JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

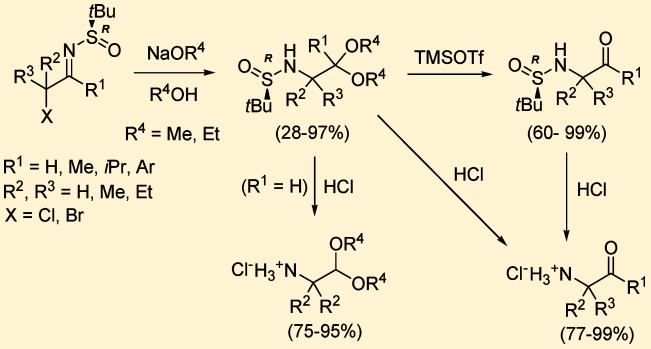
Rearrangement of *N-tert*-Butanesulfinyl α-Halo Imines with Alkoxides to *N-tert*-Butanesulfinyl 2-Amino Acetals as Precursors of *N*-Protected and *N*-Unprotected α-Amino Carbonyl Compounds

Filip Colpaert,[†] Sven Mangelinckx,[†] Bram Denolf, and Norbert De Kimpe*

Department of Sustainable Organic Chemistry and Technology, Faculty of Bioscience Engineering, Ghent University, Coupure Links 653, B-9000 Ghent, Belgium

Supporting Information

ABSTRACT: Reaction of *N-tert*-butanesulfinyl α-halo imines with alkoxides afforded new *N-tert*-butanesulfinyl 2-amino acetals in good to excellent yield. These *N-tert*-butanesulfinyl 2-amino acetals are convenient precursors for the TMSOTf-promoted synthesis of the corresponding *N*-protected α-amino aldehydes and ketones, as well as for the HCl-promoted synthesis of 2-amino acetal hydrochlorides and α-amino ketone and α-amino aldehyde hydrochlorides in high yield. Via this method, an asymmetric synthesis of (*S*)-cathinone hydrochloride (er 94:6) was achieved.



INTRODUCTION

α-Amino carbonyl compounds are important and versatile compounds that are indispensable in the synthesis of nitrogen-containing natural products and are widely used in the pharmaceutical industry.[1] Their utility stems from the broad scope of synthetic transformations that are possible with both the amino and carbonyl functional groups. Several α-amino carbonyl compounds are also known for their metabolic roles in health and disease,[2] like aminoacetone, which is putatively overproduced in patients with diabetes mellitus and *cri-du-chat* syndrome[3] and is also known as the penultimate precursor to the antitumor agent Azinomycin A.[4]

Numerous syntheses of α-amino carbonyl compounds have been developed, and new ones continue to be devised to provide access to these important chemical building blocks.[1a−h] However, most of these methods have their disadvantages. A common preparation of α-amino ketones proceeds via amination of α-halo ketones,[1c−e] in which side reactions such as dehalogenation followed by Michael addition,[1e] Favorskii type rearrangement,[5] and Voigt−Amadori rearrangement[1e] compete when certain combinations of substrates and amines are used. Amination of α-hydroxy ketones for the synthesis of α-amino ketones may give the formation of undesired crossover products and is limited by the various substitution patterns allowed in the substrates.[6] The ring-opening of alkoxy epoxides with amines resulted only in very specific α,α-dialkylated α-aminoaryl ketones,[7] while ring-opening of phenylsulfinyl epoxides with amines was limited to some α-aminoalkyl ketones and α-amino aldehydes.[8] The Neber-rearrangement of oxime tosylates and dimethylhydrazone methiodides to the corresponding azirine intermediates, followed by acid treatment, led to the synthesis of very specific *N*-unprotected α-amino ketones.[9] Very recently, a useful route toward specific α,α-unsubstituted *N*-sulfonyl α-amino ketones from terminal alkynes was developed via a rhodium(II)-catalyzed denitrogenative hydration reaction of the corresponding *N*-sulfonyl-1,2,3-triazoles.[1b]

The utility of α-amino carbonyl compounds is not without shortcomings, as nitrogen- or carbon-protecting groups are usually needed in order to prevent undesired inter- and intramolecular self-condensation reactions.[1a−h,10] 2-Amino acetals are protected α-amino carbonyl compounds and are known as useful synthetic building blocks for nitrogen-containing heterocycles.[11]

In our research group, the reaction of α-halo imines with alkoxides has been studied in detail, giving rise to a variety of 2-alkoxyaziridine intermediates, 2-amino acetals, cyclopropylamines, α-alkoxy ketones, imidates, and amides, among other compounds.[12] *C*-Oxygen-substituted aziridines are usually unstable compounds and appear primarily as intermediates en route to the final products.[13] A related reaction of interest is the Duhamel ring contraction of halogenated heterocyclic enamines with sodium methoxide leading to 2-(dimethoxymethyl)azaheterocycles via bicyclic C-methoxy-substituted aziridinium intermediates.[12g,14] However, in general, the nitrogen deprotection of the *N*-alkyl or *N*-aryl compounds after reaction of α-halo imines with alkoxides provides a limitation in the reported applications.

Received: April 11, 2012
Published: June 29, 2012

dx.doi.org/10.1021/jo300752c | J. Org. Chem. 2012, 77, 6023−6032

Scheme 1. Reactivity of *N*-*tert*-Butanesulfinyl α-Halo Imines 1 toward Alkoxides

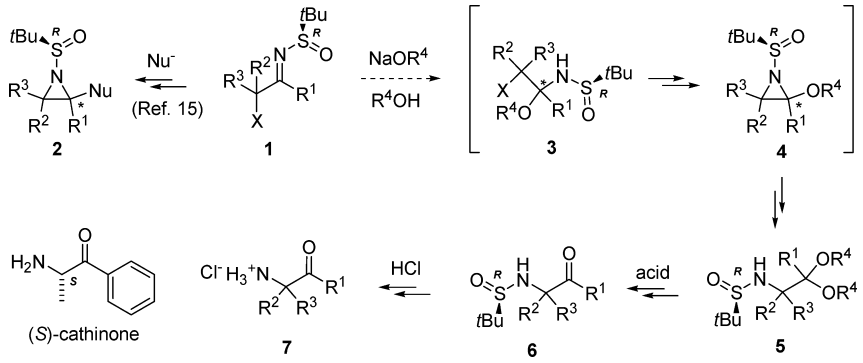
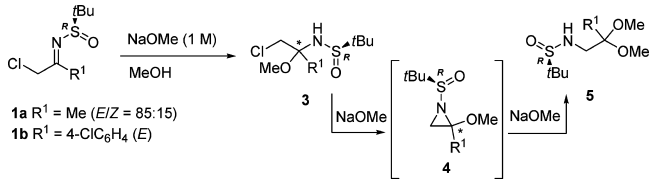


Table 1. Reaction of *N*-*tert*-Butanesulfinyl α-Chloro Imines 1a and 1b with NaOMe in MeOH



entry	NaOMe (equiv)	R^1	temp (°C)/time (h)	3/5[a]	dr 3	yield 5 (%)[b]
1	3	Me	−78/1	100:0	77:23	
2	3	Me	rt/2	0:100		**5a** (81)
3	3	Me	−40/2	100:0	41:59	
4	3	Me	−78 to rt/1	30:70	52:48	
5	1	Me	rt/1[c]	75:25[d]	50:50	
6	3	4-ClC_6H_4	−78/1	100:0	62:48	
7	3	4-ClC_6H_4	rt/2	0:100		**5b** (93)
8	3	4-ClC_6H_4	−40/1	100:0	57:43	
			+ −30/1	100:0	58:42	
			+ −20/1	100:0	57:43	
			+ −10/1	0:100		

[a]Determined via ^{1}H NMR analysis of the crude reaction mixture. [b]Isolated yield after purification via flash chromatography. [c]1 equiv of 1 M NaOMe in MeOH was added to a solution of imine **1a** in THF. [d]Incomplete conversion of 63% of imine **1a** to compounds **3** and **5**.

Recently, our and other research groups prepared a variety of chiral aziridines **2** with very good stereoselectivity via various nucleophilic addition reactions across α-chlorinated *N*-*tert*-butanesulfinyl imines **1**.[15] Nevertheless, the reactivity of α-halogenated *N*-*tert*-butanesulfinyl imines **1** toward alkoxides has never been studied. It was envisioned that reaction of *N*-*tert*-butanesulfinyl α-halo imines **1** with alkoxides would result in the synthesis of sulfinamides **3**, which cyclize to *N*-*tert*-butanesulfinyl 2-alkoxyaziridines **4**, as interesting intermediates for the formation of new *N*-*tert*-butanesulfinyl 2-amino acetals **5** (Scheme 1).

Only two synthetic methods for the synthesis of specific *N*-sulfinyl 2-aminoacetals have been reported, one via a condensation reaction of the corresponding *N*-sulfinyl imine, possessing a 2-methyl-1,3-dioxolanyl group, with an ester enolate,[16] and a second via reduction of *N*-[1-(triethoxymethyl)ethylidene]sulfinamide.[17] The 2-amino acetals **5**, together with the corresponding *N*-*tert*-butanesulfinyl α-amino aldehydes and ketones **6**, could be elaborated as new stable precursors for the synthesis of a variety of α-amino carbonyl compounds **7** (Scheme 1).

Recently, Davis and co-workers reported the synthesis of *N*-sulfinyl α-amino ketones via the addition of 2-lithio-1,3-dithianes to enantiopure sulfinimines in an effort to achieve the asymmetric synthesis of (*S*)-cathinone (Scheme 1).[18] (*S*)-Cathinone is the main active compound isolated from the leaves of *Catha edulis* (Khat) and exhibits cardiovascular activity, next to an activity similar to amphetamines and dopamine.[19] Herein, the developed synthetic pathway will be also explored toward the asymmetric synthesis of cathinone.

The expected easy removal of the *N*-*tert*-butanesulfinyl group at nitrogen is important from a practical viewpoint, especially as compared to the less convenient deprotection reactions in literature protocols. While the *N*-*tert*-butanesulfinyl group is primarily used as a chiral directing and electron-withdrawing group in the reactions of imines **1** with nucleophiles, herein the *N*-sulfinyl group is currently mainly used as a practical *N*-protective and stabilizing group (except for the asymmetric synthesis of cathinone), comparable in reactivity to a Boc group, sensu strictu.[20]

RESULTS AND DISCUSSION

Initially, the reactivity of *N*-*tert*-butanesulfinyl α-halo imines **1** toward alkoxides was studied with nonaromatic *N*-*tert*-butanesulfinyl α-chloro imine **1a** and aromatic *N*-*tert*-butanesulfinyl α-chloro imine **1b** in reactions with NaOMe (1 M in MeOH) (Table 1).

As recently described by our research group, the synthesis of the aromatic *N*-*tert*-butanesulfinyl α-chloro ketimines **1b**,**c**, as single *E*-isomers in 88−89% yield, was performed by

dx.doi.org/10.1021/jo300752c | J. Org. Chem. 2012, 77, 6023−6032

condensation of the appropriate phenacyl chlorides with (R_s)-*tert*-butanesulfinamide in the presence of 2 equiv of $Ti(OEt)_4$ in THF.[15a,g] The aliphatic *N*-*tert*-butanesulfinyl α-chloro ketimine **1a** was obtained via a similar procedure starting from α-chloro acetone in 63% yield with an *E*/*Z*-ratio of 85:15.[15i]

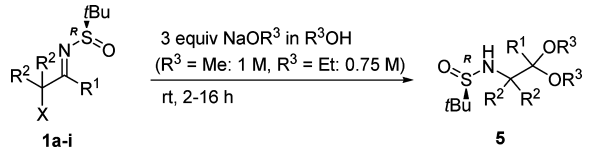
The initial reaction conditions involved the addition of 3 equiv of a freshly prepared 1 M solution of NaOMe in MeOH to *N*-sulfinyl imine **1a** at −78 °C and subsequent stirring for 1 h at −78 °C (Table 1, entry 1). After aqueous workup, the formation of *N*-*tert*-butanesulfinyl 2-chloro-1-methoxy-1-methylethylamine **3a** with a diastereomeric ratio of 77:23 (^{1}H NMR analysis) was observed. Unfortunately, sulfinamide **3a** was unstable at room temperature and was smoothly converted back to the corresponding *N*-sulfinyl imine **1a** upon standing a short time in $CDCl_3$. The moderate diastereomeric ratio obtained and the easy reversal of adduct **3** to starting imine **1** indicate that the equilibrated addition reaction is thermodynamically controlled.

On the other hand, when 3 equiv of NaOMe (1 M in MeOH) were added to *N*-sulfinyl imine **1a** at room temperature and the reaction mixture was stirred for 2 h, the corresponding *N*-*tert*-butanesulfinyl 2-amino acetal **5a** was formed (Table 1, entry 2). After purification of the reaction mixture via flash chromatography, *N*-*tert*-butanesulfinyl 2-amino acetal **5a** was isolated in 81% yield. The proposed mechanism involves the formation of the corresponding *N*-sulfinyl 2-methoxyaziridine **4a**, which undergoes spontaneous ring-opening, followed by attack of a second equivalent of NaOMe.[12g,h,l−n,13] Subsequently, in an effort to isolate or detect the intermediate *N*-sulfinyl 2-methoxyaziridine **4a**, some other reaction conditions were tested. Repeating the reaction at −40 °C for 2 h afforded a full conversion to *N*-*tert*-butanesulfinyl 2-chloro-1-methoxy-1-methylethylamine **3a** with a reversed diastereomeric ratio of 41:59 in comparison to the reaction performed at −78 °C (Table 1, entry 3). Upon performing the addition of NaOMe at −78 °C, after which the temperature was allowed to warm up to room temperature for 1 h, a mixture of sulfinamide **3a** (dr 52:48) and *N*-*tert*-butanesulfinyl 2-amino acetal **5a** in a ratio of 30:70 was obtained (entry 4). Adding 1 equiv of NaOMe instead of 3 equiv to *N*-sulfinyl imine **1a** at room temperature in THF for 1 h resulted in an incomplete conversion of 63% to a mixture of sulfinamide **3a** (dr 50:50) and 2-amino acetal **5a** in a ratio of 75:25 (entry 5). Unfortunately, no intermediate *N*-sulfinyl 2-methoxyaziridine **4a** could be detected in any of these attempted reactions, indicating the inherent instability of this highly activated aziridine **4a**.

Furthermore, when the substrate was altered from nonaromatic *N*-sulfinyl imine **1a** to aromatic *N*-sulfinyl imine **1b** and 3 equiv of 1 M NaOMe was added at −78 °C for 1 h, the corresponding *N*-*tert*-butanesulfinyl 2-chloro-1-methoxy-1-phenylethylamine **3b** was obtained after aqueous work up in a diastereomeric ratio of 62:48 (Table 1, entry 6). Similarly, sulfinamide **3b** was unstable and reverted to the corresponding *N*-sulfinyl imine **1b** upon standing overnight at room temperature in $CDCl_3$. Direct treatment of sulfinamide **3b** with various bases, either 5 equiv of K_2CO_3 in acetonitrile at room temperature for 1 h or 1.5 equiv of LiHMDS in THF at 0 °C for 1 h, did not afford the desired *N*-sulfinyl 2-methoxyaziridine **4b**, and instead *N*-sulfinyl imine **1b** was recovered as the major product.

When 3 equiv of 1 M NaOMe in MeOH were added to *N*-sulfinyl imine **1b** at room temperature for 2 h, the corresponding *N*-*tert*-butanesulfinyl 2-amino acetal **5b** was isolated in 93% yield after purification via flash chromatography (Table 1, entry 7). In an effort to determine the temperature at which sulfinamides **3** were transformed to *N*-sulfinyl 2-amino acetals **5**, the reaction of *N*-sulfinyl imine **1b** with NaOMe was repeated starting at −40 °C with a gradual increase of temperature (Table 1, entry 8). When 3 equiv of 1 M NaOMe in MeOH were added to *N*-sulfinyl imine **1b** at −40 °C for 1 h, followed by stirring at −30 °C for 1 h and subsequently at −20 °C for 1 h, sulfinamide **3b** was formed with a diastereomeric ratio of 57:43. Subsequent stirring at −10 °C for 1 h afforded a full conversion to the corresponding *N*-*tert*-butanesulfinyl 2-amino acetal **5b**, which indicates that the conversion from sulfinamide **3b** to acetal **5b** proceeds readily between −20 and −10 °C (entry 8). Subsequently, the optimized reaction conditions leading to the synthesis of *N*-*tert*-butanesulfinyl 2-amino acetals **5a** and **5b** were also applied to aromatic *N*-sulfinyl α-chloroketimines **1c** and **1f** (R^1 = C_6H_5, 2,4-$Cl_2C_6H_3$), aromatic *N*-sulfinyl α-bromoketimines **1d,e** (R^1 = 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$), nonaromatic *N*-sulfinyl α-bromoketimine **1g** (R^1 = *i*Pr), and *N*-sulfinyl α-chloro aldimines **1h,i** (R^1 = H). Furthermore, in addition to NaOMe, NaOEt (0.75 M in EtOH) was also used as a nucleophile in the corresponding alcohol as solvent (Table 2).

Table 2. Synthesis of *N*-*tert*-Butanesulfinyl 2-Amino Acetals 5



1a-i **5**

entry	X	imine **1**	R^1	R^2	R^3	time (h)	yield **5** (%)[a]
1	Cl	**1a**	Me	H	Me	2	**5a** (81)
2	Cl	**1b**	4-ClC_6H_4	H	Me	2	**5b** (93)
3	Cl	**1a**	Me	H	Et	2	**5c** (70)
4	Cl	**1b**	4-ClC_6H_4	H	Et	2	**5d** (95)
5	Cl	**1c**	C_6H_5	H	Me	2	**5e** (83)
6	Cl	**1c**	C_6H_5	H	Et	2	**5f** (97)
7	Br	**1d**	4-$MeOC_6H_4$	H	Me	2	**5g** (94)
8	Br	**1e**	4-$NO_2C_6H_4$	H	Me	2	**5h** (97)
9	Cl	**1f**	2,4-$Cl_2C_6H_3$	H	Me	2	**5i** (93)
10	Br	**1g**	*i*Pr	H	Me	2	**5j** (76)
11	Cl	**1h**	H	Me	Me	16	**5k** (96)[b]
12	Cl	**1h**	H	Me	Et	16	**5l** (77)
13	Cl	**1i**	H	Et	Me	16	**5m** (57)
14	Cl	**1i**	H	Et	Et	16	**5n** (28)

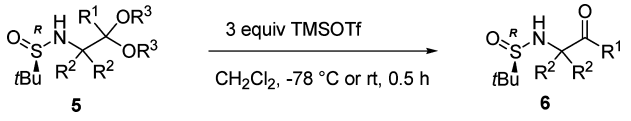
[a]Isolated yield after purification via flash chromatography. [b]Performing the same experiment starting with racemic *N*-sulfinyl aldimine **1h** led to the isolation of racemic acetal **5k** in 97% yield.

N-*tert*-Butanesulfinyl α-chloro and α-bromo imines **1d−i** were synthesized in 77−92% yield via condensation of the appropriate α-halo ketones and aldehydes with (R_s)-*tert*-butanesulfinamide in the presence of 2 equiv of $Ti(OEt)_4$ in THF.[15a,c,g] Noteworthy, since the *N*-sulfinyl group is only used as a *N*-protective and stabilizing group, the experiment for the synthesis of *N*-*tert*-butanesulfinyl 2-amino acetal **5k** (R^1 = H; R^2 = R^3 = Me) was also repeated starting from racemic *N*-sulfinyl aldimine **1h**, leading to the same result as obtained via the treatment of chiral aldimine (R_S)-**1h** with NaOMe.

dx.doi.org/10.1021/jo300752c | J. Org. Chem. 2012, 77, 6023−6032

A wide variety of *N*-*tert*-butanesulfinyl 2-amino acetals **5** were obtained in good to excellent yields after purification via flash chromatography, except for *N*-sulfinyl 2-amino acetal **5n**, which was isolated in only 28% yield because of the formation of the corresponding *N*-sulfinyl α-amino aldehyde **6i** upon column chromatography (Table 2, entry 14 and Table 3).

Table 3. Synthesis of *N*-*tert*-Butanesulfinyl α-Amino Ketones 6a−g and α-Amino Aldehydes 6h,i



5 6

entry	R^1	R^2	R^3	temp (°C)	yield **6** (%)
1	Me	H	Me	−78	**6a** (91)
2	Me	H	Et	−78	**6a** (88)
3	4-ClC_6H_4	H	Me	−78	**6b** (99)
4	4-ClC_6H_4	H	Et	−78	**6b** (92)
5	C_6H_5	H	Me	−78	**6c** (82)
6	C_6H_5	H	Et	−78	**6c** (71)
7	4-$MeOC_6H_4$	H	Me	−78	**6d** (99)
8	4-$NO_2C_6H_4$	H	Me	−78	**6e** (99)
9	2,4-$Cl_2C_6H_3$	H	Me	−78	**6f** (99)
10	*i*Pr	H	Me	−78	**6g** (76)
11	H	Me	Me	rt	**6h** (95)[a]
12	H	Me	Et	rt	**6h** (99)
13	H	Et	Me	rt	**6i** (99)
14	H	Et	Et	rt	**6i** (99)

[a]For obtaining full conversion of **5k** into **6h**, after addition of 3 equiv of TMSOTf at room temperature for 30 min, additionally two times 3 equiv of TMSOTf were added subsequently at room temperature for 30 min.

The substitution pattern of aromatic *N*-sulfinyl α-haloketimines **1b−f** seemed not to have any peculiar effect on the reaction with alkoxides to the corresponding *N*-*tert*-butanesulfinyl 2-amino acetals **5** (Table 2, entries 5−9). Even when the more steric *N*-sulfinyl α-chloroketimine **1f** (R^1 = 2,4-$Cl_2C_6H_3$) was used as an aromatic substrate with an ortho substitution, the desired *N*-*tert*-butanesulfinyl 2-amino acetal **5i** was obtained in 93% yield (Table 2, entry 9). The more bulky isopropyl group of nonaromatic *N*-sulfinyl α-bromoketimine **1g** (R^1 = *i*Pr) had no detrimental effect and the corresponding *N*-*tert*-butanesulfinyl 2-amino acetal **5j** was isolated in 76% yield (Table 2, entry 10). When *N*-*tert*-butanesulfinyl α-chloro aldimines **1h,i** were used as substrates, the reaction time had to be increased to 16 h to obtain a full conversion (Table 2, entries 11−14). The latter observation indicates that the aziridines **4** without an additional substituent at the 2-position (R^1 = H) are more difficult to form and/or are less prone toward ring-opening and further conversion to α-amino acetals **5**. Noteworthy, when KO*t*Bu was used as nucleophile instead of NaOMe and NaOEt in reaction with *N*-*tert*-butanesulfinyl α-chloro aldimines **1h,i**, complex mixtures were obtained, which contained the corresponding α,β-unsaturated imines and α,β-unsaturated aldehydes in various ratios.

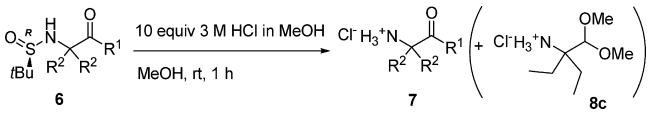
In a following step, the *N*-*tert*-butanesulfinyl 2-amino acetals **5** could be easily transformed to the corresponding *N*-*tert*-butanesulfinyl α-amino ketones **6a−g** and *N*-*tert*-butanesulfinyl α-amino aldehydes **6h,i** via a mild TMSOTf-promoted cleavage of the acetal functionality (Table 3).[21] Treatment of *N*-*tert*-butanesulfinyl 2-amino acetals **5a−j** ($R^1 \neq$ H) with 3 equiv of TMSOTf in CH_2Cl_2 at −78 °C for 0.5 h afforded the corresponding *N*-*tert*-butanesulfinyl α-amino ketones **6a−g** in 71 to 99% yield (Table 3, entries 1−10).

N-*tert*-Butanesulfinyl α-amino aldehydes **6h,i** were obtained in quantitative yield from *N*-*tert*-butanesulfinyl 2-amino acetals **5k−n** (R^1 = H) via a similar procedure, but this time TMSOTf had to be added at room temperature for 0.5 h to achieve full conversion (Table 3, entries 11−14). Exceptionally, to obtain full conversion of *N*-*tert*-butanesulfinyl 2-amino acetal **5k** into *N*-*tert*-butanesulfinyl α-amino aldehyde **6h**, after addition of 3 equiv of TMSOTf at room temperature for 30 min, two additional 3 equiv aliquots of TMSOTf were added subsequently at room temperature for 30 min, which afforded *N*-*tert*-butanesulfinyl α-amino aldehyde **6h** in 95% yield (Table 3, entry 11). Increasing the amount of TMSOTf to 10 equiv at room temperature for 30 min or increasing to reflux temperature did not afford full conversion of acetal **5k** into aldehyde **6h**.

When *N*-sulfinyl 2-amino acetal **5e** (R^1 = Ph; R^2 = H; R^3 = Me) was treated with aqueous 6 M HCl in a two-phase system with CH_2Cl_2 at room temperature for 1 h, the corresponding *N*-sulfinyl α-amino ketone **6c** was also formed but was contaminated with unidentified side products.

In a following step, *N*-*tert*-butanesulfinyl α-amino carbonyl compounds **6** were treated with HCl to achieve *N*-deprotection and formation of the corresponding hydrochlorides of α-amino ketones and aldehydes **7** (Table 4 and Scheme 2). When *N*-*tert*-

Table 4. HCl-Promoted *N*-Deprotection of *N*-*tert*-Butanesulfinyl α-Amino Carbonyl Compounds 6



6 7 8c

entry	R^1	R^2	yield **7** (%)[a]
1	Me	H	**7a** (96)
2	4-ClC_6H_4	H	**7b** (99)
3	C_6H_5	H	**7c** (92)
4	4-$MeOC_6H_4$	H	**7d** (95)
5	4-$NO_2C_6H_4$	H	**7e** (88)
6	2,4-$Cl_2C_6H_3$	H	**7f** (86)
7	*i*Pr	H	**7g** (94)
8	H	Et	**7i** + **8c**[b]

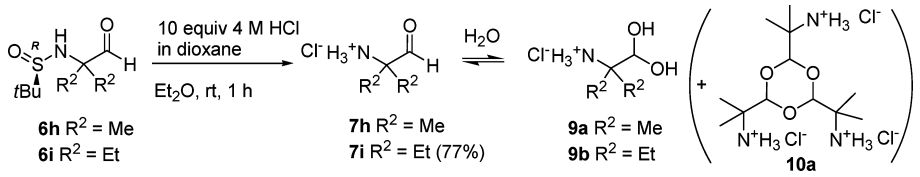
[a]Isolated yield after precipitation in Et_2O. [b]An inseparable mixture of α-amino aldehyde hydrochloride **7i** and 2-amino acetal hydrochloride **8c** in a ratio of 75:25 was obtained.

butanesulfinyl α-amino ketones **6a−g** ($R^1 \neq$ H) were treated with 10 equiv of 3 M HCl in MeOH at room temperature for 1 h, the corresponding α-amino ketone hydrochlorides **7a−g** were obtained in excellent yields (86−99%) after precipitation in dry Et_2O (Table 4, entries 1−7).

Unfortunately, when *N*-*tert*-butanesulfinyl α-amino aldehyde **6i** (R^1 = H) was treated with 3 M HCl in MeOH under the same conditions, an inseparable mixture of the desired α-amino aldehyde hydrochloride **7i** and the corresponding 2-amino acetal hydrochloride **8c** in a ratio of 75:25 was obtained. Therefore, *N*-*tert*-butanesulfinyl α-amino aldehydes **6h,i** (R^1 = H) were treated with 10 equiv of anhydrous 4 M HCl in dioxane for 1 h at room temperature in Et_2O (Scheme 2). When *N*-*tert*-butanesulfinyl α-amino aldehyde **6h** (R^2 = Me) was treated with HCl in dioxane, the formation of the desired

dx.doi.org/10.1021/jo300752c | J. Org. Chem. 2012, 77, 6023−6032

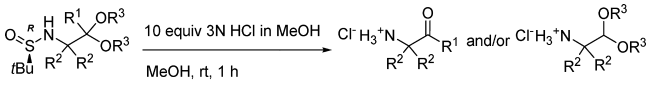
Scheme 2. HCl-Promoted *N*-Deprotection of *N*-*tert*-Butanesulfinyl α-Amino Aldehydes 6h,i



α-amino aldehyde hydrochloride **7h** was observed, but because of its high hygroscopicity, aldehyde **7h** was partially converted to the corresponding hydrate **9a**. The equilibrium of α-amino aldehydes and the corresponding hydrates is known in the literature.[22] Furthermore, a partial cyclotrimerization of aldehyde **7h** to the corresponding 1,3,5-trioxane **10a** was also observed, in addition to some other unidentified side products. In the literature it is known that the equilibrium between the free aldehyde and its trimer is highly temperature-dependent.[23] Treatment of *N*-*tert*-butanesulfinyl α-amino aldehyde **6i** (R^2 = Et) with HCl in dioxane afforded the corresponding α-amino aldehyde hydrochloride **7i**. In contrast to the synthesis of α-amino aldehyde hydrochloride **7h**, in this case no cyclotrimerization was observed and aldehyde **7i** was isolated in 77% yield after precipitation in Et_2O. Nevertheless, during ^1H NMR analysis, α-amino aldehyde hydrochloride **7i** was partially converted to the corresponding hydrate **9b**. ^1H NMR analysis of **9b** in DMSO-d_6 showed an equilibrium ratio of 80:20 between aldehyde **7i** and the corresponding hydrate **9b**, while a reversed ratio of aldehyde **7i** and the deuterated form of hydrate **9b** of 13:87 was obtained via ^1H NMR analysis in D_2O.

In order to elaborate *N*-*tert*-butanesulfinyl 2-amino acetals **5** as new stable *N*- and *C*-protected precursors for a variety of α-amino carbonyl compounds **7**, these acetals **5** were also treated with 3 M HCl in MeOH (Table 5). Treatment of *N*-*tert*-butanesulfinyl 2-amino acetals **5a–f** ($R^1 \neq H$) with 10 equiv of 3 M HCl in MeOH at room temperature for 1 h afforded the corresponding α-amino ketone hydrochlorides **7a–c** in excellent yields (89–99%) after precipitation in Et_2O (Table 5, entries 1–6). When *N*-*tert*-butanesulfinyl 2-amino acetals **5k–m** (R^1 = H) were treated with 3 M HCl in MeOH under the same conditions, the corresponding 2-amino acetal hydrochlorides **8a–c** were obtained in 75–95% yields (Table 5, entries 7–9).

Table 5. Synthesis of α-Amino Ketone and Aldehyde Hydrochlorides 7 and 2-Amino Acetal Hydrochlorides 8



5 7 8

entry	R^1	R^2	R^3	yield **7**/**8** (%)
1	Me	H	Me	**7a** (90)
2	Me	H	Et	**7a** (99)
3	4-ClC_6H_4	H	Me	**7b** (97)
4	4-ClC_6H_4	H	Et	**7b** (92)
5	C_6H_5	H	Me	**7c** (90)
6	C_6H_5	H	Et	**7c** (89)
7	H	Me	Me	**8a** (75)[a]
8	H	Me	Et	**8b** (95)
9	H	Et	Me	**8c** (81)
10	H	Et	Et	**7i** + **8d**[b]

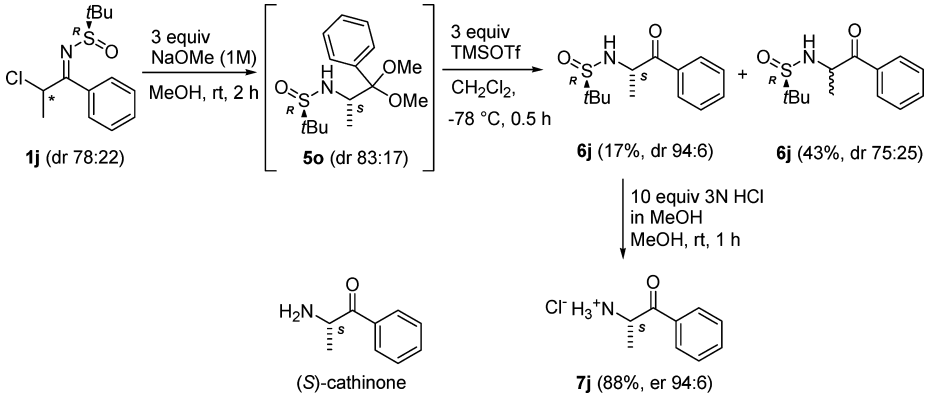
[a]Treating 2-amino acetal **5k** with 50 equiv HCl in dioxane for 16 h at room temperature in dry Et_2O afforded 2-amino acetal hydrochloride **8a** in 95% yield. [b]An inseparable mixture of α-amino aldehyde hydrochloride **7i** and 2-amino acetal hydrochloride **8d** in a ratio of 56:44 was obtained.

Treatment of *N*-*tert*-butanesulfinyl 2-amino acetal **5n** (R^1 = H) with HCl in MeOH under the same conditions afforded an inseparable mixture of the corresponding α-amino aldehyde hydrochloride **7i** and 2-amino acetal hydrochloride **8d** (Table 5, entry 10). In an effort to obtain α-amino aldehyde hydrochloride **7h** (R^1 = H, R^2 = Me), *N*-*tert*-butanesulfinyl 2-amino acetal **5k** was treated with a large excess (50 equiv) of anhydrous 4 M HCl in dioxane for 16 h at room temperature in Et_2O, but only 2-amino acetal hydrochloride **8a** was isolated in 95% yield after precipitation in dry Et_2O.

Additionally, the reactivity of *N*-*tert*-butanesulfinyl α-chloro-α-methylketimine **1j** toward alkoxides was studied in the synthesis of the corresponding *N*-*tert*-butanesulfinyl 2-amino acetal **5o** (Scheme 3). *N*-*tert*-Butanesulfinyl α-chloroketimine **1j** was synthesized in 75% yield via condensation of α-chloro propiophenone with (R_s)-*tert*-butanesulfinamide in the presence of 2 equiv of $Ti(OEt)_4$ in THF.[15a] Subsequently, when *N*-*tert*-butanesulfinyl α-chloro-α-methylketimine **1j**, which was obtained in a diastereomeric ratio of 78:22 after purification via flash chromatography, was reacted with 3 equiv of NaOMe at room temperature for 2 h, the corresponding *N*-*tert*-butanesulfinyl 2-amino acetal **5o** was formed in a diastereomeric ratio of 83:17 (Scheme 3). Unfortunately, *N*-sulfinyl 2-amino acetal **5o** seemed unstable on column and could not be isolated via flash chromatography. Instead, the corresponding *N*-sulfinyl α-amino ketone **6j** was isolated in a disappointing yield of 13% and a diastereomeric ratio of 82:18. Therefore, in a next attempt, the crude *N*-sulfinyl 2-amino acetal **5o** was treated immediately with TMSOTf in CH_2Cl_2 at −78 °C for 30 min, leading to the synthesis of the corresponding *N*-sulfinyl α-amino ketone **6j**, which can be considered as *N*-*tert*-butanesulfinyl cathinone. Unfortunately, during purification via flash chromatography, the formed diastereomers of **6j** could not be completely separated. *N*-Sulfinyl α-amino ketone **6j** was isolated as two diastereomerically enriched fractions in 43% yield (dr 75:25) and 17% yield (dr 94:6), respectively. In a last step, when *N*-sulfinyl α-amino ketone **6j** (dr 94:6) was treated with 3 M HCl in MeOH, the corresponding α-amino ketone hydrochloride **7j**, i.e. (*S*)-cathinone hydrochloride **7j**, was isolated in 88% yield after precipitation in dry Et_2O. Noteworthy, Davis and co-workers recently reported the synthesis of *N*-sulfinyl α-amino ketone **6j** in 70% yield via hydrolysis of the corresponding *N*-sulfinyl α-amino dithioacetal.[18] Nevertheless, during this hydrolysis step complete racemisation occurred, resulting from the removal of the α-proton in the α-amino carbonyl compound forming the enol.[18] Comparison of the optical rotations ($[\alpha]_D$ (*S*)-**7j** −47.2 (*c* 0.2, H_2O, er 94:6) vs −48.0 (*c* 1.0, H_2O, ee > 95%)) reported in the literature[24] confirmed the assigned absolute stereochemistry of synthesized products **6j** and **7j**.

dx.doi.org/10.1021/jo300752c | J. Org. Chem. 2012, 77, 6023–6032

Scheme 3. Reaction of *N-tert*-Butanesulfinyl α-Chloro-α-methylketimine 1j with NaOMe in MeOH, Synthesis of *N-tert*-Butanesulfinyl α-Amino Ketone 6j, and Subsequent *N*-Deprotection to (*S*)-Cathinone Hydrochloride 7j



CONCLUSIONS

In conclusion, it was demonstrated that new *N-tert*-butanesulfinyl 2-amino acetals are formed in good to excellent yield via reaction of *N-tert*-butanesulfinyl α-halo imines with alkoxides. The proposed mechanism involves formation of the corresponding *N*-sulfinyl 2-alkoxyaziridines as unstable intermediates, which open spontaneously, followed by an attack of a second equivalent of the alkoxide. These *N-tert*-butanesulfinyl 2-amino acetals were shown to act as convenient precursors for the TMSOTf-promoted synthesis of the corresponding *N*-protected α-amino aldehydes and ketones in high yield. Furthermore, the HCl-promoted synthesis of α-amino ketone and α-amino aldehyde hydrochlorides and 2-amino acetal hydrochlorides from these *N*-protected α-amino ketones and aldehydes, and the corresponding acetals, in high yield demonstrates the utility. Finally, this method was used for the asymmetric synthesis of (*S*)-cathinone (er 94:6).

EXPERIMENTAL SECTION

Synthesis of (R_S)-*N-tert*-Butanesulfinyl 2-Chloro-1-methoxyethylamines 3a–b. The synthesis of (R_S)-*N-tert*-butanesulfinyl 2-chloro-1-methoxy-1-methylethylamine **3a** is representative. To (R_S)-*N*-(2-chloro-1-methylethylidene)-*tert*-butanesulfinamide **1a** (1 equiv, 0.2 g, 1.02 mmol) at −78 °C was added 1 M NaOMe in MeOH (3 equiv, 3.06 mL, 3.06 mmol). The reaction was stirred for 1 h at −78 °C and quenched with a saturated solution of NH_4Cl (1 mL). Subsequently, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ (5 mL), and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated in vacuo to yield 0.23 g (1.02 mmol, 99%) of (R_S)-*N-tert*-butanesulfinyl 2-chloro-1-methoxy-1-methylethylamine **3a** in a diastereomeric ratio of 77:23. Because sulfinamides **3a**,**b** are unstable at room temperature and are smoothly converted back to the corresponding *N*-sulfinyl imines **1a**,**b** upon standing a short time in $CDCl_3$, only ^{1}H NMR and IR data could be reported.

(R_S)-*N-tert*-Butanesulfinyl 2-Chloro-1-methoxy-1-methylethylamine 3a. Yellow oil, 99% (0.23 g): dr 77:23; IR (cm^{-1}) ν_{max} 752, 1043, 2959, 3228; ^{1}H NMR (300 MHz, $CDCl_3$) major diastereomer δ 1.25 (9H, s), 1.57 (3H, s), 3.36 (3H, s), 3.57 (1H, d, *J* = 11.0 Hz), 3.65 (1H, d, *J* = 11.0 Hz), 3.94 (1H, br s); minor diastereomer δ 1.27 (9H, s), 1.58 (3H, s), 3.32 (3H, s, OCH_3), 3.64 (1H, d, *J* = 11.6 Hz), 3.72 (1H, d, *J* = 11.6 Hz), 4.09 (1H, br s).

(R_S)-*N-tert*-Butanesulfinyl 2-Chloro-1-methoxy-1-phenylethylamine 3b. Yellow oil, 99% (0.29 g): dr 62:48; IR (cm^{-1}) ν_{max} 749, 1070, 2980, 3196; ^{1}H NMR (300 MHz, $CDCl_3$) major diastereomer δ 1.36 (9H, s), 3.28 (3H, s), 3.71 (1H, d, *J* = 11.6 Hz), 4.10 (1H, d, *J* = 11.6 Hz), 4.33 (1H, br s), 7.34–7.52 (4H, m); minor diastereomer δ 1.27 (9H, s), 3.39 (3H, s), 3.93 (2H, s), 4.57 (1H, br s), 7.34–7.52 (4H, m).

Synthesis of (R_S)-*N-tert*-Butanesulfinyl 2-Amino Acetals 5. The synthesis of (R_S)-*N-tert*-butanesulfinyl 2,2-dimethoxypropylamine **5a** is representative. To (R_S)-*N*-(2-chloro-1-methylethylidene)-*tert*-butanesulfinamide **1a** (1 equiv, 1.0 g, 5.12 mmol) was added 1 M NaOMe in MeOH (3 equiv, 15.35 mL, 15.35 mmol) at room temperature. The reaction was stirred for 2 h at room temperature and quenched with a saturated solution of NH_4Cl (1 mL). Subsequently, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ (25 mL), and the aqueous phase was extracted with EtOAc (3 × 25 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated in vacuo. The crude product was purified via flash chromatography to yield 0.92 g (4.14 mmol, 81%) of pure (R_S)-*N-tert*-butanesulfinyl 2,2-dimethoxypropylamine **5a**. For the synthesis of (R_S)-*N-tert*-butanesulfinyl 2-amino acetals **5k–n**, the reaction time was increased to 16 h instead of 2 h. (R_S)-*N-tert*-Butanesulfinyl 2-amino acetals **5g** and **5h** were purified by recrystallization from dry Et_2O.

(R_S)-*N-tert*-Butanesulfinyl 2,2-Dimethoxypropylamine 5a. R_f = 0.22 (EtOAc). Yellow oil, yield 81% (0.92 g): $[\alpha]_D$ −49.6 (*c* 0.3, $CHCl_3$); IR (cm^{-1}) ν_{max} 1051, 2955, 3218; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (9H, s), 1.34 (3H, s), 3.04 (1H, d × d, *J* = 12.4, 8.3 Hz), 3.20 (3H, s), 3.22 (3H, s), 3.24–3.32 (1H, m), 3.37 (1H, d × d, *J* = 12.4, 4.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.3, 22.7 (3C), 48.5, 48.9, 49.3, 56.0, 100.6; MS (ES, pos. mode) *m*/*z* (%) 192 (M + H^+ − CH_3OH, 100), 246 (M + Na^+, 10). Anal. Calcd for $C_9H_{21}NO_3S$: C 48.40; H 9.48; N 6.27. Found: C 48.21; H 9.23; N 6.20.

(R_S)-*N-tert*-Butanesulfinyl 2-(4-Chlorophenyl)-2,2-dimethoxyethylamine 5b. R_f = 0.31 (EtOAc). White crystals, yield 93% (1.03 g): $[\alpha]_D$ −18.1 (*c* 0.3, $CHCl_3$); mp 124.5–124.7 °C; IR (cm^{-1}) ν_{max} 1042, 2958, 3188; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (9H, s), 2.92 (1H, d × d, *J* = 9.9, 4.4 Hz), 3.19 (3H, s), 3.20 (3H, s), 3.36 (1H, d × d, *J* = 13.2, 9.9 Hz), 3.56 (1H, d × d, *J* = 13.2, 4.4 Hz), 7.31–7.45 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.4 (3C), 49.0 (2C), 49.6, 56.0, 101.9, 128.4 (2C), 128.7 (2C), 134.2, 137.7; MS (ES, neg. mode) *m*/*z* (%) 318/320 (M − H^+, 100). Anal. Calcd for $C_{14}H_{22}ClNO_3S$: C 52.57; H 6.93; N 4.38. Found: C 52.37; H 6.71; N 4.23.

(R_S)-*N-tert*-Butanesulfinyl 2,2-Diethoxypropylamine 5c. R_f = 0.21 (petroleum ether/EtOAc 1:1). Yellow oil, yield 70% (1.26 g): $[\alpha]_D$ −56.2 (*c* 0.4, $CHCl_3$); IR (cm^{-1}) ν_{max} 1061, 2975, 3224; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 (6H, t, *J* = 7.2 Hz), 1.23 (9H, s), 1.36 (3H, s), 2.99–3.10 (1H, m), 3.29–3.57 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.4 (2C), 21.4, 22.6 (3C), 50.0, 55.9, 56.1, 100.3; MS (ES, pos. mode) *m*/*z* (%) 203 (M + H^+ − CH_3CH_2OH, 100), 274 (M + Na^+, 10). Anal. Calcd for $C_{11}H_{25}NO_3S$: C 52.56; H 10.02; N 5.57. Found: C 52.37; H 9.91; N 5.33.

(R_S)-*N-tert*-Butanesulfinyl 2-(4-Chlorophenyl)-2,2-diethoxyethylamine 5d. R_f = 0.23 (petroleum ether/EtOAc 1:1). Yellow oil, yield 95% (1.02 g): $[\alpha]_D$ −20.2 (*c* 0.4, $CHCl_3$); IR (cm^{-1}) ν_{max} 1051, 2976, 3216; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (9H, s), 1.20 (3H, t, *J* = 7.2 Hz), 1.21 (3H, t, *J* = 7.2 Hz), 2.94 (1H, d × d, *J* = 9.6, 4.1 Hz), 3.32–3.51 (5H, m), 3.56 (1H, d × d, *J* = 12.9, 4.1 Hz), 7.29–

dx.doi.org/10.1021/jo300752c | J. Org. Chem. 2012, 77, 6023–6032

7.36 (2H, m), 7.39−7.48 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.0, 15.2, 22.4 (3C), 50.3, 56.0, 56.7, 56.8, 101.4, 128.2 (2C), 128.6 (2C), 134.0, 138.6; MS (ES, neg. mode) m/z (%) 346/348 (M − H$^+$, 100). HRMS Calcd for $C_{16}H_{26}ClNO_3S$: 348.1395 [M + H]$^+$. Found: 348.1386 [M + H]$^+$.

(R_S)-*N*-*tert*-Butanesulfinyl 2,2-Dimethoxy-2-phenylethylamine 5e. R_f = 0.31 (EtOAc). Yellow crystals, yield 83% (1.22 g): $[\alpha]_D$ −25.7 (c 0.4, $CHCl_3$); mp 106.2−106.6 °C; IR (cm^{-1}) ν_{max} 1034, 2958, 3187; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (9H, s), 2.93 (1H, d × d, J = 9.9, 4.4 Hz), 3.21 (3H, s), 3.22 (3H, s), 3.40 (1H, d × d, J = 13.2, 9.9 Hz), 3.56 (1H, d × d, J = 13.2, 4.4 Hz), 7.26−7.40 (3H, m), 7.44−7.49 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.4 (3C), 48.9, 49.0, 49.7, 56.0, 102.2, 127.2 (2C), 128.2 (2C), 128.3, 138.9; MS (ES, pos. mode) m/z (%) 254 (M + H$^+$ − CH_3OH, 100), 308 (M + Na$^+$, 25). Anal. Calcd for $C_{14}H_{23}NO_3S$: C 58.92; H 8.12; N 4.91. Found: C 58.66; H 7.94; N 4.75.

(R_S)-*N*-*tert*-Butanesulfinyl 2,2-Diethoxy-2-phenylethylamine 5f. R_f = 0.25 (petroleum ether/EtOAc 1:1). Yellow oil, yield 97% (1.34 g): $[\alpha]_D$ −25.3 (c 0.3, $CHCl_3$); IR (cm^{-1}) ν_{max} 1052, 2975, 3219; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (9H, s), 1.21 (3H, t, J = 7.2 Hz), 1.22 (3H, t, J = 7.2 Hz), 2.95 (1H, d × d, J = 9.9, 4.0 Hz), 3.34−3.51 (5H, m), 3.56 (1H, d × d, J = 12.9, 4.0 Hz), 7.25−7.39 (3H, m), 7.47−7.53 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.1, 15.2, 22.4 (3C), 50.5, 55.9, 56.6, 56.7, 101.7, 127.0 (2C), 128.1 (3C), 139.9; MS (ES, pos. mode) m/z (%) 268 (M + H$^+$ − CH_3CH_2OH, 100), 336 (M + Na$^+$, 25). Anal. Calcd for $C_{16}H_{27}NO_3S$: C 61.31; H 8.68; N 4.47. Found: C 61.57; H 8.79; N 4.63.

(R_S)-*N*-*tert*-Butanesulfinyl 2,2-Dimethoxy-2-(4-methoxyphenyl)ethylamine 5g. Yellow crystals, yield 94% (2.68 g): $[\alpha]_D$ −22.2 (c 0.3, $CHCl_3$); mp 134.5−134.8 °C; IR (cm^{-1}) ν_{max} 1036, 1242, 1510, 1608, 2954, 3172; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (9H, s), 2.93 (1H, d × d, J = 9.9, 4.1 Hz), 3.18 (3H, s), 3.20 (3H, s), 3.39 (1H, d × d, J = 13.1, 9.9 Hz), 3.53 (1H, d × d, J = 13.1, 4.1 Hz), 3.82 (3H, s), 6.86−6.92 (2H, m), 7.35−7.41 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.5 (3C), 48.8, 48.9, 49.7, 52.3, 56.0, 102.1, 113.5 (2C), 128.5 (2C), 131.0, 159.5; MS (ES, pos. mode) m/z (%) 338 (M + Na$^+$, 10), 284 (M − CH_3OH, 20), 178 (M − 137, 100). Anal. Calcd for $C_{15}H_{25}NO_4S$: C 57.12; H 7.99; N 4.44. Found: C 57.34; H 7.91; N 4.65.

(R_S)-*N*-*tert*-Butanesulfinyl 2,2-Dimethoxy-2-(4-nitrophenyl)-ethylamine 5h. Yellow crystals, yield 97% (1.52 g): $[\alpha]_D$ −4.6 (c 0.5, $CHCl_3$); mp 121.7−122.0 °C; IR (cm^{-1}) ν_{max} 1042, 1347, 1520, 2958, 3188; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (9H, s), 2.98 (1H, d × d, J = 9.6, 4.7 Hz), 3.21 (3H, s), 3.25 (3H, s), 3.39 (1H, d × d, J = 13.5, 9.6 Hz), 3.64 (1H, d × d, J = 13.5, 4.7 Hz), 7.63−7.72 (2H, m), 8.19−8.29 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.4 (3C), 49.2, 49.3, 49.5, 56.1, 101.9, 123.3 (2C), 128.5 (2C), 146.5, 147.9; MS (ES, neg. mode) m/z (%) 329 (M − H$^+$, 100). Anal. Calcd for $C_{14}H_{22}N_2O_5S$: C 50.89; H 6.71; N 8.48. Found: C 50.64; H 6.49; N 8.22.

(R_S)-*N*-*tert*-Butanesulfinyl 2-(2,4-Dichlorophenyl)-2,2-dimethoxyethylamine 5i. R_f = 0.30 (petroleum ether/EtOAc 1:1). Yellow oil, yield 93% (1.48 g): $[\alpha]_D$ +4.7 (c 0.5, $CHCl_3$); IR (cm^{-1}) ν_{max} 751, 1053, 1467, 2956, 3205; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (9H, s), 2.97 (1H, d × d, J = 9.4, 5.0 Hz), 3.17 (3H, s), 3.24 (3H, s), 3.70 (1H, d × d, J = 13.8, 9.4 Hz), 3.79 (1H, d × d, J = 13.8, 5.0 Hz), 7.25 (1H, d × d, J = 8.3, 2.2 Hz), 7.40 (1H, d, J = 2.2 Hz), 7.72 (1H, d, J = 8.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.3 (3C), 45.9, 48.6, 49.0, 55.9, 101.6, 126.6, 130.8, 132.4, 132.7, 134.2, 134.9; MS (ES, pos. mode) m/z (%) 322/324/326 (M + H$^+$ − CH_3OH, 100). Anal. Calcd for $C_{14}H_{21}Cl_2NO_3S$: C 47.46; H 5.97; N 3.95. Found: C 47.67; H 6.05; N 4.07.

(R_S)-*N*-*tert*-Butanesulfinyl 2,2-Dimethoxy-3-methylbutylamine 5j. R_f = 0.27 (petroleum ether/EtOAc 1:1). Yellow oil, yield 76% (0.54 g): $[\alpha]_D$ −41.6 (c 0.2, $CHCl_3$); IR (cm^{-1}) ν_{max} 753, 1048, 1122, 1471, 2960, 3225; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (3H, d, J = 6.9 Hz), 0.98 (3H, d, J = 6.9 Hz), 1.22 (9H, s), 2.10 (1H, sept, J = 6.9 Hz), 3.11 (1H, d × d, J = 13.2, 10.5 Hz), 3.21 (3H, s), 3.25 (3H, s), 3.30−3.41 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.3, 17.4, 22.7 (3C), 32.6, 44.9, 48.5, 49.3, 55.7, 102.3; MS (ES, pos. mode) m/z (%) 220 (M + H$^+$ − CH_3OH, 100). Anal. Calcd for $C_{11}H_{25}NO_3S$: C 52.26; H 10.02; N 5.57. Found: C 52.49; H 10.31; N 5.82.

(R_S)-*N*-*tert*-Butanesulfinyl 2,2-Dimethoxy-1,1-dimethylethylamine 5k. R_f = 0.35 (EtOAc). Yellow oil, yield 96% (0.96 g): $[\alpha]_D$ −91.1 (c 0.3, $CHCl_3$); IR (cm^{-1}) ν_{max} 1067, 2954, 3304; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (3H, s), 1.20 (9H, s), 1.30 (3H, s), 3.54 (3H, s), 3.59 (3H, s), 3.63 (1H, br s), 4.14 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.6 (3C), 22.7, 22.9, 55.3, 58.5, 58.8, 58.9, 111.8; MS (ES, pos. mode) m/z (%) 238 (M + H$^+$, 100), 206 (M + H$^+$ − CH_3OH, 40). HRMS Calcd for $C_{10}H_{23}NO_3S$: 238.1471 [M + H]$^+$. Found: 238.1472 [M + H]$^+$.

(R_S)-*N*-*tert*-Butanesulfinyl 2,2-Diethoxy-1,1-dimethylethylamine 5l. R_f = 0.33 (petroleum ether/EtOAc 1:1). Yellow oil, yield 77% (0.76 g): $[\alpha]_D$ −86.8 (c 0.3, $CHCl_3$); IR (cm^{-1}) ν_{max} 1059, 1113, 2975, 3306; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (3H, s), 1.20 (9H, s), 1.23 (3H, t, J = 7.2 Hz), 1.24 (3H, t, J = 7.2 Hz), 1.32 (3H, s), 3.51−3.71 (2H, m), 3.73 (1H, br s), 3.79−3.92 (2H, m), 4.28 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.5 (2C), 22.6 (3C), 22.8 (2C), 55.3, 58.7, 66.3, 66.6, 109.1; MS (ES, pos. mode) m/z (%) 220 (M + H$^+$ − CH_3CH_2OH, 100). HRMS Calcd for $C_{12}H_{27}NO_3S$: 266.1784 [M + H]$^+$. Found: 266.1787 [M + H]$^+$.

(R_S)-*N*-*tert*-Butanesulfinyl 1-Dimethoxymethyl-1-ethylpropylamine 5m. R_f = 0.41 (EtOAc). Yellow oil, yield 57% (0.66 g): $[\alpha]_D$ −76.8 (c 0.3, $CHCl_3$); IR (cm^{-1}) ν_{max} 1064, 1450, 2918, 3310; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (3H, t, J = 7.2 Hz), 0.95 (3H, t, J = 7.2 Hz), 1.23 (9H, s), 1.48−1.89 (4H, m), 3.53 (3H, s), 3.57 (1H, br s), 3.59 (3H, s), 4.25 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.8, 8.0, 22.8 (3C), 25.3, 25.9, 56.0, 58.7, 59.0, 63.3, 111.9; MS (ES, pos. mode) m/z (%) 266 (M + H$^+$, 20), 234 (M + H$^+$ − CH_3OH, 100). HRMS Calcd for $C_{12}H_{27}NO_3S$: 266.1784 [M + H]$^+$. Found: 266.1788 [M + H]$^+$.

(R_S)-*N*-*tert*-Butanesulfinyl 1-Diethoxymethyl-1-ethylpropylamine 5n. R_f = 0.28 (petroleum ether/EtOAc 1:1). Yellow oil, yield 28% (0.42 g): $[\alpha]_D$ −67.3 (c 0.2, $CHCl_3$); IR (cm^{-1}) ν_{max} 1058, 1113, 2973, 3304; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (3H, t, J = 7.2 Hz), 0.98 (3H, t, J = 7.2 Hz), 1.19−1.27 (6H, m), 1.23 (9H, s), 1.50−1.87 (4H, m), 3.49−3.59 (1H, m), 3.64−3.74 (1H, m), 3.69 (1H, br s), 3.79−3.89 (2H, m), 4.41 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.9, 8.1, 15.5, 15.6, 22.8 (3C), 25.0, 26.0, 55.9, 63.1, 66.4, 66.7, 109.2; MS (ES, pos. mode) m/z (%) 248 (M + H$^+$ − CH_3CH_2OH, 100). HRMS Calcd for $C_{14}H_{31}NO_3S$: 294.2097 [M + H]$^+$. Found: 294.2095 [M + H]$^+$.

Synthesis of (R_S)-*N*-*tert*-Butanesulfinyl α-Amino Ketones 6a−g and 6j and (R_S)-*N*-*tert*-Butanesulfinyl α-Amino Aldehydes 6h,i. The synthesis of (R_S)-*N*-*tert*-butanesulfinyl 2-oxopropylamine **6a** is representative. To a solution of (R_S)-*N*-*tert*-butanesulfinyl 2,2-dimethoxypropylamine **5a** (1 equiv, 0.5 g, 2.24 mmol) in CH_2Cl_2 (5 mL) was added dropwise TMSOTf (3 equiv, 1.22 mL, 6.73 mmol) at −78 °C. The reaction was stirred for 30 min at −78 °C, and subsequently, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ (10 mL), and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated in vacuo. The crude product was purified via flash chromatography to yield 0.36 g (2.04 mmol, 91%) of pure (R_S)-*N*-*tert*-butanesulfinyl 2-oxopropylamine **6a**. (R_S)-*N*-*tert*-Butanesulfinyl 2-oxopropylamine **6a** was also obtained starting from (R_S)-*N*-*tert*-butanesulfinyl 2,2-diethoxypropylamine **5c** in 88% yield. For the synthesis of (R_S)-*N*-*tert*-butanesulfinyl α-amino aldehydes **6h,i**, the reaction temperature was increased to room temperature instead of −78 °C. To obtain full conversion of *N*-*tert*-butanesulfinyl 2-amino acetal **5k** into *N*-*tert*-butanesulfinyl α-amino aldehyde **6h**, after addition of 3 equiv of TMSOTf at room temperature for 30 min, two additional 3 equiv aliquots of TMSOTf were added subsequently at room temperature for 30 min. (R_S)-*N*-*tert*-Butanesulfinyl 2-(4-nitrophenyl)-2-oxoethylamine **6e** was purified by recrystallization from dry Et_2O.

(R_S)-*N*-*tert*-Butanesulfinyl 2-Oxopropylamine 6a. R_f = 0.07 (Et_2O). Yellow oil, yield 88−91% (0.36 g): $[\alpha]_D$ −97.0 (c 0.4, $CHCl_3$); IR (cm^{-1}) ν_{max} 1046, 1362, 1723, 2961, 3247; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (9H, s), 2.21 (3H, s), 3.90 (1H, d × d, J = 18.7,

dx.doi.org/10.1021/jo300752c | J. Org. Chem. 2012, 77, 6023−6032

4.4 Hz), 4.07 (1H, d × d, J = 18.7, 6.1 Hz), 4.36 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.7 (3C), 27.3, 51.8, 56.5, 203.4; MS (ES, pos. mode) m/z (%) 178 (M + H$^+$, 100). HRMS Calcd for $C_7H_{15}NO_2S$: 178.0896 [M + H]$^+$. Found: 178.0897 [M + H]$^+$.

(R_S)-*N*-*tert*-Butanesulfinyl 2-(4-Chlorophenyl)-2-oxoethylamine 6b. R_f = 0.20 (Et_2O). White crystals, yield 92−99% (0.42 g): $[\alpha]_D$ −126.9 (c 0.5, $CHCl_3$); mp 114.0−114.3 °C; IR (cm^{-1}) ν_{max} 1063, 1232, 1587, 1678, 2953, 3296; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (9H, s), 4.40−4.44 and 4.48−4.52 (1H, m), 4.57−4.65 and 4.68−4.71 (1H, m), 4.63 (1H, br s), 7.43−7.49 (2H, m), 7.84−7.91 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.8 (3C), 48.2, 56.6, 129.2 (4C), 132.8, 140.5, 193.8; MS (ES, pos. mode) m/z (%) 274/276 (M + H$^+$, 100). Anal. Calcd for $C_{12}H_{16}ClNO_2S$: C 52.64; H 5.89; N 5.12. Found: C 52.37; H 5.72; N 5.01.

(R_S)-*N*-*tert*-Butanesulfinyl 2-Oxo-2-phenylethylamine 6c. R_f = 0.37 (EtOAc). Yellow oil, yield 71−82% (0.38 g): $[\alpha]_D$ −111.2 (c 0.5, $CHCl_3$); IR (cm^{-1}) ν_{max} 1066, 1227, 1689, 2957, 3268; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (9H, s), 4.51 (1H, d × d, J = 17.6, 3.3 Hz), 4.57−4.65 (1H, m), 4.70 (1H, d × d, J = 17.6, 6.1 Hz), 7.46−7.54 (2H, m), 7.59−7.65 (1H, m), 7.92−7.97 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.8 (3C), 48.3, 56.5, 127.8 (2C), 128.9 (2C), 134.0, 134.5, 194.8; MS (ES, pos. mode) m/z (%) 240 (M + H$^+$, 100). HRMS Calcd for $C_{12}H_{17}NO_2S$: 240.1053 [M + H]$^+$. Found: 240.1053 [M + H]$^+$.

(R_S)-*N*-*tert*-Butanesulfinyl 2-(4-Methoxyphenyl)-2-oxoethylamine 6d. R_f = 0.16 (Et_2O). Yellow oil, yield 99% (0.63 g): $[\alpha]_D$ −100.7 (c 0.4, $CHCl_3$); IR (cm^{-1}) ν_{max} 749, 981, 1064, 1172, 1238, 1599, 1679, 2934, 3274; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (9H, s), 3.88 (3H, s), 4.44 (1H, d × d, J = 19.8, 5.5 Hz), 4.62 (1H, d × d, J = 19.8, 6.1 Hz), 4.64 (1H, br s), 6.93−6.98 (2H, m), 7.89−7.94 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.8 (3C), 47.8, 55.5, 56.5, 114.1 (2C), 127.5, 130.1 (2C), 164.1, 193.2; MS (ES, pos. mode) m/z (%) 270 (M + H$^+$, 100). HRMS Calcd for $C_{13}H_{19}NO_3S$: 270.1158 [M + H]$^+$. Found: 270.1161 [M + H]$^+$.

(R_S)-*N*-*tert*-Butanesulfinyl 2-(4-Nitrophenyl)-2-oxoethylamine 6e. Yellow crystals, yield 99% (0.47 g): $[\alpha]_D$ −118.6 (c 0.4, $CHCl_3$); mp 127.2−127.6 °C; IR (cm^{-1}) ν_{max} 850, 980, 1064, 1340, 1520, 1694, 2964, 3314; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (9H, s), 4.53−4.58 (1H, m), 4.54 (1H, d × d, J = 19.5, 3.9 Hz), 4.74 (1H, d × d, J = 19.5, 7.2 Hz), 8.08−8.15 (2H, m), 8.33−8.39 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.8 (3C), 48.9, 56.8, 124.1 (2C), 129.0 (2C), 138.9, 150.8, 193.8; MS (ES, pos. mode) m/z (%) 285 (M + H$^+$, 100). Anal. Calcd for $C_{12}H_{16}N_2O_4S$: C 50.69; H 5.67; N 9.85. Found: C 50.54; H 5.49; N 9.64.

(R_S)-*N*-*tert*-Butanesulfinyl 2-(2,4-Dichlorophenyl)-2oxoethylamine 6f. R_f = 0.21 (Et_2O). Yellow oil, yield 99% (0.60 g): $[\alpha]_D$ −73.2 (c 0.2, $CHCl_3$); IR (cm^{-1}) ν_{max} 751, 816, 981, 1059, 1583, 1702, 2961, 3218; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (9H, s), 4.44 (1H, d × d, J = 17.9, 3.7 Hz), 4.53 (1H, d × d, J = 6.1, 3.7 Hz), 4.61 (1H, d × d, J = 17.9, 6.1 Hz), 7.36 (1H, d × d, J = 8.3, 2.2 Hz), 7.48 (1H, d, J = 2.2 Hz), 7.64 (1H, d, J = 8.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.7 (3C), 52.0, 56.6, 127.6, 130.8, 131.2, 132.9, 134.1, 138.8, 196.3; MS (ES, pos. mode) m/z (%) 308/310/312 (M + H$^+$, 100). HRMS Calcd for $C_{12}H_{25}Cl_2NO_2S$: 308.0273 [M + H]$^+$. Found: 308.0285 [M + H]$^+$.

(R_S)-*N*-*tert*-Butanesulfinyl 3-Methyl-2-oxobutylamine 6g. R_f = 0.20 (Et_2O). Colorless oil, yield 76% (0.31 g): $[\alpha]_D$ −94.3 (c 0.3, $CHCl_3$); IR (cm^{-1}) ν_{max} 1057, 1363, 1468, 1715, 2972, 3218; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (6H, d, J = 7.2 Hz), 1.24 (9H, s), 2.66 (1H, sept, J = 7.2 Hz), 3.95 (1H, d × d, J = 18.7, 3.3 Hz), 4.11 (1H, d × d, J = 18.7, 6.1 Hz), 4.28−4.34 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.2, 18.3, 22.7 (3C), 39.0, 49.2, 56.4, 209.6; MS (ES, pos. mode) m/z (%) 206 (M + H$^+$, 100). HRMS Calcd for $C_9H_{19}NO_2S$: 206.1209 [M + H]$^+$. Found: 206.1205 [M + H]$^+$.

(R_S)-*N*-*tert*-Butanesulfinyl-2-amino-2-methylpropanal 6h. R_f = 0.09 (Et_2O). Colorless oil, yield 95−99% (0.27 g): $[\alpha]_D$ −77.1 (c 0.1, $CHCl_3$); IR (cm^{-1}) ν_{max} 1054, 1461, 1732, 2919, 3236; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (9H, s), 1.42 (3H, s), 1.44 (3H, s), 3.90 (1H, s), 9.48 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.5 (3C), 23.6, 23.7, 56.1, 62.0, 200.5; MS (ES, neg. mode) m/z (%) 190 (M − H$^+$, 80), 149 (M − 42, 100). HRMS Calcd for $C_8H_{17}NO_2S$: 192.1053 [M + H]$^+$. Found: 192.1051 [M + H]$^+$.

(R_S)-*N*-*tert*-Butanesulfinyl-2-amino-2-ethylbutanal 6i. R_f = 0.21 (Et_2O). Colorless oil, yield 99% (0.37 g): $[\alpha]_D$ −55.0 (c 0.2, $CHCl_3$); IR (cm^{-1}) ν_{max} 1055, 1458, 1730, 2966, 3221; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (3H, t, J = 7.2 Hz), 0.89 (3H, t, J = 7.2 Hz), 1.28 (9H, s), 1.77−2.03 (4H, m), 4.11 (1H, br s), 9.35 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.5, 7.7, 22.8 (3C), 27.4, 28.5, 56.5, 68.9, 201.2; MS (ES, pos. mode) m/z (%) 220 (M + H$^+$, 100). HRMS Calcd for $C_{10}H_{21}NO_2S$: 220.1366 [M + H]$^+$. Found: 220.1362 [M + H]$^+$.

(R_S)-*N*-*tert*-Butanesulfinyl 1-Methyl-2-oxo-2-phenylethylamine 6j. R_f = 0.22 (Et_2O). Colorless oil, yield 60% (43%, dr 75:25, 0.40 g + 17%, dr 94:6, 0.16 g): $[\alpha]_D$ −54.8 (c 0.4, $CHCl_3$, dr 92:8); IR (cm^{-1}) ν_{max} 700, 752, 970, 1061, 1220, 1450, 1686, 2979, 3266; ^{1}H NMR (300 MHz, $CDCl_3$) δ major (**R_S,*S*)-6j** 1.23 (9H, s), 1.56 (3H, d, J = 7.2), 4.22 (1H, d, J = 9.4 Hz), 4.96−5.09 (1H, m), 7.46−7.54 (2H, m), 7.57−7.64 (1H, m), 7.92−7.99 (2H, m); δ minor (**R_S,*R*)-6j** 1.29 (9H, s), 1.44 (3H, d, J = 7.2 Hz), 4.80 (1H, d, J = 5.0 Hz), 4.96−5.09 (1H, m), 7.46−7.54 (2H, m), 7.57−7.64 (1H, m), 7.92−7.99 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ major (**R_S,*S*)-6j** 21.5, 22.6 (3C), 54.8, 56.6, 128.6 (2C), 128.9 (2C), 133.8, 134.1, 199.1; δ minor (**R_S,*R*)-6j** 21.6, 22.7 (3C), 54.7, 55.7, 128.6 (2C), 128.9 (2C), 133.8, 134.0, 199.7; MS (ES, pos. mode) m/z (%) 254 (M + H$^+$, 100). HRMS Calcd for $C_{13}H_{19}NO_2S$: 254.1209 [M + H]$^+$. Found: 254.1207 [M + H]$^+$.

Synthesis of α-Amino Ketone Hydrochlorides 7a−g and 7j and 2-Amino Acetal Hydrochlorides 8. The synthesis of 1-aminopropan-2-one hydrochloride **7a** is representative. To a solution of (R_S)-*N*-*tert*-butanesulfinyl 2-oxopropylamine **6a** (0.20 g, 1.13 mmol) in MeOH (3 mL) was added a 3 M solution of HCl (10 equiv, 3.77 mL, 11.30 mmol) in MeOH at room temperature. The mixture was stirred for 1 h at room temperature. Subsequently, the reaction mixture was concentrated in vacuo. Precipitation in dry Et_2O afforded 0.12 g (1.09 mmol, 96%) of pure 1-aminopropan-2-one hydrochloride **7a**. 1-Aminopropan-2-one hydrochloride **7a** was also obtained starting from (R_S)-*N*-*tert*-butanesulfinyl 2,2-dimethoxypropylamine **5a** and (R_S)-*N*-*tert*-butanesulfinyl 2,2-diethoxypropylamine **5c** in 90 and 99% yield, respectively, via the same procedure. Treatment of (R_S)-*N*-*tert*-butanesulfinyl 2,2-dimethoxy-1,1-dimethylethylamine **5k**, (R_S)-*N*-*tert*-butanesulfinyl 2,2-diethoxy-1,1-dimethylethylamine **5l**, and (R_S)-*N*-*tert*-butanesulfinyl 1-dimethoxymethyl-1-ethylpropylamine **5m** with HCl in MeOH under similar conditions afforded the synthesis of 2-amino acetal hydrochlorides **8a−c**. Treating (R_S)-*N*-*tert*-butanesulfinyl 2,2-dimethoxy-1,1-dimethylethylamine **5k** with 50 equiv of HCl in dioxane at room temperature for 16 h afforded 2-amino acetal hydrochloride **8a** in 95% yield

1-Aminopropan-2-one Hydrochloride 7a. Yellow crystals, yield 90−99% (0.12 g): mp 70.8−71.1 °C vs 70.0−74.0 °C in lit.;[2S] IR (cm^{-1}) ν_{max} 1721, 2928; ^{1}H NMR (300 MHz, D_2O, int. ref CH_3CN δ 2.00) δ 2.23 (3H, s), 4.03 (2H, s); ^{13}C NMR (75 MHz, D_2O, int. ref CH_3CN δ 1.0) δ 26.6, 47.8, 204.1; MS (ES, pos. mode) m/z (%) 96 (M − HCl + Na$^+$, 100). Anal. Calcd for C_3H_8ClNO: C 32.89; H 7.36; N 12.79. Found: C 32.67; H 7.42; N 12.93. All spectroscopic data were in good agreement with reported data.[2Sa,b]

2-Amino-1-(4-chlorophenyl)ethanone Hydrochloride 7b. White crystals, yield 92−99% (0.15 g): mp 298.5−298.8 °C vs 270.0−290.0 °C in lit.;[2Sb,26] IR (cm^{-1}) ν_{max} 1250, 1467, 1588, 1681, 2979; ^{1}H NMR (300 MHz, CD_3OD, int. ref CH_3CN δ 2.00) δ 4.57 (2H, s), 7.52−7.61 (2H, m), 7.96−8.04 (2H, m); ^{13}C NMR (75 MHz, CD_3OD, int. ref CH_3CN δ 0.0) δ 45.4, 129.6 (2C), 130.1 (2C), 132.8, 141.2, 191.5; MS (ES, pos. mode) m/z (%) 170/172 (M + H$^+$ − HCl, 100). Anal. Calcd for $C_8H_9Cl_2NO$: C 46.63; H 4.40; N 6.80. Found: C 46.84; H 4.07; N 6.57. All spectroscopic data were in good agreement with reported data.[2Sb]

2-Amino-1-phenylethanone Hydrochloride 7c. Yellow crystals, yield 89−92% (0.19 g): mp 198.3−198.6 °C vs 182.0−206 °C in lit.;.[2Sb,d,27] IR (cm^{-1}) ν_{max} 759, 1241, 1504, 1696, 2866; ^{1}H NMR (300 MHz, CD_3OD, int. ref CH_3CN δ 2.00) δ 4.58 (2H, s), 7.51−7.59 (2H, m), 7.63−7.71 (1H, m), 7.98−8.04 (2H, m); ^{13}C NMR (75 MHz, CD_3OD, int. ref CH_3CN δ 0.0) δ 45.4, 128.5 (2C), 129.4 (2C), 134.3,

dx.doi.org/10.1021/jo300752c | J. Org. Chem. 2012, 77, 6023−6032

135.0, 192.5; MS (ES, pos. mode) m/z (%) 136 (M + H^+ − HCl, 100). Anal. Calcd for $C_8H_{10}ClNO$: C 55.99; H 5.87; N 8.16. Found: C 56.08; H 6.11; N 8.26. All spectroscopic data were in good agreement with reported data.[25b,27a]

2-Amino-1-(4-methoxyphenyl)ethanone Hydrochloride 7d. White crystals, yield 94% (0.18 g): mp 210.2−210.5 °C vs 195.0−205.0 °C in lit.;[25b,26b,27d] IR (cm^{-1}) ν_{max} 829, 1176, 1250, 1504, 1602, 1682, 2884, 2986; ^1H NMR (300 MHz, CD_3OD, int. ref CH_3CN δ 2.00) δ 3.86 (3H, s), 4.51 (2H, s), 7.00−7.08 (2H, m), 7.94−8.04 (2H, m); ^{13}C NMR (75 MHz, CD_3OD, int. ref CH_3CN δ 0.0) δ 44.9, 55.4, 114.6 (2C), 127.1, 130.9 (2C), 165.6, 190.7; MS (ES, pos. mode) m/z (%) 166 (M + H^+ − HCl, 100). Anal. Calcd for $C_9H_{12}ClNO_2$: C 53.61; H 6.00; N 6.95. Found: C 53.87; H 6.27; N 7.04. All spectroscopic data were in good agreement with reported data.[25b]

2-Amino-1-(4-nitrophenyl)ethanone Hydrochloride 7e. White crystals, yield 88% (0.12 g): mp 218.2−218.5 °C vs 226.0−250.0 °C in lit.;[27d,28] IR (cm^{-1}) ν_{max} 855, 1240, 1345, 1494, 1527, 1687, 2941, 3082; ^1H NMR (300 MHz, CD_3OD, int. ref CH_3CN δ 2.00) δ 4.67 (2H, s), 8.20−8.27 (2H, m), 8.34−8.41 (2H, m); ^{13}C NMR (75 MHz, CD_3OD, int. ref CH_3CN δ 0.0) δ 45.4, 123.8 (2C), 129.4 (2C), 138.1, 151.3, 191.2; MS (ES, pos. mode) m/z (%) 181 (M + H^+ − HCl, 100). Anal. Calcd for $C_8H_9ClN_2O_3$: C 44.36; H 4.19; N 12.93. Found: C 44.58; H 4.33; N 13.05.

2-Amino-1-(2,4-dichlorophenyl)ethanone Hydrochloride 7f. White crystals, yield 86% (0.17 g): mp 231.5−231.9 °C; IR (cm^{-1}) ν_{max} 815, 969, 1121, 1231, 1416, 1471, 1583, 1703, 2875, 2972; ^1H NMR (300 MHz, CD_3OD, int. ref CH_3CN δ 2.00) δ 4.53 (2H, s), 7.51 (1H, d × d, J = 8.3, 1.9 Hz), 7.65 (1H, d, J = 1.9 Hz), 7.87 (1H, d, J = 8.3 Hz); ^{13}C NMR (75 MHz, DMSO-d_6, int. ref CH_3CN δ 0.0) δ 45.7, 126.6, 129.6, 131.0, 131.3, 136.8, 191.7; MS (ES, pos. mode) m/z (%) 204/206/208 (M + H^+ − HCl, 100). Anal. Calcd for $C_8H_8Cl_3NO$: C 39.95; H 3.35; N 5.82. Found: C 40.17; H 3.52; N 6.00.

1-Amino-3-methylbutan-2-one Hydrochloride 7g. White crystals, yield 94% (0.11 g): mp 169.2−169.4 °C vs 147.0−164.0 °C in lit.;[29] IR (cm^{-1}) ν_{max} 995, 1140, 1420, 1472, 1720, 2876, 2971; ^1H NMR (300 MHz, CD_3OD, int. ref CH_3CN δ 2.00) δ 1.12 (6H, d, J = 7.2 Hz), 2.72 (1H, sept, J = 7.2 Hz), 4.01 (2H, s); ^{13}C NMR (75 MHz, CD_3OD, int. ref CH_3CN δ 0.0) δ 17.2 (2C), 38.8, 45.8, 207.1; MS (ES, pos. mode) m/z (%) 101 (M + H^+ − HCl, 100). Anal. Calcd for $C_5H_{12}ClNO$: C 43.64; H 8.79; N 10.18. Found: C 43.84; H 8.98; N 10.37.

***S*-2-Amino-1-phenyl-1-propanone Hydrochloride 7j.** White crystals, yield 88% (er 94:6, 54 mg): mp 185.3−185.9 °C vs 179.0−182.0 °C in lit.;[19a,24] $[\alpha]_D$ −47.2 (c 0.2, H_2O, er 94:6) vs $[\alpha]_D$ −48.0 (c 1.0, H_2O, ee >95%) in lit.;[19a,24] IR (cm^{-1}) ν_{max} 700, 1243, 1504, 1688, 2883; ^1H NMR (300 MHz, CD_3OD, int. ref CH_3CN δ 2.00) δ 1.53 (3H, d, J = 6.9 Hz), 5.10 (1H, q, J = 6.9 Hz), 7.51−7.61 (2H, m), 7.65−7.73 (1H, m), 7.99−8.05 (2H, m); ^{13}C NMR (75 MHz, CD_3OD, int. ref CH_3CN δ 0.0) δ 16.4, 51.4, 128.6 (2C), 129.1 (2C), 132.9, 134.5, 195.0; MS (ES, pos. mode) m/z (%) 150 (M + H^+ − HCl, 100). Anal. Calcd for $C_9H_{12}ClNO$: C 58.23; H 6.52; N 7.54. Found: C 58.31; H 6.69; N 7.68. All spectroscopic data were in good agreement with reported data.[19a,24]

2,2-Dimethoxy-1,1-dimethylethylamine Hydrochloride 8a. White crystals, yield 75−95% (78 mg): mp 135.8−136.1 °C; IR (cm^{-1}) ν_{max} 1073, 1186, 2936, 3388; ^1H NMR (300 MHz, CD_3OD, int. ref CH_3CN δ 2.00) δ 1.25 (6H, s), 3.55 (6H, s), 4.25 (1H, s); ^{13}C NMR (75 MHz, CD_3OD, int. ref CH_3CN δ 0.0) δ 20.6, 57.4, 58.2, 108.0; MS (ES, pos. mode) m/z (%) 134 (M + H^+ − HCl, 100). Anal. Calcd for $C_6H_{16}ClNO_2$: C 42.48; H 9.51; N 8.26. Found: C 42.61; H 9.88; N 8.07.

2,2-Diethoxy-1,1-dimethylethylamine Hydrochloride 8b. White crystals, yield 95% (68 mg): mp 130.8−131.2 °C; IR (cm^{-1}) ν_{max} 1057, 1505, 2884, 2977; ^1H NMR (300 MHz, CD_3OD, int. ref CH_3CN δ 2.00) δ 1.22 (6H, t, J = 7.2 Hz), 1.23−1.32 (6H, m), 3.58−3.71 (2H, m), 3.78−3.91 (2H, m), 4.37 (1H, s); ^{13}C NMR (75 MHz, CD_3OD, int. ref CH_3CN δ 0.0) δ 14.8, 21.1, 57.4, 66.7, 105.3; MS (ES, pos. mode) m/z (%) 162 (M + H^+ − HCl, 100). Anal. Calcd for $C_8H_{20}ClNO_2$: C 48.60; H 10.20; N 7.08. Found: C 48.89; H 10.37; N 7.21.

1-Dimethoxymethyl-1-ethylpropylamine Hydrochloride 8c. White crystals, yield 81% (96 mg): mp 137.3−137.6 °C; IR (cm^{-1}) ν_{max} 1072, 1112, 1507, 2910, 3363; ^1H NMR (300 MHz, CD_3OD, int. ref CH_3CN δ 2.00) δ 0.91 (3H, t, J = 7.7 Hz), 0.92 (3H, t, J = 7.7 Hz), 1.69 (2H, q, J = 7.7 Hz), 1.70 (2H, q, J = 7.7 Hz), 3.57 (6H, s), 4.35 (1H, s); ^{13}C NMR (75 MHz, CD_3OD, int. ref CH_3CN δ 0.0) δ 6.5 (2C), 24.2 (2C), 58.3 (2C), 63.2, 106.4; MS (ES, pos. mode) m/z (%) 162 (M + H^+ − HCl, 100). Anal. Calcd for $C_8H_{20}ClNO_2$: C 48.60; H 10.20; N 7.08. Found: C 48.24; H 10.03; N 6.96.

Synthesis of 2-Amino-2-ethylbutyraldehyde Hydrochloride 7i. To a solution of (R_S)-*N*-*tert*-butanesulfinyl-2-amino-2-ethylbutanal **6i** (0.10 g, 0.45 mmol) in dry Et_2O (3 mL) was added a 4 M solution of HCl (10 equiv, 1.14 mL, 4.54 mmol) in dioxane at room temperature. The mixture was stirred for 1 h at room temperature. Subsequently, the reaction mixture was concentrated in vacuo. Precipitation in dry Et_2O afforded 0.053 g (0.35 mmol, 77%) of 2-amino-2-ethylbutanal hydrochloride **7i**. ^1H NMR analysis in DMSO-d_6 showed an equilibrium between aldehyde **7i** and the corresponding 2-amino-2-ethylbutane-1,1-diol hydrochloride **9b** in a ratio of 80:20, while a reversed ratio of **7i**/**9b** 13:87 was obtained via ^1H NMR analysis in D_2O.

2-Amino-2-ethylbutanal Hydrochloride 7i. The ^1H and ^{13}C NMR spectral data of **7i** in DMSO-d_6 were obtained from a mixture of **7i** and the corresponding hydrate **9b** in a ratio of 80:20. White solid, yield 77% (53 mg): mp 199.2−199.5 °C (carbonization); IR (cm^{-1}) ν_{max} 1513, 1730, 2883; ^1H NMR (300 MHz, DMSO-d_6) δ 0.88 (6H, t, J = 7.2 Hz), 1.86 (4H, q, J = 7.2 Hz), 8.50 (3H, br s), 9.53 (1H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.8 (2C), 25.4 (2C), 66.8, 201.3; MS (ES, pos. mode) m/z (%) 116 (M + H^+, 100).

2-Amino-2-ethylbutane-1,1-diol Hydrochloride 9b. The ^1H and ^{13}C NMR spectral data of **9b** in D_2O were obtained from a mixture of **9b** and the corresponding aldehyde **7i** in a ratio of 87:13. Data: ^1H NMR (300 MHz, D_2O, int. ref CH_3CN δ 2.00) δ 0.88 (6H, t, J = 7.2 Hz), 1.69 (4H, q, J = 7.2 Hz), 5.09 (1H, s); ^{13}C NMR (75 MHz, D_2O, int. ref CH_3CN δ 0.0) δ 5.3 (2C), 22.5 (2C), 62.1, 88.3; MS (ES, pos. mode) m/z (%) 134 (M + H^+, 100).

■ ASSOCIATED CONTENT

Supporting Information

General experimental conditions and copies of ^1H NMR and ^{13}C NMR spectra for (R_S)-*N*-*tert*-butanesulfinyl 2-chloro-1-methoxyethylamines **3a**−**b**, (R_S)-*N*-*tert*-butanesulfinyl 2-amino acetals **5**, (R_S)-*N*-*tert*-butanesulfinyl α-amino ketones **6a**−**g** and **6j** and (R_S)-*N*-*tert*-butanesulfinyl α-amino aldehydes **6h**,**i**, α-amino ketone hydrochlorides **7a**−**g**, (*S*)-cathinone hydrochloride **7j**, 2-amino acetal hydrochlorides **8**, 2-amino-2-ethylbutanal hydrochloride **7i**, and 2-amino-2-ethylbutane-1,1-diol hydrochloride **9b**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Tel: +32 (0)9 264 59 51. Fax: +32 (0)9 264 62 21. E-mail: norbert.dekimpe@UGent.be.

Notes

The authors declare no competing financial interest.

[†]Postdoctoral Fellow of the Research Foundation − Vlaanderen (FWO)

■ ACKNOWLEDGMENTS

The authors are indebted to the Research Foundation − Flanders (FWO − Vlaanderen) and Ghent University (BOF) for financial support.

REFERENCES

(1) (a) Baktharaman, S.; Hili, R.; Yudin, A. K. *Aldrichim. Acta* **2008**, *41*, 109 and references therein. (b) Miura, T.; Biyajima, T.; Fujii, T.; Murakami, M. *J. Am. Chem. Soc.* **2012**, *134*, 194 and references therein. (c) Fisher, L. E.; Muchowski, J. M. *Org. Prep. Proced. Int.* **1990**, *22*, 403. (d) Katritzky, A. R.; Cheng, D.; Musgrave, R. P. *Heterocycles* **1996**, *42*, 273. (e) Mayer, D. In *Houben-Weyl, Methoden der Organischen Chemie*, 4th ed.; Müller, E. G., Ed.; Thieme: Stuttgart, 1977; Vol. *7/2c*, pp 2251−2307. (f) Gryko, D.; Chalko, J.; Jurczak, J. *Chirality* **2003**, *15*, 514. (g) Eckardt, M. In *Science of Synthesis*; Georg Thieme Verlag: Stuttgart, 2006; Vol. *25*, p 492. (h) Suffert, J. In *Science of Synthesis*; Georg Thieme Verlag: Stuttgart, 2004; Vol. *26*, p 953. (i) Besse, P.; Veschambre, H.; Dickman, M.; Chênevert, R. *J. Org. Chem.* **1994**, *59*, 8288. (j) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835. (k) Moiseev, I. K.; Makarova, N. V.; Zemtsova, M. N. *Chem. Heterocycl. Compd.* **1999**, *35*, 637.

(2) Kudrin, A. N.; Vorob'ev, V. G. *Amino Ketones*; Meditsina: Moscow, 1970; p 346.

(3) Bechara, E. J. H.; Dutra, F.; Cardoso, V. E. S.; Sartori, A.; Olympio, K. P. K.; Penatti, C. A. A.; Adhikari, A.; Assunção, N. A. *Comp. Biochem. Physiol., Part C: Pharmacol., Toxicol. Endocrinol.* **2007**, *146*, 88.

(4) Sharma, V.; Kelly, G. T.; Foulke-Abel, J.; Watanabe, C. M. H. *Org. Lett.* **2009**, *11*, 4006.

(5) (a) Stevens, C. L.; Ash, A. B.; Thuillier, A.; Amin, J. H.; Balys, A.; Dennis, W. E.; Dickerson, J. P.; Glinski, R. P.; Hanson, H. T.; Pillai, M. D.; Stoddard, J. W. *J. Org. Chem.* **1966**, *31*, 2593. (b) Stevens, C. L.; Blumbergs, P.; Monk, M. *J. Org. Chem.* **1963**, *28*, 331.

(6) Kirrmann, A.; Nouri-Bimorghi, R.; Elkik, E. *Bull. Soc. Chim. Fr.* **1969**, 2385.

(7) Stevens, C. L.; Chang, C. H. *J. Org. Chem.* **1962**, *27*, 4392.

(8) (a) Satoh, T.; Kaneko, Y.; Sakata, K.; Yamakawa, K. *Chem. Lett.* **1985**, 585. (b) Satoh, T.; Kaneko, Y.; Sakata, K.; Yamakawa, K. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 457. (c) Satoh, T.; Oohara, T.; Ueda, Y.; Yamakawa, K. *J. Org. Chem.* **1989**, *54*, 3130.

(9) (a) Parcell, R. F. *Chem. Ind.* **1963**, 1396. (b) Parcell, R. F.; Sanchez, J. P. *J. Org. Chem.* **1981**, *46*, 5229. (c) Lantos, I.; Gombatz, K.; McGuire, M.; Pridgen, L.; Remich, J.; Shilcrat, S. *J. Org. Chem.* **1988**, *53*, 4223. (d) Ueda, S.; Naruto, S.; Yoshida, T.; Sawayama, T.; Uno, H. *Chem. Commun.* **1985**, 218. (e) Zawalski, R. C.; Lisiak, M.; Kovacic, P.; Luedtke, A.; Timberlake, J. W. *Tetrahedron Lett.* **1980**, *21*, 428. (f) Morrow, D. F.; Butler, M. E.; Huang, E. C. Y. *J. Org. Chem.* **1965**, *30*, 579. (g) Ooi, T.; Takahashi, M.; Doda, K.; Maruoka, K. *J. Am. Chem. Soc.* **2002**, *124*, 7640.

(10) (a) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149. (b) Reetz, M. T. *Chem. Rev.* **1999**, *99*, 1121. (c) Hili, R.; Yudin, A. K. *J. Am. Chem. Soc.* **2006**, *128*, 14772. (d) Hili, R.; Yudin, A. K. *J. Am. Chem. Soc.* **2009**, *131*, 16404.

(11) (a) Enders, D.; Funk, R.; Klatt, M.; Raabe, G.; Hovestreydt, E. R. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 418. (b) Yamazaki, S.; Takebayashi, M. *J. Org. Chem.* **2011**, *76*, 6432. (c) Anan, H.; Tanaka, A.; Tsuzuki, R.; Yokota, M.; Yatsu, T.; Fujikura, T. *Chem. Pharm. Bull.* **1996**, *44*, 1865. (d) de la Fuente, M. C.; Pullan, S. E.; Biesmans, I.; Domínguez, D. *J. Org. Chem.* **2006**, *71*, 3963.

(12) (a) De Kimpe, N.; Verhe, R. In *The Chemistry of α-Halo Ketones, α-Halo Aldehydes, and α-Halo Imines*; Wiley: Chichester, U.K., 1988; p 496. (b) De Kimpe, N.; Schamp, N. *Org. Prep. Proced. Int.* **1979**, *11*, 115. (c) De Kimpe, N.; Verhé, R.; De Buyck, L.; Schamp, N. *Org. Prep. Proced. Int.* **1980**, *12*, 49. (d) De Kimpe, N.; Stanoeva, E.; Verhé, R.; Schamp, N. *Synthesis* **1988**, 587. (e) De Kimpe, N.; Sulmon, P.; Moëns, L.; Schamp, N.; Declerq, J.-P.; Van Meerssche, M. *J. Org. Chem.* **1986**, *51*, 3839. (f) De Kimpe, N.; Schamp, N. *Bull. Soc. Chim. Belg.* **1974**, *83*, 507. (g) De Kimpe, N.; Verhé, R.; De Buyck, L.; Moëns, L.; Schamp, N. *Tetrahedron Lett.* **1981**, *22*, 1837. (h) De Kimpe, N.; De Cock, W.; Stevens, C. *Tetrahedron* **1992**, *48*, 2739. (i) De Kimpe, N.; Schamp, N. *J. Org. Chem.* **1975**, *40*, 3749. (j) De Kimpe, N.; Verhe, R.; De Buyck, L.; Schamp, N. *Bull. Soc. Chim. Belg.* **1977**, *86*, 663. (k) De Kimpe, N.; Verhe, R.; De Buyck, L.; Schamp, N. *J. Org. Chem.* **1977**, *42*, 3704. (l) De Kimpe, N.; Verhe, R.; De Buyck, L.; Sulmon, P.; Schamp, N. *Tetrahedron Lett.* **1983**, *24*, 2885. (m) De Kimpe, N.; Verhe, R.; De Buyck, L.; Hasma, H.; Schamp, N. *Tetrahedron* **1976**, *32*, 2457. (n) De Kimpe, N.; Verhe, R.; De Buyck, L.; Moens, L.; Sulmon, P.; Schamp, N. *Synthesis* **1982**, 765. (o) De Kimpe, N.; Stanoeva, E. *Synthesis* **1994**, 695. (p) De Kimpe, N.; Boeykens, M.; Boelens, M.; De Buck, K.; Cornelis, J. *Org. Prep. Proced. Int.* **1992**, *24*, 679. (q) De Kimpe, N.; Stevens, C.; Virag, M. *Tetrahedron* **1996**, *52*, 3303. (r) De Kimpe, N.; Aelterman, W.; De Geyter, K. *J. Org. Chem.* **1997**, *62*, 5138. (s) Aelterman, W.; Giubellina, N.; Stanoeva, E.; De Geyter, K.; De Kimpe, N. *Tetrahedron Lett.* **2004**, *45*, 441.

(13) Singh, G. S.; D'hooghe, M.; De Kimpe, N. *Chem. Rev.* **2007**, *107*, 2080.

(14) (a) Dejaegher, Y.; Mangelinckx, S.; De Kimpe, N. *J. Org. Chem.* **2002**, *67*, 2075. (b) Li, J.-Y.; Zhao, B.-X.; Zhang, W.; Huang, X.-J.; Wang, Y.; Sun, P.-H.; Ye, W.-C.; Chen, W.-M. *Tetrahedron* **2012**, *68*, 3972. (c) Plaquevent, J.-C.; Giard, T.; Trancard, D.; Cahard, D. *Res. Adv. Org. Chem. 1* **2000**, 61. (d) Duhamel, L.; Poirier, J. M. *Tetrahedron Lett.* **1976**, 2437.

(15) (a) Denolf, B.; Leemans, E.; De Kimpe, N. *J. Org. Chem.* **2007**, *72*, 3211. (b) Denolf, B.; Leemans, E.; De Kimpe, N. *J. Org. Chem.* **2008**, *73*, 5662. (c) Denolf, B.; Mangelinckx, S.; Törnroos, K. W.; De Kimpe, N. *Org. Lett.* **2006**, *8*, 3129. (d) Denolf, B.; Mangelinckx, S.; Törnroos, K. W.; De Kimpe, N. *Org. Lett.* **2007**, *9*, 187. (e) Hodgson, D. M.; Kloesges, J.; Evans, B. *Org. Lett.* **2008**, *10*, 2781. (f) Chen, Q.; Li, J.; Yuan, C. *Synthesis* **2008**, 2986. (g) Leemans, E.; Mangelinckx, S.; De Kimpe, N. *Synlett* **2009**, 1265. (h) Hodgson, D. M.; Kloesges, J.; Evans, B. *Synthesis* **2009**, 1923. (i) Colpaert, F.; Mangelinckx, S.; Leemans, E.; Denolf, B.; De Kimpe, N. *Org. Biomol. Chem.* **2010**, *8*, 3251. (j) Leemans, E.; Colpaert, F.; Mangelinckx, S.; De Brabandere, S.; Denolf, B.; De Kimpe, N. *Synlett* **2011**, 674.

(16) Fujisawa, T.; Kooriyama, Y.; Shimizu, M. *Tetrahedron Lett.* **1996**, *37*, 3881.

(17) Hua, D. H.; Lagneau, N.; Wang, H.; Chen, J. *Tetrahedron: Asymmetry* **1995**, *6*, 349.

(18) Davis, F. A.; Jing, C. *ARKIVOC* **2008**, *ii*, 190.

(19) (a) Besse, P.; Veschambre, H.; Dickman, M.; Chênevert, R. *J. Org. Chem.* **1994**, *59*, 8288. (b) Kohli, J. D.; Goldberg, L. I. *J. Pharm. Pharmacol.* **1982**, *34*, 338. (c) Kalix, P. *Life Sci.* **1983**, *32*, 801.

(20) (a) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600. (b) Ferreira, F.; Botuha, C.; Chemla, F.; Perez-Luna, A. *Chem. Soc. Rev.* **2009**, *38*, 1162.

(21) Graham, M. A.; Wadsworth, A. H.; Zahid, A.; Rayner, C. M. *Org. Biomol. Chem.* **2003**, *1*, 834.

(22) (a) Fischer, E. *Chem. Ber.* **1908**, *41*, 1019. (b) Myers, A. G.; Kung, D. W.; Zhong, B. *J. Am. Chem. Soc.* **2000**, *122*, 3236.

(23) Augé, J.; Gil, R. *Tetrahedron Lett.* **2002**, *43*, 7919.

(24) (a) Kim, D. J.; Cho, B. T. *Bull. Korean Chem. Soc.* **2003**, *24*, 1641. (b) Hwang, G. I.; Chung, J.-H.; Lee, W. K. *Tetrahedron* **1996**, *52*, 12111.

(25) (a) Kazachkov, M.; Yu, P. H. *J. Chromatogr., B* **2005**, *824*, 116. (b) Han, Y.; Hu, H. *Synthesis* **1990**, 615. (c) Albert, A.; Matsuura, S. *J. Chem. Soc.* **1961**, 5131. (d) Baumgarten, H. E.; Bower, F. A. *J. Am. Chem. Soc.* **1954**, *76*, 4561.

(26) (a) Norris, T. O.; Mckee, R. L. *J. Am. Chem. Soc.* **1955**, *77*, 1056. (b) Hagedorn, I.; Eholzer, U.; Etling, H. *Chem. Ber.* **1965**, *98*, 193. (c) Cheng, S. S.; Jonsson, S.; Semeniuk, F. T. *J. Pharm. Sci.* **1962**, *51*, 108.

(27) (a) Abdalla, G. M.; Sowell, J. W. *J. Heterocycl. Chem.* **1987**, *24*, 297. (b) Castro, A. J.; Brain, D. K.; Fisher, H. D.; Fuller, R. K. *J. Org. Chem.* **1954**, *19*, 1444. (c) Smith, P. A. S.; Most, E. E. *J. Org. Chem.* **1957**, *22*, 358. (d) Baumgarten, H. E.; Petersen, J. M. *J. Am. Chem. Soc.* **1960**, *82*, 459. (e) Dhane, D. L.; Noras, K. A.; Mushrif, A. U. *Indian J. Chem.* **1975**, *13*, 858.

(28) Long, L. M.; Troutman, H. D. *J. Am. Chem. Soc.* **1949**, *71*, 247.

(29) (a) Bader, H.; Downer, J. D. *J. Chem. Soc.* **1953**, 1636. (b) Jackman, M.; Klenk, M.; Fishburn, B.; Tullar, B. F.; Archer, S. *J. Am. Chem. Soc.* **1948**, *70*, 2884.