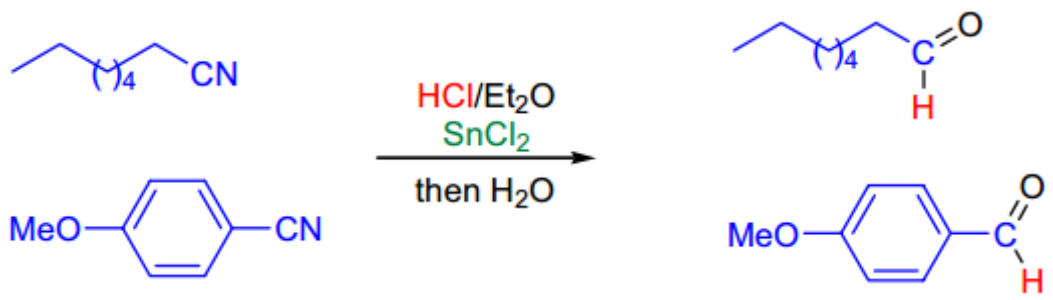
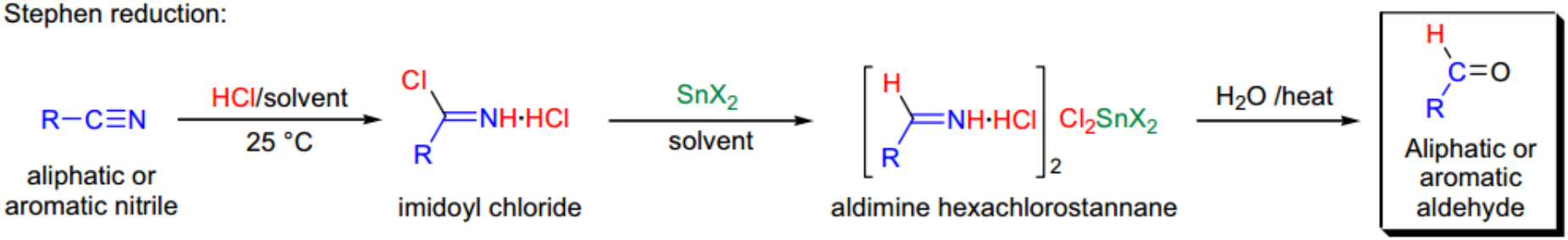
STEPHEN ALDEHYDE SYNTHESIS



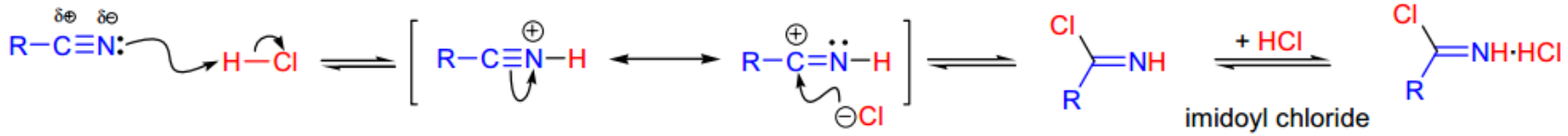
Stephen reduction:



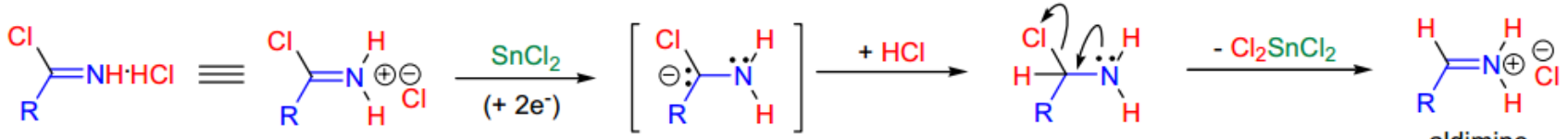
aldimine hexachlorostannane

R = 1°, 2° or 3° alkyl, aryl, heteroaryl; solvent: Et_2O, dioxane, $CHCl_3$, EtOAc; X = Cl, Br

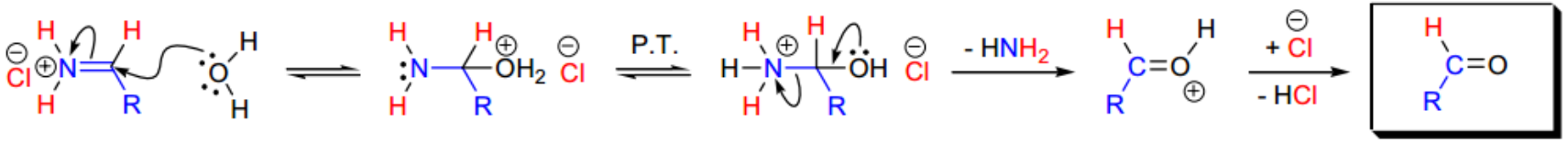
Formation of the imidoyl chloride intermediate:



Reduction of the imidoyl chloride to the aldimine:

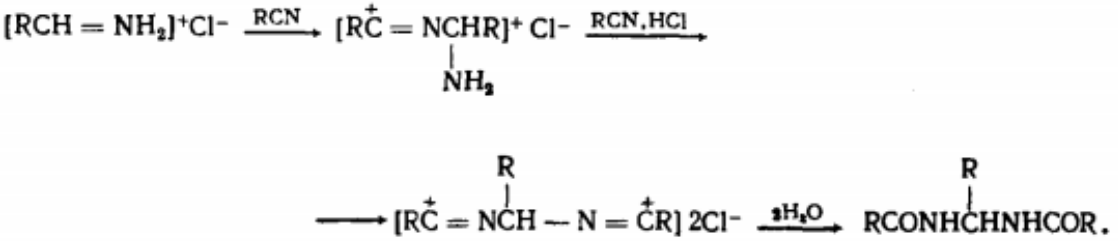


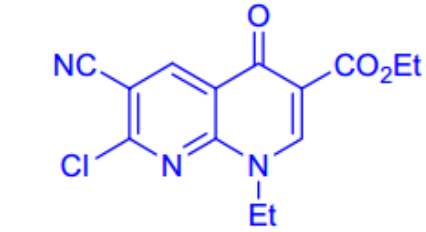
Hydrolysis of the aldimine to the corresponding aldehyde with water:



1) the original procedure has been modified: first the nitrile is dissolved in an inert solvent and the resulting solution is saturated with anhydrous HCl gas at 0 °C, then a solution of SnX2/HCl in the same solvent is added;
2) if the substrate is insoluble in a given solvent, the use of a mixture of inert solvents is recommended, most common solvents for the transformation are diethyl ether, dioxane, ethyl acetate, and chloroform;
3) the reduction products are aldimine hexachlorostannanes which usually precipitate from the reaction mixture as crystalline complexes and are readily hydrolyzed to the corresponding aldehydes with warm water;
4) the best substrates are aromatic nitriles that give moderate to good yields of the aldehyde; aliphatic nitriles tend to give lower yields primarily due to the formation of N,N‘-alkylidenbisacylamides, which are trimeric side products;
5) the yield drops sharply for aliphatic nitriles having more than six carbon atoms;
6) seldom does the Stephen reduction stop at the aldimine stage, but the reduction proceeds all the way to form the primary amine product;
7) yields are also strongly influenced by steric factors, so ortho-substituted aromatic nitriles rarely give high yield of the corresponding aldehyde;
8) the functional group tolerance is low, which renders this method only useful for robust substrates that do not have acid sensitive functional groups;
9) if a large excess of the stannous halide is used, aromatic nitro groups also undergo reduction to yield the corresponding aromatic amines.

trimeric side products

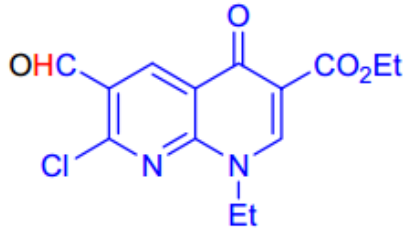




7-chloro-6-cyano-1-ethyl-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid ethyl ester

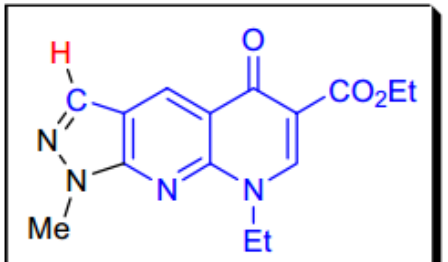
1. HCl (dry)
$SnCl_2/Et_2O$,
r.t., 2d

2. H_2O, 50 °C,
0.5h; 25%

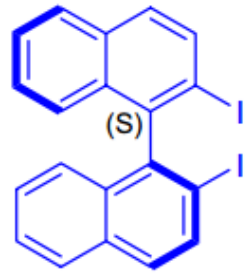


7-chloro-1-ethyl-6-formyl-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid ethyl ester

$MeNHNH_2$
EtOH, reflux
41%

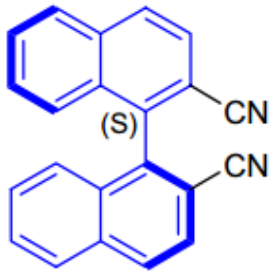


8-Ethyl-1-methyl-5-oxo-5,8-dihydro-1*H*-pyrazolo[3,4-*b*][1,8]naphthyridine-6-carboxylic acid ethyl ester



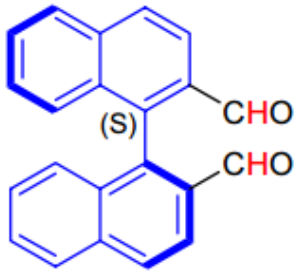
>96% *ee*

$Zn(CN)_2$, $Pd(dppf)_2$ (10 mol%)
DMF, 90 °C, 16h; 94%

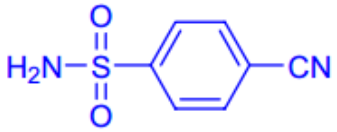


92% *ee*

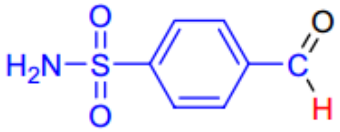
1. $SnCl_2$
(5.8 equiv)
HCl/Et_2O
r.t., 12h
2. steam, 5h; 84%



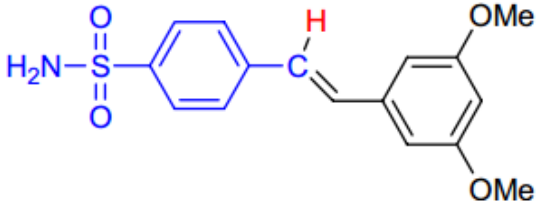
[1,1']Binaphthalenyl-2,2'-dicarbaldehyde



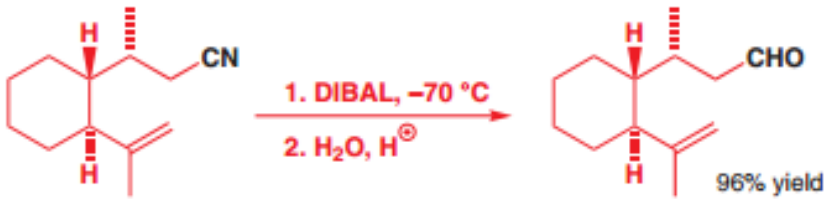
Ni-Al
HCO_2H (aq.)
86%



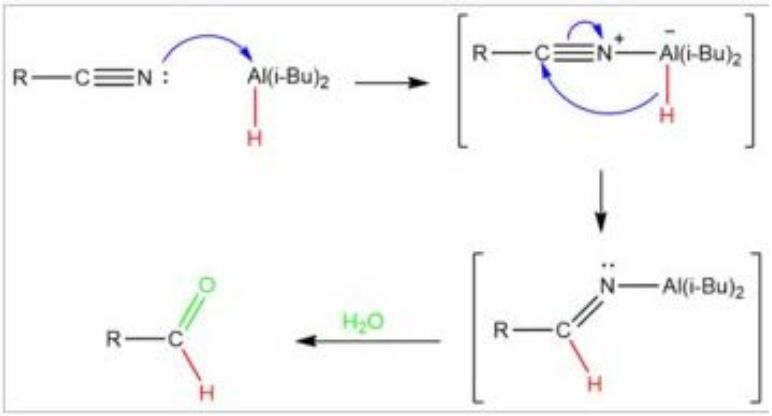
steps



trans-Stilbene benzenesulfonamide



Li(MeO)3AlH, NaH2AlEt2, et



Mind reducing agent

1

= thexyl = Thx

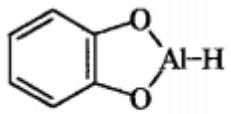
Aliphatic nitriles

Nitrile	Yield of aldehyde analyzed by 2,4-dinitrophenylhydrazine(%)
Butyro-	83
Caprylo-	95 (85)[b]
Decane-	84
Isobutyro-	72
	78[c]
	69[d]
Isovalero-	81

aromatic nitriles

Nitrile	Yield of aldehyde analyzed by 2,4-dinitrophenylhydrazine(%)
Benzo-	71 (60)[b]
	72[c]
Phthalo-	dec.
o-Tolu-	75
m-Tolu-	80
p-Tolu-	70
p-Nitrobenzo-	22
	20[d]
3-Cyanopyridine	4
	29[d]
	20[e]
4-Cyanopyridine	3
	52[d]
	48[e]
p-Carbohydroxybenzo-	91[e,f] (82)[b]

Bull. Korean Chem. Soc. 1987, 8, 301-304



Catecholalane (CA)

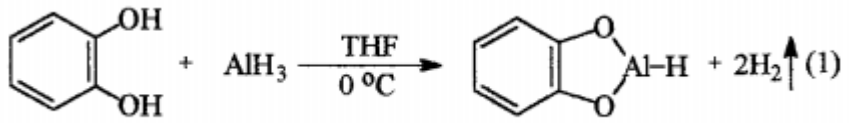
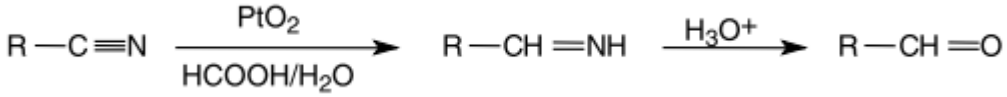
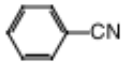
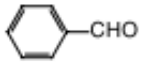
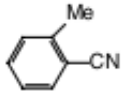
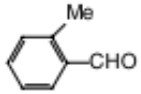
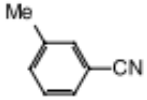
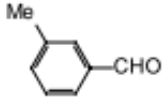
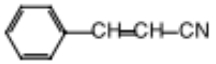
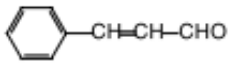
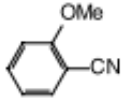
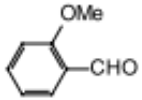
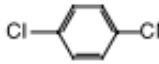
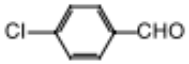
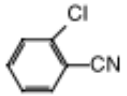
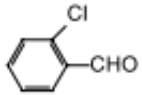
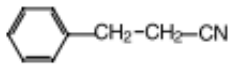
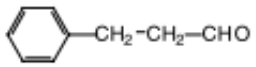


Table 1. Reduction of Nitriles to Aldehydes with Catecholalane (CA) in Tetrahydrofuran at 25 °C

Compound[a]	Time(h)	Yield(%)[b]
benzonitrile[c]	24	99,(84)[d],94[e],94[f]
4-chlorobenzonitrile[c]	24	99
2,6-dichlorobenzonitrile[g]	24	93
4-methoxybenzonitrile[c]	24	100,92[e]
o-tolunitrile[h]	24	68
	48	85
	72	95
m-tolunitrile[h]	24	92,90[e]
	48	93
terephtalonitrile[i]	24	99[e]
capronitrile[j]	24	96,(81)[d],82[f]
caprylonitrile[j]	24	92[e]
decanenitrile[j]	24	93[e]
isobutyronitrile	24	100
isovaleronitrile	24	99
trimethylacetonitrile	24	100
cyclopropanecarbonitrile	24	99
cinnamonitrile[g]	12	99

Synlett 1996, 165-166



Entry	Nitrile	Aldehyde	Reaction Time (hr)	Yield (%)
1			3	94
2			3	90
3			3	92
4			12-20	42-56
5			7	86
6			8.5	83
7			7-19	80-89
8			10-15	76-84
9			20	9

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