Metal-free Deoxygenation of Chiral Nitroalkanes: an Easy Entry to α–substituted Enantiomerically Enriched Nitriles.

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Abstract: A metal-free, mild and chemodivergent transformation involving nitroalkanes was developed. Under optimized reaction conditions, in the presence of trichlorosilane and a tertiary amine, aliphatic nitroalkanes have been selectively converted into amines or nitriles. Furthermore, when chiral β-substituted nitro compounds were reacted, the stereochemical integrity of the stereocenter was maintained and α–functionalized nitriles were obtained with no loss in enantiomeric excess. The methodology was successfully applied to the synthesis of chiral β-cyano esters, α-aryl alkylnitriles, and TBS-protected cyanohydrins, including direct precursors of four APIs (Ibuprofen, Tembamide, Aegeline and Denopamine).

Nitro derivatives are a valuable and versatile class of compounds in organic synthesis. The transformations of nitro groups into other functionalities,[1] such as their reduction or the Nef reaction[2] are therefore of primary importance, as they potentially broaden the application of nitro derivatives as useful intermediates in organic synthesis.

Our group has reported an unprecedented metal-free protocol for the reduction of nitro derivatives into amines based on the use of trichlorosilane ($HSiCl_3$),[3] an inexpensive and readily commercially available bulk chemical, widely used in the silicon industry.[4] It was observed that nitro compounds could be reduced to the corresponding amines when reacted in the presence of $HSiCl_3$ and a tertiary amine under mild reaction conditions. A systematic screening of substrates revealed that this reduction protocol is applicable to both aryl and aliphatic nitro compounds and was successfully employed in the total synthesis of complex molecules.[5]

However, with aliphatic nitro derivatives, the corresponding nitrile could be observed as a substantial reaction byproduct in variable amounts, heavily depending on the experimental conditions (nature and the stoichiometry of the base, temperature, and the structural features of the aliphatic substrate). Therefore, we decided to further investigate the reaction, in the attempt to develop an efficient protocol to convert nitro compounds in nitriles, under mild conditions.

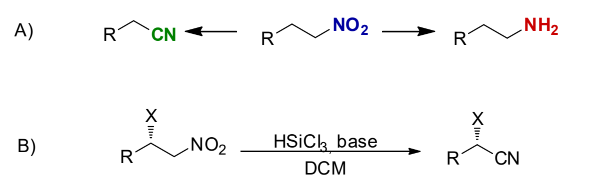
Due to their unique reactivity and activating ability, nitriles are important functional groups in organic synthesis,[6] valuable precursors for the preparation of carboxylic acids, amides, aldehydes, ketones, amidines, amines, N-containing heterocycles, or as directing groups for remote C−H activation through weak coordination. Moreover, cyanated compounds frequently find applications in medicinal, biological, physical organic, and materials chemistry.[7]

Reactions that forms C-CN bonds includes mostly substitutions and rearrangements, often requiring the use of highly toxic and difficult to handle metal-cyanides; also, dehydration reactions represent an important alternative.[6] However, most of these methods suffer from drawbacks such as harsh reaction conditions, since traditionally it is accomplished using strongly acidic dehydrating reagents; therefore, the development of a robust strategy for the synthesis of diverse functional-group-rich nitriles is highly desirable.

An interesting method for the synthesis of nitriles is the deoxygenation of nitroalkanes. Only few examples in the literature for this transformation exist, which involve different phosphorus compounds such as P_2I_4,[8] and PCl_3,[9] sulfur compounds like $Me_3SiSSiMe_3$[8] and $Na_2S_2O_4$,[10] or silyl derivatives such as Me_3SiI.[11] Transformation of optically active nitroalkanes into chiral nitriles by using benzyl bromide, KOH and nBu_4NI was reported by Carreira et al.[12]

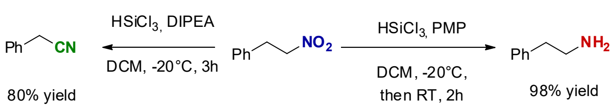
Therefore, the development of an efficient method to transform chiral nitro derivatives in the corresponding nitriles, operating under mild experimental conditions, and respectful of the stereochemical integrity of the molecule, would represent a useful entry to the synthesis of enantiomerically pure nitriles.

Herein, we report a convenient chemodivergent transformation for the selective formation of nitriles or amines starting from an aliphatic nitroalkane (Scheme 1, eq. A). Furthermore, focusing on the conversion of nitroalkanes into nitriles, we expanded reaction scope also to optically active substrates to obtain chiral enantioenriched cyano derivatives (Scheme 1, eq. B).



***Scheme* 1.** A) Chemodivergent metal-free transformation of a nitroalkane into a nitrile or an amine; B) application to the synthesis of chiral nitriles.

Our work started with the optimization of a benchmark reaction involving 2-phenylnitroethane **2a** as model substrate, in the presence of trichlorosilane ($HSiCl_3$) and diisopropylethylamine (*i*Pr_2EtN) as a base (Scheme 2). Preliminary studies revealed that 3 equivalents of base are the minimum required to give a complete conversion of the starting material and that also the temperature is a critical parameter, influencing both the reactivity and the selectivity of the system; it is necessary to keep the reaction temperature below -20°C during the exothermic addition of $HSiCl_3$. At higher temperatures, running the reaction at 0°C or at room temperature, a low selectivity was observed, and comparable amounts of nitrile and amine were obtained, with only minor preferences for one product or the other, depending on the stoichiometry and the nature of the base.

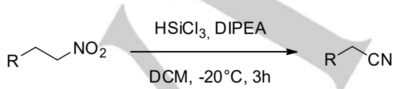


Scheme 2. Chemodivergent transformation of 2-phenylnitroethane.

The role of the base proved to be crucial for the chemoselectivity of the reaction. Using 8 mol eq. of base leads to a higher selectivity toward the nitrile, which was obtained in 80% yield with complete conversion of the starting material. The influence of the steric hindrance of the base was also investigated. The use of a much more hindered base, like pentamethylpiperidine (PMP), dramatically changed the reaction selectivity in favor of the amine. [13] This is, at the best of our knowledge, the first example of a chemodivergent transformation that starting from an aliphatic nitro compound is able to give, just changing some reaction parameters, almost complete selectivity in the formation of the amine or the cyano derivative.

While the reduction of nitro groups to give amines is a very studied and well explored topic, the deoxygenation of nitroalkanes to give nitriles is a less common transformation. A specific work-up allowed to eliminate the amine and obtain clean crude products (see supporting information). To test the applicability of the protocol, the reaction with different nitroalkanes, including compounds featuring aromatic rings (electron-rich and electron-deficient) and aliphatic chains, was performed. In all cases, the expected nitriles were isolated with moderate to good chemical yields (Table 1).[14]

Table 1. Metal-free conversion of nitroalkanes to nitriles.



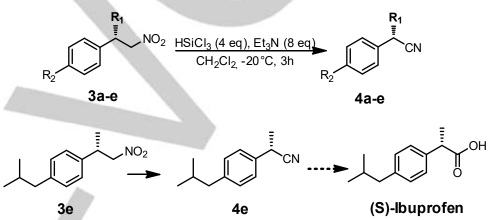
1a-e **2a-e**

Entry	Product	R	Yield %[a]
1	**2a**	Ph	80
2	**2b**	Napht	70
3	**2c**	4-Cl-Ph	51
4[b]	**2c**	4-Cl-Ph	45
5	**2d**	4-OMe-Ph	66
6	**2e**	$PhCH_2CH_2$	50
7[b]	**2e**	$PhCH_2CH_2$	66

[a] Isolated yields [b] Et_3N was used (8 mol eq.);

Our next goal was the implementation of such methodology for the deoxygenation of synthetically useful chiral nitroalkanes to afford enantioenriched nitriles. This would represent an additional challenge, since our reaction conditions involve the use of both a base and a Lewis acid, which could result in post reaction racemization. Since different catalytic, enantioselective methods for the preparation of chiral nitroalkanes are available,[15] their transformation under mild reaction conditions would represent an easy access to optically active nitriles.

The deoxygenation protocol was first tested on optically active β-alkyl nitroalkanes, derived from enantioselective reduction of disubstituted nitroalkenes. The substrates **3a-e** were reacted with 4 eq of trichlorosilane, in the presence of 8 eq. of triethylamine in dichloromethane, at -20 °C, for 3 hours and afforded the nitriles **4a-e** in fair to good yields (Scheme 3).



Scheme 3. Synthesis of enantiomerically enriched α-alkyl substituted nitriles.

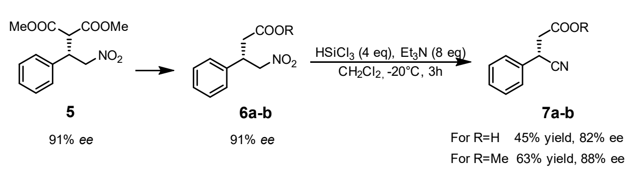
In all cases, no unreacted starting material was observed, and the products were isolated with only a very marginal loss of optical activity (enantiospecifity (*es*) always >95%,Table 2). A direct precursor of (S)-Ibuprofen (compound **4e**, entry 5) was successfully synthetized in 61% yield and without any loss in enantiomeric excess.

Table 2 Conversion of nitroalkanes to chiral α-alkyl substituted nitriles.

Entry	Prod uct	R_1	R_2	Y (%)[a]	*es* (%)[b]	*ee* **3a-e** (%)	*ee* **4a-e.** (%)
1	**4a**	Me	H	41	100	87	87
2	**4b**	Me	OMe	55	98	87	85
3	**4c**	Me	Cl	43	96	82	79
4[b]	**4d**	Et	H	57	95	85	81
5[b]	**4e**	Me	$CH_2C(Me)_2$	61	100	85	85

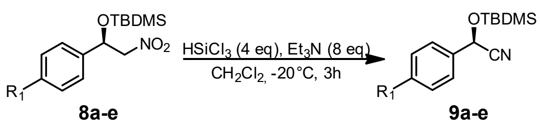
[a] Isolated yields after chromatographic purification, [b] es = enantiospecifity (ee **4** / ee **3 %**)

Well established organocatalytic methods are available for the stereoselective addition of dimethylmalonate to nitrostyrene, to afford adduct **5**, that was prepared in excellent yields and 91% *ee*.[13] Decarboxylation afforded the corresponding 4-nitro-3-phenyl butanoic acid **6a**, without any loss of stereochemical integrity (for synthetic details, see the Supporting Information).



Scheme 4. Synthesis of enantioenriched precursor of 2-aryl succinates.

The trichlorosilane-mediated deoxygenation of the carboxylic acid derivative **6a** afforded nitrile **7** in 45% yield and 82% *ee*.. When the reaction was performed on the methyl ester **6b**, methyl 3-cyano-3-phenyl ethanoate **7** was obtained in 63% yield and 88% *ee.* The reaction affords a direct precursor of enantioenriched 2-aryl succinate derivatives, valuable building blocks for the preparation of biologically active compounds, whose asymmetric catalytic synthesis is still challenging.[16]
The deoxygenation strategy was also applied to β-hydroxy nitroalkanes, protected as silylethers, that may be converted into chiral cyanohydrines. These are precursors of α–hydroxy carboxylic acids, important subunits frequently found in biologically active compounds and versatile building blocks for further transformations (Scheme 5).[17][18][19]



***Scheme* 5.** Synthesis of chiral α–silyloxy nitriles.

Chiral β-silyloxy nitroalkanes, featuring different groups on the aromatic ring, **8a-e** were synthesized by established catalytic nitroaldol reactions[13] and were reacted with trichlorosilane and triethylamine for 3 hours in DCM. All products were obtained in good yields and with no appreciable erosion of the enantiomeric excess (enantiospecifity higher than 98%, Table 3).

Table 3 Conversion of nitroalkanes to chiral α-silyloxy substituted nitriles.

Entry	Compound	R_1	Y (%)[a]	*es* (%)[b]	*Ee* **9a-e** (%)
1	**9a**	H	80	100	91
2	**9b**	Me	80	100	89
3	**9c**	OMe	70	98	87
4	**9d**	Cl	62	99	86
5	**9e**	OAllyl	54	99	74

[a] Isolated yields after chromatographic purification, [b] es = enantiospecifity

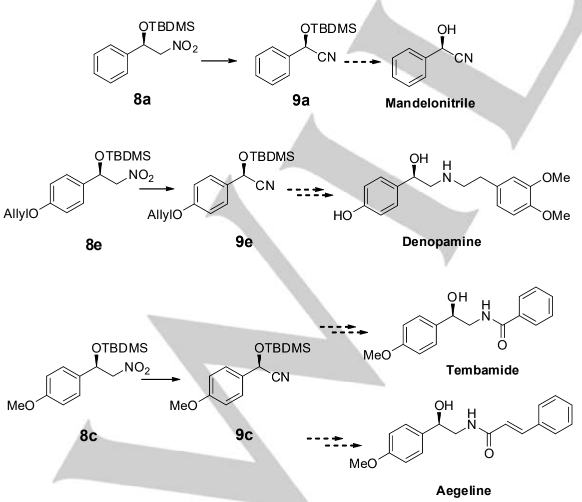


Figure 1. Chiral α-silyloxy substituted nitriles as valuable precursors of biologically active compounds.

For example, protected mandelonitrile could be prepared in 80% yield and 91% e.e. Chiral nitriles **9e** and **9c** are valuable, advanced precursors of Denopamine, and of Tembamide and Aegeline, respectively (Figure1). [20], [21]
Oximes were sometimes observed as byproduct in this reaction. This observation together with the evident effect of the base hindrance on the reaction selectivity led to the following mechanistic proposals. The oxime is in tautomeric equilibrium with the nitroso derivative, known to be the product of the first reduction step of the nitro group. From here, two more reduction steps afford the corresponding amine.[3] Alternatively, a different reaction pathway leading to the nitrile, depending on the reaction conditions, could be envisaged (mechanism A, Figure 2). This hypothesis was supported also by the fact that the oxime is a known reaction intermediate in many of the known methodologies for the transformation from nitro to nitrile.

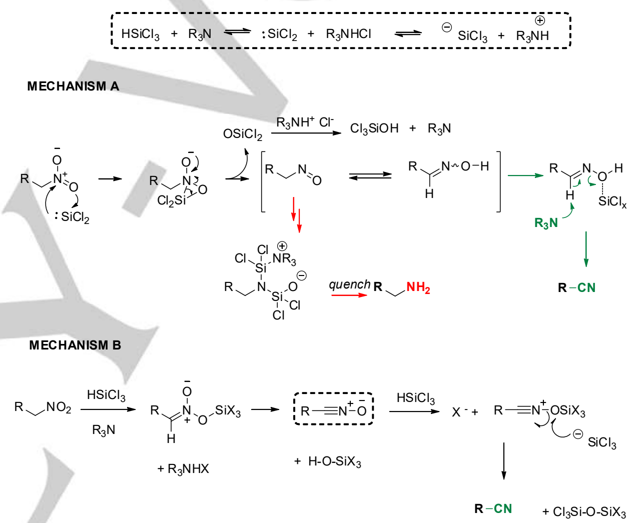


Figure 2. Two possible hypothesized mechanisms for the trichlorosilane-mediated deoxygenation of nitroalkanes to afford nitriles.

As alternative mechanism, the deprotonation of the silylated nitroalkane could lead to the formation of a nitriloxide (mechanism B); the synthesis of nitrile oxides from nitro alkanes in the presence of dehydrating agents has been described.[22, 23] Therefore, under the present conditions, with an excess of a tertiary amine and trichlorosilyl derivatives, the formation *in situ* of a nitriloxide cannot be excluded. Then, the reaction of such intermediate with a Si(II) species could account for the reductive step that generates the nitrile with the formation of a silyloxi species and reoxidation of the Si(II) atom to Si(IV).

In summary, a new chemoselective divergent methodology for the reduction of aliphatic nitro compounds into nitriles and amines has been developed. The protocol proved to be convenient for the synthesis of optically active nitriles starting from chiral nitroalkanes. The ability to access a range of optically active nitriles through a sequence that involves catalytic enantioselective reduction of nitroalkanes, or stereoselective Michael addition, followed by conversion into nitrile as described above, considerably expands the scope of such approaches to the synthesis of functionalized chiral molecules. The protocol provides access to a class of compounds that are otherwise not easily prepared by known methods in catalytic asymmetric synthesis. The salient features of the method include inexpensive bulk chemicals and metal-free conditions, thus excluding potential contamination of the product by metal impurities.

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Keywords: chiral nitriles • nitroalkanes • stereoselectivity • metal-free reaction • trichlorosilane

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[13] For further details see the Supporting Information

[14] The formation of the oxime was observed as byproduct in variable amounts (ranging between 10 - 25% yield). When the oxime was prepared and reacted under the standard experimental conditions, the nitrile was formed, but only in 50-60%, with some unreacted oxime in the mixture. The experiment may be considered as a proof that indeed the reaction goes through the oxime as intermediate, but the reaction is likely going also through another mechanism, as proposed in Figure 2.

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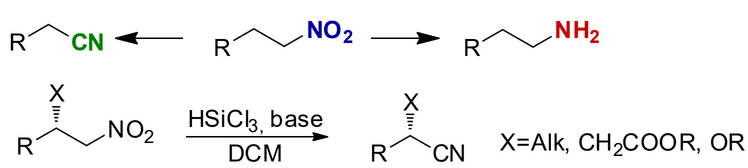

A chemoselective divergent methodology for the reduction of aliphatic nitro compounds into nitriles and amines has been developed. The protocol efficiently affords optically active nitriles starting from chiral nitroalkanes. In the reaction, inexpensive bulk chemicals are employed and the use of heavy metals is precluded, excluding potential contamination of the product by metal impurities.