FULL PAPER

Direct and Asymmetric Aldol Reactions of *N*-Azidoacetyl-1,3-thiazolidine-2-thione Catalyzed by Chiral Nickel(II) Complexes. A New Approach to the Synthesis of β-Hydroxy-α-Amino Acids

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In memory of Enrique Pedroso

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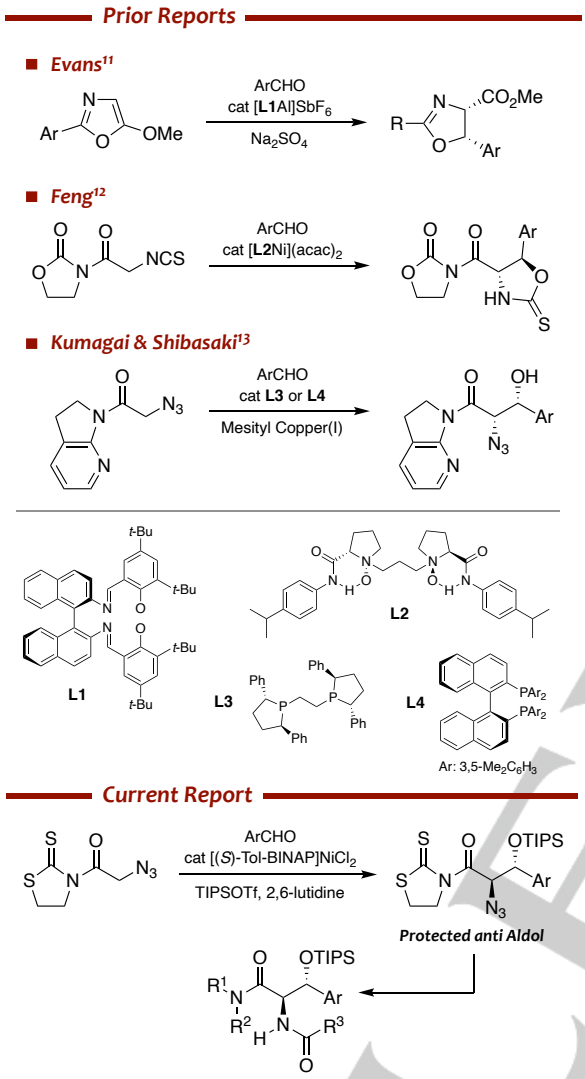
Abstract: A direct and asymmetric TIPSOTf-mediated aldol reaction of *N*-azidoacetyl-1,3-thiazolidine-2-thione with aromatic aldehydes catalyzed by a chiral nickel(II)-Tol-BINAP complex has been developed. The catalytic protocol gives the corresponding *anti* α-azido-β-silyloxy adducts with outstanding stereocontrol and in high yields. Theoretical calculations account for the stereochemical outcome of the reaction and lay the foundations for a mechanistic model. In turn, the easy removal of the thiazolidinethione yields a wide array of enantiomerically pure derivatives in a straightforward and efficient manner. Such a noteworthy character of the heterocyclic scaffold together with the appropriate manipulation of the azido group open a new route to the synthesis of di- and tripeptide blocks containing a β-aryl-β-hydroxy-α-amino acid.

Introduction

Non-proteinogenic β-aryl-β-hydroxy-α-amino acids are key building blocks in a variety of biologically active cyclodepsipeptides such as callipeltins,[1] papuamides,[2] stellatolides,[3] and others;[4,5] glycopeptide antibiotics like vancomycin;[6] and may also be used as intermediates for the asymmetric synthesis of pharmaceutical agents such as eliglustat.[7] The challenge posed by the enantioselective construction of such small but highly functionalized structures together with their remarkable activity have aroused great interest and triggered the design of a wide range of synthetic strategies.[8] Notable among them are those based on aldol reactions that take advantage of the reactivity of metal enolates. However, and despite the undeniable success of such approaches, most require stoichiometric amounts of the corresponding enolates and only a select number of methods hinge on direct, catalytic, and asymmetric transformations (Scheme 1).[9–13] As part of our ongoing project towards the development of increasingly more efficient synthetic methods under the premises dictated by the atom economy[14] and catalytic principles,[15] we have recently reported a new direct and highly enantioselective aldol reaction catalyzed by structurally simple chiral nickel(II) complexes derived from commercially available Tol-BINAP.[16] More specifically, we found that *N*-azidoacetyl-1,3-thiazolidine-2-thione is an outstanding platform from which carry out a highly stereocontrolled aldol addition to 4-methoxybenzaldehyde to produce the enantiomerically pure *anti O*-protected derivative in a high yield.[17] Importantly, the resultant aldol adduct contains an easily removable thiazolidinethione scaffold, which enables the smooth formation of an amide bond, and also an azido group, which can be considered a masked amino group and thus permits the extension of the peptide sequence employing standard procedures (Scheme 1).[18]

Herein we disclose a full account of the direct and enantioselective aldol reaction of *N*-azidoacetyl-1,3-thiazolidine-2-thione with aromatic aldehydes catalyzed by [Tol-BINAP]$NiCl_2$ in the presence of TIPSOTf and 2,6-lutidine to give enantiomerically pure *anti* α-azido-β-silyloxy adducts in high yields (Scheme 1). The outstanding stereocontrol of these reactions has been assessed through comprehensive computational studies, which provide the theoretical background to account for such a highly enantioselective transformation. Furthermore, the straightforward removal of the heterocyclic

scaffold of representative aldol adducts has given a plethora of enantiomerically pure advanced intermediates; in turn, the reduction of the azido group followed by the appropriate acylation of the resultant amino group has demonstrated their potential to participate in the synthesis of peptidic sequences.



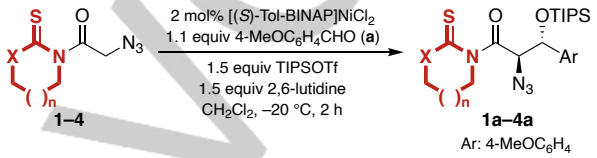
Scheme 1. Direct, asymmetric, and catalytic approaches to the synthesis of β-hydroxy-α-amino acids.

Results and Discussion

Optimization of the reaction conditions

Previous studies in our lab demonstrated that nickel(II) catalyzed carbon–carbon bond forming reactions from imide-like scaffolds require the presence of an exocyclic C=S bond.[19,20] Particularly, it was found that the *N*-azidoacetyl-1,3-thiazolidine-2-thione (**1** in Table 1) reacts with 1.1 equivalents of 4-methoxybenzaldehyde (**a**) in the presence of 2 mol% of [(*S*)-Tol-BINAP]$NiCl_2$, TIPSOTf (1.5 equivalents), and lutidine (1.5 equivalents) to give *anti aldol* adduct **1a** in a 95% yield with outstanding stereocontrol (dr > 95:5, ee 99%).[16] Despite such an excellent result, we decided to examine in detail the influence of the endocyclic heteroatom as well as the size of the heterocycle. Thus, we tested parallel reactions with *N*-azidoacetyl-1,3-oxazolidine-2-thione (**2** in Table 1) containing a five-membered oxygenated scaffold and the related six-membered counterparts (**3–4** in Table 1).[21–24] The results summarized in Table 1 indicate that the oxazolidinethione scaffold **2** (entry 2 in Table 1) is also a suitable platform to perform the aldol reaction with **a**, but a certain loss of efficiency was observed when less reactive aldehydes were employed. Surprisingly, the six-membered *N*-azidoacetyl-1,3-thiazinane-2-thione **3** and the oxygenated counterpart **4** (entry 3 and 4 respectively in Table 1) turned out to be rather unstable, which ruled them out for our purposes.[25]

Table 1. Influence of the scaffold on the aldol reaction



Entry	Starting Material	X	n	Aldol	dr (*anti*/*syn*)	*ee* [%] [a]	Yield [%] [b]
1	**1**	S	0	**1a**	> 95:5	99	95
2	**2**	O	0	**2a**	95:5	99	92
3	**3**[c]	S	1	**3a**	–	–	–
4	**4**[c]	O	1	**4a**	–	–	–

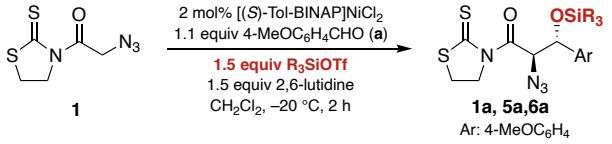
[a] Established by chiral HPLC analysis.

[b] Isolated yield.

[c] The desired *N*-acyl thioimides could not be isolated.

Following with our evaluation and keeping in mind the crucial role played by the Lewis acid, we next assessed the impact of other silyl triflates in the reaction of **1** with 4-methoxybenzaldehyde (**a**). Comparison of the results attained with TIPSOTf, TBSOTf, and TESOTf shows that they can be used interchangeably to obtain the desired aldol adducts (compare entry 1–4 in Table 2), but a slight erosion of the enantioselectivity was observed depending on the size of the silyl group. Indeed, the bulkiest TIPS group gave a single enantiomer **1a** (entry 1 in Table 2), whereas smaller groups as TBS or TES afforded the corresponding aldol adducts **5a** and **6a** with a good but poorer enantioselectivity even at low temperature (compare entry 2–4 in Table 2). Furthermore, the use of $BF_3{\cdot}OEt_2$ as an alternative Lewis acid was also explored, but both the yield and the stereocontrol obtained were too poor compared to those achieved with silyl triflates.

Table 2. Influence of the Lewis acid on the aldol reaction



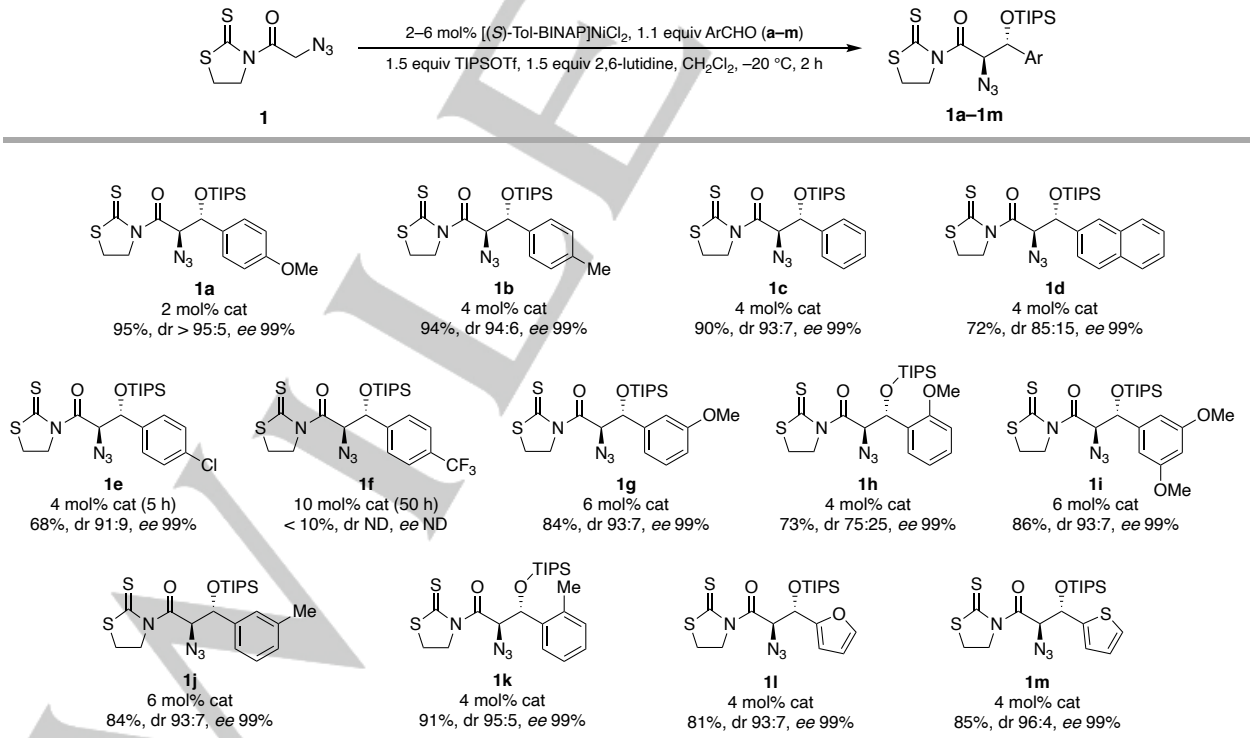
Entry	R_3SiOTf	T [°C]	*t* [h]	Aldol	dr (*anti*/*syn*)	*ee* [%] [a]	Yield [%] [b]
1	TIPSOTf	–20	2	**1a**	> 95:5	99	95
2	TBSOTf	–20	2	**5a**	> 97:3	88	95
3	TESOTf	–20	2	**6a**	> 97:3	86	90
4	TESOTf	–78	4	**6a**	> 97:3	92	83

[a] Established by chiral HPLC analysis.

[b] Isolated yield.

Scope of the aldol reaction

Having evaluated the influence of the main reagents, we explored the scope of the reaction using 1.1 equivalents of a wide array of aromatic aldehydes, 1.5 equivalents of TIPSOTf and 1.5 equivalents of 2,6-lutidine under the abovementioned conditions. To our delight, most of the aldehydes gave the enantiomerically pure *O*-protected *anti* aldol adducts with outstanding stereocontrol in high yields (Scheme 2). Noteworthily, the electronic character of the aromatic substituent plays a crucial role in the kinetics of the reaction. Indeed, an electrondonating group such as MeO (in **a**) at the *para* position led the reaction to full conversion in 2 h employing just a tiny 2 mol% of the nickel(II) complex. Less activating substituents such as alkyl or solely aryl groups (in **b–d**) required an increase in the catalyst loading up to 4 mol% to attain reproducible and comparable results. In turn, slightly deactivating chlorine (in **e**) also demanded a longer reaction time (5 h), whereas the strongly electronwithdrawing CF_3 group (in **f**) inhibited the reaction even when using 10 mol% of the catalyst. Adjusting the amount of the nickel(II) complex in the case of aldehydes containing MeO or Me groups at *meta* or *ortho* position (in **g–i** and **j–k** respectively) or heteroaromatic aldehydes (in **l** and **m**) also made the reaction possible and the corresponding *anti* aldol adducts **1g–1m** were isolated in high yields with absolute enantiocontrol (*ee* 99%).[26] These results highlight the remarkable scope of the direct and nickel–catalyzed (2–6 mol%) aldol reaction, which produces the enantiomerically pure protected *anti* aldol adducts **1a–1m** in 72–95% yield with just 1.1 equivalents of a variety of aromatic aldehydes; the only exception was the strongly electronically deactivated aldehyde 4-$CF_3C_6H_4CHO$ (**f**). Importantly, the reactions described in Scheme 2 were routinely performed at 1 mmol scale, but that of benzaldehyde (**c**) was also carried out at a 4–5 mmol scale without significant change in the stereochemical outcome (dr 93:7, *ee* 99%) or the yield (88–90%), which demonstrates the robustness of the method.



Scheme 2. Scope of the aldol reaction.

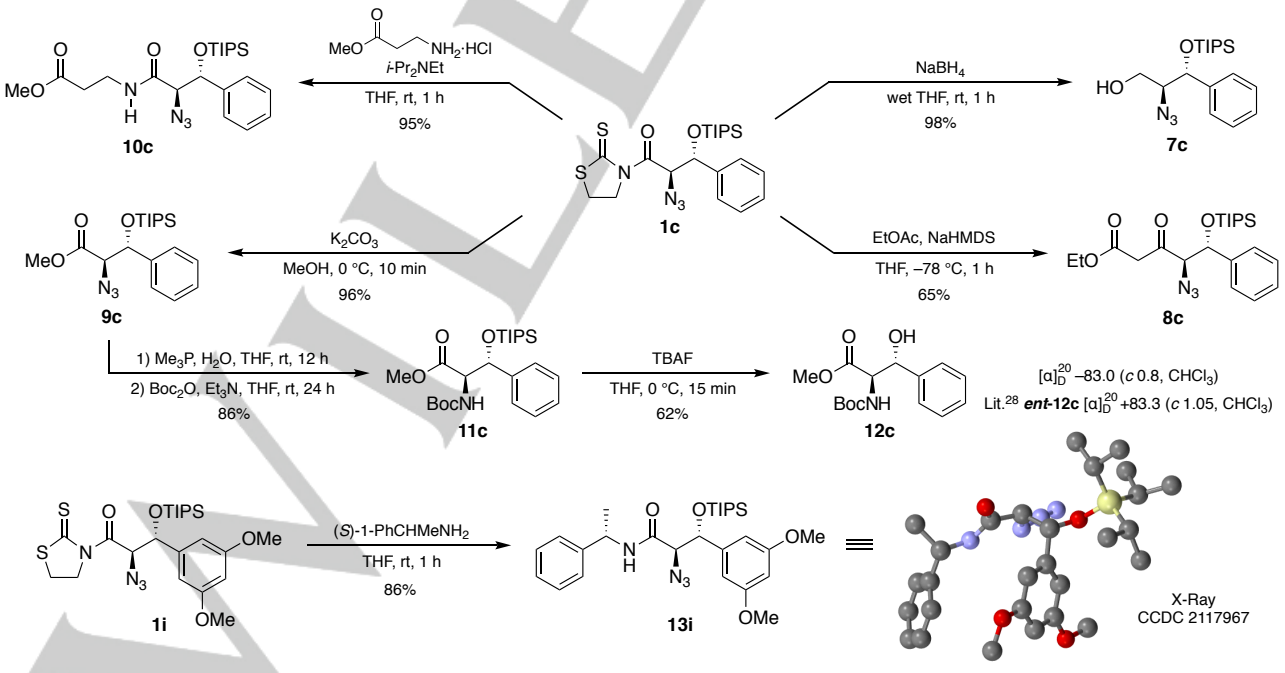
Derivatization of the aldol adducts

Once the carbon–carbon bond forming step was thoroughly studied, we focused our attention on the synthesis of enantiomerically pure compounds from model aldol substrate **1c**. The easy removal of the thiazolidinethione scaffold was instrumental in meeting such an objective and enabled a significant number of derivatives to be successfully isolated from **1c**. Thereby, alcohol **7c**, β-keto ester **8c**, methyl ester **9c**, and amide **10c** were synthesized in yields up to 98% under mild experimental conditions (Scheme 3). These results prove that hydride and carbon, nitrogen, and oxygen nucleophiles are able to displace the thiazolidinethione and may be thus employed for the preparation of advanced intermediates. Furthermore, reduction of ester **9c** with Me_3P in wet THF[27] followed by the protection of the resultant amino group afforded the β-silyloxy-α-amino ester **11c** in an 86% yield, which manifests the synthetic potential of the method to provide fully protected enantiomerically pure β-hydroxy-α-amino intermediates in a straightforward manner (Scheme 3). At this point, the configuration of the new stereocenters was firmly established by deprotection of the alcohol in **11c** with TBAF and comparison of the physical and spectroscopic data of the resultant β-hydroxy-α-amino ester **12c** with those reported in the literature (Scheme 3).[28] Eventually, X-ray analysis of crystalline amide **13i** prepared by treatment of aldol **1i** with chiral (*S*) phenylethylamine confirmed the *anti* (2*R*,3*R*) configuration of aldols **1a–1m** (Scheme 3).

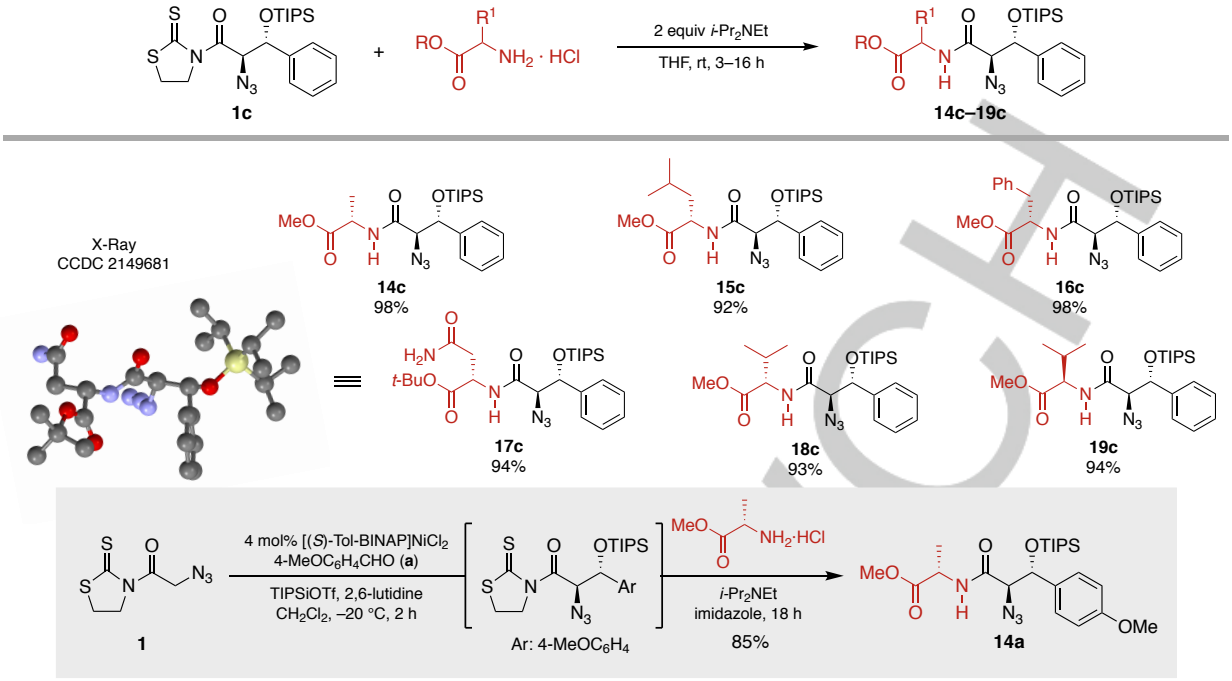
Synthesis of dipeptides from α-amino esters with primary amines

The facile synthesis of **10c** by treatment of **1c** with methyl β-alaninate (Scheme 3) led us to take advantage of the labile thiazolidinethione scaffold for the forging of amide bonds. With this in mind, we examined the synthesis of dipeptides containing β-hydroxyphenylalanine by reaction of **1c** with several α-amino ester hydrochlorides. As represented in Scheme 4 the desired dipeptides were obtained by the simple stirring of a solution of **1c**, the corresponding α-amino ester hydrochloride, and *i*-Pr_2NEt at room temperature. These results also show that the steric hindrance of the α-amino ester has a critical influence on the kinetics. Indeed, the addition of methyl alaninate was complete in only 3 h, while the other α-amino esters required longer times. Then, the reacting mixtures were routinely stirred overnight; under these conditions, dipeptides **14c–19c** were isolated in yields ranging from 92% to 98% (Scheme 4). Aside from these results, X-ray analysis of crystals from dipeptide **17c** confirmed the absolute configuration of the resultant adducts. It should be also noted that the configuration of the α-amino ester was inconsequential and both (*S*) and (*R*)-valinate esters afforded similar yields (93% and 94%) of dipeptides **18c** and **19c** respectively.

Remarkably, the isolation of the aldol adduct turned out to be unnecessary and quenching the reaction of **1** and **a** with a solution of methyl alaninate hydrochloride and stirring the resultant mixture for 18 h in the presence of *i*-Pr_2NEt and imidazole gave 85% of the expected dipeptide **14a** in a one-pot reaction (Scheme 4).



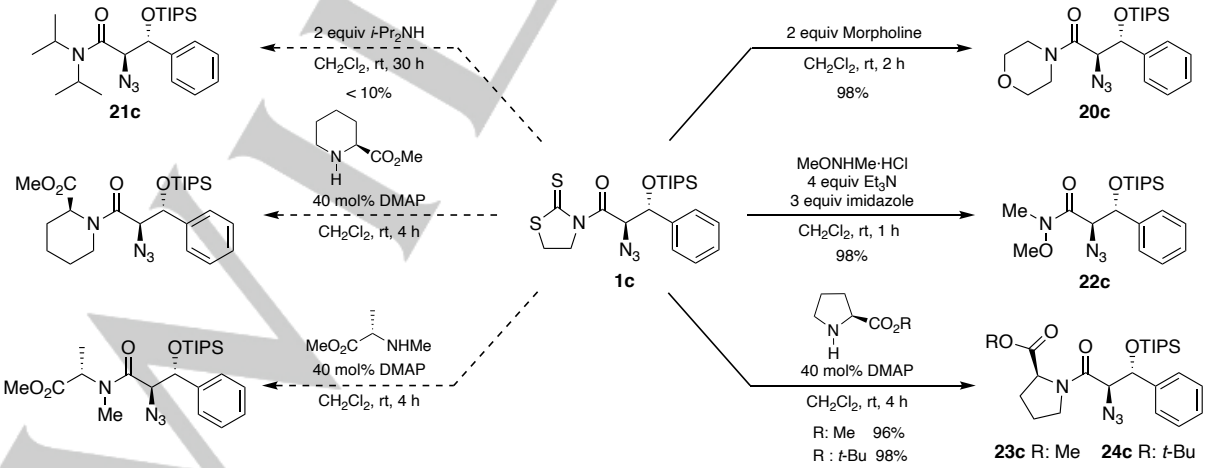
Scheme 3. Synthesis of enantiomerically pure derivatives.



Scheme 4. Synthesis of dipeptides from α-amino ester hydrochlorides.

Synthesis of amides from secondary amines

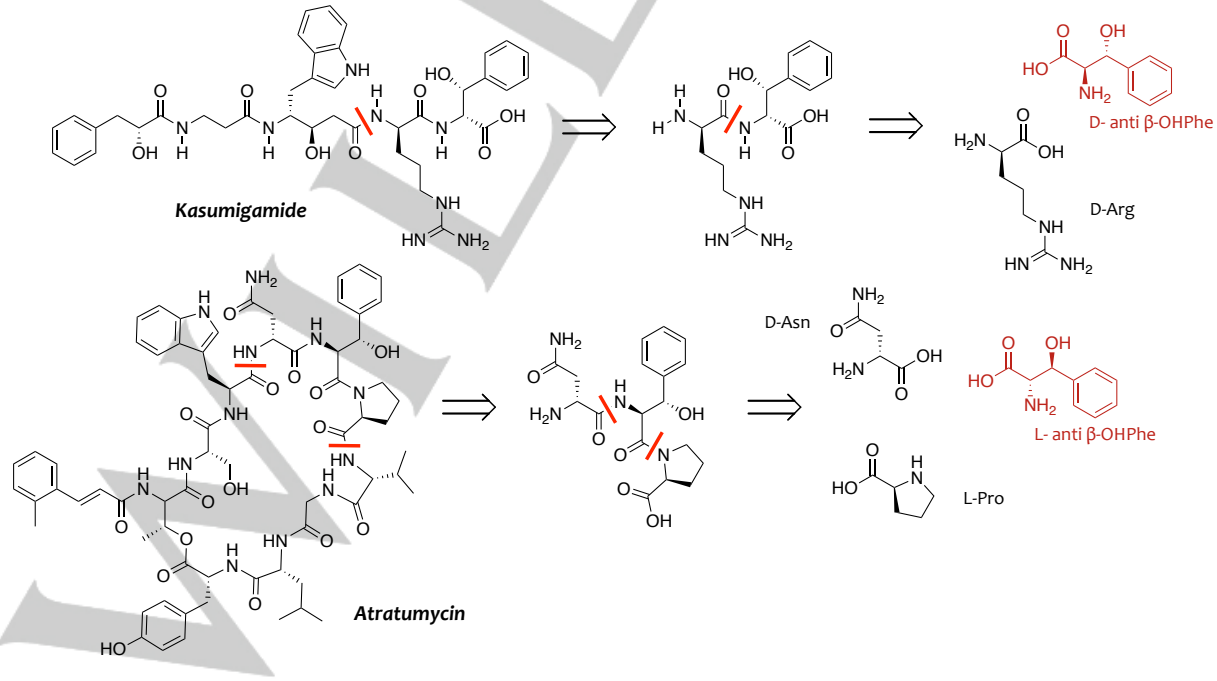
The successful construction of the amide bond using primary amines led us to explore parallel transformations involving secondary amines. In this occasion, the reaction turned out to be extremely sensitive to the steric hindrance. Preliminary experiments with morpholine and diisopropylamine showed that while the morpholine amide **20c** could be isolated in 98% yield after 2 h by simple treatment of **1c** with two equivalents of morpholine,[29] the *N*,*N*-diisopropylamide **21c** was obtained with a meagre yield under similar conditions (Scheme 5). Interestingly, the electronically poor but sterically unhindered MeONHMe furnished the Weinreb amide[30] **22c** in a quantitative yield provided that imidazole was present in the reaction mixture (Scheme 5), which evidences the key role played by the steric hindrance of the nucleophiles. In this context, further reactions with α-amino esters containing secondary amines were also troublesome. After a comprehensive analysis of the reaction of proline esters, it was found that starting free amines in the presence of DMAP provided better and more reproducible results and allowed the isolation of the corresponding peptides **23c** and **24c** in excellent yields (Scheme 5). Unfortunately, these conditions failed with esters derived from pipecolic acid and *N*-methylalanine and complex mixtures were obtained in both cases. These results prove the potential as well as the limitations of the thiazolidinethione removal with secondary amines.



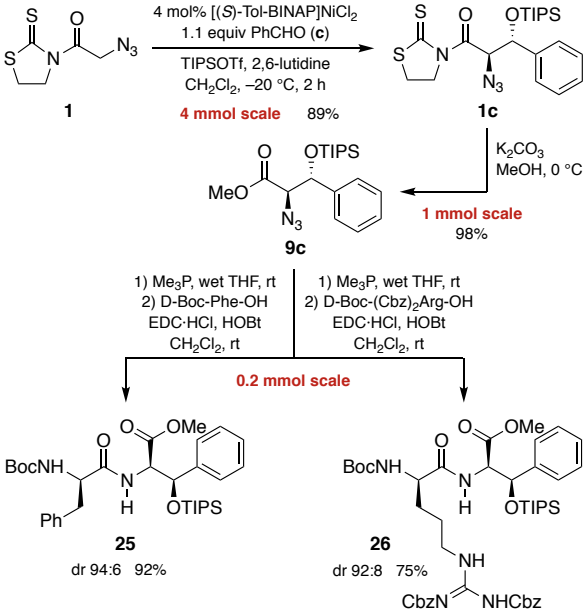
Scheme 5. Synthesis of amides from secondary amines.

Synthesis of peptidic fragments

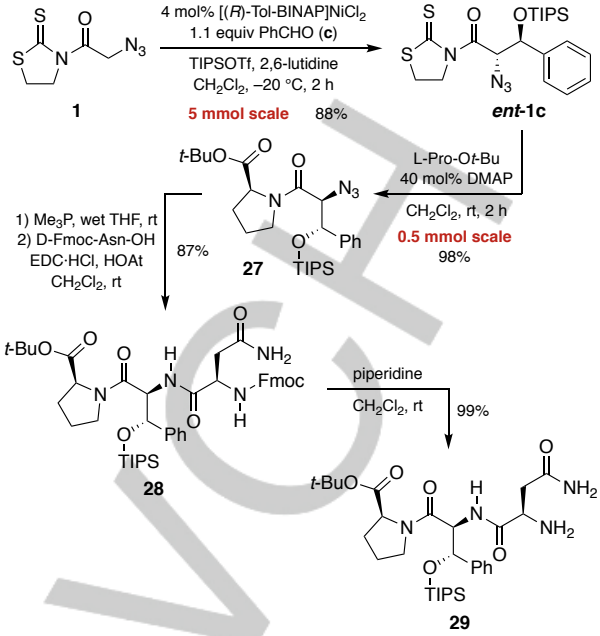
Once the main features of the method had been well defined, we tackled the synthesis of fragments of complex peptides like kasumigamide and atratumycin (Scheme 6). Kasumigamide is an antialgal tetrapeptide isolated from the freshwater cyanobacterium *Microcystis aeruginosa*,[31] whose structure has been recently revised by Kuranaga and Wakimoto.[32] In turn, atratumicyn is a cyclodepsipeptide recently isolated from the deep sea-derived bacterium *Streptomyces atratus* with significant antituberculosis and cytotoxic activity.[33] Both compounds contain an *anti* β-hydroxy-α-amino acid derived from D- and L-phenylalanine respectively, so we envisaged that the D-Arg-D-*anti*-β-OHPhe dipeptide and the D-Asn-L-*anti*-β-OHPhe-L-Pro tripeptide represented in Scheme 6 might be synthesized by merging our method and conventional peptide chemistry.[34]
Considering the need for large quantities of starting materials for the synthesis of the peptide fragments shown in Scheme 6, we first examined the gram scale aldol reaction of **1** (4 mmol) and benzaldehyde (**c**) in the presence of 4 mol% of [(*S*)-Tol-BINAP]$NiCl_2$. Remarkably, the results matched those previously attained and enantiomerically pure (dr 93:7, *ee* 99%) aldol adduct **1c** was isolated with an 89% yield at 4 mmol scale (Scheme 7). Next, the thiazolidinethione scaffold was successfully displaced in methanol, which provided α-azido-β-silyloxy ester **9c** in two steps from **1** and benzaldehyde (**c**) with an 86% overall yield. Finally, reduction of the azido group with Me_3P in wet THF under the conditions previously optimized (Scheme 3) followed by a standard coupling of the resultant amine with Boc-D-Phe-OH (EDC·HCl, HOBt) as a test reaction gave dipeptide **25** with a dr 94:6 and an excellent 92% yield (Scheme 7). Likewise, application of the same procedure to the fully protected D-arginine shown in Scheme 7 produced a slight epimerization (dr 92:8) but pure C-terminal dipeptide of kasumigamide **26** was finally isolated with a 75% yield.



Scheme 6. Retrosynthetic analysis of kasumigamide and atratumycin.



Scheme 7. Synthesis of dipeptides containing H-β-OTIPSPhe-OMe.



Scheme 8. Synthesis of a fully protected fragment of atrutamycin.

Beyond the successful completion of the synthesis of the dipeptide **26** embedded in kasumigamide, these studies proved that a straightforward access to dipeptides through the appropriate manipulation of the azido group of aldol adducts **1** was practicable. Taking advantage of such results and considering the thiazolidinethione capability to be displaced by α-amino esters for the construction of amide bonds (see Scheme 4 and Scheme 5), we next addressed the synthesis of the more challenging tripeptide D-Asn-L-*anti*-β-OHPhe-L-Pro shown in Scheme 6. In this case, [(*R*)-Tol-BINAP]$NiCl_2$-mediated gram-scale aldol reaction of **1** and benzaldehyde (**c**) afforded the desired α-azido-β-silyloxy adduct ***ent*-1c** with an 88% yield (Scheme 8). Then, treatment of ***ent*-1c** with L-Pro-O*t*-Bu gave amide **27** in a 98% yield as a 4:1 mixture of rotamers according to 1D and 2D NMR. Reduction of the azido group with Me_3P/H_2O yielded the desired amine as a 55:45 mixture of rotamers according to NMR studies, and the subsequent coupling with Fmoc-D-Asn-OH under standard conditions (EDC·HCl, HOAt) led to the fully protected tripeptide **28** in an 87% overall yield (Scheme 8). Finally, removal of the Fmoc protecting group gave the tripeptide **29** as an equimolar mixture of rotamers in a quantitative yield (Scheme 8).[35]

Theoretical studies

Once demonstrated the synthetic potential of the new method, a comprehensive computational study was carried out to account for the outstanding stereocontrol provided by the chiral nickel(II) enolate (see Supporting Information, SI-3, for details). Initially, we assessed the structure of the [(*S*)-Tol-BINAP]Ni(II) enolate from *N*-azidoacetyl-1,3-thiazolidine-2-thione. Several conformations of both the *S*,*O*-chelate and the thiazolidinone rings were optimized; the most stable is shown in Figure 1. Since the diamagnetic nature of the nickel complex was assumed, all compounds were calculated as singlet ground states. In agreement with this, the nickel atom presents a distorted square-planar environment (S_{SQ-4} = 3.7), further away from the tetrahedral one by continuous shape measures (78%). For instance, P-Ni-S and P-Ni-O opposite angles are 159° and 160°, respectively, influenced by the diphosphane bite angle (97°).[16,18c]

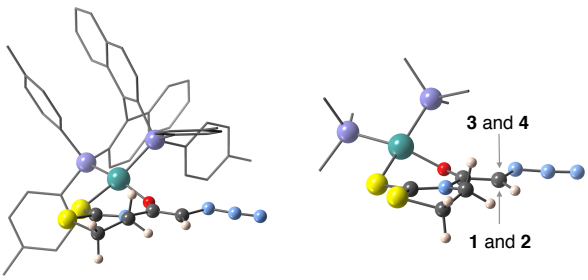


Figure 1. Optimized structure of the [(*S*)-Tol-BINAP]Ni(II) enolate from **1** (left). Detailed approaches of the electrophile to the enolate (right).

Then, we focused our attention on the reaction of the nickel(II) enolate shown in Figure 1 with an oxocarbenium intermediate arising from the coordination of a TIPS group to the carbonyl bond of *p*-methoxybenzaldehyde, [*i*-$Pr_3SiOCH(C_6H_4)$-4-OMe]$^+$. Since the carbon–carbon bond formation is kinetically controlled, four approaches were carefully examined. The relative energies

shown in Figure 2 indicated that the late transition state **TS-1** was the most preferred, in good agreement to the experimental data. Indeed, a 92:8 *anti/syn* diastereoselectivity was predicted in CH_2Cl_2 at –20 °C (and > 99:1 in gas phase) in close agreement with the experimental data (dr 95:5, see Scheme 1).

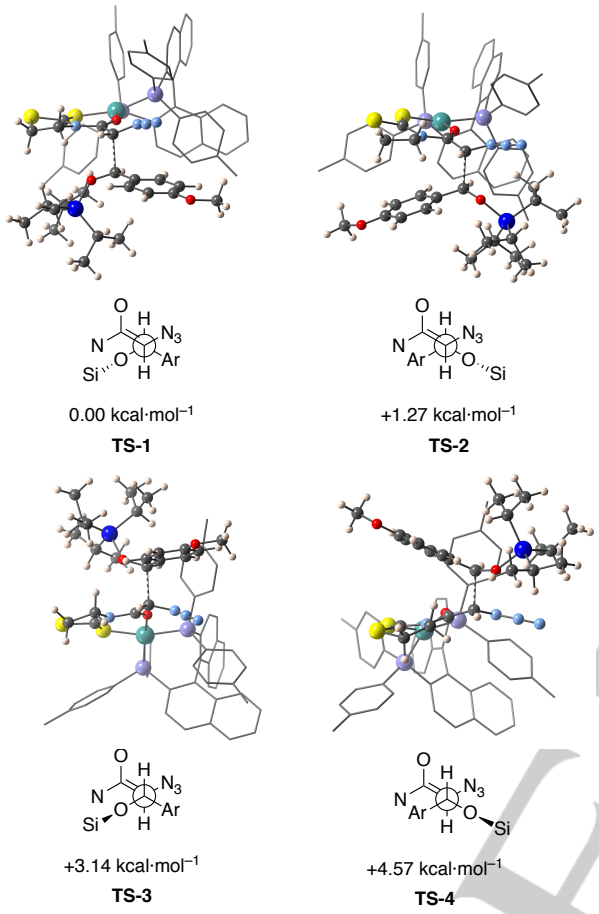
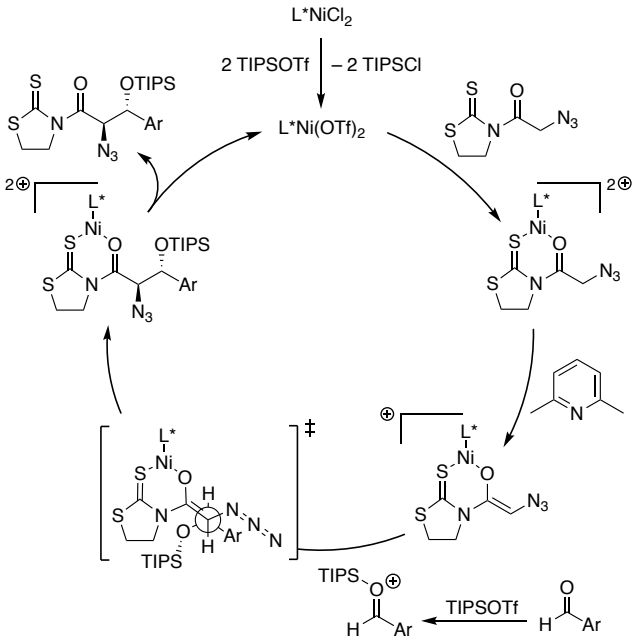


Figure 2. Accessible transition states for the reaction of **1** with **a**. The relative energies in CH_2Cl_2 are shown, taking the most stable one as reference.

The relative stability of the transition states **TS1–TS4** (Figure 2) is due to the steric bulk of the (*S*)-Tol-BINAP ligand and the TIPS group. Optimized nickel-complex shows ***π*** stacking interactions between a *p*-tolyl and naphthyl rings in the C···C range of 3.1–3.6 Å, while another *p*-tolyl group is aligned at ≈ 3.7 Å to the planar methine group. Consequently, the reaction proceeds through the external region far from the diphosphane ligand and is controlled by the interactions of the electrophile and the chelated enolate. In this context, **TS-1**, in which the TIPS–O=C moiety points towards the 1,3-thiazolidine-2-thione heterocycle and the 4-$MeOC_6H_4$ part is close to the lineal azide, is favored over the opposed **TS-2** in which the TIPS group faces the azide while the aromatic part is close to the 1,3-thiazolidine-2-thione scaffold. A detailed analysis of their molecular parameters shows that they have similar C···C distances (≈ 2.06 Å) and that only slightly different arrangements for the both methine groups (162° and 177° for **TS-1** and **TS-2**, respectively) or the conformation for dihedral angle in the carbonyl group (84° and 109°, respectively) have chemical significance, probably due to the combination of several weak interactions. In turn, opposite carbonium-approaching pathways through **TS-3** and **TS-4** are clearly unfavorable because of the changes needed to accommodate the electrophile, especially the repulsion with the *p*-tolyl group, as shown by a short C···C distance in **TS-4** (1.98 Å). The geometries around the nickel atom in all transition states remain more planar than the reactant and are always closer to square-planar than tetrahedral geometries.

To evaluate the influence of the azido group on the stereochemical outcome of the reaction, we examined analogous transition states in which the azide is replaced by a methyl group. Thus, the four transition states from *N*-propanoyl-1,3-thiazolidine-2-thione were fully reoptimized (see Supporting Information, SI-3). In this case, **TS-1-Me** became again preferred over **TS-2-Me** but the energy gap was reduced to just 1.0 kcal/mol, with **TS-3-Me** and **TS-4-Me** now localized at 2.3 and 2.5 kcal/mol higher in energy respectively. Therefore, the relative order is kept, but the propanoyl system suffers from erosion of stereocontrol due to the small differences of energy between **TS-1-Me** and **TS-2-Me** in comparison to the azide equivalent. Such results indicate that the enolate from **1** containing an azido group is particularly efficient, which accounts for the excellent stereocontrol observed in the aldol addition of **1** to aromatic aldehydes. Considering each pair of analogue structures (by side of approach, by interaction azide/methyl to methoxyphenyl or to TIPS fragments), we have not found a clear indicator to understand a single key factor determining such a difference. We just hypothesize that it might be the result of the combination of several geometric and electronic contributions. Although no significant changes in molecular geometries are appreciated, it is important to note that the C···C distances for the propanoyl-derivative are similar to a previous studied system,[16] but such distances are shortened in the *N*-azidoacetyl enolate by about 0.10 Å in all transition states, which indicates that it is a late transition state.

Overall, our calculations show the feasibility of the reaction and the accessibility of the major aldol adduct in full agreement with the experimental data. Therefore, in the basis of such calculations and the stereochemical outcome of the reaction, we are in a position to propose the mechanism for the reaction represented in Scheme 9. Initially, silyl triflate converts the nickel(II) chloride complex into the truly catalytic species.[36] Next the resultant highly electrophilic species is captured by **1** and the enhanced acidity of the Cα position of the resultant complex makes possible its deprotonation by the base. The delicate architecture unveiled by the calculations indicates that a naphthyl and a *p*-tolyl group hinder the *Si* π-face of the enolate and makes the approach of a putative oxocarbenium cation generated by the coordination of the silyl group to the carbonyl bond of the aldehyde to the *Re* π-face particularly favorable. Then, transition state **TS-1** is responsible for the observed *anti* stereochemistry of the aldol adducts. Eventually, decomplexation of the nickel(II) moiety from the final adduct allows a new catalytic cycle to restart with TON between 25–50.



Scheme 9. Proposed mechanism of the aldol reaction using L*: (*S*)-Tol-BINAP.

Conclusions

In summary, we have developed a high yielding method for the synthesis of enantiomerically pure *anti* β-aryl-β-hydroxy-α-amino acids. Such a method hinges on the direct and stereocontrolled aldol reaction of *N*-azidoacetyl-1,3-thiazolidine-2-thione with aromatic aldehydes catalyzed by a [Tol-BINAP]Ni(II) complex and the easy displacement of the heterocyclic scaffold by a broad scope of nucleophiles to efficiently produce a large number of enantiomerically pure derivatives. Importantly, the appropriate manipulation of the azido group permits the preparation of fragments of biologically active peptides in high yields. Besides such synthetic accomplishments, theoretical calculations indicate that the carbon–carbon bond formation, the crucial step of the process, evolves through an open transition state in which an oxocarbenium intermediate produced by the addition of the TIPSOTf to the aldehyde approaches to the less sterically hindered π face of a putative nickel(II) enolate; these studies unveil the clues of the method and lay the foundations for a broader approach to the enantiocontrolled construction of carbon–carbon bonds.

Experimental Section

General procedure for the Ni(II) catalyzed reaction with ArCHO

A solution of *N*-azidoacetyl thioimide **1**, an aromatic aldehyde (**a–m**, 1.1 mmol, 1.1 equiv), and [(*S*)-Tol-BINAP]$NiCl_2$ (2–6 mol%) in CH_2Cl_2 (2.5 mL) is treated with TIPSOTf (410 µL, 1.5 mmol, 1.5 equiv) and 2,6-lutidine (175 µL, 1.5 mmol, 1.5 equiv) at –20 °C under a N_2 atmosphere. The resultant solution is stirred for the appropriate time at –20 °C under a N_2 atmosphere. The reaction mixture is quenched with sat NH_4Cl (2.5 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with 0.5 M HCl (3 × 15 mL). dried (Na_2SO_4), filtered, and concentrated. The resulting brown oil is purified by column chromatography to afford the corresponding *anti* protected aldol adduct **1a–m** as a single enantiomer.

X-ray crystallographic data

Deposition numbers 2117967 (for **13i**) and 2149681 (for **17c**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

Computational methods

Multilayer ONIOM calculations were carried out using the Gaussian09. High quantum layer was defined by nickel, phosphorous and the *N*-azidoacetyl-1,3-thiazolidine-2-thione together the electrophile, while low layer includes organic frameworks of diphosphane ligand (excluding phosphorous atoms) was treated by universal field force (UFF). The hybrid density functional known as B3LYP was applied in the quantum layer, in which all-electron basis sets having triple- description with an polarization functions were used (TZVP). The geometries were fully optimized without restrictions and transition states were confirmed by vibrational analysis. Solvent effects were taken into account by PCM algorithm, keeping the optimized geometry for the gas phase.

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Keywords: Asymmetric synthesis • Aldol reaction • Catalysis • Nickel(II) complexes • Peptides

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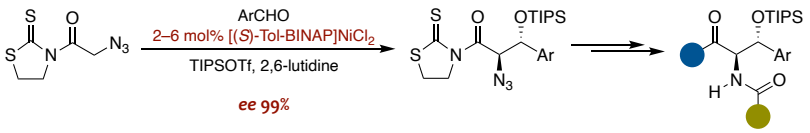

Enantiomerically pure *anti N*-β-aryl-β-silyloxy-α-azidoacetyl thioimides are efficiently prepared through a **direct** aldol reaction from *N*-azidoacetyl-1,3-thiazolidine-2-thione and a wide array of aromatic aldehydes **catalyzed** by 2–6 mol% [Tol-BINAP]Ni(II) complexes. The straightforward removal of the heterocyclic scaffold facilitates their conversion into a variety of chiral intermediates. Indeed, treatment of the resultant thioimides with α-amino ester hydrochlorides gives access to the corresponding dipeptides as well as the appropriate manipulation of the azido group yields peptidic fragments of kasumigamide and atrutamycin.