Diastereoselective Povarov-Like Reaction Involving *O*-Pivaloylated D-Galactosylimine

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Abstract: A diastereoselective Povarov-like reaction using *O*-pivaloylated β -D-galactosylamine as the chiral auxiliary is described. The three-component reaction of chiral aldimines, cyclic enol ethers and nucleophiles afforded the desired products in good yields and high content of the main isomer. This procedure provides an efficient method to obtain multifunctional molecules carrying three contiguous chiral centers in high stereoselectivity.

Keywords: asymmetric synthesis; carbohydrate auxiliary; multicomponent reactions; Povarov-like reactions; scandium triflate [Sc(OTf)₃]

The Povarov reaction, the condensation of an imine with an activated olefin, (Scheme 1, Eq. 1), has been widely used in the synthesis of tetrahydroquinoline



Scheme 1. Povarov and Povarov-like reactions.

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by Jacobsen.^[1e] In recent years, reactions trapping the oxocarbonium intermediate by an internal^[2] (Eq. 2) or external^[3] (Eq. 3) nucleophile have been developed, which are called Povarov-like reactions. Multicomponent reactions (MCRs) have many advantages, such as operational simplicity, atom economy, high efficiency of bond formation, and the access to molecular complexity from simple starting materials.^[4] The multicomponent Povarov-like reactions have been used as powerful synthetic approches to prepare structurally diverse oxacyclic scaffolds in good yields and moderate to excellent diastereomeric selectivity.^[5] For example, 4-aminobenzopyran derivatives were obtained in moderate to excellent stereoselectivity using this strategy.^[6] However, the optimal reaction conditions of Povarov-like reactions in the presence of an external nucleophile have not been systematically investigated so far.

derivatives,^[1] a representative example was reported

Carbohydrate moities have been used as effective chiral auxiliaries in many asymmetric syntheses.^[7] A remarkable example is the O-pivaloylated β -D-galactosylamine, which has been used in a variety of reactions such as Strecker reaction,^[8] Ugi reaction,^[9] Mannich reaction,^[10] and hetero-Diels-Alder reaction.^[11] Chiral homoallyl amines,^[12] α-aminophosphonic acid derivatives.^[13] and α -amino(phenyl)methyl-(phenyl)phosphinic acids^[14] were synthesized with the assistance of this chiral amine. Previous reports^[15,16] also demonstrated that O-pivaloylated β -D-galactosylamine could be used for the induction of crucial chiral centers in alkaloids through domino Mannich-Michael reactions. Recently, the asymmetric aza-Friedel-Crafts reaction of indoles assisted by O-pivaloylated β -D-galactosylamine has been reported with excellent yield and diastereoselectivity.^[17] The use of Opivalovlated β -D-galactosylamine as chiral template to promote high enantioselectivity has been well defined.



OPiv OPiv OPiv OPi റ 2a n1 equiv. Sc(OTf)₃ n₃ equiv OPiv solvent, temp OPiv MeOH 3a n2 equiv. 4aa 1a NO Content [%]^[c] Entry^[a] Yield [%][b] 2a [equiv.] 3a [equiv.] Sc(OTf)₃ [equiv.] 2 3 1 0.2 59 5 2 7.5 55 0.2 1 59 3 1.5 0.2 89.0 4 1 1.5 0.5 76 87.5 5 1 1.5 1.0 76 84.8

Table 1. Optimization of the reaction conditions for the three-component Povarov-like reaction.

^[a] All reactions were carried out with 0.15 mmol of **1a** (1 equiv.), at -78 °C in 1 mL dry dichloromethane for 72 h.

^[b] Isolated yield by column chromatography.

^[c] Content of the main product was determined by HPLC.

Herein, we describe the optimal reaction conditions of a Povarov-like three-component reaction of an Opivaloylated β -D-galactosylimine, a cyclic enol ether, and an alcoholic nucleophile.

We initially investigated the reaction of O-pivaloylated N-galactosylimine **1a** ($R^1 = NO_2$), 3,4-dihydro-2H-pyran (2a) and an excess of methanol (3a) (Scheme 1). Various ratios of 1a, 2a and 3a were investigated. The reactions were carried out at -78 °C with the catalysis by $Sc(OTf)_3$. The results revealed that good yield (76%) and high stereoselectivity (main product content 87.5%) were obtained when 1.0 equivalent of 2a, 1.5 equivalents of 3a and 0.5 equivalents of $Sc(OTf)_3$ were used (Table 1, entry 4). We found that increased amounts of 2a and **3a** resulted in lower yields (Table 1, entries 1 and 2). When the catalyst loading was increased to 0.5 equiv., the yield increased obviously but the diastereoselectivity decreased slightly (Table 1, entry 4). However, the yield did not increase and the diastereoselectivity decreased slightly when the catalyst was increased to 1.0 equiv. (Table 1, entry 5).

After optimizing the ratios of reaction components, we next identified the most suitable Lewis acid catalyst for the reaction of **1b**, **2a** and **3a**. The results showed that iron trichloride, zinc triflate, copper triflate, stannic chloride and indium trichloride provided lower yields of the product **4ba** than $Sc(OTf)_3$ (Table 2, entries 1–6). Therefore, $Sc(OTf)_3$ was the most suitable Lewis acid to catalyze the reaction. We then optimized the solvent and temperature for the reaction. The results indicated that reactions in dichloromethane, acetonitrile, 1, 2-dichloroethane and tetrahydrofuran produced **4ba** in very low yields even when the temperature was increased to -40 °C (Table 2, entries 7–10). Fortunately, when the reaction was carried out in chloroform at -40 °C, the yield increased to 82% (Table 2, entry 11). We also decreased the reaction temperature from -40 °C to -60 °C and increased the reaction time from 24 h to 48 h; the reaction proceeded smoothly with a slight decrease of yield (Table 2, entry 12). But there was no significant difference in the contents of the main product obtained at -40 °C and -60 °C (Table 2, entries 11 and 12). Considering reaction time, yield and diastereoselectivity, the optimal conditions were defined as 0.5 equiv. Sc(OTf)₃, 1.0 equiv. **2** and 1.5 equiv. **3** in dry chloroform at -40 °C for 24 h.

Under the optimized conditions, the generality of this method was examined with various aldimines, cyclic enol ethers and nucleophiles. The results are summarized in Table 3. We found that O-pivaloylated β -D-galactosylimine **1**, bearing electron-withdrawing groups such as nitro-, cyano- and halogen element groups, produced the corresponding asymmetric products in moderate to good yields and good to high diastereoselectivity. When an external nucleophile, methanol, was used, a relatively low content of the main isomer was obtained under the optimized conditions (Table 3, entries 2 and 3). However, when isopropyl alcohol was used as the nucleophile, higher yields and diastereoselectivity were observed (Table 3, entries 4) and 5), which indicated that the steric hindrance of the nucleophiles had a significant effect on diastereoselectivity. Particularly, this reaction was efficient when dihydrofuran was used.

The content of the main isomer of the desired product **4** was determined by HPLC after purification by chromatography. Three chiral centers are created during the reaction. There are eight possible diastereomers, which are *RRR*, *SRR*, *SSR*, *SSS*, *SRS*, *RRS*, *RSR* and *RSS*. Diastereomerically pure product, for





Entry ^[a]	Solvent	Time [h]	Lewis Acid	Temperature [°C]	Yield [%] ^[b]
1	CH ₂ Cl ₂	96	FeCl ₃	-78	17
2	CH ₂ Cl ₂	72	$Zn(OTf)_2$	-78	trace
3	CH_2Cl_2	72	$Cu(OTf)_2$	-78	trace
4	CH_2Cl_2	72	SnCl ₄	-78	28
5	CH_2Cl_2	72	InCl ₃	-78	34
6	CH_2Cl_2	72	$Sc(OTf)_3$	-78	41
7	CH_2Cl_2	24	$Sc(OTf)_3$	-40	45
8	CH ₃ CN	24	$Sc(OTf)_3$	-40	35
9	$Cl(CH_2)_2Cl$	24	$Sc(OTf)_3$	-35 ^[c]	49
10	THF	24	$Sc(OTf)_3$	-40	25
11	CHCl ₃	24	$Sc(OTf)_3$	-40	82 ^[d]
12	CHCl ₃	48	$Sc(OTf)_3$	-60	80 ^[e]

^[a] All reactions were carried out with 0.15 mmol of **1b**, 1 equiv. of **2a**, 1.5 equiv. of **3a** and 0.5 equiv. of Lewis acid in 1 mL dry solvent.

^[b] Isolated yield by column chromatography.

^[c] The melting point of ClCH₂CH₂Cl is -40 °C.

^[d] Content of the main product among the eight possible isomers is 83.6% determined by HPLC.

^[e] Content of the main product among the eight possible isomers is 85.3% determined by HPLC.

Table 3. The three-component Povarov-like reaction of O-pivaloylated β -D-galactosylimines.



Entry ^[a]	n	\mathbf{R}^1	\mathbb{R}^2	Yield [%] ^[b]	Content [%] ^[c]
1	2	NO_2	Me (4aa)	85	90.2
2	2	F	Me (4ca)	74	86.1
3	2	Cl	Me (4ba)	82	83.6
4	2	F	<i>i</i> -Pr (4fa)	87	94.7
5	2	Cl	<i>i</i> -Pr (4ea)	84	95.7
6	2	Br	<i>i</i> -Pr (4ga)	86	94.7
7	2	NO_2	<i>i</i> -Pr (4da)	80	$92.4 (> 99^{[d]})$
8	2	CN	<i>i</i> -Pr (4ha)	81	96.7
9	1	NO_2	Me (4ab)	90	90.7
10	1	NO_2	<i>i</i> -Pr (4db)	82	96.1
11	1	F	<i>i</i> -Pr (4fb)	76	91.9
12	1	Cl	<i>i</i> -Pr (4eb)	73	99.1
13	1	Br	<i>i</i> -Pr (4gb)	77	98.6

^[a] All reactions were carried out with 0.15 mmol of **1**, 1 equiv. of **2**, 1.5 equiv. of **3** and 0.5 equiv. of Sc(OTf)₃ in 1 mL dry CHCl₃.

^[b] Isolated yield by column chromatography.

^[c] Content of the main product among the eight possible isomers is determined by HPLC.

^[d] Content was determined by HPLC after simple recrystallization.



4ea: 95.7% content.

Scheme 2. Release of the chiral auxiliary.

example 4da (Table 3, entry 6), could be obtained after a simple recrystallization from ethanol and water.

To prepare the final product, we tested different methods to remove the auxiliary. The typical method with hydrochloric acid in methanol was not successful. We later used acetic acid-water after treatment with sodium methoxide in methanol^[13,17] (Scheme 2) which generated the desired products 5ea with high yields and without racemization. The enantiomeric ratio (er) was determined by chiral HPLC.

X-Ray diffraction analysis of a single crystal of 4aa was performed to determine the absolute configuration of the main isomer. The crystal structure of 4aa (Figure 1) shows that the absolute configuration of the main diastereomer, 2-methoxy-3-[4-nitrophenyl-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactosylamino)methyl]tetrahydro-2*H*-pyran, is $\beta SRS^{[19]}$

Based on these results, a possible reaction mechanism (Figure 2) was proposed. The preferred formation of diastereomer 4 can be explained by the postulated transition state. The scandium atom should adopt an octahedral coordination in the transition



Figure 1. X-ray structure of the product 4aa.^[18]

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Figure 2. Proposed reaction transition state.

state as shown in Figure 2.^[20] Avoiding the steric hindrance of the pivaloyl group in aldimine 1, the cyclic enol ether attacks the imine carbon from the Si face of the C=N plane. The generated oxocarbonium intermediate is subsequently attacked by the alcohol from the backside of the oxygen heterocycle, which leads to the preferred formation of diastereomer 4. The proposed mechanism indicates that the pivaloyl group plays a critical role in controlling the stereochemistry of the reaction.

In conclusion, we have optimized the reaction conditions of three component Povarov-like reactions and developed an efficient method for the preparation of chiral 2-alkoxy-3-phenyl(amino)methyltetrahydro-2H-pyran (or furan) derivatives with Sc- $(OTf)_3$ as catalyst and using *O*-pivaloylated- β -D-galactosylimine as a chiral auxiliary. High yield and diastereoselectivity were obtained with yields up to 90% and contents of the main isomer up to 99%. The octahedral coordination intermediate, which is formed with $Sc(OTf)_3$, controls the configuration of the reaction product.

Experimental Section

General Procedure for the Three-Component Povarov-Like Reaction

An oven-dried, 10-mL vial was charged with O-pivaloylated β -D-galactosylimine (0.15 mmol)and Sc(OTf)₃ (0.075 mmol). After the vessel was treated with alternating vacuum and nitrogen purge, 1 mL of dry choroform was added via a syringe, and the mixture was stirred under nitrogen at -40°C for 15 min before 3,4-dihydro-2H-pyran or 2,3-dihydro-2H-furan (0.15 mmol) and methanol or isopropyl alcohol (0.225 mmol, 1.5 equiv.) were added. The resulting solution was stirred for the indicated time until the reaction was complete as shown by TLC (usually 24 h). Then three drops of triethylamine were added and the mixture was gradually warmed to room temperature. After extraction with dichloromethane, the organic layer was washed with saturated aqueous sodium bicarbonate, dried over magnesium sulphate, filtered, and the volatiles were removed under vacuum. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 15/1), yielding the corresponding compounds 4aa-gb as a mixture

of 4–8 diastereomers (clean NMR spectra were obtained for 11 of 13 products).

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