Tetrahedron Letters 51 (2010) 1371–1373

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Sequential perfluoroalkylation and asymmetric reduction of nitriles triggered with perfluoroalkyl titanates: catalytic asymmetric synthesis of perfluoroalkyl amines

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ARTICLE INFO

Article history:
Received 7 December 2009
Revised 24 December 2009
Accepted 24 December 2009
Available online 7 January 2010

Dedicated to Professor T.V. RajanBabu for his 60's birthday on February 5th.

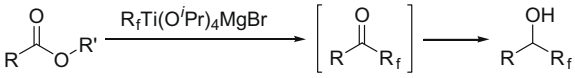
ABSTRACT

Highly enantio-enriched perfluoroalkyl amines are shown to be synthesized by perfluoroalkylation and asymmetric reduction of nitriles. Perfluoroalkylation of nitriles can be attained by the Lewis acidic perfluoroalkyl titanate reagents to give *acyclic* ketimines. Catalytic asymmetric hydrogenation of the *acyclic* ketimines affords the perfluoroalkyl amine products in up to 93% ee.

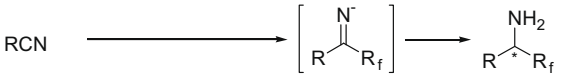
Organofluorine compounds have attracted great interest because of promising applications in biological and material science in recent years.[1] Organofluorine compounds now constitute more than 40% of pharmaceuticals on the top market and about 80% in pipelines of new drug candidates. A new term, 'fluorine scan'[2] is thus coined for the drug design. In sharp contrast, the methodological aspect of organofluorine chemistry, as the development of new methods to introduce fluorine, is still under development.

Chiral perfluoroalkyl amines potentially bear significant importance as biological targets due to the unique properties of perfluoroalkyl groups.[3] However, enantio-enriched perfluoroalkyl amines have generally been difficult to prepare and, hence, there are only limited number of approaches to those chiral perfluoroalkyl compounds.[4] A simple approach to the enantio-enriched perfluoroalkyl amines is the catalytic asymmetric hydrogenation of perfluoroalkyl imines. Although its simplicity, there are two major obstacles in the catalytic asymmetric reduction of the ketimines:[5] (1) the stereoselective preparation of perfluoroalkyl ketimines, and (2) the catalytic asymmetric hydrogenation of the resultant ketimines. The problem in synthesizing perfluoroalkyl ketimines associates with the preparation of perfluoroalkyl ketonic precursors by perfluoroalkyl metal reagents and (*Z*/*E*)-control of the ketimines derived thereof. However, the perfluoroalkyl metal reagents have generally been recognized unstable because of the α- or β-metal fluoride elimination.[6] The catalytic asymmetric hydrogenation of perfluoroalkyl *acyclic* imines is the other issue, which has been recognized to be difficult to give high enantioselectivity due to the peculiar organofluorine[1,5] and *acyclic* imine[5] functional groups.

Recently, we reported the generation of *stable* perfluoroalkyl (R_f^-) titanate-type reagents and a new type of reaction, namely, tandem[8] reductive[9] perfluoroalkylation of esters (Eq. 1).[10] Herein we report an advanced reaction sequence of *catalytic asymmetric* reduction and perfluoroalkylation triggered with the addition of the Lewis acidic titanate reagents to nitriles, which possess the same oxidation level as esters (Eq. 2):



(1)



(2)

The Lewis acidic perfluoroalkyl titanate reagents can be reactive to nitriles, hopefully in the same tandem reductive perfluoroalkylation manner.[10] However, when the perfluoroalkyl titanate reagents were reacted with nitriles at room temperature, only perfluoroalkyl ketones (**1**) were obtained quantitatively (Table 1) rather than the tandem reductive perfluoroalkylation product, namely perfluoroalkyl amines (**2**) after acidic work-up with 1*N* HCl (entries 1–3). These results indicate the formation of perfluoroalkyl imine intermediates. Without titanium tetra(iso-propoxide), the Grignard reagent did not give the perfluoroalkyl ketone (entry 4), even in the presence of the Lewis acidic cerium reagent.[11]

The imine intermediates were then isolated (Scheme 1). After perfluoroalkylation of nitrile with the perfluoroalkyl titanate reagent, acetic anhydride was added to give the perfluoroalkyl ketimine in good isolated yield, as a single (*Z*)-isomer. The (*Z*)-geometry of perfluoroalkyl ketimines was proven by the ^1H–^{19}F NOESY spectra. The formation of the single (*Z*)-isomer is attributable to hyperconjugative interaction of the lone electron pair of the

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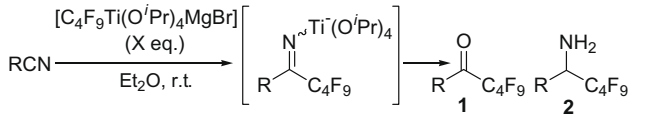
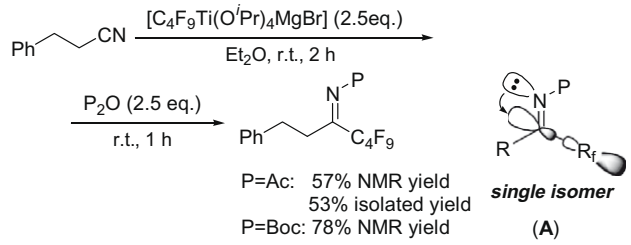
0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.12.140

Table 1
Reaction of perfluoroalkyl titanate reagents with nitriles



Entry	R	X (equiv)	Yield[a] (%)	
			1	2
1	$PhCH_2CH_2$	2.5		—
2	$PhCH_2CH_2$	4.0	Quant.	—
3	Ph	4.0	72	—
4[b]	Ph	4.0	—	—

[a] Determined by ^{19}F NMR using BTF as an internal standard.
[b] Without $Ti(O^iPr)_4$.



Scheme 1.

nitrogen into the σ* orbital of the C–C bond between imine and perfluoroalkyl group (**A**).[12] Even a generally employable Boc protecting group can also be introduced to give the Boc-protected perfluoroalkyl ketimine in good yield.

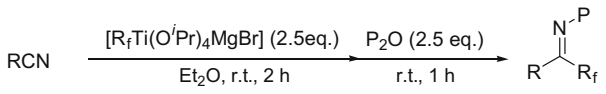
Several nitriles were then examined to give the protected (*Z*)-perfluoroalkyl ketimines (Table 2). In the case of aliphatic nitrile, acyclic perfluoroalkyl ketimines ($C_nF_{2n+1}(C_nH_{2n+1})C{=}NAc$) were obtained (entry 2). Other perfluoroalkyl groups such as C_3F_7 and C_6F_{13} could also be introduced into the perfluoroalkyl ketimines (entries 3 and 4). In the case that a Boc protecting group is employed, the corresponding Boc-protected perfluoroalkyl ketimines were obtained in good yields after aqueous rather than acidic work-up (entries 5 and 6). Even when R is sterically demanding and electron-withdrawing aromatic group,[11] the corresponding imine was also obtained in good yield (entry 5).

The highly enantio-selective synthesis of chiral *sec*-amines was realized by the catalytic asymmetric hydrogenation of the ketimines with iridinium complexes with BINAP (Ir^+-BINAPs/BAr_F^-), which generally provide only low enantioselectivity for non-fluorinated acyclic ketimines.[13] In sharp contrast, the perfluoroalkyl ketimines gave the *acyclic* perfluoroalkyl *sec*-amine in high yield and more significantly with high enantioselectivity (Table 3, entry 1). The chiral ligands, BINAP derivatives, were then screened in the hydrogenation of the model substrate. When tolBINAP was used, the perfluoroalkyl amine was obtained in good yield and higher enantioselectivity (entry 2). The xylBINAP complex gave the highest yield and enantioselectivity (entry 3).

The absolute configuration of the (*R*)-(+)-perfluorobutyl phenethyl amine (88% ee: Table 3, entry 1) was first deduced by comparison of the optical rotation of the de-protected (*R*)-(+)-hydrochloride salt ($[\alpha]_D^{25}$ +10.8) with (*S*)-(−)-trifluoromethyl amine ($[\alpha]_D^{25}$ −15.2). Furthermore, the authentic sample of (*R*)-(+)-perfluorobutyl phenethyl amine ($[\alpha]_D^{25}$ +11.5: hydrochloride salt) was prepared[4a,4b] to confirm the absolute configuration.

Several ketimines were then investigated to afford highly enantio-enriched perfluoroalkyl amines (Table 4). Even with pseudo-symmetric perfluoroalkyl ketimines ($C_nF_{2n+1}(C_nH_{2n+1})C{=}NAc$), the chiral half-perfluoroalkylated amines were obtained with high enantioselectivities (92%, 90%, and 93% ee, respectively) (entries 2–4). When the Boc protecting group was employed ($Rf(R)C{=}NBoc$), the perfluoroalkyl amines were also obtained in high enantioselectivities (entries 5 and 7). Even in the case of sterically demanding and electron-withdrawing benzonitrile-derived imine ($C_nF_{2n+1}(Ph)C{=}NBoc$), the use of acidic trifluoroethanol as a

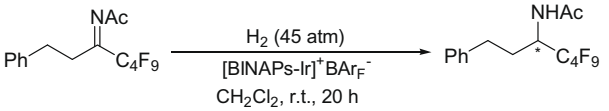
Table 2
Synthesis of the perfluoroalkyl imines



Entry	P	R	Rf	Yield[a] (%)
1	Ac	$PhCH_2CH_2$	C_4F_9	57(53)
2	Ac	C_4H_9	C_4F_9	51
3	Ac	C_3H_7	C_3F_7	51
4	Ac	C_6H_{13}	C_6F_{13}	56(56)
5	Boc	Ph	C_4F_9	78
6	Boc	$PhCH_2CH_2$	C_4F_9	73

[a] Determined by ^{19}F NMR using BTF as an internal standard. The values in the parentheses referred to isolated yields.

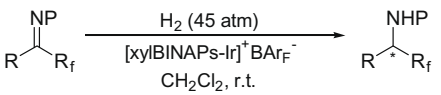
Table 3
Effect of chiral ligands



Entry	Ligand	Yield[a] (%)	ee[b] (%)
1[c]	(*S*)-BINAP	94	88 (*R*)
2[c]	(*R*)-tolBINAP	93	90 (*S*)
3[d]	(*R*)-xylBINAP	95	93 (*S*)
4[d]	(*R*)-SEGPHOS	92	88 (*S*)

[a] Isolated yields.
[b] Determined by HPLC (CHIRAL CELL OJ-H).
[c] 5 mol % of the catalyst.
[d] 3 mol % of the catalyst.

Table 4
Asymmetric hydrogenation of perfluoroalkyl imines



Entry	P	R	Rf	Yield[a] (%)	ee[b] (%)
1	Ac	$PhCH_2CH_2$	C_4F_9	95	93
2	Ac	C_4H_9	C_4F_9	88	92
3	Ac	C_3H_7	C_3F_7	97	90[c]
4	Ac	C_6H_{13}	C_3F_7	90	93
5	Boc	$PhCH_2CH_2$	C_4F_9	87	93
6	Boc	C_6H_5	C_4F_9	67	15
7	Boc	C_6H_5	C_4F_9	52	90[d]

[a] Isolated yields.
[b] Determined by HPLC (CHIRAL CELL OJ-H).
[c] Determined by chiral GC (CP-Chirasil-Dex CB).
[d] In CF_3CH_2OH.

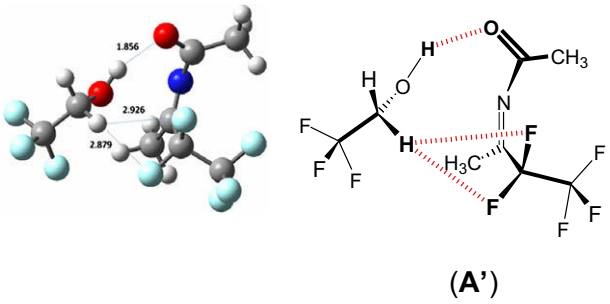


Figure 1. MP2/6-311+G(d,p) optimized geometry: F (blue), H (white), C (gray), N (purple), and O (red), respectively.

solvent[5] led to the significant increase in enantioselectivity (up to 90% ee) (entry 7). Hydrogen bonding of the carbonyl protection and perfluoroalkyl groups of the ketimines with acidic trifluoroethanol may additionally exert to fix the (*Z*)-imine geometry (vide infra),[14] leading to the increase in enantioselectivity. Otherwise, only low enantioselectivity (15% ee) was obtained (entry 6). The benzonitrile-derived imine $C_4F_9(Ph)C{=}NBoc$ might be geometrically isometrized in the absence of the acidic alcohol.

The complex between the (*Z*)-isomer of $C_2F_5(CH_3)C{=}NAc$ and trifluoroethanol was thus calculated by ab initio MP2/6-311+G(d,p) (Fig. 1). The optimized structure (**A**′) shows multi-hydrogen bonding sites in the complex. The primary interaction is of the alcohol with the acyl-protecting group (1.856 Å). The secondary interactions are of trifluoroethanol methylene hydrogen with the perfluoroalkyl fluorine atoms (2.879 Å and 2.926 Å, respectively). Although these non-bonding distances are longer than the sum of the van der Waals radii of 2.67 Å (H; 1.2 Å; F: 1.47 Å),[1a] the 'hydrogen bonding' network[14] including the weak electrostatic attraction[1a] of CH/FC type[15] stabilizes the (*Z*)-geometry of $C_2F_5(CH_3)C{=}NAc$ to prevent interconversion of (*Z*/*E*)-isomers, leading to the significant increase of enantioselectivity in acidic trifluoroethanol.[7,16,17]

In conclusion, we have developed the perfluoroalkylation and catalytic asymmetric hydrogenation of nitriles to give enantio-enriched *acyclic* perfluoroalkyl *sec*-amines. To our knowledge,[5] this is the first successful catalytic asymmetric hydrogenation of *acyclic* simple perfluoroalkyl ketimines even with the generally employable Boc protecting group.

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