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Diversity-oriented synthesis of amino acids using chiral enolates

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ABSTRACT

We report a facile diversity oriented synthesis of α- and β-amino acids, by utilizing the pluripotent α-methylene group in a chiral bicyclic lactam as our key point of transformation.

Diversity-oriented synthesis (DOS) is a facile synthetic methodology used toward the synthesis of compounds with structural diversity.[1] This is usually achieved by stereochemical and skeletal modification of the central moiety. There are mainly two strategies utilized in DOS to impart skeletal diversity, either on the basis of reagent (reagent-based approach) or the substrate (the substrate-based approach). In the reagent based approach, skeletal versatility is achieved a) either by applying a heavily functionalized motif, bearing various functionalities which, are transformed by several reagents, or b) identifying a functional group that can participate in various transformations with different reagents (*pluripotent*) (Fig. 1).[2] Hence identifying such *pluripotent* functional groups and their subsequent reaction will be a valuable addition to this methodology. Such diversity imparting chemistry which incorporates rapid structural versatility to the products (which in turn can be further transformed), could be utilized. Herein, we report the development of DOS for the synthesis of α- and β-amino acids from **1** (Meyer's oxazolidine), by implementing reagent based approach (Fig. 2).[2]

α- And β-amino acids and their derivatives are essential synthetic building blocks in organic synthesis and essay an important role in pharmaceutical research.[3] Hence the synthesis of these amino acids (natural and unnatural) continues to be the focus of intense investigation. There have been several enolate based and organo catalytic syntheses of α- and β-amino acids.[4]

Chiral oxazolines have been extensively utilized toward the asymmetric synthesis of dialkylacetic and propanoic acids, alkylbutyrolactones and valerolactones, by base mediated (nBuLi, LDA etc.) alkylation of the methylene group α- to the oxazolines.[5] It is also used toward the synthesis of β-amino acids and several heterocycles.[6] Herein we report a novel diversity oriented synthesis of α- and β-amino acid derivatives from same chiral oxazoline, in high yields and moderate stereoselectivity. The fact that we have identified a scaffold which can be tailored to different classes of amino acids for the first time, is an important highlight of the Letter.

Oxazoline **1** is prepared efficiently by condensation of methyl imidate with R-phenylglycinol in 99% ee.[7] We envision aldimine based Mannich reaction of **1** as a suitable method for the generation of appropriate intermediates (β-amino acid surrogates) which in turn can be converted to β-amino acid derivatives. In order to optimize the conditions we selected *N*-benzylbenzaldimine as the reacting intermediate. After exploring reactions with several bases at −78 °C (Table 1), we observed 2.5 equiv LDA as the most efficient protocol for the generation of the desired β-amino acid derivative **2** (entry 6). Reactions with LHMDS, KHMDS and NaHMDS resulted in extremely poor yield (entries 2, 3, and 4). LDA with LiCl as an additive (entry 5), does not really impart any more efficiency than LDA itself. However 1 equivalent of LDA (entry 1) was not good enough to obtain a decent yield and diastereoselectivity. Finally the hydrolysis of oxazoline to ester, was straightforward with 6 N HCl under refluxing condition to generate the ester **8**.

With the condition for Mannich optimized, we embarked on investigating the generic nature of the reaction. Hence we reacted **1** with different types of aldimines (viz. aryl and heteroaryl). To our

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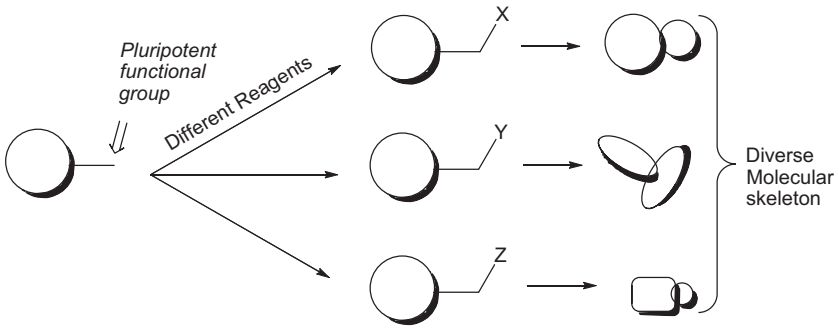


Figure 1. The reagent based approach.

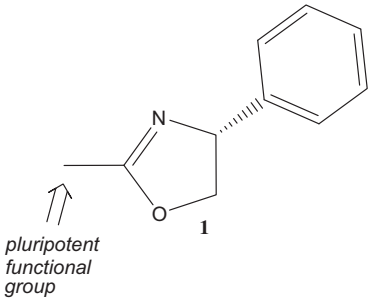
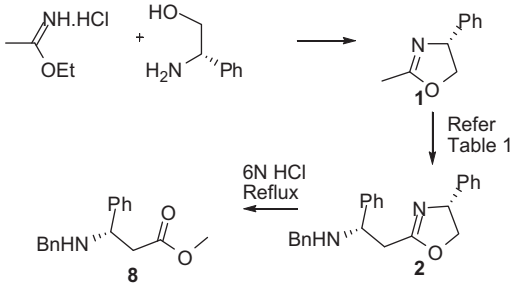


Figure 2. Chiral auxiliaries with pluripotent functional group.

Table 1
Investigation of Mannich reaction conditions and final hydrolysis



Entry	Base	Eq	*T* (°C)	Yield[a]	de[b]	Yield[a]	ee[c]
1	LDA	1	−78	40%	90%	—	—
2	LHMDS	1	−78	36%	90%	—	—
3	NaHMDS	1	−78	12%	—	—	—
4	KHMDS	1	−78	14%	—	—	—
5	LDA/LiCl	1	−78	34%	88%	—	—
6	LDA	2.5	−78	67%	90%	58%	90%

[a] Isolated yield.
[b] By HPLC.
[c] Chiral HPLC (CHIRAL PAK AD, 4.6X 250 mm, 5 μm).

satisfaction all the aldimines we used, successfully underwent Mannich reaction with good yields and decent de (Table 2). To obtain the β-amino acid derivatives these intermediates generated from Mannich reaction, were hydrolyzed with 6 N HCl. The yield of the final ester, over two steps ranged anywhere from 43% to 70%. We observed that the ee of the amino ester was same as that of the intermediate (amino acid surrogate), hence it suggests no epimerization during the hydrolysis. We also executed the Mannich reaction with *N*-benzyl-isopropaldimine (entry 5). However to our dismay, there was only 5% product conversion in LCMS. Also the pyridyl intermediate **5** (entry 4), could not be purified (as it was decomposing in the chromatography column) and was used

Table 2
Mannich reaction and hydrolysis

Entry	AAS	Yield[c] (%)	de[b] (%)	Amino esters	Yield (%)	ee[b] (%)
1	**2**	82	90	**8**	43	88
2	**3**	73	90	**9**	68	90
3	**4**	77	85	**10**	71	90
4	**5**[a]	–	–	–	62	80
5	**6**	–	–	**11**	–	–
6	**7**	70	80	**12**	52	

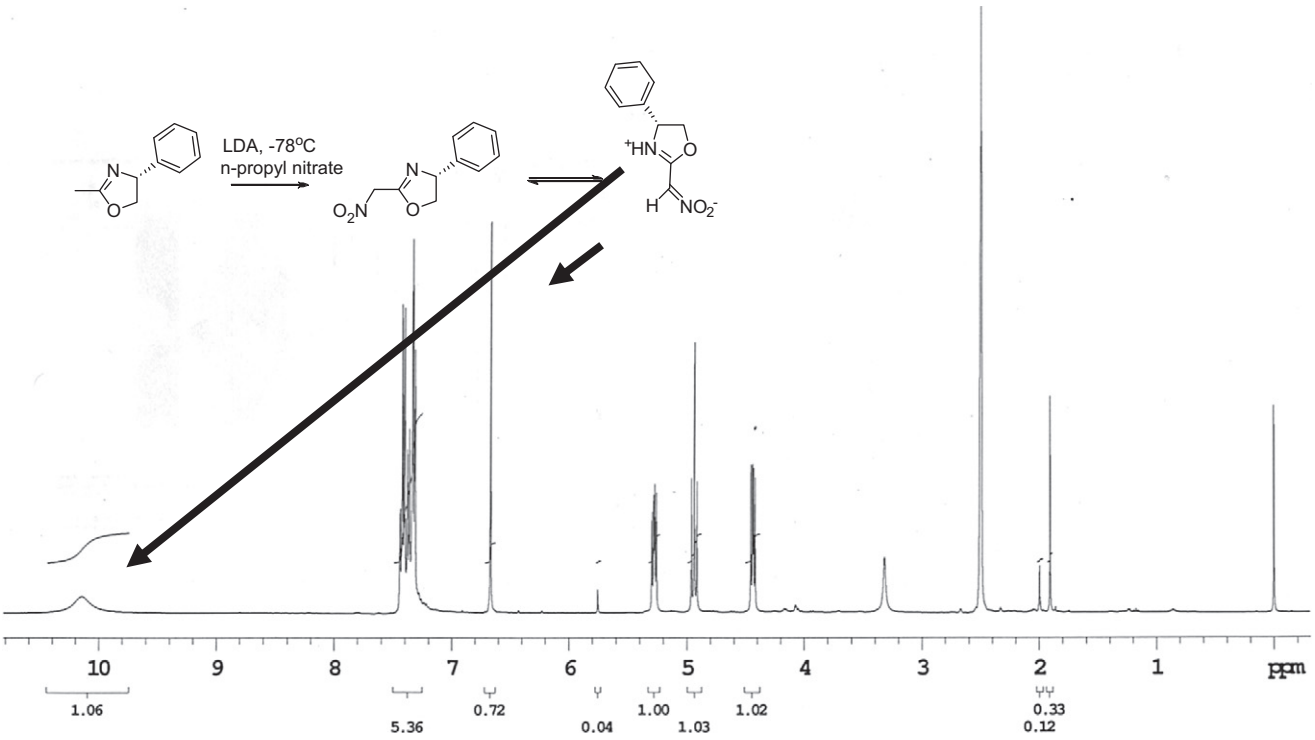
[a] Unable to isolate pure compound.
[b] By HPLC.
[c] By chiral HPLC (CHIRAL PAK AD, 4.6 × 250 mm, 5 μm).

for the final hydrolysis as crude. The absolute configuration of the β-amino acid derivatives as depicted here, was determined by comparing the SOR of **8** (SOR: $[\alpha]_{589}^{25}$ −6.1500° (MeOH, *c* 0.1) (as a representative example) with a literature value of a Boc-derivative of the same ester .[8]

For α-amino acid derivatives we envision the synthesis of chiral nitrooxazoline derivative **13**. In-turn it can be alkylated followed by hydrolysis to generate the desired α-amino ester. To that direction, we reacted chiral oxazoline **1** with n-propylnitrate (*n*-prop-ONO_2) to generate the corresponding nitro-derivative **13**.

Lithiating the resulting intermediate with LDA at −78 °C followed by 3-methylbenzyl bromide, failed to generate the desired derivative **15**. On further investigation with various bases (LDA, LHMDS, NaHMDS, KHMDS, NaH and NaOMe), in their different stoichiometric ratios and at different temperatures (0, −10, −40 and −78 °C) we observed, absolutely no reactivity of **13**. The ^{1}H NMR spectra of **13** revealed that the compound exists mostly in its dipolar structure **14** (Scheme 1). This may be due to the presence of the highly electron withdrawing $-NO_2$ and the imidate adjacent to the central methylene protons. IR and UV spectra of the compound also corroborates the same.[9] In the ^{1}H NMR we observed a broad singlet at 9–10 ppm (characteristic of the immonium ion). The proton adjacent to the $-NO_2$ appeared as a singlet at ~6.7 ppm (Scheme 1).

Consequently we decided to reverse the sequence and alkylate the oxazoline first, followed by nitration. Initial reaction with 3-methyl benzylbromide and 1 equiv LDA at −78 °C to rt provided clean alkylation by TLC. The reaction mixture was further cooled to −78 °C and was treated with LDA followed by n-propyl nitrate. To our satisfaction the desired nitro-intermediate was formed in good yields and with moderate de. Encouraged by this result, we reacted, quite a few alkyl halides with the chiral oxazoline **1**, followed by nitration with n-propylnitrate and LDA (Table 3). The general yields range from 45–76% (entry 1–8) with excellent de (>95%, entries 1–8). The relative configuration of the nitrooxazolines (**15**–**22**) as depicted in the Schemes and Tables was predicted, by the help of Meyers' hypothesis on the mode of substitution on chiral



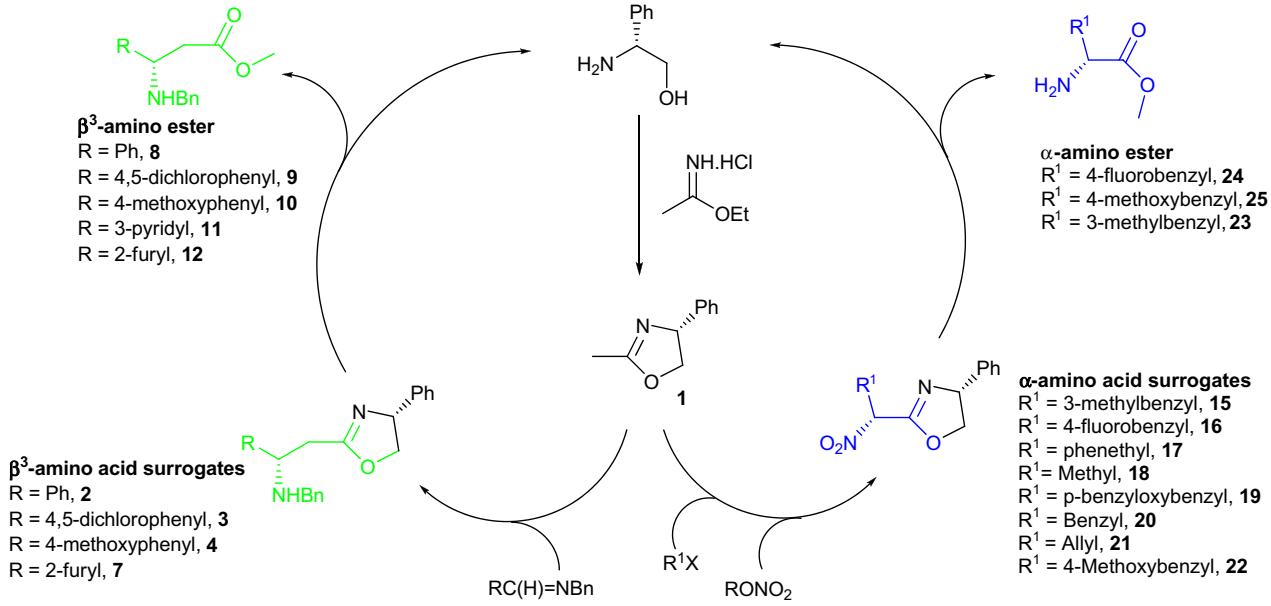
Scheme 1. Dipolar structure of chiral nitro oxazoline.

Table 3
Synthesis of α-amino acid derivatives

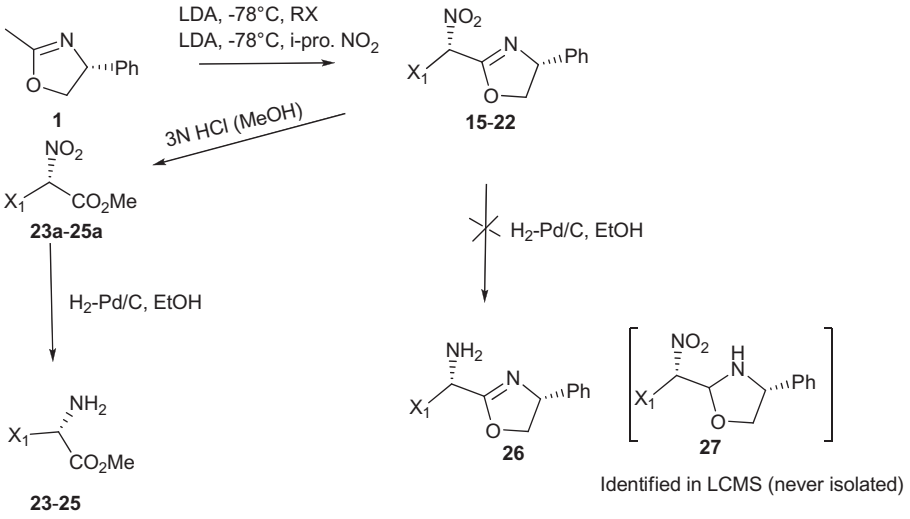
Entry	AAS	Yield[a] (%)	de[b] (%)	Amino esters	Yield[a] (%)	ee[c] (%)
1	**15**	54	99	**23**	43	90
2	**16**	87	99	**24**	68	90
3	**17**	56	99	–	–	–
4	**18**	72	95	–	–	–
6	**19**	86	99	–	–	–
7	**20**	78	95	–	–	–
8	**21**	66	98	–	–	–
9	**22**	66	98	**25**	79	82

[a] Isolated yield.
[b] Determined by HPLC.
[c] Determined by chiral HPLC (CHIRAL PAK AD, 4.6 × 250 mm, 5 μm).

oxazolines. It proposes the absolute configuration of the final acid (in our case ester) by the mode of introduction of new functionalities into the chiral oxazoline. Thus, if the group of lower priority (Cahn-Ingold-Prelog rule) is introduced first, the ester will have **S** configuration, while if the group of higher priority is introduced first, the ester will have ***R*** configuration.[5] Finally, we selected few of the intermediates as representative examples for the final conversion to the amino esters. However efforts toward reduction of the nitro to amine were disappointing, as we observed only the imine reduced oxazolidine intermediate **27** (several hydrogenation conditions and chemical reduction with Zn–AcOH; Sn–AcOH, Fe–HCl were tried). Alternatively we hydrolyzed the oxazoline to the nitro ester



Scheme 2. Reaction cycle for α- and β-amino acid.



Scheme 3. Synthesis of α-amino esters.

(**23a**–**25a**), followed by reduction of NO_2- to NH_2, via Pd-C hydrogenation at atmospheric pressure of H_2.

However, during hydrolysis we observed substantial epimerization (extent of loss of ee ~10–20%) of nitro oxazolines 15, 16 and 22 to the corresponding ester **23a–25a** (Scheme 3). Hence the ee of the final α-amino esters reduced to the range of 80–90% (Table 3).

In this Letter we have exhibited an efficient example of diversity oriented synthesis of α and β-amino acid derivatives (Scheme 2). We have utilized the versatility of chiral bicyclic lactam and the pluripotency of the α-methylene group present in it. We are presently optimizing the conditions for an effective conversion of the α-amino acid surrogates to the final derivatives without decrease in the chiral purity.

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