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Iron-Catalyzed, Chelation-Induced Remote C−H Allylation of Quinolines via 8-Amido Assistance

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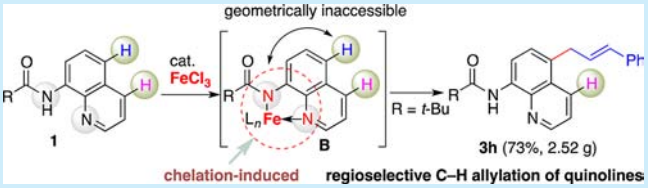
Supporting Information

ABSTRACT: An iron-catalyzed, 8-amido-enabled regiodivergent C−H allylation of quinolines is described. This reaction represents a rare example of chelation-induced geometrically inaccessible C−H functionalization, allowing for the highly regio- and stereoselective preparation of either the C5- or the C4-allylated quinoline scaffolds regiocontrolled by the catalytic systems.



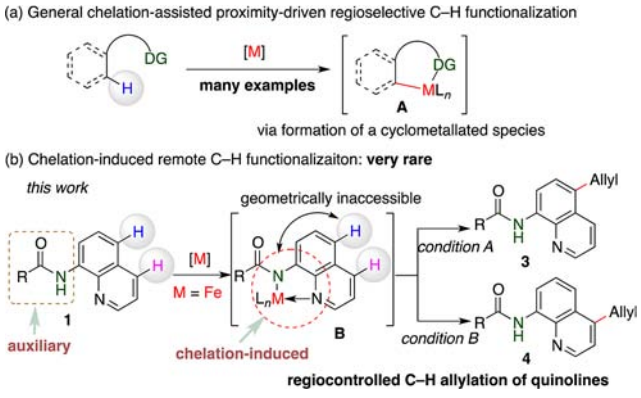
The broad distribution of quinoline scaffolds in bioactive molecules and natural products has spurred considerable efforts toward the development of efficient strategies to the functionalization of these appealing structural motifs.[1] However, because of the difficulty in the control of the regioselectivity, the C−H functionalization of quinolines poses a significant challenge but is a step-economic approach for the buildup of diversely functionalized derivatives.[2] Successful examples in the field typically focus on the transformation of C−H bonds at the C2, C3, and C8 positions of quinolines.[3] In contrast, efficient approaches to the C5- and C4-functionalization of quinolines are still rare.[4] Among the various methods for C−H transformation, the allylation of unactivated C−H bonds attracts immense attention due to its ability to incorporate valuable allyl structural motifs[5] by greatly increasing the complexity of the resulting compounds,[6−10] notably disclosed by Glorius,[9] Ma,[7a] Cramer,[7b] and Nakamura[10] via chelation-assisted C−H transformation. In view of the obvious synthetic utility for the functionalization of quinolines, the development of a C−H allylation protocol to selectively buildup the 5- or the 4-allylquinoline motifs is particularly interesting.

To achieve high regioselectivity, a general strategy is to take advantage of the chelation assistance of the auxiliary, rendering a coordinative transition metal to proximity adjacent C−H bonds, resulting in selective cleavage of a regiospecific C−H bond with the formation of a cyclometalated species **A** (Scheme 1a). In contrast, a strategy for the transformation of a geometrically inaccessible C−H bond that is located far from the coordinative metal center remains largely undeveloped, despite its unique capability in the preparation of structural motifs that are currently challenging to access by conventional means.[11] In this paper, we disclose an iron-catalyzed, chelation-induced, and site-controllable C−H allylation of quinolines via 8-amido assistance, allowing the preparation of uneasily accessible 5-allylquinoline frameworks in a highly selective manner (Scheme 1b).[12]

Since the pioneering investigation by Daugulis,[13] the bidentate chelation-assisted C−H functionalization using 8-aminoquinoline as auxiliary provides a powerful tool toward diverse molecule synthesis.[14,15] Current studies in the field typically focus on the C−H functionalization on the carboxamide scaffolds.[13−15] In contrast, the C−H transformations on the quinoline frameworks are less studied, a known C−H chlorination by a single-electron-transfer (SET) mechanism reported by Stahl.[16] We hypothesized that, after the formation of the chelation complex **B**, the amido group can undergo a property reversal from the X-type to the L-type ligand (Scheme 2). This variation may adjust the distribution of electron density on the quinoline and leads the carbon at the 5- or the 4-position to nucleophilic attack of the π-allyl species with the formation of the related imino complex **C** or **D**, which can convert into the C5- or the C4-allylated quinoline through a deprotonation and aromatization process.[17]

We started our study by examining the effect of catalysts on the reaction of 8-aminoquinoline-bearing carboxamide **1a** with commercially available cinnamyl alcohol (Table 1). In the presence of a mixture of Ru salt and $AgSbF_6$, we were pleased to

Scheme 1. Models for Chelation-Assisted C−H Functionalization



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Scheme 2. Proposed Mechanism for the Chelation-Induced C5- and C4-Allylation of 8-Aminoquinolines

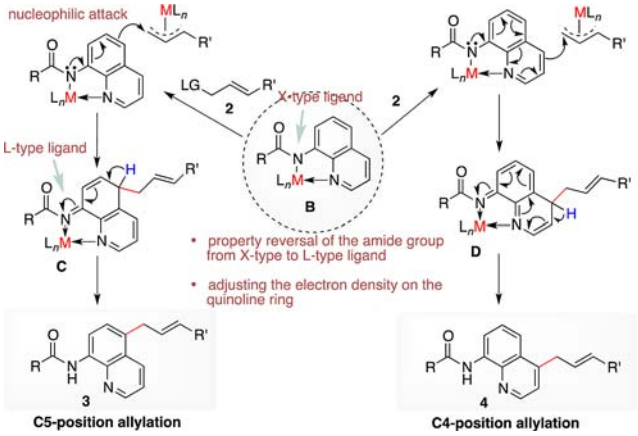
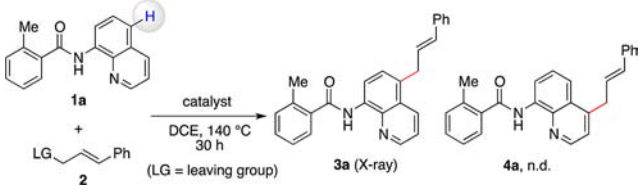


Table 1. Evaluation the Influence of Catalysts and Allyl Sources for the C5-Allylation of 8-Aminoquinolines[a,b]

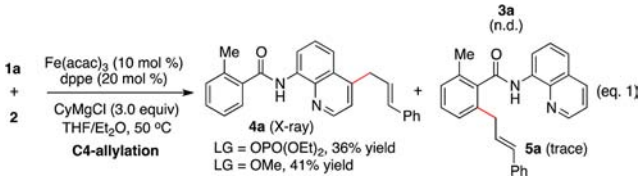


entry	LG	catalyst	yield of **3a** (%)	recovery of **1a** (%)
1[c]	OH (**2a**)	$[Ru(p\text{-cymene})Cl_2]_2$ $AgSbF_6$	53	35
2	OH	$AgSbF_6$	50	36
3	OH	$Cu(OTf)_2$	53	40
4	OH	$Ni(OTf)_2$	40	47
5	OH	$Fe(OTf)_2$	40	49
6	OH	$FeCl_3$	62	28
7	OH	$Fe(acac)_3$	trace	90
8	OH	$FeCl_2$	trace	91
9	OMe	$FeCl_3$	57	30
10	OAc	$FeCl_3$	65	26
11	OCO_2-*t*-Bu	$FeCl_3$	65	28
12	$OPO(OEt)_2$	$FeCl_3$	40	38

[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.6 mmol), catalyst (0.02 mmol), DCE (1.0 mL), 140 °C, 30 h. [b]Isolated yield. [c]$[Ru(p\text{-cymene})Cl_2]_2$ (2.5 mol %) and $AgSbF_6$ (10 mol %) were used.

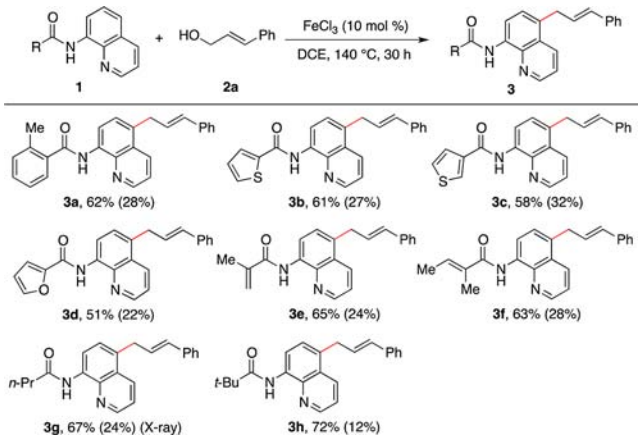
find that a C5-position allylated quinoline **3a** was formed as a single product (entry 1). Interestingly, without the Ru salt, the transformation also takes place smoothly (entry 2). At this stage, we assumed that $AgSbF_6$ could serve as a Lewis acid in promoting the transformation. Indeed, It was found that other Lewis acids such as $Cu(OTf)_2$, $Ni(OTf)_2$, and $Fe(OTf)_2$ enable improvement of the conversion (entries 3−5). Note that the use of a stronger Lewis acid of $FeCl_3$ gives a better result, providing 5-allylquinoline **3a** in good yield with complete regio- and stereoselectivity (entry 6). However, the formation of **3a** in trace amounts was observed using $Fe(acac)_3$ and $FeCl_2$ (entries 7 and 8).

Further screening showed that allyl acetate, carbonate and phosphate are suitable partners in the reaction (entries 10−13). Because of the easily accessible advantage and yielding water as a side product in the conversion, allyl alcohols were chosen as allyl electrophiles to probe the substrate scope. Interestingly, when the reaction was conducted with a low-valent iron catalytic system, the C4-allylation product **4a** was generated in combination with trace amount of *ortho*-selective α-compound **5a** (eq 1). This result is distinctive for the iron-catalyzed *ortho*-C−H allylation for the synthesis of γ-allylarenes that was disclosed by Nakamura's group.[10]



Next, we probed the influence of 8-amido scaffolds on the C−H allylation of quinolines (Scheme 3). Replacement of the aryl

Scheme 3. Influence of 8-Amido Groups on C−H Allylation[a,b]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.6 mmol), $FeCl_3$ (0.02 mmol), DCE (1 mL), 140 °C, 30 h. [b]Isolated yield. The number in parentheses is the yield of the recovered starting carboxamide.

with the thienyl and furanyl groups has only a negligible effect on the transformation (**3b−d**). A functional alkenyl moiety can be successfully incorporated into the structural motifs of the resulting allylquinolines (**3e** and **3f**). Interestingly, as compared with the related aromatic substituent-containing carboxamides, the use of alkyl-substituted substrates gives the better performance in the conversion (**3g** and **3h**).

Further exploration of the scope of quinolines revealed that the employment of *N*-methyl-protected carboxamide **6** fails to afford the allylated product, implying that the proton on the amido scaffold is indispensable for the improvement of the conversion (Figure 1). In particular, we found that *N*-(1-naphthyl)carboxamide and quinoline cannot give rise to the desired allylquinolines. This result indicates that a chelation of iron with *N*,*N*′-bidentate 8-aminoquinoline plays a predominant role in ensuring the allylation to occur effectively. Moreover, the

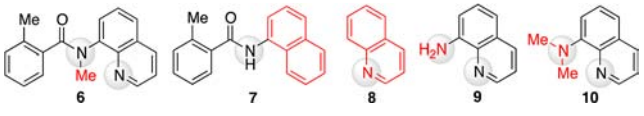


Figure 1. Ineffective substrates in the Fe-catalyzed C5-allylation.

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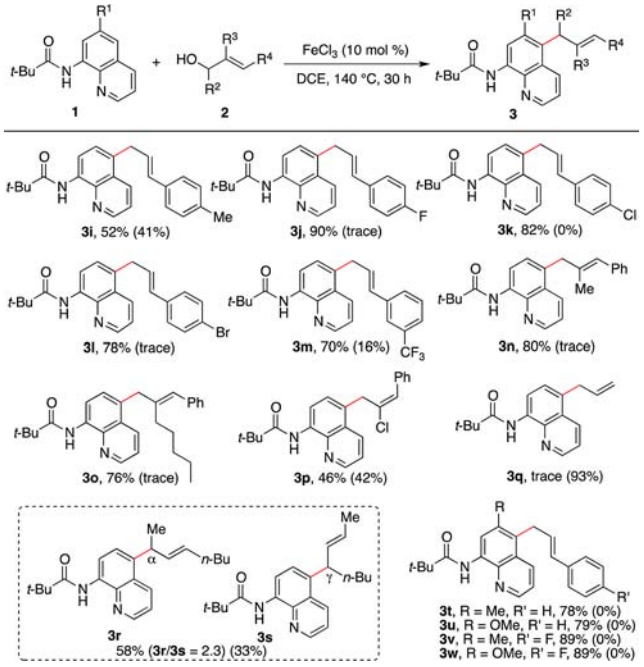
installation of electron-rich substituents such as amino and dimethylamino groups at the C8 position of quinolines hampers the conversion (**9** and **10**), suggesting that a traditional Friedel–Crafts reaction pathway by the formation of an aromatic cation may be excluded in the mechanism.

The variation of substituents on the allyl alcohols was then investigated (Scheme 4). As expected, electron-rich *p*-methyl-

Scheme 4. Iron-Catalyzed C5-Allylation of Quinolines[a,b]

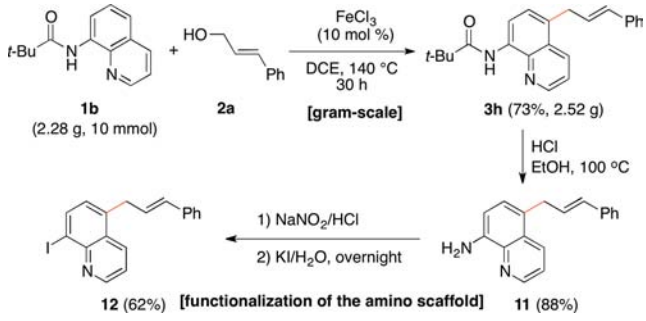


[a]Reaction conditions: **1** (0.2 mmol), **2** (0.6 mmol), $FeCl_3$ (0.02 mmol), DCE (1 mL), 140 °C, 30 h. [b]Isolated yield. The number in parentheses is the yield of the recovered starting carboxamide.

substituted cinnamyl alcohol can be employed in the allylation (**3i**). Notably, substitution of the methyl group with the electron-withdrawing fluoride remarkable accelerates the conversion, leading to the desired allylquinoline **3j** in excellent yield (90%). This result indicates that the transformation is sensitive to the substituents on the allyl scaffolds, while electron-withdrawing groups may favor the conversion due to the facilely generation of an π-allyl species with iron. Functional groups such as chloride, bromide, and trifluoromethyl are well tolerated by the reaction system (**3k–m**). 2,3-Disubstituted allyl alcohols have been shown to be suitable partners in the allylation (**3n–p**). However, simple allyl alcohol is inefficient in the reaction (**3q**). Meanwhile, the use of other simple allylic oxygens such as allyl phenyl ether, acetate, carbonates and phosphate also give the C5-allylated quinoline **3q** in trace amounts (see the Supporting Information for details). Interestingly, 3-octen-2-ol furnishes mixed α- and γ-selective coupling products **3r** and **3s**, which are thought to be generated from two different S_E2 and S_E2' pathways toward the nucleophilic attack.[18] In particular, the installation of sterically hindered methyl and methoxy group at the C6-site of quinolines has no obvious influence on reactivity and regioselectivity, giving rise to the 5-allylquinolines in good yields (**3t–w**). It is worth mentioning that the C–H allylation proceeds with complete stereoselectivity, and no relevant isomerization of the double bond to vinylquinoline derivatives was observed in these cases.

Encouraged by these results, we turned our attention to probing the postsynthetic functionalization of the amido scaffold on the resulting allylated quinolines (Scheme 5). The C–H

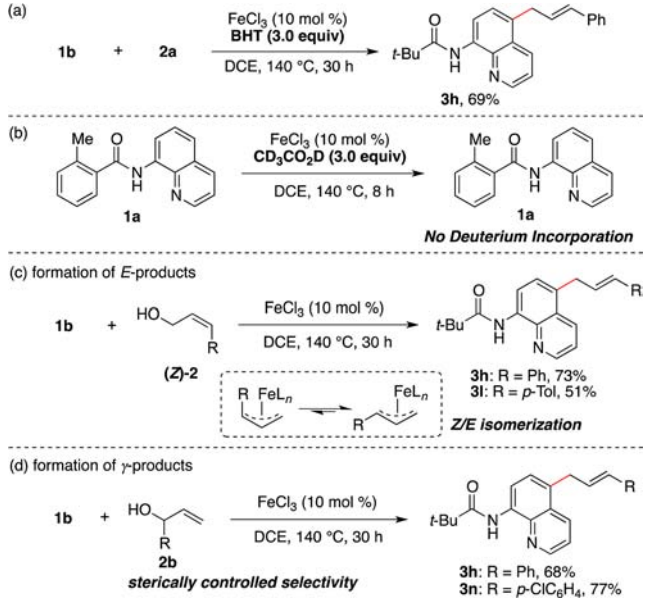
Scheme 5. Gram-Scale C–H Allylation of 1b and Synthetic Applications



allylation reaction was successfully conducted on gram scale, giving quantities of the desired 5-allylquinoline **3h** in 73% yield. Importantly, the amido scaffold on the allylated product enables facile undergoing a hydrolysis leading to the corresponding amino moiety, which was successfully converted to the synthetically useful iodo substituent via a consecutive diazotization and iodination.

As shown in Scheme 6a, the C5-allylation still carries out smoothly when the addition of 2,4-di-*tert*-butyl-4-methylphenol

Scheme 6. Mechanistic Insights



(BHT) into the catalytic system, implying that a SET pathway is less feasible in the transformation. Because no deuterium was detected by the treatment of **1a** with $FeCl_3$ and CD_3CO_2D, an irreversible C–H cleavage can be considered for the allylation (Scheme 6b). In particular, the formation of *E*-products was observed starting from *Z*-allyl alcohols, suggesting that an (π-allyl)iron species can be involved in the reaction via an isomerization to form *E*-products (Scheme 6c). In contrast with giving α-products from primary alcohols, secondary allyl alcohols **2b** lead to γ-selective linear allylquinolines, showing a sterically controlled site selectivity for the nucleophilic attack to

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the allyl alcohols (Scheme 6d). As to the low-valent Fe-catalyzed C4-allylation of quinolines, it was found that the ligands heavily influence the transformation (see the Supporting Information for more details). Unlike the Fe-catalyzed *o*-C−H allylation described by Nakamura,[10] the employment of 1,2-bis(diphenylphosphino)ethane (dppe) gives a better performance, and a zinc reagent, TMEDA·$ZnCl_2$, is not required for improving the conversion. These two factors may be responsible for the achieving a distinct C4-site-selectivity of quinolines. Meanwhile, $Fe(acac)_3$ is superior to $Fe(acac)_2$ and $Fe(OTf)_2$ in the transformation, whereas no allylated product was detected by use of $FeCl_2$.

In summary, chelation-induced reaction design has extended C−H allylation to quinoline frameworks. This iron-catalyzed, 8-amido-enabled procedure allows regiospecific C−H bonds on the quinolines to site selectively couple with allyl alcohols. It provides a controllable route for the C−H functionalization at the C5 or the C4-position of quinoline scaffolds that has rarely been explored and enables highly selectivity and scalable access to allylated quinoline derivatives using low-cost, readily available iron catalyst. Further efforts will be focused on the isolation of active intermediates and expanding the application in target-oriented molecule synthesis.

■ ASSOCIATED CONTENT

Supporting Information

Detailed optimization data; experimental procedures; characterization data of all new compounds; ORTEP drawing of **3g** and **4a**; and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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