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Chiral Phosphoric Acid–Catalyzed Enantioselective Formal [4+2] Cycloaddition between Dienecarbamates and 2–Benzothiazolimines

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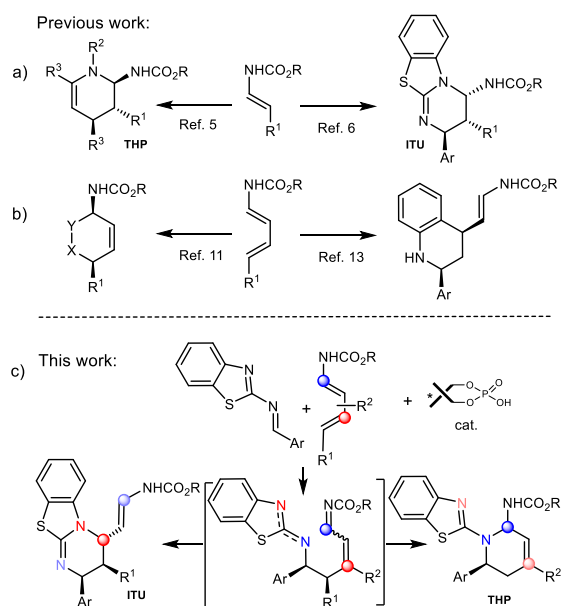
Abstract. An enantioselective chiral phosphoric acid catalyzed formal [4+2] cycloaddition between 2–benzothiazolimines and *N*–H–1,3–dienecarbamates is described. A divergence in reaction pathways was observed depending on the dienes employed. The reaction performed with 4–substituted dienes produced benzothiazolopyrimidines as major product in yields ranging from 42 to 67%, as single diastereoisomer and with enantioselectivity between 93 and 99%. The same reaction performed with 3–substituted dienes, however, gave highly enantioenriched 1,2,3,4–tetrahydroquinolines as the major products albeit with moderate diastereoselectivity.

Keywords: Dienecarbamate; Chiral phosphoric acid; cycloaddition; Heterocycle; Aza–Diels–Alder reaction

Tetrahydropyridines (THP)^[1] and benzothiazolopyrimidines^[2] have been heavily targeted since these two heterocyclic motifs provide an entry to various medicinally relevant products. In addition, benzothiazolopyrimidines, also referred to isothiouras (ITU), have been found to be excellent Lewis base organocatalysts.^[3] Therefore, a tremendous amount of effort has been devoted to develop efficient enantioselective catalytic methods for construction of both type of heterocycles. Among them, [4 + 2] cycloaddition strategies are one of the most efficient and direct ways to synthesize these corresponding heterocycles.^[4] In this context, our group reported an enantioselective synthesis of tetrahydropyridines through chiral phosphoric acid catalyzed enantioselective Diels–Alder reaction between enecarbamates and unsaturated imine (Scheme 1a, left).^[5] More recently, we disclosed a chiral phosphoric acid catalyzed [4 + 2] cycloaddition of enecarbamates with 2–benzothiazolimines leading to diverse benzothiazolopyrimidines with excellent diastereo– and enantioselectivities (Scheme 1a, right).

^[6] Due to the important biological activities of both type of azacycles and since they carry some common structural element, developing of a divergent synthetic strategy would be particularly attractive.^[7] As such, we became interested in further exploring enantioselective [4 + 2] cycloaddition strategies in this direction.

N–H 1,3–Dienecarbamates are valuable building blocks in organic synthesis. Introduced by Overman in 1978,^[8] they have since been found to be valuable units enabling the synthesis of several natural products such as perhydrogephyrotoxin, gephyrotoxin, pumiliotoxin C or amiclennomycin.^[9] As electron rich dienes, they were used as partner in various enantioselective normal electron demand [4+2] cycloadditions leading to 6–membered cyclic amines, for which chiral phosphoric acid catalysis^[10] proved to be particularly effective (Scheme 1b, left). Indeed, when opposed to dienophiles such as alkenes, quinones, nitroso or diazo compounds, they give access to valuable cyclohexenes amines or related azacycles.^[11] Interestingly, while these dienes have been essentially used a dienes in [4+2] cycloadditions (Scheme 1b, left), including in enantioselective ones, *N*–H 1,3–dienecarbamates can also act as simple ene unit. As such, Bernardi et al. reported the use of simple unsubstituted dienecarbamates^[12] in Povarov reaction leading to the synthesis of 1,2,3,4–tetrahydroquinolines (Scheme 1b, right).^[13]



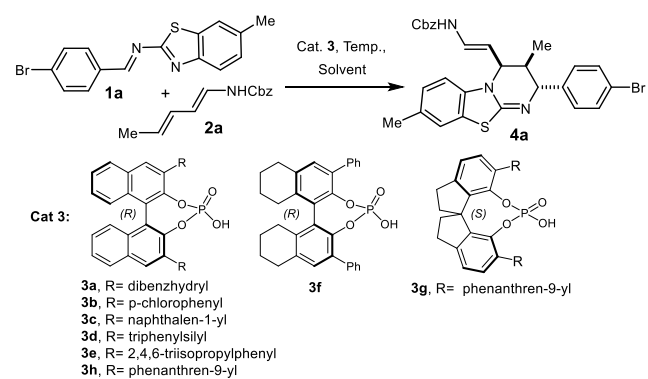
Scheme 1. Catalytic enantioselective cycloaddition involving dienecarbamates and present work.

In continuation of our research program in catalytic asymmetric reactions with dienecarbamates,^[14] we decided to explore their reactivities in connection with 2-benzothiazolimines. Indeed, these imines are versatile synthetic intermediates used for the syntheses of various heterocycles^[15] and they have been embedded in direct catalytic asymmetric annulation strategies.^[2e–h] With two latent nucleophiles (N and N'), we reasoned that they could be ideal linchpin for divergent pathways,^[7] as a common intermediate generated upon addition of a dienecarbamate onto the imine, could eventually lead by ring closure either to a tetrahydropyridine motive or benzothiazolopyrimidine skeleton (Scheme 1c). Herein, we report our findings uncovering a substrate-controlled behavior, allowing developing a highly enantioselective chiral phosphoric acid catalyzed aza-Diels-Alder for the synthesis of both, chiral benzothiazolopyrimidines or chiral tetrahydropyridines.

We initiated our work by evaluating the reaction between imine **1a** and dienecarbamate **2a** in dichloroethane at 50 °C in presence of various catalysts (Table 1). We were delighted to identify compound **4a** as the main isolable product in nearly each attempt. Careful NMR analyses lead to the conclusion that compound **4a**, isolated as a single diastereoisomer, had a 3,4-dihydro-2H-benzo[4,5]thiazolo[3,2-a]pyrimidine core in which the terminal double bond of the dienecarbamate **2a** was embedded in the cyclisation.^[16] While most chiral phosphoric acids were poorly effective, TRIP (**3e**) stood out as essentially the sole effective catalyst able to promote a reaction. Further investigation of the conditions leads to the following observations: heating the reaction at 50 °C was mandatory as no reaction occurred at RT but further increase of temperature was deleterious. 1,2-dichloroethane (DCE) proved to be a superior solvent compared to toluene.^[17] The reaction

was only marginally affected by the presence of molecular sieves (entry 5 vs 11) contrary to the relative stoichiometry of reagents that was best when using 3 equivalents of dienecarbamate **2a** (entry 5 vs 13,14). Overall, conditions established in entry 5 delivered product **4a** in 60% yield with 99% enantiomeric excess.

Table 1. Synthesis of ITU: a survey of reaction conditions.^[a]



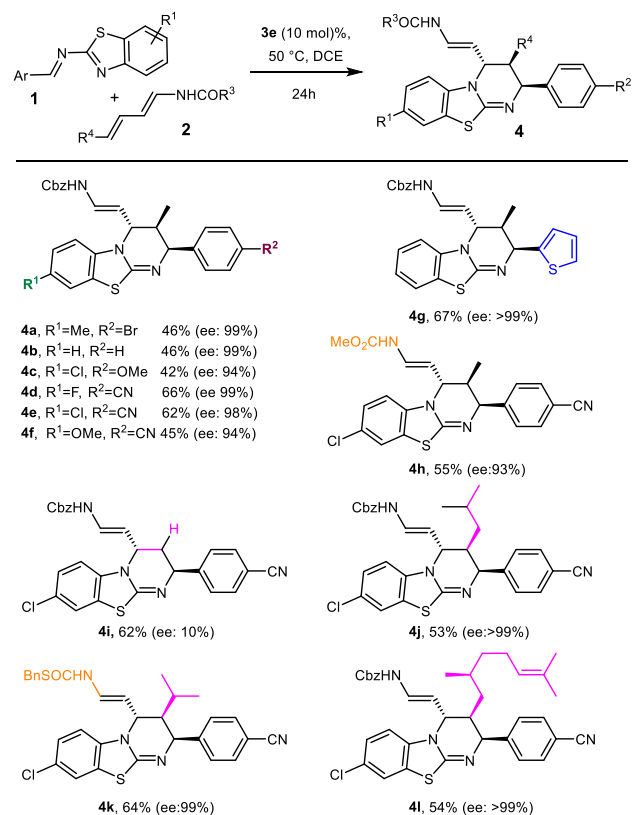
Entry	Cat	Solvent	Temp.	Yield [%] ^{b)}	ee [%] ^{c)}
1	3a	DCE	50 °C	4	
2	3b	DCE	50 °C	5	–
3	3c	DCE	50 °C	14	
4	3d	DCE	50 °C	Low	
5	3e	DCE	50 °C	60	99
6	3f	DCE	50 °C	7	
7	3g	DCE	50 °C	20	
8	3e	Toluene	50 °C	Low	
9	3e	Toluene	reflux	0%	
10 ^{d)}	3e	DCE	RT	Trace	
11 ^{e)}	3e	DCE	50 °C	61	98
12	3e	DCE	reflux	39	98
13 ^{f)}	3e	DCE	50 °C	<30	
14 ^{d)}	3e	DCE	50 °C	38	

^{a)} General conditions: Cat **3** (0.01 mmol), **1a** (0.2 mmol), **2a** (0.6 mmol) in solvent (1 mL), temperature, 24h. ^{b)} ¹H NMR yields, determined with 1,3,5-trimethoxybenzene as internal standard. d.r. > 98:2 in all cases, determined by ¹H NMR analysis. ^{c)} Enantiomeric excess determined by HPLC on a chiral stationary phase; see the Supporting Information for details. ^{d)} **2a** (0.4 mmol). ^{e)} 0.2g molecular sieve (4Å). ^{f)} **2a** (0.3 mmol).

With the optimal reaction conditions established, we next investigated the substrate scope of the reaction by employing various imines **1** and 1,3-dien-1-yl carbamate **2**. As can be seen in table 2, imines tolerated various substituents such as methoxy, methyl, cyanide or halogens either at the benzo[d]thiazol-2-yl or at the aromatic ring. However, incorporation of *ortho* substitution at either aromatic end of imines ((*o*-tolyl)methanimine or 4-methylbenzo[d]thiazol-2-yl) was not tolerated. Presence of electron withdrawing group seems beneficial in terms of yield (compounds **4d** and **4e**), but overall, the reaction proceeded with acceptable yields in each case and importantly with excellent enantioselectivity (up to 99%).

Heteroaromatic thiophene was also fully compatible allowing building compound **4g** in 67% yield with near perfect enantioselectivity.

Table 2. Scope of the organocatalytic enantioselective regioselective [4+2] cyclization for the synthesis of ITU.^[a]



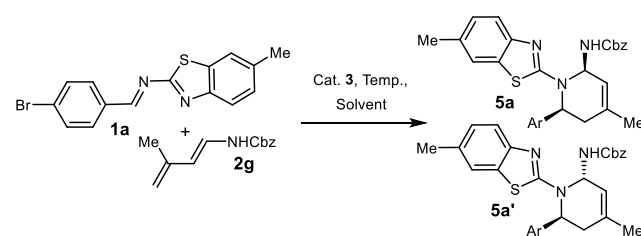
a) General conditions: table 1 entry 5; yields refer chromatographically pure products; absolute configuration is speculative.

Various 1,3-dien-1-yl carbamates **2** were subsequently evaluated. Besides benzyl-protected carbamate (NHCBz), methylcarbamate or *S*-benzylcarbamothioate were well tolerated and the corresponding benzothiazolopyrimidines (**4h** and **4k**) were, isolated in good yields and excellent stereoselectivities. Pleasingly, 1,3-dien-1-yl carbamate **2** with more or less sterically demanding δ -substituted alkyl side chains such as methyl, isobutyl, isopropyl or 2,6-dimethylhept-5-enyl performed uneventfully (compounds **4j**–**4l**). Of note, presence of an additional chiral center in the side chain of dienecarbamate does not affect the enantioselectivity as observed for **4i** ((*S*)-(-)-citronellal derived), obtained with equal enantiomeric excess compared to **4j** (>99% ee). Presence of δ -substituent on the dienecarbamate proved however to be mandatory for enantioselectivity, as use of benzyl (*E*)-buta-1,3-dien-1-ylcarbamate **2c** furnished the corresponding cycloadduct **4i** in descent yield (62%) but almost as racemate (ee: 10%). It is also worth noting that in general yields are moderate mainly due to the

difficulty to purify the relative polar products in presence of excess of carbamates.

Following this last result, we surmised that substitution on the diene could be a handle to modulate or diverge from the ITU-pathway and therefore decided to investigate the behavior of benzyl (*E*)-(3-methylbuta-1,3-dien-1-yl)carbamate **2g**, bearing a methyl substituted at the γ -position. To our delight, under the initially established conditions (Table 1, entry 5), this diene did not form any benzo[4,5]thiazolo[3,2-*a*]pyrimidine adduct, but instead, we were able to isolate the tetrahydropyridin-2-ylcarbamates adduct **5a** as single diastereoisomer. The modest yield (38%) and limited enantioselectivity (40%) prompted us to reinvestigate the conditions (Table 3).

Table 3. Synthesis of 4-aminotetrahydroquinoline: a survey of reaction conditions.^{a)}



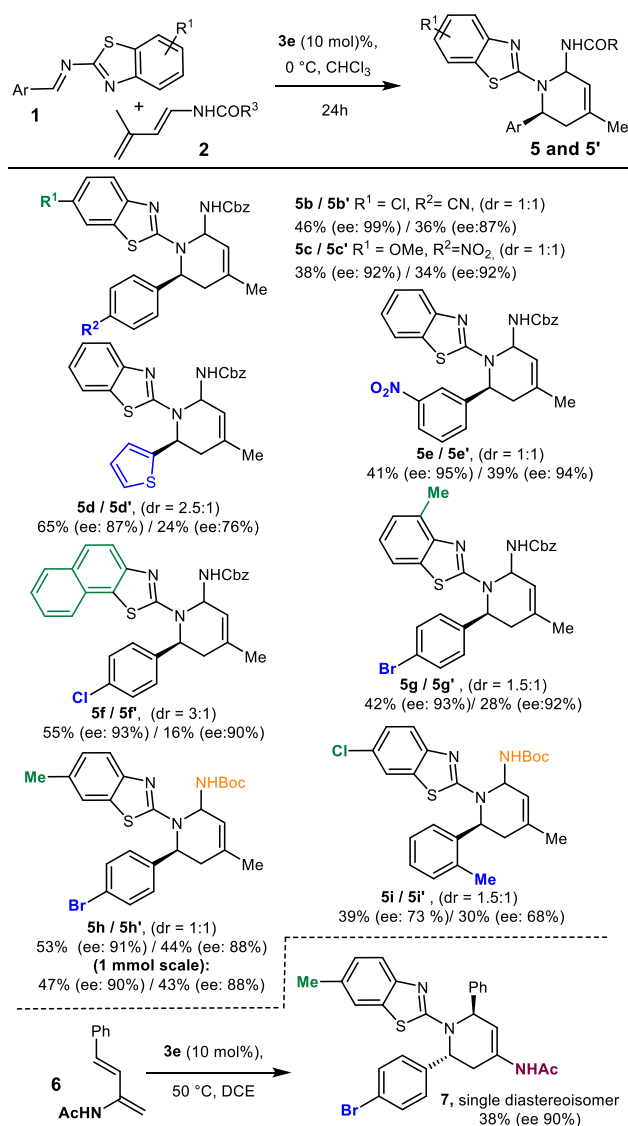
Entry	Cat	Solvent	Temp	dr ^{b)}	5a	5a'
					Yield [%] ^{c)}	Yield [%] ^{c)}
					(ee [%] ^{d)})	(ee [%] ^{d)})
1 ^{d)}	3e	DCE	50 °C	-	38 (40)	(-)
2	3e	DCE	25 °C	-	40 (60)	trace
3	3e	DCE	0 °C	1.5:1	20 (90)	14 (nd)
4	3e	DCE	45 °C	-	<10 (97)	nd
5	3e	CHCl ₃	0 °C	2:1	40 (92)	21 (88)
6	3b	CHCl ₃	0 °C	1.3:1	39 (46)	28 (10)
7	3c	CHCl ₃	0 °C	1:1	27 (45)	18 (25)
8	3h	CHCl ₃	0 °C	1:1.1	36 (22)	28 (10)

a) General conditions: **3** (0.01 mmol), **1a** (0.2 mmol), **2g** (0.4 mmol) in solvent (1 mL), at a defined temperature, 24h. b) Estimated from crude ¹H NMR analysis. c) Yields refer to chromatographically pure products. d) Enantiomeric excess determined by HPLC on a chiral stationary phase: see the Supporting Information for details. e) **2a** (0.6 mmol).

Lowering the temperature was in this case possible and had a clear beneficial impact on enantioselectivity, delivering compound **5a** with 90% or 97% ee at 0°C or -45°C, respectively (entries 2–4). Yields remained however low and examination of reactions revealed the presence of a second compound **5a'**. Diastereomeric relationship between **5a** and **5a'** was established based on analytical data (see SI) and on the fact that **5a'** converted to **5a** at 50°C, but with substantial degradation. Solvent was found to be important for the overall yield of the transformation. Indeed, performing the reaction at 0°C but switching from DCE to CHCl₃ as supporting media allowed to isolate **5a** in 40% yield with 92% ee and 21% of **5a'**

with 88% ee. Finally, while other chiral phosphoric acid did promote the reaction, none was superior to TRIP catalyst (**3e**) (entries 5–8).

Table 4. Scope of the organocatalytic enantioselective [4+2] cyclization for the synthesis of THP.^{a)}



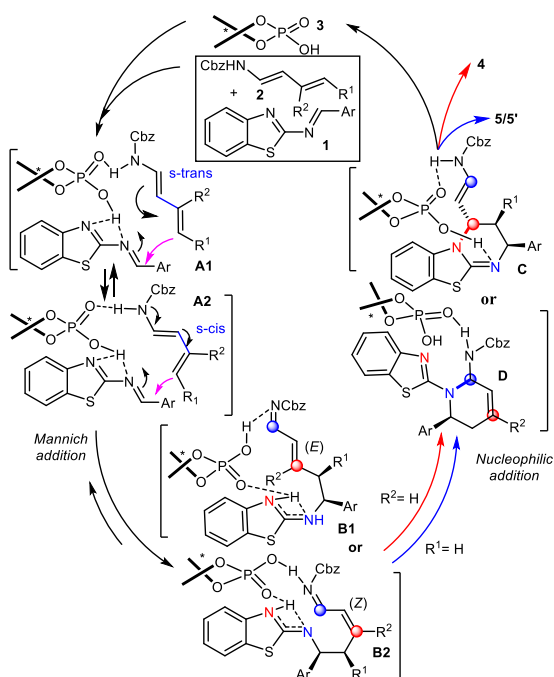
^{a)} General conditions: table 3, entry 5; dr is estimated from crude ¹H NMR analysis, yields refer chromatographically pure products; absolute configuration based on X-ray of compound **5b'**.

Various *N*-(benzo[d]thiazol-2-yl)-1-phenylmethanimines **1** were subsequently engaged with diene **2g** under these novel conditions (Table 4). The reaction proved to be quite general furnishing in each case two separable diastereoisomers in a good overall yield (from 61% to 97%). Diverse functional groups such as methyl, OMe, CN, NO₂ or halides, positioned at the benzothiazole unit or at the terminal aryl of imine precursor, proved all compatible. Interestingly, compound **5f/5f'** and compound **5g/5g'** derived from sterically demanding 4-methylbenzo- or naphthathiazoles, could also be isolated uneventfully. 2-Methylbenzaldehyde derived imine could be also used

as demonstrated with the synthesis of compounds **5i/5i'**; enantioselectivity (73% and 68%, respectively) was however reduced in that case probably for steric reason. *tert*-Butoxycarbonyl-protected diene carbamate **2h** was also a competent precursor, furnishing compounds **5h/5h'** in excellent yield. Overall, diastereoselection remained low but a few examples proved to be significant. As such, an almost equal amount of individual stereoisomers **5c** and **5c'** were produced in the reaction, contrary to compound **5f** and **5f'** isolated in 55% and 16%, respectively (d.r.: 3/1). Nevertheless, it should be mentioned that enantioselectivity was in each case high (>76%), reaching even 99% for compound **5b**. One diastereoisomer showed consistently a slightly lower enantioselectivity than the second one in pair of diastereoisomers. We also demonstrated that the reaction could be easily performed on a 1.0 mmol scale by synthesizing cycloadduct **5h/5h'**, obtained in comparable yields (90% vs 97% overall yield) and with equal selectivity, thus demonstrating the practicality of this process. In addition, use of (*E*)-*N*-(4-phenylbuta-1,3-dien-2-yl)acetamide (**6**) was also conducive to a tetrahydropyridin-2-yl framework. Conditions applied for ITU syntheses (Table 1, entry 5) were however required furnishing compound **7** in a modest 38% yield but as a single diastereoisomer with 90% enantiomeric excess.^[18]

A plausible reaction mechanism, accounting for both scaffolds, is depicted in Scheme 2. A two-step mechanism, reported for various (aza)-Diels-Alder reaction and in line with our previous study on benzothiazolopyrimidines, can be proposed.^[6, 13b, 19] Presence of aldehyde traces in the crude reaction mixture possibly arising from the hydrolysis of intermediates (**B1/B2**) brings support to this 2-step mechanism. According to many precedents in phosphoric acid-catalyzed process, and in line with a bifunctional activation mode^[10, 11a, 20] formation of a ternary complex **A** involving imine **1**, dienecarbamate **2** and phosphoric acid catalyst **3** could initiate the transformation. Within the spatially defined complex **A**, a dual activation mode will promote a stereoselective vinylogous Mannich reaction. This step could be reversible explaining the low enantioselectivity observed in the case of **4i**. The bond-forming event will be conducive to complex **B** containing the first enantio-defined bond and an unsaturated iminium. In a second event, intramolecular 1,2- or 1,4-addition of a defined nitrogen of the benzo[d]thiazol-2-amine residue onto the conjugated iminium will furnish either intermediate **C** or **D**. Configuration of the conjugated iminium in complex **B** could be advanced to justify individual pathways. Indeed, within the hydrogen bond network, an *E*-configured adduct (**B1**) could fold into a conformation where one nitrogen (Red) is in close proximity of the 4-position of the iminium and would cyclize to **C**. Presence of a substituent (R²) at the γ -position of the dienecarbamate will disfavor this *E*-configuration and probably slow down cyclisation. In this latter case, intermediate **B2** presenting a *Z*-

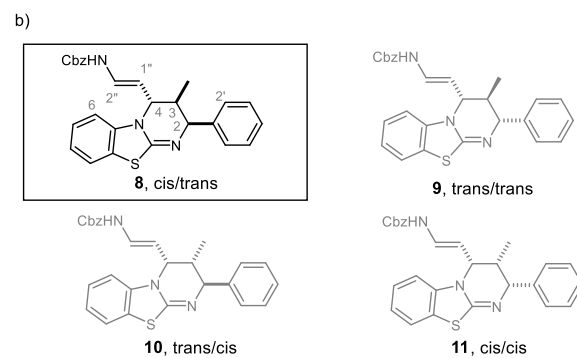
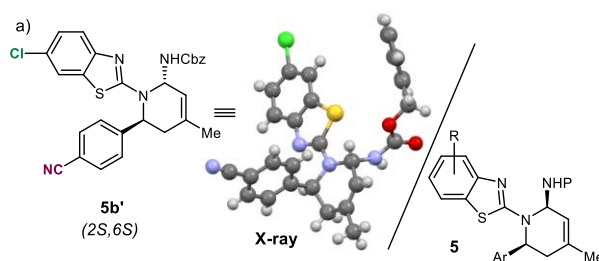
configuration could be favored and, based on proximity, would cyclize through 1,2 addition. Formation of individual **B1/B2** complexes could be in line with an initial *s-trans* or *s-cis* conformation of the dienecarbamate. It should be noted E/Z stereochemical arguments have been suggested from DFT-calculation in related Mukaiyama–Mannich reaction involving γ -substituted vinylketene silyl acetals.^[21] Catalyst control, through a chiral anchoring environment present in complex **B**, could explain the high diastereoselectivity observed for compound **4** (single diastereoisomer). The same could hold for compound **5'**, which could subsequently epimerize to **5** under the reaction condition. Indeed, partial conversion ($\approx 20\%$) of isolated **5a'** to **5a** was observed upon standing in CDCl₃ for 3 days. Catalyst decomplexation should finally close the cycle. Because of the difference in basicity of individual product, release of compound **5** and C_{1'}/C_{2'} allowed excluding the *cis-cis* (**11**) and *trans-trans* (**9**) configurations. Furthermore, two coupling constants ($J_{2-3} = 3.6$ Hz and $J_{3-4} = 6.2$ Hz), extracted from the ¹H NMR spectra of compound **4f**, furnished additional geometrical information: the first value should be in line with a dihedral angle around 50°, while the second value would require a dihedral angle close to 70°. ^[25] Such values were incompatible with those found in **9** and **10**, which therefore can also be excluded. Overall, these results tend to indicate that the *cis-trans* relationship of compound **8** presents the best matching relative stereochemistry compared to compound **4f**. Further DFT calculations on additional conformers of the encarbamate side chain in compound **8** allowed the identification of the most stable conformers, representing more than 98.8% of Boltzmann distribution, that were perfectly fitting with all measured data. As such, considering that compounds **5** and **4** share a common initial bond forming event, a (2*S*,3*R*,4*R*) absolute configuration can be suggested for this series of compounds.



Scheme 2. Mechanistical proposal for the divergent enantioselective aza-DA reactions.

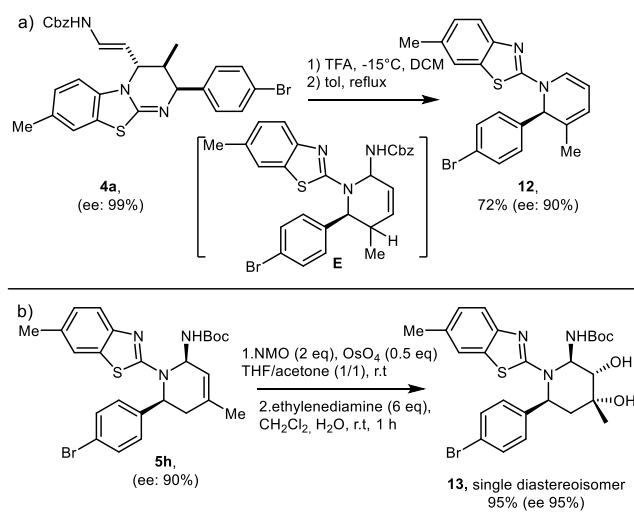
We finally turned our attention to stereochemical determination of compounds **4** and **5**. A suitable crystal of compound **5b'** could be grown and elucidated by X-ray analysis revealing a (2*S*,6*S*) absolute configuration (scheme 3, a).^[22] A *cis* relationship was therefore assigned to the corresponding diastereoisomer **5b** and in analogy, to the entire series, with (2*S*,6*R*) absolute configuration.^[23] Despite considerable efforts, we were not able to get suitable crystals from any compound **4**. A combination of experimental and computational approaches was there for adopted to establish the relative configuration of the series.^[24] Extensive NMR studies were undertaken with a

representative isothiourea (**4f**). In parallel, we performed a conformational search by restrained molecular dynamics in explicit solvent on each possible diastereoisomer of ITUs (*cis/trans* **8**, *trans/trans* **9**, *trans/cis* **10**, and *cis/cis* **11**, Scheme 3, b) considering pseudo axial or pseudo equatorial arrangements, followed by DFT calculations for geometry optimization of the most representative conformers using Gaussian09 (see supporting information). Comparison of information from experimental data and computed structures allowed to make several conclusions. Large set of cross peaks experimentally observed in the NOESY spectra of compound **4f** were found to be compatible with all possible configurations when considering both axial or equatorial arrangements. However, an experimentally observed signal assigned to hydrogens belonging to C₂ and C_{1'}/C_{2'} allowed excluding the *cis-cis* (**11**) and *trans-trans* (**9**) configurations. Furthermore, two coupling constants ($J_{2-3} = 3.6$ Hz and $J_{3-4} = 6.2$ Hz), extracted from the ¹H NMR spectra of compound **4f**, furnished additional geometrical information: the first value should be in line with a dihedral angle around 50°, while the second value would require a dihedral angle close to 70°. ^[25] Such values were incompatible with those found in **9** and **10**, which therefore can also be excluded. Overall, these results tend to indicate that the *cis-trans* relationship of compound **8** presents the best matching relative stereochemistry compared to compound **4f**. Further DFT calculations on additional conformers of the encarbamate side chain in compound **8** allowed the identification of the most stable conformers, representing more than 98.8% of Boltzmann distribution, that were perfectly fitting with all measured data. As such, considering that compounds **5** and **4** share a common initial bond forming event, a (2*S*,3*R*,4*R*) absolute configuration can be suggested for this series of compounds.



Scheme 3. Stereochemical considerations.

Interestingly we could further transform ITU **4a** into 1,2-dihydropyridine^[26] **12** (scheme 4, a). As such, treatment of enantioenriched **4a** (99% ee) with an excess of TFA (3 equiv) in DCM, followed by refluxing the crude salt in toluene furnished compound **12** in 72% yield and 90% ee. A slight decrease in enantioselectivity was observed during the reaction, but could be contained by rapidly stopping the reaction at full conversion (followed by TLC). Indeed, racemization of pure product **12** was found to occur upon prolonged heating. The mechanism transforming **4a** to **12** was not investigated, but could involve a ring opening, the formation of an intermediate tetrahydropyridine **E** and a 1,4-elimination of benzyl carbamate. We also demonstrated that tetrahydropyridines adduct **5** could be further derivatized by considering a diastereoselective dihydroxylation (scheme 4, b). Dioxygenated piperidines **13** could be cleanly synthesized from compound **5h** following an osmium mediated/diamine hydrolysis sequence and isolated in 95%.^[27] Compound **13**, which bears four-controlled stereocenters, including a tetrasubstituted one, was isolated in 95% yield. It is of note that an enrichment took place during the process, probably through a Horeau amplification,^[28] as starting from compound **5h** having 90% ee, compound **13** reached 95% ee. The relative stereochemistry between the substituents on C₂ and C₃ in **13** was tentatively assigned as *trans* based upon the presumed steric effect of the starting material.



Scheme 4. Post-transformations.

In conclusion, we have explored enantioselective phosphoric acid-catalyzed aza-Diels-Alder processes involving diene carbamates and 2-benzothiazolimines. A divergent cycloaddition pathway, depending on the substitution of the diene carbamate has been uncovered, leading either to tetrahydropyridine or 3,4-dihydro-2H-benzo[4,5]thiazolo[3,2-a]pyrimidine scaffold. The transformation provides enantioselectivity ranging from 68 to 99% over a broad range of precursors.

Experimental Section

General procedure for the synthesis of Isothioureas **4**:

To a solution of imine **1** (1.0 equiv.) and catalyst **3e** (0.1 equiv.) in dry 1,2-DCE (0.1 M) was added dienecarbamate **2** (3.0 equiv.). The reaction mixture was heated to 50 °C and stirred for 24 h under argon. The reaction mixture was cooled to room temperature, concentrated under reduced pressure and the crude was directly purified by flash chromatography (SiO₂, heptane/ethyl acetate mixture) as to afford pure product **4**.

General procedure for the synthesis of 4-methyl-1,2,3,6-tetrahydropyridine **5** and **5'**:

To a solution of imine **1** (1.0 equiv.) and catalyst **3e** (0.1 equiv.) in dry CHCl₃ (0.1 M) was added dienecarbamate **2** (2.0 equiv.). The reaction mixture was cooled to 0 °C and stirred for 48 h under argon. The reaction mixture was warmed to room temperature, concentrated under reduced pressure and the crude was directly purified by flash chromatography (SiO₂, heptane/ethyl acetate mixture) to afford the two separable pure product **5** and **5'**.

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