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Asymmetric synthesis of cetirizine dihydrochloride†

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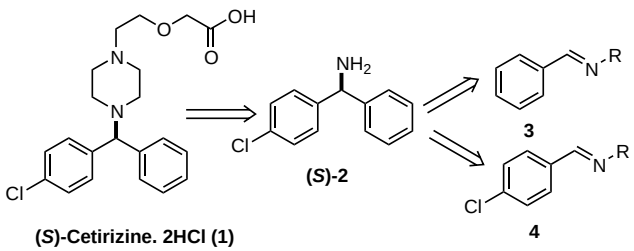
Abstract—Practical route technology for the preparation of (*S*)-cetirizine·2HCl via diastereoselective organometallic addition to *N*-*tert*-butanesulfinyl aldimines is disclosed.

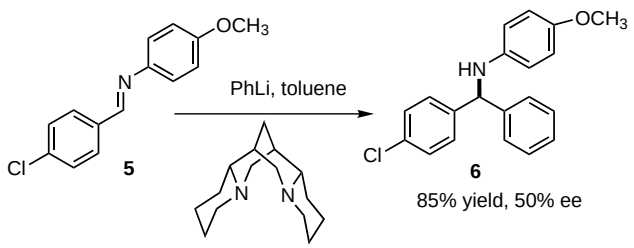
Cetirizine dihydrochloride (**1**; 2-[2-[[4-[(4-chlorophenyl)-phenylmethyl]-1]piperazinyl]ethoxy]-acetic acid) is a non-sedating histamine H1-receptor antagonist used for the treatment of allergies.[1] Preliminary results indicate that the levorotatory enantiomer of cetirizine displays a better pharmacological profile than the racemic mixture, and is currently marketed as Xyzal™ in Europe. Previous syntheses of single enantiomer cetirizine have relied on resolution,[2] or a stoichiometric heavy metal.[3] We sought an asymmetric synthesis that would allow the preparation of either enantiomer employing pharmaceutically acceptable reagents. Recently, we reported on a preparative chiral high-performance liquid chromatography (HPLC) approach to the large-scale production of both enantiomers of cetirizine dihydrochloride.[4] Herein we report our efforts on the asymmetric synthesis via aryl organometallic addition to the appropriate *N*-*tert*-butanesulfinyl aldimines.[5]

The conversion of enantiomerically enriched amine **2** (available via diastereomeric crystallization with tartaric acid) to **1** has been reported.[2b] Therefore, we sought an asymmetric synthesis of **2**.[6] The most appealing approach is an enantioselective/diastereoselective addition of an organometallic reagent to imine **3** or **4** (Scheme 1). The advantage to this approach is that by changing the imine/organometallic partner, either enantiomer can be produced. That is, the reaction of the imine of 4-chlorobenzaldehyde with metallobenzene will give the opposite enantiomer as the reaction of the benzaldehyde imine with the 4-chlorometallobenzene. Organometallic addition to an aldimine in the presence of an external chiral chaperone is known to proceed with high selectivity.[7] Preliminary experiments adding phenyllithium to imine **5** in the presence of stoichiometric sparteine were promising (Scheme 2; stereochemistry of **6** is based on Ref. 6c). However, attempts to remove the *p*-methoxyphenyl ring resulted in benzylic oxidation and the destruction of the newly formed stereocenter rather than deprotection.

In parallel, chiral auxiliary based approaches were investigated.[8] Sulfinimines have also been shown to be



Scheme 1.



Scheme 2.

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† This paper is dedicated to Professor Carl R. Johnson on the occasion of his retirement.

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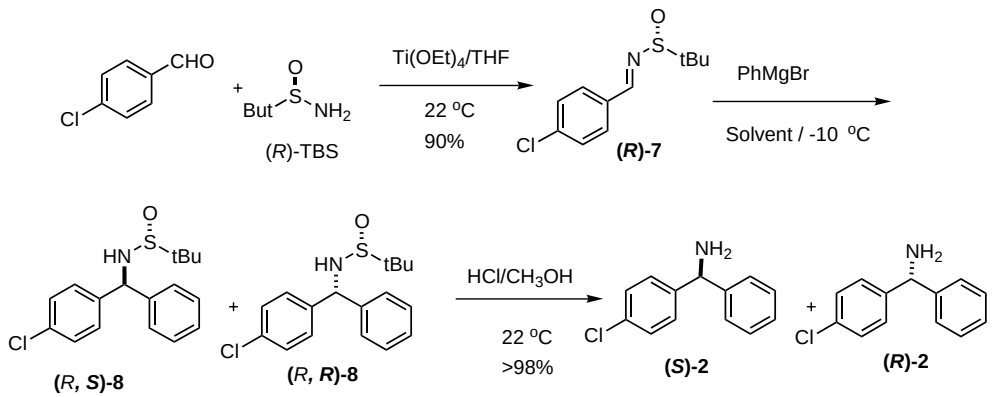


Scheme 3.

efficient chiral auxiliaries for the preparation of chiral non-racemic amines.[9] Condensation of (*R*)-*t*-butyl sulfinamide [(*R*)-TBS] with 4-chlorobenzaldehyde provides imine (*R*)-**7**. Initial efforts are focused on the effects of the solvent on the addition of phenyl magnesium bromide and the establishment of the absolute stereochemistry of the major isomer of **8** (Scheme 3).

As depicted in Table 1, reaction of PhMgBr with 4-chlorobenzaldehde in tetrahydrofuran, diethylether and toluene provided comparable diastereoselectivity at −10°C with complete conversion. After optimization of the temperature and solvents, it was found that with the addition of the PhMgBr to (*R*)-**7** at −20°C, followed by aging at 0°C in toluene, a 91:9 diastereoselectivity was observed. The major diastereomer could be crystallized from hexanes to provide diastereopure material in >65% yield. Single crystal X-ray analysis was performed to confirm that the absolute configuration at the newly formed stereocenter was (*S*) (Fig. 1). After establishment of the absolute stereochemistry of the diastereomeric mixture of sulfinamides [(*R*,*S*)-**8**:(*R*,*R*)-**8**=91:9], a mild hydrolysis condition was developed. Exposure of **8** to 2N HCl in MeOH provided a 91:9 ratio of corresponding amine **2** in 87% without any epimerization of the stereocenter (Table 1).[10]

At this point, the diastereoselective addition reaction with organometallic reagents was re-examined. Ellman and co-workers have reported that the minor diastereomer formed by the addition of the Grignard reagent was the major diastereomer formed in the reaction with the lithium reagent (albeit with low selectivity in this case).[10] Addition of phenyllithium to imine **7** and subsequent treatment with acidic methanol resulted in an 82% yield with a 38:62 ratio of (*S*)-**2**:(*R*)-**2**. It is important to note that the addition of Lewis acids can alter the diastereoselectivity of the organometallic addition. A variety of Lewis acids were screened in both the Grignard and lithium reactions. The reactions of phenyl Grignard with **7** in the presence of a Lewis acid showed decreased diastereoselectivity. On the other hand, an increased diastereoselectivity was observed when Lewis acids (such as $AlMe_3$, $BF_3{\cdot}OEt_3$ or $ZnCl_2$) were used in the additions of phenyllithium reactions (Table 2). In this study, it is clear that without any additives, the PhMgBr addition process to (*R*)-**7** was highly complementary to the trimethylaluminum- or $BF_3{\cdot}OEt_2$-mediated phenyllithium addition process.

As outlined in Scheme 4, condensation of (*R*)-TBS with benzaldehyde provided (*R*)-*N*-(benzylidine)-*t*-butylsulfinamide [(*R*)-**9**] in an 85% yield. Treatment of 4-chlorophenyl magnesium bromide with (*R*)-**9** in toluene at −20 to 0°C provided a 15:85 ratio of (*R*,*S*)-**8**:(*R*,*R*)-**8**;

Table 1. Effect of solvent on the diastereoselectivity of PhMgBr addition to (*R*)-**7** at −10°C

Entry	Solvent	% Conversion	Dr
1	Dichloromethane	76	90:10
2	Toluene	>95	86:14
3	THF	>95	82:18
4	Heptane	67	79:21
5	Diethyl ether	>95	89:11

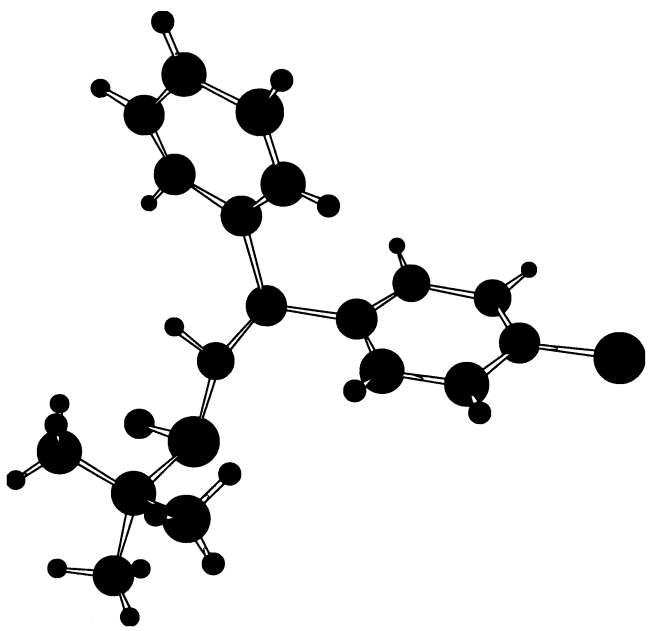
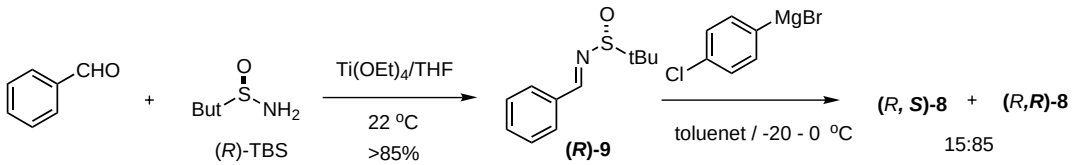


Fig. 1. X-Ray of (*R*,*S*)-sulfinamide-**8** (major diastereomer from PhMgBr addition process).

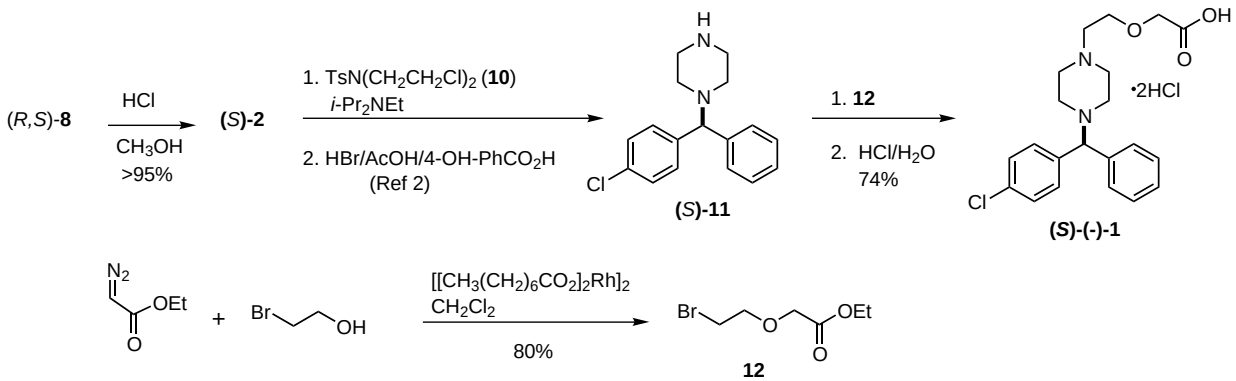
Table 2. Addition of organometallic reagents to *N*-sulfinylimine (*R*)-**7** in toluene

Lewis acid[b]	PhMgBr[a]		PhLi[a]	
	Er[c] (configuration)	Yield (%)	Er[c] (configuration)	Yield (%) (% conversion)
None	91:9 (*S*:*R*)	78	62:38 (*R*:S)	82 (95)
$AlMe_3$	81:19 (*S*:*R*)	75	93:7 (*R*:S)	80 (95)
$BF_3{\cdot}OEt_2$	72:28 (*S*:*R*)	78	89:11 (*R*:S)	88 (95)
$Cu(OTf)_2$	61:39 (*S*:*R*)	64	52:48 (*R*:S)	(90)
$ZnCl_2$	60:40 (*S*:*R*)	70	81:11 (*R*:S)	(10)
$Mg(OTf)_2$	61:39 (*S*:*R*)	72	51:49 (*S*:*R*)	(95)
$Ti(O\text{-}i\text{-}Pr)_4$	73:27 (*S*:*R*)	71	59:41 (*R*:*S*)	(95)

[a] Reactions with Grignard reagents were performed at −20 to 0°C, reactions with lithium reagents were performed at −78°C.
[b] One equivalent of Lewis acid was complexed with sulfinimine **7** for 30 min at 25°C and then the reaction was cooled to the appropriate temperature.
[c] Er of compound **2** was determined by Chiral pak AS 9:1 of hexane:IPA, rate 1 ml/min at 222 nm.



Scheme 4.



Scheme 5.

and following the hydrolysis of sulfinamide resulted in (*R*)-**2** in 70% ee. The major diastereomer obtained in this process is similar to the trimethylaluminum-mediated phenyllithium addition process to (*R*)-**7**, and is complementary to the PhMgBr addition to (*R*)-**7**.

After development of the preparation of either enantiomer of **2**, our attention was focused on the completion of the synthesis of (*S*)-cetirizine. (*S*)-(−)-cetirizine dihydrochloride was prepared as illustrated in Scheme 5. The diastereopure (*S*,*R*)-sulfinamide **8**, obtained from the direct PhMgBr addition to (*R*)-**7**, was then deprotected with HCl/MeOH to give (*S*)-**2** in an excellent yield. Amine **2** was then bis-alkylated with **10** and deprotected to provide piperidine (*S*)-**11** according to a known procedure.[2b] Upon treatment of ethyldiazoacetate in dichloromethane with a 0.1 mol% of rhodium octanoate in the presence of 2-bromoethanol, ester **12** was provided in an 80% yield.[11] Ester **12** was alkylated with **11** to furnish cetirizine ethyl ester. Acidic hydrolysis of ester provided (*S*)-(−)-cetirizine dihydrochloride in an excellent yield, confirming the previously proposed absolute configuration ($[\alpha]_D^{20}$ −0.68 (*c* 5, H_2O).[5]

In conclusion, we have demonstrated an inexpensive and practical asymmetric process for the preparation of (*S*)-citirizine·2HCl, utilizing Davis–Ellman-type sulfinamide chemistry. The scope and limitation of generating optically active diaryl amines for medicinally valuable targets, utilizing either enantiopure alkyl or aryl sulfinamides, are under evaluation.

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