Direct, Enantioselective, and Nickel(II) Catalyzed Reactions of N-Azidoacetyl Thioimides with Trimethyl Orthoformate. A New Combined Methodology for the Rapid Synthesis of Lacosamide and Derivatives

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Abstract: A direct and highly enantioselective reaction of N-azidoacetyl-1,3-thiazolidine-2-thione with trimethyl orthoformate catalyzed by Tol-BINAPNiCl₂ in the presence of TESOTf and 2,6-lutidine is reported. The heterocyclic scaffold can be easily removed by addition of a wide array of amines to give the corresponding enantiomerically pure 2-azido-3,3-dimethoxypropanamides in high yields. Appropriate manipulation of the N-benzyl amide derivative provides an efficient access to the antiepileptic agent lacosamide through a new enantioselective C–C bond-forming process. DFT computational studies uncover clues for the understanding of the remarkable stereocontrol of the addition of a nickel(II) enolate to a putative oxocarbenium intermediate from trimethyl orthoformate.

Introduction

Despite the tremendous advancements in the asymmetric and catalytic construction of carbon–carbon bonds achieved during the last years, there is still a need for versatile methods that will enable the synthesis of a broad range of molecular architectures.[1–3] In this context, Evans[4] and Shibasaki[5] have convincingly established that both thiazolidinethione and azaindoline are suitable scaffolds to carry out direct and highly enantioselective aldol reactions catalyzed by chiral nickel(II) and copper(II) complexes respectively. Inspired by such studies, we have recently reported that simple N-propanoyl-1,3-thiazine-2-thione is a valuable platform from which to carry out direct and enantioselective carbon–carbon bond forming reactions with a plethora of cationic reagents using 1–5 mol% of robust and easy to handle [(R)-DTBM-SEGPHOS]NiCl₂.[6] Particularly, the direct addition to trimethyl orthoformate activated by TESOTf produces a single enantiomer of the corresponding adduct in 90% yield (Scheme 1A). Furthermore, former evidence on similar reactions based on chiral N-acyl 1,3-thiazolidine-2-thiones catalyzed by (Me₃P)₂NiCl indicated that the N-azidoacetyl counterpart was particularly suitable to provide highly stereocontrolled transformations (Scheme 1B),[7] which resulted in being especially appealing due to the well known instability of metal enolates from those substrates.[8–10] In view of such results, we envisaged that the azido group might be used as a masked amino group to synthesize enantiomerically pure α-amino acids or derivatives in a straightforward manner.[11] Thus, aiming to expand the scope of such processes, we launched a project to develop direct, enantioselective, and nickel(II) catalytic reactions of N-azidoacetyl thioimides with carbendenium and oxocarbenium intermediates.

We hereby describe our first results on the enantioselective addition of N-azidoacetyl thioimides to trimethyl orthoformate and the application of this method to the synthesis of lacosamide[12,13] and several related compounds as a proof of concept (Scheme 1C).
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N-propanoyl thioimides indicated that the 6-membered thiazinanethione was slightly more selective and active than the 5-membered thiazolidinethione counterpart.[8] Unfortunately, we were unable to synthesize the corresponding N-azidoacetyl-1,3-thiazinan-2-thione. The use of both azidoacetic acid and EDC as a coupling agent or azidoacetyl chloride and triethylamine at 0 °C under conditions previously described led to a complex mixture and no presence of the desired product. Conducting the reaction at –20 °C showed signs of product formation (the solution turned yellow as expected along with a new TLC spot) but when either warmed or quenched the solution turned black and the product could not be detected in the crude mixture. These results suggest that whilst the N-azidoacetyl thiazinanethione might be initially formed at –20 °C it is unstable at room temperature and therefore not viable.

For that reason, we moved to evaluate various 5-membered scaffolds. Five different heterocycles were chosen to assess the influence of the heteroatoms as well as geminal dimethyl groups in the direct addition to trimethyl orthoformate. Importantly, all candidates were acylated smoothly and the ensuing N-azidoacetyl derivatives 1–5 shown in Scheme 2 were completely stable and could be satisfactorily isolated in a pure form.

Then, we evaluated the reactivity of 1–5 with trimethyl orthoformate and commercially available (Me₆P₃)NiCl₂. Taking advantage of our former experience, TESOTf was chosen to both activate the nickel(II) complex via ligand exchange and to create the required oxocarbenium electrophile from the trimethyl orthoformate.[14] Then, the addition of N-azidoacetyl derivatives 1–5 to trimethyl orthoformate in the presence of 2,6-lutidine and TESOTf was initially tested with 2.5 mol% of achiral (Me₆P₃)NiCl₂ for a relatively short reaction time of 2.5 h to better grasp the differences between the scaffolds. The results are summarized in Table 1.

### Results and Discussion

**Direct and Ni(II) catalyzed addition of N-azidoacetyl thioimides to trimethyl orthoformate**

Our experience from the carbon–carbon bond forming reactions of N-propanoyl thioimides indicated that the 6-membered thiazinanethione was slightly more selective and active than the 5-membered thiazolidinethione counterpart.[8] Unfortunately, we were unable to synthesize the corresponding N-azidoacetyl-1,3-thiazinan-2-thione. The use of both azidoacetic acid and EDC as a coupling agent or azidoacetyl chloride and triethylamine at 0 °C under conditions previously described led to a complex mixture and no presence of the desired product. Conducting the reaction at –20 °C showed signs of product formation (the solution turned yellow as expected along with a new TLC spot) but when either warmed or quenched the solution turned black and the product could not be detected in the crude mixture. These results suggest that whilst the N-azidoacetyl thiazinanethione might be initially formed at –20 °C it is unstable at room temperature and therefore not viable.

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**Table 1. Direct and nickel(II) catalyzed addition of N-azidoacetyl derivatives to trimethyl orthoformate.**

| Entry | Starting Material | X | Y | R | Product | Yield [%] |
|-------|------------------|---|---|---|---------|-----------|
| 1     | 1                | O | O | H | 6       | < 5       |
| 2     | 2                | S | O | H | 7       | 39        |
| 3     | 3                | S | S | H | 8       | 61        |
| 4     | 4                | S | O | Me| 9       | < 10      |
| 5     | 5                | S | S | Me| 10      | < 10      |

[a] Isolated yield.

As expected, oxazolidinone 1 gave low conversion in the nickel catalyzed reaction and the starting material was recovered unaltered (entry 1 in Table 1), which further confirmed the need for an exocyclic sulphur atom (X = S in Table 1). The endocyclic sulfur (Y = S in Table 1) also held a key importance as the isolated yield from thiazolidinethione 3 was considerably higher than that attained from oxazolidinethione 2 (compare entry 2 and 3 in Table 1). This concurred with previous results making the sulphur–sulphur combination (X, Y = S in Table 1) superior.[14] Eventually, it was thought that the introduction of geminal dimethyl groups at C4 in 4 and 5 might improve the stereochemical outcome of the addition, but the conversion observed for both compounds was too low to be deemed useful (entry 4 and 5 in Table 1). Therefore, these results pointed to the N-azidoacetyl-1,3-thiazolidine-2-thione (3) as the most appropriate substrate to conduct the enantioselective trimethyl orthoformate reaction.

**Scheme 2. Synthesis of N-azidoacetyl scaffolds.**
Direct, enantioselective, and Ni(II) catalyzed addition of N-azidoacetyl-1,3-thiazolidine-2-thione to trimethyl orthoformate

Having chosen the scaffold from which to carry out the desired addition, we next screened the chiral ligands necessary to achieve the highest enantioselectivity. The ligands tested were the traditional DIOP as well as the BINAP and SEGPHOS families. The required chiral complexes L’NiCl₂ were prepared via the simple reflux of the chiral diphosphine ligand and NiCl₂ in acetonitrile. These were compared to the achiral (Me₂P)₂NiCl₂ and both the enantioselectivity and efficiency were evaluated, which is summarized in Table 2.

| Entry | L⁺ | Yield [%] | ee [%] |
|-------|----|-----------|--------|
| 1     | (Me₂P)₂ | 61 | – |
| 2     | (+)-DIOP | < 5 | nd |
| 3     | (R)-BINAP | 78 | 94 |
| 4     | (R)-Tol-BINAP | 80 | 96 |
| 5     | (R)-Xyl-BINAP | 72 | 92 |
| 6     | (R)-SEGPHOS | 61 | 88 |
| 7     | (R)-DTBM-SEGPHOS | 52 | 94 |

[a] Isolated yield. [b] Established by chiral HPLC analysis. [c] Full conversion. [d] Incomplete conversion, ca 85%.

Initially, DIOP gave almost no conversion and was therefore discarded (entry 2 in Table 2). The BINAP family performed much better in terms of activity and gave full conversion and good yields in all cases (entry 3–5 in Table 2). Importantly, the enantioselectivity was high, especially with Tol-BINAP, which gave an 80% yield (entry 4 in Table 2). Instead, the SEGPHOS family gave worse results with respect to conversion, yield, and selectivity (entry 6 and 7 in Table 2) and provided the desired adduct 8 in modest yields (52–61%) with a somewhat eroded stereocentre (ee 88–94%). The conclusion of the ligand screening left Tol-BINAP as the most selective diphosphine and highest yielding and therefore [(R)-Tol-BINAP]NiCl₂ was selected as the complex of choice for this reaction.

We next analyzed the catalytic loading and temperature to complete the optimization of the reaction conditions. As shown in Table 3, the catalyst loading could be decreased to 2 mol% without adverse effects; further reduction showed incomplete conversion and a decrease in the yield of 8. In turn, raising the temperature led to the formation of a side product resulting from the nucleophilic attack of the exocyclic sulphur atom of the thiazolidine thionone heterocycle on the oxocarbenium species, which leads to an S-methyl alkylation product. Interestingly, we had previously observed a similar reaction when working with the N-propanol thiazinanethione scaffold (see Scheme 1),[6] whose nucleophilic character was more pronounced and the reaction had to be conducted at –40 °C. Alongside this study, the (S)-C₂ configuration of the resultant adduct 8 was initially established through chemical correlation.

| Entry | n (mol%) | T (°C) | Yield [%] |
|-------|----------|--------|-----------|
| 1     | 3.0      | –20    | 81        |
| 2     | 2.5      | –20    | 80        |
| 3     | 2.0      | –20    | 82        |
| 4     | 1.5      | –20    | 69        |
| 5     | 2.0      | 0      | 59        |
| 6     | 2.5      | 20     | 53        |

[a] Isolated yield. [b] Established by chiral HPLC analysis. [c] Full conversion.

Once established the main framework of the reaction, we focused our attention to the synthesis of lacosamide (vide infra). Since exploratory studies indicated that the required configuration was the opposite to that provided by [(R)-Tol-BINAP]NiCl₂ we moved to use the (S) enantiomer. Then, we tackled the scale-up of the reaction and a comprehensive analysis of the experimental conditions. Importantly, the progressive increase of the reaction from 1 to 3, and up to 6 mmol of N-azidoacetyl thiazolidinethione 3 with trimethyl orthoformate in the presence of 2 mol% [(S)-Tol-BINAP]NiCl₂ showed that ent-8 could be isolated with an 85% yield and 96% ee at 6 mmol scale by stirring the reaction mixture at –20 °C for 2.5 h (Scheme 3).[15]

Mechanistically, this reaction may be occurring via an Sn2-like pathway, in which the TESOTf plays a key role.[15] Indeed, the silyl triflate activates the chiral nickel(II) complex, [(S)-Tol-BINAP]NiCl₂, to form the true catalytic species, [(S)-Tol-BINAP]Ni[OTf]₂, shown in Scheme 4. Complexation with the thioimide in the presence of 2,6-lutidine 85% ee 96% at 6 mmol scale by stirring the reaction mixture at –20 °C for 2.5 h (Scheme 3).[15]

Scheme 3. Direct and enantioselective addition of N-azidoacetyl thioimide 3 to trimethyl orthoformate catalyzed by [(S)-Tol-BINAP]NiCl₂.

Table 3. Direct and enantioselective addition of thioimide 3 to trimethyl orthoformate catalyzed by [(R)-Tol-BINAP]NiCl₂.

Table 2. Influence of nickel(II) ligands on the addition of N-azidoacetyl thioimide 3 to trimethyl orthoformate.

Table 3. Direct and enantioselective addition of thioimide 3 to trimethyl orthoformate catalyzed by [(R)-Tol-BINAP]NiCl₂.

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DFT Calculations

Taking into account the mechanism described in Scheme 4, we carried out computational studies for an accurate understanding of the outstanding stereocontrol provided by the Tol-BINAP catalyst. Assuming that the reaction proceeds through the addition of a nickel(II) Z-enolate of \([(R)-\text{Tol-BINAP}]\text{Ni(N-azidoacetyl-1,3-thiazolidine-2-thione)}^+\) (Figure 1) to an oxocarbenium intermediate from trimethyl orthoformate, a theoretical study has been carried out. Importantly, NMR spectra of \([(R)-\text{Tol-BINAP}]\text{NiCl}_2\) were an undeniable proof for its diamagnetic character and molecular geometries for the Z-enolate have therefore been calculated in the singlet ground state. Several conformations have been optimized for S,O-chelate and thiazolidinethione rings with a nickel environment closer to square-planar coordination, resulting in a range of 8 kcal mol\(^{-1}\) for Gibbs free energies in solution. Taking the most stable one, it shows an important deviation for the planarity evaluated by continuous shape measures (\(S_{\text{SQ}} = 3.7\)), and P–Ni–S and P–Ni–O angles are 159º and 160º, respectively, clearly influenced by the P–Ni–P bite angle of the diphosphine ligand (97º).

Figure 1. Addition of a Z-nickel(II) enolate to an oxocarbenium intermediate.
To understand the reaction between HC\((\text{OMe})_2\)^+ and \([((R)-\text{Tol-BINAPNi(N(N-azidooacetetyl-1,3-thiazolidine-2-thione)})]^+\), we have analyzed the corresponding energy profile. Since the electrophilic oxocarbenium can be approached by two \(\pi\)-faces of the nickel enolate (I and II), and it can also present three different relative orientations for the methoxy groups, six transition states were proposed and fully characterized. They are shown in Figure 1, together with the corresponding relative Gibbs free energies in dichloromethane solution. Several transition states present energies included within a range of less than 1 kcal·mol\(^{-1}\), and we could anticipate the reaction evolving by different pathways. In the three first transition states (I.a, I.b, and I.c), the electrophile is approached on the same side of the nickel(II) enolate from the N-azidooacetetyl-1,3-thiazolidine-2-thione giving the same stereoisomer with different orientations for the methyl groups, but their small differences suggest that the three pathways all participate in the reaction (calculated values are about 74, 16, and 7\%, respectively). However, the three transition states for the opposite side, and therefore the other enantiomer (II.a, II.b, and II.c), are higher in energy and their contributions clearly become smaller. According to the energetic distribution of the six transition states, estimation for the ratio of final products at \(-20^\circ\text{C}\) would be 97:3, in excellent agreement to experimental data (er 98:2). These results can be explained by the steric hindrance caused by the \((R)-\text{Tol-BINAP}\) diphosphine. The optimized conformation of the nickel-complex presents two \(\pi-\pi\) stacking interaction between p-toly and naphthyl aromatic rings (3.2–3.6 Å), whereas another p-toly substituent is aligned at \(-3.8\) Å to the planar methine group of the nickel-complex (see Supporting Information). This situation is also reproduced for other conformations of the reactant blocking only one \(\pi\)-face for reaction pathway (<3.5 kcal·mol\(^{-1}\)). Consequently, those transition states in which the oxocarbenium is approaching from the external region become more stable than those from the internal one by geometric requirements (I and II, respectively). In the first cases, geometries for nickel remain closer to reactant, while the latter becomes the most planar environment. Thus, the excellent stereocontrol observed for such a reaction hinges on the position of one of the p-toly substituents blocking the \(\text{Re}\ \pi\)-face of the nickel(II) Z-enolate. With a fully optimized procedure in hand and a complete understanding of the keys for the remarkable stereocontrol, the attention was then paid to the synthesis of lacosamide.

**Lacosamide**

**Retrosynthetic Analysis**

The development of new enantioselective carbon–carbon bond forming reactions from \(\text{N-azidoacetetyl thioimidies}\) may offer a lucrative route towards biologically \(\alpha\)-amino acid derivatives. One of such compounds is the antiepileptic agent lacosamide (Scheme 5). First synthesized in 1996, lacosamide\(^{[1]}\) and structurally related compounds show an important anticonvulsant activity\(^{[2]}\) for which they have recently received great attention.\(^{[3]}\) Despite such an interest, most of the synthetic approaches reported up to now rely on the appropriate treatment of \(\text{D-serine}\) or other starting materials from the chiral pool.\(^{[4]}\) Alternatively, a few syntheses involve kinetic resolution steps\(^{[5]}\) or are based on asymmetric reactions applied to substrates containing the required carbon backbone.\(^{[6]}\) However, none of them hinge on the enantioselective construction of the C2–C3 bond. Hence, seeing the potential for an enantioselective synthesis with the utility of easily accessible derivatives without any methodological changes, we envisaged that the retrosynthetic analysis depicted in Scheme 5, based on our newly developed orthof orm reaction and the easy removal of the thiazolidinethione scaffold\(^{[22,23]}\) might allow us to gain access to lacosamide and a wide array of structurally related compounds keeping the C3 methyl ether that is apparently essential to their antiepileptic activity.

**Previous Retrosynthetic Analyses**

| [\(\text{EiO}\)] | \(\text{MeO=CH=NH=O}\) | \(\text{HC(OMe)_2}^+\) |
|---|---|---|
| \(\text{HO}\) | \(\text{OH}\) | \(\text{MeOH}\) |
| \(\text{S} \) | \(\text{N} \) | \(\text{N} \) |
| \(\text{S} \) | \(\text{N} \) | \(\text{N} \) |
| \(\text{OH} \) | \(\text{HO}\) | \(\text{MeOH}\) |

**Our Approach: C2–C3 Constructive Retrosynthetic Analysis**

**Scheme 5. Retrosynthetic analyses of lacosamide.**

**Preliminary Studies**

With the asymmetric reaction fully optimized, we turned our attention toward the removal of the 1,3-thiazolidine-2-thione moiety with an amine to form the amide group present in lacosamide and its derivatives. We started the assessment using benzylamine as a model, which would form the required N-benzyl amide for lacosamide, in two differing routes. One would involve the displacement of the scaffold from the purified product with benzylamine, while an advanced one-pot process would be based on the quenching of the carbon–carbon bond forming reaction with benzylamine to directly furnish the desired amide (Scheme 6).

Both steps of the sequential approach proceeded smoothly (Scheme 6). Indeed, the desired N-benzylpropanamide 11 a was isolated with a 73% overall yield using a stoichiometric amount of benzylamine (a). In turn, the one-step process needed an excess of amine and a careful monitoring by TLC to make sure that the starting \(\text{N-azidoacetetyl thiazolidine}\) 3 had completely reacted before adding the amine. This is a key requirement. If full conversion is not achieved before the addition of the amine it can
lead to the formation of the corresponding N-azidoacetyl amide, which is difficult to separate from the product. Taking into account such premises, the one-pot process allowed an increase in the yield over the sequential process and produced benzylamide 11a with an 88% overall yield and ee 96% at a 3 mmol scale (Scheme 6).

Scheme 6. First steps towards lacosamide.

Six more amines (b–g) were then applied in this transformation and the results are summarized in Scheme 7. Different reaction times were required for each substrate; however, they only varied between 1 h and 3 h to reach full conversion. The methodology supported various primary amines, alkylic and aromatic variants both gave excellent results (11a–d, 11g); furthermore, the use of chiral amines provided the corresponding amides as a single diastereomer (11c and 11g). Secondary amines were also tolerated, with a slight decrease in the yield, and the pyrrolidine amide 11e as well as the morpholine amide 11f were both obtained with good yields. Furthermore, the displacement with a chiral amino ester derived from leucine afforded the diastereomerically pure peptidic product 11g with a remarkable 79% yield.

Scheme 7. Amide-like derivatives prepared by treatment of the reaction mixture with primary and secondary amines.

Importantly, X-ray analysis of crystals from amide 11c confirmed the configuration of the new Ca stereocenter (Figure 2).

Figure 2. X-Ray of amide 11c.

The reduction of the dimethyl acetal to the corresponding methyl ether with TiCl4 and Et3SiH was the next step in the synthetic pathway towards lacosamide. First, the reaction was examined using the benzylamide derivative 11a as a model. Low conversion was observed when using only 1.5 equivalents of both TiCl4 and Et3SiH (entry 1 in Table 4). Furthermore, it became clear that the reaction needed temperatures above 0 °C to function (compare entry 2–4 in Table 4). Therefore, the addition of 2.5 equivalents of TiCl4 and Et3SiH was tested via two routes. We found that the addition of an extra equivalent of both TiCl4 and Et3SiH after 4 h led to an increase in the conversion and yield (entry 5 in Table 4), while the initial use of 2.5 equivalents at the beginning of the reaction provided full conversion and a 57% yield (entry 6 in Table 4). Using these conditions, we were able to run this reaction on 9 mmol scale with a comparable yield (entry 7 in Table 4).

**Table 4. Acetal reduction of N-benzyl amide 11a**

| Entry | Equiv TiCl4 | Equiv Et3SiH | T (°C) | t (h) | Yield [%][a] | ee [%][b] |
|-------|-------------|--------------|--------|-------|-------------|-----------|
| 1     | 1.5         | 1.5          | –20    | 6     | < 5         | nd        |
| 2     | 1.5         | 1.5          | 0–20   | 16    | 5–16        | 5–96      |
| 3     | 2.0         | 2.0          | 0–20   | 16    | 27–41       | 27–41     |
| 4     | 2.0         | 2.0          | 0–20   | 16    | 27–41       | 27–41     |
| 5     | 1.5+1       | 20           | 4+12   | 46    | 46–61       | 46–61     |
| 6     | 2.5         | 2.5          | 20     | 16    | 57–76       | 57–76     |
| 7     | 2.5         | 2.5          | 20     | 16    | 54–76       | 54–76     |

[a] Isolated yield. [b] Established by chiral HPLC analysis. [c] Initial loading of 1.5 equiv of TiCl4 and Et3SiH followed by 1 equiv of both reagents 4 h later. [d] Addition at 9 mmol scale.

With the model compound optimized, we strove to expand the scope to the amides 11b–g. Unfortunately, the use of these reaction conditions on N-hexyl amide 11b led to incomplete conversion and the corresponding methyl ether 12b was isolated.
in 42% yield. Thus, we conducted a finetuning of the optimization to achieve a more general protocol. The use of 4 equivalents of TiCl₄ and Et₃SiH led to full conversion, but with a yield lower than expected (entry 1 in Table 5). This made us suspect that some of the product was not being liberated in the workup, possibly due to the formation of titanium complexes, which led us to scrutinize the quench of the reaction mixture. We found that the yield improved when the mixture was left stirring for 3.5 h after the quench (compare entry 1 and 2 in Table 5). Moreover, the use of NH₄F instead of NH₄Cl provided a 60% yield of product 12b after 3.5 h (entry 4 in Table 5); no further improvement was observed at longer times (compare entry 4 and 5 in Table 5).

| Table 5. Work-up of the reaction. |
|----------------------------------|
| Entry | Quenching reagent | t (h) | Yield of 12b [%] |
|-------|------------------|------|-----------------|
| 1     | sat NH₄Cl        | 0.15 | 42              |
| 2     | sat NH₄Cl        | 3.5  | 50              |
| 3     | 25% w/w NH₄F     | 0.5  | 47              |
| 4     | 25% w/w NH₄F     | 3.5  | 60              |
| 5     | 25% w/w NH₄F     | 7    | 57              |

[a] Stirring time after quench. [b] Isolated yield.

This advance combined with the use of four equivalents of TiCl₄ and Et₃SiH provided a general procedure for the reduction of the acetol that was applied to the remaining amides 11. Unfortunately, the morpholine amide 11f turned out to be unsuitable and gave a considerably lower yield of product 12f that was inseparable from the starting material (Scheme 8). In turn, the peptide fragment 11g provided the corresponding product 12g with a slightly lower yield of 46%, which can be attributed to its higher complexity. Apart from these cases, the tolerance of the reaction to these conditions was high and the majority of the β-methoxy amides 12 were isolated with yields of around 60%, as shown in Scheme 8.

The final step in the synthesis of lacosamide and its derivatives involved the conversion of the azido group into an acetamide using a Staudinger reaction and subsequent in situ acylation (Scheme 9). Such a transformation proved very reliable and lacosamide (13a) was isolated as planned with a yield of 86%. The application of such a one-pot reduction and protective sequence gave also excellent results when applied to other amides 12 and afforded the desired acetamido derivatives in 80–90% yields for all of the examples except 12g. This decrease is unsurprising owing to the complexity of the molecule compared to the other examples and so a yield of 70% is very respectable. Again, the tolerance for the method was wide, with the primary, secondary, alkyl and aryl amides all giving excellent yields.

Scheme 9. Azide reduction and acylation of amides 12.

This completed the synthesis of lacosamide as summarized in Scheme 10. The final route consists of five reactions in a three-step synthetic sequence with an overall yield of 43% and complete optical purity after recrystallization, making it a highly efficient process. Furthermore, due to the development of the adaptable methodology we were able to synthesize five other derivatives of lacosamide without any significant change in the reaction conditions. The number of derivatives able to be made by this method are considerably larger due to there being three points of divergence in the synthesis: the ortho ester addition, the amine displacement of the scaffold, and the protection of the Staudinger product. By changing either the ortho ester, amine, or acyl agent a new derivative can thus be synthesized with ease.
Conclusion

A direct, catalytic, and highly enantioselective addition of N-azidoacetoyl-1,3-thiazolidine-2-thione to trimethyl orthoformate has been reported. Interestingly, the reaction proceeds through a nickel(II) enolate from Tol-BINAPNICl2 in which the α-azido group remains stable, which provides facile access to a variety of enantioselectively pure α-amino acid derivatives. Theoretical calculations have uncovered the origin of such an outstanding stereocontrol. Furthermore, the thiazolidinethione scaffold may be easily removed by a wide array of amines to give enantiomerically pure 2-azido-3,3-dimethoxyamides through a simple reaction in which the heterocycle acts as a coupling reagent. The synthetic potential of such an approach is demonstrated by converting the N-benzyl amide into the antiepileptic agent lacosamide based on a novel C2–C3 bond forming reaction and the synthesis of several previously unsynthesized derivatives.

Experimental Section

General procedure for the Ni(II) catalyzed reaction with trimethyl orthoformate and in situ scaffold removal

A solution of 3 (606 mg, 3.0 mmol) and [(S)-Tol-BINAP]Cl2 (48 mg, 0.06 mmol, 2 mol%) in CH2Cl2 (7.5 mL) under N2 was cooled to −20 °C and trimethyl orthoformate (360 µL, 3.3 mmol), TESOTf (1.0 mL, 4.4 mmol), and 2,6-lutidine (520 µL, 4.5 mmol) were added dropwise after 1, 3, and 7 min respectively. The reaction mixture was stirred at −20 °C and after 2.5 h, or complete conversion by TLC, warmed to 0 °C, and the corresponding amine (9.0 mmol, 3 equiv) was slowly added. The resultant mixture was stirred for 10 min at 0 °C and then at room temperature for 0.5–3 h. It was quenched with sat NH4Cl (3 mL), diluted with H2O (30 mL), and extracted with CH2Cl2 (3 x 30 mL), and then with brine (30 mL). The organic layer was dried (Na2SO4), filtered, and concentrated. The resulting brown oil was purified by column chromatography to afford pure amides 11a–g.

X-ray crystallographic data

CCDC 1984006 contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

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Keywords: Asymmetric synthesis • C–C bond forming reactions • Catalysis • Lacosamide • Synthetic methods

Computational methods

ONIOM calculations were carried out using the Gaussian09 package. High quantum layer is defined by nickel, phosphorous and the N-azidoacetoyl-1,3-thiazolidine-2-thione together the electrophile in the reaction pathway, while low layer includes organic frameworks of diphosphine ligand (excluding phosphorous atoms) by treated by universal field force (UFF). The hybrid density functional known as B3LYP was applied. The all-electron basis sets having triple-ζ quality with an extra polarization function were used for all elements (TZVP). The geometries were fully optimized without restrictions and transition states were confirmed by vibrational analysis. Solvent effects of dichloromethane were taken into account by PCM algorithm, keeping the optimized geometry for the gas phase (single-point calculations). Continuous shape measures were calculated with the SHAPE program, which provides quantitative information of how much the environment is deviated from an ideal polyhedron.

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A direct, enantioselective, and catalytic approach to the synthesis of α-amino acids in which an achiral 1,3-thiazolidine-2-thione is used for the sake of attaining high yields is reported. Such a scaffold also acts as coupling reagent to give in a single step enantiomerically pure amide derivatives, which can then be converted into biologically active compounds as lacosamide in a rapid and straightforward manner.

\[
\begin{align*}
\text{S} & \xrightarrow{\text{HC(OOMe)}_2, 2 \text{ mol\% } [\text{S}-(\text{S})-\text{Tol-BINAP}]\text{NiCl}_2, \text{TESOTf, 2,6-lutidine}} \text{R}^1\text{NHR}^2
\end{align*}
\]

single step
\[\text{ee} \geq 96\%
\]

Lacosamide
\[\text{R}^1: \text{Bn} \quad \text{R}^2: \text{H}
\]