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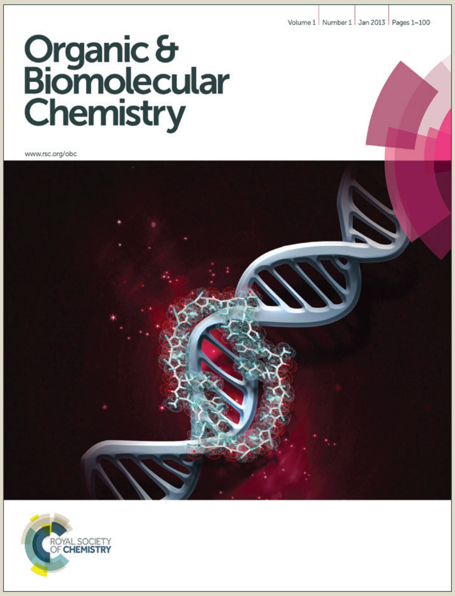

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Visible Light Mediated sp^3 C-H Bond Functionalization of N-Aryl-1,2,3,4-tetrahydroisoquinolines via Ugi-type Three-component Reaction

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Abstract: An efficient and high yield process for sp^3 C-H bond functionalization of N-aryl-1,2,3,4-tetrahydroisoquinolines was disclosed through a visible light mediated photoredox Ugi-type reaction with carboxylic acids and isonitriles under aerobic conditions, by employing $Ru(bpy)_3Cl_2$ as photoredox catalyst and CH_3CN as solvent. CH_3CN was found to be crucial for the process and good to excellent yields were achieved for a large variety of N-aryl-1,2,3,4-tetrahydroisoquinolines, carboxylic acids, and isonitriles. The developed methodology was attractive for synthesis of a library of 1,2,3,4-tetrahydroisoquinolines.

Keywords: Photoredox catalysis; C-H bond functionalization; Ugi-type reaction; 1,2,3,4-tetrahydroisoquinoline; visible light mediated reaction

Introduction

Because of ubiquity of C-H bond in organic molecules, its direct functionalization to synthesize complex products, without prior introduction of activating groups, has attracted the attention of synthetic chemists.[1] Among the research area of C-H bond activation, direct functionalization of sp^3 C-H bond adjacent to nitrogen atom in general and of 1,2,3,4-tetrahydroisoquinoline in particular, represent one of the forefront directions,[2] as 1,2,3,4-tetrahydroisoquinoline represents one of the privileged heterocyclic skeleton and a variety of its natural and unnatural derivates exhibited good biological activities.[3] A large number of novel methods, focusing on new catalysts[4] (such as CuBr, $FeCl_3$, SO_2Cl_2, and I_2), oxidants[5] (such as MnO_2 and DDQ), photoredox catalysis,[6] or enantioselective alternatives,[7] were developed for this transformation since the pioneering work of Murahashi[2f,2h,8] and Li.[9] Despite the progress made thus far, sp^3 C-H bond functionalization of 1,2,3,4-tetrahedroisoquinoline through a multi-component reaction process was quite limited.[10]

Recently, visible light mediated photoredox catalysis has received much attention. As a result, a variety of novel transformations could be carried out under mild conditions in the presence of photoredox catalyst and visible light.[11] Despite the progress made thus far, to the best of our knowledge, photoredox-catalyzed multi-component process for C-H bond functionalization was scarce.[12] Recently, Rueping and co-workers[13] reported a visible light photoredox-catalyzed three-component reaction of tertiary amine, isonitriles, and carboxylic acids, leading to sp^3 C-H functionalization of tertiary amine, by using $[Ir(ppy)_2byp]PF_6$ as the catalyst and blue LEDs as the light source. Inspired by this novel work, we envisioned that sp^3 C-H bond functionalization of N-aryl-1,2,3,4-tetrahydroisoquinolines might be achieved with appropriate photoredox catalyst and light source through a Ugi-type reaction process. We reported herein a visible light mediated Ugi-type three-component process for efficient and high yield sp^3 C-H bond functionalization of N-aryl-1,2,3,4-tetrahydroisoquinolines.

Results and Discussion

At the beginning of this study, the reaction conditions in terms of solvent was optimized using N-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline **1a**, cyclohexyl isonitrile **2a**, and acetic acid **3a** as the model substrates in the presence of 1 mol% of $Ru(bpy)_3Cl_2$ under visible light. According to the results illustrated in Table 1, it could be concluded that the reaction solvent played critical role for the process. Among the solvent screened, CH_3CN afforded the desired product **4a** in the best isolated yield of 95% (entry 1), while toluene, CH_2Cl_2, and THF were not the good choice of solvent, as much lower yields were observed even prolonging the reaction time (entries 2-4). As reported in literature, iodine is an excellent catalyst in sp^3 C-H bond functionalization of 1,2,3,4-tetrahydroisoquinoline under aerobic conditions,[4c] thus it was then tried as the catalyst for the present Ugi-type three components reaction. However, only 1-cyclohexylaminocarbonyl-N-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline, formed through the nucleophilic addition of isonitrile to in-situ generated iminium iodide, was isolated in 62% and 53% yields (92% and 84% yields based on the recovered **1a)** in MeOH and CH_3CN, respectively (entries 5-6, see supporting information). Attempts to improve the reaction conversion and yield, such as increasing the iodine loading to 30mol% and raising reaction temperature to 80 °C were unsuccessful.

With the optimal conditions in hand, the substrate scope of the process was then investigated with varieties of N-aryl-1,2,3,4-tetrahydroisoquinolines **1**, isonitriles **2**, and carboxylic acids **3**. Firstly, the substrate scope of acids **3** was carried out and the results are depicted in Scheme 1. Acrylic acid and *trans*-cinnamic acid were firstly tried under the optimized conditions, the desired products **4b** and **4c** were isolated in 68% and 84% yields, respectively. Benzoic acids with different substituents were then investigated. To our delight, the process was compatible with benzoic acids with both electron-donating and electron-withdrawing groups, afforded the corresponding products **4d-j** in good to excellent yields, ranging from 69% to 86%. For example, the reaction of N-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline, cyclohexyl isonitrile, and 2-methoxybenzoic acid or 4-methoxybenzoic acid in the presence of $Ru(bpy)_3Cl_2$ (1 mol%) in CH_3CN provided products **4e** and **4f** in 81% and 85% yields, respectively. While the reaction of N-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline, cyclohexyl isonitrile and 3-nitrobenzoic acid afforded the desired product **4i** in 69% yield under the same conditions. The structure of **4i** was unambiguously assigned by X-ray crystallography as shown in Figure 1. Two kinds of heterocyclic acids, such as nicotinic acid and 2-furoic acid were then subjected to the reactions, the reactions underwent smoothly and the desired products **4k** and **4l** were isolated in excellent yield of 98% and 73%, respectively. The structure of **4k** was also confirmed by X-ray crystallography as shown in Figure 1.

Having examined the scope of the visible light mediated Ugi-type three components reaction with carboxylic acids, we then investigated the compatibility of different N-ary-1,2,3,4-tetrahydroisoquinolines. Thus, several kinds of N-ary-1,2,3,4-tetrahydroisoquinolines were then prepared through Buchwald-Hartwig amination of 1,2,3,4-isoquinoline and aryl iodide catalyzed by CuI in the presence of glycol and K_3P_4 in isopropyl alcohol.[14] The isolated N-ary-1,2,3,4-tetrahydroisoquinolines were then subjected to the present visible light mediated three components reaction and the results were illustrated in Scheme 2. To our delight, N-ary-1,2,3,4-tetrahydroisoquinolines with different substitutions were compatible and the corresponding products could be isolated in good to excellent yields. For example, the reaction of N-(3-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline, cyclohexyl isonitrile and acetic acid in the presence of 1mol% of $Ru(bpy)_3Cl_2$ in CH_3CN afforded product **4m** in 71% yield. Under the same reaction conditions, N-phenyl-1,2,3,4-tetrahydroisoquinoline and N-(4-methylphenyl)-1,2,3,4-tetrahydroisoquinoline gave the corresponding products **4n** and **4o** in better isolated yields of 86% and 84%, respectively. Moreover, N-aryl-1,2,3,4-tetrahydroisoquinolines bearing halides (3-F, 4-Cl, and 4-Br) also showed good compatibility, affording products **4p**, **4q**, and **4r** in good to excellent yields.

To further demonstrate the generality of the newly developed photoredox catalysis procedure, our attention was then turned to the substrate scope of isonitriles. Thus, several phenyl isonitriles with different substituents were prepared through dehydration of the corresponding N-aryl formamides[15] in the presence of PPh_3, I_2, and

Et_3N in CH_2Cl_2.[16] As shown in Scheme 3, phenyl isonitriles with both electron-donating group (4-OMe) and electron-withdrawing group (4-CN) afforded the desired products **4s** and **4t** in excellent yields of 80% and 88%, respectively. Delightedly, other four kinds of phenyl isonitriles (4-Cl, 3-Cl, 4-Br, and 4-OCF_3) were also compatible and good to excellent yields were observed. Moreover, when benzyl isonitrile was employed, the desired **4y** was isolated in 92% yield.

As illustrated in Figure 2, the plausible reaction pathway for the present visible light mediated Ugi-type three components reaction began with the photoexcitation of $Ru(bpy)_3^{2+}$ to $^*Ru(bpy)_3^{2+}$ under irradiation of visible light, which oxidizing N-aryl-1,2,3,4-tetrahydroisoquinoline **1** to its radical cation **A** through single-electron transfer and $^*Ru(bpy)_3^{2+}$ specie itself was reduced to $Ru(bpy)_3^{+}$. In the presence of oxygen, $Ru(bpy)_3^{+}$ was then oxidized to the ground state $Ru(bpy)_3^{2+}$ to complete the catalytic cycle and meanwhile, generated superoxide specie, which oxidize the radical cation **A** to the reactive iminium cation intermediate **B** through abstracting a hydrogen atom and an electron. The subsequent nucleophilic attach of isonitrile to intermediate **B** formed nitrillium ion **C**, which was trapped by carboxylic acids to form the key intermediate **D**. Subsequent rearrangement of intermediate **D** via nucleophilic attack of nitrogen atom to carbonyl carbon afforded the final imide product **4**.

Conclusion

In conclusion, we have developed an efficient and high yield process for sp^3 C-H bond functionalization of 1,2,3,4-tetrahydroisoquinolines. The process highlighted visible light mediated and photoredox catalyzed three-component Ugi-type reaction under aerobic conditions. Using CH_3CN as solvent was found to be crucial to achieve high yields. Moreover, the developed process was compatible with a wide range of N-ary-1,2,3,4-tetrahydroisoquinolines, carboxylic acids, and isonitriles, and should be attractive for synthesis of libraries of 1,2,3,4-tetrahydroisoquinolines. Applying visible light mediated photoredox catalysis to other multi-component reaction for efficient synthesis of complex molecules is under investigation.

Experimental

Typical experimental procedure: To a 10 mL reaction vial was charged with magnetic stir bar, acetonitrile (2 mL), N-aryl-1,2,3,4-tetrahydroisoquinoline (0.25 mmol), acids (0.3 mmol), isonitriles (0.3 mmol), and $Ru(bpy)_3Cl_2$ (0.0025 mmol). After stirring at room temperature overnight under visible light irradiation (Philiphs household lamp, 12w), the reaction mixture was directly purified by column chromatography on silica gel to provide the corresponding products **4**.

Acknowledgements

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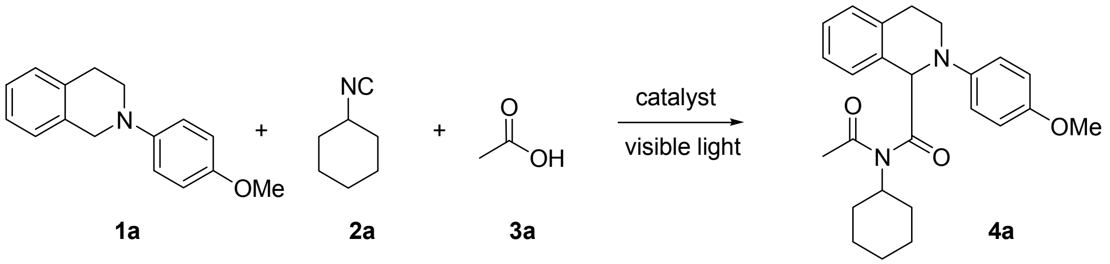
Table 1. Optimization of reaction conditions.[a]



Entry	Catalyst	Solvent	t (h)	yield (%)[c]
1	$Ru(bpy)_3Cl_2$	CH_3CN	15	95
2	$Ru(bpy)_3Cl_2$	Toluene	43	39
3	$Ru(bpy)_3Cl_2$	CH_2Cl_2	70	64
4	$Ru(bpy)_3Cl_2$	THF	70	60
5[b]	I_2	MeOH	72	0(62, 92[d])
6[b]	I_2	CH_3CN	72	0(53, 84[d])

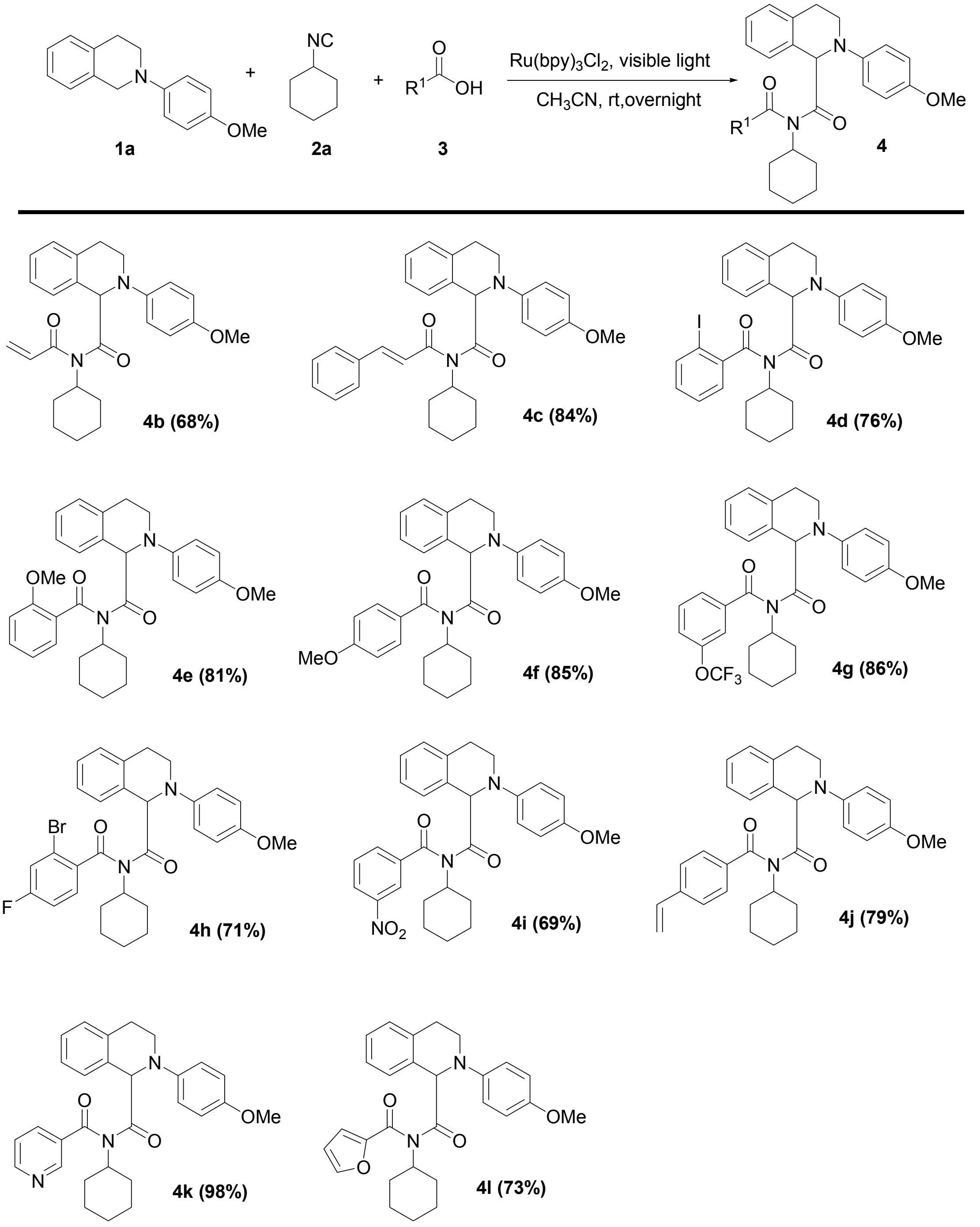
[a] Reaction conditions: N-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (0.25 mmol), cyclohexyl isonitrile (0.3 mmol), acetic acid (0.3 mmol), $Ru(bpy)_3Cl_2$ (1 mol%), visible light, room temperature.

[b] 10 mol% of I_2 was used as catalyst.

[c] Isolated yield and the yield in parentheses is for 1-cylcohexylaminocarbonyl-N-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline.

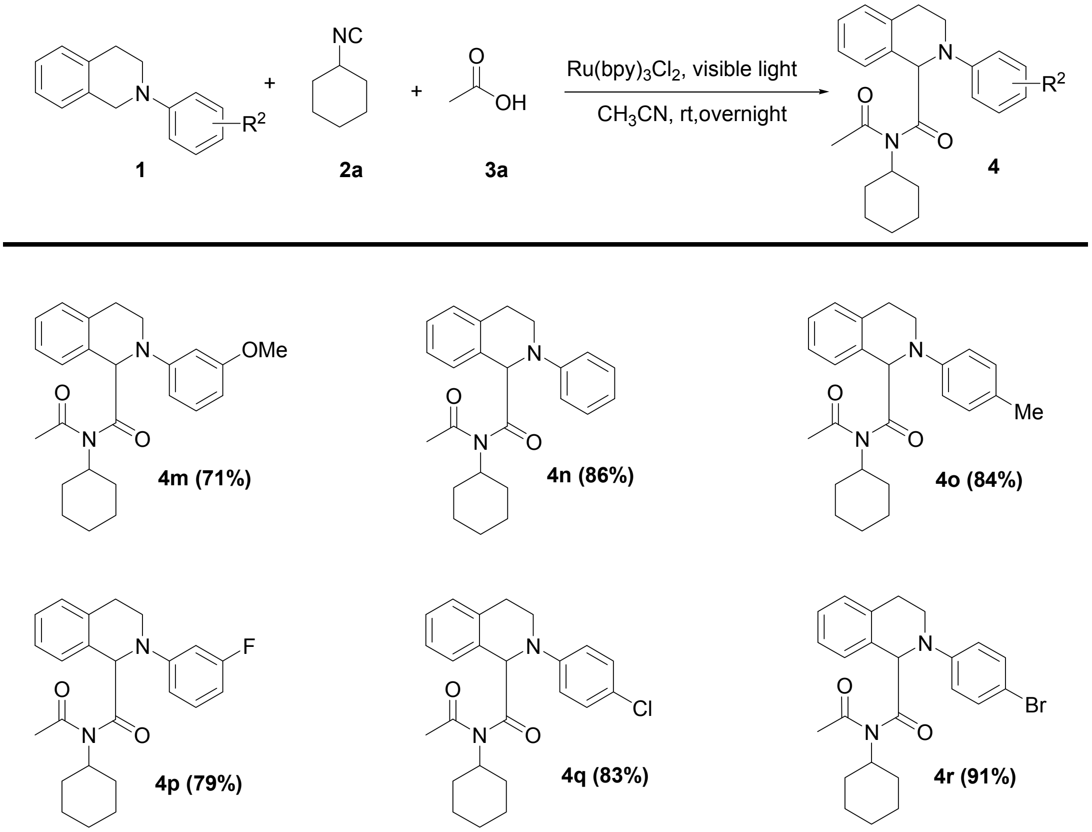
[d] Yield based on the recovered **1a**.

Scheme 1. Investigation of substrate scope of visible light mediated sp^3 C-H bond functionalization of N-aryl-1,2,3,4-tetrahydroisoquinoline with different acids.[a]



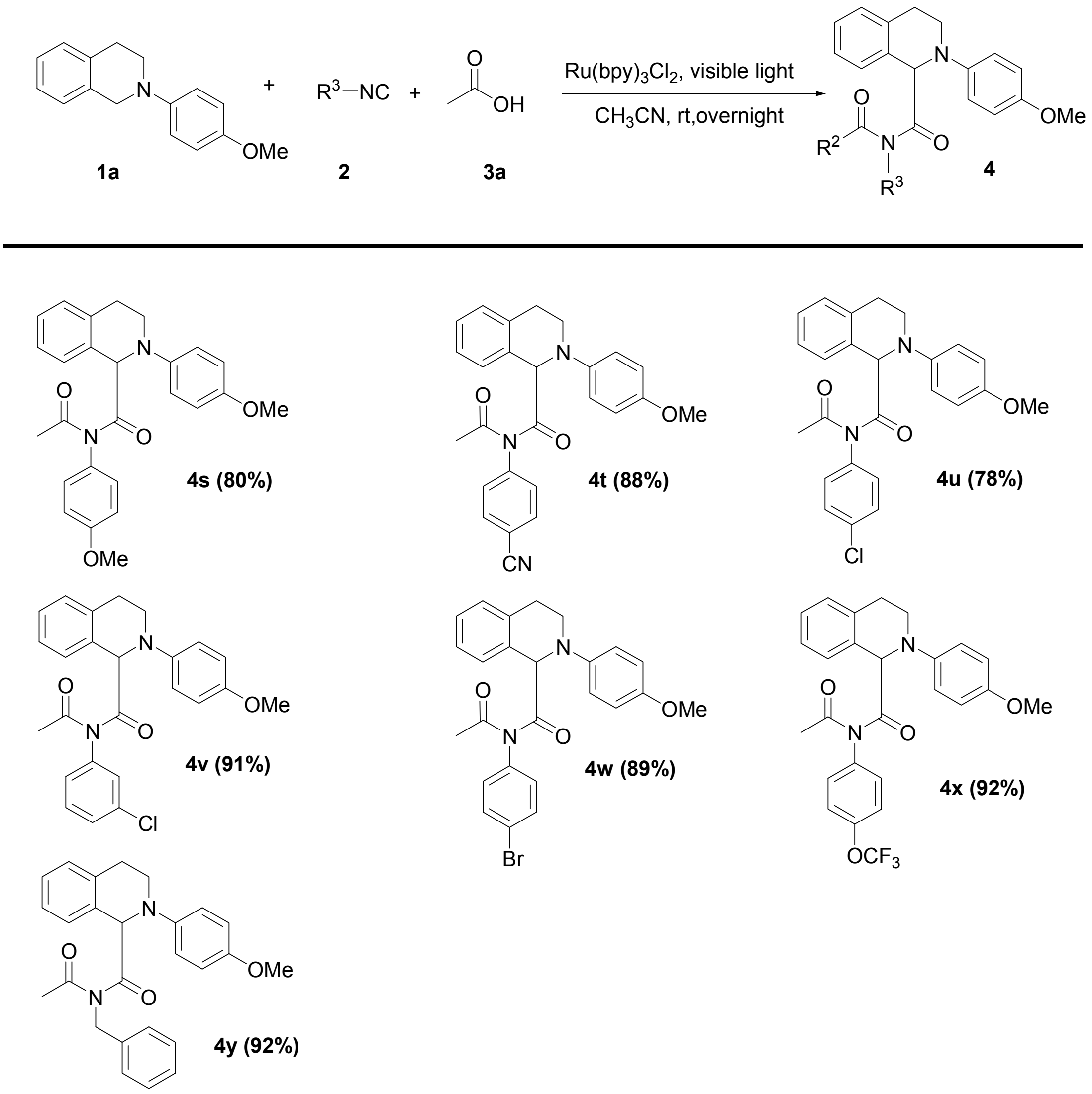
[a] Reaction conditions: N-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (0.25 mmol), cyclohexyl isonitrile (0.3 mmol), carboxylic acids **3** (0.3 mmol), Ru(bpy)$_3$Cl$_2$ (1 mol%), CH$_3$CN, visible light, room temperature, overnight.

Scheme 2. Investigation of substrate scope with different N-aryl-1,2,3,4-tetrahydroisoquinolines.[a]



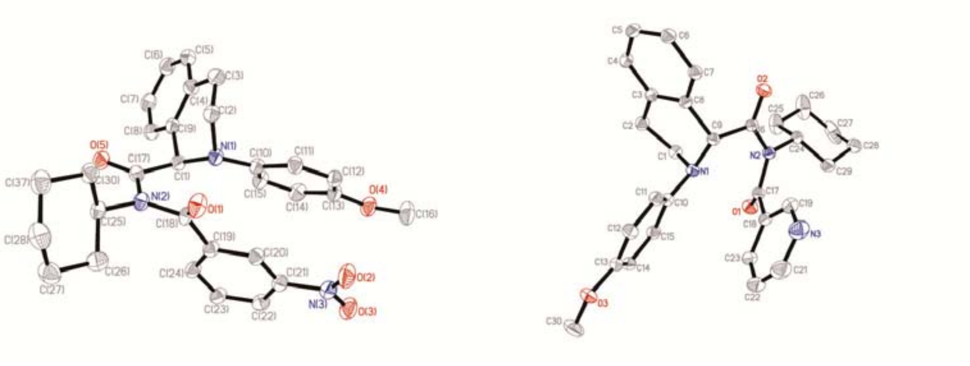
[a] Reaction conditions: N-aryl-1,2,3,4-tetrahydroisoquinoline **1** (0.25 mmol), cyclohexyl isonitrile (0.3 mmol), acetic acid (0.3 mmol), Ru(bpy)$_3$Cl$_2$ (1 mol%), CH$_3$CN, visible light, room temperature, overnight.

Scheme 3. Investigation of substrate scope with different isonitriles.[a]



[a] Reaction conditions: N-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (0.25 mmol), isonitriles **2** (0.3 mmol), acetic acid (0.3 mmol), Ru(bpy)$_3$Cl$_2$ (1 mol%), CH$_3$CN, visible light, room temperature, overnight.

Figure 1. Crystal structures of compounds **4i** and **4k**.



4i

4k

Figure 2. Plausible mechanism for visible light mediated Ugi-type three components reaction.