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First asymmetric SmI_2-induced cross-coupling of $Cr(CO)_3$ aromatic nitrone complexes with carbonyl compounds

Murielle Chavarot,[a] Michaël Rivard,[a] Françoise Rose-Munch,*[a] Eric Rose[a] and Sandrine Py[b]

[a] *Laboratoire de Chimie Organique, UMR 7611, Université P. et M. Curie, Tour 44 1er étage, BP181, 4 Place Jussieu, F-75252 Paris CEDEX 05, France. E-mail: rosemun@ccr.jussieu.fr*

[b] *LEDSS, UMR 5616, Université J. Fourier, BP53, F-38041 Grenoble CEDEX 9, France*

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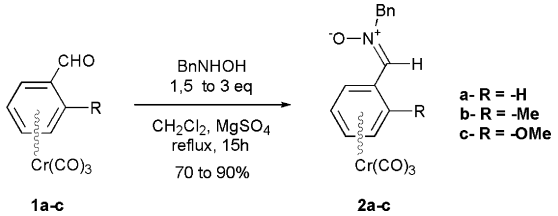
The SmI_2-induced cross-coupling of $Cr(CO)_3$-complexed nitrones with carbonyl compounds is described. This highly chemo- and diastereoselective reaction affords enantiopure β-amino alcohol complexes in excellent yields.

β-Amino alcohols are an important class of ligands for asymmetric synthesis.[1] Their synthesis usually relies on transformations of the chiral pool, thus limiting diversity in their design. Their *N*-hydroxylamino derivatives have been far less studied, presumably because of the lack of methods for their direct synthesis. Therefore, new methods for the asymmetric synthesis of a wide range of compounds in these two classes are highly desirable. Recently, one of us reported a reductive cross-coupling of nitrones with carbonyl compounds, yielding the corresponding *racemic* β-*N*-hydroxylamino or β-amino alcohols with high efficiency.[2]

In this communication, we wish to describe the first asymmetric version of the SmI_2-induced coupling of nitrones with carbonyl compounds, based on chiral induction using planar chiral (η^6-arene) chromium tricarbonyl complexes.[3] Such complexes have emerged as valuable and versatile auxiliaries for several reasons: i) the preparation of enantiopure planar chiral complexes is well described, either by resolution of racemic mixtures,[4] by diastereoselective complexation[4,5] or by asymmetric synthesis;[6] ii) they proved to be efficient building blocks for organic synthesis as they induce high diastereoselectivities in a large variety of reactions;[7] iii) decomplexation of the arene ring is easily performed at the end of the synthesis.

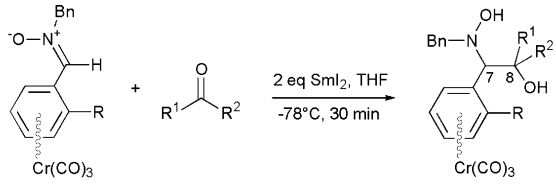
Although the chiral information could be introduced, in principle, either on the carbonyl or on the nitrone partner, organometallic nitrones were chosen as chiral substrates.[8] Compared to the tricarbonylchromium complexed aldehydes or imines, very few planar-chiral nitrones have been described to date. To the best of our knowledge, most of these examples are limited to *N*-methyl-derivatives, that were used either in 1,3-dipolar cycloaddition reactions,[9] or for the NMR determination of the enantiomeric purity of their aldehyde precursors.[10] Various *N*-benzyl-nitrones **2** were prepared (Scheme 1) by condensation of *N*-benzylhydroxylamine with the corresponding racemic tricarbonylchromium benzaldehyde derivatives **1**.[11] When the achiral organometallic nitrone **2a** was reacted with acetone and SmI_2,† the desired β-hydroxylamino alcohol **3a** was obtained in 65% yield (entry 1, Table 1) and no significant amount of any organometallic by-product was isolated.

The *ortho*-substituted nitrones **2b** and **2c** were also reacted with



Scheme 1

Table 1 Cross-coupling of nitrones with carbonyl compounds



Entry	Nitrone	R	R^1	R^2	Product	Yield (%)[a]	d.r.[b]
1	**2a**	H	Me	Me	**3a**	65	—
2	**2b**	Me	Me	Me	**3b**	95	> 95 : 5
3	**2c**	OMe	Me	Me	**3c**	93	> 95 : 5
4	**2b**	Me	$-(CH_2)_5-$		**3d**	88	> 95 : 5
5	**2b**	Me	*t*Bu	H	**3e**	96	> 95 : 5[c]
6	**2b**	Me	Et	H	**3f**	83[e]	> 95 : 5[d]

[a] After purification. [b] At C^7, determined by ^1H NMR analysis of the crude mixtures. [c] Diastereoisomeric ratio at C^8 > 95 : 5. [d] Diastereoisomeric ratio at C^8 = 70 : 30. [e] Crude yield.

acetone† (entries 2 and 3), giving the pure β-*N*-hydroxylamino alcohols **3b** and **3c** in yields ⩾ 90%. The coupling reaction is fast, highly chemoselective, and completely diastereoselective, within the limits of ^1H NMR analysis of crude materials. Using cyclohexanone instead of acetone as the coupling partner (entry 4) did not modify reactivity or selectivity. The reaction of nitrone **2b** with aldehydes was also highly chemoselective and led to the corresponding β-*N*-hydroxylamino alcohols **3e** and **3f** in excellent yields (entries 5 and 6). Remote diastereoselectivity at the carbon C^8 bearing the alcohol functionality seems to be dependent on the size of the R^2 group: while a single diastereomer was isolated from the coupling of **2b** with pivalaldehyde, a 70 : 30 diastereomeric mixture was obtained from propionaldehyde.

X-Ray analysis of crystals of the racemic β-*N*-hydroxylamino alcohol **3c**[12] (Fig. 1) allowed the determination of its relative configuration, and an (*S*) configuration was revealed for the newly created stereogenic benzylic carbon, coupled with the (*pS*) configuration of the chromium complex.[13] The NMR spectrum

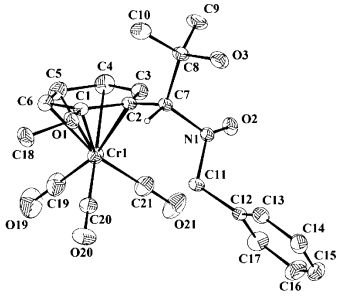


Fig. 1 X-Ray structure of β-*N*-hydroxylamino alcohol **3c**.

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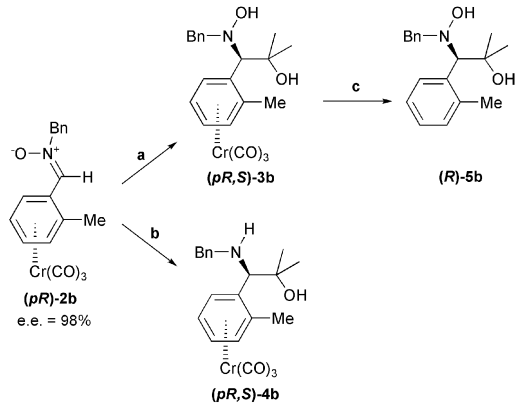

Scheme 2 *Reagents and conditions:* **a**: 1 eq MeCOMe, 2eq SmI_2, THF, −78 °C, 30 min. **b**: 1 eq MeCOMe, 6 eq SmI_2, THF, −78 °C to RT, 15 h. **c**: pyridine, reflux.

of these crystals corresponded to the spectrum of the most abundant diastereoisomer.

The observed diastereoselectivity is in agreement with the previously accepted transition state models for nucleophilic additions to aldehydes and imines,[7,14] as well as for [1,3]-dipolar cycloadditions of nitrones,[9] and originates in the following factors: due to steric hindrance, the *ortho*-substituent governs the conformation of the nitrone group, which adopts an *anti* orientation, coplanar with the aromatic ring; additionally, as the $Cr(CO)_3$ moiety blocks one face of the arene, the carbonyl partner preferentially approaches the substrate on the opposite face.

Interestingly, using an excess of SmI_2, β-amino alcohols **4** could be directly prepared with good overall yields (**4a**, 60%; **4b**, 81%) in a one-pot sequence,† by reduction of the *in situ* generated hydroxylamine. It is noteworthy that when the reaction was performed in identical conditions with the corresponding *N*-benzylimine complex, the expected β-amino alcohol was not isolated at all but a 40 : 60 mixture of diamine (homocoupling) and benzylic amine (two-electron-reduction of the imine) was obtained. This observation is in good agreement with the studies realised by Uemura *et al.*[15]

These promising results prompted us to use an enantiopure nitrone as starting material. The enantiopure *ortho*-methyl benzaldehyde complex was synthesized according to the procedure developed a few years ago in our group.[4] The corresponding nitrone was prepared as before, by condensation with *N*-benzylhydroxylamine, with no racemisation.[10]

Nitrone **(*pR*)-2b**[16,17] was first reacted with acetone and two equivalents of SmI_2† (Scheme 2) to yield the enantiopure β-*N*-hydroxylamino alcohol **(*pR*,*S*)-3b**[17] in 95% yield. Decomplexation of the chromium entity occurred quantitatively, giving access to β-*N*-hydroxylamino alcohol **(*R*)-5b**.[17] When six equivalents of SmI_2 were used in the reaction mixture, the corresponding β-amino alcohol complex **(*pR*,*S*)-4b**[17] was also isolated in excellent yield.

In conclusion, the reductive cross-coupling of $Cr(CO)_3$-complexed nitrones with carbonyl compounds is very efficient. It allows for the chemo- and enantioselective synthesis of β-*N*-hydroxylamino or β-amino alcohols under mild conditions. The use of planar chiral substrates induces excellent diastereoselectivities in the C–C bond formation. We are currently extending the scope of this synthetically useful reaction to various carbonyl compounds.

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Notes and references

† *Typical procedure for the reductive cross-coupling*: A solution of nitrone (0.5 mmol in 10 mL) and of the carbonyl compound (1 equiv.) in THF was cooled to −78 °C. A solution of SmI_2 (0.1 mol L^{-1}, 10 mL, 2 equiv.) in THF was then added drop by drop. The mixture was stirred at −78 °C for 30 min before being quenched by addition of saturated solutions of $Na_2S_2O_3$ (10 mL) and $NaHCO_3$ (10 mL). The yellow mixture was extracted by AcOEt. The combined organic layers were washed with a saturated aqueous NaCl solution and dried over $MgSO_4$. After concentration *in vacuo*, the crude mixture was purified either by washing with cyclohexane (**3b**, **3c** and **3e**) or by chromatography on silica gel (**3a**, **3d** and **3f**) to afford the pure β-*N*-hydroxylamino alcohols.
For the one-pot synthesis of β-amino alcohols, 6 equivalents of SmI_2 were used, and the reaction mixture was stirred for 30 min at −78 °C, then 15 hours at room temperature.

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