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Stereoselective Radical-Radical Coupling Reactions of Metallated Imidazolines

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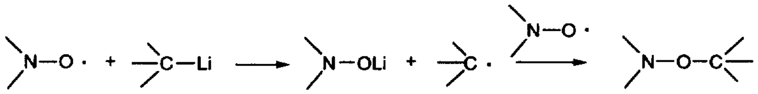
Abstract: *Dianions derived from chiral imidazolines **1a-c**, undergo selective one-electron oxidation reactions in the presence of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) and form metallated radical species. Depending on the reaction conditions the radical intermediate is trapped stereoselectively by TEMPO, or undergoes a dimerization reaction.*

Keywords: Asymmetric reactions; Carbanions; Electron transfer; Radicals and radical reactions.

We recently described that C_2 symmetric imidazolines are valuable chiral inductors in asymmetric metallation-alkylation processes[1]. As a logical extension of this work, it was hypothesized that these chiral systems may additionally have some use in asymmetric radical reactions.[2]

Metallated organic intermediates can be transformed into organic free-radicals by one electron oxidation.[3] The transformation of dimetallated intermediates into metallated organic radicals is not fully understood, and remains unexplored on a preparative scale. Difficulties arise from the thermal instability of the intermediate organometallic species under the reaction conditions and additionally, from a chemical incompatibility with the oxidizing agent. Our attention has been turned towards stable organic radicals, such as nitroxy radicals[4], as one-electron oxidizing agents. Despite reports that some alkylsamarium, benzylzinc, benzylcopper[5] and alkyllithium compounds[6] reacts with TEMPO *via* chemically induced electron transfer (CET), the reaction has received only limited attention[7].



We wish to report here that in the presence of TEMPO, dianions derived from chiral imidazolines **1a-c**[8], undergo selective one electron oxidation and form a radical anion species, which either can be trapped by TEMPO, or may undergo dimerization. The oxidation reaction, and the following alkylation reaction are fast, being virtually instantaneous at -78°C. By addition of an approximatively 1.8 molar equivalents of TEMPO solution (saturated in hexane) the orange colour of the dianion disappears, and the red colour of the oxidant appears. The addition rate of the oxidizing agent has a dramatic influence on the reaction. While addition of the TEMPO solution in one portion at -78°C gives rise to the formation of the hydroxylated compounds[9,10] **3a-c**, (yields 51-47 % respectively), slow addition of the oxidizing agent to the dianion derived from **1a**, over 6 hours using a syringe pump, and at -78°C, resulted in the formation of an asymmetric dimer as the major product[11] in 48% yield. In both cases 35-38% of unreacted starting materials were also recovered.

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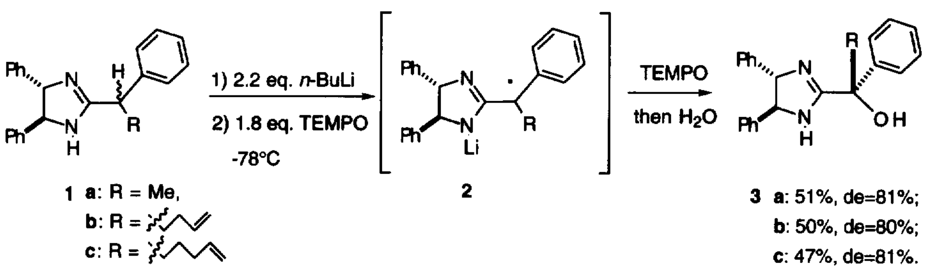

The scope of this oxidation reaction seems to be limited. Lithiated intermediates derived from ethyl phenylacetate and/or benzyl cyanide do not undergo the hydroxylation reaction. Under the routinely used conditions only unreacted starting materials were recovered from the mixture.

The configuration of the newly formed asymmetric center was established by chemical correlation, using the earlier developed alkylation-fragmentation sequence, and was assigned as depicted in the scheme. Moreover, the comparison of the ^{1}H NMR spectrum of **3a** with that of the compound resulting from oxidation of **1a** using 1.1 molar equiv. of Davis' oxaziridine (THF, -78°C, 74%, de≥95%), showed that the stereochemistry is consistent in both cases with the stereochemistry of alkylation of dianions using alkyl halides as electrophiles.

The high diastereoselectivity of this radical-radical coupling reaction is surprising. It is generally accepted, that, in free-radical reactions, the stereoselection occurs *after* the formation of the radical in a kinetically controlled process[12]. Understandably, the principal body of our knowledge on stereoselective radical coupling reactions is based on reactions of reasonably slow rates, such as hydrogen- or allyl-transfer reactions. Chiral systems which allow stereoselective radical-radical couplings, which usually have rates close to diffusion are indeed elusive. This lack of selectivity is a notorious and basic problem in these processes. This communication wishes to provide an example, that at least in some cases, good control can be obtained for such a type of reaction[13].

References and footnotes:

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8 Starting materials were prepared and the dilithiations were performed according to the procedures previously outlined.[1a] Accordingly dilithiation of imidazolines was performed in THF using *n*-BuLi at -25°C, without addition of other complexing agents such as TMEDA, or metal salt.

9 The formation of the hydroxylated derivative was attributed to the fragmentation/decomposition of the intermediate *N*-oxy adduct. The instability of this intermediate was anticipated on the basis of the considerable steric congestion of the TEMPO adduct. The isolation of the primary adduct with TEMPO was unsuccessful.

10 We were unable to isolate cyclized products i.e. in which the transient radical would be trapped by an olefin side chain. This result is probably due to the fast intermolecular trapping comparing to the relatively slow cyclization reaction.

11 The regiochemistry of this reaction follows the dimerization pattern of the trityl radical (Gomberg's radical), as it was ascertained by ^{1}H and ^{13}C NMR.

12 Similar to polar reactions, complexing agents such as Lewis acids may increase stereoselectivity by stabilizing one of the conformers, and/or select reaction paths by modulating the activation energy gap of the given reaction.

13 For a related stereoselective TEMPO trapping experiment see: Jahn, U.; Hartmann, P. *Chem. Commun.* **1998**, 209.