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Traceless Directing-Group Strategy in the Ru-Catalyzed, Formal [3 + 3] Annulation of Anilines with Allyl Alcohols: A One-Pot, Domino Approach for the Synthesis of Quinolines

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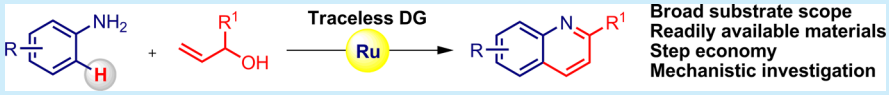
Supporting Information

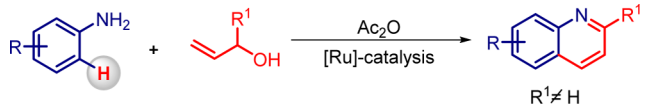


ABSTRACT: A unique, ruthenium-catalyzed, [3 + 3] annulation of anilines with allyl alcohols in the synthesis of substituted quinolines is reported. The method employs a traceless directing group strategy in the proximal C−H bond activation and represents a one-pot Domino synthesis of quinolines from anilines.

Utilization of directing groups to guide site selectivity in C−H activation reactions is probably the most widely employed approach in the area of C−H functionalization. Of the various methods or mechanisms put forward for C−H activation, heteroatom-directed (or chelation-controlled) proximal bond activation by transition-metal catalysts remains the principal choice of synthetic chemists.[1] The method obviously suffers from limitations since installation and the inevitable removal of the directing group lowers the step-economy of the transformation. Often, the directing groups cannot be removed from the products and continue to be a part of them, thereby limiting the synthetic utility of such methods. Of late, the concept of traceless directing group has gained precedence,[2] whereby the step economy of the entire process of C−H functionalization is maintained at a high level. In this regard, transient directing groups too have made a mark in organic synthesis.[3,4]

Nitrogen heterocycles are a ubiquitous part of a majority of pharmaceutically relevant molecules even as they are biologically very significant.[5a] Of these, quinolines are one of the most common *N*-heterocycles found in drug molecules.[5b,c] The synthesis of substituted quinolines has been the subject of widespread interest, spanning well over a century.[6] Several classical as well as modern syntheses of these heterocycles have been described in literature.[7,8] Of these, the Doebner−von Miller modification of the Skraup-quinoline synthesis is a unique reaction.[7a−e] We describe herein a one-pot, domino approach for the synthesis of substituted quinolines via proximal C−H bond activation in which a traceless directing-group methodology has been employed in the ruthenium-catalyzed [3 + 3] annulation of anilines with allyl alcohols (Scheme 1). This methodology provides a completely different product substitution pattern when compared to the Doebner−von Miller synthesis. Allyl alcohols are extremely useful building blocks in organic synthesis and have been widely employed as coupling partners in C−H functionalization reactions, very often functioning as latent α,β-unsaturated carbonyl compounds.[9]

Scheme 1. Traceless Directing Group in One-Pot Domino Synthesis of Quinolines



The alkene moiety of the allyl alcohols has been primarily utilized for Heck-type coupling reactions and the allylic hydroxyl functional group transforms very often into a carbonyl group in the same transformation. Allyl alcohols have also been employed for oxidative (or dehydrogenative) Heck-type coupling reactions thereby resulting in oxidative alkylations of C−H bonds.[10,11] Of these, the works of Jiang,[10] Glorius,[11a] Jeganmohan,[11b] Kim,[11c] and Sundararaju[11d] are noteworthy. Allyl alcohols have also been employed as allylating agents in C−H functionalization reactions, thereby obviating the need for prefunctionalization of either of the coupling partners.[12a,13] Saa and Kim independently reported the use of the allyl acetates in the rhodium-catalyzed C−H functionalization of anilides, resulting in the synthesis of indoles.[14] In this context, Stone had reported a unique method wherein *o*-halo anilines were coupled with allyl alcohols in a two-step sequence to lead to quinolines.[15] Ackermann and co-workers demonstrated the synthesis of quinolines utilizing acetanilides and enones as coupling partners in an *ortho*-selective C−H alkenylation−cyclization cascade.[16] The present method utilizes allyl alcohols as latent α,β-unsaturated carbonyl compounds in the *ortho*-selective C−H functionalization of anilines, thereby leading to substituted quinolines in a one-pot domino-type synthesis (Scheme 1). The highlight of the synthesis is the use of a

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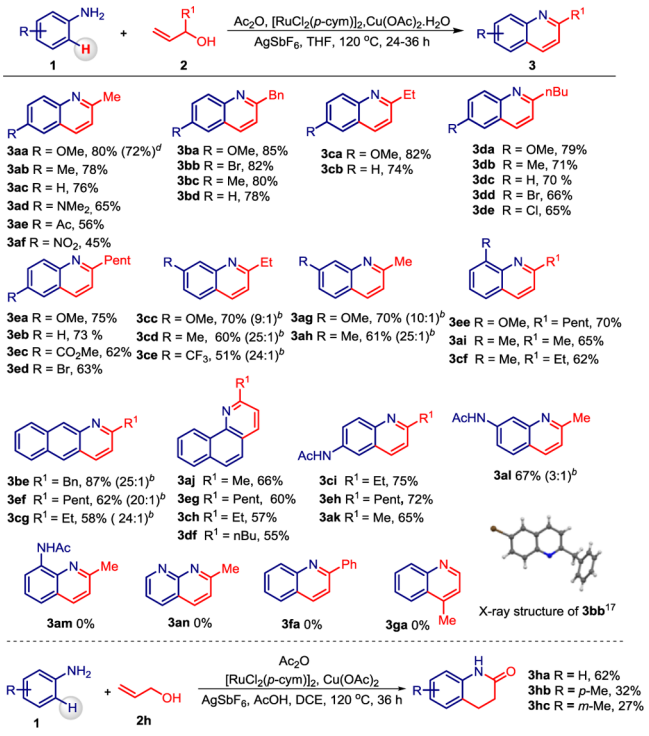
traceless directing group without the need for any prefunctionalization of any of the coupling partners. This method also removes the need for rather labile α,β-unsaturated carbonyl compounds.

Taking inspiration from our previous work on C−H allylation of indoles,[12] we extensively scanned a variety of reaction conditions, among which the cationic ruthenium catalyst provided the best results (see Supporting Information for further details). The reaction worked best only with the ruthenium catalyst, and other catalysts that were scanned did not yield the desired results. The use of copper acetate as co-oxidant was essential for the transformation, and in particular the hydrate form was essential for the annulation to proceed to completion. Of all the additives scanned, $AgSbF_6$ worked the best. Of the solvents scanned, THF worked best for the transformation. Although addition of AcOH resulted in good yields of the product, the use of $AgSbF_6$ (0.5 equiv) proved sufficient to circumvent the use of protic media for the reaction. Use of lower equivalents of $AgSbF_6$ led to slower rates of annulation.

The reaction had a broad substrate scope and worked very well for most of the anilines scanned (Scheme 2). Electronic

Scheme 2. Substrate Scope[a,c]



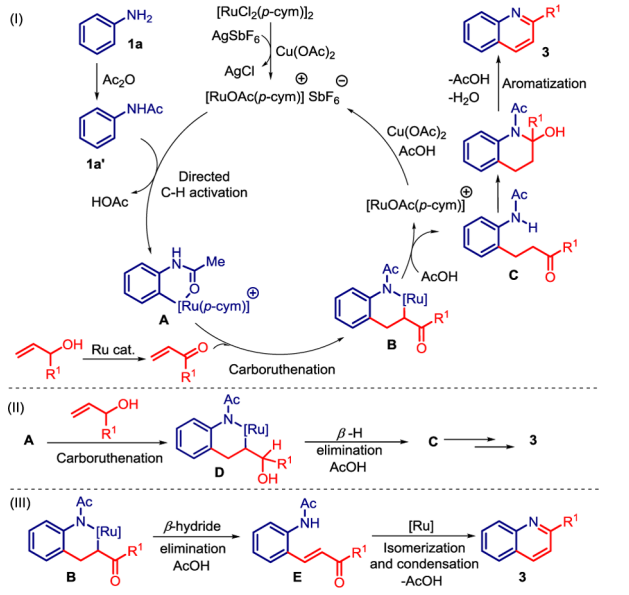
[a]Unless otherwise mentioned all reactions were performed with **1a** (0.3 mmol), **2a** (0.6 mmol), catalyst (0.015 mmol), oxidant (0.6 mmol), and additive (0.15 mmol) in 1.5 mL solvent, in a sealed tube. [b]Regioisomeric ratio determined by GCMS and NMR. [c]All yields are isolated yields. [d]Reaction performed on 1 mmol scale.

factors were well tolerated on the aniline. Steric factors were also well tolerated, and the reaction worked well for *ortho*-substituted anilines as well (**3ee**, **3ai**, **3cf**, Scheme 2).

The reaction yielded a good outcome with *para*- and *meta*-phenylenediamines (**3ci**, **3eh**, **3ak**, **3al**, Scheme 2); however, it failed to produce good outcomes for *ortho*-phenylenediamine and pyridin-2-amine (**3am**, **3an**, Scheme 2). The reaction worked well for most of the allyl alcohols that were scanned. A notable exception was the 1-phenyl-prop-2-en-1-ol, which failed to yield the desired product (**3fa,** Scheme 2). The reaction was rather sensitive to steric crowding on the allyl alcohol, and substituents on the alkene part of the allyl alcohol were not good additions to the substrate scope (**3ga**, Scheme 2). Unsubstituted allyl alcohol yielded quinolones (**3ha−c**, Scheme 2), which came as a surprise to us. However, such an example of this type of outcome was reported by Glorius and co-workers under Rh(III) catalysis.[11a] The substrate scope with unsubstituted allyl alcohol was not very promising since the reaction was rather slow. Preforming the acetanilide in this case did not help. We also attempted to apply the developed strategy to acetyl directed *ortho* C−H functionalization of phenols and thiophenols, but the desired products were not observed.

The reaction is postulated to proceed by a mechanism depicted below in Scheme 3. The formation of acetanilide from

Scheme 3. Proposed Mechanisms



the parent aniline installs the *N*-acyl group that would be the traceless directing group in the transformation. Directed C−H activation assisted by this weak-coordinating group leads to the ruthenacycle **A**. It is also possible that the activation at the ortho position is a result of a combination of an electrophilic C−H activation pathway[18,19b] and the CMD (concerted metalation deprotonation) pathway.[19] The oxidation of allylic alcohols to enones by transition metal catalysts is well documented in literature.[20] Carboruthenation of the enone leads to the intermediate **B** which upon protonolysis leads to **C**. This anilide then cyclizes onto the ketone functional group followed by dehydration and aromatization to lead to the product quinoline.

It is possible that carboruthenation with the allylic alcohol results in **D** which after β-H elimination could lead to **C** (Scheme 3, Pathway II). An alternate pathway involving a β-hydride elimination to generate an oxidative-Heck product **E** (Fujiwara−Moritani type pathway)[21a,b] can also be postulated (Scheme 3, Pathway III).[21c] This product could undergo an olefin isomerization under the reaction conditions, followed by condensation with the ketone functional group to directly lead to the product quinoline. Incidently, when 3 equiv of 1-

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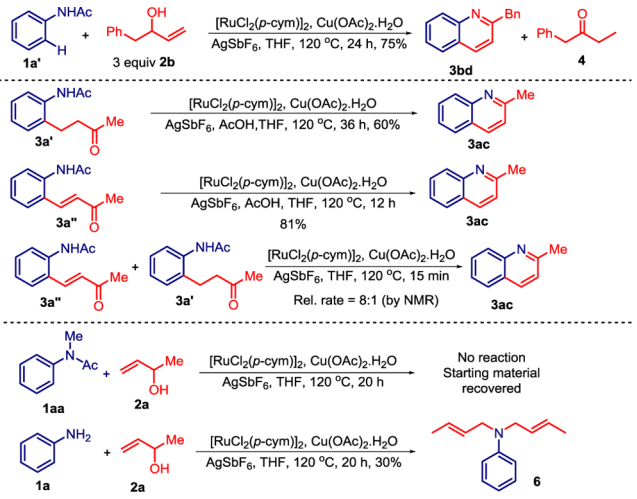
phenylbut-3-en-2-ol were used under standard conditions, ketone **4** was detected and isolated (Scheme 4), clearly

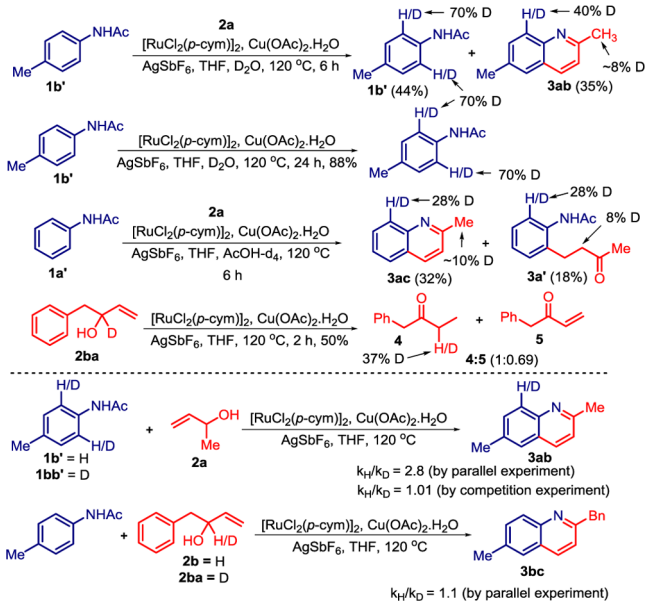
Scheme 4. Control Reactions



indicating that the oxidation of the allylic alcohol was the initial step in this pathway. This points to a C−H alkylation pathway (Scheme 3) being the predominant pathway. It could also be possible that the pathway via the oxidative-Heck product involves a rapid isomerization and cyclization to yield the product. Each of these plausible intermediates resulted in the desired product under the reaction conditions (Scheme 4). A competition reaction involving the two plausible intermediates resulted in a relative rate of 8:1, indicating that **3a″** may be a short-lived intermediate (Scheme 4). *N*-Alkyl anilines did not yield any desired product (Scheme 4).

The acyl directing group was necessary for the transformation as was obvious from the reaction of the free aniline in the absence of Ac_2O (Scheme 4), where only an *N*-allylation reaction was observed. In order to study the plausible pathway for the transformation, studies were conducted to determine the reversibility of the C−H activation/metalation step. The reaction yielded 70% of *ortho*-deuteration when the reaction was carried out in the presence of D_2O (Scheme 5). The high level of deuteration observed at the *ortho*-position of the recovered starting material clearly indicated that the metalation was reversible. No deuteration was observed in absence of the catalyst and additive, thereby ruling out H−D exchange via an S_EAr mechanism. Some deuteration was observed at the α-position of the carbonyl which could be attributed to the deuteration via keto−enol tautomerization (Scheme 5). Oxidation of deuterated allyl alcohol **2ba** (Scheme 5) led to deuterium incorporation at the α-position, pointing to [Ru-D] insertion into **5**. The rate of this oxidation was much faster that the observed rate of the overall transformation indicating that Pathway II (Scheme 3) may not be a possibility. Studies were conducted to determine whether the cleavage of $C(sp^2)$−H was involved in the rate-determining step. Although parallel reactions indicated that the C−H bond cleavage was the rate-limiting step, competition reactions indicated otherwise (Scheme 5). The cleavage of the C−H bond bearing the hydroxy functional group in the allylic alcohol was also not rate limiting (Scheme 5). Studies undertaken to determine the effect of substituents on the rate of the transformation indicated a mild dependency on electronic nature of the substituent.[22]

Scheme 5. Reversibility and Kinetic Studies



The Hammett reaction constant ρ was −0.69, which indicates that the annulation of the anilide onto the ketone may be involved in the rate-limiting step (Figure 1) and the fact

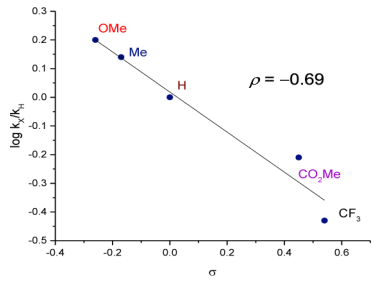


Figure 1. Hammett plot.

that the annulation is retarded by electron-withdrawing substituents on the aniline. The fact that steric effects on the allylic alcohol needed to be optimal indicated that two steps were critical to the transformation, the carboruthenation and the annulation steps.

In summary, we have developed a unique, traceless (transient) directing group strategy for a one-pot domino synthesis of substituted quinolines from anilines and allyl alcohols, utilizing a ruthenium-catalyzed C−H functionalization strategy as the key step. The method is efficient, has high step economy and a broad scope, and uses simple materials. The transformation is quite unique since it incorporates several chemical steps in one pot: installation of the directing group, oxidation of the allyl alcohol, *ortho*-C−H functionalization, annulation, removal of the directing group, and oxidation/aromatization to the final product.

■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures and full spectroscopic data for all new compounds (PDF)
Crystal structure data (X-ray) for compound **3bb** (CIF)

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Notes

The authors declare no competing financial interest.

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