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Tetrahedron: *Asymmetry* 15 (2004) 3823–3825

Indium-mediated diastereoselective addition of allyl bromides to enantiomerically pure *N-tert*-butylsulfinyl aldimines

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Received 27 September 2004; accepted 27 October 2004
Available online 24 November 2004

Abstract—The reaction of different *N-tert*-butylsulfinyl aldimines **1** with allyl bromides **2** and indium powder in THF at 60 °C affords, after hydrolysis with water, the corresponding *N-tert*-butylsulfinylamines **3** with high chemical yields and diastereoselectivities.

1. Introduction

The addition of allyl metal derivatives to imines[1] is an effective method for the synthesis of homoallylic amines, which are compounds of interest themselves because they can be intermediates in the synthesis of other nitrogenated materials.[2] The asymmetric version of these processes can be achieved by using chiral auxiliaries or under asymmetric catalysis, with either chiral amines or amine derivatives (amino alcohols, amino esters, amino sugars, hydrazines and oximes) being the chiral auxiliaries of choice. Imines are less electrophilic than carbonyls meaning that they are less reactive towards nucleophiles. However this can be overcome by either using electrophilic imines or by modulating the strength of the nucleophile by choosing the appropriate metal bonded to the organic fragment.[3] For instance, in the case of *N*-sulfonyl aldimines the nucleophilic additions take place smoothly.[4] More recently, *N-tert*-butylsulfinyl aldimines have found high applicability in synthesis[5] as electrophiles because of the possibility of preparing both enantiomers in large scale processes following the methodology developed by Ellman and co-workers[6] and also because the chiral auxiliary can be easily removed under acidic conditions. In this context, Li and Batey reported the highly diastereoselective allylation of *N-tert*-butylsulfinyl aldimines with potassium allyltrifluoroborate in the presence of boron trifluoride etherate.[7] On the other hand, indium metal has attracted considerable attention since 1988 when it was used for the first time as a mediating reagent in the addition of allyl bromides to carbonyl compounds under Barbier-type reaction conditions.[8] Since then, it has been used also for promoting the addition of other allylic systems to different electrophilic functional groups and as a reducing reagent.[9] Other important advantages of indium over other metals are that it tolerates aqueous solvents and air exposure without oxidising, meaning there is no need for specific activation, and that it shows low toxicity. Recently, Cook et al. have reported the indium-mediated diastereoselective allylation of hydrazones, using oxazolidinones derived from aminoalcohols as chiral auxiliaries with excellent diastereoselectivities.[10] Taking into account these antecedents we considered it of interest to study the indium-mediated addition of allyl bromides to simple enantiopure *N-tert*-butylsulfinyl aldimines. To the best of our knowledge, the only examples of allylindium intermediates addition to *N-tert*-butylsulfinyl aldimines have been provided by Grigg and co-workers in their study of three-component palladium–indium-mediated diastereoselective cascade allylation of imines with allenes and aryl iodides.[11] They found excellent diastereoselectivities in these processes, especially those which occurred intramolecularly, with chiral highly substituted pyrrolidines and piperidines being synthesised in this way.

2. Results and discussion

Starting materials (*R*)-*N-tert*-butylsulfinyl aldimines **1** were prepared in high yields from readily available (*R*)-1,1-dimethylethanesulfinamide[12] and the

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doi:10.1016/j.tetasy.2004.10.031

corresponding aldehyde in dichloromethane at room temperature, in the presence of excess anhydrous magnesium sulfate (5 equiv) and a catalytic amount of PPTS (0.05 equiv). During the condensation no racemisation was observed the aldimines isolated exclusively as the (*E*)-imine isomers.[6c,13]

We first investigated the reaction conditions for the allylation of the benzaldehyde derivative **1d** by treatment with allyl bromide **2a** in the presence of indium metal. Based on our previous experience with indium-mediated allylation of aldimines,[14] we used 1.3 equiv of indium metal and 1.3 equiv of allyl bromide, THF being the solvent of choice. It was supposed that in these processes the formation of an allylindium intermediate[15] was facilitated in aqueous media, although in the cases of using water or a water/THF mixture, hydrolysis of the starting (*R*)-*N*-*tert*-butylsulfinyl aldimine **1d** occurred, yielding benzaldehyde and other reaction products derived from it. In contrast, the allylation of *N*-sulfonyl imines performed in aqueous media[16] has already been reported. Regarding the temperature, although the reaction does not progress significantly at room temperature while at 40 °C it takes 12 h to drive it to completion, complete conversion was achieved at 60 °C after 4 h without loss of stereoselectivity. The diastereomeric ratio of the reaction product **3g** was found to be 94:6 (Scheme 1, Table 1, entry 7), determined both by 300 MHz ^{1}H NMR spectroscopy and GLC with a chiral capillary column from the crude reaction mixture,[17] both results being coincident. Similar yields and diastereomeric ratios were found for a variety of aldimines **1a–c** using both allyl and methallyl bromides **2a** and **2b**, respectively (Scheme 1 and Table 1). It is noteworthy that enantiopure *N*-*tert*-butylsulfinyl amines **3** can be separated from the diastereomeric reaction mixture by using conventional silica gel column chromatography.

A six-membered ring chelation control model (Fig. 1) is consistent with a high level of stereocontrol as well as with the configuration of the newly created stereogenic centre. Coordination of indium to nitrogen increases the reactivity of the electrophilic centre of the imine, while the coordination of the metal to the oxygen of the sulfinyl group is responsible for the face selectivity. We assume that the nucleophilic attack takes place in all cases to the *Si* face of the imino group. Similar transition states have been proposed by others in the case of nucleophilic allylation to aldimines.[18]

In order to determine the configuration of the newly created stereogenic centre, the removal of the chiral auxiliary from sulfinamide **3g** under acidic conditions yielded the homoallylic amine **4g** in almost quantitative yield (Scheme 2) its specific rotation $\{[\alpha]_D^{22} = -37$ (*c* 0.74, $CH_2Cl_2)\}$ was consistent with that provided in the literature for (*S*)-1-phenylbut-3-en-1-amine $\{[\alpha]_D^{22} = -42$ (*c* 0.5, $CH_2Cl_2)\}$.[19]

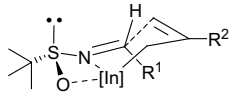
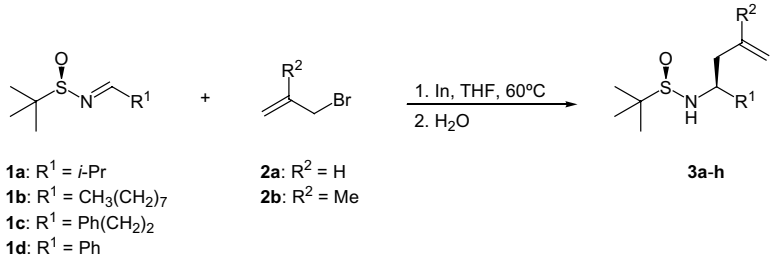


Figure 1.

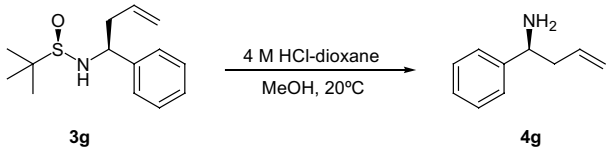


Scheme 1.

Table 1. Preparation of sulfinamides **3**

Entry	Starting aldimine	Allylic bromide	Product[a]						
			No	R^1	R^2	dr[b]	R_f[c]	$[\alpha]_D^{20}$ (*c*)[d]	Yield (%)[e]
1	**1a**	**2a**	**3a**	*i*-Pr	H	92:8	0.31	−65 (0.59)	84
2	**1a**	**2b**	**3b**	*i*-Pr	Me	88:12	0.36	−89 (1.10)	82
3	**1b**	**2a**	**3c**	$CH_3(CH_2)_7$	H	96:4	0.32	−50 (0.42)	91
4	**1b**	**2b**	**3d**	$CH_3(CH_2)_7$	Me	95:5	0.39	−59 (1.82)	86
5	**1c**	**2a**	**3e**	$Ph(CH_2)_2$	H	91:9	0.25	−44 (0.68)	79
6	**1c**	**2b**	**3f**	$Ph(CH_2)_2$	Me	90:10	0.26	−69 (0.62)	83
7	**1d**	**2a**	**3g**	Ph	H	94:6[f]	0.28	−148 (0.85)	94
8	**1d**	**2b**	**3h**	Ph	Me	93:7	0.29	−147 (0.55)	91

[a] All products were >95% pure (GLC and 300 MHz ^{1}H NMR).
[b] Diastereomeric ratio was determined by ^{1}H NMR spectroscopy.
[c] Silica gel, hexane/ethyl acetate: 2/1.
[d] In CH_2Cl_2; in parenthesis concentration given in g/100 mL.
[e] Isolated yield after column chromatography (silica gel, hexane/ethyl acetate) based on the starting material **1**.
[f] Diastereomeric ratio was also determined by GLC with a chiral capillary column, see text above and Ref. 17.



3g 4g

Scheme 2.

3. Conclusion

In conclusion, we have reported herein that the indium-mediated allylation of different (*R*)-*N*-*tert*-butylsulfinyl aldimines takes place under mild reaction conditions with high diastereoselectivity to yield homoallylic sulfinamides **3** while the sulfinyl group can be removed easily under acidic conditions to give primary homoallylic amines. Studies are currently in progress trying to extend this methodology to the synthesis of different nitrogenated compounds by using other allylic, benzylic and propargylic bromides.

Acknowledgements

This work was generously supported by the Generalitat Valenciana (project no GV01-443).

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