Asymmetric Synthesis

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Chiral 4-Phenyl-2-trifluoromethyloxazolidine: A High-Performance Chiral Auxiliary for the Alkylation of Amides**

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Chiral-auxiliary-based alkylation at the α-position of amides remains the strategy of choice for the preparation of various building blocks useful for the synthesis of bioactive compounds. Oxazolidinones[1] and related heterocyclic structures,[2] sultames,[3] and amino alcohols, such as pseudoephedrine,[4] count among the most efficient chiral auxiliaries reported. The use of oxazolidines as chiral auxiliaries for the diastereoselective alkylation of amide enolates has rarely been reported.[5] This is probably due to the harsh reaction conditions required for the removal of the aminoacetal functional group and its low stability. Although the introduction of fluorine atoms into molecules dramatically perturbs their physical and chemical properties,[6] little is known about the use of fluorine-containing chiral auxiliaries in asymmetric synthesis.[7] Chiral 2-trifluoromethyloxazolidines were first reported by Mikami and co-workers[8] and have recently found several applications as synthons in the stereoselective synthesis of chiral trifluoromethylated amines and amino acids.[9] We now report their use as chiral auxiliaries for highly diastereoselective alkylation reactions of amide enolates. The introduction of the trifluoromethyl group in the 2-position of the oxazolidine ring is intended to increase its stability to hydrolysis and to enable the chiral auxiliary to be recovered. Unique effects of the fluorinated group on the diastereoselectivity are also expected.

The starting *N*-acyloxazolidines **2a–d** and **3a–d** were conveniently prepared by an acylation reaction of a diastereomeric mixture of the corresponding 2-trifluoromethyloxazolidines **1**[8a] (Scheme 1). The separation of (2*S*,4*R*)-**1** and (2*R*,4*R*)-**1** was quite difficult. However, after the acylation reaction, the separation of both the 2,4-*trans* and 2,4-*cis* diastereomers was achieved very efficiently by chromatography on silica gel (eluent: cyclohexane/ethyl acetate, 9:1). With this eluent system, the R_f value of each acylated diastereomer varied from 0.13 to 0.23. Each diastereomer

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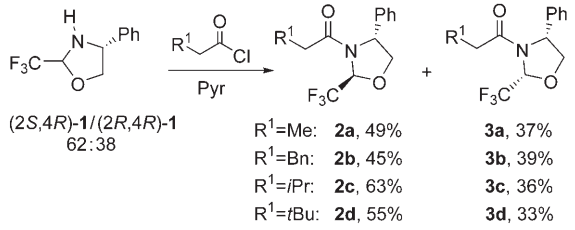
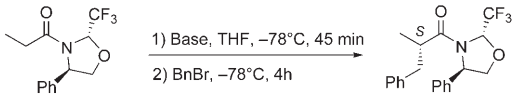


Scheme 1. Synthesis of *N*-acyl oxazolidines **2a–d** and **3a–d**. pyr = pyridine.

2a–d and **3a–d** was then obtained in good yield as the pure isolated product.

The benzylation of the *Z* enolate using the 2,4-*trans*-oxazolidine (2*S*,4*R*)-**1** as the chiral auxiliary, performed under standard conditions, occurred in good yield and with complete diastereoselectivity (Table 1). The *S* configuration of the new

Table 1: Highly diastereoselective benzylation of *N*-propanoyl oxazolidine **2a**.



2a (*S*)-**4a**

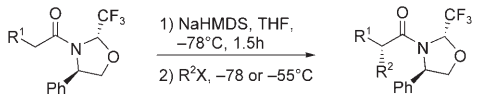
Entry	Base[a]	Yield [%][b]	*de* [%][c]
1	LiHMDS	82	>99 (*S*)
2	NaHMDS	85	>99 (S)
3	KHMDS	63	>99 (S)

[a] 1.9 equivalents. [b] Yield of the isolated product. [c] One single diastereomer was detected by GC analysis of the crude reaction mixture.

stereogenic center was assigned after removal of the chiral auxiliary (see below). LiHMDS, NaHMDS, and KHMDS (HMDS = hexamethyldisilazane) proved to be the most suitable bases for this reaction. Difluoromethylene compounds that resulted from a base-mediated dehydrofluorination were detected as side products when lithium diisopropylamide (LDA) was used.

The NaHMDS-promoted alkylation of **2a** was then performed with various halogenated derivatives (Table 2). The alkylation was completely diastereoselective with ethyl iodide and allyl bromide (entries 1 and 2). The conversion and the stereoselectivity decreased when methoxymethyl (MOM) bromide was used (entry 3). However, the stereoselectivity could be raised up to 90% *de* by adding 1,3-dimethyltetrahydro-2-pyrimidinone (DMPU) as a cosolvent (entry 4). The reaction of **2a** with more hindered branched alkyl halides, such as isobutyl iodide (entry 5) and isopropyl iodide (entry 6), occurred in good yield and was also completely stereoselective. However, with these less reactive electrophiles, the reaction had to be performed at higher temperature (−55 °C) with longer reaction times and with 4–8 equivalents of alkyl halide. The influence of various substituents on the amide moiety was then investigated. The (*R*)-**4a** epimer was also obtained in good yield with complete diastereoselectivity by the complementary strategy which

Table 2: Diastereoselective alkylation reactions of *N*-acyl oxazolidines **2a–d**.

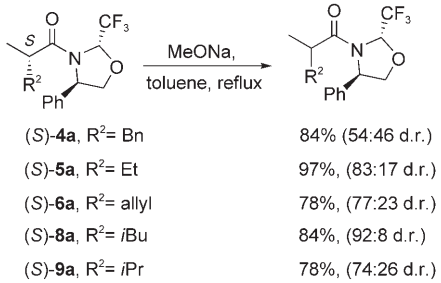


Entry	Substrate	R^2X	Product	Yield [%][a]	*de* [%]
1	**2a**, R^1 = Me	EtI[b]	(*S*)-**5a**	78	>99[c]
2	**2a**, R^1 = Me	allylBr[b]	(*S*)-**6a**	88	>98[d]
3	**2a**, R^1 = Me	MOMBr[b]	(*S*)-**7a**	60[e]	54[e]
4	**2a**, R^1 = Me	MOMBr[b,f]	(*S*)-**7a**	50[e]	90[g]
5	**2a**, R^1 = Me	*i*BuI[h]	(*S*)-**8a**	74	>99[c]
6	**2a**, R^1 = Me	*i*PrI[i]	(*S*)-**9a**	76[j]	>99[c]
7	**2b**, R^1 = Bn	MeI[b]	(*R*)-**4a**	78	>99[c]
8	**2c**, R^1 = *i*Pr	BnBr[b]	(*R*)-**4c**	71	>99[c]
9	**2d**, R^1 = *t*Bu	BnBr[k]	(*R*)-**4d**	56[l]	>99[c]

[a] Yield of isolated product. [b] Condiditions: 1.9 equivalents, −78 °C, 2–6 h. [c] One single diastereomer was detected by GC analysis of the crude reaction mixture. [d] One single diastereomer was detected by ^{19}F and ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [e] Conversion of **2a** = 66%. [f] Reaction performed in the presence of DMPU as a cosolvent. [g] GC analysis of the crude reaction mixture. [h] Conditions: 4 equivalents, −55 °C, 24 h. [i] Conditions: 8 equivalents, −55 °C, 35 h. [j] Conversion = 95%. [k] Conditions: 4 equivalents, −55 °C, 35 h. [l] Conversion = 62%.

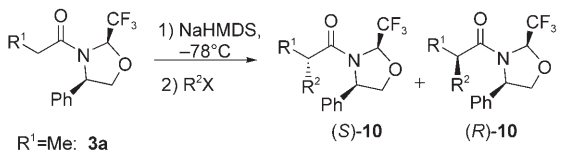
proceeded through the methylation reaction of 3-phenylpropanoylamide (**2b**; entry 7). This result highlights the great potential of this (*R*)-phenylglycinol-based fluorinated oxazolidine as a chiral auxiliary for asymmetric alkylation reactions. The benzylation of the isopropyl-substituted amide **2c** was performed under standard conditions to give (*R*)-**4c** in good yield with a total diastereoselectivity (entry 8). The benzylation of the more hindered *tert*-butyl-substituted amide **2d** occurred also with complete diastereoselectivity, but required a higher temperature (−55 °C), a longer reaction time, and 4 equivalents of alkyl halide (entry 9).

The complete diastereoselectivity of the alkylation reactions was confirmed by epimerization reactions of **4–6a**, **8**, and **9a** (Scheme 2).[10] These side-chain epimers were not detected by GC or NMR spectroscopic analysis of the crude mixture of the alkylation reaction.



Scheme 2. Epimerization reactions of **4–6a**, **8**, and **9a**.

The results of the alkylation reactions using the 2,4-*cis*-oxazolidine (2*R*,4*R*)-**1** as the chiral auxiliary were somewhat disappointing (Scheme 3). The stereoselectivity of the benzylation of **3a** was very low and no stereoselectivity was induced



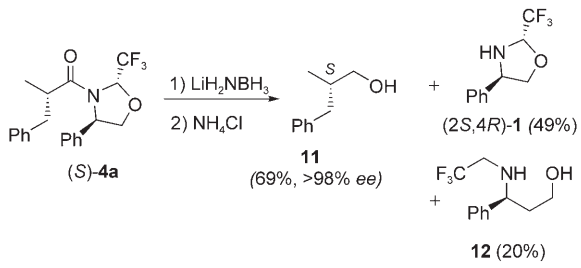
R¹=Me: **3a**
R¹=Bn: **3b**

R¹	R²X	Yield [%]	(*S*)-**10**/(*R*)-**10** (d.r.)
Me	BnBr	55	69:31
Bn	MeI	66	50:50

Scheme 3. Alkylation reactions of *N*-propanoyl oxazolidines **3a**, **b**.

during the methylation of **3b**. It is worthwhile noting that the same major *S* diastereomer was obtained from the benzylation of (2*S*,4*R*)-**2a** and (2*R*,4*R*)-**3a**. This underlines the preponderant influence of the configuration at C4 in the chiral auxiliary on the stereoselective induction. The pseudo-C_2 symmetry of the 2,4-*trans*-oxazolidine could be an explanation of its high performance as a chiral auxiliary. With this auxiliary, the same diastereotopic face of the enolate is shielded around the C1–N3 bond in both major conformations.

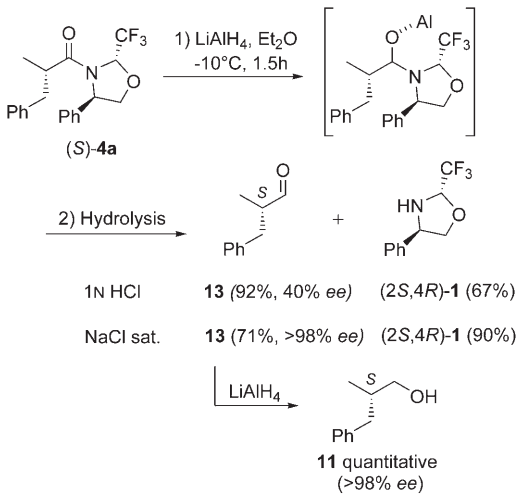
Key features of the use of this fluorinated oxazolidine as a chiral auxiliary that warrant future synthetic study are its removal and recovery. As all the standard methods known for the hydrolysis of amide bonds in acidic or basic media failed to give the corresponding carboxylic acid or caused epimerization, we examined reductive conditions. First lithium amidotrihydroborate (LiH_2NBH_3),[11] which transforms tertiary amides into the corresponding primary alcohols, was used (Scheme 4). With this reagent, the expected *S* alcohol **11**



Scheme 4. Removal of the chiral auxiliary from (*S*)-**4a** with LiH_2NBH_3.

was obtained in enantiomerically pure form,[12] provided that the reaction was performed at 0 °C.[13] Unfortunately, the chiral auxiliary **1** was only recovered in 49% yield and the amino alcohol **12** that resulted from the reduction of the oxazolidine **1** was obtained in 20% yield.

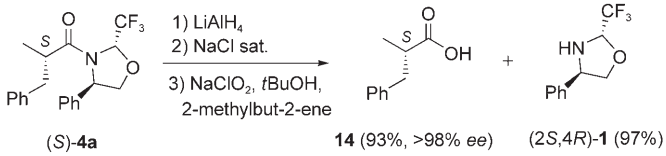
This over-reduction of the chiral auxiliary could be easily avoided by using $LiAlH_4$ (Scheme 5). Under these conditions, aldehyde **13** was selectively obtained in good yield without any epimerization when the hydrolysis step was performed in a neutral medium. The *S* configuration of **13** was assigned by comparison with literature data[14] of the Mosher ester of the alcohol **11** obtained by quantitative reduction of **13** with $LiAlH_4$. The chiral auxiliary (2*S*,4*R*)-**1** was very efficiently recovered in 90% yield. It is important to note that neither the complete reduction of the amide group into an amine nor



Scheme 5. Removal of the chiral auxiliary from (*S*)-**4a**, thus selectively giving aldehyde **13** in enantiomerically pure form.

the reduction of the oxazolidine ring occurred. The key intermediate of this reaction should be an aluminum hemiacetal, which is stable under the reaction conditions. The corresponding hemiacetal is then hydrolyzed[15] to give the expected aldehyde and the fluorinated oxazolidine in high yield. The hydrolysis should be performed under neutral rather than acidic conditions to avoid epimerization. As the aldehyde **13** could be quantitatively reduced into alcohol **11** and the chiral auxiliary was very efficiently recovered, this two-step procedure proved to be more efficient than the direct reduction of (*S*)-**4a** with LiH_2NBH_3.

The corresponding enantiopure carboxylic acid (*S*)-**14**[16] was also obtained in high yield and enantiomeric excess from (*S*)-**4a** in a two-step procedure, which involved the reduction of (*S*)-**4a** with $LiAlH_4$ followed by the oxidation of the aldehyde (Scheme 6). The chiral auxiliary was recovered in 97% yield.



Scheme 6. Removal of the chiral auxiliary from (*S*)-**4a**, thus selectively giving carboxylic acid **14** in enantiomerically pure form.

In summary, we have reported the use of a 2-trifluoromethyloxazolidine as a chiral auxiliary for the first time. Alkylation reactions of the corresponding amides occurred with extremely high diastereoselectivity. As representative target molecules, (*S*)-α-methylbenzenepropanal, (*S*)-β-methylbenzenepropanol, and (*S*)-α-methylbenzenepropanoic acid were obtained in high yield in enantiopure form. Moreover, the highly stable fluorinated oxazolidine was conveniently recovered in high yield. Further investigations into understanding the extremely high diastereoselectivity and other

synthetic applications are underway and will be reported in due course.

Experimental Section

General procedure for the alkylation reactions: The oxazolidine **2a–c** (1.19 mmol) was dissolved in THF (10 mL) under argon and cooled down to −78 °C. NaHMDS was added dropwise (1.1 mL, 2 M in THF, 2.24 mmol), the reaction mixture was stirred for 45 min–1.5 h at this temperature, and the electrophile (2.24 mmol) was added slowly. The reaction mixture was stirred for a further 2 h at −78 °C, quenched with a saturated solution of NH_4Cl (15 mL), and extracted with diethyl ether (2 × 30 mL) and dichloromethane (30 mL). The combined organic layers were dried over $MgSO_4$, evaporated under reduced pressure, and the resulting crude mixture was purified by filtration through a short pad of silica gel (20 g).

Reductive cleavage of (*S*)-**4a**: (*S*)-**4a** (400 mg, 1.1 mmol) was dissolved in anhydrous diethyl ether (10 mL) under argon and the solution was cooled down to −10 °C. $LiAlH_4$ (167 mg, 4.4 mmol) was added slowly and the reaction mixture was stirred for 1.5 h at −10 °C. A saturated solution of NH_4Cl (10 mL) was added dropwise at −10 °C, and the solution was vigorously stirred for 2.5 h at room temperature. At this stage, the intermediate hemiacetal could be detected. The aqueous layer was extracted with diethyl ether (2 × 20 mL) and dichloromethane (20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The resulting crude mixture was purified by column chromatography (cyclohexane/diethyl ether 98:2–95:5) to afford **13** as a colorless oil (116 mg, 71 %) and (2*S*,3*R*)-**1** (213 mg, 90 %).

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