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Copper-Catalyzed Cyanomethylation of Substituted Tetrahydroisoquinolines with Acetonitrile

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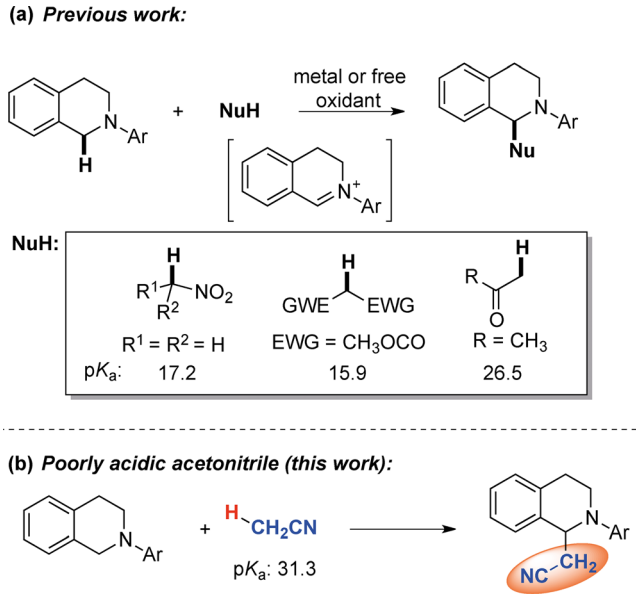
Abstract: A novel method for the synthesis of cyanomethylated tetrahydroisoquinolines has been developed with mild reaction conditions, good yields and a broad substrate scope. Acetonitrile, a common solvent, is for the first time used as a pronucleophile for this type of two sp^3 C–H bonds cross-dehydrogenative coupling (CDC) reaction. A new oxidative system ($CuCl_2$/TEMPO/Cs_2CO_3) has been established by our group, in which the mild TEMPO reagent was found to be a highly efficient oxidant.

Keywords: acetonitrile; cyanomethylation; sp^3 C–H bond activation; TEMPO; tetrahydroisoquinolines

Tetrahydroisoquinolines (THIQs) are among the most common skeletons in natural compounds with various biological activities.[1] Therefore, the development of new methods for functionalizing THIQs is of tremendous significance in organic chemistry. During the past decade, oxidative cross-dehydrogenative coupling (CDC) has received considerable attention for attaining C-1 substituted THIQs.[2] This methodology provides an efficient way to form a C–C bond directly through activating two C–H bonds and coupling the fragments without special leaving groups. Since the pioneering works reported by Murahashi[3a] and Li,[3b] substantial reaction systems have emerged and a large number of pronucleophile species (NuH)[4–16] have been discovered to react with iminium intermediates which are believed to be generated from the oxidation of tertiary amines. Concerning the coupling of two sp^3 C–H bonds, the oxidative CDC reactions of THIQs with different types of C(sp^3)–H bonds remain a big challenge. In most cases, highly active nucleophiles such as nitromethane[6] and malonate[8] serve as sp^3 C–H coupling partners. It is noteworthy that these active nucleophiles have an acidic proton which exhibits low pK_a values {pK_a (CH_3NO_2) = 17.2,[17a] pK_a [$CH_2(COOCH_3)_2$] = 15.9[17b] in DMSO} [Scheme 1, (a)]. In sharp contrast, there are very limited examples[18] for using unactivated sp^3 C–H bonds as the pronucleophile to couple with THIQ due to the unactivated sp^3 C–H bonds possessing high pK_a values.

Cyanomethylation is a pretty useful reaction in organic synthesis due to the importance of the cyano group in medicinal and synthetic organic chemistry.[19,20a] An ideal approach is to employ acetonitrile, the simplest alkyl nitrile, directly by activating the sp^3 C–H bond. In fact, however, acetonitrile is generally viewed as an inert chemical reagent and used as a sol-

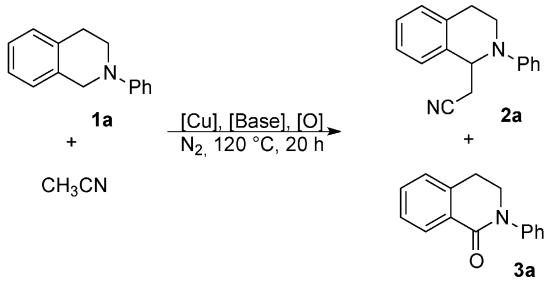


Scheme 1. CDC reactions by activating two sp^3 C–H bonds.

vent frequently. Due to its high pK_a value [pK_a (CH_3CN) = 31.3[17a] in DMSO], it is relatively difficult to be used as a pronucleophile. And the related reports are still rare and limited.[20] To the best of our knowledge, there are no examples of CDC reactions between THIQs and acetonitrile. Thus, we become interested to meet this challenge. Herein we report a Cu-catalyzed C(sp^3)–C(sp^3) bond formation between substituted THIQs and acetonitrile, for the first time, in the presence of TEMPO as an oxidant and Cs_2CO_3 as a base, which is a new system for the cross-dehydrogenative coupling (CDC) reaction [Scheme 1, (b)].

Initially, we selected *N*-phenyl-1,2,3,4-tertrahydroisoquinoline (**1a**) as a model substrate to optimize the conditions. In considering acetonitrile's high pK_a value, we systematically surveyed reaction parameters by screening bases, oxidants, and copper salts under a nitrogen atmosphere. To our delight, when substrate **1a** was subjected to the initial conditions with CuCl (20 mol%), KO-*t*-Bu (1.0 equiv.), and TBHP (1.5 equiv.) in CH_3CN (2 mL) solvent at 120 °C, it afforded the desired cyanomethylated product **2a** in 11% yield. However, a side reaction occurred along with our designed pathway. An oxidative by-product **3a** was predominantly formed in 62% yield (Table 1, entry 1). In order to suppress the formation of **3a**, a variety of bases were first tested (Table 1, entries 2–5). When using Cs_2CO_3 as a base, a promising result was obtained, providing **2a** in 34% yield and a trace amount of **3a** (Table 1, entry 5). It was suggested that the oxygen atom in the molecule of **3a** comes from TBHP. In this context, we examined other oxidants, which are not peroxides, to avoid the generation of side product **3a**. Various oxidants, such as benzoquinone (BQ), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), ceric ammonium nitrate (CAN), $K_2S_2O_8$, and 2,2,6,6-tetramethylpiperidine 1-oxyl free radical (TEMPO), were tested. TEMPO proved to be particularly effective to give **2a** in 62% yield without forming **3a** (Table 1, entry 10). Further optimization showed that this reaction was significantly improved with $CuCl_2$ as a catalyst to give the desired product **2a** in 87% yield and no trace amount of **3a** was observed (Table 1, entry 11). Additionally, CuBr, $Cu(OAc)_2$, and $Cu(OTf)_2$ also gave the acceptable yields (Table 1, entries 12–14). When decreasing the temperature to 100 °C, or reducing the amount of copper salt or Cs_2CO_3 or TEMPO, the reactions gave slightly inferior yields (Table 1, entries 15–18). Notably, the reaction yield was dramatically decreased in the absence of copper salt or TEMPO, implying that this reaction might proceed through a radical pathway (Table 1, entries 19 and 21). However, no reaction occurs without Cs_2CO_3, indicating that Cs_2CO_3 is essential for the two sp^3 C–H bonds coupling reaction (Table 1, entry 20).

Table 1. Optimization of the reaction conditions.[a]

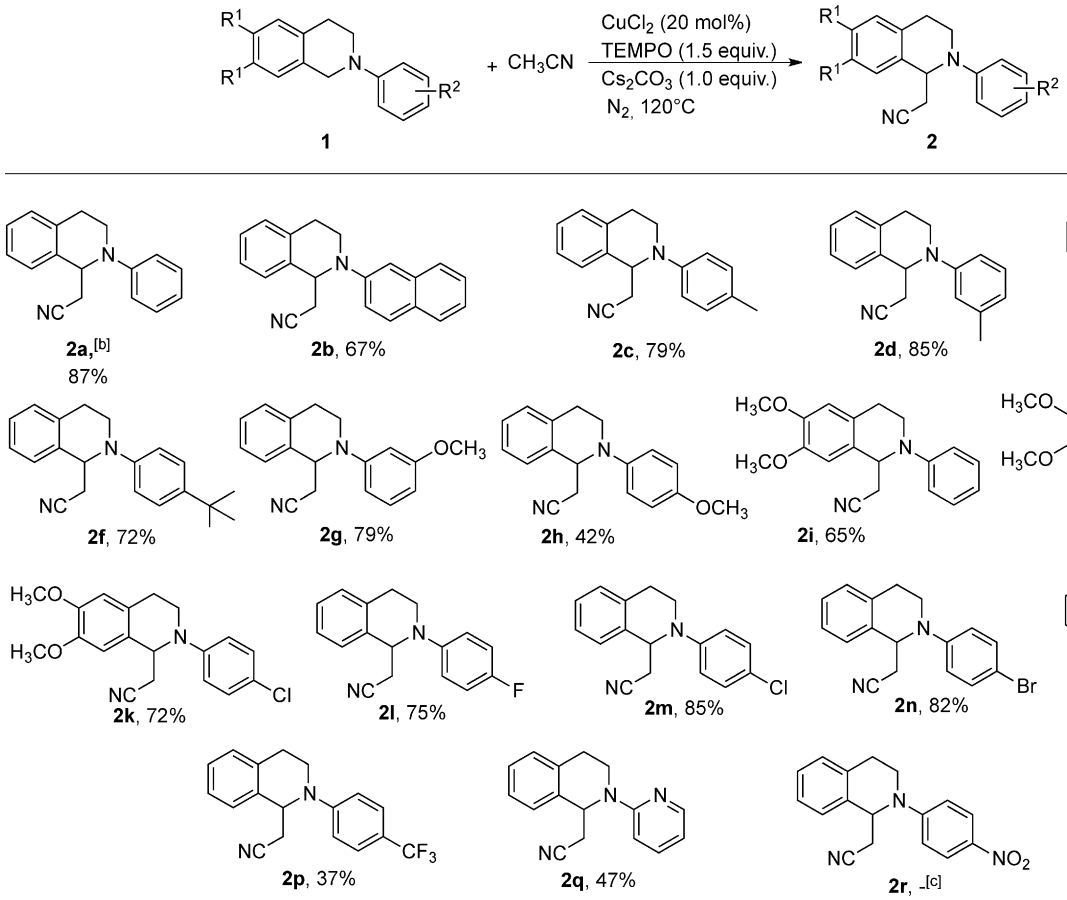


Entry	[Cu] (20 mol%)	[Base] (1 equiv.)	[Oxidant] (1.5 equiv.)	Yield[b] 2a	Yield[b] 3a
1	CuCl	KO-*t*-Bu	TBHP	11%	62%
2	CuCl	NaO-*t*-Bu	TBHP	8%	59%
3	CuCl	Na_2CO_3	TBHP	n. d.	trace
4	CuCl	K_2CO_3	TBHP	trace	trace
5	CuCl	Cs_2CO_3	TBHP	34%	trace
6	CuCl	Cs_2CO_3	BQ	n. d.	n. d.
7	CuCl	Cs_2CO_3	DDQ	n. d.	n. d.
8	CuCl	Cs_2CO_3	CAN	n. d.	n. d.
9	CuCl	Cs_2CO_3	$K_2S_2O_8$	n. d.	n. d.
10	CuCl	Cs_2CO_3	TEMPO	62%	n. d.
11	**$CuCl_2$**	**Cs_2CO_3**	**TEMPO**	**87%**	**n. d.**
12	CuBr	Cs_2CO_3	TEMPO	73%	n. d.
13	$Cu(OAc)_2$	Cs_2CO_3	TEMPO	76%	n. d.
14	$Cu(OTf)_2$	Cs_2CO_3	TEMPO	56%	n. d.
15[c]	$CuCl_2$	Cs_2CO_3	TEMPO	42%	n. d.
16[d]	$CuCl_2$	Cs_2CO_3	TEMPO	62%	n. d.
17[e]	$CuCl_2$	Cs_2CO_3	TEMPO	70%	n. d.
18[f]	$CuCl_2$	Cs_2CO_3	TEMPO	70%	n. d.
19	--	Cs_2CO_3	TEMPO	31%	n. d.
20	$CuCl_2$	--	TEMPO	n. d.	n. d.
21	$CuCl_2$	Cs_2CO_3	--	14%	n. d.

[a] *Conditions:* **1a** (0.1425 mmol, 30 mg), CH_3CN (2 mL).
[b] Isolated yield; n.d. = not detected.
[c] 100 °C.
[d] $CuCl_2$ (10 mol%).
[e] Cs_2CO_3 (50 mol%).
[f] TEMPO (1.0 equiv.).

Next, we attempted to explore the scope and generality of this catalytic two sp^3 C–H bonds coupling with acetonitrile as a pronucleophile under the $CuCl_2$/TEMPO/Cs_2CO_3 system (Table 2). Gratifyingly, a variety of *N*-substituted tetrahydroisoquinolines (THIQs) reacted well with CH_3CN under the standard conditions to afford the desired products in good yields (Table 2). When THIQ is substituted with a naphthyl group (**1b**) at the nitrogen atom, or phenyl groups with alkyl substituents such as Me (**1c**, **1d**), *i*-Pr (**1e**), or *t*-Bu (**1f**), the corresponding oxidative coupling products were obtained in 67–85% yields (**2b**–**2f**). Substrate **1g** with 3-methoxyphenyl on nitrogen gave the target product in 79% yield (**2g**). To our surprise, when tetrahydroisoquinoline (THIQ) was installed with 4-methoxyphenyl on the nitrogen, it resulted in

Table 2. Scope of substituted THIQs.[a]

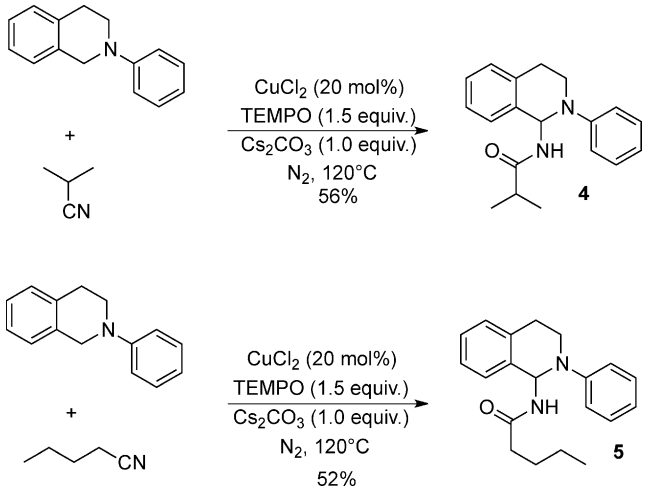


[a] *Conditions:* **1** (0.25 mmol), CH_3CN (3.5 mL), $CuCl_2$ (20 mol%), TEMPO (1.5 equiv.), Cs_2CO_3 (1.0 equiv.), isolated yields.
[b] **1a** (0.1425 mmol), CH_3CN (2 mL).
[c] Complex mixture.

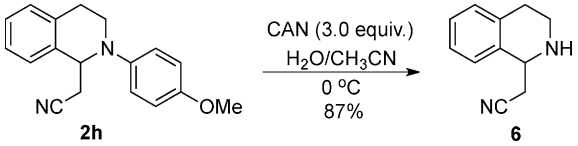
a low yield (**2h**, 42%). When the more electron-rich compound **1j** was used as the substrate, the reaction gave a complex mixture. The possible reason was considered to be that the electron-rich phenyl group on the nitrogen is prone to form an imine cation intermediate, but it results in a decrease of the electrophilic property of the imine cation. On the other hand, weak electron-withdrawing groups on the phenyl ring such as F, Cl, and Br could give the corresponding products (**2k**–**2n**) with good yields (72–85%). Nevertheless, once strong electron-withdrawing groups such as OCF_3 (**1o**) and CF_3 (**1p**) were attached on the phenyl ring, the desired products were obtained with inferior yields (55% for **2o**, 37% for **2p**). The substrate with an electron-poor pyridyl group also gave an inferior yield (47% for **2q**). We speculate that the strong electron-withdrawing groups on the nitrogen are unfavorable to form an imine cation intermediate due to the decrease of electron density on the nitrogen with a strongly electron-poor aryl ring (for details, please see the Supporting Information). This speculation was proved by substrate **1r** which has an extremely strong electron-withdrawing group (NO_2) and led to complicated mixture under the standard conditions. In the case of *N*-methyltetrahydroisoquinoline (**1s**), we did not find the corresponding cyanomethylated product.

We then performed reactions with isobutyronitrile and *n*-pentanenitrile under the optimal conditions. Unexpectedly, we obtained the amide products **4** and **5** rather than the corresponding cyanoalkylated compounds (see Scheme 2). We inferred that the nitrile was first transformed to an amide followed by coupling with an imine cation intermediate.[14a]

Actually, the removal of the *N*-aryl substituent is significant for expanding the full value of this method. According to the reported method,[12b] the aryl group (*p*-methoxyphenyl) of **2h** could be readily removed with CAN to generate the secondary amine **6** (see the Supporting Information) which is the intermediate for the synthesis of various nitrogen-containing substances of both natural and synthetic origin[21] (87% yield, Scheme 3).



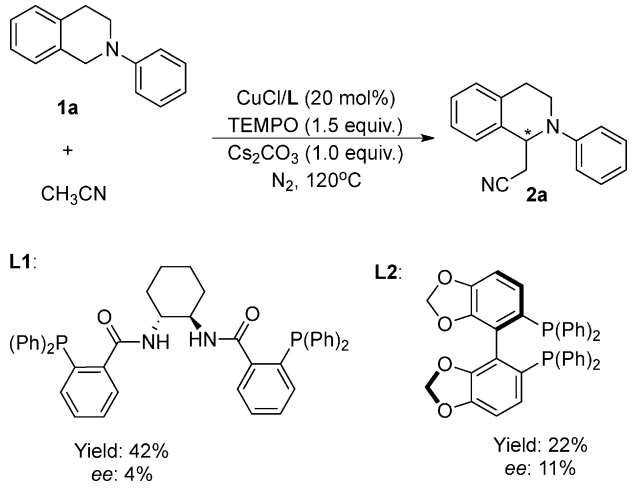
Scheme 2. The reaction of other alkyl nitriles.



Scheme 3. The removal of **2h**'s aryl group.

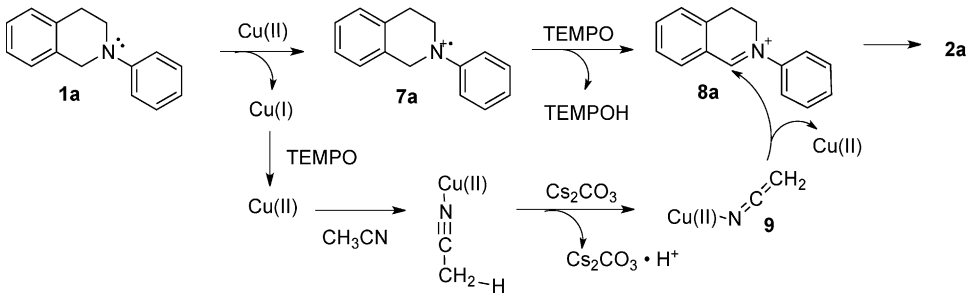
Interestingly, a stereocenter was established at the C-1 position after cyanomethylation.[5a,d,7a,h,9b,11a,14c] Therefore, we attempted to explore the catalytic asymmetric 1-cyanomethlation of THIQs by adding a chiral ligand into the system (Scheme 4). By varying the chiral ligands, we found that the use of ligand **L1** produced a moderate yield (46%) and low enantioselectivity (4% *ee*). Pleasingly, slightly increased enantioselectivity was obtained (11% *ee*) when using chiral ligand **L2**. Given the fact that the reaction could proceed without copper salt (see Table 1, entry 19), it may be hard to realize high enantioselectivity at the current stage. However, this promising result means that the catalytic asymmetric 1-cyanomethylation of THIQs is plausible.

On the basis of previous mechanistic studies[2,22] and our investigation on this reaction by GC, we propose a plausible reaction pathway as shown in Scheme 5: **1a** was transformed to **7a** by single electron transfer (SET) followed by TEMPO abstracting a hydrogen of **7a** to yield the iminium cation **8a** and TEMPOH which was determined by GC (see the Supporting Information). Due to the coordination ability of nitriles to copper metal, we speculate that acetonitrile was activated by the Cu salt and deprotonated by Cs_2CO_3 to generate the nucleophile **9** which couples with the intermediate **8a** to generate the desired product **2a**. Accordingly, the sp^3 C–H activation of acetonitrile is probably promoted by both copper species and base.[20g]



Scheme 4. Asymmetric cyanomethylation.

In conclusion, we have developed a novel method for the synthesis of cyanomethylated tetrahydroisoquinolines. Acetonitrile, a common solvent, was first used as a pronucleophile for this type of two sp^3 C–H bonds CDC reaction. During this investigation, an efficient system ($CuCl_2$/TEMPO/Cs_2CO_3) has been established by our group. The mild TEMPO reagent was found to be a highly efficient oxidant. This reaction has mild reaction conditions, good yields and a broad substrate scope for the coupling of tetrahydroisoquinolines with acetonitrile.



Scheme 5. Plausible reaction mechanism.

Experimental Section

General Procedure for CDC of THIQs and Alkyl Nitriles

Corresponding 2-substituted tetrahydroisoquinoline (0.25 mmol), $CuCl_2$ (7 mg, 20 mol%), Cs_2CO_3 (82 mg, 1 equiv.), alkyl nitrile (3.5 mL), and TEMPO (58.5 mg, 1.5 equiv.) were added into a Schlenk tube which was evacuated and back filled with nitrogen at room temperature. Then the reaction tube was sealed. The tube was heated up to 120 °C for 20 h. After cooling to room temperature, the solid material was removed by filtration and washed with 30 mL of ethyl acetate. The combined organic layers were evaporated, and the resulting crude product was purified by column chromatography on silica gel to give the products.

All products (**2a**–**2i**, **2k**–**2q**, **4**, and **5**) were unknown compounds. When we performed the reaction with isobutyronitrile and *n*-pentanenitrile, the amount of the substrate used was 0.2 mmol and 2 mL isobutyronitrile or *n*-pentanenitrile were added.

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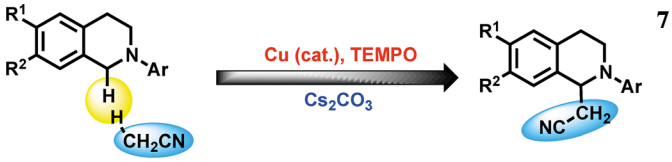

- the coupling of two sp^3 C–H bonds
- acetonitrile as a pronuclephile in CDC reaction for the first time
- TEMPO: a mild oxidant