[16] M. Kunitake, K. Kotoo, O. Manabe, T. Muramatsu, N. Nakashima, *Chem. Lett.* **1993**, 1033 – 1036; C. J. Easton, S. F. Lincoln, A. G. Meyer, H. Onagi, *J. Chem. Soc. Perkin Trans. 1* **1999**, 2501 – 2506; C. Heim, A. Affeld, M. Nieger, F. Vögtle, *Helv. Chim. Acta* **1999**, *82*, 746 – 759; A. H. Parham, B. Windisch, F. Vögtle, *Eur. J. Org. Chem.* **1999**, 1233 – 1238.

[17] Nonrotaxane α-CD and β-CD – stilbene complexes photoisomerize in aqueous solution (W. Herrmann, S. Wehrle, G. Wenz, *Chem. Commun.* **1997**, 1709 – 1710) but not in the solid β-CD complex; M. S. Syamala, S. Devanathan, V. Ramamurthy, *J. Photochem.* **1986**, *34*, 219 – 229.

[18] J. W. Happ, M. T. McCall, D. G. Whitten, *J. Am. Chem. Soc.* **1971**, *93*, 5496 – 5501.

[19] We have not detected phenanthrene formation from **3** or **3** $\subset \alpha$-CD, even after irradiation in the presence of iodine.

[20] We have been unable to separate the *E* and *Z* isomers of **3** $\subset \alpha$-CD. NOE measurements were carried out on a photogenerated mixture of both isomers, of known composition, which facilitates comparison of the strengths of NOEs in the two isomers; see Supporting Information.

[21] The ratios $\Phi_{E\rightarrow Z}/\Phi_{Z\rightarrow E}$ for **3** and **3** $\subset \alpha$-CD were evaluated from the *E*/*Z* ratios of their photostationary states. Values of $\Phi_{E\rightarrow Z}$ were obtained by comparing the initial rates of photoisomerization with that of *E*-stilbene in cyclohexane ($\Phi_{E\rightarrow Z} = 0.50$; S. Malkin, E. Fischer, *J. Phys. Chem.* **1964**, *68*, 1153 – 1163) during irradiation under identical conditions; see Supporting Information.

[22] The $\Phi_{E\rightarrow Z}$ in compounds **3** and **3** $\subset \alpha$-CD is lower than that in simple stilbene because of the 4,4′-diaryl substitution; see: G. Gauglitz, R. Goes, W. Stooss, R. Raue, *Z. Naturforsch. A* **1985**, *40*, 317 – 323.

[23] A similar reduction in $\Phi_{E\rightarrow Z}$ was reported in a cationic azobenzene rotaxane, compared to the free dumbbell, but in that case it was attributed to radiationless decay by charge-transfer states, rather than to steric hindrance.[9]

Samarium Diiodide-Induced Reductive Cross-Coupling of Nitrones with Aldehydes and Ketones**

Géraldine Masson, Sandrine Py,* and Yannick Vallée*

The use of nitrones as free-radical traps (spin traps) is well known. Nitrones have been designed to react with oxygen radicals to lengthen their half-lives and allow their detection in EPR studies.[1] They have also been used as in vivo protective agents against radicals generated by oxidative stress.[2] Surprisingly, nitrones have seldom been involved in radical reactions aimed to create C–C bonds,[3, 4] even though the addition of radicals to other C=N bonds is known.[5] We decided to explore the possibility of reductive cross-coupling between nitrones and carbonyl compounds, promoted by samarium diiodide, to produce vicinal amino alcohols. Vicinal amino alcohol fragments are common in natural products, and a preparation of these compounds by C–C bond formation (similar to the pinacol coupling reaction) is highly desirable.

The intramolecular reductive coupling of aldehydes or ketones with oximes,[6] hydrazones,[7] and imines[8] is well documented. These couplings have been accomplished with different degrees of stereoselectivity and generally yield the *trans* α-amino alcohol derivatives as the major products. The mechanism of this reaction is generally assumed to involve the initial formation of a ketyl radical by a single electron tranfer (SET) from the reducing agent, followed by its addition to the C=N double bond.

The intermolecular cross-coupling of C=O and C=N groups, on the other hand, has been far less successful in the past because of competitive homocoupling or formation of reduction products. Pedersen and Roskamp[9] used $NbCl_3 \cdot$ DME as a two-electron reducing agent to synthesize efficiently a variety of amino alcohols from the corresponding aldimines and ketones or aldehydes. The method was less efficient with aliphatic imines, and it failed with sterically hindered substrates. Electroreductive methods have also been employed to couple carbonyl compounds with aromatic aldimines, aliphatic aldoximes and ketoximes, and nitrones.[10] Samarium(II) diiodide (SmI_2) is another reducing agent which has been used with varying degrees of success in reductive cross-couplings involving carbonyl compounds and imine derivatives. It was initially reported to give poor selectivity in reductive couplings involving imines,[11, 12] the main side reaction being reduction to the corresponding amines. SmI_2 was employed for the aminomethylation of aliphatic aldehydes and ketones with *O*-benzylformaldoxime in the presence of hexamethylphosphoramide (HMPA) and an alcohol (2 equiv), but this reaction could not be extended to other oximes.[13] The cross-coupling of aromatic aldimines with nonaromatic ketones could be induced by SmI_2 under mild conditions, provided that NiI_2 was used as an additive in the reaction mixture.[14] Recently, Taniguchi and Uemura showed that SmI_2-promoted reductive coupling of aromatic aldehydes and imine derivatives was an efficient and selective way to prepare vicinal amino alcohols, provided that the imine derivatives were aromatic *N*-sulfonylimines, as these substrates exhibit a suitable redox potential for selective cross-coupling.[15]

Here we disclose our preliminary results on SmI_2-induced cross-coupling of nitrones with aldehydes or ketones. Because of its good oxophilicity, samarium(II) diiodide was chosen as the SET reagent to mediate the reductive coupling of nitrones with carbonyl compounds. It was supposed that coordination of a samarium(III) ketyl radical to the oxygen atom of the nitrone and of the C=O group would favor the reaction and might induce good stereoselectivities in the coupling reactions.

To verify these assumptions we first conducted an intramolecular reaction by treating a 0.04 M solution of ketonitrone **1**[16] in THF with 2 equiv of SmI_2 at $-78\,^{\circ}C$ (Scheme 1). Cyclization proceeded rapidly (1 h) to yield 2-[benzyl(hydroxy)amino]-1-methylcyclohexanol (**2**) as a single diastereoisomer in almost quantitative yield. Moreover, treatment

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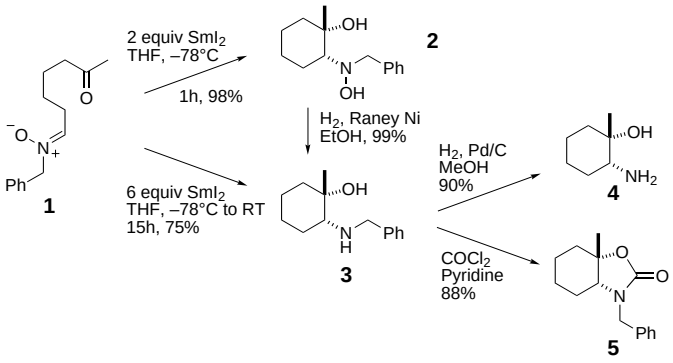
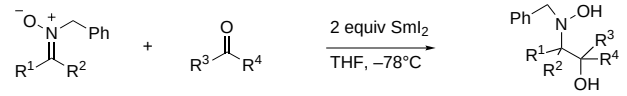


Scheme 1. Synthesis of cyclic α-*N*-hydroxyamino and α-amino alcohols by intramolecular coupling of ketonitrone **1**.

of **1** with 6 equiv of SmI_2 at room temperature[17] directly afforded the amine **3**, albeit in lower yield.

This pinacol-like reductive coupling took place under very mild conditions, with no need for additives such as alcohols or the toxic co-solvent HMPA, which was essential for the coupling of oximes and hydrazones to carbonyl compounds. It is noteworthy that in this case the product has a *cis* configuration,[18] which suggests that the reaction pathway is different from that generally assumed for other imine derivatives.

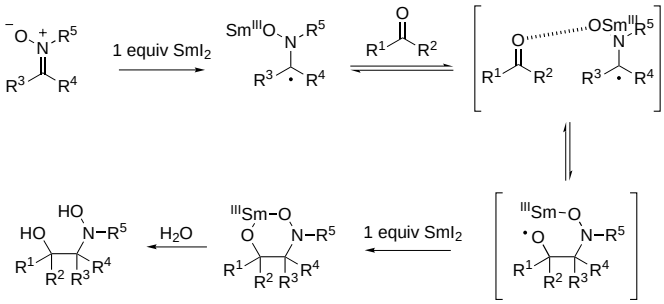
Encouraged by this result, we turned our efforts to the more challenging intermolecular cross-coupling of nitrones with a variety of carbonyl compounds (Scheme 2, Table 1). We found that both aromatic and aliphatic nitrones are effective



Scheme 2. Intermolecular reductive cross-coupling of nitrones and carbonyl compounds.

substrates for efficient and selective cross-coupling, not only with ketones, but also with aldehydes. When prochiral substrates were used, a mixture of diastereoisomers was obtained. The reactions are fast and highly chemoselective: no side products such as homocoupling or reduction products were isolated in any case. When both aldehyde and ketone functionalities were present in the substrate, coupling occurred selectively with the aldehyde (entries 14 and 15). Reactions with aromatic nitrones were faster. No limitations on the nature of substrates were revealed in this study, and even "bis-quaternary" amino alcohols could be prepared efficiently (entries 12 and 13). Interestingly, the presence of a proton source such as a remote hydroxy group in substrates does not impair the progress of this reaction (entry 10). The coupling can even be conducted in the presence of *tert*-butyl alcohol (entry 8, see footnote).

Based on the stability of the aminoxyl radical possibly formed by addition of R$^\bullet$ to the nitrone group and on the good electrophilicity of nitrones compared to that of imines, oximes, or hydrazones, we initially postulated a mechanism in which the first step is the formation of a ketyl radical from the carbonyl compound, followed by addition to the nitrone, and reduction of the resulting aminoxyl radical. However, several experiments indicate that the initial SET occurs at the nitrone group (Scheme 3). First, when benzylbenzylidene



Scheme 3. Proposed mechanism for the reductive cross-coupling of nitrones and carbonyl compounds.

amine *N*-oxide was treated under the described conditions in the absence of carbonyl compound its dimerization product was isolated in 73% yield. Second, reactions involving an α-cyclopropylketone as the carbonyl substrate yielded the expected cross-coupling products with no trace of ring opening, which suggests that the mechanism does not involve a ketyl radical (entries 4, 5, and 9). Finally when a 1,6-dicarbonyl substrate was treated with a nitrone (entries 14 and 15), only the α-*N*-hydroxyamino alcohols resulting from the coupling of the nitrone with the aldehyde were isolated (80–84% yied), and no intramolecular pinacol coupling occurred.

In conclusion, we have demonstrated that nitrones are the substrates of choice for the reaction with a variety of aldehydes and ketones under SmI_2-promoted reductive coupling conditions. This reaction provides a new method to prepare highly substituted and unsymmetrical vicinal *N*-hydroxyamino and amino alcohols. Its mechanism involves chemoselective SET from SmI_2 to the nitrone group, followed by addition of the resulting species to aldehydes or ketones. We are currently studying the scope and limitations of this reaction in the field of asymmetric synthesis. This process should be of interest both in the synthesis of natural products and in the design of new diversely substituted chiral ligands.

Experimental Section

A stirred and carefully deoxygenated solution of nitrone (*N*-alkylidenebenzylamine *N*-oxide, 0.5 mmol) in dry THF (10 mL) was cooled to $-78\,^\circ C$ under argon. Then the carbonyl compound (0.5 mmol) and a solution of SmI_2 (0.1 mol L^{-1}, 10 mL, 1 mmol) in THF were added. The temperature was kept at $-78\,^\circ C$ until the reaction was judged to be complete by TLC, and then saturated aqueous solutions of $Na_2S_2O_3$ (20 mL) and $NaHCO_3$ (20 mL) were added. The yellow mixture was extracted with AcOEt (3×50 mL), and the combined layers were washed with a saturated aqueous solution of NaCl and dried over $MgSO_4$. Filtration, concentration in vacuo and purification by chromatography on silica gel afforded the expected α-*N*-hydroxyamino alcohol(s) as single products (or as mixtures of diastereomers). All new compounds gave spectroscopic and analytical data in agreement with the assigned structures.

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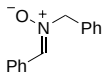
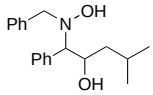
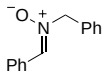
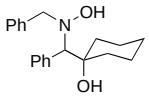
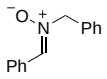
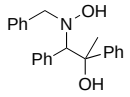
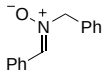
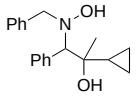
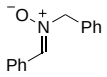
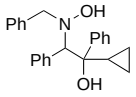
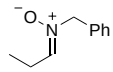
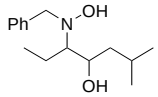
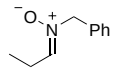
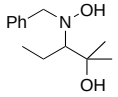
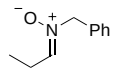
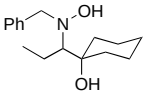
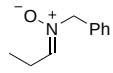
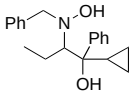
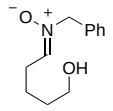
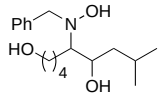
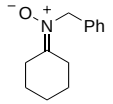
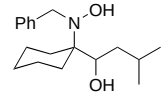
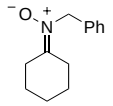
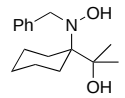
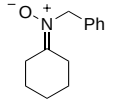
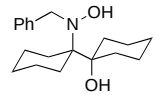
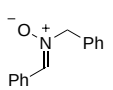
Table 1. Preparation of α-*N*-hydroxyamino alcohols by selective cross-coupling of nitrones with carbonyl compounds.

Entry	Nitrone	Carbonyl Compound	*N*-Hydroxyamino alcohol	Time	Yield	d.r.[a]
1				1 h	75 %	1:1
2				1 h	80 %	–
3				1 h	91 %	7:3
4				5 min	93 %	1:1
5				20 min	99 %	3:2
6				2 h	92 %	1:1
7				1 h	69 %	–
8[b]				2 h30	74 %	–
9				2 h	79 %	3:2
10				2 h	83 %	1:1
11				2 h	98 %	–
12				2 h	98 %	–
13				2 h	77 %	–
14				5 min	80 %	1:1
15				3 h	84 %	3:2

[a] According to ^{1}H NMR analysis of the crude materials. [b] The same result was obtained when *t*BuOH (2 equiv) was added to the reaction mixture before addition of SmI_2.

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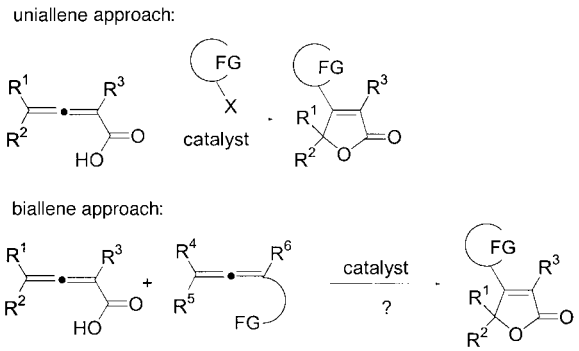
Oxidative Cyclization – Dimerization Reaction of 2,3-Allenoic Acids and 1,2-Allenyl Ketones: An Efficient Synthesis of 4-(3′-Furanyl)butenolide Derivatives**

Shengming Ma* and Zhanqian Yu

Allenes are a class of compounds with interesting reactivities owing to the presence of two cumulative carbon-carbon double bonds.[1] As a result of the axial chirality as well as the substituent-loading capability, allenes show great potential in organic synthesis in terms of chirality transfer[2] and diversity. Recently, we[3–5] and others[6–14] established the cycloisomerization of functionalized allenes and the coupling – cyclization of functionalized allenes with organic halides for the synthesis of carbo- and heterocyclic compounds based on transition-metal-catalyzed or mediated cyclization of functionalized allenes.[14] However, to the best of our knowledge, no protocol has been established in the area of cyclization – dimerization reactions between two different classes of functionalized allenes to give interesting cyclic compounds in a single step (Scheme 1). The formidable *challenge* is to match the reactivities of two different classes of allenes.



Scheme 1. Cyclization – dimerization reactions of functionalized allenes to give butenolide derivatives.

With this idea in mind, we screened different combinations of several functionalized allenes, for example, 2,3-allenoic acids,[3] 2,3-allenols,[4a,b] 2,3-allenamides,[4c] and 1,2-allenyl ketones.[5] Fortunately, after numerous trial and error reactions, we observed the $[PdCl_2(MeCN)_2]$-catalyzed (5 mol %)

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