SmI_2-Mediated Reductive Cross-Coupling Reactions of α-Cyclopropyl Nitrones

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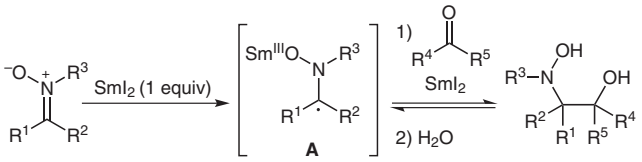
Abstract: Three new α-cyclopropyl nitrones have been synthesized as mechanistic probes for reductive cross-coupling reactions of nitrones. The α-cyclopropylcarbinyl radical intermediate formed by single electron transfer from SmI_2 to these nitrones is not prone to ring opening, due to a unique stabilization by the vicinal N–O–Sm system. Consequently, β-cyclopropyl hydroxylamines could be prepared in high yield from α-cyclopropyl nitrones.

Key words: nitrone, samarium diiodide, reductive coupling reaction, mechanistic probes, cyclopropyl group

Samarium(II) iodide is a powerful single electron transfer agent, that has been used for a vast range of one-step and cascade transformations.[1] Despite the 30 years history of SmI_2 chemistry since its introduction by Kagan,[2] the mechanism of many SmI_2-mediated reactions remains equivocal. Depending on the nature of substrates, the formation of radical, anionic, or organosamarium intermediates has been postulated or confirmed by mechanistic studies.[3] Cyclopropyl ketones have proved to be convenient mechanistic probes for radical intermediates,[4] as the cyclopropylcarbinyl → homoallyl radical rearrangement of cyclopropyl-substituted ketyl radical anions is a kinetically favored process.[5] Cyclopropyl ring opening has served for probing the formation of ketyl radical intermediates upon treatment of α-cyclopropyl ketones with SmI_2,[6] and it has also been used advantageously in the synthesis of complex natural products.[7] However, Handa et al. demonstrated that SmI_2-mediated intramolecular pinacol coupling of cyclopropyl ketones to form five-membered rings is such a fast process, that cyclization competes favorably with ring opening.[8]

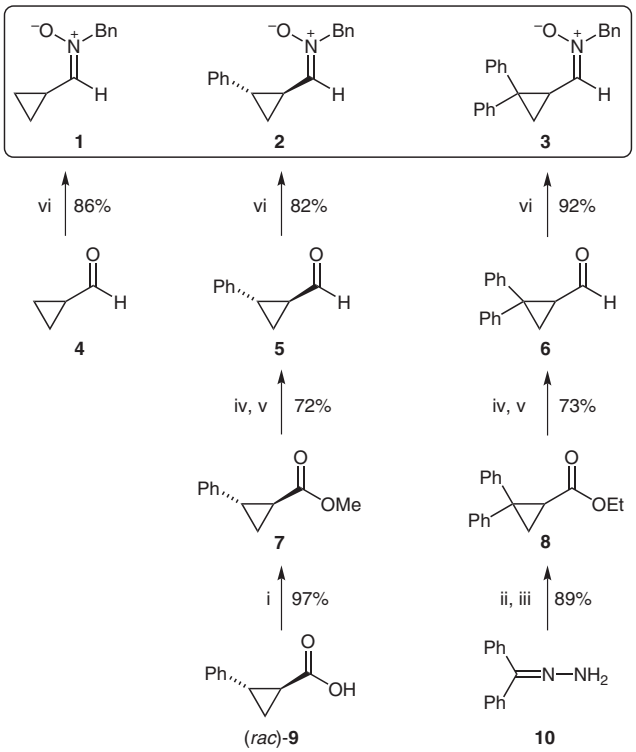
Previously, we have reported the chemoselective cross-coupling of nitrones with carbonyl compounds in the presence of SmI_2 (Scheme 1),[9] as an efficient method to access vicinal amino alcohols derivatives.[10] The formation of radical **A** was proposed to be the first step of the process.

Intermediate **A** can be considered as an imino equivalent of ketyl radical anions. It was thus expected that upon treatment with SmI_2, α-cyclopropyl nitrones could undergo cyclopropane ring opening during the reductive coupling reactions of nitrones with aldehydes, ketones[9] or α,β-unsaturated esters.[11] To the best of our knowledge, the reactivity of α-cyclopropyl imine derivatives under reductive conditions has not been investigated yet.



Scheme 1 SmI_2-mediated cross-coupling of nitrones and carbonyl compounds

Herein, we present the synthesis of α-cyclopropyl nitrones **1**–**3** (Scheme 2), as potential mechanistic probes for SmI_2-mediated reactions of nitrones. As the rate of cyclopropyl ketyl opening depends on the nature of the substituents on the cyclopropane ring (2-phenyl cyclopropyl ketyl opens



Scheme 2 Synthesis of α-cyclopropyl nitrones **1**–**3**. *Reagents and conditions*: (i) $SOCl_2$, MeOH, reflux; (ii) MnO_2, $MgSO_4$, CH_2Cl_2; (iii) ethyl acrylate, pentane; (iv) $LiAlH_4$, THF, 0 °C to r.t.; (v) Dess–Martin, CH_2Cl_2; (vi) BnNHOH, $MgSO_4$, CH_2Cl_2.

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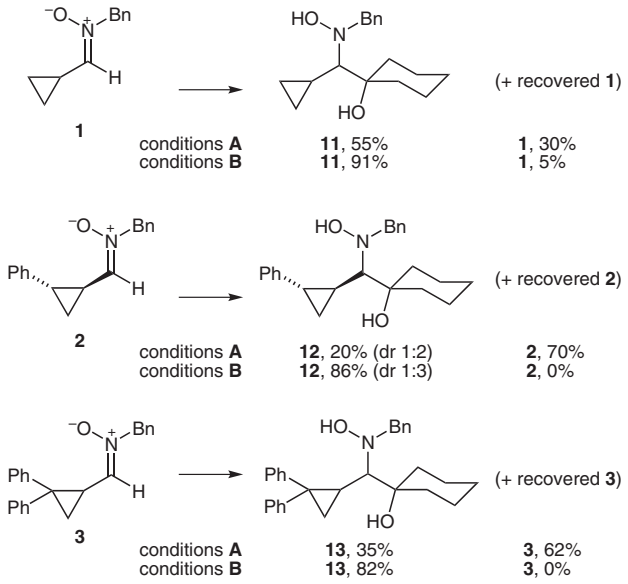
significantly faster than unsubstituted cyclopropyl ketyl radical),[12] it was assumed that the rate of ring opening in α-cyclopropyl nitrones would also be related to its degree of substitution, by analogy.

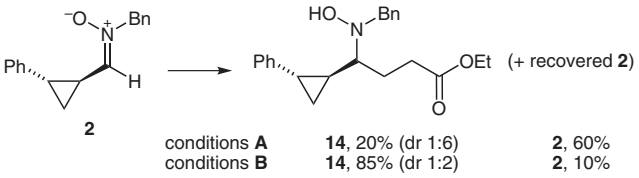
α-Cyclopropyl nitrones **1–3** were prepared by reaction of *N*-benzylhydroxylamine with the corresponding α-cyclopropyl carbaldehydes **4–6** (Scheme 2).[13] While cyclopropane carbaldehyde (**4**) is commercially available, its mono- and disubstituted derivatives **5**[14] and **6**[15] were synthesized from (*rac*)-*trans*-2-phenylcyclopropane carboxylic acid (**9**) and benzophenone hydrazone (**10**), respectively.

Nitrones **1–3** were first subjected to SmI_2-mediated reductive cross-coupling with cyclohexanone (Scheme 3, conditions **A**).[16] In all cases, only the β-cyclopropyl-β-*N*-hydroxyamino alcohols **11–13** were isolated as products, with no trace of opened-ring products. The reactivity of α-cyclopropyl nitrones in the presence of samarium diiodide thus contrasts with the reactivity of the corresponding α-cyclopropyl carbonyl compounds.[6] Disappointingly, in these reactions, the conversions were reproducibly modest in conditions **A**. However, as previously observed,[9b,11] the introduction of water in reaction media[17] led to a significant improvement of the yields (82–91%) in β-cyclopropyl-β-*N*-hydroxyamino alcohols **11–13** (Scheme 3, conditions **B**).[16] Again, no opened-ring product was detected. At this stage, it was assumed that, like in Handa's studies,[8] the SmI_2-mediated reaction of nitrones with carbonyl compounds was a fast process that could compete favorably with the radical ring opening of the cyclopropyl group.



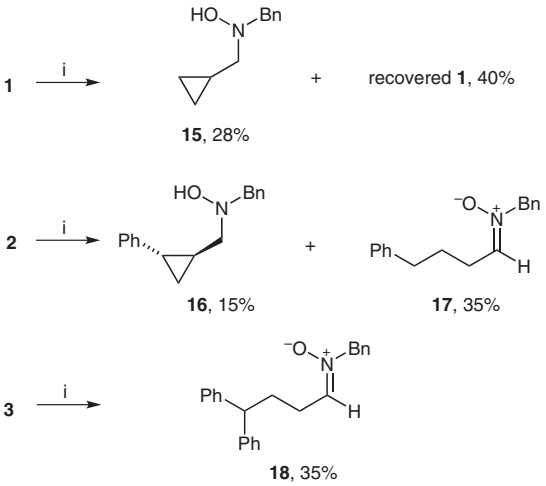
Scheme 3 SmI_2-mediated reductive cross-coupling of α-cyclopropyl nitrones **1–3** with cyclohexanone. Conditions **A**: cyclohexanone (1.5 equiv), SmI_2 (2.2 equiv), THF, –78 °C, 3 h; Conditions **B**: cyclohexanone (1.5 equiv), SmI_2 (3.0 equiv), H_2O (16.0 equiv), THF, –78 °C, 3 h.

The SmI_2-mediated reductive coupling of nitrones with α,β-unsaturated esters being a slower process when compared to the coupling of nitrones with aldehydes and ketones, it was thought that ring opening of the cyclopropyl group could compete with cross-coupling in this case.[11a] Nitrone **2** was thus reacted with ethyl acrylate under similar conditions (Scheme 4). However, again the cross-coupling reaction was favored over cyclopropyl opening, and the γ-*N*-hydroxyamino ester **14** was obtained in 85% yield (Scheme 4, conditions **B**).



Scheme 4 SmI_2-mediated reductive cross-coupling reactions between α-cyclopropyl nitrone **2** and ethyl acrylate. Conditions **A**: ethyl acrylate (1.5 equiv), SmI_2 (2.2 equiv), THF, –78 °C, 3 h; Conditions **B**: ethyl acrylate (1.5 equiv), SmI_2 (3.0 equiv), H_2O (8.0 equiv), THF, –78 °C, 3 h.

As noted by Guibé and co-workers,[3a] the non-observation of products arising from cyclopropyl opening does not necessarily mean that radical species are not formed. Moreover, kinetic studies on cyclopropyl ring opening have generally been conducted with free radical anions, and may not transpose to samarium-bound species. In order to evaluate the feasibility of reductive ring opening in nitrones **1–3**, the latter were next treated by SmI_2 in the absence of carbonyl or α,β-unsaturated ester partner, to avoid the competition of cross-coupling reactions with α-cyclopropyl ring opening (Scheme 5).



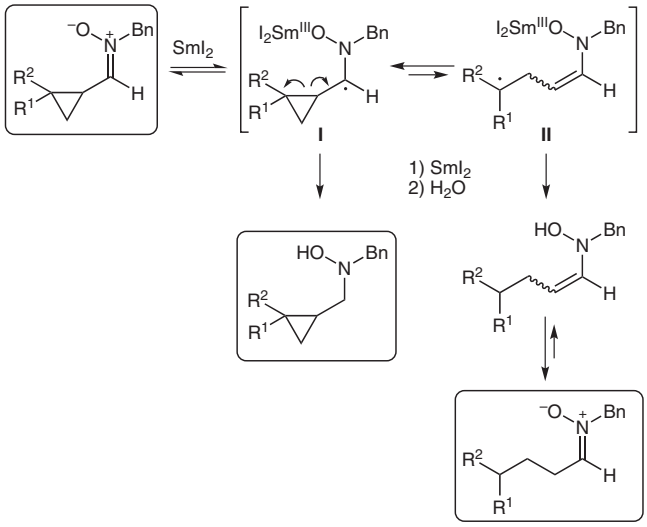
Scheme 5 SmI_2-mediated reactions of α-cyclopropyl nitrones **1–3**. *Reagents and conditions*: (i) SmI_2 (3.0 equiv), H_2O (16.0 equiv), THF, –78 °C, 3 h.

In conditions **A**, no transformation occurred, and starting nitrones were recovered intact (not shown in Scheme). In the presence of water (conditions **B**), nitrones **1–3** exhibited different reactivity pattern, depending on their sub-

stituents on the cyclopropyl ring. Under treatment with SmI_2 (3 equiv) in the presence of water (16 equiv) at –78 °C, nitrone **1** was partially reduced to the corresponding *N*-hydroxylamine **15** (28%); no opened-ring product was detected in the reaction mixture, and 40% of starting material was recovered. Under the same conditions, the phenyl-substituted nitrone **2** was transformed into *N*-hydroxylamine **16** (15%) and nitrone **17** (35%); nitrone **3** yielded nitrone **18** (35%) as the only identified product. Nitrones **17** and **18** do result from α-cyclopropyl ring opening from SmI_2-mediated reduction of nitrones **2** and **3**, respectively, and their isolation supports the formation of a radical intermediate of type **A** (see Scheme 1). However, it appears that the ring opening of this radical is not favored, presumably due to stabilization by delocalization on the neighboring heteroatomic centers. Stabilization of radicals α to nitrogen atoms has been documented.[18] In the present system, a unique sharing of π-electrons in the semi-occupied and lone pair orbitals can be admitted not only between the C and N centers, but also with the O and Sm centers, resulting in increased stabilization of the α-cyclopropyl radical **I** versus homoallyl radical **II** (Scheme 6). Consequently, the predominant formation of β-*N*-hydroxyamino cyclopropyl derivatives from SmI_2-mediated reduction of nitrones could be related to the predominance of intermediate **I** over **II** ([**I**] >> [**II**], Scheme 6). Only in cases where **II** benefits from stabilization of the homoallyl radical by substitution with phenyl group(s) the products resulting from the cyclopropyl → homoallyl radical rearrangement (i.e. **17** and **18**) could be isolated. This result is surprising in light of the Curtin–Hammet principle that would predict that **I** and **II** being in rapid equilibrium, the proportion of the products should depend only on the kinetic rate of their respective bimolecular coupling (or reduction) towards the products. In such case, one would reasonably expect that **II**, which is less stabilized, would react faster than **I**, and that opened-ring products would predominate.

In this work, it was expected that the SmI_2-promoted reduction of α-cyclopropyl nitrones would yield products resulting from cyclopropyl → homoallyl radical rearrangement, by analogy with aldehydes or ketones. However, it was found that such rearrangement is disfavored, probably due to stabilization of the cyclopropyl radical by delocalization onto the α-N–O–Sm system. As a consequence, cyclopropyl nitrones can be successfully employed in intermolecular SmI_2-mediated cross-coupling reactions to allow a versatile synthetic access to α-cyclopropyl carbinylamine derivatives. The latter are important building blocks for medicinal chemistry, as conformationally constrained analogues of biologically active amines or hydroxylamines.[19]

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.



Scheme 6 Proposed mechanism for the SmI_2-mediated reduction of α-cyclopropyl nitrones

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The CNRS, the Université Joseph Fourier, and the Agence Nationale pour la Recherche (grant ANR-05-JCJC-0130-01) are acknowledged for financial support.

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(16) **General Procedure for the Coupling Reaction of Nitrones 1–3 and Cyclohexanone**; **Conditions A**: To a stirred and carefully deoxygenated solution of nitrone **1–3** (0.20 mmol) and cyclohexanone (0.30 mmol) in anhyd THF (5 mL), a 0.1 M solution of SmI_2 (0.44 mmol) was added at –78 °C under argon. After 3 h, sat. solutions of $Na_2S_2O_3$ (5 mL) and $NaHCO_3$ (5 mL), and EtOAc (20 mL) were added. After extraction, the organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Column chromatography yielded racemic products **11–13** (EtOAc–pentane, 1:4) and recovered nitrones **1–3** (MeOH–EtOAc, 5:95). **Conditions B**. The same procedure was used, but degassed H_2O (3.20 mmol) was added before SmI_2 addition (0.6 mmol).

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