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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 1375–1378

$NaIO_4$-mediated asymmetric bromohydroxylation of α,β-unsaturated carboxamides with high diastereoselectivity: a short route to (−)-cytoxazone and droxidopa

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Received 24 October 2006; revised 11 December 2006; accepted 19 December 2006
Available online 23 December 2006

Abstract—The $NaIO_4$-mediated asymmetric bromohydroxylation of α,β-unsaturated carboxamides was achieved using lithium bromide as the bromine source under acidic conditions at rt to afford the corresponding chiral α-bromo-β-hydroxy carboxamides. Excellent yields (77–90%) and diastereoselectivities (up to 10:1) along with exclusive control over regio- as well as *anti*-selectivity are the main features with a good scope of substrates. The method has successfully been applied in the enantioselective syntheses of two biologically important molecules, viz (−)-cytoxazone and L-*threo*-DOPS (droxidopa).

The 1,2-functionalization of electron-deficient olefins (e.g., α,β-unsaturated acid derivatives) by the selective addition of two different functional groups, such as water and halogens (halohydroxylation) in a highly regio- and enantioselective manner, constitutes an important transformation in organic synthesis.[1] Such chiral α-halo-β-hydroxy carboxamides are versatile precursors, which could readily be transformed into epoxides, ketones, and unusual β-hydroxy-α-amino acids.[2] The asymmetric bromohydroxylation of alkenes, a potentially straightforward method to obtain such halohydrins, is scarce and known only for limited chiral substrates.[3] Biologically, haloperoxidases, such as vanadium bromoperoxidase (V-BrPO),[4] are known to catalyze the $2e^-$ oxidation of halides by H_2O_2, resulting in the concomitant halogenation of organic substrates, probably accounting for the biosynthesis of numerous halogenated marine natural products including terpenes, indoles, and phenols. Several catalytic functional mimics of V-BrPO have been reported.[5] Recently, Hajra et al.[6] reported diastereoselective syntheses of vicinal halohydroxy derivatives of α,β-unsaturated carboxylic acids. However, the asymmetric version of halohydrin reactions suffers from several disadvantages such as low diastereoselectivities (dr = 2:1), use of expensive metal salts (Ag, Yb), stoichiometric amounts of corrosive Br_2/*N*-halosuccinimides or the formation of large amounts of organic and inorganic waste.[6] We have described sodium metaperiodate ($NaIO_4$)-mediated enantioselective halohydroxylation of alkenes (encapsulated in β-cyclodextrin) using alkali metal halides with moderate enantioselectivity (56% ee).[7a]

In continuation of our interest in $NaIO_4$-mediated oxyfunctionalization of organic compounds,[7] we report herein the first 'transition metal-free' procedure for the asymmetric bromohydroxylation of α,β-unsaturated carboxamides with $NaIO_4$ as the oxidant and LiBr as the halogen source under ambient conditions in a highly regio- and diastereoselective manner, to afford the corresponding chiral α-bromo-β-hydroxy carboxamides (Table 1). After initial experimentation, (4*S*)-*N*-cinnamoyl-4-benzyl-2-oxazolidinone (**1a**), readily derived from the Evans' chiral auxiliary obtainable from (*S*)-phenylalanine,[8] was subjected to oxidative bromination in the presence of 0.3 equiv. $NaIO_4$ in a 2:1 mixture of CH_3CN and water and LiBr (1.2 equiv) under acidic conditions (aq HCl), to afford the corresponding bromohydrins **2a** and **3a** in 81% combined yield and high diastereoselectivity (dr = 5.5:1) (Scheme 1). A mixture of CH_3CN and H_2O (2:1 ratio) was found to be the best solvent system for the formation of bromohydrins. There was a marginal increase in the diastereomeric

Keywords: $NaIO_4$; Asymmetric bromohydroxylation; Carboxamide; Cytoxazone; Droxidopa.
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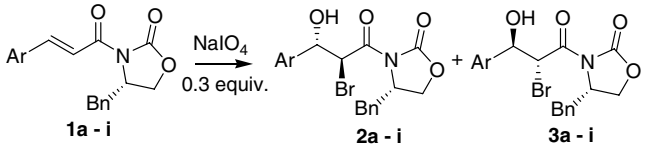
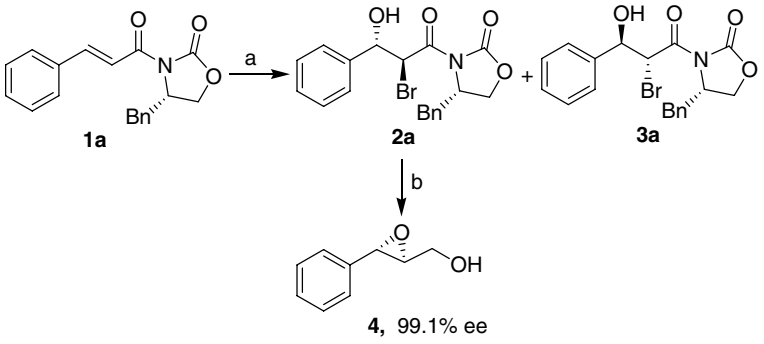
doi:10.1016/j.tetlet.2006.12.109

Table 1. $NaIO_4$-mediated[a] asymmetric bromohydroxylation of α,β-unsaturated carboxamides with LiBr



Entry	Substrate (Ar)	Ratio (**2**:**3**)[b]	Yield[c] (%)
a	C_6H_5	5.5:1	81
b	4-MeO–C_6H_4	10:1	90
c	4-CH_3–C_6H_4	9:1	86
d	3,4-Dimethoxy-C_6H_3	7:1	82
e	4-Cl–C_6H_4	6:1	77
f	3,4,5-Trimethoxy-C_6H_2	6:1	86
g	3,4-(O–CH_2–O)–C_6H_3	5:1	84
h	3,4-Dibenzyloxy-C_6H_3	6:1	87
i	Furan	5:1	82

[a] Reaction conditions:[17] carboxamides **1a**–**i** (5 mmol), LiBr (6 mmol), 35% aq HCl (0.5 mL), CH_3CN/H_2O (2:1), 25 °C, 3 h.
[b] Diastereomeric ratios were determined by GC.
[c] Combined isolated yield of **2** and **3**.

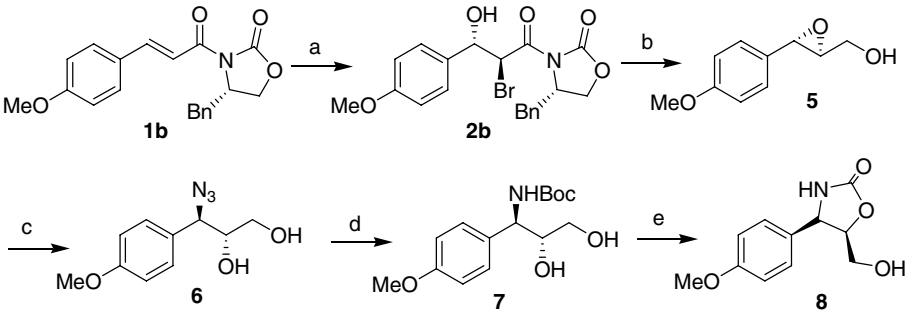


$[\alpha]^{D}_{25}$ -50.58 (*c* 1, $CHCl_3$)

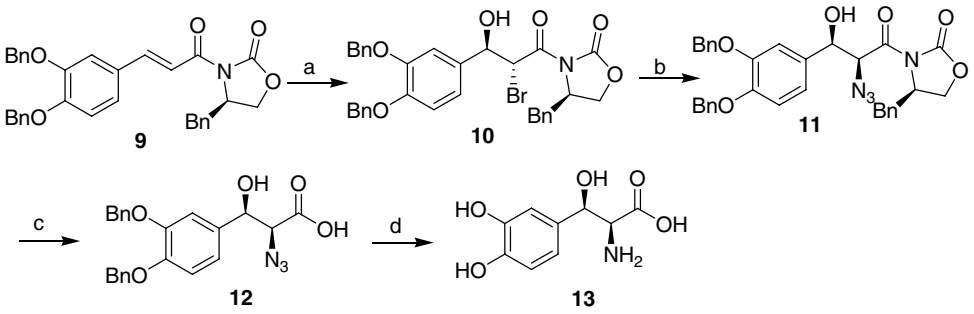
Scheme 1. Reagents and conditions: (a) $NaIO_4$ (0.3 equiv), LiBr (1.2 equiv), H^+, CH_3CN/H_2O (2:1), 25 °C, 81%, dr = 6:1; (b) $LiBH_4$, Et_2O, THF, MeOH, 0 °C, 1.5 h then 10% NaOH, 25 °C, 85%.

ratio (dr = 6.5:1) when bromohydroxylation of **1a** was conducted at 10 °C, however, lower conversion resulted. In order to confirm the resulting configuration of the diastereomers obtained, the oxazolidinones **2a** and **3a** were separated by column chromatography and subsequently **2a** was subjected to reduction with $LiBH_4$ under basic conditions to give the chiral epoxy alcohol **4** in 99.1% ee (determined by chiral HPLC using a Chiralcel OD column).[9] Encouraged by this result, several (4*S*)-*N*-cinnamoyl-4-benzyl-2-oxazolidinones (entries **1a**–**i**) with electron-donating and withdrawing substituents on the aromatic nucleus were prepared and then subjected to asymmetric bromohydroxylation to produce the corresponding bromohydrins **2** and **3** in excellent yields and high diastereoselectivities (Table 1). With all the substrates studied, the reaction proceeded in a highly regiospecific manner, the hydroxyl group adding at the benzylic position, exclusively. No traces of dibromide were observed in all the substrates screened. Monosubstituted electron-donating groups at the *para* position (e.g., OMe, CH_3) gave the maximum diastereoselectivities of 10:1 and 9:1, respectively (Table 1, entries b and c).

It was of interest to apply the present methodology to the enantioselective synthesis of both (−)-cytoxazone (**8**) and L-*threo*-DOPS (**13**). (−)-Cytoxazone (**8**) exhibits cytokine modulating activity by inhibiting the signalling pathway of Th2 cells. Since Th2 cells play a major role in mediating the immune response to allergens, (−)-cytoxazone could be a useful lead compound for the development of therapeutic agents for atopic dermatitis and asthma. Due to its potent bioactivity and relatively simple structure, several methods for the synthesis of (−)-cytoxazone have been reported.[10] L-*threo*-DOPS [(2*S*,3*R*)-3,4-dihydroxy phenylserine] (**13**), an alternative biological precursor of norepinephrine, is useful in treating disorders of the central and sympathetic nervous systems. For example, orthostatic hypotension, characterized by adrenergic deficiency and certain symptoms of Parkinson's disease, can be alleviated by treatment with L-*threo*-DOPS.[11] To the best of our



Scheme 2. Reagents and conditions: (a) $NaIO_4$ (0.3 equiv), LiBr, H^+, CH_3CN:H_2O (2:1), 25 °C, 1 h, 82%; (b) $LiBH_4$, Et_2O, THF, MeOH, 0 °C, 1.5 h then 10% NaOH, 25 °C, 86%; (c) NaN_3, NH_4Cl, MeOH, H_2O, 80 °C, 3 h, 84%; (d) (i) 10% Pd/C, MeOH, 25 °C, 12 h; (ii) $(Boc)_2O$, Et_3N, CH_2Cl_2, 25 °C, 2 h, 77% (2 steps); (e) NaH, THF, 25 °C, 2 h, 89%.



Scheme 3. Reagents and conditions: (a) $NaIO_4$ (0.3 equiv), LiBr, H^+, CH_3CN:H_2O (2:1), 25 °C, 1 h, 75%; (b) NaN_3, DMF, 60 °C, 4 h, 82%; (c) LiOH, 30% H_2O_2, THF, H_2O, 0 °C, 2 h, 88%; (d) 10% Pd/C, MeOH, 25 °C, 12 h, 94%.

knowledge, there are only two reports in the literature[12] which describe the asymmetric synthesis of L-*threo*-DOPS.

For the synthesis of (−)-cytoxazone, carboxamide **1b** was subjected to oxidative bromohydroxylation ($NaIO_4$, LiBr, H^+) to produce bromohydrin **2b**[18] with excellent diastereoselectivity (dr = 10:1) in an isolated yield of 82%. The chiral auxiliary in **2b** was removed by reduction with $LiBH_4$ followed by treatment with 10% NaOH[13] to give epoxy alcohol **5** in 86% yield; $[\alpha]_D^{25}$ −12.5 (*c* 1.1, $CHCl_3$). The regiospecific opening[14] of epoxide **5** with azide produced azido alcohol **6** in 84% yield. Azido alcohol **6** was then converted to (−)-cytoxazone (**8**) {mp 118–121 °C; $[\alpha]_D^{25}$ −71 (*c* 1, MeOH); lit.[10] mp 118–121 °C; $[\alpha]_D^{25}$ −71 (*c* 1, MeOH)} in 99.2% ee (determined by chiral HPLC using a Chirasphere® column) using a standard sequence of reactions, viz. azide reduction and amine protection followed by cyclization[15] (Scheme 2).

For the preparation of droxidopa, carboxamide **9** prepared from (*R*)-phenylalanine[8] was subjected to oxidative bromohydroxylation to produce bromohydrin **10**[18] in the ratio dr = 6:1. Nucleophilic displacement of bromide group in **10** with sodium azide in DMF furnished azido alcohol **11** in 82% yield; $[\alpha]_D^{25}$ −17 (*c* 1, $CHCl_3$). Subsequent removal of the chiral auxiliary with LiOH and 30% H_2O_2[16] followed by azide reduction and deprotection of the benzyl groups with 10% Pd/C, H_2 (1 atm) in MeOH furnished L-*threo*-DOPS **13** {mp 232–233 °C; $[\alpha]_D^{25}$ −39 (*c* 0.4, 1 N HCl); lit.[12b] mp 232–235 °C; $[\alpha]_D^{25}$ −39 (*c* 0.4, 1 N HCl)} in 94% yield and >99% ee (Scheme 3).

In conclusion, we have described the $NaIO_4$-mediated asymmetric bromohydroxylation of α,β-unsaturated carboxamides[17,18] with high regio- and diastereoselectivity using Evans' chiral auxiliary and LiBr as the halogen sources. The methodology avoids the use of heavy metals and molecular bromine as well as *N*-halosuccinimides as halogen sources. The enantioselective syntheses of two medicinally important molecules, (−)-cytoxazone **8** and droxidopa **13**, were achieved using the present protocol. This method should find application in the synthesis of various biologically active organic molecules.

Acknowledgements

S.G. and N.V.S. thank CSIR, New Delhi, for the award of research fellowships. The authors are thankful to Dr. B. D. Kulkarni, Deputy Director, for his support and encouragement.

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17. General experimental procedure for bromohydroxylation of α,β-unsaturated carboxamides: To a stirred solution of α,β-unsaturated carboxamide (5 mmol), $NaIO_4$ (1.5 mmol), and 35% aq HCl (0.5 mL) in CH_3CN/H_2O (2:1, 30 mL) at 25 °C, LiBr (6 mmol) was added portionwise. The reaction was monitored by TLC. After completion of the reaction, it was diluted with water and extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with 5% sodium thiosulfate (30 mL) followed by brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude bromohydrin products, which were then purified by column chromatography on silica gel (60–120 mesh) eluting with petroleum ether and ethyl acetate (7:3) to afford pure products **2** and **3**.
18. All the compounds listed in Table 1 and **4**–**13** were characterized by NMR and FT-IR spectroscopy. Spectral data for selected new compounds:
anti-(4*S*,2′*S*,3′*S*)-3-[2′-Bromo-3′-hydroxy-3′-(4-methoxyphenyl)-propionyl]-4-benzyloxazolidin-2-one (**2b**): Yield: 84%; solid; mp: 103 °C; $[\alpha]_D^{25}$ +7.76 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$): *v* 3602, 3019, 2927, 2400, 1785, 1701, 1604, 1498, 1384, 1215, 1111, 1021, 757, 668 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.76 (dd, $J = 9.0$, 13.7 Hz, 1H), 3.21 (dd, $J = 3.6$, 13.7 Hz, 1H), 3.37 (d, $J = 6.3$ Hz, 1H), 3.89 (s, 3H), 4.15–4.31 (m, 2H), 4.68–4.74 (m, 1H), 5.12 (d, $J = 7.6$ Hz, 1H), 5.86 (d, $J = 8.0$ Hz, 1H), 6.90 (d, $J = 8.3$ Hz, 2H), 7.10–7.40 (m, 7H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 37.12, 44.56, 55.24, 56.00, 66.02, 74.08, 111.30, 127.20, 128.72, 129.18, 131.86, 132.62, 137.17, 152.36, 155.70, 168.75; Analysis: $C_{20}H_{20}BrNO_5$ requires C, 55.31; H, 4.64; Br, 18.40; N, 3.23. Found: C, 55.59; H, 4.48; Br, 18.01; N, 3.54.
anti-(4*R*,2′*R*,3′*R*)-3-[2′-Bromo-3′-hydroxy-3′-(3,4-bis(benzyloxy)phenyl)-propionyl]-4-benzyloxazolidin-2-one (**10**): Yield: 75%; gum; $[\alpha]_D^{25}$ −52.75 (*c* 3.0, $CHCl_3$); IR ($CHCl_3$): *v* 3502, 3019, 2926, 2252, 1787, 1496, 1383, 1250, 1160, 1107, 911, 794, 737 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.77 (dd, $J = 9.5$, 13.5 Hz, 1H), 3.25 (dd, $J = 3.3$, 13.5 Hz, 1H), 3.58 (br s, 1H), 4.03–4.12 (m, 2H), 4.47–4.58 (m, 1H), 5.10 (s, 2H), 5.15 (s, 2H), 5.48 (d, $J = 7.1$ Hz, 1H), 6.02 (d, $J = 6.1$ Hz, 1H), 7.09–7.44 (m, 18H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 36.82, 43.82, 54.94, 66.03, 71.03, 71.09, 73.32, 114.11, 114.47, 118.11, 127.21, 127.33, 127.49, 127.81, 127.95, 128.38, 128.45, 128.86, 129.37, 130.73, 134.58, 136.23, 136.52, 148.25, 149.52, 152.28, 168.40; Analysis: $C_{33}H_{30}BrNO_6$ requires C, 64.29; H, 4.90; Br, 12.96; N, 2.27. Found: C, 64.01; H, 5.21; Br, 12.69; N, 2.49.