Enantioselective, Catalytic Multicomponent Synthesis of Homoallylic Amines Enabled by Hydrogen-Bonding and Dispersive Interactions

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Supporting Information Placeholder

ABSTRACT: We report a one-step catalytic, enantioselective method for the preparation of homoallylic *N*-Boc amines directly from acetals. Reactive iminium ion intermediates are generated *in situ* through the combination of an acetal, a chiral thiourea catalyst, trialkylsilyl triflate, and *N*-Boc carbamate, and are subsequently trapped by a variety of allylsilane nucleophiles. No homoallylic ether byproducts are detected, consistent with allylation of the iminium intermediate being highly favored over allylation of the intermediate oxocarbenium ion. Acetals derived from aromatic aldehydes possessing a variety of functional groups and substitution patterns yield homoallylic amines with excellent levels of enantiomeric enrichment. Experimental and computational data are consistent with an anchoring hydrogen-bond interaction between the protoiminium ion and the amide of the catalyst in the enantiodetermining transition state, and with stereodifferentiation achieved through specific non-covalent interactions (NCIs) with the catalyst pyrenyl moiety. Evidence is provided that the key NCI in the major pathway is a π-stacking interaction, contrasting with the cation–π interactions invoked in previously studied reactions promoted by the same family of aryl-pyrrolidino-H-bond-donor catalysts.

Enantioselective imine allylation provides a most attractive approach to the synthesis of chiral homoallylic amines, which are versatile intermediates for the synthesis of a wide variety of valuable, nitrogen-containing compounds.[1] As an alternative to effective strategies engaging stoichiometric chiral auxiliaries and additives[2,3] considerable effort has been directed toward the development of catalytic methods for the enantioselective allylation of aldimines (Figure 1A).[4] Most successful approaches have relied on additions to isolated imines, which may be challenging to access and purify due to their hydrolytic sensitivity.[5] Enantioselective allylation of iminium intermediates generated in situ from stable precursors represents an attractive alternative (Figure 1B).[6,7] To date, only a few such enantioselective, three-component coupling reactions have been reported, with notable examples from the groups of List, who employed a chiral disulfonimide catalyst;[8a] Feng, who applied a C_2-symmetric Sc(III) Lewis acid complex,[8b] and Schaus, who achieved enantioselective Petasis-type imine allylations with chiral biphenol catalysts.[8c] Herein we report the successful implementation of an alternative and potentially generalizable strategy that relies on the cooperative action of silyl triflate Lewis acids and chiral H-bond-donor (HBD) catalysts for the direct synthesis of highly enantioenriched homoallylic amines directly from readily available acetal precursors (Figure 1C).

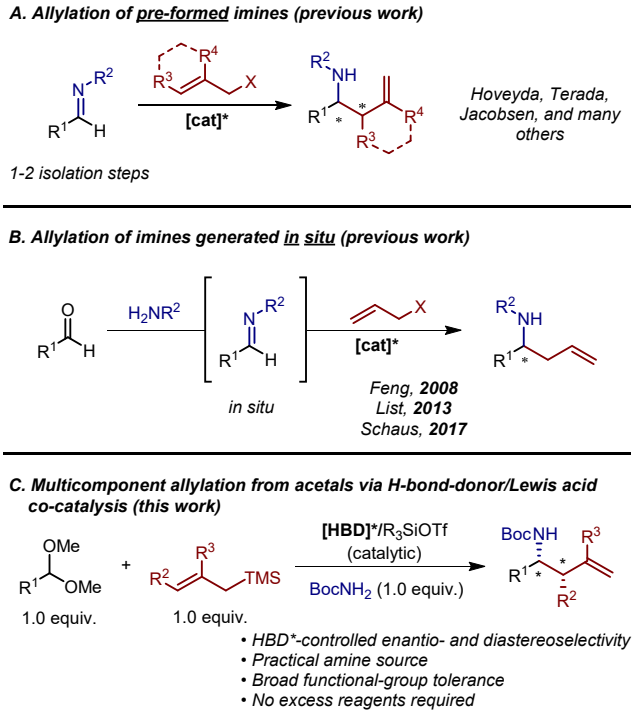

Figure 1. Approaches to imine allylation. A. Classical approach via pre-formed imine substrates. B. Examples of imine allylation via *in situ* generation of iminium species from aldehyde precursors. C. Multicomponent allylation reactions from acetals via chiral H-bond donor ([HBD]*)-silyl triflate co-catalysis.

We recently identified a Lewis acid–chiral dual HBD co-activation strategy that allows highly reactive cationic intermediates to be generated from stable electrophilic precursors and subsequently engaged in enantioselective nucleophilic addition reactions.[9] The approach relies on association of the HBD to a silyl triflate or halide to produce a Lewis acid with enhanced reactivity. Activation of weak electrophiles produces an HBD-associated ion pair, and direct trapping of the cationic electrophile may thus proceed enantioselectively to yield the desired product. We

hypothesized that an oxocarbenium ion generated under the catalytic conditions could be converted to an iminium ion in the presence of a suitable *N*- nucleophile, and that the intermediate thus generated could be trapped in situ and chemoselectively with an allylsilane reagent to afford the desired homoallylic amine product.

Reaction investigations were initiated using acetal **1a** and methallylsilane **2a** as model substrates. The identity of the amine source was found to be crucial for reactivity and chemoselectivity, with carbamates uniquely effective in affording the desired homoallylic amine products.[10] The enantioselectivity of the reaction was sensitive to the alkyl group on the carbamate, with highest levels obtained with $BocNH_2$ (Table S2). Notably, the reaction proceeded to high conversion with equimolar quantities of acetal **1a**, methallylsilane **2a**, and $BocNH_2$. Enantioselectivities were insensitive to the identity of the trialkylsilyl triflate, and TESOTf selected due to its ease of use. With the basic reaction parameters thus identified, an extensive survey of chiral dual-HBD catalysts revealed that chiral thioureas harboring arylpyrrolidine motifs afforded **3a** in the highest e.e. (Figure 2). As seen previously in other reactions promoted by this class of catalysts,[9] we observed a positive correlation between the expanse of the aryl substituent on the pyrrolidine and enantioselectivity, leading to the identification of (4-pyrenyl)pyrrolidino thiourea **4f** as optimal (95% e.e.). However, in sharp contrast with other reactions, the identity of the dual H-bond donor had very little effect on reaction outcome, with the corresponding urea (**5f**) and squaramide (**6f**) catalysts promoting the model reaction with very similar levels of enantioselectivity. This and other unique features of the observed catalyst-enantioselectivity effects signaled an unusual mechanism of stereoinduction, as will be analyzed further below.

The scope of the new multicomponent homoallylic amine synthesis was investigated under the optimized conditions (Figure 3). Consistently high enantioselectivity was achieved with arylaldehyde dimethylacetals bearing a wide variety of substitution patterns (**3a**–**3l**, 94–99% e.e.). The reaction was compatible with potentially reactive functional groups on the substrates such as esters (**3j**), phenols (**3l**), and *N*-, *O*-, and *S*-heteroaromatic groups (**3n**–**3s**), with the corresponding desired products obtained efficiently and with high enantioselectivities. The methodology was extended successfully to the acetal derived from the conjugated cyclohexene carboxaldehyde to afford the corresponding allylic amine product in good yield and enantioselectivity (**3m**). However, acetals derived from aliphatic aldehydes displayed poor reactivity and afforded homoallylic amine products in <55% e.e.[11] Aldehydes also participate effectively as electrophiles in the reaction, providing the corresponding homoallylic amine products with the same levels of enantioselectivity as the corresponding dimethyl acetals, albeit in 10-30% lower conversion and yields (see Supporting Information).

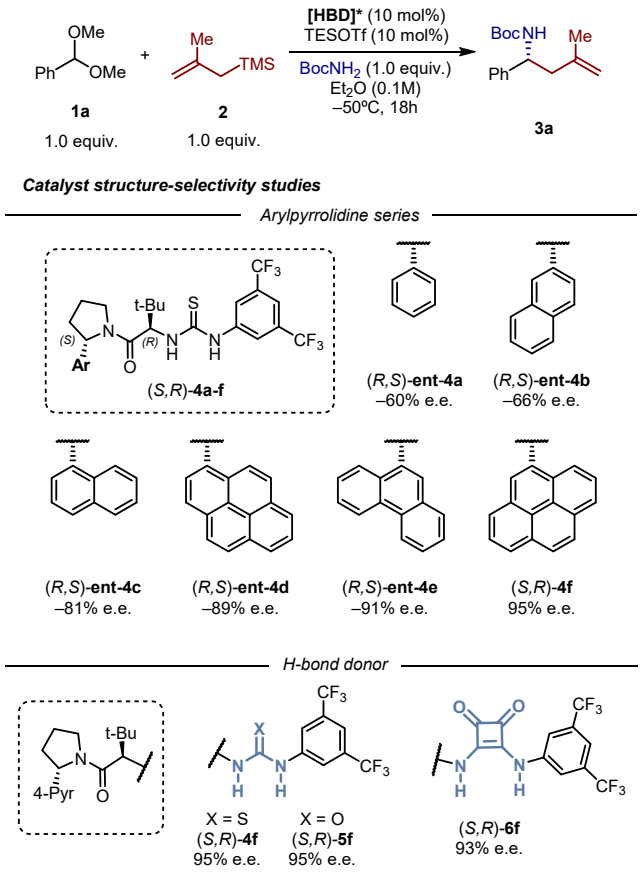

Figure 2. Chiral H-bond donor ([HBD]*) catalyst-structure-enantioselectivity relationship studies: variation of aryl pyrrolidine and H-bond donor identity.

The nucleophilic allylsilane component of the coupling reaction could also be varied to other 2-substituted derivatives (**3t**-**3u**) while maintaining excellent enantioselectivities. Reactions with the prochiral 2,3-disubstituted allyltrimethylsilane (**3w**) proceeded with both high enantioselectivity and excellent diastereoselectivity (>50:1 d.r.). The latter observation is noteworthy given the likelihood that these allylation reactions proceed via open transition states (see discussion below, Figure 5C), and the fact that the same reaction carried out in the absence of thiourea **4f** was found to proceed with significantly lower diastereoselectivity (5:1 d.r.). None of the homoallylic amine product was obtained when the less nucleophilic parent allyltrimethylsilane was employed.

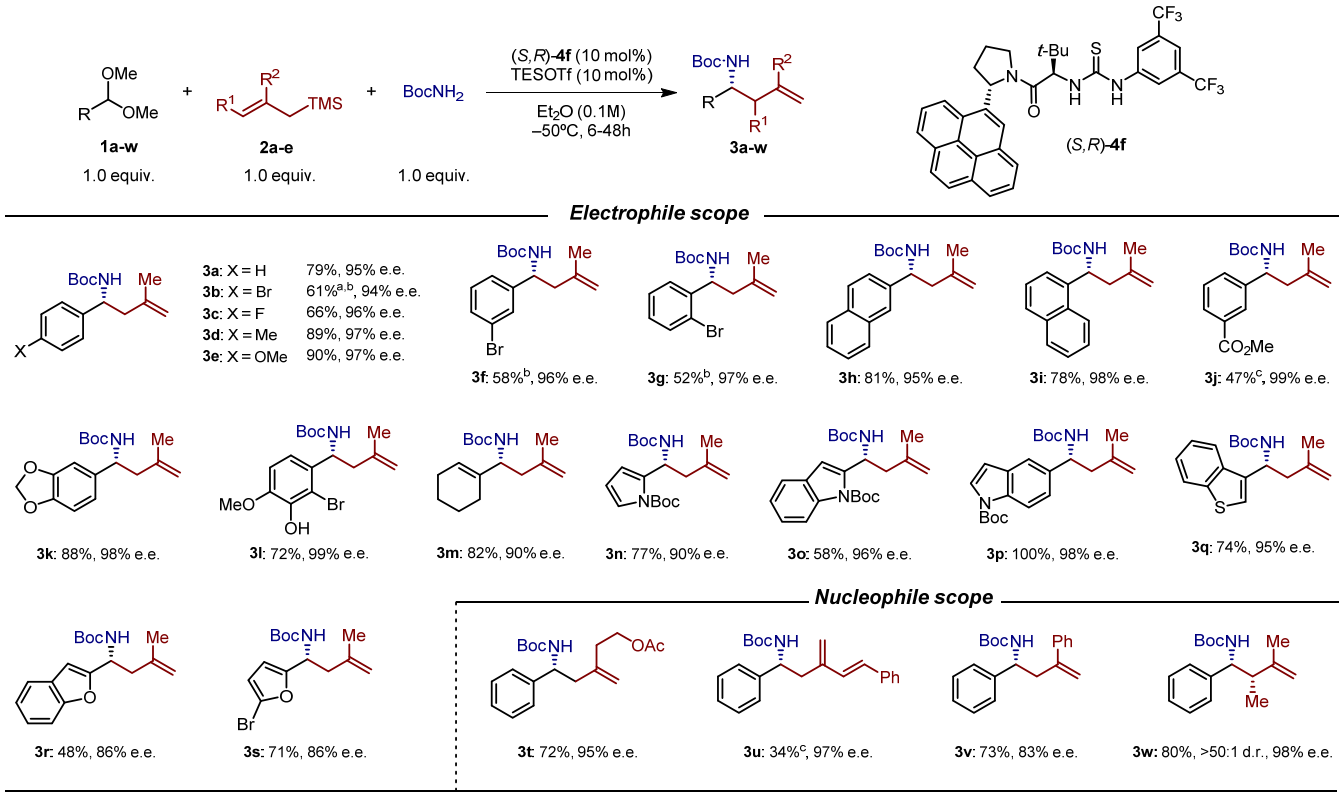

Figure 3. Reaction scope. Enantioselectivity was determined by chiral HPLC analysis of purified product on commercial columns (see Supporting Information for separation conditions). Conditions: acetal **1a-w** (0.3 mmol), $BocNH_2$ (0.3 mmol), **2a-e** (0.3 mmol), TESOTf (0.03 mmol), **4f** (0.03 mmol), Et_2O (0.1M), cooled to −50°C, 6h or 18h (see Supporting Information for details). [a] run for 24h. [b] run at −25°C. [c] run for 48h.

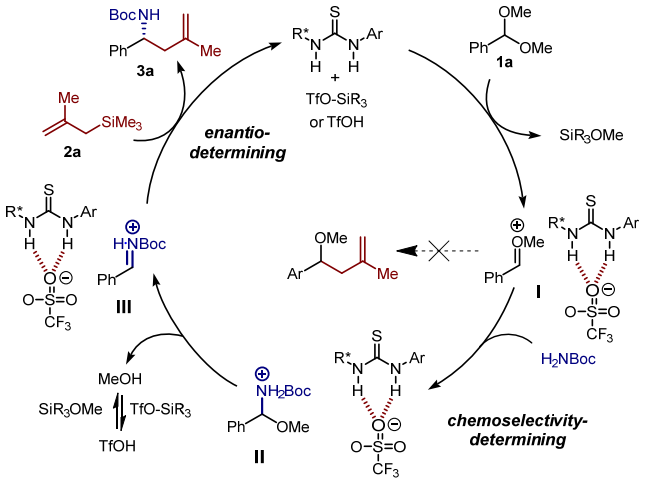

Figure 4. Proposed catalytic cycle for the multicomponent allylation reaction; R = Me, Et.

A proposed catalytic cycle for the multicomponent allylation reaction is depicted in Figure 4. The cooperative action of dual H-bond donors and silyl triflates has been shown to promote activation of simple acetals to afford oxocarbenium ion intermediates such as **I**,[9a] which in the present system are intercepted by $BocNH_2$ en route to the iminium ion pair **III**. Qualitative observations that reaction rates are increased with electron-rich acetal substrates and are independent of [$BocNH_2$] are consistent with either rate-limiting generation of oxocarbenium ion **I** or breakdown of the hemiaminal intermediate (**II** → **III**). While exclusive formation of homoallylic amines was observed with allylsilanes such as **2a**, stronger π-nucleophiles such as silyl enol ethers and silyl ketene acetals[11] afforded mixtures of amine- and ether-containing products (Table S10). The relative reactivity of the π-C-centered nucleophile versus the N-centered nucleophile (i.e. $BocNH_2$) toward **I** thus determines chemoselectivity. The key iminium ion intermediate **III** is poised to undergo enantiodetermining coupling with methallylsilane **2a** to afford the observed homoallylic amine **3a**. The MeOH generated stoichiometrically in the breakdown of heminaminal **II** may give rise to a TfOH co-catalyzed pathway. Indeed, almost identical enantioselectivities were obtained using TfOH as co-catalyst (Table S9).

It is to be expected and indeed generally observed that the identity of the H-bond donor motif has a profound effect on reaction outcomes in asymmetric HBD catalysis.[13] For example, squaramides have been shown to induce substantially higher enantioselectivities than analogous urea and thiourea catalysts in previously reported HBD/silyl triflate co-catalyzed reactions.[9d,f] It is therefore intriguing that the urea, thiourea, and squaramide analogs **4f-6f** all catalyze the multicomponent homoallyl amine synthesis with very similar levels of enantioselectivity (Figure 2, bottom). In an effort to elucidate the basis for this unexpected insensitivity to the identity of the presumed

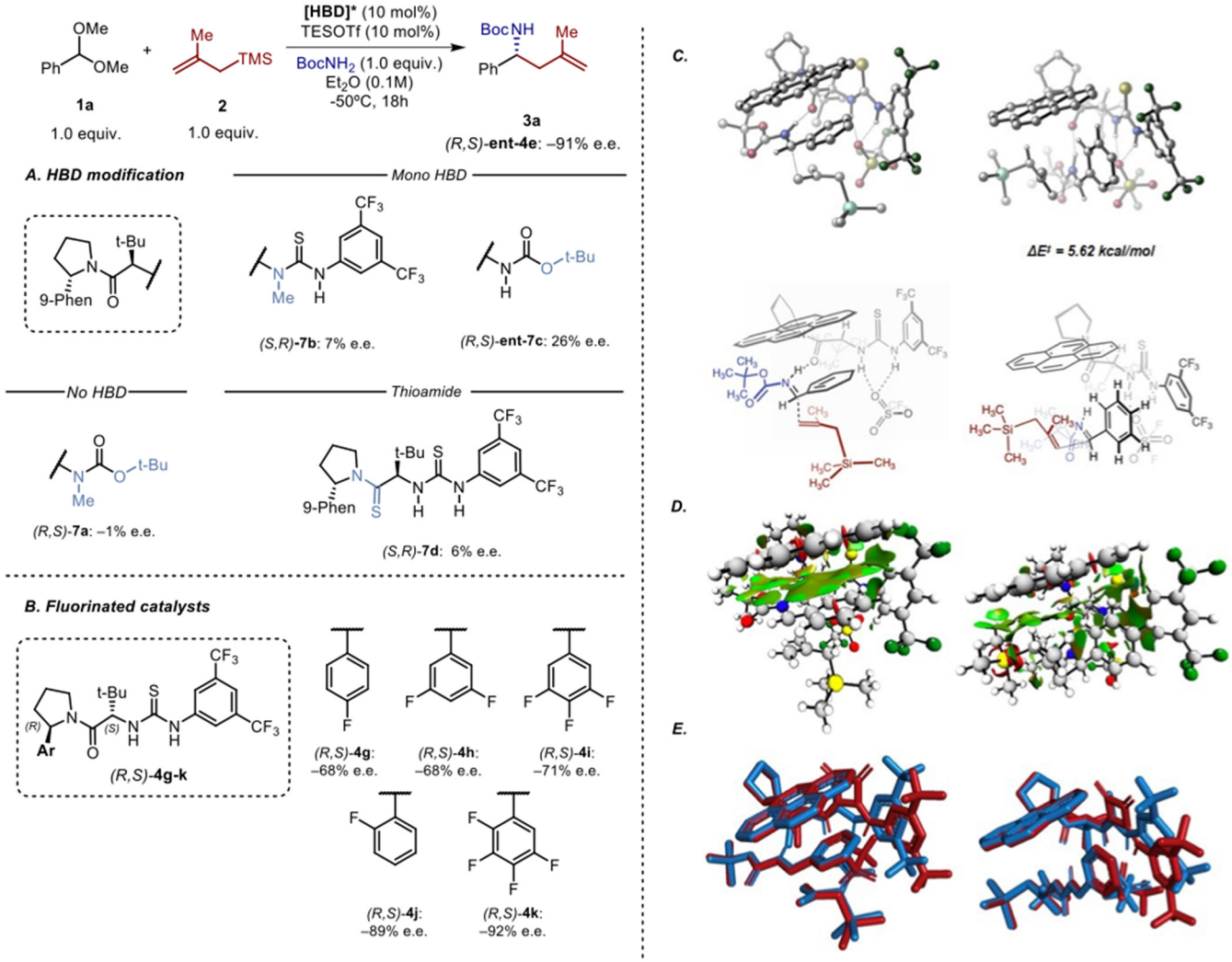

Figure 5. Catalyst structure-enantioselectivity and computational studies. A. Effects of changes to the HBD and amide motif. B. Effects of perturbing the electronic properties of the aryl-pyrrolidine moiety through fluorination. C. Computed lowest energy transition states of the enantiodetermining iminium ion allylation step with catalyst (*R,S*)-**4f**. See Supporting Information for details of the computational analyses. D. Non-covalent interaction (NCI) analysis of lowest energy transition states of catalyst (*R,S*)-**4f** showing different extent of dispersive interactions between the 4-pyrenyl moiety of the catalyst and the substrate. E. Overlay of the computed lowest energy transition states (left: major pathway, right: minor pathway) for thiourea catalyst (*R,S*)-**4f** (blue) and the analogous squaramide catalyst (*R,S*)-**6f** (red).

catalytic engine, we carried out a systematic analysis of the HBD motif (Figure 5). Reactions run with **7a**, a compound lacking any HBD component, yielded essentially racemic product, while variants in which the dual HBD was substituted with a single HBD (as in **7b** or **7c**) were poorly enantioselective.

While the above results indicate that a dual HBD motif may be necessary for attaining high enantioselectivity, they provide no explanation for the unexpected similarity in outcomes with the urea, thiourea, and squaramide analogs. We hypothesized that other catalyst components must therefore be playing crucial roles in enantioinduction. The ability of catalysts in this class to act as hydrogen-bond acceptors through the amide moiety has been proposed in other reactions and is supported by numerous computational models.[9b,9f,14] To test whether such an interaction plays a role in the present system, we prepared and evaluated catalyst **7d** bearing a thioamide in place of the amide.[15] Product **3a** was obtained with drastically lower e.e. with the thioamide catalyst in the model reaction (Figure 5a), consistent with the participation of an explicit interaction between the amide on the catalyst and the protioiminium ion intermediate **III** in the enantiodetermining transition state.

Positive correlations between reaction enantioselectivity and the expanse of the aryl substituent of the arylpyrrolidino HBD catalysts (e.g., Figure 2, **4a**–**4f**) have been noted previously, and in each instance have been ascribed to selective cation–π interactions in the enantiodetermining transition state.[9b,9f,16] We therefore assumed initially that the same type of NCI played a key role in the present system. However, fluorine substitution on the arene had little effect on enantioselectivity within sterically similar arylpyrrolidine derivatives (68-71% e.e. for the mono-, 3,5-di-, and 3,4,5-trifluoro derivatives **4g**–**4i**, vs. 60% e.e. for the parent phenyl **4a**; 89-92% e.e. for 2-fluoro-substituted derivatives **4j**–**4k** vs. 81-95% e.e. with 1-napthyl, 9-anthryl, or pyrenyl derivatives **4c**–**4f**, Figures 2 and 5). Arene fluorination is known to disrupt cation–π interactions,[17] so

these results appear to rule out key cation–π interactions in the enantiodetermining event in the present system, and indicate participation of other, previously undocumented, selective interactions with the aryl pyrrolidine.

A DFT computational study was undertaken to glean insight into the nature of the enantiodetermining interactions (Figure 5C). Lowest energy transition state (TS) structures for both the major and minor enantiomeric pathways were identified (see Supporting Information for details). The anchoring amide–iminium hydrogen–bonding interaction deduced from the catalyst structure-enantioselectivity studies (*vide supra*) was captured and is present in both TS structures. A face-face π–stacking interaction between the substrate arene and the catalyst arylpyrrolidine is evident in the major TS, while the minor transition state adopts a T-shaped orientation between the same arenes. A non-covalent interaction (NCI) analysis[18] reveals extensive reduced density gradients between the aromatic rings of the catalyst and the substrate in the major TS, consistent with the presence of van der Waals-type interactions (Figure 5D, green region). Transition state models generated for thiourea- (**4f**) and squaramide- (**6f**) promoted pathways reveal the same secondary interactions and remarkably similar geometries, differing only in the positioning of the triflate and the aniline-derived component of the catalyst (Figure 5E). On the basis of the experimental and computational data, we conclude that the combination of coulombic, H-bonding, and dispersive π-stacking interactions are involved in the HBD-R_3SiOTf co-catalyzed aza-Sakurai reaction, with the latter playing the determining role in enantioinduction.

We have developed an efficient and selective catalytic method for the synthesis of enantioenriched, homoallylic *N*-Boc amines in one pot from acetals based on the cooperative action of achiral Lewis/Brønsted acid and chiral dual HBD catalysts. The high levels of enantioselectivity and diastereoselectivity across a broad range of substrates render the new protocol applicable to the preparation of valuable homoallylic amine derivatives. Strong evidence was obtained for a previously unidentified mode of enantioinduction with the arylpyrrolidino-HBD catalysts, highlighting the privileged nature of these scaffolds in their ability to induce high levels of stereocontrol through distinct mechanisms.[19]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI (XXXX).
Experimental procedures and characterization data for new compounds (PDF)

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Notes

The authors declare no competing financial interests.

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(11) A representative survey of less-effective substrates is provided in Figure S1.

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