Lewis acid enhancement by hydrogen-bond donors for asymmetric catalysis

Steven M. Banik, Anna Levina, Alan M. Hyde, Eric N. Jacobsen

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) (7, 8). However, because of the generally weak Bronsted 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 silylum 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 donor catalysis in reactions of ion-pair intermediates, this approach would open the door to a wide variety of enantioselective catalytic reactions.

Department of Chemistry and Chemical Biology, Harvard University, Cambridge, MA 02138, USA.* These authors contributed equally to this work.
†Corresponding author. Email: jacobsen@chemistry.harvard.edu

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-butyldimethylsilyl 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 expansion 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 stereocchemical 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...
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 acetal substrates 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 (1H 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 1H NMR (Fig. 3C). As expected given the known anion-binding properties of squaramides (29), NBu4OTf forms a stable complex with 5g in CD2Cl2 (Fig. 3C, entry 1). However, TESOTf was found to bind 4000 times as tightly as NBu4OTf (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 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 silyl 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 tetralkylammonium triflate. Under the conditions of catalysis, the activated silyl species may be associated directly with the squaramide, such as in Fig. 3F, and/or with the solvent. In either case, the complex between 5 and trialkyl silyl triflate (R3SiOTf) is expected to be more Lewis acidic than R3SiOTf 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 oxallyl 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 oxallyl cation and involves the reaction with furan. The basis

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 NBu4OTf and TESOTf, and of 6g with TESOTf. These provide evidence for cooperative binding of TESOTf to 5g. Experiments were conducted at 23°C in CD2Cl2. (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.
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 oxallyl cation followed by ring closure (fig. S22). The structures corresponding to the lowest-energy transition states for the first, selectivity-determining C–C bond-forming step in the addition of furan to an oxallyl cation intermediate, leading to the experimentally observed major enantiomer. 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.

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.

Fig. 4. Proposed mechanism. (A) Proposed catalytic cycle for the enantioselective, catalytic (4+3) reactions with 5-R3SiOTf 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 oxallyl 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.
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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. Science, this issue p. 761; see also p. 720

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