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Substrate Control in Enantioselective and Diastereoselective Aldol Reaction by Memory of Chirality: A Rapid Access to Enantiopure β-Hydroxy Quaternary α-Amino Acids

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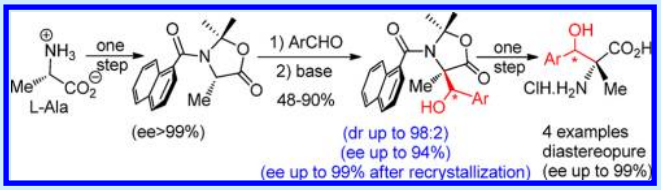
Supporting Information

ABSTRACT: An asymmetric aldol reaction by memory of chirality is reported with a substrate control of stereoselectivity by aldehyde and rationalized. Starting from L-alanine, several diastereopure and enantioenriched β-hydroxy quaternary α-amino acids have been obtained in three steps. The initial chirality of L-alanine is memorized through the dynamic axial chirality of tertiary aromatic amide.



Quaternary α-amino acids are a large class of compounds that include many biologically active members and thus have attracted much attention of research groups.[1] Among the quaternary α-amino acids, β-hydroxy amino acids occupy a special place as they are present in several interesting natural active compounds such as lactacystin, kaitocephalin, or sphingofungin, etc. (Figure 1).[2]

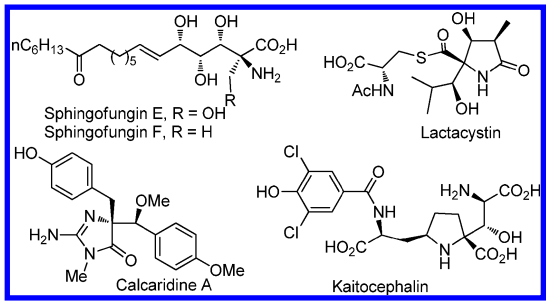
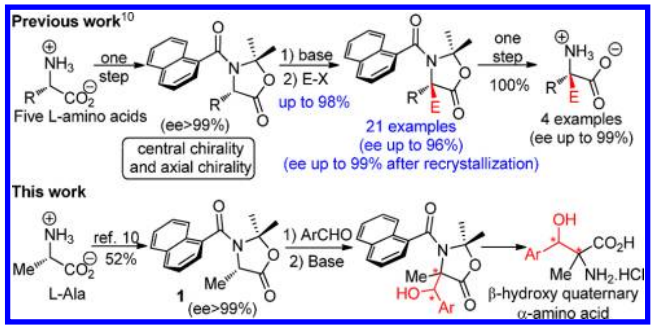


Figure 1. Structures of biologically active natural β-hydroxy quaternary α-amino acids.

The aldol reaction seems to be a straightforward access to the quaternary β-hydroxy amino acids, and classical approaches for their stereoselective synthesis have been described.[3] Methods using only the initial chirality of a starting α-amino acids such as the self-regeneration of stereocenters developed by Seebach[4] or the memory of chirality (MOC)[5] have also been employed. A reaction proceeding with memory of chirality has been defined by Carlier as "a formal substitution at a sp^3 stereogenic center that proceeds stereospecifically, even though the reaction proceeds by trigonalization of that center, and despite the fact that no other permanently chiral elements are present in the system". A few examples of aldol reactions have been described so far with the MOC principle, the earliest reported reactions being intramolecular.[6] Recently, Ghorai[7] succeeded in intermolecular aldol reaction but with low stereoselectivities, and Kawabata's intermolecular aldol reaction led to oxazolidinone formation with inversion of configuration in high yields and stereoselectivities.[8] However, these oxazolidinones were not hydrolyzed. In our group, we have developed a three-step MOC synthesis of quaternary α-amino acids based on the dynamic axial chirality of tertiary aromatic amides.[9] We have performed alkylation of oxazolidinones derived from natural amino acids and got quaternary α-amino acids in high yields and enantiomeric excesses.[10] We describe herein the extension of this methodology to the aldol reaction, which is a greater challenge as a second asymmetric center is formed (Scheme 1).

We chose L-alanine as the starting amino acid as our previous studies showed that the corresponding enolate was more configurationally stable, and this could be used later in the total synthesis of sphingofungin F, a bioactive molecule known to have potent antifungal activity and also inhibitory activity against serine palmitoyl transferaes (SPT).[2b] We synthesized

Scheme 1. Previous Work on Memory of Chirality and Application to Aldol Reaction



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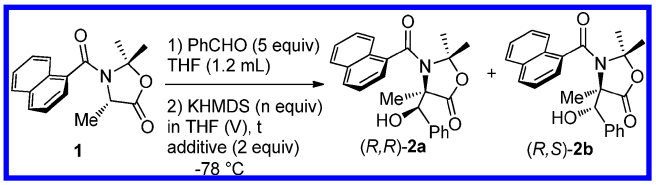
oxazolidinone **1** as previously described and then tried to optimize the aldol reaction conditions by using benzaldehyde. Oxazolidinone **1** exists as four conformers (*P,cis*:*M,cis*:*P,trans*:*M,trans*) in solution at −78 °C with *P,cis* being major.

The initial experiment, the addition of KHMDS in THF and DME to a solution of **1** in THF under argon at −78 °C and quenching by acetic acid, was disappointing as we observed only a trace of **2a**,**b**. The yields were improved by replacing acetic acid with NH_4Cl, and then removed the acidic residues by washing with 5% $NaHCO_3$ solution to avoid the acidic cleavage of the oxazolidinone ring. We tried various conditions to further improve the yield, ee and dr (Table 1).

Table 1. Optimization of Aldol Reaction of Oxazolidinone 1 with Benzaldehyde[a]



entry	*n*	vol (mL)	additive	*t* (min)	dr[b]	ee[c] (%) **2a**/**2b**	yield[d] (%)
1[e,f]	1.0	0.35	DME	10	83:17	83/79	71
2[e,f]	1.5	1.5	DME	10	86:14	84/74	85
3[e,f]	2.0	1.7	DME	10	83:17	79/73	90
4[e–g]	2.0	1.7		10	72:28	83/82	57
5[e–h]	2.0	1.7		10	75:25	84/79	80
6[e–g,i]	2.0	1.7		10	82:18	34/18	78
7[j,k]	1.5	0.52		10	66:34	68/46	80
8[k–m]	1.5	0.52		10	**89:11**	**83/75**	**78**
9[k,l]	1.5	0.52		12	75:25	83/79	82
10[l,n]	1.5	0.52		12	80:20	72/64	85

[a]General procedures: To a stirred solution of oxazolidinone **1** (0.35 mmol) in THF (1.2 mL) at −78 °C was added benzaldehyde (5 equiv) just before adding a solution of KHMDS (n equiv) in THF (V mL) dropwise (over 2 min), and the mixture was stirred for *t* min at −78 °C. [b]Ratio **2a**/**2b** determined by chiral stationary-phase HPLC on the crude product. [c]Ee of **2a**/**2b** determined by chiral stationary-phase HPLC after purification. [d]Combined yield of **2a** and **2b**. [e]Addition of a precooled KHMDS solution via canula. [f]Toluene was removed from the commercially available solution of KHMDS and replaced by THF. [g]Washed with $NaHCO_3$ 1% solution. [h]Benzaldehyde distilled from CaH_2 just before use. [i]Identical to general procedure, except that KHMDS is added first and benzaldehyde is then added after 1.5 min. [j]Direct and rapid addition of a room temperature KHMDS solution. [k]Commercially available 1 M solution of KHMDS in THF was used. [l]Direct and slow addition of a room temperature KHMDS solution. [m]Relative configuration of dia **a** determined by X-ray. [n]Benzaldehyde was added to **1** in THF at RT and cooled to −78 °C.

The addition of a precooled solution of base in THF and DME (2 equiv, diluted to avoid freezing at −78 °C) to a solution of oxazolidinone and electrophile (5 equiv) in THF gave the expected aldol **2a** and **2b** in 71% combined yield, with a dr of 83:17 (separable diastereomers) and ee of 83 and 79%, respectively (Table 1, entry 1); 1.5 equiv of KHMDS was sufficient to ensure good conversion (Table 1, entries 1−3). DME, as an additive, was excluded from the reaction for simplification (Table 1, entries 3 and 4). The quality of benzaldehyde was essential for a better yield (Table 1, entries 4 and 5). Precooling of the base solution did not considerably improve the stereoselectivity of the reaction (we subsequently increased the amount of solvent to avoid freezing, but dilution of the reaction led to decrease of the dr). Therefore, a direct addition of commercially available uncooled KHMDS solution via syringe to the mixture of **1** and benzaldehyde simplified the condition. This allowed us to perform a more concentrated reaction as dilution led to lowering of dr. Addition of the aldehyde after deprotonation was deleterious for the enantiomeric excess (Table 1, entry 6), and this is probably significant of the enolate racemization. Besides, a rapid addition of the base led to a decrease of stereoselectivity (Table 1, entry 7) probably because a rapid addition of an uncooled base, coupled with an exothermic deprotonation reaction, should induce warming and thereby enolate racemization. Slow addition of an uncooled base improved the enantio- and diastereoselectivity (Table 1, entries 7 and 8). Going from 10 to 12 min of reaction decreased the dr and improved the yield (Table 1, entries 8 and 9). This is perhaps due to the reaction of the minor conformers. We also observed a change of enantio- and diastereoselectivity depending on the temperature at which the benzaldehyde and the oxazolidinone were mixed (Table 1, entries 9 and 10). To understand this, we performed two ^1H NMR experiments. Premixing oxazolidinone **1** and benzaldehyde (5 equiv) in THF-d_8 at RT and recording the ^1H NMR spectrum at −78 °C showed two aldehyde peaks, probably due to the presence of free and complexed aldehyde. Moreover, we observed several conformational changes in the oxazolidinone part (more visible for the acidic proton and for the dimethyl group). The conformational change could have happened because of the $\pi-\pi$ interaction between the naphthoyl group and the benzaldehyde in a complexed form. Whereas when benzaldehyde is mixed with oxazolidinone **1** at −78 °C and the spectra are recorded at the same temperature, we did not observe any such effects (see Supporting Information). We tried other solvents (ether or DME) and addition of a Lewis acid or other bases (KHMDS in toluene or LiHMDS gave no product at all) but observed no improvement. Thus the best conditions are the ones of entry 8.

We next performed the MOC aldol reactions successfully with various aromatic or heteroaromatic aldehydes and cinnamaldehyde. Two aliphatic aldehydes (isobutyraldehyde and pivalaldehyde) were unsuccessfully tested. Moreover, a reactive ketone, 1-Me-isatin, also reacted well (Table 2, entry 15), allowing the generation of two contiguous quaternary centers, but the diketone benzyl was found unreactive. For each aldehyde, we separately optimized the reaction time to get the best results (for ee, dr, and yields), other conditions being kept constant (Table 2). From these results, the ee of the major diastereomer is often superior to 80% and is up to 94% (Table 2, entry 13). Fortunately, all the diastereomers were separable by chromatography. In most of the cases, the products coexisted as conformers, and it is confirmed by the variable-temperature ^1H NMR experiments (see Supporting Information).

On the other hand, the dr is highly dependent on the aldehyde; from *o*-Br (**a** major) to *o*-F (**b** major), there is a diastereo switching, and for furan aldehyde, the diastereoselectivity is completely opposite (Table 2, entries 6, 11, and 12). Thiophene aldehyde lies in the borderline. 1-Methyl-isatin showed the same trend at lower reaction concentration (Table 2, entry 15). As we found for benzaldehyde (Table 1), both dilution and reversal of mode of addition of electrophile led to decrease and reversal of dr (Table 2, entry 16).

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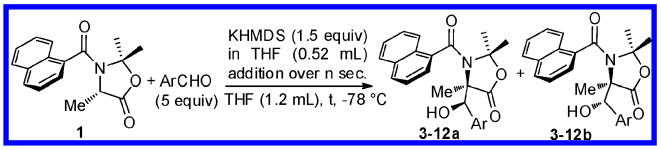
Table 2. Aldol Reaction of Oxazolidinone 1 with Aldehydes or 1-Me-isatin



entry	Ar-	*n* (s)	*t* (min)	comp	dr	ee[a] (%)	yield[b] (%)
1	*o*-Me-C_6H_4-CHO	60	12	**3**	>98:2[c]	78/–	48
2	*o*-Me-C_6H_4-CHO	120	12	**3**	>98:2[c]	82[d]/–	48
3	*p*-OMe-C_6H_4-CH	120	12	**4**	88:12[c]	73/56	67
4	*m*-Br-C_6H_4-CHO	150	15	**5**[e]	92:8[c]	79/65	90
5	*m*-Br-C_6H_4-CHO	240	15	**5**	87:13[c]	89/68	72
6	*o*-Br-C_6H_4-CHO	95	12.5	**6**[f]	93:7[g]	75/90	81
7	*p*-Me-C_6H_4-CHO	95	512	**7**	80:20[c]	78[d]/73	56
8	*p*-Me-C_6H_4-CHO	120	12	**7**	78:22[c]	82/78	73
9	3-pyridine-CHO	105	12	**8**	79:21[g]	85/92	71
10	2-thiophene-CHO	105	12	**9**	50:50[g]	75/71	68
11	*o*-F-C_6H_4-CHO	120	15	**10**[e]	30:70[c]	88/78	56
12	2-furan-CHO	105	8	**11**[h]	15:85[c]	83/93[i]	68
13	2-furan-CHO	105	12	**11**	10:90[c]	77/94[j]	75
14	Ph-CH=CH-CHO	90	12	**12**	83:17[c]	87/65	99
15	1-Me-isatin	120	12	**13**	42:58[c]	53/87	49[k]
16	1-Me-isatin	120	8	**13**	68:32[c]	58/78	80[l]

[a]Ee of diastereomers **a**/**b** determined by chiral stationary-phase HPLC after purification. [b]Combined yield of both diastereomers. [c]Dr **a**/**b** (**a** being the less polar) determined by ^{1}HNMR on the crude product. [d]Recrystallization allowed improvement of ee for **3a**: ee >99%, yield = 66%; for **7a**: ee = 93%, yield = 70%. [e]Relative configuration of dia **a** determined by X-ray. [f]Absolute configuration of dia **a** determined by X-ray. [g]Dr **a**/**b** (**a** being the less polar) determined by chiral stationary-phase HPLC on the crude product. [h]Relative configuration of dia **b** determined by X-ray. [i]Ee observed for the crude product: 86/96.[11] [j]Ee observed for the crude product: 91/95. [k]1-Me-isatin was sparingly soluble at −78 °C. [l]1-Me-isatin (3 equiv) in 2.2 mL of THF was added after KHMDS.

Several aldol compounds were recrystallized to determine relative and absolute configurations by X-ray structures. Compounds **2a** and **5a** crystallized as racemic leading to the determination of the relative configuration (either *RR* or *SS*) and to an improvement of the ee in the mother liquor (mother liquor: **2a** (yield = 90%; ee = 98%); **5a** (yield = 78%; ee = 95%)). Compounds **6a** (yield = 74%; ee >99%), **10a** (yield = 80%; ee >99%), and **11b** (yield = 60%; ee >99%) were obtained as enantiopure by recrystallization. The X-ray structures (Figure 2) showed that compounds **2a**, **5a**, **6a**, and **10a** possess the same relative configuration, and for **6a** (which possesses a bromine atom), the configuration of the first asymmetric center is retained (*R*), as observed for alkylation reactions. Moreover, the relative configuration of **11b** was opposite to the previous one. Considering the resemblance of the ^{1}H NMR spectra for each diastereomer in all aldol products, we extended the preceding stereochemistry to all compounds (including for compound **13**).

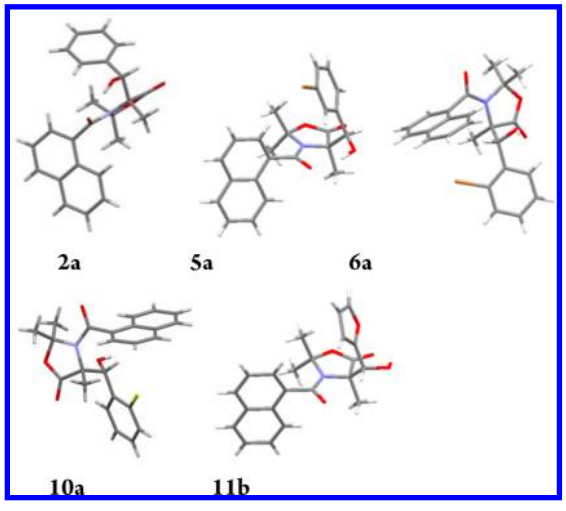


Figure 2. X-ray structures of compounds **2a** and **5a** (racemic, major enantiomer shown), **6a**, **10a**, and **11b** (enantiopure).

The observed stereochemistry can be explained by a Zimmerman−Traxler transition state (Figure 3). As already

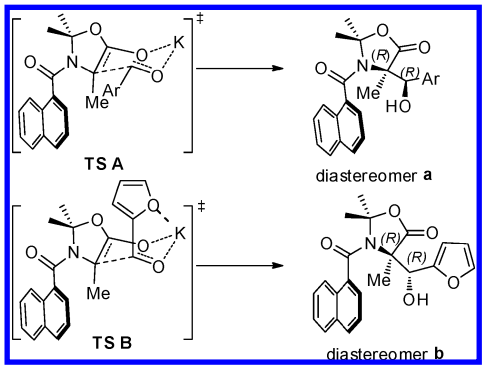


Figure 3. Explanation for the observed stereoselectivity: the favored transition states **TS A** leading to diastereomer **a** and **TS B** leading to diastereomer **b** are presented.

rationalized for alkylation,[10] the initial orientation of the naphthoyl group is retained during enolate formation and induces an electrophile approach through the opposite face (leading to the observed retention of configuration for the α-carbon). In the chairlike Zimmerman−Traxler transition state **TS A**, due to the presence of the five-membered ring and the dimethyl group in it, the C−N bond is pseudoequatorial,

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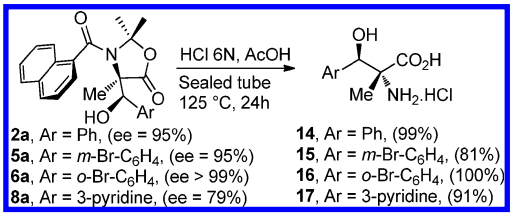
whereas the methyl group is pseudoaxial. The aromatic ring of the approaching aldehyde can orient in pseudoequatorial position, leading to the observed major diastereomer **a**.

This pseudoequatorial position (**TS A**) of the aromatic ring is even more favored when the aromatic ring is hindered such as with the *o*-Me-phenyl and *o*-Br-phenyl groups and allowed an almost perfect diastereoselectivity (Table 2, entries 1 and 6). Surprisingly, we observed a reversal of diastereoselectivity when the phenyl group is substituted at the ortho position with fluorine atom (**10b** is major, Table 2, entry 11). This was also the case when furan aldehyde was used as an electrophile (Table 2, entries 12 and 13). When a donor atom is present at the aromatic ring, there could be an extra anchoring interaction between the pseudoaxial aromatic ring and the metal, thereby stabilizing the **TS B**, resulting in the major formation of diastereomer **b**. For 3-pyridine aldehyde, the coordinating atom is away from the coordinating position. For thiophene aldehyde, both **TS A** and **TS B** may be equally possible. **TS B** must be favored for the *o*-fluorobenzaldehyde but not for the *o*-bromobenzaldehyde (**6a** is major, entry 6), as *o*-Br is too bulky compared to *o*-F. To our knowledge, this type of diastereocontrol by the aldehyde has not been observed so far for aldol reactions with a chairlike transition state, but a similar case has been described for allylation reaction of aldehydes.[12] Four compounds were hydrolyzed in one step and led to β-hydroxy quaternary α-amino acids as hydrochloride in good to excellent yields (Scheme 2).

Scheme 2. Hydrolysis of Diastereopure Aldol Compounds: Access to β-Hydroxy Quaternary α-Amino Acids



2a, Ar = Ph, (ee = 95%)
5a, Ar = *m*-Br-C_6H_4, (ee = 95%)
6a, Ar = *o*-Br-C_6H_4, (ee > 99%)
8a, Ar = 3-pyridine, (ee = 79%)

14, Ar = Ph, (99%)
15, Ar = *m*-Br-C_6H_4, (81%)
16, Ar = *o*-Br-C_6H_4, (100%)
17, Ar = 3-pyridine, (91%)

We have presented here an efficient synthesis of β-hydroxy quaternary α-amino acids, using only the initial chirality of the starting α-amino acid. This is the first example of a MOC aldol reaction that allows the synthesis of the final compounds in three steps, and several β-hydroxy quaternary α-amino acids have been obtained in diastereopure and enantioenriched form. We have moreover highlighted a surprising substrate control of the stereoselectivity from the aldehyde side which, to our knowledge, has not been so far described in the aldol reaction. An explanation of the observed stereoselectivity has been proposed. Extension of this reaction to other amino acids is currently under investigation.

■ ASSOCIATED CONTENT

Supporting Information

Crystallographic data of compounds **2a**, **5a**, **6a**, **10a**, and **11b** and experimental details and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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