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Diastereoselective Reductions

Diastereoselective Reductive Amination of Aryl Trifluoromethyl Ketones and α-Amino Esters

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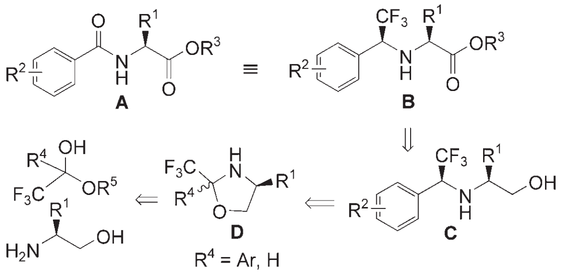
The optimization of new drug entities depends on the manipulation of the potency, selectivity, adsorption, and metabolic properties of lead structures. One of the most commonly employed strategies for accomplishing these objectives involves the incorporation of fluorinated moieties into drug candidates, which often has a profound influence on their in vivo performance.[1] As such, there has been intense interest in the stereoselective inclusion of fluorinated fragments into small organic molecules.[2] One particularly important functionality employed in these endeavors is the bulky and highly electron withdrawing trifluoromethyl group, which is capable of dramatically perturbing the electronic properties of neighboring atoms. Given the ubiquitous nature of α-amino acids in biologically active compounds, it is not surprising that there have been a number of reports describing the stereoselective incorporation of the trifluoromethyl group into simple amino acids, as well as more complex polypeptides.[3] In this way, Zanda and co-workers have shown that 2,2,2-trifluoroethylamines can act as a nonbasic amide surrogate, and have made use of this strategy in the development of novel peptidomimetics.[3a–e] This approach has also recently been employed in the development of potent and selective cathepsin K inhibitors for the treatment of osteoporosis, where the planar amide functionality of the parent compound **A** has been replaced with a stereogenic 2,2,2-trifluoroethyl moiety (Scheme 1).[4] Amidation of the *S,S* isomer **B** of these novel α-amino acids affords particularly potent cathepsin K inhibitors, but it is likely that future applications would benefit from stereoselective access to either isomer of this intriguing class of compounds.



Scheme 1. Trifluoroethylamines as amide equivalents.

While a number of methods for preparing the corresponding β-amino alcohols **C** from 1,3-oxazolines **D** have been described in the literature (Scheme 1),[4,5] these approaches have a number of drawbacks. Initial reports involved condensation of trifluoroacetadehyde hemiacetals and β-amino alcohols to afford approximately 1.5:1 mixtures of diastereomeric oxazolines (Scheme 1, $R^4 = H$).[5b] Chromatographic separation of the diastereomers, followed by stereoselective addition of an organolithium species then afforded the desired amino alcohols with excellent levels of diastereoselectivity. Recent reports from our research describe alternative protocols which avoid the need for the separation of the diastereomeric oxazolines;[4b,5a,6] however, these methodologies still require the use of expensive trifluoroacetaldehyde hemiacetals, are limited to substrates containing functionality which is compatible with organolithium reagents, and require oxidation of the amino alcohols to the amino acids. Mikami and co-workers have shown that 1,3-oxazolines derived from readily available trifluoroacetophenones can be converted into the same types of amino alcohols by selective reduction (Scheme 1, $R^4 = Ar$);[5c] however, this approach again relies on the chromatographic separation of mixtures of diastereomeric oxazolines followed by treatment with a relatively harsh reagent ($LiAlH_4$).

We felt that the simplest approach to α-amino acids **B** would involve a reductive amination between 2,2,2-trifluoroacetophenones and α-amino esters.[7] Two key challenges had to be addressed to achieve this objective. First, suitable conditions for the formation of an imine between the sensitive α-amino esters and 2,2,2-trifluoroacetophenones needed to be developed and, second, stereoselective conditions needed to be identified for reduction of the imine. Herein we describe an unprecedented K_2CO_3-mediated formation of a trifluoromethylketimine and complementary reduction protocols for direct access to either the *R,S* or *S,S* diastereomers of 1-aryl-2,2,2-trifluoroethyl-substituted amino acids **B**.

Initial efforts to form imines between 2,2,2-trifluoroacetophenones and α-amino esters were hampered by decomposition under the harsh conditions typically required to dehydrate the robust aminal intermediates **E** (Scheme 2).[7,8] The yields of the desired imines were less than 30% and we were unable to separate them from reaction by-products. However, we were pleased to discover that the aminal

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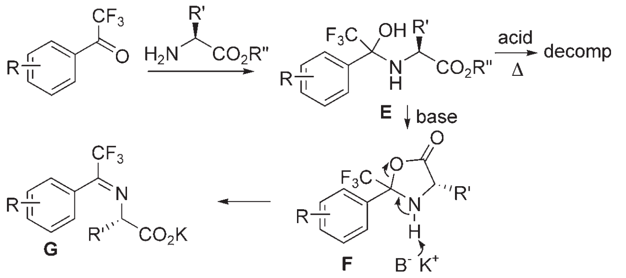
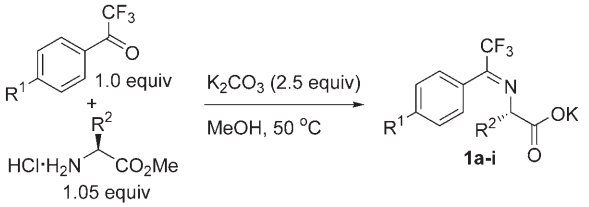
Supporting information for this article (experimental details) is available on the WWW under http://www.angewandte.org or from the author.



Scheme 2. Imine/potassium carboxylate formation under basic conditions.

intermediate could be converted smoothly in the presence of a mild base (K_2CO_3/MeOH, 50 °C) into the imine/potassium carboxylates **G**, presumably via oxazolidinone **F** (Scheme 2). This protocol was employed to prepare imines **1a–i** in good yields (Table 1).[9] The enantiomeric excess of compounds **1a–e**, **1g**, and **1i** was determined by chiral HPLC analysis of the corresponding methyl esters formed by treating the potassium salts with iodomethane. The optical purity of **1f** was assessed by chiral HPLC analysis of the reduction compounds formed in Table 3, entry 6 and Table 4, entry 6. It was not possible to achieve baseline separation of the ester analogues of **1h**, but by inference we assume this compound to also have greater than 94 % *ee*.

Table 1: Imine/potassium carboxylate formation.

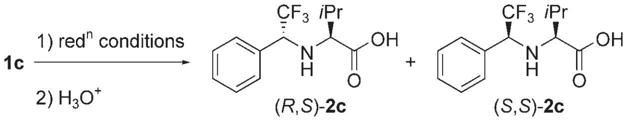


Entry	1	R^1	R^2	*t* [h]	Conv. [%] (% yield)[a]	*ee* [%][b]
1[c]	**a**	H	Me	2	> 95 (65)	96
2	**b**	H	*i*Bu	8	> 95 (84)	96
3	**c**	H	*i*Pr	8	> 95 (88)	> 99.5
4[c]	**d**	Br	Me	4	> 95[d]	94
5	**e**	Br	*i*Bu	16	> 95[d]	97
6	**f**	Br	*i*Pr	16	> 95 (89)	> 99.5[e]
7[c]	**g**	MeO	Me	1	> 95[d]	98
8	**h**	MeO	*i*Bu	4	> 95[d]	n.d.
9	**i**	MeO	*i*Pr	4	> 95[d]	> 99.5

[a] Based on a ^{1}H NMR spectroscopic assay using mesitylene as an internal standard. [b] Determined by chiral HPLC analysis of the corresponding methyl ester. [c] Reactions were performed at ambient temperature with 1.2 equiv of K_3PO_4. [d] The crude imine carboxylate was reduced directly without purification. [e] Determined by HPLC analysis of the reduction products **2f**. n.d. = not determined.

With these substrates in hand, we turned our attention to their diastereoselective reduction, with **1c** used as a model compound (Table 2). Conventional reduction conditions including catalytic hydrogenation, (*S*)-CBS-catalyzed reduction,[10] Red-Al, and $NaBH_4$ afforded the *R*,*S* diastereomer preferentially.[11] The most convenient *R*,*S*-selective protocol involved slow addition of water to a mixture of **1c** and $NaBH_4$ in THF over 3 h (Table 2, entry 5),[12] which afforded the desired product in 86 % yield as a 25:1 mixture of diastereomers. Interestingly, the addition of a Lewis acid ($ZnCl_2$) in the presence of $NaBH_4$ gave a 3:1 preference for the *S*,*S* diastereomer (Table 2, entry 6). This opened the intriguing possibility of accessing either diastereomer from the same imine starting material (see below).

Table 2: Development of *R*,*S*-selective imine reductions.

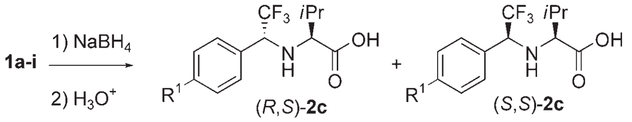


Entry	Redⁿ conditions	Conv. [%] (% yield)	*R*,*S*/*S*,*S*[a]
1	H_2, $Pd(OH)_2/C$	60	2:1
2	CatB-H, (*S*)-CBS[b]	100	5:1
3	Red-Al, THF[c]	100 (40)	26:1
4	$NaBH_3CN$,CH_3CN	100	1:1
5	$NaBH_4$, THF[d]	100 (86)	25:1
6	$NaBH_4/ZnCl_2$,THF	100	1:3

[a] Determined by ^{19}F NMR spectroscopy. [b] 0.5 equiv of H_2SO_4 was added to dissolve the subtsrate. CatB-H = catecholborane, CBS = Corey–Bakshi–Shibata catalyst. [c] Red-Al = 65 wt % sodium bis(2-methoxyethoxy)aluminum hydride in toluene. [d] 5 % H_2O (v/v) was added by syringe pump over 3 h.

Subjecting imines **1a–i** to the $NaBH_4$ reduction protocol showed there to be no significant dependence on the electronic properties of the starting materials. However, steric factors were found to be highly influential, with substrates derived from valine giving better selectivity than those derived from leucine, which were more selective than those derived from alanine (Table 3).

Table 3: Substrate scope for the *R*,*S*-selective imine reductions.[a]

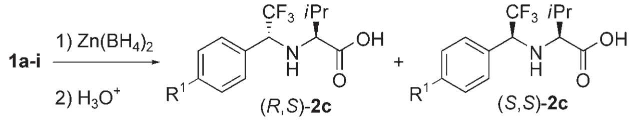


Entry	Substrate	Yield [%][b]	*R*,*S*/*S*,*S*[c]
1	**1a**	58	10:1
2	**1b**	79	19:1
3	**1c**	86	25:1
4	**1d**	46	4:1
5	**1e**	76	17:1
6	**1f**	91	46:1
7	**1g**	53	4:1
8	**1h**	79	19:1
9	**1i**	75	33:1

[a] $NaBH_4$ (8 equiv), THF, then H_2O (5 % v/v), 3 h addition. [b] Yield of isolated product from 2,2,2-trifluoromethylacetophenones. [c] As determined by ^{19}F NMR spectroscopy.

As mentioned above, reduction of **1c** with a $NaBH_4/ZnCl_2$ mixture gave modest selectivity for the *S*,*S* isomer. Addition of a preformed solution of $Zn(BH_4)_2$ to suspensions of **1c** in a variety of solvents revealed the reduction in CH_3CN to be particularly *S*,*S* selective, and gave an 8:1 mixture of diastereomers at ambient temperature. Lowering the reaction temperature to −40 °C improved the ratio to 21:1. The reaction could be run as a one-pot procedure in which the crude suspensions of the imines in MeOH were diluted with CH_3CN ($MeOH/CH_3CN$ 1:5), cooled to −40 °C, and treated with a 1 M solution of $Zn(BH_4)_2$ in 1,2-dimethoxyethane. These conditions were applied to imines **1a**–**i** and the results are detailed in Table 4. The diastereoselectivity ranged from 8:1–21:1 and, unlike the $NaBH_4$ procedure, did not show a pronounced dependence on either steric or electronic factors.

Table 4: Substrate scope for the *S*,*S*-selective imine reductions.[a]



Entry	Substrate	Yield [%][b]	*R*,*S*/*S*,*S*[c,d]
1	**1a**	45	1:15
2	**1b**	90	1:13
3	**1c**	92	1:21
4	**1d**	46	1:8
5	**1e**	76	1:12
6	**1f**	80	1:12
7	**1g**	48	1:8
8	**1h**	76	1:16
9	**1i**	72	1:13

[a] $Zn(BH_4)_2$ (2.0 equiv), $CH_3CN/MeOH$ (5:1), −40 °C, 3 h. [b] Yield of isolated product from 2,2,2-trifluoromethylacetophenones. [c] As determined by ^{19}F NMR spectroscopy. [d] In all cases, the ratios improved to greater than 100:1 by recrystallization of the Cy_2NH salts. Cy = cyclohexyl.

Ab initio calculations were performed (6-31 + G(d,p)) using **1a** as a model to better understand the observed sense of diastereoselectivity.[13] These studies suggest that the lowest energy conformation of the imine carboxylates has the methine proton co-planar with the imine face (Figure 1 a). As a result, the *si* face is flanked by the potassium (or sodium) carboxylate functionality, which is smaller than R^2. As a result, when a nonchelating reductant such as $NaBH_4$ is employed the hydride attacks the *si* face. This proposal is consistent with the observed dependence of the stereoselectivity on the steric bulk of the R^2 substituent.

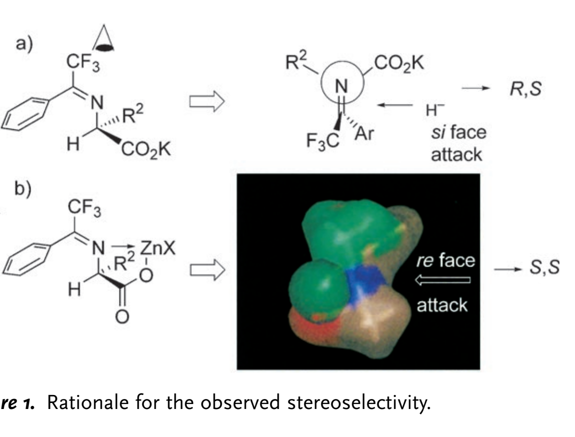


Figure 1. Rationale for the observed stereoselectivity.

To better understand the reversal in selectivity observed upon switching from $NaBH_4$ to $Zn(BH_4)_2$ ab initio calculations were performed on a substrate where the Na^+ or K^+ counterion was replaced with $ZnCl^+$ (Figure 1 b). These calculations showed that the same overall conformation was preferred, with the methine proton still eclipsing the imine, but now the $ZnCl^+$ counterion forms a chelate with the imine lone pair of electrons so that the ion is positioned to effectively shield the *si* face of the imine, thus allowing for attack at the *re* face.[14]

In conclusion, we have developed practical protocols for a reductive amination of 2,2,2-trifluoroacetophenones and α-amino esters which features a novel base-mediated formation of an imine and allows for stereoselective access to either the *R*,*S* or *S*,*S* diastereomers of the resulting amino acids by careful choice of the reducing agent. Preliminary mechanistic studies have offered some possible explanations for the observed sense of stereoselectivity for each reduction protocol. These methodologies provide rapid access to an important class of biologically active compounds. Furthermore, the simplicity and flexibility of this approach, along with the availability of a wide variety of 2,2,2-trifluoroacetophenones and α-amino esters should make these fluorinated α-amino acids appealing targets for future investigations.

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[9] While the imines could generally be isolated, it was not necessary to do so and the crude suspensions were carried directly into the borohydride reductions. Analysis of the the imine carboxylate **1b** by ^{1}H NMR spectroscopy shows an NOE interaction between the proton α to the carboxylate and the *ortho* protons of the aromatic ring, which is consistant with the proposed *E* isomer. Ab initio calculations (6-31 + G(d,p)) also show this isomer to be favored by about 6 kcal mol^{-1}.

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[14] Initially, we assumed that the presence of Zn ions allowed access to the *Z* isomer, which might be expected to undergo reduction with the opposite sense of selectivity (see Ref. [5b]). While we can not rule out the possibility that traces of the *Z* imine are formed and that this isomer undergoes reduction much faster with $Zn(BH_4)_2$ than does the major *E* isomer, we feel this is unlikely for the following reasons: 1) mixtures of *E* and *Z* imines derived from trifluoroacetaldehyde (fluoral) required about 60 minutes at ambient temperature to equilibrate to the thermodynamically preferred *E* isomer; 2) mixing the imine carboxylates with zinc salts such as $Zn(OTf)_2$ or $ZnCl_2$ resulted in a downfield shift of the proton α to the carboxylate group (the rest of the spectra remain largely unchanged), presumably as a result of coordination of the carboxylate with Zn, but analysis of this complex still shows an NOE interaction between this proton and the *ortho* protons of the aromatic ring, which is indicative of an *E* imine.