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Asymmetric Hydrogenation of α-Primary and Secondary Amino Ketones: Efficient Asymmetric Syntheses of (−)-Arbutamine and (−)-Denopamine

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Abstract: Two β-receptor agonists (−)-denopamine and (−)-arbutamine were prepared in good yields and enantioselectivities by asymmetric hydrogenation of unprotected amino ketones for the first time by using Rh catalysts bearing electron-donating phosphine ligands. A series of α-primary and secondary amino ketones were synthesized and hydrogenated to produce various 1,2-amino alcohols in good yields and with good enantioselectivies. This Rh electron-donating phosphine-catalyzed asymmetric hyderogenation represents one of the most promising and convenient approaches towards the asymmetric synthesis of chiral amino alcohols.

Keywords: amino alcohols · asymmetric catalysis · enantioselectivity · hydrogenation · ketone

Introduction

Chiral 1,2-amino alcohols are important building blocks for a large number of pharmaceutical and natural products,[1] such as arbutamine, denopamine, dexsotalol, and nebivolol. The efficient preparation of enantiomerically pure 1,2-amino alcohols is one of the most challenging tasks in organic synthesis. Among various synthetic methods, transition-metal-catalyzed asymmetric hydrogenation of corresponding α-amino ketones represents one of the most effective and promising approaches.[2] Despite the remarkable success achieved by Noyori and others in the Ru-catalyzed hydrogenation of tertiary or N-acyl amino ketones,[3] direct asymmetric hydrogenation of unprotected primary and secondary amino ketones has been less extensively studied and only limited substrate scope has been reported.[4] A hydrogenation method without protection–deprotection of the amino group is highly desired for the practical syntheses of useful molecules bearing amino alcohol moieties. One of the major concerns of this methodology is that the unprotected amine group can poison the transition-metal catalysts and result in low catalytic activity. Recently, we have revealed that electron-donating phosphines, such as TangPhos (1,1′-di-*tert*-butyl-[2,2′]-diphospholane), DuanPhos (2,2′-di-*tert*-butyl-2,3,2′,3′-tetrahydro-1*H*,1′*H*-[1,1′]biisophosphindolyl), binapine (4,4′-di-*tert*-butyl-4,4′,5,5′-tetrahydro-3,3′-bi-3*H*-dinaphtho[2,1-*c*:1′,2′-*e*]phosphesin), and DuPhos (1,2-bis(2,5-dimethylphospholano)benzene) could facilitate the dissociation of the amine group[2d,5] and their Rh complexes could serve as good catalysts in the asymmetric hydrogenation of unprotected β-amino ketones.[5b] As a result of our extended studies, herein, we would like to report our asymmetric syntheses of two β-receptor agonists, (−)-denopamine and (−)-arbutamine based on an efficient hydrogenation of unprotected α-amino ketones. The scope of this methodology was also explored with Rh catalysts bearing various electron-donating phosphine ligands on both α-primary and secondary amino ketones. In most cases, high enantioselectivities and catalyst activities (up to 95% *ee*, 4000 TON; *ee* = enantiomeric excess) were achieved.

Results and Discussion

(−)-Denopamine and (−)-arbutamine are useful β-receptor agonists for the treatment of congestive heart failure and were chosen as the synthetic targets for our direct hydrogenation method. Some conventional syntheses of these com-

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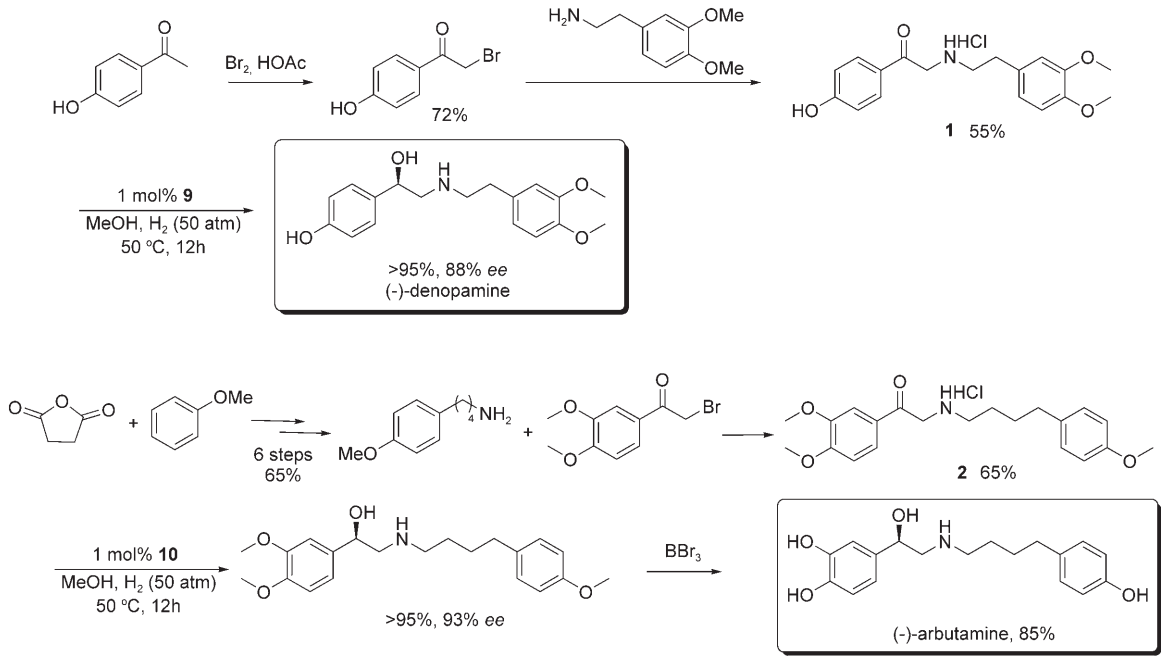
Supporting information for this article contains compound characterization data and is available on the WWW under http://www.chemeurj.org/ or from the author.

pounds involved optical resolution.[6] A few asymmetric approaches with organometallic catalysts were also reported with either moderate selectivities or tedious protection and deprotection steps.[3a,7] To explore the direct hydrogenation strategy, two corresponding prochiral amino ketones **1** and **2** were synthesized and subjected to hydrogenation (Scheme 1). After a survey of the Rh catalysts bearing electron-donating phosphines from both our lab and commercial sources, we were pleased to find that good yields of the amino alcohol products were obtained in general and the best enantioselectivities were achieved with Me-DuPhos and Et-DuPhos.[8] Thus, (−)-denopamine and (−)-arbutamine were synthesized efficiently in good overall yields and enantioselectivities. Although the enantioselectivities could be improved further for practical applications, the current results clearly elucidate the potentness of the asymmetric hydrogenation of unprotected α-amino ketones as a convenient approach for the synthesis of chiral bioactive molecules containing 1,2-amino alcohol functionalities.

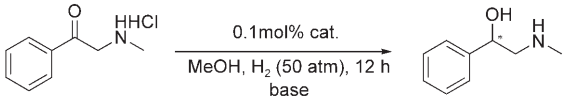
The results from the syntheses of (−)-denopamine and (−)-arbutamine prompted us to explore the scope of the hydrogenation of unprotected α-amino ketones in detail. Thus, a number of α-secondary amino ketones were synthesized and studied in the hydrogenation reaction. The 2-methylaminoacetophenone hydrochloride (**3a**) was chosen as the standard substrate to optimize the hydrogenation conditions. Among all the catalysts screened, [Rh(binapine)(cod)]·BF_4 (**5**) (cod = cyclooctadiene) exhibited the best enantioselectivity (>95% yield, 95% *ee*, Table 1, entry 1). Pd or Ir catalysts with a binapine ligand did not exhibit any activity (entries 5 and 6). Notably lower *ee* values were observed with [Rh(Me-DuPhos)(cod)]·BF_4 (**9**), [Rh(Et-DuPhos)(cod)]·BF_4 (**10**), and [Rh(DuanPhos)(cod)]·BF_4 (**11**) (85, 89, and 40% *ee*, respectively, entries 7–9). Adjusting the hydrogen pressure and reaction temperature did not affect the *ee* or yield when 1.0 mol% catalyst was used. The hydrogenation reaction was also largely solvent dependent. Methanol was the only solvent that gave both good *ee* values and complete conversions during our screening. Other solvents, such as ethanol and 2,2,2-trifluoroethanol provided diminished results. The effect of the base in the hydrogenation reaction was also examined. Organic bases such as triethyl amine (TEA) and strong inorganic bases such as $CsCO_3$ and KO*t*Bu only resulted in undesired dark gummy products (entries 10–12). Taken together with the literature reports,[9] these observations strongly implied that the fast neutralization of the substrates would generate a high concentration of free amino ketones which would undergo side reactions competing with the desired hydrogenation reaction. The absence or catalytic amount of a base resulted in notably lower conversions and *ee* values (entries 15 and 16). Inorganic bases with suitable pK_a were beneficial to this transformation both in terms of yield and enantioselectivity. Among the bases examined, K_2CO_3 gave the best results while $NaHCO_3$ and $KHCO_3$ afforded similar yields but slightly lower *ee* values (entries 1, 13, and 14).

When a series of substrates with different substituents on the aromatic ring were subjected to the optimized hydrogenation conditions, complete conversions and over 90% *ee* values were observed in most cases by using only 0.1 mol% of **5**. It was observed that the substrates with *ortho* substituents generally resulted in notably lower enantioselectivities (84 and 41% *ee*, Table 2, entries 2 and 5). We suspected that the *ortho* substituents might interfere with the preferred coordination of the carbonyl group to the metal center and lead to lower facial selectivity. This observation was also



Scheme 1. Syntheses of (−)-arbutamine and (−)-denopamine.

Table 1. Asymmetric hydrogenation of α-secondary amino ketone **3a**.

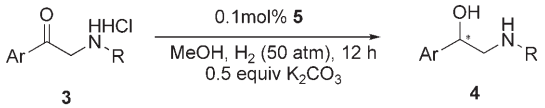


3a **4a**

Entry[a]	Catalyst	Base[b]	Yield [%][c]	*ee* [%][d]
1	[Rh((*S*)-binapine)(cod)]·BF_4 (**5**)	K_2CO_3	>95	95
2	[Rh((*S*)-binapine)Cl]$_2$ (**6**)	K_2CO_3	>95	93
3	[Rh((*S*)-binapine)SO_2Me]$_2$ (**7**)	K_2CO_3	>95	95
4	[Rh((*S*)-binapine)Tos]$_2$ (**8**)	K_2CO_3	>95	93
5	[Pd((*S*)-binapine)]	K_2CO_3	0	N/A
6	[Ir((*S*)-binapine)]	K_2CO_3	0	N/A
7	[Rh((*S,S*)-Me-DuPhos)(cod)]·BF_4 (**9**)	K_2CO_3	>95	85
8	[Rh((*S,S*)-Et-DuPhos)(cod)]·BF_4 (**10**)	K_2CO_3	>95	89
9	[Rh((*R,R,S,S*)-DuanPhos)(nbd)]·SbF_6 (**11**)	K_2CO_3	>95	40
10	**5**	TEA	<10	N/A
11	**5**	KO*t*Bu	<10	N/A
12	**5**	$CsCO_3$	<10	N/A
13	**5**	$NaHCO_3$	>95	90
14	**5**	$KHCO_3$	>95	92
15[e]	**5**	K_2CO_3 (10 mol%)	>95	90
16[e]	**5**	no base	90	54

[a] The hydrogenation was carried out under the described conditions for each entry with 0.1 mol% of Rh precatalyst following the general procedure. [b] 0.5 equiv of K_2CO_3 were used and 1.0 equiv for other bases [c] Yields were determined by ^{1}H NMR spectroscopy of the crude product. [d] The enantiomeric excess of **4** was determined by chiral HPLC after conversion to the corresponding N-acyl derivatives (see the Experimental Section). [e] 0.2 mol% of catalyst was used.

Table 2. Asymmetric hydrogenation of α-secondary amino ketones **3**.



3 **4**

Entry[a]	Ar	R	Yield [%][b]	*ee* [%] (config.)[c]
1	C_6H_5 (**3a**)	Me	>95 (**4a**)	95 (*S*)
2	2-$CH_3OC_6H_4$ (**3b**)	Me	>95 (**4b**)	84
3	3-$CH_3OC_6H_4$ (**3c**)	Me	>95 (**4c**)	92
4	4-$CH_3OC_6H_5$ (**3d**)	Me	>95 (**4d**)	91
5	2-ClC_6H_5 (**3e**)	Me	>95 (**4e**)	41
6	3-ClC_6H_5 (**3f**)	Me	>95 (**4f**)	84
7	4-ClC_6H_5 (**3g**)	Me	>95 (**4g**)	90
8	2-naphthyl (**3h**)	Me	>95 (**4h**)	89
9	C_6H_5 (**3i**)	Et	>95 (**4i**)	84
10[d]	C_6H_5 (**3a**)	Me	>95 (85[e], **4a**)	94 (*S*)

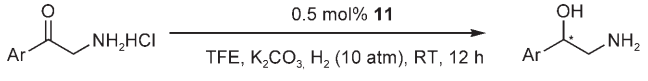
[a] The hydrogenation was carried out with 0.1 mol% of **5** as the precatalyst in the presence of 0.5 equiv of K_2CO_3 for 12 h. [b] Yields were based on ^{1}H NMR spectroscopy of the crude product. [c] The enantiomeric excess was determined by chiral HPLC after conversion to the corresponding N-acyl derivative (see the Supporting Information). The absolute configuration of **4a** was determined by comparing the sign of optical rotation of the corresponding N-acyl derivative with reported data. [d] 0.025 mol% of **5** was used. [e] Isolated yield.

consistent with the previously reported hydrogenation reactions dealing with substrates bearing an α-aryl group, such as α-aryl enamides.[10] To test the effect of the alkyl group on nitrogen, 2-ethylaminoacetophone hydrochloride (**3i**) was subjected to the optimized hydrogenation conditions. The reaction yield remained excellent (>95%), while the *ee* dropped to 84% when using catalyst **5** (entry 9).

To demonstrate the potential practical applications of this methodology, a hydrogenation was performed on substrate **3a** with an even lower catalyst loading (0.025 mol%, *S*/*C*=4000; *S*/*C*=ratio of substrate/catalyst). Complete conversion and retained *ee* was observed under the previously determined optimized conditions. Despite of the difficulties in the separation of amino alcohol products, an 85% isolated yield was still achieved and over a 3400 turnover number was obtained in 12 h with 94% *ee* (Table 2, entry 10).

Prompted by the high yields and selectivities we observed in the hydrogenation of the α-secondary amino ketones with Rh catalytic systems, we subsequently switched our exploration to the hydrogenation of α-primary amino ketones.[4] Commercially available 2-amino-1-phenylethanone hydrochloride (**12a**) was examined as a standard substrate to optimize the hydrogenation conditions. A large variety of Rh catalysts and reaction conditions were screened[11] and the best results were obtained with 0.5 mol% [Rh(DuanPhos)(nbd)]·SbF_6 (**11**) (nbd=norbornadiene) catalyst and 0.5 equivalents of K_2CO_3. The use of 2,2,2-trifluoroethanol (TFE) as the solvent resulted in a much higher *ee* than other alcoholic solvents. Under 10 atm H_2 at room temperature for 12 h, 88% *ee* was observed with virtually complete conversion (Table 3, entry 1). Rh catalysts with other commercially

Table 3. Asymmetric hydrogenation of α-primary amino ketones **12**.



12 **13**

Entry[a]	Ar	Yield [%][b]	*ee* [%] (config.)[c]
1	C_6H_5 (**12a**)	>95 (**13a**)	88 (*S*)
2	4-$CH_3OC_6H_4$ (**12b**)	>95 (**13b**)	71
3	3-$CH_3OC_6H_4$ (**12c**)	>95 (**13c**)	83
4	2,5-$CH_3OC_6H_5$ (**12d**)	>95 (**13d**)	71
5	4-$CH_3C_6H_5$ (**12e**)	>95 (**13e**)	90
6	2-naphthyl (**12f**)	>95 (**13f**)	87
7	4-CNC_6H_5 (**12g**)	>95 (**13g**)	64
8	4-BrC_6H_5 (**12h**)	>95 (**13h**)	76
10[d]	C_6H_5 (**12a**)	>95 (80[e], **13a**)	84 (*S*)

[a] The hydrogenation was carried out with 0.5 mol% of **11** as the precatalyst in the presence of 0.5 equiv of K_2CO_3 for 12 h. [b] Yields were based on ^{1}H NMR spectroscopy of the crude product. [c] The enantiomeric excess was determined by GC analysis using a Chiral Select 1000 column after conversion to the corresponding N-trifluoroacyl or N,O-bis-trifluoroacyl derivative (see the Supporting Information). The absolute configuration of **13a** was determined by comparing the sign of optical rotation with reported data. [d] 0.02 mol% of **11** was used. [e] Isolated yield.

available ligands, such as **9** and **10**, gave slightly lower *ee* values (80 and 85% *ee*, respectively). When the hydrogenation was performed with a lower catalyst loading (0.02 mol%, $S/C=5000$), 80% isolated yield was still obtained with a slightly lower *ee* (>4000 TON, 84% *ee*, Table 3, entry 9).

A series of substrates with different substituents on the aromatic ring were synthesized in good yields through two steps[12] and were subsequently hydrogenated under the optimized conditions previously determined. Most of the substrates were reduced efficiently with 0.5 mol% of catalyst **11** (Table 3). Although the enantioselectivities are only from moderate to good (64–90% *ee*), this hydrogenation still represents a promising approach for the facial syntheses of free 1,2-amino alcohols.

Conclusion

Two β-receptor agonists (−)-denopamine and (−)-arbutamine were prepared in good yields and enantioselectivities by asymmetric hydrogenation of unprotected amino ketones by using Rh catalysts possessing electron-donating phosphine ligands. The generality of this methodology was elucidated by the hydrogenation of a series of α-primary and secondary amino ketones producing various 1,2-amino alcohols in good yields and enantioselectivies. This methodology represents one of the most promising and convenient approaches towards the asymmetric synthesis of chiral amino alcohols. At present, Rh–Binapine, –DuanPhos, and –DuPhos complexes are generally the catalysts of choice, though a ligand screening is needed for optimal enantioselectivity for different types of substrates. Further catalyst screening and studies into the applications of these catalysts towards the hydrogenation of other types of unprotected amino ketones are currently ongoing and will be reported in due course.

Experimental Section

General methods: All reactions and manipulations were performed in a nitrogen-filled glove box or under a nitrogen atmosphere by using Schlenk techniques unless otherwise noted. Column chromatography was performed by using Sorbent silica gel 60 Å (230×450 mesh). ^{1}H and ^{13}C NMR spectral data were recorded on Bruker DPX-300, CDPX-300, AMX-360, and DRX-400 MHz spectrometers. Chemical shifts were reported in ppm upfield to tetramethylsilane with solvent resonance as the internal standard. MS spectra were recorded on a KRATOS mass spectrometer MS 9/50 for LR-APCI and HR-APCI.

General procedure for asymmetric hydrogenation of α-amino ketones: $[Rh(cod)_2]\cdot BF_4$ (40.6 mg, 0.1 mmol) and (*S*)-binapine (73.4 mg, 0.1 mmol) were dissolved in degassed dichloromethane (2 mL) in a Schlenk tube under nitrogen. After stirring at room temperature for 1 h, degassed hexanes (10 mL) were added and the resulting precipitates were filtered under nitrogen to give the complex as an orange solid (90.0 mg, 90% yield). This orange complex was stored in a nitrogen filled glovebox for further usage.

The complex (5.0 mg, 0.005 mmol) was dissolved in degassed anhydrous MeOH (5 mL) in a glovebox. A 4 mL ample was then charged with a half-inch stir bar, substrate (0.2 mmol), a stoichiometric amount of base, the preformed complex solution (0.2 mL for $S/C=1000$, 2 mL for $S/C=100$), and MeOH to reach 2 mL. The vial was transferred to an autoclave which was charged with H_2 (50 atm). The hydrogenation was performed at 50°C for 12 h. After carefully releasing the H_2, the solvent was removed under reduced pressure. The yield was determined by ^{1}H NMR spectroscopy of the crude product.

General procedure for the preparation of α-secondary amino ketone hydrochlorides: A solution of 2-bromoacetophenone (2 g, 10 mmol) in CH_3CN (4 mL) was added to a solution of methylamine (8 M solution in absolute alcohol, 2.5 mL, 20 mmol, 2 equiv) in CH_3CN (3 mL) at 0°C. The solution was stirred at 0°C for 5 min (or monitored by TLC until complete conversion). Dry diethyl ether (100 mL) was added and the resulting precipitates were filtered. The filtration was evaporated under vacuum until a small amount of liquid was left. Dry ether was added to dissolve the residue and HCl solution (1 M solution in dry ether, 10 mL) was added dropwise at 0°C. The precipitate was filtered and then washed with acetone. Recrystallization in hot absolute alcohol gave the product as a white crystalline solid.

General procedure for the preparation of racemic 1,2-secondary amino alcohols: $NaBH_4$ (190 mg, 5 equiv) was added in small portions to a solution of 2-methylamino-1-phenylethanone hydrochloride (200 mg, 1 mmol) in methanol (15 mL). The resulting mixture was stirred at RT for 4–6 h until completion. The reaction was quenched with water and most of the methanol was removed under vacuum. The aqueous solution was then extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave the crude product as a white powder. Purification by column chromatography (EtOAc/MeOH/NH_3 aq 20:4:1) gave a pure racemic amino alcohol product.

General procedure for the derivatization of 1,2-amino alcohols: Acetic anhydride (28 μL, 1.5 equiv) was added to a CH_2Cl_2 solution of the α-amino alcohol (0.2 mmol). The resulting mixture was stirred at RT for 2–4 h until completion. The solvent was removed under vacuum and the crude product was purified by silica-gel column chromatography (EtOAc).

General procedure for the preparation of α-primary amino ketone hydrochlorides: NaN_3 (0.78 g, 12 mmol) was added to a solution of 2-bromo-3′-methoxyacetophenone (2.29 g, 10 mmol) in DMSO (10 mL) at 10°C in one portion. The reaction mixture was allowed to warm to RT and stirred for 2 h. After 20 mL of H_2O had been added, the resulting mixture was extracted with EtOAc (30 mL×2). The combined organic layers were washed with H_2O (20 mL×2), dried over Na_2SO_4, and concentrated to provide the crude azide intermediate as a pale-yellow solid in quantitative yield (1.91 g). This product directly underwent hydrogenation without purification. HCl in diethyl ether (2.0 M, 6.0 mL) and catalytic amount of 10% Pd/C were added to a solution of the product in MeOH (8 mL). The hydrogenation was performed in an autoclave under 3 bars of hydrogen at RT for 5 h. After carefully releasing the hydrogen, the reaction mixture was filtered and concentrated to dryness. The residue was vigorously stirred with EtOAc (25 mL) at RT for 2 h, and then filtered and washed with EtOAc to provide **12c** as an off-white solid (1.58 g, 78%).

General procedure for the preparation of racemic 1,2-primary amino alcohols: $NaBH_4$ (83 mg, 2.18 mmol) was added to a solution of **12a** (375 mg, 2.18 mmol) in MeOH (5 mL) at 0°C. The resulting mixture was stirred at 0°C for 30 min before quenching with saturated NH_4Cl solution (2 mL). The solvent was partially removed under reduced pressure. The residue was basicified with NaOH (1 N, 5 mL) and extracted with CH_2Cl_2 (10 mL×3). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford **13a** as a white solid (254 mg, 85%). The analytical sample was obtained by purification through a short silica-gel plug (EtOAc/MeOH/TEA 10:10:1).

General procedure for the preparation of (±)-2,2,2-trifluoro-*N*-(2-hydroxy-2-phenylethyl)acetamide: Trifluoroacetic anhydride (46 μL, 0.33 mmol) was added to a solution of **13a** (45 mg, 0.33 mmol) in CH_2Cl_2 (3 mL) at RT. The reaction mixture was stirred at RT for 10 min. After removal of the solvent, the desired N-trifluoroacyl derivative was isolated

by flash column chromatography on silica gel (hexanes/EtOAc 80:10) for subsequent chiral GC analysis.

General procedure for the preparation of (±)-trifluoroacetic acid 1-(4-bromophenyl)-2-(2,2,2-trifluoroacetylamino) ethyl ester: Trifluoroacetic anhydride (96 μL, 0.69 mmol) was added to a solution of **13h** (50 mg, 0.23 mmol) in CH_2Cl_2 (3 mL) at RT. The reaction mixture was stirred at RT for 1 h. After removal of the solvent, the desired N,O-bistrifluoroacyl derivative was isolated by flash column chromatography on silica gel (hexanes/EtOAc 80:10) for subsequent chiral GC analysis.

Acknowledgement

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