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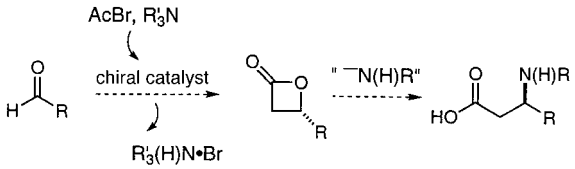
Enantioselective β-Amino Acid Synthesis Based on Catalyzed Asymmetric Acyl Halide – Aldehyde Cyclocondensation Reactions**

Scott G. Nelson* and Keith L. Spencer

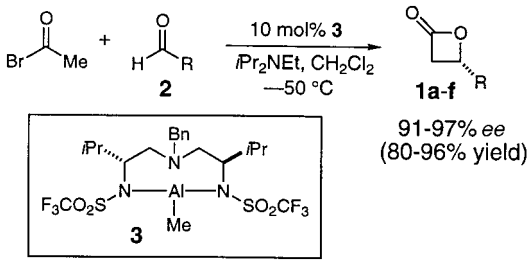
Optically active β-amino acids have become increasingly prevalent features in small-molecule chemotherapeutic agents[1] and are integral components of peptidic materials that have unique structural properties.[2] As a result, efficient and economical preparation of enantiomerically enriched β-amino acids has become the focus of numerous synthesis studies.[3, 4] The amine-mediated S_N2 ring opening of β-lactones presents an especially attractive and straightforward entry to compounds that contain β-amino carbonyl functionalities [Eq. (1)].[5, 6] However, the evolution of this strategy as



(1)

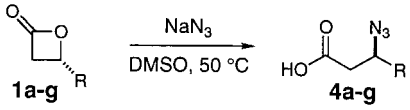
a general asymmetric synthesis of β-amino acids has been limited by the availability of the requisite optically active β-lactone electrophiles.[7] Herein we describe the union of catalytic asymmetric acyl halide – aldehyde cyclocondensation reactions with azide- or sulfonamide-anion-mediated ring opening of the derived enantiomerically enriched β-lactones as an economical and efficient asymmetric synthesis of N-protected β-amino acids.

Catalyzed enantioselective acyl halide – aldehyde cyclocondensation (AAC) reactions have recently been reported to provide convenient access to β-lactones with high enantiomeric purities [Eq. (2)].[8] We envisioned that integrating the



(2)

catalytic asymmetric AAC reaction technology with the reactivity of nitrogen-based nucleophiles toward β-lactones would represent a general asymmetric synthesis of β-amino acid derivatives. Thus, a series of enantiomerically enriched β-lactones **1** were prepared by the asymmetric cyclocondensation of acetyl bromide and a variety of aldehyde electrophiles **2** catalyzed by the Al^{III} triamine complex **3** (Table 1). Based on pioneering observations by the groups of Vederas and Seebach,[5a–c] azide ion was evaluated initially as a suitable nucleophile for effecting the desired S_N2 mode of 2-oxetanone ring opening. Reacting the optically active β-lactones **1a–f** with sodium azide (2.0 equiv) in DMSO (50 °C) promoted efficient S_N2 lactone ring opening to directly afford the β-azido acids **4a–f** in 78 – 95 % yield [Eq. (3)].[9] Azide-induced



(3)

ring opening was insensitive to the structure of the lactone alkyl substituent; lactones bearing aliphatic unbranched, alkoxy-substituted, α-branched,[10] and β-branched alkyl sub-

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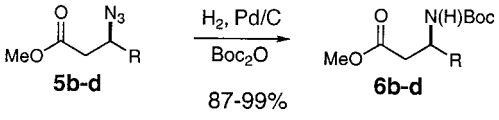
Table 1. Asymmetric catalyzed AAC and azide-mediated ring-opening reactions.

Entry	Aldehyde **2** (R)	*ee* [%] (**1**)[a] (Yield [%])	Yield [%] (**4**)[b] (Config.)	*ee* [%] (**4**)
1	**a** ($BnOCH_2$)	91 (88)	94 (*R*)	92[c]
2	**b** ($PhCH_2CH_2$)	97 (96)	95 (*S*)	93[c]
3	**c** (Me_2CHCH_2)	95 (95)	95 (*S*)	97[d]
4	**d** ($CH_3CH_2CH_2$)	96 (95)	78 (*S*)	
5	**e** ($CH_3(CH_2)_3$)	97 (80)	83 (*S*)	
6	**f** ($CH_2CH(CH_2)_8$)	94 (96)	87 (*S*)	
7	**g** (cC_6H_{11})	99 (48)[e]	93 (*R*)	

[a] Lactones **1** were prepared and assayed by using the procedures described in ref. [8a] (except lactone **1g**). [b] Reported yields are for compounds obtained from the acid–base extractive workup of the azide ring-opening reactions. [c] Enantiomer ratio deteremined by chiral-phase HPLC (Chiralcel OD-H column) of the corresponding methyl ester. [d] Enantiomer ratio deteremined by chiral-phase HPLC (Chiralcel OD-H column) of the corresponding benzyl ester. [e] Lactone **1g** was obtained by the resolution procedure described in ref. [10a].

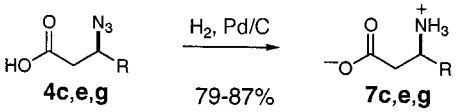
stituents are subject to efficient lactone ring opening with the anticipated inversion of configuration (Table 1).[11] Product isolation and purification was facilitated by acid–base partitioning of the β-azido acid reaction products; the β-azido acids typically emerge from the extractive workup in $>95\%$ purity.[12]

The optically active β-azido acids **4** can be further derivatized or protected to correctly format the carboxylic acid and amino functions for subsequent transformations. Upon converting the azido acids **4b–d** to the corresponding methyl esters **5b–d** (CH_2N_2, Et_2O), transforming the azide residue to the carbamate-protected amine was achieved by catalyzed hydrogenolysis of the β-azido esters **5b–d** in the presence of di-*tert*-butyl dicarbonate (Boc_2O) to afford the *N*-Boc-protected β-amino acid derivatives **6b–d** in 87–99% yield [Eq. (4)].[13] The free β-amino acid salts **7c**, **e**, **g** were



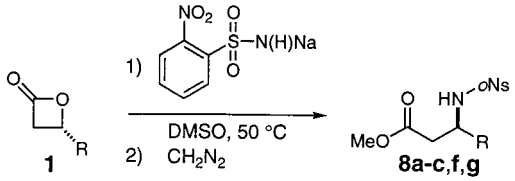
(4)

obtained in 79–87% yield by Pd^0-catalyzed hydrogenolysis of the β-azido acids **4c**, **e**, **g** [Eq. (5)]. Note that the optically active β-azido acids emerge from the lactone ring-opening reaction appropriately derivatized for direct coupling at the carboxylate terminus, while the acid protection–azide reduction sequence formats the resulting β-amino esters for amide-bond construction at the nitrogen terminus.



(5)

In anticipation of the demands that multistep synthesis applications might place on the β-amino acid derivatives emerging from this procedure, we were interested in developing methods for directly installing the protected β-amine function in the correct oxidation state. Ring opening of optically active β-lactones with stabilized amine anions would afford an asymmetric synthesis of β-amino acids in which the nitrogen function would be directly introduced bearing an electron-withdrawing protecting group. Sulfonamide anions were expected to possess the correct electronic properties to allow S_N2 β-lactone ring opening to predominate relative to the alternative ring-opening pathway involving nucleophilic attack at the lactone carbonyl group.[14] Accordingly, the anion derived from *o*-nitrobenzenesulfonamide was selected as a suitable nitrogen nucleophile based on the utility of nosylate (*o*-nitrobenzenesulfonyl, *o*Ns) groups as easily removable nitrogen protecting groups [Eq. (6)].[15] Reacting the enan-



(6)

tiomerically enriched β-lactones **1a–c**, **f** with the sodium salt of *o*-nitrobenzenesulfonamide in DMSO (50 °C) afforded the N-protected β-amino acids **8a–c**, **f** in good yields (64–83%) accompanied by little ($\leq 10\%$) to none of the imide product arising from carbonyl addition (Table 2).[16] Steric bulk

Table 2. Sulfonamide-anion-mediated lactone ring opening.

Entry	Lactone **1** (R)	Yield [%] (**8**)[a] (Config.)	*ee* [%] (**8**)[b] (*ee* [%] (**1**))
1	**a** ($BnOCH_2$)	64 (*R*)	
2	**b** ($PhCH_2CH_2$)	72 (*S*)	≥ 95 (97)
3	**c** (Me_2CHCH_2)	74 (*S*)	93 (95)
4	**f** ($CH_2CH(CH_2)_8$)	83 (*S*)	
5	**g** (cC_6H_{11})	43 (*R*)[c]	≥ 95 (99)

[a] Reported values are for chromatographically purified compounds. [b] Enantiomer ratios deteremined by ^1H NMR analysis of corresponding (*S*)-α-methoxyphenylacetamides; see ref. [16]. [c] 38% of regioisomer formed.

adjacent to the electrophilic carbon atom, however, alters the regioselectivity of nucleophilic addition to the β-lactones; sulfonamide anion addition to the cyclohexyl-substituted lactone **1g** suffers from significant competition between the S_N2 and carbonyl addition reaction pathways (Table 2, entry 5).[17] In this regard, the azide-mediated ring-opening reactions that do not exhibit substrate-dependent regioselectivity represent attractive complements to sulfonamide anion addition reactions. Since *o*-nitrobenzenesulfonyl-protected nitrogen functionalities are conveniently unmasked with thiolate ion, this procedure constitutes a convenient two-step synthesis of versatile N-protected β-amino acids.[18]

The asymmetric AAC–amine ring-opening sequence provides an operationally simple and economical enantioselective synthesis of β-amino acid derivatives. The availability of either enantiomer of the cyclocondensation catalyst **3** affords convenient access to β-amino acids in either enantiomeric series.

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Experimental Section

General procedure for S_N2 addition of NaN_3 to β-lactones **1**: To a solution of NaN_3 (72 mg, 2.0 mmol, 2.0 equiv) in anhydrous DMSO (3.4 mL) at 50 °C was added β-lactone **1** (176 mg, 1.0 mmol, final concentration 0.3 M) by syringe. The resulting homogeneous solution was stirred until all the lactone had been consumed as monitored by TLC (ca. 6 h). After the reaction mixture had been cooled to ambient temperature, saturated aqueous $NaHCO_3$ (3 mL) was added. The resulting heterogeneous mixture was triturated with water until all the precipitated salts dissolved. The resulting mixture was extracted with ethyl acetate (2×5 mL) and the aqueous layer was separated and acidified with 1M HCl. The acidic aqueous layer was extracted with ethyl acetate (3×5 mL) and the combined organic portions were washed with water (2×5 mL) and brine (2×5 mL). The organic portion was dried (Na_2SO_4) and evaporated in vacuo to afford the β-azido acid **4**.

General procedure for S_N2 addition of *o*-nitrobenzenesulfonamide (monosodium salt) to β-lactones **1**: To a suspension of *o*-nitrobenzenesulfonamide (monosodium salt; 700 mg, 3.13 mmol, 2.0 equiv) and activated powdered 4 Å molecular sieves (200 mg) in anhydrous DMSO (5.2 mL, in lactone) at 50 °C was added β-lactone **1** (200 mg, 1.56 mmol, final concentration 0.3 M) by syringe. The resulting suspension was stirred until all the lactone had been consumed as monitored by TLC (ca. 5 h). After the reaction mixture had been cooled to ambient temperature, 1M aqueous HCl (5 mL) was added and the resulting mixture was extracted with ethyl acetate (3×5 mL). The combined organic extracts were washed with water (2×5 mL) and brine (2×5 mL). The organic layer was separated, dried (Na_2SO_4), and concentrated in vacuo to afford a yellow solid. The solid was triturated with chloroform and the insoluble material (*o*-nitrobenzenesulfonamide) removed by filtration. The filtrate was concentrated in vacuo to afford the crude β-sulfonamido acid. The crude acid was dissolved in ethyl acetate and a solution of CH_2N_2 in diethyl ether was added until a yellow color persisted. Glacial acetic acid was added to decolorize the reaction mixture and the volatiles were evaporated in vacuo to afford the β-sulfonamido ester **8** as a yellow oil that was purified by column chromatography (hexanes/ethyl acetate, 65:35).

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[11] The absolute configuration of β-azido acids **4b** – **d** was established by conversion to the corresponding *N*-Boc-protected amino esters **5b** – **d** (1. CH_2N_2; 2. H_2, Boc_2O, Pd/C) and correlation of their optical rotation to those of authentic samples of known configuration. The configuration of azido acid **4e** was established similarly by conversion to the corresponding *N*-Boc-protected amino acid (1. H_2, 10% Pd/C; 2. Boc_2O, Et_3N). The configuration of the remaining β-azido acids (**4a**, **f**, **g**) was assigned by analogy to these determinations.

[12] To verify that lactone ring opening was proceeding with rigorous inversion of configuration, the enantiomeric purities of azides **4a** – **c** were determined by chiral-phase HPLC (Chiralcel OD-H column) of the methyl esters derived from **4a** and **4b**, and the benzyl ester derived from **4c**.

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[16] The enantiomeric purities of the β-sulfonamido esters **8b**, **c**, **g** were determined by integrating representative signals in the ^1H NMR spectrum of the corresponding (*S*)-α-methoxyphenylacetamides. The diastereomeric (*S*)-α-methoxyphenylacetamides were prepared from **8** by sulfonamide deprotection (PhSH, K_2CO_3, DMF) followed by coupling the derived β-amino ester with (*S*)-α-methoxyphenylacetic acid (dicyclohexyl carbodiimide, 5 mol% 4-(dimethylamino)pyridine).

[17] Attempts to introduce carbamate-protected nitrogen residues by addition of benzylcarbamate- or *tert*-butylcarbamate-derived anions afforded β-hydroxy imide products derived from predominant carbonyl addition.

[18] Sulfonamide deprotection (PhSH, K_2CO_3, DMF) of representative β-sulfonamido esters **8** proceeded in 80 – 90% yield.