ORGANIC LETTERS

2007
Vol. 9, No. 2
187−190

Asymmetric Synthesis of Cyclopropylamines Starting from *N*-Sulfinyl α-Chloro Ketimines

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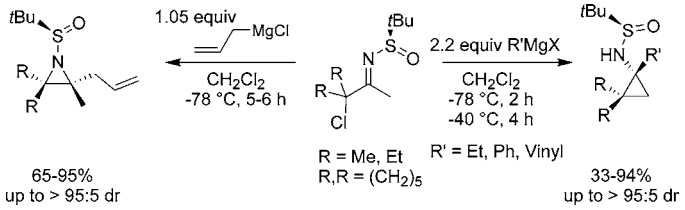
Received September 6, 2006

ABSTRACT



Treatment of novel chiral *N*-sulfinyl α-chloro ketimines with Grignard reagents resulted in the synthesis of chiral *N*-(1-substituted cyclopropyl)-*tert*-butanesulfinamides in acceptable to good yields and diastereoselectivity via 1,3-dehydrohalogenation and subsequent addition of the Grignard reagent to the intermediate cyclopropylideneamine. Only in the case of allylmagnesium chloride did the reaction lead to aziridines in high yield. Further deprotection toward *N*-unprotected 1-substituted cyclopropylamines was established, and the absolute configuration was determined.

The use of cyclopropylamines and their stereoselective synthesis are of considerable interest in recent years.[1] Besides their occurrence as pharmaceutical or agrochemical subunits, the highly strained cyclopropylamines are also synthesized for their use as chiral resolving agents or as synthetic intermediates for further reactions.[2] Additionally, the potential to control local conformation by restricting the number of rotational degrees is progressively applied in computational modeling systems. Hence, the need for such small, chiral molecules is of great interest.[3]

From earlier research, it is known that the synthesis of cyclopropylamines can be achieved in acceptable yield upon treatment of *N*-alkyl α-halo imines with alkoxides.[4] However, the cyclopropylamine synthesis via reaction of Grignard reagents with α-halo imines is unprecedented. It has been established that the moderate reactivity and stereoselectivity, often observed when *N*-alkyl imines are used, can substantially be improved by using the corresponding *N*-sulfinyl imines.[5] A lot of work in this area has been performed by the Ellman[6] and Davis groups.[7] Despite the good results leading to numerous publications, almost no attention has been given to *N*-sulfinyl α-halo imines. Only few halogenated *N*-sulfinyl imines have been synthesized, and the few examples reported have not been thoroughly studied toward their reactivity.[8] However, the potential of halo-

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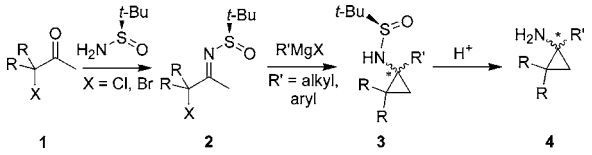
10.1021/ol0622054 CCC: $37.00
Published on Web 01/03/2007

genated imines as starting material to synthesize aziridines or cyclopropylamines, among other interesting compounds, in a simple and straightforward manner has been described extensively.[9] Chiral α-halo imines have not been used in this respect. In addition, *N*-sulfinyl deprotection, under mild conditions, after reaction, providing unprotected cyclopropylamines or aziridines is advantageous for further reaction.

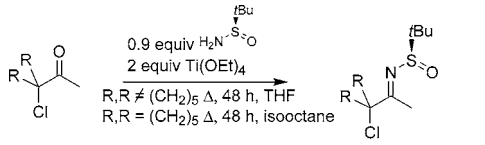
In this paper, the chiral synthesis of 1-alkyl- and 1-aryl-cyclopropylamines is elaborated for the first time starting from α-halo imines (Scheme 1).

Scheme 1. Purpose of the Research



N-Sulfinyl α-chloro ketimines (R_S)-**2**, a new class of functionalized *N*-sulfinyl imines, were synthesized via condensation of α-chloro ketones **1** with (R_S)-*tert*-butanesulfinamide in the presence of 2 equiv of $Ti(OEt)_4$ (Scheme 2). Ketimines (R_S)-**2a**,**b** were synthesized in high yields (82−91%) when stirred for 48 h at reflux temperature in dry THF, while ketone **1c** had to be stirred at 98 °C for 48 h in isooctane to form ketimine (R_S)-**2c** in 89% yield (Scheme 2). The ketimines (R_S)-**2** were isolated after removal of the titanium species after aqueous workup, and after distillation to remove the small excess of ketones **1** used. The latter ketones were synthesized according to literature procedures.[10] No epimerization at the sulfinyl center occurred during the synthesis of imines **2** as was checked for with lanthanide shift reagent $Eu(hfc)_3$.

Scheme 2. Synthesis of *N*-Sulfinyl α-Chloro Ketimines (R_S)-**2**

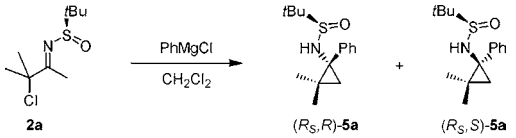


1a R = Me — **2a** R = Me (91%)
1b R = Et — **2b** R = Et (82%)
1c R,R = $(CH_2)_5$ — **2c** R,R = $(CH_2)_5$ (89%)

All ketimines (R_S)-**2a**−**c** were obtained as exclusively E-isomers and could be stored for long periods (>1 year) of time at low temperature (−40 °C).

These new chiral ketimines (R_S)-**2** were tested for their reactivity upon treatment with Grignard reagents. Therefore, addition of 1.05 equiv of PhMgCl to ketimine (R_S)-**2a**, dissolved in CH_2Cl_2, at −78 °C and subsequent stirring for 4 h at this temperature, afforded *N*-sulfinyl 1-phenylcyclopropylamine (R_S,*R*)-**5a** in 10% yield with excellent diastereoselectivity (95:5 dr) after aqueous NH_4Cl workup. Yet, most of the starting ketimine (43%) was recovered under these conditions (Table 1, entry a). As reported in Table 1, changing temperature, time, and the amount of Grignard reagent added resulted in a substantial improvement of the isolated yields of the formed cyclopropylamine (R_S,*R*)-**5a**. Judging from the reaction mechanism (vide infra), 2 equiv of Grignard reagent is consumed in the synthesis of 1-phenylcyclopropylamine **5a**. Subsequently, higher amounts of Grignard reagent were added (Table 1, entries a−c). If more than 2.2 equiv of PhMgCl were added, yields of cyclopropylamine (R_S,*R*)-**5a** formed dropped. Side reactions became more pronounced and were detrimental for purification by flash chromatography. Extended reaction times did improve the yields significantly (entry b vs e). However, changing the temperature turned out to be a more promising alternative. Better results were obtained if the reaction was performed at −40 °C, under the sole condition that the reagent was added at −78 °C (Table 1, entries d,f−i). Addition of 2.2 equiv of PhMgCl at −40 °C afforded the cyclopropylamine (R_S,*R*)-**5a** in reasonable yield (59%) but with inferior diastereoselectivity. Again, the purification by flash chromatography was more tedious and disadvantageous for the isolated yield of the cyclopropylamine (R_S,*R*)-**5a**. Changing the solvent (toluene, Et_2O, and THF) or the concentration did not improve the yield or the diastereoselectivity of the reaction.

Table 1. Synthesis of Cyclopropylamine **5a** via Addition of PhMgCl Across *N*-Sulfinyl α-Chloro Ketimine (R_S)-**2a**



entry	PhMgCl (equiv)	T (°C)	time (h)	yield[a] (%) (dr)[b]
a	1.05	−78	4	10 (95:5)
b	2.2	−78	4	28 (96:4)
c	3	−78	4	17 (−)
d	2.2	−40	4	59 (80:20)
e	2.2	−78	8	47 (95:5)
f	2.2	−78/−40	2/4	70 (95:5)
g	2.2	−78/−40	0.4/4	71 (92:8)
h	2.2	−78/rt	2/4	27 (82:18)
i	2.2	−78/−40/rt	2/4/12	67 (95:5)

[a] Determined by a mass balance after chromatography. [b] Determined by NMR analysis of the reaction mixture.

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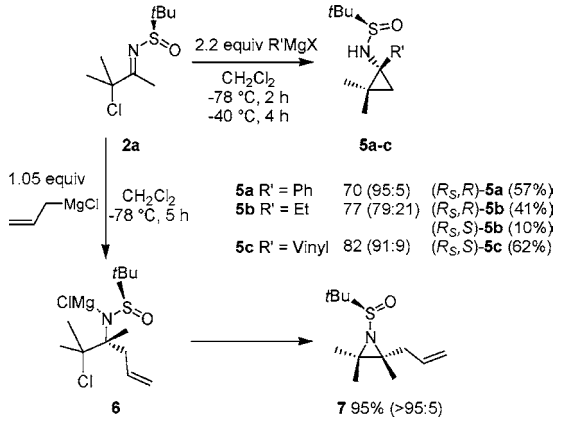
The best results were obtained if 2.2 equiv of PhMgCl were added across ketimine (R_S)-**2a** in dichloromethane at −78 °C. Subsequent stirring for 2 h at −78 °C and 4 h at −40 °C afforded 1-phenylcyclopropylamine (R_S,R)-**5a** after aqueous NH_4Cl workup in high yield (70%) and excellent diastereoselectivity (95:5 dr).

In order to explore the scope of the Grignard addition reaction across ketimine (R_S)-**2a**, a variety of different Grignard reagents were evaluated. The optimized reaction conditions, found in the addition reaction of PhMgCl across ketimine (R_S)-**2a**, were applied for EtMgCl, EtMgBr, and vinylMgBr upon addition of *N*-sulfinyl α-chloro ketimine (R_S)-**2a** (Scheme 3), affording the substituted *N*-sulfinyl

Scheme 3. Addition of Grignard Reagents to Chiral *N*-Sulfinyl α-Chloro Ketimine **2a**



cyclopropylamines (R_S,R)-**5b** and (R_S,S)-**5c** in high yield (77−82%) with good diastereoselectivity (79:21−91:9).

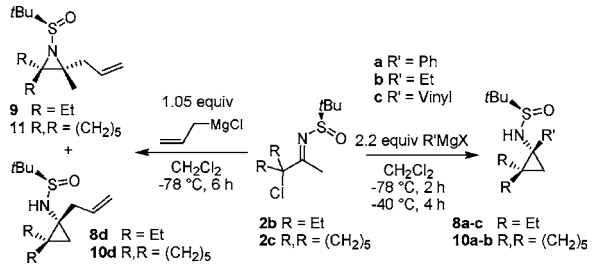
Changing EtMgCl to EtMgBr resulted in the formation of a less complicated reaction mixture. Still, with reference to the other nucleophiles used, the stereoselectivity of the addition of EtMgBr was lower (Scheme 3). As a result, both diastereomers **5b** were obtained.

The cyclopropylamines (R_S,R)-**5a**,**b** and (R_S,S)-**5c** formed were isolated as a single compound after flash chromatography. Consequently, the yields dropped significantly during purification. Only 1-phenylcyclopropylamine (R_S,R)-**5a** could be obtained by recrystallization of the reaction mixture in diethyl ether. Upon treatment of ketimine (R_S)-**2a** with 2.2 equiv of allylMgCl in dichloromethane at −78 °C for 2 h and subsequent reaction for 4 h at −40 °C, *N*-(1-allylcyclopropyl)-*tert*-butanesulfinamide (R_S,R)-**5d** was not formed. Ketimine (R_S)-**2a** was attacked at the imine function without preceding α-deprotonation. The intermediate *β*-halo *N*-sulfinamide **6** was in situ ring closed toward the corresponding *N*-sulfinyl 2-allylaziridine (R_S,R)-**7**. A closely related synthesis of chiral aziridines by the use of Grignard reagents and *N*-sulfinyl α-chloro aldimines has recently been described by us.[11]

Better yields of 2-allylaziridine (R_S,R)-**7** were obtained if the Grignard reagent was added in a small excess (1.05 equiv instead of 2.2 equiv) and the mixture stirred for longer periods at −78 °C (5 h).

The steric bulk of ketimines (R_S)-**2b**,**c**, upon treatment with Grignard reagents, resulted in good diastereoselectivities of the cyclopropylamines formed (Table 2). However, the yields

Table 2. Addition of Grignard Reagents to *N*-Sulfinyl α-Chloro Ketimines **2b**,**c**



entry	imine	R′	product	yield[a] (%) (dr)[b]	yield[c] (%)
a	**2b**	Ph	**8a**	50 (95:5)	(R_s,R)-**8a** (38)
b	**2b**	Et	**8b**	57 (79:21)	(R_s,R)-**8b** (30)
c	**2b**	vinyl	**8c**	62 (91:9)	(R_s,S)-**8c** (37)
d	**2b**	allyl	**9**	91 (95:5)	(R_s,R)-**9** (84)
e	**2c**	Ph	**10a**	44 (96:4)	(R_s,R)-**10a** (31)
f	**2c**	Et	**10b**	42 (81:19)	(R_s,R)-**10b** (23)
g	**2c**	allyl	**11**	83 (93:7)	(R_s,R)-**11** (65)[d]

[a] Determined by a mass balance of the reaction mixture. [b] Determined by NMR analysis of the reaction mixture. [c] Determined by a mass balance after chromatography. [d] Cyclopropylamine (R_S,R)-**10d** was isolated in 2% yield.

of the cyclopropylamines isolated dropped significantly. Troublesome purification by flash chromatography was inevitable. Though various solvent mixtures were used, all attempts to isolate and identify the side products failed. Upon treatment of ketimine (R_S)-**2b** in dichloromethane with 1.05 equiv of allylMgCl the 2-allylaziridine **9** was isolated in 84% yield and 95:5 dr after completion of the reaction at −78 °C (6 h). Noteably, some of the 1-allylcyclopropylamine (R_S,R)-**8d** was observed by ^{1}H NMR (3%) but the formed side product could not be isolated. Reaction of ketimine (R_S)-**2c** with 1.05 equiv of allylMgCl at −78 °C afforded 1-allylspiro-[2.5]octan-1-amine (R_S,R)-**10d** after flash chromatography in low yield (2%) in addition to 2-allylazaspiro[2.5]octane (R_S,R)-**11** (65%).

It is proposed that the cyclopropanation reaction proceeds via a Favorskii-type reaction mechanism (Scheme 4).[12] Hence, the first equivalent of Grignard reagent acts as a base, an unprecedented reaction in this field. A proton in α-position of the imino function of ketimines (R_S)-**2** is abstracted, the resulting 1-azaallylic anion **12**−**13** undergoing chloride expulsion to produce the intermediate *N*-(cyclopropylidene)-

(11) Denolf, B.; Mangelinckx, S.; Törnroos, K. W.; De Kimpe, N. *Org. Lett.* **2006**, *8*, 3129.

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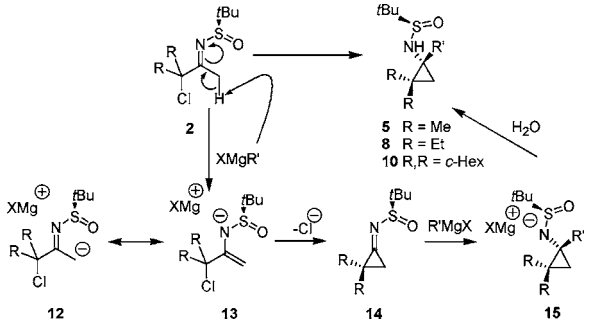
Scheme 4. Proposed Favorskii-Type Reaction Mechanism

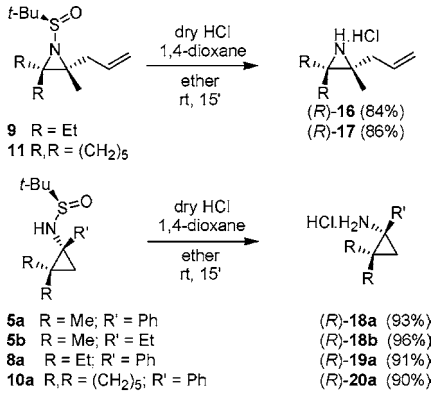


tert-butanesulfinamide **14**, which is attacked by the second equivalent of Grignard reagent across the reactive imino function of **14** giving rise to cyclopropylamine **5**, **8**, or **10** after aqueous NH_4Cl workup. The highly strained Favorskii-type intermediate **14**, in combination with the bulky *tert*-butanesulfinyl group, results in the formation of an enantio-enriched cyclopropylamine **5**, **8**, or **10**.

All attempts to isolate the intermediate *N*-cyclopropylidene sulfinamide **14** failed. Addition of different bases (1.05 equiv of PhMgCl, BuLi, or NaH) yielded a complex reaction mixture wherein the cyclopropyl protons in ^{1}H NMR, or the imino function, specific at 1800 cm^{-1} in IR, were not observed. By use of Ellman's procedure,[13] the intermediate aza enolate **12**−**13** of imine **2a** (R = Me) was trapped with benzaldehyde affording *N*-[2-chloro-1-(2-hydroxy-2-phenyl-ethyl)-2-methylpropylidene]-*tert*-butanesulfinamide in a 2:1 mixture of diastereomers.

The chiral *N*-sulfinyl allylaziridines (R_S,*R*)-**9** and -**11** and *N*-sulfinyl cyclopropylamines **5**, **8**, and **10** could be deprotected by simple treatment with a saturated solution of dry HCl in 1,4-dioxane. Stirring for 15 min at room temperature afforded the HCl salts of the aziridines **16** and **17** or the cyclopropylamines **18**−**20** in high yield (>85%) and purity (85−95%) (Scheme 5).

Scheme 5. Sulfinyl Deprotection in 1,4-Dioxane·HCl



Without any of the cyclopropylamines (*R*)-**18**−**20** or aziridines (*R*)-**16** and -**17** being reported in literature, the absolute configuration had to be determined. From the X-ray diffraction analysis of the formed cyclopropylamine (R_S,*S*)-**5c** the absolute configuration of the structure was undoubtedly characterized as (R_S,*S*)-*N*-(*tert*-butanesulfinyl)cyclopropylamine **5c**. This configuration can be predicted via a chelation-controlled transition state **A** (Figure 1), which is the general intermediate proposed for additions to non-functionalized *N*-sulfinyl imines.[5,6,14]

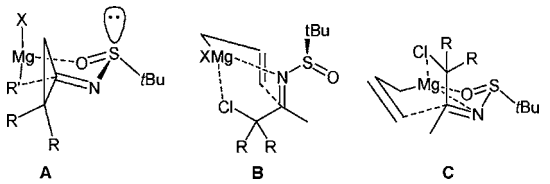


Figure 1. Proposed transition states during the reaction

Though it is was not possible to prove the absolute configuration of allylaziridines **16** and **17**, the (R_S,*R*)-stereochemistry is assumed in analogy with the stereochemistry obtained during the synthesis of similar aziridines from chiral aldimines.[11] The reversal of stereochemical outcome of the reaction is attributed to the α-coordinating ability of the chlorine atom as is depicted in Figure 1 (transition state **B** and **C**) and is analogous to the results obtained with other *N*-sulfinyl imines containing an α-coordinating group, such as a nitrogen or oxygen atom.[14a,15]

In conclusion, an efficient synthesis of *N*-sulfinyl α-chloro ketimines was developed. Upon treatment of *N*-sulfinyl α-chloro ketimines (R_S)-**2** with Grignard reagents, chiral *N*-(1-substituted cyclopropyl)-*tert*-butanesulfinamides **5**, **8**, and **10** were synthesized in acceptable to good yields with good diastereoselectivity via 1,3-dehydrohalogenation to a cyclopropylideneamine intermediate which underwent addition of organomagnesium nucleophiles with high selectivity. Only in the case of allylmagnesium chloride did the reaction lead to aziridines (R_S,*R*)-**7**, **9**, and **11** in high yield. Further deprotection toward the *N*-unprotected cyclopropylamines **18**−**20** was established and the absolute configuration was determined.

Acknowledgment. Research funded by a Ph.D. grant of the Institute for the Promotion of Innovation through Science and Technology in Flanders (IWT-Vlaanderen).

Supporting Information Available: Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0622054

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