REPORT

ORGANIC CHEMISTRY

Lewis acid enhancement by hydrogen-bond donors for asymmetric catalysis

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Small-molecule dual hydrogen-bond (H-bond) donors such as ureas, thioureas, squaramides, and guanidinium ions enjoy widespread use as effective catalysts for promoting a variety of enantioselective reactions. However, these catalysts are only weakly acidic and therefore require highly reactive electrophilic substrates to be effective. We introduce here a mode of catalytic activity with chiral H-bond donors that enables enantioselective reactions of relatively unreactive electrophiles. Squaramides are shown to interact with silyl triflates by binding the triflate counterion to form a stable, yet highly Lewis acidic, complex. The silyl triflate-chiral squaramide combination promotes the generation of oxocarbenium intermediates from acetal substrates at low temperatures. Enantioselectivity in nucleophile additions to the cationic intermediates is then controlled through a network of noncovalent interactions between the squaramide catalyst and the oxocarbenium triflate.

Chiral hydrogen-bond (H-bond) donors can catalyze enantioselective nucleophile-electrophile addition reactions either by direct complexation with neutral electrophiles or by anion binding to generate chiral ion-pair intermediates (Fig. 1A) (*1*, *2*). However, because of the generally weak Brønsted acidity of the catalysts (*3*, *4*), these approaches commonly require highly electrophilic substrates with labile carbon-heteroatom (σ or π) bonds (*2*). We considered whether the anion-binding principle could be applied in a fundamentally different way to enhance the reactivity of Lewis acids such as silyl triflates through association of a chiral H-bond donor with the triflate. This strategy could facilitate the generation of highly reactive cationic intermediates from relatively stable precursors, while still enabling enantiocontrol through noncovalent interactions with the chiral catalyst. We report here the realization of this idea in the discovery of cooperative reactivity between silyl triflates and chiral squaramides and its application to a series of enantioselective reactions involving oxocarbenium ion intermediates.

Silyl triflates are readily available Lewis acids with broad application in organic synthesis (*5*, *6*). The reactivity of these reagents is enhanced through incorporation of more weakly coordinating anionic ligands such as disulfonimides, as demonstrated initially by Ghosez in racemic Diels-Alder reactions (*7*–*9*). List and co-workers extended this advance to enantioselective catalysis through the design of chiral disulfonimide counteranions that associate with the active silylium species (*10*, *11*). We envisaged an alternative approach wherein association of a chiral H-bond donor with the triflate anion would generate a charge-separated complex with enhanced Lewis acidity relative to silyl triflate alone. Given the outstanding chiral induction properties of H-bond donors in reactions of ion-pair intermediates, this approach would open the door to a wide variety of enantioselective catalytic

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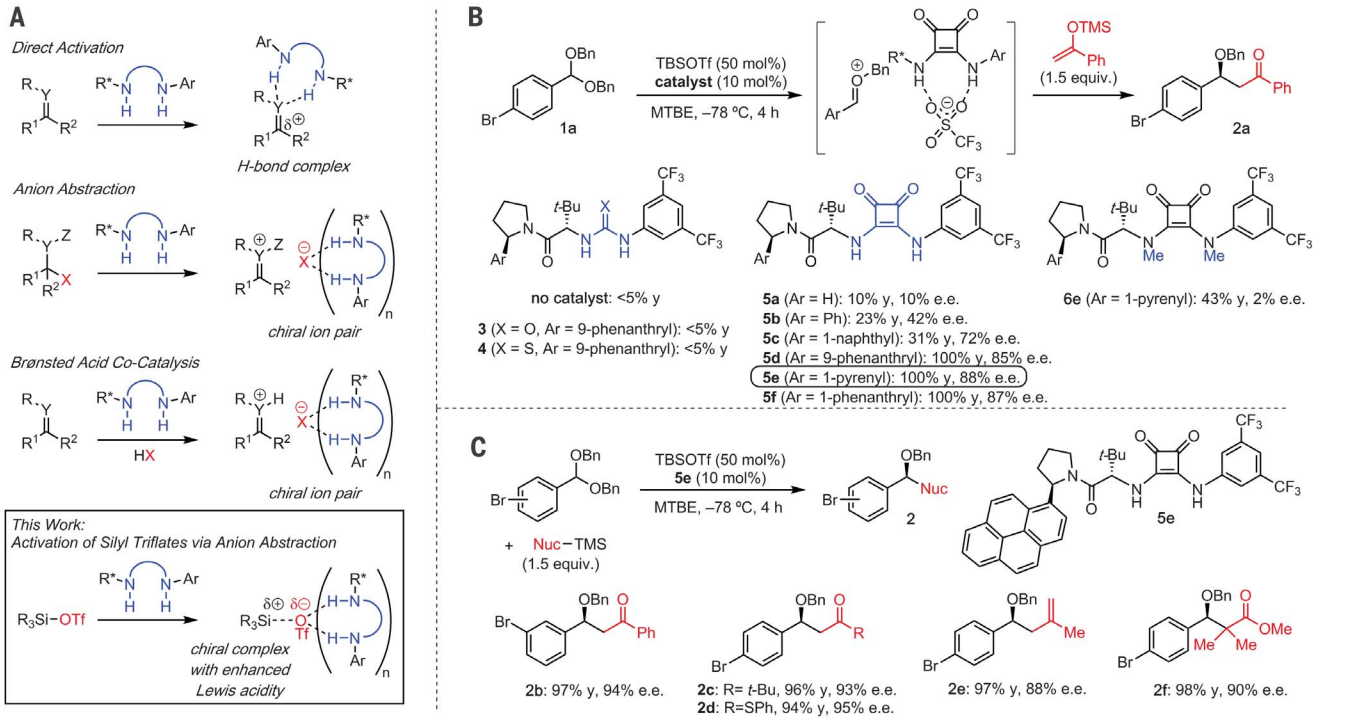

Fig. 1. Reactivity concept and reaction development. (**A**) Existing strategies for electrophile activation using chiral dual hydrogen-bond donor catalysts and the approach explored in this study using anion binding to generate a reactive, cationic metal or metalloid center as a chiral ion pair. (**B**) Proof-of-concept in the silyl triflate–promoted Mukaiyama aldol reaction of an acetal, with examples from optimization studies of the chiral squaramide catalysts. (**C**) Representative examples of enantioselective alkylation reactions of acetals promoted by TBSOTf and catalyzed by **5e**.

reactions. We sought to apply this activation principle to the generation of oxocarbenium ions from stable acetals for the Mukaiyama aldol reaction, a prototypical Lewis acid–promoted process (*12*, *13*); the trimethylsilyl enol ether derived from acetophenone and 4-bromobenzaldehyde dibenzyl acetal (**1a**) were selected as model substrates (Fig. 1B). Under the optimized reaction conditions [–78°C, methyl *tert*-butyl ether (MTBE)], the combination of chiral squaramide (*14*) derivatives (**5**) and silyl triflates [e.g., *tert*-butyldimethysilyl trifluoromethanesulfonate (TBSOTf), 50 mole %] was particularly effective at promoting the enantioselective reaction; no reaction was observed with TBSOTf either alone or in the presence of representative urea (**3**) and thiourea (**4**) catalysts under the same conditions. Reactivity and enantioselectivity were strongly responsive to the expanse of the arylpyrrolidine substituent on the squaramide, with pyrenyl catalyst **5e** being optimal [100% conversion, 88% enantiomeric excess (e.e.)]. The importance of the H-bond donor motif of the catalyst was established through evaluation of **6e**, the *N*,*N*′-dimethyl squaramide analog of **5e**, which promoted the aldol addition but afforded nearly racemic product. This observation of moderate reactivity but negligible enantioselectivity with **6e** suggests that the Lewis basic properties of the squaramide catalysts may play a role in enhancing the Lewis acidity of the silyl triflate (*15*, *16*) but that the H-bond donor properties are essential for effective stereochemical control.

This strategy for generating oxocarbenium ion intermediates from stable acetals and engaging them in enantioselective alkylation reactions was readily extended to other classes of nucleophiles (Fig. 1C). With **5e** and TBSOTf (*17*) as the silyl triflate promoter, allyl silane, silyl enol ether, and silyl ketene acetal nucleophiles engaged in highly enantioselective reactions with electrophiles derived from **1** (for expanded substrate scope, see fig. S1). Effective enantiocontrol in alkylations of oxocarbenium ions was thus achieved with alkylating reagents spanning five orders of magnitude of nucleophilicity (N = 3.78 to 9.00) (*18*).

We sought to test the generality of H-bond donor–silyl triflate cooperativity in a highly demanding synthetic context and selected (4+3) cycloadditions for examination. These reactions provide an attractive approach to functionalized seven-membered carbocyclic frameworks (*19*, *20*), and limited success in the development of enantioselective, catalytic variants has been achieved despite important pioneering efforts (*21*–*23*). A protocol analogous to the one described above for Mukaiyama aldol–type reactions of acetals (*24*, *25*) was applied successfully to the reaction of oxyallyl cation precursors (**7**) with furan derivatives (**8**) to generate bicyclic (4+3) cycloadducts (**9**) in good yield and high enantioselectivity as single diastereomers (Fig. 2). Substituted oxyallyl cation precursors and three-substituted furans, in particular, afforded products with the highest enantioselectivity (**9b** to **9k**). As observed in the Mukaiyama-type reactions, squaramides were

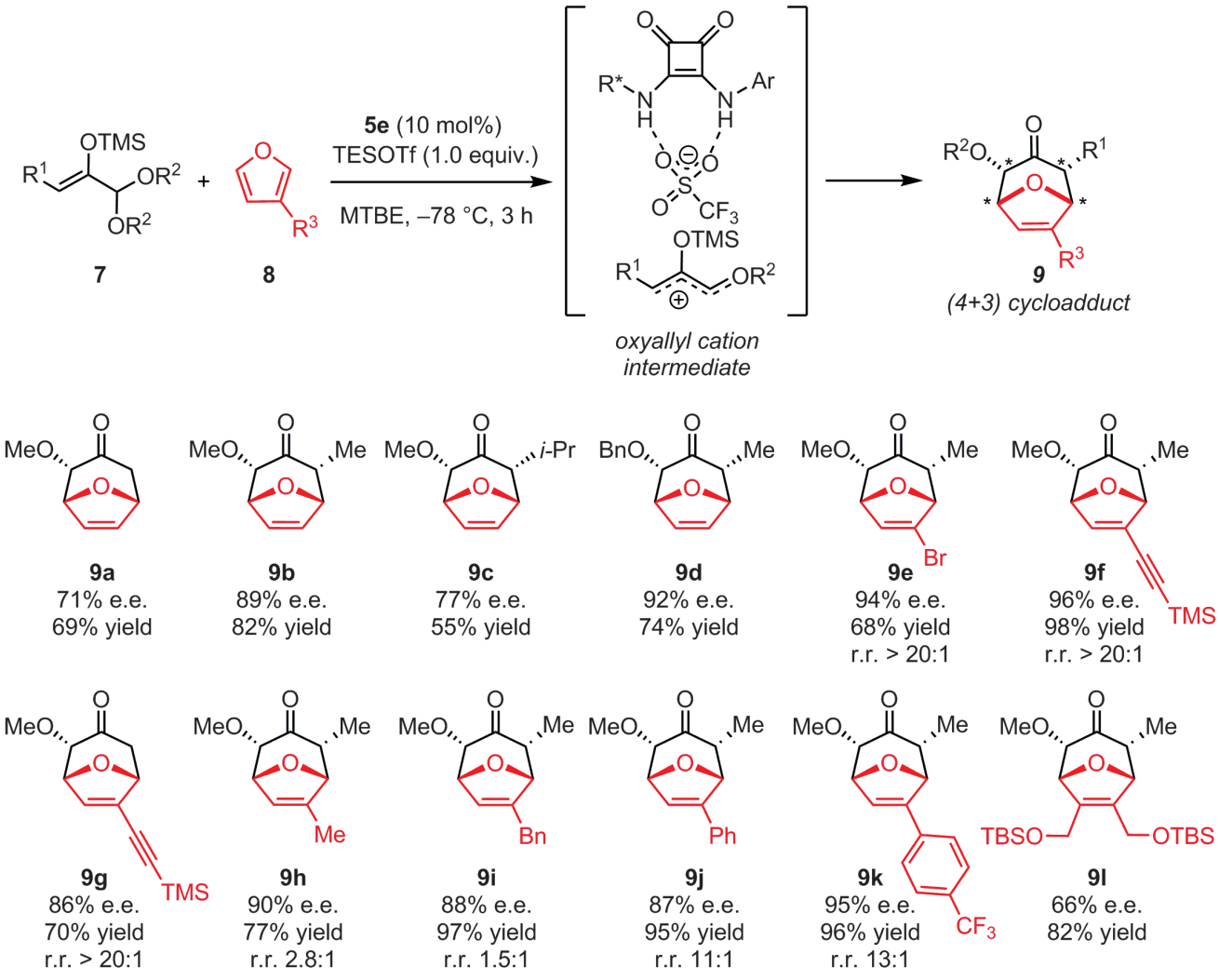

Fig. 2. (4+3) Cycloaddition substrate scope. Cooperative reactivity of squaramide catalysts and silyl triflate Lewis acids in enantioselective (4+3) cycloadditions via oxyallyl cation intermediates; r.r. is the regioisomeric ratio. In all cases, only the indicated diastereomer was detectable. Absolute stereochemistry was assigned by x-ray crystallographic analysis of a 9b and a crystalline derivative of 9e.

particularly effective as catalysts, and a strong dependence of reactivity and enantioselectivity on catalyst structure was observed, with squaramide derivative **5e** again affording optimal results (fig. S7).

The results presented in Figs. 1 and 2 reveal that the cooperative action of squaramide H-bond donors with silyl triflates can serve to catalyze a variety of enantioselective transformations of acetals and may offer a general approach to catalytic generation and asymmetric reaction of cationic intermediates from relatively stable precursors. Given the potential utility of this approach, we undertook a careful analysis of the (4+3) cycloaddition to glean insight into the underlying catalytic mechanism. The reaction that generates bicyclic adduct **9g** was selected for kinetic analysis because it proceeds with rates conveniently monitored by in situ infrared (IR) spectroscopy. A first-order kinetic dependence on acetal and a zero-order dependence on furan were observed (figs. S14 and S15), together with saturation kinetics with respect to [TESOTf] (Fig. 3A, left) and a first-order dependence on squaramide **5e**. The recently reported method of Burés for determination of reaction order in [**5e**] proved particularly convenient in this regard (Fig. 3A, right) (*26*).

The kinetic data for the (4+3) cycloaddition are consistent with a pre-equilibrium formation of a resting-state complex between the squaramide catalyst and TESOTf and rate-limiting reaction of this complex with the acetal substrate (*27*). To assess this model and the nature of this complex, the interaction between the H-bond donor catalyst and TESOTf was examined spectroscopically. Titration experiments were performed with catalyst **5g**, which provided well-resolved proton nuclear magnetic resonance (^{1}H NMR) spectra and displayed similar kinetic behavior to **5e** (*28*). Application of the method of continuous variation revealed a 1:1 binding interaction between TESOTf and **5g** (Fig. 3B). In this manner, 1:1 binding was established between different squaramide and triflate sources, and the binding constants were determined from titration experiments quantified by ^{1}H NMR (Fig. 3C). As expected given the known anion-binding properties of squaramides (*29*), NBu_4OTf forms a stable complex with **5g** in CD_2Cl_2 (Fig. 3C, entry 1). However, TESOTf was found to bind 4000 times as tightly as NBu_4OTf (Fig. 3C, entry 2), an indication that simultaneous binding of both the triflate and the trialkyl silyl component may be occurring in the complex. Further evidence for a direct squaramide-silicon interaction is provided by the observation that the dimethylated squaramide derivative **6g**, which lacks H-bond donor capabilities, also forms a complex with TESOTf. Titration of a solution of **5g** in MTBE at –78°C with TESOTf was also monitored by in situ IR spectroscopy, with disappearance of the absorbances attributed to the squaramide carbonyl groups observed upon addition of TESOTf (Fig. 3D) (*30*). Taken together, the kinetic and binding studies are consistent with an unexpectedly strong 1:1 complex between

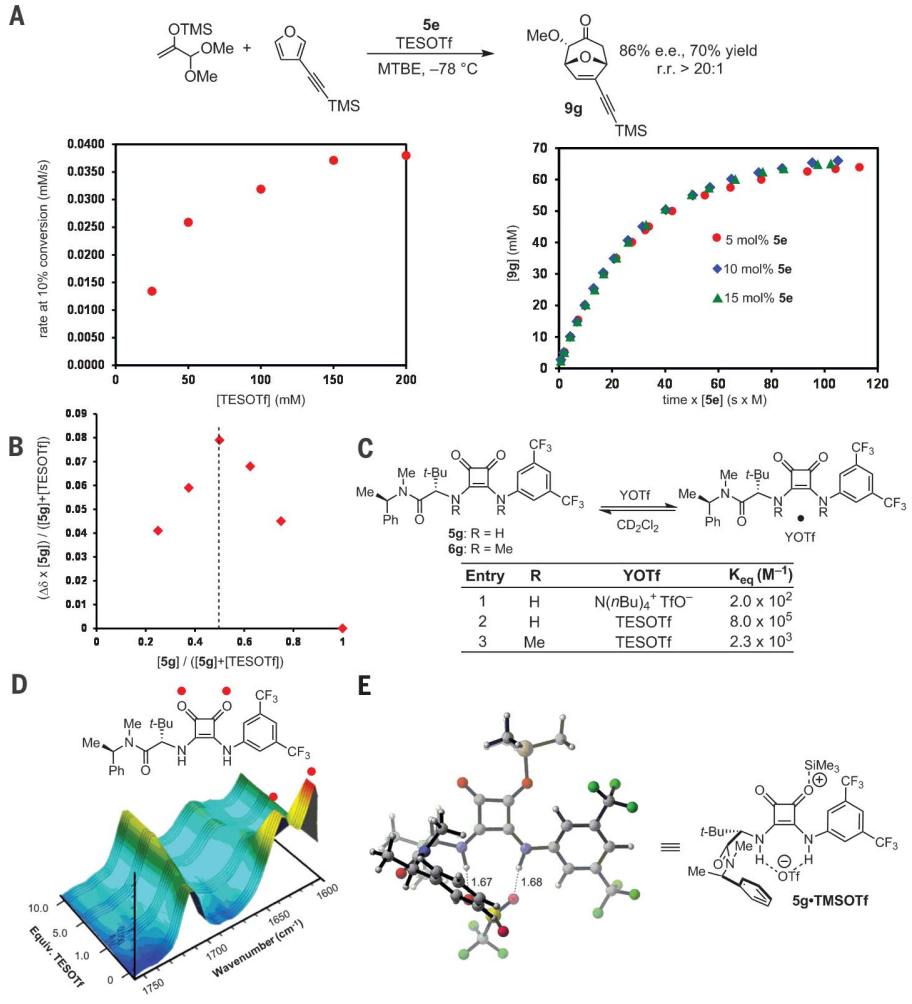

Fig. 3. Mechanistic studies. (**A**) Kinetic analysis of a model (4+3) cycloaddition reaction promoted by **5e**. The reaction rate obeys a first-order dependence on [**5e**] as determined using the Burés method and displays saturation in [TESOTf]. (**B**) Job plot for the binding of TESOTf to **5g** indicating a 1:1 binding stoichiometry. (**C**) Equilibrium constants for the binding of **5g** with NBu_4OTf and TESOTf, and of **6g** with TESOTf. These provide evidence for cooperative binding of TESOTf to **5g**. Experiments were conducted at 23°C in CD_2Cl_2. (**D**) IR spectra monitoring addition of TESOTf to catalyst **5g** at –78°C in MTBE. (**E**) Lowest-energy ground-state structure of **5g** bound to TMSOTf. Calculations were performed at the B3LYP/6-31G(d) level. Structures of alternative, higher-energy complexes are provided in fig. S22.

TESOTf and **5** as the resting state of the catalyst in the reactions outlined in Figs. 2 and 3.

Computational modeling of the 1:1 complex between **5g** and trimethylsilyl trifluoromethanesulfonate (TMSOTf) using density functional theory (DFT) revealed a minimum energy structure in which the silyl triflate is dissociated heterolytically, with the triflate anion engaged by nearly symmetrical dual H-bonding interactions (1.67 and 1.68 Å) and the corresponding silylium cation associated covalently with the more Lewis basic of the carbonyls in the squaramide moiety (Fig. 3E). This dual interaction mode may account for the enhanced affinity of the squaramide for the silyl triflate relative to tetra-alkylammonium triflate. Under the conditions of catalysis, the activated silylium species may be associated directly with the squaramide, such as in Fig. 3E, and/or with the solvent. In either case, the complex between **5** and trialkyl silyl triflate (R_3SiOTf) is expected to be more Lewis acidic than R_3SiOTf alone due to the stabilization of the triflate anion by the H-bond donor.

The catalytic cycle depicted in Fig. 4A is consistent with the kinetic and binding studies outlined above. The silyl triflate-squaramide complex serves as the resting state of the catalyst and as a potent Lewis acid that promotes acetal ionization. Post-rate-determining reaction of the oxyallyl cation intermediate with the furan affords the (4+3) cycloadduct. Based on the observation that similar e.e.'s are obtained with different trialkyl silyl triflate promoters (fig. S5), it is proposed that the enantioselectivity-determining step occurs after formation of the oxyallyl cation and involves the reaction with furan. The basis

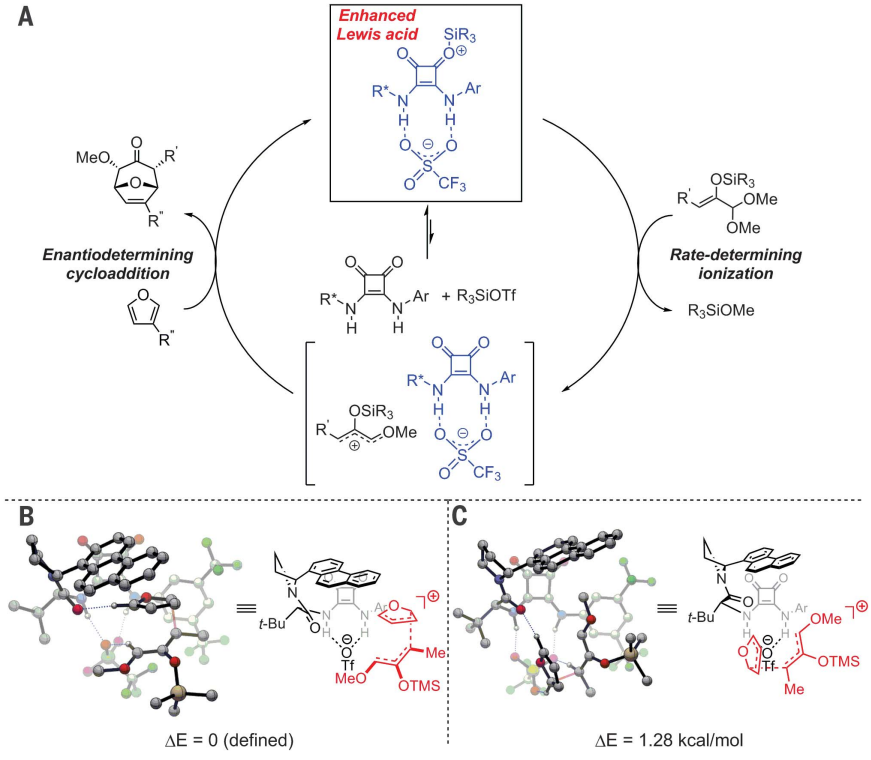

Fig. 4. Proposed mechanism. (**A**) Proposed catalytic cycle for the enantioselective, catalytic (4+3) reactions with **5**•R_3SiOTf acting as an enhanced Lewis acid. (**B**) Lowest-energy transition structure for the first, selectivity-determining C–C bond-forming step in the addition of furan to an oxyallyl cation intermediate, leading to the experimentally observed major enantiomer. (**C**) Corresponding transition structure leading to the minor enantiomer. Structures were calculated at the B3LYP/6-31G(d) level of theory, with uncorrected electronic energies at the M062x/6-31+G(d,p) level.

for stereoinduction in the cycloaddition reaction was probed computationally using DFT with ***5f*** as the squaramide catalyst. Consistent with previous studies on (4+3) cycloadditions of furan and alkoxy silyloxyallyl cations (*31*, *32*), the calculations converge on a stepwise mechanism involving initial nucleophilic attack by furan at the vinyl terminus of the oxyallyl cation followed by ring closure (fig. S22). The structures corresponding to the lowest-energy transition states for the first, enantioselectivity-determining C–C bond-forming step en route to the major and minor enantiomers of product are presented in Fig. 4, B and C, respectively. Single-point calculations at the M062X/6-31+G(d,p) level of theory reproduce both the sense and magnitude ($\Delta\Delta E^{\ddagger}_{calc}$ = 1.28 kcal/mol) of enantioinduction determined experimentally. Both transition states display a network of hydrogen-bonding interactions between the oxyallyl fragment and the triflate counterion, as well as between furan and the amide backbone of the catalyst. However, the positioning of the furan nucleophile in proximity to the aromatic substituent of the catalyst in the major transition state suggests a stabilizing interaction between the furan and the catalyst. Such an interaction is absent in the minor one and may thus be a key factor responsible for enantioselectivity (*33*, *34*).

The interaction between simple silyl triflates and squaramide H-bond donors produces a highly reactive Lewis acid complex capable of activating acetals to produce chiral catalyst-associated oxocarbenium ion intermediates. Enantioselectivity in reactions of these intermediates can be achieved through the interplay of noncovalent interactions between the H-bond donor catalyst and both components of the ion pair. Enhancement of the intrinsic reactivity of Lewis acids represents a potentially powerful strategy for the development of asymmetric reactions proceeding through high-energy cationic intermediates.

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27. On the basis of the binding data depicted in Fig. 3, C and D, rate saturation in the catalytic reaction would be expected to occur at lower [TESOTf] than what is observed in Fig. 3A. One possible explanation for this discrepancy is that the acetal substrate might undergo initial conversion to a mixed sulfonate acetal [i.e., RCH(OMe)(OTf)], which then undergoes ionization to generate the oxocarbenium intermediate (see fig. S16). This scenario fits within the general catalytic cycle proposed in Fig. 4A and does not require any changes to the mechanistic conclusions outlined herein.
28. The enantioselective reaction proceeds most effectively and remains homogeneous in ethereal solvents such as MTBE. However, gel formation was observed at high concentrations. Accordingly, the quantitative binding measurements were carried out in CD_2Cl_2 to ensure complete solubility of all components and to avoid competing reactions between TESOTf and solvent.
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SUPPLEMENTARY MATERIALS

www.sciencemag.org/content/358/6364/761/suppl/DC1
Materials and Methods
Supplementary Text
Figs. S1 to S23
Tables S1 to S9
References (*35*–*52*)

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Lewis acid enhancement by hydrogen-bond donors for asymmetric catalysis

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Lewis acid catalysis tackled by tag team

Molecular catalysts with two closely spaced nitrogen-hydrogen groups can act like a tweezer, activating a carbon center by latching onto a leaving group through double hydrogen bonding and then pulling it away. In the resultant ion pair, the shape of the catalyst can bias an ensuing reaction to favor just one of two possible mirror-image products. Banik *et al.* used this motif to activate a Lewis acid cocatalyst, pulling a leaving group off silicon instead of carbon (see the Perspective by Mattson). The combined pair of catalysts is more effective for reactions such as asymmetric cycloadditions that involve weaker leaving groups on carbon.

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