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Oxidation of Amino Diols Mediated by Homogeneous and Heterogeneous TEMPO

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M. P. and R. C. dedicate this work to Professor Carsten Bolm.

Abstract: The conversion of amino diols to aminohydroxy acids by oxidation of the primary hydroxy group mediated by homogeneous and heterogeneous TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl radical) is reported. The synthesis uses NaOCl as primary oxidant and TEMPO, either dissolved in the homogeneous phase or entrapped in a sol-gel matrix, as catalytic mediator. Homogeneous TEMPO is suitable for the oxidation of aliphatic methylamino diols, while the hybrid organic-inorganic silica sol-gel catalysts are more selective mediators for the oxidation of benzylic amino diols like the potent antibiotic chloramphenicol which, under homogeneous conditions, are unselectively oxidized to benzoic acids.

Keywords: amino alcohols; chloramphenicol; heterogeneous catalysis; ormosil; oxidation; sol-gel; TEMPO

Introduction

Enantiomerically pure β-amino-α-hydroxy acids and α-amino-β-hydroxy acids are of considerable importance being essential components of medicinally useful products.[1] The synthesis of these non-proteinogenic amino acids can be achieved from appropriate amino diols by oxidation of the primary hydroxyl group to carboxylic acid. However, such oxidation generally requires previous protection of the amino *and* of the secondary hydroxy groups and these multiple-step procedures afford the desired product with moderate yields.[2] On the other hand, exploiting the known selectivity of TEMPO-mediated oxidations in an alkaline environment,[3] the selective oxidation with TEMPO/NaOCl of the primary alcohol function to carboxylic acid in polyol systems can be carried out in one step[4] and also the oxidation of *N*-protected 3-amino-1,2-diols has been studied.[5]

No examples could be found in the literature of oxidation mediated by TEMPO of 3-phenyl-substituted 2-amino-1,3-propanediols, probably due to competitive oxidation of the benzylic alcohol moiety in these systems. We now report the synthesis of β-amino-α-hydroxy acids and α-amino-β-hydroxy acids by oxidation of selected amino alcohols mediated by homogeneous and heterogeneous TEMPO with NaOBr (NaOCl and a catalytic amount of Br^-) as stoichiometric oxidant (Scheme 1), and show once again how the sol-gel encapsulation of the organic nitroxyl radical in hybrid organic-inorganic silica matrices can be effectively exploited to obtain the desired products with yields and selectivity which are *higher* than those observed in the corresponding homogeneous conversion.

Results and Discussion

The utility of the oxidation of *N*-Boc-3-methylamino-1,2-diols and *N*-Boc-2-methylamino-1,3-diols with homogeneous TEMPO/NaOCl was confirmed using a regioisomeric mixture (75:25) of the amino diols **1a** and **2a** with 10 mol % TEMPO (a relatively high amount, employed to maximize the reaction rate and minimize degradation).[6] Due to instability of the aminohydroxy acids, esterification *in situ* was carried out prior to chromatographic purification and the methylaminohydroxy esters **3a** (81% calculated from **1a**) and **4a** (78% calculated from **2a**) were isolated as pure compounds and no unselective oxidation products could be detected.

Then, we attempted the oxidation of the commercially available chloramphenicol **2b**, a potent antibiotic containing a benzylic alcohol moiety. In this reaction (followed by esterification) the corresponding ester **4b** was isolated in 31% yield only; and the oxidation of

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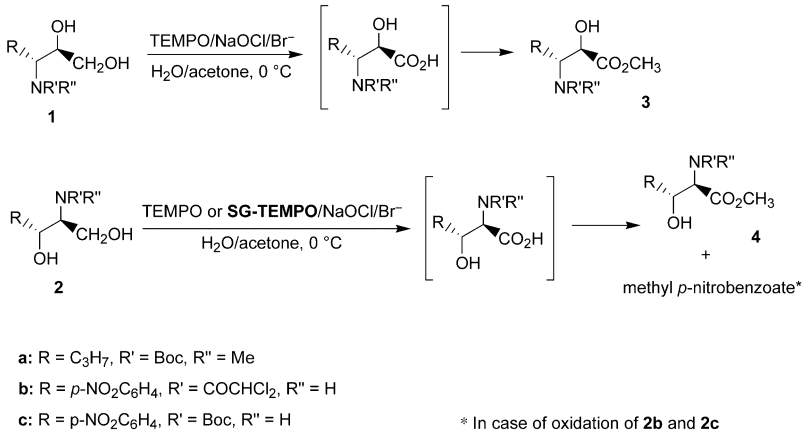

Scheme 1. Synthesis of β-amino-α-hydroxy esters **3** and α-amino-β-hydroxy esters **4**.

the *N*-Boc protected amino diol **2c** afforded the ester **4c** with a similar yield (38%). In both cases an abundant amount of methyl-*p*-nitrobenzoate (37%) was isolated as a result of the oxidation of the benzylic alcohol moiety (Scheme 1).

Since the homogeneous TEMPO/bleach reaction protocol in water/acetone, when applied to the conversion of chloramphenicol **2b** and the benzylic amino alcohol **2c**, yields the moderate selectivity reported above, we reasoned that a heterogeneous TEMPO catalyst might improve the selectivity by separating the catalyst from the reactants, and decided to use the new sol-gel entrapped catalysts which were found in a recent report to be selective oxidation mediators in the Anelli–Montanari oxidation of alcohols to carbonyls (Table 1).[7]

The experimental results confirmed the validity of the above mentioned expectations (Table 2). Hence, for instance, while the oxidation of chloramphenicol using homogeneous TEMPO/NaOCl in water/acetonitrile (buffered by $NaHCO_3$ to pH 9.1) yields only 31% of the corresponding ester (37% of chloramphenicol was degraded to benzoic ester), the use of sol-gel silica entrapped TEMPO after the same reaction time (8 h) yields 45% of chloramphenicol carboxylic ester and only 27% of degradation product after 14 h (entries 1 and 2, Table 2). A selectivity increase could be further enhanced using *acetone* in place of acetonitrile as organic co-solvent (entry 3, Table 2).

Organically modified silicates (ormosils) doped with TEMPO, in particular, were reported as better catalytic oxidants in the biphasic system water/CH_2Cl_2 than the corresponding unmodified doped SiO_2 gel,[7] and we also decided to verify this result in the amino alcohol oxidation in the monophasic water/acetone solution.

With the catalytic ormosil SG-TEMPO-1 (a sol-gel silica matrix in which 25% of the Si atoms bear a covalently bonded CH_3 group) in place of the unmodified SiO_2 gel SG-TEMPO-0, the selectivity was practically unchanged (entries 4 and 3 in Table 2, respectively); using the doped 75% propyl-modified gel SG-TEMPO-P (entry 5) a 56% yield of chloramphenicol carboxylic ester **4b** was obtained along with 26% of benzoic ester in 14 h. A further improvement in selectivity was achieved after the same reaction time by the use of the microporous, fully methyl-modified gel SG-TEMPO-2 and a 64% yield of the ester **4b** (entry 6) and only 20% of benzoic ester were eventually obtained (no substrate is left unreacted; above yields are calculated after product isolation which of course is not quantitative).

Similarly to what was observed in the biphasic H_2O/CH_2Cl_2 system, the sol-gel ormosils proved to be remarkably stable, with increasing alkylation of the silica matrix promoting the stability of the resulting catalyst. Moreover, in water/acetone also the *unmodified* silica-encapsulated TEMPO (SG-TEMPO-0) retained its initial high activity upon the first oxidative reaction run,

Table 1. Textural properties and composition of the catalytic ormosils doped with TEMPO.

Catalyst	Organosilane[a]	DF[b] [mmol/g]	S_{BET} [m^2/g]	V_p [cm^3/g]
SG-TEMPO-0	0% MTMS	0.27	217	1.24
SG-TEMPO-1	25% MTMS	0.28	213	1.19
SG-TEMPO-2	100% MTMS	0.30	267	1.25
SG-TEMPO-P	75% PTMS	0.25	75	0.38

[a] Molar percentages relative to TMOS (tetramethyl orthosilicate) used in each gel preparation; MTMS (methyltrimethoxysilane), PTMS (propyltrimethoxysilane).
[b] Degree of functionalization based on the assumption of complete radical encapsulation during the sol-gel catalyst synthesis.

Table 2. Yields in the oxidation of chloramphenicol with NaOCl/NaBr mediated by homogeneous and sol-gel entrapped TEMPO.

Entry	Catalyst	Chloramamphenicol carboxylic ester **4b** [%]	*p*-Nitrobenzoic ester [%]	Time [h]
1	TEMPO[a]	31	37	8
2	SG-TEMPO-0[b]	45	27	14
3	SG-TEMPO-0[c]	55	24	14
4	SG-TEMPO-1[c]	52	20	14
5	SG-TEMPO-P[c]	56	26	14
6	SG-TEMPO-2[c]	64	20	14

[a] Reaction conditions: 2 mmol of substrate, 10 mol % TEMPO, 20 mL of aqueous $NaHCO_3$ (5% w/w), 20 mL acetonitrile; NaOCl 2.2 equivs.; NaBr 10 mol %; T = 0 °C.
[b] 10 mol % entrapped TEMPO.
[c] Acetone is the co-solvent, 10 mol % entrapped TEMPO.

probably due to the action of acetone which moderates the alkalinity of the bicarbonate solution (with OH^- attacking the siloxane Si–O–Si bonds in the silica structure).

In each catalytic run mediated by the doped ormosils no leaching of encapsulated radicals in solution was observed, as shown also by the lack of further reactivity of the reaction filtrate obtained upon separation of the catalyst from the reaction mixture; hence, for instance, the SG-TEMPO-2 catalyst could be reused in all the 7 catalytic runs in which it was employed without any significant loss in activity. Accordingly, no degradation of the ormosil structure in the buffered alkaline reaction environment (pH 9.1) was observed by EPR and FTIR analysis of the catalyst prior to and after 7 reaction runs (which may be compared to the chemical behavior of materials like hydrophilic MCM-41-grafted TEMPO which is unusable[8] above pH 8 due to dissolution of the crystalline silica).

Encapsulation of an active species within the sol-gel cages of silica, in fact, results in chemical sponges showing chromatographic properties (which adsorb and concentrate the reagents at the cages surface where reactions take place) and higher chemical and physical stability of the entrapped molecules relative to those observed in solution.[9] This is particularly relevant here, since the continuous decrease in activity of TEMPO anchored (through a slow heterogeneous reaction) to the pores surface of commercial aminopropyl-silica was recently proved to be due to *intermolecular* quenching of the radicals anchored in proximity at the material surface;[10] in contrast, the homogeneous sol-gel encapsulation process disperses and protects the dopant species *within* nanoporous silica cages, allowing also the use of gels with higher catalytic loads without loss in the material activity.[7]

To explain the origin of the increased selectivity upon the catalyst entrapment in hydrophobic sol-gel matrices (which has been observed also in other cases)[11] *three* factors are known to play a major role: i) the effect of the spatial confinement of the narrow pores, imposing a specific approach of the substrate to the catalyst; ii) the participation of the intra-cage silanol and alkyl groups in hindering free tumbling of the substrate molecule, while directing a specific orientational approach to the catalytic species through the chemical interactions (hydrogen bonds etc.) between the substrate and the pore/cage surface; and iii) the hydrophilic-lipophilic balance (HLB) of the material surface.

In the present case, it might be that the polar $-CH_2OH$ heads of the hydrophobic amino alcohol molecules diffuse orientating towards the active oxoammonium ion (formed upon the action of BrO^-) tethered at the surface of the hydrophobic cage. Indeed, within the sol-gel cage organically modified by the alkyl groups, the entrapped radical senses a hydrophobic environment since the alkyl groups concentrate at the cage surface,[12] and it is precisely in this *inner* surface that reactions take place due to internal porosity (1.25 mL/g) and accessibility of the cages (267 m^2/g of SG-TEMPO-2 *vs.* a few m^2/g of the outer surface regions of the gel).

On the other hand, the enhanced hydrophobicity of the silica cages diminishes the amount of hindering *intra-cage* hydrogen bonds between Si–OH groups and between silanols and water molecules, and this enhances the freedom of the encapsulated TEMPO by providing the needed flexibility[9a,11] which is crucial in ensuring the selectivity for primary alcohols due also to the cyclic reaction mechanism[3] of TEMPO-mediated oxidations at alkaline pH. A thorough study of the influence of the pH on the (heterogeneous) reaction will be reported separately.

Finally, it is also relevant in the light of possible applications to note that the sol-gel encapsulation of the nitroxyl radicals in hydrophobic silica matrices markedly protects them against quenching due to a lesser degree of silane radical formation during the sol-gel synthesis of the materials,[7] while the versatility of the sol-gel process has already allowed the introduction of "2nd generation" sol-gel doped hybrid materials for commer-

cial applications[13] which now include also fine chemistry catalytic conversions.[14]

Conclusion

The catalytic TEMPO/NaOCl oxidation protocol can be applied to the conversion of aliphatic amino diols to valuable aminohydroxy acids in good yields (65–80%) and selectivity in aqueous acetone as reaction medium. Ormosils doped with TEMPO are recyclable heterogeneous catalysts for the same conversion and can *also* be applied to the oxidation of amino diols containing a benzylic alcohol moiety such as 3-phenyl-substituted 2-amino-1,3-diols, with enhanced product selectivity of 3:1 when, under homogeneous conditions, these species are unselectively degraded to benzoic acids. The best performing catalysts are fully methyl-modified hybrid silica gels which afford higher yields of hydroxy acids and better selectivity than homogeneous TEMPO. An interpretation of the findings is given to provide guidelines in the preparation of efficient TEMPO-based solid oxidation catalysts.

Considering the importance of the amino diol oxidation products[1] and the advantages of heterogeneous oxidation catalysis,[15] these results further demonstrate the versatility of sol-gel organic-inorganic silica hybrid catalysts doped with TEMPO as practical oxidation catalysts which are likely to soon find commercial applications in the fine chemicals and catalysis industries.[16]

Experimental Section

Unless otherwise specified, materials were purchased from commercial suppliers and used without further purification. Solvents were distilled prior to use and flash chromatography was performed using silica gel (60 Å, 230–240 mesh).

Preparation of *N*-Protected Amino Diols

To a solution of a regioisomeric mixture (75:25) of (2*R*,3*R*)-3-methylamino-1,2-hexanediol and (2*R*,3*R*)-2-methylamino-1,3-hexanediol (12.7 mmol) in $CHCl_3$ (10 mL) was added dropwise a solution of di-*tert*-butyl dicarbonate (2.76 g, 12.7 mmol) in $CHCl_3$ (5 mL). After 24 h stirring at room temperature the solvent was concentrated under vacuum to leave a residue, which was chromatographed over silica gel (NEt_3 pre-treated 2% v/v) using hexane/EtOAc as eluent to afford a mixture of the *N*-Boc amino diols **1a** and **2a** (75:25). By the same procedure the (1*S*,2*S*)(+)-2-amino-1-(4-nitrophenyl)-1,3-propanediol afforded the amino diol **2c**.

Oxidation Procedure

Method A (homogenous conditions): To a solution of the amino diol (2.03 mmol) in acetonitrile or acetone (20 mL) containing TEMPO (0.2 mmol) was added a 5% aqueous $NaHCO_3$ solution (20 mL) buffered to pH 9.1. The mixture was cooled to 0 °C and NaOCl (5.3 mL, *ca.* 13% w/w) was added dropwise over 15 min while following the reaction by TLC. The mixture was acidified with a 10% aqueous tartaric acid solution (10 mL), extracted with EtOAc (3 × 10 mL), dried over $NaSO_4$ and concentrated under reduced pressure. The crude product was used for the following reaction without further purification.

Method B (heterogeneous conditions): The catalyst SG-TEMPO-2 (300 mg, 20 μmol) and KBr (0.2 mmol) were added to a flask containing acetone (20 mL) and amino diol (2.03 mmol) and further combined with a 5% aqueous $NaHCO_3$ solution (20 mL) buffered to pH 9.1. The mixture was stirred and NaOCl (5.3 mL, 13% w/w) was added dropwise over 15 min while following the reaction by TLC. When the reaction was complete, the catalyst was filtered and washed with H_2O, MeOH and acetone (2 mL each), air-dried and reused as such in a consecutive oxidation run. The crude product was isolated as mentioned above and used for the following reaction without further purification.

Esterification of Aminohydroxy Acids

A solution of the crude product (1.1 mmol) in DMF (1 mL) cooled to 0 ^{0}C was added with 1.1 mmol K_2CO_3 (0.16 g) and left under stirring for 10 min prior to addition of iodomethane (0.14 mL, 2.3 mmol). The mixture was stirred for 45 min, allowed to warm to room temperature and kept under further stirring for 90 min after which EtOAc (10 mL) and H_2O (10 mL) were added, allowing the separation of two layers. The organic extract was washed with brine (2 × 10 mL), dried ($NaSO_4$) and concentrated under reduced pressure to give a residue, which was purified by chromatography on silica gel using hexane/EtOAc.

Analyses

Melting points are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at either 300 MHz or 400 MHz corresponding to 75 MHz or 100 MHz resonance frequencies for ^{13}C NMR. Chemical shifts are reported in delta (δ) units, parts per million (ppm) downfield from trimethylsilane or to the center of the 77.00 ppm triplet of $CDCl_3$. ^{13}C NMR spectra were routinely run with broadband decoupling. Optical rotations were measured at room temperature. High-resolution mass spectral (HRMS) data are reported as *m/e* (relative intensity). The ionization modes used in mass spectroscopy were electron impact (EI) or chemical ionization (CI) at 70 eV.

(2*R*,3*R*)-3-[*N*-(*tert*-Butoxycarbonyl)-*N*-(methyl)amino]-1,2-hexanediol (1a) and (2*R*,3*R*)-2-[*N*-(*tert*-Butoxycarbonyl)-*N*-(methyl)amino]-1,3-hexanediol (2a)

Regioisomeric mixture 75:25, yield: 68%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, J = 7.1 Hz, $3H_{1a}$ + $3H_{2a}$), 1.25 (m, $2H_{1a}$ + $2H_{2a}$), 1.39 (s, $9H_{2a}$), 1.45 (s, $9H_{1a}$), 1.52 (m, $2H_{1a}$ + $2H_{2a}$), 2.40 (s, $3H_{1a}$), 2.66 (s, $3H_{2a}$), 2.82 (bs, $2H_{1a}$ + $2H_{2a}$), 3.50–3.89 (m, $4H_{1a}$ + $4H_{2a}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5 (c_{1a}), 13.6 (c_{2a}), 18.8 (t_{2a}), 19.2 (t_{1a}), 27.5 (c_{1a}),

28.3 (c_{2a}), 29.1 (c_{2a}), 29.5 (t_{1a}), 31.0 (c_{1a}), 36.6 (t_{2a}), 55.7 (d_{1a}), 56.0 (d_{2a}), 63.2 (t_{1a}), 64.1 (t_{2a}), 72.4 (d_{1a}), 72.7 (d_{2a}), 80.0 (s_{2a}), 80.3 (s_{1a}), 156.0 (s_{2a}), 157.8 (s_{1a}); IR (KBr): $\nu = 3439$, 1674 cm^{-1}; HRMS (CI): calcd. for $C_{12}H_{26}NO_4$ [M+1]: 248.1861; found: 248.1868.

(2*R*,3*R*)-2-[*N*-(*tert*-Butoxycarbonyl)amino]-3-(4-nitrophenyl)-1,3-propanediol (2c)

Yield: 70%; white solid; mp 113–114 °C; $[\alpha]_D^{25}$: −22.0 (*c* 1, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.15$ (s, 3H), 3.6 (m, 3H), 3.8 (bs, 1H), 4.6 (bs, 1H), 5.1 (s, 1H), 5.3 (s, 1H), 7.4 (d, $J = 8$ Hz, 2H), 8.05 (d, $J = 8$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 28.0$ (c), 56.7 (d), 62.8 (t), 72.0 (d), 80.1 (s), 123.3 (d), 126.8 (d), 147.0 (s), 149.2 (s), 156.2 (s); IR (KBr): $\nu =$ 3422, 2978, 1680, 1520, 1346 cm^{-1}; HRMS (CI): calcd. for $C_{14}H_{21}N_2O_6$ [M+1]: 313.1399; found: 313.1413.

Methyl (2*R*,3*R*)-3-[*N*-(*tert*-Butoxycarbonyl)-*N*-(methyl)amino]-2-hydroxyhexanoate (3a)

By method A; yield: 81% (calculated from **1a**); colorless oil; $[\alpha]_D^{25}$: +25.9 (*c* 1.83, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.87$ (t, $J = 7.1$ Hz, 3H), 1.23 (m, 2H), 1.41 (s, 9H), 1.70 (m, 2H), 2.71 (s, 3H), 3.63 (s, 3H), 4.37 (m, 1H), 4.71 (d, $J =$ 5.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.5$ (q), 19.2 (t), 28.2 (q), 30.7 (t), 31.1 (q), 51.9 (q), 57.2 (d), 58.7 (d), 79.9 (s), 156.3 (s), 172.5 (s); IR (KBr): $\nu = 3350$, 1700, 1657 cm^{-1}; HRMS (CI): calcd. for $C_{13}H_{26}NO_5$ [M+1]: 276.1811; found: 276.1814.

Methyl (2*R*,3*R*)-2-[*N*-(*tert*-Butoxycarbonyl)-*N*-(methyl)amino]-3-hydroxyhexanoate (4a)

By method A; yield: 78% (calculated from **2a**); colorless oil; $[\alpha]_D^{25}$: −40.3 (*c* 2.73, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.84$ (t, $J = 7.1$ Hz, 3H), 1.12–1.22 (m, 4H), 1.42 (s, 9H), 2.70 (s, 3H), 3.69 (s, 3H), 4.44 (c, $J = 7.0$ Hz, 1H), 4.75 (d, $J =$ 7.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.8$ (c), 18.2 (t), 28.1 (c), 34.4 (c), 35.0 (t), 52.1 (c), 65.4 (d), 69.7 (d), 80.7 (s), 154.6 (s), 172.9 (s); IR (KBr): $\nu = 3425$, 1735, 1675 cm^{-1}; HRMS (CI): calcd. for $C_{13}H_{26}NO_5$ [M]: 276.1811, found 276.1810.

Methyl (2*S*,3*R*)-2-[*N*-(Dichloroacetyl)amino]-3-hydroxy-3-(4-nitrophenyl)propanoate (4b)

By methods A and B, yields are reported in Table 2; white solid; mp 160–161 °C; $[\alpha]_D^{25}$: +16.4 (*c* 0.73, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 3.79$ (s, 3H), 4.82 (dd, $J = 9.2$ and 2.7 Hz, 1H), 5.45 (dd, $J = 4.5$ and 2.7 Hz, 1H), 6.50 (d, $J =$ 4.5 Hz, 1H, exchanged with D_2O), 6.61 (s, 1H), 7.74 (d, $J =$ 8.6 Hz, 2H), 8.23 (d, $J = 8.6$ Hz, 2H), 9.03 (d, $J = 9.2$ Hz, 1H, exchanged with D_2O); ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 53.7$ (c), 60.2 (d), 67.3 (d), 73.5 (d), 124.7 (d), 128.6 (d), 149.2 (s), 150.1 (s), 166.9 (s), 171.3 (s); IR (KBr): $\nu = 3402$, 2954, 1689, 1647, 1540, 1317 cm^{-1}; HRMS (EI): calcd for $C_{12}H_{13}N_2O_6Cl_2$ [M+1]: 351.0150; found: 351.0142.

Methyl (2*S*,3*R*)-2[*N*-(*tert*-Butoxycarbonyl)amino]-3-hydroxy-3-(4-nitrophenyl)propanoate (4c)

By method A; yield: 38%; by method B (SG-TEMPO-2); yield: 57%; white solid; mp 96–97 °C; $[\alpha]_D^{25}$: −23.8 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.20$ (s, 9H), 3.68 (s, 3H), 4.30 (bs, 1H), 4.50 (d, $J = 4.5$ Hz, 1H), 5.30 (s, 1H), 5.50 (d, $J = 4.5$ Hz, 1H), 7.61 (d, $J = 8.6$ Hz, 2H), 8.23 (d, $J = 8.6$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 28.0$ (c), 52.9 (c), 59.4 (d), 72.9 (d), 80.5 (s), 123.6 (d), 127.6 (d), 147.5 (s), 148.0 (s), 155.8 (s), 171.0 (s); IR (KBr): $\nu = 3436$, 2965, 1710, 1665, 1517, 1328 cm^{-1}; HRMS (EI): calcd for $C_{15}H_{21}N_2O_7$ [M]: 341.1348; found: 341.1353.

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[14] Similar catalytic materials are already finding commercial applications: The U. S. fine chemicals manufacturer Avecia, for instance, recently licensed Johnson Matthey's sol-gel technology for preparing organic-inorganic silica hybrid gels doped with chiral ligands for the synthesis of valuable cyanohydrins from ketones, see: M. Rouhi, *Chem. Eng. News* **2004**, *82* (*07*), 20.
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[16] Silica gels functionalized with TEMPO for alcohol oxidations produced by the Canadian company Silicycle Inc. are commercialized by the chemical supplier Aldrich (see: *ChemFiles* **2002**, Vol. *2*, no. 6). Silica gels offer several technical advantages over well-known gel-type resins being solvent-independent (rigid porous structure and no swelling), no non-specific binding (high yield) and with a high density of functional groups (small volume of gel required). See also: http://www.silicycle.com/html/english/products/produit detail.php?pro id=177.

