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Tetrahedron Letters 46 (2005) 7849–7852
Tetrahedron Letters

# Auxiliary strategies for the preparation of β-amino alcohols with reductive cross-coupling and a synthesis of (−)-cytoxazone

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Received 16 August 2005; revised 1 September 2005; accepted 1 September 2005

**Abstract**—Imine auxiliaries including chiral *N-tert*-butanesulfinyl imines have been successfully utilized to provide stereochemical control to the reductive cross-coupling of imines with aldehydes or ketones. This methodology has been applied to the synthesis of (−)-cytoxazone.

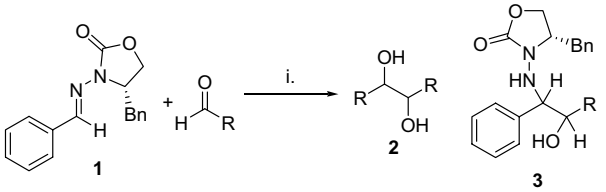

The application of auxiliaries has successfully controlled the stereochemical outcomes in a range of radical reactions.[1] We considered this to be a potential approach towards the preparation of β-amino alcohols from the reductive coupling of imines and carbonyls.[2] β-Amino alcohols are a frequent functional motif in natural products and drugs of significant biological activity[3–5] and have thus merited much synthetic attention.[6–9] However, few approaches offered potential access to β-amino alcohols with high stereoselectivity for either diastereoisomer as secondary or tertiary alcohols and incorporating a carbon–carbon bond forming event. This potential is present in the 'Pinacol-type' cross-coupling discussed in this paper.

This ideal picture has been fraught with difficulties of chemo- and diastereo- control.[2] There are a very limited number of examples encompassing enantio-control. Uemura et al. have utilized enantiopure ferrocenyl[10,11] and $Cr(CO)_3$ aromatic aldehydes,[12] thus prohibiting a wider range of aldehydes for coupling such as aliphatic aldehydes. We viewed the introduction of the chiral auxiliary on the imine nitrogen as offering a more flexible strategy and there existed numerous enantiopure amine precursors. During preparation of this manuscript a similar plan was achieved by Xu and Lin et al.[13]

Identification of an enantiopure auxiliary that would provide high stereocontrol for the cross-coupling reaction was crucial. Initially oxazolidinones (Scheme 1) (e.g., **1**) were focused upon in light of the success that Friestad et al. have found in radical alkylations.[14]

Aromatic aldehydes (e.g., benzaldehyde) were found to be too reactive and only gave a homocoupled product (Table 1; entry 1). However aliphatic aldehydes (Scheme 1) provided more promise and gave moderate to excellent diastereoselectivity, but problematically in poor yield (Table 1; entries 2 and 3).

Amongst other auxiliaries studied were chiral *N-tert*-butanesulfinyl imines (**4**) first used by Ellman et al. with great effect in alkylation.[15] Recently, Xu et al. have, utilized this as an auxiliary with high stereocontrol in homocoupling[16] and cross-coupling with nitrones.[17] Thus this auxiliary was selected for cross-coupling initially with aldehydes (Scheme 2).




**Scheme 1.** The synthesis of a β-amino alcohol by the cross-coupling of aldehydes with an imine oxazolidinone auxiliary. Reagents and conditions: i. $SmI_2$, $^tBuOH$, THF, $ZnX_2$ (see Table 1), 25 °C.

*Keywords*: Reductive cross-coupling; *N-tert*-Butanesulfinyl imine; Chiral auxiliary; Cytoxazone; Pinacol.
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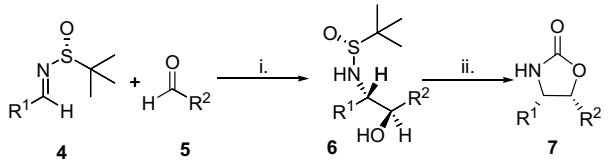
0040-4039/$ - see front matter © 2005 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2005.09.002

**Table 1.** Cross-coupling of aldehydes with an imine oxazolidinone auxiliary shown in Scheme 1

| Entry | Reagent/product | Diastereomeric ratio (dr)[a] | Yield (%) |
|---|---|---|---|
| 1 | X = Br, **2** R = Ph | — | 90 |
| 2 | X = Br, **3** R = $^{n}$Bu | 20:1 | 30 |
| 3 | X = Cl, **3** R = $^{i}$Pr | 5:1 | 46 |

[a] Diastereomeric ratio determined by $^{1}$H NMR.




**Scheme 2.** The synthesis of a β-amino alcohol by the cross-coupling of aldehydes with an imine (*R*)-*N*-*tert*-butanesulfinyl auxiliary. Reagents and conditions: i. $SmI_2$, $^{t}$BuOH, THF, −78 °C; ii. (a) HCl, MeOH, 25 °C (b) triphosgene, $Et_3N$, DCM, 25 °C.

Given the experiences with the oxazolidinone auxiliary (**1**) aromatic aldehydes were avoided. The cross-coupling in Table 2; entry 2 was studied, initially at −20 °C giving only 21% yield of the β-amino alcohol (**6** $R^1$ = Ph, $R^2$ = $^{i}$Pr). However, reduction of the reaction temperature to −78 °C saw a dramatic improvement. The reaction displayed very good diastereoselectivity (14:1) and chromatography allowed isolation of a single diastereomer (**6** $R^1$ = Ph, $R^2$ = $^{i}$Pr) in high yield (91%) (Scheme 2).

Following this success, the phenyl imine (**4** $R^1$ = Ph) was cross-coupled with a variety of aliphatic aldehydes. Trends in the reactions of **5**, from $R^2$ = Et to $R^2$ = $^{i}$Pr to $R^2$ = $^{t}$Bu (Table 2; entries 1–2–3) suggested that an increase in size of the substituent in close proximity of the aldehyde's α-carbon displayed increased diastereoselectvity. Thus the aldehyde with the bulkiest substituent (**5** $R^2$ = $^{t}$Bu) provided the highest diastereoselectivity, but regrettably at the cost of a low yield and a comparatively long reaction time (Table 2; entry 3). Increase in the size of the aldehyde further from the α-carbon gave a slight reduction in diastereoselectivity (e.g., Table 2; entry 1 compared to entry 4, or entry 2 compared to entry 6). Pentanal (**5** $R^2$ = $^{n}$Bu) was also found to give good diastereoselectvity (Table 2; entry 5) when coupled with phenyl imine (**4** $R^1$ = Ph).

Variation of the aromatic (*R*)-*N*-*tert*-butanesulfinyl imine (**4**) was sought in an attempt to improve the diastereoselectivity of the cross-coupling even further. The poorest aldehyde (**5** $R^2$ = $^{s}$Bu), in terms of the cross-coupling's diastereoselectivity (Table 2; entry 4), was the partner for this study. The introduction of electron-withdrawing substituents on the phenyl ring such as *p*-chloro (Table 2; entry 8) caused a slight decrease in the diastereoselectivity and yield of the cross-coupling reaction. However, electron-donating substituents on the phenyl ring such as *p*-methoxy (Table 2; entry 9) provided a significant improvement in the diastereoselectivity of β-amino alcohol formation.

An aliphatic (*R*)-*N*-*tert*-butanesulfinyl imine was also prepared (**4** $R^2$ = $^{i}$Pr) and was coupled with **5** ($R^2$ = $^{i}$Pr) with good diastereoselectivity (Table 2; entry 11). The (*R*)-*N*-*tert*-butanesulfinyl auxiliary was removed under acidic conditions and the resulting amino alcohol was protected as the oxazolidinone **7** ($R^1$ = $R^2$ = $^{i}$Pr) in high yield. The *cis*-diastereomer had been previously synthesized,[18] and its $H^1$ and $C^{13}$ NMR data matched **7** ($R^1$ = $R^2$ = $^{i}$Pr). Crystallization of **6** ($R^1$ = *p*-$MeOC_6H_4$, $R^2$ = $^{s}$Bu) from ether allowed investigation by X-ray analysis (Fig. 1) and demonstrated the *anti*-diastereomer to be the major diastereomer.

A derivative of aldehyde **5** ($R^2$ = $CH_2OBn$), which contained a protected alcohol was perceived to have greater synthetic utility and cross-coupling with **4** ($R^1$ = Ph) gave good diastereoselectivity and yield (Table 2; entry 7). Improved diastereoselectivity of the cross-coupling was again observed when the *p*-methoxy substituent was introduced to the phenyl ring (**4** $R^1$ = *p*-$MeOC_6H_4$) (Table 2; entry 10). Repeating this coupling with *epi*-**4** ($R^1$ = *p*-$MeOC_6H_4$), removal of the auxiliary and transformation to the oxazolidinone followed by deprotection of the primary alcohol gave a high yield of (−)-cytoxazone (**8**, Scheme 3).[19,20] Cytoxazone is a cytokine modulator, which has been isolated from *Streptomyces* sp. and has been shown to inhibit Th2 cell's signalling pathway.[21,22]

**Table 2.** Cross-coupling of aldehydes with an imine (*R*)-*N*-*tert*-butanesulfinyl auxiliary shown in Scheme 2

| Entry | $R^1$ | $R^2$ | Reaction time (h) | Dr[a] crude | Dr[a] after separation | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | Ph | Et | 4 | 8:1 | 9:1 | 90 |
| 2 | Ph | $^{i}$Pr | 3 | 14:1 | >25:1 | 91 |
| 3 | Ph | $^{t}$Bu | 20 | >25:1 | >25:1 | 31 |
| 4 | Ph | $^{i}$Bu | 3 | 6:1 | 10:1 | 86 |
| 5 | Ph | $^{n}$Bu | 3 | 8:1 | 9:1 | 69 |
| 6 | Ph | $^{c}C_6H_{11}$ | 3 | 7:1 | >25:1 | 88 |
| 7 | Ph | $BnOCH_2$ | 3 | — | 10:1 | 70 |
| 8 | *p*-$ClC_6H_4$ | $^{s}$Bu | 3 | 5:1 | 10:1 | 73 |
| 9 | *p*-$MeOC_6H_4$ | $^{s}$Bu | 4 | 14:1 | >25:1 | 83 |
| 10 | *p*-$MeOC_6H_4$ | $BnOCH_2$ | 8 | 15:1 | >25:1 | 85 |
| 11 | $^{i}$Pr | $^{i}$Pr | 10 | 8:1 | >25:1 | 51 |

[a] Diastereomeric ratio determined by $^{1}$H NMR.

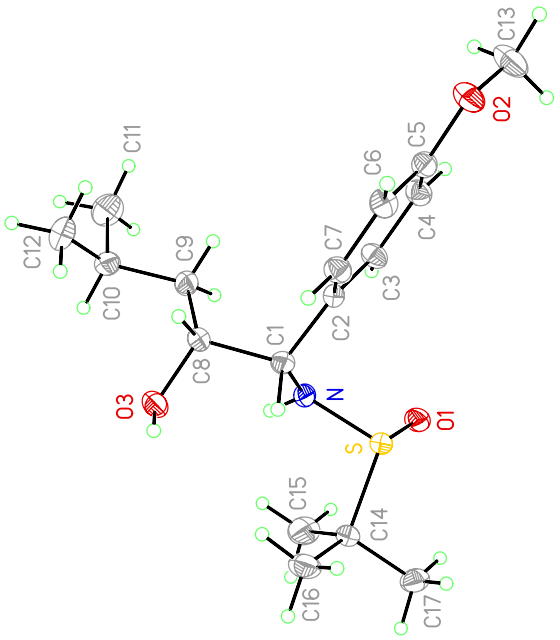
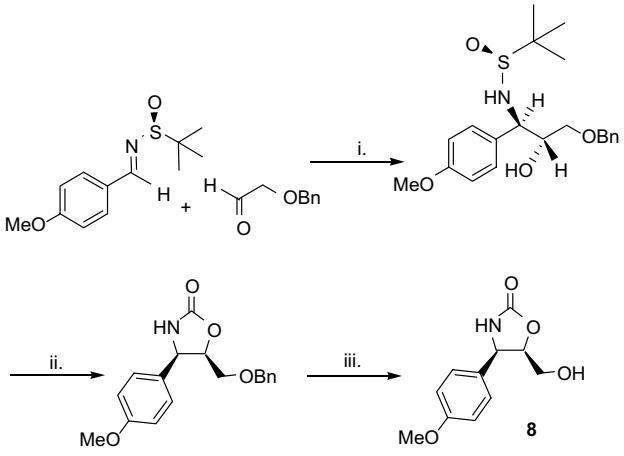
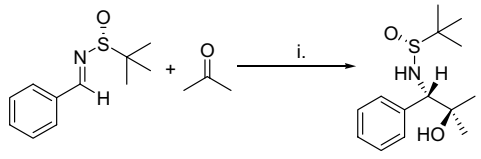



**Figure 1.** The ORTEP image of β-amino alcohol **6** ($R^1 = p$-$MeOC_6H_4$, $R^2 = {}^s$Bu).




**Scheme 3.** The synthesis of (−)-cytoxazone. Reagents and conditions: i. $SmI_2$, $^t$BuOH, THF, −78 °C (83%); ii. (a) HCl, MeOH, 25 °C (b) Triphosgene, $Et_3N$, DCM, 25 °C (85%); iii. $Pd(OH)_2/C$, $H_2$(g), MeOH (86%).

Application of the chiral *N-tert*-butanesulfinyl imine auxiliary was further diversified with its coupling of ketones (Scheme 4). Acetone was crossed coupled with the imine (Scheme 4) initially in poor yield but variation of




**Scheme 4.** The synthesis of a β-amino alcohol by the cross-coupling of ketones with an imine (*R*)-*N-tert*-butanesulfinyl auxiliary. Reagents and conditions: i. $SmI_2$, $^t$BuOH, THF, −78 °C.

**Table 3.** Cross-coupling of ketones with an imine *N-tert*-butanesulfinyl auxiliary shown in Scheme 4

| Entry | Additive | Reaction time (h) | Yield (%) |
|---|---|---|---|
| 1 | — | 10 | 33 |
| 2 | $Et_3N$ | 2 | 53 |
| 3 | TMEDA | 0.5 | 56 |

an amine additive resulted in a faster reaction that gave the β-amino alcohol as a single diastereomer in moderate yield (Table 3).

The very efficient synthesis of β-amino alcohols by the highly stereoselective cross-coupling of *N-tert*-butanesulfinyl imine and aldehyde (complementing Uemura's methodology[12,11]) offers a broad scope towards numerous natural product/drug targets, which our group is in the process of exploiting. The imine ketone cross-coupling is being studied further with unsymmetric ketones.

## Acknowledgements

Financial support from the Department of Chemistry and the Research Allocation Committee, University of New Mexico is gratefully acknowledged. We would like to thank Eileen Duesler for assistance with X-ray analysis.

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.09.002.

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