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A Convenient and Highly Productive Aminohydroxylation Protocol Employing an Osmium-Diamine Catalyst

Kilian Muñiz,[a,c,*] Iriux Almodovar,[c,d] Jan Streuff,[a,c] and Martin Nieger[b]

[a] Institut de Chimie, Université Louis Pasteur, 4 rue Blaise Pascal, 67070 Strasbourg Cedex, France
Fax: (+33)-3-9024-1526; e-mail: muniz@chimie.u-strasbg.fr
[b] Institut für Anorganische Chemie der Universität Bonn, Gerhard-Domagk-Str. 1, 53121 Bonn, Germany
[c] Kekulé-Institut für Organische Chemie und Biochemie, Gerhard-Domagk-Str. 1, 53121 Bonn, Germany
[d] Departamento de Química Orgánica y Físicoquímica, Facultad de Ciencias Químicas y Farmaceúticas, Universidad de Chile, casilla 233, Santiago 1, Chile

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Abstract: *In situ* generated osmium-diamine chelates from 2,3-diaminopropionic acid or diaminosuccinic acid represent efficient catalysts for the highly productive aminohydroxylation of alkenes. The reaction can be employed with various osmium salts and successful catalyst recycling was demonstrated for a representative example. The catalyst design derives from the general structural features of recently investigated osmium complexes from alkene diamination reactions.

Keywords: amino alcohols; aminohydroxylation; diamines; homogeneous catalysis; osmium

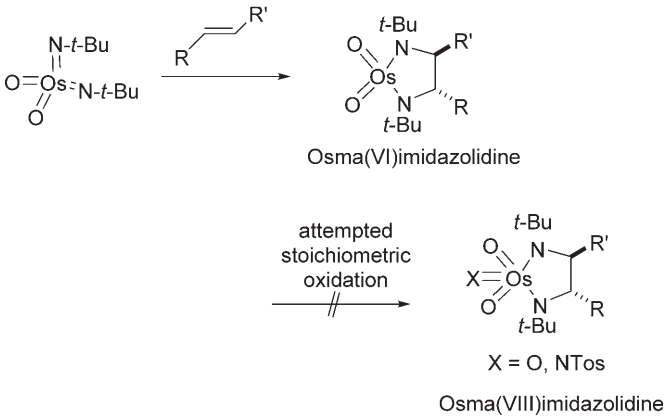


Figure 1. Osmaimidazolidine product from alkene diamination and stability towards stoichiometric re-oxidation.

Recently, we have intensively investigated the diamination of alkenes employing preformed bis- and tris-(*tert*-butylimido)osmium(VIII) oxidants.[1] These reagents induce a completely chemoselective reaction in favour of diamination[2] and lead to monomeric osmium-diamine chelates with an unprecedented stability (Figure 1).[3] The inherent properties of these products prompted us to examine whether or not such compounds themselves could act as catalyst precursors for oxidation chemistry. However, the extremely low tendency of the osma(VI)imidazolidine group to undergo oxidation at the central Os atom – a consequence of electronic saturation due to the basic alkyl substituents at the neighbouring nitrogens – has so far prevented their use as efficient oxidation catalysts for alkene functionalisation.[4,5] In order to overcome this problem, the incorporation of amino groups with lower lone pair donating ability was envisioned.

To this end, it was decided to replace the rather basic *tert*-alkyl substituents at nitrogen and construct osmium catalysts from suitable osmium precursors such as $OsCl_3$, $K_2[OsO_2(OH)_4]$ or OsO_4 by complexation to bistosylated diaminocarboxylic acids (structure **A**, Figure 2). Tosylamides have recently emerged as a successful *leitmotif* in ligand design undergoing rapid coordination to transition metal centres. The sulfonyl group enhances the acidity of the N–H bond, but does not effect the desired sp^3-hybridisation at nitrogen.[6–8]

The choice of the free carboxylic acid motif was made since recent work by Sharpless and Fokin had shown that some special substrate classes exist such as acrylic acids and their amide derivatives, respectively. These substrates do not react under standard AD and AA conditions.[9] Instead, oxidation of these compounds occurs exclusively in a competing secondary catalytic cycle which is independent of the usual *Cinchona* alkaloid ligands. Consequently, certain carboxylic acids bearing 2,3-diol or aminohydroxy functionalities were introduced as bidentate ligands for the efficient oxidation of other olefins.[10]

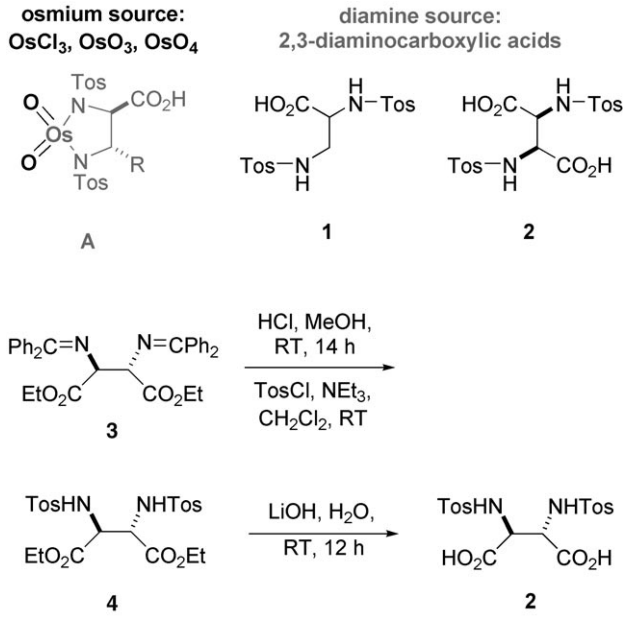


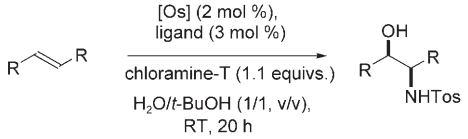
Figure 2. Diaminocarboxylic acids for *in situ* formation of osmaimidazolidine catalysts **A**.

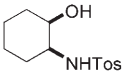
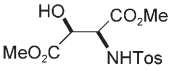
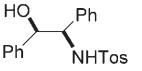
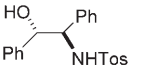
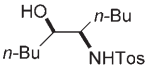
Conversion of commercially available diaminopropionic acid into its *N*,*N*′-bistosylated derivative **1** employing a literature procedure[11] led to a first ligand following the concept outlined in Figure 2. In a similar manner, ligand **2** was synthesised from the known compound **3**[12] followed by a sequence of tosylation (X-ray analytical confirmation of conformation for intermediate **4**)[13] and ester hydrolysis.[14]

Active catalysts were then prepared *in situ* by complexation of preformed ligands **1** and **2** displaying free carboxylic acid units to OsO_4, $K_2[O_2Os(OH)_4]$ and $OsCl_3$, three commercially available Os sources which were found to be equally successful for this purpose.[15] Due to the easier handling, osmium trichloride and the osmate salt were used in subsequent reactions. Thus, with diamino ligands **1** or **2** (1.5 equivs., relative to Os) and in the presence of one equivalent of chloramine-T as terminal oxidant, clean aminohydroxylation of a variety of olefins was accomplished with complete conversion. For example, cyclohexene, dimethyl fumarate, stilbenes and 5-decene underwent aminohydroxylation in high yields upon precipitation (Table 1). The reaction still worked well with a catalyst loading of as low as 0.2 mol%. Even on the basis of its rather small ligand scaffold, enantiopure **1** induced a 32% *ee* in the asymmetric aminohydroxylation of cyclohexene.

In most of these cases, the products were isolated by filtration leaving the remaining filtrate with the osmium catalyst for potential use in a subsequent further aminohydroxylation. In order to prove the feasibility of such catalyst re-use, the oxidation of cyclohexene was successfully carried out for five consecutive runs (82 to 78% chemical yield, Figure 3).

Table 1. Aminohydroxylation of symmetrical olefins.



Substrate	Ligand	Os Source	Product	Yield [%][a]
cyclohexene	**1**	$OsCl_3$		82
	1[b]	$OsCl_3$		80
	1	$K_2[OsO_2(OH)_4]$		82
	2	$OsCl_3$		77
	2	$K_2[OsO_2(OH)_4]$		75
dimethyl fumarate	**1**	$OsCl_3$		87
(*E*)-stilbene	**2**	$K_2[OsO_2(OH)_4]$		93
(*Z*)-stilbene	**1**	$OsCl_3$		90
(*E*)-5-decene	**2**	$K_2[OsO_2(OH)_4]$		92

[a] Precipitated material at 100% olefin conversion.
[b] With 0.2 mol% catalyst loading, 48 h reaction time.

This result represents a rare example for the re-use of osmium-based oxidation catalysts. Thus far, there have been reports on the immobilisation of chiral *Cinchona* alkaloid ligands,[16] however, these approaches require the subsequent addition of osmium amounts. Elegant concepts as those from Kobayashi and Jacobs use encapsulated[17] or heterogeneously bound[18] osmium tetroxide for repeated dihydroxylation reactions. However, application in aminohydroxylation remains to be investigated.

Finally, the aminohydroxylation protocol was employed for non-symmetrical olefins (Table 2). Here, oxidation of methyl, *tert*-butyl and isopropyl cinnamate proceeded smoothly within 14 h with quantitative conversion to give the corresponding amino alcohols in high isolated yield after precipitation. The obtained regioisomeric ratios were found to be independent of the use of ligand **1** or **2**. Phenyl cinnamate gave an essentially 1:1-mixture of regioisomers. Apparently, the influence of the phenyl ester on regioselectivity from the related first cycle aminohydroxylation

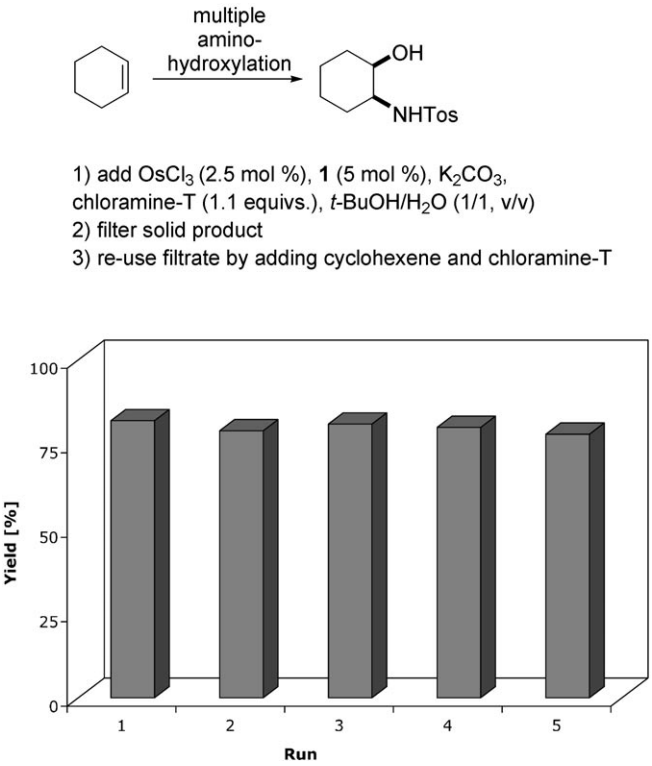
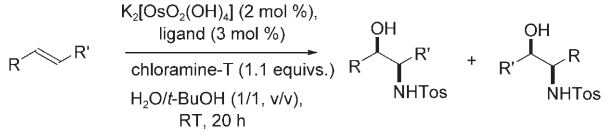
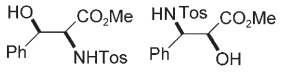
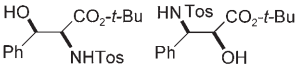
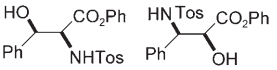
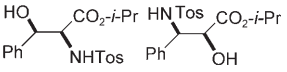
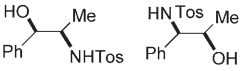
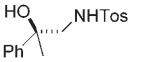


Figure 3. Re-use of an osmium catalyst for consecutive aminohydroxylation of cyclohexene.

Table 2. Aminohydroxylation of unsymmetrical olefins.



Substrate	Ligand	Products	Regio-selectivity[a]	Yield [%][b]
methyl cinnamate	1		1:1.4	82
	2		1:1.4	87
t-butyl cinnamate	1		1:1.6	78
	2		1:2.0	81
phenyl cinnamate	2		1:1	77
i-propyl cinnamate	1		1:1.7	86
β-methylstyrene	1		1:1.2	88
	2		1:1.4	85
α-methylstyrene	1		100:0	88
	2		100:0	93

[a] Determined from the crude ^{1}H NMR.
[b] Combined yield of both regioisomers after precipitation (at 100 % alkene conversion).

with acetamide-derived nitrenes does not apply favourably in the present case. β-Methylstyrene gave high yields and moderate regioselectivities as well. α-Methylstyrene led to the selective formation of a regioisomeric product due to steric control with the hydroxy group being placed at the quaternary stereocentre for reactions with both ligands **1** and **2**.

The postulated catalytic cycle for the observed highly productive aminohydroxylation is depicted in Figure 4. It is initiated by formation of osma(VI)imidazolidine **B** from free **1** or **2** and an osmium source in agreement with the expected general catalyst structure **A**. This undergoes oxidation to form the actual osma(VIII)imidazolidine catalyst **C**. Subsequent aminohydroxylation gives the intermediate **D** which upon hydrolytic cleavage affords the free amino alcohol product and regenerates catalyst precursor **B**. This final step requires preferential hydrolysis of the azaglycolate structure over the imidazolidine core which is in agreement with the observed relative stabilities of related osmium complexes from stoichiometric reactions.[19] Both the five-membered ring chelate and the free carboxylate are prerequisites for achievement of high reactivity and catalyst stability. Application of *N,N'*-bistosylethylenediamine and 2,4-bis(tosylamino)-butanoic acid as ligands led to complete loss of catalyst activity.

Compared with the previous diol or amino alcohol-based ligands,[10] we postulate two differences regarding bistosylated diamino acids as ligands. First, on the basis of the unprecedented stability of monomeric osmaimidazolidines, all the osmium should be bound exclusively to the diamine ligand and no ligand scrambling to yield bis(diamino) complexes can take place. This is of major importance since ligand exchange has been observed for related glycolate and azaglycolate complexes[4,5,20] thereby releasing uncomplexed osmium.

Secondly, the turnover limiting step should be the reoxidation to Os(VIII), hence the regeneration of catalyst **C** from **B**. Therefore, the catalyst system described herein consists of a delicate balance between the inherent properties of osmaimidazolidines: while the diamino entity ensures hydrolytic stability of the Os-diamine chelate, the tosyl substituents ensure the reoxidation of the catalytically prerequisite Os(VIII) centre.[21]

In summary, we have described the first use of *in situ* generated chiral osmaimidazolidines as homogeneous oxidation catalysts. Concerning yields, catalyst loading and regioselectivities, our results compare well with the ones from former azaglycolate catalysts.[9,10] Chemoselectivities are excellent for this pro-

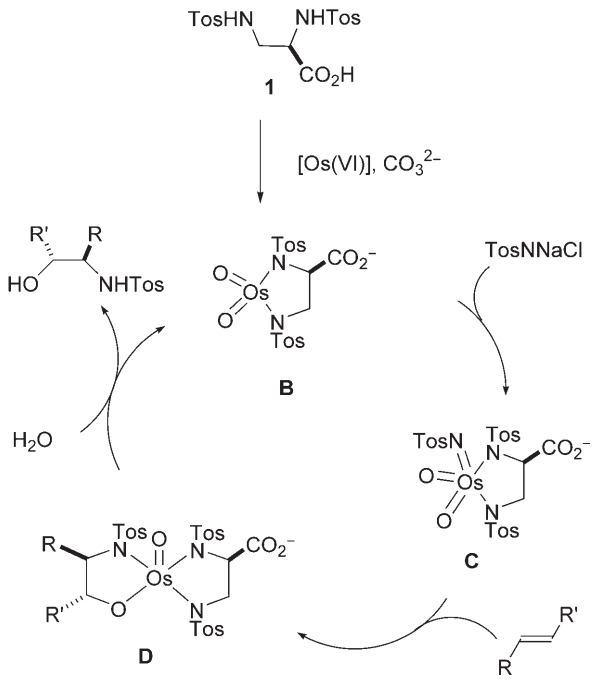


Figure 4. Postulated catalytic cycle for aminohydroxylation. Ligand **1**, osmate source and geometry of intermediate **D** shown arbitrarily.

cess with no diol formation ever being observed.[22] While regioselectivities and enantiomeric induction for this second cycle catalysis is still much lower than for the established *Cinchona* alkaloid based AA protocol,[6] the present diaminocarboxylic acid motif offers room for future ligand optimisation. Investigation on related structures based on different diamino entities are currently under investigation.

Experimental Section

Diethyl [2,3-Bis(tosylamino)]succinate (4)

Racemic diethyl [2,3-bis(diphenylmethylene-amino)] succinate[12] (2.66 g, 5 mmol) was dissolved in commercially available methanolic HCl solution (30 mmol, 6 equivs.) and stirred for 24 h at room temperature. The solvent was removed under reduced pressure and the remaining oily residue taken up in two portions of absolute dichloromethane (20 mL each) to remove remaining acid. All solvents were removed under reduced pressure and the residue was dissolved in absolute dichloromethane (40 mL) followed by addition of triethylamine (10 mL) and toluenesulfonyl chloride (3.42 g, 18 mmol, 3.6 equivs.) and stirring at room temperature overnight. It was worked-up by addition of water (100 mL) and extraction with dichloromethane. The combined organic phases were separated, dried with $MgSO_4$ and evaporated to dryness under reduced pressure. Column chromatography (silica gel, hexanes/ethyl acetate, 75/25, v/v) gave a white product which was crystallised from ethyl acetate to give colourless prisms; yield: 2.15 g (84%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.69$ (d, $J = 8.34$ Hz, 2H), 7.28 (d, $J = 8.34$ Hz, 2H), 5.50 (d, $J = 8.40$ Hz, 1H), 4.36 (d, $J = 8.40$ Hz, 2H), 3.95–4.15 (m, 2H), 2.41 (s, 3H), 1.16 (t, $J = 7.13$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 167.7$, 149.7, 144.0, 136.2, 130.0, 129.7, 127.4, 63.0, 57.8, 21.5, 13.8; MS (EI, eV): m/z (%) = 512.1 (0.25% [M^+]), 439.1 (0.75%), 357.1 (5%) 256.1 (100%), 155,0 (100%), 102.0 (80%). IR (KBr): $\nu =$ 3405, 2970, 2909, 2366, 2355, 1451, 1230, 1100 cm^{-1}; HR-MS: $m/z = 512.1284$, calcd. for $C_{22}H_{28}N_2O_8S_2$: 512.1287 $g\,mol^{-1}$.

2,3-Bis(tosylamino)succinic Acid (2)

Diethyl [2,3-bis(tosylamino)]succinate (1.00 g, 19.5 mmol) was dissolved in a 2M aqueous LiOH and stirred for 40 h at room temperature. The solution was filtered through cotton wool and made acidic by addition of 3M HCl solution. Placing the resulting solution in the freezer overnight resulted in precipitation of the title compound in form of a white solid; yield: 508 mg (11.1 mmol, 57%). ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.28$ (s, 6H), 4.22 (s, 2H), 7.31 (d, $J = 8.5$ Hz, 4H), 7.69 (d, $J = 8.5$ Hz, 4H), 13.04 (brs, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 21.40$, 58.02, 127.17, 129.69, 138.29, 143.13, 169.26.

General Experimental Procedure for Aminohydroxylation in the Presence of *N,N′*-Bistosyldiaminopropionic Acid or 2,3-Bis(tosylamino)succinic Acid

To a solution of of the ligand (**1** or **2**, 0.15 mmol) and potassium osmate (36.8 mg, 0.1 mmol) in 6 mL of water/*tert*-butyl alcohol (1/1, v/v) at room temperature was added potassium carbonate (41.5 mg, 0.3 mmol) and the resulting mixture stirred at room temperature for 15 min. Chloramine-T (1.55 g, 5.5 mmol) was then added in one portion, at which point the reaction mixture turned bright yellow. The olefin (5.0 mmol) was added in one portion and the resulting mixture stirred for the periods given in Table 1 and Table 2. [For reaction times longer than 10 h, the pH is adjusted to 8 after this period. Reactions employing osmium trichloride as catalyst source were carried out with an initial addition of 125 mg of potassium carbonate.]

Generally, the products crystallised from the reaction mixture and were isolated by simple filtration. If desired, the crude reaction mixtures can be extracted with dichloromethane. Column chromatography of the crude product with solvent mixtures of hexanes/ethyl acetate gives analytically pure samples.

Supporting Information

Detailed experimental procedures, synthesis of ligands **1** and **2**, product characterisation and data on X-ray analysis.

Acknowledgements

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est, and to Stefan Kürpig for initial work on the synthesis of ligand ***2****.*

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[13] Crystallographic data (excluding structure factors) for the structure of **4** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-297486. Copies of the data can be obtained free of charge at [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: int. code +44–1223/336–033; e-mail:].

[14] See Supporting Information for full description of ligands **1** and **2**.

[15] See Supporting Information for full description on screening experiments.

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[21] Initial screening experiments (included as Table S2 in the supporting information) indicate that related reactivity can be obtained for reoxidation with NMO as well. In view of the established high development of the dihydoxylation reaction[4] further investigation in this direction appears less important.

[22] Structurally more elaborate acrylates bearing heteroaromatic substituents such as 2-pyridinyl react on very slow rate (<15% conversion after 96 h). Current work aims to overcome these problems. For a discussion on first cycle aminohydroxylation of such substrates, see: D. Raatz, C. Innertsberger, O. Reiser, *Synlett* **1999**, 1907.

