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Direct, Catalytic Enantioselective Nitroaldol (Henry) Reaction of Trifluoromethyl Ketones: An Asymmetric Entry to α-Trifluoromethyl-Substituted Quaternary Carbons

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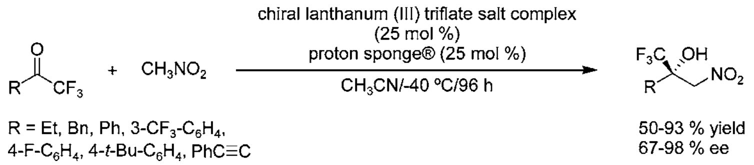
ABSTRACT



Herein we describe the first direct, catalytic enantioselective nitroaldol (Henry) reaction of simple α-trifluoromethyl ketones with nitromethane using a chiral monometallic lanthanum(III) triflate salt complex, namely [(Δ,*S*,*S*,*S*)-Binolam]$_3$·La(OTf)$_3$, as enantioselective catalyst. The resulting α-trifluoromethyl tertiary nitroaldols were obtained in moderate to high yields (up to 93%) and enantioselectivities (up to 98% ee). These adducts are versatile chiral building blocks and may be reduced (NiCl$_2$/NaBH$_4$) to their *β*-amino-α-trifluoromethyl tertiary alcohols without loss of enantiomeric purity.

Organofluorine chemistry is an important field of research owing to the wide range of applications of organofluorine compounds.[1] Among them, trifluoromethyl-substituted molecules constitute a particularly interesting class of compounds because of their relevant properties[2] for the pharmaceutical and agrochemical areas. On the other hand, the development of new methods for the construction of carbon quaternary centers is a matter of current interest.[3] Accordingly, the asymmetric synthesis of α-trifluoromethyl tetrasubstituted carbons[4] has attracted much attention, mainly because of the emergence of drugs such as Efavirenz (anti-HIV),[5] a chiral α-trifluoromethyl tertiary alcohol in which the -CF$_3$ moiety is located at an asymmetric tetrasubstituted carbon center. Methodologies for accessing this sort of asymmetric tetrasubstituted carbon atoms via enantioselective catalysis have

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only recently begun to be explored, and further development is clearly needed.[6]

To date, the most common approach to build a chiral carbon bearing a -CF_3 group relies on the asymmetric addition of organometallic compounds to prochiral α-trifluoromethyl-substituted ketones, imines, and the like.[7] The nitroaldol (Henry) reaction[8] of simple ketones is difficult because of the attenuated reactivity of such compounds,[9] and also to the strong tendency toward undergoing a retronitroaldol reaction under basic conditions.[10] Nevertheless, we envisioned that our recently reported chiral, monometallic lanthanide(III) triflate salt complexes[11] might avoid the latter difficulty and thus be able to promote a direct catalytic enantioselective nitroaldol (Henry) reaction[12] upon trifluoromethyl ketones to the desired enantiomerically enriched α-trifluoromethyl tertiary alcohols.[13] Our expectations were based not only on the activated nature of trifluoromethyl ketones as electrophiles but also on the large size of the -CF_3 (halfway between an isopropyl and a *tert*-butyl group),[2a,4a] and the ligating potentialities of the -$COCF_3$ moiety.[14]

Herein we describe the first apparently general, direct enantioselective nitroaldol (Henry) reaction of simple trifluoromethyl ketones[15] and demonstrate that the enantiomerically enriched α-trifluoromethyl tertiary nitroaldols thereby obtained are themselves amenable of chemical manipulation (reduction) into other useful chiral building blocks, however with some unwanted, though not unexpected, result in one particular case (see later).

Recently, we reported on the straightforward formation of shelf stable, though nevertheless kinetically labile, highly symmetric, chiral-at-metal complexes **2Ln** in combining 3 equiv of 3,3′-bis-diethylaminomethyl-2,2′-dihydroxy-1,1′-dinaphthalene **1** (“binolam”)[16] with 1 equiv of a lanthanide(III) triflate,[17] which are armed with an array of acid and basic sites (Lewis acid−Brönsted acid−Lewis base: LABALB) (Figure 1). In particular, the enantiopure lanthanum derivative [(Δ,*S*,*S*,*S*)-Binolam]$_3$·La(OTf)$_3$ **2La** was found to be ideally suited to catalyze the direct nitroaldol (Henry) reaction between nitromethane and aldehydes in an enantioselective manner.[11]

Having found that the nitroaldol reaction catalyzed by **2Ln** did not proceed satisfactorily with simple ketones, we decided to explore the enantioselective nitroaldol reaction upon the more reactive trifluoromethyl ketones, using **2La** as catalyst under the conditions previously reported for common aldehydes. A promising result (79% yield and 52% ee) was obtained for the commercially available 1,1,1-trifluoromethyl-2-butanone **3a** when working at room temperature. After considerable adjustment of variables, the optimal working conditions were fixed as indicated.[18] Following the recent reports by Soloshonok advising on the potential self-disproportionation of nonracemic mixtures of

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[6] Except for hydrocyanation, direct catalytic asymmetric synthesis of tetrasubstituted carbons are restricted to α-keto (or imino) carbonyl compounds or α-keto phosphonates. Nitroaldol reactions: (a) Christensen, C.; Juhl, K.; Jørgensen, K. A. *Chem. Commun.* **2001**, 2222−2223. (b) Christensen, C.; Juhl, K.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 4875−4881. (c) Choudary, B. M.; Ranganath, K. V. S.; Pal, U.; Kantam, M. L.; Sreedhar, B. *J. Am. Chem. Soc.* **2005**, *127*, 13167−13171. (d) Li, H.; Wang, B.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 732−733. (e) Mandal, T.; Samanta, S.; Zhao, C.-G. *Org. Lett.* **2007**, *9*, 943−945. Aldol reactions: (f) Zhuang, W.; Saaby, S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4476−4478. (g) Tokuda, O.; Kano, T.; Gao, W.-G.; Ikemoto, T.; Maruoka, K. *Org. Lett.* **2005**, *7*, 5103−5105. (h) Tang, Z.; Cun, L.-F.; Cui, X.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *Org. Lett.* **2006**, *8*, 1263−1266. (i) Samanta, S.; Zhao, C.-G.; *J. Am. Chem. Soc.* **2006**, *128*, 7442−7443. Alkynylation reaction: (j) Jiang, B.; Chen, Z.; Tang, X. *Org. Lett.* **2002**, *4*, 3451−3453.

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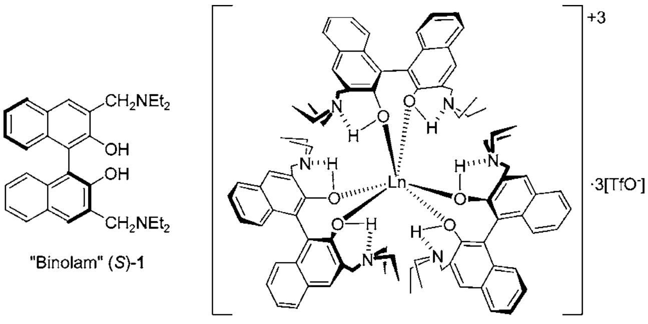


"Binolam" (*S*)-**1**

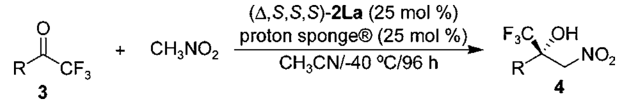
[(Δ,*S*,*S*,*S*)-Binolam]$_3$·Ln(OTf)$_3$ **2Ln**

Figure 1. Chiral monometallic lanthanide(III) triflate salt complexes **2Ln** of bifunctional "Binolam" (*S*)-**1**.

trifluoromethyl-substituted compounds,[19] we ran the "enantiomer self-disproportionation test" recommended, using chloroform as eluant. Since no self-disproportionation was observed (each of the six 4-mL fractions collected gave almost identical enantiomeric excesses when examined by chiral HPLC), all samples were treated along this protocol.

To explore the scope and limitations of the reaction, these optimized reaction conditions were then applied to various alkyl, aryl, and alkynyl α-trifluoromethyl ketones **3a**−**g** (noncommercially available compounds **3f**, **3g** were synthesized by applying the procedure reported by Creary).[20] As illustrated in Table 1, the enantiomeric excesses of the α-trifluoromethyl tertiary nitroaldols **4** so obtained can be qualified as good in most cases (in every single case, to further avoid trace self-disproportionations, a sample of the whole product was injected into the HPLC instrument for measuring ee values). As to the scope, alkyl α-trifluoromethyl ketones **3a**, **3b** (entries 1−2) were found to be suitable substrates for reaction. Aryl **3c**, **3e**, **3f**, and alkynyl **3h** α-trifluoromethyl ketones also gave good results (entries 3, 5−6) with the exception of the 3-trifluoromethyl derivative **3d** (entry 4), for which case the resulting nitroaldol **4d** was shown to have an enantiomeric excess of 67% only (two independent runs gave identical results). In our view, this unexpected result suggests that the extra -CF$_3$ moiety on the benzene ring might be interfering with the -COCF$_3$ unit in ligating a key center on the catalyst. The spectroscopic and analytical properties of the α-trifluoromethyl tertiary nitroaldols **4a**−**g** (except for the case of **4c**, all compounds have not been described in the literature) so obtained are fully consistent with the assigned structures.

Table 1. Enantioselective Nitroaldol Condensations of Trifluoromethyl Ketones **3a**−**g**[18]



entry	R (ketone **3**)	product **4**	yield (%)^a	ee (%)^b
1	Et (**3a**)	**4a**	55	85 (*S*)
2	Bn (**3b**)	**4b**	93	92 (*S*)
3	Ph (**3c**)	**4c**	78	96 (*S*)
4	3-CF$_3$-C$_6$H$_4$ (**3d**)	**4d**	55	67 (*S*)
5^c	4-F−C$_6$H$_4$ (**3e**)	**4e**	68	97 (*S*)
6	4-*t*-Bu−C$_6$H$_4$ (**3f**)	**4f**	50	98 (*S*)
7	PhC≡C (**3g**)	**4g**	82	80 (*S*)

^{a} Isolated yields after column chromatography. ^{b} Determined by chiral HPLC (Daicel Chiralpak AS-H or Chiralcel OJ-H columns). The absolute configuration of **4c** was established to be (*S*) after conversion in **5c** and X-ray analysis. Accordingly, the absolute configuration of the remaining nitroaldols **4** is tentatively assigned to be (*S*) as well. ^{c} Reaction performed at −30 °C, 7 days.

The long reaction times needed for completion (less reactive aryl ketones did not fully convert after 96 h) posed the question of the possible role of retroaldol reactions upon the observed ee's. In this regard it is worth mentioning that under the conditions of operation there is not substantial retronitroaldol reaction, as shown for the case of nitroaldol **4c** (96% ee) which after being submitted to the standard reaction conditions, was recovered in excellent chemical yield (99%) and proved to have identical enantiomeric purity (96% ee) by chiral HPLC as the starting nitroaldol **4c**. Moreover, we have found that no retroaldolization occurred during column chromatography.

To determine the absolute configuration of nitroaldols **4**, we decided to look for assignment by chemical correlation. After some experimentation with different reducing agents we found that compound **4c** (96% ee) could be efficiently reduced with nickel boride[21] (NiCl$_2$/NaBH$_4$) in methanol with apparent complete retention of the stereochemistry, as proved by chiral HPLC upon the resulting **5c** (94.5% ee). Its optical rotation ($[\alpha]^{25}_{D}$ +40.5 (*c* 0.765, CHCl$_3$)) revealed that its absolute configuration should be opposite to that reported by Solladié for a partially enriched sample.[22] Eventually, we were able to crystallize from chloroform our β-amino-α-trifluoromethyl derivative **5c**, and its absolute configuration was unambiguously established to be (*S*) by recourse to X-ray analysis (Figure 2).[23] By analogy, the absolute configuration

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[18] Typically, to a solution of [(Δ,*S*,*S*,*S*)-Binolam]$_3$·La(OTf)$_3$ **2La** (260 mg, 0.1325 mmol, 25 mol%, 0.25 equiv) in dry CH$_3$CN (5 mL), at -40 °C, under argon, proton sponge (475 μL, 0.1325 mmol, 25 mol%, 0.25 equiv, 280 mM solution in dry CH$_3$CN) was added. After stirring for 5 min, the corresponding trifluoromethyl ketone **3a**−**g** (0.53 mmol, 1 equiv) and excess nitromethane (291 μL, 5.3 mmol, 10 equiv) were added, and the mixture stirred for 96 h. The reaction mixture was then quenched with the appropriate amount of TFA (0.265 mmol, 0.50 equiv) followed by evaporation to dryness. The crude mixture was purified by flash chromatography on a silica gel column using CHCl$_3$ as eluant, thereby affording the α-trifluoromethyl tertiary nitroaldols **4a**−**g**. Full experimental details are provided as Supporting Information.

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[21] *Handbook of Reagents for Organic Synthesis: Oxidizing and Reducing Agents*; Burke, S. D., Danheiser, R. L., Eds.; Wiley: Chichester, England 1999; pp 246−250.

[22] The absolute configuration of a partially enriched sample of **5c** ($[\alpha]^{18}_{D}$ -15.1, (*c* 0.762, CHCl$_3$)) has been reported to be (*R*). See: Mioskowski, C.; Solladie, G. *Tetrahedron* **1973**, *29*, 3669−3674.

[23] CCDC 662278 ((*S*)-**5c**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.com.uk/data_request/cif. See the Supporting Information.

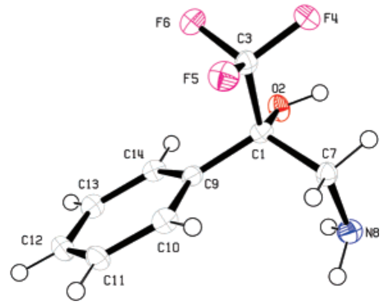
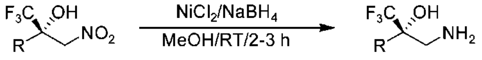


Figure 2. X-ray crystallographic structure of (*S*)-**5c**. Ellipsoids drawn at the 50% probability level. Flack parameter = 0.01(16).

of the remaining β-amino-α-trifluoromethyl derivatives **5** obtained in our work (see later) have also been assigned to be (*S*). Accordingly, the absolute configuration of nitroaldol **4c** is assumed to be (*S*). The absolute configuration of the remaining nitroaldols **4** have been tentatively assigned to be (*S*) as well.

To further extend the usefulness of the enantiomerically enriched α-trifluoromethyl tertiary nitroaldols **4** as building blocks for the pharmaceutical and agrochemical industries, we have explored their reduction to the corresponding β-amino-α-trifluoromethyl tertiary alcohols **5**. We eventually found that the nitroaldol products **4b**, **4c**, **4f**, **4g** could be efficiently reduced with nickel boride ($NiCl_2/NaBH_4$) in methanol with apparent complete retention of the stereochemistry as proved by chiral HPLC (Scheme 1). Under these conditions, the phenylpropargyl alcohol **4g** underwent complete reduction of the acetylene unit to the corresponding phenylethyl derivative **5g**. The spectroscopic and analytical properties of the resulting enantiomerically enriched β-amino-α-trifluoromethyl tertiary alcohols (except for **5c**, all compounds have not been described in the literature) are fully consistent with the assigned structures.

Scheme 1. Reduction ($NiCl_2/NaBH_4$) of Enantiomerically Enriched α-Trifluoromethyl Tertiary Nitroaldols **4** to Their β-Amino-α-trifluoromethyl Derivatives **5**



(*S*)-**4** (*S*)-**5**

4b: R = Bn (92% ee)
4c: R = Ph (96% ee)
4f: R = 4-*t*-Bu-C_6H_4 (98% ee)
4g: R = PhC≡C (80% ee)

5b: R = Bn (78%, 84% ee)
5c: R = Ph (79%, 94.5% ee)
5f: R = 4-*t*-Bu-C_6H_4 (87%, 97% ee)
5g: R = $Ph(CH_2)_2$ (61%, 72% ee)

As of today, we do not have mechanistically relevant data other than that reported previously for the nitroaldol reaction upon aldehydes,[11] which suggested that under the above reaction conditions the actual catalyst is the deprotonated precatalyst as shown by NMR and MS. In our view, this species could either promote (a) an enantioselective nitroaldol condensation or (b) a kinetic resolution upon the racemic nitroaldol.[10] In accordance with the results shown above we have found that racemic nitroaldol **4c** did not undergo noticeable kinetic resolution under the standard reaction conditions, thus leaving the enantioselective nitroaldol condensation as the only plausible reaction mechanism. Therefore, at this point we can only speculate on the dual role that this species might play in ligating both nitromethane and the α-trifluoromethyl ketone. The latter, as suggested above, may act as a chelating electrophile, thus providing a source for adequate facial discrimination. Kinetic studies are needed to further substantiate a detailed mechanistic hypothesis.

In summary, we have developed the first direct, enantioselective nitroaldol (Henry) reaction of simple trifluoromethyl ketones and nitromethane using a chiral, monometallic lanthanum(III) triflate salt complex. The resulting α-trifluoromethyl tertiary nitroaldols were obtained in moderate to high yields and enantioselectivities. These nitroaldol adducts are versatile chiral building blocks and may be reduced with nickel boride to the corresponding enantiomerically enriched β-amino-α-trifluoromethyl tertiary alcohols without loss of enantiomeric purity. This methodology adds a new entry to the existing ones toward enantiomerically pure quaternary centers. Further investigations on the usefulness of chiral monometallic lanthanide (III) triflate salt complexes are ongoing.

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Supporting Information Available: Detailed experimental procedures, characterization data of all new compounds and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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