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ABSTRACT

Tetrabutylammonium phthalimide-*N*-oxyl (TBAPINO) was found to catalyze trimethylsilyl cyanide addition to a variety of aldehydes and ketones in high to excellent yields. The reaction proceeds smoothly under mild conditions by employing 1.0 mol% of the organocatalyst at room temperature within very short reaction times. Due to the high solubility of the tetrabutylammonium phthalimide-*N*-oxyl in organic solvents, a significant improvement in the catalytic activity of the phthalimide-*N*-oxyl (PINO) nucleophile was observed.

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1. Introduction

Cyanohydrins serve as key intermediates in the synthesis of many biologically important compounds such as α -hydroxy acids, α -hydroxy aldehydes or ketones, α -amino acids, and β -amino alcohols [1–31] or ferroelectrics and liquid crystals [7]. However, it has been proved that the direct synthesis of cyanohydrins from carbonyl compounds and HCN is difficult due to not only the inherent thermodynamic instability of the products [15] but also the toxicity of HCN [22]. To overcome these problems, cyanohydrins from carbonyl compounds are generally prepared in *O*-protected form. The cyanosilylation of carbonyl compounds is particularly suitable since the silyl protecting groups can be removed under very mild reaction conditions. Therefore, the most commonly used method to prepare cyanohydrin silyl ethers involves catalytic addition of trimethylsilyl cyanide (TMSCN) to carbonyl compounds [2–31]. It is therefore not surprising that many catalysts have been developed for this transformation [29].

Transfer of a cyano group from TMSCN to carbonyl compounds can be catalyzed by a plethora of catalysts including achiral or chiral Lewis acids [2–14], Lewis bases [16–18] and double activating or bifunctional catalytic systems [19–21]. However, many of these methods suffer from several disadvantages such as the use of heavy or expensive metal catalysts [4–6,10–13], prolonged reaction times or poor yield of the products [4,12,13,19], the requirement

for an anhydrous solvent or inert atmosphere [4,11,12], and hygroscopic nature of the catalysts [17,18]. On the other hand, organocatalytic protocols for cyanosilylation for carbonyl compounds which mainly exert their catalytic activity through Lewis base catalysis have received considerable attention in the recent years [22–31]. Organocatalysis is often associated with high efficiency, mild reaction conditions, inexpensive and environmentally benign reagents, simple experimental operations and potential for large scale reaction. However, development of new organocatalysts which operate under milder conditions is a challenge attracting much attention. We have recently developed alkali metal salts of phthalimide-*N*-oxyl (PINO) and *p*-toluenesulfate as efficient catalysts for cyanosilylation of carbonyl compounds [23,24] or cyclo-trimerization of isocyanates [32,33] under mild conditions. In continuation of our interest to develop new generation and more efficient nucleophilic organocatalysts for these industrially important reactions, we herein disclose the first application of tetrabutylammonium phthalimide-*N*-oxyl (TBAPINO) as a metal-free organocatalyst for the addition of TMSCN to carbonyl compounds under extremely mild conditions (Scheme 1).

2. Experimental

2.1. General

FT IR spectra were recorded as KBr pellets on a Shimadzu FT IR-8400S spectrometer. ¹H NMR (500 MHz) and ¹³C NMR (125 MHz) spectra were obtained using a Bruker DRX-500 AVANCE spectrometer. All NMR spectra were determined in CDCl₃ or DMSO at ambi-

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