

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

Saul F. Teloxa,^[a] Stuart C. D. Kennington,^[a] Marc Camats,^[a] Pedro Romea,^{*,[a]} Fèlix Urpí,^{*,[a]} Gabriel Aullón,^[b] and Mercè Font-Bardia^[c]

Dedicated to Prof. Sergio Castillón

[a] S. F. Teloxa, S. C. D. Kennington, M. Camats, P. Romea, F. Urpí
Department of Inorganic and Organic Chemistry, Section of Organic Chemistry
Universitat de Barcelona
Carrer Martí i Franqués 1-11, 08028 Barcelona (Catalonia, Spain)
E-mail: pedro.romea@ub.edu; felix.urpi@ub.edu
Homepage: http://www.qo.ub.edu/grups/SSNP/en/qui_som_presentacio.html

[b] G. Aullón
Department of Inorganic and Organic Chemistry, Section of Inorganic Chemistry
Universitat de Barcelona
Carrer Martí i Franqués 1-11, 08028 Barcelona (Catalonia, Spain)

[c] M. Font-Bardia
X-Ray Diffraction Unity. CCiTUB
Universitat de Barcelona
Carrer Solé i Sabarís 1-3, 08028 Barcelona (Catalonia, Spain)

Supporting information for this article is given via a link at the end of the document.

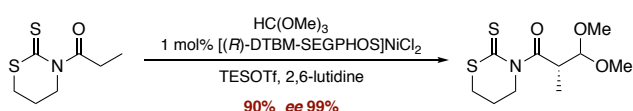
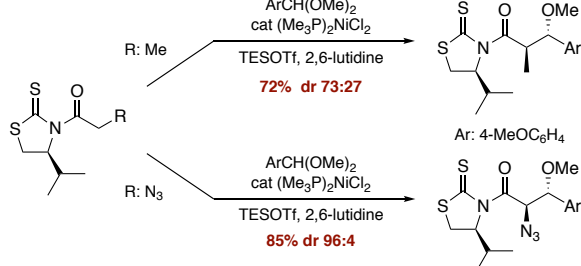
Abstract: A direct and highly enantioselective reaction of *N*-azidoacetyl-1,3-thiazolidine-2-thione with trimethyl orthoformate catalyzed by Tol-BINAPNiCl₂ in the presence of TESOTf and 2,6-lutidine is reported. The heterocyclic scaffold can be easily removed by addition of a wide array of amines to 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

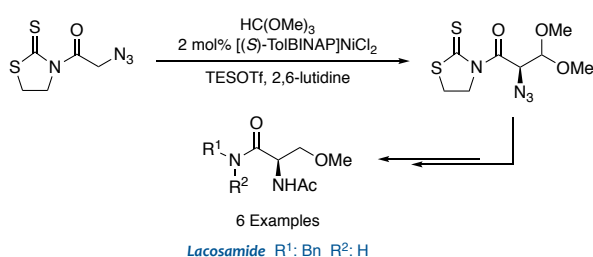
Despite the tremendous advancements in the asymmetric and catalytic construction of carbon–carbon bonds achieved during the last years, there is still a need for versatile methods that will enable the synthesis of a broad range of molecular architectures.^[1–3] In this context, Evans^[4] and Shibasaki^[5] 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(I) complexes respectively. Inspired by such studies, we have recently reported that simple *N*-propanoyl-1,3-thiazinane-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)₂NiCl₂ 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 carbenium 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).

A. Prior work^[6]B. Prior work^[7]

C. This work



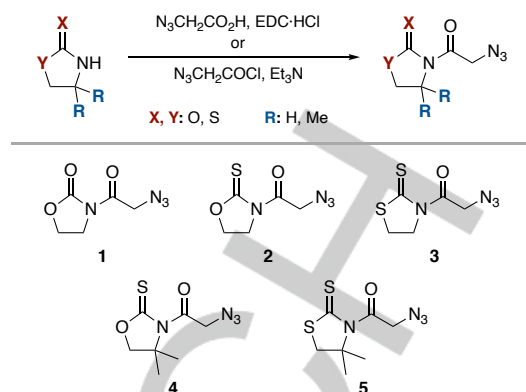
Scheme 1. Direct and stereoselective reactions from *N*-acyl thioimides catalyzed by nickel(II) complexes.

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.^[6] Unfortunately, we were unable to synthesize the corresponding *N*-azidoacetyl-1,3-thiazinane-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.



Scheme 2. Synthesis of *N*-azidoacetyl scaffolds.

Then, we evaluated the reactivity of **1–5** with trimethyl orthoformate and commercially available (Me₃P)₂NiCl₂. 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 (Me₃P)₂NiCl₂ 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.

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

Entry	Starting Material	X	Y	R	Product	Yield [%] ^[a]
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

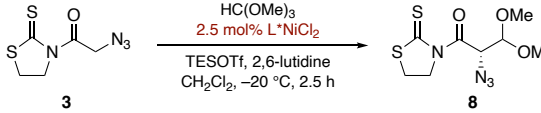
[a] Isolated yield.

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.

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^*NiCl_2 were prepared via the simple reflux of the chiral diphosphine ligand and $NiCl_2$ in acetonitrile. These were compared to the achiral $(Me_3P)_2NiCl_2$ and both the enantioselectivity and efficiency were evaluated, which is summarized in Table 2.

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

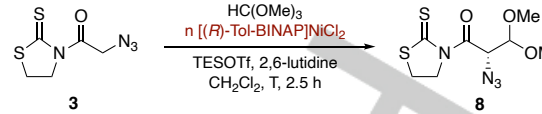
			
Entry	L^*	Yield [%] ^[a]	ee [%] ^[b]
1	$(Me_3P)_2$	61	–
2	(+)-DIOP	< 5	nd
3	(<i>R</i>)-BINAP	78 ^[c]	94
4	(<i>R</i>)-Tol-BINAP	80 ^[c]	96
5	(<i>R</i>)-Xyl-BINAP	72 ^[c]	92
6	(<i>R</i>)-SEGPHOS	61 ^[d]	88
7	(<i>R</i>)-DTBM-SEGPHOS	52 ^[d]	94

[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 stereocontrol (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] $NiCl_2$ was selected as the complex of choice for this reaction.

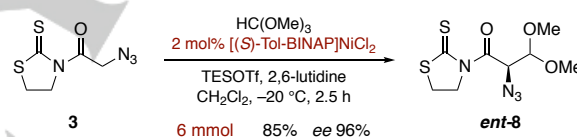
We next analyzed the catalytic loading and temperature to complete the optimization of the reaction conditions. As shown in Table 3, the catalyst loading could be decreased to 2 mol% without adverse effects; further reduction showed incomplete conversion and a decrease in the yield of **8**. In turn, raising the temperature led to the formation of a side product resulting from the nucleophilic attack of the exocyclic sulphur atom of the thiazolidinethione 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*-propanoyl thiazinanethione scaffold (see Scheme 1),^[6] whose nucleophilic character was more pronounced and the reaction had to be conducted at $-40\text{ }^\circ\text{C}$. Alongside this study, the (*S*)-C2 configuration of the resultant adduct **8** was initially established through chemical correlation.

Table 3. Direct and enantioselective addition of thioimide **3** to trimethyl orthoformate catalyzed by [(*R*)-TolBINAP] $NiCl_2$.

			
Entry	n (mol%)	T ($^\circ\text{C}$)	Yield [%] ^[a]
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

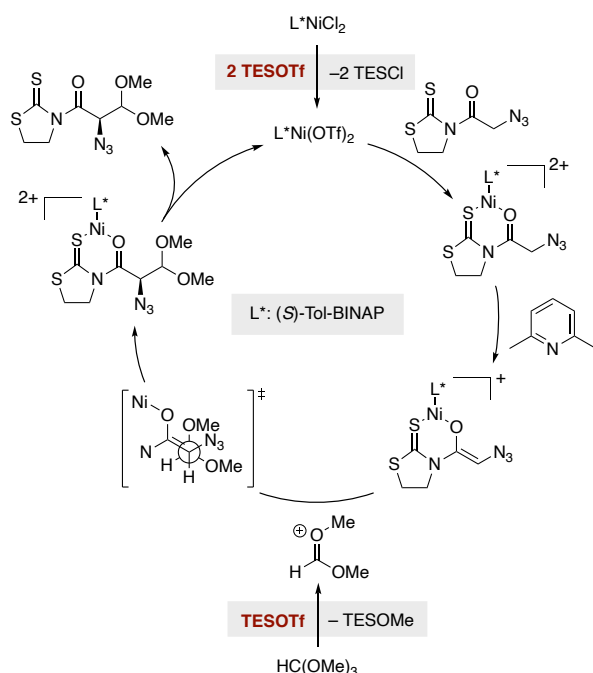
[a] Isolated yield.

Once established the main framework of the reaction, we focused our attention to the synthesis of iacosamide (vide infra). Since exploratory studies indicated that the required configuration was the opposite to that provided by [(*R*)-Tol-BINAP] $NiCl_2$ 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] $NiCl_2$ showed that **ent-8** could be isolated with an 85% yield and 96% ee at 6 mmol scale by stirring the reaction mixture at $-20\text{ }^\circ\text{C}$ 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] $NiCl_2$.

Mechanistically, this reaction may be occurring via an S_N1 -like pathway, in which the TESOTf plays a key role.^[16] Indeed, the silyl triflate activates the chiral nickel(II) complex, [(*S*)-Tol-BINAP] $NiCl_2$, 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 triggers the formation of a nickel(II) *Z*-enolate, able to add to an oxocarbenium intermediate, $HC(OMe)_2^+$, generated in situ by the reaction of TESOTf with methyl orthoformate. The approach of such an electrophile to the *Re* face of the enolate leads to the formation of the carbon–carbon bond and the further release of the desired adduct allows for the regeneration of the active nickel(II) complex to start a new catalytic cycle.^[17]



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 $[(R)\text{-Tol-BINAP}]\text{Ni}(N\text{-azidoacetyl-1,3-thiazolidine-2-thione})^+$ (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 ($S_{\text{SQ-4}} = 3.7$), and P–Ni–S and P–Ni–O angles are 159° and 160°, respectively, clearly influenced by the P–Ni–P bite angle of the diphosphine ligand (97°).

Scheme 4. Proposed mechanism for the reaction.

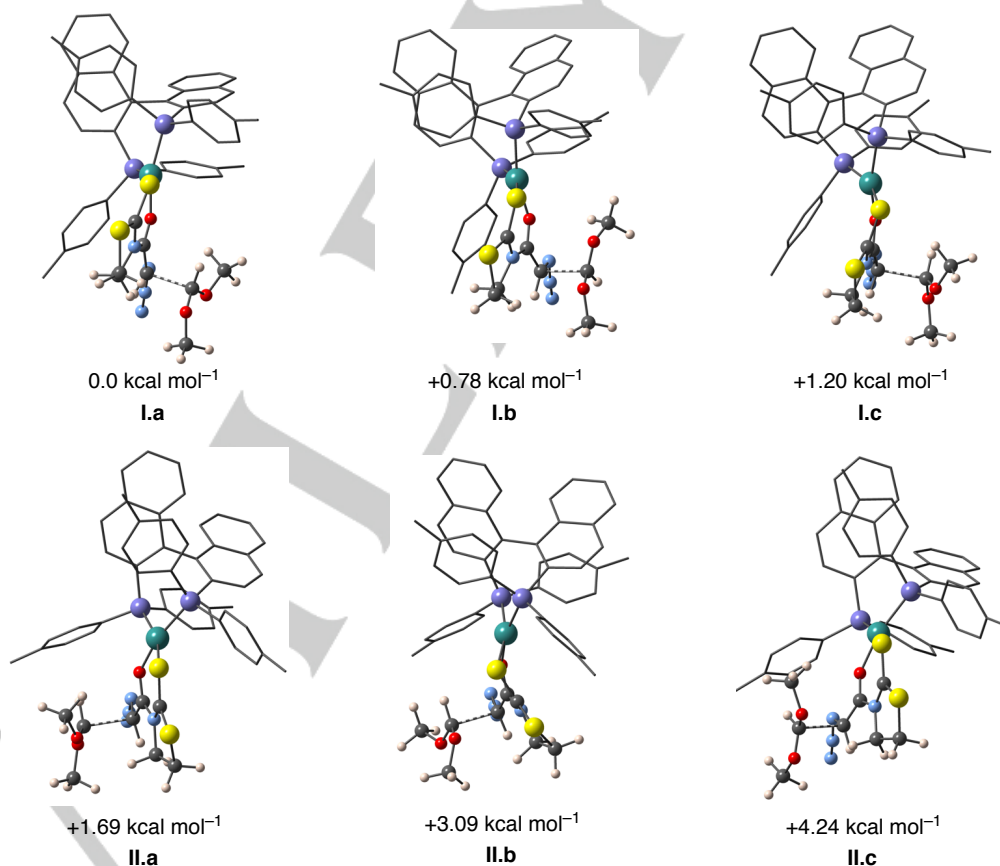


Figure 1. Addition of a Z-nickel(II) enolate to an oxocarbenium intermediate

FULL PAPER

To understand the reaction between HC(OMe)_2^+ and $[(R)\text{-Tol-BINAP}]\text{Ni}(N\text{-azidoacetyl-1,3-thiazolidine-2-thione})]^+$, we have analyzed the corresponding energy profile. Since the electrophilic oxocarbenium can be approached by two π -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 $1\text{ kcal}\cdot\text{mol}^{-1}$, 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*-azidoacetyl-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 $-20\text{ }^\circ\text{C}$ 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*)-Tol-BINAP diphosphine. The optimized conformation of the nickel-complex presents two π - π stacking interaction between *p*-tolyl and naphthyl aromatic rings (3.2–3.6 Å), whereas another *p*-tolyl substituent is aligned at $\sim 3.8\text{ Å}$ 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 π -face for reaction pathway ($< 3.5\text{ kcal}\cdot\text{mol}^{-1}$). 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*-tolyl substituents blocking the *Re* π -face of the nickel(II) Z-enolate.

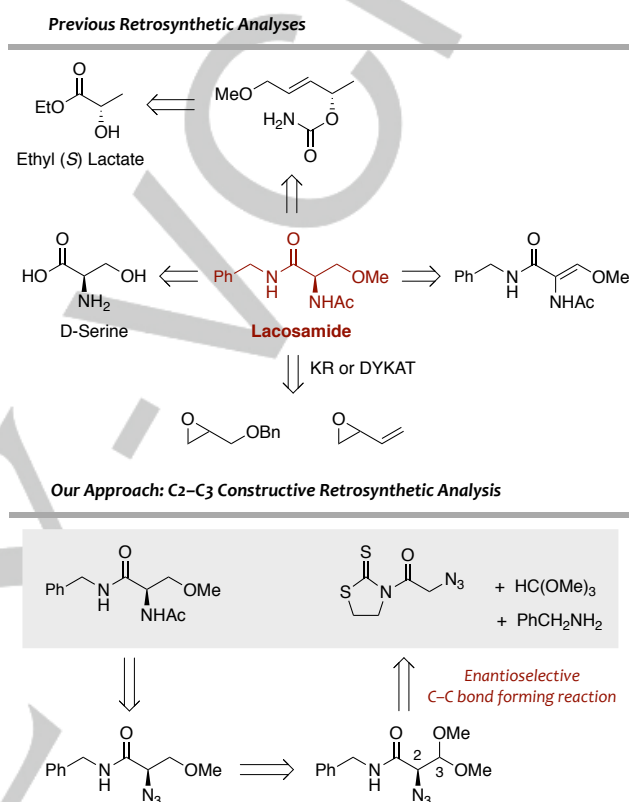
With a fully optimized procedure in hand and a complete understanding of the keys for the remarkable stereocontrol, the attention was then paid to the synthesis of lacosamide.

Lacosamide

Retrosynthetic Analysis

The development of new enantioselective carbon–carbon bond forming reactions from *N*-azidoacetyl thioimides may offer a lucrative route towards biologically active α -amino acid derivatives. One of such compounds is the antiepileptic agent lacosamide (Scheme 5). First synthesized in 1996, lacosamide^[12] and structurally related compounds show an important anticonvulsant activity^[18] for which they have recently received great attention.^[13] Despite such an interest, most of the synthetic approaches reported up to now rely on the appropriate treatment of D-serine or other starting materials from the chiral pool.^[18,19] Alternatively, a few syntheses involve kinetic resolution steps^[20] or are based on asymmetric reactions applied to substrates containing the required carbon backbone.^[21] 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 orthoformate 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.



Scheme 5. Retrosynthetic analyses of lacosamide.

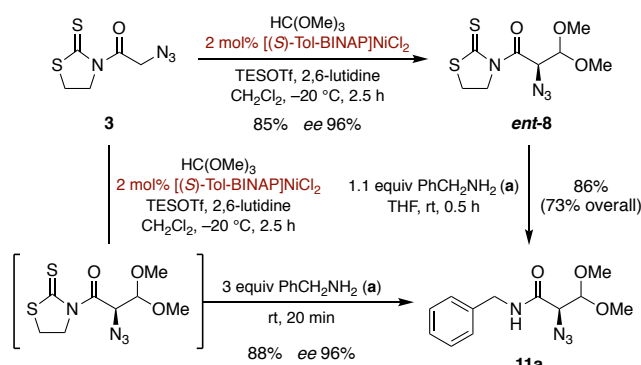
Preliminary Studies

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 **11a** 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 *N*-azidoacetyl 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

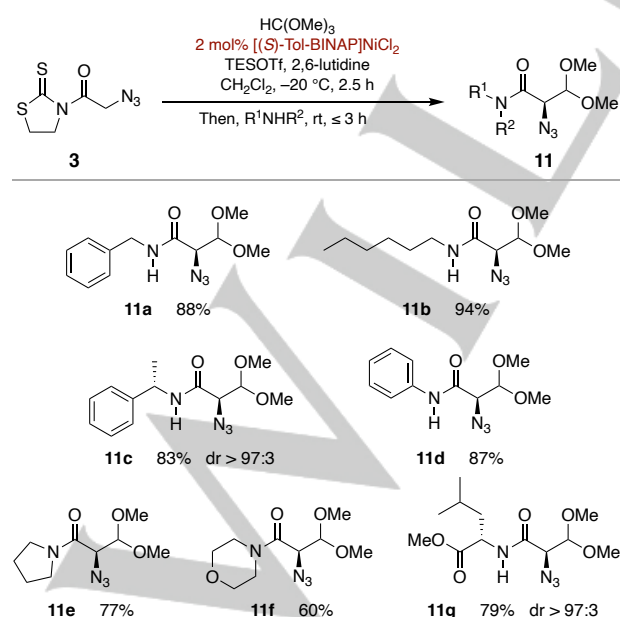
FULL PAPER

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).



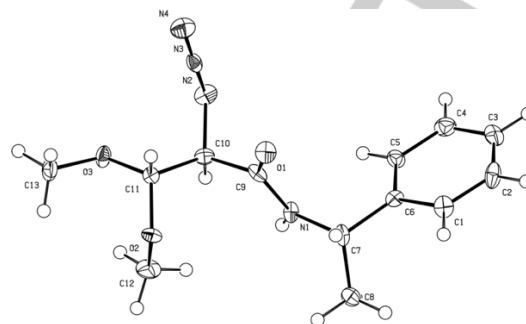
Scheme 6. First steps towards lacosamide.

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, alkyl 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 C α stereocenter (Figure 2).



FULL PAPER

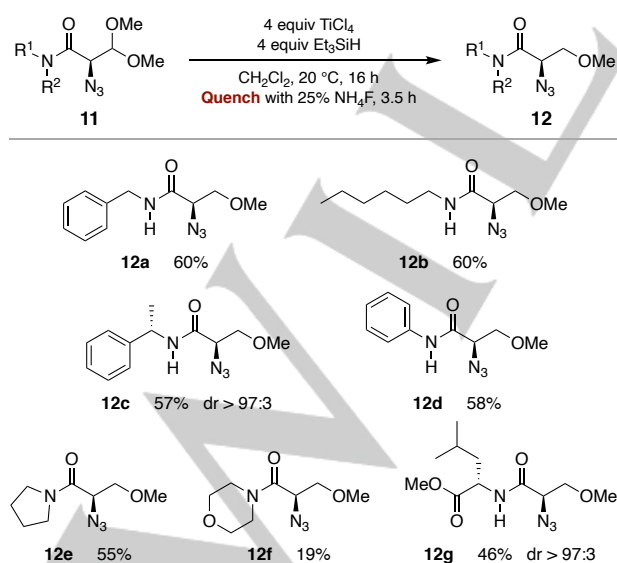
in 42% yield. Thus, we conducted a finetuning of the optimization to achieve a more general protocol. The use of 4 equivalents of TiCl_4 and Et_3SiH led to full conversion, but with a yield lower than expected (entry 1 in Table 5). This made us suspect that some of the product was not being liberated in the workup, possibly due to the formation of titanium complexes, which led us to scrutinize the quench of the reaction mixture.^[26] 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 NH_4F instead of NH_4Cl 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	<i>t</i> (h) [a]	Yield of 12b [%] [b]
1	sat NH_4Cl	0.15	42
2	sat NH_4Cl	3.5	50
3	25% w/w NH_4F	0.5	47
4	25% w/w NH_4F	3.5	60
5	25% w/w NH_4F	7	57

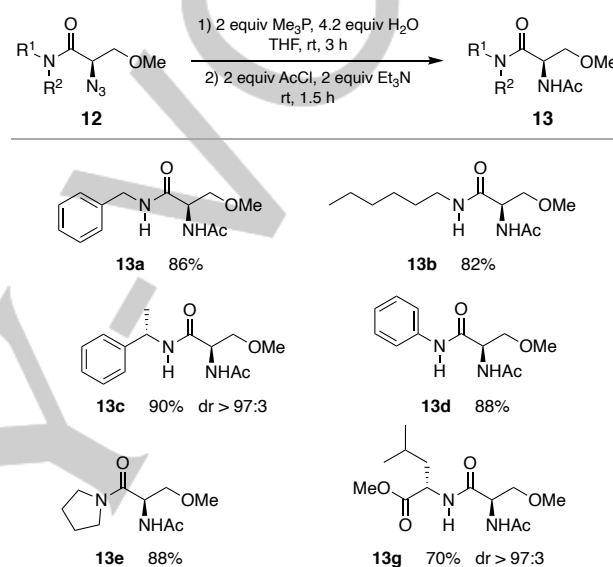
[a] Stirring time after quench. [b] Isolated yield.

This advance combined with the use of four equivalents of TiCl_4 and Et_3SiH provided a general procedure for the reduction of the acetal 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.



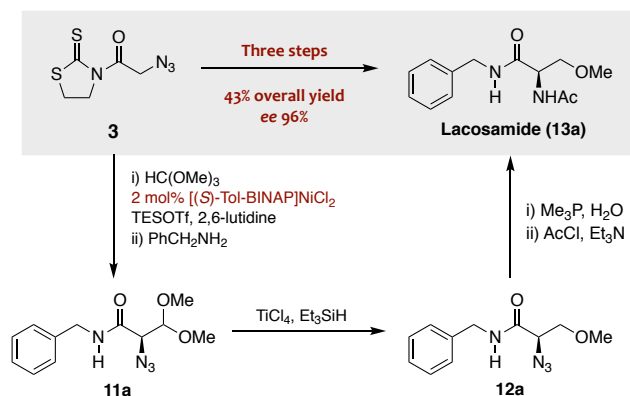
Scheme 8. Acetal reduction of amides **11**.

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).^[27] 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.



Scheme 10. Lacosamide synthesis.

Conclusion

A direct, catalytic, and highly enantioselective addition of *N*-azidoacetyl-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 enantiomerically 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]NiCl₂ (48 mg, 0.06 mmol, 2 mol%) in CH₂Cl₂ (7.5 mL) under N₂ was cooled to –20 °C and trimethyl orthoformate (360 μ L, 3.3 mmol), TESOTf (1.0 mL, 4.4 mmol), and 2,6-lutidine (520 μ L, 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 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.

Computational methods

ONIOM calculations were carried out using the Gaussian09 package.^[28] High quantum layer is defined by nickel, phosphorous and the *N*-azidoacetyl-1,3-thiazolidine-2-thione together the electrophile in the reaction pathway, while low layer includes organic frameworks of diphosphane ligand (excluding phosphorous atoms) by treated by universal field force (UFF).^[29] The hybrid density functional known as B3LYP was applied.^[30] The all-electron basis sets having triple- ζ quality with an extra polarization function were used for all elements (TZVP).^[31] 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,^[32] keeping the optimized geometry for the gas phase (single-point calculations).

Continuous shape measures were calculated with the SHAPE program,^[33] that provides quantitative information of how much the environment is deviated from an ideal polyhedron.

Acknowledgements

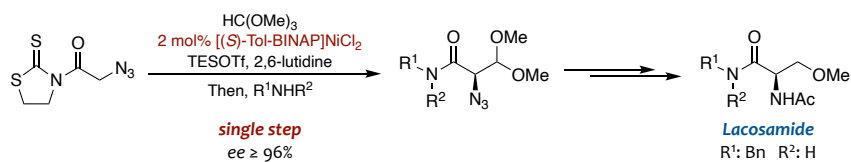
Financial support from the Spanish Ministerio de Ciencia, Innovación y Universidades (MCIU)/Agencia Estatal de Investigación (AEI)/Fondo Europeo de Desarrollo Regional (FEDER, UE) (Grant No. CTQ2015-65756-P, Grant No. PGC2018-094311-B-I00, and Grant No. PGC2018-093863-B-C21), and the Generalitat de Catalunya (2017SGR 271 and 2017SGR 1289) as well as doctorate studentships to S. F. T. (CONACYT–México, Grant Number 438357) and S. C. D. K. (FI, Generalitat de Catalunya).

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

- [1] a) E. M. Carreira, L. Kvaerno in *Classics in Stereoselective Synthesis*, Wiley-VCH, Weinheim, **2009**; b) P. J. Walsh, M. C. Kozlowski in *Fundamentals in Asymmetric Catalysis*, University Science Books, Sausalito, **2009**.
- [2] a) E. M. Carreira, *Chem. Rev.* **2015**, *115*, 8945–8945; b) E. Keinan, D. Pappo, *Isr. J. Chem.* **2018**, *58*, 7–10.
- [3] L. W. Hernandez, D. Sarlah, *Chem. Eur. J.* **2019**, *25*, 13248–13270.
- [4] a) D. A. Evans, C. W. Downey, J. L. Hubbs, *J. Am. Chem. Soc.* **2003**, *125*, 8706–8707; b) D. A. Evans, R. J. Thomson, *J. Am. Chem. Soc.* **2005**, *127*, 10506–10507.
- [5] N. Kumagai, M. Shibasaki, *Synthesis* **2019**, *51*, 185–193.
- [6] S. C. D. Kennington, A. J. Taylor, P. Romea, F. Urpí, G. Aullón, M. Font-Bardia, L. Ferré, J. Rodrigalvarez, *Org. Lett.* **2019**, *21*, 305–309.
- [7] a) J. Fernández-Valparís, J. M. Romo, P. Romea, F. Urpí, H. Kowalski, M. Font-Bardia, *Org. Lett.* **2015**, *17*, 3540–3543; b) J. Fernández-Valparís, P. Romea, F. Urpí, M. Font-Bardia, *Org. Lett.* **2017**, *19*, 6400–6403.
- [8] For a first report of a stoichiometric Ti-mediated aldol reaction from a chiral *N*-azidoacetyl thiazolidinethione, see: J. Patel, G. Clavé, P.-Y. Renard, X. Franck, *Angew. Chem. Int. Ed.* **2008**, *47*, 4224–4227; *Angew. Chem.* **2008**, *120*, 4292–4295.
- [9] For direct and enantioselective C–C bond-forming reactions from α -azido 7-azaindolylacetamide catalyzed by chiral copper(I) complexes, see: a) K. Weidner, Z. Sun, N. Kumagai, M. Shibasaki, *Angew. Chem. Int. Ed.* **2015**, *54*, 6236–6240; *Angew. Chem.* **2015**, *127*, 6334–6338; b) Z. Sun, K. Weidner, N. Kumagai, M. Shibasaki, *Chem. Eur. J.* **2015**, *21*, 17574–17577; c) H. Noda, F. Amemiya, K. Weidner, N. Kumagai, M. Shibasaki, *Chem. Sci.* **2017**, *8*, 3260–3269.
- [10] For an example of organocatalytic aldol reaction from α -azidoacetone, see: A. Martínez-Castañeda, K. Kedziora, I. Lavandera, H. Rodríguez-Solla, C. Concellón, V. del Amo, *Chem. Commun.* **2014**, *50*, 2598–2600.

- [11] For a proof of the scope of such a proposal using a chiral thiazolidinethione, see: J. Fernández-Valparis, P. Romea, F. Urpí, *Eur. J. Org. Chem.* **2019**, 2745–2752.
- [12] Lacosamide was first reported as a potent anticonvulsant drug, see: D. Choi, J. P. Stables, H. Kohn, *J. Med. Chem.* **1996**, 39, 1907–1916.
- [13] For a recent overview on the synthesis of (*R*)-lacosamide, see: E. K. Aratikla, A. K. Bhattacharya, *Org. Process Res. Dev.* **2020**, 24, 17–24.
- [14] J. M. Romo, E. Gálvez, I. Nubiola, P. Romea, F. Urpí, M. Kindred, *Adv. Synth. Catal.* **2013**, 355, 2781–2786.
- [15] The reaction at 6 mmol scale required a longer time (5 h) to get a yield of 85%.
- [16] For the key role of R_3SiOTf in the conversion of nickel(II) chlorides into the corresponding triflates, see: a) T. Suzuki, Y. Hamashima, M. Sodeoka, *Angew. Chem. Int. Ed.* **2007**, 46, 5435–5439; *Angew. Chem.* **2007**, 119, 5531–5535; b) Y. Hamashima, T. Nagi, R. Shimizu, T. Tsuchimoto, M. Sodeoka, *Eur. J. Org. Chem.* **2011**, 3675–3678.
- [17] Similar mechanistic schemes have previously been proposed, see References 4, 6, and 7.
- [18] a) S. V. Andurkar, J. P. Stables, H. Kohn, *Tetrahedron: Asymmetry* **1998**, 9, 3841–3854; b) S. V. Andurkar, J. P. Stables, H. Kohn, *Bioorg. Med. Chem.* **1999**, 7, 2381–2389; c) P. Morieux, J. P. Stables, H. Kohn, *Bioorg. Med. Chem.* **2008**, 16, 8968–8975; d) C. Salomé, E. Salomé-Grosjean, K. D. Park, P. Morieux, R. Swendiman, E. DeMarco, J. P. Stables, H. Kohn, *J. Med. Chem.* **2010**, 53, 1288–1305.
- [19] a) S. Stecko, *J. Org. Chem.* **2014**, 79, 6342–6346; b) E. K. Aratikla, A. K. Bhattacharya, *Tetrahedron Lett.* **2015**, 56, 5802–5803; c) H. Jeong, N. N. Yadav, H.-J. Ha, *Synthesis* **2017**, 49, 1264–1272; d) A. Yang, F. Hu, Z. Li, M. Chen, J. Cai, L. Wang, T. Zhang, C. Zhao, F. Zhang, *Org. Process Res. Dev.* **2019**, 23, 818–824; e) M.-D. Chen, A.-J. Yang, Z. Li, F.-F. Hu, J.-T. Yang, S.-H. Gao, F.-L. Zhang, C.-J. Zhao, *ACS Omega* **2019**, 4, 6546–6550.
- [20] a) M. Muthukrishnan, M. Mujahid, M. Sasikumar, P. Mujumdar, *Tetrahedron: Asymmetry* **2011**, 22, 1353–1357; b) Z. Y. Wang, L. S. Xu, J. Z. Liu, H. J. Zhang, J. Ghao, Q. Liu, Q. C. Jiao, *Chem. Res. Chinese Univ.* **2012**, 28, 833–836; c) Y. Garg, S. K. Pandey, *J. Org. Chem.* **2015**, 80, 4201–4203.
- [21] a) P. Etayo, J. L. Núñez-Rico, A. Vidal-Ferran, *Organometallics* **2011**, 30, 6718–6725; b) S. B. Wadavrao, A. Narikimalli, A. V. Narsaiah, *Synthesis* **2013**, 45, 3383–3386; c) H. Wehlan, J. Oehme, A. Schäfer, K. Rossen, *Org. Process Res. Dev.* **2015**, 19, 1980–1986.
- [22] Chiral thiazolidinethiones were introduced and identified as easily removable chiral auxiliaries in asymmetric synthesis by Nagao and Fujita, see: Y. Nagao, W. M. Dai, M. Ochiai, S. Tsukagoshi, E. Fujita, *J. Org. Chem.* **1990**, 55, 1148–1156.
- [23] For the removal of thiazolidinethione chiral auxiliaries, see: a) A. Cosp, P. Romea, P. Talavera, F. Urpí, J. Vilarrasa, M. Font-Bardia, X. Solans, *Org. Lett.* **2001**, 3, 615–617; b) I. Larrosa, P. Romea, F. Urpí, D. Balsells, J. Vilarrasa, M. Font-Bardia, X. Solans, *Org. Lett.* **2002**, 4, 4651–4654; c) M. T. Crimmins, A. M. R. Dechert, *Org. Lett.* **2009**, 11, 1635–1638; d) T. J. Harrison, S. Ho, J. L. Leighton, *J. Am. Chem. Soc.* **2011**, 133, 7308–7311.
- [24] For an overview on organosilane-mediated reductions, see: G. L. Larson, J. L. Fry, *Org. React.* **2008**, 71, 1–737.
- [25] For classical examples on the reduction of acetals and related groups with $TiCl_4/Et_3SiH$, see: a) M. D. Lewis, J. K. Cha, Y. Kishi, *J. Am. Chem. Soc.* **1982**, 104, 4976–4978; b) A. Mori, K. Ishihara, H. Yamamoto, *Tetrahedron Lett.* **1986**, 27, 987–990; c) J. A. Robl, M. P. Cimarusti, L. M. Simpkins, H. N. Weller, Y. Y. Pan, M. Malley, J. D. DiMarco, *J. Am. Chem. Soc.* **1994**, 116, 2348–2355; d) A. I. Meyers, M. A. Tschantz, G. P. Brengel, *J. Org. Chem.* **1995**, 60, 4359–4362.
- [26] For the use of NH_4F to quench reactions involving titanium salts, see: a) M. Brenner, D. Seebach, *Helv. Chim. Acta* **1999**, 82, 2365–2379; b) A. Gómez-Palomino, A. Barrio, P. García-Lorente, P. Romea, F. Urpí, M. Font-Bardia, *Eur. J. Org. Chem.* **2017**, 5776–5784.
- [27] Y. G. Gololobov, L. F. Kasukhin, *Tetrahedron* **1992**, 48, 1353–1406.
- [28] M. J. Frisch *et al.*, *Gaussian 09 (Revision B. 1)*. Gaussian Inc.: Wallingford CT 2010.
- [29] a) F. Maseras, K. Morokuma, *J. Comput. Chem.* **1995**, 16, 1170–1179; b) S. Dapprich, I. Komáromi, K. S. Byun, K. Morokuma, M. J. Frisch, *J. Mol. Struct.–Theochem.* **1999**, 461–462, 1–21.
- [30] a) A. D. Becke, *J. Chem. Phys.* **1993**, 98, 5648–5652; b) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, 37, 785–789.
- [31] A. Schäfer, C. Huber, R. Ahlrichs, *J. Chem. Phys.* **1994**, 100, 5829–5835.
- [32] J. Tomasi, B. Mennucci, R. Cammi, *Chem. Rev.* **2005**, 105, 2999–3094.
- [33] M. Llunell, D. Casanova, J. Cirera, P. Alemany, S. Alvarez, *SHAPE (versión 2.0)*, Barcelona, **2010**.

Entry for the Table of Contents



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.