Umpolung of C-N Bonds

SmI_2-Induced Umpolung of the C=N Bond: First Reductive Conjugate Addition of Nitrones to α,β-Unsaturated Esters**

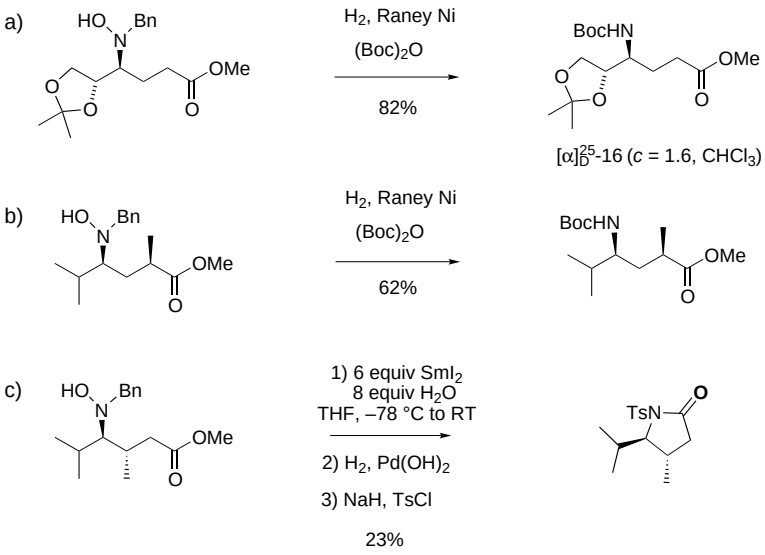
Géraldine Masson, Pascale Cividino, Sandrine Py, and Yannick Vallée**

Polarity inversion of organic functional groups is of great interest because it allows added flexibility in the design of complex synthetic schemes. While the umpolung of carbonyl groups is well documented,[1] a similar inversion of the C=N bond has been demonstrated in significantly fewer examples.[2,3] We have recently reported a general and high-yielding pinacol-type heterocoupling of nitrones with aldehydes and ketones in presence of SmI_2 that produces the corresponding β-*N*-hydroxyamino alcohols.[4] In that work, nitrones proved to be far superior to imines,[5] oximes,[6] and hydrazones[7] for the *intermolecular* cross-coupling reaction with carbonyl partners. Concerning the mechanism of this coupling, evidence was found that SmI_2 first reduces the nitrone, as opposed to the carbonyl component, to generate an α-aza-nucleophilic species (radical or anion), which then adds to the C=O bond of the aldehyde or ketone. Herein we demonstrate that *nitrone umpolung* chemistry can be extended to other electrophiles, namely α,β-unsaturated esters, to generate important γ-amino ester derivatives.

Owing to its finely tunable reactivity, samarium(II) diiodide has found wide application in organic synthesis[8] since the seminal work by Kagan and co-workers in the early 1980s.[9] In particular, this mild reducing agent has become a popular reagent for the reductive addition of carbonyl compounds to a variety of electrophilic species, as exemplified by the conjugate addition to α,β-unsaturated acid derivatives.[10] Owing to the apparent persistency of the nitrone-derived species generated upon treatment with SmI_2, it appeared that they might undergo addition to electron-deficient alkenes and alkynes.

Indeed, when a solution of an aliphatic nitrone and ethyl acrylate in THF at −78 °C was treated with two equivalents of SmI_2, the γ-*N*-hydroxyamino ester resulting from conjugate addition was isolated in about 75% yield (Table 1, entries 1, 2, and 4). An attempt to accelerate the addition by running the reaction at higher temperature led to the corresponding oxazinanone as the main product (Table 1, entry 3). However, the desired products were obtained with dramatically increased reaction rates by addition of a proton source such as water (Table 1, entries 5, 6, 8, and 9). The effect of water[9,11] was particularly significant in the reductive additions of a hydroxy-containing nitrone (Table 1, entry 5) and a ketonitrone (Table 1, entry 6) to ethyl acrylate. In both examples, reaction times were shorter (7-fold and 12-fold, respectively) and yields were much better in the presence of this safe and convenient additive.

The possibility of 1,2-diastereomeric induction was next addressed by using carbohydrate-derived nitrones as substrates. A recently described D-mannose-derived (*E*)-aldonitrone[12] reacted with ethyl acrylate (Table 1, entry 7) to afford a 75:25 mixture of diastereomers, thus offering a new, reasonably stereoselective route to diversely substituted sugar mimics (azasugars).[13] Similarly, the (*R*)-2,3-*O*-isopropylidene-D-glyceraldehyde-derived nitrone[14] added to ethyl acrylate with good diastereoselectivity (Table 1, entry 8) and yielded an important intermediate[15,16] for the synthesis of Vigabatrin,[17] a potent and selective GABA-transaminase inhibitor used for treatment and prevention of epilepsy. The relative stereochemistry displayed in the product in entry 8 of



Scheme 1. Determination of the stereochemistry of the products in entries 8 (a), 9 (b), and 11 (c) of Table 1. See text for details. Boc = *tert*-butyloxycarbonyl.

Table 1 was determined by reduction of the hydroxylamine and carbamoylation to give a known[15a] Boc-protected γ-amino ester (Scheme 1a).

Following these encouraging results, the addition of nitrones to substituted acrylates was studied. Both methyl methacrylate (Table 1, entries 9, 10), and (*E*)-methyl crotonate (entry 11) proved to be good acceptors. Furthermore, their reactions displayed excellent diastereoselectivities, and afforded the 2- and 3-substituted-γ-*N*-hydroxyamino acid derivatives respectively, in > 95% purity. The relative stereochemistry (Table 1, entry 9) was assigned by hydrogenation/

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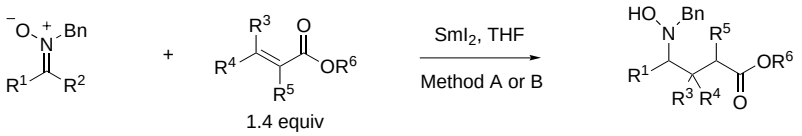
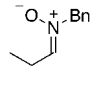
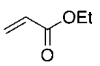
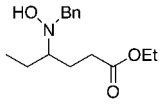
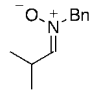
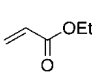
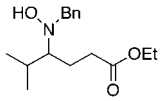
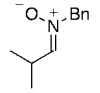
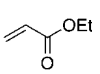
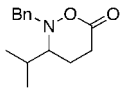
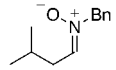
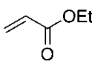
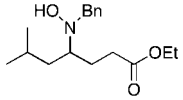
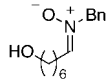
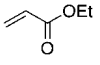
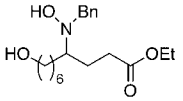
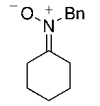
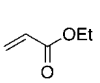
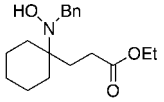
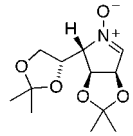
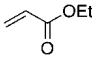
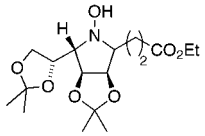
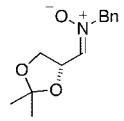
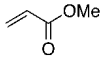
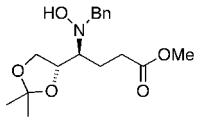
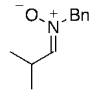
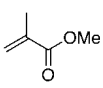
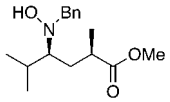
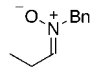
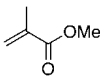
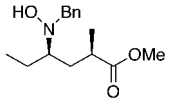
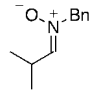
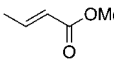
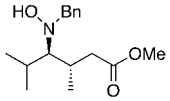
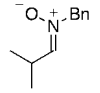
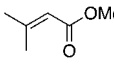
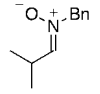
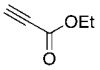
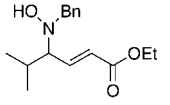
Table 1: Preparation of γ-*N*-hydroxyamino esters by reductive conjugate addition of nitrones to α,β-unsaturated esters.



Entry	Nitrone	Electrophile	Product	Method[a]	*t* [h]	Yield [%][b] (d.r.)[c]
1				A	10	76
2				A	10	75
3				A[d]	7	58
4				A	9	74
5				A B	7 1	60 73
6				A B	96 8	45 55
7				B	5	63 (75:25)
8				A B	7 1	72 (90:10) 81 (85:15)
9				A B	7 2	29 (>95:5) 74 (>95:5)
10				B	3	76 (>95:5)
11				B	2.5	66 (>95:5)
12				B	3	54
13				A B	8 0.5	<10 71
14				B	7	58

carbonylation reactions of the product (Scheme 1b) and comparison to a known carbamate.[18] In the case of the product in entry 10 (Table 1), although the proposed assignment should be considered tentative, it is most likely as depicted by analogy with that in entry 9 (Table 1). To determine the stereochemistry of the product in entry 11, the product was cyclized into a pyrrolidinone (Scheme 1c) in which the observed coupling constant ($J_{4,5} = 7.7$ Hz) is indicative[19] of a *trans* relationship. The method, however, seems to reach a limit with β,β-disubstituted esters, as no addition product was detected with 3,3-dimethyl acrylate (Table 1, entry 12); the starting nitrone merely undergoes reduction. The outcome of this reaction strongly suggests a mechanism for these additions that involves initial reduction of the nitrone followed by conjugate addition, rather than initial reduction of the α,β-unsaturated ester and addition of the resulting radical anion to the nitrone.

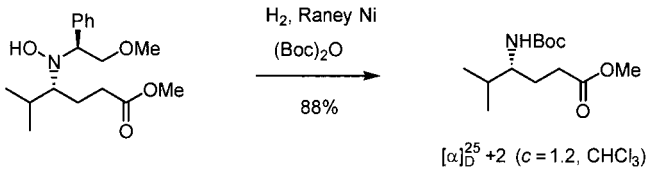
While intramolecular SmI_2-induced conjugate additions to α,β-acetylenic esters have been reported to be sluggish[20] and have allowed only the elaboration of five-membered rings,[21] no examples of the intermolecular version of these additions have been disclosed. It is noteworthy that the conjugate addition of nitrone-derived α-azanucleophilic species to propiolates in presence of water proceeded smoothly (Table 1, entries 13, 14)

[a] Method A: A solution of the nitrone and α,β-unsaturated ester in THF at −78 °C was treated with two equivalents of SmI_2, and the reaction mixture was then kept at −78 °C for the indicated reaction time. Method B: A solution of the nitrone, α,β-unsaturated ester and degassed water (8 equiv) in THF at −78 °C was treated with three equivalents of SmI_2, and the reaction mixture was then kept at −78 °C for the indicated reaction time. [b] Yields of isolated product after column chromatography. [c] According to ^{1}H NMR analysis of the crude products. [d] The reaction mixture was allowed to reach −50 °C over 7 h.

to produce the corresponding γ-*N*-hydroxyamino-α,β-ethylenic esters as single isomers (100% *E*). The effect of water in these additions was even more dramatic than in those above: the presence of eight equivalents of water resulted in both a remarkable acceleration of the reaction and an improvement of the yield (<10% to 71%). The products represent versatile intermediates for the synthesis of a variety of naturally occurring γ-amino-α,β-ethylenic and γ-amino-α,β-dihydroxy acid derivatives.[22]

To achieve enantioselectivity in the synthesis of γ-amino acid derivatives, nitrones bearing a chiral auxiliary at the nitrogen center were prepared and treated with ethyl acrylate (Table 2).[23] These additions proceeded in good yield[24] to afford diastereomeric γ-*N*-hydroxyamino esters, which could be separated by column chromatography (Table 2, entries 1–4). In the case of entry 4 (and by analogy entry 5), the major diastereomer was assigned the depicted stereochemistry from its conversion to a known derivative (Scheme 2).[25]

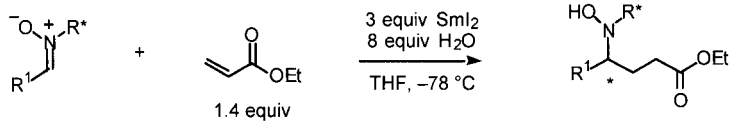
When the 1-(triisopropylphenyl)ethyl auxiliary[26] was used, an excellent diastereoselectivity (>95:5) was observed (Table 2, entry 6); a single-crystal X-ray crystallographic analysis of the major diastereomer provided its relative configuration.[27]

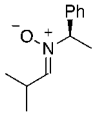
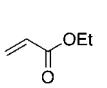
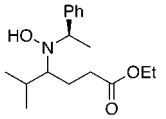
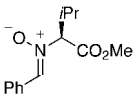
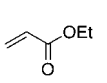
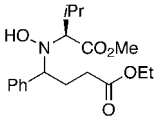
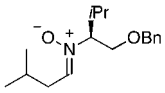
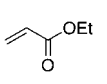
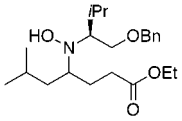
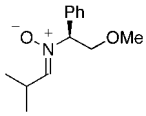
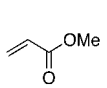
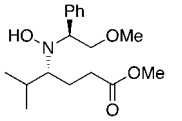
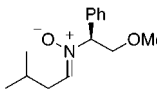
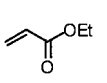
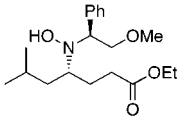
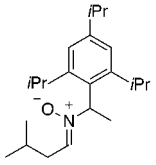
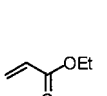
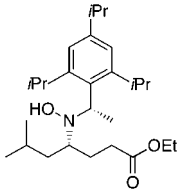


Scheme 2. Determination of the stereochemistry of the product in entry 4 of Table 2.

In conclusion, reduction of nitrones by SmI_2 yields α-azacarbon nucleophiles that undergo efficient and highly selective intermolecular conjugate addition to acrylic and propiolic esters. Outstanding diastereoselectivities are observed and the use of chiral auxiliaries at the nitrogen center provides an expedient, enantioselective approach to γ-amino acid derivatives. The 4-substituted, 2,4-disubstituted, and 3,4-disubstituted γ-*N*-hydroxyamino and γ-amino acid derivatives[16] produced by this novel, direct method should find considerable application, both as synthetic intermediates and as precursors of conformationally defined, protease-resistant γ-peptides.[28] Current work is aimed at extending this method to other unsaturated systems.

Table 2: Reductive conjugate addition of chiral nitrones to ethyl acrylate.



Entry	Nitrone	Electrophile	Product	*t* [h]	Yield [%]	d.r.[a]
1				2	78	75:25[b]
2				0.5	36	70:30
3				4.5	56	60:40
4				3	96	85:15
5				3.25	84	85:15
6[c]				11.5	73	>95:5

[a] According to ^{1}H NMR analysis of the crude product. [b] In this case the diastereomeric ratio (d.r.) could not be determined from ^{1}H NMR analysis of the crude material because of signal overlap and was therefore based on the yields of the isolated diastereomers. [c] In this case the chiral nitrone was used as a racemic mixture.

Experimental Section

Preparation of 0.1M SmI_2 in THF:[29] A suspension of samarium powder (4 g, 26.6 mmol) and I_2 (5 g, 19.7 mmol) in dry THF (200 mL) was vigorously stirred at room temperature for at least 2 h, during which time the color changed from yellow-brown to green and finally to blue. Titration of this SmI_2 solution was performed with a 0.1M solution of I_2 in THF (the end point is reached when the solution turns yellow and SmI_3 precipitates).

General procedure for intermolecular conjugate addition of nitrones to acrylic and propiolic esters: A stirred and carefully deoxygenated solution of the nitrone (*N*-alkylidenebenzylamine-*N*-oxide) (0.5 mmol) in dry THF (10 mL) was cooled to −78°C under argon. The unsaturated ester (0.7 mmol), water (4 mmol, degassed by boiling under a stream of argon for 30 min) when method B was employed, and a solution of SmI_2 (ca. 0.1M, 10 mL, 1 mmol) in THF were then added. The temperature was kept at −78°C until the reaction was judged to be complete by TLC, whereupon a saturated aque-

ous solution of $Na_2S_2O_3$ (30 mL) was added. The yellow mixture was extracted with AcOEt (3 × 50 mL) and the combined organic layers were washed with a saturated aqueous solution of NaCl, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the resulting residue by chromatography on silica gel afforded the expected γ-*N*-hydroxyamino ester as a single product (or a mixture of diastereomers). All new compounds gave spectroscopic and analytical data in agreement with the assigned structures.

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