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Highly Diastereoselective Synthesis of β-Carboxy-γ-lactams and Their Ethyl Esters via $Sc(OTf)_3$-Catalyzed Imino Mukaiyama-Aldol Type Reaction of 2,5-Bis(trimethylsilyloxy)furan with Imines

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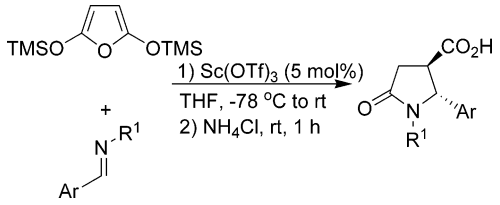
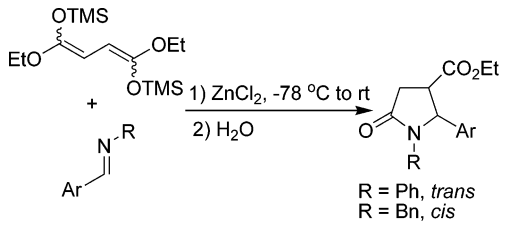


Functionalized γ-lactams are found to be crucial intermediates in the synthesis of biologically important natural products. We herein described a highly diastereoselective synthesis of β-carboxy-γ-lactams and their ethyl ester derivatives, in high yields with high diastereomeric ratio, via the Mukaiyama-aldol type reaction of 2,5-bis(trimethysilyloxy)furan with imines, employing $Sc(OTf)_3$ as a catalyst.

The construction of γ-lactam functionality has been a topic of great interest for many years since the γ-lactam unit is a prominent structural feature found in a number of biologically active natural products.[1] In addition, functionalized γ-lactams have also proven to be attractive synthetic targets, and crucial intermediates in the synthesis of numerous natural products.[1] Therefore, considerable efforts were directed to a great number of synthetic approaches to γ-lactam synthons. As they are considered the general methods for assembling γ-lactam unit, they are based on Rh-catalyzed intramolecular C−H insertion of diazo derivatives,[2] Pd-catalyzed cyclization,[3] *N*-heterocyclic carbene catalyzed addition of enals to imines,[4] addition of homoenolates to imines,[5] ring expansion of β-lactams,[6] and cycloaddition strategies.[7]

Recently, we have developed an alternative approach to β-carboethoxy-γ-lactam synthesis. The methodology is based on the reaction of bis(trimethylsilyloxy)-1,4-diethoxy-1,3-butadiene with imines via imino Mukaiyama-aldol type reaction mediated by $ZnCl_2$. Regarding the stereochemical outcome, the relative stereochemistry of the carboethoxy group at C-β and the aryl group at C-γ depends on the type of substituent on the nitrogen atom of the imines (eq 1).[8]



(1)

We now report our findings on a highly diastereoselective synthesis of the trans isomers of β-carboxy-γ-aryl-γ-lactams and their ethyl esters from the reaction of 2,5-bis(trimethylsilyloxy)furan (**1**) and imines catalyzed by $Sc(OTf)_3$. The 2,5-bis(trimethylsilyloxy)furan (**1**) was prepared according to the previously reported procedure.[9a] It has been used for the synthesis of γ-hydroxybutenolides[9] and as diene for the Diels−Alder reactions.[10] With 2,5-bis(trimethylsilyloxy)furan (**1**) in hand, we next examined the Lewis acid suitable for promoting the reaction. A collection of Lewis acids, i.e., $Ti(O^iPr)_4$ and $M(OTf)_x$, were tested and *N*-benzylimine derived from benzaldehyde was selected as a model substrate (Table 1). Compound **1** was treated with a THF solution of imine **2a** and Lewis acid at −78 °C and the reaction was allowed to proceed at room temperature (16 h). After being exposed to acidic aqueous stirring (NH_4Cl) at room temperature for 1 h followed by conventional workup, it provided γ-lactamcarboxylic acid **3a** with excellent diastereoselectivity (99:1 of trans:cis), which was

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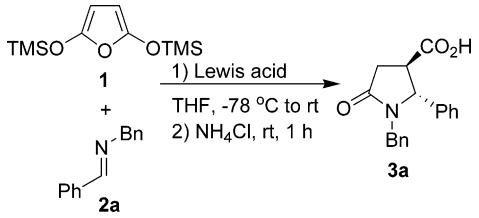
TABLE 1. Screening of Lewis Acids



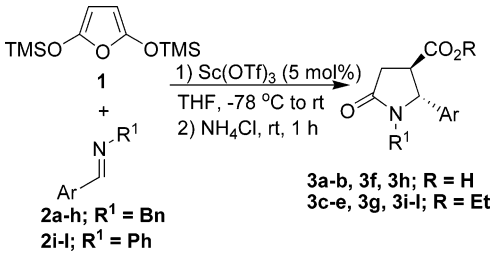
entry	Lewis acid[a]	yield (%);[b] trans:cis[c]
1	$Ti(O^iPr)_4$	60; 99:1
2	$Sc(OTf)_3$	86; 99:1
3	$Yb(OTf)_3$	67; 99:1
4	$Zn(OTf)_2$	74; 99:1
5	$In(OTf)_3$	80; 99:1

[a] 100 mol % for $Ti(O^iPr)_4$ and 5 mol % for $M(OTf)_x$. [b] Isolated yields after crystallization from ^{i}PrOH. [c] Determined by integration of the ^{1}H NMR (300 MHz) spectra of the crude products before crystallization.

determined by integration of the ^{1}H NMR (300 MHz) spectra of the crude product. Pure *trans*-**3a**, with yields ranging from 60% to 86% depending on the types of Lewis acid employed, was obtained after single crystallization from ^{i}PrOH. A stoichiometric amount of $Ti(O^iPr)_4$ showed moderate reactivity, affording lactam **3a** in moderate yield (60%, Table 1, entry 1). Metal triflates, $Yb(OTf)_3$, $Zn(OTf)_2$, $In(OTf)_3$, and $Sc(OTf)_3$, as catalysts gave better results (67−86%, Table 1, entries 2−5). Among these, $Sc(OTf)_3$ was found to be the best catalyst. In addition, $Sc(OTf)_3$-catalyzed Mukaiyama-aldol reactions and imine activation are extensively documented.[11]

The $Sc(OTf)_3$-catalyzed imino Mukaiyama-aldol type reaction of 2,5-bis(trimethylsilyloxy)furan (**1**) was further studied with other imine substrates and the results were summarized in Table 2. The diastereomeric ratios in all cases as shown in Table 2 were established from the ^{1}H NMR integration of the crude materials of the γ-lactamcarboxylic acids. The γ-lactam products were isolated either as the carboxylic acid derivative in the case when the crystallization was allowed or as ethyl ester by exposure of the crude mixture to $SOCl_2$ (3 equiv) in ethanol, −78 °C to room temperature for 5 h, followed by chromatographic purification and crystallization. Measurement of the diastereomeric ratios of the ethyl ester derivatives by ^{1}H NMR integration of the crude materials confirmed that no epimerization took placed under the esterification reaction conditions employed. Finally, relative stereochemistry of the γ-lactam products was established and assigned by analogy with our previous work.[8] Generally, *N*-benzylimine substrates (Table 2, entries 1−8) produced γ-lactam products with good to moderate yields (63−89%) with high diastereoselectivity (trans:cis = 99:1) except for *N*-benzylimine derived from 3,4-dimethoxybenzaldehyde (Table 2, entry 4, inseparable mixture of trans:cis = 90:10). From the experimental results, there is no obvious relationship between the electron density of the Ar group of the arylimine substrates and the yields of the corresponding γ-lactam products. The reaction of *N*-phenylimime also proceeded under the same reaction conditions, however,

TABLE 2. $Sc(OTf)_3$-Catalyzed Reaction of Compound 1 with Imines 2a−*l*



entry	imine 2	imine Ar	lactam 3	yield (%);[a] trans:cis[b]
1	**2a**	C_6H_5	**3a**	86; 99:1
2	**2b**	4-$MeOC_6H_4$	**3b**	72; 99:1
3	**2c**	3-$MeOC_6H_4$	**3c**	74; 99:1
4	**2d**	3,4-$(MeO)_2C_6H_3$	**3d**	65; 90:10
5	**2e**	4-MeC_6H_4	**3e**	70; 99:1
6	**2f**	4-ClC_6H_4	**3f**	89; 99:1
7	**2g**	4-$NO_2C_6H_4$	**3g**	63; 99:1
8	**2h**	2-furyl	**3h**	75; 99:1
9	**2i**	C_6H_5	**3i**	60; 80:20
10	**2j**	4-$MeOC_6H_4$	**3j**	70; 80:20
11	**2k**	3,4-$MeOC_6H_3$	**3k**	60; 80:20
12	**2*l***	4-ClC_6H_4	**3l**	65; 90:10

[a] Isolated yields of the acid or ethyl ester derivatives. [b] Determined by integration of the ^{1}H NMR (300 MHz) spectra of the crude lactamcarboxylic acids before crystallization or exposure to esterification.

with lower yields and diminished diastereoselectivity (60−70% yields with trans:cis = 80:20 to 90:10; Table 2, entries 9−12). These results are in sharp contrast to our earlier work on the $ZnCl_2$-catalyzed reaction of bis(trimethylsilyloxy)-1,4-diethoxy-1,3-butadiene with *N*-benzyl- and *N*-phenylimimes (eq 1).[8] It is worth emphasizing that in the present work the trans isomer is preferentially formed regardless of the type of substituent (phenyl or benzyl) on the imine nitrogen. Even though the diastereoselectivities are moderate in case of *N*-phenylamine, pure diastereomer can be obtained by simple chromatographic purification.

On the basis of our previous report and our current studies, the possible mechanistic pathway of the imino Mukaiyama-aldol reaction of 2,5-bis(trimethylsilyloxy)furan (**1**) and imines catalyzed by $Sc(OTf)_3$ is illustrated in Scheme 1. The reaction was proposed to proceed via the staggered acyclic transition state.[12] It is assumed that the $Sc(OTf)_3$ occupied a coordination site on the nitrogen atom of the imine such that it is cis to the Ar group of the imine carbon. Now 2,5-bis(trimethylsilyloxy)furan (**1**) can approach the imine by transition state **4A** or **4B**. It is envisioned that the diastereoselectivity was governed by the steric effect caused by repulsion interaction of the $Sc(OTf)_3$ and the carbon atom (C_β) of the furan ring. Therefore, transition state **4A** is more favorable by positioning the least steric hydrogen atom at C_β of the furan ring being cis to the $Sc(OTf)_3$, leading preferably to trans γ-lactam after aqueous workup. The reaction of *N*-phenylimines with compound **1** leading to lower diastereoselection may result from slow cyclization due to the low nucleophilicity of the nitrogen atom. Thus, the equilibration at the stereogenic α-carbon adjacent to the anhydride group occurred.

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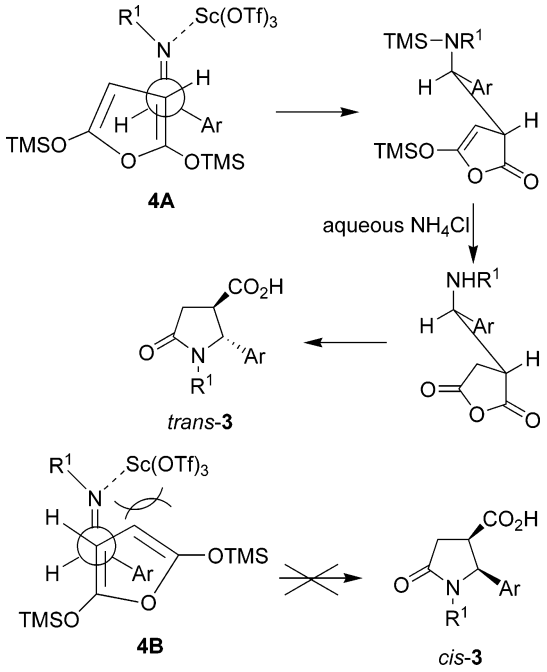
SCHEME 1



In summary, we have developed an efficient and highly diastereoselective synthesis of β-carboxy-γ-aryl-γ-lactams and their ethyl esters from the reaction of 2,5-bis(trimethylsilyloxy)-furan and imines catalyzed by $Sc(OTf)_3$. The methodology offers an alternative and efficient method for the synthesis of functionalized γ-lactams in terms of simplicity of the procedure, readily available starting materials, mild reaction conditions, and high diastereoselectivity. A study of the enantioselective synthesis of this type of γ-lactam is currently underway.

Experimental Section

General Procedure for the Reaction of 2,5-Bis(trimethylsilyloxy)furan (1) with Imines, Using $Sc(OTf)_3$ as a Catalyst. To a 50 mL round-bottomed flask charged with $Sc(OTf)_3$ (49 mg, 0.05 mmol) was added a solution of imine (1 mmol) in THF (1 mL) at room temperature. The mixture was further stirred at room temperature under an argon atmosphere for 30 min. The mixture was brought to −78 °C (dry ice−acetone) and a solution of 2,5-bis(trimethylsilyloxy)furan (**1**) (0.244 g, 1 mmol) in THF (2 mL) was added dropwise. The resulting mixture was slowly warmed to room temperature and stirred overnight. After 16 h, saturated aqueous NH_4Cl (2 mL) was added and the mixture was stirred at room temperature for 1 h before it was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with water (3 × 30 mL) and brine (30 mL) and dried over anhydrous Na_2SO_4. Removal of solvents (aspirator then vacuo) yielded a crude γ-lactamcarboxylic acid whose diastereomeric ratio was determined by ^{1}H NMR integration. The crude material was purified by crystallization to yield the acid derivative or conversion to ethyl ester derivative ($SOCl_2$, EtOH, −78 °C to rt) before chromatographic purification when the crystallization of the first formed acid was found difficult.

Preparation of 1-Benzyl-5-oxo-2-phenylpyrrolidine-3-carboxylic Acid (3a). To a 50 mL round-bottomed flask charged with $Sc(OTf)_3$ (49 mg, 0.05 mmol) was added a solution of imine **2a** (0.195 g, 1 mmol) in THF (1 mL) at room temperature. The mixture was further stirred at room temperature under an argon atmosphere for 30 min. The mixture was brought to −78 °C (dry ice−acetone) and a solution of 2,5-bis(trimethylsilyloxy)furan (**1**) (0.244 g, 1 mmol) in THF (2 mL) was added dropwise. The resulting mixture was slowly warmed to room temperature and stirred overnight. After 16 h, saturated aqueous NH_4Cl (2 mL) was added and the mixture was stirred at room temperature for 1 h before it was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with water (3 × 30 mL) and brine (30 mL) and dried over anhydrous Na_2SO_4. After removal of the solvents, the diastereomeric ratio of the crude γ-lactamcarboxylic acid **3a** was determined by ^{1}H NMR integration to consist of a 99:1 mixture of trans:cis isomer. A pure trans isomer of **3a** was obtained after single crystallization from ^{i}PrOH (0.253 g, 86%, mp 171−172 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−6.95 (m, 10H), 5.09 (d, J = 14.7 Hz, 1H), 4.63 (d, J = 5.6 Hz, 1H), 3.47 (d, J = 14.7 Hz, 1H), 3.15−3.05 (m, 1H), 3.00−2.75 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7, 173.0, 138.6, 135.4, 129.2, 128.7, 128.6, 128.4, 127.7, 127.0, 63.5, 45.6, 44.5, 33.5. IR (KBr) ν_{max} 3448, 3033, 1731, 1655 cm^{-1}. MS m/z (%) relative intensity 296 ([M + 1]$^+$, 5), 295 ([M]$^+$, 30), 204 (100), 147 (22), 146 (51), 132 (29), 119 (19), 118 (60), 117 (13), 115 (22), 104 (45), 91 (42), 77 (11), 65 (14). HRMS (ESI-TOF) calcd for $C_{18}H_{17}NO_3Na$ [M + Na]$^+$ 318.1106, found 318.1110.

Preparation of Ethyl 5-Oxo-1,2-diphenylpyrrolidine-3-carboxylate (3i). To a 50 mL round-bottomed flask charged with $Sc(OTf)_3$ (49 mg, 0.05 mmol) was added a solution of imine **2i** (0.185 g, 1 mmol) in THF (1 mL) at room temperature. The mixture was further stirred at room temperature under an argon atmosphere for 30 min. The mixture was brought to −78 °C (dry ice−acetone) and a solution of 2,5-bis(trimethylsilyloxy)furan (**1**) (0.244 g, 1 mmol) in THF (2 mL) was added dropwise. The resulting mixture was slowly warmed to room temperature and stirred overnight. After 16 h, saturated aqueous NH_4Cl (2 mL) was added and the mixture was stirred at room temperature for 1 h before it was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with water (3 × 30 mL) and brine (30 mL) and dried over anhydrous Na_2SO_4. After removal of the solvents, the diastereomeric ratio of the crude γ-lactamcarboxylic acid was determined by ^{1}H NMR integration to consist of an 80:20 mixture of trans:cis isomers. The ethyl ester derivative was then prepared according to General Procedure A: Thionyl chloride (0.2 mL, 3 mmol) was added dropwise to a stirred −78 °C dry EtOH (20 mL) solution. To this mixture was added a solution of a crude γ-lactamcarboxylic acid in dry EtOH (5 mL). The reaction mixture was allowed to warm to room temperature under an argon atmosphere. After 5 h, EtOH was removed (aspirator). The residue was quenched by slow addition of saturated aqueous Na_2CO_3 at 0 °C. The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with H_2O (25 mL) and brine (25 mL), dried (Na_2SO_4), filtered, and concentrated. A crude ethyl ester residue was purified by preparative thin-layer chromatography (SiO_2, 20% EtOAc in hexanes, triple runs). The higher R_f was *trans*-**3i** (0.161 g, 52%, a pale yellow solid, mp 115−116 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, J = 7.6 Hz, 2H), 7.35−7.19 (m, 7H), 7.06 (t, J = 7.5 Hz, 1H), 5.53 (d, J_{trans} = 4.6 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.20−2.80 (m, 3H), 1.27 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.15, 172.09, 139.7, 137.5, 129.0, 128.7, 128.2, 126.1, 125.3, 122.7, 65.8, 61.6, 46.4, 34.3, 14.1. IR ($CHCl_3$) ν_{max} 1731 (C═O of ester), 1698 (C═O of amide) cm^{-1}. MS m/z (%) relative intensity 310 ([M + 1]$^+$, 24), 309 ([M]$^+$ 97), 236 (100), 208 (99), 180 (71), 91 (24), 77 (38), 50 (11). Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.79; H, 6.25; N, 4.41. The lower R_f was *cis*-**3i** (25 mg, 8%, a pale yellow oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, J = 7.9 Hz, 2H) 7.35−7.10 (m, 7H), 7.06 (t, J = 7.3 Hz, 1H), 5.48 (d, J_{cis} = 8.8 Hz, 1H), 3.88−3.65 (m, 3H), 3.32 (dd, J = 17.3, 10.2 Hz, 1H), 2.72 (dd, J = 17.3, 8.8 Hz, 1H), 0.99 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 169.5, 137.8, 136.2, 128.7, 128.62, 128.60, 127.0, 125.3, 122.1, 65.1, 61.0, 43.7, 32.9, 13.7. IR (neat) ν_{max} 1732 (C═O of ester), 1707 (C═O of amide) cm^{-1}. MS m/z (%) relative

intensity 310 ([M + 1]$^+$, 29), 309 ([M]$^+$, 75), 281 (51), 236 (100), 208 (78), 91 (21), 77 (33), 65 (3). HRMS (ESI-TOF) calcd for $C_{19}H_{19}NO_3Na$ [M + Na]$^+$ 332.1263, found 332.1263.

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Supporting Information Available: Experimental details and characterization data of compound **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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