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Asymmetric catalysis

Direct, Stereodivergent, and Catalytic Michael Additions of Thioimides to α,β-Unsaturated Aldehydes – Total Synthesis of Tapentadol

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Dedicated to Professor Jaume Vilarrasa.

Abstract: Direct and stereodivergent Michael additions of *N*-acyl 1,3-thiazinane-2-thiones to α,β-unsaturated aldehydes catalyzed by chiral nickel(II) complexes are reported. The reactions proceed with a remarkable regio-, diastereo-, and enantioselectivity, so access to any of the four potential Michael stereoisomers is granted through the appropriate choice of the chiral ligand of the nickel(II) complex. Simple removal of the heterocyclic scaffold furnishes a wide array of either *syn* or *anti* enantiomerically pure derivatives, which can be exploited for the asymmetric synthesis of biologically active compounds, as demonstrated in a new approach to tapentadol. In turn, a mechanism, based on theoretical calculations, is proposed to account for the stereochemical outcome of these transformations.

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Introduction

It is certainly the case that, at present, new methods in Organic Synthesis must be devised with the compelling need for *selectivity*, since they are expected to act in a masterful manner to produce the desired transformation at a specific site without affecting other parts of the molecule.[1,2] In this scenario, the simultaneous control over the *regio-* and *stereoselectivity* of a particular reaction often presents a formidable challenge. A case in point involves conjugated carbonyl compounds. Indeed, they may undergo nucleophilic attacks at either the carbonyl or the conjugated position, namely 1,2- versus 1,4-additions, which usually entail the installation of up to two stereocenters.[3,4] Faced with the complexity of satisfying both selective requirements, the importance of substrate choice has been empirically acknowledged. Actually, traditional wisdom contends that α,β-unsaturated ketones or esters predominantly participate in 1,4-additions, while the more reactive aldehyde counterparts are prone to evolve through the alternative 1,2-pathway.[5–8] Therefore, it should be no surprise that, despite undeniable interest, just a small number of reports describe regio- and stereoselective Michael additions of acyclic carbonyl compounds to α,β-unsaturated aldehydes. So far, none of the currently reported methods take advantage of metal enolates[9,10] and contrarily hinge on organocatalytic approaches, proceeding through the iminium mode of action, in which the carbonyl bond of the electrophile is temporarily replaced by the iminium counterpart. Indeed, pioneering studies by Palomo on the intermolecular *anti* Michael addition of aldehydes to enals catalyzed by a proline derivative demonstrated the feasibility of such a strategy.[11,12] A little later, Barbas reported a comprehensive study on the addition of activated thioesters of aryl acetic acids to cinnamaldehyde, catalyzed by the Jørgensen-Hayashi amine to provide the *anti* Michael adducts with diastereoselectivities up to 3:1 and variable enantiocontrol.[13,14] Consequently, the development of new methods to successfully achieve 1,4-additions in both a regio- and stereoselective manner to provide both *anti* and *syn* Michael adducts is still necessary to grant access to new valuable molecular architectures, unattainable with current methodologies.[15]

In this context and beyond the abovementioned challenges, the interest in a particular stereoselective carbon-carbon bond forming reaction is nowadays increasingly associated to the ability to provide any of the potential stereoisomers,[16] ideally under the premises of Atom Economy[17] and Green Chemistry.[18] In this context, stereodivergent dual catalysis[19,20] has recently emerged as an engaging option for obtaining any stereoisomer in transformations in which up to two new stereocenters are installed.[21] In principle, such a conceptual framework requires the use of distinct chiral catalysts acting on a single set of precursors to exercise independent control on the absolute configuration of the stereocenters formed. Lee has recently demonstrated the gains and opportunities of such an approach in a highly regio- and stereoselective Michael addition of pentafluorophenyl aryl acetates to α,β-unsaturated aldehydes through the appropriate combination of a proline derivative and a chiral Lewis base (see Eq 1 in Scheme 1).[22] Unfortunately, the profile of the nucleophilic partner is once again restricted to relatively acidic aryl acetic esters,[13] so new approaches are needed to enable the enantioselective formation of carbon-carbon bonds through the addition of a wide array of carbonyl compounds to the conjugated position of α,β-unsaturated aldehydes.

Considering the benefits of a process with a wider scope and the lack of *regio-* and *stereoselective* Michael additions of metal enolates to α,β-unsaturated aldehydes, we envisaged that a close, but less stringent version, of the aforementioned stereodivergent dual catalytic model might be successful. This would entail a single transition-metal catalytic model in such a way that the simple change of the chiral ligand would give access to all the potential stereoisomers in a highly regio- and stereocontrolled manner.[16,23]

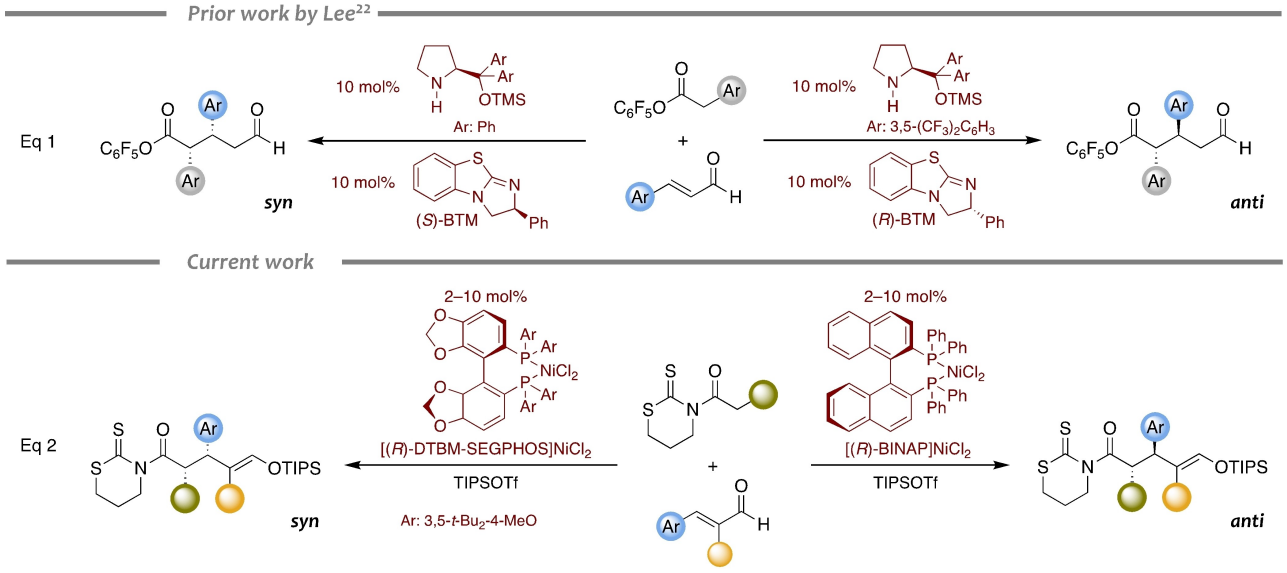
Herein, we report that direct and asymmetric Lewis acid-mediated Michael additions of *N*-acyl 1,3-thiazinane-2-thiones to α,β-unsaturated aldehydes catalyzed by nickel(II) complexes, containing chiral diphosphines 5,5′-bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole (DTBM-SEGPHOS) or 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP), produce, at will, enantiomerically pure *syn* or *anti* stereoisomers in good to high yields (Eq 2 in Scheme 1). Importantly, the aldehyde group is transformed through its activation and becomes a protected silyl enol ether in the resultant Michael adduct, which facilitates further transformations and thus enhances the synthetic usefulness of the method.

Results and Discussion

Preliminary Studies and Optimization

During our studies on the direct, asymmetric, and silyl triflate-mediated aldol reactions from *N*-acyl thiazinanethiones catalyzed by chiral nickel(II) complexes,[24] mixtures of aldol and Michael adducts and other unidentified by-products were obtained when cinnamaldehyde (**a**) was used as the electrophilic partner. In turn, parallel theoretical calculations showed that the participation of C1 and C3 for the LUMO of the silyl-activated cinnamaldehyde were similar (Figure 1). All in all, these signs encouraged us to make further efforts towards the search of selective 1,4-additions.

Therefore, we first explored the regiochemical outcome of the Michael additions using the achiral $(Me_3P)_2NiCl_2$ complex under differing conditions. To our surprise, the silyl triflate proved to be crucial. Indeed, the use of a sterically hindered silyl triflate such as triisopropylsilyl triflate (TIPSOTf) produced the desired Michael adduct with remarkable regioselectivity, while less bulky trimethylsilyl triflate



Scheme 1. Direct and Stereodivergent Michael Additions to α,β-Unsaturated Aldehydes. TMS = trimethylsilyl, TIPS = triisopropylsilyl, TIPSOTf = triisopropylsilyl triflate.

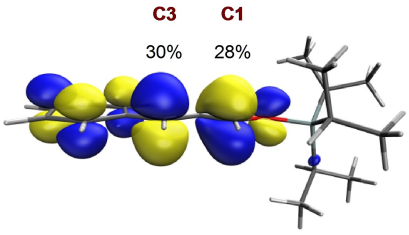


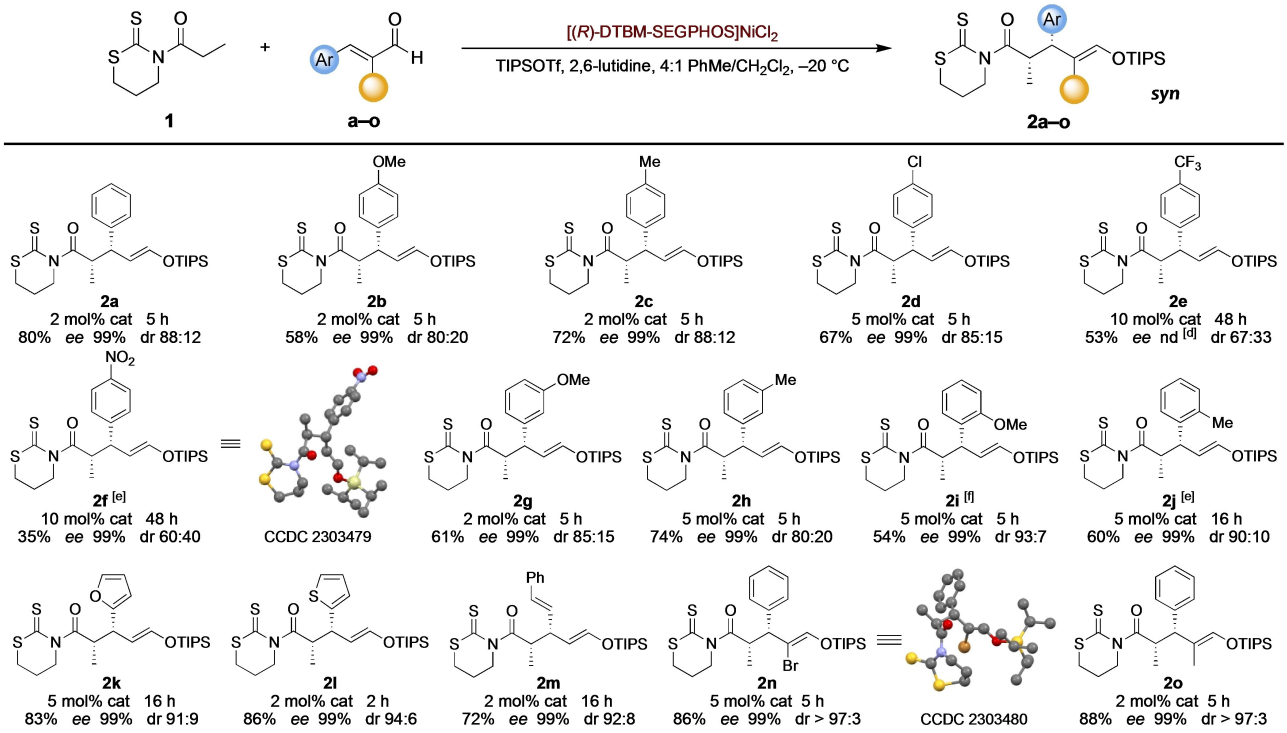
Figure 1. LUMO of [PhCH=CHCHO-TIPS]$^+$.

(TMSOTf) showed opposing selectivity (see Table S1). The scaffold turned out to play a key role too; the thiazinanethione[25] and thiazolidinethione adducts proved to be the most selective, with the former being more efficient in terms of the kinetics of the process (see Table S1).[26] Having identified the pairing of thiazinanethione/TIPSOTf as the best combination for obtaining Michael adducts, we next assessed the influence of chiral nickel(II) catalysts. We were pleased to observe that all chiral catalysts examined produced the desired 1,4-addition with absolute regioselectivity. Furthermore, the diastereoselectivity heavily depended both on the solvent and the ligand (see Table S2) to such an extent that [DTBM-SEGPHOS]$NiCl_2$ in 4:1 toluene/CH_2Cl_2 gave the *syn* Michael adduct (*syn*/*anti* 88:12). Such a solvent mixture also turned out to be the most appropriate when [BINAP]$NiCl_2$ was used; but however, this catalyst led to the *anti* counterpart instead (*syn*/*anti* 15:85). Finally, and most importantly, both the *syn* and *anti* diastereomers were obtained enantiomerically pure (*ee* 99%). All together, these results proved that we could access at will, in a highly stereoselective manner, any of the four possible Michael stereoisomers, with absolute regiocontrol, by just switching between [DTBM-SEGPHOS]$NiCl_2$ and [BINAP]$NiCl_2$ and choosing the appropriate enantiomer of the ligand (Eq 2 in Scheme 1).

Scope

Having established an unusual, direct, and stereodivergent Michael addition to cinnamaldehyde (**a**), we moved to examine the scope of the reaction catalyzed by [(*R*)-DTBM-SEGPHOS]$NiCl_2$ (Scheme 2). Unfortunately, α,β-unsaturated aldehydes containing an alkyl group, a heteroatom, or an ester group at the β position proved unsuitable.[27] On the contrary, β-aryl-α,β-unsaturated aldehydes **a**–**o** turned out to be excellent substrates and all the corresponding *syn* diastereomers **2a**–**o** were easily isolated in enantiomerically pure form by column chromatography except for trifluoromethyl-derived aldehyde **e**.

Indeed, most of these aldehydes, with the single exception of *ortho* methoxy aldehyde **i**, reacted with



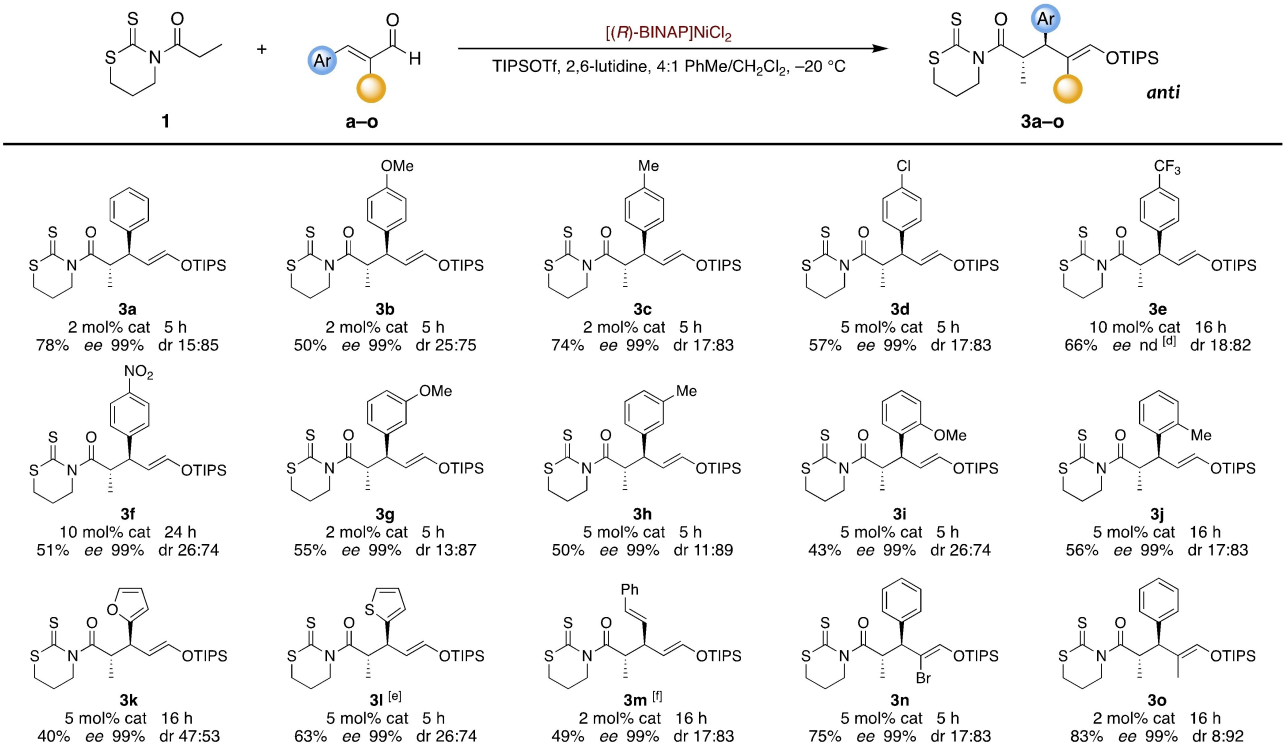
Scheme 2. TIPSOTf-Mediated Michael additions of *N*-propanoyl thiazinanethione **1** to α,β-unsaturated aldehydes catalyzed by [(*R*)-DTBM-SEGPHOS]$NiCl_2$.[a–c]

[a] Isolated yields of the enantiomerically pure **2a**–**o** syn adducts are shown. [b] Enantiomeric excess established by chiral HPLC. [c] Diastereomeric ratio (syn/anti) established by ^{1}H NMR analysis. [d] It was impossible to determine the ee by chiral HPLC. [e] Conversion: 85–90%. [f] rr (1,4:1,2) 87:13.

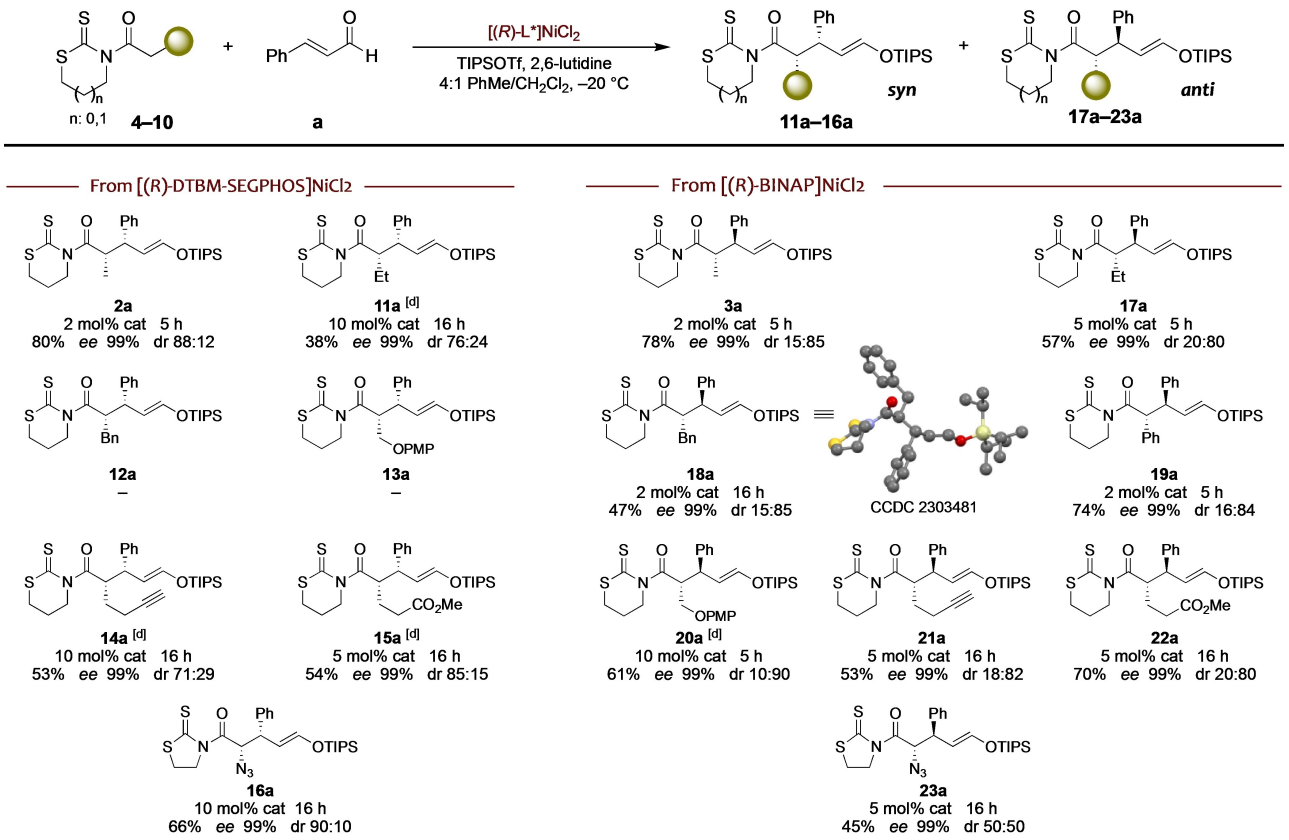
absolute regiocontrol (rr 1,4:1,2 > 99:1) to provide enantiomerically pure (*ee* 99 %) *syn* Michael adducts **2a–o** in good to high yields. As shown in Scheme 2, the electronic character of the substituents at the *para* position of the aromatic ring has a profound effect on the kinetics of the process. Indeed, electron-donating groups seen in **a–c** required a low catalyst loading of 2 mol % to reach completion in 5 h. Aldehyde **d**, containing chlorine as a slightly electron-withdrawing group, required 5 mol % of the catalyst, while the stronger trifluoromethyl or nitro groups, in **e** and **f** respectively, demanded 10 mol % of the catalyst and reaction times up to 48 h. Even better results were achieved with aldehydes **k** and **l** containing an heteroaromatic ring of furane or thiophene, which allowed for the isolation of enantiomerically pure *syn* adducts **2k** and **2l** in yields of 83–86 %. Noteworthily, the method tolerated the placement of substituents at the *meta* and even the *ortho* position and adducts **2g–j** were obtained under similar conditions and with results close to the corresponding *para* substituted counterparts **2b** and **2c**. Eventually, α,β-γ,δ-unsaturated aldehyde **m**, which could potentially undergo 1,4- and 1,6-attacks, proved to be an excellent substrate since it led to a single regioisomer **2m** with outstanding stereocontrol (dr 92:8, *ee* 99 %) in a 72 % yield. Finally, α-substituted aldehydes **n** and **o** also participated in totally stereocontrolled reactions and provided diastereomerically and enantiomerically pure (dr > 97:3, *ee* 99 %) *syn* Michael products **2n** and **2o** in yields of 86–88 %. It is worth highlighting that the absolute configuration of Michael adducts **2** was firmly established through X-ray analysis of crystals from **2f** and **2n**.[28]

An analogous study was carried out using [(*R*)-BINAP]$NiCl_2$. Results summarized in Scheme 3 show that both the regio- and the enantiocontrol provided by this complex are as good as those imparted by the former. Furthermore, these reactions proved to be faster than those catalyzed by [DTBM-SEGPHOS]$NiCl_2$ and, for instance, the addition to the reluctant aldehyde **f** was, this time, complete in 24 h. The diastereoselectivities were high and close to those of the *syn* series, while the isolated yields of the enantiomerically pure *anti* diastereomers **3a–o** ranged from moderate to high. From a general point of view, the access to the enantiomerically pure *anti* configuration utilizing [BINAP]$NiCl_2$ combines perfectly with that provided by the [DTBM-SEGPHOS]$NiCl_2$ complex and makes the overall method a stereodivergent strategy for Michael additions to α,β-unsaturated aldehydes (Eq 2 in Scheme 1).

Finally, we met the challenge of expanding both procedures to other *N*-acyl thiazinanethiones. Results summarized in Scheme 4 indicate that the reaction catalyzed by [DTBM-SEGPHOS]$NiCl_2$ generally provides the expected *syn* stereoisomers but is highly sensitive to the steric hindrance of the Cα group. A case in point was *N*-butanoyl thiazinanethione **4**, which required a fivefold increase of the



Scheme 3. TIPSOTf-Mediated Michael additions of *N*-propanoyl thiazinanethione **1** to α,β-unsaturated aldehydes catalyzed by [(*R*)-BINAP]$NiCl_2$.[a–c] [a] Isolated yields of the enantiomerically pure **3a–o** anti adducts are shown. [b] Enantiomeric excess established by chiral HPLC. [c] Diastereomeric ratio (syn/anti) established by ^{1}H NMR analysis. [d] It was impossible to determine the ee by chiral HPLC. [e] Reaction temperature of −40 °C. [f] rr (1,4:1,6): 70:30.



Scheme 4. TIPSOTf-Mediated Michael additions of *N*-acyl thiazinanethiones **4**–**10** to cinnamaldehyde (**a**) catalyzed by chiral nickel(II) complexes.[a–c] [a] Isolated yields of the enantiomerically pure syn or anti adducts are shown. [b] Enantiomeric excess established by chiral HPLC. [c] Diastereomeric ratio (syn/anti) established by ^{1}H NMR analysis. [d] rr (1,4:1,2): ca 90:10.

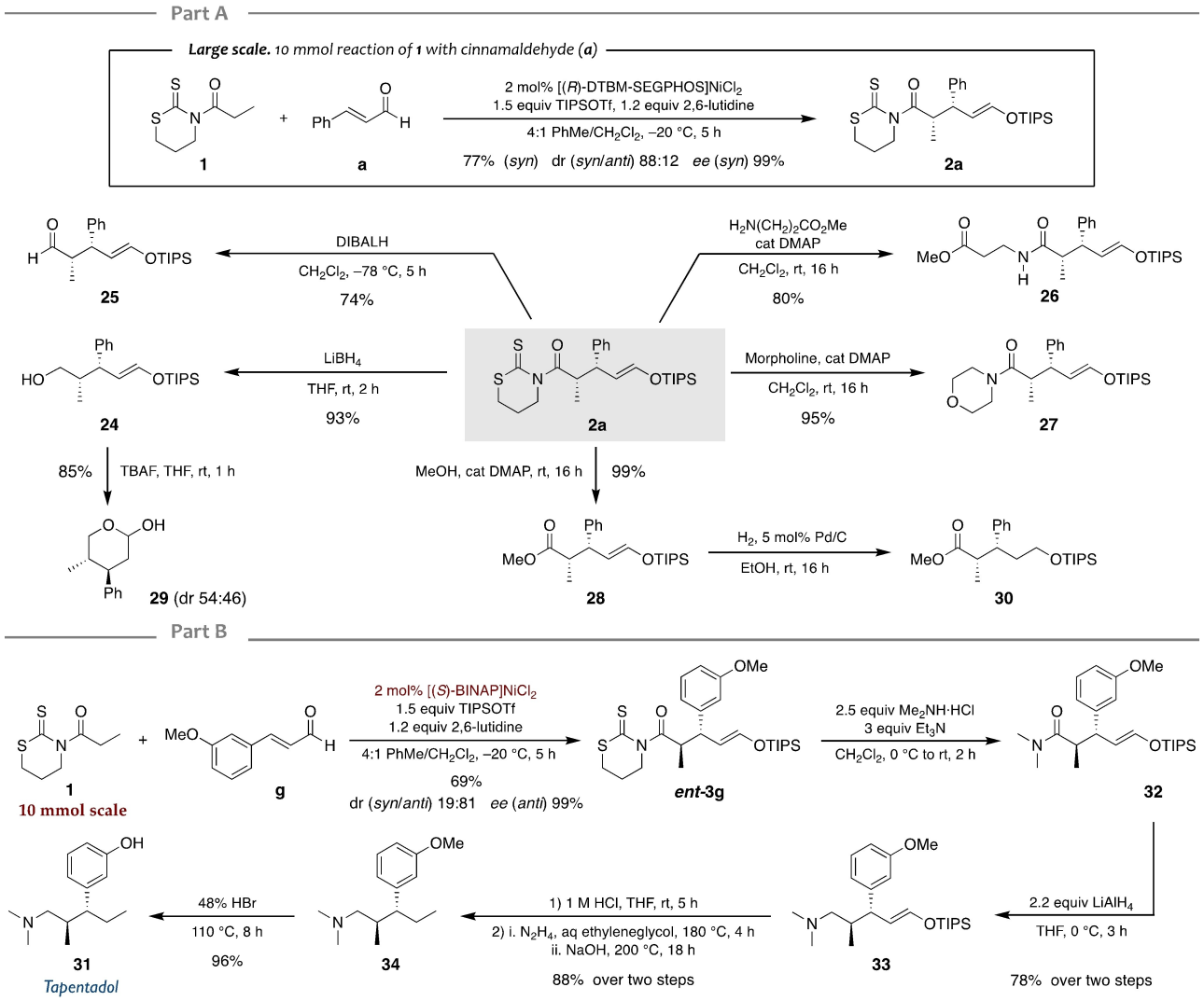
catalyst loading with respect to *N*-propanoyl thiazinanethione **1**, to produce *syn* Michael adduct **11a** with a poorer regioselectivity (rr 1,4:1,2 90:10) and a lower diastereoselectivity (dr 76:24) in a much lower 38 % yield. In turn *syn* adducts **12a** and **13a** possessing bulky groups were not obtained, whereas *N*-phenylacetic thioimide **6** surprisingly gave *anti* **19a** as the major stereoisomer. Other substrates with less sterically hindered substituents performed better and gave the corresponding enantiomerically pure *syn* stereoisomers **14a**–**15a** in good yields. In turn, the results achieved with α-azidoacetyl thiazolidinethione **10**[29] were particularly noteworthy, as the expected *syn* diastereomer **16a** was obtained with excellent stereocontrol (dr 90:10, *ee* 99 %) and an isolated yield of 66 %.

Parallel reactions catalyzed by [BINAP]$NiCl_2$ were less dependent on the steric bulk of the substrate and using 2–5 mol % of catalyst, enantiomerically pure *anti* adducts **17a**–**23a** were isolated in yields of 50–75 % with high selectivity except in the case of α-azido thiazolidinethione **10**, which produced an equimolar mixture of *syn* and *anti* stereoisomers, and thioimide **7**, which produced a slight erosion of the regioselectivity of *anti* **20a**. Importantly, the absolute configuration of *anti* adduct **18a** was corroborated through X-ray analysis.[28]

Synthetic Applications

With two fully optimized procedures in hand, we next assessed the removal of the heterocyclic scaffold to yield a variety of chiral intermediates. Initially, the reaction catalyzed by [(*R*)-DTBM-SEGPHOS]$NiCl_2$ was scaled up to get large quantities of model *syn* stereoisomer **2a** in order to test the transformations represented in Part A of Scheme 5. We were pleased to observe that the Michael addition of **1** to cinnamaldehyde (**a**) worked perfectly at a 10 mmol scale, allowing the isolation of enantiomerically pure **2a** in a 77 % yield, which proves the robustness of the method. Then, its reduction with $LiBH_4$ or diisobutylaluminium hydride (DIBALH) afforded alcohol **24** or aldehyde **25** respectively in high yields. In turn, secondary and tertiary amides **26** and **27** or methyl ester **28** were easily prepared by simple treatment with the required amines or methanol in the presence of 4-dimethylaminopyridine (DMAP). Finally, the resultant silyl enol moiety turned out to be strategic and its appropriate manipulation afforded hemiacetal **29** (dr 54:46) and the saturated and protected δ-hydroxy ester **30** in excellent yields.

As part of these efforts, we also considered the application of the *anti* procedure to the synthesis of commercially available tapentadol **31** (Part B of Scheme 5), an opioid drug with strong analgesic effects used for the



Scheme 5. Transformations of Michael adducts. Synthesis of tapentadol. TBAF = tetrabutylammonium fluoride.

treatment of pain in several diseases.[30] Our retrosynthetic analysis hinged on the strategic disconnection of both stereocenters through a Michael reaction.[31,32]

Thus, the first step involved the stereocontrolled Michael addition of thioimide **1** to (*E*)-3-(3-methoxyphenyl)-2-propenal (**g**) catalyzed by 2 mol % of [(*S*)-BINAP]$NiCl_2$ at a 10 mmol scale (Part B of Scheme 5). Interestingly, the scale was important and enantiomerically pure *anti* ***ent*-3g** was isolated in this case with a slightly better diastereomeric ratio (dr *syn*/*anti* 19:81) and a significantly higher yield of 69 % than those obtained at 1 mmol scale (see Scheme 3). Smooth removal of the heterocycle in ***ent*-3g** with dimethylamine gave amide **32** in a quantitative yield. Then, it was reduced with $LiAlH_4$ to provide amine **33** in a 78 % yield. Treatment of the silyl enol ether with 1 M HCl for 5 h led to the corresponding aldehyde, which was immediately submitted to a Wolff–Kishner reduction using the Huang-Minlon modification[33] to obtain deoxygenated amine **34** in an 88 % two-step yield. Eventually, demethylation of **34** with 48 % HBr under standard conditions led to tapentadol **31** in a 96 % yield, whose spectroscopic and physical data matched those reported in the literature. Importantly, our synthetic sequence takes advantage of a highly stereocontrolled Michael addition to furnish enantiomerically pure tapentadol with an overall yield of 45 % in six steps.[34,35]

Theoretical Calculations. Mechanism

Once the wide scope and the synthetic interest of the Michael addition had been established, we focused our attention to unraveling the mechanistic basis of such a stereodivergent transformation.

With this idea in mind, we initially evaluated the potential reacting centers of the triisopropylsilyl (TIPS)-activated cinnamaldehyde (**a**), a suitable model of the putative electrophilic partner. Interestingly, contributions of both the C1 and C3 carbons turned out be almost identical (Figure 1), which indicated that the outstanding regioselectivity observed within the present study must rely mostly on

the steric bulk of the TIPS group, which is in accordance with the trend summarized in Table S1.

Building on this initial information, we then carried out a comprehensive analysis of the transition states involved in the addition of the chiral nickel enolates from thioimide **1** to the TIPS-activated cinnamaldehyde.

Initially, we optimized the molecular geometry of the singlet state of [{(*R*)-Diphos}Ni(thiazinanethione)]$^+$ enolates in which the Diphos ligands are the chiral chelating disphosphines (DTBM-SEGPHOS or BINAP). Four conformations were optimized for the *S*,*O*-chelate and the thiazinane rings (see Figure S1). All the conformations from the BINAP-derived enolate were in a range of 3 kcal mol^{-1}, the two most stable resulting in a slightly distorted square-planar geometry for nickel ($S_{SQ\text{-}4}$ <3.0). However, a completely different energetic ordering was found for the DTBM-SEGPHOS counterpart, likely due to the large steric character of the diphosphine substituents, which suggests that other factors may play an important role in stabilizing each conformation.

Following previous results, the four minima for each catalyst were taken into account to compute the transition states of the additions to the activated cinnamaldehyde, [(*i*-Pr$_3$Si)O=CHCH=CHPh]$^+$. The approach of such an oxocarbenium intermediate generated four transition states for each conformation considering the two π diastereotopic faces of the nickel enolate and the relative arrangement of the groups at the β position of the electrophile.

Then, sixteen transition states for the nickel enolate containing the DTBM-SEGPHOS ligand were calculated (see Figure S2). Interestingly, the most stable among them involves the approach of the *Re* π face of the enolate to the *Si* π face of the activated cinnamaldehyde (namely **TS-D3** in Figure 2, top), in which the TIPS group is directed towards the thiazinane ring. This leads to the *syn* **2a** stereoisomer. In turn, the alternative approach giving access to the *anti* **3a** diastereomer (**TS-C1**, see Figure S2) places the phenyl group close to the heterocycle and turns out to be disfavored by +0.9 kcal mol^{-1}. Other transition states engaging the opposite *Si* π-face of the enolate are higher in energy (from +2.5 to +3.4 kcal mol^{-1}) and exhibit a different conformation of the nickel-chelate ring. The Boltzmann distribution of all these transition states indicates that only two of them truly participate in the reaction, **TS-D3** and **TS-C1**, which predicts a *syn*/*anti* diastereomeric ratio of 85:14 (**2a**/**3a**) at −20 °C with others which would lead to the opposing enantiomer contributing less than 1 %. These results nicely match the experimental results summarized in Scheme 2 (dr 88:12, *ee* 99 %).

In turn, a parallel study for the BINAP-derived enolate predicted that the major stereoisomer should be *anti* **3a**, opposite to that obtained from DTBM-SEGPHOS. The molecular geometries of the resultant transition states along with their relative Gibbs free energies in solution in a range of 20 kcal mol^{-1} are shown in Figure S3. In this case, the most favorable transition state (namely **TS-A1** in Figure 2, bottom) involves the approach of the *Re* π face of the enolate to the *Re* π face of the activated cinnamaldehyde in which the thiazinane ring is close to the phenyl group and

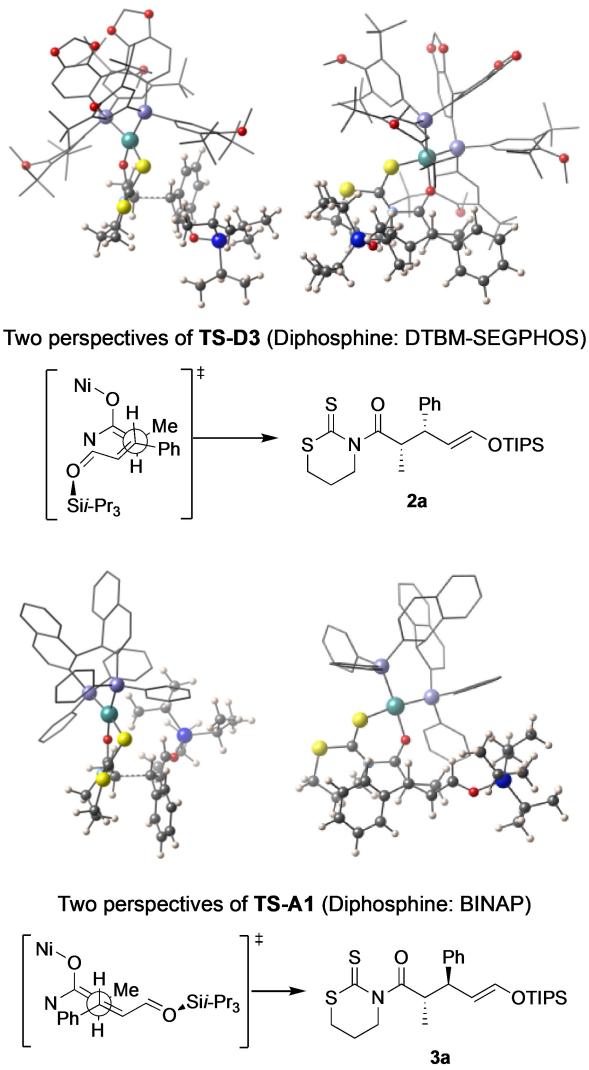


Figure 2. Transition states leading to the *syn* and the *anti* stereoisomers.

far from the bulky TIPS group of the electrophile. This produces the *anti* **3a** stereoisomer in full accordance with the experimental results. Surprisingly, other transition states show energies too high to participate in the stereochemical outcome of the reaction, so *anti* **3a** is expected to be the only stereoisomer. These results account for the amazing enantiocontrol observed throughout these reactions, but the lack of prediction for the minor *syn* **2a** counterpart indicates that minor influences should be also considered.

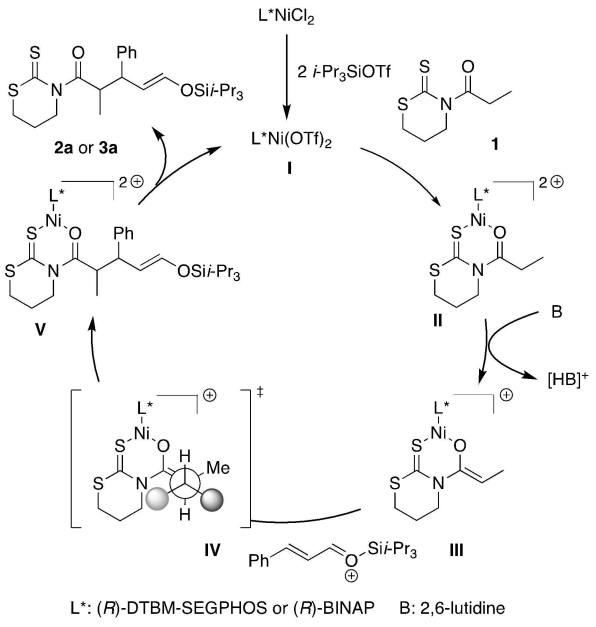
Despite the fact that the reasons accounting for the stereochemical outcome of the reaction are manifold, the analysis of the transition states of the carbon-carbon bond forming step provide clues for a better understanding of the overall process. Indeed, assuming that the reaction proceeds through an open transition state involving a chelated enolate in which the nickel geometry is mostly square planar, conformations of the thiazinane heterocycle may be of paramount importance to determine distinct approaches to the activated electrophile; this is particularly crucial for the

DTBM-SEGPHOS enolate. Furthermore, chiral ligands containing phosphines with bulky *tert*-butyl groups, such as the DTBM-SEGPHOS and the related 2,2′-bis[bis(4-methoxy-3,5-di-*tert*-butylphenyl)phosphino]-4,4′,6,6′-tetramethoxy-1,1′-biphenyl (DTBM-GARPHOS, see Table S2), play a crucial role to steer the stereochemical outcome towards the *syn* **2a** stereoisomer, through a transition state in which, in a counterintuitive manner, the thiazinane ring is close to the TIPS group (Figure 2, top).

The abovementioned transition states are consistent with a mechanism represented in Scheme 6 in which a silyl-activated cinnamaldehyde approaches a chelated nickel(II) enolate from thioimide **1** through the open transition states shown in Figure 2. Indeed, taking advantage of Sodeoka's findings[36] on the activation of nickel(II) chloride complexes with silyl triflates, the chiral nickel(II) chloride complexes employed in this study generate in situ nickel(II) triflate **I**, the real catalytic species. Coordination of **I** with **1** produces chelate **II**, which can be deprotonated by 2,6-lutidine to produce the nickel(II) enolate **III**. Then, the *Re* π-face of **III** approaches the activated aldehyde through the open transition states **IV** in which the distribution of the substituents determines the configuration of the new β stereocenter in **V**. Eventually, release of the L*Ni group gives the desired Michael adduct (**2a** or **3a**) and the nickel(II) triflate **I** necessary for a new catalytic cycle.

Conclusion

We have developed a direct and asymmetric TIPSOTf-mediated Michael addition of thioimides to α,β-unsaturated aldehydes catalyzed by chiral nickel(II) complexes possessing DTBM-SEGPHOS or BINAP ligands. The reaction shows remarkable regio- and stereochemical control, and delivers at will any of the potential *syn* or *anti* stereoisomers, depending on the chiral ligand, in a highly efficient stereodivergent manner. In turn, the resultant adducts can be smoothly converted into a wide array of enantiomerically pure derivatives that can be used for the synthesis of biologically active compounds, as demonstrated in a new approach to tapentadol. Finally, theoretical studies clarify the mechanistic intricacies of such a transformation and provide arguments for a proper understanding of the observed stereodivergency.



Scheme 6. Proposed mechanism.

Supporting Information

The authors have cited additional references within the Supporting Information.[37–48]

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

If our manuscript is accepted, a copy of a preprinted version will be available in the repository of the Universitat de Barcelona

Keywords: Michael addition · asymmetric catalysis · nickel complexes · stereodivergent synthesis · tapentadol

[1] a) T. Newhouse, P. S. Baran, R. W. Hoffmann, *Chem. Soc. Rev.* **2009**, *38*, 3010–3021; b) D. S. Peters, C. R. Pitts, K. S. McClymont, T. P. Stratton, C. Bi, P. S. Baran, *Acc. Chem. Res.* **2021**, *54*, 605–617.

[2] K. C. Nicolaou, J. S. Chen, *Classics in Total Synthesis III*, Wiley-VCH, Weinheim, **2011**.

[3] For enantioselective and catalytic aldol additions, see: Y. Yamashita, T. Yasukawa, W.-J. Yoo, T. Kitanosono, S. Kobayashi, *Chem. Soc. Rev.* **2018**, *47*, 4388–4480.

[4] For enantioselective and catalytic Michael Reactions, see: a) E. Reyes, U. Uria, J. L. Vicario, L. Carrillo, in *Organic Reactions*, *Vol. 90* (Ed.-in-Chief: S. E. Denmark), John Wiley & Sons, Hoboken, **2016**, pp. 1–898; b) K. Zheng, X. Liu, X. Feng, *Chem. Rev.* **2018**, *118*, 7586–7656.

[5] J. Clayden, N. Greeves, S. Warren, in *Organic Chemistry*, Oxford University Press, Oxford, **2012**.

[6] P. Perlmutter, in *Conjugate Addition Reactions in Organic Synthesis*, Pergamon Press, Oxford, **2013**.

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

[8] For an insightful switch of regioselectivity in the asymmetric addition of aldehydes to enals, see: T. Kano, H. Maruyama, R. Sakamoto, K. Maruoka, *Chem. Commun.* **2015**, *51*, 10062–10065.

[9] For rare examples of Michael additions of metal enolates of activated carbonylic compounds to acrolein, see: a) M. Sawamura, H. Hamashima, Y. Ito, *J. Am. Chem. Soc.* **1992**, *114*, 8295–8296; b) Y. Motoyama, Y. Koga, K. Kobayashi, K. Aoki, H. Nishiyama, *Chem. Eur. J.* **2002**, *8*, 2968–2975.

[10] A few examples of Michael additions of cyclic β-keto esters to acrolein and crotonaldehyde have been described, see: Y. Hamashima, D. Hotta, N. Umebayashi, Y. Tsuchiya, T. Suzuki, M. Sodeoka, *Adv. Synth. Catal.* **2005**, *347*, 1576–1586.

[11] C. Palomo, A. Landa, A. Mielgo, M. Oiarbide, A. Puente, S. Vera, *Angew. Chem. Int. Ed.* **2007**, *46*, 8431–8435.

[12] For an early report on Michael additions of cyclic β-keto esters to α,β-unsaturated aldehydes catalyzed by cinchona derivatives, see: F. Wu, R. Hong, J. Khan, X. Liu, L. Deng, *Angew. Chem. Int. Ed.* **2006**, *45*, 4301–4305.

[13] D. A. Alonso, S. Kitagaki, N. Utsumi, C. F. Barbas III, *Angew. Chem. Int. Ed.* **2008**, *47*, 4588–4591.

[14] For other studies on organocatalytic Michael additions to enals, see: a) S. Cabrera, E. Reyes, J. Alemán, A. Milelli, S. Kobbelgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2008**, *130*, 12031–12037; b) S. Duce, I. Alonso, A. M. Lamsabhi, E. Rodrigo, S. Morales, J. L. G. Ruano, A. Poveda, P. Mauleón, M. B. Cid, *ACS Catal.* **2018**, *8*, 22–34, and references therein.

[15] For other organocatalytic approaches based on preformed enolates, see: a) S. P. Brown, N. C. Goodwin, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, *125*, 1192–1194; b) W. Wang, H. Li, J. Wang, *Org. Lett.* **2005**, *7*, 1637–1639.

[16] a) L. Lin, X. Feng, *Chem. Eur. J.* **2017**, *23*, 6464–6482; b) M. Bihani, J. C.-G. Zhao, *Adv. Synth. Catal.* **2017**, *359*, 534–575; c) I. P. Beletskaya, C. Nájera, M. Yus, *Chem. Rev.* **2018**, *118*, 5080–5200.

[17] B. M. Trost, *Science* **1991**, *254*, 1471–1477.

[18] a) P. T. Anastas, M. M. Kirchhoff, *Acc. Chem. Res.* **2002**, *35*, 686–694; b) B. M. Trost, *Acc. Chem. Res.* **2002**, *35*, 695–705.

[19] S. Krautwald, E. M. Carreira, *J. Am. Chem. Soc.* **2017**, *139*, 5627–5639.

[20] X. Huo, G. Li, X. Wang, W. Zhang, *Angew. Chem. Int. Ed.* **2022**, *61*, e202210086.

[21] For a milestone report, see: S. Krautwald, D. Sarlah, M. A. Schafroth, E. M. Carreira, *Science* **2013**, *340*, 1065–1068.

[22] B. Kim, Y. Kim, S. Y. Lee, *J. Am. Chem. Soc.* **2021**, *143*, 73–79.

[23] For a recent example on aldol reaction, see: M. A. Rahman, T. Cellnik, B. B. Ahuja, L. Li, A. R. Healy, *Sci. Adv.* **2023**, *9*, eadg8776.

[24] S. C. D. Kennington, S. F. Teloxa, M. Mellado-Hidalgo, O. Galeote, S. Puddu, M. Bellido, P. Romea, F. Urpí, G. Aullón, M. Font-Bardia, *Angew. Chem. Int. Ed.* **2021**, *60*, 15307–15312.

[25] S. C. D. Kennington, O. Galeote, M. Mellado-Hidalgo, P. Romea, F. Urpí, *Org. Synth.* **2021**, *98*, 374–390.

[26] For other examples showing the key role of the heterocycle, see a) 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; b) M. Mellado-Hidalgo, E. A. Romero-Cavagnaro, S. Nageswaran, S. Puddu, S. C. D. Kennington, A. M. Costa, P. Romea, F. Urpí, G. Aullón, M. Font-Bardia, *Org. Lett.* **2023**, *25*, 659–664.

[27] Starting materials were recovered in these cases, which suggests that such α,β-unsaturated aldehydes are not properly activated with TIPSOTf under the reaction conditions.

[28] Deposition numbers 2303479 (for **2f**), 2303480 (for **2n**), and 2303481 (for **18a**) contain 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.

[29] Thiazolidinethione was employed because of the unexpected instability of the *N*-azidoacetyl thiazinanethione counterpart, see: S. F. Teloxa, M. Mellado-Hidalgo, S. C. D. Kennington, P. Romea, F. Urpí, G. Aullón, M. Font-Bardia, *Chem. Eur. J.* **2022**, *28*, e202200671.

[30] a) T. M. Tzschentke, T. Christoph, B. Kögel, K. Schiene, H.-H. Hennies, W. Englberger, M. Haurand, U. Jahnel, T. I. F. H. Cremers, E. Friderichs, J. De Vry, *J. Pharmacol. Exp. Ther.* **2007**, *323*, 265–276; b) S. M. Hoy, *Drugs* **2012**, *72*, 375–393; c) U. Freo, P. Romualdi, H. G. Kress, *J. Pain. Res.* **2019**, *12*, 1537–1551; d) J. Santos, J. Alarcão, F. Fareleira, A. Vaz-Carneiro, J. Costa, *Cochrane Database Syst. Rev.* **2015**, CD009923; e) P. J. Wiffen, S. Derry, K. Naessens, R. F. Bell, *Cochrane Database Syst. Rev.* **2015**, CD011460.

[31] For a review on metal-catalyzed asymmetric Michael additions in natural products synthesis, see: C. Hui, F. Pu, J. Xu, *Chem. Eur. J.* **2017**, *23*, 4023–4036.

[32] For an overview on synthetic approaches to tapentadol, see: P. P. Graczyk, O. Zbrojkiewicz, S. Nerdinger, *Tetrahedron: Asymmetry* **2017**, *28*, 387–400.

[33] Huang-Minlon, *J. Am. Chem. Soc.* **1946**, *68*, 2487–2488.

[34] For a recent and highly efficient total synthesis of tapentadol (eight steps, 47 %) based on the asymmetric coupling of 1,3-dienes with pentafluorophenyl acetates, see: Q. Zhang, M. Zhu, W. Zi, *Chem.* **2022**, *8*, 2784–2796.

[35] For a recent formal synthesis of tapentadol based on an asymmetric hydrogenation of an α-methyl-β-ketoamide, see: L. Zhang, Z. Wang, Z. Han, K. Ding, *Angew. Chem. Int. Ed.* **2020**, *59*, 15565–15569.

[36] T. Suzuki, Y. Hamashima, M. Sodeoka, *Angew. Chem. Int. Ed.* **2007**, *46*, 5435–5439.

[37] C. F. H. Allen, C. O. Edens Jr, *Org. Synth.* **1945**, *25*, 92–94.

[38] K. Ando, H. Watanabe, X. Zhu, *J. Org. Chem.* **2021**, *86*, 6969–6973.

[39] H. Iida, Y. Akatsu, K. Mizukami, S. Natori, M. Matsukawa, K. Takahashi, *Synth. Commun.* **2016**, *46*, 581–585.

[40] Q. Zhang, R. Zhang, G. Tian, J. Li, F. Zhu, X. Jiang, J. Shen, EP2671878-A1 **2016**.

[41] K. C. Nicolaou, A. Li, D. J. Edmonds, G. S. Tria, S. P. Ellery, *J. Am. Chem. Soc.* **2009**, *131*, 16905–16918.

[42] C. Srivari, S. M. Prathama, K. K. Ramagonolla, S. Genji, US20220177413-A1, **2022**.

[43] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman,

J. V. Ortiz, J. Cioslowski, D. J. Fox, *Gaussian 09 (Revission D.1)*; Gaussian Inc.: Wallingford CT **2010**.
[44] 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**, *462*, 1–21.
[45] 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.
[46] A. Schäfer, C. Huber, R. Ahlrichs, *J. Chem. Phys.* **1994**, *100*, 5829–5835.
[47] J. Tomasi, B. Mennucci, R. Cammi, *Chem. Rev.* **2005**, *105*, 2999–3094.
[48] M. Llunell, D. Casanova, J. Cirera, P. Alemany, S. Alvarez, *SHAPE* (version 2.0), Barcelona, **2010**.

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Research Articles

Asymmetric catalysis

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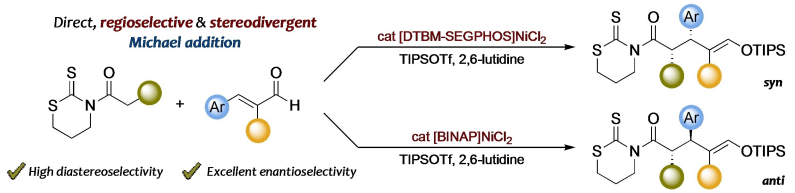
Direct, Stereodivergent, and Catalytic Michael Additions of Thioimides to α,β-Unsaturated Aldehydes – Total Synthesis of Tapentadol



The direct, triisopropy silyl triflate (TIPSOTf)-mediated, regioselective and stereodivergent Michael additions of thioimides to α,β-unsaturated aldehydes catalyzed by chiral nickel complexes give any of the potential *syn* and *anti* diastereomers, at will, with good to high yields. The resultant adducts can be easily transformed into a wide array of enantiomerically pure intermediates ready to participate in the asymmetric synthesis of biologically active compounds.

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