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Green Organocatalytic Synthesis of Indolines and Pyrrolidines from Alkenes

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Abstract: Employing a green and efficient 2,2,2-trifluoroacetophenone-catalyzed oxidation of alkenes, which utilizes H_2O_2 as the green oxidant, a novel and sustainable synthesis of indolines and pyrrolidines was developed. This constitutes a cheap, general and environmentally-friendly protocol for the synthesis of substituted nitrogen-containing heterocycles. A variety of substitution patterns, both aromatic and aliphatic moieties, are well tolerated leading to the desired nitrogen heterocycles in good to excellent yields.

Keywords: Organocatalysis; Oxidation; Pyrrolidine; Green Chemistry; H_2O_2

Pyrrolidines and indolines are widely existing structural motifs in a number of pharmaceuticals, biologically important molecules and natural products (Figure 1).[1] The indoline moiety constitutes a very useful and versatile scaffold in organic synthesis, since it is usually embedded in a wide range of designed bioactive compounds and natural products (Figure 1). In the former case, an indoline derivative has been proven to exhibit anticancer properties,[2] while strychnine is a notorious natural product bearing the indoline scaffold (Figure 1).[1,3] Furthermore, the simpler structure of pyrrolidine is also present in the natural amino acid proline, which except from its role in enzymes and proteins, is being considered as a key molecule in Organocatalysis.[4] In addition, pyrrolidine is encountered in numerous natural products, such as kainic acid[5] and coccinine[6] (Figure 1).

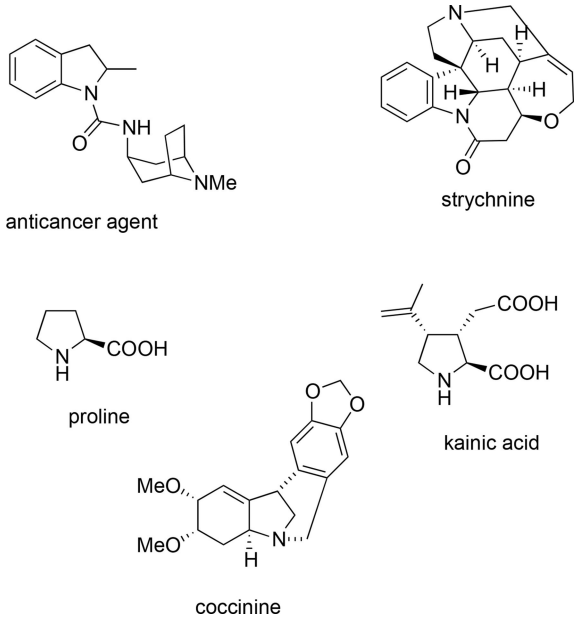
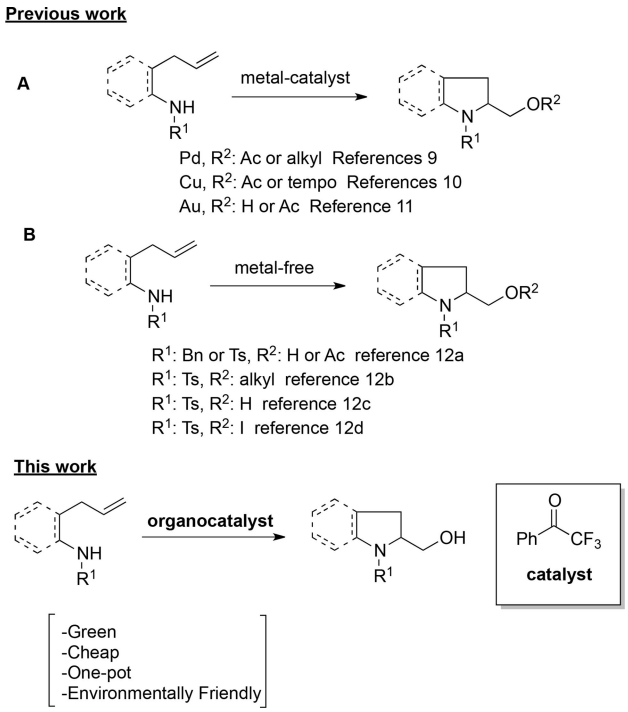


Figure 1. Representative molecules containing the indoline or the pyrrolidine moiety.

As a consequence of their vivid occurrence in numerous compounds, their existence in a significant proportion of biologically active molecules and due to their synthetic utility, a plethora of synthetic approaches have been devised for the synthesis of both indolines and pyrrolidines (Scheme 1). One of the most common synthetic approaches to these nitrogen heterocycles constitutes the oxidative difunctionalization of unactivated alkenes. Among the most powerful transformations in modern organic chemistry are alkenes' vicinal difunctionalization.[7] It comes as no surprise that metal-catalyzed processes have the lion's share towards the synthesis of these nitrogen heterocycles (indolines and pyrrolidines) involving either osmium,[8] palladium,[9] copper[10] or gold[11] (Scheme 1, **A**). Despite the widespread popularity of these protocols, metal toxicity and high levels of inorganic waste make their application harmful for the environ-

ment. A few metal-free approaches for the synthesis of these nitrogen heterocycles have also emerged in the literature,[12] but they heavily depend on the stoichiometric use of iodine reagents[12a,b,d] or Oxone[12c] (Scheme 1, **B**). Although no metal contamination can be expected by these transformations, the stoichiometric amount of acid waste remains. To our surprise, there is no single literature report (stoichiometric or catalytic) employing H_2O_2 as the oxidant for such a transformation, although this will have as an obvious advantage that the only byproduct of the method would be water. Probably, this is due to the inability of H_2O_2 to perform oxidations by itself and it has to be activated by a catalyst.[13]

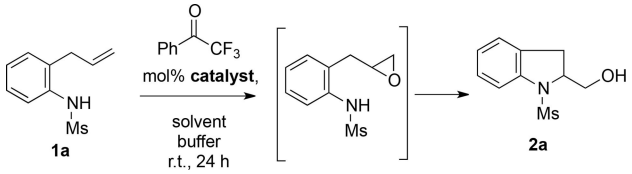


Scheme 1. Synthetic approaches for the synthesis of indolines and pyrrolidines.

We have been actively involved in the field of Organocatalysis and very recently reported a cheap, green and environmentally friendly protocol for various oxidations employing H_2O_2 as the green oxidant, whose only by-product is water and 2,2,2-trifluoroacetophenone as the organocatalyst.[14] We envisaged we could extend this organocatalytic oxidative protocol via the introduction of an one-pot procedure for the isolation of indolines and pyrrolidines (Scheme 1, bottom).

We envisaged that, H_2O_2 could be activated by 2,2,2-trifluoroacetophenone to perform an epoxidation. Once the intermediate epoxide is formed, and upon the basic conditions of the reaction, taking into consideration the orthogonal choice of the nitrogen protecting group, so that in situ deprotonation will occur, an intramolecular ring opening reaction would afford the desired cyclized compound bearing a hydroxy moiety (Scheme 1, bottom and Table 1). In general, this oxidation protocol would be environmentally friendly, having as the only byproduct, water. In addition, this will lead to an unprotected alcohol that can be easily transformed to a variety of functional groups.

Table 1. Optimization of the reaction conditions for the synthesis of indoline **2a** from **1a**.[a]



Entry	Catalyst (mol%)	MeCN/H_2O_2 (equiv.)	Solvent	Yield[b] (%)
1	10	12	tBuOH	68
2	0	12	tBuOH	traces
3	10	16	tBuOH	93
4	10	16	MeCN	91
5	10	16	EtOAc	65
6	10	16	MeOH	11
7	10	16	THF	28
8	10	16	$CHCl_3$	37

[a] All reactions were carried out with **1a** (0.50 mmol), 2,2,2-trifluoro-1-phenylethanone (10 mol%, 0.05 mmol), solvent (0.4 mL), aqueous buffer solution (0.4 mL, 0.6 M K_2CO_3–4×10^{-4} M EDTA disodium salt), acetonitrile and 30% aqueous H_2O_2. The reaction mixture was left stirring for 18 hours.

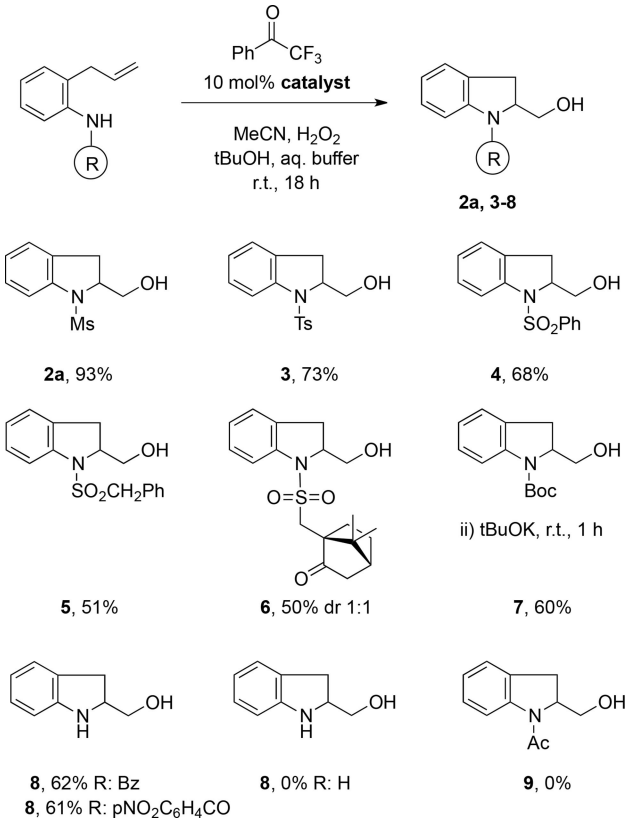
[b] Isolated yield.

Surprisingly, there are only sparse reports for the synthesis of indolines and pyrrolidines bearing a free hydroxyl moiety.[11,12a,c,15]

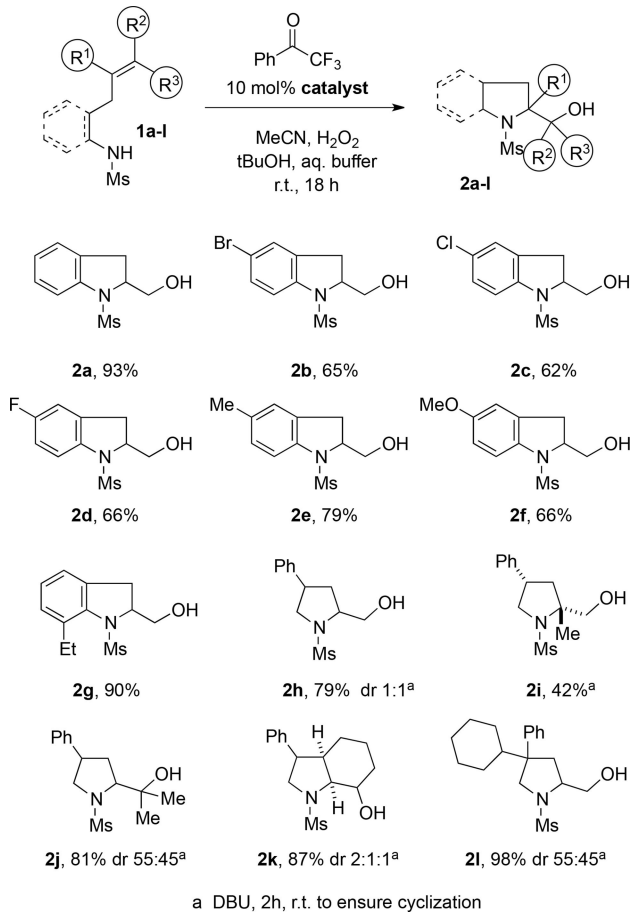
We initiated our study utilizing mesyl-protected allyl aniline **1a**, easily-prepared from aniline, in our optimized reaction conditions for the epoxidation reaction (Table 1, entry 1).[14c] At the beginning, the alkene is epoxidized, while in the basic pH of aqueous buffer, mesyl aniline is deprotonated (pK_a of $MeSO_2$ Ph ~12.9 DMSO, usually lower in H_2O) and thus subsequent ring opening of the epoxide leads to cyclization to **2a** in good yield without requiring additional reagents or heating (Table 1, entry 1). The choice of the mesyl-group was not made in vain, since additionally to the appropriate adjustment to the acidity of the NH for the deprotonation and the subsequent cyclization, it is thought to be a "difficult" substrate for this reaction. In most literature reports,

the Ts- or the Ns-protecting group is employed, while the mesyl-group is known to lead to poor yield or no reaction.[9,10] 2,2,2-Trifluoroacetophenone is indispensable for this protocol, since if it is omitted, traces of the product are observed (Table 1, entry 2). Increasing the amount of MeCN and H_2O_2 led to almost quantitative reaction yield (Table 1, entry 3). Various organic co-solvents were tested along with the aqueous buffer and only MeCN led to similar high yield (Table 1, entries 4–8).

Having in hand the optimum reaction conditions, we further explored how the nature of the protecting group affects the reaction outcome (Scheme 2). Although the tosyl-protecting group is frequently employed in literature, in our case the indoline **3** was isolated in slightly lower yield than **2a**. This can be attributed to the fact, that some deprotection of the tosyl group was observed under the reaction conditions, while no reaction takes place when the amine is unprotected (Scheme 2). Other-sulfonyl based protecting groups can be also employed with similar success (**4**–**6**). It has to be noted that when the enantiopure camphorsulfonate was used, no selectivity was observed (1:1 dr of **6**), which is probably due to the fact that the chiral center is not in close proximity to the generated chiral center and thus no chiral induction is transferred. When the Boc-group was employed, as a typical member of the urethane protecting groups, the epoxidation took place, but the BocNH is not acidic enough to be deprotonated, and thus no cyclization occurs. Thus, the intermediate epoxide can be isolated. Alternatively, once the epoxidation reaction is completed, addition of tBuOK performs the deprotonation



Scheme 2. Green Organocatalytic synthesis of indolines – nature of the protecting group.



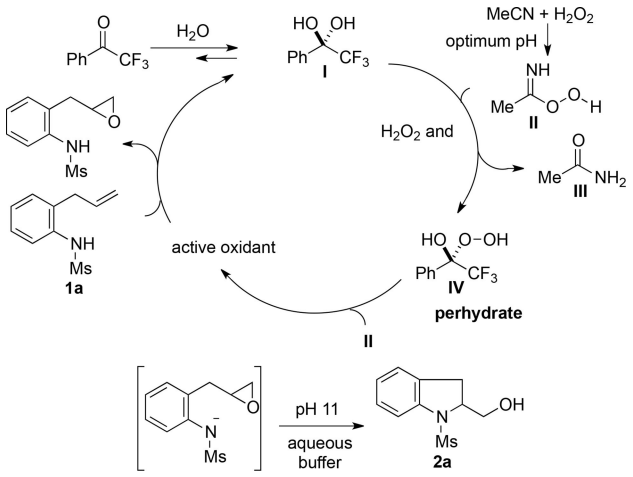
Scheme 3. Green Organocatalytic synthesis of indolines and pyrrolidines – substrate scope.

and furnishes the cyclized product **7**. When benzoyl or *p*-nitrobenzoyl protection was employed, after epoxidation and cyclization, an additional deprotection is taking place leading to unprotected aminoalcohol **8** in good yields in both cases. Again, deprotection occurs after epoxidation and cyclization, since the free allylaniline does not undergo the cyclization step. Unfortunately, simple acetyl protection cannot be employed, since no cyclized product is formed.

Once the optimum protecting group was found, we focused on exploring the substrate scope of this new green and sustainable protocol (Scheme 3). Initially, a number of substituted aromatic allyl-mesyl-protected anilines (**1a**–**g**) were utilized (Scheme 3). In all cases,

the products were isolated in high to excellent yields. Attempts to render the process asymmetric, utilizing the commercially available Shi's epoxidation catalyst, led to poor asymmetric induction.[16] Halogen substitution at the *para* position led to substituted indolines **2b**–**d** in good yields. Electron donating groups, such as alkyl or methoxy were well tolerated leading to compounds **2e** and **2f** in similarly good yields. If the substitution is moved to the *ortho* position, indoline **2g** was isolated in excellent yield. Next, a series of aliphatic mesyl-protected homoallyl amines were employed leading to substituted pyrrolidines **2h**–**l** (Scheme 3). In some cases in these aliphatic mesyl amines, a mixture of cyclized product and epoxide was present in crude NMR. Thus, to ensure cylization and higher yield of the pyrrolidine, the reaction mixture was treated with DBU to ensure cyclization. In the case of **2h**, a mixture of diastereomers was isolated in high yield. Again, attempts to render the process asymmetric led to poor yield and low enantioselectivity.[16] One can envisage an easy access to 4-substituted proline derivatives after oxidation of the hydroxy group to acid. When the alkene is α,α-disubstituted, as the case of **1i**, trisubstituted pyrrolidine **2i** that carries a tetrasubstituted carbon atom was isolated as a single diastereomer in moderate yield. Probably a preferred cyclization is taking place, leading to the cyclization of only one diastereomer. Trisubstituted alkene **1j** led to high yield of pyrrolidine **2j**, albeit with low diastereoselectivity. Pyrrolidine **2j** closely resembles Jorgensen-Hayashi's diaryl prolinols, which are known to be potent organocatalysts.[4] This approach can lead to substituted derivatives on the pyrrolidine ring of these molecules. When cyclic alkene **1k** (1:1 mixture of diastereomers) was employed, bicyclic compound **2k** was isolated in high yield as a mixture of diastereomers. This constituted an interesting entry in the rapid assembly of polyfunctionalized bicyclic scaffolds for numerous applications, such as bioactive compounds or new catalysts and ligands. Finally, trisubstiuted pyrrolidines, such as **2l** that carries a quaternary center on the pyrrolidine ring can be formed by this protocol in almost quantitative yield.

To summarize the events that take place in this procedure, a proposed reaction mechanism is shown in Scheme 4. In the aqueous environment of the reaction, 2,2,2-trifluoroacetophenone affords diol **I**. Then, and in the appropriate pH, MeCN reacts with H_2O_2 to afford **II**, which in conjunction with H_2O_2 oxidizes **I** to perhydrate **IV**.[14] Then, another molecule of **II** reacts with **IV** affording the active oxidant of the protocol, which epoxides alkenyl-mesyl-protected aniline **1a**. The structure of the active oxidant of the oxidation protocol is still unknown. The possibility of a dioxirane intermediate cannot be ruled out,[17] although we have recently reported that this is highly unlikely to be true.[14e] Then, and upon the basic conditions, deprotonation occurs leading to a ring opening of the epoxide with simultaneous cyclization to indoline **2a**.



Scheme 4. Proposed reaction mechanism.

In conclusion, a highly sustainable and green protocol was developed for the conversion of alkenyl protected anilines into polysubsituted indolines or pyrrolidines using H_2O_2 as the oxidant. Since H_2O_2 is poor by itself to perform oxidations, our synthetic approach utilizes a cheap and commercially available metal-free organic molecule (2,2,2-trifluoroacetophenone) as the catalyst to activate H_2O_2. Our approach reports the one-pot epoxidation of alkenyl-protected amines followed by an in situ ring opening/cyclization process leading to nitrogen heterocycles in good to excellent yields. After an extensive study of the nature of the protecting group, a variety of substitution patterns is well tolerated leading to indolines and pyrrolidines in good to high yields. This novel approach of combining our organocatalytic oxidation protocol in one-pot transformations leading to products of high molecular complexity is currently being pursued in our laboratories.

Experimental Section

Experimental DetailsAlkene (0.50 mmol) was placed in a round bottom flask and dissolved in *tert*-butanol (0.4 mL). 2,2,2-Trifluoro-1-phenylethanone (8.7 mg, 0.05 mmol), aqueous buffer solution (0.4 mL, 0.6 M K_2CO_3–4×10^{-4}M EDTA disodium salt), acetonitrile (0.40 mL, 8.00 mmol) and 30% aqueous H_2O_2 (0.84 mL, 8.00 mmol) were added consecutively. The reaction mixture was left stirring for 18 hours at room temperature. The product was purified by column chromatography (30–50% EtOAc in Pet. Ether). For aliphatic substrates, after reaction completion, DBU (1.00 mmol) was added and the reaction mixture was left

stirring at room temperature for 2 h before column chromatography

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UPDATES

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