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Organocatalysis

2,2,2-Trifluoroacetophenone as an Organocatalyst for the Oxidation of Tertiary Amines and Azines to *N*-Oxides

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Abstract: A cheap, mild and environmentally friendly oxidation of tertiary amines and azines to the corresponding *N*-oxides is reported by using polyfluoroalkyl ketones as efficient organocatalysts. 2,2,2-Trifluoroacetophenone was identified as the optimum catalyst for the oxidation of aliphatic tertiary amines and azines. This oxidation is chemoselective and proceeds in high-to-quantitative yields utilizing 10 mol% of the catalyst and H_2O_2 as the oxidant.

Introduction

N-Oxides are key components for ubiquitously used materials such as toilet soaps, toothpastes, detergents, shampoos, cosmetics, and also found in products for biomedical applications.[1] They are also employed as oxidants to accomplish important reactions, such as the osmium-catalyzed dihydroxylation of olefins,[2a] the ruthenium-catalyzed oxidation of alcohols,[2b] the Mn-salen-catalyzed epoxidation of olefins[2c] and the Pauson–Khand reaction.[2d] The most common approach for the synthesis of these compounds is the oxidation of amines (Figure 1) employing stoichiometric amounts of per-

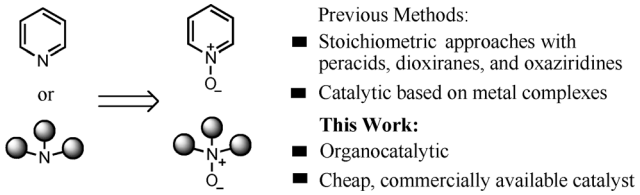

Figure 1. Approaches for the synthesis of *N*-oxides.

acids,[3a,b] activated H_2O_2,[3c] dioxiranes[3d–f] or oxaziridines.[3g] These reagents are inexpensive but usually generate large amounts of waste. Transition-metal-catalyzed processes have been also developed.[4] Among them Re,[4a] Ti,[4b] W,[4c] Ru[4d] and V[4e] are the most commonly employed. The flavin family is the only class of organic molecules utilized as catalysts for the oxidation of aliphatic tertiary amines.[5] From an environmental standpoint, the use of precious and potentially hazardous metals can have a great impact, especially in products of pharmaceutical interest, for which any metal contamination is unacceptable. An additional drawback of the abovementioned procedures is that most of these methods are limited to either aliphatic tertiary amines or azines, and only a handful of methods can be applied in both series of substrates. Although organocatalysis has provided elegant solutions to a number of reactions,[6] research on oxidation is less documented. A few examples exist in literature, dealing mainly with the epoxidation reaction.[7–10]

Perhydrates and dioxiranes are among the most promising organic oxidants,[7] which derive from ketones in conjunction with an oxygen source. In most cases, a large excess (over 5 equiv) is required for oxidations to reach completion. Attempts to reduce the amount of the reaction promoter have met with limited success. Indeed, the groups of Denmark,[8] Yang,[9] and Shi[10] have provided elegant solutions to epoxidation reactions. Today, there is an increasing demand to use oxidants such as H_2O_2, which are environmentally friendly and do not give rise to any waste products. Our aim was the development of a general strategy that enables the use of substoichiometric amounts (10 mol%) of an organic compound as the catalyst, to provide a synthetically versatile and operationally trivial mode of activation of H_2O_2.

Results and Discussion

We have been previously engaged in the synthesis of activated ketones as potent and selective enzyme inhibitors.[11,12] Coupled with our own previous experience in organocatalysis,[13] we envisaged the use of activated ketones as catalysts. Hydrogen peroxide by itself is a poor oxidant for organic oxidations. Thus, it has to be coupled with a catalyst to create a reactive intermediate that will efficiently carry out the oxidation (Scheme 1). Nitriles have been employed for such activation.[3c,14] Perfluoroketones have been employed in the past for oxidation reactions, but usually in stoichiometric amounts.[15,16] For amine oxidation in particular, they have been employed only for the oxidation of azines,[15] and in some cases in stoi-

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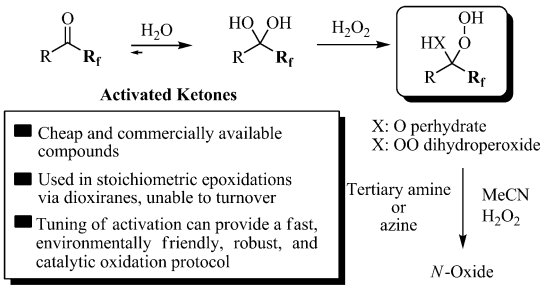


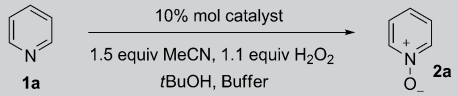
Scheme 1. Design of the synthesis of *N*-oxides.

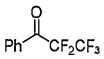
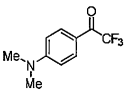
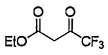
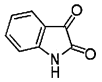
chiometric quantities.[15a] It is known that perfluoroalkyl ketones in an aqueous environment exist mainly in their hydrate form. We believed that this hydrate could react with hydrogen peroxide to form either a perhydrate or a dihydroperoxide. It was postulated that this perhydrate will react with MeCN and H_2O_2 to generate a reactive oxidant species that will perform the oxidation and will regenerate the catalyst to be employed in another catalytic cycle.

To test our hypothesis, activated ketones were tested as catalysts for the oxidation of pyridine to pyridine *N*-oxide by using H_2O_2 as the oxidant (Table 1). When the catalyst was omitted from the reaction, the product formed in low yields (entry 1, Table 1). 2,2,2-Trifluoroacetophenone furnished the best results, because pyridine *N*-oxide was formed in a quantitative yield (entry 2, Table 1). Increasing the amounts of acetonitrile and H_2O_2 provided a quantitative yield in just 4 h (entry 3, Table 1). Decreasing the activation of the carbonyl led to decreased yields, whereas the use of polyfluoroalkyl substituents led to similar high yields (entries 4–7, Table 1). Acetophenone led to low yields, highlighting the need of the perfluoroalkyl moiety to activate the carbonyl compound to act as the oxidation catalyst (entry 8, Table 1). Similar results were obtained when acetone was employed (result not shown). Other activated compounds as diketones, ketoacids, ketoesters, and ketoamides were also tested but in all cases low-to-moderate yields were obtained (entries 9–14, Table 1).

Once the optimum reaction conditions were identified, the substrate scope of the oxidation was explored (Scheme 2). Initially substituted pyridines (**1a**–**1i**) were utilized leading to **2a**–**2i**. Substitution at either position had no effect on the reaction outcome affording the products in almost quantitative yield (**2a**–**2d**). Disusbstituted pyridines can also be oxidized in excellent yields, except in the case of 2,5-disubstituted pyridines in which the steric bulkiness of the substituents have an impact in the reaction yield (**2f**). Other functional groups can be tolerated as substituents since no byproducts were observed and the *N*-oxides were obtained in excellent yields (**2g**–**2i**). Quinoline and isoquinoline behave similarly in the reaction, leading to excellent yields, whereas bipyridine can be doubly oxidized (**2j**–**2l**). One of the main disadvantages of the existing methods is their lack of generality, since they are usually employed either for azines or aliphatic tertiary amines. Our protocol provides an excellent solution to this end, since aliphatic tertiary amines are also good substrates for oxidation in our protocol

Table 1. Activated ketones as catalysts for the oxidation of pyridine to pyridine *N*-oxide.

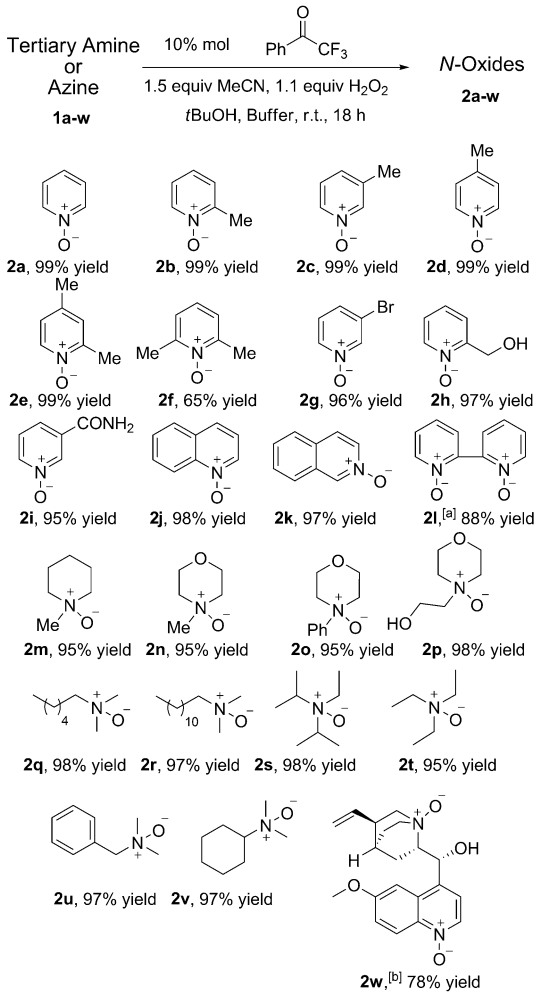


Entry	Catalyst	Yield [%][a]	*t* [h]
1	No catalyst	29	18
2		>99(99)	18
3[b]		>99(99)	4
4		92	18
5		53	18
6		95	18
7		27	18
8		28	18
9		44	18
10		43	18
11		39	18
12		41	18
13		46	18
14		38	18

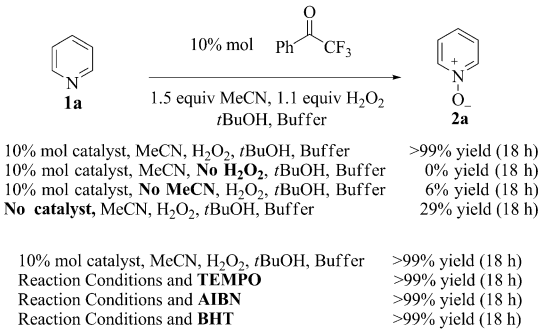
[a] Yield was determined by GC-MS analysis; the yield of the isolated product is given in parenthesis. [b] Two equivalents of MeCN and H_2O_2 were utilized.

(**2m**–**2w**).[17] Cyclic tertiary amines were oxidized to the corresponding *N*-oxides in high to excellent yields (**2m**–**2p**). Mixed long linear aliphatic- and short non-linear aliphatic alkyl amines, as well as symmetrical amines are well-tolerated leading to excellent yields (**2q**–**2v**). To further extend this methodology, quinine was also employed (**2w**). The double oxidation product (*N*,*N*′-oxide) was isolated in high yield, whereas the double bond was left intact, indicating the chemoselectivity of the method towards the formation of the *N*-oxides.

To elucidate the reaction mechanism, control experiments were carried out (Scheme 3). In the absence of H_2O_2, no reaction took place, confirming that H_2O_2 is the oxidant of the reaction. However, H_2O_2 by itself or in combination with the catalyst was not capable of performing the oxidation, because in the absence of MeCN, oxidation is negligible. The amount of the acetonitrile is of critical importance because at least one



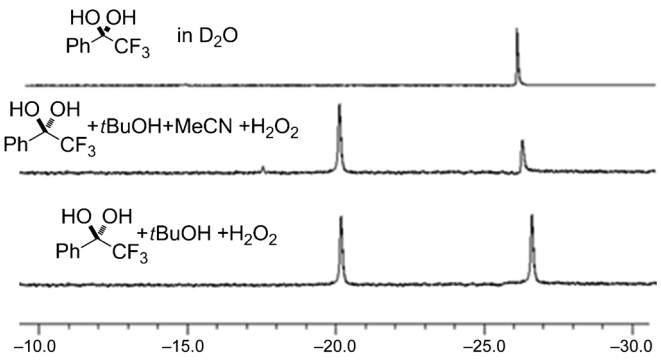
Scheme 2. Substrate scope of the oxidation. Isolated yields. [a] MeCN (3.0 equiv), H_2O_2 (2.2 equiv). [b] MeCN (8.0 equiv), H_2O_2 (8.0 equiv).



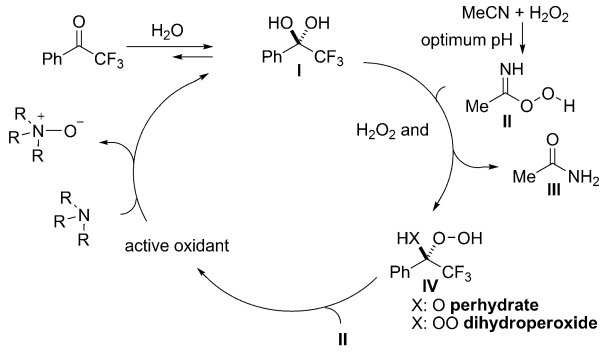
Scheme 3. Mechanistic investigation of the reaction.

equivalent of MeCN is required to result in full oxidation of the starting material.[18] We assume that an intermediate is formed, which is a peroxycarboximidic acid, similar to the intermediate that Payne and co-workers have proposed in their epoxidation reaction.[3c] This intermediate is sluggish in promoting the reaction by itself, since in the absence of the catalyst only 29% yield was obtained. Evidence that supports the peroxycarboximidic acid intermediate is the observation of the formation of acetamide at the end of the reaction both by GC-MS analysis and ^{1}H NMR spectroscopy. At this stage, the crucial role of the pH of the solution has to be highlighted for the peroxycarboximidic acid intermediate to be generated (see Supporting Information). To eliminate the possibility of radical intermediates in this protocol, a number of control experiments were performed (Scheme 3). The reaction outcome was independent on the addition of the radical traps ((2,2,6,6-tetramethyl-piperidin-1-yl)oxyl (TEMPO), azobisisobutylonitrile (AIBN), and 3,5-di-*tert*-butyl-4-hydroxytoluene (BHT) indicating that this protocol does not involve any radical intermediates.

Stemming from previous acquired knowledge,[11,12] it was postulated that perfluoroalkyl aryl ketones exist mainly in their hydrate form in the aqueous environment of the reaction. Indeed, ^{19}F NMR spectroscopic experiments showed that although in organic solvents the equilibrium lies towards the ketone form, in the aqueous medium of the reaction, the hydrate was the main form (Scheme 4, see also the Supporting Information). Thus, the perfluoroalkyl ketone is hydrated in the presence of water leading to hydrate form **I** (Scheme 5). Once



Scheme 4. ^{19}F NMR spectroscopic experiments to probe the active oxidant species.

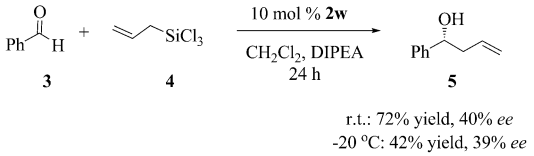


Scheme 5. Proposed reaction mechanism.

the optimum pH is utilized, acetonitrile and H_2O_2 react to form peroxycarboximidic acid **II**. The hydrate form of the perfluoroalkyl ketone is oxidized by H_2O_2 and **II** forming perhydrate **IV** and leaving as a byproduct from the peroxycarboximidic acid, acetamide **III**. Following the reaction mixture by ^{19}F NMR spec-

troscopy and upon addition of *t*BuOH and MeCN, no change was observed. However, once H_2O_2 was added, a new peak was immediately observed in ^{19}F NMR spectrum (Scheme 4). The same peak is observed when H_2O_2 is added to the reaction mixture in the absence of MeCN (see also the Supporting Information). This peak is assigned to perhydrate **IV**, which can be formed from the diol with H_2O_2, but it is not capable to perform the oxidation by itself as highlighted in Scheme 3. Perhydrate **IV** then reacts with **II** forming the active oxidant species of the oxidation.[19] Upon addition of the tertiary amine, the oxidation occurs to the corresponding *N*-oxides. Finally, *N*-oxide is obtained and at the same time recycling of the catalyst occurs through generation of the hydrate **I**. If the tertiary amine is not added in the reaction medium, the perhydrate is transformed to another species, the dihydroperoxide (based on the observation of ^{19}F NMR spectroscopic analysis, see the Supporting Information).

To highlight the importance of the products of this protocol, *N*-oxide **2w** was employed as the catalyst in the enantioselective allylation of benzaldehyde (Scheme 6). The activation of



Scheme 6. Asymmetric allylation of aldehydes utilizing **2w** as the catalyst.

allyltrichlorosilane by catalytic amounts of Lewis base, especially aromatic *N*-oxides, has already been demonstrated in the asymmetric allylation of aromatic aldehydes.[20] Although a number of chiral quinoline oxides have been tested for this reaction, simple *N*-oxides deriving from the Cinchona alkaloid family have not been reported. Herein, *N*-oxide **2w**, which has been prepared by our protocol, was tested as the catalyst for the asymmetric allylation of benzaldehyde. In unoptimized reaction conditions, it was found that 10 mol% of **2w** can promote the reaction at room temperature affording the product in high yields but low enantioselectivities. A decrease in the temperature did not lead to any improvement.

Conclusion

A highly selective organocatalytic oxidation protocol of tertiary amines and azines to *N*-oxides is described. Perfluoroalkyl aryl ketones can be employed as catalysts (10 mol%) in such a reaction leading to excellent-to-quantitative yields in short reaction times under mild reaction conditions. The substrate scope of the reaction is very general and a variety of aliphatic tertiary amines and azines can be tolerated. The mechanism of the reaction was studied and active intermediates are proposed.

Experimental Section

General procedure for the oxidation of tertiary amines and azines to *N*-oxides

Amine (1.00 mmol) was placed in a round-bottom flask followed by 2,2,2-trifluoro-1-phenylethanone (17.4 mg, 0.10 mmol). *tert*-Butanol (0.5 mL), aqueous buffer solution (0.5 mL, 0.6 M K_2CO_3/4× 10^{-5} M EDTA tetrasodium salt), acetonitrile (0.08 mL, 1.50 mmol) and 30% aqueous H_2O_2 (0.13 mL, 1.10 mmol) were added consecutively. The reaction mixture was left stirring for 18 h. The crude product was purified using flash column chromatography or alumina (10–40% EtOAc in petroleum ether) to afford the desired product.

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Keywords: green chemistry · hydrogen peroxide · *N*-oxides · organocatalysis · oxidation

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[18] For full experimental procedure, catalyst screening, reaction optimization, mechanistic investigations, and full NMR spectroscopic data, see the Supporting Information.
[19] For a possible structure of the active oxidant species, see the Supporting Information.
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