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Direct and Enantioselective Aldol Reactions Catalyzed by Chiral Nickel(II) Complexes

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

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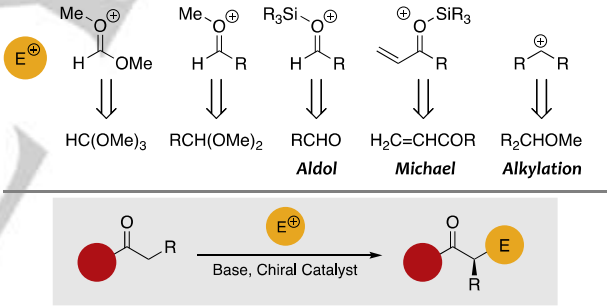
Abstract: A direct and asymmetric aldol reaction of *N*-acyl thiazinanethiones with aromatic aldehydes catalyzed by chiral nickel(II) complexes is documented. The reaction gives the corresponding *O*-TIPS protected *anti* aldol adducts in high yields and with a remarkable stereocontrol and atom economy. 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 account for the observed high stereocontrol.

The 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 were generated in the reaction mixture and evolve through similar open transition states (Scheme 1).

In this context, 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 direct and highly enantioselective aldol reactions with aromatic aldehydes catalyzed by chiral nickel(II) complexes in which the resultant protected aldol compounds are selectively obtained with remarkable atom economy. Importantly, this reaction gives access *in a single step* to protected *anti* aldol adducts and supplements *syn* methods previously described by 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 1. Direct and Enantioselective Carbon–Carbon Bond Forming Reactions from Carbonylic Compounds

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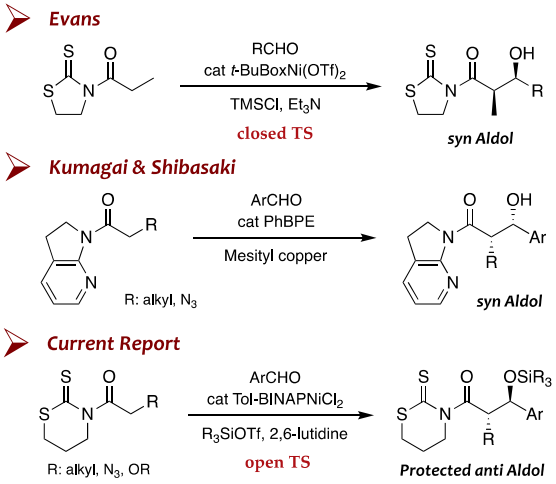
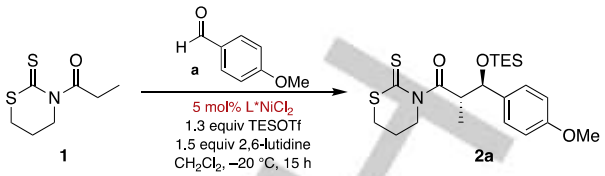


Scheme 2. Direct and enantioselective aldol reactions catalyzed by chiral metal complexes.

Exploratory experiments using *N*-propanoyl derivatives of several achiral heterocycles, 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 produce similar results, the slower kinetics observed for the thiazolidinethione made the thiazinanethione counterpart the best choice for further developments (see Table SI-1).[9]

Then, we examined the stereocontrol provided by different of 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 that are properly 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] 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 $DIOPNiCl_2$ (entry 2 in Table 1). Indeed, achiral $(Me_3P)_2NiCl_2$ provided a mixture of silyl aldol adducts with a remarkable diastereomeric ratio (dr 88:12) from which racemic *anti* adduct **2a** was isolated with a 79% yield (entry 1 in Table 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 performed much better and afforded an 80:20 *anti*/*syn* mixture (compare entry 3 and 4 in Table 1); in addition, the absolute stereocontrol was outstanding and enantiomerically pure (*ee* ≥ 98%) 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, the Tol-BINAP ligand being the most appropriate in terms of stereocontrol and yield (compare entries 5–7 in Table 1).

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



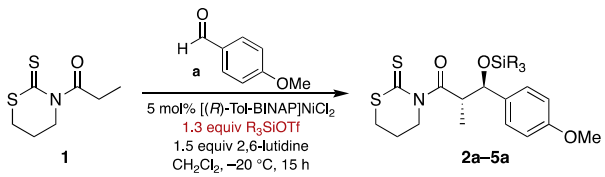
1 **2a**

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) analysis. [b] Established by chiral HPLC analysis. [c] Isolated yield.

The impact of the bulk of ligands in the reaction led us to explore the influence of the activating Lewis acid. We thus assessed the 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 SI-2). On the contrary, we observed a significant change of selectivity when [(*R*)-Tol-BINAP]$NiCl_2$ was used instead. Indeed, 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 (compare entry 1–4 in Table 2). In turn, enantiocontrol was excellent for all these reagents.

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



1 **2a–5a**

Entry	R_3SiOTf	*anti* Adduct	dr[a]	*ee anti*[b]	Yield *anti* (%)[c]
1	TESOTf	**2a**	80:20	98	76
2	TMSOTf	**3a**	73:27	nd	nd
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) analysis. [b] Established by chiral HPLC analysis. [c] Isolated yield.

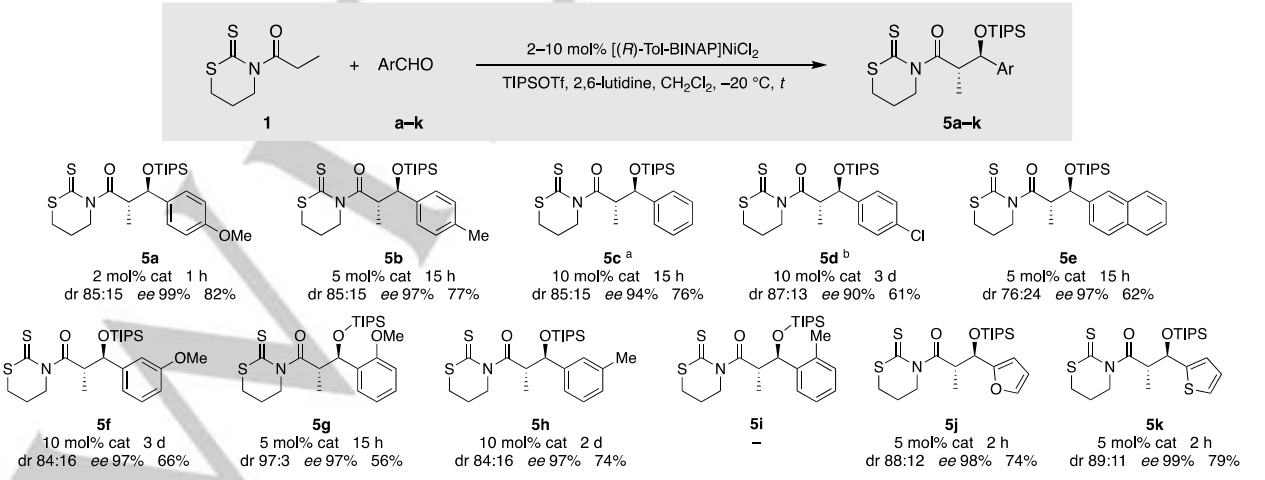
We also evaluated other variables. The temperature had a modest positive effect on the diastereomeric ratio when cooled to –40 °C but duly decreased the rate of reaction, so we maintained –20 °C as the reaction temperature. Finally, a comprehensive evaluation of the different variables considered together indicated that the reaction of *N*-propanoyl thiazinanethione **1** with **a** in the

presence of 2 mol% of [(*R*)-Tol-BINAP]$NiCl_2$, 1.3 equivalents of TIPSOTf, and 1.5 equivalents of 2,6-lutidine in only 1 h at –20 °C afforded the protected *anti* aldol adduct **5a** in 82% yield with an excellent stereocontrol (dr 85:15, *ee* 99%).

With the reaction conditions optimized for **a**, we moved to evaluate the scope of the reaction with other aromatic aldehydes.[12] Results summarized in Table 3 prove that the reaction is sensitive both to the electronic character and the steric hindrance of the substituents of the aromatic aldehyde. Indeed, electron donating groups at the *para* position enabled highly stereocontrolled aldol reactions (dr 85:15 and *ee* up to 99%) and permitted the isolation of enantiomerically pure *anti* adducts **5a** and **5b** in 82% and 77% respectively. Benzaldehyde (**c**) required an increase in catalyst loading to 10 mol% to attain similar results, but the more deactivated 4-chlorobenzaldehyde (**d**) only provided *anti* adduct **5d** with a 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 owing to the formation of a by–product arising from the attack of the nucleophilic exo sulfur atom to the activated aldehyde. In turn, more electron-rich 2-naphthaldehyde (**e**) gave adduct **5e** in a remarkable 62% yield and *ee* 97% by using 5 mol% of catalyst. Other isomers of **a** were also assessed with satisfactory results. As expected, the 3-methoxy (**f**) turned out to be less reactive but gave the corresponding *anti* adduct **5f** in 66% yield with 10 mol% of the catalyst after three days. More surprisingly, 2-methoxybenzaldehyde (**g**) led to **5g** as a single stereoisomer (dr 97:3 and *ee* 97%) in a 56% yield using 5 mol% of the catalyst. Parallel aldol reaction of *meta*-tolyl aldehyde **h** proceeded efficiently, but the *ortho* counterpart **i** resulted to be completely inactive and did not afford the desired adduct **5i**. This indicates that bulky groups close to the carbonyl group hinder the approach to the enolate, whereas 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, as the furan **j** and thiophene **k**, afforded the *anti* aldol adducts **5j** and **5k** in high yields after 2 h by 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%) as well as the catalyst loading requiring an increase 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 (*ee* 94–99%) protected *anti* adducts **19a–22a** were isolated in good to high yields (62–76%). Finally, the presence of a strong electron withdrawing α-CF_3 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 trialled 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 pleasure, thiazolidinethione-based substrates **14–16** (m = 0 in Table 4) also gave excellent results. Indeed, and in spite of requiring a longer reaction time, *N*-propanoyl thiazolidinethione **14** (R: Me) and the more bulky **15** (R: CH_2CHMe_2) also afforded the corresponding aldol adducts **25a** and **26a** with high yields and *ee* (99 and 95% 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, *ee* 99%) with a 93% yield.[13]

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



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

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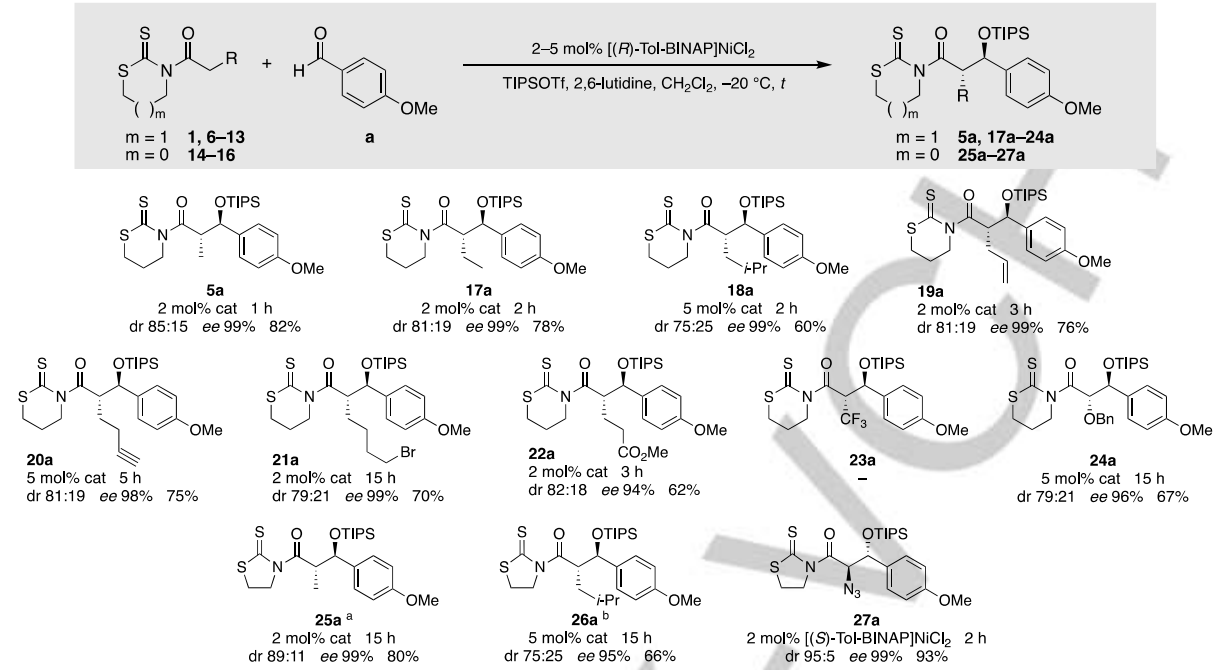
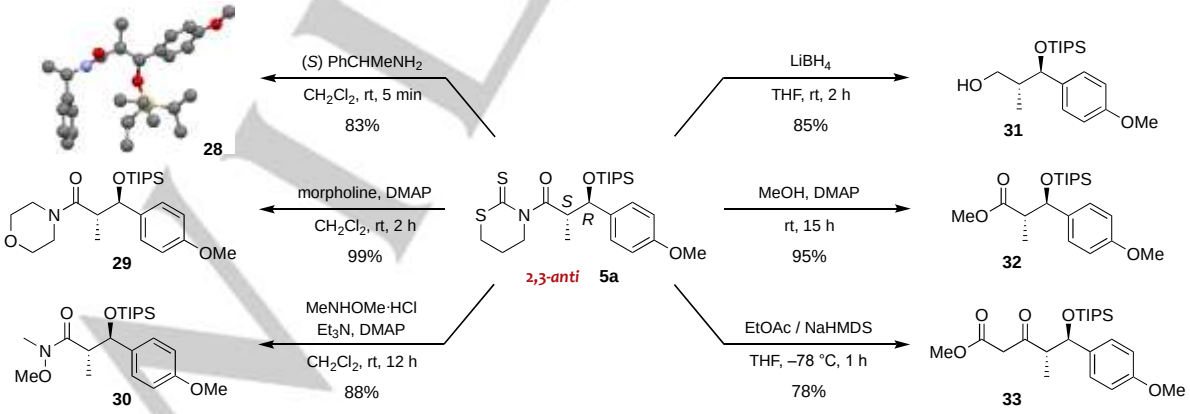
Table 4. TIPSOTf-Mediated aldol reaction of *N*-acyl-1,3-thiazinane-2-thiones with 4-methoxybenzaldehyde (**a**).



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

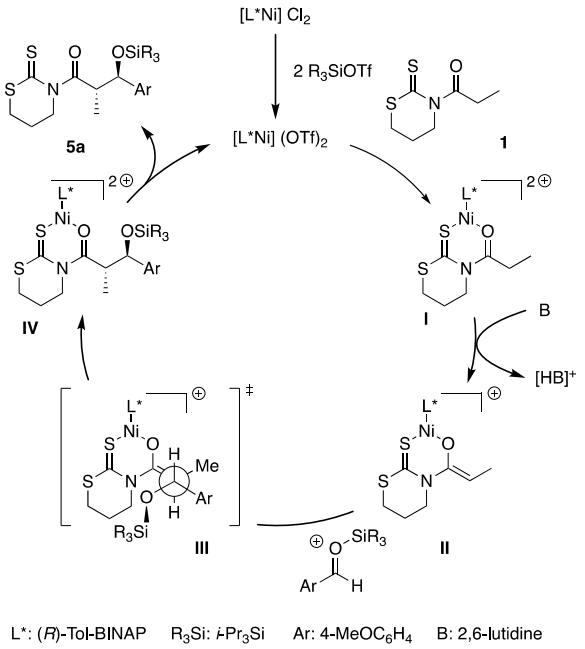
The configuration of **5a** was established as the (2*S*,3*R*) *anti* adduct through an X-ray analysis of the benzyl amide derivative **28**,[14] easily prepared via nucleophilic displacement of the scaffold of **5a** with (*S*)-1-phenyl-1-ethylamine (Scheme 3).[15] Furthermore, amides **29** and **30** were isolated in up to 99% yield after reaction with morpholine and *N*-methoxy-*N*-methyl amine 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 an 85% yield, methyl ester **32** was obtained in a 95% yield by simple stirring of **5a** in methanol, whereas the sodium enolate of ethyl acetate was used to deliver the β-keto ester **33** with 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. With the proposed catalytic cycle depicted in Scheme 4, in which 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 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 to the *Re* π-face of the square planar nickel(II) enolate **II** (Scheme 4).



Scheme 3. Removal of the scaffold and conversion of aldol adducts into enantiomerically pure compounds.

Importantly, the approach to the opposite *Si* π-face is ≈ 3 kcal mol^{-1} less stable, which accounts for the excellent enantiocontrol achieved across all the reactions.



Scheme 4. Mechanistic hypothesis.

In summary, we have developed a direct and asymmetric aldol reaction of *N*-acyl thiazinanethiones and thiazolidinethiones with aromatic aldehydes in the presence of TIPSOTf and promoted by [(*R*)-Tol-BINAP]NiCl$_2$. This reaction gives the corresponding *O*-TIPS protected *anti* aldol adducts with high yields and diastereoselectivity and an excellent enantiocontrol up to *ee* 99%. 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.

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Keywords: aldol reaction• direct reaction • asymmetric catalysis • nickel • thiazinanethione

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

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[14] For the X-ray data, see Supporting Information. Crystallographic data for adduct amide **28** have been also deposited at Cambridge Crystallographic Data Centre as supplementary publication number CCDC 2062607.

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

[16] ONIOM calculations were carried out using the Gaussian09 package. High quantum layer at 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 frameworks of diphosphane ligand was treated by universal field force. For further details, see Supporting Information.

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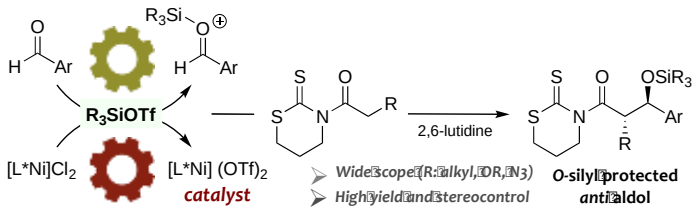
Entry for the Table of Contents



Appropriate and simultaneous activation of robust and easily to handle [Tol-BINAP]$NiCl_2$ and aromatic aldehydes with TIPSOTf orchestrate a direct, asymmetric, and catalytic aldol reaction from a wide array of *N*-acyl-1,3-thiazinane-2-thiones leading to the corresponding TIPS-protected *anti* aldol adducts in a highly efficient and atom economy manner.