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Oxidation of the inert sp^3 C–H bonds of tetrahydroisoquinolines through C–H activation relay (CHAR): construction of functionalized isoquinolin-1-ones†

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A TBN/O_2-initiated oxidation of the relatively inert 3,4-C–H bonds of THIQs was accomplished, in which the existence of an α-phosphoric ester group is crucial to enable dioxygen trapping and intramolecular HAT (C–H activation relay, CHAR), realizing the synthesis of a series of isoquinolin-1-ones in high yields. The mechanistic study confirmed that the formation of the 3,4-double bond is mediated by the CHAR process. This work provides a new strategy to achieve remote C–H bond activation.

Recently, direct functionalization of C–H bonds has constituted a promising atom- and step-economic strategy for the rapid construction of complex and functionalized compounds.[1,2] However, due to their inherently low reactivity, activation of the inactive sp^3 C–H bonds remains a big challenge. As an effective supplement to transition-metal catalysis, free radical reactions show broad prospects in sp^3 C–H bond activation and have been a focus of various research studies, which have established numerous elegant methodologies.[2–4] With the deepening research, organic chemists have not been content with activation of the relatively active sp^3 C–H bonds, such as the C–H bonds adjacent to nitrogen or oxygen atoms, and the activation of inactive and remote C–H bonds through intramolecular hydrogen-atom transfer (HAT) has attracted great attention.[4]

It is well known that the considerable difference in bond dissociation energies (BDE) between the starting materials and the products is one of the most important driving forces of radical reactions.[5] Therefore, heteroatom-centered radicals must be initially generated to trigger further remote C–H functionalization by intramolecular HAT (Fig. 1, eqn (1)).[6] However, either harsh reaction conditions or prefunctionalized starting materials are needed to generate the heteroatom-centered radicals, which restricts the wide application of intramolecular HAT. So we questioned whether a carbon-centered free radical could be generated through oxidation of the active C–H bond under mild conditions, followed by intramolecular HAT to propagate further functionalization of the inert C–H bond. However, a challenge exists. The radical intermediate derived from oxidation of the active C–H bond is commonly more stable than that from the inert position; therefore, this process is generally unfavorable. However, in the presence of O_2, the coupling between dioxygen and the radical center could generate a peroxide radical (with rate constant of about 10^9 M^{-1} s^{-1}) to initiate further intramolecular HAT.[5a] With this strategy, named C–H activation relay (**CHAR**), we reported isatin synthesis by the aerobic oxidation of glycine esters in 2016, in which the relatively inert C–H bond is activated through the **CHAR** process.[7] We think that this strategy might be a new way to realize remote C–H bond activation under mild conditions (Fig. 1, eqn (2)).

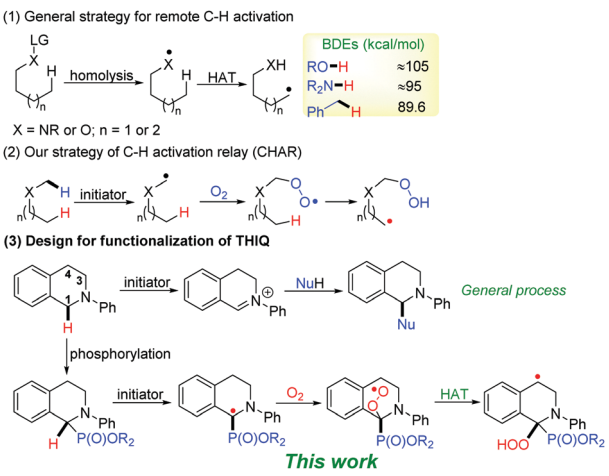

Fig. 1 Strategies for C–H activation relay.

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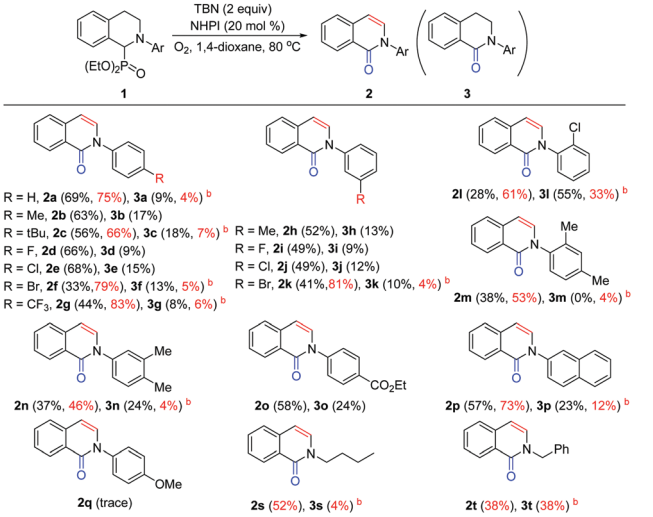
According to our previous research,[7,8] substrates suitable for **CHAR** should meet several criteria: (1) at least one C–H bond in the substrate should be active enough to be oxidized to a radical under mild conditions; (2) the generated radical should be stabilized to couple with dioxygen and not easily oxidized to a carbocation; (3) the product should be as stable as possible to provide sufficient driving force. Based on these considerations, the functionalization of tetrahydroisoquinolines (THIQ) aroused our interest. In the past decade, THIQs, as a kind of model substrate, have been studied widely.[9,10] However, most research concentrated on functionalization of the C–H bond adjacent to nitrogen (1-position), and the oxidation of C–H bonds on the 3- or 4-position still remains unprecedented. From the literature, we know that under mild conditions, a radical center could be generated on the 1-position and captured by dioxygen to provide the desired peroxide radical. However, the existence of α-H and the relatively electron-rich nature will accelerate generation of the iminium intermediate through secondary electron transfer or elimination of a peroxide, which will intercept the designed HAT (Fig. 1, eqn (3)). So we reasoned that if an electron-withdrawing group is installed on 1-position, on one hand, the radical intermediate would be further stabilized by captodative effect, and on the other hand, the formation of iminium intermediate would be inhibited, for the electron-withdrawing group will destabilize the electron-poor carbocation intermediate. If so, the desired HAT might occur and achieve functionalization of the C–H bonds on the 3- and 4-positions. Considering the availability of the starting material, we decided to perform the reaction of an α-phosphorylated THIQ to test our design.

At the outset, the aerobic oxidation of **1a** was chosen as a model reaction to optimize the reaction conditions, and the results are provided in (ESI†). The results show that using TBN (*tert*-butylnitrite)/O_2 as the catalyst system,[11,12] the expected product **2a** was afforded in 69% isolated yield, although the direct oxidative Wittig reaction is inevitable, giving the corresponding amide **3a** in 9% yield (Scheme 1).[12,13]

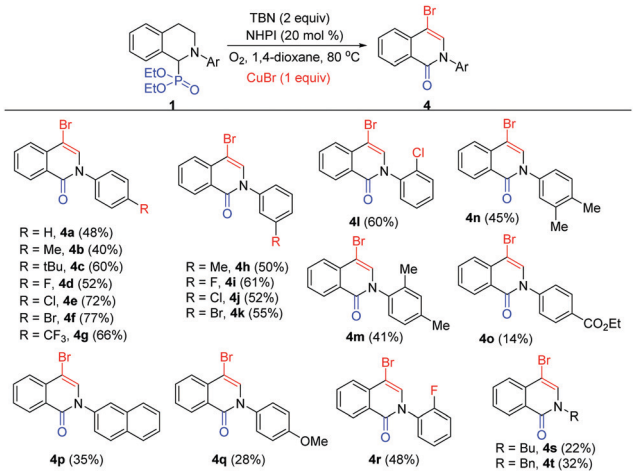
With the best reaction conditions established, various substituted THIQs were evaluated. The alkyl electron-donating groups, such as methyl and *tert*-butyl, enhanced the conjugation between the lone-pair electrons on nitrogen and the radical intermediate, giving the desired products in higher yields, although the direct oxidative Wittig reaction was also inevitable (**2a–2c**). The reaction efficiency was reduced by electron-withdrawing groups, and the isoquinolin-1-ones were obtained in lower yields (**2d–2g**). The substituents on *meta*-position could also be tolerated in this reaction, providing the expected products in acceptable yields (**2h–2k**). In the existence of *ortho*-groups, the intramolecular HAT process was partly inhibited, and the undesired **3l** was obtained in 55% yield. Although no **3m** was detected in the case of **1m**, the yield of the desired product **2m** was also lower. The reaction of 3,4-dimethyl THIQ gave **2n** in comparable yield, with poor selectivity. The substrates with ester and naphthyl groups were also suitable in this reaction, affording the corresponding products in moderate yields (**2o–2p**). When the methoxyl group was connected on



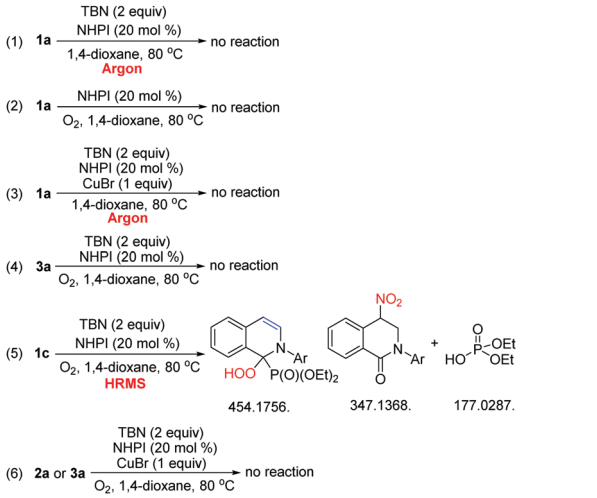
Scheme 1 Substrate scope of THIQs for the formation of isoquinolin-1-ones.[a] [a] Reaction conditions: **1** (0.5 mmol), TBN (1 mmol), NHPI (20 mol%), 1,4-dioxane (5 mL), 80 °C under O2 for 24 h, isolated yield. [b] The yields highlighted in red were obtained in the presence of 2 equivalents of TEMPO instead of NHPI.

the phenyl ring, the reaction became messy, and only trace amount of the desired product was detected (**2q**). Although the exact reason remains unknown, it is attributed to the oxidative deprotection of the *N*-PMP group, leading to the complicated side-reactions. The reactions of *N*-alkyl THIQs were also tested, and the desired products **2s** and **2t** were obtained in 52% and 38% yields, respectively. These results show that even in the absence of *N*-aryl groups, which are beneficial to stabilizing the generated radical intermediates, the current catalyst system can be applied to more general substrates. Overall, the desired reaction was mainly intercepted by the direct oxidative Wittig reaction, and reinforcing the intramolecular HAT is crucial to increase the reaction efficiency. Fortunately, we accidentally found that the addition of a stoichiometric amount of TEMPO can efficiently increase the yield of product **2** (catalytic amount of TEMPO is not beneficial to the reaction, see ESI†). Therefore, using **1c** as the model substrate, the effect of TEMPO was studied, and when the amount of TEMPO was increased to 2 equivalents, selectivity was obviously improved (for details, see ESI†). Then, some representative examples were tested in the presence of 2 equivalents of TEMPO, and in most cases, the reaction efficiency was improved dramatically (highlighted in red, Scheme 1). Although the exact reason remains unknown, the existence of TEMPO at high concentration might accelerate formation of the C=C double bond, providing sufficient driving force for the desired HAT.[14]

Encouraged by the success of 3,4-functionalization of THIQs, we decided to introduce more functional groups on the 3- or 4-position to provide platforms for later modification. In 2018, Yan and co-workers reported an interesting synthesis of 4-bromo-1,2-dihydroisoquinolines through a copper-catalyzed atom-transfer process.[15] Inspired by this work, the model reaction of **1c** was performed in the presence of copper catalyst, and as our design, the 4-bromodihydroisoquinolin-1-one



Scheme 2 Substrate scope of THIQs for the formation of 4-bromoisoquinolin-1-ones.[a] [a] Reaction conditions: **1** (0.5 mmol), TBN (1 mmol), NHPI (20 mol%), CuBr (1 equiv.), 1,4-dioxane (5 mL), 80 °C under O_2 for 24 h, isolated yield.



Scheme 3 Control experiments.

4c was obtained through copper-catalyzed atom-transfer reaction.[16] After optimization of the reaction conditions (see ESI†), the results showed that 20 mol% of NHPI is sufficient to give the desired product **4c** in 60% yield (Scheme 2). It is worth noting that CuBr might accelerate the formation of the desired product, and no direct oxidative Wittig product **3c** was detected.

Then, the reactions of various substrates were tested (Scheme 2). Overall, both electron-donating and -withdrawing groups are well tolerated in this reaction, providing the desired products in acceptable yields (**4a–4g**). The substituents on *meta*- and *ortho*-positions did not affect the reaction efficiency, and the HAT proceeded smoothly to yield the 4-bromodihydroisoquinolin-1-ones (**4h–4n** and **4r**). The ester group reduced the reaction efficiency, giving the expected product in low yield (**4o**). The electron-rich aryl groups were also tolerated in this reaction, and the corresponding isoquinolin-1-ones were isolated in moderate yields (**4p–4q**). This reaction could also be applied to the *N*-alkyl THIQs (**4s–4t**), albeit the yields of the desired products were lower.

To uncover the details of the reaction mechanism, several control experiments were performed (Scheme 3). In the absence of dioxygen and TBN, respectively, no reaction occurred even in the presence of CuBr (eqn (1)–(3)), which suggested that dioxygen and TBN are both crucial to initiate this C–H functionalization. Using **3a** as the starting material, no reaction occurred under the standard conditions, indicating that **3a** is not the intermediate, and intramolecular HAT is the key process to realize functionalization of the 3,4-C–H bonds (eqn (4)). To observe the reaction intermediates, the reaction mixture was detected by HRMS, and several important species were confirmed to be involved in the reaction process (eqn (5)). The existence of the peroxide intermediate implied the participation of HAT process in functionalization of the 3,4-C–H bonds. Under TBN-initiated reaction conditions, nitro radical, as a persistent radical, will exist inevitably;[11,12] therefore, a nitrated intermediate was observed by HRMS, suggesting that after the HAT, a carbon-centered radical **E** (see ESI†) was formed. In addition, the oxidative Wittig reaction leading to the formation of the carbonyl group was also confirmed by the existence of the corresponding phosphate. For the bromination reaction, the reactions of **2a** and **3a** were conducted under the standard conditions, respectively; however, no reaction occurred (eqn (6)). These results showed that **2** and **3** are not the intermediates, and the bromination process is prior to the formation of 3,4-double bond. Based on these results and the literature precedents,[10–12] a radical-mediated mechanism was proposed (see ESI†).

In summary, using TBN/O_2 as the catalyst system, an unprecedented C–H bond functionalization of THIQ was developed through C–H activation relay process, synthesizing a series of dihydroisoquinolin-1-ones and 4-bromodihydroisoquinolin-1-ones. According to the mechanistic study, dioxygen trapping and further intramolecular HAT process (**CHAR**) are key steps to realize the functionalization of C–H bonds on the 3- and 4-positions. This **CHAR** strategy successfully avoids the use of prefunctionalized starting material to generate heteroatom-centered free radicals, accomplishing the shift of radical center from the active position to the inert position. We believe that **CHAR** might provide a useful way to accomplish remote C–H bond activation. However, it should be confessed that the direct Wittig reaction seriously affected the reaction efficiency, and the introduction of phosphate ester group is far from the best choice to implement the **CHAR** strategy. Further screening of the α-substituents, attempts to construct more complicated structures, and mechanistic studies are still underway in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

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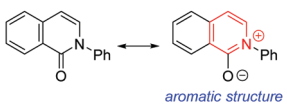
14 The aromaticity of the products might provide a strong driving force to the oxidation of 3,4-C–H bonds.



aromatic structure

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