Amino Acids as Nitrogen Sources

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Amino Acid-Based Reoxidants for Aminohydroxylation: Application to the Construction of Amino Acid–Amino Alcohol Conjugates**

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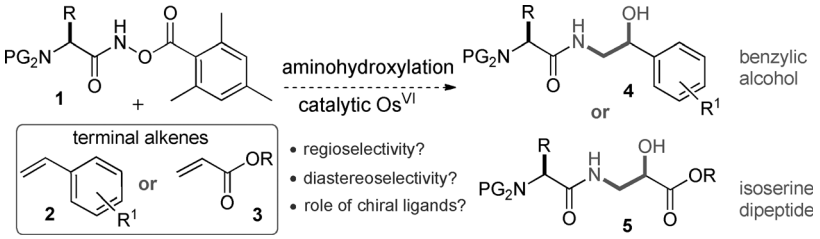
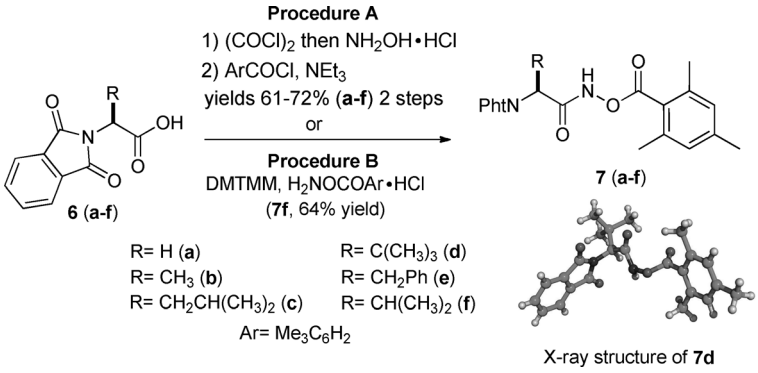
In recent years, there has been a surge in reports of methodology aimed at synthesizing the 1,2-amino alcohol motif.[1] Despite numerous studies, this key unit is still highly sought after because of its occurrence in many different organic compounds of value ranging from natural products to pharmaceutical agents.[2] Methods that allow for the regioselective and stereospecific addition of nitrogen and oxygen across a double bond are rare, and continue to be influenced by the osmium-catalysed aminohydroxylation reaction.[3] Recent developments of this reaction have witnessed the introduction of N-O based reoxidants for osmium that have made the process much more reliable and high-yielding.[4] Herein, we report for the first time the use of natural amino acids as a scaffold for such reoxidants, allowing their conjugation with alkenes in a regio- and stereocontrolled process. This sequence enables rapid access to well-defined and enantiopure amino alcohols using a transition metal and a chiral ligand in catalytic amounts.



Scheme 1. Amino acids as stable reoxidants and nitrogen sources for aminohydroxylation? PG: protecting group.



Scheme 2. Conversion of amino acids into reoxidants for aminohydroxylation.

We set out to explore the role of amino acids **1** as nitrogen sources in the aminohydroxylation reaction and to search for the factors that control both the regio- and stereoselectivity of the process (Scheme 1). We chose two classes of terminal alkenes, namely substituted styrenes **2** and acrylate esters **3**, as the alkene partners because the product amino acid conjugates are potentially useful in synthesis, especially in medicinal chemistry.[5]

Early work had shown that the nitrogen atom of an amino acid should be doubly protected in order to give the best results in aminohydroxylation. Therefore, the synthetic route began with the conversion of an amino acid into its phthalimide-protected form (phthalic anhydride, 93–100% yield[6]) and subsequent transformation of the free carboxylic acid into an *O*-acyl hydroxamic acid reoxidant (Scheme 2). Taking the case of L-valine and L-alanine as examples, procedure A took place without significant racemization and the products were formed in 94–98% *ee*. An exception to this reactivity involved the use of α-phenylglycine, which could not be coupled to hydroxylamine derivatives without significant racemization. An alternative pathway (procedure B) to the activated amino acids involved the separate formation of *O*-mesitoyl hydroxylamine (as its HCl salt),[7] which could be coupled to the free acid using a peptide-coupling agent (DMTMM);[8] in the case examined (**7f**), this reagent gave no racemization in the product, but was less convenient to use on a large scale. X-ray analysis proved the identity of compound **7d**.[9]

Armed with these amino acid-based reoxidants, we were then able to examine their behavior in aminohydroxylation reactions. In the first instance we chose to examine the combination of L-valine-derived reoxidant **7f** with *p*-methoxystyrene (**8**; Table 1). A screen of the solvents that are typically used in aminohydroxylation showed that aqueous THF gave the best results in terms of high yield and

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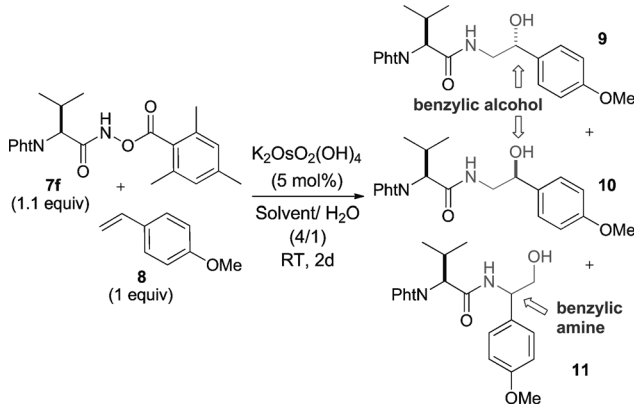
Table 1: Addition of L-valine-based reoxidant **7 f** to **8**.

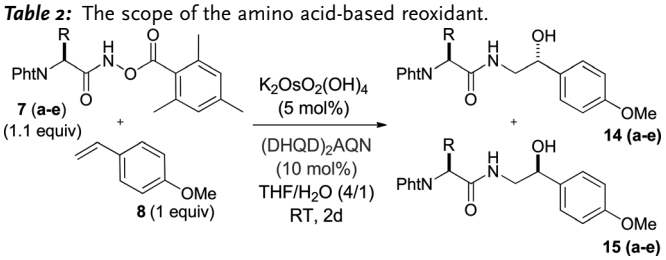


Entry	Solvent/Ligand	(**9**+**10**):**11**[a]	Yield [%] (d.r., **9**:**10**)
1	THF	33:1	91 (2:1)
2	THF/$(DHQD)_2AQN$[b]	13:1	89 (15:1)
3	THF/$(DHQ)_2AQN$[b]	6.5:1	72 (1:1.3)

[a] The diastereoselectivity within the minor regioisomer **11** was not determined but the structure of one isomer was proven by X-ray crystallography.[9] [b] 10 mol% of chiral ligand was used throughout. Alternative spacer groups such as PHAL and PYR gave inferior selectivities (see the Supporting Information).

regioselectivity for the benzylic alcohols **9** and **10** (Table 1, entry 1). This high regioselectivity for benzylic alcohols makes our reaction complementary to past procedures which tend to give benzylic amines.[10,11] Moreover, we also discovered that the low levels of diastereoselectivity for **9** imparted by the chiral amino acid reoxidant could be augmented by the addition of a catalytic amount of Sharpless' chiral ligands (the optimal result was obtained with $(DHQD)_2AQN$ giving d.r. = 15:1, Table 1, entry 2).[3d,11] While this particular combination clearly represents a matched pairing of ligand and amino acid substrate, the use of $(DHQ)_2AQN$ was less successful and could only overturn the facial bias of the system to a small degree (Table 1, entry 3). The identity of the major regio- and diastereomer **9** was proven by X-ray crystallography which revealed that the configuration at the benzylic center is that to be expected using a DHQD-based ligand.[9,11] Moreover, the identity of the alternative diastereomer **10** was confirmed when a 2:1 mixture of **9** and **10** was oxidized to a single benzylic ketone **12** upon treatment with Dess–Martin periodinane (DMP) (Scheme 3). Finally, in order to prove the synthetic utility of the sequence, the major diastereomer **9** was deprotected using hydrazine[12] to furnish **13** without detectable epimerization of the stereogenic centers (Scheme 3).

Table 2: The scope of the amino acid-based reoxidant.

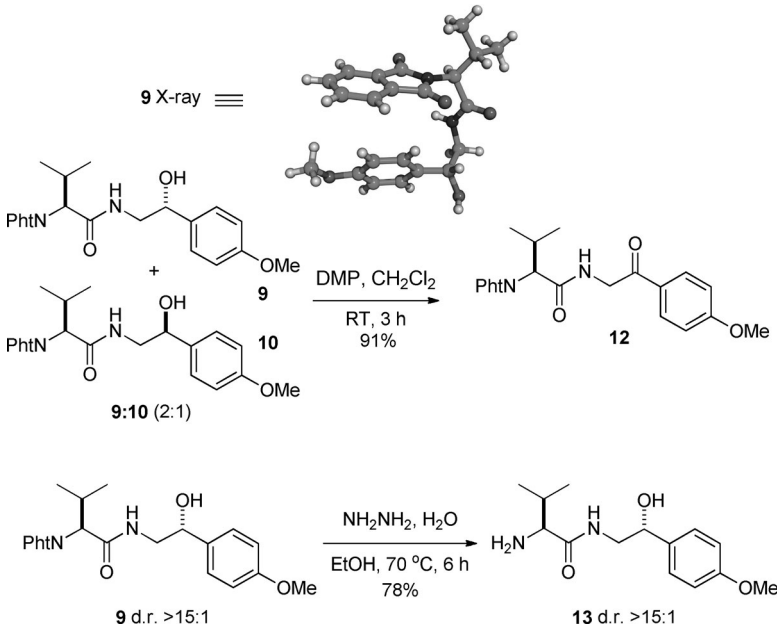


R	Regioselectivity	d.r. (**14**:**15**)	Yield [%]
H (**a**)	5:1	–	72
CH_3 (**b**)	14:1	6:1	79
$CH_2CH(CH_3)_2$ (**c**)	12:1	4:1	81
$C(CH_3)_3$ (**d**)	9:1	10:1	64
CH_2Ph (**e**)	8:1	6:1	68

Next, we explored the range of amino acids that were compatible with this sequence, using **8** as a convenient alkene substrate (Table 2; all amino acids were activated as shown in Scheme 2). Although α-phenylglycine did give good yields in this sequence (Table 2, last entry) it is not shown above because of problems associated with racemization during active-ester formation (see above). The identity of the major diastereomer was assumed by analogy to the L-valine example above; in each case, aminohydroxylation without a chiral ligand gave high regioselectivity but low diastereoselectivity. This bias could be reenforced with a matching DHQD-based ligand (only the results employing the DHQD ligand are shown in Table 2).

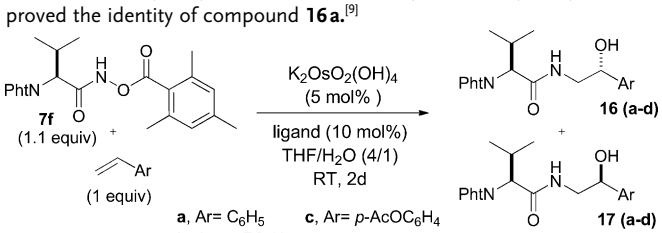
As before, oxidation of a mixture of diastereomers from the reactions shown in Table 2 gave, in each case, a single benzylic ketone thus allowing us to assign the peaks in the ^1H NMR spectra that were attributable to diastereomers as opposed to regioisomers. Clearly, the amino acids glycine, L-alanine, L-leucine, L-*tert*-butylglycine, and L-phenylalanine are all compatible with this methodology.

Next, we examined the range of substituted styrenes that would react with the L-valine-based reoxidant **7 f** to gauge the generality of the method for this class of alkenes (Table 3). The



Scheme 3. Proof of regioselectivity and phthalimide deprotection.

Table 3: Aminohydroxylation of substituted styrenes; X-ray analysis proved the identity of compound **16a.**[9]



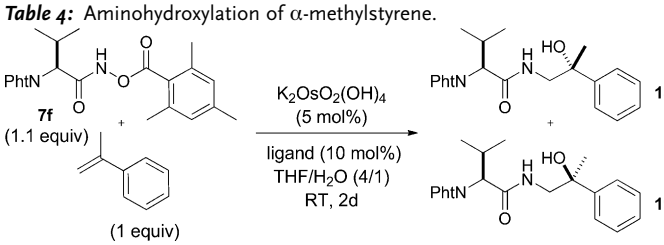
a, Ar= C_6H_5 **c**, Ar= *p*-$AcOC_6H_4$
b, Ar= *p*-FC_6H_4 **d**, Ar= 2-naphthyl

Ar	Ligand	Regioselectivity	d.r. (**16**:**17**)	Yield [%]
C_6H_5	–	20:1	1.5:1	80
C_6H_5	$(DHQD)_2AQN$	15:1	13:1	75
C_6H_5	$(DHQ)_2AQN$	7:1	1:1.4	68
p-FC_6H_4	–	15:1	2:1	81
p-FC_6H_4	$(DHQD)_2AQN$	17:1	6:1	79
p-FC_6H_4	$(DHQ)_2AQN$	15:1	1:1.3	71
p-$AcOC_6H_4$	–	13:1	1.5:1	80
p-$AcOC_6H_4$	$(DHQD)_2AQN$	12:1	8:1	78
p-$AcOC_6H_4$	$(DHQ)_2AQN$	6:1	1:2	69
2-naphthyl	–	18:1	2:1	79
2-naphthyl	$(DHQD)_2AQN$	13:1	12:1	77
2-naphthyl	$(DHQ)_2AQN$	7:1	1:1.3	70

placement of groups at the *para*-position on the aromatic ring, or the introduction of alternative aromatic motifs did not affect the outcome of the sequence, which revealed that: 1) high regioselectivity for the benzylic alcohol was maintained throughout; 2) the matching effect of DHQD-based ligands was supported; 3) the mismatching effect of DHQ-based ligands was observed. In each case, the subsequent oxidation of a mixture of diastereomers gave a single benzylic ketone (see the Supporting Information).

If we used a 1,1-disubstituted alkene, such as α-methylstyrene, the aminohydroxylation still proceeded with high regioselectivity and adequate stereoselectivity with either diastereomer **18** or **19** being accessible (Table 4). Note that in this case, the regiochemistry of the major isomers was assigned by NMR experiments, and the configuration at the newly formed stereogenic center is assumed to be that as shown (that is, under the control exerted by the chiral ligands[13]).

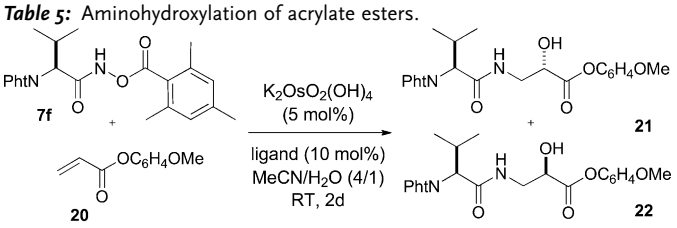
Table 4: Aminohydroxylation of α-methylstyrene.



Ligand	Regioselectivity	d.r. (**18**:**19**)	Yield [%]
–	25:1	2:1	64
$(DHQD)_2AQN$	11:1	3:1	62
$(DHQ)_2AQN$	8:1	1:2	53

Changing the terminal alkene substrate from being electron-rich to being electron-deficient enabled the synthesis of dipeptides containing valine and isoserine, because the imido–osmium oxidant placed the bulky amino acid at the terminus of the alkene during aminohydroxylation (Table 5).

Table 5: Aminohydroxylation of acrylate esters.



Ligand	Regioselectivity	d.r. (**21**:**22**)	Yield [%]
–	9:1	1.5:1	83
$(DHQD)_2AQN$	8:1	10:1	84
$(DHQ)_2AQN$	15:1	1:4	68
$(DHQ)_2PHAL$	12:1	1:5	82

We found that the aminohydroxylation of aryl acrylate ester **20** was especially productive and allowed valine–isoserine residues **21** and **22** to be prepared. Finding acetonitrile to be the optimal solvent, we observed matching (DHQD) and mismatching (DHQ) effects as before, and the selection of a particular ligand allowed the formation of either L-**21** or D-**22** amino acids at will.[14] In this case, the DHQ ligand was better matched with a PHAL spacer rather than with an AQN spacer, which was not the case with the styrene derivatives. It is hoped that this new approach to making peptides will have several uses in organic synthesis.[15]

In conclusion, we have shown that protected amino acids are viable nitrogen sources and reoxidants for the intermolecular aminohydroxylation reaction, with high levels of regio- and stereoselectivity being achieved during the oxidation of both electron-rich and electron-deficient terminal alkenes. The sequence enables the conjugation of amino acids and alkenes in a concise manner, and will lead to the efficient and rapid synthesis of amino acid–amino alcohol conjugates which are expected to have widespread use in organic synthesis. Further investigations regarding the scope of substrates with non-terminal alkenes are currently ongoing.

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