Synthetic Methods

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Chiral Phosphoric Acid Catalyzed Transfer Hydrogenation: Facile Synthetic Access to Highly Optically Active Trifluoromethylated Amines**

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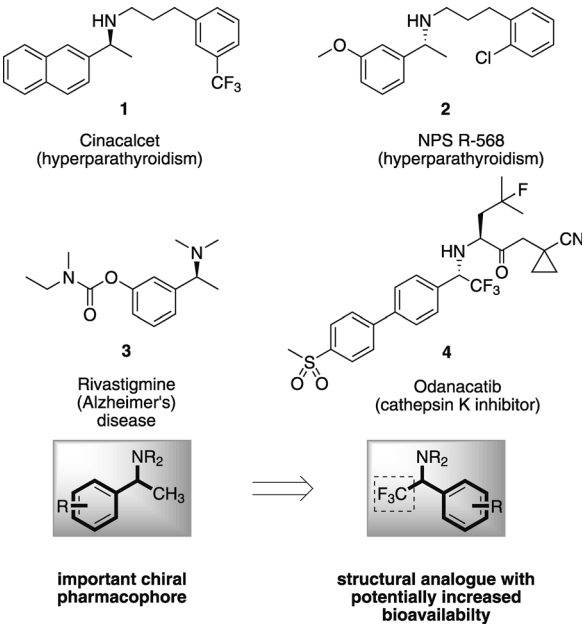
Chiral amines represent an important structural motif that can be found in a vast number of biologically active compounds.[1] Many well-established drugs that are applicable in a diverse number of areas rely on this prominent pharmacophore. Among them are Cinacalcet (**1**) and NPS R-568 (**2**; hyperparathyroidism), Rivastigmine (**3**; Alzheimer's and Parkinson's disease), and Odanacatib (**4**; cathepsin K inhibitor; Scheme 1).



Scheme 1. Selected examples of α-methyl chiral amine based pharmaceuticals.

Over the last decades, fluorinated compounds have attracted considerable attention in pharmaceutical as well as agrochemical research.[2a–e] The incorporation of fluorine into a biologically active molecule causes minimal steric alterations yet constructively changes its physicochemical properties, thus generally leading to increased metabolic stability as well as improved membrane permeation by the functionalized molecule.[2b,c,d,e] In this context, trifluoromethylated amines became the subject of special interest since it was recently found that they can act as nonbasic amide bond surrogates with improved bioavailability.[2b] The application of this strategy by Zanda et al. yielded a new kind of peptidomimetic, on which the development of novel cathepsin K inhibitors for the treatment of osteoporosis were based (Scheme 1).[3]

As a result of the constantly growing demand for new and structurally diverse trifluoromethylated amines for pharmaceutical and agrochemical purposes, we envisaged the development of a general yet efficient method for the preparation of these compounds. Whereas several research groups have already reported excellent contributions concerning the asymmetric metal-[4] and organocatalyzed[5–7] reduction of ketimines as well as the reductive amination of ketones, the use of perfluoroalkylated ketimines and ketones as substrates in the latter transformations has been much less investigated.[8] Hughes et al. and Xu et al. developed a diastereoselective reductive amination of aryl trifluoromethyl ketones.[9] During the preparation of this manuscript, the research group of Bräse[10] and later that of Zhou[11] reported an achiral Lewis acid mediated reductive amination of aromatic trifluoromethyl ketones and an enantioselective palladium-catalyzed hydrogenation of perfluorinated nonactivated ketimines, respectively. Although the yields as well as the enantioselectivities are good to high, in the latter contribution the drawbacks are the use of relatively high pressures of hydrogen and the expensive and toxic transition-metal catalyst for the transformation.

We report herein the first asymmetric phosphoric acid catalyzed synthesis of aromatic and heteroaromatic trifluoromethylated amines and their application to the synthesis of a perfluoroalkylated analogue of NPS R-568.

As a result of our recent finding that benzothiazolines are able to reduce C=N bonds efficiently, we envisaged their use as a hydride source in this transformation.[12] At the outset of our studies, different chiral phosphoric acid catalysts were screened in the presence of benzothiazoline **6a** and ketimine **5a**, and it was revealed that the catalyst (*R*)-**8** was the most suitable. One of the major advantages of employing benzothiazolines as the hydride donor lies in the potential to fine-tune their electronic and steric properties. Therefore, various benzothiazoline derivatives (**6a–d**) were tested for their activity and selectivity and the results are summarized in Table 1. Whereas high yield (68%) and good enantioselec-

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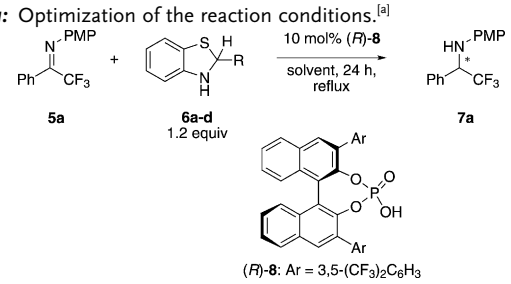
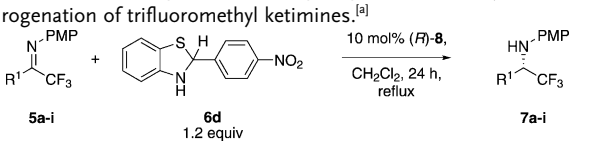
Table 1: Optimization of the reaction conditions.[a]



Entry	Thiazoline	R	Solvent	Yield [%][b]	*ee* [%][c]
1	**6a**	Ph	toluene	28[d]	84
2	**6b**	4-$MeOC_6H_4$	toluene	51	82
3	**6c**	4-ClC_6H_4	toluene	68[d]	87
4	**6d**	4-$NO_2C_6H_4$	toluene	44	92
5	**6d**	4-$NO_2C_6H_4$	CH_2Cl_2	89	96

[a] Reaction conditions: trifluoromethyl ketimine **5a** (0.2 mmol), benzothiazoline **6a-d** (0.24 mmol), (*R*)-**8** (10 mol%), solvent (2 mL) at reflux temperature. [b] If not otherwise noted, the yield is of the isolated product **7a** after preparative TLC. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Determined from the ^{1}H NMR spectrum of the crude reaction mixture. PMP = *para*-methoxyphenyl.

Table 2: Substrate scope for the chiral phosphoric acid catalyzed transfer hydrogenation of trifluoromethyl ketimines.[a]

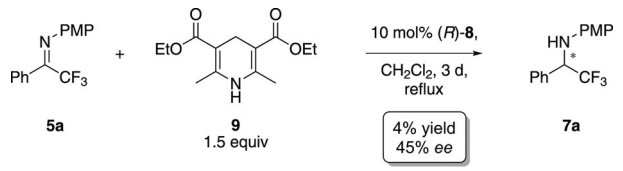


Entry	Imine	R^1	Yield [%][b]	*ee* [%][c]
1	**5a**	Ph	89	96 (+)
2	**5b**	4-ClC_6H_4	91	98 (+)
3	**5c**	4-BrC_6H_4	89	97 (+)
4	**5d**	4-$CF_3C_6H_4$	77	97 (+)
5	**5e**	4-MeC_6H_4	89	97 (+)
6	**5f**	3-$MeOC_6H_4$	97	97 (+) (*S*)[d]
7	**5g**	4-$MeOC_6H_4$	94	98 (+)
8	**5h**	2-naphthyl	99	97 (+)
9	**5i**	2-thienyl	72	97 (+)

[a] Reaction conditions: trifluoromethyl ketimine **5a–i** (0.2 mmol), benzothiazoline **6d** (0.24 mmol), (*R*)-**8** (10 mol%), CH_2Cl_2 (2 mL) at reflux temperature. [b] Yields are of the isolated products **7a–i** after preparative TLC. [c] Determined by HPLC analysis on a chiral stationary phase. [d] The absolute configuration was determined by comparison to data reported in the literature.[8h]

tivity (87% *ee*) could be obtained with benzothiazoline **6c** (entry 3, Table 1), the use of the more-electron-deficient 4-nitrophenyl benzothiazoline **6d** resulted in a lower yield (44%), albeit with a better enantioselectivity (92% *ee*; entry 4, Table 1). To our delight, changing the solvent from toluene to dichloromethane improved both the yield and enantioselectivity significantly (entry 5, Table 1).

Interestingly, employing the commonly used transfer hydrogenation agent, the Hantzsch ester (**9**), under the same reaction conditions resulted in only a trace amount of **7a** (4%) with diminished enantioselectivity (45% *ee*; Scheme 2). This result clearly points to the distinct differences in the reactivity between **6d** and **9**, and shows that an appropriate choice of hydride source is crucial for the outcome of this transformation.[13]



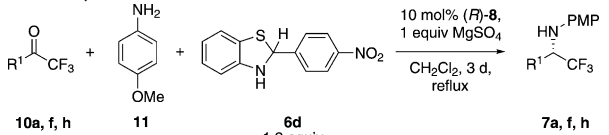
Scheme 2. Transfer hydrogenation of trifluoromethyl ketimine with Hantzsch ester (**9**).

With the optimized reaction conditions in hand, a range of trifluoromethyl ketimines **5a–j** were tested in this reaction (Table 2). Whereas the yields and enantioselectivities were similar for halogenated ketimines **5b** (entry 2, Table 2) and **5c** (entry 3), the employment of substrate **5d**, which bears a stronger electron-withdrawing aromatic substituent (entry 4), resulted in a diminished yield (77%) but similar enantioselectivity (97% *ee*). The electron-rich ketimines **5e–g** showed good to excellent results (89–99% yield) and overall excellent enantioselectivities (97–98% *ee*; entries 5–7, Table 2). Heteroaromatic imine **5i** is viable for this transformation although its use results in a lower reactivity (72% yield) and high enantioselectivity (97% *ee*; entry 10, Table 2).

Next, we investigated the possibility of creating the required N-PMP-protected ketimines in situ in the manner of a direct reductive amination; a simpler and more practical version of this protocol. To our delight, subjecting 2,2,2-trifluoromethyl acetophenone (**10a**) and *p*-anisidine (**11**) in the presence of $MgSO_4$ to the optimized reaction conditions (10 mol% (*R*)-**8**, CH_2Cl_2, reflux) resulted in the formation of **7a** in very good yield (92%) and with excellent enantioselectivity (95% *ee*; entry 1, Table 3). Although this transformation requires a longer reaction time (3 d), the yields and the enantioselectivities are as high as those for the reduction of the preformed imines (entries 1–3, Table 3).

In additional experiments, we focused on the synthesis of a perfluoroalkylated analogue of NPS R-568, (*S*)-**14**, to underscore the synthetic utility of this method. NPS R-568

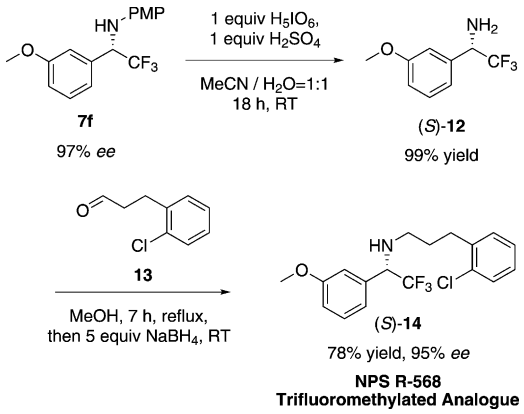
Table 3: Chiral phosphoric acid catalyzed reductive amination of trifluoromethyl ketones.[a]



Entry	Ketone	R^1	Yield [%][b]	*ee* [%][c]
1	**10a**	Ph	92	95 (+)
2	**10f**	3-$MeOC_6H_4$	82	93 (+)-(*S*)
3	**10h**	2-naphthyl	95	96 (+)

[a] Reaction conditions: trifluoromethyl ketone **10a**,**f**, or **h** (0.2 mmol), benzothiazoline **6d** (0.24 mmol), (*R*)-**8** (10 mol%), CH_2Cl_2 (2 mL) at reflux temperature. [b] Yields are of the isolated products **7a**,**f**, and **h** after preparative TLC. [c] Determined by HPLC analysis on a chiral stationary phase.

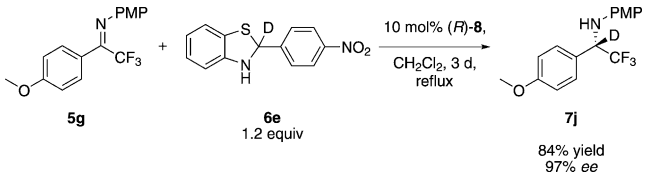
(**2**) belongs to the drug class of type II calcimetics and has been approved for use in the treatment of hyperparathyroidism in patients with kidney disease as well as hypercalcemia in patients with parathyroid carcinoma.[14] The deprotection of **7f** with orthoperiodic acid[15] worked smoothly and resulted in the primary amine **12** in a quantitative yield (99%). The absolute configuration was determined to be *S* by comparing the optical rotation of **12** to that reported in the literature.[8h,16] Next, the reductive amination of (*S*)-**12** with aldehyde **13** afforded compound (*S*)-**14** in 78% yield without significant loss of enantioselectivity (95% *ee*; Scheme 3). Notably, the synthesis of the NPS R-568 trifluoromethyl analogue (*S*)-**14** was accomplished by this route without the use of any expensive and toxic transition-metal catalysts or reagents.



Scheme 3. Synthesis of the trifluoromethylated analogue [(*S*)-**14**] of NPS R-568 (**2**).

Despite the possibility of fine-tuning the reactivity of benzothiazoline to enable the adaptation to the steric and electronic demands of the catalytic system, the use of deuterated benzothiazoline for the enantioselective incorporation of deuterium in a molecule represents another synthetic advantage of the present method. Treatment of trifluoromethyl ketimine **5g** and the readily available deuterated benzothiazoline **6e**[17] with **8** (10 mol%) furnished the α-deuterio-α-trifluoromethylated amine **7j** in slightly diminished yield (72%) and with excellent enantioselectivity (97%) under somewhat modified standard reaction conditions (Scheme 4).[18] This outcome strongly supports the hydride (deuteride) mechanism for the transfer hydrogenation of ketimines with benzothiazoline.[7h,i,12]

In summary, we have developed the first organocatalytic, highly enantioselective transfer hydrogenation and reductive amination of trifluoromethyl imines and trifluoromethyl ketones, respectively. The corresponding α-trifluoromethylated amines could be obtained in good to excellent yields (72–99%) with overall excellent enantioselectivities (96–98%), and represent important synthetic building blocks as well as valuable pharmaceutical intermediates. Furthermore, the synthetic applicability of the developed method was demonstrated in a short yet efficient synthesis of a CF_3 analogue of the pharmaceutical compound NPS R-568. In additional experiments it could be shown that the developed method is also suitable for the enantioselective incorporation of deuterium into prochiral trifluoromethyl ketimines.



Scheme 4. Chiral phosphoric acid catalyzed synthesis of α-deuterio-α-trifluoromethylated amine **7k**.

Experimental Section

Typical procedure for the transfer hydrogenation of trifluoromethyl ketimines: In a dry, nitrogen-flushed Schlenk tube, trifluoromethyl ketimine (0.2 mmol), 2-(4-nitrophenyl)-2,3-dihydrobenzothiazoline (**6d**; 62 mg, 0.24 mmol), and chiral phosphoric acid (*R*)-**8** (15 mg, 0.02 mmol) were dissolved in absolute CH_2Cl_2 (2 mL). After being stirred for 24 h at 55 °C, the reaction mixture was quenched with aq. 10% $NaHCO_3$ (2 mL) and extracted three times with ethyl acetate (5 mL). The combined organic phases were dried and concentrated in vacuo. The resulting crude reaction mixture was purified by preparative TLC (eluent: *n*-hexane/ethyl acetate 15:1) to yield the corresponding trifluoromethylated amine.

Typical procedure for the reductive amination of trifluoromethyl ketones: In a dry, nitrogen-flushed Schlenk tube, trifluoromethyl ketone (0.2 mmol), 4-methoxyaniline **11** (25 mg, 0.2 mmol), 2-(4-nitrophenyl)-2,3-dihydrobenzothiazoline (**6d**; 62 mg, 0.24 mmol), and chiral phosphoric acid (*R*)-**8** (15 mg, 0.02 mmol) were dissolved in 2 mL of absolute CH_2Cl_2. $MgSO_4$ (24 mg, 0.2 mmol) was added and the reaction mixture was stirred for 3 d at 55 °C after which the typical work-up procedure was performed.

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[16] By analogy the absolute configurations for the trifluoromethylated amines **7a–i** are proposed to be *S*.

[17] For the synthesis of 2-deuterio-2-(4-nitrophenyl)-2,3-dihydrobenzothiazoline **6e** see the Supporting Information.

[18] Reaction conditions: trifluoromethyl ketimine **5g** (0.13 mmol), benzothiazoline **6e** (0.16 mmol), (*R*)-**8** (10 mol%), CH_2Cl_2 (2 mL) at reflux temperature.

