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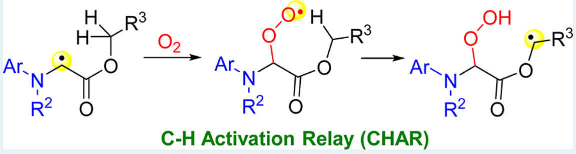
C−H Activation Relay (CHAR): An Efficient Construction of Isatin Skeleton by Aerobic Oxidation of Glycine Esters

Xiaodong Jia,*[†,‡] Yingzu Zhu,[‡] Yu Yuan,[†] Xuewen Zhang,[†] Shiwei Lü,[‡] Liang Zhang,[‡] and Liangliang Luo[‡]

[†]College of Chemistry and Chemical Engineering, Yangzhou University, Yangzhou, Jiangsu 225002, China
[‡]College of Chemistry and Chemical Engineering, Northwest Normal University, Lanzhou, Gansu 730070, China

Supporting Information

ABSTRACT: Directed by the strategy of C−H activation relay (CHAR), an efficient construction of isatin skeleton was developed through catalytic oxidation of glycine esters. The mechanistic study reveals that the oxidation of the relatively active C−H bonds initiated the followed activation of remote and inert C−H bonds, and an intramolecular 1,6-hydrogen shift was involved as a key step.



KEYWORDS: *C−H activation, aerobic oxidation, glycine ester, isatin, 1,6-hydrogen shift*

The ubiquitous and diverse nature of C−H bonds in complex organic compounds makes C−H bond activation an attractive approach to C−C and C−X bonds, providing some novel synthetic disconnections for constructions of organic molecules.[1−3] However, due to their relatively inert nature, the selective activation and functionalization of C−H bonds is still a challenge in organic synthesis. Beside sp^2 C−H activation,[2] which was mainly conducted through the use of transition-metal-mediated reactions, activation of sp^3 C−H bonds is a tougher task.[3,4] Generally, by transition-metal-promoted transformations, the existence of an appropriate directing group is crucial to achieve activity and selectivity control, and great improvements have been achieved in the past decade.[3]

Another method to promote sp^3 C−H activation is through a free-radical-mediated process. The high bond energy of sp^3 C−H bonds makes them difficult to break, and activating groups are needed, such as nitrogen, oxygen and so on, for the generated radical can be stabilized by the adjacent heteroatoms through the lone-pair electrons. Second, the selectivity of C−H functionalization mediated by radical processes is problematic. Due to the reactivity and selectivity, the functionalization of the C−H bonds adjacent to nitrogen, oxygen, and phenyl group has attracted extensive attention, and a variety of applicable transformations have been developed.[4] However, activation of the inert C−H bonds is still a great problem.

It is well-known that the intramolecular 1,5- or 1,6-hydrogen atom shift, which undergoes a six- and seven-membered ring, respectively, is a common process in radical chemistry, and in some cases, was used in functionalization of remote and inert C−H bonds.[5] So we wondered whether we can initially generate a radical on an active position and then trigger the remote and inactive C−H functionalization through intramolecular hydrogen atom abstraction, which was named C−H activation relay (CHAR, Figure 1, eq 1). It will be a new way to achieve C−H activation and selectivity control.

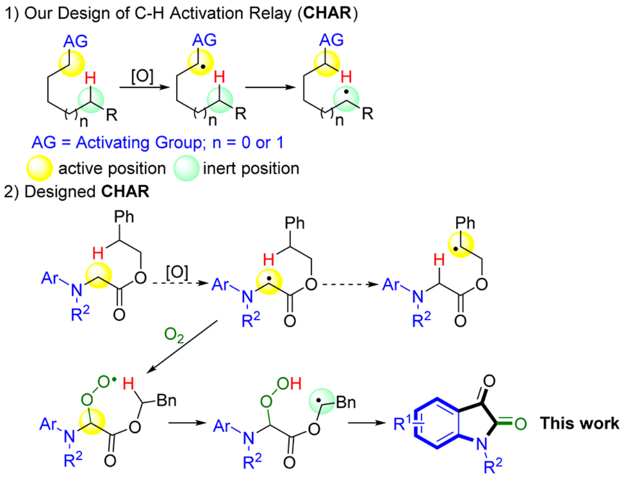


Figure 1. Design of C−H activation relay (CHAR).

In recent years, our group has developed several related methodologies using *N*-arylglycine derivatives, building a series of heterocyclic structures.[6] In these investigations, we found that the C−H bonds adjacent to nitrogen in *N*-glycine are reactive and easy to be oxidized to the corresponding radicals or iminiums. So we speculate whether this active position could act as the first runner in a relay-race, launching further C−H oxidation. Then, phenethyl *N*-methyl-*N*-phenylglycinate was designed to test the possibility of CHAR (Figure 1, eq 2). Different from our initial design, an isatin product was detected, which means that not only the C−H bonds adjacent to nitrogen but also the C−H and C−O bonds in ester were activated. After evaluation of the reaction mechanism, we found that after

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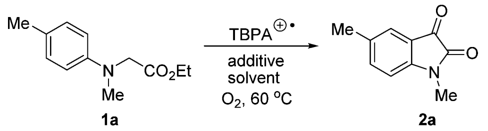
oxidation of *N*-arylglycine ester, a radical intermediate is generated, which is trapped by dioxygen. Then an intramolecular 1,6-H shift occurs via 7-membered transition state (CHAR). This process is preferred, for the driving force of this H-shift from the inert sp^3 C−H bonds is the formation of a stronger O−H bond (about 103 kcal/mol) than C−H bond (about 96 kcal/mol) in alkyl groups.[7] Encouraged by this promising result, we tried the more accessible substrate, ethyl *N*-arylglycinate (**1a**), and to our delight, the isatin was isolated in 57% yield (Table 1, entry 1).

Table 1. Optimization of Reaction Conditions[a]



entry	initiator (mol %)	additive (mol %)	solvent	time (h)	yield (%)[b]
1	10	no	CH_3CN	78	57
2	20	no	CH_3CN	52	73
3	30	no	CH_3CN	28	82
4	CAN[c]	no	CH_3CN	24	13
5	TBHP[c]	no	CH_3CN	48	n.d.
6	30	$InCl_3$ (10)	CH_3CN	52	90
7	30	$FeCl_3$ (10)	CH_3CN	120	trace
8	30	TFA (10)	CH_3CN	20	75
9	30	$InCl_3$ (10)	DCM	79	87
10	30	$InCl_3$ (10)	DCE	29	58
11	30	$InCl_3$ (10)	THF	29	14
12	10	no	MeOPh	50	95
13	10	no	MeOPh	60	trace[d]
14	TDBPA$^{+\cdot}$	no	MeOPh	50	65

[a] Unless otherwise specified, the reaction was carried out with **1a** (0.1 mmol) in the presence of TBPA$^{+\cdot}$ and anhydrous solvent (1.0 mL); [b] Yield of crude product ^{1}HNMR using 1,3,5-trimethoxylbenzene as internal standard; [c] 1 equivalent of the oxidant was used; [d] The reaction was performed under argon.

Although the first synthesis of isatin could be traced back to 1840,[8] the construction of isatin motif still attracted extensive attentions, and some newly improved protocols have been developed.[9−12] However, some limitations also exist in these efficient approaches, such as inaccessible starting materials, harsh reaction conditions, expensive reagents, and narrow substrate scope. Therefore, the synthesis of structurally diverse isatins through more simple and applicable methods is still highly desirable. Herein, we demonstrate a radical cation salt initiated CHAR to give isatins in good yields.

Our efforts toward this CHAR to isatins initially focused on intramolecular cyclization of *N*-aryl-*N*-methylglycinate (Table 1). Under tris(4-bromophenyl)aminium hexachloroanti-monate (TBPA$^{+\cdot}$)-induced conditions, the desired isatin was obtained in 57% yield after 78 h (Table 1, entry 1). This encouraging result prompted us to optimize the reaction conditions further. It was found that the loading of the initiator exerts an important impact on the outcome of this transformation. Higher catalyst loading led to better yields and shorter reaction time (entries 2−3). Evaluation of other initiators show that TBPA$^{+\cdot}$ is more efficient to promote the aerobic oxidation (entries 4 and 5). To further increase the reaction efficiency, some additives were tested. Addition of $InCl_3$ exerts positive effect on the reaction, and the yield of the desired isatin increased to 90% at the cost of elongated reaction time (entry 6). Various solvents, such as DCM, DCE, THF, were then examined (entries 9−11), and MeCN is still the best solvent. Interestingly, we found that anisole is an excellent solvent in this transformation, which is superior in yield, catalyst loading, and reaction time (compare entry 12 with entry 1). Although the exact reason remains unknown, the electron-rich nature of anisole might be beneficial for stabilizing the electron-deficient intermediate. In the absence of dioxygen, no desired product was detected, and the starting material was recovered in 95% yield, implying that O_2 is crucial to oxidation of the sp^3 C−H bonds (entry 13). More oxidizing tris(2,4-dibromophenyl)amine radical cation (TDBPA$^{+\cdot}$, entry 14) was also tested, and the desired product **2a** was isolated in lower yield (65%) together with some unidentified byproducts. It is attributed that the stronger radical cation would result in some undesired side reactions. So we chose TBPA$^{+\cdot}$ (10 mol %) and O_2 in anisole as the optimized conditions.

With the best conditions established, the scope of substituted glycine esters was investigated. First, the substituent effect on anilines was examined, and the results were compiled in Scheme 1. Electron-donating groups enhanced the reaction efficiency, giving the desired products in good to excellent yields (**2a** to **2c**). Slightly lower yields were obtained, when electron-withdrawing groups were connected (**2d** to **2f**). However, if strong EWGs (NO_2, CF_3, and CO_2Me) were introduced, the reaction efficiency was reduced dramatically, and only a trace amount of products were detected (not shown in Scheme 1). The reason was attributed to the fact that the conjugation between the lone pair electrons of nitrogen and the generated radical is weakened. These results supported our hypothesis that the oxidation of the active C−H bond enabled the subsequent C−H bond activation. Then we investigated the substrate scope with respect to the *N*-groups. Straight *N*-groups do not affect the reaction, giving isatin in high yields (**2g** to **2l**). Bulky groups such as the *iso*-butyl, cyclohexylmethyl, and neopentyl analogues performed as well in good to excellent yields under the optimized conditions, and the isatin products were isolated in 90% (**2m**), 80% (**2n**), and 86% (**2o**) yields, respectively. The efficiency of this reaction was not decreased, when the diethyl diacetate was employed, providing the desired products in 71% yields (**2p**). In accord with the reported results, the absence of *para*-groups would reduce the yields of the desired products significantly (**2q** and **2r**).[6,13]

To test the selectivity of CHAR, phenethyl group was installed on nitrogen, which has another active benzyl position that might disturb the expected 1,6-H shift process (Scheme 2, upper). The reaction became complicated, and only a trace of the desired product **2t** was detected. It is attributed to the fact that the 1,6-H shift on the benzylic C−H bonds might compete with the desired process. To enhance the desired 1,6-H shift, benzyl ester was subjected to standard oxidation conditions, and the reaction occurred smoothly, yielding the desired products in 67% yields (**2t**). A similar result was obtained in the synthesis of *N*-cyclopropyl isatin (Scheme 1, **2s**). As we know, 1,5-H shift, which mediated by six-membered ring, is faster than 1,6-H shift.[8] So we designed an ethyl *N*-benzylglycinate (**1u**) to test the competition of 1,5- and 1,6-H shift (Scheme 2, lower). As expected, the former process was totally disturbed, and the reaction became complicated, yielding the desired isatin in only 19% yield together with a variety of unidentified compounds. When benzyl ester was employed, the expected process was enhanced, providing **2u** in 81% yield. The reason for this finding is that the introduction of the phenyl group could increase the activity of the C−H bonds adjacent to oxygen and further stabilize the generated radical intermediate.

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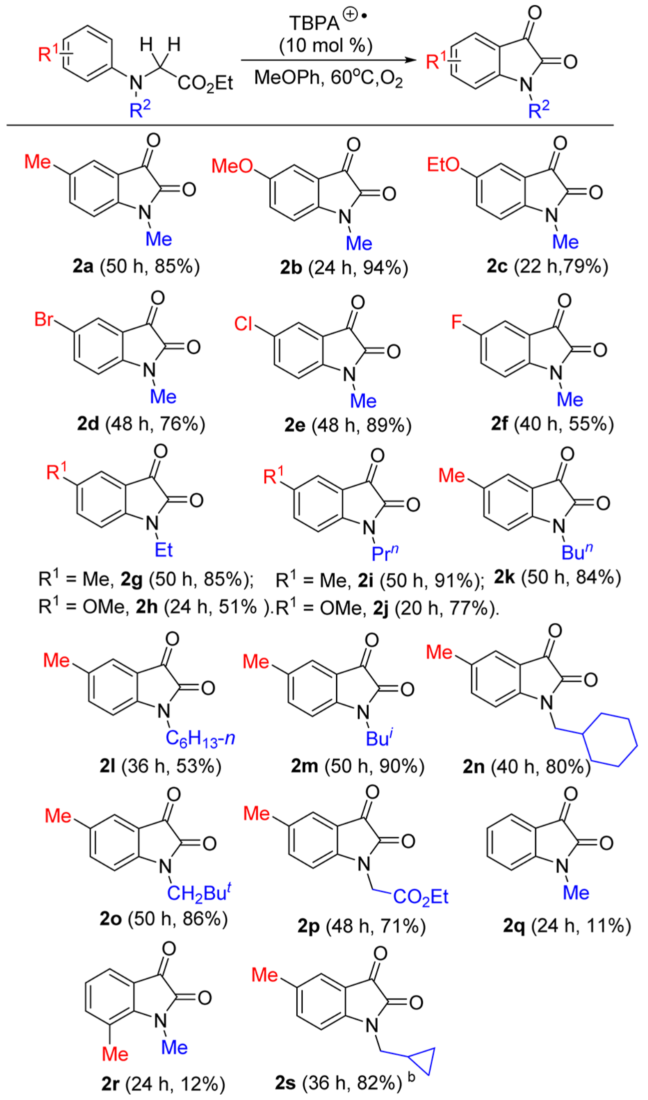
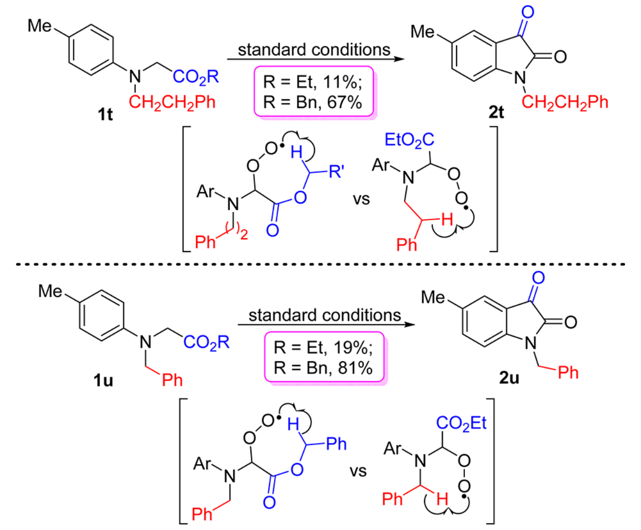
Scheme 1. Reaction of Alkyl *N*-Arylglycinates[a]



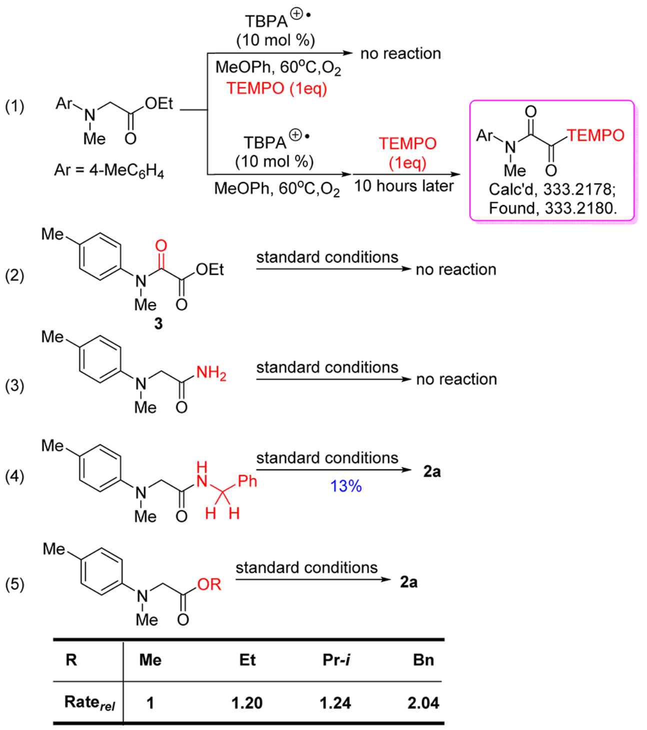
[a]Reaction conditions: **1** (1 mmol), TBPA$^{+\cdot}$ (10 mol %), anisole (5 mL), 60 °C under O$_2$, isolated yield; [b]The corresponding benzyl ester was used.

Scheme 2. Competition Reactions of Glycine Esters[a]



[a]Reaction conditions: **1** (1 mmol), TBPA$^{+\cdot}$ (10 mol %), anisole (5 mL), 60 °C under O$_2$, isolated yield.

Scheme 3. Control Experiments

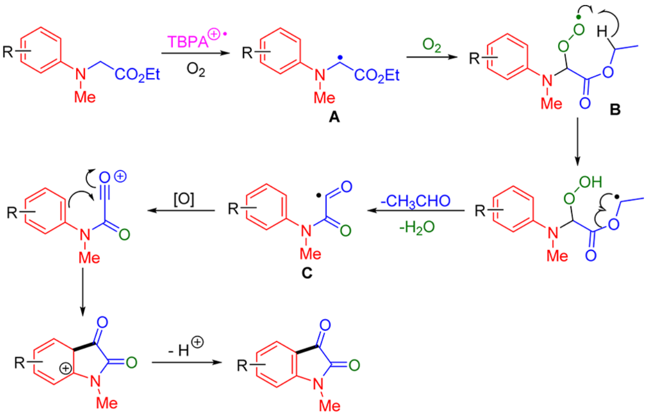


R	Me	Et	Pr-*i*	Bn
Rate$_{rel}$	1	1.20	1.24	2.04

To understand the mechanism, a series of control reactions were conducted, as shown in Scheme 3. It was found that the addition of TEMPO (1 equiv) inhibits the reaction, suggesting a single-electron-transfer pathway might be involved in this reaction (eq 1 in Scheme 3). To further confirm the involvement of radical intermediate, TEMPO (2 equiv) was added 10 h after the reaction was conducted, and then we performed HRMS experiments to detect the capture product (eq 1). We are delighted to observe the signal at m/z 333.2180 (calcd for $C_{19}H_{28}N_2O_3 + H^+$, 333.2178); this signal is related to the mass of an acyl radical trapped by TEMPO, implying that the C−O bond in ester was activated. When the corresponding benzyl ester was used, the eliminated benzaldehyde and its oxidative product, benzoic acid, were detected by chromatography−mass spectrometry. Then the standard oxidative condition was applied to **3** (eq 2), and no reaction occurred, which completely excluded the possibility of direct intramolecular Friedel−Crafts reaction of glycine ester. Glycine amide shows no reactivity (eq 3), whereas the corresponding *N*-benzylamide gave **2a** in 13% yield (eq 4). The relative rate of different esters was then measured (eq 5), and in accordance with the above observations, the benzyl esters gave the fastest rate (for details, see Supporting Information), whereas the *tert*-butyl ester gave only trace of the expected product (not shown in Scheme 3). These results show that the α-H adjacent to ester or amide is crucial to formation of isatin, which supports the existence of 1,6-H shift in this CHAR.

On the basis of the above results, a possible mechanism was proposed (Scheme 4). In the presence of dioxygen, the relatively active C−H of glycine ester is oxidized by radical cation salt,[14] yielding a radical intermediate **A**. Second, **A** is trapped by dioxygen to produce a peroxide radical **B**. After the intramolecular 1,6-H shift, the C−H bond adjacent to oxycarbonyl group is activated, followed by β-cleavage and elimination of

Scheme 4. Proposed Mechanism



water, providing an acyl radical **C**. This species is further oxidized to a carbonyl cation, and then an intramolecular Friedel−Crafts type cyclization occurs. After a proton loss and rearomatizaion, the isatin product is afforded.

In conclusion, designed by CHAR, an efficient construction of isatin skeleton was developed from accessible glycine esters. The examination of its scope shows good substrate generality and functional group tolerance. The mechanistic studies revealed that the oxidation of the relatively active C−H bonds initiates the subsequent activation of remote and inert C−H bonds. Therefore, this reaction provides a new way to achieve C−H activation and the corresponding selectivity control. Further applications of this reaction and more designs of CHAR are still underway in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.6b01781.

Experimental details and spectroscopic data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jiaxd1975@163.com.

Notes

The authors declare no competing financial interest.

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