Organic Synthesis

# Convenient Transformation of Optically Active Nitroalkanes into Chiral Aldoximes and Nitriles**

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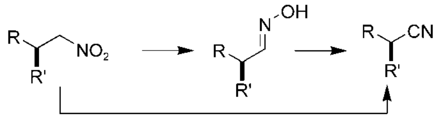
The chemistry of nitro compounds forms the basis of a number of well-known processes, such as the Henry or the Nef reactions.[1] Transformations such as the latter permit the interconversion between nitro and other functional groups and are therefore of prime importance. They make possible the application of nitroalkanes as useful intermediates in synthesis. There has been intense activity in the development of catalytic, enantioselective methods for the preparation of chiral nitroalkanes.[2,3] The use of optically active organonitro compounds would significantly benefit from the availability of methods for their conversion under mild conditions into other chiral compound classes. Herein we report a convenient heavy-metal-free transformation of optically active nitroalkanes into chiral aldoximes at room temperature by employing inexpensive reagents: benzyl bromide, KOH, and 5 mol% $n$Bu$_4$NI (Scheme 1). This also makes possible a one-pot conversion of nitroalkanes into optically active nitriles.



***Scheme 1.*** Transformation of optically active nitroalkanes into chiral aldoximes and nitriles in the absence of heavy metals.

The most commonly employed methods for the reduction of primary nitroalkanes to oximes involve the use of Bu$_3$SnH, Se/NaBH$_4$, CS$_2$, or SnCl$_2$ (often in combination with thiophenol).[4,5] Our interest in the synthesis and use of optically active nitroalkanes as chiral building blocks has led us to focus on the development of milder, more convenient alternatives.

In analogy to the Kornblum oxidation that uses DMSO, 2-nitropropane has been employed for the conversion of benzyl halides into benzaldehydes.[6] The applications of this transformation have been solely focused on the halide partners and their oxidation to aldehydes. No study has appeared that addresses the scope of the nitroalkanes that may be successfully employed.[7] This leaves a number of critical issues

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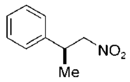
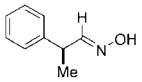
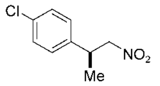
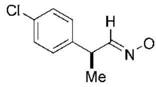
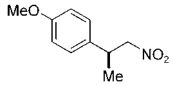
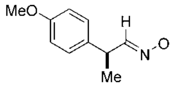
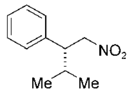
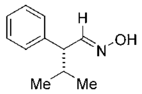
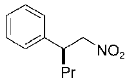
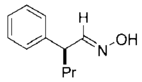
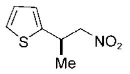
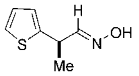
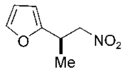
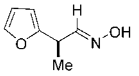
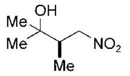
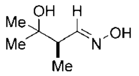
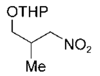
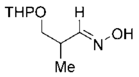
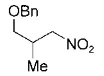
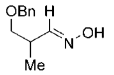
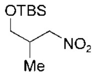
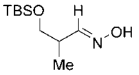
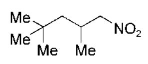
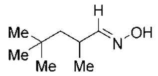
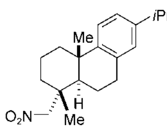
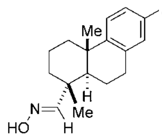
unresolved that would be important for the successful implementation of such methodology for the reduction of a range of synthetically useful chiral nitroalkanes. In this respect, first, it was not clear whether the process would be generally applicable for non-benzylic primary nitroalkanes. Second, a chief concern when using optically active β-substituted nitroalkanes was whether the stereochemical integrity of the compound would be preserved.

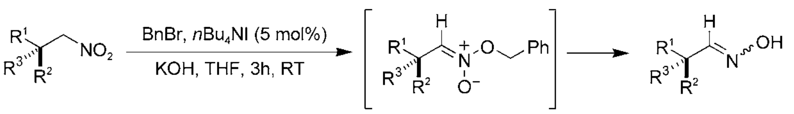
In initial investigations, treatment of 2-phenyl-1-nitropropane with benzyl bromide and KOH in THF in the presence of 5 mol% $n\mathrm{Bu_4NI}$ at room temperature led to the formation of the corresponding aldoxime in 3 h and with 72% yield. The use of soluble amine bases failed to give product, whereas the heterogeneous conditions KOH/THF proved optimal in promoting aldoxime formation for a broad range of substrates. As shown in Table 1, optically active nitroalkanes including aromatic (electron-rich and electron-deficient), heteroaromatic, branched and unbranched aliphatic substrates, as well as substrates that incorporate unprotected alcohol functionalities were successfully reduced. Furthermore, it was demonstrated (Table 1, entry 13) that a nitroalkane which bears a quaternary center in the β-position was successfully reduced under these conditions, despite the longer reaction times needed (24 h compared to 3 h). Importantly, by means of a chiral HPLC assay, we determined that no racemization occurred during the process. This is particularly important for entries 1–7 (Table 1) as they involve intermediates in which an acidic C–H bond is rendered labile by both the *O*-alkylnitronate [Eq. (1), $R^3 = H$] and aryl groups. Also, nitroarenes are unreactive under these conditions.[8] Consequently, the method we describe provides a chemoselective reduction of nitroalkanes, which in effect reverses the reactivity pattern seen with traditional reductants.

Chiral oxime products serve as a source of aldehydes and chiral nitrile oxides [Eq. (2)].[9,10] Chiral nitrile oxides have been shown to be convenient starting materials for the synthesis of ketides in highly diastereoselective [3+2] dipolar cycloadditions with allylic alcohols. The ability to access a range of optically active oximes through a sequence that involves catalytic enantioselective reduction of nitroalkenes followed by their conversion into oximes as described above considerably expands the scope of such approaches to the synthesis of polyketides.

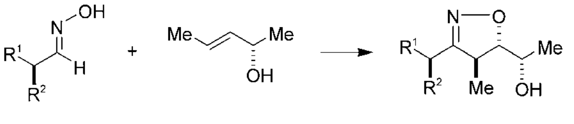
***Table 1:*** Conversion of nitroalkanes into oximes [Eq. (1)].[a]

| Entry | Substrate | Product | Yield [%] |
|---|---|---|---|
| 1 |  |  | 72 |
| 2 |  |  | 80 |
| 3 |  |  | 69 |
| 4 |  |  | 81 |
| 5 |  |  | 80 |
| 6 |  |  | 76 |
| 7 |  |  | 75 |
| 8 |  |  | 60 |
| 9 |  |  | 78 |
| 10 |  |  | 65 |
| 11 |  |  | 70 |
| 12 |  |  | 73 |
| 13 |  |  | 56 |

[a] Typical reaction conditions: BnBr (1.1 equiv), KOH (1.05 equiv), and $n\mathrm{Bu_4NI}$ (5 mol%) in THF at room temperature. THP = tetrahydropyran, Bn = benzyl, TBS = *t*-butyldimethylsilyl.



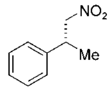
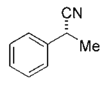
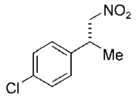
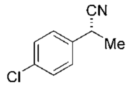
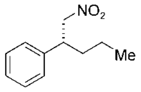
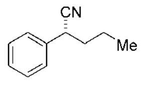
(1)



(2)

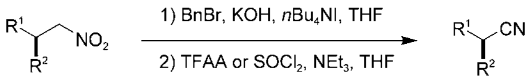
To further expand the application of the reduction protocol described above, we examined the possibility of carrying out a one-pot transformation of nitroalkanes into nitriles through the oxime. Of particular concern again was whether the desired nitrile could be isolated without loss of optical purity. The screening of a variety of dehydrating reagents revealed that by using trifluoroacetic anhydride (TFAA) or thionyl chloride and base (e.g. $NEt_3$), efficient formation of nitriles through the dehydration of the aldoximes occurs.[11] Thus, following treatment of the starting organonitro compound with benzyl bromide, KOH, and $n\mathrm{Bu_4NI}$ in THF (3 h at room temperature) and when the consumption of the nitroalkane was judged to be complete, the simple addition of $SOCl_2$ or TFAA [Eq. (3) and Table 2] leads directly to nitriles in preparatively useful yields without loss of optical activity as

*Table 2:* One-pot transformation of chiral nitroalkanes into nitriles.[a]

| Entry | Substrate | Reagent | Product | Yield [%] |
|---|---|---|---|---|
| 1 |  | TFAA |  | 62 |
| 2 | | $SOCl_2$ | | 66 |
| 3 |  | TFAA |  | 63 |
| 4 | | $SOCl_2$ | | 69 |
| 5 |  | TFAA |  | 73 |
| 6 | | $SOCl_2$ | | 72 |

[a] Typical reaction conditions: BnBr (1.1 equiv), KOH (1.05 equiv), $n\mathrm{Bu_4NI}$ (5 mol%) in THF, room temperature, 3 h; then TFAA (trifluoroacetic anhydride) or $SOCl_2$ (4.5 equiv), $NEt_3$ (9 equiv), −20°C, 12 h.

verified by chiral HPLC assays. The overall protocol provides access to a class of compounds that are otherwise not easily accessed by known methods in catalytic asymmetric synthesis.[12]


(3)

In summary, we have documented a convenient protocol for the synthesis of optically active aldoximes and nitriles starting from chiral nitroalkanes. The salient features of the method include: 1) the reaction can be performed at room temperature under ambient atmosphere, 2) inexpensive reagents are employed (BnBr, KOH, $n\mathrm{Bu_4NI}$), and 3) the use of heavy metals is precluded. This provides an environmentally friendly reaction that excludes the potential contamination of the products by metal impurities. Given the ongoing advances in catalytic asymmetric synthesis that involve nitro compounds, the methodology described herein expands their possibilities for conversion into valuable synthetic targets.

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**Keywords:** chirality · nitro compounds · oximes · reduction · synthetic methods

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[8] No reaction was observed by $^1$H NMR spectroscopy when nitrobenzene was treated with benzyl bromide (1.1 equiv), KOH (1.05 equiv), and $n\mathrm{Bu_4NI}$ (5 mol%) in THF at room temperature for 6 h.

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