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Direct sp^3 C–H acroleination of *N*-aryl-tetrahydroisoquinolines by merging photoredox catalysis with nucleophilic catalysis†

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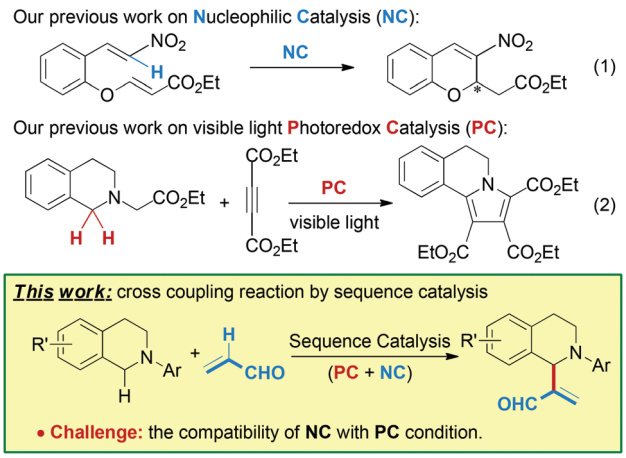
Sequence catalysis merging photoredox catalysis (PC) and nucleophilic catalysis (NC) has been realized for the direct sp^3 C–H acroleination of *N*-aryl-tetrahydroisoquinoline (THIQ). The reaction was performed under very mild conditions and afforded products in 50–91% yields. A catalytic asymmetric variant was proved to be successful with moderate enantioselectivities (up to 83 : 17 er).

The development of efficient and sustainable processes to construct new C–C bonds has attracted considerable attention from the chemical community.[1] From the viewpoint of green catalysis, visible light photoredox catalysis (PC) is an ideal complement to the conventional thermal procedures.[2,3] Particularly, sequence catalysis by merging PC with other catalytic models has become extremely powerful in direct functionalizations of inert C–H bonds.[4,5] Pioneered by the Stephenson group,[6] *N*-aryl-tetrahydroisoquinoline (THIQ) has been widely employed as the testing platform[5] to verify the feasibility of sequence catalysis (Scheme 1).[7] Notably, Rueping and coworkers have developed direct Mannich reactions of THIQs with methyl ketones by integrating PC with enamine catalysis.[5g] Since then, sequence catalysis combining PC and N-heterocyclic carbene (NHC) catalysis,[5d] H-bonding catalysis[5a] and transition metal catalysis[5e,f] have been successfully developed by the groups of Rovis, Rueping, Stephenson and Jacobsen, respectively, to install the carbonyl, alkynyl or methyl ester moiety into C–H bonds adjacent to a N-atom. Despite these impressive advances, sequence catalysis involving visible light photoredox catalysis has not achieved its full potential.

Over the past few decades, nucleophilic catalysis (NC) has grown at a dramatic pace in C–C formation reactions.[8] Encouraged by our success of both NC (eqn (1))[9] and PC (eqn (2)),[10] we recently questioned whether it might be possible to merge these two powerful catalytic models, with the goal of direct functionalization of inactive C–H bonds. Inspired by elegant work from the Wang group on the tertiary amine/copper co-catalysed oxidative olefination reaction of THIQ,[11] we chose the same transformation to test our proposal. The challenge is the compatibility of a nucleophilic catalyst under PC conditions since traditional nucleophilic catalysts (*i.e.* DABCO and PPh_3) might be oxidized in the presence of oxidative radicals (*vide infra*).



The acroleination of sp^3 C–H bonds of THIQs was evaluated using *N*-phenyl tetrahydroisoquinoline **1a** and acrolein **2a** as the substrates in the presence of different nucleophilic catalysts, photocatalysts, and oxidants (Table 1). It was found that oxidized isoquinoline, 2-phenyl-3,4-dihydroisoquinolin-1(2*H*)-one, was isolated as the major product when $Ru(bpy)_3Cl_2{\cdot}6H_2O$ (**I**) was employed as the photoredox catalyst and oxygen was used as the oxidant (Table 1, entry 1). To our delight, the proposed acroleination reaction did proceed when $BrCCl_3$ was introduced as the oxidant (Table 1, entry 2: 49% yield). To address the compatibility of nucleophilic catalysts with photoredox catalysts and oxidants, we examined the stoichiometric reaction of nucleophilic catalysts, DABCO and PPh_3, with

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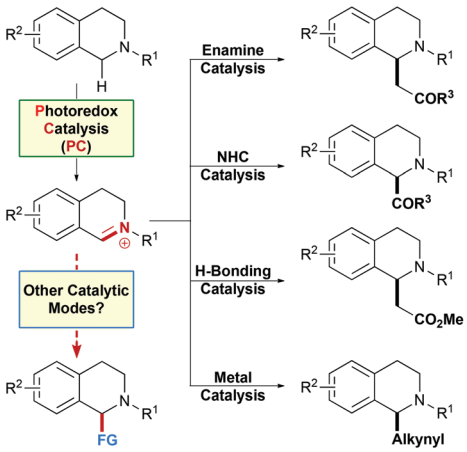


Scheme 1 Representative examples of functionalization of C–H bonds of THIQ *via* PC-based sequence catalysis.

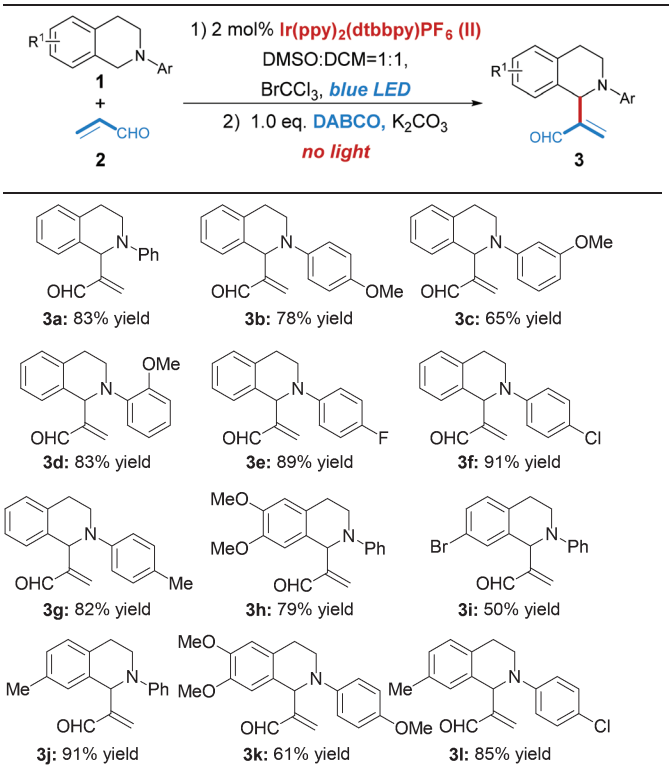
Table 1 Optimization of reaction conditions[a]

Entry	Photoredox catalyst	Nucleophilic catalyst	Oxidant	Solvent	Yield[b] (%)
1	**I**	DABCO	O_2	DMF	n.d.
2[c]	**I**	DABCO	$BrCCl_3$	DMF	49
3	**I**	DABCO	$BrCCl_3$	DMF	75
4	**I**	DBU	$BrCCl_3$	DMF	Trace
5	**I**	PPh_3	$BrCCl_3$	DMF	71
6	**II**	DABCO	$BrCCl_3$	DMF	79
7	**III**[d]	DABCO	$BrCCl_3$	DMF	11
8	**IV**[e]	DABCO	$BrCCl_3$	DMF	73
9	**II**	DABCO	$BrCCl_3$	MeCN	69
10	**II**	DABCO	$BrCCl_3$	THF	46
11	**II**	DABCO	$BrCCl_3$	DMSO	79
12	**II**	DABCO	$BrCCl_3$	DCM	79
13	**II**	**DABCO**	**$BrCCl_3$**	**DMSO–DCM = 1 : 1**	**83**

[a] Reaction conditions: **1a** (0.5 mmol), photoredox catalyst (2 mol%), $BrCCl_3$ (3.0 equiv.) in solvent (2 mL), blue LED irradiation at r.t., 3 h, then no light, **2a** (5.0 equiv.), nucleophilic catalyst (1.0 equiv.), K_2CO_3 (1.0 equiv.). [b] Yield of isolated product. [c] Reaction conditions: **1a** (0.5 mmol), photoredox catalyst (2 mol%), **2a** (5.0 equiv.), nucleophilic catalyst (1.0 equiv.), K_2CO_3 (1.0 equiv.) and oxygen (1 atm) or $BrCCl_3$ (3.0 equiv.) in DMF (2 mL) under blue LED irradiation at r.t. [d] Esion Y (**III**). [e] $Ru(bpy)_3PF_6$ (**IV**).

$BrCCl_3$ under PC conditions. The results indicated that DABCO decomposed completely in the presence of $BrCCl_3$ under irradiation of blue light, but remains unchanged without blue light. In addition, PPh_3 disappears quickly with or without the blue light irradiation. Thus, one-pot operation was applied to the designed reaction: **1a** was mixed with $BrCCl_3$ and $Ru(bpy)_3Cl_2{\cdot}6H_2O$ (**I**) to generate the iminium intermediates *in situ* under PC conditions, and then DABCO,

Table 2 Substrate scope[a]

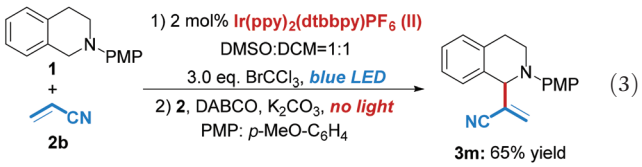


[a] Reaction conditions: **1** (0.5 mmol), $Ir(ppy)_2(dtbbpy)PF_6$ (**II**) (2 mol%), $BrCCl_3$ (3.0 equiv.) in solvent (2 mL), blue LED irradiation at r.t., 3 h, then no light, **2** (5.0 equiv.), DABCO (1.0 equiv.), K_2CO_3 (1.0 equiv.).

acid acceptor (K_2CO_3) and **2a** were added to the reaction mixture after removing blue LED irradiation.[5a,f] To our delight, by this manipulation an increased yield of product **2a** was achieved (75% yield, Table 1, entry 3). In addition, the effect of different photosensitizers and nucleophilic catalysts was explored, and the results showed that the combination of $Ir(ppy)_2(dtbbpy)PF_6$ (**II**) and DABCO was the best (Table 1, entries 4–8). To further improve the reaction efficiency, different reaction media were screened. As presented in Table 1, the reaction was applicable with a variety of different solvents such as MeCN, THF, DCM, and DMSO (entries 9–13). The use of a mixed solvent (DMSO–DCM = 1 : 1) gave the best result (83% yield, Table 1, entry 13).[12]

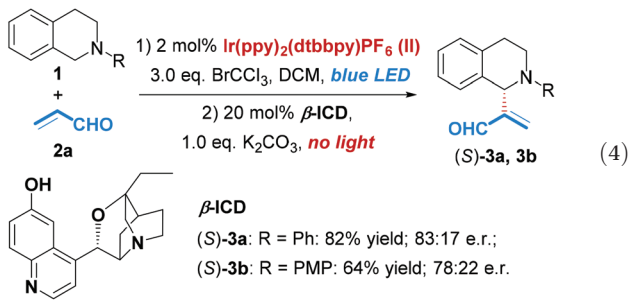
Under the optimal reaction conditions, the scope of N-substituted THIQs for this acroleination reaction was next examined. The electronic nature of the aromatic substituents on the nitrogen atom shows no pronounced effect on the overall reaction outcomes. As highlighted in Table 2, substrates bearing an electron-donating (*p*-OMe) or electron-withdrawing group (*p*-F) on the phenyl rings participate in this transformation efficiently (**3b**: 78% yield, **3e**: 89% yield). Moreover, this acroleination reaction tolerated the *o*-OMe group well (**3d**: 83% yield), which did not show a steric hindrance for the addition step. Though an undetermined by-product was isolated from the resultant mixture in the case of *m*-OMe substituted

substrate **1c**, the desired product was still obtained in a good isolated yield (**3c**: 65% yield). Incorporation of chloro and methyl substituents at the *para*-position of the *N*-phenyl group is possible without loss in reaction efficiency (**3f**: 91% yield; **3g**: 82% yield). Perhaps more importantly, significant structural variation on the tetrahydroquinoline scaffold can also be realized. A variety of substituents can be successfully incorporated on the THIQ at different positions (**3h**: 79% yield, **3i**: 50% yield, **3j**: 91% yield, **3k**: 61% yield and **3l**: 85% yield). Notably, when acrylonitrile was used instead of acrolein, the reaction could also proceed well and the desired product was obtained in 65% yield (eqn (3)).



(3)

A catalytic asymmetric acroleination has been carried out by using a chiral nucleophilic catalyst. With the use of 20 mol% β-isocupreidine (β-**ICD**) as the nucleophilic catalyst, the reaction afforded the enantioenriched (*S*)-**3a** and (*S*)-**3b** (eqn (4), **3a**: 82% yield, 83 : 17 er; **3b**: 64% yield, 78 : 22 er), respectively.



(4)

Conclusions

In summary, we have developed the first example of sequence catalysis by merging visible light photoredox catalysis and nucleophilic catalysis. This process is able to directly assemble acrolein to the sp^3 C–H at the α-position of tertiary amines in moderate to excellent yields (52–93%). The primary trial on catalytic asymmetric acroleination of THIQ was realized with moderate enantioselectivity.

Acknowledgements

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