Chiral Brønsted Acid Catalyzed Enantioselective Dehydrative Nazarov-type Electrocyclization of Aryl and 2-Thienyl Vinyl Alcohols

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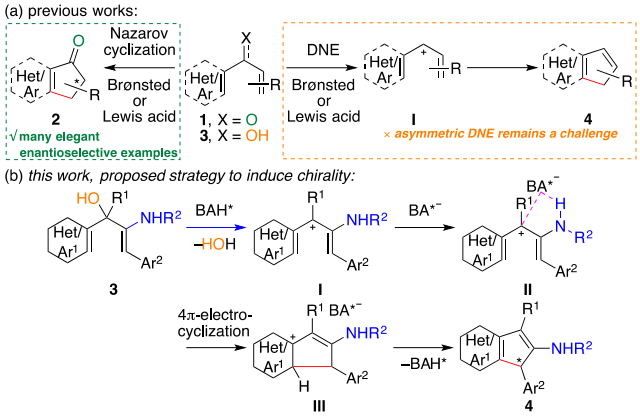
Supporting Information Placeholder

ABSTRACT: An efficient chiral Brønsted acid-catalyzed enantioselective dehydrative Nazarov-type electrocyclization (DNE) of electron-rich aryl- and 2-thienyl-β-amino-2-en-1-ols is described. The 4π conrotatory electrocyclization reaction affords access to a wide variety of the corresponding 1*H*-indenes and 4*H*-cyclopenta[*b*]thiophenes in excellent yields of up to 99% and enantiomeric excess (ee) values of up to 99%. Experimental and computational studies based on a proposed intimate contact ion-pair species that is further assisted by hydrogen bonding between the amino group of the substrate cation and chiral catalyst anion provide insight into the observed product enantioselectivities.

INTRODUCTION

The Nazarov cyclization of divinyl and (hetero)aryl vinyl ketones mediated by a Brønsted or Lewis acid is among one of the most powerful and efficient methods for the synthesis of cyclopentenone derivatives (Scheme 1).[1–6] A reflection of this is its frequent use in synthetic strategies to natural and synthetic compounds of current biological and materials interest containing the structural motif or as a building block.[2,3] This functional group transformation has also inspired the development of new 4π electrocyclization processes that has included the DNE of electron-rich divinyl and (hetero)aryl vinyl alcohols to cyclopenta-1,3-dienes (Scheme 1a).[4–6] Unlike the Nazarov cyclization, an asymmetric variant of the DNE reaction, either by using a chiral auxiliary or catalyst, by contrast, has so far remained a challenge (Scheme 1a).[3,5]

Scheme 1. The Nazarov Cyclization and DNE of Divinyl and (Hetero)aryl Vinyl Ketones and Alcohols



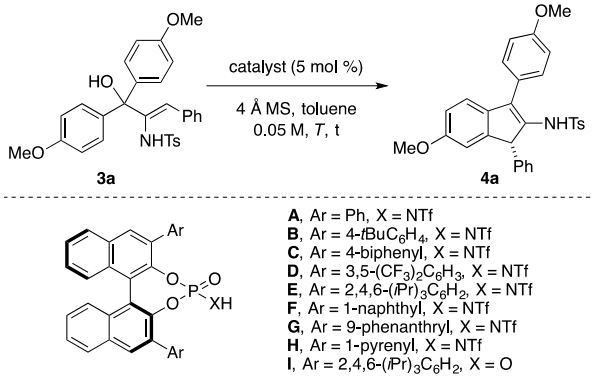
From a mechanistic viewpoint, the Brønsted acid-mediated DNE reaction is thought to involve initial protonation of the alcohol motif in the electron-rich substrate by the catalyst (Scheme 1a). This is followed by elimination of a molecule of water to give the substrate cation, with one or more of the remaining pendant electron-rich (hetero)aryl or vinyl groups facilitating the dehydration step by stabilizing the putative carbocationic species. Subsequent 4π conrotatory electrocyclization would then deliver the cyclopenta-1,3-dienyl ring system with product enantioselectivity believed to be determined by this latter step. However, this has often been thought to be challenging due to the limited stereoelectronic interactions creating a poorly-defined stereochemical environment in the proposed acyclic precursor **I** shown in Scheme 1a.[4i] In this context, we were drawn to the potential enantioselective DNE chemistry of this compound class with a pendant amino group catalyzed by a chiral Brønsted acid (BAH*, Scheme 1b).[1,6] We reasoned this would provide the corresponding intimate ion-pair species **II** in which the amino group of the associated cation of the substrate and anion of the chiral catalyst can additionally participate in hydrogen bonding interactions. With the chiral Brønsted acid anion now occupying one face of the substrate cation as a result, this might then allow asymmetric induction in the ensuing pericyclic reaction step to be accomplished to give the pentacyclic product in an enantioselective manner. Herein, we report the details of this study that offers an expedient route to these two potentially useful members of the 1*H*-indene and 4*H*-cyclopenta[*b*]thiophene compound family in excellent yields and enantioselectivities.[7] A density functional theory (DFT) calculation on the origin of the observed product enantioselectivities is also presented.

RESULTS AND DISCUSSION

We began our studies by examining the chiral Brønsted acid-mediated enantioselective DNE of **3a** to establish the optimum reaction conditions (Table 1). This initially revealed subjecting the substrate to 5 mol % of chiral *N*-triflyl phosphoramide (*S*)-**A**, 4 Å molecular sieves (MS) in toluene at 25 °C for 1 h gave **4a** in 95% yield and an ee value of 63% (entry 1). The structure and absolute stereochemistry of the carbocyclic adduct

was determined by NMR measurements and X-ray crystallographic analysis of two closely related products *vide infra*.[8] An examination of other chiral Brønsted acid catalysts showed the performance of (*S*)-**B**, (*S*)-**C**, (*S*)-**D**, (*S*)-**E**, (*S*)-**F**, (*S*)-**G** and (*S*)-**H** for 1–12 h gave product yields of 74–99% along with ee values of 30–73% (entries 2, 3, and 9–13). Likewise, the analogous control reactions mediated by (*S*)-**C** in which toluene was replaced by dichloromethane or 1,2-dichloroethane as the solvent were found to give product yields of 92 and 94% along with ee values of 40 and 45%, respectively (entries 4 and 5). Our subsequent studies found that repeating the (*S*)-**C**-catalyzed reaction in toluene as the solvent at –60 °C for 36 h gave the best result, providing the 1*H*-indene product in 95% yield and 95% ee (entry 7). However, increasing the reaction temperature to –40 °C for 24 h or decreasing it to –78 °C for 48 h was found to lead to slightly lower product yields of 94 and 82% and ee values of 91 and 82%, respectively (entries 6 and 8). In a final control experiment with the less acidic chiral phosphoric acid (*S*)-**I** as the catalyst, no reaction was detected

Table 1. Optimization of the Reaction Conditions for the Chiral Brønsted Acid-Mediated Asymmetric DNE of 3a[a]



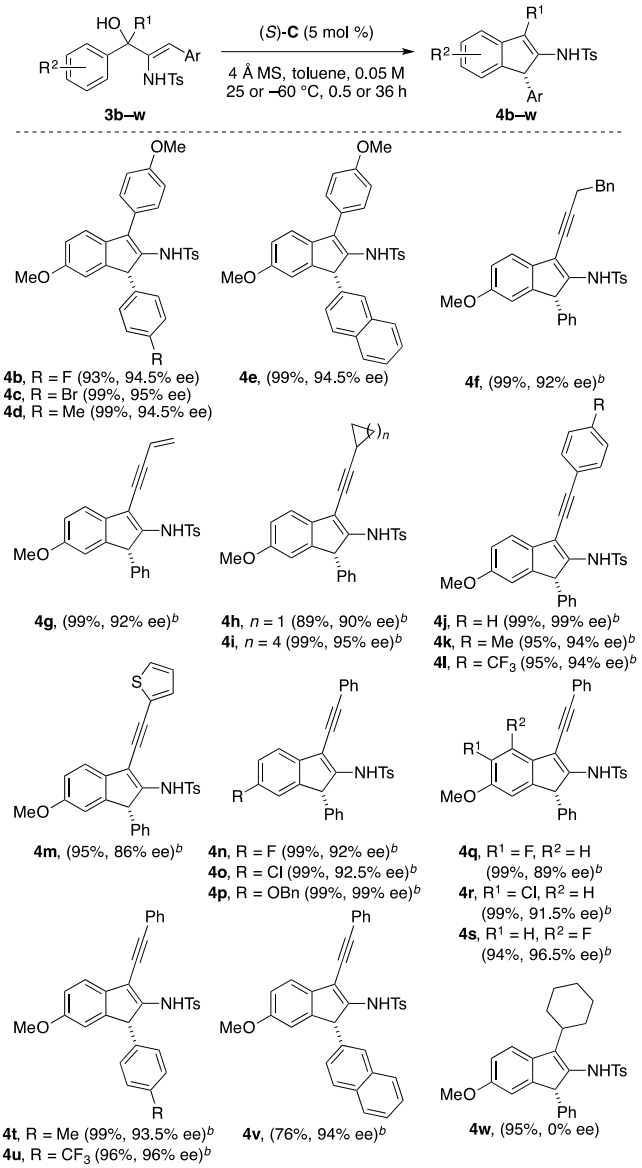
entry	catalyst	*T* (°C)	t (h)	yield (%)[b]	ee (%)[c]
1	(*S*)-**A**	25	1	95	63
2	(*S*)-**B**	25	1	95	35
3	(*S*)-**C**	25	1	99	73
4[d]	(*S*)-**C**	25	1	92	40
5[e]	(*S*)-**C**	25	1	94	45
6	(*S*)-**C**	–40	24	94	91
7	(*S*)-**C**	–60	36	95	95
8	(*S*)-**C**	–78	48	82	82
9	(*S*)-**D**	25	1	93	30
10	(*S*)-**E**	25	12	97	58
11	(*S*)-**F**	25	1	74	66
12	(*S*)-**G**	25	1	99	60
13	(*S*)-**H**	25	1	97	54
14	(*S*)-**I**	25	24	-[f]	-

[a]All reactions were performed at the 0.1 mmol scale with 5 mol % of catalyst, 4 Å MS (100 mg) in toluene (2 mL) at given temperature and time. [b]Isolated yield. [c]Ee values were determined using an AD-H chiral column (eluent: *n*hexane:*i*PrOH = 9:1). [d]Reaction conducted with CH_2Cl_2 as the solvent. [e]Reaction conducted with $(CH_2Cl)_2$ as the solvent. [f]No reaction detected by TLC analysis and ^{1}H NMR measurements with recovery of **3a** in 99% yield.

and the substrate was recovered in near quantitative yield (entry 14).

With the reaction conditions established, we next sought to evaluate the generality of the present procedure using a series of electron-rich aryl-*β*-amino-2-en-1-ols **3b**-**w** (Table 2). Overall, the (*S*)-**C**-catalyzed reaction conditions were shown to be broad, providing a family of 1*H*-indenes **4b**–**w** containing a variety of substitution patterns in excellent yields and ee values from the corresponding substrates. Reactions of starting materials with a pendant *para*-substituted electron-withdrawing phenyl (**3b**,**c**), *p*tolyl (**3d**), or 2-naphthyl (**3e**) group at the alkenyl carbon center were found to react well, giving **4b**–**e** in 93–99% yield and 94.5–95% ee. Likewise, electron-rich substrates containing an acetylenic motif with a

Table 2. Enantioselective DNE of Aryl-*β*-amino-2-en-1-ols 3b–w Catalyzed by (*S*)-C[a]

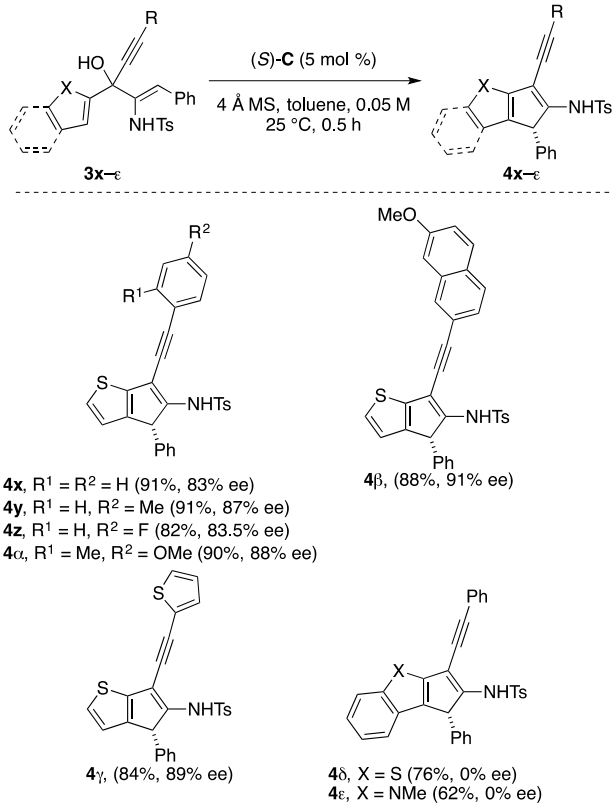


[a]All reactions were performed at the 0.1 mmol scale with 5 mol % of (*S*)-**C**, 4 Å MS (100 mg) in toluene (2 mL) at –60 °C for 36 h. Values in parentheses denote isolated product yields and ee values determined using an AD-H chiral column (eluent: *n*hexane:*i*PrOH = 9:1). [b]Reaction conducted at 25 °C for 0.5 h.

phenethyl (**3f**), vinyl (**3g**), cycloalkyl (**3h**,**i**), aryl (**3j**–**l**), or 2-thienyl (**3m**) substituent in place of an anisyl group were found to have minimal influence on the outcome of the reaction. In these experiments, which could be conducted at 25 °C, the corresponding 1*H*-indene products **4f**–**m** were afforded in 89–99% yield and 86–99% ee with the (8*R*) absolute configuration of **4j** established by X-ray crystallography.[8] Added to this, starting 1,4-enynols containing an aryl motif with electron-donating and/or -withdrawing substituent at various positons of the ring at the carbinol or alkynyl carbon center, as in **3n**–**v**, gave the corresponding carbocycles **4n**–**v** in 76–99% yield and 89–99% ee. The reaction of **3w** containing a cyclohexyl motif at the carbinol carbon center was the only instance to give the corresponding 1*H*-indene adduct **4w** as a racemate in 95% yield.

Having established the generality of the reaction conditions that gave 1*H*-indenes, we next examined the scope of the methodology for the enantioselective synthesis of 4*H*-cyclopenta[*b*]-fused heterocycles (Table 3). With this in mind, the (*S*)-**C**-mediated enantioselective DNE of electron-rich 2-thienyl-substituted 1,4-enynols **3x**–α in which the alkyne motif contained an aryl group were first examined. This led us to find that the corresponding *S*-heterocycles **4x**–α could be furnished in 82–91% yield and 83–88% ee. Under similar conditions, the reaction of substrates with a pendant 7-methoxy-2-naphthyl (**3**β) or 2-thienyl (**3**γ) on the acetylenic carbon center

Table 3. Enantioselective DNE of 2-Heteroaryl-*β*-amino-2-en-1-ols 3x–ε Catalyzed by (*S*)-C[a]



[a]All reactions were performed at the 0.1 mmol scale with 5 mol % of (*S*)-**C**, 4 Å MS (100 mg) in toluene (2 mL) at 25 °C for 36 h. Values in parentheses denote isolated product yields and ee values, determined using an AD-H chiral column (eluent: *n*hexane:*i*PrOH = 9:1).

gave **4**β and **4**γ in respective yields of 88 and 84% and ee values of 91 and 89%. The reactions of substrates containing a 2-benzothienyl (**3**δ) or *N*-methyl indolyl (**3**ε) group in place of the 2-thienyl moiety at the carbinol carbon center were observed to be the only exception. In these experiments, the corresponding tricyclic adducts **4**δ and **4**ε were afforded as a racemate in respective yields of 76 and 62%. On the other hand, in all the above experiments, no other cyclic adducts that could be formed from competitive arylation of the aryl vinyl group of the substrate or product isomerization was detected by ^{1}H NMR analysis of the crude mixtures.

A tentative mechanistic rationale for the origin of the product enantioselectivities obtained in the present chiral Brønsted acid-catalyzed asymmetric DNE reactions is presented in Figure 1. Using **3j** as a representative example, this might initially involve protonation of the substrate by the chiral Brønsted acid to give the carbocationic species **Ij** and **Ij'** and the catalyst anion (*S*)-**C'** on release of a molecule of water. Building on the premise put forward in Scheme 1b that chiral induction might then be achieved in the ion-pair species forming step, this would give the four possible conformers **IIj**$_a$, **IIj**$_b$, **IIj'**$_a$ and **IIj'**$_b$. In all four cases, we surmise that the amino motif hydrogen atom in the ion-pair species acts as a directing group through its ability to hydrogen bond with the catalyst anion, thereby determining whether it sits on the *re* or *si* face of the

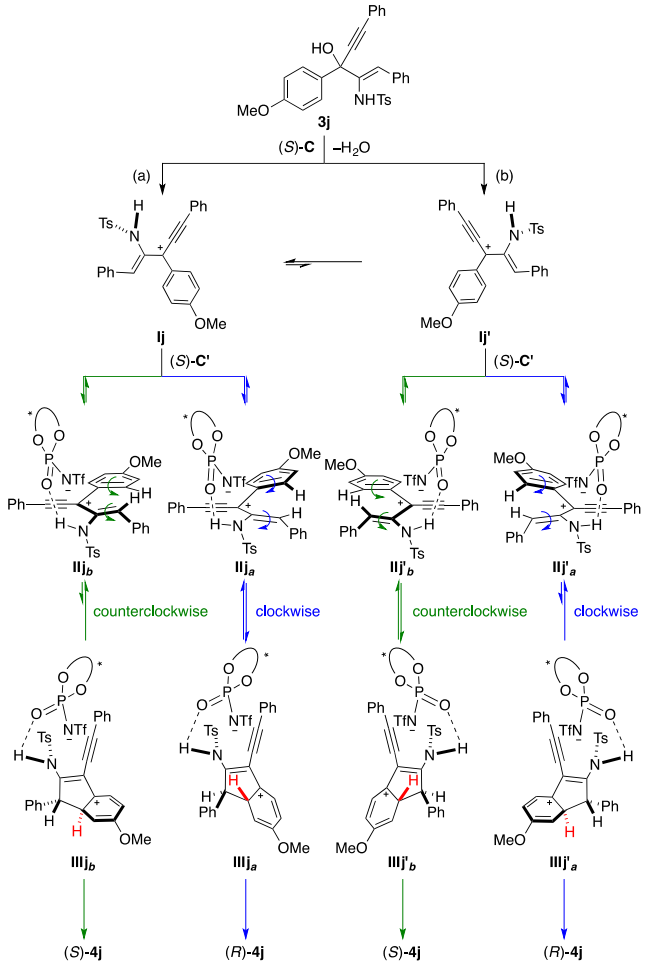
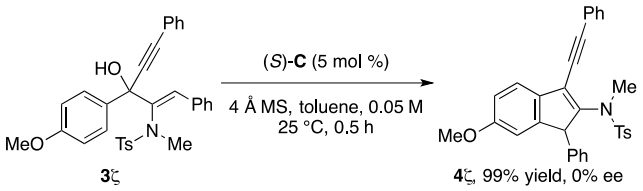


Figure 1. Proposed mechanistic rationale for the product enantioselectivities obtained for the (*S*)-**C**-catalyzed asymmetric DNE of electron-rich aryl- and 2-thienyl-*β*-amino-2-en-1-ols represented by **3j**.

substrate cation. For **IIj**$_a$, clockwise 4π conrotatory electrocyclization of the ion-pair species would lead to **IIIj**$_a$ being formed with the resulting acidic aryl proton (labeled red in Figure 1a) and chiral Brønsted acid anion positioned on the same face of the cyclic adduct. This is important as we reason it would permit the facile deprotonation and re-aromatization of the Wheland-type intermediate **IIIj**$_a$ by the chiral Brønsted acid anion to deliver the product (*R*)-**4j**.[9] Conversely, the counterclockwise pericyclic reaction of **IIj**$_b$ would give **IIIj**$_b$ whereby the acidic aryl proton and chiral Brønsted acid anion are now situated on the opposite faces of the carbocyclic cation. As a consequence, this might prevent the deprotonation step from occurring and the formation of this cyclic carbocation is anticipated to lead to a dead end unless it undergoes the reverse reaction. A second possibility is that intermediate **IIIj**$_b$ could be deprotonated if water serves as a base, the ability of which is dependent on the size of the water cluster $(H_2O)_n$ involved in the process. However, this was thought to be less likely based on our experience predicting such deprotonations to require an activation energy of ca 17 kcal/mol, which is higher than that required for the conversion of **IIj**$_a$ → **IIIj**$_a$ *vide infra*. As illustrated in Figure 1b for the pathways involving **IIj'**$_a$ and **IIj'**$_b$, a similar rationale would account for the preferential outcome of the enantiomer (*S*)-**4j**. In this regard, our hypothesis predicts that product formation can only come from pathways involving the ion-pair species **IIIj**$_a$ and **IIIj'**$_b$ with the dominant ion-pair species in solution being the former in view of a product ee value of 99%. It also implies that the catalyst anion may not preferentially occupy one face of the substrate cation in an ion-pair species containing a tertiary amino substituent. In the absence of the directing group, this might subsequently allow both the clockwise and counterclockwise pericyclic reaction pathways to be operative in equal measure and give the product as a racemate. Consistent with this are our findings in a control reaction with the *N*,*N*-disubstituted substrate **3**ζ under the (*S*)-**C**-catalyzed conditions described in Scheme 2, which gave **4**ζ in 99% yield and 0% ee. The posited involvement of the ion-pair species **II** would explain the marked differences in product ee values obtained for the reactions of **3a** in toluene, dichloromethane and 1,2-dichloroethane detailed in Table 1, entries 3–5. It might be expected that is an increase in interactions between the substrate cation and catalyst anion with the reaction medium as the solvent dielectric constant (ε) increases on going from toluene (ε = 2.4, 290 K) to dichloromethane (ε = 9.2, 288 K) and 1,2-dichloroethane (ε = 11.0, 288 K).[10] As a consequence, this may disrupt the ability of the substrate cation and catalyst anion to form a tight ion-pair species, resulting in a decrease in product ee values. We reason a similar rationale could be in play in the reactions of **3w**, **3**δ and **3**ε that led to the corresponding products being obtained as a racemate. The presence of a bulky cyclohexyl or benzofused ring in these substrates might provide sufficient unfavorable steric interactions to prevent the substrate cation and catalyst anion forming the requisite intimate ion-pair species **II**.

Scheme 2. Control Experiment with 3ζ



To verify the proposed mechanistic rationale for the observed product enantioselectivities outlined in Figure 1, we performed a series of DFT calculations. As summarized in Figure 2, a number of transition states and intermediates were

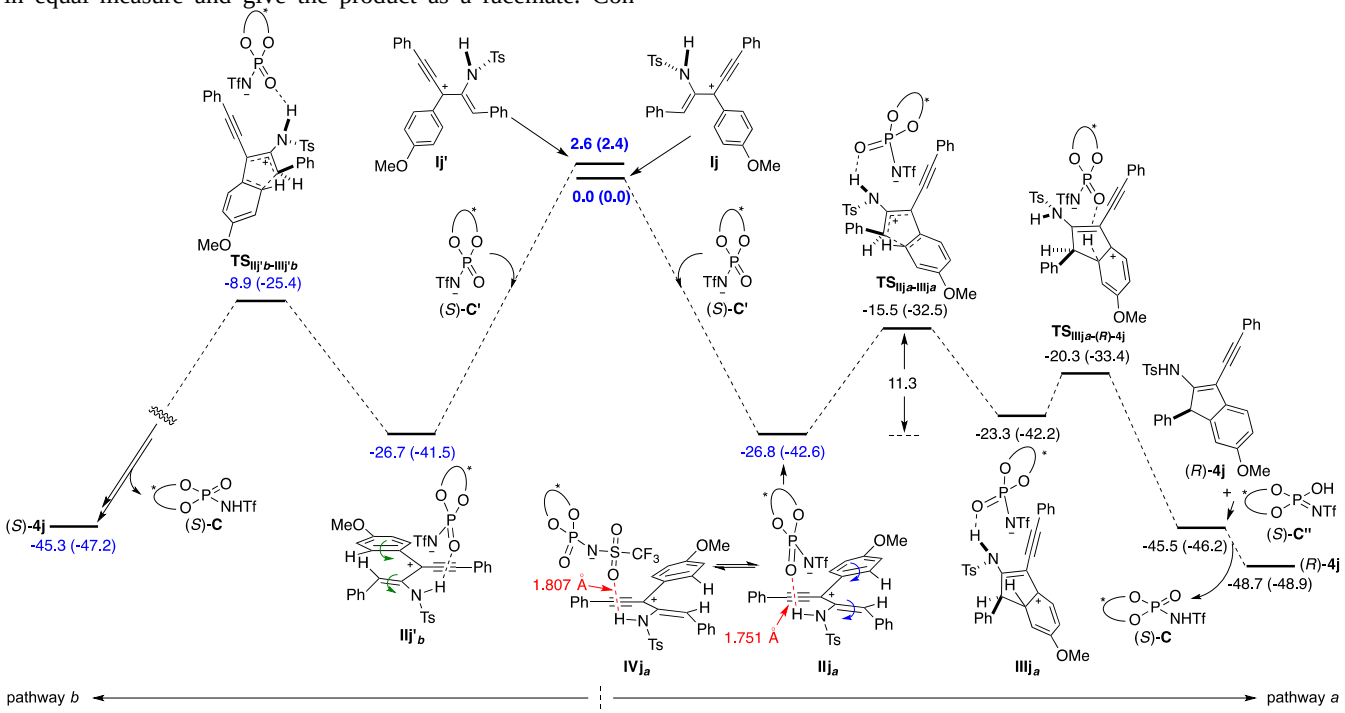


Figure 2. Energy profile of pathways *a* and *b* for the (*S*)-**C**-catalyzed enantioselective DNE of **3j** to (*R*)-**4j** and (*S*)-**4j**, respectively. Structures **IIj** and **IVj** show short P=O···HN and S=O···HN interactions (1.751, 1.807 Å) that indicate hydrogen bonding. The relative Gibbs and potential energies (in parentheses) obtained from M06-CPCM/6-31+G(d,p)//B3LYP-CPCM/6-31G(d) calculations are given in kcal/mol and bond lengths in Å.

produced in the two possible reaction pathways *a* and *b* from **Ij** and **Ij'** to the corresponding (*R*) and (*S*) enantiomers of **4j**. On the basis of these calculations, pathway *a* was revealed to be favored with rotation from **Ij** to **Ij'** shown to be endergonic by 2.6 kcal/mol. Accordingly, the latter conformer was found to be sparsely populated, which is in good agreement with our experimental findings showing (*R*)-**4j** being afforded in 99% ee. This was followed by the interaction of the substrate cation with (*S*)-**C'**, which lowers the energy of the carbocationic species by >26 kcal/mol. As such, the ensuing ion-pair species **IIj***a* functioned as a thermodynamic sink that prevented interconversion between the two substrate cation conformers. In the ion-pair species, the chiral Brønsted acid anion was found to be located on the *re* face of the substrate cation due to hydrogen bonding interactions between the former and the latter, as evidenced by a P=O···HN bond distance of 1.751 Å. The ion-pair species **IVj***a* depicted in Figure 2, the most stable among other possible interactions, was also considered. However, this latter hydrogen bonded ion-pair species was thought to be less likely as it was found to be 5.4 kcal/mol less stable and had a slightly longer S=O···HN bond distance of 1.807 Å. Our calculations further suggested clockwise 4π conrotatory electrocyclization of **IIj***a* to **IIIj***a* occurred through **TS**$_{\mathbf{IIj}a\text{–}\mathbf{IIIj}a}$ with an energy barrier of 11.3 kcal/mol. For the reaction steps after the formation of the Wheland-type intermediate **IIIj***a*, the Brønsted acid anion was found to play a crucial role in the deprotonation of the adduct. By accepting the aryl proton sitting on the same face of the catalyst anion, this provided the product (*R*)-**4j** and (*S*)-**C''** *via* **TS**$_{\mathbf{IIIj}a\text{–}(\mathbf{R})\text{-}\mathbf{4j}}$ with an energy barrier of 3.0 kcal/mol. This implied that the re-aromatization process was more facile than the preceding carbocyclic ring forming step. Regeneration of the chiral Brønsted acid catalyst was readily achieved through tautomerization of (*S*)-**C''**, which was found to be exergonic by 3.2 kcal/mol.

In a second set of calculations in the absence of (*S*)-**C**, the activation energy required for the 4π electrocyclization step was demonstrated to increase by 6.1 kcal/mol, as shown in Figure 3a. This suggested that the interaction between the cation of the substrate and the anion of the catalyst in **TS**$_{\mathbf{IIj}a\text{–}\mathbf{IIIj}a}$ was stronger than that in **IIj***a*. Repeating these calculations for

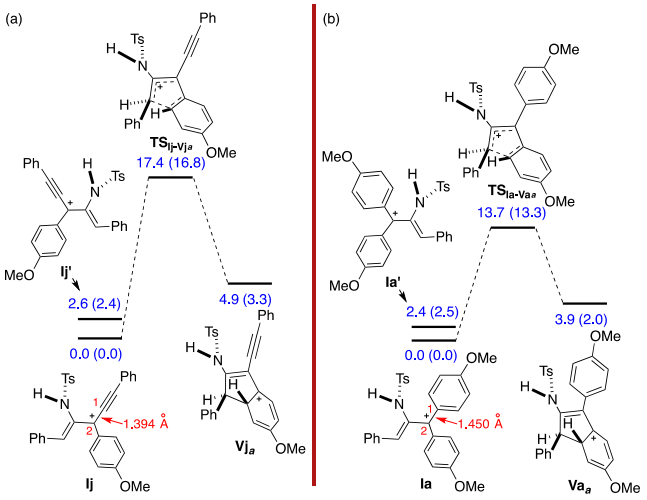


Figure 3. Energy profiles for the 4π conrotary electrocyclization step of (a) **3j** and (b) **3a** in the absence of (*S*)-**C**. The relative Gibbs and potential energies (in parentheses) obtained from M06-CPCM/6-31+G(d,p)//B3LYP-CPCM/6-31G(d) calculations are given in kcal/mol and bond lengths in Å.

3a in the absence of the Brønsted acid revealed the pericyclic reaction step required an activation energy of 13.7 kcal/mol (Figure 3b). This implied that **3a** was intrinsically more reactive than **3j** toward carbocyclic ring formation and is in good agreement with the need for lower experimental temperatures of –60 °C to achieve chiral induction in such diaryl-substituted substrates. The source of this greater reactivity was attributed to the steric demand of the aryl ring limiting its ability to stabilize the cationic charge by π-conjugation in **Ia**, as corroborated by the much longer C1–C2 bond distance in the carbocation species than in **Ij** (*cf.* Figures 3a and 3b). As with **3j**, the experimentally observed product enantioselectivity obtained from **3a** was found to be a result of conformer **Ia** being 2.4 kcal/mol more stable than that of conformer **Ia'**.

In a final set of calculations, the Gibbs energy on forming **IVj***a* from **Ij** and (*S*)-**C'** was determined to be –13.3 and –30.8 kcal/mol at the B3LYP-CPCM/6-31+G(d,p)//B3LYP-CPCM/6-31G(d) and B3LYP-D3-CPCM/6-31+G(d,p)//B3LYP-CPCM/6-31G(d) level, respectively. While the analogous calculations could not be accomplished for the formation of **IIj***a*, these findings nonetheless indicated that the dispersive interactions implied in Scheme 1b are operative and play a key role in the stability of the ion-pair species.

Interestingly, our DFT studies also revealed that if the stereoelectronic nature of the amino substituent in the substrate was changed by replacing the *N*-Ts motif with a *N*-Boc group, as in **3**η shown in Scheme 3 and Figure S1 in the Supporting Information (SI), a switch in the stereochemical outcome of the reaction should be observed. Calculations for the substrate in the absence of (*S*)-**C** at the M06-CPCM/6-31+G(d,p)//B3LYP-CPCM/6-31G(d) and B3LYP-CPCM/6-311+G(d,p)//B3LYP-CPCM/6-31G(d) level found **I**η**'** to be more stable than **I**η by 0.5 and 1.9 kcal/mol, respectively, which implied the (*S*)-enantiomer would be afforded as the major product. Pleasingly, this was supported by our subsequent findings in experiments with **3**η and its 2-naphthyl substituted analogue **3**θ catalyzed by (*S*)-**C** under the conditions described in Scheme 3. In these test reactions, the corresponding 1*H*-indene adducts **4**η and **4**θ were furnished in respective yields of 95 and 85% and ee values of 80 and 87% with the (8*S*) absolute configuration of the former ascertained by X-ray crystallography.[8]

Scheme 3. (*S*)-C-Catalyzed Asymmetric DNE of 3η and 3θ

CONCLUSIONS

In summary, we have developed a chiral Brønsted acid-catalyzed method for the asymmetric synthesis of 1*H*-indenes and 4*H*-cyclopenta[*b*]thiophenes from the respective electron-rich aryl- and 2-thienyl-*β*-amino-2-en-1-ols. The excellent product ee values were achieved by realizing the first example of an enantioselective DNE from a posited chiral ion-pair species to asymmetrically assemble the bicyclic ring system. Our studies suggest the origin of the observed product enantioselectivity was initially due to the more stable conformation of the substrate cation. The ensuing ion-pair species then acted as

a thermodynamic sink to prevent interconversion between these two conformers. Also instrumental was the role of the amino group in the substrate cation in directing the chiral catalyst anion to preferentially sit on one face of the adduct and the ability of the latter to efficiently facilitate re-aromatization to give the product. We envision that the present synthetic method will encourage the further development of asymmetric strategies in reactions where there is such intrinsic low directionality through the installation of a directing group.

EXPERIMENTAL SECTION

General Considerations. All reactions were performed in oven-dried glassware under a nitrogen atmosphere. Unless specified, all reagents and starting materials were purchased from commercial sources and used as received. The chalcones used in the synthesis of substrates **3** and chiral Brønsted acids **A-I** were prepared following literature procedures.[11,12] Toluene was freshly distilled from sodium/benzophenone. Analytical thin layer chromatography (TLC) was performed using precoated silica gel plate. Visualization was achieved by UV light (254 nm). Flash chromatography was performed using silica gel and gradient solvent system (*n*hexane:EtOAc as the eluent). ^{1}H and ^{13}C NMR spectra were recorded on 300 and 400 MHz spectrometers. Chemical shifts (ppm) were recorded with tetramethylsilane (TMS) as the internal reference standard. Multiplicities are given as: s (singlet), br s (broad singlet), d (doublet), t (triplet), dd (doublet of doublets) or m (multiplet). The number of protons (n) for a given resonance is indicated by *n*H and coupling constants are reported as a *J* value in Hz. Infrared spectra were taken on a IR spectrometer. High resolution mass spectra (HRMS) were obtained on a LC/HRMS TOF spectrometer using simultaneous electrospray (ESI). Ee values were determined by high performance liquid chromatography (HPLC) analysis using a AD-H column. Optical rotations were measured in $CHCl_3$ on a polarimeter with a sodium vapor lamp at 589 nm and 10 cm cell (c given in g/100 mL).

General Procedure for (*S*)-C-Catalyzed Asymmetric DNE of Aryl Vinyl Alcohols 3a–3e, 3η, 3θ and 3w. To a round-bottom flask was charged the substrate (0.1 mmol), chiral Brønsted acid (*S*)-**C** (3.9 mg, 0.005 mmol, 5 mol %) and 4 Å MS (100 mg) followed by the addition of toluene (2 mL) at –60 °C. The reaction mixture was stirred at this temperature for 36 h. On completion, the reaction mixture was quenched with $NaHCO_3$ (8.4 mg, 0.1 mmol). After warming to room temperature, the reaction mixture was directly passed through a silica gel column (eluent: *n*hexane/EtOAc = 8:1) to give the title compound.

General Procedure for (*S*)-C-Catalyzed Asymmetric DNE of Aryl Vinyl Alcohols 3f–3v and 3x–3ζ. To a round-bottom flask was charged the substrate (0.1 mmol), chiral Brønsted acid (*S*)-**C** (3.9 mg, 0.005 mmol, 5 mol %) and 4 Å MS (100 mg) followed by the addition of toluene (2 mL) at 25 °C. The reaction mixture was allowed to stir at room temperature for 30 min. Upon completion, the reaction mixture was directly passed through a silica gel column (eluent: *n*hexane/EtOAc = 8:1) to give the title compound.

ASSOCIATED CONTENT

Detailed experimental procedures, characterization data and ^{1}H and ^{13}C NMR spectra for all starting materials and products, raw DFT data, XYZ coordinates, and the CIF files for **4j** and **4**η. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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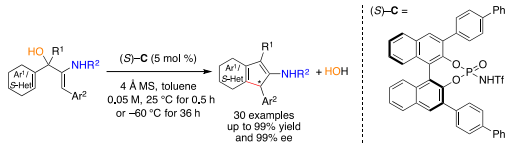
TOC


HO
R1
NHR2
Ar1
S-Het
Ar2
(S)–C (5 mol %)
4 Å MS, toluene
0,05 M, 25 °C for 0,5 h
or –60 °C for 36 h
R1
Ar1
S-Het
NHR2
Ar2
+ HOH
30 examples
up to 99% yield
and 99% ee
(S)–C =
Ph
O
P
O
O
NHTf
Ph