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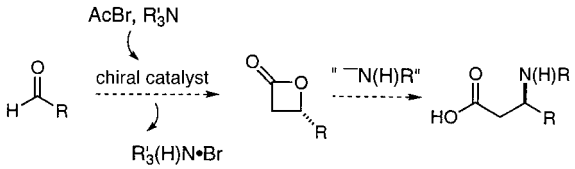
Enantioselective β-Amino Acid Synthesis Based on Catalyzed Asymmetric Acyl Halide – Aldehyde Cyclocondensation Reactions**

Scott G. Nelson* and Keith L. Spencer

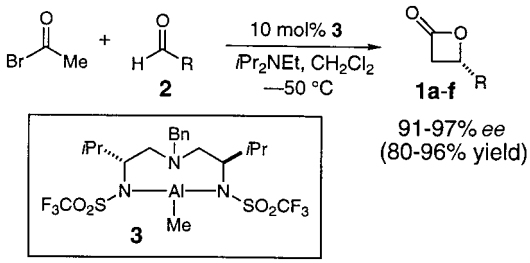
Optically active β-amino acids have become increasingly prevalent features in small-molecule chemotherapeutic agents[1] and are integral components of peptidic materials that have unique structural properties.[2] As a result, efficient and economical preparation of enantiomerically enriched β-amino acids 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)

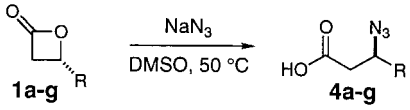
a general asymmetric synthesis of β-amino acids has been limited by the availability of the requisite optically active β-lactone electrophiles.[7] Herein we describe the union of catalytic asymmetric acyl halide – aldehyde cyclocondensation reactions with azide- or sulfonamide-anion-mediated ring opening 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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[**] The National Science Foundation (CHE-9875735) and the University of Pittsburgh are gratefully acknowledged for support of this work. We thank Prof. Peter Wipf for helpful discussions during the preparation of this manuscript.

Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/angewandte/ or from the author.

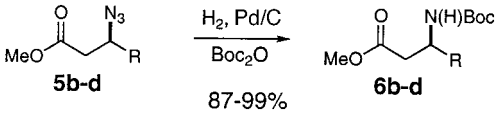
Table 1. Asymmetric catalyzed AAC and azide-mediated ring-opening reactions.

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].

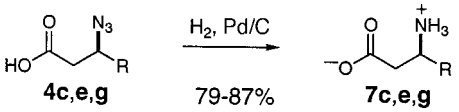
stituents are subject to efficient lactone ring opening with the anticipated inversion of configuration (Table 1).[11] Product isolation and purification was facilitated by acid–base partitioning of the β-azido acid reaction products; the β-azido acids typically emerge from the extractive workup in $>95\%$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



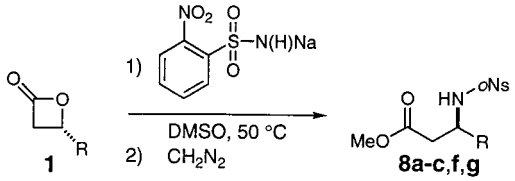
(4)

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.

  0570-0833/00/3907-1324 $ 17.50+.50/0 *Angew. Chem. Int. Ed.* **2000**, *39*, No. 7

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).

Received: October 15, 1999 [Z14153]

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[10] β-Lactones possessing α-branched substituents are not obtained in sufficiently high enantioselectivities from the catalyzed AAC reactions to be generally useful. Lactone **1g** was readily prepared from the enzyme-mediated resolution of the racemic β-lactone that was derived from the achiral AAC reaction, see: a) S. G. Nelson, K. L. Spencer, *J. Org. Chem.* **2000**, *65*, 1227 – 1230; see also: b) N. Sakai, S. Ageishi, H. Isobe, Y. Hayashi, Y. Yamamoto, *J. Chem. Soc. Perkin Trans. 1* **2000**, 71 – 77.

[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.