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First asymmetric aminohydroxylation of acrylamides

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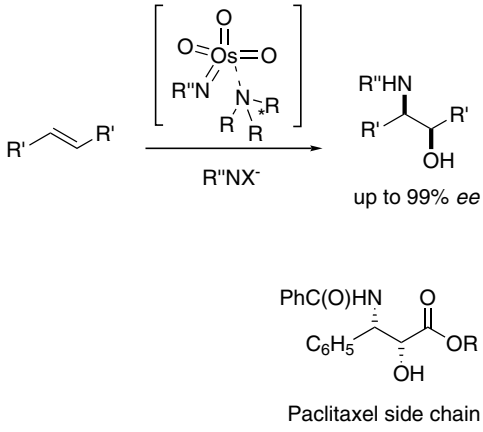
Abstract—The first examples of the asymmetric aminohydroxylation of acryl amides are reported. This was accomplished with chiral acrylamides as substrates, which undergo diastereoselective oxidative transformation within the so-called 'second catalytic cycle' with diastereomeric excesses reaching 100:0. The reaction relies solely on the stereochemical information provided by the enantiomerically pure starting materials. A stereochemical model for the observed asymmetric induction is provided.

1. Introduction

Asymmetric oxidation represents a powerful tool for the defined introduction of heteroatoms into carbon skeletons.[1] With traditional investigation focussing on oxygen-transfer, recent advances in the area of oxidative nitrogen incorporation has put these transformations at the centre of current research.[2]

Osmium(VIII) catalysis represents a particularly successful approach to oxidative alkene functionalisation. In particular, asymmetric dihydroxylation represents a highly developed synthetic tool for the conversion of an alkene into a vicinal diol entity.[3] The simultaneous introduction of an amino and hydroxy group through the related aminohydroxylation process follows the general pathways of dihydroxylation and employs an imidoosmium catalyst.[4,5] The enantioselective variant of this process requires the use of a chiral cinchona alkaloid based ligand.[4–6] Recent synthetic applications of this protocol include the synthesis of various serine and *iso*-serine derivatives from acrylates, among which figures the synthesis of the side chain of the powerful anticancer drug Paclitaxel (Taxol®) from cinnamate as the most prominent example (Scheme 1).[7] In 1997, Sharpless reported that α,β-unsaturated amides and acrylic acids do not undergo enantioselective aminohydroxylation, but are oxidised in the so-called second catalytic cycle. For this particular class of substrates, chiral catalyst control cannot provide optically active amino alcohols.[8,9] Therefore, all products from the oxidative conversion of this type of substrate under aminohydroxylation conditions are racemic. We herein report the first examples of an asymmetric aminohydroxylation of chiral acrylamides.



Scheme 1. Sharpless aminohydroxylation of olefins.[4,5] R_3N^* represents a chiral cinchona alkaloid ligand.

2. Results and discussion

To achieve an asymmetric course during the aminohydroxylation of acrylamides, attention was turned towards chiral substrates. To this end, the condensation of

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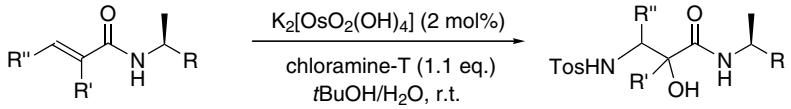
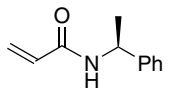
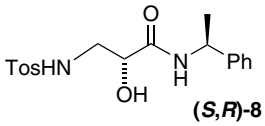
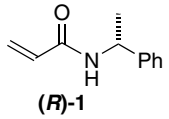
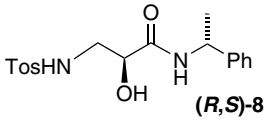
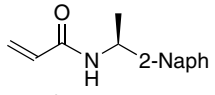
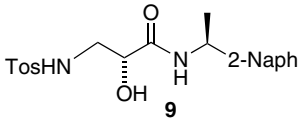
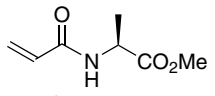
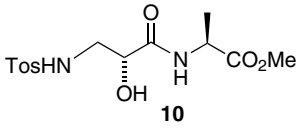
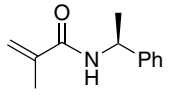
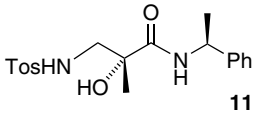
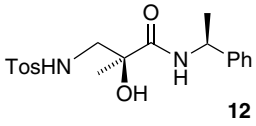
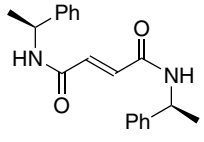
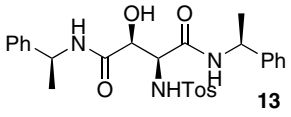
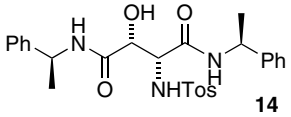
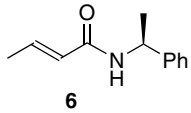
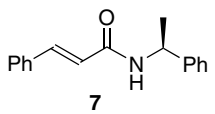
various unsaturated acid chlorides with commercially available α-aryl ethylamines led to the synthesis of amides **1**, **2** and **4**–**7**. Likewise, compound **3** was obtained from alanine methyl ester. Oxidative conversion of these compounds in the presence of only 2 mol % of potassium osmate and 1.1 equiv of chloramine-T as

Table 1. Aminohydroxylation of chiral, non-racemic acryl amides



Entry	Substrate	Product(s)	Yield (%)[a]	Regioisomeric ratio[b]	Dr[b]
1	 **(*S*)-1**	 **(*S*,*R*)-8**	84	100:0	100:0
2	 **(*R*)-1**	 **(*R*,*S*)-8**	81	100:0	100:0
3	 **2**	 **9**	88	100:0	12:1
4	 **3**	 **10**	96	100:0	7:1
5	 **4**	 **11**	79	100:0	1:3:1
		 **12**			
6	 **5**	 **13**	92	—	1:1
		 **14**			
7	 **6**	All four stereoisomers	77	50:50	1.1:1.1:1:1
8	 **7**	All four stereoisomers	86	50:50	1.1:1:1:1

Products from entries 7 and 8 were not separated.

[a] Isolated yield at 100% conversion.

[b] Determined from the crude ^{1}H NMR spectrum.

reoxidant and nitrogen source in a solvent mixture of *tert*-butanol and water led to the expected aminohydroxylation reaction. Complete conversion was observed for all substrates and the desired amino alcohol products were obtained after reductive work-up (Table 1).

As expected, the addition of a standard cinchona alkaloid based ligands such as $(DHQ)_2PHAL$ or $(DHQ)_2AQN$ did not alter the reaction course indicating that observation by Sharpless on the ligands unsuitability for acrylamide substrates is valid for chiral acrylamides as well.[8] In the absence of any ligand, unsubstituted acrylamides, such as compounds **1**, **2** and **3** gave complete regioselective aminohydroxylation with the amino group positioned at the terminal carbon (Table 1, entries 1–4). In addition, acryl amide **1** from α-phenyl ethylamine led to complete diastereoselectivity regarding the newly established stereogenic centre.[10] Moreover, the product from the aminohydroxylation of **3** offers the synthesis of the *iso*-serine-alanine dipeptide analogue **10**. The complete regioselectivity in these reactions is restricted to acryl and methacryl amides, respectively. Aminohydroxylation reactions of 3-substituted α,β-unsaturated amides, such as crotoyl derivative **5** or cinnamoyl derivative **6** lacked any selectivity (entries 7 and 8), while the acryl amides give diastereoselectivities ranging from 100:0 to 7:1. This stereochemical preference of an acrylic derivative over higher substituted derivatives matches the experimental outcome for related diamination reactions observed by us in reactions with preformed trisimidoosmium reagents.[11]

The results obtained from the aminohydroxylation of fumaryl amide **4** revealed the formation of two stereoisomers. Due to the absence of regioselectivity issues for this substrate, these two isomers must represent diastereomers with regards to the facial selection in the oxidation step. Again, the substitution pattern of the alkene prevents the formation of a product with diastereomeric excess. In view of the complete regio and diastereoselectivity in the aminohydroxylation of **1**, product **8** was submitted to X-ray analysis and a (2*R*)-configuration was established (Fig. 1). The complete stereoselectivity in the aminohydroxylation of **1** and the high stereodiscriminations in the related reactions of **2** and **3** are noteworthy.

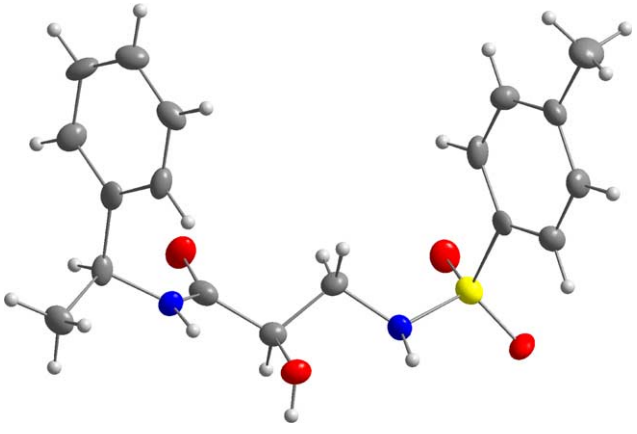


Figure 1. Solid state structure of (*S*,*R*)-**8**.[12]

A definite mechanistic background for this surprising reaction outcome remains to be established. Within this context, we have recently investigated the stereochemical course of self-replication of chiral *iso*-serine derivatives and concluded that for acrylic substrates. the stereochemical course cannot be governed efficiently by the stereochemical information of the azaglycolate entity itself.[13] In view of the high inductions observed in the aminohydroxylation of **1**, **2** and **3**, the chiral amine auxilary from the amide group must therefore exercise a decisive influence on the overall stereochemical course of this catalysis.

We propose that the reaction presented herein may proceed through the catalytic cycle as depicted in Figure 2. It is initiated by the aminohydroxylation of **1** with $O_3OsNTos$, as obtained in situ from the osmate and chloramine-T, to give osma(VI)azaglyolate **A**. Reoxidation with chloramine-T forms the imidoosmium catalyst as the osma(VIII)azaglycolate **B**. This oxidises **1** in a completely stereoselective manner to arrive at the diaste-

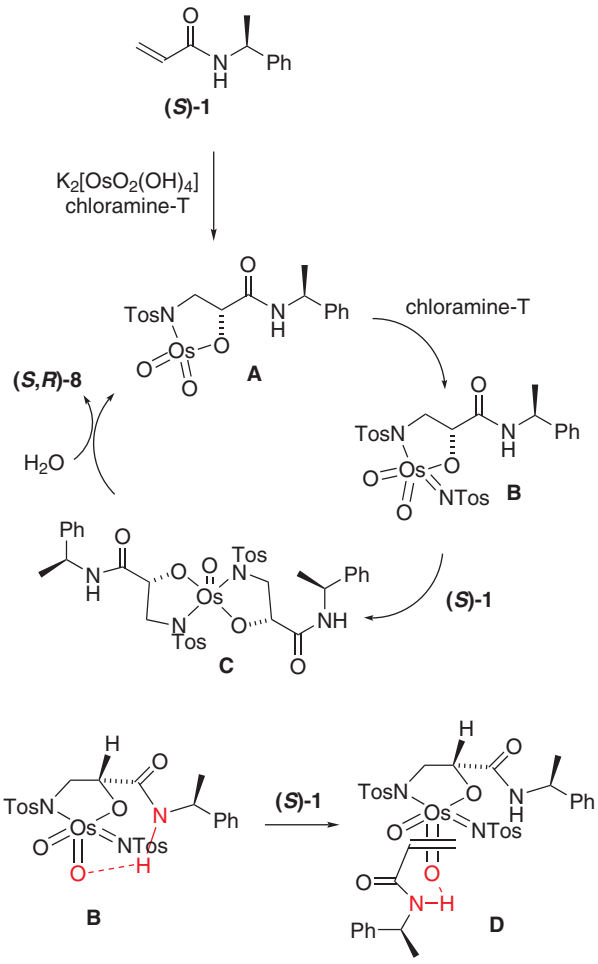


Figure 2. Catalytic cycle and proposed transition state for aminohydroxylation.

reomerically pure bisazaglycolate **C**. Subsequent hydrolysis of this intermediate releases the free amino alcohol product **8** and regenerates **A** to close the catalytic cycle. Since **8** is produced as a single stereoisomer, intermediate **C** must be homochiral, that is, it must contain two azaglycolate ligands of identical absolute configuration. Therefore, the catalytic aminohydroxylation of acrylamide **1** with catalyst **B** represents the rare case of a truly stereoselective self-replication of a chiral ligand.[13] As mentioned before, we deduced a pronounced role of the amide on the overall stereochemical course of the reaction. This should be influential at two stages. First, the conformation of the square-planar intermediate **B** might be organised from intramolecular hydrogen bonding between the non-transferable oxo-ligand and the amide-NH group.[14]

While this does not necessarily need to be the only conformation in solution, the kinetic preference of **B** is sufficient to dominate the catalysis. Within the subsequent step of olefin aminohydroxylation, the observed complete face selectivity might again arise from a preorganisation through hydrogen bonding. Obviously, such a preorganisation seems to be strongly influenced by additional substituents as in the cases of substrates **6** and **7**. It agrees well with a substrate, such as **5**, which due to its symmetrical amide substitution pattern cannot distinguish the prochiral olefin faces through hydrogen bonding. In addition, *N*-phenyl-*N*-(α-phenylethyl)-acrylamide as substrate only showed low conversion and no stereoselectivity (1:1-mixture and 14% yield after 36 h), which strengthens the importance of an amide NH on the overall catalytic course.

3. Conclusion

In summary, we have described the first asymmetric aminohydroxylations of chiral, non-racemic acryl amides, which proceed exclusively in the second cycle. The assumed stereoselectivity model of hydrogen bonding should lead to a potential design of new ligands for this type of oxidation catalysis.[15] Mechanistic investigation along these lines is currently under investigation.

Acknowledgements

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9. Fokin, V. V.; Sharpless, K. B. *Angew. Chem Int. Ed.* **2001**, *40*, 3455.
10. Selected analytical data: (−)-**8**: $[\alpha]_D = -50$ (*c* 0.3, acetone). ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 1.36$ (d, $J = 7.0$ Hz, 3H), 2.36 (s, 3H), 2.67–2.76 (m, 1H), 2.94–2.99 (m, 1H), 3.91–4.00 (m, 1H), 4.89 (quin, $J = 4.7$ Hz, 1H), 5.73 (d, $J = 6.0$ Hz, 1H), 7.19–7.48 (m, 8H), 7.65 (s, 1H), 7.68 (s, 1H), 8.05 (d, $J = 8.1$ Hz, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 21.4$, 22.5, 47.2, 48.0, 71.0, 126.4, 127.0, 128.6, 130.0, 137.9, 143.0, 144.7, 171.0. IR (KBr): 3471, 3325, 3304, 3032, 2985, 2929, 2870, 1653, 1527, 1456, 1408, 1315, 1213, 1161, 1109, 1090, 1018, 937, 872, 815, 769, 706, 671 cm^{-1}. MS (EI, eV): *m*/*z* (%): 362.2 (12) [M]$^+$, 347.2 (3), 251.2 (1), 214.2 (17), 207.2 (20), 179.2 (52), 155.1 (44), 139.1 (3), 120.2 (55), 105.2 (100), 91.2 (45), 75.1 (13), 60.2 (7). HRMS: calcd for $C_{19}H_{22}N_2O_4S$: 362.1300. Found: 362.1297. Compound **13**: $[\alpha]_D = -141$ (*c* 0.23, MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 1.22$ (d, $J = 6.97$ Hz, 3H), 1.28 (d, $J = 6.97$ Hz, 3H), 2.36 (s, 3H), 4.19 (m, 2H), 4.72 (m, 2H), 7.14–7.30 (m, 12H), 7.61 (d, $J = 8.28$ Hz, 2H), 7.68 (d, = 8.10 Hz, 1H), 7.96 (d, $J = 7.73$ Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 21.1$, 22.1, 22.5, 48.0, 48.3, 59.1, 72.3, 125.9, 126.1, 126.7, 126.8, 128.25, 128.31, 129.4, 142.6, 143.9, 144.2, 168.1, 169.7. IR (KBr): 3417, 3290, 3062, 3028, 2974, 2960, 2927, 1659, 1539, 1508, 1448, 1427, 1336, 1161, 1078, 1022, 941, 761, 698, 557 cm^{-1}. MS (EI, eV): *m*/*z* (%): 509.3 [M]$^+$, 362.2 (8), 361.2 (25), 355.2 (5), 332.2 (10), 318.2 (2), 257.1 (15), 240.1 (1), 215.2 (5), 214.1 (15), 191.2 (4), 177.2 (20), 161.1 (1), 155.1 (10), 139.1 (4), 132.1 (0), 120.2 (25), 105.1 (100), 91.1 (10), 79.1 (5), 73.1 (1), 60.1 (8), 57.2 (1). HRMS: calcd for $C_{27}H_{31}N_3O_5S$: 509.1984. Found: 509.1989. Compound **14**: $[\alpha]_D = -78$ (*c* 0.1, DMSO). ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 1.04$ (d, $J = 6.97$ Hz, 3H), 1.37 (d, $J = 6.97$ Hz, 3H), 2.32 (s, 3H), 4.24 (m, 2H), 4.64 (m, 1H), 4.90 (quin, $J = 6.97$, 1H),

7.15–7.37 (m, 12H), 7.57 (d, $J = 8.28$ Hz, 2H), 7.73 (d, $J = 7.73$ Hz, 1H), 7.93 (d, $J = 8.29$ Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 20.9$, 21.8, 31.2, 47.6, 48.1, 59.6, 72.01, 125.87, 125.97, 126.06, 126.49, 126.56, 128.05,128.1, 129.2, 142.4, 143.6, 167.6, 169.4. IR (KBr): 3400, 3301, 3055, 3030, 2976, 2960, 2922, 1659, 1544, 1500, 1443, 1336, 1161, 1079, 1021, 936, 771 cm^{-1}. MS (EI, eV): m/z (%): 509.3 $[M]^+$, 362 (3), 361 (26), 332 (10), 257 (15), 215.2 (11), 214.1 (15), 191.2 (4), 177.2 (20), 161.1 (1), 155.1 (10), 120.2 (25), 105.1 (100), 91.1 (10), 79.1 (5), 60.1 (8). HRMS: calcd for $C_{27}H_{31}N_3O_5S$: 509.1984. Found: 509.1991.

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12. Details concerning the X-ray analysis of **8**: Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-279068. Copies of the data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambrigde CB2 1EZ, UK; Fax: int. code +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk].
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