The Diastereoselective Barbier-Type Addition to Chiral N-Tosylimines

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Abstract: The Barbier approach was used for diastereoselective formation of allylamino acid derivatives. The stereochemical models for nucleophilic addition to N-tosylimines bearing various chiral auxiliaries such as (2R)-bornano-10,2-sultam, (R)-8-phenylmenthol, and 10-N,N-dicyclohexylsulfamoyl-(R)-isoborneol are proposed.

Key words: chiral auxiliaries, imines, nucleophilic additions, organometallic reagents, stereoselectivity

The demand for stereochemically pure, nonproteogenic amino acids in pharmaceutical industry triggers intensive research effort in this area. The methodology that uses specifically glyoxyloyl-derived imines for nucleophilic addition provides a straightforward route to target amino acids. Many 1,2-nucleophilic asymmetric additions of organometallic compounds to chiral imines were exploited involving Grignard reagents, organozinc compounds, etc. in enantioselective and diastereoselective ways.1 Recently, the Barbier reagents were applied for the reactions of O-alkylated oximes with the assistance of chiral auxiliaries.2,3 Imines having the stereogenic center (responsible for the asymmetric induction) connected to the nitrogen atom4 were also used in the Barbier-type addition.

In our previous reports on the stereoselectivity of N-glyoxyloyl-(2R)-bornano-10,2-sultam in nucleophilic addition6 and hetero-Diels–Alder reaction, 7,8 we described a stereochemical substantiation of asymmetric induction and the benefits of using (2R)-bornano-10,2-sultam as a chiral auxiliary. 10-N,N-Dicyclohexylsulfamoyl-(R)-isobornyl glyoxylate was found less beneficial, in terms of diastereoselectivity, for the nucleophilic addition of allytrimethylsilane to the carbonyl group.9 We have recently reported the diastereoselective hetero-Diels–Alder reaction of N-tosylimine derivatives of N-glyoxyloyl-(2R)-bornano-10,2-sultam that showed very high diastereofacial differentiation.10 Then we focused our attention on nucleophilic addition reactions of allytrimeth-
ysilane to imines bearing chiral auxiliaries.\textsuperscript{11,12} In the present work, we decided to conduct the comparative studies concerning three different chiral auxiliaries as carriers of chirality in the asymmetric Barbier reaction. The procedure requires mild, nonbasic conditions for the nucleophilic attack and affords high stereoselectivities. The asymmetric induction in this reaction results from coordination of the electron lone-pair at nitrogen with zinc; this can be modulated by chelation with another heteroatom (C=O, SO\textsubscript{2}) to form a rigid transition state.

The N-tosylimines were obtained from the corresponding derivatives of glyoxylic acid using the method introduced recently by Holmes et al.\textsuperscript{13} The reaction of compounds 1a,\textsuperscript{14,15} 1b,\textsuperscript{16–19} and 1e\textsuperscript{9} with p-toluenesulfonyl isocyanate (2), in refluxing toluene, afforded the expected imines 3a,\textsuperscript{10} 3b,\textsuperscript{20} and 3c,\textsuperscript{12} respectively (Scheme 1). Table 1 presents the results of the Barbier addition of allylzinc bromide (4) and 2,2-dimethylallylzinc bromide (5) to the imines 3a-c. The more sterically-demanding zinc derivative 5 gave the better diastereoselectivities and, in the case of (R)-8-phenylmenthyl ester 3b, allylamine (S)-7b was obtained with excellent asymmetric induction. Imines 3a and 3b, derived from (2R)-bornano-10,2-sultam and 10-N,N-dicyclohexylsulfamoyl-(R)-isoborneol, respectively, gave relatively low asymmetric inductions. All results presented in Table 1 confirm the superiority of \(\gamma\)-substituted allyl nucleophiles.

\begin{table}
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\small
\begin{tabular}{cccccc}
\hline
Entry & N-Tosylimine & Allylic Reagent & Yield (\%) & Diastereoisomeric Ratio of Adducts C-2' (S,R) \\
\hline
1 & 3a & 4 & 46 & 6a & 60:40 \\
2 & 3a & 5 & 63 & 7a & 70:30 \\
3 & 3b & 4 & 57 & 6b & 71:29 \\
4 & 3b & 5 & 50 & 7b & 100:0 \\
5 & 3c & 4 & 50 & 6c & 42:58 \\
6 & 3c & 5 & 55 & 7c & 88:12 \\
\hline
\end{tabular}
\caption{Results of the Barbier-Type Addition to Chiral Imines}
\end{table}

In order to rationalize the stereoechemical course of allylic addition to the imine derived from N-glyoxyloyl-(2R)-bornano-10,2-sultam (1a), we propose two chelates of type A and B (Figure 1) that lead to opposite diastereoisomers and explain the low diastereoselectivities in entries 1 and 2. The explanation involves an analogy to the proposed rationale for the hetero-Diels–Alder reaction that is based on two concepts: (a) the sterically controlled approach of the thermodynamically more stable SO\textsubscript{2}/CO antiperiplanar, CO/CHNTs \(s\)-\(cis\) planar conformer A, as proposed by Oppolzer et al.\textsuperscript{21}and by Curran et al.\textsuperscript{22} for N-acryloyl- and N-crotonoyl-(2R)-bornano-10,2-sultam; and (b) the high reactivity of the less stable SO\textsubscript{2}/CO synperiplanar, CO/CHNTs \(s\)-\(cis\) planar conformer B, reinforced by the cooperative stereoelectronic effect, as recently formulated by Chapuis et al.\textsuperscript{7,8}for N-glyoxyloyl-(2R)-bornano-10,2-sultam (1a).

Oppolzer has earlier proposed,\textsuperscript{23} that the most favorable conformation was reached when the alkoxy C–H bond was \(\text{syn}\)-periplanar to the C=O moiety of the ester (as supported by recent X-ray analysis).\textsuperscript{24} As a consequence, all these groups possess an identical sterically-induced \(C_s\)-\(si\) topology, where the (E)-C=N bond is \(s\)-\(cis\) to that of the C=O bond. The PM3 calculations confirmed the thermodynamic stability and higher reactivity of the \(s\)-\(cis\) over \(s\)-\(trans\) conformer for N-benzyl protonated analogues.\textsuperscript{25}

Since the zinc reagent presumably forms the 5-membered chelate with oxygen and nitrogen (Figure 2), the following rationale is proposed. The (R)-8-phenylmenthyl chiral auxiliary (cf. 1b) provides excellent diastereoselectivities that hypothetically result from the \(\pi\)-\(\pi\) stacking between the aryl moiety and the reacting site.\textsuperscript{26} The \(\text{pro-R}\) side is effectively shielded by the aryl moiety. Moreover, the chelation by zinc additionally stabilizes the transition state shown below.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{structure1.png}
\caption{Structure of 5-membered Zn-chelate derived from 1b.}
\end{figure}

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The configuration 2\(^S\) of the major diastereoisomer 6a and 2\(^R\) of the major diastereoisomer 6c were earlier determined by X-ray analysis.\textsuperscript{17} The absolute configuration of the adduct 6b was obtained by converting the two major diastereoisomers 6a and 6b, and the minor diastereoisomer 6c to alcohol 8, and comparing the optical rotations of the respective products (Scheme 2). A similar approach was used for the series of adducts 7. The configuration 2\(^S\) of 7a was determined by X-ray analysis (Figure 3). The absolute configurations of adducts 7b and 7c were obtained by converting all derivatives 7a, 7b, and 7c to alcohol 9 and comparing the optical rotations of the respective products (Scheme 2).
combined organic extracts were washed with NaHCO₃, dried (MgSO₄) and rotary-evaporated under reduced pressure. The products were purified by flash chromatography using 30% Et₂O-hexane as an eluent for the adducts of the imine derived from N-glyoxoyloyl-(2R)-bornano-10,2-sultam (1a) as well as 10-N,N-dicyclohexylsulfamoyl-(R)-isobornyl glyoxylate (Ic), and using 10% EtOAc-hexane as an eluent for the adduct of the imine derived from (R)-8-phenylmethyl glyoxylate (Ib). The separate diastereoisomers were thus obtained.

Scheme 2

**Figure 3** Crystal Structure of Compound 7a.

The reagent-grade solvents, CH₂Cl₂, hexanes, EtOAc, THF, were distilled prior use. All the reported NMR spectra were recorded on a Varian Gemini spectrometer at 200 MHz (1H NMR) and at 50 MHz (13C NMR). The chemical shifts are reported in δ relative to the TMS signal at δ = 0.00 (1H NMR) or δ = 0.00 (13C NMR). The IR spectra were obtained on a Perkin-Elmer 1640 FTIR spectrophotometer. The major bands are reported in cm⁻¹. Mass spectra were obtained on an AMD-604 Intectra instrument using the EI or LSIMS technique. Chromatography was performed on silica gel (Kieselgel 60, 200–400 mesh). Optical rotations were recorded using a Jasco DIP-360 polarimeter with a thermally jacketed 10 cm cell. All air- or moisture-sensitive reactions were carried out using flame-dried glassware under argon.

**N-Toluenesulfonilimines 3a–c; General Procedure**

To a stirred solution of the corresponding glyoxylate (1.5 mmol) in toluene in an ice bath, were added the Barbier reagent 4 or 5 [prepared in situ by reacting metallic zinc (126 mg, 2 mmol) and corresponding allyl bromide (1.5 mmol) at 0 °C in THF]. The reaction mixture was stirred for 12 h at 0 °C. The reaction was quenched by dropwise addition of 10% HCl. The aqueous phase was extracted with EtO and the combined organic extracts were washed with NaHCO₃, dried (MgSO₄) and rotary-evaporated under reduced pressure. The products were purified by flash chromatography using 30% Et₂O-hexane as an eluent for the adducts of the imines derived from N-glyoxoyloyl-(2R)-bornano-10,2-sultam (1a) as well as 10-N,N-dicyclohexylsulfamoyl-(R)-isobornyl glyoxylate (Ic), and using 10% EtOAc-hexane as an eluent for the adduct of the imine derived from (R)-8-phenylmethyl glyoxylate (Ib). The separate diastereoisomers were thus obtained.

N-[2(R)-N'-p-Toluenesulfonfallylglycinoyl-(2R)-bornano-10,2-sultam [(R)-6a]

Mp 154–157 °C (hexane–EtOAc); [α]D⁰ +28.2 (c = 1, CHCl₃). All IR, 1H NMR, 13C NMR, EI-MS, and analytical data were identical with those obtained by us earlier.

N-[2(R)-N'-p-Toluenesulfonfallylglycinoyl-(2R)-bornano-10,2-sultam [(S)-6a]

Mp 120–123 °C (hexane–EtOAc); [α]D⁰ +34.6 (c = 1, CHCl₃). All IR, 1H NMR, 13C NMR, EI-MS, and analytical data were identical with those obtained by us earlier.

N-[2(R)-N'-p-Toluenesulfonallylglycine 8-(R)-Phenylmethyl Ester [(S)-6b]

Oil; [α]D⁰ +20.6 (c = 1, CHCl₃). All IR, 1H NMR, 13C NMR, EI-MS, and analytical data were identical with those obtained by us earlier.

N-[2(R)-N'-p-Toluenesulfonfallylglycinoyl-(2R)-Isobornyl Ester [(R)-6c]

Mp 171–172 °C; [α]D⁰ –29.2 (c = 1, CHCl₃). All IR, 1H NMR, 13C NMR, EI-MS, and analytical data were identical with those obtained by us earlier.

N-[2(R)-N'-p-Toluenesulfonfallylglycinoyl-(2R)-Isobornyl Ester [(S)-6c]

Mp 167–168 °C; [α]D⁰ –14.0 (c = 1, CHCl₃). All IR, 1H NMR, 13C NMR, EI-MS, and analytical data were identical with those obtained by us earlier.

N-[2'(R)-N'-p-Toluenesulfonallylglycinoyl-(2R)-bornano-10,2-sultam [(R)-7a]

Oil; [α]D⁰ –29.0 (c = 1, CHCl₃).

IR (KBr): 3292, 2962, 2884, 1688, 1339, 1162 cm⁻¹.

1H NMR (200 MHz, CDCl₃): δ = 7.81 (dAB, J = 8.2 Hz, 2H), 7.25 (dAB, J = 8.4 Hz, 2H), 5.97 (m, 1H), 5.15–4.98 (m, 3H), 4.23 (br s, 1H), 3.74 (br s, 1H), 3.54–3.28 (m, 2H), 2.41 (s, 3H), 2.06–1.80 (m, 2H), 5.87 (m, 1H), 5.20–5.01 (m, 3H), 4.41 (d, J = 10.2, 1H), 3.75–3.58 (m, 1H), 3.52–3.28 (m, 2H), 2.40 (s, 3H), 2.06–1.80 (m, 5H), 1.43–0.80 (m, 14H).

13C NMR (50 MHz, CDCl₃):

67 = 170.0, 142.4, 129.5, 127.7, 115.5, 104.0, 52.2, 47.2, 47.7, 44.5, 41.1, 38.4, 33.1, 26.3, 24.7, 23.2, 21.6, 20.6, 20.0.

13C NMR DEPT (50 MHz, CDCl₃): δ = 124.2 (CH), 129.5 (CH), 127.7 (CH), 115.5 (CH₂), 60.4 (CH₂), 52.8 (CH₂), 52.2 (CH₂), 38.4, 33.1 (CH₃), 26.3 (CH₃), 24.7, 23.2, 21.6, 20.6, 20.0.

MS (EI): m/z = 101 (M + Na⁺), 517 (M + Na⁺), 425 (42), 252 (48), 155 (94), 91 (100), 69 (42), 41 (29).

HRMS (EI): m/z calcd for C₃₂H₃₄NO₇Na₂S₂ (M + Na): 517.1806; found: 517.1801.

N-[2'(S)-N'-p-Toluenesulfonallylglycinoyl-(2R)-bornano-10,2-sultam [(S)-7a]

Mp 131–134 °C (hexane–EtOAc); [α]D⁰ +31.4 (c = 1, CHCl₃).

1H NMR (200 MHz, CDCl₃): δ = 7.82–7.72 (m, 2H), 7.27–7.19 (m, 2H), 5.87 (m, 1H), 5.20–5.01 (m, 3H), 4.41 (d, J = 10.2, 1H), 3.75–3.58 (m, 1H), 3.52–3.28 (m, 2H), 2.40 (s, 3H), 2.06–1.80 (m, 5H), 1.43–0.80 (m, 14H).

5.16–5.00 (m, 2 H), 4.59 (qAB, dAB, m, 2 H), 4.42 (td, J = 8.4 Hz, 1 H), 5.51–5.32 (m, 2 H), 4.98–4.08 (d, J = 16.9 Hz, 1 H), 2.70 (dAB, J = 8.4 Hz, 1 H), 3.08–2.98 (m, 1 H), 2.43 (s, 3 H), 0.97 (s, 3 H).

HRMS (EI): m/z calcd for C14H21NNaO3S (M + Na): 306.1134; found: 306.1152.


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References
(30) The crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-194392. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax (+44)1223336033; e-mail: deposit@ccdc.cam.ac.uk].