Direct and Asymmetric Nickel(II) Catalyzed Construction of Carbon–Carbon Bonds from N-Acyl Thiazinanethiones

Stuart C. D. Kennington,† Adam J. Taylor,‡ Pedro Romea,*‡ Felìx Urpí,*† Gabriel Aullón,‡ Mercè Font-Bardia,§ Laura Ferrè,† and Jesus Rodríguez-Vázquez†,

† Department of Inorganic and Organic Chemistry, Section of Organic Chemistry, and Institute of Biomedicine (IBUB), University of Barcelona. Carrer Martí i Franquès 1-11, 08028 Barcelona, Catalonia, Spain
‡ Department of Inorganic and Organic Chemistry, Section of Inorganic Chemistry, University of Barcelona. Carrer Martí i Franquès 1-11, 08028 Barcelona, Catalonia, Spain
§ Unitat de Difracció de RX, CCITUB, Universitat de Barcelona. Carrer Solé i Sabarés 1-3, 08028 Barcelona, Catalonia, Spain

Supporting Information Placeholder

ABSTRACT: A wide array of new N-acyl thiazinanethiones are employed in a number of direct and enantioselective carbon–carbon bond forming reactions catalyzed by nickel(II) complexes. The electrophilic species are mostly prepared in situ from ortho esters, methyl ethers, acetals, and ketals, which makes the overall process highly efficient and experimentally straightforward. Theoretical calculations indicate that the reactions proceed through an open transition state in a S_N1-like mechanism. The utility of this novel procedure has been demonstrated by the asymmetric preparation of synthetically useful intermediates and the total synthesis of peperomin D.

The stereocontrolled construction of carbon–carbon bonds from metal enolates holds a prominent position among carbon backbone forming methods in asymmetric synthesis.4 Unfortunately, most of the reported methods hinge on the stoichiometric generation of the enolate and subsequent reaction with the chosen electrophile, so they do not meet the current demands for economy in synthesis.5 Organocatalysis does meet such challenges,6 but the source of nucleophiles is often restricted to aldehydes and a few privileged compounds.7 Hence, there is a lack of direct, catalytic, and asymmetric transformations based on metal enolates from non–activated carboxylic derivatives. In this context, pioneering studies underlined the benefits of working with easily removable scaffolds attached to the carboxylic moiety.5–7 This led Kobayashi to use amides in highly enantioselective aldol and Michael additions,8 similarly Evans described aldol reactions and orthoester alkylations from N-acyl thiazolidineethiones,9 Kumagai and Shibasaki also reported a number of reactions based on 7-azaindoline amides.10,11 Inspired by such precedents and taking advantage of our

Scheme 1. Direct, Asymmetric, and Catalytic C–C Bond Forming Reactions

We were aware from the very beginning that such a challenging process called for: (a) the catalytic formation of an enolate possessing the necessary chiral environment in parallel to (b) the generation of the required electrophile for (c) the installation of up to two
new stereocenters whilst (d) minimizing undesired reactions. Therefore, we carried out a careful examination of all the species involved in such a process.

Exploratory studies on the addition of \( N \)-propanoyl derivatives \( 1a \text{--} 5a \) to \( 4,4' \)-dimethoxybenzyldihydroxyl methyl ether in the presence of commercially available (Me\(_2\)P)\(_2\)NiCl\(_2\) demonstrated the crucial role of the exocyclic C=S bond (Scheme 2). Indeed, oxazolidinone \( 1a \) and thiazolidinone \( 2a \) did not react at all, whereas thiazolidinethione \( 4a \) and thiazenanthione \( 5a \) were converted into the alkylated products quantitatively.

**Scheme 2. Assessment of the Scaffold**

\[
\begin{align*}
\text{Y} & \quad \text{N} & \quad \text{O} & \quad \text{Ar} \\
\text{1a} & \quad \text{2a} & \quad \text{3a} & \quad \text{4a} & \quad \text{5a} \\
\text{O} & \quad \text{N} & \quad \text{S} & \quad \text{N} & \quad \text{S} \\
\end{align*}
\]

\( \text{Conversion established by 'H NMR analysis of the reaction mixture} \)

Therefore, we focused our attention on the alkylation of \( 4a \) and \( 5a \) promoted by a few chiral complexes (L*\( \text{NiCl}_2 \) in Table 1), easily prepared by simple heating of mixtures of \( \text{NiCl}_2 \) and the corresponding diphosphines in CH\(_3\)CN. Initial screening of the reaction conditions revealed that both substrates were appropriate platforms to carry out such alkylations. Thereby, treatment of thiazolidinethione \( 4a \) with \( 4,4' \)-dimethoxybenzyldihydroxyl methyl ether, TESOTf, and 2,6-lutidine in the presence of 5 mol % L*\( \text{NiCl}_2 \) at \(-20^\circ\text{C}\) for 15 h produced the quantitative and enantioselective (ee up to 96%) conversion into the alkylated adduct \( 9a \) (entries 1--3 in Table 1). Even better, parallel reactions from thiazenanthione \( 5a \) afforded adduct \( 10a \) as a simple enantiomer (entries 4--6 in Table 1). Importantly, the temperature could be raised to \( 0^\circ\text{C} \) without any detrimental effect, which enabled us to dramatically reduce the reaction time and to scale down the catalyst loading (compare entries 6--9 in Table 1). Eventually, the alkylation of \( 5a \) with a mere 1 mol % of \([\text{R}(-)\text{DTBM-SEGPHOS}]\text{NiCl}_2\) took place at \( 0^\circ\text{C} \) in just 10 min and gave \( 10a \) with a 98% ee and a 96% yield after chromatographic purification (entry 8 in Table 1).

The optimized conditions were then applied to a broad array of \( N \)-acyl thiazenanthiones \( 5 \) (Table 2). The reaction proved to be sensitive to the bulk of the acyl group, so the catalyst loading had to be increased to 10 mol % for the sterically hindered (R: \( i\)-Pr) thiazenanthione \( 5d \) (compare entries 1--4 in Table 2). Otherwise, it tolerated the presence of common functional groups as alkenes, alkynes, and carboxylic esters as well as C\(\alpha\)-benzyl or phenyl ethers, in most cases with an outstanding enantiocontrol (ee up to 98%) and yields from 78 to 96% (entries 5--9 in Table 2). Unfortunately, the synthesis of the azidoacetyl thiazenanthione counterpart proved troublesome, but a parallel alkylation reaction was carried out successfully with the \( N \)-azidoacetyl thiazenothione \( 4j \).

**Table 1. Initial Trials on the Direct and Asymmetric Reactions Catalyzed by Chiral Nickel(II) Complexes**

| entry | substrate | L*\( \text{NiCl}_2 \) | mol % | temp (°C) | \( t \) (h) | ee (%)\(^a\) | conversion (%)\(^b\) | yield (%)\(^c\) |
|-------|-----------|----------------------|-------|-----------|-----------|-----------|----------------|-------------|
| 1     | 4a        | [(R)\text{-BINAP}]\text{NiCl}_2 | 5     | -20       | 15        | 94        | > 97           |             |
| 2     | 4a        | [(R)\text{-TolBINAP}]\text{NiCl}_2 | 5     | -20       | 15        | 95        | > 97           |             |
| 3     | 4a        | [(R)\text{-DTBM-SEGPHOS}]\text{NiCl}_2 | 5     | -20       | 15        | 96        | > 97           |             |
| 4     | 5a        | [(R)\text{-BINAP}]\text{NiCl}_2 | 5     | -20       | 15        | 96        | > 97           |             |
| 5     | 5a        | [(R)\text{-TolBINAP}]\text{NiCl}_2 | 5     | -20       | 15        | 98        | > 97           |             |
| 6     | 5a        | [(R)\text{-DTBM-SEGPHOS}]\text{NiCl}_2 | 5     | -20       | 15        | 98        | > 97           |             |
| 7     | 5a        | [(R)\text{-DTBM-SEGPHOS}]\text{NiCl}_2 | 2     | -20       | 1         | 98        | > 97           |             |
| 8     | 5a        | [(R)\text{-DTBM-SEGPHOS}]\text{NiCl}_2 | 1     | 0         | 0.2       | 98        | > 97           |             |
| 9     | 5a        | [(R)\text{-DTBM-SEGPHOS}]\text{NiCl}_2 | 1     | 20        | 0.2       | 92        | > 97           |             |

\(^a\) Established by chiral HPLC. \(^b\) Established by \(^1\)H NMR. \(^c\) Isolated yield after column chromatography.
Table 2. Direct and Enantioselective Alkylation with (4-MeOPh)$_2$CHOMe Catalyzed by a Chiral Nickel(II) Complex

| entry | substrate | $R$ | mol % L$^*$NiCl$_2$ | $t$ (h) | adduct | ee (%) | yield (%)$^b$ |
|-------|-----------|-----|----------------------|--------|--------|---------|-------------|
| 1     | 5a        | Me  | 1                    | 0.2    | 10a    | 98      | 96          |
| 2     | 5b        | Et  | 2                    | 2      | 10b    | 95      | 88          |
| 3     | 5c        | Bn  | 2                    | 2      | 10c    | 96      | 81          |
| 4     | 5d        | i-Pr | 10                  | 2      | 10d    | 98      | 78          |
| 5     | 5e        | (CH$_3$)$_2$CH=CH$_2$ | 2      | 2      | 10e    | 98      | 78          |
| 6     | 5f        | (CH$_3$)$_2$CCH | 2      | 2      | 10f    | 98      | 96          |
| 7     | 5g        | (CH$_3$)$_2$CO$_2$Me | 2      | 2      | 10g    | 95      | 78          |
| 8     | 5h        | OPh | 10                  | 2.5    | 10h    | 95      | 85          |
| 9     | 5i        | OBn | 2                    | 4      | 10i    | 95      | 93          |
| 10    | 4j        | N$_3$ | 2                  | 2      | 9j    | 95      | 93          |

$^a$ Established by chiral HPLC. $^b$ Isolated yield after column chromatography.

(entry 10 in Table 2). Significantly, the results for 10i and 9j make this alkylation a new approach to the asymmetric synthesis of $\alpha$-hydroxy and $\alpha$-amino acids respectively (entries 9 and 10 in Table 2).

The thiazinanethione scaffold of the products 10 was easily removed to release alkylated products (Scheme 3). Indeed, reduction of 10a with NaBH$_4$ led to alcohol 11a with a yield of 87%, whereas treatment of 10a with methanol afforded ester 12a with a 96% yield. In turn, ($S$)-$\alpha$-methylbenzylamine and morpholine reacted smoothly with 10a to produce amides 13a and 14a respectively in yields up to 96%. At this point, absolute configuration of adducts 10 was firmly established by chemical correlation of 11a–12a and X-ray analysis of amide 13a. Interestingly, thiazinanethione may also act as a coupling reagent and permitted us to obtain dia stereomerically pure $N$-acyl amino acid 15f by simple addition of methyl ($S$) leucinate to adduct 10f with an 89% yield.

Once the feasibility of the catalytic and asymmetric alkylation of 5 with 4,4'-dimethoxybenzhydryl methyl ether was established, we examined the synthetic potential of such a transformation through the use of other electrophiles represented in Scheme 1. The reactions with trimethyl orthoformate, a dimethyl ketal, and a tropylum salt, which involve the installation of a single stereocenter, proceeded smoothly and led to enantio merically pure adducts 16a–18a (ee $\geq$97%) after slight adjustments of the former experimental conditions (Scheme 4). More concretely, the reaction with trimethyl orthoformate was carried out at $-40^\circ$C to suppress the competitive alkylation of the exocyclic C=S bond, whereas the addition to the dimethyl ketal lasted for six hours, probably because of the steric bulk of the o xo...
An $S_N1$-like mechanism based on the approach of cat
ionic reagents to the $Re$ face of a putative chiral nickel enolate accounts for all these results. [(R)-DTBMSEGPHOS]NiCl$_2$ is a robust and bench stable nickel(II) complex with a distorted square planar geometry which can be seen in the crystal structure obtained; it does not catalyse the alkylation reaction but it is easily activated in situ with TESOTf to produce the true catalyst containing two triflate ligands. Coordination of this species to the thioimide moiety enhances the acidity of $5$ and facilitates the deprotonation of the $C\alpha$ position. At the same time, the TESOTf reacts with the benzhydryl methyl ether and produces the corresponding carbocation, which in turn adds to the nickel(II) enolate. Once the carbon-carbon bond is formed, the alkylated adduct $10a$ is released and the nickel(II) complex may start a new catalytic cycle (Scheme 5).

Eventually, we considered the synthesis of peperomin D ($20$ in Scheme 6), a secologan metabolite isolated from *Peperomia glabillae*. Featuring a five membered lactone with a benzhydryl appendage at the $\beta$ position, we envisaged that it might be synthesized through alklylation of thiazinanethione $5k$ with the appropriate benzhydryl methyl ether in the presence of [(S)-DTBMSEGPHOS]NiCl$_2$. Indeed, quenching the reaction mixture with LiBH$_4$ gave chemoselectively the hydroxy ester $21$, which was then treated with Amberlyst resin to obtain the desired lactone $22$ with an excellent stereocontrol (95% ee) and a 51% yield. Remarkably, just a single chromatographic purification was required. The installation of the $\alpha$-stereocenter was next accomplished by substrate-controlled alkylation of $22$ with MeI, which allowed us the isolation of enantiomerically pure peperomin D $20$ with an overall yield of 42% over three steps.

In summary, we have demonstrated the utility of $N$-acyl thiazinanethiones in a number of direct, chemo- and enantioselective carbon-carbon bond forming reactions usually promoted by 1–5 mol % of [DTBMSEGPHOS]NiCl$_2$. The thiazinanethione scaffold can be smoothly released from the resulting adducts to provide a broad array of enantiomerically pure intermediates. Theoretical studies suggest that these transformations proceed through an open transition state in an $S_N1$-like mechanism, in which the configuration of the $\alpha$-stereocenter is absolutely controlled by the chiral biphosphine. The efficiency of such an alkylation has been proved in the total synthesis of peperomin D, a five membered lactone containing two stereocenters.
ASSOCIATED CONTENT
The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and characterization data (PDF).

AUTHOR INFORMATION
Corresponding Authors
* pedro.romea@ub.edu
* felix.urpi@ub.edu

Present Addresses
◊ Adam J. Taylor: University of Glasgow
◊ Jesus Rodriíguez-Varela: Department of Chemistry, University of Cambridge, United Kingdom

Funding Sources
No competing financial interests have been declared.

ACKNOWLEDGMENT
Financial support from the Spanish Ministerio de Economía y Competitividad (Grant No. CTQ2015-65759-P) and the Generalitat de Catalunya (2017SGR 271) as well as a doctorate studentship to S. C. D. K. (Generalitat de Catalunya) and an Erasmus+ grant to A. J. Taylor are acknowledged.

Dedicated to the memory of recently deceased Professor Josep Castells.

REFERENCES
(1) Carreira, E. M.; Kvaerno, L. In Classics in Stereoselective Synthesis. Wiley-VCH, Weinheim, 2009.
(2) (a) Trost, B. M. The atom economy – a search for synthetic efficiency. Science 1991, 254, 1471–1477. (b) Trost, B. M. Atom Economy–A Challenge for Organic Synthesis: Homogeneous Catalysis Leads the Way. Angew. Chem. Int. Ed. Engl. 1995, 34, 259–281.
(3) (a) Beeson, T. D.; Mastracchio, A.; Hong, J.-B.; Ashton, K.; MacMillan, D. W. C. Enantioselective Organocatalysis Using SOMO Activation. Science 2007, 316, 582–585. (b) Nicewicz, D. A.; Mac-Millan, D. W. C. Merging PhotoRedox Catalysis with Organocatalysis: The Direct Asymmetric Alkylation of Aldehydes. Science 2008, 322, 77–80.
(4) Ooi, T.; Maruoka, K. Recent Advances in Asymmetric Phase-Transfer Catalysis. Angew. Chem. Int. Ed. 2007, 46, 4222–4266.
(5) (a) Yamada, Y. M. A.; Yoshikawa, N.; Sasaï, H.; Shibasaki, M. Direct Catalytic Asymmetric Aldol Reactions of Aldehydes with Unmodified Ketones. Angew. Chem. Int. Ed. Engl. 1997, 36, 1871–1872. (b) Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasaï, H.; Shibasaki, M. Direct Catalytic Asymmetric Aldol Reaction. J. Am. Chem. Soc. 1999, 121, 4168–4178.
(6) (a) Trost, B. M.; Ito, H. A Direct Catalytic Enantioselective Aldol Reaction via a Novel Catalyst Design. J. Am. Chem. Soc. 2000, 122, 12003–12004. (b) Trost, B. M.; Bartlett, M. J. ProPhenol-Catalyzed Asymmetric Additions by Spontaneously Assembled Dinuclear Main Group Metal Complexes. Acc. Chem. Res. 2015, 48, 688–701.
(7) (a) Harada, S.; Handa, S.; Matsunaga, S.; Shibasaki, M. Direct Catalytic Asymmetric Mannich-Type Reactions of N-(2-Hydroxyacetyl)pyrrole as an Ester-Equivalent Donor. Angew. Chem. Int. Ed. 2005, 44, 4365–4368. (b) Morimoto, H.; Lu, G.; Aoyama, N.; Matsunaga, S.; Shibasaki, M. Lanthanum Aryloxide/Pybox-Catalyzed Direct Asymmetric Mannich-Type Reactions Using a Trichloro-
NiCl$_2$–Binap/R$_3$SiOTf/2,6-Lutidine. Angew. Chem. Int. Ed. 2007, 46, 5435–5439.

(19) Theoretical calculations were carried out using QM/MM algorithm methodology to localise the transition states. These show that one of the phosphine ligands hinders the approach of said carbocation to the Si face of the enolate ($\Delta\Delta G^\dagger \approx 2.7$ kcal mol$^{-1}$) and thus determines the $\pi$-face selectivity of the addition. For details of theoretical calculations, see Supporting Information.

(20) Delle Monache, F.; Compagnone, R. S. A Secolignan from Peperomia Glabella. Phytochemistry 1996, 43, 1097–1098.

(21) For a previous total synthesis of peperomin D, see Sibi, M. P.; Johnson, M. D.; Punniyamurthy, T. Enantioselective synthesis of peperomins A, C, D, and analogs – Examination of diastereoselective cuprate conjugate additions to $N$-enoyl-4-diphenylmethyl-2-oxazolidinones. Can. J. Chem. 2001, 79, 1546–1555.
NiCl₂

TESOTf, 2,6-lutidine
CH₂Cl₂, 0 °C

> 94% ee