Visible light mediated photocatalytic oxidative coupling reaction of *N*-phenyl tetrahydroisoquinoline with β-keto acids

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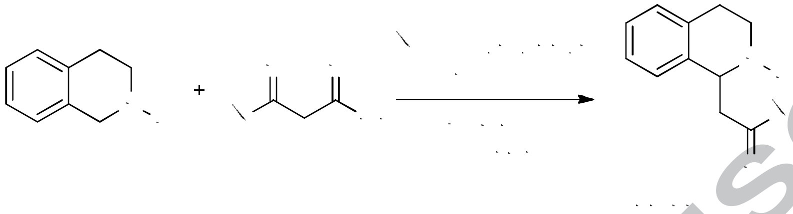

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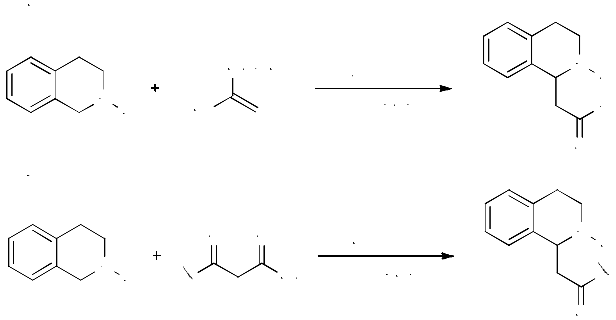
ABSTRACT

A visible light mediated photocatalytic oxidative coupling reaction of *N*-phenyl tetrahydroisoquinoline with β-keto acids has been developed. This approach provides a mild and operationally simple access to the synthesis of C1-acylmethylated tetrahydroisoquinolines.

The direct transformation of C–H into C–C bonds has recently received significant attention in the fields of organic and medicinal chemistry.[1] In particular, the direct oxidative cross-dehydrogenative coupling (CDC) of two C–H bonds can be an atom-economic and environmentally benign approach in organic synthesis.[2] Since the pioneering work on CDC demonstrated by Murahashi and Li groups on oxidative iminium formation from tetrahydroisoquinoline (THIQ) derivatives,[3] various nucleophiles have been utilized to combine the iminium intermediates to construct new C–C bonds under Mannich-type protocols.[4]

The application of visible light mediated photoredox catalysis has emerged as a novel and efficient tool for chemical transformations due to its natural abundance, mild and relatively clean reaction conditions, and high reactivity.[5] In this context, the visible-light photocatalytic C–H functionalization of α-carbon atom of an amino group became a valuable extension of conventional oxidation reactions.[6] Several groups reported the visible light photocatalytic CDC of the THIQs with aliphatic ketones and α-trifluofomethyl β-fluorinated *gem*-diol in the presence of photocatalysts.[7] Recently, the Xia group has reported visible light mediated phenacylmethylation to form C1-phenacylmethylated THIQ derivatives from the reaction of enol silanes with *N*-phenyl tetrahydroisoquinolines (Scheme 1a).[8] The decarboxylative additions of β-keto acids as of ketones or ketone enolate equivalents have received much attention.[9] However, the decarboxylative alkylation of β-keto acids to THIQs remains elusive. We envisioned the decarboxylative Mannich-type reaction of the β-keto acids to the C1-acylmethylated THIQs by visible light mediated photocatalytic CDC (Scheme 1b).

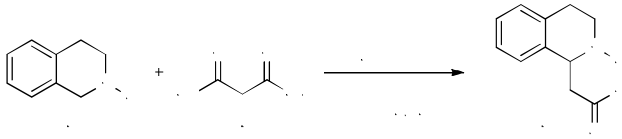
As part of a research program related to redox reaction, we recently reported the internal redox reaction via C–H bond activation[10] and photoredoxcatalytic functionalization/ring expansion.[11] In this letter, we wish to describe visible light mediated photocatalytic C1-acylmethylation of THIQs.



Scheme 1. Strategies for the visible light mediated photocatalytic phenacylmethylation of THIQs.

To determine suitable reaction conditions for the visible light mediated photocatalytic oxidative coupling reaction of THIQs, we examined the visible light mediated photocatalytic reaction of *N*-phenyl tetrahydroisoquinoline (**1**) with 3-oxo-3-phenylpropanoic acid (**2a**) in the presence of 3 mol % photocatalyst under visible light irradiation with blue LEDs (5 W, max = 455 nm) in MeOH at room temperature. By screening photocatalysts (Table 1, entries 1-6), we found that $Ru(bpy)_3Cl_2·6H_2O$ was the best photocatalyst for oxidative coupling reaction, affording the corresponding product **3a** in 83% yield (Table 1, entry 3). Among the solvents evaluated (Table 1, entries 3 and 7-14), the best result was achieved when the reaction was conducted in MeOH (Table 1, entry 3). Reducing the photocatalyst loading to 1 mol % had little influence on the yield (Table 1, entry 15). The control experiment showed that the reaction could not proceed in the absence of a photocatalyst and

Table 1. Optimization of photocatalytic oxidative coupling reaction [a]



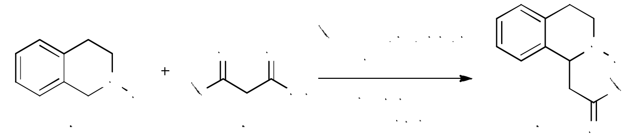
entry	photocatalyst	solvent	time (h)	yield (%)[b]
1	$Ru(bpy)_3(PF_6)_2$	MeOH	7	60
2	$Ru(phen)_3Cl_2{\cdot}H_2O$	MeOH	7	56
3	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	MeOH	7	83
4	*fac*-Ir(ppy)$_3$	MeOH	7	25
5	fluorecein	MeOH	7	15
6	eosin Y	MeOH	7	23
7	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	EtOH	10	41
8	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	*i*-PrOH	10	58
9	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	CH_3CN	15	30
10	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	DMF	15	12
11	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	DMSO	15	15
12	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	acetone	15	38
13	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	CH_2Cl_2	15	27
14	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	THF	15	29
15[c]	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	MeOH	7	82
16[d]	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	MeOH	7	35
17[e]	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	MeOH	7	0
18	-	MeOH	7	0
19	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	MeOH	7	34

[a] Reaction conditions: *N*-phenyl tetrahydroisoquinoline (**1**, 0.3 mmol), 3-oxo-3-phenylpropanoic acid (**2a**, 0.6 mmol), photocatalyst (0.009 mmol), solvent (2.0 mL) at room temperature under visible light irradiation. [b] Isolated yield. [c] 1 mol % photocatalyst loading. [d] 0.1 mol % photocatalyst loading. [e] The reaction was performed in the dark.

visible light (Table 1, entries 17-18). Under nitrogen after degassing, the reaction gave reduced yield. It is indicate that oxygen may play a role in the mechanism but is not explicitly required (Table 1, entry 19). Therefore, the optimized conditions entailed the use of 1 mol % of $Ru(bpy)_3Cl_2{\cdot}6H_2O$ as a photocatalyst in MeOH at room temperature for 7 h (Table 1, entry 15).

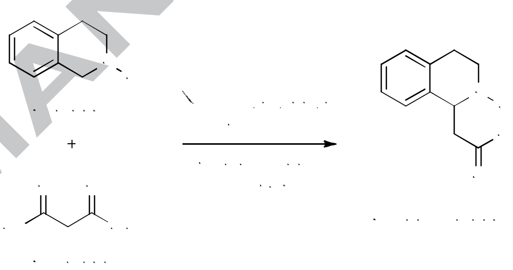
With the optimal reaction conditions in hand, we investigated the scope of this visible light mediated photocatalytic oxidative coupling reaction of *N*-phenyl tetrahydroisoquinoline (**1**) with 3-oxoalkanoic acid **2** in the presence of 1 mol % of $Ru(bpy)_3Cl_2{\cdot}6H_2O$ under light irradiation with blue LEDs in MeOH at room temperature.[12] As shown in Table 2, various 3-oxoalkanoic acid **2** with electron-withdrawing or electron-donating aryl groups furnished the corresponding migration products with moderate to good yields (65-82%, Table 2, entries 1-7). The naphthyl- and heteroaryl-substituted β-keto acids provided the desired products with high yields (75-86%, Table 2. entries 8-10). In addition, alkyl-substituted β-keto acid-like 3-oxopentanoic acid (**1k**) participated in this reaction to afford the corresponding products **3k** in 65% yield (Table 2. entry 11).

Table 2. Variation of substrates **2**[a,]



entry	2, R	time (h)	yield (%)[b]
1	Ph	7	**3a**, 82
2	4-Br,C_6H_4	7	**3b**, 82
3	4-Cl,C_6H_4	7	**3c**, 66
4	4-F,C_6H_4	7	**3d**, 78
5	4-NO_2,C_6H_4	7	**3e**, 65
6	4-Me,C_6H_4	7	**3f**, 75
7	4-OMe,C_6H_4	15	**3g**, 73
8	1-naphthyl	15	**3h**, 86
9	2-furyl	15	**3i**, 80
10	2-thienyl	24	**3j**, 75
11	CH_3CH_2	24	**3k**, 65

[a] Reaction conditions: *N*-phenyl tetrahydroisoquinoline (**1**, 0.3 mmol), 3-oxo-alkanoic acid **2** (0.6 mmol), photocatalyst (0.003 mmol), solvent (2.0 mL) at room temperature under visible-light irradiation. [b] Isolated yield



Scheme 2. Gram scale photocatalytic oxidative coupling reaction of *N*-phenyl tetrahydroisoquinoline (**1**) with 3-oxo-3-phenylpropanoic acid (**2a**).

The present method is operationally simple and efficient and, thus, may be valuable for practical chemical synthesis. As shown in Scheme 2, when *N*-phenyl tetrahydroisoquinoline (**1**) was treated with 3-oxo-3-phenylpropanoic acid (**2a**) the optimal reaction conditions, the reaction proceeded smoothly to afford the desired 1-phenyl-2-(2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)ethanone (**3a**) at the gram scale with 81% yield (Scheme 2).

In conclusion, we have developed a novel and environmentally benign process for the visible light mediated photoredox catalyzed oxidative coupling reaction of *N*-phenyl tetrahydroisoquinoline (**1**) with 3-oxoalkanoic acid acid **2** in the presence of 1 mol % of $Ru(bpy)_3Cl_2{\cdot}6H_2O$. Current studies are aimed at developing a related asymmetric version of photocatalytic oxidative coupling reaction for the efficient buildup of molecular complexity.

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12. General procedure for the visible-light mediated photocatalytic oxidative coupling reaction of N-phenyl tetrahydroisoquinoline with β-keto acids: An oven-dried flask was equipped with a magnetic stir bar, *N*-phenyl tetrahydroisoquinoline (**1a**, 63 mg, 0.3 mmol), Ru(bpy)$_3$Cl$_2$·6H$_2$O (2.3 mg, 0.003 mmol), 3-oxoalkanoic acid (**2**, 0.6 mmol) and MeOH (2 mL) under air atmosphere. The reaction mixture was allowed to stir for 7-24 h under irradiation of blue LEDs (5 W). After the reaction was finished, the mixture was added ammonium chloride and extracted with ethyl acetate. The organic layers were dried over Na$_2$SO$_4$, concentrated in vacuum and purified by chromatography on silica gel (ethyl acetate:n-hexane = 1:20) to afford the C1-acylmethylated THIQs **3**.

Supplementary Material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org

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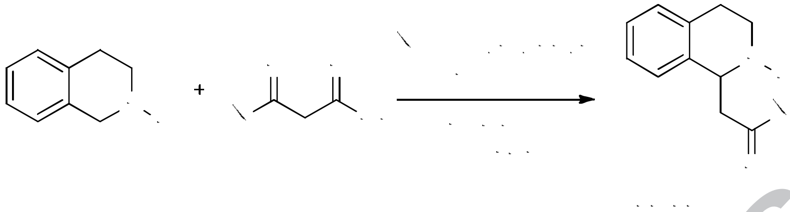

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Highlight

1. We have developed the photocatalyzed alkylation of tetrahydroquinoline derivatives.
2. Moderate to high yields (**3a-3k**, 65-86%) observed.
3. This reaction proceeded under mild conditions (1 mol % photocatalyst with blue LEDs at room temperature)