

A catalytic highly enantioselective direct synthesis of 2-bromo-2-nitroalkan-1-ols through a Henry reaction†

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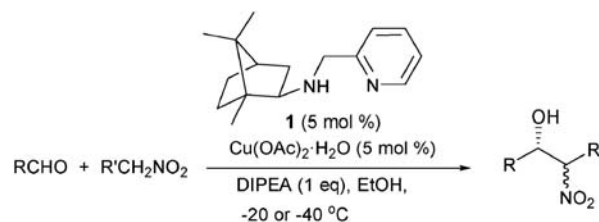
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Highly enantiomerically enriched 2-bromo-2-nitroalkan-1-ols are prepared by direct condensation of aliphatic and aromatic aldehydes with bromonitromethane in the presence of a catalytic amount of copper(II) acetate and a C_1 -symmetric camphor-derived amino pyridine ligand.

The reaction between a nitroalkane and a carbonyl compound, the so called Henry or nitro-aldol reaction, provides β -hydroxy nitroalkanes that are valuable intermediates for the synthesis of polyfunctionalized molecules and biologically active compounds.¹ In the last years, a number of catalytic enantioselective procedures for this reaction have been developed, most of them involving aldehydes and nitromethane² or, to a lesser extent, other unfunctionalized nitroalkanes.³ However, the use of functionalized nitroalkanes has been little studied. The addition of bromonitromethane to a carbonyl compound appears as an attractive method to prepare 2-bromo-2-nitroalkan-1-ols. This kind of compound shows activity against bacteria⁴ and other microorganisms, such as algae and fungi, and hence they are used as industrial microbicides⁵ in oil and gas wells,⁶ paper manufacture,⁷ fertilizers,⁸ and are included in a number of patented formulations for photographic and printing materials.⁹

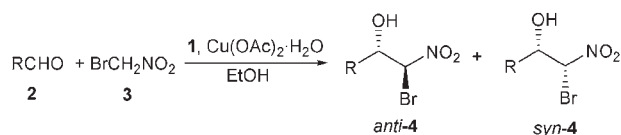
Bromonitroalkanols are normally obtained by bromination of the corresponding nitroalkanols with bromine,¹⁰ in a procedure that may lead to double bromination giving 2,2-dibromo-2-nitroalkanols as by-products. 2-Bromo-2-nitroalkan-1,3-diols have been prepared by double nitro-aldol addition of bromonitromethane to aldehydes under pH-controlled conditions.¹¹ On the other hand, controlled mono-addition of bromonitromethane to aldehydes has been achieved under heterogeneous acidic (one example) or basic (two examples) catalysis,¹² and very recently by NaI catalysis under very mild conditions.¹³ However, despite the effect of the absolute stereochemistry on the biological activity of chiral compounds, a procedure for the synthesis of 2-bromo-2-nitroalkan-1-ols in enantiomerically enriched form has not been reported to date, with the only exception of one example of diastereoselective addition of bromonitromethane to a chiral 2-amino aldehyde.¹³



Scheme 1 Nitro-aldol reaction between nitroalkanes and aldehydes catalyzed by copper(II) acetate and amino pyridine ligand **1**.

Recently our group has developed new ligands for the asymmetric metal-catalyzed Henry (or nitro-aldol) reaction.¹⁴ We have found that the catalytic system formed by copper(II) acetate and a camphor-derived C_1 -symmetric amino pyridine ligand **1** catalyzes the addition of nitromethane and other nitroalkanes to aliphatic and aromatic aldehydes with very high enantioselectivity, up to 98% ee, under very advantageous experimental conditions (Scheme 1).¹⁵ From these results, we envisioned that the reaction between bromonitromethane and aldehydes using this catalytic system could provide the expected 2-bromo-2-nitroalkan-1-ols in highly enantioenriched form.

The reaction between bromonitromethane (**3**) and benzaldehyde (**2a**) was used for the optimization process (Scheme 2, R = Ph). Initially, the reaction was carried out under similar conditions to those used in our previous work with nitromethane, which involved the use of 1 eq. of diisopropylethylamine (DIPEA) in ethanol at -40 °C. We were very pleased to observe that, after 7 h, the reaction was almost completed affording compound **4a** as an *anti* : *syn* 1 : 1 diastereomeric mixture with 67 and 74% ee, respectively. The enantioselectivity of the reaction was lower than that obtained in the reaction of nitromethane with benzaldehyde (98% ee) under identical conditions.¹⁵ We hypothesized that this lower enantioselectivity may be due to the competitive uncatalyzed addition of the bromonitromethane nitronate which should be present in higher concentration than in the case of nitromethane. As anticipated, a reduction in the amount of base minimized this side reaction and the expected product **4a** was obtained with increased enantioselectivity (Table 1, entries 2–4). The amount



Scheme 2 Catalytic enantioselective synthesis of 2-bromo-2-nitroalkan-1-ols by addition of bromonitromethane to aldehydes.

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Table 1 Asymmetric addition of bromonitromethane to benzaldehyde (R = Ph) catalyzed by copper(II) acetate and ligand **1** according to Scheme 2. Optimization^a

Entry	Additive	T/°C	t/h	Conv. (%) ^b	Anti : syn ^b	ee (%) ^c
1	DIPEA (1 eq)	-40	7	>99	52 : 48	67/74
2	DIPEA (60 mol%)	-40	7	>99	64 : 36	73/70
3	DIPEA (20 mol%)	-40	7	>99	52 : 48	77/77
4	DIPEA (10 mol%)	-40	7	>99	42 : 58	86/93
5	NaI (10 mol%)	-20	40	>99	31 : 69	89/90
6	CsF (10 mol%)	-20	6	>90	31 : 69	79/81
7	—	-40	40	>99	60 : 40	95/93
8	—	0	2	>99	59 : 41	84/78

^a All experiments were carried out under nitrogen: 0.5 mmol of **2**, 0.025 mmol of Cu(OAc)₂·H₂O, 0.025 mmol of **1**, 5.0 mmol of **3** and additive in 2 mL of EtOH. ^b Determined by ¹H NMR. ^c Determined by HPLC.

of DIPEA could be decreased to 10 mol% with respect to the aldehyde without any noticeable decrease of the reaction rate, the addition product **4a** being obtained in 86 and 93% ee for the *anti* and *syn* isomers, respectively (entry 4). When NaI was used in place of DIPEA, compound **4a** was obtained with similar enantiomeric excesses but with higher diastereoselectivity, although the reaction required more time (entry 5). Similar results were obtained when CsF, with the more basic fluoride ion, was used as the base. Finally, it was observed that the acetate ion of the copper salt was able to promote the reaction without the need for an external base. Under these conditions, compound **4a** was obtained as a 6 : 4 *anti* : *syn* mixture in 95/93% ee, respectively (entries 7 and 8). Note that the reactions without base and with NaI gave different major diastereomers (entries 5 and 7); however, this was not a general trend (*vide infra*).

Substrate scope was studied under “base-free” conditions.† A variety of aromatic and heteroaromatic aldehydes were found to be suitable substrates,¹⁶ with the reaction providing the expected bromonitroalkanol **4** in high to quantitative yields (Tables 1 and 2, entries 1–16). 2-Methoxybenzaldehyde reacted especially fast, indicating a possible chelating effect of the substrate with the catalyst. The reaction products **4** were obtained as mixtures of *anti* and *syn* diastereomers with moderate to good diastereoselectivities and very high enantiomeric excesses (near or above 90% ee) for both diastereomers. Only 4-nitrobenzaldehyde (entry 14) gave the condensation product **4m** with low ee. A substituent at the *ortho*- or *meta*-position favored the *syn* products (with the exception of 3-methoxybenzaldehyde, entry 8), while *para*-substituted benzaldehydes gave the *anti* isomers as the major products. The reaction with 2-chlorobenzaldehyde was also tested with the addition of 10 mol% NaI (entry 5); however an inversion of the diastereoselectivity with respect to the reaction in absence of additives was not observed in this case. Remarkably, the reaction could also be performed with unbranched and even branched or sterically hindered aliphatic aldehydes (entries 17–20). In these cases, the reaction needed to be carried out at higher temperature (0 °C) and the resulting products were obtained in high yield and good enantiomeric excesses, only slightly below the ee values obtained with aromatic aldehydes. Finally, the reaction with the α,β -unsaturated aldehyde, cinnamaldehyde (**2t**), afforded exclusively the 1,2-addition product **4t** in almost quantitative

Table 2 Asymmetric addition of bromonitromethane to aldehydes catalyzed by copper(II) acetate and ligand **1**. Substrate scope^a

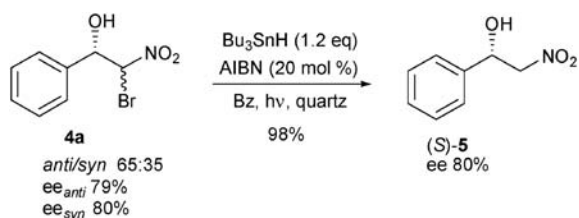
Entry	Aldehyde	T/°C	t/h	Yield (%) ^b	ee (%) ^c	anti : syn ^c
1	Benzaldehyde (2a)	-40	40	99	60 : 40	95/93
2	2-Methylbenzaldehyde (2b)	-40	40	99	16 : 84	98/96
3	2-Methoxybenzaldehyde (2c)	-40	4	95	21 : 79	94/95
4	2-Chlorobenzaldehyde (2d)	-40	45	80	13 : 87	94/97
5 ^e	2-Chlorobenzaldehyde (2d)	0	24	92	15 : 85	93/88
6	2-Nitrobenzaldehyde (2e)	-40	45	86	15 : 85	88/96
7	3-Methylbenzaldehyde (2f)	-40	45	99	32 : 68	94/97
8	3-Methoxybenzaldehyde (2g)	-40	45	98	61 : 39	94/94
9	3-Chlorobenzaldehyde (2h)	-40	45	97	41 : 59	94/nd
10	3-Nitrobenzaldehyde (2i)	-40	45	72	40 : 60	87/94
11	4-Methylbenzaldehyde (2j)	-40	40	83	70 : 30	89/92
12	4-Methoxybenzaldehyde (2k)	-40	45	95	63 : 37	93/94
13	4-Chlorobenzaldehyde (2l)	-40	45	95	69 : 31	90/90
14	4-Nitrobenzaldehyde (2m)	-40	45	85	64 : 36	44/38
15	Thiophene-2-carbaldehyde (2n)	-40	45	99	36 : 64	89/95
16	Thiophene-3-carbaldehyde (2o)	-40	45	99	32 : 68	91/95
17	Decanal (2p)	0	24	95	54 : 46	83/91
18	Dihydrocinnamaldehyde (2q)	0	24	99	54 : 46	87/87
19	Isovaleraldehyde (2r)	0	16	97	57 : 43	86/92
20	Cyclohexanecarbaldehyde (2s)	0	16	99	66 : 34	90/91
21	Cinnamaldehyde (2t)	-40	40	99	32 : 68	81/96

^a All experiments were carried out under nitrogen: 0.5 mmol of **2**, 0.025 mmol of Cu(OAc)₂·H₂O, 0.025 mmol of **1**, 5.0 mmol of **3**, in 2 mL of EtOH. ^b Isolated yield of **4**. ^c Determined by ¹H NMR. ^d Determined by HPLC. ^e 10 mol% NaI, conditions as in Table 1, entry 5.

yield, good diastereoselectivity and high ee for both diastereomers (entry 21). It should be noted that although a 90% pure technical bromonitromethane containing 10% nitromethane was used in all the reactions, no products arising from the addition of nitromethane were observed in the reaction mixtures.

The *anti* : *syn* diastereomeric ratio was determined from the integration of the ¹H NMR signals for the protons adjacent to the OH and NO₂ groups corresponding to each diastereomer. The coupling constants (*J*) between these protons appear in the 7.5–9.0 Hz range for the *anti* isomer and in the 2.1–5.4 Hz range for the *syn* isomer. These *J* values are in good agreement with those calculated from the dihedral angles (~180° for the *anti* and ~45° for the *syn* isomers) between H1 and H2 in the lower-energy conformation,¹⁷ and with those observed for related 2-alkyl-2-nitroalkan-1-ols.^{3,15}

The absolute stereochemistry of bromonitroalkanol **4a** was determined by chemical conversion into the known compound (*S*)-**5**, via reductive dehalogenation (Scheme 3). Treatment of a 65 : 35 *anti* : *syn* mixture of **4a** (79% ee for the *anti* isomer, 80% ee for the *syn* isomer) with Bu₃SnH in the presence of AIBN¹⁸ afforded (*S*)-**5** in almost quantitative yield and 80% ee,¹⁹ showing that the configuration of the carbon atom bearing the hydroxyl group was *S* in both the *anti* and *syn* diastereomers. Similar results were obtained with compounds **4b,f,j,s** indicating the existence of a common stereochemical



Scheme 3 Determination of the absolute stereochemistry of compound **4a**.

pathway regardless of the location of the substituent on the aromatic ring or the aromatic/aliphatic nature of the aldehyde. The stereochemistry for the rest of compounds **4** was assigned as 1*S* on the assumption of this uniform reaction mechanism. The absolute stereochemistry of compounds **4** is in agreement with the preferential approach of the nitronate from the *Re* face of the aldehyde carbonyl group according to our previously proposed mechanism.¹⁵

In summary, we have developed the first general procedure for the enantioselective synthesis of 2-bromo-2-nitroalkan-1-ols, which are compounds with important practical applications. The procedure involves the Henry reaction between bromonitromethane and aldehydes in the presence of a low load (5 mol%) of a catalytic system, recently developed in our laboratory, that uses copper(II) acetate and a readily available camphor-derived amino pyridine ligand. The reaction is general in scope providing the expected products with high to quantitative yields and good to excellent enantioselectivities with a broad range of aromatic, heteroaromatic, aliphatic and unsaturated aldehydes.

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Notes and references

‡ A solution of amino pyridine **1** (6.7 mg, 0.025 mmol) in absolute ethanol (2 mL) was added to Cu(OAc)₂·H₂O (5.0 mg, 0.025 mmol) contained in a Schlenk tube under nitrogen. The mixture was stirred for 1 h at room temperature until the formation of a deep blue solution. Benzaldehyde (**2a**, 53 μL, 0.5 mmol) was added and the reaction flask introduced in a bath at -40 °C. After 5 min, 90% pure technical bromonitromethane (**3**, 0.39 mL, 5 mmol) was added and the reaction mixture was stirred for 40 h. The mixture was treated with 1 M aqueous HCl (15 mL) and extracted with dichloromethane (3 × 15 mL). The organic layer was washed with brine (20 mL), dried over MgSO₄ and concentrated under reduced pressure to give **4a** (121 mg, 99%).

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