ORGANIC LETTERS

2009
Vol. 11, No. 15
3254−3257

The Chiral Auxiliary *N*-1-(1′-Naphthyl)ethyl-*O*-*tert*-butylhydroxylamine: A Chiral Weinreb Amide Equivalent

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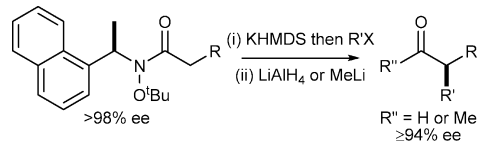
Received May 26, 2009

ABSTRACT



The chiral auxiliary *N*-1-(1′-naphthyl)ethyl-*O*-*tert*-butylhydroxylamine is readily prepared from *N*-hydroxyphthalimide in four steps, with resolution giving access to both enantiomers in >98% ee, on a multigram (>25 g) scale. Conversion to a range of *N*-acyl derivatives, followed by highly diastereoselective alkylation (≥94% de) gives the corresponding chiral, 2-substituted derivatives as single diastereoisomers (>98% de) after chromatography. Reductive cleavage with $LiAlH_4$ allows direct access to chiral aldehydes, and treatment with MeLi gives chiral methyl ketones in excellent enantiopurity (≥94% ee). The auxiliary can be recovered in >98% ee and recycled.

The use of stoichiometric chiral auxiliaries remains a highly important method of asymmetric synthesis. Among the most generally applicable and commonly used auxiliaries for enolate reactions are Oppolzer's camphor-derived sultam **1**[1] and Evans's 4-substituted-oxazolidin-2-ones **2a**.[2] Whereas these auxiliaries can be cleaved to yield carboxylic acids, esters, and alcohols in a single chemical transformation,[1,2] access to aldehydes and ketones generally requires at least two steps.[3] In order to address this limitation, we have demonstrated that incorporation of a 4-alkyl-5,5-dimethyl functionality within the basic oxazolidin-2-one framework

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10.1021/ol901174t CCC: $40.75
Published on Web 07/16/2009

confers several beneficial properties upon the resultant SuperQuat family of chiral auxiliaries **2b**[4,5] (e.g., increased levels of stereoinduction[6] and resistance to endocyclic ring cleavage)[7] and enables an *N*-acyl SuperQuat to function as a masked aldehyde equivalent upon treatment with DIBAL-H.[8] Perhaps the most widely utilized chiral auxiliary based procedure for the direct synthesis of enantiopure aldehydes and ketones is Enders's *S*AMP and *R*AMP hydrazone method.[9] Other contributions to this area were made by Larcheveque and Meyers, who demonstrated that ephedrine[10] and pseudoephedrine,[11] respectively, act as useful chiral auxiliaries, and Masamune, who developed the chiral benzopyranoisoxazolidine auxiliary **4** to facilitate the direct preparation of aldehydes and ketones from the corresponding *N*-acyl derivatives in a single cleavage step[12] (Figure 1). We

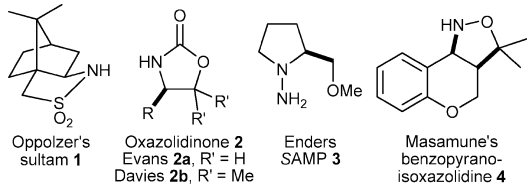
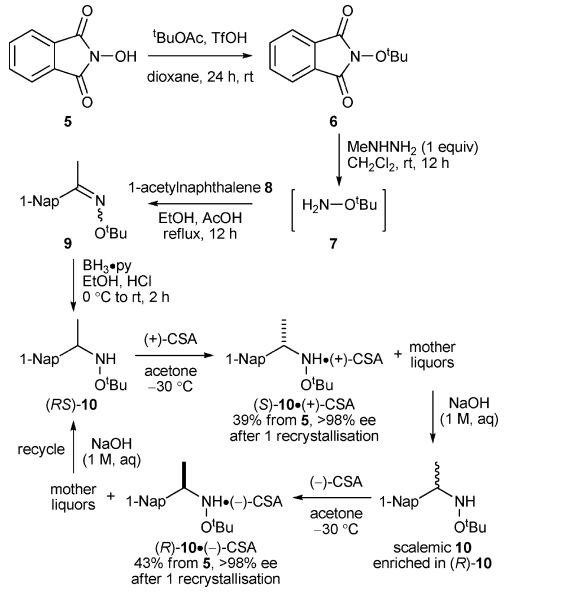


Figure 1. Chiral auxiliaries **1**−**4**.

became interested in the development of a novel auxiliary capable of functioning as a chiral Weinreb amide equivalent and report herein *N*-1-(1′-naphthyl)ethyl-*O*-*tert*-butylhydroxylamine, which fulfils this criterion.

The antipodes of *N*-1-(1′-naphthyl)ethyl-*O*-*tert*-butylhydroxylamine **10** were prepared in four steps from inexpensive, commercially available starting materials, followed by resolution. *N*-Hydroxyphthalimide **5** was *O*-alkylated by treatment with excess *tert*-butyl acetate in dioxane and trifluoromethansulfonic acid[13] to give **6** in quantitative yield. Release of *O*-*tert*-butylhydroxylamine **7** was achieved using a stoichiometric amount of methylhydrazine. Subsequent addition of ketone **8** to the reaction flask, followed by AcOH and heating at reflux, gave oxime ether **9** as a 5:1 mixture of geometric isomers. Reduction of the crude reaction mixture with borane−pyridine complex and ethanolic HCl[14] gave (*RS*)-**10**. Resolution was achieved by cooling a solution of (*RS*)-**10** and (+)-camphorsulfonic acid [(+)-CSA] in acetone to −30 °C,[15] to afford the single diastereoisomeric salt (*S*)-**10**•(+)-CSA as crystals. After basification and re-extraction of the mother liquors, treatment of the residue with (−)-CSA under identical conditions afforded the antipode (*R*)-**10**•(−)-CSA as a single diastereoisomer. A second crop of (*S*)-**10**•(+)-CSA and (*R*)-**10**•(−)-CSA was obtained, and after a subsequent recrystallization from acetone, both enantiomers of **10** were isolated as their pure CSA salts in very high yield from **5** [39% (out of a maximum of 50%) for (*S*)-**10**•(+)-CSA and 43% (out of a maximum of 50%) for (*R*)-**10**•(+)-CSA] and in >98% ee[16] {for (*S*)-**10**•(+)-CSA, $[\alpha]_D^{23}$ +63.2 (*c* 1.1 in $CHCl_3$); for (*R*)-**10**•(−)-CSA, $[\alpha]_D^{24}$ −63.0 (*c* 1.1 in $CHCl_3$)}. In addition to being a highly efficient and operationally simple resolution procedure, crystallization of the CSA salts of the antipodes of **10** provided an excellent purification procedure and allowed the complete synthetic sequence to be performed without the need for chromatography (Scheme 1). The relative configuration within (*R*)-**10**•(−)-CSA was determined unambiguously by single crystal X-ray analysis, with the absolute (*R*)-configuration of the auxiliary assigned from the known absolute configuration of the (−)-CSA (Figure 2).

Scheme 1. Preparation of Hydroxylamine Auxiliary (*RS*)-**10** and Resolution via the Diastereoisomeric CSA Salts[a]



[a] 1-Nap = 1-naphthyl.

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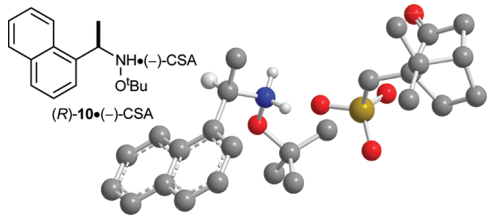
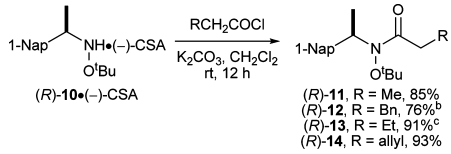


Figure 2. Chem3D representation of the single crystal X-ray structure of (*R*)-**10**•(−)-CSA (some H atoms omitted for clarity).

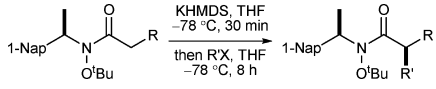
Acylation of **10** with a range of acid chlorides was readily achieved directly from the CSA salt using K_2CO_3 in CH_2Cl_2 (Scheme 2). The acyl derivatives **11**−**14** were deprotonated with KHMDS in THF at −78 °C to afford pale yellow enolate solutions. Enolates of **11**−**14** proved to be highly reactive, undergoing rapid nucleophilic substitution with a range of alkyl halides at −78 °C. Benzylation of the *N*-propanoyl derivative (*R*)-**11** gave (2*S*,1′*R*)-**15** in 96% de, whereas methylation of the *N*-hydrocinnamoyl derivative (*R*)-**12** gave the diastereoisomer (2*R*,1′*R*)-**18** in 94% de.[17] Chromatographic purification of the crude reaction mixtures gave **15** and **18** as single diastereoisomers (>98% de) in each case (Table 1). In the racemic series, the relative (2*RS*,1′*RS*)-configuration within **18** was unambiguously proven by single crystal X-ray analysis (Figure 3), which therefore also allowed

Scheme 2. Acylation of (*R*)-**10**•(−)-CSA[a]



[a] 1-Nap = 1-naphthyl. [b] Reaction performed in both enantiomeric series. [c] Reaction performed in the opposite enantiomeric series.

Table 1. Diastereoselective Alkylation Reactions Employing Chiral Auxiliary (*R*)-**10**[d]



	R	R′X	product	de %[b]	yield (de) %[c]
(*R*)-**11**	Me	BnBr	(2*S*,1′*R*)-**15**	96	95 (>98)
(*R*)-**11**	Me	ArCH$_2$Br	(2*S*,1′*R*)-**16**	95	71 (>98)
(*R*)-**11**	Me	allylBr	(2*S*,1′*R*)-**17**	96	94 (>98)
(*R*)-**12**	Bn	MeI	(2*R*,1′*R*)-**18**	94	85 (>98)
(*R*)-**12**[d]	Bn	EtI	(2*R*,1′*R*)-**19**[d]	96	89 (>98)
(*R*)-**13**[d]	Et	BnBr	(2*S*,1′*R*)-**20**[d]	96	86 (>98)
(*R*)-**14**	allyl	MeI	(2*R*,1′*R*)-**21**	95	72 (>98)
(*R*)-**14**	allyl	BnBr	(2*S*,1′*R*)-**22**	95	91 (>98)

[a] 1-Nap = 1-naphthyl; Ar = *o*-BrC$_6$H$_4$. [b] Crude. [c] Purified. [d] Reaction performed in the opposite enantiomeric series.

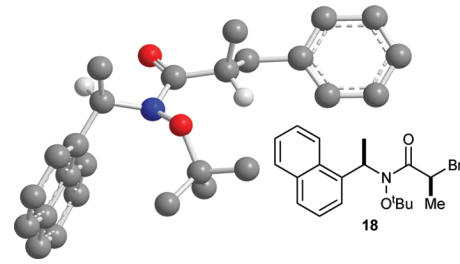
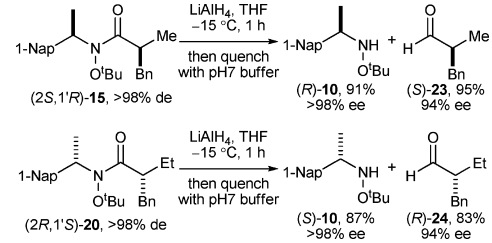


Figure 3. Chem3D representation of the single crystal X-ray structure of (2*RS*,1′*RS*)-**18** (some H atoms omitted for clarity).

unambiguous assignment of the relative configuration within the diastereoisomer **15**. The absolute (2*R*,1′*R*)- and (2*S*,1′*R*)-configurations within homochiral **18** and **15** were thus assigned from the known (*R*)-configuration of the chiral auxiliary. Further alkylation reactions gave the 2-substituted derivatives **16**, **17**, and **19**−**22** with uniformly high diastereoselectivities, with chromatographic purification giving single diastereoisomers in each case (Table 1). The absolute configurations within **16**, **17**, and **19**−**22** were assigned by analogy to those unambiguously established for **15** and **18**.

Treatment of the 2-substituted products (2*S*,1′*R*)-**15** and (2*R*,1′*S*)-**20** with excess $LiAlH_4$ in THF at −78 °C for 1 h followed by quenching with a pH 7 phosphate buffer solution allowed clean production of the known chiral aldehydes (*S*)-**23** and (*R*)-**24**: very little (<5%) or none of the over-reduced alcohol products were observed in the ^{1}H NMR spectra of the crude reaction mixtures. The auxiliary **10** was recovered in high yield and enantiopurity (>98% ee)[16] by precipitation of the CSA salt from pentane,[18] leaving the aldehyde in solution, giving (*S*)-**23**[5b,19] and (*R*)-**24**[5b] in 94% ee[20] in both cases (Scheme 3).

Scheme 3. Cleavage of **15** and **20** to give Homochiral Aldehydes **23** and **24**[a]

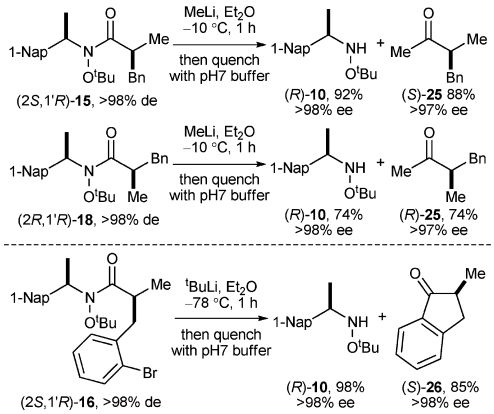


[a] 1-Nap = 1-naphthyl.

Treatment of (2*S*,1′*R*)-**15** and (2*R*,1′*R*)-**18** with MeLi (3 equiv) in Et_2O at −10 °C allowed cleavage to afford the corresponding enantiomeric ketones (*S*)-**25**[21] and (*R*)-**25**[21] in high yield and excellent enantiomeric purity (>97% ee)[22]

after chromatographic separation from the auxiliary. Addition of ^{t}BuLi to *o*-bromobenzyl derivative (2*S*,1′*R*)-**16** promoted halogen−lithium exchange and cyclization, giving 2-methylindanone (*S*)-**26**[23] in 85% yield and >98% ee[22] after distillation (Scheme 4).

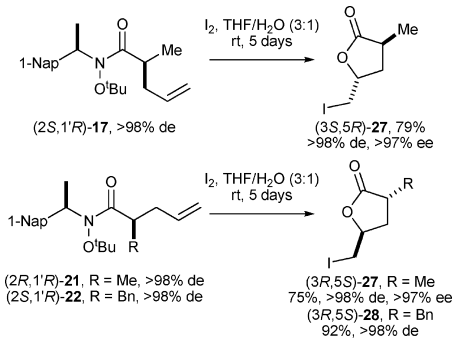
Scheme 4. Cleavage of **15**, **16**, and **18** to give Homchiral Ketones **25** and **26**[a]



[a] 1-Nap = 1-naphthyl.

Treatment of (2*S*,1′*R*)-**17** and (2*R*,1′*R*)-**21** with iodine gave the enantiomeric iodomethyl lactones (3*S*,5*R*)-**27**[24] and (3*R*,5*S*)-**27**[24] in 82% de in each case, and in excellent yield and diastereo- and enantiopurity (≥75%, >98% de, >97% ee)[22] after chromatographic purification.[25] Similar treatment of (2*S*,1′*R*)-**22** with iodine gave a single diastereoisomeric lactone (3*R*,5*S*)-**28**,[24a,26] which was isolated in 92% yield.[25] The selectivity upon formation of the C(5)-stereogenic center within lactones **27** and **28** appears to be controlled only by the steric bulk of the alkyl group at C(3), which is in accordance with the observations of Yoshida[24a] and in our system is independent of the configuration within the chiral auxiliary (Scheme 5).

Scheme 5. Cleavage of **17**, **21**, and **22** to give Iodolactones[a]



[a] 1-Nap = 1-naphthyl.

In conclusion, *N*-acyl derivatives of the chiral auxiliary *N*-1-(1′-naphthyl)ethyl-*O*-*tert*-butylhydroxylamine undergo highly diastereoselective enolate alkylations and behave as chiral Weinreb amide equivalents in subsequent cleavage reactions upon reduction or treatment with an organometallic reagent. The auxiliary is readily prepared on a multigram (>25 g) scale in either enantiomeric form, in four steps that require no chromatographic purification. *N*-Acylation of the auxiliary and alkylation of the enolates of the resultant derivatives proceeds with excellent levels of diastereoselectivity. The alkylation products may be transformed directly into chiral aldehydes, ketones, and iodolactones of high enantiomeric purity. The auxiliary is recovered from these cleavage reactions in >98% ee and may be recycled. *N*-1-(1′-Naphthyl)ethyl-*O*-*tert*-butylhydroxylamine should prove to be a valuable addition to the field of asymmetric synthesis. Investigations to establish the origins of the high levels of diastereoselectivity observed in these enolate alkylation reactions and further synthetic applications of this auxiliary in asymmetric synthesis are currently in progress within our laboratory.

Acknowledgment. The authors would like to thank AstraZeneca for a CASE studentship (D.H.), Ajinomoto Co., Inc. for funding (W.K.), and the Oxford Chemical Crystallography Service for the use of their X-ray diffractometers.

Supporting Information Available: Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Control of the temperature is critical to the success of this resolution procedure, as an alternative polymorph of the salt, leading to racemic **10**, is produced at higher temperatures.

(16) The enantiomeric excess of **10** was determined by ^{1}H NMR spectroscopic analysis in the presence of (*S*)-*O*-acetylmandelic acid as a chiral shift reagent and comparison with an authentic racemic sample.

(17) Alkylation diastereoselectivities were readily determined from peak integration of the ^{1}H NMR spectrum of the crude reaction mixtures (and the pure products); relatively large chemical shift differences between the *tert*-butyl singlets of the diastereoisomeric products facilitated this analysis.

(18) Alternatively, the aldehyde and **10** are separable by distillation.

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(20) The enantiomeric excesses of (*S*)-**23** and (*R*)-**24** were determined by reduction and conversion of the resultant alcohol to the corresponding Mosher's ester; see: Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543. Full details are contained within Supporting Information.

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(22) The enantiomeric excesses of (*S*)-**25**, (*R*)-**25**, (*S*)-**26**, (3*S*,5*R*)-**27**, and (3*R*,5*S*)-**27** were determined by chiral GC analysis.

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(25) In these cases, partial oxidation of the auxiliary **10** to the oxime **9** occurred under the reaction conditions. A mixture of **9** and **10** was thus isolated after chromatography, in addition to the desired iodolactones **27** and **28**.

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