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$Cu(OTf)_2$ Catalyzed Trimethylsilyl Cyanide Addition to Carbonyl Compounds

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Abstract: Copper (II) triflate was found to catalyze Trimethylsilyl cyanide addition to a variety of ketones and aldehydes at rt in an efficient manner.

Cyanohydrins are important in organic synthesis as it provides an handle for conversion into various other functional groups, and are usually synthesized by addition of trimethylsilyl cyanide (TMSCN) to carbonyl groups in the presence of Lewis acids.[1-3] Very recently, it was reported that $Yb(OTf)_3$ catalyzes TMSCN addition to aldehydes and some aliphatic ketones, however, it failed to catalyze TMSCN addition to aromatic ketones.[2] For example, acetophenone failed to react with TMSCN in the presence of $Yb(OTf)_3$ at rt. While working on enantioselective addition of TMSCN to carbonyls using chiral metal complexes, we discovered that $Cu(OTf)_2$ catalyzes the addition of TMSCN to aldehydes, aliphatic ketones, and aromatic ketones in a smooth manner, and we herein disclose our results.

In a typical procedure, benzaldehyde (1 mmol) was treated with TMSCN (1.3 mmol) in the presence of $Cu(OTf)_2$ (5 mol %) in dry CH_2Cl_2 (2 mL) at rt for 3 h. The reaction mixture was concentrated and taken in 1 mL MeCN and 1 mL of of 1N HCl and stirred at 0 °C for few minutes till the TMS ether got hydrolyzed. It was extracted with ethylacetate, washed with water, brine, and dried. Solvent removal and purification over silica gel column gave pure cyanohydrin (81% yield).[4] In a similar fashion, we tried TMSCN addition to a variety of aldehydes and found that the reaction was very smooth (Table). We extended the reaction to a variety of ketones also. Aliphatic ketones reacted with TMSCN in CH_2Cl_2 smoothly,[5] however reaction of aromatic ketones with TMSCN was slow and required longer period of time. We quickly found out that switching the solvent to MeCN helped the reaction a lot in terms of reducing the reaction time. So, we carried out all the reactions of ketones in MeCN, and results are summarized in the table. It was observed that 5 mol% of $Cu(OTf)_2$ is optimum for the reaction. Use of higher or lower amount of the catalyst decreased the yield of cyanohydrin. It was also observed that other copper salt such as $CuCl_2$ did not catalyze the TMSCN addition to carbonyl group.

In conclusion, $Cu(OTf)_2$ is an efficient catalyst for TMSCN addition to aldehydes and ketones under milder conditions. Although a variety of Lewis acids are known for this reaction, $Cu(OTf)_2$ has a great potential for extension into asymmetric version of the reaction which is also at progress in our laboratory.

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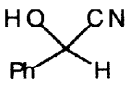
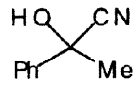
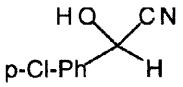
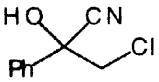
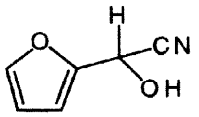
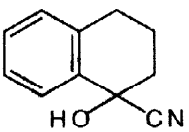
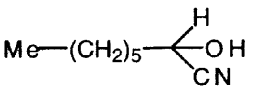
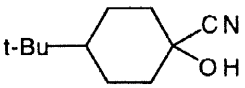
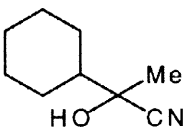
Table: $Cu(OTf)_2$ Catalyzed TMSCN Addition to Carbonyl Compounds[a]

Entry	Cyanohydrins	Time (h)	Yield (%)	Entry	Cyanohydrins	Time (h)	Yield (%)
1.		03	81	6.		20	85
2.		03	75	7.		30	82
3.		03	75	8.		50	80
4.		02	70	9.		02	95
5. PhCH=CH-CHOH(CN)		03	75	10.		03	84

[a]Reaction of aldehydes was done in CH_2Cl_2 and of ketones in MeCN at rt.

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2. Wang, D.; Yang, Y. *Synlett* **1997**, 1379.

3. For uncatalyzed reaction of TMSCN with aldehydes in MeCN, see: Manju, K.; Trehan, S. *J. Chem. Soc., Perkin Trans. 1*, **1995**, 2383.

4. Although we could also isolate TMS ether of cyanohydrin by quenching the reaction mixture with water, the isolated yield was low due to partial cleavage of silyl group to cyanohydrin. In fact, partial cleavage of TMS group was even observed during tlc run.

5. The reaction of 4-tert.-butylcyclohexanone with TMSCN in MeCN was complete in 2h whereas in CH_2Cl_2 it took 3h at rt.