Direct and Enantioselective Aldol Reactions Catalyzed by Chiral Nickel(II) Complexes
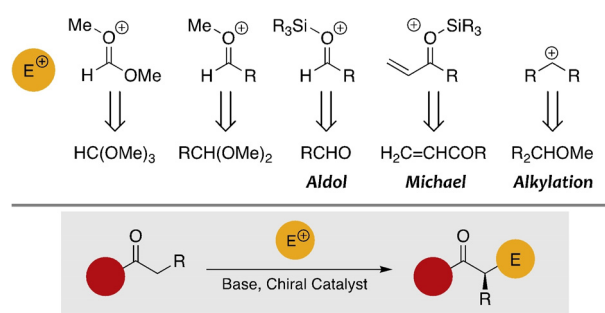
Stuart C. D. Kennington, Saul F. Teloxa, Miguel Mellado-Hidalgo, Oriol Galeote, Sabrina Puddu, Marina Bellido, Pedro Romea,* Fèlix Urpí,* Gabriel Aullón, and Mercè Font-Bardia

Dedicated to Professor David A. Evans on the occasion of his 80th birthday

Abstract: *A direct and asymmetric aldol reaction of N-acyl thiazinanethiones with aromatic aldehydes catalyzed by chiral nickel(II) complexes is reported. The reaction gives the corresponding O-TIPS-protected anti-aldol adducts in high yields and with remarkable stereocontrol and atom economy. Furthermore, the straightforward removal of the achiral scaffold provides enantiomerically pure intermediates of synthetic interest, which involve precursors for anti-α-amino-β-hydroxy and α,β-dihydroxy carboxylic derivatives. Theoretical calculations explain the observed high stereocontrol.*

$\mathcal{T}$he enantioselective construction of the carbon backbone of chiral molecules has been at the forefront of organic synthesis in the last decades. It is therefore hardly surprising that classical transformations such as aldol and Michael reactions or Diels–Alder cycloadditions still hold a prominent position among the most important synthetic methods.[1] In this context, the continuing demand for increasingly more efficient procedures in accordance with the premises dictated by selectivity and economy in synthesis[2,3] has given rise to the development of a plethora of catalytic methods for the enantioselective construction of carbon–carbon bonds.[4] Unfortunately, the scope of most of them is rather narrow, which hampers further development and prevents a comprehensive exploitation of their possibilities. Thus, considering the benefits arising from a general approach, we envisaged that metal enolates from a single platform might participate in a number of direct, enantioselective, and catalytic transformations provided that the appropriate electrophiles are generated in the reaction mixture and evolve through similar open transition states (Scheme 1).
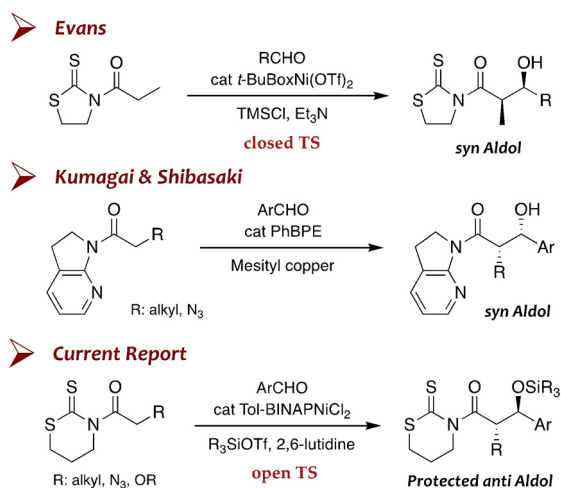
[*] Dr. S. C. D. Kennington, Dr. S. F. Teloxa, M. Mellado-Hidalgo,
    O. Galeote, S. Puddu, M. Bellido, Prof. P. Romea, Prof. F. Urpí
    Department of Inorganic and Organic Chemistry
    Section of Organic Chemistry
    Universitat de Barcelona
    Carrer Martí i Franqués 1–11, 08028 Barcelona (Spain)
    E-mail: pedro.romea@ub.edu
            felix.urpi@ub.edu
    Prof. G. Aullón
    Department of Inorganic and Organic Chemistry
    Section of Inorganic Chemistry
    Universitat de Barcelona
    Carrer Martí i Franqués 1–11, 08028 Barcelona (Spain)
    Dr. M. Font-Bardia
    X-ray Diffraction Unity, CCiTUB, Universitat de Barcelona
    Carrer Solé i Sabarís 1–3, 08028 Barcelona (Spain)

Scheme 1. Direct and enantioselective carbon–carbon bond-forming reactions from carbonylic compounds.

In this context, the activated aldehydes shown in Scheme 1 might react with carbonylic species in the presence of a base and a chiral catalyst to undergo direct and stereocontrolled aldol reactions.[5] With this aim, we have identified *N*-acyl thiazinanethiones as worthy substrates for our purposes and we now describe our findings on the direct and highly enantioselective aldol reactions of aromatic aldehydes catalyzed by chiral nickel(II) complexes in which the resultant protected aldol compounds are obtained selectively with remarkable atom economy. Importantly, this reaction gives access in a single step to protected *anti*-aldol adducts and supplements the *syn*-methods previously described by the groups of Evans,[6] and Kumagai and Shibasaki (Scheme 2).[7,8] Furthermore, the reaction shows a wide scope for the nucleophilic partner, which also permits the obtention of enantiomerically pure protected α-azido-β-hydroxy and α,β-dihydroxy derivatives in high yields under mild conditions (Scheme 2).

Scheme 2. Direct and enantioselective aldol reactions catalyzed by chiral metal complexes.

Exploratory experiments using *N*-propanoyl derivatives of several achiral heterocycles, triethylsilyltrifluoromethane sulfonate (TESOTf), and $(Me_3P)_2NiCl_2$ proved the feasibility of our approach for a direct and stereocontrolled aldol reaction as well as the advantage of thiazolidinethione and thiazinanethione over other heterocyclic scaffolds. In this respect, and despite both scaffolds producing similar results, the slower kinetics observed with the thiazolidinethione made the thiazinanethione counterpart the best choice for further developments (see Table S1 in the Supporting Information).[9]

We then examined the stereocontrol provided by different chiral nickel(II) complexes. It is important to highlight that these complexes are robust, easy to handle and prepare from the corresponding chiral ligands and $NiCl_2$, and are activated in the reaction mixture at the same time as the aldehyde by simple treatment with a silyl triflate.[10] Therefore, the role of the silyl triflate is twofold, since it activates the aldehyde as well as converting the nickel(II) chloride complex into the true catalytic species.[11] The results summarized in Table 1

show that *N*-propanoyl thiazinanethione **1** reacts with 4-methoxybenzaldehyde (**a**) in the presence of minute amounts of a large array of nickel(II) complexes, with the exception of $DIOPNiCl_2$ (Table 1, entry 2). Indeed, achiral $(Me_3P)_2NiCl_2$ provided a mixture of silyl aldol adducts with a remarkable diastereomeric ratio (dr 88:12) from which the racemic *anti*-adduct **2a** was isolated in 79% yield (Table 1, entry 1), whereas other chiral complexes also catalyzed the desired aldol reaction with full conversion. Interestingly, the steric hindrance of the chiral ligands plays a key role in the stereochemical outcome of the reaction. Indeed, the DTBM-SEGPHOS diphosphine gave an equimolar mixture of *anti* and *syn* diastereomers, whereas the less bulky SEGPHOS ligand performed much better and afforded an 80:20 *anti/syn* mixture (Table 1, entries 3 and 4); in addition, the absolute stereocontrol was outstanding and enantiomerically pure ($\geq$ 98% *ee*) aldol adduct **2a** was isolated in both cases. Furthermore, the BINAP family gave much more consistent results, although the stereochemical outcome of the reaction slightly depended on the bulk of the ligand, with the Tol-BINAP ligand being the most appropriate in terms of stereocontrol and yield (Table 1, entries 5–7).
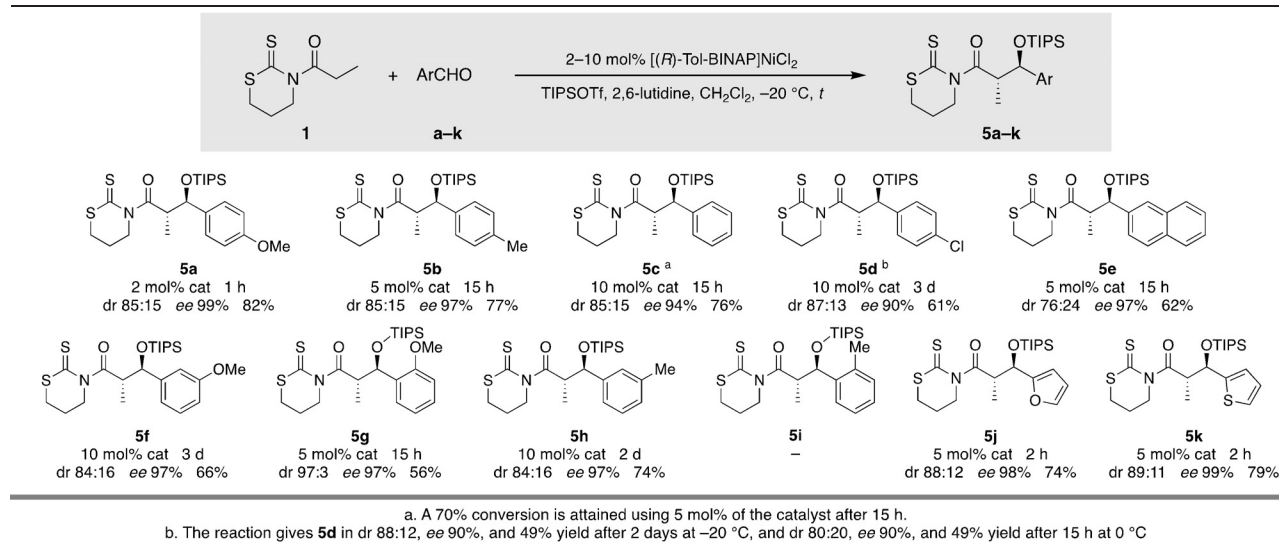
The impact of the bulk of ligands on the reaction led us to explore the influence of the activating Lewis acid. We thus assessed commercially available TMS, TBS, TES, and TIPS triflates. In the reaction with $(Me_3P)_2NiCl_2$, all these silyl triflates—except TMSOTf, which produced similar diastereomeric ratios but larger amounts of deprotection—can be used interchangeably (see Table S2). In contrast, we observed a significant change in the selectivity when [(*R*)-Tol-BINAP]-$NiCl_2$ was used instead. Indeed, the stereoselectivity depends upon the silyl triflate: less bulky TMSOTf and TBSOTf gave lower diastereoselectivities than TESOTf, whereas the bulkiest TIPSOTf increased the diastereomeric ratio up to 85:15 (Table 2, entries 1–4). Furthermore, the enantiocontrol was excellent for all these reagents.

We also evaluated other variables. The temperature had a modest positive effect on the diastereomeric ratio on cooling to −40°C but duly decreased the rate of reaction, so −20°C was used as the reaction temperature. Finally,

Table 1: Influence of the chiral nickel(II) complex on the stereochemical outcome of the aldol reaction.

Entry	L*	*anti/syn*[a]	*ee* **2a** [%][b]	Yield **2a** [%][c]
1	$(Me_3P)_2NiCl_2$	88:12	–	79
2	(+)-$DIOPNiCl_2$	88:12	< 5	< 10
3	(*R*)-SEGPHOS	80:20	98	67
4	(*R*)-DTBM-SEGPHOS	50:50	99	43
5	(*R*)-BINAP	80:20	97	75
6	(*R*)-Tol-BINAP	80:20	98	76
7	(*R*)-Xyl-BINAP	83:17	83	71

[a] Established by ^{1}H NMR (400 MHz) spectroscopic analysis. [b] Established by chiral HPLC analysis. [c] Yield of isolated product.

Table 2: Influence of the Lewis acid in the stereochemical outcome of the aldol reaction.

Entry	R_3SiOTf[e]	*anti* Adduct	dr[a]	*ee anti* [%][b]	Yield *anti* [%][c]
1	TESOTf	**2a**	80:20	98	76
2	TMSOTf	**3a**	73:27	nd[d]	nd[d]
3	TBSOTf	**4a**	75:25	99	67
4	TIPSOTf	**5a**	85:15	99	80

[a] *anti/syn* ratio established by ^{1}H NMR (400 MHz) spectroscopic analysis. [b] Established by chiral HPLC analysis. [c] Yield of isolated product. [d] Not determined. [e] TES = triethylsilyl, TMS = trimethylsilyl, TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl.

Table 3: TIPSOTf-mediated aldol reaction of **1** with aromatic aldehydes.

5a 2 mol% cat 1 h dr 85:15 *ee* 99% 82%	**5b** 5 mol% cat 15 h dr 85:15 *ee* 97% 77%	**5c** [a] 10 mol% cat 15 h dr 85:15 *ee* 94% 76%	**5d** [b] 10 mol% cat 3 d dr 87:13 *ee* 90% 61%	**5e** 5 mol% cat 15 h dr 76:24 *ee* 97% 62%
5f 10 mol% cat 3 d dr 84:16 *ee* 97% 66%	**5g** 5 mol% cat 15 h dr 97:3 *ee* 97% 56%	**5h** 10 mol% cat 2 d dr 84:16 *ee* 97% 74%	**5i** –	**5j** 5 mol% cat 2 h dr 88:12 *ee* 98% 74%

5k
5 mol% cat 2 h
dr 89:11 *ee* 99% 79%

a. A 70% conversion is attained using 5 mol% of the catalyst after 15 h.
b. The reaction gives **5d** in dr 88:12, *ee* 90%, and 49% yield after 2 days at −20 °C, and dr 80:20, *ee* 90%, and 49% yield after 15 h at 0 °C

a comprehensive evaluation of the different variables considered together indicated that the reaction of *N*-propanoyl thiazinanethione **1** with **a** in the presence of 2 mol% [(*R*)-Tol-BINAP]NiCl₂, 1.3 equiv TIPSOTf, and 1.5 equiv 2,6-lutidine for only 1 h at −20 °C afforded the protected *anti*-aldol adduct **5a** in 82% yield with excellent stereocontrol (dr 85:15, 99% *ee*).

With the reaction conditions optimized for **a**, we moved to evaluate the scope of the reaction with other aromatic aldehydes.[12] The results summarized in Table 3 prove that the reaction is sensitive to both the electronic character and the steric hindrance of the substituents on the aromatic aldehyde. Indeed, electron-donating groups at the *para* position enabled highly stereocontrolled aldol reactions (dr 85:15 and up to 99% *ee*) and permitted the isolation of enantiomerically pure *anti*-adducts **5a** and **5b** in yields of 82% and 77%, respectively. Benzaldehyde (**c**) required an increase in the catalyst loading to 10 mol% to attain similar results, whereas the more deactivated 4-chlorobenzaldehyde (**d**) only provided *anti*-adduct **5d** in 61% yield after three days at −20 °C or a modest 49% yield when the reaction was carried out at 0 °C for 15 h, as a result of the formation of a by-product arising from the attack of the nucleophilic exo sulfur atom on the activated aldehyde. In turn, the more-electron-rich 2-naphthaldehyde (**e**) gave adduct **5e** in a remarkable 62% yield and 97% *ee* on using 5 mol% of the catalyst. Other isomers of **a** were also assessed and gave satisfactory results. As expected, the 3-methoxy derivative (**f**) turned out to be less reactive, but gave the corresponding *anti*-adduct **5f** in 66% yield after three days when 10 mol% of the catalyst was used. More surprisingly, 2-methoxybenzaldehyde (**g**) led to **5g** as a single stereoisomer (dr 97:3 and 97% *ee*) in 56% yield when using 5 mol% of the catalyst. A parallel aldol reaction of *meta*-tolyl aldehyde **h** proceeded efficiently, but the *ortho* counterpart **i** was found to be completely inactive and did not afford the desired adduct **5i**. This indicates that bulky groups close to the carbonyl group hinder approach to the enolate;

we speculate that the outstanding results from **g** may be due to the formation of a chelated oxocarbenium intermediate in which the *ortho* substituent remains far from the carbonyl center. Finally, aromatic aldehydes containing π-electron-rich heterocycles, such as furan **j** and thiophene **k**, afforded the *anti*-aldol adducts **5j** and **5k** in high yields after 2 h when using 5 mol% of the nickel(II) complex.

Once the feasibility of the enantioselective *anti* aldol reaction had been demonstrated, we assessed the influence of the substituents of the acyl group on the addition of *N*-acyl thiazinanethiones **6**–**13** to **a**. The results shown in Table 4 highlight the key role of steric bulk in the stereochemical outcome of the aldol reaction. Indeed, the enantioselectivity is consistently excellent for the *N*-acyl thiazinanethiones **6**–**8**, but the diastereoselectivity and consequently the yield are eroded from **5a** (R = Me: dr 85:15, 82%) to **17a** (R = Et: dr 81:19, 78%) and **18a** (R = *i*Bu: dr 75:25, 60%) and the catalyst loading needed to be increased from 2 mol% to 5 mol%. Moreover, the chemoselectivity is excellent and the presence of common functional groups such as alkenes, alkynes, halides, or esters does not have a noticeable influence, so enantiomerically pure (94–99% *ee*) protected *anti*-adducts **19a**–**22a** were isolated in good to high yields (62–76%). Finally, the presence of a strong electron-withdrawing α-CF₃ group inhibits the reaction, but the α-benzyloxy derivative affords the *anti*-adduct **24a** in a highly efficient manner, which provides straightforward access to protected *anti*-α,β-dihydroxy compounds. At this stage, we tested introducing an azido group at the α-position. Unfortunately, all our attempts failed, and we were obliged to consider the use of the thiazolidinethione scaffold. As previously mentioned, such a heterocycle enables aldol reactions but with slower kinetics than the thiazinanethione counterpart. To our delight, thiazolidinethione-based substrates **14**–**16** (m = 0 in Table 4) also gave excellent results. Indeed, and despite requiring a longer reaction time, *N*-propanoyl thiazolidinethione **14** (R = Me) and the more bulky derivative **15** (R =

Table 4: TIPSOTf-mediated aldol reaction of *N*-acyl-1,3-thiazinane-2-thiones with 4-methoxybenzaldehyde (**a**).
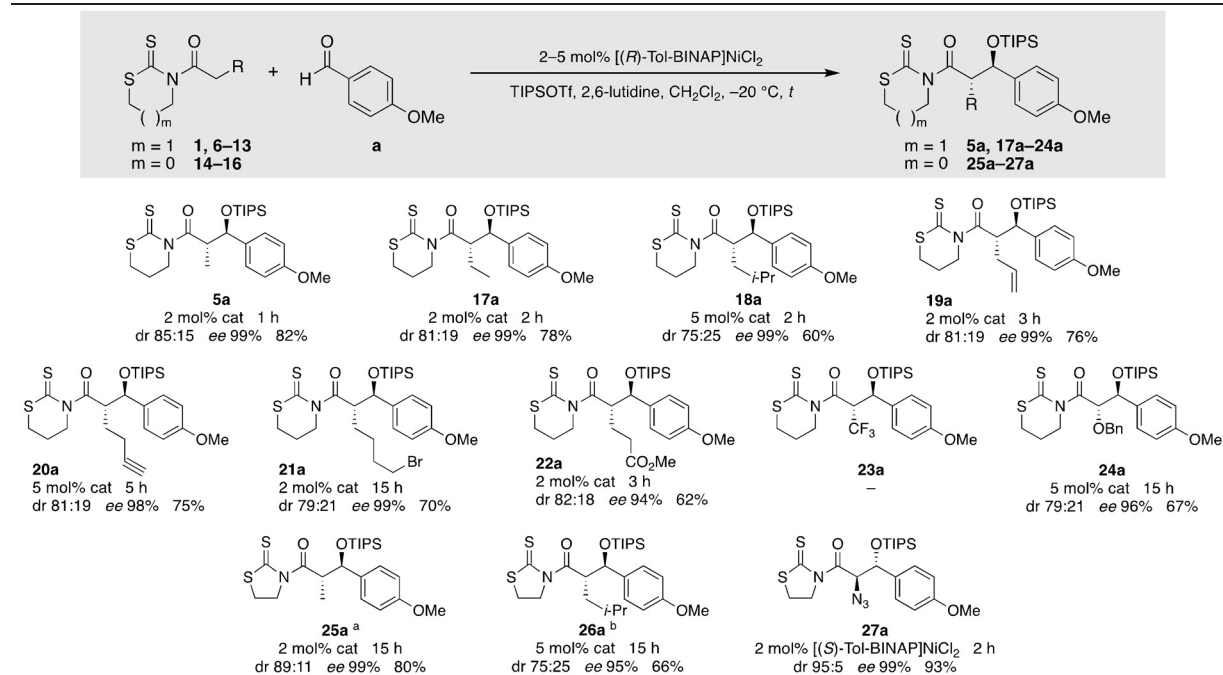

a. The conversion in 1 h was 20%. b. The conversion in 5 h was 35%.

CH_2CHMe_2) also afforded the corresponding aldol adducts **25a** and **26a** with high yields and enantioselectivity (99% and 95% *ee*, respectively). Finally, the azido thiazolidinethione **16** (R = N_3) proved especially successful and afforded in just 2 h the α-azido-β-silyloxy adduct **27a** virtually as a single stereoisomer (dr 95:5, 99% *ee*) in a yield of 93%.[13]

The configuration of **5a** was established as the (2*S*,3*R*)-*anti*-adduct through X-ray analysis of the benzyl amide derivative **28**,[14] which was easily prepared by nucleophilic displacement of the scaffold of **5a** with (*S*)-1-phenyl-1-ethylamine (Scheme 3).[15] Furthermore, amides **29** and **30** were isolated in up to 99% yield after reaction with morpholine and *N*-methoxy-*N*-methylamine, respectively. In addition, aldol **5a** was also converted into a wide array of

enantiomerically pure derivatives of synthetic interest. As shown in Scheme 3, treatment of **5a** with LiBH$_4$ gave alcohol **31** in 85% yield, methyl ester **32** was obtained in 95% yield by simply stirring **5a** in methanol, whereas the sodium enolate of ethyl acetate was used to deliver the β-keto ester **33** in a remarkable 78% yield. All together, these transformations prove the easy removal of the thiazinanethione scaffold and the synthetic utility of the aldol adducts.

Having demonstrated the wide scope and synthetic interest of the aldol reaction, we focused our attention on its mechanism. The proposed catalytic cycle is depicted in Scheme 4, where the TIPSOTf plays a dual role as the trigger for the generation of the catalytic species as well as the activating Lewis acid for the aldehyde. We carried out
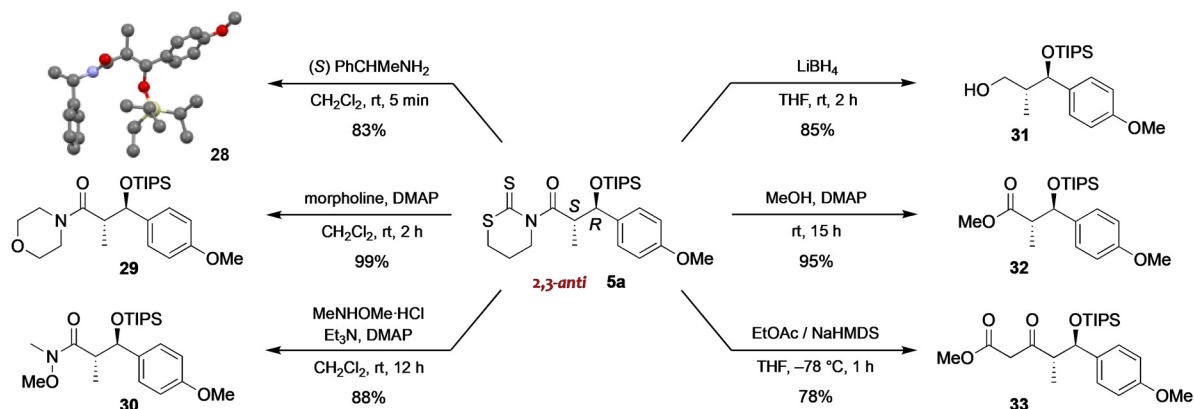
Scheme 3. Removal of the scaffold and conversion of aldol adducts into enantiomerically pure compounds.
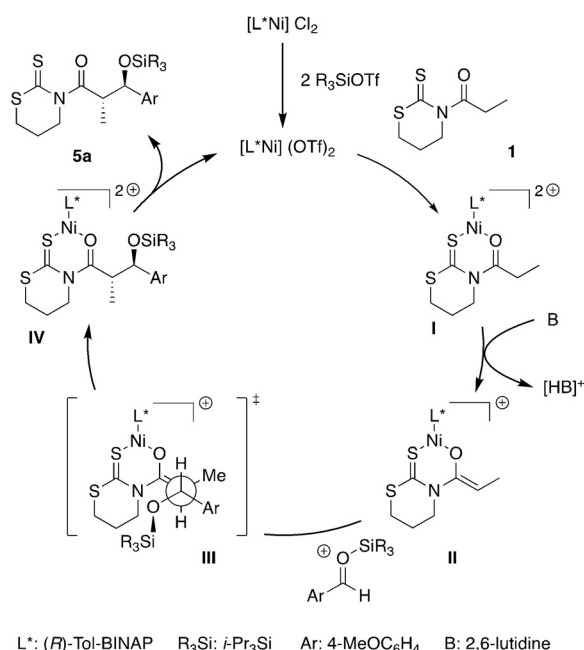
Scheme 4. Mechanistic hypothesis.

a comprehensive computational study of the carbon–carbon bond-forming step.[16] These calculations indicated that the reaction evolves through an open transition state **III**, in which the activated aldehyde approaches the *Re* π-face of the square-planar nickel(II) enolate **II** (Scheme 4). Importantly, the approach to the opposite *Si* π-face is about 3 kcal mol⁻¹ less stable, which accounts for the excellent enantiocontrol achieved in all the reactions.

In summary, we have developed a direct and asymmetric aldol reaction of *N*-acyl thiazinanethiones and thiazolidine-thiones with aromatic aldehydes in the presence of TIPSOTf and promoted by [(*R*)-Tol-BINAP]NiCl₂. This reaction gives the corresponding *O*-TIPS-protected *anti*-aldol adducts in high yields and diastereoselectivity as well as with an excellent enantiocontrol up to 99% *ee*. The wide scope of the reaction permits the use of *N*-acyl groups containing alkenes, alkynes, halides, or esters, as well as α-azido and α-hydroxy substituents, which provides a simple and quick access to *anti*-α-azido-β-silyloxy and α-alkoxy-β-silyloxy moieties. Furthermore, the heterocyclic scaffold can be easily removed to give enantiomerically pure intermediates. Finally, theoretical studies indicate that the carbon–carbon bond-forming step proceeds through an open transition state, in which the steric interactions play a crucial role.

Conflict of interest

The authors declare no conflict of interest.

Keywords: aldol reaction · asymmetric catalysis · direct reaction · nickel · thiazinanethiones

[1] E. M. Carreira, L. Kvaerno, *Classics in Stereoselective Synthesis*, Wiley-VCH, Weinheim, **2009**.

[2] a) B. M. Trost, *Science* **1991**, *254*, 1471–1477; b) P. A. Wender, B. L. Miller, *Nature* **2009**, *460*, 197–201; c) N. Z. Burns, P. S. Baran, R. W. Hoffmann, *Angew. Chem. Int. Ed.* **2009**, *48*, 2854–2867; *Angew. Chem.* **2009**, *121*, 2896–2910; d) Y. Hayashi, *Chem. Sci.* **2016**, *7*, 866–880.

[3] T. Newhouse, P. S. Baran, R. W. Hoffmann, *Chem. Soc. Rev.* **2009**, *38*, 3010–3021.

[4] For leading references, see a) D. W. C. MacMillan, *Nature* **2008**, *455*, 304–308; b) J. T. Mohr, M. R. Krout, B. M. Stoltz, *Nature* **2008**, *455*, 323–332; c) M. Silvi, P. Melchiorre, *Nature* **2018**, *554*, 41–49.

[5] a) B. M. Trost, C. S. Brindle, *Chem. Soc. Rev.* **2010**, *39*, 1600–1632; b) B. M. Trost, C.-I. Hung, G. Mata, *Angew. Chem. Int. Ed.* **2020**, *59*, 4240–4261; *Angew. Chem.* **2020**, *132*, 4268–4291.

[6] 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.

[7] a) K. Weidner, N. Kumagai, M. Shibasaki, *Angew. Chem. Int. Ed.* **2014**, *53*, 6150–6154; *Angew. Chem.* **2014**, *126*, 6264–6268; b) Z. Liu, T. Takeuchi, R. Pluta, F. A. Arteaga, N. Kumagai, M. Shibasaki, *Org. Lett.* **2017**, *19*, 710–713.

[8] a) N. Kumagai, M. Shibasaki, *Chem. Eur. J.* **2016**, *22*, 15192–15200; b) N. Kumagai, M. Shibasaki, *Synthesis* **2019**, *51*, 185–193.

[9] For related studies on the key role of the 1,3-thiazinane-2-thione scaffold, see 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.

[10] T. Suzuki, Y. Hamashima, M. Sodeoka, *Angew. Chem. Int. Ed.* **2007**, *46*, 5435–5439; *Angew. Chem.* **2007**, *119*, 5531–5535.

[11] For other examples, see a) J. M. Romo, E. Gálvez, I. Nubiola, P. Romea, F. Urpí, M. Kindred, *Adv. Synth. Catal.* **2013**, *355*, 2781–2786; b) J. Fernández-Valparís, J. M. Romo, P. Romea, F. Urpí, H. Kowalski, M. Font-Bardia, *Org. Lett.* **2015**, *17*, 3540–3543.

[12] Aliphatic aldehydes reacted sluggishly under the reaction conditions. In turn, α,β-unsaturated aldehydes afforded complex mixtures.

[13] Metal enolates from α-azido carbonyl compounds are rarely used because of their lack of stability. For leading examples, see a) J. Patel, G. Clavé, P.-Y. Renard, X. Franck, *Angew. Chem. Int. Ed.* **2008**, *47*, 4224–4227; *Angew. Chem.* **2008**, *120*, 4292–4295; b) K. Weidner, Z. Sun, N. Kumagai, M. Shibasaki, *Angew. Chem. Int. Ed.* **2015**, *54*, 6236–6240; *Angew. Chem.* **2015**, *127*, 6334–6338.

[14] For the X-ray data, see the Supporting Information. Deposition Number 2062607 (for **28**) contains 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 www.ccdc.cam.ac.uk/structures.

[15] The minor isomer was confirmed as the (2*S*,3*S*)-*syn*-aldol product by chemical correlation.

[16] ONIOM calculations were carried out using the Gaussian09 package. High quantum layer B3LYP/TZPV was applied to nickel, phosphorus, and the *N*-acyl thiazinanethione together with the electrophile in the reaction pathway, while low layer including organic substituents of the diphosphane ligand was treated by universal field force. For further details, see the Supporting Information.