h, under N_2; isolated yields, [b]24 h. [c]60 °C. [d]70 °C.

Considering that many di- or monofluoroethoxyl group containing compounds have important biological activities and these motifs widely exist in pharmaceutically relevant molecules,[12] we successively employed difluoroethanol **4b** and monofluoroethanol **4c** as nucleophiles in the four-component reaction. The experiments demonstrated that aniline **1b** or **1c**, acetic anhydride **2a**, and propenol **3a** were able to undergo the cascade reaction smoothly with **4b** or **4c** to give corresponding di- or monofluoroethoxyl tetrahydroquinolin **5bb−cc** in 50−73% yields (Scheme 3). Trichloroethanol **4d** also performed the reaction to give α-trichloroethoxyl tetrahydroquinoline **5cd** in a 58% yield, which was lower than that of **5ca** using trifluoroethanol **4a** (Scheme 2 and Scheme 3). Various common primary alcohols such as ethanol **4e**, pentanol **4f**, isobutanol **4g**, neopentanol **4h**, and cyclopropanemethanol **4i** also underwent the four-

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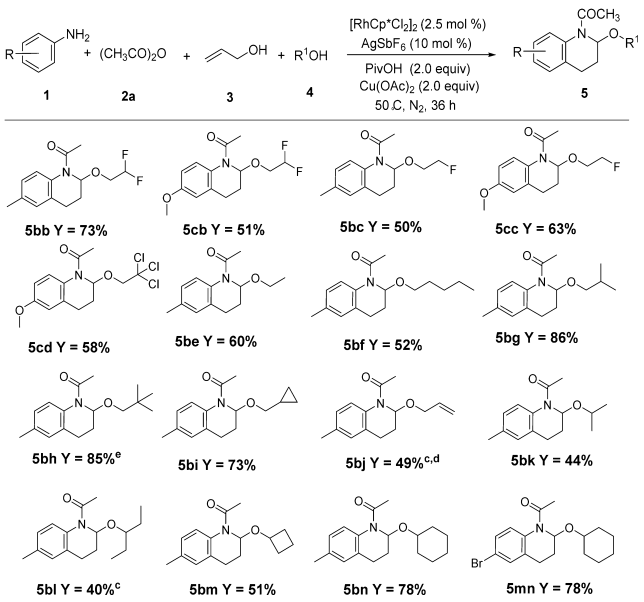
Scheme 3. Scope of Alcohols 4 in the Cascade Reaction[a,b]

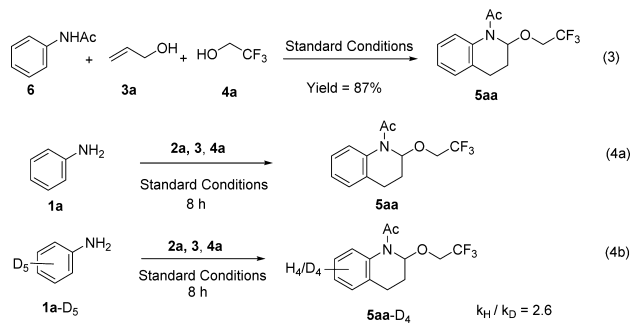


[a]Reaction conditions: **1** (0.10 mmol), **2a** (0.20 mmol), **3** (0.30 mmol), **4** (1.5 mL), $[RhCp^*Cl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), PivOH (2.0 equiv), $Cu(OAc)_2$, (2.0 equiv), 50 °C, for 36 h, under N_2. [b]Isolated yields, [c]60 °C. [d]**3** (0.50 mmol), **4j** (0.50 mmol). S = 1,4-dioxane (1.5 mL). [e]**4h** (0.50 mmol), S = 1,4-dioxane (1.5 mL).

component reaction expediently to give α-alkoxyl tetrahydroquinolines **5be–bi** in 52–86% yields. When excess allylic alcohol (5.0 equiv) was employed as both a C–H functionalization reagent and a nucleophile, equivalent trifluoroethanol **4a** was still needed; otherwise, no α-allyloxyl tetrahydroquinolines **5bj** was obtained. With respect to secondary alcohols, both chain **4k–l** and cyclic **4m–n** alcohols underwent the cascade reaction readily to give **5bk–mn** in 40–78% yields (Scheme 3).

To gain insight into the mechanistic pathway of the four-component reaction, we conducted control experiments by using *N*-phenyl acetamide **6** instead of aniline **1a** and acetic anhydride **2a** (Scheme 4, eq 3). As expected, *N*-phenyl

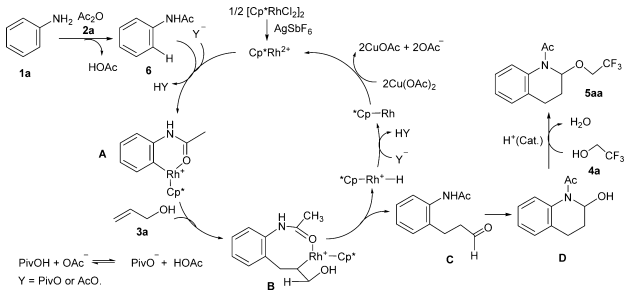
Scheme 4. Primary Mechanistic Study



acetamide **6** performed the desired cascade reaction with propanol **3** and trifluoroethanol **4a** smoothly to give **5aa** in good yields. The experimental results support that the acetyl group could function as a directing group in the C–H functionalization. Furthermore, parallel reactions using equimolar amounts of **1a** and **1a**-D_5 under the optimized conditions were conducted respectively, and the value of the kinetic isotope effect (KIE) is 2.6. The KIE result suggests that the C–H functionalization may be a rate-determining step in the cascade C–H functionalization/cyclization/nucleophilic substitution reaction (Scheme 4, eq 4a and eq 4b).

Referring to the preceding literature reports,[13,14] a plausible mechanism for the cascade C–H functionalization/cyclization/nucleophilic substitution reaction of aniline **1a**, acetyl anhydride **2a**, propenol **3**, and trifluoroethanol **4a** is depicted in Scheme 5.

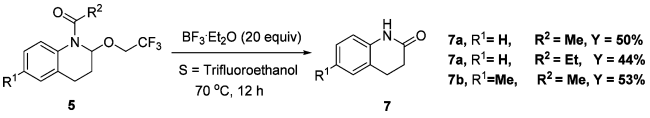
Scheme 5. Plausible Mechanism



First, aniline **1a** reacts with acetyl anhydride **2a** to give *N*-phenylacetamide **6**, forming a directing group in intermediate **6**. Then, Cp^*Rh^{2+} could activate α-C(sp^2)–H in phenylacetamide **6** to form a six-membered rhodacycle intermediate **A**. Insertion of propenol **3** into the rhodacycle intermediate **A** results in an eight-membered rhodacycle intermediate **B**. β-H Elimination of rhodacycle intermediate **B** gives propanalated *N*-phenyl acetamide intermediate **C** and HRh^+Cp^*. After the addition of a carboxylate anion onto $HRh^{2+}Cp^*$, loss of carboxylic acid (HY) by reductive elimination may lead to Cp*Rh. Cp*Rh then is oxidized into Cp^*Rh^{2+} for catalytic recycle by $Cu(OAc)_2$. For intermediate **C**, the nitrogen in the acetamido group may undergo nuceophilic addition onto the carbonyl group in the propanal moiety to form α-hydroxyl tetrahydroquinoline intermediate **D**. Finally, trifluoroethanol **4a** undergoes a nucleophilic substitution reaction with intermediate **D** in the presence of a Brønsted acid, producing desired α-alkoxyl tetrahydroquinoline **5aa**.

Acetyl and propionyl groups as directing groups in α-alkoxyl tetrahydroquinolines **5ba** and **5pa** were readily removed by treatment of $BF_3{\cdot}Et_2O$ (Scheme 6). However, with the

Scheme 6. Disconnection of Directing Group in α-Allyloxyl Tetrahydroquinolines 5



disconnection of the acetyl or propionyl group, the trifluoroethyl group in **5** was also removed to give dihydroquinolinones **7**, which are core structures in a large number of natural products and marketed drugs or their candidates.[15]

To understand the nucleophilicities of different alcohols **4** in the four-component reaction, two alcohols **4** (10 equiv) were added together with **1b**, **2a**, and **3** under the standard conditions. The competitive experiment of ethanol **4e** with isobutanol **4g** indicates that the nucleophilicity of **4e** is similar and about 1.3 times as much as that of **4g** in the cascade reaction, and the chemical selectivity between **4e** and **4g** is poor (Scheme 7, eq 5). The competitive experiments of ethanol **4e**

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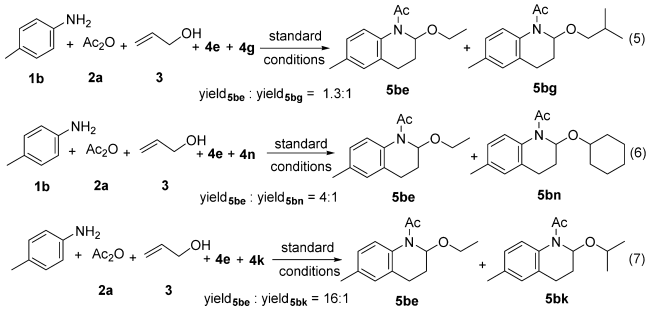
Scheme 7. Nucleophilicities and Chemical Selectivities between Two Alcohols 4 for the Cascade Reaction



with cyclohexanol **4n** and **4e** with isopropanol **4k** indicate that the nucleophilicity of **4e** is about 4 times as much as that of **4n**, and 16 times as much as that of **4k**, and the chemical selectivity between **4e** and **4k** is excellent (Scheme 7, eqs 6 and 7). Therefore, it can be concluded that the nucleophilicity order of some alcohols **4** in the cascade reaction is as follows: ethanol **4e** > isobutanol **4g** > cyclohexanol **4n** > isopropanol **4k** (also see SI). The results suggest that the nucleophilic substitution in the cascade reaction is more sensitive to the steric hindrance of alcohols as nucleophiles.

In conclusion, we have developed a new four-component cascade C−H functionalization/cyclization/nucleophilic substitution reaction by the strategy of *in situ* directing group formation, constructing α-alkoxyl tetrahydroquinolines **5** from four basic starting materials in one reaction. By the rhodium catalytic system, the cascade reaction of anilines **1**, carboxylic anhydrides **2**, propenol **3**, and alcohols **4** was able to proceed smoothly to afford efficient and convenient synthesis of α-alkoxyl tetrahydroquinolines **5** in moderate to excellent yields. The plausible mechanism involving rhodium(III) catalytic C−H functionalization and double nucleophilic attacks is also proposed for the cascade reaction. The nucleophilicity order of some alcohols **4** is obtained for the cascade reaction. Owing to the advantages of simple substrates, mild reaction conditions, moderate to excellent yields, and a highly efficient synthesis, the novel four-component reaction may have potential applications in the synthesis of related natural products and the production of pharmaceuticals.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00226.

Experimental procedures, characterization data, and spectra of ^{1}H NMR, ^{13}C NMR, and HRMS for new products (PDF)

X-ray crystallographic data for **3e** (CIF)

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Notes

The authors declare no competing financial interest.

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