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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 15 (2004) 3485–3487

# An enantioselective synthesis of nitrogen protected 3-arylserine esters

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Received 30 March 2004; revised 17 May 2004; accepted 7 October 2004

**Abstract**—A method for the preparation of (2*R*,3*S*) nitrogen protected arylserine esters is described. The method consists of rhodium mediated insertion of *tert*-butylcarbamate into the corresponding 3-keto-2-diazoester, affording the *N*-protected α-amino-β-ketoester, followed by asymmetric reduction/dynamic resolution to afford the corresponding *N*-protected 3-arylserine esters in good chemical yield, and in most cases high enantiomeric excess.


## 1. Introduction

As part of an ongoing research project, a direct route to a variety of chiral *threo* 3-arylserine derivatives of general structure **3** was required. It was envisioned that these compounds could be derived from the asymmetric reduction/dynamic resolution[1,2] of the corresponding α-amino-β-ketoester derivative **2**. Although several methods for the preparation of α-amino-β-ketoesters are known,[3] all of the reported methods employed strongly basic or acidic conditions, which limits the scope of the method. Pearson and Zigmantas[4] reported the synthesis of ethyl 3-(4-chlorophenyl)-2-*tert*-butyloxycarbonylaminopropionate via an asymmetric aminohydroxylation protocol, which gave excellent enantioselectivity but relatively poor yields. This compound was used to introduce the C-ring of ristocetin A as well as served as the linchpin in the construction of the key macrocyclic linkage. We envisioned the substrates of general formula **2** could be readily obtained under neutral conditions via the insertion of a rhodium carbenoid, derived from diazoesters of structure **1** into the N–H bond of *tert*-butyl carbamate, as outlined in Scheme 1.

## 2. Results and discussion

Moody and co-workers[5,6] have reported the rhodium-mediated variant of this reaction with alcohols, amines, amides and thiols, with these reactions working well. The requisite α-diazo-β-ketoesters **1a**–**g** were readily synthesized from the corresponding β-ketoesters using mesyl azide and triethylamine under standard conditions.[7]

In turn, the β-ketoester starting materials were either commercially available or synthesized via the tin(II) mediated condensation of ethyl diazoacetate and the corresponding benzaldehyde derivative.[8]

After some experimentation it was discovered that the rhodium(II) octanoate was a superior catalyst for the insertion reaction and results are outlined in Table 1. The reaction appears to be applicable to both electron donating and electron withdrawing substituents on the aromatic ring with a variety of functional groups tolerated.

With the required α-amino-β-ketoester intermediates in hand we began to study the asymmetric reduction/kinetic resolution step. Noyori et al.[1] have described this procedure using a BINAP/ruthenium system, though the method employs high pressure hydrogenation. A more recent report has described this transformation under hydrogen transfer conditions,[2] although the number of examples reported was very limited and the chiral

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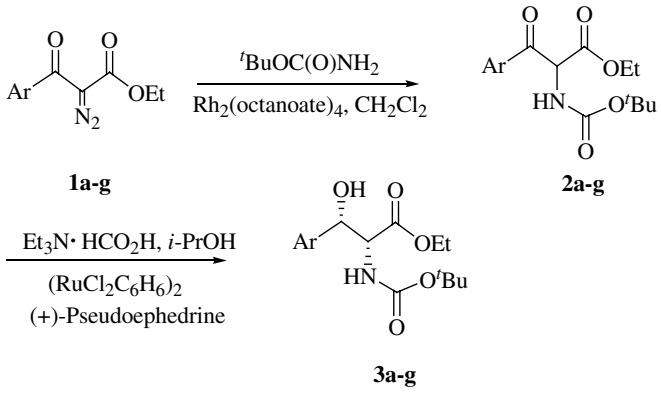
doi:10.1016/j.tetasy.2004.10.005




**Scheme 1.**

**Table 1.** Rhodium-mediated insertion of *tert*-butyl carbamate into diazoesters **1a**–**g**

| Product | Ar | R | Yield[a] (%) |
|---|---|---|---|
| **2a** | Phenyl | *t*-Bu | 63 |
| **2b** | 3-Trifluoromethylphenyl | *t*-Bu | 56 |
| **2c** | 4-Nitrophenyl | *t*-Bu | 57 |
| **2d** | 2-Furyl | *t*-Bu | 82 |
| **2e** | 3-Methoxyphenyl | *t*-Bu | 70 |
| **2f** | 4-Chlorophenyl | *t*-Bu | 65 |
| **2g** | 3,4-Methylenedioxyphenyl | *t*-Bu | 46 |
| **2h** | 4-(2-Phthalimido)ethoxy | *t*-Bu | 70 |

[a] All compounds were determined pure by $^1$H NMR and mass spectral analysis.

**Table 2.** Asymmetric reduction/dynamic resolution of **2a**–**g**

| Product | Yield[a] (%) | Diastereomeric excess[b] (%) | Enantiomeric excess[c] (%) | Rotation (EtOH, 25 °C)[d] |
|---|---|---|---|---|
| **3a** | 78 | >95 | 85 | +20.4 (*c* 1.1) |
| **3b** | 50 | >95 | 81 | +16.6 |
| **3c** | 77 | >95 | 84 | +29.7 |
| **3d** | 72 | 87 | 42 | +9.1 |
| **3e** | 52 | >95 | 83 | +15.9 |
| **3f** | 76 | >95 | 84 | +26.3 |
| **3g** | 66 | 87 | 87 | +15.8 |
| **3h** | 45 | 91 | 85 | +20.9 |

[a] All compounds were >95% HPLC purity and had consistent $^1$H NMR and mass spectra.

[b] Determined by NMR analysis of the corresponding deprotected hydrochloride salt. In most cases the NMR resonances for the C-3 methine protons of the *erythro* isomer were 0.05–0.08 ppm upfield relative to the corresponding *threo* isomer. The two exceptions were the salts derived from compounds **3c** and **3e** and which had resonances of 0.04 and 0.06 ppm downfield, respectively.

[c] Determined by NMR analysis of the corresponding Mosher ester.

[d] *c* 0.5, unless otherwise indicated.

ligands of choice were based on Noyori's C-2 symmetric diamines. Although the diamine precursors to these ligands are commercially available, the cost was envisioned as somewhat prohibitive, especially if the reduction were to be run on larger scale, and the method necessitated the synthesis of the catalyst. With these factors in mind, our efforts focused on the use of ephedrine and pseudoephedrine derived ligands, as these ligands have been reported to give excellent enantioselectivities in the reduction of aromatic ketones.[9] Furthermore, they are inexpensive, and can be potentially used directly without further chemical modification. An initial ligand screen, using **1a** as the reduction substrate, revealed that while most ephedrine and pseudoephedrine derived ligands did afford some degree of enantioselection, (+)-pseudoephedrine gave superior enantioselectivities. Results from the (+)-pseudoephedrine mediated asymmetric reduction/dynamic resolution of substrates **1a**–**g** are outlined in Table 2.

The reduction reaction appears quite diverse and a variety of functionality was tolerated.

Diastereoselectivity was generally excellent, with little of the *erythro* isomer being observed in most cases by $^1$H NMR analysis of either the initial reduction product or the deprotected amino-ester hydrochloride salt. The enantioselectivity of the reduction was also high, with enantiomeric excesses greater than 90% being observed in virtually all cases. An exception to this was the furyl derivative **2d**, with good diastereoselectivity but modest enantioselectivity being observed. Following the analysis method of Dale and Mosher,[10] an (*S*)-configuration was assigned at the 3-position for products derived from (+)-pseudoephedrine mediated chiral reduction. As the ruthenium catalyzed transfer hydrogenation of protected α-amino-β-ketoesters has been reported to be *threo* selective,[2] this translates to an (*R*)-configuration at the 2-centre to give an absolute configuration of 2*R*,3*S*. However, a discrepancy was observed in the comparison of the observed rotation of +20.4 (*c* 1.1, EtOH) for **1a** to the reported value[11] of +8.5 (*c* 1.1, EtOH). The exact reason for this discrepancy was unclear and further efforts to corroborate our stereochemical assignment were made. Thus, **2a** was converted to ethyl (2*R*,3*S*)-2-amino-3-hydroxy-3-phenylpropionate hydrochloride, readily obtained by treatment with 4 M hydrogen chloride in dioxane. This material was found to have a specific rotation of +32.6 (25 °C, *c* 1.0, $H_2O$), which corresponded well to the literature value[12] of −30.0 (18 °C, *c* 2.0, $H_2O$) for the 2*S*,3*R* antipode. Further treatment of this compound with 2 equivalents of lithium hydroxide in water at 0 °C afforded (2*R*,3*S*)-2-amino-3-hydroxy-3-phenylpropionic acid. The specific rotation of this material was found to be +50.0 (25 °C,

*c* 2.0, 6 M HCl), which is also in good agreement with the reported[11,13] literature values of +52.0 (*c* 0.8, 6 M HCl) and +50.2 (20 °C, *c* 2.0, 6 M HCl). These observations further corroborated our initial assignment of 2*R*,3*S* based on Mosher ester analysis.

## 3. Conclusion

In conclusion, we have reported a general synthesis of *threo*-aryl serine derivatives that appears applicable to a variety of substrates. The method gives a rapid entry into *threo*-3-arylserine derivatives with a high degree of diastereoselectivity and enantioselectivity. As both enantiomers of pseudoephedrine are readily available, both antipodes of the final compounds should be attainable.

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