Samarium diiodide-induced intramolecular pinacol coupling of dinitrones: synthesis of cyclic *cis*-vicinal diamines†

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Pinacol coupling of alkyl dinitrones mediated by SmI$_2$ was achieved in the presence of a proton source allowing the synthesis of cyclic vicinal diamines with good *cis*-selectivity.

Cyclic vicinal diamines are important constituents in numerous biologically active compounds of medicinal value, as well as in a multitude of chiral auxiliaries and chiral ligands.[1] Most of the methods described for the synthesis of cyclic vicinal diamines rely on the creation of the C–N bond, by reductive amination,[2] electrophilic amination,[3] nucleophilic amination to conjugated π-systems,[4] olefin oxidation by dinitrogen tetroxide,[5] or intermolecular 1,2-diamination of alkenes.[6] Approaches involving C–C bond formation using the reductive coupling of imine species have also been developed, although only in specific cases involving the preparation of ethylenediamine containing ring systems.[7]

Previous reports from the Vallée/Py group and us have demonstrated the ability of alkyl nitrones to undergo SmI$_2$-mediated intermolecular radical addition to various acceptors such as carbonyl compounds producing vicinal amino alcohols,[8] and α,β-unsaturated amides or esters resulting in the synthesis of γ-*N*-hydroxyamino amides or esters.[9,10] Moreover, Xu and coworkers have described the asymmetric synthesis of vicinal diamines by SmI$_2$-promoted reductive cross-coupling of alkyl nitrones to chiral sulfinyl imines,[11] although the reactions appear limited to aryl substrates. In this communication, we disclose an alternative method for the preparation of this important class of cyclic compounds *via* a *cis*-selective intramolecular pinacol type coupling of dinitrones promoted by the single electron reducing agent, samarium diiodide.[12]
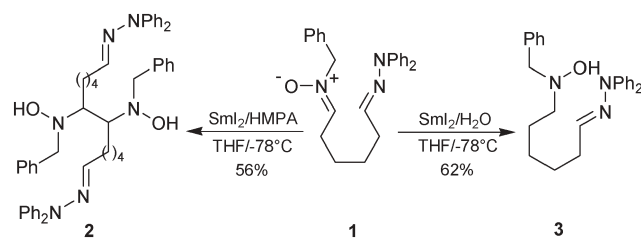
Taking into consideration the previous work on SmI$_2$-promoted intramolecular cyclisations of ketyl-hydrazones[13] or ketyl-oximes[14] for the formation of five-, six- and seven-membered cyclic amino alcohols, initial efforts were focused on the ability of a nitrone group to undergo intramolecular coupling with either a hydrazone or oxime. Hence, the nitrone hydrazone **1** was first submitted to conditions reported by Sturino and Fallis[13a] for promoting ring formation (SmI$_2$ 2.4 equiv./HMPA 8 equiv.). The major product was surprisingly not the cyclic compound but the dihydroxylamine **2** from intermolecular pinacol coupling. The use of a proton source such as H$_2$O (8 equiv.) resulted in the reduction of the nitrone to the hydroxylamine hydrazone **3** (Scheme 1).

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Attempts to promote the cyclisation of oxime **4** with *t*-BuOH (8 equiv.) as proton source led only to the simple reduction of the nitrone, whereas addition of butyl acrylate provided the γ-hydroxylamino ester **6** with 40% yield (Scheme 2) suggesting indeed that the nitrone was undergoing reduction.
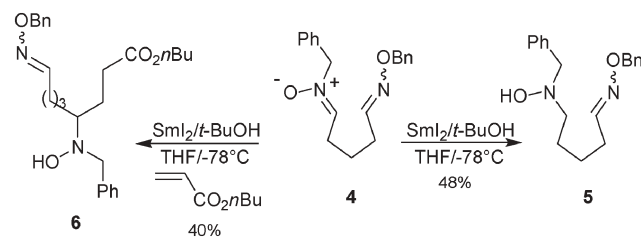
As the dinitrone **7** was obtained as a side product in the synthesis of **4**, but is also available by the condensation of glutaraldehyde with *N*-benzylhydroxylamine (see ESI), this compound was submitted to reductive conditions. Whereas no intramolecular pinacol coupling occurred at −78 °C with SmI$_2$, the reaction led at 0 °C to the corresponding cyclopentyl diamine **8** in 48% yield with good *cis*-selectivity (10 : 1) (Table 1, entry 2).

The desired product was obtained with dramatically increased reaction rates in the presence of an additive (entries 3, 5 and 6), except for *t*-BuOH (entry 4). Inclusion of methanol afforded the desired cyclic compound with a *cis* : *trans* ratio up to 19 : 1 and 76% yield (entry 6). The *cis*-relationship between the two vicinal nitrogens of the major cyclic product was determined by a single crystal X-ray structure analysis of the corresponding cyclic urea **9a**, prepared by a two-step procedure from **8** involving N–O bond cleavage with excess SmI$_2$ and cyclisation with phosgene (Fig. 1).‡

This intramolecular pinacol coupling was then applied to various dialdonitrones **7** in order to study the influence of the ring size, as well as the presence of heteroatoms in the ring. In order to avoid product mixtures from a competing reaction involving the over-reduction of the *N*-hydroxylamines to the corresponding amines, the intramolecular couplings were carried out with excess
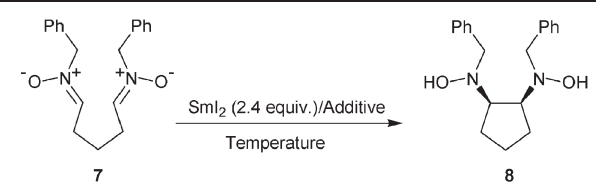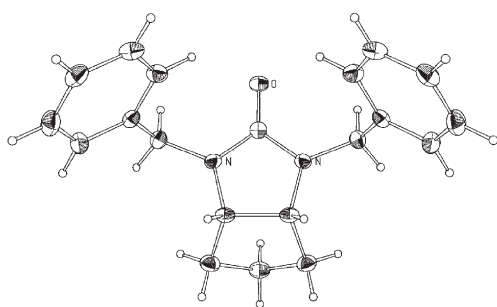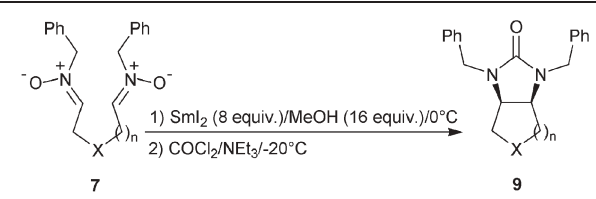

Scheme 1 Attempts to cyclise the nitrone hydrazone **1**.

Scheme 2 Attempt to cyclise the nitrone oxime **4**.

Table 1 Optimisation of cyclisation conditions promoted by SmI_2

Entry	Additive (equiv.)	Temperature	Time/h	Yield/%	d.r. (cis : trans)[a]
1	—	−78 °C	20	0	—
2	—	0 °C	1	48	10 : 1
3	H_2O (10)	0 °C	0.08	60	6 : 1
4	t-BuOH (10)	0 °C	3	56	4 : 1
5	HMPA (10)	0 °C	0.75	47	7 : 1
6	MeOH (10)	0 °C	0.75	76	> 19 : 1

[a] Determined by ^{1}H NMR.

Fig. 1 X-ray crystal structure representation of the urea **9a**.
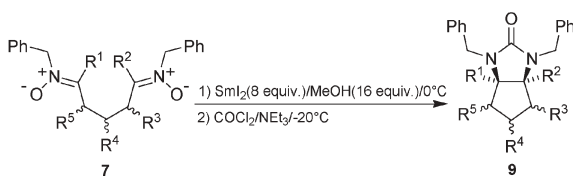
Table 2 Influence of the ring size

Entry	Dinitrone	n	X	Product	Yield/%	d.r. (cis : trans)[a]
1	**7b**	0	CH_2	**9b**	32	> 19 : 1
2	**7a**	1	CH_2	**9a**	66	> 19 : 1
3	**7c**	1	O	**9c**	52	5 : 1
4	**7d**	1	NBoc	**9d**	59	> 19 : 1
5	**7e**	2	CH_2	**9e**	43[b]	5 : 1
6	**7f**	3	CH_2	**9f**	35	3 : 1

[a] Determined by ^{1}H NMR. [b] Result obtained with t-BuOH as additive.

SmI_2 (8 equiv.) in 14 h at 0 °C. Without isolation, the intermediary cyclic diamines were subjected to phosgene generating the cyclic ureas **9** with yields ranging from 32 to 66% (three steps) and cis : trans ratios up to 19 : 1 (Table 2). In general, the highest yields were obtained for the 5-membered ring products (entries 2–4) where the yields dropped upon formation of both smaller and larger rings.

Following these encouraging results, the intramolecular pinacol coupling of various aldonitrones and ketonitrones was examined as illustrated in Table 3. Cyclisation of the symmetrical aldonitrone **7g** gave the tricyclic structure **9g** with an *endo*-selectivity (entry 1).

The dinitrones of entries 2 and 3 imply that the synthesis of unsymmetrical ureas can be achieved in good yields and diastereoselectivities. The *trans*-relationship between the methyl substituent and the amine groups of **9i** was confirmed by NOE studies.[15] The ring formation between aldonitrone and ketonitrone moieties was also shown possible with slightly lower yields, but an acceptable cis : trans selectivity was still maintained (entries 4 and 5). Finally, the pinacol coupling of diketonitrones afforded in

Table 3 Pinacol coupling of various aldo- and ketonitrones

Entry	Dinitrone	Product	Yield/%	d.r. (cis : trans)[a]
1	**7g**	**9g**	52	4 : 1[b]
2	**7h**	**9h**	58	4 : 1
3	**7i**	**9i**	65[c]	> 19 : 1 (> 9 : 1)[d]
4	**7j** Z/E 69:31	**9j**	42	7 : 1
5	**7k**	**9k**	44	5 : 1
6	**7l** ZZ/ZE/EE 1:2:1	**9l**	28	4 : 1
7	**7m** Z/E 1:1	—	—	—

[a] Determined by ^{1}H NMR. [b] *endo : exo* ratio. [c] Result obtained with H_2O as additive. [d] *anti : syn* ratio.
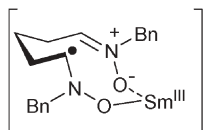
Fig. 2 Plausible transition state for the intramolecular SmI_2-promoted pinacol cyclisation of dinitrones.

the case of dinitrone **7l** the desired cyclic urea **9l** with a low yield and a d.r. of 4 : 1 (entry 6), whereas no cyclisation took place in the case of dinitrone **7m** (entry 7). Single crystal X-ray structure analysis of the compound **9l** again allowed confirmation of the *cis*-stereoselectivity observed for this SmI_2-induced intramolecular pinacol coupling.§

To explain the *cis*-selectivity observed in these reactions, we propose a plausible chelated transition state invoking coordination of the Sm(III) of the nitrone radical anion to the oxygen of the other nitrone as depicted in Figure 2. Similar chelated transition states have been proposed for the *cis*-selective pinacol coupling of dicarbonyl compounds.[16]

In summary, we have developed an intramolecular pinacol coupling of alkyl dinitrones allowing the synthesis of cyclic diamines with good to excellent *cis*-stereoselectivities. Attempts to find conditions suitable for the preparation of the corresponding *trans*-isomers using this reductive cyclisation process are in progress and will be reported in due course.

Notes and references

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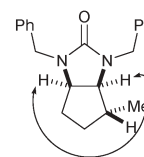
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