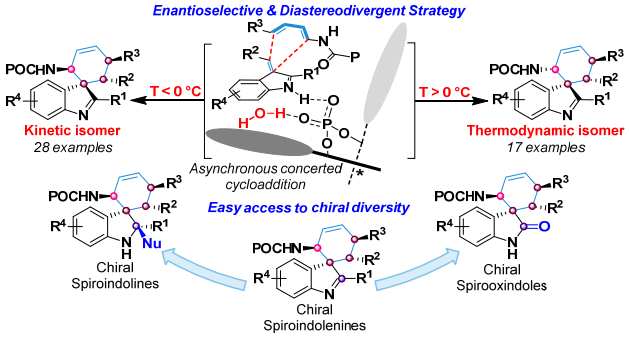
Enantioselective and Diastereo-divergent Synthesis of Spiro-indolenines *via* Chiral Phosphoric Acid-Catalyzed Cycloaddition

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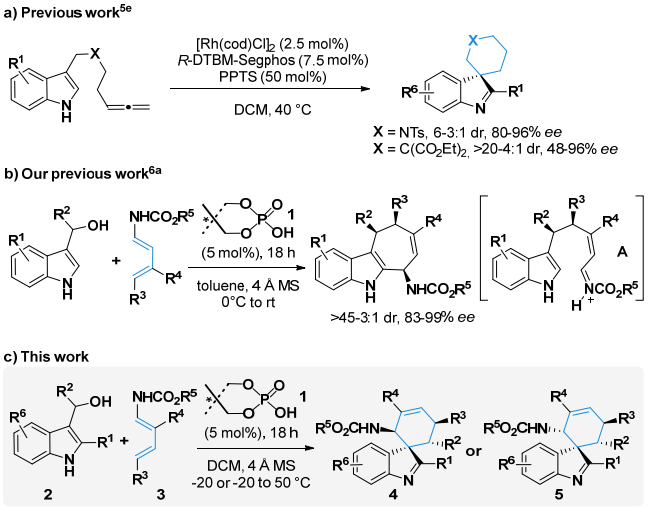
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ABSTRACT: A diastereodivergent and enantioselective synthesis of chiral spirocyclohexyl-indolenines with four contiguous stereogenic centers is achieved by a chiral phosphoric acid catalyzed cycloaddition of 2-susbtituted 3-indolylmethanols with 1,3-dienecarbamates. Modular access to two different diastereoisomers with high enantioselectivities was obtained by careful choice of reaction conditions. Their functional group manipulation provides an efficient access to enantioenriched spirocyclohexyl-indolines and -oxindoles. The origins of this stereocontrol have been identified using DFT calculations, which reveal an unexpected mechanism compared to our previous work dealing with enecarbamates.



Chiral spiro indoles derived units are important structural motifs encountered in various naturally occurring alkaloids as well as biologically active compounds.[i] They are key intermediates for the synthesis of numerous natural products.[ii] The development of direct and efficient catalytic methods for their enantioselective synthesis has therefore attracted the attention of synthetic organic chemists. A number of enantioselective methodologies have been successively reported over the years.[iii] However, in contrast to spirocyclohexyl-oxindoles,[iv] asymmetric strategies for building related indolines and indolenines are limited in number.[v] In 2017, Gandon, Guinchard et *al.*[5a] reported an example of Au(I)-catalyzed enantioselective cyclizations of *N*-propargyl tryptamines, providing the corresponding spiroindolenines in moderate yield and enantioselectivity (up to 68% *ee*). The same year, Zheng, You et *al.*[5b] developed an efficient method for synthesizing spirocyclohexyl-indolenines based on Ir-catalyzed asymmetric dearomatization of bis(indol-3-yl)allylic carbonates. One year later, the same group disclosed an enantioselective dearomatization of indolyl dihydropyridines using chiral phosphoric acid catalysis to afford various spiroindolines with high yields and enantioselectivities.[5c] More recently, Wei, Shi et *al*. developed an elegant enantioselective desymmetrization of bis(indol-3-yl)-allenes catalyzed by a chiral Au complex, which afforded fused spirocyclohexyl derivatives with high enantioselectivities.[5d] Despite these achievements and while derivatives containing a heteroatom in the spirocyclohexyl ring were produced, catalytic asymmetric syntheses of all-spirocarbocyclic indoline derivatives have remained extremely scarce. To the best of our knowledge, only very recently Breit *et al.* achieved a stereoselective synthesis of unfused spirocarbocyclic indolenines though rhodium-catalyzed cyclization of *N*-allenyltryptamines and 3-allenylindoles, delivering a moderate to high level of enantio- and diastereoselectivity (Scheme 1, a).[5e] Indeed, the enantioselective construction of highly substituted spirocarbocycles with the control of multiple stereocenters, including the quaternary spirocenter, in a single assembly step from easily accessible starting materials remains a significant challenge.

Scheme 1. Enantioselective catalytic synthesis of spirocyclohexyl-indolines and -indolenines

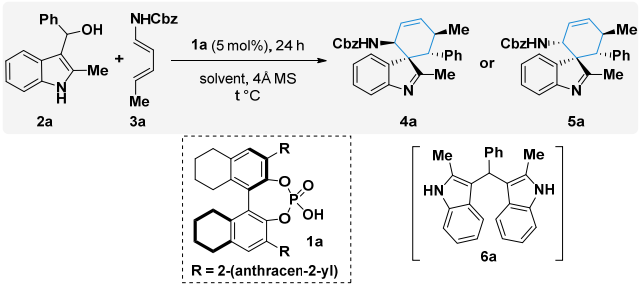


Recently, we disclosed an efficient enantioselective synthesis of cyclohepta[*b*]indoles involving a chiral phosphoric acid-catalyzed formal (4+3)-cycloaddition of 3-indolylmethanols with 1,3-dienecarbamates (Scheme 1, b).[via,vii,viii,ix] Mechanistic investigations provided evidence for a two-step reaction process involving vinylogous addition of the diene to a vinyliminium ion[x] generated *in situ* from the 3-indolylmethanol, followed by an intramolecular C_2-indole alkylation of the resulting imine **A**. Based on this, we reasoned that incorporation of a substituent at the C_2 position of the indole moiety may promote electrophilic substitution at C_3 rather than C_2 and may lead to an efficient synthesis of enantioenriched spirocarbocyclic indolenines. Herein we report a highly enantioselective synthesis of polysubstituted spirocyclohexyl-indolenines having up to four contiguous stereocontrolled chiral centers, including a quaternary one, in satisfying yields and with excellent enantio- and diastereoselectivity (Scheme 1, c). DFT computations and experimental studies provided a clear mechanistic picture of the transformation and revealed an unexpected activation mode by the chiral phosphoric acid catalyst.

Initially, (2-methyl-1*H*-indol-3-yl)(phenyl)methanol (**2a**) and benzyl (penta-1,3-dien-1-yl)carbamate (**3a**) were chosen as model substrates to evaluate our hypothesis (Table 1, entry 1). Pleasingly, performing the reaction at 0 °C with (*S*)-H_8-BINOL-phosphoric acid catalyst **1a** delivered the desired spirocyclohexyl-indolenines **4a** and **5a** as a mixture of diastereomers (2.2:1 ratio) with high enantioselectivity, albeit with a relatively moderate yield. Lower yields were due to the competitive formation of about 10−25% of bis-indole **6a**, presumably formed *via* the retro-Friedel-Crafts reaction of **1a** followed by C_2-alkylation of the resulting 2-methyl-indole. This side reaction could be significantly reduced at lower temperature (-20 °C), thereby improving the yield, but interestingly the reaction produced exclusively the diastereomer **4a** with still a good 92% *ee*. Neither concentrating nor diluting the reaction mixture did affect the yield and enantioselectivity (entries 3 and 4). Molecular sieves was not mandatory for the transformation, but was found to slightly increase yields and enantioselectivity (entry 5). Since changing the ratio between both starting materials only marginally affected the reaction outcome (entry 6 vs entry 2), for practical reasons, we adopted a 1.2:1 ratio between **2a**:**3a** for subsequent evaluations. Extensive screening of catalysts and solvents did not improve the yield and enantioselectivity (see Supporting Information, Table S1 and S2). Lowering the reaction temperature did not have a positive impact on both yield and enantioselectivity (entries 7 and 8). However, additional investigation showed that the diastereoselectivity was completely switched at room temperature to form exclusively **5a** in high enantioselectivity (entry 9). The retro-Friedel-Crafts

side reaction accounts for the modest yield (54%) obtained under these last conditions. To our delight, diastereomer **5a** could be produced in a significantly improved 70% yield, along with only 10% of side product **6a**, when the reaction was initially performed at -20° C in DCE and subsequently heated to 60 °C for 3 h (entry 10). This clearly established that **4a** is a kinetic adduct while **5a** represents the thermodynamic one. Furthermore, no erosion of enantioselectivity was observed during the thermodynamic equilibration. The robustness of this diastereodivergent enantioselective[xi] transformation was demonstrated by a larger scale synthesis of compound **4a** (1 mmol, 70% yield, 94% *ee,* entry 11), and **5a** (0.5 mmol, 70% yield, 94% *ee,* entry 12).

Table 1. Optimization of catalytic enantioselective synthesis of spiroindolenines.



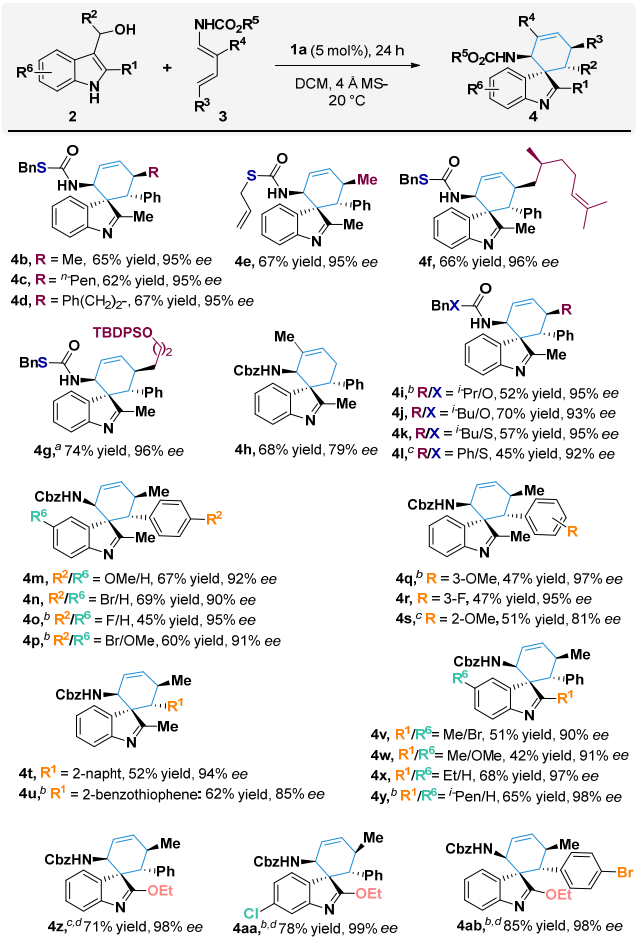
entry	t °C	**4a** yield (%)[b]	**4a** *ee* (%)[c,d]	**5a** yield (%)[b]	**5a** *ee* (%)[c,d]
1[a]	0	44	92	20	90
2[a]	-20	69	92	_	_
3[a,e]	-20	67	92	_	_
4[a,f]	-20	69	92	_	_
5[a,g]	-20	63	90	_	_
6[h]	-20	70	92	_	_
7[h]	-30	69	92	_	_
8[h]	-40	64	88	_	_
9[h]	rt	_	_	54	86
10[i]	-20 then 60	_	_	70	93
11[h,j]	-20	70[d]	94	_	_
12[i,k]	0 to 60	_	_	70	94

[a] General conditions: **2a** (0.10 mmol), **3a** (0.15 mmol) and **1a** (5 mol%) in DCM (0.05 M). [b] Yield of isolated pure product after chromatography. [c] **4a** refers to absolute (1*S*,2*S*,5*R*,6*R*) configuration, **5a** refers to (1*S*,2*R*,5*R*,6*R*) configuration, assigned by X-ray crystal-structure analysis of **4a** and **5a** (see Supporting Information). [d] Determined by HPLC analysis on a chiral stationary phase. [e]C = 0.1 M. [f] C = 0.025 M. [g] Without 4 Å MS. [h] General conditions: **2a** (0.12 mmol), **3a** (0.10 mmol) and **1a** (5 mol%) in DCM (0.05 M). [i] General condition: **2a** (0.10 mmol), **3a** (0.12 mmol) and **1a** (5 mol%) in DCE (0.05 M) at -20 °C for 24 h, then heated at 60 °C for 3 h. [j]With 1 mmol of **2a**. [k] With 0.5 mmol of **2a**.

Having established the optimal reaction conditions for the formation of the kinetic spiro-product **4**, we next explored the substrate scope with a diverse set of dienecarbamates **3**. In all cases, the β spirocyclohexyl-indolenines **4a-4l** were obtained with excellent diastereo- and enantioselectivity (Table 1). The *N*-thiobenzyl- and *N*-thioallyl-carbamate-substituted dienes were also tolerated, affording the corresponding spiroproducts **4b** to **4e** in similar yields and enantioselectivity. Use of dienecarbamates **4c** and **4d** substituted by linear alkyl groups at the 4-position altered neither yield nor stereoselectivity (95% *ee* and >95:5 *dr*). Additional functional groups such as remote unsaturation

(**4f**) and silyl ether (**4g**) were also well tolerated. Notably, the enantioenriched dienecarbamate (prepared from (*S*)-citronellal) participated in the reaction with equal efficiency. The presence of an additional chiral center did not influence the enantioselective process. Meanwhile, dienes carrying bulkier alkyl groups (such as ^{i}-Pr and ^{i}-Bu) were found to be compatible with the reaction. The corresponding enantioenriched spiroproducts **4i**-**4k** could be obtained in moderate to good yields, albeit requiring longer reaction times. Subsequently, 4-phenyl-substituted and 4-unsubstituted dienes were studied and the respective products **4l** and **4h** were isolated in relatively lower yield or enantioselectivity, respectively.

Scheme 2. Scope of the enantioselective synthesis of kinetic spirocyclohexyl-indolenines 4.



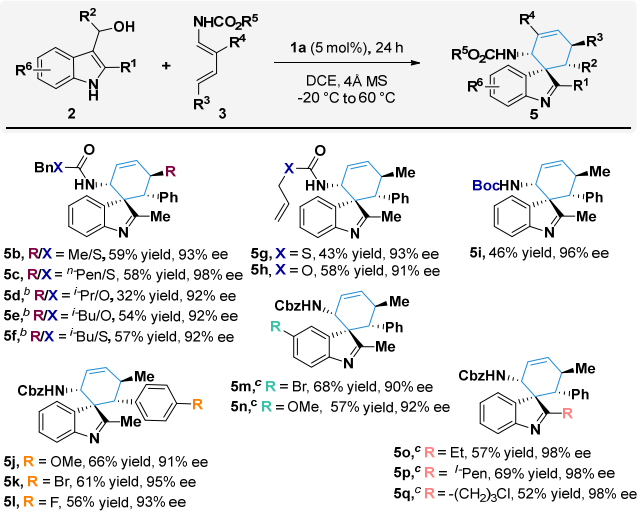
[a] On 0.05 mmol scale. [b] For 48 h. [c] At 0 °C for 48 h. [d] Without 4 Å MS.

Extension of this enantioselective transformation to other 2-alkylindole-3-methanols **2** was successful. Indolyl methanol containing various aryl groups on the side chain with either an electron-donating group or halide group at the *ortho*-, *meta*-, and *para*-positions gave the desired products **4m-4s** in moderate to good yields and high stereoselectivities. Moreover, the presence of the 2-naphthyl or benzothiophene group was found to be suitable and the corresponding spiroproducts **4t-4u** were obtained in lower yields but still with excellent enantioselectivity. Methoxy or halo (Br, Cl) substitution at the aromatic core of the indoles was also tolerated as exemplified with the synthesis of compound **4m, 4v-4w** and **4aa,** obtained in moderate to good yields but with excellent enantioselectivities. Notably, various C_2-substituted 3-indolylmethanols bearing diverse alkyl groups, such as ethyl and isopentyl, reacted smoothly to produce the corresponding spiroproducts **4x** and **4y** in decent yields with excellent enantiomeric excesses. Use of 2-phenylindolyl precursor was however not tolerated,

and only degradation of this latter was observed. In contrast, when 2-ethoxyindole derivatives were used, we were pleased to see that the reaction proceeded smoothly to give the corresponding products **4z**-**4ab** in higher yields (71-85% yield) with excellent enantioselectivities (up to 99% *ee*).

The reaction scope for the synthesis of thermodynamic spiroproducts **5** was also examined. As shown in Scheme 3, 4-substituted dienecarbamates **3** were converted to corresponding products **5b-5f** in low to good yields with excellent enantioselectivities. As previously observed, the diene bearing an ^{i}-Pr group delivered product **5c** with a decreased yield, presumably due to the steric hindrance of its bulky side chain. Changing the carbamate group from benzyl to allyl (**5g** and **5h**) and ^{t}-Bu (**5i**) led to similar yields and enantiomeric excesses. A variety of thermodynamic spiroproducts (**5j** to **5m**) was obtained with high enantio- and diastereoselectivities from selected 2-alkylindole-3-methanols. This demonstrated that electron-rich and -poor substituents either on the indole core (**5m** and **5n**) or on the aryl moiety (**5i**-**5k**) were well tolerated. It is also worth noting that our methodology is compatible with various alkyl substituents at the C_2-position of indoles (**5o** to **5q**).

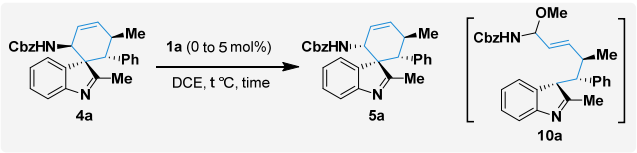
Scheme 3. Scope of the enantioselective synthesis of thermodynamic spirocyclohexyl-indolenines 5.



[a] At 0 °C for 24 h, then at 60 °C for 3h. [b] At -20 °C for 24 h, then at 60 °C for 12 h. [c] At -20 °C for 48 h, then at 60 °C for 3 h.

Control experiments confirmed that the two diastereomers **4** and **5** were formed under kinetic and thermodynamic conditions, respectively. Epimerization could be monitored by heating pure spiroproduct **4a** at various temperatures in DCE (Table 2). In the absence of catalyst, no epimerization occurred at room temperature after 15 h while total epimerization of **4a** to thermodynamic product **5a** was observed in the same amount of time at 60 °C. However, the phosphoric acid catalyst seems to favor the isomerization. Indeed, a complete epimerization took place at room temperature and at 60 °C in respectively 15 h (entry 2) and 5 min (entry 7) in the presence of 5 mol% of **1a**. In addition, the isomerization of **4a** was complete at 35 °C in the absence of catalyst **1a** applying a 405 nm irradiation (80% NMR yield of **5a** after 6 h, entry 4). Interestingly, the reaction performed in MeOH under such conditions resulted in the formation of the hemiaminal **10a**; this trapped iminium intermediate spontaneous cyclizes after its isolation (15% yield) in the NMR tube (entry 5).

Table 2. Control Experiments Confirm Kinetic and Thermodynamic Product Formation.[a]

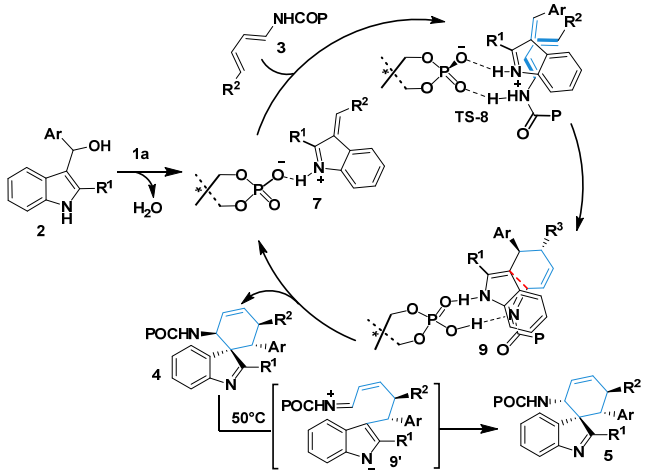


entry	**1a** (x mol%)	t °C	time	**5a** conv. (%)[b]	**5a** yield (%)[b]
1	0	rt	15 h	0	_
2	5	rt	15 h	100	100
3	0	35	15 h	0	_
4	0	35	6 h[c]	100	80
5	0	35	18 h[c,d]	20	ND
6	0	60	15 h	100	100
7	5	60	5 min	100	100

[a] General condition: **4a** (0.05 mmol) and **1a** (5 mol%) in DCE (0.05 M). [b] Conversion and yields determined by ^{1}H NMR spectroscopy using Bn_2O as standard intern. [c] irradiated with EvoluChem, P206-18-1 at 405 nm, 28 mW/cm^2.[d] In MeOH.

Based on these experiments and our previous mechanistic studies,[6] a catalytic cycle of the enantioselective spirocyclization was proposed. Even though we were not able to identify any iminium (or trapped intermediate **10a**) under the catalyzed process (see Supporting Information, Scheme S2)[xii] we privileged a stepwise mechanism. The vinylindoliniminium ion is formed upon initial chiral phosphoric acid **1a** mediated dehydration of 2-alkyl-3-indolylarlymethanols **2**, furnishing complex **7** (Scheme 4). Then, dienecarbamate **3** reacts with the vinyliminium complex **7** to form the iminium intermediate **8**. The latter undergoes an intramolecular C_3 aza-alkylation of indolylmethane delivering iminium **9** that produces the desired β spirocyclohexyl-indolenines **4**. Finally, the kinetic product isomerizes to yield the thermodynamically more stable spiroproduct **5** via iminium intermediate **9'**. The stepwise isomerization mechanism is consistent with the isolation of intermediate **10a**.

Scheme 4. Plausible reaction mechanism.



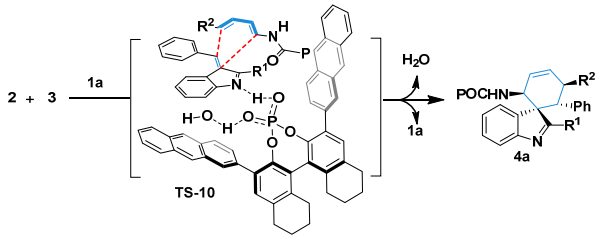
A computational study was undertaken at the M06-2X/6-311+G(d,p)//M06-2X/6-31G(d) level of theory in order to get deeper insight into the mechanism and importantly to rationalize the observed stereochemistry of **5**. Initial calculations investigated according the above mechanism did however

furnish a conflicting result, as it provided systematically the wrong enantiomer. The details are provided in the Supporting Information (Schemes S3 to S6). As such it questioned the dual activation of the vinyliminium and the dienecarbamate by the chiral phosphoric acid **1a** (**TS-**8, Scheme 4). This finding required the reevaluation of the mechanism of this spirocyclization. Our novel set of computations clearly indicated that the process of water abstraction from the indolylalcohol had to be taken into account and that the resulting H-bonded water molecule could play a major role in the stereoselectivity.[xiii,xiv] Figure 1 shows what we believe fully rationalizes our experimental findings. As reference system, we chose indolylmethanol **2a**, the s-*trans* diene **3a** and the model catalyst **1b**. The s-*cis* diene **3a**' was found 3.0 kcal/mol less stable than **3a**. The formation of a H-bond between the alcohol functionality of **2a** and the acidic proton of **1b** leads to **B**, with the release of 4.8 kcal/mol of free energy. Cleavage of the C-O bond provides intermediate **C**,[xv] which is of course axially chiral by the phosphate side, but this especially induces planar chirality as the water molecule is located on the lower face of the vinylindoliniminium ion framework when the Me group is oriented to the right. The corresponding transition state, $\mathbf{TS_{BC}}$, lies at 12.5 kcal/mol on the free energy surface and this step is endergonic by 4.3 kcal/mol. The diastereomers of **B** and **C**, **B'** and **C'**, are shown on the lower energy profile. While these intermediates are virtually as stable as **B** and **C**, $\mathbf{TS_{B'C'}}$ is 0.9 kcal/mol less stable than $\mathbf{TS_{BC}}$. An adduct is then formed between **3a'** and the vinylindoliniminium species **C** or **C'**, which can only occur on the face opposite to water. Of note, in **D** and **D'**, the carbamate is oriented as to give an *endo* adduct in the Diels-Alder sense of the word. The *exo*-orientation did not allow any subsequent C-C bond formation. **D'** is markedly less stable than **D** by 4.3 kcal/mol (from -0.9 to 3.4 kcal/mol). The last step is an asynchronous (4+2) cycloaddition furnishing the spiro adduct **E** or **E'**, which are equally stable. However, $\mathbf{TS_{DE}}$ is 4.2 kcal/mol more stable than $\mathbf{TS_{D'E'}}$ (from 12.1 to 16.3 kcal/mol). Comparison of these two profiles clearly indicates that the formation of **E** is kinetically preferred over that of **E'**. The absolute configuration of **E** matches that of the experimentally observed kinetic product (KP) **4a** (*R,R* configuration), located at -12.5 kcal/mol on the free energy surface. The corresponding thermodynamic product (TP) **5a** was found at -14.3 kcal/mol. While the *S* enantiomer of **B** shown in the upper part of Figure 1 reacts faster than the *R* enantiomer depicted in the lower part, we observed no kinetic resolution in this transformation. Thus, the two profiles must be connected in some way by transition states of lower energies than those already discussed to allow a dynamic kinetic resolution. We found indeed than **C** and **C'** are in fast equilibrium (see the Supporting Information, Scheme S7).Thus, based on these computations and all the other options summarized in the Supporting Information, we can conclude that the planar chirality of the vinylindoliniminium ion intermediate controls the enantioselectivity of the formal cycloaddition reaction.

To experimentally confirm that no specific Lewis base activation of the dienecarbamate was required for overall reactivity, we performed a series of experiments involving other Brønsted acid catalysts (see the Supporting Information, Scheme S1 and Table S3). When TFA (50 mol%) was employed, a 1:1 mixture of **4a** and **5a** were formed in 47% yield. In addition, the reaction conducted in the presence of (+)-CSA (20 mol%) led to **4a** in 51% yield with 28% *ee*. These results are in full agreement with the computed transition state in which the chiral phosphate counterion controls the stereochemical outcome of the reaction. They also concur with a mono-activation of **2** by the catalyst.[xvi]

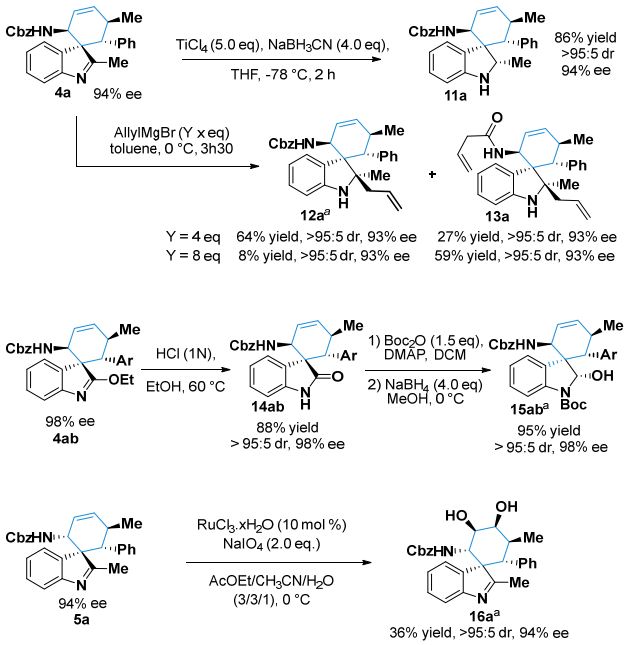
In light of these experimental and computational data, the initially proposed mechanism (Scheme 4) was adjusted as shown in scheme 5. As originally proposed, the reaction begins with the formation of a chiral vinyliminium phosphate ion pair upon treatment of **2** with catalyst **1a**. However, in contrast to our initial thought, water stays coordinate to **1a**, generating a stable complex, which undergoes the addition of the dienecarbamate **2** in an asynchronous concerted manner through a well-organized transition state **TS-10**. Finally, the catalyst **1a** is liberated upon release of water, which is trapped by molecular sieves.

Scheme 5. Revisited reaction mechanism.



The value of kinetic and thermodynamic spirocyclic compound **4a, 4ab** and **5a,** prepared by the novel catalytic process was further illustrated by performing various stereospecific transformations (Scheme 6).

Scheme 6. Stereospecific Derivatizations of Spiroindolenines into Spiroindolines and Spirooxindoles



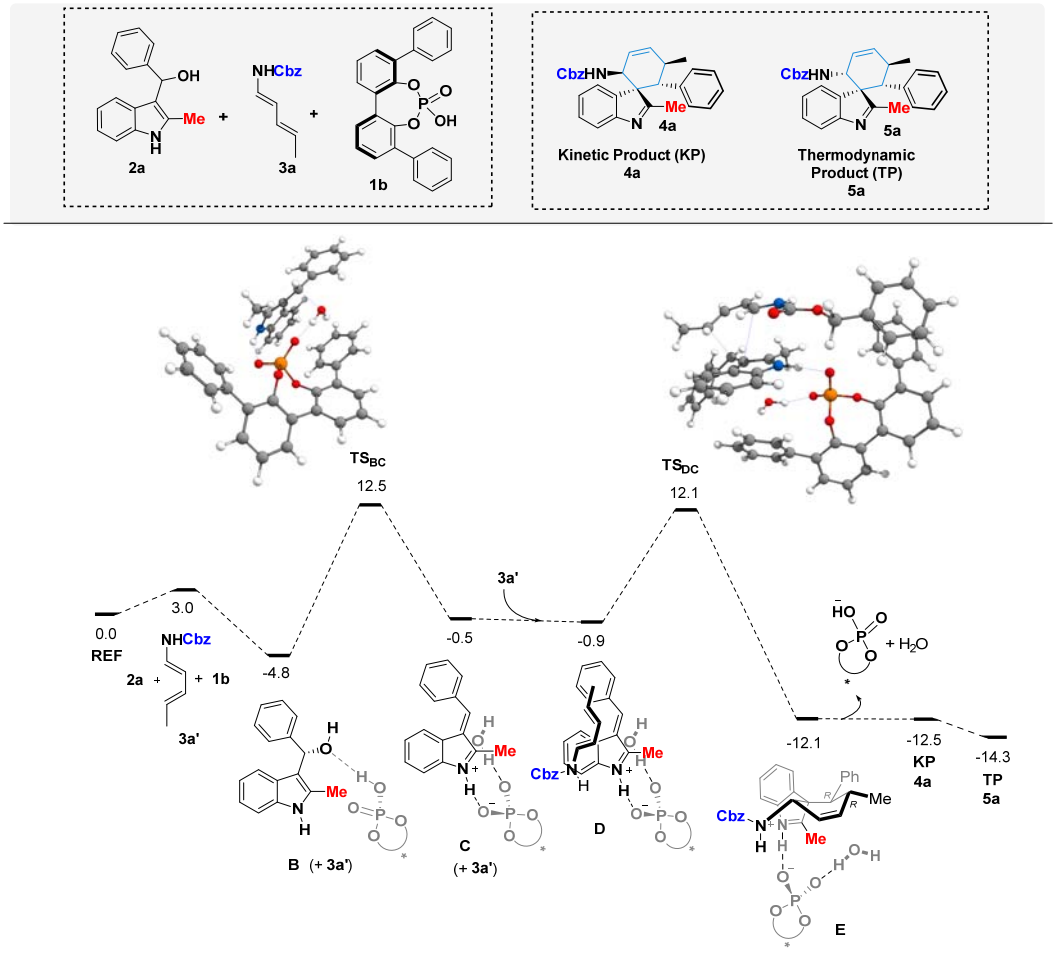
[a] The relative configuration was assigned by NOESY experiments (See Supporting Information).

For instance, chiral spiroindolenine **4a** was reduced with $NaBH_3CN$ and $TiCl_4$ to provide the corresponding indolenine **11a** in 84% yield as a single diastereomer bearing five fully defined stereocenters and with no erosion of enantioselectivity. The absolute configuration of **11a** was confirmed by X-ray diffraction. The reduction was also realized in a sequential one-pot process, which avoids the purification of the spiroindolenine **4a**. Under sequential process, the spiroindoline **11a** was isolated in 58% overall yield (corresponding to the sum of the yields of individual step) with 90% *ee* as a single diastereomer (See Supporting Information). Addition of allylmagnesium bromide to **4a** proceeded with complete diastereoselectivity leading to the formation of two products: the expected allylated spiroindoline **12a** and the double allylated spiroindoline **13a** in a 7:3 ratio, respectively. Both products were readily separated by column chromatography and isolated without loss of enantioselectivity. When an excess of allylmagnesium bromide was used, the double allylated spiroindoline **13a** was formed as major compound in better yield. In addition, the acetamidate product **4ab** was submitted to hydrolysis and the spirooxindole **14ab** was produced in good yield with no loss of enantioselectivity. The resulting product **14ab** was protected with Boc and then reduced with $NaBH_4$ to give the spiro-aminal **15ab** with excellent diastereoselectivity (>95:5). Finally, the thermodynamic

spiroproduct **5a** could undergo a dihydroxylation to give the highly substituted enantioenriched spiroproduct **16a** in moderate yield albeit with full diastereocontrol of six contiguous stereogenic centers give the spiro-aminal **15ab** with excellent diastereoselectivity (>95:5). Finally, the thermodynamic spiroproduct **5a** could undergo a dihydroxylation to give the highly substituted enantioenriched spiroproduct **16a** in moderate yield albeit with full diastereocontrol of six contiguous stereogenic centers

CONCLUSION

In summary, we developed a novel enantioselective and diastereodivergent spirocyclizations of 2-susbtituted 3-indolylmethanols with 1,3-dienecarbamates by a chiral phosphoric acid. In this reaction, a variety of valuable chiral polysubstituted spirocyclohexyl-indolenines bearing four contiguous stereogenic centers, including one spiro quaternary center, were conveniently constructed with excellent enantioselectivities and diastereoselectivities. The [4+2] cycloaddition, can be directed to different diastereomers of the spiroindolenine simply through temperature change, moving from kinetic to thermodynamic control. Besides, chiral spiroindolenines were amenable to further transformations and converted into enantioenriched spiroindolenines and spirooxindoles. DFT calculation and experimental findings corroborate an asynchronous concerted mechanism with a mono activation of chiral phosphoric acid. Finally, this also revealed the fundamental role played by a water molecule in the transition state accounting for the enantioselectivity.



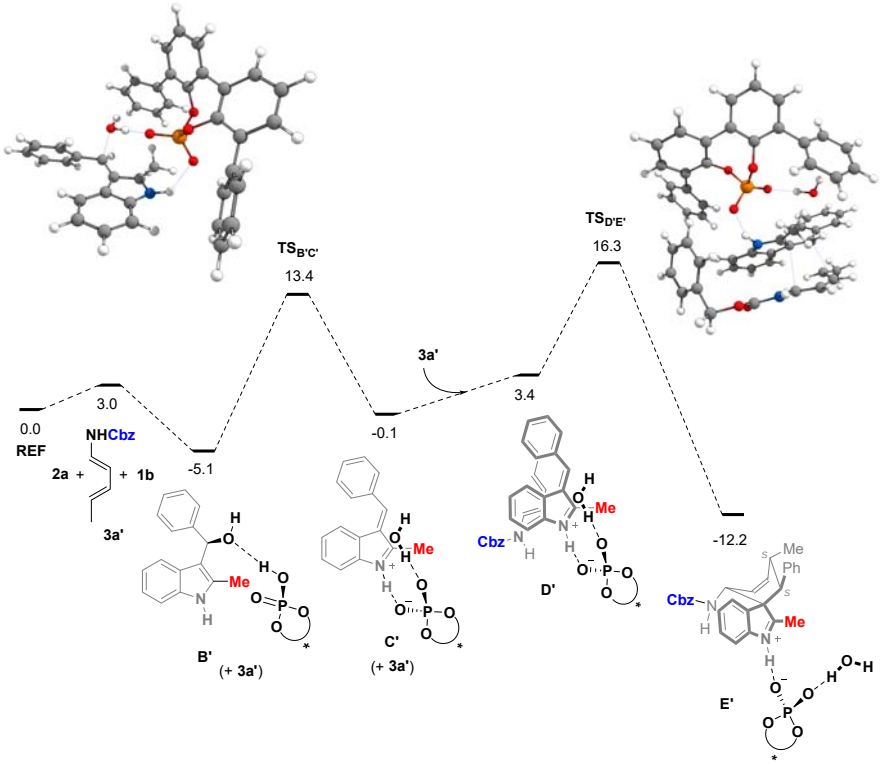


Figure 1. Computed free energy profiles (ΔG_{253}, kcal/mol).

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([xii]) No reaction occurred when the reaction was performed in MeOH as solvent.

([xiii]) Reaction performed best in presence of MS, but is also very effective in its absence (Table 1, entry 5). Reaction was also effective in presence of 5 equivalent of H2O (see supporting information, Scheme S2).

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([xv]) Of note, the cationic part of **E** has a *trans* configuration with respect to the exocyclic C=C bond. The *cis* isomer is less stable by 2.1 kcal/mol.

([xvi]) Tertiary-dienecarbamates were tested in the reaction (See the Supporting Information, Scheme S1) and no product was formed presumably due to their lower reactivity compared to the secondary counterparts. For diminished nucleophilicity of tertiary enamides, See ref 8e and 8f.