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Acetic Acid Promoted Metal-Free Aerobic Carbon−Carbon Bond Forming Reactions at α-Position of Tertiary Amines

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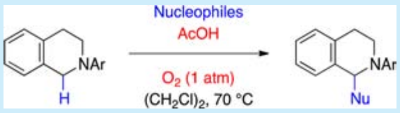
S *Supporting Information*

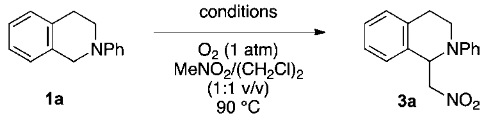
ABSTRACT: The oxidative functionalization of the benzylic C−H bonds in tetrahydroisoquinolines and tetrahydro-*β*-carboline derivatives was investigated. C−C bond forming reactions proceeded with a range of nucleophiles (nitroalkane, enol silyl ether, indole, allylstannane, and tetrabutylammonium cyanide) under metal-free conditions and an oxygen atmosphere. Acetic acid caused a significant acceleration effect.



The development of a novel C−C bond-forming reaction is one of the most important topics in the field of organic chemistry because C−C bond formation is a fundamental organic reaction. Most of the reactions require the special activation of a substrate as a nucleophile, an electrophile, or a precursor of a reactive species (such as a radical), which causes unnecessary waste, costs, and laborious experimental operations. In addition, cross-coupling reactions generally need transition metal catalysts and special ligands.[1] Recently, cross-dehydrogenative coupling (CDC) reactions,[2] which can introduce a substituent through the cleavage of a C−H bond under redox conditions without the introduction of a leaving group,[3] have received considerable attention because they are more environmentally friendly than other available reactions. If molecular oxygen can be used as an oxidant, the reaction only produces hydrogen peroxide, which decomposes to form water. These advantages inspired the synthetic community to develop aerobic CDC reactions.[2] A number of CDC reactions at C(sp^3)−H bonds adjacent to tertiary amines have been developed, including Murahashi's seminal contribution using Ru catalysts.[4] Most of these reactions involve strong oxidants, such as DDQ,[5] 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO) salt,[6] (diacetoxyiodo)benzene,[7] iodine,[8] or sulfuryl chloride;[9] transition metal catalysts, such as Ru,[4] Cu,[10] Fe,[11] Rh,[12] Au,[13] Pt,[14] V,[15] or Mo;[16] or photocatalysts, such[16] as $Ir(ppy)_2(dtbbpy)^+$[17a−e] or eosin Y.[17f] Tremendous efforts have been made to develop novel CDC reactions, but few metal-free aerobic CDC reactions with broad scopes have been reported. One such example is the recently disclosed Klussmann's aerobic oxidative C−C bond-forming reaction at the benzylic methylene in xanthenes, acridines, and tetrahydroisoquinoline derivatives with an acid catalyst and no metal catalyst or oxidant.[18] Stephenson reported that a quite slow aerobic oxidative aza-Henry reaction proceeded without a catalyst or oxidant.[17b] Here, we describe the versatile metal-free oxidative C−C bond-forming reactions of tetrahydroisoquinoline and tetrahydro-*β*-carboline derivatives that proceed at atmospheric pressure under oxygen and in the presence of acetic acid.

We recently found that Grubbs' catalyst works as a precatalyst for the catalytic oxidation of tertiary amines under an oxygen atmosphere.[19] This prompted us to examine the wider applicability of this aerobic catalytic oxidation reaction using an oxidative aza-Henry reaction with *N*-phenyltetrahydroisoquinoline **1a** as a model reaction (Table 1). As expected, heating a mixture of **1a** and a Hoveyda−Grubbs second generation catalyst in a 1:1 (v/v) mixture of nitromethane **2** and 1,2-dichloroethane under an oxygen atmosphere provided the aza-Henry product **3a** in low yield (Table 1, entry 1). After further investigation, we found that the conversion rate was dramatically increased in the presence of 10 equiv of acetic acid and the starting material **1a** was completely consumed after only 3.5 h to give **3a** in 84% yield (Table 1, entry 2). Surprisingly, a control experiment in the absence of the catalyst provided **3a** with a comparable yield and conversion rate. These results contrasted with those in Klussmann's seminal report on aerobic metal-free oxidative C−C bond formation, the coupling reactions between **1a** and ketones in that work giving low to modest yields using catalytic trifluoromethanesulfonic acid or methanesulfonic acid under a pressurized oxygen atmosphere.[18]

Table 1. Preliminary Experiments on Oxidative Aza-Henry Reaction



entry	catalyst (mol %)	additive (equiv)	time (h)	yield (%)[a]
1	Hoveyda−Grubbs second catalyst (5)	–	30	24[b]
2	Hoveyda−Grubbs second catalyst (5)	AcOH (10)	3.5	84
3	–	AcOH (10)	3.5	71

[a] Isolated yield. [b] The starting compound **1a** was recovered in 62% yield.

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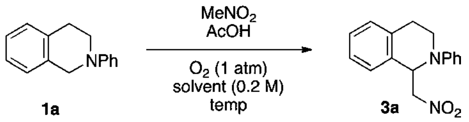
Intrigued by these unexpected results, we performed a detailed optimization study on the acetic acid promoted oxidative aza-Henry reaction (Table 2). First, **1a** was treated with 10 equiv of acetic acid in a mixture of nitromethane and 1,2-dichloroethane at different temperatures (Table 2, entries 1−4). The yield of product **3a** was slightly better (80%) when the reaction was conducted at 70 °C (Table 2, entry 2). The reaction required a long reaction time at 50 °C and rt (Table 2, entries 3 and 4). The amount of nitromethane could be decreased to 10 equiv (Table 2, entry 5). The best yield of product **3a** (92%) was obtained when a mixture of **1a**, 10 equiv of nitromethane, and 5 equiv of acetic acid in 1,2-dichloroethane was heated to 70 °C (Table 2, entry 6). These optimal conditions were also applicable in a gram scale reaction (Table 2, entry 7).

Table 2. Optimization of Reaction Conditions and Control Experiments



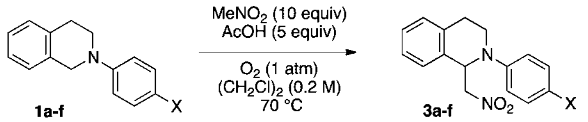
entry	AcOH (equiv)	$MeNO_2$ (equiv)	solvent	temp (°C)	time (h)	yield (%)[a]
1	10	–	$MeNO_2/(CH_2Cl)_2$ (1:1 v/v)[b]	90	3.5	71
2	10	–	$MeNO_2/(CH_2Cl)_2$ (1:1 v/v)[b]	70	3	80
3	10	–	$MeNO_2/(CH_2Cl)_2$ (1:1 v/v)[b]	50	7	81
4	10	–	$MeNO_2/(CH_2Cl)_2$ (1:1 v/v)[b]	rt	160	72
5	10	10	$(CH_2Cl)_2$	70	6	67
6	5	10	$(CH_2Cl)_2$	70	18	92
7[c]	5	10	$(CH_2Cl)_2$	70	20	86
8[d]	5	10	$(CH_2Cl)_2$	70	144	53
9[e]	5	10	$(CH_2Cl)_2$	70	168	2[f]
10	1	10	$(CH_2Cl)_2$	70	70	63
11	0	10	$(CH_2Cl)_2$	70	168	14[g]
12	–	10	AcOH	70	24	54
13	5	10	none	70	42	57

[a] Isolated yield. [b] The initial concentration of **1a** was 0.1 M. [c] Gram scale reaction. [d] Reaction was conducted under air. [e] Reaction was conducted under argon after degassing by performing freeze−pump−thaw cycles. [f] The starting **1a** was recovered in 98% yield. [g] The starting **1a** was recovered in 70% yield.

We then conducted control experiments (Table 2, entries 8−13) to investigate the importance of oxygen and acetic acid. The conversion rate became much lower under an air atmosphere, and 6 days were required to consume all of **1a** (Table 2, entry 8). The reaction gave product **3a** in only 2% yield under an argon atmosphere, and 98% of **1a** was recovered even after a week (Table 2, entry 9). We also found that the conversion rate was strongly dependent on the amount of acetic acid present (Table 2, entries 5, 6, 10, and 11). However, the use of acetic acid as the solvent was not effective (Table 2, entry 12). Finally, we analyzed the metals that were present as contaminants in the reaction mixture by inductively coupled plasma optical emission spectrometry, to determine the possibility that redox-active metallic impurities acted as catalysts. Redox-active transition metals, including V, Mn, Fe, Cu, Ru, and Pd, were not detected in our quantitative analyses (the detection limit was 0.05 ppm), which we believe eliminated the possibility that these metals were involved in this oxidative process.[20]

Next, we investigated the substituent effect of the *N*-aryl moiety in the tetrahydroisoquinoline derivatives on the aza-Henry reaction and found that a variety of substituents, including electron-donating and electron-withdrawing groups, were compatible with the reaction conditions (Table 3). Substrates **1b** and **1c**, which bear an electron-donating methyl group and methoxy group, respectively, on the *para* position of the *N*-phenyl group had high conversion rates and provided the desired products **3b** and **3c** in moderate yields (Table 3, entries 2 and 3). Introducing a bromo or methoxycarbonyl group also allowed the reaction to proceed, resulting in products **3d** and **3e**, respectively, in high yields (Table 3, entries 4 and 5). Substrate **1f**, which has a powerful electron-withdrawing nitro group, was poorly reactive, and the desired product **3f** was obtained in only 30% yield even after 120 h (Table 3, entry 6).

Table 3. Substituent Effects of *N*-Aryl Moiety of Tetrahydroisoquinoline



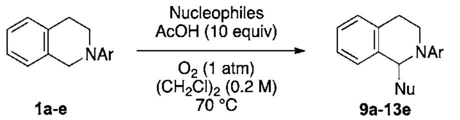
entry	substrate	X	product	time (h)	yield (%)[a]
1	**1a**	H	**3a**	18	92
2	**1b**	CH_3	**3b**	2	56
3	**1c**	OCH_3	**3c**	2.5	47
4	**1d**	Br	**3d**	18	90
5	**1e**	CO_2CH_3	**3e**	18	95
6	**1f**	NO_2	**3f**	120	30[b]

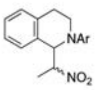
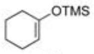
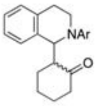
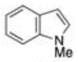
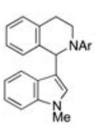
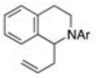
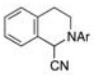
[a] Isolated yield. [b] Starting material **1f** was recovered in 70% yield.

Having obtained the basic information on the acetic acid promoted aerobic metal-free oxidative aza-Henry reaction, we focused our attention on the applicability of this metal-free oxidative process to other C−C bond forming reactions. A wide range of nucleophiles were found to be suitable for this oxidative coupling process (Table 4). Nitroethane could be used in the oxidative aza-Henry reaction, giving products **9a** and **9e** in good yields as diastereomeric mixtures (Table 4, entries 1 and 2). An aza-Mannich-type reaction proceeded smoothly with enol silyl ether **5** to provide product **10e** in a moderate yield (Table 4, entry 3). In addition, the indole derivative **6** proved to be a suitable nucleophile for an oxidative Friedel−Crafts reaction, giving products **11a−c** in 71−79% yields (Table 4, entries 4−6). We were also able to apply the reaction to an oxidative allylation reaction, the reaction with allyltributylstannane **7**, giving products **12a−c** in moderate to good yields (Table 4, entries 7−9). Furthermore, the oxidative coupling took place smoothly using tetrabutylammonium cyanide **8** to give Strecker products **13a** and **13e** in good yields (Table 4, entries 10 and 11).

Further investigations were conducted to expand the scope of the substrates. First, tetrahydro-*β*-carboline **14** was found to be a suitable substrate for the reaction. The allylation reaction using allyltributylstannane **7** proceeded with 20 equiv of acetic acid to afford product **15** in a modest yield (Scheme 1). The oxidative Strecker reaction with tetrabutylammonium cyanide **8** proceeded well to provide **16** in good yield. In addition, a simple *N*-heterocyclic compound, pyrrolidine derivative **17**, gave the corresponding oxidative Strecker product **18** in a modest yield.

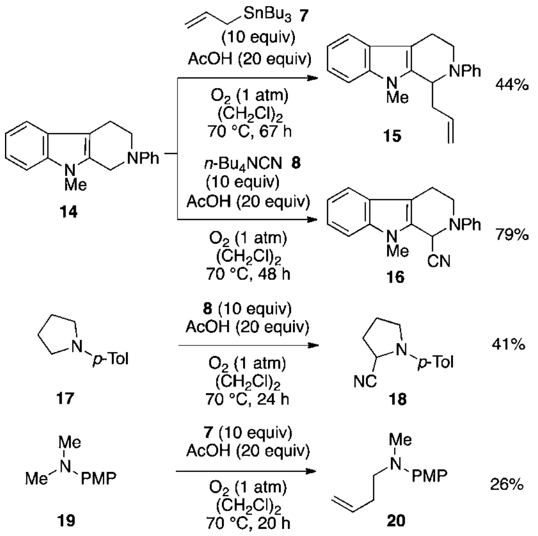
Table 4. Oxidative Coupling of *N*-Aryltetrahydroisoquinoline with Various Nucleophiles



entry	nucleophile (equiv)	substrate		product (Ar)	time (h)	yield (%)[a]
1[b]	$EtNO_2$ **4** (10)	**1a**		**9a**[c] (C_6H_5)	33	72
2[b]		**1e**		**9e**[d] ($4\text{-}MeO_2CC_6H_4$)	66	73
3[e]	 **5** (5)	**1e**		**10e**[f] ($4\text{-}MeO_2CC_6H_4$)	120	47
4	 **6** (5)	**1a**		**11a** (C_6H_5)	30	78
5[g]		**1b**		**11b** ($4\text{-}MeC_6H_4$)	27	71
6[g]		**1c**		**11c** ($4\text{-}MeOC_6H_4$)	10.5	79
7	*n*-$Bu_3SnAllyl$ **7** (5)	**1a**		**12a** (C_6H_5)	63	51
8[g]		**1b**		**12b** ($4\text{-}MeC_6H_4$)	33	61
9[g]		**1c**		**12c** ($4\text{-}MeOC_6H_4$)	5.5	70
10	*n*-Bu_4NCN **8** (5)	**1a**		**13a** (C_6H_5)	23	87
11		**1e**		**13e** ($4\text{-}MeO_2CC_6H_4$)	54	77

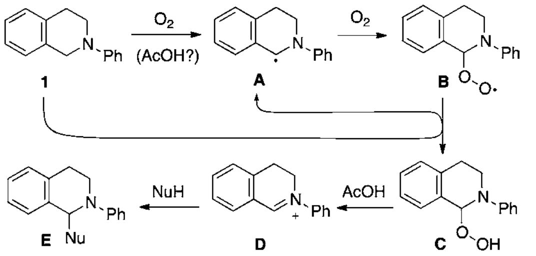
[a] Isolated yield. [b] AcOH (5 equiv) was used. [c] The diastereomeric ratio (dr) was 2:1. [d] The dr was 3:2. [e] The initial concentration of **1e** was 0.3 M. [f] The dr was 1:1. [g] The reaction was performed in CH_2Cl_2 at 50 °C.

Scheme 1. Oxidative Coupling of Tertiary Amines

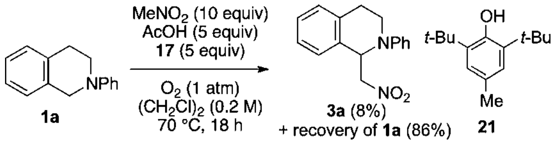


Significantly, *N,N*-dimethylaniline derivative **19** was feasible to the oxidative allylation and the reaction gave *N*-homoallylaniline derivative **20**.

Scheme 2. Proposed Mechanisms for Oxidative Coupling in the Presence of Acetic Acid and Molecular Oxygen

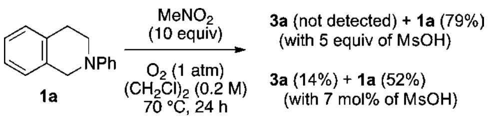


Scheme 3. Effects of a Radical Inhibitor on the Aza-Henry Reaction



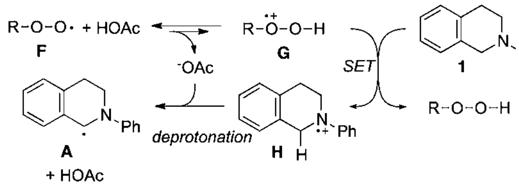
A plausible mechanism for the acetic acid promoted metal-free aerobic C−C bond-forming reaction has not yet been fully elucidated, but the reaction may proceed through a benzylic radical species **A** generated by the autoxidation of **1** (Scheme 2).[21] A reaction of the product with molecular oxygen, H-abstraction from the benzylic CH_2 in another molecule of **1**, and elimination of hydrogen peroxide would provide the iminium ion species **D**,[22,23] which should form a C−C bond with various nucleophiles. The involvement of the intermediate radical species **A** was proven by a control experiment in the presence of a radical inhibitor, 2,6-di-*tert*-butyl-4-methylphenol **21** (Scheme 3). The conversion rate was substantially lower in this reaction than in the reaction without **21**, and product **3a** was obtained in only 8% yield after the standard reaction time, while the starting material **1** was recovered in 86% yield.

Scheme 4. Oxidative Aza-Henry Reaction in the Presence of a Strong Acid



There would be two processes in the proposed reaction mechanism (Scheme 2) in which acetic acid might participate to accelerate the reaction. One is the formation of iminium ion **D** by protonation of the peroxide **C** (Scheme 2). A similar explanation was proposed by Klussmann et al. for the acid-catalyzed metal-free aerobic coupling of xanthenes. Our results were very different from the results reported by Klussmann et al. when they used stronger acids, and we found that using methanesulfonic acid instead of acetic acid did not allow the oxidative aza-Henry reaction to occur effectively in a reaction with an excess or a catalytic amount of methanesulfonic acid (Scheme 4).[24,25] The other process involved would be the generation of the benzylic radical **A** during the autoxidation step. Given the facts that neither peroxide **C** nor the corresponding hemiaminal was detected and that 70% of starting material **1a** remained even after a week under conditions without acetic acid (Table 1, entry 11), it seems likely that the process in which the benzylic radical **A** is generated is the rate-determining process and that acetic acid either accelerates this process or accelerates both steps (**1** to **A** and **C** to **D**)(Scheme 2). In analogy to the acetic acid promoted acceleration of the oxidation of phenol with peroxyl radicals that was recently disclosed by Pratt et al.,[26] we wonder whether the acetic acid might work in a way that acetic acid could protonate a peroxyl radical **F** (although the initiation process is unclear) to generate **G**, which would facilitate single electron transfer from **1** to give an aminium radical species **H**, followed by deprotonation of the benzylic proton of **H** with the acetate anion to provide **A** (Scheme 5). This mechanism would operate better with a weaker acid than with a stronger acid because a weaker acid should have a reasonably basic conjugated base that could be involved in the deprotonation of **H** to generate radical species **A**.[24,25]

Scheme 5. Proposed Mechanisms for the Generation of the Benzylic Radical Species A in the Presence of Acetic Acid



In summary, we have established an oxidative C–C bond-forming reaction that occurs at a benzylic C–H bond adjacent to a tertiary amine. The utility of the reaction was fully demonstrated by applying it to a wide range of C–C bond-forming reactions with various nucleophiles and substrates. Significantly, the reaction proceeds in the presence of only acetic acid and molecular oxygen, and no metal catalyst or external oxidant is required. Further investigations are currently in progress, which are aimed at expanding the scope of this environmentally friendly reaction and elucidating the mechanisms involved.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and procedures, compound characterization data, copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This materials is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(24) For a series of experiments using various Brønsted acids including acid–base conditions, see the SI.

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