Stereoselective and Catalytic Synthesis of \textit{anti} \( \beta \)-Alkoxy-\( \alpha \)-Azido Carboxylic Derivatives

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Supporting Information Placeholder

ABSTRACT: Direct addition of a chiral N-azidoacetyl thiazolidinethione to a variety of dialkyl acetics catalyzed by a commercially available and structurally simple nickel(II) complex gives access in good yields and a highly stereocontrolled manner to \textit{anti} \( \beta \)-alkoxy-\( \alpha \)-azido carboxylic derivatives which, in turn, can be easily converted into a wide array of enantiomerically pure compounds.

\textit{Anti} \( \beta \)-hydroxytyrosine derivatives are key structural motifs in a variety of biologically active compounds, ranging from structurally simple 3-acyltetramic acids\(^1\) to much more complex vancomycin antibiotics\(^2\) or cyclodepsipeptides such as stellatolides (Figure 1).\(^3\)

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\begin{align*}
\text{S} & \quad \text{N} & \quad \text{O} & \quad \text{N}_3 \\
\text{cat. (Me}_3\text{P)}_2\text{NiCl}_2 & \quad \text{TESOTf, 2,6-lutidine} & \quad \text{S} & \quad \text{N} & \quad \text{O} & \quad \text{N}_3 \\
\text{R}_1 & \quad \text{R}\end{align*}
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Figure 1. \textit{anti} \( \beta \)-Hydroxytyrosine fragments in natural products

It should therefore come as no surprise that their synthesis has attracted much attention, but, despite considerable effort, that goal has remained elusive. Lipton reported a single example of a highly enantioselective and diastereoselective synthesis of \textit{anti} \( \beta \)-methoxytyrosine through asymmetric aziridination of the TBS-protected methyl \( p \)-coumarate followed by ring opening in methanol.\(^4\) In turn, Hamada found that \( \alpha \)-amino-\( \beta \)-aryl-\( \beta \)-keto esters can be hydrogenated through dynamic kinetic resolution in the presence of a chiral iridium catalyst to give the corresponding \textit{anti} \( \alpha \)-amino-\( \beta \)-hydroxy acids as a single diastereomer with excellent enantiocontrol;\(^5\) however, the high pressure and long reaction time required (100 atm for four days) have thwarted further applications. Alternative aldol-based approaches might seem much more promising, but their scope is still very limited.\(^6\) Maruoka reported the enantioselective synthesis of \textit{anti} \( \alpha \)-amino-\( \beta \)-hydroxy acids through aldol reactions from a glycine Schiff base catalyzed by a chiral quaternary ammonium salt, but aromatic aldehydes turned out to be unsuitable substrates.\(^7\) More recently, Kumagai and Shibasaki have described a highly diastereoselective and enantioselective catalytic aldol reaction of \( \alpha \)-azido 7-azaindolinyacetamide; but this is restricted to ortho-substituted aromatic aldehydes.\(^8\) In the face of this lack of experimentally simple and broad ranging synthetic methods, we envisaged that the direct addition of chiral \( N \)-glycyl thiazolidinethiones to dialkyl acetics catalyzed by nickel(II) complexes might afford \textit{anti} \( \beta \)-alkoxy-\( \alpha \)-amino carboxylic derivatives.\(^9\)\(^,\)\(^10\)\(^,\)\(^11\) Herein, we report that (Me\(_3\)P)\(_2\)NiCl\(_2\) triggers the stereocontrolled addition of a chiral \( N \)-2-azidocarboxyl thiazolidinethione (NPG: N\(_3 \)) in Scheme 1) to aromatic and propargylic dialkyl acetals to give \textit{anti} \( \beta \)-alkoxy-\( \alpha \)-azido adducts\(^12\) which, in turn, can be easily converted into a plethora of enantiomerically pure intermediates.
Scheme 1. Direct and catalyzed addition of N-(2-azaacetyl) thiazolidinethiones to dialkyl acetals

Exploratory experiments indicated that most of the amino protecting groups (NPG: Boc, Fmoc, Z, and Bz in Scheme 1) were unsuitable for our purposes. Only nickel(II) catalyzed addition of phthaloyl and azido derivatives, 1 and 2 respectively in Scheme 2,11 to the dimethyl acetal of p-anisaldehyde (a), which gave the desired adducts in good yields. Unfortunately, and despite our efforts, we did not succeed in exerting proper stereocontrol over the configuration of the β-stereocenter from 1, and adduct 3a was isolated as a 67:33 diastereomeric mixture in an overall yield of 89% (Scheme 2). In contrast, N-2-azidoacetyl-4-isopropyl-1,3-thiazolidine-2-thione 2 gave adduct 4a as a 96:4 mixture of diastereomers with a 60% yield (Scheme 2).

Scheme 2. Preliminary results

Following comprehensive optimization, we finally found that the direct reaction of 2 with the acetal a (1.1 equivalents) using 5 mol % of commercially available (Me₂P)₂NiCl₂, 1.5 equivalents of TESOTT and 2,6-lutidine for 15 h at –20 °C led to a 96:4 diastereomeric mixture from which the pure anti adduct 4a was isolated with an 85% yield (Scheme 3). Once the synthesis of such a β-methoxytyrosine precursor had been completed, we next applied the abovementioned conditions to a variety of dimethyl acetals from aromatic aldehydes. As shown in Scheme 3, the methoxy-substituted acetals a–c revealed the dramatic influence of the electronic character of the aryl group on the outcome of these additions. Indeed, the diastereomeric ratio dropped from 96:4 to 73:27 and improved again to 82:18 when we passed from 4-OMe to 3-OMe and 2-OMe acetals respectively (compare 4a–c in Scheme 3). In accordance with such a trend, piperonal and 4-NMe₂ dimethyl acetals, d and e respectively, also furnished the anti adducts 4d and 4e in high diastereomeric ratios and yields (Scheme 3). The less activated tolyl and phenyl acetals, f and g respectively, afforded the anti adducts with a progressively poorer stereoccontrol; whereas the deactivated 4-chloro dimethyl acetal (h) required 20 mol % of (Me₂P)₂NiCl₂ to obtain 4h with a meager 15% yield (Scheme 3). Finally, the alkyl group R did not have any effect on these reactions. Indeed, the allyl and benzyl acetals, i and j respectively, gave the corresponding anti adducts 4i and 4j with diastereoselectivities and yields close to those for the dimethyl acetal a (Scheme 3).14

Thiazolidinethiones are renowned among the chiral auxiliaries for their ease of removal,15 so 4a was smoothly converted into the enantiomerically pure alcohol 5, ester 6, and keto ester 7 under mild conditions (Scheme 4). Furthermore, treatment of 4a with (S)-α-methylbenzylamine afforded amide 8, whose X-ray analysis permitted us to establish the anti configuration of 4. In turn, a parallel reaction with 1 equivalent of methyl leucinate hydrochloride gave the dipeptide 9 with a 96% yield in a straightforward manner (Scheme 4).

Scheme 3. Diastereoselective and nickel(II) catalyzed addition of (S) N-2-azidoacetyl-4-isopropyl-1,3-thiazolidine-2-thione (2) to dialkyl acetals of aromatic aldehydes
Aiming to expand the scope of this transformation, we then focused our attention on other acetals. Since Schreiber reported that cobalt-derived propargylic acetals easily undergo $S_n$-like reactions, we envisaged that their use might provide access to a much larger range of compounds. Thus, we were pleased to observe that model cobalt phenylpropargylddehyde diethyl acetal (k) participated in a highly stereoselective reaction with 2. Indeed, its direct addition to 2 using 10 mol % of $(Me_3P)_2NiCl_2$, 2.2 equivalents of TESOTf, and 1.5 equivalents of 2,6-lutidine provided diastereomerically pure 10k with 73% yield (Scheme 5). These conditions were further applied to a number of acetals k–t possessing a wide array of functional groups to obtain 10k–t as single diastereomers in high yields, with the exception of 10m, from the simple propargylddehyde diethyl acetal (Scheme 5). All together, these results show that the addition of 2 catalyzed by a nickel(II) complex to properly activated acetals provides a totally stereocinated access to highly functionalized anti $\beta$-alkoxy-$\alpha$-azido carboxylic derivatives.

Importantly, the resulting adducts 10 can be transformed into a variety of advanced intermediates. As shown in Scheme 6, appropriate manipulation of adduct 10k produced the Boc-protected amino alcohol 11 in a 48% overall yield. This can then be hydrogenated to the alkyl 12 or $Z$-allenyl derivative 13 in excellent yields. Unfortunately, the obtention of the E-counterpart 14 was much more troublesome. Attempts to reduce the triple bond with Na/NH$_3$ or by means of ruthenium catalysts were unsuccessful; it was finally achieved by treatment with LiAIH$_4$ but in a poor yield (E/Z 90:10, 30%, 64% brsm). Alternatively, 10n was smoothly converted into the terminal alkenne 15, which underwent a cross-metathesis reaction with 1-hexene to produce the $E$-alkene 16. Finally, we also took advantage of the anti adduct 10u containing an alkoxy group close to the cobalt-activated triple bond to carry out Pauson-Khand cyclization that furnished the densely functionalized cyclopentenone 17 in a 57% yield under very mild conditions (Scheme 6). All together, these results prove that adducts 10 are suitable materials to access to a wide array of enantiomerically pure anti 3-alkoxy-2-amino hydroxy derivatives.

In summary, direct Lewis acid-mediated reaction of N-2-azidoacetyl-4-isopropyl-1,3-thiazolidine-2-thione 2 with aromatic and propargylic acetals catalyzed by 5–10 mol % of a structurally simple nickel(II) complex provides the corresponding anti $\alpha$-alkoxy-$\beta$-azido derivatives in good yield with high stereocentral. In turn, the resultant adducts can be converted into a variety of enantiomerically pure intermediates in a straightforward manner.
ASSOCIATED CONTENT

Supporting Information
Complete experimental procedures, physical, and spectroscopic data for 2, adducts 4a-j, 10k–u, derivatives 5–9, 11–17, as well as X-ray of 8 (PDF).
Copies of 1H and 13C spectra for new compounds (PDF)
The Supporting Information is available free of charge on the ACS Publications website.

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Notes
The authors declare no competing financial interest.

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(12) The addition probably proceeds through the antiperiplanar approach of a putative oxocarbenium intermediate to a chelated nickel(II) enolate, as described in Reference 10a and 11b.
(14) For other Lewis acid-mediated additions to dibenzyl acetal see: Gálvez, E.; Parelló, R.; Romea, P.; Urpi, F. Synlett 2008, 2951.
(16) Crystallographic data for amide 8 has been deposited at the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1574237. A copy of the data can be obtained free of charge on application to CCDC (e-mail: deposit@ccdc.cam.ac.uk).


(19) Acetals k-t have been synthesized in accordance with standard procedures and purified by column chromatography, see: (a) Varghese, V.; Saha, M.; Nicholas, K. M. *Org. Synth.* 1989, 67, 141. (b) Reference 17 and 18.

