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Chlorine, an atom economical auxiliary for asymmetric aldol reactions†

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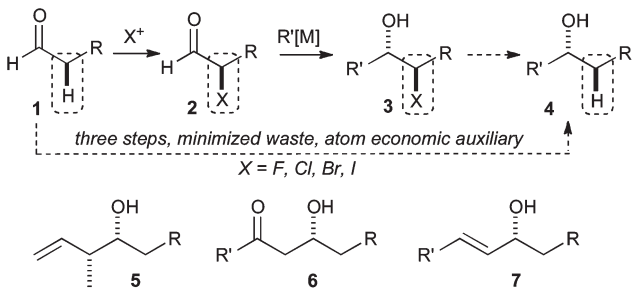
An auxiliary strategy has been developed for asymmetric reactions of aldehydes in which the auxiliary itself is not chiral, but a single chlorine atom introduced *via* organocatalytic α-chlorination. The stereodirecting influence of the chlorine atom is then exploited prior to its removal by radical reduction. This strategy is demonstrated in the synthesis of several aldols (92–99% ee) and the natural products (+)-dihydroyashabushiketol and (+)-solistatin.

Introduction

Chiral auxiliaries play an important role in organic synthesis by enabling many transformations to proceed with a predictable sense and level of enantioselectivity.[1] Perhaps most recognizable are the Evans auxiliaries[2] that are routinely exploited in polyketide synthesis, and variants of this classic reaction facilitate the enantioselective synthesis of most stereoisomeric aldols.[3] Despite the successes of these and other chiral auxiliaries, their use in asymmetric synthesis is often disfavoured due to costs associated with employing a stoichiometric amount of chiral reagent, and the inherently low overall atom economy[4] of these processes. Considering that the primary role of a chiral auxiliary is to impart diastereoselectivity to otherwise non-selective reactions,[1] we envisioned an alternative auxiliary approach to asymmetric synthesis in which the *auxiliary itself is not chiral, but a single atom introduced through a catalytic asymmetric reaction*. In this way, the use of stoichiometric amounts of expensive chiral pool materials would be avoided, and the overall mass balance of the asymmetric process improved. For example, temporary replacement of an α-hydrogen of an aldehyde with a halogen atom (*e.g.*, **1** → **2**, Scheme 1) *via* organocatalysis[5,6] could be coupled with a well-established diastereoselective reaction of the resulting α-haloaldehyde (*e.g.*, crotylation,[7] aldol reaction,[8] or 1,2-addition[9]). Subsequent removal of the halogen (*e.g.*, **3** → **4**) would then provide optically enriched secondary alcohols relevant to polyketide synthesis (*e.g.*, **5**–**7**). The development of this strategy and its demonstration in atom and step economical syntheses of the natural products (+)-dihydroyashabushiketol and (-+)-solistatin are described below.



Scheme 1 A single atom auxiliary for asymmetric synthesis.

Results and discussion

Considering the relative stability, stereodirecting ability,[9a,10] and ease of asymmetric synthesis of individual α-haloaldehydes,[5] we began these investigations with the preparation of several racemic α-chloroaldehydes using the procedure described by Jørgensen.[6b] Addition of lithium enolates[8g] or lithium derivatives of acetonitrile to these compounds provided the chlorohydrins **10**–**14** in good to excellent yield and diastereoselectivity. While reduction of the C–Cl bond in α-chlorocarbonyl compounds with Zn/HOAc is well known,[11] and the C–Cl bond in a number of chlorohydrin-containing carbohydrates has been reduced,[12] only one report documents the reduction of a racemic β-ketochlorohydrin using Bu_3SnH/AIBN, in which no yields were provided.[8b] This latter reaction is likely complicated by competing furan formation at elevated temperatures[8b,8i] and, unfortunately, radical reduction of **10** using a combination of AIBN and Bu_3SnH resulted largely in decomposition. Based on the improved halogen-abstracting ability of the radical generated from tris(trimethylsilyl)silane

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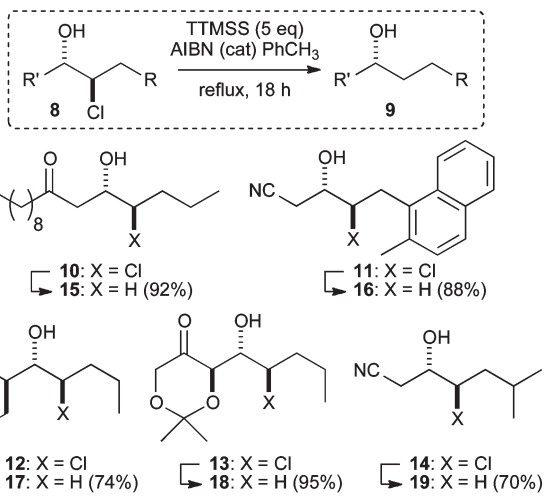
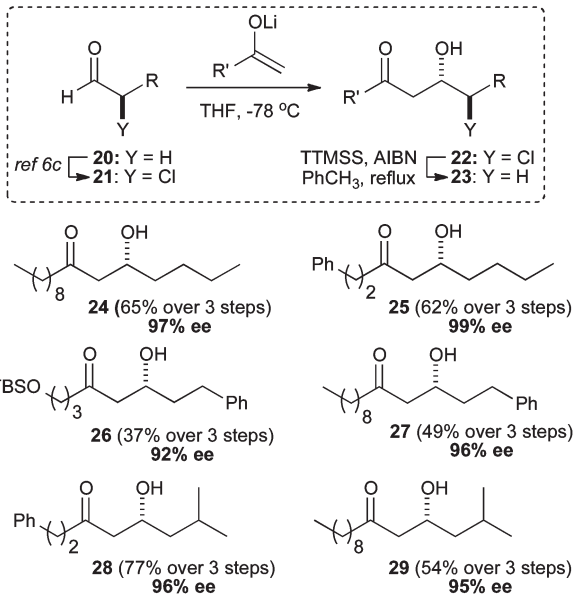
(TTMSS),[13] the reduction of β-keto- and β-nitrilechlorohydrins **10–14** were also examined using TTMSS and, after some optimization, we were delighted to find that the chloromethine function in each of these compounds could be reduced without competing formation of furans or side reactions involving other functional groups in the molecules (*e.g.*, ketone, nitrile, acetonide). In this way, the β-hydroxyketones **15–19** were produced in good to excellent yield.

The results summarized in Scheme 2 inspired us to apply this chlorine-auxiliary approach to asymmetric methyl ketone aldol reactions, which are among the more challenging asymmetric aldol reactions.[14] As depicted in Scheme 3, chlorination of pentanal, hydrocinnamaldehyde, and isovaleraldehyde using MacMillan's asymmetric SOMO α-chlorination procedure[6c] afforded the corresponding α-chloroaldehydes, which subsequently engaged in high yielding aldol reactions with lithium enolates[8g] derived from 2-undecanone, 4-phenyl-2-butanone, and 5-(*t*-butyldimethylsilyloxy)-2-pentanone to afford a small collection of optically enriched β-ketochlorohydrins. Radical reduction of the chloromethine function in each of these latter compounds proceeded smoothly using the optimized reaction conditions to provide the β-hydroxyketones **24–29** in good to excellent overall yield and enantiomeric excess, as determined by chiral GC or HPLC analysis. Based on the relative ease with which this process is executed, its functional group tolerability, and the high level of optical purity of the resulting β-hydroxyketones, this approach represents a viable alternative to existing chiral auxiliary-based strategies for asymmetric aldol synthesis.

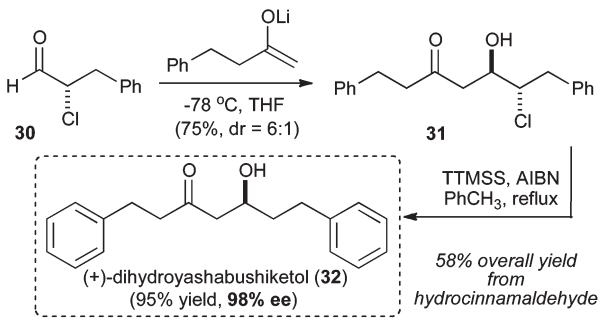
As depicted in Scheme 4, the chlorine-auxiliary strategy was applied to a short asymmetric synthesis of (+)-dihydroyashabushiketol (**32**), a diarylheptanoid that was originally isolated[15] from the deciduous plant *Alnus firma* and has demonstrated a variety of potentially useful biological activities.[16] In 2011, the first asymmetric synthesis of (+)-**32** was reported that involved a six-step sequence of reactions including the use of Oppolzer's sultam auxiliary to control the absolute stereochemistry



Scheme 2 TTMSS reduction of β-keto- and β-nitrilechlorohydrins.



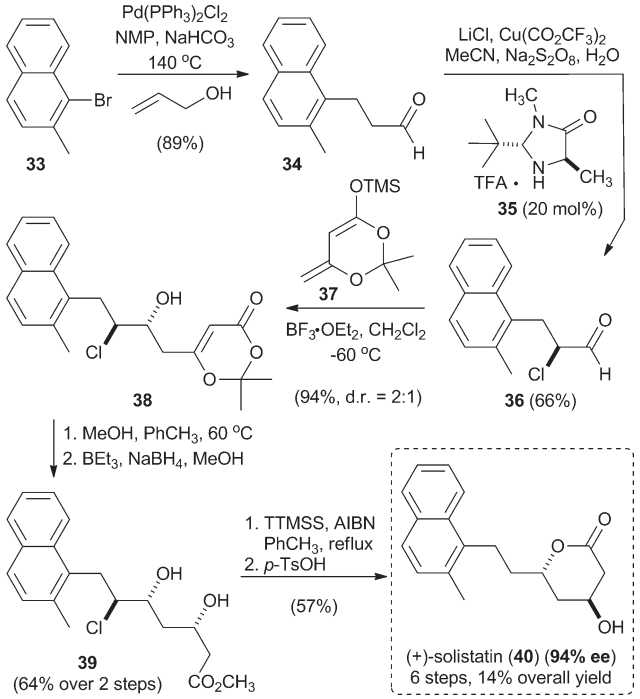
Scheme 3 Chlorine auxiliary approach to asymmetric aldol reactions.



Scheme 4 A short synthesis of (+)-dihydroyashabushiketol (**32**).

of a 1,3-dipolar cycloaddition.[16a] Notably, the chiral auxiliary represented 49% of the molecular weight of the cycloaddition product. As depicted in Scheme 4, treatment of (*S*)-2-chlorohydrocinnamaldehyde (**30**)[6c] with the lithium enolate derived from 4-phenyl-2-butanone, afforded the ketochlorohydrin **31** in good yield. Reduction of the chloromethine function in **31** proceeded smoothly to provide (+)-dihydroyashabushiketol (**32**) in excellent yield and optical purity (98% ee). It is worth highlighting that this three-step synthesis (from hydrocinnamaldehyde) also proceeds in excellent overall yield (58%), and that the auxiliary (Cl) represents only 11% of the molecular weight of the aldol adduct **31**.

The chlorine-auxiliary approach was further demonstrated in a short total synthesis of (+)-solistatin (**40**). Isolated from the cheese-associated fungus *Penicillium solitum*,[17] solistatin is an inhibitor of cholesterol biosynthesis and structurally similar to other HMG CoA reductase inhibitors (*e.g.*, simvastatin and lovastatin).[18] In 2007 a 17-step synthesis of solistatin was reported that exploited sequential catalytic asymmetric Overman esterification reactions.[19] As outlined in Scheme 5, chlorination of **34** using MacMillan's SOMO α-chlorination



Scheme 5 Total synthesis of (+)-solistatin (**40**).

procedure[6c] afforded the chloroaldehyde **36**. Reaction of **36** with the dianion derived from methyl acetoacetate gave the corresponding β-ketochlorohydrin (not shown) in modest yield (40%) and diastereoselectivity (dr = 3 : 1). While use of the enol silyl ether **37**[20] failed to improve the diastereoselectivity of this reaction, the Mukaiyama aldol[8d] reaction depicted in Scheme 5 provided the desired chlorohydrin **38** in good isolated yield (63%). Methanolysis, followed by 1,3-*syn*-selective reduction[21] of the resulting β-hydroxyketone gave the chlorodiol **39**. Radical reduction of the chloromethine function in **39** proceeded smoothly to provide a mixture of (+)-solistatin (**40**) and the corresponding methylester (not shown). Brief treatment of this mixture with *p*-TsOH afforded (+)-solistatin (**40**) in good yield and enantiomeric excess (94% ee).

Conclusion

We have demonstrated that the asymmetric chlorination of aldehydes can be partnered sequentially with diastereoselective aldol reactions and chloromethine reduction to afford β-hydroxyketones in excellent overall yield and enantioselectivity. This process should serve as an alternative to chiral auxiliary-based aldehyde coupling reactions. Specifically, in contrast to traditional chiral auxiliary approaches, stoichiometric amounts of chiral pool materials are not required, and the overall mass balance of the asymmetric process is significantly improved. The efficiency of the chlorine-auxiliary approach has been demonstrated in short total syntheses of both (+)-dihydroyashabushiketol (**32**) (3 steps) and (+)-solistatin (**40**) (6 steps). The extension of this work to include other asymmetric transformations of aldehydes is currently underway in our laboratory, and the results of these efforts will be reported in due course.

Acknowledgements

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